Host genetics in susceptibility to respiratory infectious diseases

Gelemanović, Andrea

Doctoral thesis / Disertacija

2019

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Split, School of Medicine / Sveučilište u Splitu, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:171:574158

Rights / Prava: In copyright / Zaštićeno autorskim pravom.

Download date / Datum preuzimanja: **2024-03-28**

SVEUČILIŠTE U SPLITU
MEDICINSKI FAKULTET
UNIVERSITAS STUDIORUM SPALATENSIS
FACULTAS MEDICA

Repository / Repozitorij:

MEFST Repository

UNIVERSITY OF SPLIT

dabar
DIGITALNI AKADEMSKI ARHIVI I REPOZITORIJI

UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

Andrea Gelemanović

HOST GENETICS IN SUSCEPTIBILITY TO RESPIRATORY INFECTIOUS DISEASES

Doctoral thesis

Split, 2019

The work of this doctoral thesis has been carried out at the Department of Public Health at the University of Split School of Medicine in Split, Croatia during the years 2015 – 2018, under the supervision of Associate Professor Ozren Polašek, MD, MPH, PhD. It has been submitted for the evaluation to the Committee for evaluation of doctoral thesis of University of Split School of Medicine, in order to obtain a PhD title. This work was supported by the Croatian Science Foundation grant 8445 and 8875, and the EU FP7 grant PREPARE (grant 602525).

Acknowledgments

First of all, a very special thanks to my mentor Associate Professor Ozren Polašek for his great contribution to my scientific education, enthusiastic support and guidance throughout this amazing journey. His advices and deep knowledge on any aspect of scientific research were greatly appreciated and of tremendous help.

I would like to thank all of the professors of the TRIBE doctoral program, especially to TRIBE directors Professor Damir Sapunar and Associate Professor Livia Puljak, for their helpful and critical discussions about my work.

A huge thanks to all of my co-workers, with always some positive advices and pleasant moments spent at the Department.

I would also like to thank the WP6 group within the PREPARE project, for their valuable advices, comments and numerous discussions during our meetings, it has been a pleasure to be part of such great group of international research enthusiasts.

And finally, I would like to thank the most my family and friends, for understanding, patience and support during my endless years of studies. Thank you for always being there for me and support my aspiration to achieve the highest goals.

Contents

List of Abbreviations v

List of Tables vi

List of Figures vii

List of Appendices viii

1 INTRODUCTION 1

1.1 Genetics of infectious diseases 3

1.2 Global burden of respiratory infectious diseases 4

1.3 Systematic review and meta-analysis 6

2 AIMS 10

3 METHODS 11

3.1 Protocol and registration 11

3.2 Literature database search 11

3.2.1 Information sources 11

3.2.2 Search details 11

3.2.2.1 PubMed search strategy 12

3.2.2.2 Web of Knowledge search strategy 14

3.2.2.3 Scopus search strategy 14

3.3 Eligibility criteria 15

3.3.1 Inclusion criteria 15

3.3.2 Exclusion criteria 16

3.4 Data extraction process 17

3.5 Disease model 19

3.6 Risk of bias in individual studies 21
3.7 Meta-analysis 23
3.8 Risk of bias across studies 24
4 RESULTS 25
4.1 Study selection 25
4.2 Quantitative synthesis (meta-analysis) 26
4.2.1 RISEdb description 26
4.2.1.1 Publication year and journal 28
4.2.1.2 Disease category and pathogen species 29
4.2.1.3 Demographics of subjects 30
4.2.1.4 Disease model 32
4.2.1.5 Risk of bias in individual studies (CSI scores) 33
4.2.1.6 Genes and SNPs 35
4.2.2 Meta-analysis 36
4.3 Qualitative synthesis 39
5 DISCUSSION 41
6 CONCLUSION 48
7 SUMMARY 49
8 SAŽETAK 50
9 REFERENCES 51
10 APPENDICES 86
11 RESUME 141

List of Abbreviations

BFDP	Bayesian false-discovery probability
CAP	Community-acquired pneumonia
CI	Confidence interval
COME/ROM	Chronic otitis media with effusion/recurrent otitis media
CSI	Confounding-Selection-Information risk bias scale
GWAS	Genome-wide association study
HC	Healthy control
HHC	Household contact
HCW	Health-care worker
HWE	Hardy-Weinberg equilibrium
I^2	Inconsistency index
OM	Otitis media
OR	Odds ratio
PCR	Polymerase chain reaction
PMID	PubMed identifier
PTB	Pulmonary tuberculosis
QC	Quality control
RISE	Respiratory Infection SuscEptibility database
RSV	Respiratory syncytial virus
SARS	Severe acute respiratory syndrome
SNP	Single nucleotide polymorphism
UCB	Umbilical cord blood

List of Tables

Table 1 Categories of exclusion criteria with explanations..... 17

Table 2 Explanation of extracted variables from each study..... 17

Table 3 Disease model categories 20

Table 4 Domains and grades of CSI score..... 21

Table 5 Demographics of subjects included in RISEdb 31

Table 6 Summary of disease model per each disease category 32

Table 7 Information domain of CSI score stratified by disease category 35

Table 8 Most frequently analysed genes per each disease category 36

Table 9 Significant and noteworthy results of random-effects meta-analyses 38

List of Figures

Figure 1 Number of published studies using keywords „systematic review“ and „meta-analysis“ 9

Figure 2 Simplified scheme of disease model 20

Figure 3 PRISMA guidelines study flowchart and data extraction process scheme 27

Figure 4 Distribution of included studies in RISEdb according to publication year 28

Figure 5 Distribution of included studies in RISEdb according to the publication year and stratified per disease 29

Figure 6 CSI scores for pooled and per each disease category 34

List of Appendices

Table A.1 List of appendices provided on CD as part of electronic version of this Thesis... 86

Table A.2 Short summary of articles included in quantitative synthesis 87

Table A.3 Random-effects meta-analyses results, allelic model, disease susceptibility 107

Table A.4 Random-effects meta-analyses results, dominant model, disease susceptibility 110

Table A.5 Random-effects meta-analyses results, recessive model, disease susceptibility 113

Table A.6 Random-effects meta-analyses results, heterozygote advantage model, disease susceptibility.....116

Table A.7 Random-effects meta-analyses results, various models, subset analysis 118

Table A.8 Overview of family-based and linkage studies that investigated host genetic factors for respiratory infectious diseases.....133

Table A.9 Overview of genome-wide association studies that investigated host genetic factors for respiratory infectious diseases.....137

Figure A.1 Forest and funnel plot for *IL4* (rs2070874) in allelic model of RSV meta-analysis 119

Figure A.2 Forest and funnel plot for *IL4* (rs2243250) in allelic model of RSV meta-analysis, stratified on European ethnicity.....120

Figure A.3 Forest and funnel plot for *IFNG* (rs2430561) in allelic model of tuberculosis meta-analysis.....121

Figure A.4 Forest and funnel plot for *TLR2* (rs5743708) in allelic model of tuberculosis meta-analysis.....122

Figure A.5 Forest and funnel plot for *IFNG* (rs2430561) in dominant model of tuberculosis meta-analysis....123

Figure A.6 Forest and funnel plot for *IFNG* (rs2430561) in recessive model of tuberculosis meta-analysis....124

Figure A.7 Forest and funnel plot for *CCL2* (rs1024611) in heterozygote advantage model of tuberculosis meta-analysis, stratified on admixed populations....125

Figure A.8 Forest and funnel plot for *IFNG* (rs2430561) in allelic model of pooled diseases meta-analysis....126

Figure A.9 Forest and funnel plot for *IL4* (rs2070874) in allelic model of pooled diseases meta-analysis....127

Figure A.10 Forest and funnel plot for *IFNG* (rs2430561) in dominant model of pooled diseases meta-analysis....128

Figure A.11 Forest and funnel plot for *TLR2* (rs3804099) in dominant model of pooled diseases meta-analysis....129

Figure A.12 Forest and funnel plot for *IFNG* (rs2430561) in recessive model of pooled diseases meta-analysis....130

Figure A.13 Forest and funnel plot for *IL4* (rs2070874) in recessive model of pooled diseases meta-analysis....131

Figure A.14 Forest and funnel plot for *CCL2* (rs1024611) in heterozygote advantage model of tuberculosis meta-analysis....132

1 INTRODUCTION

Through history infectious diseases have been shaping the course of human evolution, and despite a long-lasting research and major advances in the field of infectious diseases, they still represent one of the major threats to human health in the 21st century. Reason for that is that infectious diseases are characterized by many unique features – they are caused by a single agent, they can easily be transmitted among people, they have possibility to cause epidemics and pandemics, they can be prevented and eradicated, but also new ones may emerge, and they can coevolve in other animal species (1-3).

It has long been known that the infectious diseases are caused by different pathogens, but clinical variability in disease occurrence and treatment outcomes between individuals represents the main problem to this understanding. Few theories which are overlapping are explaining this variability. Louis Pasteur in 1867-1868 first established the microbiological theory, and at that time the newly established paradigm was that microbes alone are causing infectious diseases (4). This was confirmed with Robert Koch's discovery of the pathogen causing tuberculosis in 1882 and his postulates that the pathogen have to be found in all patients and not in healthy individuals (5). This however was not sufficient in explaining clinical variability among individuals in the course of the disease, until another Pasteur's discovery of prevention the infectious disease with the use of attenuated microbes in form of vaccine. Understanding that individuals can be immunized with less virulent but similar microbes or by a small inoculum of the same microbe and thus survive the infection that is virulent enough to kill other individuals, now known as acquired immunity, led to the formation of immunological theory (4, 5). René Dubos in 1955 tried a different approach to explain the interindividual variability during the course of infection, and can be thought of a pioneer in the study of microbiota in the gastrointestinal tract (5) which led him to made foundations to ecological theory. This theory takes into account the various environmental variation (e.g. lifestyle), and also includes dual infections (5). Finally, understanding that infections can be asymptomatic led to the development of

genetic theory in the early 20th century, with main assumption that germline immunity variability determines susceptibility or resistance to a microbe (4), however the first Mendelian inborn errors of immunity were described in the 1950s (5).

In recent years it has become evident that there is a polygenic side to the understanding of infectious diseases and the impact of infections to human genome. It is hypothesized that life-threatening primary infections of childhood result from single-gene inborn errors of immunity, and that symptomatic reactivation and secondary infections in young adults may result from the impact of a major locus, whereas in older adults the cause may be more polygenic. Other components, such as ecological and somatic variations are thought to be important for disease determinism in adults. Also, when comparing contribution of host and microbe genetics to the clinical outcome of the infectious diseases it is thought that individual with strong genetic vulnerability (single-gene variant) may develop disease after infection with weakly virulent microbe, and individual with low level of genetic vulnerability may develop disease only when infected with highly virulent microbe (4). This means that severe infections can gradually shape the human genome and common variants will be spreading by natural selection, but rare variants are the ones that will form life-threatening genetic form of disease (5). From an evolutionary point of view, it is important to mention that pathogens that diminish reproductive potential drive selection on genetic variants that affect resistance, and such selection is most evident for pathogens with a long evolutionary history with humans (malaria, smallpox, cholera, tuberculosis, leprosy). Some pathogens will cause acute diseases (smallpox, cholera) and when cured will represent little additional threat. On the other hand, pathogens causing malaria, tuberculosis and leprosy, can be chronic infections which will impair nutrition, growth, cognitive development and fertility (2). Taking all that into account, research of host genetic profile is vital in the field of infectious diseases, as not only it would provide a better knowledge to disease mechanism and pathways, but it also possesses the strength to improve current intervention and prevention measures since the global burden of infectious diseases is still very high with over 10 million deaths annually.

1.1 Genetics of infectious diseases

Infections elicit some of the strongest known selective pressures on human genomes (6), predominantly in childhood by removing the most susceptible individuals from population (7), and it has considered that virus-human interactions drove up to 30% of human genome evolution since viruses often uses host pathways to complete their replication cycles (8). It is thus no surprise that there is an increased interest in the last decade of 20th century for understanding the host genetics in infectious disease pathogenesis in order to elucidate the strong inter-individual differences in susceptibility to infectious disease (9, 10). This was first confirmed by adoption, twin and heritability studies (11, 12), and the two main types of study designs broadly used today are candidate gene, and in lesser extent genome-wide approach. So far, majority of studies have adopted a candidate gene approach where the choice of candidate gene may arise from animal data, results of whole genome sequencing studies, clinical data or biological plausibility. Between 2001 and 2010, over 4,000 candidate-gene studies were published, where major focus was on tuberculosis (13). However, these studies often provided very conflicting results (7, 14). Some of the major problems these studies suffered from included low study power, high risk of publication bias, differences in study designs, especially cases and controls recruitment schemes, which altogether led to frequent bias and confounding, genotyping inaccuracies, and substantial problems in phenotype definition, especially in the case of tuberculosis (15-17). There is evidence of very unfavourable effect-to-bias ratios, where the magnitude of bias exceeds that of the sought effect (18).

In order to overcome some of the issues in candidate gene studies, genome-wide association studies (GWAS) represents a better and more advanced strategy as there is no previous assumption on the involved genes (hypothesis-free approach) and it allows novel or unconsidered genes to be identified. Also, it allows millions of single nucleotide polymorphisms (SNPs) to be mapped across human genome in many individuals to find genetic variations associated with particular disease. This large-scale approach using GWAS became possible due to huge progress in genomic technologies, such as DNA arrays and next-generation sequencing (6, 10, 19, 20). Unfortunately, due to its complexity, progress in the field of GWAS studies of susceptibility to infectious diseases has been much

slower than similar studies of various other diseases and traits (19), as there is only a small number of such studies with almost no replication of results between them (7, 21, 22).

In addition, majority of the published studies relied on a single genetic marker as the only disease predictor. Their main methodological limitation was the adherence to the "common disease, common variant" hypothesis, which states that majority of genetic variation is due to differences in common genes of low penetrance, while the contrasting hypothesis, "common disease, rare variant" postulates that majority of disease susceptibility will be defined by the rare variants of much stronger penetrance (23). The current overview of the published studies suggests that rare variants are likely to have stronger effect, explaining some methodological restraints that were obtained by adherence to common variants hypothesis (24). Another major issue is that insights derived from the fields of clinical infectology, microbiology, immunology, epidemiology, as well as clinical, evolutionary and population genetics remained largely isolated from one another (4, 19, 25), preventing systematic understanding of the entire field.

Understanding the host genetic side could be an invaluable tool in clinical medicine, especially because susceptibility to an infectious agent lies at least partly hidden or masked in inborn errors or immune response (26, 27). This renders infectious diseases a high-ranking research priority, especially respiratory ones, having in mind the mobility of modern human population, the ever changing pathogen nature, and a large potential to cause epidemics and pandemics.

1.2 Global burden of respiratory infectious diseases

Respiratory infectious diseases are a leading cause of mortality and morbidity worldwide, with 2.7 million deaths reported in 2013, and influenza and pneumonia represents the main cause of death among young children and elderly (28).

Although there was an evidence of nearly 25% reduction in the incidence of community-acquired childhood pneumonia in 2010 when comparing to the previous decade (29), pneumonia is still one of the main childhood mortality causes, and is estimated for 120 million episodes and 1.3 million of lethal outcomes globally (30).

Similarly, it is estimated that respiratory syncytial virus (RSV) is responsible for 33.8 million of episodes of newly diagnosed acute lower respiratory infections worldwide in children under 5 years (31), with a minimum of 3.4 million severe cases requiring hospital admission. Infection with RSV can manifest in a range of clinical picture, from a mild cold to severe cases of bronchiolitis or pneumonia, but it is considered that almost all children by two years of age have been infected with it (8).

Influenza virus is an excellent example of a seasonal virus, with about 20% of the human population infected every year presenting with moderate symptoms, however, a small percentage with experience severe respiratory distress or additional complications (8). In addition, influenza constantly presents a threat to initiate a pandemic, with the 1918 Spanish influenza has been considered one of the largest ever recorded pandemic, responsible for 25-100 million deaths (32, 33). Also, in the last 60 years there have been three pandemics: the H2N2 outbreak in 1957 which caused 100,000 deaths, the H3N2 outbreak in 1968 which caused 700,000 deaths, and the most recent H1N1 pandemic in 2009 which caused over 15,000 deaths (28).

Human coronavirus infections are generally considered to be responsible for a low percentage of annual upper and lower respiratory infections, with severe outcomes in children, elderly and immunocompromised patients (34). This situation changed with appearance of severe acute respiratory syndrome (SARS) Coronavirus, clinically presented as atypical pneumonia, which was initially present in horseshoe bat population and then transmitted to humans through intermediate hosts (35). Consequently, it was an example of how quickly a novel respiratory pathogen can spread globally (36), when an outbreak occurred in 2003 resulting in about 8,000 cases and an overall mortality rate of 10% (35).

Tuberculosis is an example of highly adaptive pathogen, which managed to coevolve with humans, possibly as far as the initial waves of human migrations out of Africa (37-39). Interestingly, clinical presentation of tuberculosis can be very variable. Some individuals will not become infected regardless of high levels of exposure of *M. tuberculosis*, while about 5% of infected individuals will develop clinical symptoms within two years of infection and as such is often associated with extrapulmonary form of disease. Most of the infected people will develop latent infection, and only about 5 – 10% will develop a

pulmonary clinical form of tuberculosis later in life which is characterized with extensive lung damage (40). Due to its unique features, tuberculosis still remains one of the major issues in public health, as it is estimated in 2013 that 9 million people globally is infected, with 1.5 million deaths annually, and possibly as much as third of all living humans being latent carriers (41).

For all of the above mentioned respiratory infectious diseases, there has been numerous genetic studies performed, either as candidate gene, expression, *in vitro* or animal studies, and multiple genes have been proposed to be involved in the pathogenesis. Since the aim of this Thesis is limited to only human candidate gene type of studies in order to summarize all currently available knowledge on the influence of SNPs to infection susceptibility using the rigid and best possible methodology, it is beyond the scope of this Thesis to mention the results of previous studies at this stage.

1.3 Systematic review and meta-analysis

Clinical evidence can be ranked according to the impact of various biases, and in the hierarchy of evidence, systematic reviews and meta-analyses are on the top, meaning that they represent the strongest evidence with the minimum risk of bias (42).

With the extreme publication growth of scientific literature on a daily basis, there is a large need for a comprehensive review studies which would facilitate, accelerate and guide the future research on any topic of interest. This is in particular important for health sciences, as it is usually impossible for clinicians to keep up with the literature. By definition a systematic review is a review that is based on a clearly defined question, involves a systematic and comprehensive search of the literature, grade their quality and summarizes the evidence with the rigid methodology, usually with meta-analysis (43, 44). The key features of systematic review are to provide a reader with synthesis of all relevant studies on a specific topic and the reproducible methodology. Exactly for this specific qualities, a systematic review is distinguished form the traditional narrative reviews which can often suffer from bias in selecting the relevant literature on the basis of author's personal choice. To show the necessity and importance of systematic reviews, there is an

organization named the Cochrane Collaboration (www.cochrane.org) which supports and promotes evidence-based healthcare decisions by producing high-quality systematic reviews and meta-analyses. Cochrane reviews are published in the Cochrane Database of Systematic Reviews, and they published a detailed methodological framework for preparing a systematic review named The Cochrane Handbook for Systematic Reviews of Interventions (45).

There are eight major steps in performing a systematic review (43, 44), with an emphasis that they should be performed by at least two authors to minimize the risk of bias:

- Step 1: Formulate a clear review question;
- Step 2: Define inclusion and exclusion criteria;
- Step 3: Develop search strategy and perform the search in several electronic databases;
- Step 4: Select relevant studies first by screening the Title and Abstract section against the inclusion criteria, and any study that met the inclusion criteria should be read in full;
- Step 5: Extract the necessary information from the selected relevant studies;
- Step 6: Assess the quality of included studies;
- Step 7: Synthesize the evidence, preferably by using meta-analysis approach;
- Step 8: Interpret the main findings.

Meta-analysis represents a statistical procedure that summarizes the results of several independent studies, with usually more precise outcome estimates of effect than any individual study included in the analysis (42). Most commonly used measures of effect are the risk ratio (RR), which is the ratio between two incidence proportions, and the odds ratio (OR), which is calculated as the number of exposed individuals divided by the number of unexposed individuals in both cases and controls group. A measure of effect below 1 implies that the risk of the outcome is lower in exposed individuals than in unexposed individuals, and vice versa. Any measure of effect is accompanied by a measure of the

precision of the estimate, the confidence interval (CI), and can be explained in a way that the 95% CI is the interval of values in which the true measure of effect is likely to lie with a probability of 95% (46).

Meta-analysis can be performed under the assumption of fixed effects or random effects model, where fixed effects model is based on the assumption that the effect is expected to be the same for each study and that the study populations are homogeneous, while random effects model assumes a distribution of effects which results from heterogeneity between the studies. In addition, in the random effects model, studies are weighted according to the inverse variance and the heterogeneity parameter, while a fixed effects model uses only inverse variance. Most commonly used method for fixed effects model is the Mantel-Haenzel method, while for random effects model is the DerSimonian and Laird method (42, 47).

Additional analyses that go alongside meta-analysis include heterogeneity and publication bias analysis. In order to test the heterogeneity between the studies, often inconsistency index I^2 is used, which describes the percentage of total variation across studies, and values above 75% are considered as substantial heterogeneity. Meta-analysis results are often presented in a graphical form as forest plot, where overall and per each study effect size is shown with its 95% confidence interval. With the overall effect size, heterogeneity measure is displayed as well. The solid vertical line in forest plots corresponds to no effect (measure of effect is 1.0), so if the confidence interval includes 1, then the difference between the groups is not statistically significant at the level of P=0.05. Another graphical representation commonly used in meta-analysis is the funnel plot, which is used to visually assess the publication bias, and is interpreted to be of symmetric inverted funnel shape if no publication bias is present (42, 47).

When PubMed search was performed using keywords „systematic review" or „meta-analysis" (restricted to appearance in Titles), it is evident that these types of studies are in large growth in the last two decades (Figure 1).

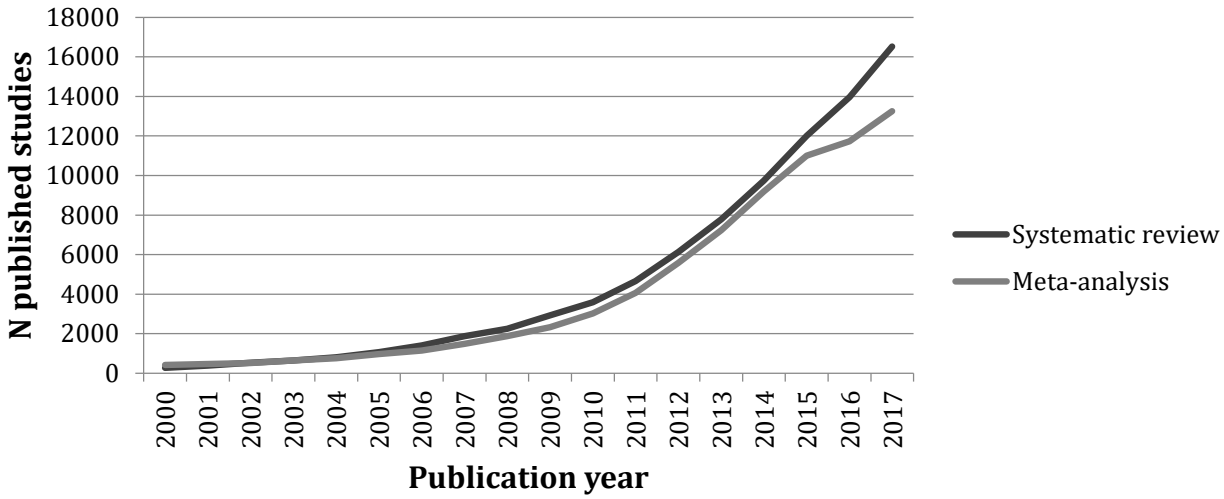


Figure 1 Number of published studies using keywords „systematic review“ and „meta-analysis“ (Medline search performed on December 17, 2018 (48))

2 AIMS

The main aim of this Thesis is the identification of genes involved in respiratory infectious diseases pathways in order to better understand the complex network of interaction between a pathogen causing infectious disease and genetic factors in humans. The impact of this Thesis lies in better understanding of disease determinants, which could not only be used to identify individuals at greater risks, but also to provide better knowledge of the disease mechanisms which offer potential for future development of novel prevention and therapy approaches.

This aim was achieved by performing a comprehensive systematic review with meta-analyses to provide field synopsis of the current knowledge of host genetic factors implicated in susceptibility to respiratory infectious diseases. Five respiratory infections were the main interest of this Thesis, selected for its great threat to human populations and possibility to cause epidemics (tuberculosis, influenza, pneumonia, SARS, RSV infection). Because of that, a special focus was set on the comparative analysis of these different pathogens and diseases, in order to increase the understanding of both common and disease-specific pathways. Analysis was additionally complemented by stratifying included individuals on the basis of their ethnicity, gender and age, in order to discover if some additional host genetic factors are important for disease susceptibility in certain sub-populations.

Secondary aims of this Thesis are to develop a new risk of bias scoring scheme which is appropriate for genetic studies, to develop a comprehensive Respiratory Infection SuscEptibility database (RISEdb) which will be made publicly available and to provide a critical overview of the entire field and give guidelines for improvement of future studies in understanding of the infectious disease development, progression and outcome.

3 METHODS

Methods were performed according to our recent paper (49), where the author of this Thesis is a joint first author, with some modifications and extensions.

3.1 Protocol and registration

Key features of this systematic review were registered prospectively in PROSPERO, an international database of systematic reviews with a health related outcome (https://www.crd.york.ac.uk/prospero/), as the record CRD42014009072.

3.2 Literature database search

3.2.1 Information sources

Three bibliographic databases were used as an information source for this systematic review: PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Web of Science (http://wok.mimas.ac.uk) and Scopus (http://www.scopus.com). Also, a search of the HuGe Literature Finder (http://www.hugenavigator.net) was performed in order to identify the articles that might have been missed in other databases. Additionally, the list of potentially relevant articles was supplemented by hand search of their references. In any case of potentially relevant article which reported insufficient information, e-mails were sent to authors of these studies and asked for clarifications or raw data sharing.

3.2.2 Search details

Two authors (of which one is the author of this thesis) first jointly performed the literature databases search and then separately performed study selection, which was supervised by the third author (mentor of this thesis) and if any discrepancies were found

in any step between the two authors, the third one was resolving the issues. Search terms can most simply be divided into three major units: 1) polymorphism; 2) susceptibility; and 3) type of respiratory infection, with various synonyms in order to get the most comprehensive results and not to miss relevant studies. This was supplemented by restricting the search to humans, articles published in English language and the date of publication. To search in HuGe database, it is only needed to put the keyword of a respiratory infection of interest and to restrict the publication year, thus its search strategy was not shown.

Search was originally restricted to begin with January 01, 2000 as it was the time when the genotyping technology emerged and there was a boom in candidate gene studies (50, 51). Search was performed in three stages: initially on May 06 2014, with first update on August 25, 2015 and second update on July 26, 2018. After each search, the duplicates were removed and the articles were firstly checked for inclusion by reading the Title and Abstract. After exclusion of non-relevant articles, the rest were read in full and screened against the inclusion criteria.

Regardless of the search being performed in multiple stages, the data were in the end analysed together with careful exclusion of duplicated articles retrieved in two overlapping searches (as only in PubMed one can select the exact dates of publication, while in Web of Knowledge, Scopus and HuGe one can only select the year of publication). Thus, the search strategy presented in this Thesis was set to end with 2018 as an example of what this search would look like if it was performed all at once. Systematic review was conducted and written under the PRISMA reporting guidelines (52).

3.2.2.1 PubMed search strategy

"DNA"[MeSH Terms] OR SNP[All Fields] OR "polymorphism"[All Fields] OR "polymorphism, single nucleotide"[MeSH Terms] OR "single nucleotide polymorphism"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR "genetic polymorphism"[All Fields] OR "genes"[MeSH Terms] OR "genes"[All Fields] OR "gene"[All Fields] OR variant[All Fields] OR "genotype"[MeSH Terms] OR "alleles"[MeSH Terms] OR "alleles"[All Fields] OR "allele"[All Fields] OR "genomics"[MeSH Terms] OR "genomics"[All Fields] OR "genetic"[All

Fields] OR "exome"[MeSH Terms] OR "exome"[All Fields] OR "base sequence"[MeSH Terms] OR "sequence"[All Fields]

AND

"Disease Susceptibility"[Mesh Terms] OR "susceptibility"[All Fields] OR "susceptibility"[All Fields] OR "sensitivity"[All Fields] OR "risk"[MeSH Terms] OR "risk"[All Fields] OR severity[All Fields] OR "association"[MeSH Terms] OR "association"[All Fields] OR "mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]

AND

"respiratory tract infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract infection"[All Fields] OR ("respiratory"[All Fields] AND "infection"[All Fields]) OR "respiratory infection"[All Fields] OR "pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "otitis media"[MeSH Terms] OR ("otitis"[All Fields] AND "media"[All Fields]) OR "otitis media"[All Fields] OR "bronchitis"[MeSH Terms] OR "bronchitis"[All Fields] OR "bronchiolitis"[MeSH Terms] OR "bronchiolitis"[All Fields] OR "common cold"[MeSH Terms] OR ("common"[All Fields] AND "cold"[All Fields]) OR "common cold"[All Fields] OR "pharyngitis"[MeSH Terms] OR "pharyngitis"[All Fields] OR "pleurisy"[MeSH Terms] OR "pleurisy"[All Fields] OR "pleuritis"[All Fields] OR "glottis"[MeSH Terms] OR "glottis"[All Fields] OR "sinusitis"[MeSH Terms] OR "sinusitis"[All Fields] OR "tonsillitis"[MeSH Terms] OR "tonsillitis"[All Fields] OR "pharyngitis"[MeSH Terms] OR "pharyngitis"[All Fields] OR "influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields] OR "flu"[All Fields] OR "streptococcus pneumoniae"[MeSH Terms] OR ("streptococcus"[All Fields] AND "pneumoniae"[All Fields]) OR "streptococcus pneumoniae"[All Fields] OR "pneumococcus"[All Fields] OR "orthomyxoviridae infections"[MeSH Terms] OR ("orthomyxoviridae"[All Fields] AND "infections"[All Fields]) OR "orthomyxoviridae infections"[All Fields] OR "coronavirus infections"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronavirus infections"[All Fields] OR "severe acute respiratory syndrome"[MeSH Terms] OR ("severe"[All Fields] AND "acute"[All Fields] AND "respiratory"[All Fields] AND "syndrome"[All Fields]) OR "severe acute respiratory syndrome"[All Fields] OR "SARS"[All Fields] OR "respiratory syncytial virus infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "syncytial"[All Fields] AND "virus"[All Fields] AND "infections"[All Fields]) OR "respiratory syncytial virus infections"[All Fields] OR "RSV"[All Fields] OR "rhinovirus"[MeSH Terms] OR "rhinovirus"[All Fields] OR "tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR "mycobacterium"[MeSH Terms] OR "mycobacterium"[All Fields] OR "haemophilus"[MeSH Terms] OR "haemophilus"[All Fields] OR "hemophilus"[All Fields] OR "legionella"[MeSH Terms] OR "legionella"[All Fields] OR ("chlamydia"[MeSH Terms] OR "chlamydia"[All Fields]) AND ("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields]) OR "paramyxoviridae infections"[MeSH Terms] OR ("paramyxoviridae"[All Fields] AND "infections"[All Fields]) OR "paramyxoviridae infections"[All Fields] OR "parainfluenza"[All Fields] OR "adenoviridae"[MeSH Terms] OR "adenoviridae"[All Fields] OR "adenovirus"[All Fields] OR "adenoviridae infections"[MeSH Terms] OR ("adenoviridae"[All Fields] AND "infections"[All Fields]) OR "adenoviridae infections"[All Fields] OR "mycoplasma

pneumoniae"[MeSH Terms] OR ("mycoplasma"[All Fields] AND "pneumoniae"[All Fields]) OR "mycoplasma pneumoniae"[All Fields]

AND

"humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]

AND

"2000/01/01"[PDAT] : "3000"[PDAT]

AND

English[lang]

3.2.2.2 Web of Knowledge search strategy

TOPIC: (DNA OR SNP OR gene OR variant OR polymorphism OR genotype OR allele OR genetic OR genom* OR exom* OR sequenc*)

AND

TOPIC: (susceptib* OR sensitiv* OR association OR sever* OR mortality OR risk)

AND

TOPIC: (respiratory tract infection OR respiratory infection OR Pneumonia OR otitis media OR bronchitis OR bronchiolitis OR common cold OR pharyngitis OR pleurisy OR pleuritis OR glottis OR sinusitis OR tonsillitis OR influenza OR flu OR streptococcus pneumoniae OR pneumococcus OR orthomyxovir* OR coronavir* OR severe acute respiratory syndrome OR SARS OR respiratory syncytial virus OR RSV OR rhinovirus OR tuberculosis OR mycobacterium OR haemophilus OR legionella OR chlamydia pneumonia OR paramyxovir* OR parainfluenza OR adenovir* OR mycoplasma)

AND

human

AND

YEAR PUBLISHED:(2000-2018)

AND

LANGUAGE:(English)

3.2.2.3 Scopus search strategy

TITLE-ABS-KEY(DNA OR SNP OR gene OR variant OR polymorphism OR genotype OR allele OR genetic OR genom* OR exom* OR sequenc*)

AND

TITLE-ABS-KEY(susceptib* OR sensitiv* OR associate* OR sever* OR mortality OR risk)

AND

TITLE-ABS-KEY(respiratory tract infection OR Pneumonia OR otitis media OR bronchitis OR bronchiolitis OR common cold OR pharyngitis OR pleurisy OR pleuritis OR glottis OR sinusitis OR tonsillitis OR influenza OR flu OR streptococcus OR pneumococcus OR orthomyxovir* OR coronavir* OR severe acute respiratory syndrome OR SARS OR respiratory syncytial virus OR RSV OR rhinovirus OR tuberculosis OR mycobacterium OR haemophilus OR legionella OR chlamydia pneumonia OR paramyxovir* OR parainfluenza OR adenovir* OR mycoplasma)

AND

(human)

AND

PUBYEAR > 1999

AND

LANGUAGE(english)

3.3 Eligibility criteria

An extensive and systematic search of all published studies related to association of host genetics in development or outcome of respiratory tract infectious diseases was performed. Focus was several major respiratory infectious diseases (tuberculosis, pneumonia, influenza, RSV infection and SARS) that represent a major threat to human population and have an epidemic potential.

3.3.1 Inclusion criteria

To be included in quantitative synthesis (meta-analysis), studies needed to be candidate gene studies where association between host genetic polymorphisms and development or outcome of respiratory tract infectious diseases was examined. Respiratory tract infectious diseases of interest were tuberculosis, pneumonia, RSV, SARS and influenza, but studies where a syndrome phenotype was reported, such as pneumonia, without the specific pathogen information was also included. Studies needed to report the number of cases and controls for every analysed genotype. Preferably, studies needed to

report the number of each genotype (major homozygote, heterozygote, minor homozygote), but if studies reported only allelic counts they were also included. Studies had to be based on biallelic single-nucleotide polymorphisms (SNP) or biallelic insertion-deletion marker type, and performed on previously healthy subjects (although in some cases certain comorbidities were present but these studies were accordingly graded for possible risk of bias).

Family-based and linkage studies, as well as genome-wide association studies (GWAS) were initially excluded due to inability to analyse such studies jointly in appropriate format. However, these studies were retained in qualitative synthesis and their main findings were provided in form of short tabular summary.

3.3.2 Exclusion criteria

Several criteria were used to exclude non-relevant studies: studies based on non-biallelic marker types, those that reported aggregated haplotypes, those that reported gene expression profiles, animal and *in vitro* studies, studies that reported any outcome in previously affected patients (e.g. HIV/AIDS, immunodeficiency syndromes, asthma, fungal infections, nosocomial infections (ventilator-associated, VAP or hospital-acquired, HAP), studies reporting pathogen genotypes only or host-pathogen interactions, studies reported on non-respiratory infection sites (e.g. extra-pulmonary tuberculosis, meningitis, invasive pneumococcal disease), studies reported prior to the year 2000 and studies not written in English language. Additionally, in order to remove redundant data or publications all studies that were obviously reporting previously published results were excluded.

As reasons of exclusion needs to be reported for all studies excluded after the stage of full-text reading, above mentioned exclusion criteria are grouped into several categories which are shown in Table 1.

Table 1 Categories of exclusion criteria with explanations

Comment	Explanation
Wrong marker type	HLA, KIR, IGHG2, MBL haplotypes, short tandem repeats, microsatellites
Wrong study type	Expression studies, animal models, *in vitro* studies, challenge studies, other study types that are not case-control
Wrong phenotype	Different or unclear clinical forms of tuberculosis, latent tuberculosis, non-tuberculous mycobacterial infections (NTM), fungal infections, asthma, sepsis, HIV patients, invasive pneumococcal disease (IPD), nosocomial pneumonia (ventilator-associated, VAP or hospital-acquired, HAP), different phenotypes pooled together
Insufficient information	No genetic data provided, no clear genotype or allele counts, data combined as haplotypes only, no risk allele reported, data reported in graphs instead of numerical tables
Not relevant	Case reports, conference material, editorial material, support paper, database tool, articles not referring to host genetic susceptibility

3.4 Data extraction process

A total of 42 pieces of information were extracted from each study, which can be grouped in six categories, i.e. article characteristics, study characteristics, risk of bias and disease model, statistical information, SNP/gene information, genotyping information. Detailed explanation of extracted information is shown in Table 2. The database was made publicly available in the on-line RISEdb – Respiratory Infection SuscEptibility database, available at http://www.prepare-europe.eu/risedb.

Table 2 Explanation of extracted variables from each study

Group	Extracted variables
Article characteristics	RISEdb unique ID
	First author
	Title
	Publication year

Group	Extracted variables
	Journal
	PMID
Study characteristics	Country of origin
	Ethnicity (European, Asian, African, South American or Admixed)
	Sampling period
	Disease
	Pathogen species
	Diagnostics information
	Genotyping information
	Cases selection criteria
	Number of cases
	Controls selection criteria
	Number of controls
	Age stratification (infants, children, adults, elderly or mixed)
	Gender stratification (females, males or both)
Risk of bias and disease model	CSI score (with detailed explanation of grade per category)
	Disease model
Statistical information	Type of statistical test used
	Multivariate adjustment (yes or no)
SNP/gene information	Gene
	SNP identifier
	Major homozygote genotype (GAA)
	Heterozygote genotype (GAa)
	Minor homozygote genotype (Gaa)
	Major allele (AAA)
	Minor allele (Aaa)
Genotyping information	Number of cases GAA
	Number of cases GAa
	Number of cases Gaa
	Number of controls GAA
	Number of controls GAa
	Number of controls Gaa
	Number of cases AAA

Group	Extracted variables
	Number of cases Aaa
	Number of controls AAA
	Number of controls Aaa
	Number of cases GAA+Gaa
	Number of controls GAA+Gaa

To ensure data integrity, all the extracted data were entered into RISE database by two authors and checked by the third. Each study that entered the RISE database (extracted for quantitative synthesis) was indexed with a unique identification code – RISEdb ID. As studies were entering the RISE database on the rule "one SNP – one line in database entry", some studies provided more than one data point and were represented with more than one data entry in the RISE database, so there are significantly more lines in the database than the number of included studies.

The data were in most cases extracted in the raw format as genotype counts, but in cases where such information was not provided, genotype counts were calculated from the reported percentages and sample sizes. If more cases or control groups were analysed in one study and the data on genotype counts were available for each group, multiple data points were entered into RISE database from the same study, especially in case of having discovery and replication datasets.

3.5 Disease model

In order to better understand the various steps in diseases pathogenesis, all data points were classified according to the disease model. Simplified scheme of explanation of disease model is shown in Figure 2 (modified according to Casadevall and Pirofski (53)). First step is exposure of the host to a pathogen, which unfortunately cannot be estimated precisely. The second step is the infection susceptibility which is defined as the ability of a pathogen to enter the host and it defines whether infection will progress to asymptomatic,

or it will cause a disease with more or less severe symptoms (severity step). Last step is the disease outcome which can lead to recovery or death.

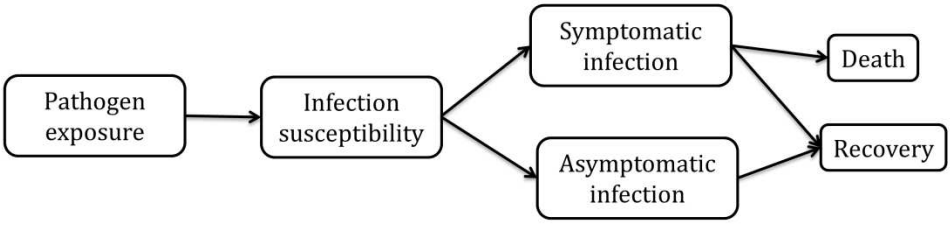


Figure 2 Simplified scheme of disease model

For the purposes of this study several categories of disease model were created in order to minimize the heterogeneity between studies and to maximize the importance of genetic polymorphisms in each step of the disease model. Three major categories were identified: studies that investigated infectious disease susceptibility, disease severity or disease mortality. In addition, there was a subset of methodologically better studies where controls were of known exposure to the pathogen. Detailed explanation of disease model categories is shown in Table 3.

Table 3 Disease model categories

Disease model category	Cases status	Controls status
Healthy exposed controls		
21	Exposed and tested positive healthy controls	Exposed and tested negative healthy controls
Disease susceptibility		
30	Infected cases	Healthy controls
3E	Infected cases	Possibly exposed controls or exposed controls but status not known
31	Infected cases	Exposed and tested negative healthy controls
31/2	Infected cases	Exposed and tested positive/negative healthy

Disease model category	Cases status	Controls status
		controls
32	Infected cases	Exposed and tested positive healthy controls
33	Recurrent cases	Newly diagnosed cases
Disease severity		
41/2	Severe infected cases	Exposed and tested positive/negative healthy controls
43	Severe infected cases	Mild infected cases
Disease mortality		
50	Deceased infected cases	Healthy controls
53	Deceased infected cases	Mild infected cases
54	Deceased infected cases	Severe infected cases

3.6 Risk of bias in individual studies

A study may be prone to three main domains of errors and bias – confounding, selection bias and information bias, and these were the basis of a newly developed score for purposes of assessing the risk of bias (author of this Thesis was one of the authors involved in the development). The novel score was entitled Confounding-Selection-Information bias score (CSI) and it major elements are shown in Table 4.

Table 4 Domains and grades of CSI score

Domain	Level A grade	Level B grade	Level C grade
Confounding risk	No apparent confounding (or possible confounding properly adjusted for) AND no indication of population stratification	Some degree of confounding OR some indication of population stratification	Detectable levels of confounding OR indication of strong population stratification
Selection bias risk	Controls drawn from general population	Controls drawn from structured sampling	No description on controls recruitment

Domain	Level A grade	Level B grade	Level C grade
	AND satisfy HWE	frame (e.g. hospital) AND satisfy HWE	OR fail HWE
Information bias risk	I1: Cases status verified by highly specific molecular methods (e.g. PCR) I2: Controls status verified by highly specific molecular methods (e.g. PCR) I3: Favourable genotyping quality control results	I1: Cases status established on the basis of less specific methods (e.g. guidelines, cultures) I2: Controls status established on the basis of less specific methods (e.g. no history of disease) I3: Partial genotyping quality control results	I1: No clear definition of cases I2: No description of disease status in controls I3: No indication of genotyping reproducibility

The elements of the score were developed on the basis of several previous studies (54), various assessment scores (Venice criteria for assessing cumulative epidemiologic evidence in genetic associations (55), Newcastle-Ottawa case-control scale (56), Cochrane risk of bias tool (45)), and previously established quality scores in genetic epidemiology (57). Neither of these tools provided a good fit for the risk of bias assessment in observational studies in genetic epidemiology, so elements were taken from previous scales to derive a new one. In line with Venice criteria, all three domains were scored with one of the three grades of credibility: high – graded as A, intermediate – graded as B, or weak – graded as C. This scheme provided estimates ranging from the best AAA to worst CCC score, which was applied to every data point in RISE database. Since information bias can affect several aspects of the study, this domain was divided into three separate sub-scores, relating to cases and controls selection and genotyping quality control procedures, with the worst of all three defining the overall information bias risk. All CSI scoring was done independently by two authors, and all discrepancies were settled by a third author.

As an additional quality control check, Hardy-Weinberg equilibrium (HWE) was re-calculated for every control set included in the analysis, using a two tailed chi-square test or an exact test, when appropriate. Those data points that failed HWE test at the level of $P<0.05$ were downgraded to C in the CSI score, in order to reflect possible methodological

limitations of failed HWE (which indicates both the risk for selection and/or information bias). In disease severity models, where cases from single study were classified as moderate or severe and controls as mild, Selection domain of the CSI score was not determined. Such data points were assigned 0 as selection risk bias, as there was no selection process involved, but a *post-hoc* division of overall cases.

3.7 Meta-analysis

In order to better understand the host genetic influence on gene-disease association, four separate genetic models were used in meta-analysis and subsequently compared: allelic, dominant, recessive and heterozygote advantage (58, 59). Model selection was based on commonly used allelic model ('A' *versus* 'a'), two additional models that assume different inheritance effects (dominant 'AA' *versus* 'Aa+aa', and recessive 'aa' *versus* 'Aa+AA'), followed by the heterozygote advantage ('Aa' *versus* 'AA+aa'), as previous studies reported such results (60-62).

A series of meta-analyses was then performed for all SNPs where four or more data points were available for a single SNP. Meta-analysis was performed for each disease separately but also for all the investigated respiratory infections pooled together. All of the analyses were performed separately for each disease model, along with "expanded" models to go in line with three major research questions of disease susceptibility, disease severity and disease mortality. Whenever appropriate (four or more data points available for a single SNP), a subset analyses were performed limiting the input data according to gender (males, females), age (children, adults) and ethnicity (European, Asian, African) in order to see if there are additional genetic polymorphisms influencing the disease susceptibility in a certain sub-population. Assuming differences in study designs and ethnic composition of individual studies, random effect meta-analysis model was used; however, fixed-effects model was also calculated in order to compare the results. To measure heterogeneity between the studies, I^2 statistics and corresponding confidence intervals were used. Visual representation of meta-analysis results in form of forest plots (63) was used. Due to

substantial requirements for appropriate use of publication bias analysis methods (64), publication bias was only examined visually in form of funnel plots (65).

In order to account for multiple testing as a result of numerous meta-analyses and different genetic models being performed, Bayesian false-discovery probability (BFDP) (66) was used. It was calculated for nominally significant results only, with a BFDP-level threshold for noteworthiness of 0.2. BFDP was calculated using two prior probabilities, with medium/low prior level (0.05 to E-03), consistent with a candidate gene; and very low prior level (E-04 to E-06), consistent with a random SNP. The advantage of this approach over the commonly used corrections is that it is not dependent on the number of tests performed, as it relies on odds ratios and confidence intervals for calculation.

All analyses were performed in R, version 3.2.2 (67). Meta-analysis was performed with 'meta' package, version 4.8-1 (68), with *metabin*, *forest* and *funnel* functions. Hardy-Weinberg equilibrium testing was performed with 'HardyWeinberg' package, version 1.6.1 (69, 70), with *HWExactMat* or *HWChisqMat* functions, based on the cell expected frequencies. BFDP was performed 'gap' package, version 1.1-22 (66), with *BFDP* function.

3.8 Risk of bias across studies

To assess the meta-analysis credibility for nominally significant results, Venice criteria (55) was used. Study power was assessed on the basis of sample sizes (with sample sizes of up to a 1,000 graded as C, 1,001-10,000 graded as B, and over 10,001 graded as A). Heterogeneity was based on I^2 statistics (graded as A in case of 0-25%, B in case of 26-50% and C in case of I^2 being over 50%), while the third score domain was fixed as C (weak credibility), due to very prevalent risk of bias in primary studies.

4 RESULTS

4.1 Study selection

After all three search stages were combined, 37,188 articles were identified through database search, with 5,621 articles identified through PubMed (15.1%), 17,913 through Web of Knowledge (48.2%), 11,835 through Scopus (31.8%), and 1,819 through HuGe (4.9%). After duplicates were excluded, 30,307 articles remained for screening for inclusion by reading the Title and Abstract. At this stage, a total of 29,013 articles were excluded for not being relevant. The remaining set of 1,026 articles was supplemented by hand search of their references, which led to additional 268 articles to screen for inclusion. In total, 1,294 articles were read in full and screened against inclusion criteria.

In addition, a total of 142 e-mails were sent to authors of articles which were classified as potentially relevant, but which had reported insufficient information, in order to ask for clarifications or data sharing. This resulted in 10 responses only (7.0%), where four were rejections, two which did not satisfy the inclusion criteria and four which clarified or shared the raw data. Authors who provided additional information in order to clarify the information reported in the articles were: Eileen Hoal and Marlo Möller (Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; RISE0109), Riny Janssen and Hennie Hodemaekers (Center for Health Protection, National Institute for Public Health and the Environment, Bilthoven, the Netherlands; RISE0329), Meghan Baker and Megan Murray (Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; RISE0791) and Antony Payton (Centre for Integrated Genomic Medical Research, The University of Manchester, Manchester, UK) and Enitan D Carrol (Institute of Infection and Global Health, University of Liverpool, Liverpool, UK; RISE0517).

After reading the selected 1,294 articles in full, 831 of them were excluded due to various reasons (explanation of exclusion criteria are additionally clarified in Table 1): 184

due to the wrong phenotype (22.2%), 151 due to review type of article (18.2%), 136 due to wrong marker type (16.4%), 87 due to wrong study type (10.5%), 76 due to insufficient information provided (9.1%), 61 due to not being relevant (7.3%), 61 due to systematic review and/or meta-analysis type of article (7.3%), 48 due to language different than English (5.8%), 15 due to duplicated publication or data (1.8%), and 12 due to being not retrievable in full-text (1.4%). Full list of excluded articles (alongside with included articles) at this stage with reasons for exclusion is shown as Supplementary material (Table e-A.2) available on CD as part of electronic version of this Thesis.

In total, 463 articles were included in qualitative synthesis, which included 22 family-based and linkage studies and 16 GWAS studies, while 425 articles were used in data extraction process and included in quantitative synthesis (meta-analysis).

The whole process of study selection with numbers of excluded articles at each stage is shown in Figure 3.

4.2 Quantitative synthesis (meta-analysis)

4.2.1 RISEdb description

From 425 studies included in the quantitative synthesis step, a total of 2,402 data points were extracted, which represents RISE database. Short summary of the included studies is shown in Table A.2, with general information for each study: RISEdb unique identification number, the last name of the first author, publication year, disease of interest, ethnicity, gender and age of included cases and controls, CSI score, disease model, number of genes and SNPs analysed, and reference. A full RISEdb is given as a Supplementary material (Table e-A.3) available on CD as part of electronic version of this Thesis.

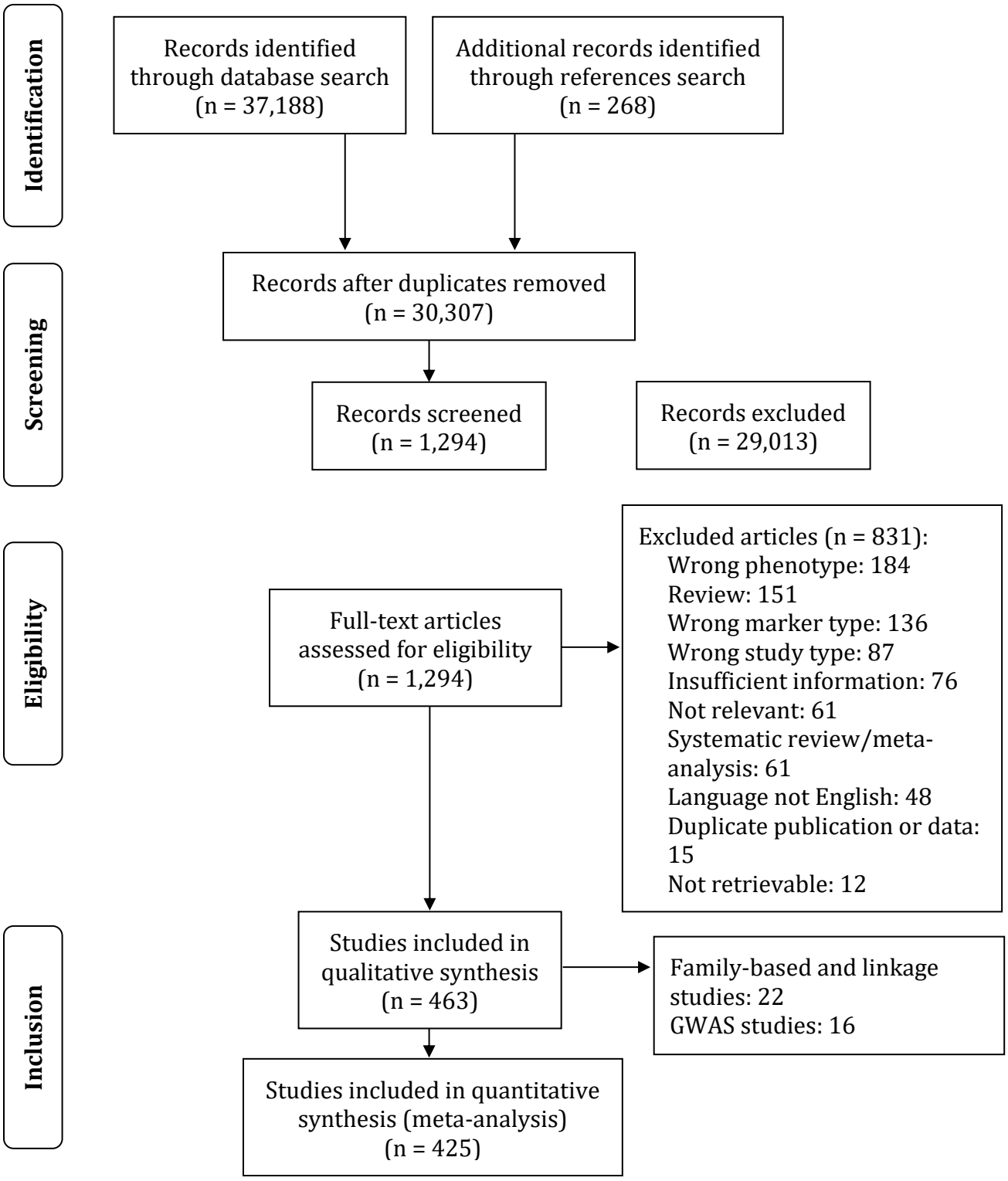


Figure 3 PRISMA guidelines study flowchart and data extraction process scheme

4.2.1.1 Publication year and journal

Distribution of included studies in RISEdb according to publication year is shown in Figure 4, and the same graph stratified by disease is shown in Figure 5. A trend of growth in the number of candidate gene studies published in the field of respiratory infectious diseases is visible, with the most studies published in the year 2012, and an additional peak of such publications in the year 2007. After 2012, publication of such candidate gene studies is steadily decreasing, with the lowest nine studies published in the year 2015. When comparing publications per year and stratified per disease category, it is evident that there is an evenly percentage every year of published studies on tuberculosis, pneumonia and RSV. As expected, studies on SARS were published in a timespan from 2004 to 2011, starting immediately after the 2003 SARS outbreak (71, 72). Surprisingly, even though influenza is very well-known for its pandemic possibilities and there have been several influenza pandemic reports in the last 500 years (73), candidate gene studies on influenza, in line with very rigid inclusion and exclusion criteria of this systematic review, only started to be published from 2012.

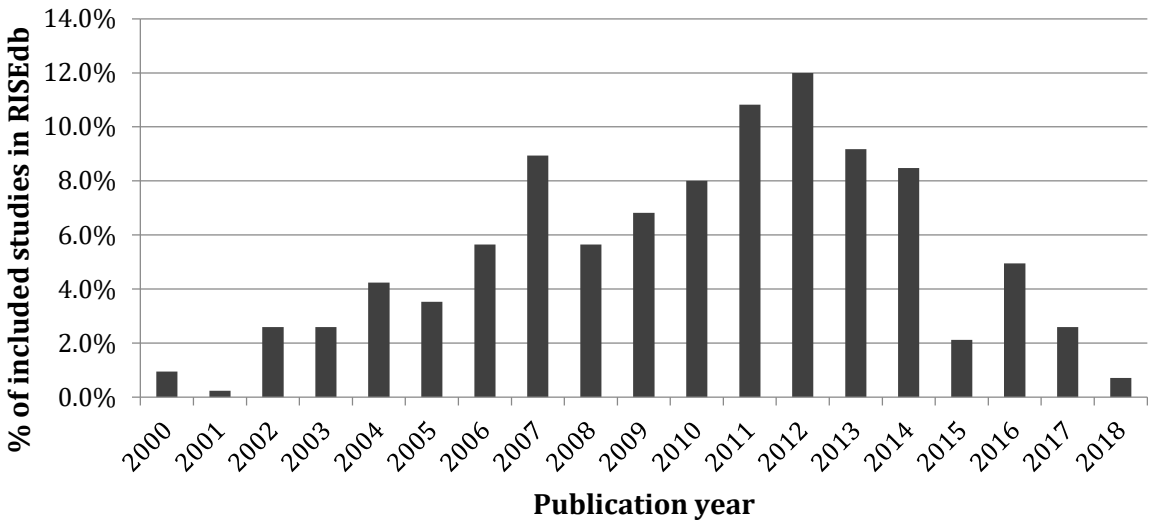


Figure 4 Distribution of included studies in RISEdb according to publication year

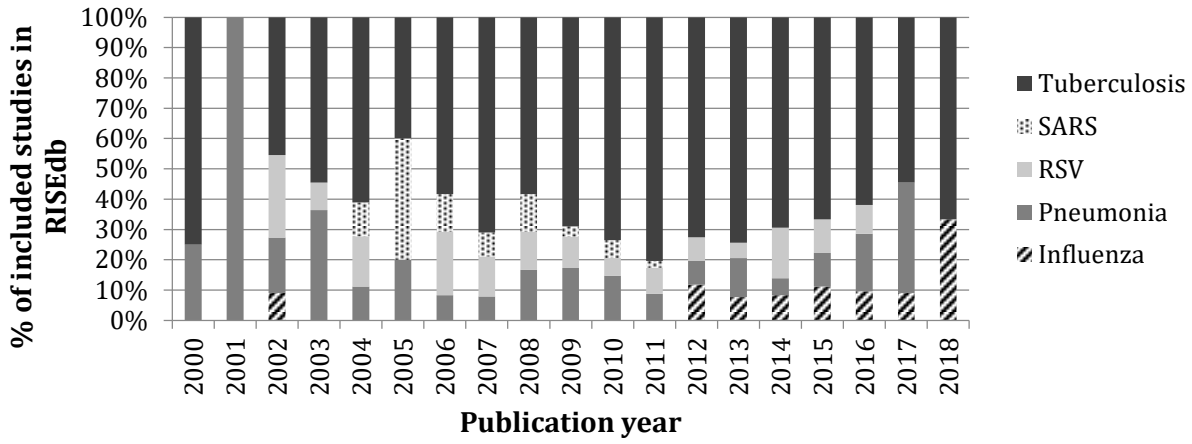


Figure 5 Distribution of included studies in RISEdb according to the publication year and stratified per disease

When comparing the journals where these studies were published, 32.7% of the studies were published in the „top" eight journals (classified as such if there were more than 10 published studies): Journal of Infectious Diseases (26 studies, 6.1%, IF= 5.345[5.186]), PLoS One (22 studies, 5.2%, IF= 2.766[2017]), Infection, Genetics and Evolution (19 studies, 4.5%, IF= 2.545[2017]), International Journal of Immunogenetics (17 studies, 4.0%, IF=1.000[2017]), BMC Infectious Diseases (15 studies, 3.5%, IF= 2.620[2017]), International Journal of Tuberculosis and Lung Disease (15 studies, 3.5%, IF= 2.392[2017]), Tuberculosis (14 studies, 3.3%, IF= 2.727[2017]), and Human Immunology (11 studies, 2.6%, IF= 1.994[2017]).

4.2.1.2 Disease category and pathogen species

The majority of the studies addressed tuberculosis (1,565 data points, 65.1%), followed by RSV (294 data points, 12.2%), pneumonia (261 data points, 10.9%), SARS (201 data point, 8.4%), and influenza (81 data point, 3.4%). With regards to reported pathogen, all studies on SARS had SARS coronavirus identified, 99.5% data points on tuberculosis had *Mycobacterium tuberculosis* identified (the rest was composition of various pathogens from Mycobacterial lineage), 98.0% data points on RSV had RSV identified (the rest was mixture

of RSV and human rhinovirus (HRV)), and 91.4% data points on influenza had H1N1 identified (3.7% data points had H3N2, 2.5% data points had H7N9, and the rest was either not reported or a composition of several influenza viruses). The situation for pneumonia is the most complicated one, as 54.0% data points had identified several bacterial and/or viral causative pathogens, high as 29.9% data points did not report causative pathogen, while 7.7% data points identified *Legionella pneumophila*, 6.9% data points identified *Streptococcus pneumoniae*, and 1.5% data points identified *Mycoplasma pneumoniaeas* the causative pathogen. As pneumonia can be of very diverse clinical signs and symptoms, due to simplicity and increasing the sample size, several diseases were grouped together and are analysed as "pneumonia", which in total corresponds to 52 data points (19.9%) of various disease: otitis media, various lower respiratory tract infections, bronchiolitis, bronchiectasis, tonsillitis, obstructive tonsillar hypertrophy, thoracic empyema, chronic obstructive bronchitis, and Legionnaire's disease.

4.2.1.3 Demographics of subjects

Demographics of included subjects (cases and controls) – ethnicity, gender and age distribution, reported as number of data points in RISEdb is shown in Table 5.

Regarding the ethnicity, majority of the studies are focusing on subjects of Asian ethnicity (1,138 data points, 47.4%), followed by Europeans (513 data points, 21.4%), admixed population (445 data points, 18.5%), Africans (281 data points, 11.7%), and subjects of native South American descend (25 data points, 1.0%). Data points were classified as admixed population if the subjects were from South or North America (unless explicitly stated as subjects of native South American descend), Australia, and in cases where studies explicitly reported of including subjects of several different origins. When stratified per disease category, all subjects in SARS studies were Asians, and majority of subjects in tuberculosis studies were Asians (54.9%), while majority of subjects in pneumonia and RSV studies were Europeans (65.5% and 65.3, respectively). Studies on influenza do not have such strong stratification regarding subjects' origin (44.4% Europeans, 34.6% admixed, 21.0% Asians).

Only minority of included studies reported data separated by gender, leading to only 40 (1.7%) and 64 (2.6%) data points reported for women only and men only, respectively. When stratified by disease category, all data points on influenza and pneumonia, 98.6% data points on RSV, 95.5% data points on tuberculosis, and 85.6% data points on SARS reported joined results (both women and men).

Majority of studies were done on adults (1,895 data points, 78.9%), however almost 11% of data points had combined children and adult subjects (either joined together in cases and controls group, or e.g. as having children in cases group and adults in controls group as it was a very common case for RSV studies, 52.7%).

Table 5 Demographics of subjects included in RISEdb (reported as number of data points with percentages in brackets)

	Influenza	**Pneumonia**	**RSV**	**SARS**	**Tuberculosis**
Ethnicity					
Admixed	28 (34.6)	32 (12.3)	70 (23.8)	-	315 (20.1)
African	-	25 (9.6)	4 (1.4)	-	252 (16.1)
Asian	17 (21.0)	33 (12.6)	28 (9.5)	201 (100.0)	859 (54.9)
European	36 (44.4)	171 (65.5)	192 (65.3)	-	114 (7.3)
South American	-	-	-	-	25 (1.6)
Gender					
Mixed	81 (100.0)	261 (100.0)	290 (98.6)	172 (85.6)	1494 (95.5)
Women	-	-	2 (0.7)	17 (8.4)	21 (1.3)
Men	-	-	2 (0.7)	12 (6.0)	50 (3.2)
Age					
Adults	66 (81.5)	156 (59.8)	-	201 (100.0)	1472 (94.1)
Children	10 (12.3)	67 (25.7)	33 (11.2)	-	14 (0.9)
Elderly	3 (3.7)	22 (8.4)	-	-	-
Infants	-	3 (1.1)	106 (36.1)	-	-
Mixed	2 (2.5)	13 (5.0)	155 (52.7)	-	79 (5.0)

In disease susceptibility models where controls were healthy individuals, majority of the data were addressing to healthy individuals (HC, 1,613 data points, 75.1%), followed by household contacts (HHC, 205 data points, 9.5%), mixed category of several control groups used (188 data points, 8.8%), health-care workers (HCW, 84 data points, 3.9%), and umbilical cord blood samples (UCB, 59 data points, 2.7%).

4.2.1.4 Disease model

Majority of the studies were attributable to infectious disease susceptibility model (2,104 data points, 87.6%), followed by disease severity model (204 data points, 8.4%), disease mortality model (47 data points, 2.0%), while the rest was based on comparison of seropositive and seronegative controls (47 data points, 2.0%). Detailed summary of the number of data points per each disease model stratified by disease category is shown in Table 6.

Table 6 Summary of disease model per each disease category (reported as number of data points with percentages in brackets)

Disease model category	Influenza	Pneumonia	RSV	SARS	Tuberculosis
Healthy exposed controls					
21	-	1 (0.4)	-	6 (3.0)	40 (2.6)
Disease susceptibility					
30	44 (54.3)	155 (59.4)	247 (84.0)	85 (42.3)	1,176 (75.1)
3E	-	17 (6.5)	-	1 (0.5)	52 (3.3)
31	-	-	-	41 (20.4)	39 (2.5)
31/2	8 (9.9)	-	-	10 (5.0)	122 (7.8)
32	-	1 (0.4)	-	6 (3.0)	96 (6.1)
33	-	-	-	-	4 (0.3)
Expanded 30 (30+3E+31+31/2+32)	52 (64.2)	173 (66.3)	247 (84.0)	143 (71.1)	1,485 (94.9)
Disease severity					

Disease model category	Influenza	Pneumonia	RSV	SARS	Tuberculosis
41/2	4 (4.9)	-	-	-	-
43	18 (22.2)	56 (21.4)	47 (16.0)	44 (21.9)	35 (2.2)
Disease mortality					
50	-	10 (3.8)	-	-	-
53	3 (3.7)	19 (7.3)	-	5 (2.5)	1 (0.1)
54	4 (5.0)	2 (0.8)	-	3 (1.4)	-

4.2.1.5 Risk of bias in individual studies (CSI scores)

For 2,094 data points (87.2%) all three CSI score domains were scored. For the rest of the data points, where cases were classified as severe or deceased, Selection domain of CSI score was not determined, as there was no selection process involved, so those data points were assigned 0 in Selection domain. There were 264 data points (12.9%) that failed HWE test ($P<0.05$), and those studies had their Selection domain of CSI score downgraded to C (58 data points were downgraded, as the rest already had the score C in Selection domain).

When all three CSI score domains were scored, only 122 data points (5.1%) had credible CSI score (having only A or B grades in all three domains), while the remaining had at least one C grade and was immediately considered to be of weak credibility. Disease-specific CSI profiles indicated that studies on tuberculosis, pneumonia and influenza were of slightly better quality, while studies on RSV and SARS were slightly worse. CSI scores for all data points and separated by disease category are in details shown in Figure 6.

Since Information domain of CSI score is divided in three sub-domains, majority of the data points were assigned B grade for I1 (cases status was verified on the basis of less specific diagnostic methods, e.g. guidelines, microbiology cultures; 1,936 data points, 92.4%), B grade for I2 (controls status verified on the basis of less specific diagnostic methods, e.g. tuberculin skin test, no history of disease; 1,289 data points, 61.5%), and C grade for I3 (no genotyping QC performed; 1,256 data points, 59.9%). Detailed classification of Information domain of CSI score separated by disease is shown in Table 7.

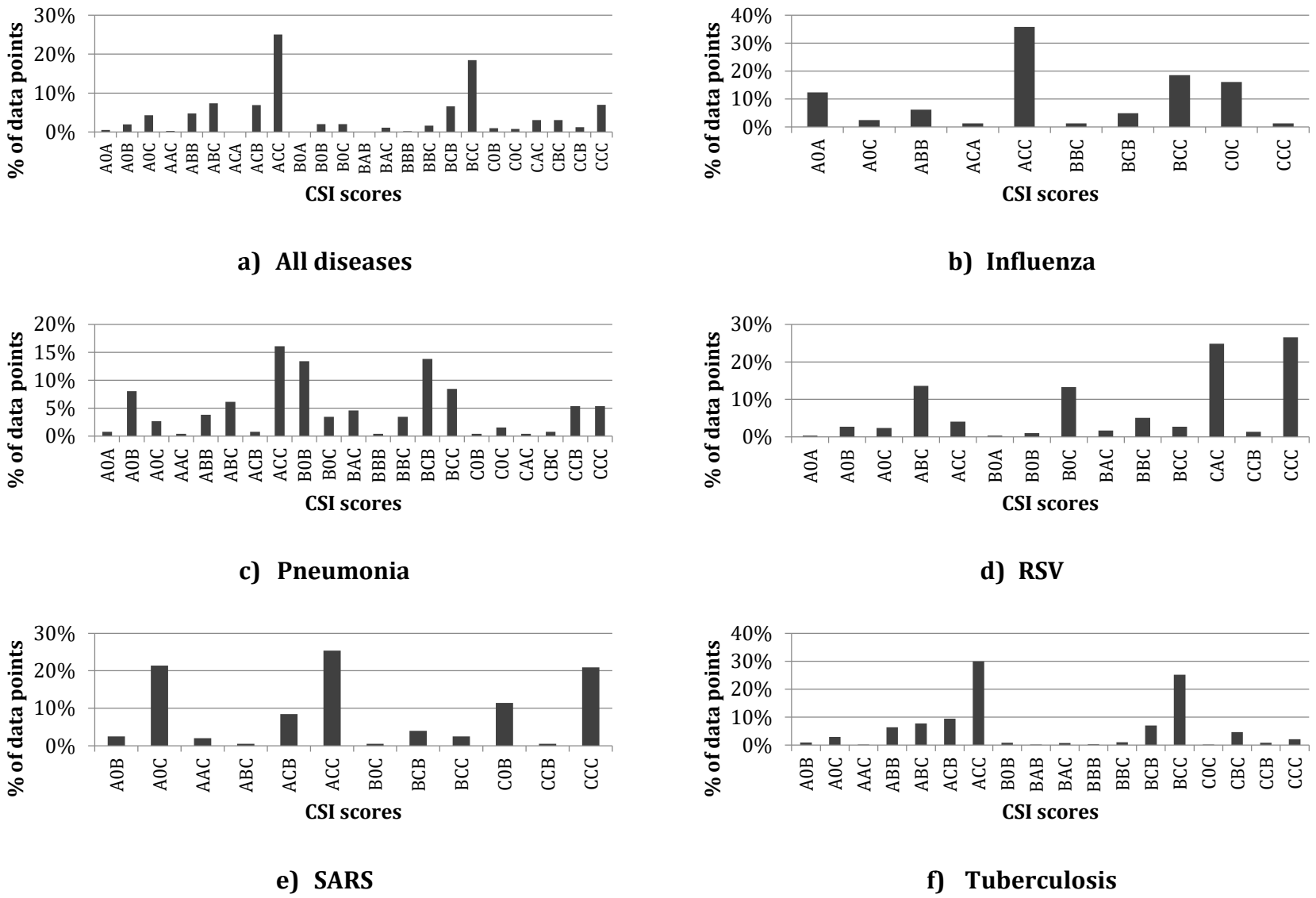


Figure 6 CSI scores for pooled and per each disease category (Confounding-Selection-Information risk of bias scale; grades of credibility: A – high, B – intermediate, C – weak, 0 – *post-hoc* stratification of cases in disease severity models)

Table 7 Information domain of CSI score stratified by disease category (reported as number of data points with percentages in brackets)

Grade	Influenza	Pneumonia	RSV	SARS	Tuberculosis
I1 – diagnostic information of cases					
A	45 (80.4)	10 (5.5)	26 (11.0)	-	13 (0.9)
B	11 (19.6)	152 (83.5)	206 (87.7)	124 (96.1)	1,443 (96.6)
C	-	20 (11.0)	3 (1.3)	5 (3.9)	38 (2.5)
I2 – diagnostic information of controls					
A	7 (12.5)	-	-	-	21 (1.4)
B	12 (21.4)	102 (56.0)	29 (12.3)	53 (41.1)	1,093 (73.2)
C	37 (66.1)	80 (44.0)	206 (87.7)	76 (58.9)	380 (25.4)
I3 – genotyping QC					
A	15 (26.8)	85 (46.7)	149 (63.4)	83 (64.3)	402 (26.9)
B	-	14 (7.7)	4 (1.7)	-	88 (5.9)
C	41 (73.2)	83 (45.6)	82 (34.9)	46 (35.7)	1004 (67.2)

4.2.1.6 Genes and SNPs

Overall, there were 288 different genes in the data, with most frequent results for *IL10* (126 data points, 5.3%), *TNFA* (116 data points, 4.8%), *VDR* (101 data points, 4.2%), *SLC11A1* (97 data points, 4.0%), and *SP110* (88 data points, 3.7%). Three most frequently analysed genes per each disease category is shown in Table 8.

A total of 1,000 different SNPs were recorded in the database, but only 124 met the inclusion criteria of at least four data points per SNP (the numbers changed according to the disease model and disease category used to perform meta-analysis, which is explained later in the chapter 4.2.2 Meta-analysis).

Table 8 Most frequently analysed genes per each disease category (reported as number of data points with percentages in brackets)

Influenza		Pneumonia		RSV		SARS		Tuberculosis	
Gene	**N (%)**	**Gene**	**N (%)**	**Gene**	**N (%)**	**Gene**	**N (%)**	**Gene**	**N (%)**
TNFA	11 (13.6)	*IL6*	26 (10.0)	*IL4*	23 (7.8)	*ACE2*	29 (14.4)	*IL10*	98 (6.3)
PIK3CG	9 (11.1)	*IL10*	15 (5.8)	*TLR4*	17 (5.8)	*TNFA*	26 (12.9)	*SLC11A1*	97 (6.2)
SFTPD	9 (11.1)	*MYLK*	14 (5.4)	*IL13* & *STPA1*	13 (4.4)	*FCER2*	25 (12.4)	*VDR*	90 (5.8)

4.2.2 Meta-analysis

After checking all combinations of possible meta-analyses (stratified by disease category, disease model and when applicable, to either ethnicity, age and/or gender), only 50 models passed the threshold of having at least four data points (studies) per SNP. Thus, a total of 200 meta-analyses were performed in all four genetic models (allelic, dominant, recessive, heterozygote advantage). In addition to analysing each investigated disease separately, all the analysis was performed on pooled diseases, in order to understand if there are any universal genetic polymorphisms that are responsible for (respiratory) infections susceptibility in broader sense.

Due to lack of at least four published studies per SNP, meta-analysis was not performed for disease mortality model. Same, no subset analysis was possible when stratified to age or gender (except in case of disease susceptibility model with pooled diseases and stratified to only children cases, two SNPs in *TLR4* gene were available for meta-analysis).

In analysis of disease susceptibility model (expanded 30 model was used), there was a total of 1,146 data points in meta-analysis, with a total of 233 nominally significant results under random-effects assumption (20.3%; 70 in allelic, 66 in dominant, 50 in recessive, and 47 in heterozygote advantage model). Results of nominally significant results of random-effects meta-analyses are shown in Tables A.3, A.4, A.5 and A.6. Out of these nominally significant results, only 4 genes retained noteworthiness for the mid/low

BFDP level, which are shown in Table 9. Two SNPs (rs2070874 and rs2243250) of *IL4* gene were shown to be significant for RSV in allelic model, while rs2070874 was also associated with pooled diseases set in allelic and recessive model. Second gene, *IFNG*, was significantly associated with tuberculosis and pooled diseases set in allelic, dominant and recessive models (rs2430561). The third one was *TLR2* gene, where rs5743708 was significant for tuberculosis in allelic model, while rs3804099 was significant for pooled disease set in dominant model. Finally, gene *CCL2* (rs1024611) was significant for tuberculosis in heterozygote advantage model. No strong publication bias was detected for any of the noteworthy SNPs, when visually examining funnel plots.

Subset analysis of each disease model included under disease susceptibility model in order to analyse methodologically better studies with controls of known exposure to the pathogen, was possible for tuberculosis under model 21 (exposed seropositive controls *vs.* seronegative controls), tuberculosis and pooled disease set under model 31/2 (infected cases *vs.* mixed exposed seropositive and seronegative healthy controls), and tuberculosis under model 32 (infected cases *vs.* exposed seropositive healthy controls). Five genes were nominally significant under random-effects assumption (three for tuberculosis and model 32, two for pooled disease set and model 31/2; Table A.7), but only one remained noteworthy after BFDP calculation. It is a gene *CCL2* (rs1024611; Table 9) for tuberculosis in heterozygote advantage model when comparing the cases to exposed seropositive healthy controls (model 32).

Meta-analyses for disease severity models (43), could only be performed for pooled disease set and pneumonia, and there was only one nominally significant result – gene *IL10* (rs1800896; Table A.7) for pooled disease in recessive model.

All forest and funnel plots for 14 noteworthy significant results are shown at the end of this Thesis in Chapter Appendices (Figure A.1-A.14).

Complete sets of results for all disease models for both fixed- and random-effects meta-analysis are available on CD as part of electronic version of this Thesis (Table e-A.4 – e-A.9).

Table 9 Significant and noteworthy results of random-effects meta-analyses

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
Disease model: expanded 30 (disease susceptibility)											
RSV; allelic model											
IL4	rs2070874	C/T	4	1125	2627	-	8.91E-06	0.69 [0.58, 0.81]	0.007 (0.271)	24.7	BAC
IL4	rs2243250	C/T	4	1082	2729	European	6.04E-05	0.76 [0.66, 0.87]	0.046 (0.718)	0	BAC
Tuberculosis; allelic model											
IFNG	rs2430561	A/T	26	4914	5012	-	1.50E-07	1.31 [1.19, 1.46]	0.001 (0.054)	54.2	BCC
TLR2	rs5743708	A/G	6	1727	1684	-	3.30E-07	3.21 [2.05, 5.02]	0.066 (0.788)	0	BAC
Tuberculosis; dominant model											
IFNG	rs2430561	A/T	25	4774	4931	-	9.20E-06	1.44 [1.22, 1.69]	0.009 (0.329)	61.9	BCC
Tuberculosis; recessive model											
IFNG	rs2430561	A/T	25	4774	4931	-	1.21E-05	0.71 [0.61, 0.83]	0.017 (0.471)	15.2	BAC
Tuberculosis; heterozygote advantage model											
CCL2	rs1024611	A/G	5	2195	2031	Admixed	2.26E-07	0.72 [0.63, 0.81]	0.000 (0.004)	0	BAC
Pooled diseases; allelic model											
IFNG	rs2430561	A/T	28	5487	5878	-	1.71E-06	1.34 [1.19, 1.51]	0.002 (0.080)	70.8	BCC
IL4	rs2070874	C/T	7	1672	3514	-	1.35E-04	0.75 [0.65, 0.87]	0.087 (0.834)	40.0	BBC
Pooled diseases; dominant model											
IFNG	rs2430561	A/T	27	5347	5797	-	2.24E-05	1.46 [1.23, 1.74]	0.025 (0.575)	71.8	BCC
TLR2	rs3804099	C/T	10	2062	2555	-	9.44E-05	1.40 [1.18, 1.65]	0.048 (0.724)	0	BAC
Pooled diseases; recessive model											
IFNG	rs2430561	A/T	27	5347	5797	-	8.93E-06	0.68 [0.57, 0.81]	0.018 (0.491)	39.6	BBC
IL4	rs2070874	C/T	5	1277	2513	-	7.79E-08	1.800 [1.45, 2.22]	0.000 (0.014)	0	BAC
Disease model: 32 (exposed healthy seropositive controls)											
Tuberculosis; heterozygote advantage model											
CCL2	rs1024611	A/G	4	1529	1570	-	2.65E-06	0.71 [0.62, 0.82]	0.004 (0.162)	0	BAC

* reference/alternate allele

4.3 Qualitative synthesis

A total of 22 family and linkage-based studies were identified, out of which 12 for tuberculosis, six for otitis media, three for RSV, and one for pneumonia and influenza. Studies on tuberculosis were either genome-wide (two studies), or were focused on larger chromosome regions (including chromosomes 2, 5, 10, 11, 15, 17, 20, and X) or specific gene (*SLC11A1* (two studies), *TNF* (three studies), and *IL12RB1*). Studies on otitis media investigated regions on chromosomes 3, 10 (two studies), 19 (three studies), genes *SLC11A1, Evi1*, *Fbxo11*, and four *SMAD*, while one study was genome-wide linkage study. Out of three studies on RSV, two were conducted within the same research group, but with different families included in the analysis, so there is a replication of promotor SNP in *IL8* gene. Overview of these studies with short description of study design and main findings are shown in Table A.8. In general, there is no overlap in of results within these studies.

Additional 16 GWAS studies were identified, 11 on tuberculosis, three on pneumonia, two on otitis media, and one on influenza. Five genome-wide significant results were recorded for tuberculosis, belonging to genes *WT1, ASAP1, HLA, RGS12 and MFN2*, with only gene *WT1* being replicated in an independent study. Two genome-wide significant results were recorded for pneumonia, both SNPs belonging to *HLA* gene cluster. GWAS on otitis media and influenza did not yield any genome-wide significant result. Detailed overview of GWAS study description with main findings is summarized in Table A.9.

There was also 61 published (systematic review and) meta-analyses identified, of which majority addressed genetic susceptibility to tuberculosis (52 studies, 85.2%). However, these meta-analyses investigated infection susceptibility in much wider set of clinical appearances, often with manifestations not restricted to respiratory tract, and were thus not directly comparable to this study. Overall, out of 52 meta-analyses on tuberculosis there were 24 analysed genes (number of published meta-analyses was given in brackets): *P2X7* (7), *CD14* (5), *VDR* (5), *TNF* (4), *HLA-DRB1* (3), *IFNG* (3), *IL10* (3), *MCP1* (3), *SLC11A1* (3), *CCL5* (2), *CD209* (2), *IL18* (2), *MBL* (2), *TLR2* (2), and per one published study for *CCL2*, *HLA-DQ*, *IL12B*, *IRGM*, *NOD2*, *SP110*, *TIRAP*, *TLR1*, *TLR4*, *TLR6*. Four meta-analyses were

focused on pneumonia (1 study analysed several SNPs, 1 study on *TNF*, and two studies on *ACE*), two meta-analyses focused on RSV bronchiolitis (with investigated genes *VDR*, *TLR4*, *CD14*), one meta-analyses focused on influenza and gene *IFITM1*, while the last two meta-analyses were focusing on various infectious diseases and its association to *SLC11A1* and *IL27*. Most surprisingly, majority of these meta-analyses were only focusing on one gene and in most cases on only one SNP.

5 DISCUSSION

Work presented in this Thesis represents a direct continuation of our recently published paper (49), where the author of this Thesis is a joint first author. As such, this is the first, most comprehensive and up to date (with literature included up to July 26, 2018) systematic review and meta-analysis of published studies investigating host genetic single nucleotide polymorphisms (SNPs) implicated in five respiratory infectious diseases, selected on the basis of their great impact and burden on human health and on the possibility to cause pandemics – tuberculosis, influenza, pneumonia, respiratory syncytial virus (RSV) infection, and severe acute respiratory syndrome (SARS) coronavirus.

One of the novelty, and thus strength, presented here lies in this approach by selecting several respiratory infections which made possible to analyse the shared respiratory infectious disease mechanisms and pathways, besides the disease-specific analyses. Contrary, majority of the published studies included within this review were focused on only one pathogen (and in great number of cases only one gene and/or SNP), ignoring the possibility of that various pathogens might and do utilize the same host mechanisms by comparing various diseases.

After a rigorous multiple testing correction, there were in total four genes that retained their significance (Table 9). Gene *IFNG* with its SNP rs2430561 was investigated in 28 different studies which in meta-analysis included more than 11,000 individuals, and as such showed significance in tuberculosis and pooled diseases model, all under three different genetic models (except heterozygote advantage). *IL4* gene showed to be significant in RSV (with two SNPs in allelic model – rs2070874, and rs2243250 in European population), and in pooled diseases model (rs2070874, in allelic and recessive model). Two SNPs in *TLR2* gene retained significance in tuberculosis (rs5743708, in allelic model), and in pooled diseases model (rs3804099, in dominant model). All noteworthy genes were identified in the disease susceptibility model, while the significance of the fourth gene, *CCL2*, was also identified in a subset analysis of methodologically better studies, where

controls were of known exposure, healthy but seropositive (rs1024611, in heterozygote advantage model).

IFNG is part of the large interferon gene family that has initially been discovered to have a role in antiviral gene expression while encoding cytokines that plays an important role in modulating innate and adaptive immune response (74). Several studies suggested direct involvement of *IFNG* in tuberculosis development, where IFN-γ cytokines are synthesized in response to mycobacterial stimulation displaying protective characteristics and that *IFNG*-deficient mice suffer from severe *M. tuberculosis* infection (75). As shown with the number of studies investigating this crucial gene, there is evidence that *M. tuberculosis* may evade human response if it successfully inhibits the IFNG signalling pathway (76).

IL4 gene has been previously described to have a vital role in the shaping of immune response, as it promotes and stimulates both T-cell and B-cell differentiation and provides balance between Th1 and Th2 (77). This is very important to be optimally and strictly regulated as Th1-type cytokines are producing proinflammatory response, and without the counteract of anti-inflammatory response of Th2, it would lead to uncontrolled tissue damage (78). Alterations in this gene have most commonly been associated with the increased risk of allergies and atopy (79). Furthermore, few animal studies already showed a direct role of *IL4* in infection pathogenesis – one study showed that RSV induce basophil accumulation and *IL4* expression (80), while another showed that *IL4*-deficient mice were more susceptible to *Legionella pneumophila* and had increased mortality rates compared to controls (81).

TLR2 is a member of large family of genes involved in pathogen recognition and signalling cascade of innate immune response (82), and it is well-known that cell wall components of most Gram-positive bacteria can activate *TLR2* inflammatory response by releasing cytokines and chemokines (83). As confirmed within this study, there have been previous reports of the *TLR2* importance in the immune response to tuberculosis (84). However, it seems that *TLR2* effects are very context-specific, as *TLR2*-deficient mice did not have their clinical outcomes altered (85). Interestingly, despite *TLR2* being closely

linked to *CD14* mechanisms (82), this study did not show any significant associations with *CD14*.

Lastly, *CCL2* has been previously associated with diseases that included granuloma formation (86, 87), monocytic infiltrations (88), and migration and retention of monocytes in particular locations (89), all of which is a feature of tuberculosis (90), and its association with tuberculosis is confirmed in this study. Other studies suggest the importance of *CCL2* in various other infectious diseases – *CCL2*-overexpressing mice showed an improved pneumococcal clearance and survival (91), while in mice influenza challenge study it was shown to be a major mediator in H7N9 infection (92). Taking this into account, it is evident that *CCL2* should get more research focus and that human studies of respiratory diseases, other than tuberculosis, should also consider investigating this gene as a promising therapeutic target.

The results of this study fit into previously implied mechanisms of respiratory infections, where *CCL7-CCL2-CCR2* axis was described to have a critical role in *IL4* production and immune response regulation in both fungal (93) and viral infections (94), as well as tumours (95). Also, a role of IFNG can be seen here for its known regulation of *CCL2* chemokine synthesis (96). This could represent the most interesting translatable mechanism towards clinical application across the wider spectrum of respiratory infectious diseases. In addition, the only significant results from GWAS studies, *WT1* gene, implied in susceptibility to tuberculosis (97, 98), has been described to be under control of *CCL2* (99), which could, at least partly, explain the relationship between some infections and tumours (100).

An overview of family and linkage-based studies suggested frequent differences in study designs, marked by dissimilarities in phenotype definitions, marker types and analytic approaches. Regardless, the association of *SLC11A1* with tuberculosis was replicated in two studies (101, 102), with another study on otitis media (103) which clearly shows the need to take into account the shared pathways when investigating the infection susceptibility of respiratory tract (Table A.8). Regarding GWAS studies, there was only one significant and replicated result, located in an intergenic region near *WT1* gene (rs2057178), associated with tuberculosis (97, 98). There was an additional significant

association with HLA gene cluster with tuberculosis (104-106) and pneumonia (106, 107), however, no SNPs were replicated between these studies. Other reported genome-wide significant signals were not replicated in independent cohorts (Table A.9). This is probably due to largely underpowered study designs, as the sample sizes are rarely exceeding 1,000 cases or controls, but more importantly there are still major methodological barriers that were simply transferred from the candidate gene study designs. Up-scaling the study in terms of genetic resolution (from single or just a few SNPs to hundreds of thousands and millions of SNPs in GWAS), increase in the sample size and use of more advanced analytic and statistical methods will not likely provide a meaningful step forward before the main methodological and study design limitations are solved, e.g. when it comes to sample selection. Also, as infectious diseases fall in the field of complex diseases, there is a high level of genetic complexity present (108), and one must be aware of duality between rare Mendelian variants, which may confer complete immunity, but have very low prevalence in a population (109), and common variants, which usually have much lower explained variance, and therefore have a limited capacity for clinical intervention.

It is also interesting to see the publication bias towards tuberculosis studies, and even though other diseases investigated within this Thesis are also shown to have a substantial burden on human health, it is surprising in which extent are they understudied (at least in the frames of rigid inclusion criteria selected within the scope of this work). It is also necessary to stress that even though there is a substantial number of published meta-analysis on tuberculosis, how much is lost in context of complex genetic pathways, as in most cases these meta-analyses were only focusing on either one gene or even only on one SNP. It is of utmost urgency to systematically improve the whole field and to focus on a wider picture, as it is clear that there is a complex network of multiple genes and SNPs involved in susceptibility to any given infectious disease. What this work also identified as being extremely underpowered is the fact that majority of published studies were focused on disease susceptibility, but only a very few added up the next step in the infection cycle, and that is disease severity and mortality. It is obvious that there should be an additional level of complexity and a separate network of genes and SNPs that will distinguish between

those individuals that are susceptible to infection but will only develop a mild clinical outcome and those that will develop a severe disease with possible fatal outcome.

In order to improve any of the above mentioned steps, the absolutely crucial step is to improve primary study design in a stringent evidence-based manner, as almost 95% of all extracted data points in this work suffered from a strong risk of bias or confounding in at least one domain that was graded. The improvements must be undertaken in almost all aspects of study design, including better clinical definitions and phenotyping, improved controls selection and diagnostics, appropriate statistical analysis, the use of novel molecular technologies and better reporting with larger sample sizes obtained through consortia development. Firstly, there is a need to improve phenotype definitions and criteria for diagnosis, alongside with the use of proper diagnostics to validate a causal pathogen. It would also be interesting to use proxy and extreme phenotypes (110), which was used in HIV, with exposed uninfected subjects, long-term non-progressors, fast progressors and elite controllers (111-113). One of the largest identified issues was that very often controls are only referred to as "healthy", with no mention of any diagnostic procedure undertaken to validate their status. Also, it was quite common to use dissimilar diagnostic procedures for classification of cases and controls, so the selection of controls and diagnostic process must be thoroughly improved and harmonized. In order to have a study design from which valid conclusions can be made, protocols must be harmonized and standardized between cases and controls. Even then there is some possibility of not having appropriate controls as there may be many issues which researches often ignore. This can include misdiagnosed controls, pre-disease sampling (in cases when controls are sampled before an epidemic outbreak or use of cord blood samples as controls when cases are adults – in both scenarios controls are thought to have the same chance of becoming cases under the assumption of an equal risk across the population), controls who are susceptible but were unexposed to pathogen (and would fall into cases category if exposed to pathogen), controls who are susceptible but insufficiently exposed to pathogen (in cases of less virulent pathogens), controls who are susceptible but vaccinated and resistant, and finally, controls with latent undetected infections or a mild disease who will not require healthcare. Taking into account all these possible scenarios, a careful selection and

diagnostics of controls is one of the best strategies to improve genetic studies of infectious diseases, and definitely the best option would be to include controls that were known to be exposed to the same pathogen as cases. In addition, data analysis should be improved, the use of various novel –*omics* technologies is highly desirable (114), but that should be accompanied with replication efforts in an unlinked population. When very complex genetic background of infectious diseases is coupled with huge errors and biases arising from study designs, as showed with this work, there will be a very low number of significant results and accumulation of large amount of poorly usable evidence. Therefore, it is clear that the best way forward is to improve primary studies, which can have a very positive effect on gene discovery.

In addition, there should be very stringent framework about reporting, where all relevant information have to be reported, and manuscript prepared against a given set of criteria such as STREGA (115), STROBE-ME (116) or STREIS (117). Another layer of improvement may come from the creation of large-scale consortia and enable data sharing, that would be based on harmonized protocols and standardized analysis framework which would provide the best opportunity to substantially move forward the entire field and to maximize understanding of the host genetics involvement in the infectious disease development, progression and outcome. Naturally, the proposed methodology improvements from this work are applicable to any infectious disease research, and can also be applied to other –*omics* fields besides genomics.

Despite the best efforts of conducting this systematic review with very stringent criteria, there are still numerous limitations. Firstly, a very diverse field of several respiratory infections was reviewed, and there is a chance that some relevant articles are missed, regardless of a very detailed and several times adjusted search strategy. This was partially fixed with extensive hand search of selected relevant articles references; however, the problem remains in cases when it was impossible to obtain a full text article or raw data in cases when insufficient data were provided within the article. Since the scope of this work was only focused on single nucleotide polymorphisms, there is a whole array of genetic information missed since markers such as HLA or KIR were excluded, along with short tandem repeats, microsatellites or haplotypes. Also, even with the best effort of

excluding studies that reported patients having comorbidities, there are still some such studies that were included in the meta-analysis in the end. This work also completely ignored any information on pathogen, and studies reporting various pathogens as causal were pooled together, however, a subset analysis should be performed in order to overcome this issue since there may be some differences in the genetic response depending on the causal pathogen regardless of the same clinical outcome (e.g. pneumonia). Any limitation might have a very negative impact on effect-to-bias ratio and bias may be several orders of magnitude greater than the effect size. In attempt to minimize this, a very stringent analytic approach was used including very rigid threshold and multiple testing correction, random-effects meta-analysis, and extremely stringent quality assessment scoring of individual studies. Also, due to inconsistency in reporting, it was impossible to adjust the analysis for basic covariates, such as age, sex and comorbidity information, or to perform stratified analysis as only few studies reported the data separately for men and women, or children and adults, in studies with no age limitation. Finally, this study completely ignored any pathogen information (118), including microbiome even though novel studies are suggesting that lungs are not sterile and that respiratory tract microbiome could have a great impact on health and disease (119).

6 CONCLUSION

This Thesis represents the first, most comprehensive and up to date field synopsis of the host genetics influence on the susceptibility to respiratory infectious diseases. Four genes (*IL4, TLR2, IFNG* and *CCL2*) retained their significance after a stringent and as much as possible unbiased methodological framework for either pooled respiratory infections (influenza, pneumonia, RSV, SARS, tuberculosis), tuberculosis, and/or RSV infection alone. These findings are based on the inclusion from 4,000 up to 11,000 individuals in meta-analysis per single SNP, and as various ethnicities are included they truly represent a global findings indispensable in the susceptibility to various respiratory infections.

In addition, as part of this Thesis, a new risk of bias scoring scheme is developed, named CSI – Confounding-Selection-Information risk bias scale, which is fully appropriate to assess all various aspects of risk of bias which can arise form genetic studies, as none of the previously published and widely acceptable scores are unable to do.

The main part of this Thesis, a comprehensive Respiratory Infection SuscEptibility database (RISEdb) was made publicly available and searchable.

Also, this Thesis aimed to provide a critical overview and guidelines for improvement of future primary studies, which could be useful and extended to genetic studies of all infectious diseases.

Finally, results of this Thesis represent the first step in understanding the host side of the host-pathogen interactions, and only by a fully interdisciplinary approach by combining various host –*omics* with pathogen –*omics* there is a possibility to truly move forward the entire field and enable the development of personalized infectious disease medicine.

7 SUMMARY

Background and aim: With substantial global burden of respiratory infectious diseases on human health, it is important to elucidate all the factors involved in their susceptibility and pathogenesis. Frequently used approach is to study host genetic polymorphisms, but results of such studies were often inconsistent. The aim of this Thesis was to provide the most comprehensive and up to date field synopsis on involvement of host genetics to respiratory infections (tuberculosis, influenza, pneumonia, RSV, SARS) susceptibility.

Methods: 425 studies were identified as relevant and meta-analysed from the total of 30,307 studies identified in a systematic search of four bibliographic databases and stringently assessed for risk of bias using the novel Confounding-Selection-Information risk of bias scale.

Results: In random-effects meta-analysis four genes retained their significance after multiple testing correction: *IL4* for RSV (rs2070874, OR [95% CI] = 0.69 [0.58, 0.81]; rs2243250, OR [95% CI] = 0.76 [0.66, 0.87]) and pooled respiratory infections (rs2070874, OR [95% CI] = 0.75 [0.65, 0.87]), *TLR2* for tuberculosis (rs5743708, OR [95% CI] = 3.21 [2.05, 5.02]) and pooled respiratory infections (rs3804099, OR [95% CI] = 1.40 [1.18, 1.65]), *IFNG* for tuberculosis (rs2430561, OR [95% CI] = 1.31 [1.19, 1.46]) and pooled respiratory infections (rs2430561, OR [95% CI] = 1.34 [1.19, 1.51]), and within a subset analysis of methodologically better studies *CCL2* was significant for tuberculosis (rs1024611, OR [95% CI] = 0.71 [0.62, 0.82]).

Conclusion: The *IFNG-IL4-TLR2-CCL2* axis could represent a highly interesting target for translation towards clinical use. However, this conclusion is based on a very low credibility of evidence with almost 95% of identified studies showed a string risk of bias or confounding. Recommendations for future studies in this field are to build upon large-scale collaborations, but also to substantially improve primary study design, in order to produce reproducible and clinically translatable evidence.

8 SAŽETAK

Uvod i cilj: Kako zarazne bolesti dišnog sustava i dalje predstavljaju ogroman teret na globalno ljudsko zdravlje, neophodno je istražiti sve čimbenike koji pridonose podložnosti i patogenezi. Analiza genetskih čimbenika je čest pristup, no rezultati takvih studija su većinom nedosljedni. Stoga je cilj ove doktorske disertacije provesti najopsežniji i najrecentniji pregled literature o ulozi ljudskih genetskih čimbenika na podložnost zaraznim bolestima dišnog sustava (tuberkuloza, gripa, upala pluća, RSV, SARS).

Metode: 425 studija se pokazalo značajnima te su uključene u meta-analizu od ukupno 30,307 studija pronađenih prilikom sustavnog pregleda četiri bibliografske baze podataka, te je njihov rizik od pristranosti strogo procijenjen uporabom nove ljestvice za procjenu rizika od pristranosti (*Confounding-Selection-Information risk of bias scale*).

Rezultati: Rezultati meta-analize nasumičnog učinka pokazali su kako su četiri gena zadržali svoju značajnost nakon ispravka statističke značajnosti zbog problema višestrukog testiranja: *IL4* za RSV (rs2070874, OR [95% CI] = 0.69 [0.58, 0.81]; rs2243250, OR [95% CI] = 0.76 [0.66, 0.87]) i u udruženom modelu (svih pet bolesti zajedno) (rs2070874, OR [95% CI] = 0.75 [0.65, 0.87]), *TLR2* za tuberkulozu (rs5743708, OR [95% CI] = 3.21 [2.05, 5.02]) i u udruženom modelu (rs3804099, OR [95% CI] = 1.40 [1.18, 1.65]), *IFNG* za tuberkulozu (rs2430561, OR [95% CI] = 1.31 [1.19, 1.46]) i u udruženom modelu (rs2430561, OR [95% CI] = 1.34 [1.19, 1.51]), te unutar metodološki boljih studija *CCL2* se pokazao značajnim za tuberkulozu (rs1024611, OR [95% CI] = 0.71 [0.62, 0.82]).

Zaključak: *IFNG-IL4-TLR2-CCL2* os bi mogla predstavljati značajnu metu za translaciju prema kliničkoj upotrebi. No, rezultati ovog rada se temelje na veoma niskoj vjerodostojnosti dokaza budući da skoro 95% uključenih studija pokazuju snažan rizik od pristranosti. Smjernice za buduća istraživanja u ovom području uključuju udruživanje u veće kolaboracijske centre, no također je potrebno značajno poboljšati ustroj primarnih istraživanja, kako bi se proizveli dokazi koji su ponovljivi, te se mogu prenijeti u kliničku upotrebu.

9 REFERENCES

1. Fauci AS, Morens DM. The Perpetual Challenge of Infectious Diseases. The New England Journal of Medicine 2012;366:454-61.

2. Karlsson EK, Kwiatkowski DP, Sabeti PC. Natural selection and infectious disease in human populations. Nat Rev Genet 2014;15:379-93.

3. Morens DM, Folkers GK, Fauci AS. The challenge of emerging and re-emerging infectious diseases. Nature 2004;430:242-9.

4. Casanova JL, Abel L. The genetic theory of infectious diseases: a brief history and selected illustrations. Annu Rev Genomics Hum Genet 2013;14:215-43.

5. Casanova JL. Human genetic basis of interindividual variability in the course of infection. Proc Natl Acad Sci U S A 2015;112:E7118-27.

6. Hill AVS. Evolution, revolution and heresy in the genetics of infectious disease susceptibility. Philosophical Transactions of the Royal Society B 2012;367:840-9.

7. Chapman SJ, Hill AV. Human genetic susceptibility to infectious disease. Nat Rev Genet 2012;13:175-88.

8. Kenney AD, Dowdle JA, Bozzacco L, i sur. Human Genetic Determinants of Viral Diseases. In: Bonini NM, editor. Annual Review of Genetics, Vol 512017. p. 241-63.

9. Cooke GS, Hill AV. Genetics of susceptibility to human infectious disease. Nat Rev Genet 2001;2:967-77.

10. Burgner D, Jamieson SE, Blackwell JM. Genetic susceptibility to infectious diseases: big is beautiful, but will bigger be even better? The Lancet Infectious diseases 2006;6:653-63.

11. Sorensen TI, Nielsen GG, Andersen PK, Teasdale TW. Genetic and environmental influences on premature death in adult adoptees. N Engl J Med 1988;318:727-32.

12. Albright FS, Orlando P, Pavia AT, Jackson GG, Albright LAC. Evidence for a heritable predisposition to death due to influenza. Journal of Infectious Diseases 2008;197:18-24.

13. Rowell JL, Dowling NF, Yu W, Yesupriya A, Zhang L, Gwinn M. Trends in population-based studies of human genetics in infectious diseases. PLoS One 2012;7:e25431.

14. Heitzeneder S, Seidel M, Forster-Waldl E, Heitger A. Mannan-binding lectin deficiency - Good news, bad news, doesn't matter? Clin Immunol 2012;143:22-38.

15. Colhoun HM, McKeigue PM, Davey Smith G. Problems of reporting genetic associations with complex outcomes. Lancet 2003;361:865-72.

16. Barry CE, Boshoff HI, Dartois V, i sur. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nature Reviews Microbiology 2009;7:845-55.

17. Affandi JS, Price P, Waterer G. Can immunogenetics illuminate the diverse manifestations of respiratory infections? Therapeutic advances in respiratory disease 4 2010;4:161-76.

18. Ioannidis JP, Greenland S, Hlatky MA, i sur. Increasing value and reducing waste in research design, conduct, and analysis. Lancet 2014;383:166-75.

19. Manry J, Quintana-Murci L. A genome-wide perspective of human diversity and its implications in infectious disease. Cold Spring Harb Perspect Med 2013;3:a012450.

20. Hill AV. Aspects of genetic susceptibility to human infectious diseases. Annu Rev Genet 2006;40:469-86.

21. Thye T, Owusu-Dabo E, Vannberg FO, i sur. Common variants at 11p13 are associated with susceptibility to tuberculosis. Nature Genetics 2012;44:257-9.

22. Thye T, Vannberg FO, Wong SH, i sur. Genome-wide association analyses identifies a susceptibility locus for tuberculosis on chromosome 18q11.2. Nature Genetics 2010;42:739-41.

23. Schork NJ, Murray SS, Frazer KA, Topol EJ. Common vs. rare allele hypotheses for complex diseases. Curr Opin Genet Dev 2009;19:212-9.

24. Manolio TA, Collins FS, Cox NJ, i sur. Finding the missing heritability of complex diseases. Nature 2009;461:747-53.

25. Quintana-Murci L, Alcais A, Abel L, Casanova JL. Immunology in natura: clinical, epidemiological and evolutionary genetics of infectious diseases. Nat Immunol 2007;8:1165-71.

26. Alcais A, Abel L, Casanova JL. Human genetics of infectious diseases: between proof of principle and paradigm. Journal of Clinical Investigation 2009;119:2506-14.

27. Alcais A, Quintana-Murci L, Thaler DS, Schurr E, Abel L, Casanova JL. Life-threatening infectious diseases of childhood: single-gene inborn errors of immunity? Ann N Y Acad Sci 2010;1214:18-33.

28. Ascough S, Paterson S, Chiu C. Induction and Subversion of Human Protective Immunity: Contrasting Influenza and Respiratory Syncytial Virus. Front Immunol 2018;9.

29. Rudan I, O'Brien KL, Nair H, i sur. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. J Glob Health 2013;3:010401.

30. Walker CL, Rudan I, Liu L, i sur. Global burden of childhood pneumonia and diarrhoea. Lancet 2013;381:1405-16.

31. Nair H, Nokes DJ, Gessner BD, i sur. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010;375:1545-55.

32. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. Bull Hist Med 2002;76:105-15.

33. Patterson KD, Pyle GF. The geography and mortality of the 1918 influenza pandemic. Bull Hist Med 1991;65:4-21.

34. Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. Journal of Pathology 2015;235:185-95.

35. Schafer A, Baric RS, Ferris MT. Systems approaches to coronavirus pathogenesis. Current Opinion in Virology 2014;6:61-9.

36. Poon LL, Guan Y, Nicholls JM, Yuen KY, Peiris JS. The aetiology, origins, and diagnosis of severe acute respiratory syndrome. Lancet Infect Dis 2004;4:663-71.

37. Le Chevalier F, Cascioferro A, Majlessi L, Herrmann JL, Brosch R. Mycobacterium tuberculosis evolutionary pathogenesis and its putative impact on drug development. Future Microbiol 2014;9:969-85.

38. Gagneux S. Host-pathogen coevolution in human tuberculosis. Philos Trans R Soc Lond B Biol Sci 2012;367:850-9.

39. Hershberg R, Lipatov M, Small PM, i sur. High functional diversity in Mycobacterium tuberculosis driven by genetic drift and human demography. PLoS Biol 2008;6:e311.

40. Abel L, El-Baghdadi J, Bousfiha AA, Casanova JL, Schurr E. Human genetics of tuberculosis: a long and winding road. Philosophical Transactions of the Royal Society B-Biological Sciences 2014;369.

41. Zumla A, George A, Sharma V, Herbert RH, Oxley A, Oliver M. The WHO 2014 global tuberculosis report--further to go. Lancet Glob Health 2015;3:e10-2.

42. Haidich AB. Meta-analysis in medical research. Hippokratia 2010;14:29-37.

43. Uman LS. Systematic reviews and meta-analyses. J Can Acad Child Adolesc Psychiatry 2011;20:57-9.

44. Khan KS, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. J R Soc Med 2003;96:118-21.

45. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. 2011.

46. Tripepi G, Jager KJ, Dekker FW, Wanner C, Zoccali C. Measures of effect: Relative risks, odds ratios, risk difference, and 'number needed to treat'. Kidney International 2007;72:789-91.

47. Zwahlen M, Renehan A, Egger M. Meta-analysis in medical research: potentials and limitations. Urol Oncol 2008;26:320-9.

48. Corlan AD. Medline trend: automated yearly statistics of PubMed results for any query. 2004.

49. Patarcic I, Gelemanovic A, Kirin M, i sur. The role of host genetic factors in respiratory tract infectious diseases: systematic review, meta-analyses and field synopsis. Scientific Reports 2015;In Press.

50. Daly AK, Day CP. Candidate gene case-control association studies: advantages and potential pitfalls. Br J Clin Pharmacol 2001;52:489-99.

51. LaFramboise T. Single nucleotide polymorphism arrays: a decade of biological, computational and technological advances. Nucleic Acids Res 2009;37:4181-93.

52. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

53. Casadevall A, Pirofski LA. Host-pathogen interactions: basic concepts of microbial commensalism, colonization, infection, and disease. Infect Immun 2000;68:6511-8.

54. Sagoo GS, Little J, Higgins JP. Systematic reviews of genetic association studies. Human Genome Epidemiology Network. PLoS Med 2009;6:e28.

55. Ioannidis JP, Boffetta P, Little J, i sur. Assessment of cumulative evidence on genetic associations: interim guidelines. Int J Epidemiol 2008;37:120-32.

56. Wells GA, Shea B, O'Connell D, i sur. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013.

57. Bogardus ST, Jr., Concato J, Feinstein AR. Clinical epidemiological quality in molecular genetic research: the need for methodological standards. JAMA 1999;281:1919-26.

58. Horita N, Kaneko T. Genetic model selection for a case-control study and a meta-analysis. Meta Gene 2015;5:1-8.

59. Clarke GM, Anderson CA, Pettersson FH, Cardon LR, Morris AP, Zondervan KT. Basic statistical analysis in genetic case-control studies. Nat Protoc 2011;6:121-33.

60. Chan VS, Chan KY, Chen Y, i sur. Homozygous L-SIGN (CLEC4M) plays a protective role in SARS coronavirus infection. Nat Genet 2006;38:38-46.

61. Prugnolle F, Manica A, Charpentier M, Guegan JF, Guernier V, Balloux F. Pathogen-driven selection and worldwide HLA class I diversity. Curr Biol 2005;15:1022-7.

62. Fumagalli M, Pozzoli U, Cagliani R, i sur. Parasites represent a major selective force for interleukin genes and shape the genetic predisposition to autoimmune conditions. J Exp Med 2009;206:1395-408.

63. Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. BMJ 2001;322:1479-80.

64. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ 2007;176:1091-6.

65. Sterne JA, Sutton AJ, Ioannidis JP, i sur. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.

66. Wakefield J. A Bayesian measure of the probability of false discovery in genetic epidemiology studies. Am J Hum Genet 2007;81:208-27.

67. Team RC. R: A language and environment for statistical computing. Vienna, Austria2013.

68. Schwarzer G. meta: An R package for meta-analysis. R News 2007;7:40-5.

69. Graffelman J, Camarena JM. Graphical tests for Hardy-Weinberg equilibrium based on the ternary plot. Hum Hered 2008;65:77-84.

70. Graffelman J. Exploring Diallelic Genetic Markers: The HardyWeinberg Package. Journal of Statistical Software 2015;64:1-23.

71. Heymann DL. The international response to the outbreak of SARS in 2003. Philos Trans R Soc Lond B Biol Sci 2004;359:1127-9.

72. Shaw K. The 2003 SARS outbreak and its impact on infection control practices. Public Health 2006;120:8-14.

73. Taubenberger JK, Morens DM. Influenza: the once and future pandemic. Public Health Rep 2010;125 Suppl 3:16-26.

74. Tau G, Rothman P. Biologic functions of the IFN-gamma receptors. Allergy 1999;54:1233-51.

75. Cavalcanti YV, Brelaz MC, Neves JK, Ferraz JC, Pereira VR. Role of TNF-Alpha, IFN-Gamma, and IL-10 in the Development of Pulmonary Tuberculosis. Pulm Med 2012;2012:745483.

76. Ting LM, Kim AC, Cattamanchi A, Ernst JD. Mycobacterium tuberculosis inhibits IFN-gamma transcriptional responses without inhibiting activation of STAT1. J Immunol 1999;163:3898-906.

77. Choi P, Reiser H. IL-4: role in disease and regulation of production. Clin Exp Immunol 1998;113:317-9.

78. Berger A. Th1 and Th2 responses: what are they? BMJ 2000;321:424.

79. Hershey GK, Friedrich MF, Esswein LA, Thomas ML, Chatila TA. The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. N Engl J Med 1997;337:1720-5.

80. Moore ML, Newcomb DC, Parekh VV, i sur. STAT1 negatively regulates lung basophil IL-4 expression induced by respiratory syncytial virus infection. J Immunol 2009;183:2016-26.

81. Newton C, McHugh S, Widen R, Nakachi N, Klein T, Friedman H. Induction of interleukin-4 (IL-4) by legionella pneumophila infection in BALB/c mice and regulation of tumor necrosis factor alpha, IL-6, and IL-1beta. Infect Immun 2000;68:5234-40.

82. van Bergenhenegouwen J, Plantinga TS, Joosten LA, i sur. TLR2 & Co: a critical analysis of the complex interactions between TLR2 and coreceptors. J Leukoc Biol 2013;94:885-902.

83. Kovach MA, Standiford TJ. Toll like receptors in diseases of the lung. Int Immunopharmacol 2011;11:1399-406.

84. Underhill DM, Ozinsky A, Smith KD, Aderem A. Toll-like receptor-2 mediates mycobacteria-induced proinflammatory signaling in macrophages. Proc Natl Acad Sci U S A 1999;96:14459-63.

85. Oliveira-Nascimento L, Massari P, Wetzler LM. The Role of TLR2 in Infection and Immunity. Front Immunol 2012;3:79.

86. Hussain R, Ansari A, Talat N, Hasan Z, Dawood G. CCL2/MCP-I genotype-phenotype relationship in latent tuberculosis infection. PLoS One 2011;6:e25803.

87. Deshmane SL, Kremlev S, Amini S, Sawaya BE. Monocyte chemoattractant protein-1 (MCP-1): an overview. J Interferon Cytokine Res 2009;29:313-26.

88. Xia M, Sui Z. Recent developments in CCR2 antagonists. Expert Opin Ther Pat 2009;19:295-303.

89. Paiva CN, Figueiredo RT, Kroll-Palhares K, i sur. CCL2/MCP-1 controls parasite burden, cell infiltration, and mononuclear activation during acute Trypanosoma cruzi infection. J Leukoc Biol 2009;86:1239-46.

90. Sampath P, Moideen K, Ranganathan UD, Bethunaickan R. Monocyte Subsets: Phenotypes and Function in Tuberculosis Infection. Front Immunol 2018;9:1726.

91. Winter C, Taut K, Srivastava M, i sur. Lung-specific overexpression of CC chemokine ligand (CCL) 2 enhances the host defense to Streptococcus pneumoniae infection in mice: role of the CCL2-CCR2 axis. J Immunol 2007;178:5828-38.

92. Lai C, Wang K, Zhao Z, i sur. C-C Motif Chemokine Ligand 2 (CCL2) Mediates Acute Lung Injury Induced by Lethal Influenza H7N9 Virus. Front Microbiol 2017;8:587.

93. Szymczak WA, Deepe GS, Jr. The CCL7-CCL2-CCR2 axis regulates IL-4 production in lungs and fungal immunity. J Immunol 2009;183:1964-74.

94. Ladinig A, Lunney JK, Souza CJ, Ashley C, Plastow G, Harding JC. Cytokine profiles in pregnant gilts experimentally infected with porcine reproductive and respiratory syndrome virus and relationships with viral load and fetal outcome. Vet Res 2014;45:113.

95. Wang H, Nemoto-Sasaki Y, Kondo T, Akiyama M, Mukaida N. Potential involvement of monocyte chemoattractant protein (MCP)-1/CCL2 in IL-4-mediated tumor immunity through inducing dendritic cell migration into the draining lymph nodes. Int Immunopharmacol 2003;3:627-42.

96. Rauch I, Muller M, Decker T. The regulation of inflammation by interferons and their STATs. JAKSTAT 2013;2:e23820.

97. Thye T, Owusu-Dabo E, Vannberg FO, i sur. Common variants at 11p13 are associated with susceptibility to tuberculosis. Nat Genet 2012;44:257-9.

98. Chimusa ER, Zaitlen N, Daya M, i sur. Genome-wide association study of ancestry-specific TB risk in the South African Coloured population. Hum Mol Genet 2014;23:796-809.

99. Asai H, Fujiwara H, An J, i sur. Co-introduced functional CCR2 potentiates in vivo anti-lung cancer functionality mediated by T cells double gene-modified to express WT1-specific T-cell receptor. PLoS One 2013;8:e56820.

100. de Martel C, Ferlay J, Franceschi S, i sur. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012;13:607-15.

101. Cervino AC, Lakiss S, Sow O, Hill AV. Allelic association between the NRAMP1 gene and susceptibility to tuberculosis in Guinea-Conakry. Ann Hum Genet 2000;64:507-12.

102. Greenwood CM, Fujiwara TM, Boothroyd LJ, i sur. Linkage of tuberculosis to chromosome 2q35 loci, including NRAMP1, in a large aboriginal Canadian family. Am J Hum Genet 2000;67:405-16.

103. Rye MS, Wiertsema SP, Scaman ES, i sur. Genetic and functional evidence for a role for SLC11A1 in susceptibility to otitis media in early childhood in a Western Australian population. Infect Genet Evol 2013;16:411-8.

104. Sveinbjornsson G, Gudbjartsson DF, Halldorsson BV, i sur. HLA class II sequence variants influence tuberculosis risk in populations of European ancestry. Nature Genetics 2016;48:318-22.

105. Qi H, Zhang YB, Sun L, i sur. Discovery of susceptibility loci associated with tuberculosis in Han Chinese. Hum Mol Genet 2017;26:4752-63.

106. Tian C, Hromatka BS, Kiefer AK, i sur. Genome-wide association and HLA region fine-mapping studies identify susceptibility loci for multiple common infections. Nat Commun 2017;8:599.

107. Anderson D, Fakiola M, Hales BJ, Pennell CE, Thomas WR, Blackwell JM. Genome-wide association study of IgG1 responses to the choline-binding protein PspC of Streptococcus pneumoniae. Genes and Immunity 2015;16:289-96.

108. Casanova JL, Abel L. Human genetics of infectious diseases: a unified theory. EMBO J 2007;26:915-22.

109. Picard C, Casanova JL, Abel L. Mendelian traits that confer predisposition or resistance to specific infections in humans. Curr Opin Immunol 2006;18:383-90.

110. Rietveld CA, Esko T, Davies G, i sur. Common genetic variants associated with cognitive performance identified using the proxy-phenotype method. Proc Natl Acad Sci U S A 2014;111:13790-4.

111. van Manen D, van 't Wout AB, Schuitemaker H. Genome-wide association studies on HIV susceptibility, pathogenesis and pharmacogenomics. Retrovirology 2012;9:70.

112. Aouizerat BE, Pearce CL, Miaskowski C. The search for host genetic factors of HIV/AIDS pathogenesis in the post-genome era: progress to date and new avenues for discovery. Curr HIV/AIDS Rep 2011;8:38-44.

113. An P, Winkler CA. Host genes associated with HIV/AIDS: advances in gene discovery. Trends Genet 2010;26:119-31.

114. Polasek O. Future of biobanks - bigger, longer, and more dimensional. Croat Med J 2013;54:496-500.

115. Little J, Higgins JP, Ioannidis JP, i sur. STrengthening the REporting of Genetic Association Studies (STREGA): an extension of the STROBE statement. PLoS Med 2009;6:e22.

116. Gallo V, Egger M, McCormack V, i sur. STrengthening the Reporting of OBservational studies in Epidemiology: Molecular Epidemiology STROBE-ME. An extension of the STROBE statement. J Epidemiol Community Health 2012;66:844-54.

117. Hollenbach JA, Mack SJ, Gourraud PA, i sur. A community standard for immunogenomic data reporting and analysis: proposal for a STrengthening the REporting of Immunogenomic Studies statement. Tissue Antigens 2011;78:333-44.

118. Kodaman N, Sobota RS, Mera R, Schneider BG, Williams SM. Disrupted human-pathogen co-evolution: a model for disease. Front Genet 2014;5:290.

119. Dickson RP, Erb-Downward JR, Martinez FJ, Huffnagle GB. The Microbiome and the Respiratory Tract. Annu Rev Physiol 2016;78:481-504.

120. Bellamy R. Identifying genetic susceptibility factors for tuberculosis in Africans: a combined approach using a candidate gene study and a genome-wide screen. Clinical Science 2000;98:245-50.

121. Gao PS, Fujishima S, Mao XQ, i sur. Genetic variants of NRAMP1 and active tuberculosis in Japanese populations. International Tuberculosis Genetics Team. Clin Genet 2000;58:74-6.

122. Ryu S, Park YK, Bai GH, Kim SJ, Park SN, Kang S. 3 ' UTR polymorphisms in the NRAMP1 gene are associated with susceptibility to tuberculosis in Koreans. International Journal of Tuberculosis and Lung Disease 2000;4:577-80.

123. Yee AM, Phan HM, Zuniga R, Salmon JE, Musher DM. Association between FcgammaRIIa-R131 allotype and bacteremic pneumococcal pneumonia. Clin Infect Dis 2000;30:25-8.

124. Waterer GW, Quasney MW, Cantor RM, Wunderink RG. Septic shock and respiratory failure in community-acquired pneumonia have different TNF polymorphism associations. Am J Respir Crit Care Med 2001;163:1599-604.

125. Choi EH, Lee HJ, Yoo T, Chanock SJ. A common haplotype of interleukin-4 gene IL4 is associated with severe respiratory syncytial virus disease in Korean children. J Infect Dis 2002;186:1207-11.

126. Delgado JC, Baena A, Thim S, Goldfeld AE. Ethnic-specific genetic associations with pulmonary tuberculosis. J Infect Dis 2002;186:1463-8.

127. Lahti M, Lofgren J, Marttila R, i sur. Surfactant protein D gene polymorphism associated with severe respiratory syncytial virus infection. Pediatr Res 2002;51:696-9.

128. Li CM, Campbell SJ, Kumararatne DS, i sur. Association of a polymorphism in the P2X7 gene with tuberculosis in a Gambian population. J Infect Dis 2002;186:1458-62.

129. Liaw YS, Tsai-Wu JJ, Wu CH, i sur. Variations in the NRAMP1 gene and susceptibility of tuberculosis in Taiwanese. Int J Tuberc Lung Dis 2002;6:454-60.

130. Lio D, Marino V, Serauto A, i sur. Genotype frequencies of the+874T -> A single nucleotide polymorphism in the first intron of the interferon-gamma gene in a sample of Sicilian patients affected by tuberculosis. European Journal of Immunogenetics 2002;29:371-4.

131. Lofgren J, Ramet M, Renko M, Marttila R, Hallman M. Association between surfactant protein A gene locus and severe respiratory syncytial virus infection in infants. J Infect Dis 2002;185:283-9.

132. Morimoto S, Okaishi K, Onishi M, i sur. Deletion allele of the angiotensin-converting enzyme gene as a risk factor for pneumonia in elderly patients. Am J Med 2002;112:89-94.

133. Onishi M, Morimoto S, Yang J, i sur. Association of angiotensin-I converting enzyme DD genotype with influenza pneumonia in the elderly. Geriatrics and gerontology international 2002;2:8-15.

134. Quasney MW, Waterer GW, Dahmer MK, i sur. Intracellular adhesion molecule Gly241Arg polymorphism has no impact on ARDS or septic shock in community-acquired pneumonia. Chest 2002;121:85S-6S.

135. Selvaraj P, Chandra G, Kurian SM, Reetha AM, Charles N, Narayanan PR. NRAMP1 gene polymorphism in pulmonary and spinal tuberculosis. Current Science 2002;82:451-4.

136. Akahoshi M, Nakashima H, Miyake K, i sur. Influence of interleukin-12 receptor beta1 polymorphisms on tuberculosis. Hum Genet 2003;112:237-43.

137. Gallagher PM, Lowe G, Fitzgerald T, i sur. Association of IL-10 polymorphism with severity of illness in community acquired pneumonia. Thorax 2003;58:154-6.

138. Hawn TR, Verbon A, Lettinga KD, i sur. A common dominant TLR5 stop codon polymorphism abolishes flagellin signaling and is associated with susceptibility to legionnaires' disease. J Exp Med 2003;198:1563-72.

139. Hoebee B, Rietveld E, Bont L, i sur. Association of severe respiratory syncytial virus bronchiolitis with interleukin-4 and interleukin-4 receptor α polymorphisms. Journal of Infectious Diseases 2003;187:2-11.

140. Lopez-Maderuelo D, Arnalich F, Serantes R, i sur. Interferon-gamma and interleukin-10 gene polymorphisms in pulmonary tuberculosis. Am J Respir Crit Care Med 2003;167:970-5.

141. Ozbas-Gerceker F, Tezcan I, Berkel AI, i sur. The effect of mannose-binding protein gene polymorphisms in recurrent respiratory system infections in children and lung tuberculosis. Turk J Pediatr 2003;45:95-8.

142. Rossouw M, Nel HJ, Cooke GS, van Helden PD, Hoal EG. Association between tuberculosis and a polymorphic NFkappaB binding site in the interferon gamma gene. Lancet 2003;361:1871-2.

143. Scola L, Crivello A, Marino V, i sur. IL-10 and TNF-alpha polymorphisms in a sample of Sicilian patients affected by tuberculosis: implication for ageing and life span expectancy. Mech Ageing Dev 2003;124:569-72.

144. Selvaraj P, Chandra G, Kurian SM, Reetha AM, Narayanan PR. Association of vitamin D receptor gene variants of BsmI, ApaI and FokI polymorphisms with susceptibility or resistance to pulmonary tuberculosis. Current Science 2003;84:1564-8.

145. Waterer GW, ElBahlawan L, Quasney MW, Zhang Q, Kessler LA, Wunderink RG. Heat shock protein 70-2+1267 AA homozygotes have an increased risk of septic shock in adults with community-acquired pneumonia. Crit Care Med 2003;31:1367-72.

146. Yuan FF, Wong M, Pererva N, i sur. FcγRIIA polymorphisms in Streptococcus pneumoniae infection. Immunology and Cell Biology 2003;81:192-5.

147. Awomoyi AA, Nejentsev S, Richardson A, i sur. No association between interferon-gamma receptor-1 gene polymorphism and pulmonary tuberculosis in a Gambian population sample. Thorax 2004;59:291-4.

148. Ben-Ali M, Barbouche MR, Bousnina S, Chabbou A, Dellagi K. Toll-like receptor 2 Arg677Trp polymorphism is associated with susceptibility to tuberculosis in Tunisian patients. Clin Diagn Lab Immunol 2004;11:625-6.

149. Bikmaeva AR, Sibiryak SV, Khusnutdinova EK. Insertion polymorphism of the CYP2E1 gene in patients with infiltrative pulmonary tuberculosis from Bashkortostan. Molecular Biology 2004;38:196-9.

150. Chiu RW, Tang NL, Hui DS, i sur. ACE2 gene polymorphisms do not affect outcome of severe acute respiratory syndrome. 2004;50:1683-6.

151. Fitness J, Floyd S, Warndorff DK, i sur. Large-scale candidate gene study of tuberculosis susceptibility in the Karonga district of northern Malawi. Am J Trop Med Hyg 2004;71:341-9.

152. Gomi K, Tokue Y, Kobayashi T, i sur. Mannose-binding lectin gene polymorphism is a modulating factor in repeated respiratory infections. Chest 2004;126:95-9.

153. Hoebee B, Bont L, Rietveld E, i sur. Influence of promoter variants of interleukin-10, interleukin-9, and tumor necrosis factor-alpha genes on respiratory syncytial virus bronchiolitis. J Infect Dis 2004;189:239-47.

154. Hull J, Rowlands K, Lockhart E, i sur. Haplotype mapping of the bronchiolitis susceptibility locus near IL8. Hum Genet 2004;114:272-9.

155. Itoyama S, Keicho N, Quy T, i sur. ACE1 polymorphism and progression of SARS. Biochem Biophys Res Commun 2004;323:1124-9.

156. Liu W, Cao WC, Zhang CY, i sur. VDR and NRAMP1 gene polymorphisms in susceptibility to pulmonary tuberculosis among the Chinese Han population: a case-control study. Int J Tuberc Lung Dis 2004;8:428-34.

157. Newport MJ, Allen A, Awomoyi AA, i sur. The toll-like receptor 4 Asp299Gly variant: no influence on LPS responsiveness or susceptibility to pulmonary tuberculosis in The Gambia. Tuberculosis (Edinb) 2004;84:347-52.

158. Ogus AC, Yoldas B, Ozdemir T, i sur. The Arg753GIn polymorphism of the human Toll-like receptor 2 gene in tuberculosis disease. European Respiratory Journal 2004;23:219-23.

159. Pacheco E, Fonseca C, Montes C, Zabaleta J, Garcia LF, Arias MA. CD14 gene promoter polymorphism in different clinical forms of tuberculosis. FEMS Immunol Med Microbiol 2004;40:207-13.

160. Quasney MW, Waterer GW, Dahmer MK, i sur. Association between surfactant protein B + 1580 polymorphism and the risk of respiratory failure in adults with community-acquired pneumonia. Crit Care Med 2004;32:1115-9.

161. Roth DE, Soto G, Arenas F, i sur. Association between vitamin D receptor gene polymorphisms and response to treatment of pulmonary tuberculosis. J Infect Dis 2004;190:920-7.

162. Selvaraj P, Chandra G, Jawahar MS, Rani MV, Rajeshwari DN, Narayanan PR. Regulatory role of vitamin D receptor gene variants of Bsm I, Apa I, Taq I, and Fok I polymorphisms on macrophage phagocytosis and lymphoproliferative response to mycobacterium tuberculosis antigen in pulmonary tuberculosis. J Clin Immunol 2004;24:523-32.

163. Tal G, Mandelberg A, Dalal I, i sur. Association between common Toll-like receptor 4 mutations and severe respiratory syncytial virus disease. J Infect Dis 2004;189:2057-63.

164. Tso HW, Lau YL, Tam CM, Wong HS, Chiang AK. Associations between IL12B polymorphisms and tuberculosis in the Hong Kong Chinese population. J Infect Dis 2004;190:913-9.

165. Awomoyi AA, Charurat M, Marchant A, i sur. Polymorphism in IL1B: IL1B-511 association with tuberculosis and decreased lipopolysaccharide-induced IL-1beta in IFN-gamma primed ex-vivo whole blood assay. J Endotoxin Res 2005;11:281-6.

166. Chan KC, Tang NL, Hui DS, i sur. Absence of association between angiotensin converting enzyme polymorphism and development of adult respiratory distress syndrome in patients with severe acute respiratory syndrome: a case control study. BMC Infect Dis 2005;5:26.

167. Cipriano C, Caruso C, Lio D, i sur. The -308G/A polymorphism of TNF-alpha influences immunological parameters in old subjects affected by infectious diseases. Int J Immunogenet 2005;32:13-8.

168. Correa PA, Gomez LM, Cadena J, Anaya JM. Autoimmunity and tuberculosis. Opposite association with TNF polymorphism. J Rheumatol 2005;32:219-24.

169. Flores-Villanueva PO, Ruiz-Morales JA, Song CH, i sur. A functional promoter polymorphism in monocyte chemoattractant protein-1 is associated with increased susceptibility to pulmonary tuberculosis. J Exp Med 2005;202:1649-58.

170. Gomez LM, Anaya JM, Martin J. Genetic influence of PTPN22 R620W polymorphism in tuberculosis. Hum Immunol 2005;66:1242-7.

171. Hamano E, Hijikata M, Itoyama S, i sur. Polymorphisms of interferon-inducible genes OAS-1 and MxA associated with SARS in the Vietnamese population. Biochem Biophys Res Commun 2005;329:1234-9.

172. Ip WK, Chan KH, Law HK, i sur. Mannose-binding lectin in severe acute respiratory syndrome coronavirus infection. J Infect Dis 2005;191:1697-704.

173. Itoyama S, Keicho N, Hijikata M, i sur. Identification of an alternative 5'-untranslated exon and new polymorphisms of angiotensin-converting enzyme 2 gene: lack of association with SARS in the Vietnamese population. Am J Med Genet A 2005;136:52-7.

174. Korytina GF, Yanbaeva DG, Babenkova LI, Etkina EI, Victorova TV. Genetic polymorphisms in the cytochromes P-450 (1A1, 2E1), microsomal epoxide hydrolase and glutathione S-transferase M1, T1, and P1 genes, and their relationship with chronic bronchitis and relapsing pneumonia in children. J Mol Med (Berl) 2005;83:700-10.

175. Schaaf B, Rupp J, Muller-Steinhardt M, i sur. The interleukin-6 -174 promoter polymorphism is associated with extrapulmonary bacterial dissemination in Streptococcus pneumoniae infection. Cytokine 2005;31:324-8.

176. Shin HD, Park BL, Kim YH, Cheong HS, Lee IH, Park SK. Common interleukin 10 polymorphism associated with decreased risk of tuberculosis. Exp Mol Med 2005;37:128-32.

177. Yuan FF, Tanner J, Chan PK, i sur. Influence of FcgammaRIIA and MBL polymorphisms on severe acute respiratory syndrome. Tissue Antigens 2005;66:291-6.

178. Zhang W, Shao L, Weng X, i sur. Variants of the natural resistance-associated macrophage protein 1 gene (NRAMP1) are associated with severe forms of pulmonary tuberculosis. Clin Infect Dis 2005;40:1232-6.

179. Zhang H, Zhou G, Zhi L, i sur. Association between mannose-binding lectin gene polymorphisms and susceptibility to severe acute respiratory syndrome coronavirus infection. J Infect Dis 2005;192:1355-61.

180. Amirzargar AA, Rezaei N, Jabbari H, i sur. Cytokine single nucleotide polymorphisms in Iranian patients with pulmonary tuberculosis. Eur Cytokine Netw 2006;17:84-9.

181. Barreiro LB, Neyrolles O, Babb CL, i sur. Promoter variation in the DC-SIGN-encoding gene CD209 is associated with tuberculosis. Plos Medicine 2006;3:230-5.

182. Chapman SJ, Khor CC, Vannberg FO, i sur. PTPN22 and invasive bacterial disease. Nat Genet 2006;38:499-500.

183. Chen WJ, Yang JY, Lin JH, i sur. Nasopharyngeal shedding of severe acute respiratory syndrome-associated coronavirus is associated with genetic polymorphisms. Clin Infect Dis 2006;42:1561-9.

184. Chong WP, Ip WK, Tso GH, i sur. The interferon gamma gene polymorphism +874 A/T is associated with severe acute respiratory syndrome. BMC Infect Dis 2006;6:82.

185. Druszczynska M, Strapagiel D, Kwiatkowska S, i sur. Tuberculosis bacilli still posing a threat. Polymorphism of genes regulating anti-mycobacterial properties of macrophages. Pol J Microbiol 2006;55:7-12.

186. Etokebe GE, Bulat-Kardum L, Johansen MS, i sur. Interferon-gamma gene (T874A and G2109A) polymorphisms are associated with microscopy-positive tuberculosis. Scand J Immunol 2006;63:136-41.

187. Gomez LM, Camargo JF, Castiblanco J, Ruiz-Narvaez EA, Cadena J, Anaya JM. Analysis of IL1B, TAP1, TAP2 and IKBL polymorphisms on susceptibility to tuberculosis. Tissue Antigens 2006;67:290-6.

188. Hawn TR, Dunstan SJ, Thwaites GE, i sur. A polymorphism in Toll-interleukin 1 receptor domain containing adaptor protein is associated with susceptibility to meningeal tuberculosis. J Infect Dis 2006;194:1127-34.

189. He J, Feng D, de Vlas SJ, i sur. Association of SARS susceptibility with single nucleic acid polymorphisms of OAS1 and MxA genes: a case-control study. BMC Infect Dis 2006;6:106.

190. Henao MI, Montes C, Paris SC, Garcia LF. Cytokine gene polymorphisms in Colombian patients with different clinical presentations of tuberculosis. Tuberculosis (Edinb) 2006;86:11-9.

191. Hsu YH, Chen CW, Sun HS, Jou R, Lee JJ, Su IJ. Association of NRAMP 1 gene polymorphism with susceptibility to tuberculosis in Taiwanese aboriginals. J Formos Med Assoc 2006;105:363-9.

192. Krueger M, Puthothu B, Heinze J, Forster J, Heinzmann A. Genetic polymorphisms of adhesion molecules in children with severe RSV-associated diseases. Int J Immunogenet 2006;33:233-5.

193. Liu W, Zhang F, Xin ZT, i sur. Sequence variations in the MBL gene and their relationship to pulmonary tuberculosis in the Chinese Han population. Int J Tuberc Lung Dis 2006;10:1098-103.

194. Ozturk C, Aksu G, Berdeli A, Kutukculer N. Fc gamma RIIa, IIIa and IIIb polymorphisms in Turkish children susceptible to recurrent infectious diseases. Clin Exp Med 2006;6:27-32.

195. Puthothu B, Krueger M, Heinze J, Forster J, Heinzmann A. Impact of IL8 and IL8-receptor alpha polymorphisms on the genetics of bronchial asthma and severe RSV infections. Clin Mol Allergy 2006;4:2.

196. Puthothu B, Forster J, Heinzmann A, Krueger M. TLR-4 and CD14 polymorphisms in respiratory syncytial virus associated disease. Dis Markers 2006;22:303-8.

197. Puthothu B, Krueger M, Forster J, Heinzmann A. Association between severe respiratory syncytial virus infection and IL13/IL4 haplotypes. J Infect Dis 2006;193:438-41.

198. Puthothu B, Krueger M, Heinze J, Forster J, Heinzmann A. Haplotypes of surfactant protein C are associated with common paediatric lung diseases. Pediatr Allergy Immunol 2006;17:572-7.

199. Selvaraj P, Prabhu Anand S, Jawahar MS, Chandra G, Banurekha B, Narayanan PR. Promoter polymorphism of IL-8 gene and IL-8 production in pulmonary tuberculosis. Current Science 2006;90:952-4.

200. Taype CA, Castro JC, Accinelli RA, Herrera-Velit P, Shaw MA, Espinoza JR. Association between SLC11A1 polymorphisms and susceptibility to different clinical forms of tuberculosis in the Peruvian population. Infect Genet Evol 2006;6:361-7.

201. Thye T, Browne EN, Chinbuah MA, i sur. No associations of human pulmonary tuberculosis with Sp110 variants. J Med Genet 2006;43:e32.

202. Vaid M, Kaur S, Taruna M, i sur. Association of SP-D, MBL and I-NOS genetic variants with pulmonary tuberculosis. Indian Journal of Human Genetics 2006;12:105-10.

203. Vidyarani M, Selvaraj P, Prabhu Anand S, Jawahar MS, Adhilakshmi AR, Narayanan PR. Interferon gamma (IFNgamma) & interleukin-4 (IL-4) gene variants & cytokine levels in pulmonary tuberculosis. Indian J Med Res 2006;124:403-10.

204. Alagarasu K, Selvaraj P, Swaminathan S, Raghavan S, Narendran G, Narayanan PR. Mannose binding lectin gene variants and susceptibility to tuberculosis in HIV-1 infected patients of South India. Tuberculosis (Edinb) 2007;87:535-43.

205. Awomoyi AA, Rallabhandi P, Pollin TI, i sur. Association of TLR4 polymorphisms with symptomatic respiratory syncytial virus infection in high-risk infants and young children. J Immunol 2007;179:3171-7.

206. Babb C, Keet EH, van Helden PD, Hoal EG. SP110 polymorphisms are not associated with pulmonary tuberculosis in a South African population. Hum Genet 2007;121:521-2.

207. Babb C, van der Merwe L, Beyers N, i sur. Vitamin D receptor gene polymorphisms and sputum conversion time in pulmonary tuberculosis patients. Tuberculosis (Edinb) 2007;87:295-302.

208. Ben-Ali M, Barreiro LB, Chabbou A, i sur. Promoter and neck region length variation of DC-SIGN is not associated with susceptibility to tuberculosis in Tunisian patients. Hum Immunol 2007;68:908-12.

209. Chan KY, Ching JC, Xu MS, i sur. Association of ICAM3 genetic variant with severe acute respiratory syndrome. J Infect Dis 2007;196:271-80.

210. Chu SF, Tam CM, Wong HS, Kam KM, Lau YL, Chiang AK. Association between RANTES functional polymorphisms and tuberculosis in Hong Kong Chinese. Genes Immun 2007;8:475-9.

211. Emonts M, Wiertsema SP, Veenhoven RH, i sur. The 4G/4G plasminogen activator inhibitor-1 genotype is associated with frequent recurrence of acute otitis media. Pediatrics 2007;120:e317-23.

212. Fernando SL, Saunders BM, Sluyter R, i sur. A polymorphism in the P2X7 gene increases susceptibility to extrapulmonary tuberculosis. Am J Respir Crit Care Med 2007;175:360-6.

213. Gomez LM, Sanchez E, Ruiz-Narvaez EA, Lopez-Nevot MA, Anaya JM, Martin J. Macrophage migration inhibitory factor gene influences the risk of developing tuberculosis in northwestern Colombian population. Tissue Antigens 2007;70:28-33.

214. Harishankar M, Selvaraj P, Rajeswari DN, Anand SP, Narayanan PR. Promoter polymorphism of IL-18 gene in pulmonary tuberculosis in South Indian population. Int J Immunogenet 2007;34:317-20.

215. Hwang JH, Kim EJ, Kim SY, i sur. Polymorphisms of interferon-gamma and interferon-gamma receptor 1 genes and pulmonary tuberculosis in Koreans. Respirology 2007;12:906-10.

216. Inoue Y, Shimojo N, Suzuki Y, i sur. CD14 -550 C/T, which is related to the serum level of soluble CD14, is associated with the development of respiratory syncytial virus bronchiolitis in the Japanese population. J Infect Dis 2007;195:1618-24.

217. Janssen R, Bont L, Siezen CL, i sur. Genetic susceptibility to respiratory syncytial virus bronchiolitis is predominantly associated with innate immune genes. J Infect Dis 2007;196:826-34.

218. Kusuhara K, Yamamoto K, Okada K, Mizuno Y, Hara T. Association of IL12RB1 polymorphisms with susceptibility to and severity of tuberculosis in Japanese: a gene-based association analysis of 21 candidate genes. Int J Immunogenet 2007;34:35-44.

219. Lee J, Kim HR, Min JW, i sur. Lack of association between matrix metalloproteinase 8 promoter polymorphism and bronchiectasis in Koreans. Journal of Korean Medical Science 2007;22:667-71.

220. Leung KH, Yip SP, Wong WS, i sur. Sex- and age-dependent association of SLC11A1 polymorphisms with tuberculosis in Chinese: a case control study. BMC Infect Dis 2007;7:19.

221. Mak JC, Leung HC, Sham AS, i sur. Genetic polymorphisms and plasma levels of transforming growth factor-beta(1) in Chinese patients with tuberculosis in Hong Kong. Cytokine 2007;40:177-82.

222. Moller M, Nebel A, Kwiatkowski R, van Helden PD, Hoal EG, Schreiber S. Host susceptibility to tuberculosis: CARD15 polymorphisms in a South African population. Mol Cell Probes 2007;21:148-51.

223. Moller M, Kwiatkowski R, Nebel A, van Helden PD, Hoal EG, Schreiber S. Allelic variation in BTNL2 and susceptibility to tuberculosis in a South African population. Microbes Infect 2007;9:522-8.

224. Moran A, Ma X, Reich RA, Graviss EA. No association between the +874T/A single nucleotide polymorphism in the IFN-gamma gene and susceptibility to TB. Int J Tuberc Lung Dis 2007;11:113-5.

225. Ng MW, Zhou G, Chong WP, i sur. The association of RANTES polymorphism with severe acute respiratory syndrome in Hong Kong and Beijing Chinese. BMC Infect Dis 2007;7:50.

226. Nino-Moreno P, Portales-Perez D, Hernandez-Castro B, i sur. P2X7 and NRAMP1/SLC11 A1 gene polymorphisms in Mexican mestizo patients with pulmonary tuberculosis. Clin Exp Immunol 2007;148:469-77.

227. Oh JH, Yang CS, Noh YK, i sur. Polymorphisms of interleukin-10 and tumour necrosis factor-alpha genes are associated with newly diagnosed and recurrent pulmonary tuberculosis. Respirology 2007;12:594-8.

228. Paulus SC, Hirschfeld AF, Victor RE, Brunstein J, Thomas E, Turvey SE. Common human Toll-like receptor 4 polymorphisms - Role in susceptibility to respiratory syncytial virus infection and functional immunological relevance. Clinical Immunology 2007;123:252-7.

229. Prabhu Anand S, Selvaraj P, Jawahar MS, Adhilakshmi AR, Narayanan PR. Interleukin-12B & interleukin-10 gene polymorphisms in pulmonary tuberculosis. Indian J Med Res 2007;126:135-8.

230. Puthothu B, Forster J, Heinze J, Heinzmann A, Krueger M. Surfactant protein B polymorphisms are associated with severe respiratory syncytial virus infection, but not with asthma. BMC Pulm Med 2007;7:6.

231. Rosas-Taraco AG, Revol A, Salinas-Carmona MC, Rendon A, Caballero-Olin G, Arce-Mendoza AY. CD14 C(-159)T polymorphism is a risk factor for development of pulmonary tuberculosis. J Infect Dis 2007;196:1698-706.

232. Sahiratmadja E, Baak-Pablo R, de Visser AW, i sur. Association of polymorphisms in IL-12/IFN-gamma pathway genes with susceptibility to pulmonary tuberculosis in Indonesia. Tuberculosis (Edinb) 2007;87:303-11.

233. Sahiratmadja E, Wieringa FT, van Crevel R, i sur. Iron deficiency and NRAMP1 polymorphisms (INT4, D543N and 3'UTR) do not contribute to severity of anaemia in tuberculosis in the Indonesian population. Br J Nutr 2007;98:684-90.

234. Sallakci N, Coskun M, Berber Z, i sur. Interferon-gamma gene+874T-A polymorphism is associated with tuberculosis and gamma interferon response. Tuberculosis (Edinb) 2007;87:225-30.

235. Soborg C, Andersen AB, Range N, i sur. Influence of candidate susceptibility genes on tuberculosis in a high endemic region. Mol Immunol 2007;44:2213-20.

236. Szeszko JS, Healy B, Stevens H, i sur. Resequencing and association analysis of the SP110 gene in adult pulmonary tuberculosis. Hum Genet 2007;121:155-60.

237. Thuong NT, Hawn TR, Thwaites GE, i sur. A polymorphism in human TLR2 is associated with increased susceptibility to tuberculous meningitis. Genes Immun 2007;8:422-8.

238. Vejbaesya S, Chierakul N, Luangtrakool P, Sermduangprateep C. NRAMP1 and TNF-alpha polymorphisms and susceptibility to tuberculosis in Thais. Respirology 2007;12:202-6.

239. Wilbur AK, Kubatko LS, Hurtado AM, Hill KR, Stone AC. Vitamin D receptor gene polymorphisms and susceptibility M. tuberculosis in native Paraguayans. Tuberculosis (Edinb) 2007;87:329-37.

240. Yende S, Angus DC, Ding J, i sur. 4G/5G plasminogen activator inhibitor-1 polymorphisms and haplotypes are associated with pneumonia. Am J Respir Crit Care Med 2007;176:1129-37.

241. Yuan FF, Boehm I, Chan PK, i sur. High prevalence of the CD14-159CC genotype in patients infected with severe acute respiratory syndrome-associated coronavirus. Clin Vaccine Immunol 2007;14:1644-5.

242. Amanatidou V, Sourvinos G, Apostolakis S, i sur. RANTES promoter gene polymorphisms and susceptibility to severe respiratory syncytial virus-induced bronchiolitis. Pediatr Infect Dis J 2008;27:38-42.

243. Asai S, Abe Y, Fujino T, i sur. Association of the SLC11A1 Gene Polymorphisms With Susceptibility to Mycobacterium Infections in a Japanese Population. Infectious Diseases in Clinical Practice 2008;16:230-4.

244. Castiblanco J, Varela DC, Castano-Rodriguez N, Rojas-Villarraga A, Hincapie ME, Anaya JM. TIRAP (MAL) S180L polymorphism is a common protective factor against developing tuberculosis and systemic lupus erythematosus. Infect Genet Evol 2008;8:541-4.

245. Cosar H, Ozkinay F, Onay H, i sur. Low levels of mannose-binding lectin confers protection against tuberculosis in Turkish children. Eur J Clin Microbiol Infect Dis 2008;27:1165-9.

246. Ding S, Li L, Zhu X. Polymorphism of the interferon-gamma gene and risk of tuberculosis in a southeastern Chinese population. Hum Immunol 2008;69:129-33.

247. Farnia P, Pajand O, Anoosheh S, i sur. Comparison of Nramp1 Gene Polymorphism among TB Health Care Workers and Recently Infected Cases; Assessment of Host Susceptibility. Tanaffos 2008;7:19-24.

248. Garcia-Laorden MI, Sole-Violan J, Rodriguez de Castro F, i sur. Mannose-binding lectin and mannose-binding lectin-associated serine protease 2 in susceptibility, severity, and outcome of pneumonia in adults. J Allergy Clin Immunol 2008;122:368-74, 74 e1-2.

249. Helminen M, Nuolivirta K, Virta M, i sur. IL-10 gene polymorphism at -1082 A/G is associated with severe rhinovirus bronchiolitis in infants. Pediatr Pulmonol 2008;43:391-5.

250. Herb F, Thye T, Niemann S, i sur. ALOX5 variants associated with susceptibility to human pulmonary tuberculosis. Hum Mol Genet 2008;17:1052-60.

251. Kumar V, Khosla R, Gupta V, Sarin BC, Sehajpal PK. Differential association of tumour necrosis factor-alpha single nucleotide polymorphism (-308) with tuberculosis and bronchial asthma. Natl Med J India 2008;21:120-2.

252. Li H, Tang NL, Chan PK, i sur. Polymorphisms in the C-type lectin genes cluster in chromosome 19 and predisposition to severe acute respiratory syndrome coronavirus (SARS-CoV) infection. J Med Genet 2008;45:752-8.

253. Mailaparambil B, Krueger M, Heinze J, Forster J, Heinzmann A. Polymorphisms of toll like receptors in the genetics of severe RSV associated diseases. Dis Markers 2008;25:59-65.

254. Mokrousov I, Sapozhnikova N, Narvskaya O. Mycobacterium tuberculosis co-existence with humans: making an imprint on the macrophage P2X(7) receptor gene? Journal of Medical Microbiology 2008;57:581-4.

255. Nejentsev S, Thye T, Szeszko JS, i sur. Analysis of association of the TIRAP (MAL) S180L variant and tuberculosis in three populations. Nat Genet 2008;40:261-2; author reply 2-3.

256. Roth DE, Jones AB, Prosser C, Robinson JL, Vohra S. Vitamin D receptor polymorphisms and the risk of acute lower respiratory tract infection in early childhood. J Infect Dis 2008;197:676-80.

257. Selvaraj P, Vidyarani M, Alagarasu K, Prabhu Anand S, Narayanan PR. Regulatory role of promoter and 3' UTR variants of vitamin D receptor gene on cytokine response in pulmonary tuberculosis. J Clin Immunol 2008;28:306-13.

258. Selvaraj P, Alagarasu K, Harishankar M, Vidyarani M, Nisha Rajeswari D, Narayanan PR. Cytokine gene polymorphisms and cytokine levels in pulmonary tuberculosis. Cytokine 2008;43:26-33.

259. Selvaraj P, Alagarasu K, Harishankar M, Vidyarani M, Narayanan PR. Regulatory region polymorphisms of vitamin D receptor gene in pulmonary tuberculosis patients and normal healthy subjects of south India. Int J Immunogenet 2008;35:251-4.

260. Shin HD, Cheong HS, Park BL, i sur. Common MCL1 polymorphisms associated with risk of tuberculosis. BMB Rep 2008;41:334-7.

261. Tang F, Liu W, Zhang F, i sur. IL-12 RB1 genetic variants contribute to human susceptibility to severe acute respiratory syndrome infection among Chinese. PLoS One 2008;3:e2183.

262. Thuong NT, Dunstan SJ, Chau TT, i sur. Identification of tuberculosis susceptibility genes with human macrophage gene expression profiles. PLoS Pathog 2008;4:e1000229.

263. van de Garde EM, Endeman H, Deneer VH, i sur. Angiotensin-converting enzyme insertion/deletion polymorphism and risk and outcome of pneumonia. Chest 2008;133:220-5.

264. Wang S, Wei M, Han Y, i sur. Roles of TNF-alpha gene polymorphisms in the occurrence and progress of SARS-Cov infection: a case-control study. BMC Infect Dis 2008;8:27.

265. Yuan FF, Marks K, Wong M, i sur. Clinical relevance of TLR2, TLR4, CD14 and FcgammaRIIA gene polymorphisms in Streptococcus pneumoniae infection. Immunol Cell Biol 2008;86:268-70.

266. Alagarasu K, Selvaraj P, Swaminathan S, Raghavan S, Narendran G, Narayanan PR. CCR2, MCP-1, SDF-1a & DC-SIGN gene polymorphisms in HIV-1 infected patients with & without tuberculosis. Indian J Med Res 2009;130:444-50.

267. Alagarasu K, Selvaraj P, Swaminathan S, Narendran G, Narayanan PR. 5' regulatory and 3' untranslated region polymorphisms of vitamin D receptor gene in south Indian HIV and HIV-TB patients. J Clin Immunol 2009;29:196-204.

268. Ansari A, Talat N, Jamil B, i sur. Cytokine gene polymorphisms across tuberculosis clinical spectrum in Pakistani patients. PLoS One 2009;4:e4778.

269. Chen J, Xu Z, Ou X, Wang M, Yang X, Li Q. Mannose-binding lectin polymorphisms and recurrent respiratory tract infection in Chinese children. Eur J Pediatr 2009;168:1305-13.

270. Endeman H, Cornips MC, Grutters JC, i sur. The Fcgamma receptor IIA-R/R131 genotype is associated with severe sepsis in community-acquired pneumonia. Clin Vaccine Immunol 2009;16:1087-90.

271. Forton JT, Rowlands K, Rockett K, i sur. Genetic association study for RSV bronchiolitis in infancy at the 5q31 cytokine cluster. Thorax 2009;64:345-52.

272. Intemann CD, Thye T, Niemann S, i sur. Autophagy gene variant IRGM -261T contributes to protection from tuberculosis caused by Mycobacterium tuberculosis but not by M. africanum strains. PLoS Pathog 2009;5:e1000577.

273. Lamsyah H, Rueda B, Baassi L, i sur. Association of PTPN22 gene functional variants with development of pulmonary tuberculosis in Moroccan population. Tissue Antigens 2009;74:228-32.

274. Lee SH, Han SK, Shim YS, Yim JJ. Effect of matrix metalloproteinase-9 -1562C/T gene polymorphism on manifestations of pulmonary tuberculosis. Tuberculosis (Edinb) 2009;89:68-70.

275. Merza M, Farnia P, Anoosheh S, i sur. The NRAMPI, VDR and TNF-alpha gene polymorphisms in Iranian tuberculosis patients: the study on host susceptibility. Braz J Infect Dis 2009;13:252-6.

276. Moller M, Nebel A, Valentonyte R, van Helden PD, Schreiber S, Hoal EG. Investigation of chromosome 17 candidate genes in susceptibility to TB in a South African population. Tuberculosis (Edinb) 2009;89:189-94.

277. Naslednikova IO, Urazova OI, Voronkova OV, i sur. Allelic polymorphism of cytokine genes during pulmonary tuberculosis. Bull Exp Biol Med 2009;148:175-80.

278. Payton A, Payne D, Mankhambo LA, i sur. Nitric oxide synthase 2A (NOS2A) polymorphisms are not associated with invasive pneumococcal disease. BMC Med Genet 2009;10:28.

279. Puthothu B, Bierbaum S, Kopp MV, i sur. Association of TNF-alpha with severe respiratory syncytial virus infection and bronchial asthma. Pediatr Allergy Immunol 2009;20:157-63.

280. Sadki K, Lamsyah H, Rueda B, Lahlou O, El Aouad R, Martin J. CD209 Promoter Single Nucleotide Polymorphism-336A/G and the Risk of Susceptibility to Tuberculosis Disease in the Moroccan Population. International Journal of Human Genetics 2009;9:239-43.

281. Sanchez-Castanon M, Baquero IC, Sanchez-Velasco P, i sur. Polymorphisms in CCL5 promoter are associated with pulmonary tuberculosis in northern Spain. Int J Tuberc Lung Dis 2009;13:480-5.

282. Sapru A, Hansen H, Ajayi T, i sur. 4G/5G polymorphism of plasminogen activator inhibitor-1 gene is associated with mortality in intensive care unit patients with severe pneumonia. Anesthesiology 2009;110:1086-91.

283. Selvaraj P, Alagarasu K, Swaminathan S, Harishankar M, Narendran G. CD209 gene polymorphisms in South Indian HIV and HIV-TB patients. Infect Genet Evol 2009;9:256-62.

284. Tang NL, Fan HP, Chang KC, i sur. Genetic association between a chemokine gene CXCL-10 (IP-10, interferon gamma inducible protein 10) and susceptibility to tuberculosis. Clin Chim Acta 2009;406:98-102.

285. Thye T, Nejentsev S, Intemann CD, i sur. MCP-1 promoter variant -362C associated with protection from pulmonary tuberculosis in Ghana, West Africa. Hum Mol Genet 2009;18:381-8.

286. Thye T, Browne EN, Chinbuah MA, i sur. IL10 haplotype associated with tuberculin skin test response but not with pulmonary TB. PLoS One 2009;4:e5420.

287. Thye T, Scarisbrick G, Browne EN, i sur. CTLA4 autoimmunity-associated genotype contributes to severe pulmonary tuberculosis in an African population. PLoS One 2009;4:e6307.

288. Tian M, Liu F, Wen GY, Shi SY, Chen RH, Zhao DY. Effect of variation in RANTES promoter on serum RANTES levels and risk of recurrent wheezing after RSV bronchiolitis in children from Han, Southern China. Eur J Pediatr 2009;168:963-7.

289. Trajkov D, Trajchevska M, Arsov T, i sur. Association of 22 cytokine gene polymorphisms with tuberculosis in Macedonians. Indian J Tuberc 2009;56:117-31.

290. Vidyarani M, Selvaraj P, Raghavan S, Narayanan PR. Regulatory role of 1, 25-dihydroxyvitamin D3 and vitamin D receptor gene variants on intracellular granzyme A expression in pulmonary tuberculosis. Exp Mol Pathol 2009;86:69-73.

291. Vollstedt S, Yuliwulandari R, Okamoto K, i sur. No evidence for association between the interferon regulatory factor 1 (IRF1) gene and clinical tuberculosis. Tuberculosis (Edinb) 2009;89:71-6.

292. Wang Y, Yan J, Shi Y, i sur. Lack of association between polymorphisms of MASP2 and susceptibility to SARS coronavirus infection. BMC Infect Dis 2009;9:51.

293. Xiao J, Sun L, Jiao W, i sur. Lack of association between polymorphisms in the P2X7 gene and tuberculosis in a Chinese Han population. FEMS Immunol Med Microbiol 2009;55:107-11.

294. Yende S, Angus DC, Kong L, i sur. The influence of macrophage migration inhibitory factor gene polymorphisms on outcome from community-acquired pneumonia. FASEB J 2009;23:2403-11.

295. Anggraini R. 3 ' UTR Polymorphism of NRAMP1 Gene and Susceptibility to Lung Tuberculosis among Patients and Nurses in Surabaya , Indonesia. Indonesian journal of tropical and infectious disease 2010;1:17-22.

296. Banoei MM, Mirsaeidi MS, Houshmand M, i sur. Vitamin D receptor homozygote mutant tt and bb are associated with susceptibility to pulmonary tuberculosis in the Iranian population. Int J Infect Dis 2010;14:e84-5.

297. Chan KY, Xu MS, Ching JC, i sur. CD209 (DC-SIGN) -336A>G promoter polymorphism and severe acute respiratory syndrome in Hong Kong Chinese. Hum Immunol 2010;71:702-7.

298. Chapman SJ, Vannberg FO, Khor CC, i sur. Mannose-binding lectin genotypes: lack of association with susceptibility to thoracic empyema. BMC Med Genet 2010;11:5.

299. Che N, Li S, Gao T, i sur. Identification of a novel IRGM promoter single nucleotide polymorphism associated with tuberculosis. Clin Chim Acta 2010;411:1645-9.

300. Chen J, Deng Y, Zhao J, i sur. The polymorphism of IL-17 G-152A was associated with childhood asthma and bacterial colonization of the hypopharynx in bronchiolitis. J Clin Immunol 2010;30:539-45.

301. Ching JCY, Chan KYK, Lee EHL, i sur. Significance of the Myxovirus Resistance A (MxA) Gene-123C > A Single-Nucleotide Polymorphism in Suppressed Interferon beta Induction of Severe Acute Respiratory Syndrome Coronavirus Infection. Journal of Infectious Diseases 2010;201:1899-908.

302. Ganachari M, Ruiz-Morales JA, Gomez de la Torre Pretell JC, Dinh J, Granados J, Flores-Villanueva PO. Joint effect of MCP-1 genotype GG and MMP-1 genotype 2G/2G increases the likelihood of developing pulmonary tuberculosis in BCG-vaccinated individuals. PLoS One 2010;5:e8881.

303. Garcia-Elorriaga G, Carrillo-Montes G, Mendoza-Aguilar M, Gonzalez-Bonilla C. Polymorphisms in tumor necrosis factor and lymphotoxin A in tuberculosis without and with response to treatment. Inflammation 2010;33:267-75.

304. Hatta M, Ratnawati, Tanaka M, Ito J, Shirakawa T, Kawabata M. NRAMP1/SLC11A1 gene polymorphisms and host susceptibility to Mycobacterium tuberculosis and M. leprae in South Sulawesi, Indonesia. Southeast Asian J Trop Med Public Health 2010;41:386-94.

305. Lian Y, Yue J, Han M, Liu J, Liu L. Analysis of the association between BTNL2 polymorphism and tuberculosis in Chinese Han population. Infect Genet Evol 2010;10:517-21.

306. Lofgren J, Marttila R, Renko M, Ramet M, Hallman M. Toll-like receptor 4 Asp299Gly polymorphism in respiratory syncytial virus epidemics. Pediatr Pulmonol 2010;45:687-92.

307. Lu A, Wang L, Zhang X. Haplotype of IL-8 -251T and 781C is associated with the susceptibility to respiratory syncytial virus. J Trop Pediatr 2010;56:242-6.

308. Ma MJ, Xie LP, Wu SC, i sur. Toll-like receptors, tumor necrosis factor-alpha, and interleukin-10 gene polymorphisms in risk of pulmonary tuberculosis and disease severity. Hum Immunol 2010;71:1005-10.

309. Madach K, Aladzsity I, Szilagyi A, i sur. 4G/5G polymorphism of PAI-1 gene is associated with multiple organ dysfunction and septic shock in pneumonia induced severe sepsis: prospective, observational, genetic study. Crit Care 2010;14:R79.

310. Marashian SM, Farnia P, Seyf S, Anoosheh S, Velayati AA. Evaluating the role of vitamin D receptor polymorphisms on susceptibility to tuberculosis among iranian patients: a case-control study. Tuberk Toraks 2010;58:147-53.

311. Moller M, Flachsbart F, Till A, i sur. A functional haplotype in the 3'untranslated region of TNFRSF1B is associated with tuberculosis in two African populations. Am J Respir Crit Care Med 2010;181:388-93.

312. Moller M, Nebel A, van Helden PD, Schreiber S, Hoal EG. Analysis of eight genes modulating interferon gamma and human genetic susceptibility to tuberculosis: a case-control association study. BMC Infect Dis 2010;10:154.

313. Mosaad YM, Soliman OE, Tawhid ZE, Sherif DM. Interferon-gamma +874 T/A and interleukin-10 -1082 A/G single nucleotide polymorphism in Egyptian children with tuberculosis. Scand J Immunol 2010;72:358-64.

314. Najmi N, Kaur G, Sharma SK, Mehra NK. Human Toll-like receptor 4 polymorphisms TLR4 Asp299Gly and Thr399Ile influence susceptibility and severity of pulmonary tuberculosis in the Asian Indian population. Tissue Antigens 2010;76:102-9.

315. Prabhu Anand S, Harishankar M, Selvaraj P. Interferon gamma gene +874A/T polymorphism and intracellular interferon gamma expression in pulmonary tuberculosis. Cytokine 2010;49:130-3.

316. Russell R, Quasney MW, Halligan N, i sur. Genetic variation in MYLK and lung injury in children and adults with community-acquired pneumonia. Pediatr Crit Care Med 2010;11:731-6.

317. Sadki K, Lamsyah H, Rueda B, i sur. Analysis of MIF, FCGR2A and FCGR3A gene polymorphisms with susceptibility to pulmonary tuberculosis in Moroccan population. J Genet Genomics 2010;37:257-64.

318. Sambasivan V, Murthy KJ, Reddy R, Vijayalakshimi V, Hasan Q. P2X7 gene polymorphisms and risk assessment for pulmonary tuberculosis in Asian Indians. Dis Markers 2010;28:43-8.

319. Selvaraj P, Harishankar M, Singh B, Jawahar MS, Banurekha VV. Toll-like receptor and TIRAP gene polymorphisms in pulmonary tuberculosis patients of South India. Tuberculosis (Edinb) 2010;90:306-10.

320. Sharma S, Kumar V, Khosla R, Kajal N, Sarin B, Sehajpal P. Association of P2X7 receptor +1513 (A-->C) polymorphism with tuberculosis in a Punjabi population. Int J Tuberc Lung Dis 2010;14:1159-63.

321. Sole-Violan J, de Castro F, Garcia-Laorden MI, i sur. Genetic variability in the severity and outcome of community-acquired pneumonia. Respir Med 2010;104:440-7.

322. Taype CA, Shamsuzzaman S, Accinelli RA, Espinoza JR, Shaw MA. Genetic susceptibility to different clinical forms of tuberculosis in the Peruvian population. Infect Genet Evol 2010;10:495-504.

323. Vallinoto AC, Graca ES, Araujo MS, i sur. IFNG +874T/A polymorphism and cytokine plasma levels are associated with susceptibility to Mycobacterium tuberculosis infection and clinical manifestation of tuberculosis. Hum Immunol 2010;71:692-6.

324. Wang CH, Lin HC, Lin SM, i sur. MMP-1(-1607G) polymorphism as a risk factor for fibrosis after pulmonary tuberculosis in Taiwan. Int J Tuberc Lung Dis 2010;14:627-34.

325. Wang J, Tang S, Shen H. Association of genetic polymorphisms in the IL12-IFNG pathway with susceptibility to and prognosis of pulmonary tuberculosis in a Chinese population. Eur J Clin Microbiol Infect Dis 2010;29:1291-5.

326. Wang X, Cao Z, Jiang J, i sur. AKT1 polymorphisms are associated with tuberculosis in the Chinese population. Int J Immunogenet 2010;37:97-101.

327. Xue Y, Zhao ZQ, Wang HJ, i sur. Toll-like receptors 2 and 4 gene polymorphisms in a southeastern Chinese population with tuberculosis. Int J Immunogenet 2010;37:135-8.

328. Zembrzuski VM, Basta PC, Callegari-Jacques SM, i sur. Cytokine genes are associated with tuberculin skin test response in a native Brazilian population. Tuberculosis 2010;90:44-9.

329. Abhimanyu, Jha P, Jain A, Arora K, Bose M. Genetic association study suggests a role for SP110 variants in lymph node tuberculosis but not pulmonary tuberculosis in north Indians. Hum Immunol 2011;72:576-80.

330. Abhimanyu, Mangangcha IR, Jha P, i sur. Differential serum cytokine levels are associated with cytokine gene polymorphisms in north Indians with active pulmonary tuberculosis. Infect Genet Evol 2011;11:1015-22.

331. Adams LA, Moller M, Nebel A, i sur. Polymorphisms in MC3R promoter and CTSZ 3'UTR are associated with tuberculosis susceptibility. Eur J Hum Genet 2011;19:676-81.

332. Afzal MS, Anjum S, Salman A, i sur. Interleukin-10 gene promoter polymorphism as a potential host susceptibility factor in Pakistani patients with pulmonary tuberculosis. African Journal of Biotechnology 2011;10:14706-10.

333. Akgunes A, Coban AY, Durupinar B. Human leucocyte antigens and cytokine gene polymorphisms and tuberculosis. Indian J Med Microbiol 2011;29:28-32.

334. Ampuero S, Luchsinger V, Tapia L, Palomino MA, Larranaga CE. SP-A1, SP-A2 and SP-D gene polymorphisms in severe acute respiratory syncytial infection in Chilean infants. Infect Genet Evol 2011;11:1368-77.

335. Anoosheh S, Farnia P, Kargar M. Association between TNF-Alpha (-857) Gene Polymorphism and Susceptibility to Tuberculosis. Iranian Red Crescent Medical Journal 2011;13:243-8.

336. Ansari A, Hasan Z, Dawood G, Hussain R. Differential combination of cytokine and interferon- gamma +874 T/A polymorphisms determines disease severity in pulmonary tuberculosis. PLoS One 2011;6:e27848.

337. Aydin S, Aslan I, Yildiz I, i sur. Vitamin D levels in children with recurrent tonsillitis. Int J Pediatr Otorhinolaryngol 2011;75:364-7.

338. Ben Selma W, Harizi H, Bougmiza I, i sur. Interferon gamma +874T/A polymorphism is associated with susceptibility to active pulmonary tuberculosis development in Tunisian patients. DNA Cell Biol 2011;30:379-87.

339. Ben-Selma W, Harizi H, Boukadida J. MCP-1 -2518 A/G functional polymorphism is associated with increased susceptibility to active pulmonary tuberculosis in Tunisian patients. Mol Biol Rep 2011;38:5413-9.

340. Ben-Selma W, Harizi H, Boukadida J. Association of TNF-alpha and IL-10 polymorphisms with tuberculosis in Tunisian populations. Microbes Infect 2011;13:837-43.

341. Ben-Selma W, Harizi H, Bougmiza I, Ben Kahla I, Letaief M, Boukadida J. Polymorphisms in the RANTES gene increase susceptibility to active tuberculosis in Tunisia. DNA Cell Biol 2011;30:789-800.

342. Ben-Selma W, Ben-Kahla I, Boukadida J, Harizi H. Contribution of the P2X7 1513A/C loss-of-function polymorphism to extrapulmonary tuberculosis susceptibility in Tunisian populations. FEMS Immunol Med Microbiol 2011;63:65-72.

343. Curtis J, Kopanitsa L, Stebbings E, i sur. Association analysis of the LTA4H gene polymorphisms and pulmonary tuberculosis in 9115 subjects. Tuberculosis 2011;91:22-5.

344. Dai Y, Zhang X, Pan H, Tang S, Shen H, Wang J. Fine mapping of genetic polymorphisms of pulmonary tuberculosis within chromosome 18q11.2 in the Chinese population: a case-control study. BMC Infect Dis 2011;11:282.

345. Dalgic N, Tekin D, Kayaalti Z, i sur. Arg753Gln polymorphism of the human Toll-like receptor 2 gene from infection to disease in pediatric tuberculosis. Hum Immunol 2011;72:440-5.

346. Dalgic N, Tekin D, Kayaalti Z, Cakir E, Soylemezoglu T, Sancar M. Relationship between toll-like receptor 8 gene polymorphisms and pediatric pulmonary tuberculosis. Dis Markers 2011;31:33-8.

347. de Wit E, van der Merwe L, van Helden PD, Hoal EG. Gene-gene interaction between tuberculosis candidate genes in a South African population. Mamm Genome 2011;22:100-10.

348. Endeman H, Meijvis SC, Rijkers GT, i sur. Systemic cytokine response in patients with community-acquired pneumonia. Eur Respir J 2011;37:1431-8.

349. Feng WX, Mokrousov I, Wang BB, i sur. Tag SNP polymorphism of CCL2 and its role in clinical tuberculosis in Han Chinese pediatric population. PLoS One 2011;6:e14652.

350. Garcia-Laorden MI, Rodriguez de Castro F, Sole-Violan J, i sur. Influence of genetic variability at the surfactant proteins A and D in community-acquired pneumonia: a prospective, observational, genetic study. Crit Care 2011;15:R57.

351. Han M, Yue J, Lian YY, Zhao YL, Wang HX, Liu LR. Relationship between single nucleotide polymorphism of interleukin-18 and susceptibility to pulmonary tuberculosis in the Chinese Han population. Microbiol Immunol 2011;55:388-93.

352. Hashemi M, Sharifi-Mood B, Nezamdoost M, i sur. Functional polymorphism of interferon-gamma (IFN-gamma) gene +874T/A polymorphism is associated with pulmonary tuberculosis in Zahedan, Southeast Iran. Prague Med Rep 2011;112:38-43.

353. Hashimoto K, Katayose M, Sakuma H, i sur. Uteroglobulin-related protein 1 and severity of respiratory syncytial virus infection in children admitted to hospital. J Med Virol 2011;83:1086-92.

354. Hattori S, Shimojo N, Mashimo T, i sur. Relationship between RANTES polymorphisms and respiratory syncytial virus bronchiolitis in a Japanese infant population. Jpn J Infect Dis 2011;64:242-5.

355. Intemann CD, Thye T, Forster B, i sur. MCP1 haplotypes associated with protection from pulmonary tuberculosis. BMC Genet 2011;12:34.

356. Kang TJ, Jin SH, Yeum CE, i sur. Vitamin D Receptor Gene TaqI, BsmI and FokI Polymorphisms in Korean Patients with Tuberculosis. Immune Netw 2011;11:253-7.

357. Kobayashi K, Yuliwulandari R, Yanai H, i sur. Association of CD209 polymorphisms with tuberculosis in an Indonesian population. Hum Immunol 2011;72:741-5.

358. Kresfelder TL, Janssen R, Bont L, Pretorius M, Venter M. Confirmation of an association between single nucleotide polymorphisms in the VDR gene with respiratory syncytial virus related disease in South African children. J Med Virol 2011;83:1834-40.

359. Li D, Wang T, Song X, i sur. Genetic study of two single nucleotide polymorphisms within corresponding microRNAs and susceptibility to tuberculosis in a Chinese Tibetan and Han population. Hum Immunol 2011;72:598-602.

360. Liang L, Zhao YL, Yue J, i sur. Association of SP110 gene polymorphisms with susceptibility to tuberculosis in a Chinese population. Infect Genet Evol 2011;11:934-9.

361. Liang L, Zhao YL, Yue J, i sur. Interleukin-10 gene promoter polymorphisms and their protein production in pleural fluid in patients with tuberculosis. FEMS Immunol Med Microbiol 2011;62:84-90.

362. Ma MJ, Wang HB, Li H, i sur. Genetic variants in MARCO are associated with the susceptibility to pulmonary tuberculosis in Chinese Han population. PLoS One 2011;6:e24069.

363. Naderi M, Hashemi M, Karami H, i sur. Lack of association between rs1024611 (-2581 A/G) polymorphism in CC-chemokine Ligand 2 and susceptibility to pulmonary Tuberculosis in Zahedan, Southeast Iran. Prague Med Rep 2011;112:272-8.

364. Noumsi GT, Tounkara A, Diallo H, Billingsley K, Moulds JJ, Moulds JM. Knops blood group polymorphism and susceptibility to Mycobacterium tuberculosis infection. Transfusion 2011;51:2462-9.

365. Selvaraj P, Alagarasu K, Singh B, Afsal K. CCL5 (RANTES) gene polymorphisms in pulmonary tuberculosis patients of south India. Int J Immunogenet 2011;38:397-402.

366. Singh A, Gaughan JP, Kashyap VK. SLC11A1 and VDR gene variants and susceptibility to tuberculosis and disease progression in East India. Int J Tuberc Lung Dis 2011;15:1468-74, i.

367. Solé-Violán J, García-Laorden MI, Marcos-Ramos JA, i sur. The Fcγ receptor IIA-H/H131 genotype is associated with bacteremia in pneumococcal community-acquired pneumonia. Critical Care Medicine 2011;39:1388-93.

368. Solgun HA, Tastemir D, Aksaray N, Inan I, Demirhan O. Polymorphisms in NRAMP1 and MBL2 genes and their relations with tuberculosis in Turkish children. Tuberk Toraks 2011;59:48-53.

369. Stagas MK, Papaetis GS, Orphanidou D, i sur. Polymorphisms of the NRAMP1 gene: distribution and susceptibility to the development of pulmonary tuberculosis in the Greek population. Med Sci Monit 2011;17:PH1-6.

370. Thye T, Niemann S, Walter K, i sur. Variant G57E of mannose binding lectin associated with protection against tuberculosis caused by Mycobacterium africanum but not by M. tuberculosis. PLoS One 2011;6:e20908.

371. Uciechowski P, Imhoff H, Lange C, i sur. Susceptibility to tuberculosis is associated with TLR1 polymorphisms resulting in a lack of TLR1 cell surface expression. J Leukoc Biol 2011;90:377-88.

372. Zheng R, Zhou Y, Qin L, i sur. Relationship between polymorphism of DC-SIGN (CD209) gene and the susceptibility to pulmonary tuberculosis in an eastern Chinese population. Hum Immunol 2011;72:183-6.

373. Zhu X, Wang Y, Zhang H, i sur. Genetic variation of the human alpha-2-Heremans-Schmid glycoprotein (AHSG) gene associated with the risk of SARS-CoV infection. PLoS One 2011;6:e23730.

374. Alavi-Naini R, Salimi S, Sharifi-Mood B, Davoodikia AA, Moody B, Naghavi A. Association between the CD14 gene C-159T polymorphism and serum soluble CD14 with pulmonary tuberculosis. Int J Tuberc Lung Dis 2012;16:1383-7.

375. Antonopoulou A, Baziaka F, Tsaganos T, i sur. Role of tumor necrosis factor gene single nucleotide polymorphisms in the natural course of 2009 influenza A H1N1 virus infection. Int J Infect Dis 2012;16:e204-8.

376. Arji N, Busson M, Iraqi G, i sur. The MCP-1 (CCL2) -2518 GG genotype is associated with protection against pulmonary tuberculosis in Moroccan patients. J Infect Dev Ctries 2012;6:73-8.

377. Bahari G, Hashemi M, Taheri M, Naderi M, Eskandari-Nasab E, Atabaki M. Association of IRGM polymorphisms and susceptibility to pulmonary tuberculosis in Zahedan, Southeast Iran. ScientificWorldJournal 2012;2012:950801.

378. Baker MA, Wilson D, Wallengren K, i sur. Polymorphisms in the gene that encodes the iron transport protein ferroportin 1 influence susceptibility to tuberculosis. J Infect Dis 2012;205:1043-7.

379. Ben-Selma W, Boukadida J. IL23R(Arg381Gln) functional polymorphism is associated with active pulmonary tuberculosis severity. Clin Vaccine Immunol 2012;19:1188-92.

380. Ben-Selma W, Ben-Abderrahmen Y, Boukadida J, Harizi H. IL-10R1 S138G loss-of-function polymorphism is associated with extrapulmonary tuberculosis risk development in Tunisia. Mol Biol Rep 2012;39:51-6.

381. Ben-Selma W, Harizi H, Letaief M, Boukadida J. Age- and gender-specific effects on NRAMP1 gene polymorphisms and risk of the development of active tuberculosis in Tunisian populations. Int J Infect Dis 2012;16:e543-50.

382. Carroll SR, Zald PB, Soler ZM, Milczuk HA, Trune DR, MacArthur CJ. Innate immunity gene single nucleotide polymorphisms and otitis media. Int J Pediatr Otorhinolaryngol 2012;76:976-9.

383. Esposito S, Molteni CG, Giliani S, i sur. Toll-like receptor 3 gene polymorphisms and severity of pandemic A/H1N1/2009 influenza in otherwise healthy children. Virol J 2012;9:270.

384. Everitt AR, Clare S, Pertel T, i sur. IFITM3 restricts the morbidity and mortality associated with influenza. Nature 2012;484:519-23.

385. Faber TE, Schuurhof A, Vonk A, i sur. IL1RL1 gene variants and nasopharyngeal IL1RL-a levels are associated with severe RSV bronchiolitis: a multicenter cohort study. PLoS One 2012;7:e34364.

386. Gurbuzler L, Sogut E, Koc S, i sur. Manganese-superoxide dismutase and glutathione peroxidase 1 polymorphisms in recurrent tonsillitis and tonsillar hypertrophy. Int J Pediatr Otorhinolaryngol 2012;76:1270-3.

387. Hijikata M, Shojima J, Matsushita I, i sur. Association of IFNGR2 gene polymorphisms with pulmonary tuberculosis among the Vietnamese. Hum Genet 2012;131:675-82.

388. Horne DJ, Randhawa AK, Chau TT, i sur. Common polymorphisms in the PKP3-SIGIRR-TMEM16J gene region are associated with susceptibility to tuberculosis. J Infect Dis 2012;205:586-94.

389. Kobayashi K, Yuliwulandari R, Yanai H, i sur. Association of TLR polymorphisms with development of tuberculosis in Indonesian females. Tissue Antigens 2012;79:190-7.

390. Kouhpayeh HR, Hashemi M, Hashemi SA, i sur. R620W functional polymorphism of protein tyrosine phosphatase non-receptor type 22 is not associated with pulmonary tuberculosis in Zahedan, southeast Iran. Genet Mol Res 2012;11:1075-81.

391. Li Y, Yuan T, Lu W, Chen M, Cheng X, Deng S. Association of tuberculosis and polymorphisms in the promoter region of macrophage migration inhibitory factor (MIF) in a Southwestern China Han population. Cytokine 2012;60:64-7.

392. Liu Y, Shao Y, Yu B, Sun L, Lv F. Association of PBEF gene polymorphisms with acute lung injury, sepsis, and pneumonia in a northeastern Chinese population. Clin Chem Lab Med 2012;50:1917-22.

393. Martin-Loeches I, Sole-Violan J, Rodriguez de Castro F, i sur. Variants at the promoter of the interleukin-6 gene are associated with severity and outcome of pneumococcal community-acquired pneumonia. Intensive Care Med 2012;38:256-62.

394. Mishra G, Poojary SS, Raj P, Tiwari PK. Genetic polymorphisms of CCL2, CCL5, CCR2 and CCR5 genes in Sahariya tribe of North Central India: an association study with pulmonary tuberculosis. Infect Genet Evol 2012;12:1120-7.

395. Morales-Garcia G, Falfan-Valencia R, Garcia-Ramirez RA, i sur. Pandemic influenza A/H1N1 virus infection and TNF, LTA, IL1B, IL6, IL8, and CCL polymorphisms in Mexican population: a case-control study. BMC Infect Dis 2012;12:299.

396. Nuolivirta K, He Q, Vuononvirta J, Koponen P, Helminen M, Korppi M. Toll-like receptor 3 L412F polymorphisms in infants with bronchiolitis and postbronchiolitis wheezing. Pediatr Infect Dis J 2012;31:920-3.

397. Ogarkov O, Mokrousov I, Sinkov V, Zhdanova S, Antipina S, Savilov E. 'Lethal' combination of Mycobacterium tuberculosis Beijing genotype and human CD209 -336G allele in Russian male population. Infect Genet Evol 2012;12:732-6.

398. Overodder H, Naver L. Clara cell protein 10 polymorphism is not associated with severe respiratory syncytial virus infection. Acta Paediatr 2012;101:34-7.

399. Pakasi TA, Melani A, Bramantyo A, i sur. Distribution of D543N NRAMP1 polymorphism in tuberculosis patients from Kupang , east region of Indonesia. Medical journal of Indonesia 2012:160-5.

400. Pan H, Dai Y, Tang S, Wang J. Polymorphisms of NOD2 and the risk of tuberculosis: a validation study in the Chinese population. Int J Immunogenet 2012;39:233-40.

401. Png E, Alisjahbana B, Sahiratmadja E, i sur. Polymorphisms in SP110 are not associated with pulmonary tuberculosis in Indonesians. Infect Genet Evol 2012;12:1319-23.

402. Rathored J, Sharma SK, Singh B, i sur. Risk and outcome of multidrug-resistant tuberculosis: vitamin D receptor polymorphisms and serum 25(OH)D. Int J Tuberc Lung Dis 2012;16:1522-8.

403. Sanchez D, Lefebvre C, Rioux J, Garcia LF, Barrera LF. Evaluation of Toll-like receptor and adaptor molecule polymorphisms for susceptibility to tuberculosis in a Colombian population. Int J Immunogenet 2012;39:216-23.

404. Schuurhof A, Bont L, Hodemaekers HM, i sur. Proteins involved in extracellular matrix dynamics are associated with respiratory syncytial virus disease severity. Eur Respir J 2012;39:1475-81.

405. Selvaraj P, Alagarasu K, Singh B. Stromal cell-derived factor-1 (SDF-1/CXCL12) gene polymorphisms in pulmonary tuberculosis patients of south India. Int J Immunogenet 2012;39:26-31.

406. Shah JA, Vary JC, Chau TT, i sur. Human TOLLIP regulates TLR2 and TLR4 signaling and its polymorphisms are associated with susceptibility to tuberculosis. J Immunol 2012;189:1737-46.

407. Singh V, Gaur R, Mittal M, i sur. Absence of nucleotide-binding oligomerization domain-containing protein 2 variants in patients with leprosy and tuberculosis. Int J Immunogenet 2012;39:353-6.

408. Singla N, Gupta D, Joshi A, Batra N, Singh J, Birbian N. Association of mannose-binding lectin gene polymorphism with tuberculosis susceptibility and sputum conversion time. Int J Immunogenet 2012;39:10-4.

409. Singla N, Gupta D, Joshi A, Batra N, Singh J. Genetic polymorphisms in the P2X7 gene and its association with susceptibility to tuberculosis. Int J Tuberc Lung Dis 2012;16:224-9.

410. Songane M, Kleinnijenhuis J, Alisjahbana B, i sur. Polymorphisms in autophagy genes and susceptibility to tuberculosis. PLoS One 2012;7:e41618.

411. Souza CF, Noguti EN, Visentainer JE, Cardoso RF, Petzl-Erler ML, Tsuneto LT. HLA and MICA genes in patients with tuberculosis in Brazil. Tissue Antigens 2012;79:58-63.

412. Taheri M, Hashemi-Shahri SM, Hamzehnejadi M, i sur. Lack of association between interleukin-18 -607 C/A gene polymorphism and pulmonary tuberculosis in Zahedan, Southeast Iran. Prague Med Rep 2012;113:16-22.

413. Thuong NT, Hawn TR, Chau TT, i sur. Epiregulin (EREG) variation is associated with susceptibility to tuberculosis. Genes Immun 2012;13:275-81.

414. Velez Edwards DR, Tacconelli A, Wejse C, i sur. MCP1 SNPs and pulmonary tuberculosis in cohorts from West Africa, the USA and Argentina: lack of association or epistasis with IL12B polymorphisms. PLoS One 2012;7:e32275.

415. Verma VK, Taneja V, Jaiswal A, i sur. Prevalence, distribution and functional significance of the -237C to T polymorphism in the IL-12Rbeta2 promoter in Indian tuberculosis patients. PLoS One 2012;7:e34355.

416. Wang D, Zhou Y, Ji L, i sur. Association of LMP/TAP gene polymorphisms with tuberculosis susceptibility in Li population in China. PLoS One 2012;7:e33051.

417. Wang C, Jiang T, Wei L, i sur. Association of CTLA4 gene polymorphisms with susceptibility and pathology correlation to pulmonary tuberculosis in Southern Han Chinese. Int J Biol Sci 2012;8:945-52.

418. Xue Y, Zhao ZQ, Chen F, i sur. Polymorphisms in the promoter of the CD14 gene and their associations with susceptibility to pulmonary tuberculosis. Tissue Antigens 2012;80:437-43.

419. Zaki HY, Leung KH, Yiu WC, Gasmelseed N, Elwali NE, Yip SP. Common polymorphisms in TLR4 gene associated with susceptibility to pulmonary tuberculosis in the Sudanese. Int J Tuberc Lung Dis 2012;16:934-40.

420. Zhang G, Zhou B, Wang W, i sur. A functional single-nucleotide polymorphism in the promoter of the gene encoding interleukin 6 is associated with susceptibility to tuberculosis. J Infect Dis 2012;205:1697-704.

421. Zhang X, Jiang F, Wei L, i sur. Polymorphic allele of human MRC1 confer protection against tuberculosis in a Chinese population. Int J Biol Sci 2012;8:375-82.

422. Zhao M, Jiang F, Zhang W, i sur. A novel single nucleotide polymorphism within the NOD2 gene is associated with pulmonary tuberculosis in the Chinese Han, Uygur and Kazak populations. BMC Infect Dis 2012;12:91.

423. Zhou J, To KK, Dong H, i sur. A functional variation in CD55 increases the severity of 2009 pandemic H1N1 influenza A virus infection. J Infect Dis 2012;206:495-503.

424. Zuniga J, Buendia-Roldan I, Zhao Y, i sur. Genetic variants associated with severe pneumonia in A/H1N1 influenza infection. Eur Respir J 2012;39:604-10.

425. Abhimanyu, Bose M, Komal, Varma-Basil M. Lack of association between IL17A and IL17F polymorphisms and related serum levels in north Indians with tuberculosis. Gene 2013;529:195-8.

426. Alexandra SG, Georgiana DC, Nicoleta C, Daniela PM, Traian S, Veronica S. Apa I and Taq I polymorphisms of VDR (vitamin D receptor) gene in association with susceptibility to tuberculosis in the Romanian population. Romanian Biotechnological Letters 2013;18:7956-62.

427. Ali S, Hirschfeld AF, Mayer ML, i sur. Functional genetic variation in NFKBIA and susceptibility to childhood asthma, bronchiolitis, and bronchopulmonary dysplasia. J Immunol 2013;190:3949-58.

428. Bahari G, Hashemi M, Taheri M, i sur. Association of P2X7 gene polymorphisms with susceptibility to pulmonary tuberculosis in Zahedan, Southeast Iran. Genet Mol Res 2013;12:160-6.

429. Boechat AL, Ogusku MM, Sadahiro A, dos Santos MC. Association between the PTPN22 1858C/T gene polymorphism and tuberculosis resistance. Infect Genet Evol 2013;16:310-3.

430. Bowdish DM, Sakamoto K, Lack NA, i sur. Genetic variants of MARCO are associated with susceptibility to pulmonary tuberculosis in a Gambian population. BMC Med Genet 2013;14:47.

431. Cai L, Deng SL, Liang L, i sur. Identification of genetic associations of SP110/MYBBP1A/RELA with pulmonary tuberculosis in the Chinese Han population. Hum Genet 2013;132:265-73.

432. Capparelli R, De Chiara F, Di Matteo A, Medaglia C, Iannelli D. The MyD88 rs6853 and TIRAP rs8177374 polymorphic sites are associated with resistance to human pulmonary tuberculosis. Genes and Immunity 2013;14:504-11.

433. da Cruz HL, da Silva RC, Segat L, i sur. MBL2 gene polymorphisms and susceptibility to tuberculosis in a northeastern Brazilian population. Infect Genet Evol 2013;19:323-9.

434. Garcia-Elorriaga G, Vera-Ramirez L, del Rey-Pineda G, Gonzalez-Bonilla C. -592 and -1082 interleukin-10 polymorphisms in pulmonary tuberculosis with type 2 diabetes. Asian Pac J Trop Med 2013;6:505-9.

435. Hashemi M, Eskandari-Nasab E, Moazeni-Roodi A, Naderi M, Sharifi-Mood B, Taheri M. Association of CTSZ rs34069356 and MC3R rs6127698 gene polymorphisms with pulmonary tuberculosis. Int J Tuberc Lung Dis 2013;17:1224-8.

436. Jahantigh D, Salimi S, Alavi-Naini R, Emamdadi A, Owaysee Osquee H, Farajian Mashhadi F. Association between TLR4 and TLR9 gene polymorphisms with development of pulmonary tuberculosis in Zahedan, southeastern Iran. ScientificWorldJournal 2013;2013:534053.

437. Ji LD, Chai PF, Zhou BB, i sur. Lack of association between polymorphisms from genome-wide association studies and tuberculosis in the Chinese population. Scand J Infect Dis 2013;45:310-4.

438. Korytina GF, Akhmadishina LZ, Viktorova EV, i sur. Extracellular matrix remodeling genes polymorphisms and risk of chronic bronchitis and recurrent pneumonia in children. J Hum Genet 2013;58:467-74.

439. Leandro AC, Rocha MA, Lamoglia-Souza A, VandeBerg JL, Rolla VC, Bonecini-Almeida Mda G. No association of IFNG+874T/A SNP and NOS2A-954G/C SNP variants with nitric oxide radical serum levels or susceptibility to tuberculosis in a Brazilian population subset. Biomed Res Int 2013;2013:901740.

440. Lee SW, Chuang TY, Huang HH, i sur. Interferon gamma polymorphisms associated with susceptibility to tuberculosis in a Han Taiwanese population. J Microbiol Immunol Infect 2014.

441. Liu Y, Li S, Zhang G, i sur. Genetic variants in IL1A and IL1B contribute to the susceptibility to 2009 pandemic H1N1 influenza A virus. BMC Immunol 2013;14:37.

442. Lopes MQP, de Figueiredo Teixeira RL, de Miranda AB, i sur. Influence of the Interferon – Gamma (IFN – γ) and Tumor Necrosis Factor Alpha (TNF – α) Gene Polymorphisms in TB Occurrence and Clinical Spectrum. Tuberculosis: Current issues in diagnosis and management 2013:79-103.

443. Martinez-Ocana J, Olivo-Diaz A, Salazar-Dominguez T, i sur. Plasma cytokine levels and cytokine gene polymorphisms in Mexican patients during the influenza pandemic A(H1N1)pdm09. J Clin Virol 2013;58:108-13.

444. Meenakshi P, Ramya S, Shruthi T, i sur. Association of IL-1beta +3954 C/T and IL-10-1082 G/A cytokine gene polymorphisms with susceptibility to tuberculosis. Scand J Immunol 2013;78:92-7.

445. Metanat M, Nejad MN, Salehi M, Moazen J, Sanei-Moghaddam E, Arbabi N. Comparison of Genetic Polymorphisms of TNF-alpha and IL-10 Genes Between Tuberculosis Patients and Healthy Blood Donors. Archives of clinical infectious diseases 2013;8:1-5.

446. Mhmoud N, Fahal A, van de Sande WJ. Association of IL-10 and CCL5 single nucleotide polymorphisms with tuberculosis in the Sudanese population. Trop Med Int Health 2013;18:1119-27.

447. Misch EA, Verbon A, Prins JM, Skerrett SJ, Hawn TR. A TLR6 polymorphism is associated with increased risk of Legionnaires' disease. Genes Immun 2013;14:420-6.

448. Naderi M, Hashemi M, Hazire-Yazdi L, i sur. Association between toll-like receptor2 Arg677Trp and 597T/C gene polymorphisms and pulmonary tuberculosis in Zahedan, Southeast Iran. Braz J Infect Dis 2013;17:516-20.

449. Nuolivirta K, Vuononvirta J, Peltola V, i sur. Toll-like receptor-2 subfamily genotypes are not associated with severity of bronchiolitis or post-bronchiolitis wheezing in infants. Acta Paediatr 2013.

450. Ocejo-Vinyals JG, de Mateo EP, Hoz MA, i sur. The IL-17 G-152A single nucleotide polymorphism is associated with pulmonary tuberculosis in northern Spain. Cytokine 2013;64:58-61.

451. Peng R, Yue J, Han M, Zhao Y, Liu L, Liang L. The IL-17F sequence variant is associated with susceptibility to tuberculosis. Gene 2013;515:229-32.

452. Salnikova LE, Smelaya TV, Golubev AM, Rubanovich AV, Moroz VV. CYP1A1, GCLC, AGT, AGTR1 gene-gene interactions in community-acquired pneumonia pulmonary complications. Mol Biol Rep 2013;40:6163-76.

453. Salnikova LE, Smelaya TV, Moroz VV, Golubev AM, Rubanovich AV. Functional polymorphisms in the CYP1A1, ACE, and IL-6 genes contribute to susceptibility to community-acquired and nosocomial pneumonia. Int J Infect Dis 2013;17:e433-42.

454. Sanchez D, Lefebvre C, Garcia LF, Barrera LF. Variants in the IFN gamma transcription factor genes TBET, STAT1, STAT4, and HLX and the risk of pulmonary tuberculosis in a Colombian population: a case-control study. Biomedica 2013;33:259-67.

455. Song X, Li S, QuCuo M, i sur. Association between SNPs in microRNA-machinery genes and tuberculosis susceptibility in Chinese Tibetan population. Mol Biol Rep 2013;40:6027-33.

456. Taheri M, Kouhpayeh HR, Hosseinalizadeh T, Naderi M, Bahari G, Hashemi M. A Functional Polymorphism in Promoter of the CXCL10 Gene (-135 G / A) Associated With Pulmonary Tuberculosis. Archives of Clinical Infectious Diseases 2013;8:1-4.

457. Tapia LI, Ampuero S, Palomino MA, i sur. Respiratory syncytial virus infection and recurrent wheezing in Chilean infants: a genetic background? Infect Genet Evol 2013;16:54-61.

458. Velayati AA, Farnia P, Farahbod AM, i sur. Association of Receptors, Purinergic P2X 7 and Tumor Necrosis Factor-Alpha Gene Polymorphisms in Susceptibility to Tuberculosis Among Iranian Patients. Archives of clinical infectious diseases 2013;8:1-8.

459. Wang X, Tang NL, Leung CC, i sur. Association of polymorphisms in the Chr18q11.2 locus with tuberculosis in Chinese population. Hum Genet 2013;132:691-5.

460. Wu F, Zhang W, Zhang L, i sur. NRAMP1, VDR, HLA-DRB1, and HLA-DQB1 gene polymorphisms in susceptibility to tuberculosis among the Chinese Kazakh population: a case-control study. Biomed Res Int 2013;2013:484535.

461. Yang Y, Li X, Cui W, i sur. Potential association of pulmonary tuberculosis with genetic polymorphisms of toll-like receptor 9 and interferon-gamma in a Chinese population. BMC Infect Dis 2013;13:511.

462. Zhang X, Li X, Zhang W, i sur. The novel human MRC1 gene polymorphisms are associated with susceptibility to pulmonary tuberculosis in Chinese Uygur and Kazak populations. Mol Biol Rep 2013;40:5073-83.

463. Zhang YH, Zhao Y, Li N, i sur. Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with severe influenza in Chinese individuals. Nat Commun 2013;4:1418.

464. Arji N, Busson M, Iraqi G, i sur. Genetic diversity of TLR2, TLR4, and VDR loci and pulmonary tuberculosis in Moroccan patients. J Infect Dev Ctries 2014;8:430-40.

465. Carpenter D, Taype C, Goulding J, i sur. CCL3L1 copy number, CCR5 genotype and susceptibility to tuberculosis. Bmc Medical Genetics 2014;15.

466. Chen J, Wilson ES, Dahmer MK, i sur. Lack of association of the caspase-12 long allele with community-acquired pneumonia in people of African descent. PLoS One 2014;9:e89194.

467. Ciencewicki JM, Wang XT, Marzec J, i sur. A genetic model of differential susceptibility to human respiratory syncytial virus (RSV) infection. Faseb Journal 2014;28:1947-56.

468. da Silva RC, Segat L, da Cruz HLA, i sur. Association of CD209 and CD209L polymorphisms with tuberculosis infection in a Northeastern Brazilian population. Molecular Biology Reports 2014;41:5449-57.

469. Drysdale SB, Prendergast M, Alcazar M, i sur. Genetic predisposition of RSV infection-related respiratory morbidity in preterm infants. Eur J Pediatr 2014.

470. Etokebe GE, Bulat-Kardum L, Munthe LA, Balen S, Dembic Z. Association of variable number of tandem repeats in the coding region of the FAM46A gene, FAM46A rs11040 SNP and BAG6 rs3117582 SNP with susceptibility to tuberculosis. PLoS One 2014;9:e91385.

471. Feng Y, Wang FL, Pan HQ, i sur. Obesity-associated gene FTO rs9939609 polymorphism in relation to the risk of tuberculosis. Bmc Infectious Diseases 2014;14.

472. Goutaki M, Haidopoulou K, Pappa S, i sur. The role of TLR4 and CD14 polymorphisms in the pathogenesis of respiratory syncytial virus bronchiolitis in greek infants. Int J Immunopathol Pharmacol 2014;27:563-72.

473. Herrera-Ramos E, Lopez-Rodriguez M, Ruiz-Hernandez JJ, i sur. Surfactant protein A genetic variants associate with severe respiratory insufficiency in pandemic influenza A virus infection. Crit Care 2014;18:R127.

474. Hu X, Shang M, Zhou J, i sur. Association of genetic variants in wnt signaling pathway with tuberculosis in chinese han population. PLoS One 2014;9:e93841.

475. Joshi L, Ponnana M, Penmetsa SR, Nallari P, Valluri V, Gaddam S. Serum vitamin D levels and VDR polymorphisms (BsmI and FokI) in patients and their household contacts susceptible to tuberculosis. Scand J Immunol 2014;79:113-9.

476. Khan AU, Aslam MA, Hussain I, i sur. Role of Toll-like receptor 2 (-196 to -174) polymorphism in susceptibility to pulmonary tuberculosis in Pakistani population. Int J Immunogenet 2014;41:105-11.

477. Lopez Campos GN, Velarde Felix JS, Sandoval Ramirez L, i sur. Polymorphism in cathelicidin gene (CAMP) that alters Hypoxia-inducible factor (HIF-1alpha::ARNT) binding is not associated with tuberculosis. Int J Immunogenet 2014;41:54-62.

478. Lu J, Pan H, Chen Y, i sur. Genetic polymorphisms of IFNG and IFNGR1 in association with the risk of pulmonary tuberculosis. Gene 2014;543:140-4.

479. Mahmoud AA, Ali AHK. Vitamin D receptor gene polymorphism and 25 hydroxy vitamin D levels in Egyptian patients with pulmonary tuberculosis. Egyptian Journal of Chest Diseases and Tuberculosis 2014;63:651-5.

480. Marr N, Hirschfeld AF, Lam A, Wang S, Lavoie PM, Turvey SE. Assessment of genetic associations between common single nucleotide polymorphisms in RIG-I-like receptor and IL-4 signaling genes and severe respiratory syncytial virus infection in children: a candidate gene case-control study. Plos One 2014;9:e100269.

481. Mills TC, Rautanen A, Elliott KS, i sur. IFITM3 and susceptibility to respiratory viral infections in the community. J Infect Dis 2014;209:1028-31.

482. Naderi M, Hashemi M, Taheri M, Pesarakli H, Eskandari-Nasab E, Bahari G. CD209 promoter -336 A/G (rs4804803) polymorphism is associated with susceptibility to pulmonary tuberculosis in Zahedan, southeast Iran. J Microbiol Immunol Infect 2014;47:171-5.

483. Park SK, Park CS, Lee HS, i sur. Functional polymorphism in aldehyde dehydrogenase-2 gene associated with risk of tuberculosis. BMC Med Genet 2014;15:40.

484. Qrafli M, Amar Y, Bourkadi J, i sur. The CYP7A1 gene rs3808607 variant is associated with susceptibility of tuberculosis in Moroccan population. Pan Afr Med J 2014;18:1.

485. Randolph AG, Yip WK, Falkenstein-Hagander K, i sur. Vitamin D-binding protein haplotype is associated with hospitalization for RSV bronchiolitis. Clin Exp Allergy 2014;44:231-7.

486. Rangel-Ramirez VV, Garcia-Sepulveda CA, Escalante-Padron F, i sur. NKG2C gene deletion in the Mexican population and lack of association to respiratory viral infections. Int J Immunogenet 2014;41:126-30.

487. Sabri A, Grant AV, Cosker K, i sur. Association study of genes controlling IL-12-dependent IFN-gamma immunity: STAT4 alleles increase risk of pulmonary tuberculosis in Morocco. J Infect Dis 2014.

488. Sanchez D, Lefebvre C, Garcia LF, Rioux J, Barrera LF. Crohn's disease susceptibility variants in Colombian tuberculosis patients. International Journal of Tuberculosis and Lung Disease 2014;18:89-94.

489. Seshadri C, Thuong NT, Yen NT, i sur. A polymorphism in human CD1A is associated with susceptibility to tuberculosis. Genes Immun 2014;15:195-8.

490. Shen C, Qi H, Sun L, i sur. A 3'UTR Polymorphism of IL-6R Is Associated with Chinese Pediatric Tuberculosis. Biomed Res Int 2014;2014:483759.

491. Singh B, Chitra J, Selvaraj P. CCL2, CCL3 and CCL4 gene polymorphisms in pulmonary tuberculosis patients of South India. Int J Immunogenet 2014;41:98-104.

492. Sivangala R, Ponnana M, Thada S, i sur. Association of cytokine gene polymorphisms in patients with tuberculosis and their household contacts. Scand J Immunol 2014;79:197-205.

493. Sulaja BDM, Chauhan UK. rs 10735810 of Vitamin D Receptor (VDR) Gene : Association with Pulmonary Tuberculosis in Children. Journal of Infection and Molecular Biology 2014;2:32 - 4.

494. To KK, Zhou J, Song YQ, i sur. Surfactant protein B gene polymorphism is associated with severe influenza. Chest 2014;145:1237-43.

495. Varahram M, Farnia P, Nasiri MJ, Karahrudi MA, Dizagie MK, Velayati AA. Association of Mycobacterium Tuberculosis Lineages with IFN-gamma and TNF-alpha Gene Polymorphisms among Pulmonary Tuberculosis Patient. Mediterr J Hematol Infect Dis 2014;6:e2014015.

496. Yang HY, Li H, Wang YG, i sur. Correlation analysis between single nucleotide polymorphisms of pulmonary surfactant protein A gene and pulmonary tuberculosis in the Han population in China. Int J Infect Dis 2014;26:31-6.

497. Zhang Y, Li X, Wu Z, Fan H. Association between ACE I/D polymorphism and pulmonary tuberculosis in Chinese population. Mol Biol Rep 2014.

498. Zhao L, Chu H, Xu X, Yue J, Li H, Wang M. Association between single-nucleotide polymorphism in CISH gene and susceptibility to tuberculosis in Chinese Han population. Cell Biochem Biophys 2014;68:529-34.

499. Zidan HE, Elbehedy RM, Azab SF. IL6-174 G/C gene polymorphism and its relation to serum IL6 in Egyptian children with community-acquired pneumonia. Cytokine 2014;67:60-4.

500. Campo M, Randhawa AK, Dunstan S, i sur. Common Polymorphisms in the CD43 Gene Region Are Associated with Tuberculosis Disease and Mortality. Am J Respir Cell Mol Biol 2015;52:342-8.

501. Cheng ZS, Zhou J, To KKW, i sur. Identification of TMPRSS2 as a Susceptibility Gene for Severe 2009 Pandemic A(H1N1) Influenza and A(H7N9) Influenza. Journal of Infectious Diseases 2015;212:1214-21.

502. Jiang DB, Wubuli A, Hu X, i sur. The variations of IL-23R are associated with susceptibility and severe clinical forms of pulmonary tuberculosis in Chinese Uygurs. BMC Infect Dis 2015;15.

503. Li W, Guo LY, Li HR, i sur. Polymorphism rs2239185 in vitamin D receptor gene is associated with severe community-acquired pneumonia of children in Chinese Han population: a case-control study. Eur J Pediatr 2015;174:621-9.

504. Liu XT, Ren L, Zhou LL, Xiao QY, Deng Y, Liu EM. ORMDL3 variants associated with bronchiolitis susceptibility in a Chinese population. Genet Mol Res 2015;14:19155-62.

505. Liu Q, Wang J, Sandford AJ, i sur. Association of CYBB polymorphisms with tuberculosis susceptibility in the Chinese Han population. Infect Genet Evol 2015;33:169-75.

506. Trifunovic VS, Buha I, Jovanovic D, i sur. VARIANTS IN VDR AND NRAMP1 GENES AS SUSCEPTIBILITY FACTORS FOR TUBERCULOSIS IN THE POPULATION OF SERBIA. Genetika-Belgrade 2015;47:1021-8.

507. Wu JD, Lu LJ, Zhang L, i sur. Single Nucleotide Polymorphisms in P2X7 Gene Are Associated with Serum Immunoglobulin G Responses to Mycobacterium tuberculosis in Tuberculosis Patients. Disease Markers 2015.

508. Zhao Y, Bu H, Hong K, i sur. Genetic polymorphisms of CCL1 rs2072069 G/A and TLR2 rs3804099 T/C in pulmonary or meningeal tuberculosis patients. Int J Clin Exp Pathol 2015;8:12608-20.

509. Azab SF, Abdalhady MA, Elsaadany HF, i sur. Interleukin-10 -1082 G/A gene polymorphisms in Egyptian children with CAP: A case-control study. Medicine (Baltimore) 2016;95:e4013.

510. Chou SC, Ko HW, Lin YC. CRP/IL-6/IL-10 Single-Nucleotide Polymorphisms Correlate with the Susceptibility and Severity of Community-Acquired Pneumonia. Genet Test Mol Biomarkers 2016;20:732-40.

511. da Silva RC, da Cruz HLA, Brandao LAC, i sur. DEFB1 gene polymorphisms and tuberculosis in a Northeastern Brazilian population. Brazilian Journal of Microbiology 2016;47:389-93.

512. de Lima DS, Ogusku MM, Sadahiro A, Pontillo A. Inflammasome genetics contributes to the development and control of active pulmonary tuberculosis. Infection Genetics and Evolution 2016;41:240-4.

513. Gaio V, Nunes B, Pechirra P, i sur. Hospitalization risk due to respiratory illness associated with genetic variation at IFITM3 in patients with influenza A(H1N1)pdm09 infection: A case-control study. PLoS One 2016;11.

514. Georgitsi MD, Vitoros V, Panou C, i sur. Individualized significance of the -251 A/T single nucleotide polymorphism of interleukin-8 in severe infections. Eur J Clin Microbiol Infect Dis 2016;35:563-70.

515. High M, Cho HY, Marzec J, i sur. Determinants of host susceptibility to murine respiratory syncytial virus (RSV) disease identify a role for the innate immunity scavenger receptor MARCO gene in human infants. EBioMedicine 2016;11:73-84.

516. Holscher C, Heitmann L, Owusu-Dabo E, i sur. A Mutation in IL4RA Is Associated with the Degree of Pathology in Human TB Patients. Mediators of Inflammation 2016.

517. Jafari M, Nasiri MR, Sanaei R, i sur. The NRAMP1, VDR, TNF-alpha, ICAM1, TLR2 and TLR4 gene polymorphisms in Iranian patients with pulmonary tuberculosis: A case-control study. Infection Genetics and Evolution 2016;39:92-8.

518. Lee SW, Chuang TY, Huang HH, Liu CW, Kao YH, Wu LSH. VDR and VDBP genes polymorphisms associated with susceptibility to tuberculosis in a Han Taiwanese population. Journal of Microbiology Immunology and Infection 2016;49:783-7.

519. Liu C, He T, Rong YX, i sur. Association of Mannose-binding Lectin Polymorphisms with Tuberculosis Susceptibility among Chinese. Sci Rep 2016;6.

520. Liu AH, Li J, Bao FK, i sur. Single nucleotide polymorphisms in cytokine MIF gene promoter region are closely associated with human susceptibility to tuberculosis in a southwestern province of China. Infection Genetics and Evolution 2016;39:219-24.

521. Lopez-Rodriguez M, Herrera-Ramos E, Sole-Violan J, i sur. IFITM3 and severe influenza virus infection. No evidence of genetic association. European Journal of Clinical Microbiology & Infectious Diseases 2016;35:1811-7.

522. Lu YJ, Zhu YW, Wang X, i sur. FOXO3 rs12212067: T > G Association with Active Tuberculosis in Han Chinese Population. Inflammation 2016;39:10-5.

523. Meyer CG, Reiling N, Ehmen C, i sur. TLR1 Variant H305L Associated with Protection from Pulmonary Tuberculosis. PLoS One 2016;11.

524. Ren GX, You JT, Gong XF, i sur. SP110 and PMP22 polymorphisms are associated with tuberculosis risk in a Chinese-Tibetan population. Oncotarget 2016;7:66100-8.

525. Smelaya TV, Belopolskaya OB, Smirnova SV, i sur. Genetic dissection of host immune response in pneumonia development and progression. Sci Rep 2016;6:35021.

526. Thuong NTT, Tram TTB, Dinh TD, i sur. MARCO variants are associated with phagocytosis, pulmonary tuberculosis susceptibility and Beijing lineage. Genes and Immunity 2016;17:419-25.

527. Yuan LY, Ke ZQ, Ma J, Guo Y, Li Y. IRGM gene polymorphisms and haplotypes associate with susceptibility of pulmonary tuberculosis in Chinese Hubei Han population. Tuberculosis 2016;96:58-64.

528. Zhang M, Lu Y, Zhang X, Lu A, Wang L, Chen C. Interleukin-4 polymorphism is associated with severity of respiratory syncytial virus infection. J Paediatr Child Health 2016;52:25-9.

529. Zhu XK, Guo W, Ren GX, i sur. P2X7R Gene Polymorphisms Are Associated with Increased Risk of Pulmonary Tuberculosis in the Tibetan Chinese Population. American Journal of Tropical Medicine and Hygiene 2016;95:1016-20.

530. Abouzeid H, Alkholy UM, Abdou MA, i sur. Angiotensin-converting enzyme insertion/deletion gene polymorphism in Egyptian children with CAP: A case-control study. Pediatr Pulmonol 2017;52:1592-8.

531. Amiri A, Sabooteh T, Shahsavar F, Anbari K, Pouremadi F. Mannose-Binding Lectin (MBL) gene polymorphisms in susceptibility to pulmonary tuberculosis among the Lur population of Lorestan Province of Iran. Genomics Data 2017;12:146-50.

532. Azar AF, Jazani NH, Bazmani A, Vahhabi A, Shahabi S. Polymorphisms in Beta-2 Adrenergic Receptor Gene and Association with Tuberculosis. Lung 2017;195:147-53.

533. Mao ZR, Zhang SL, Feng B. Association of IL-10 (-819T/C, -592A/C and -1082A/G) and IL-6 -174G/C gene polymorphism and the risk of pneumonia-induced sepsis. Biomarkers 2017;22:106-12.

534. Mehrbod P, Eybpoosh S, Fotouhi F, Targhi HS, Mazaheri V, Farahmand B. Association of IFITM3 rs12252 polymorphisms, BMI, diabetes, and hypercholesterolemia with mild flu in an Iranian population. Virol J 2017;14.

535. Qrafli M, Asekkaj I, Bourkadi JE, El Aouad R, Sadki K. New variant identified in major susceptibility locus to tuberculosis on chromosomal region 8q12-q13 in Moroccan population: a case control study. BMC Infect Dis 2017;17.

536. Rolandelli A, Del Pino REH, Pellegrini JM, i sur. The IL-17A rs2275913 single nucleotide polymorphism is associated with protection to tuberculosis but related to higher disease severity in Argentina. Sci Rep 2017;7.

537. Seshadri C, Thuong NTT, Mai NTH, i sur. A polymorphism in human MR1 is associated with mRNA expression and susceptibility to tuberculosis. Genes and Immunity 2017;18:8-14.

538. van Kempen G, Meijvis S, Endeman H, i sur. Mannose-binding lectin and l-ficolin polymorphisms in patients with community-acquired pneumonia caused by intracellular pathogens. Immunology 2017;151:81-8.

539. Zhao J, Zhang W, Shen L, Yang X, Liu Y, Gai Z. Association of the ACE, GSTM1, IL-6, NOS3, and CYP1A1 polymorphisms with susceptibility of mycoplasma pneumoniae pneumonia in Chinese children. Medicine (Baltimore) 2017;96:e6642.

540. Zheng XZ, Li TC, Chen YZ, i sur. Genetic polymorphisms of the P2X7 gene associated with susceptibility to and prognosis of pulmonary tuberculosis. Infection Genetics and Evolution 2017;53:24-9.

541. Garcia CC, Tavares LP, Dias ACF, i sur. Phosphatidyl Inositol 3 Kinase-Gamma Balances Antiviral and Inflammatory Responses During Influenza A H1N1 Infection: From Murine Model to Genetic Association in Patients. Front Immunol 2018;9.

542. Hsieh MH, Ou CY, Hsieh WY, i sur. Functional Analysis of Genetic Variations in Surfactant Protein D in Mycobacterial Infection and Their Association With Tuberculosis. Front Immunol 2018;9.

543. Roodposhti SZ, Motalleb G, Nikokar I. Rs4073 single nucleotide polymorphism of interleukin-8 (CXCL8/IL-8) and susceptibility to pulmonary tuberculosis in Gilan, Northern Iran. Gene Reports 2018;11:127-30.

544. Bellamy R, Beyers N, McAdam K, i sur. Genetic susceptibility to tuberculosis in Africans: A genome-wide scan. Proceedings of the National Academy of Sciences of the United States of America 2000;97:8005-9.

545. Hull J, Thomson A, Kwiatkowski D. Association of respiratory syncytial virus bronchiolitis with the interleukin 8 gene region in UK families. Thorax 2000;55:1023-7.

546. Hull J, Ackerman H, Isles K, i sur. Unusual haplotypic structure of IL8, a susceptibility locus for a common respiratory virus. Am J Hum Genet 2001;69:413-9.

547. El Baghdadi J, Remus N, Benslimane A, i sur. Variants of the human NRAMP1 gene and susceptibility to tuberculosis in Morocco. International Journal of Tuberculosis and Lung Disease 2003;7:599-602.

548. Daly KA, Brown WM, Segade F, i sur. Chronic and recurrent otitis media: a genome scan for susceptibility loci. Am J Hum Genet 2004;75:988-97.

549. Jamieson SE, Miller EN, Black GF, i sur. Evidence for a cluster of genes on chromosome 17q11-q21 controlling susceptibility to tuberculosis and leprosy in Brazilians. Genes and Immunity 2004;5:46-57.

550. Miller EN, Jamieson SE, Joberty C, i sur. Genome-wide scans for leprosy and tuberculosis susceptibility genes in Brazilians. Genes Immun 2004;5:63-7.

551. Remus N, El Baghdadi J, Fieschi C, i sur. Association of IL12RB1 polymorphisms with pulmonary tuberculosis in adults in Morocco. Journal of Infectious Diseases 2004;190:580-7.

552. Casselbrant ML, Mandel EM, Jung J, i sur. Otitis media: a genome-wide linkage scan with evidence of susceptibility loci within the 17q12 and 10q22.3 regions. BMC Med Genet 2009;10:85.

553. Cobat A, Gallant CJ, Simkin L, i sur. Two loci control tuberculin skin test reactivity in an area hyperendemic for tuberculosis. J Exp Med 2009;206:2583-91.

554. Mahasirimongkol S, Yanai H, Nishida N, i sur. Genome-wide SNP-based linkage analysis of tuberculosis in Thais. Genes and Immunity 2009;10:77-83.

555. Thomas NJ, DiAngelo S, Hess JC, i sur. Transmission of surfactant protein variants and haplotypes in children hospitalized with respiratory syncytial virus. Pediatr Res 2009;66:70-3.

556. Ridruechai C, Mahasirimongkol S, Phromjai J, i sur. Association analysis of susceptibility candidate region on chromosome 5q31 for tuberculosis. Genes Immun 2010;11:416-22.

557. Chen WM, Allen EK, Mychaleckyj JC, i sur. Significant linkage at chromosome 19q for otitis media with effusion and/or recurrent otitis media (COME/ROM). BMC Med Genet 2011;12:124.

558. Rye MS, Wiertsema SP, Scaman ES, i sur. FBXO11, a regulator of the TGFbeta pathway, is associated with severe otitis media in Western Australian children. Genes Immun 2011;12:352-9.

559. Cobat A, Hoal EG, Gallant CJ, i sur. Identification of a major locus, TNF1, that controls BCG-triggered tumor necrosis factor production by leukocytes in an area hyperendemic for tuberculosis. Clin Infect Dis 2013;57:963-70.

560. Rye MS, Scaman ES, Thornton RB, i sur. Genetic and functional evidence for a locus controlling otitis media at chromosome 10q26.3. BMC Med Genet 2014;15:18.

561. Cobat A, Poirier C, Hoal E, i sur. Tuberculin Skin Test Negativity Is Under Tight Genetic Control of Chromosomal Region 11p14-15 in Settings With Different Tuberculosis Endemicities. Journal of Infectious Diseases 2015;211:317-21.

562. Rubicz R, Yolken R, Drigalenko E, i sur. Genome-wide genetic investigation of serological measures of common infections. European Journal of Human Genetics 2015;23:1544-8.

563. Thye T, Vannberg FO, Wong SH, i sur. Genome-wide association analyses identifies a susceptibility locus for tuberculosis on chromosome 18q11.2. Nat Genet 2010;42:739-41.

564. Mahasirimongkol S, Yanai H, Mushiroda T, i sur. Genome-wide association studies of tuberculosis in Asians identify distinct at-risk locus for young tuberculosis. J Hum Genet 2012;57:363-7.

565. Png E, Alisjahbana B, Sahiratmadja E, i sur. A genome wide association study of pulmonary tuberculosis susceptibility in Indonesians. BMC Med Genet 2012;13:5.

566. Rye MS, Warrington NM, Scaman ES, i sur. Genome-wide association study to identify the genetic determinants of otitis media susceptibility in childhood. PLoS One 2012;7:e48215.

567. Allen EK, Chen WM, Weeks DE, i sur. A genome-wide association study of chronic otitis media with effusion and recurrent otitis media identifies a novel susceptibility locus on chromosome 2. J Assoc Res Otolaryngol 2013;14:791-800.

568. Chimusa ER, Zaitlen N, Daya M, i sur. Genome-wide association study of ancestry-specific TB risk in the South African Coloured population. Human Molecular Genetics 2014;23:796-809.

569. Chen Y, Zhou J, Cheng ZS, i sur. Functional variants regulating LGALS1 (Galectin 1) expression affect human susceptibility to influenza A(H7N9). Sci Rep 2015;5.

570. Curtis J, Luo Y, Zenner HL, i sur. Susceptibility to tuberculosis is associated with variants in the ASAP1 gene encoding a regulator of dendritic cell migration. Nature Genetics 2015;47:523-U128.

571. Grant AV, Sabri A, Abid A, i sur. A genome-wide association study of pulmonary tuberculosis in Morocco. Human Genetics 2016;135:299-307.

572. Hayden LP, Cho MH, McDonald MN, i sur. Susceptibility to Childhood Pneumonia: A Genome-Wide Analysis. Am J Respir Cell Mol Biol 2017;56:20-8.

573. Mekonnen E, Bekele E, Stein CM. Novel polymorphisms in TICAM2 and NOD1 associated with tuberculosis progression phenotypes in Ethiopian populations. Global Health Epidemiology and Genomics 2018;3.

10 APPENDICES

Table A.1 List of appendices provided on CD as part of electronic version of this Thesis

1) **Table e-A.1** Complete list of abbreviations
2) **Table e-A.2** List of 1,294 articles that were read in full and assessed for eligibility with reasons of exclusion
3) **Table e-A.3** Complete RISE database with 425 studies included in quantitative synthesis (in total 2,402 data points with 59 extracted and re-calculated variables)
4) **Table e-A.4** Complete meta-analyses results, allelic model, disease susceptibility
5) **Table e-A.5** Complete meta-analyses results, dominant model, disease susceptibility
6) **Table e-A.6** Complete meta-analyses results, recessive model, disease susceptibility
7) **Table e-A.7** Complete meta-analyses results, heterozygote advantage model, disease susceptibility
8) **Table e-A.8** Complete meta-analyses results, various models, subset analysis
9) **Table e-A.9** Complete meta-analyses results, various models, disease severity

Table A.2 Short summary of articles included in quantitative synthesis (Disease model and CSI abbreviations are explained in Tables 3 and 4, respectively)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0001	Bellamy	2000	Tuberculosis	African	Mixed	Adults	ACC	30	2 (3)	(120)
RISE0007	Gao et al.	2000	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(121)
RISE0017	Ryu et al.	2000	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (2)	(122)
RISE0023	Yee et al.	2000	Pneumonia	Admixed	Mixed	Adults	BBC	30	1 (1)	(123)
RISE0042	Waterer et al.	2001	Pneumonia	Admixed	Mixed	Adults	B0C	53	2 (2)	(124)
RISE0047	Choi et al.	2002	RSV	Asian	Mixed	Mixed	CCC	30	3 (10)	(125)
RISE0048	Delgado et al.	2002	Tuberculosis	Asian	Mixed	Adults	ACC	32	5 (10)	(126)
RISE0055	Lahti et al.	2002	RSV	European	Mixed	Infants	ACC	30	1 (3)	(127)
RISE0056	Li et al.	2002	Tuberculosis	African	Males	Adults	CBC	30	1 (6)	(128)
RISE0057	Liaw et al.	2002	Tuberculosis	Asian	Mixed	Adults	BBC	30	1 (5)	(129)
RISE0059	Lio et al.	2002	Tuberculosis	European	Mixed	Adults	ACC	30	1 (1)	(130)
RISE0060	Lofgren et al.	2002	RSV	European	Mixed	Infants	ABC	30	2 (6)	(131)
RISE0065	Morimoto et al.	2002	Pneumonia	Asian	Mixed	Elderly	BCC	30	2 (2)	(132)
RISE0067	Onishi et al.	2002	Influenza	Asian	Mixed	Elderly	ACA	30, 43, 54	1 (1)	(133)
RISE0069	Quasney et al.	2002	Pneumonia	Admixed	Mixed	Adults	B0C	43, 53	1 (1)	(134)
RISE0073	Selvaraj et al.	2002	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(135)
RISE0081	Akahoshi et al.	2003	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (4)	(136)
RISE0088	Gallagher et al.	2003	Pneumonia	European	Mixed	Adults, elderly	ABC	30, 43, 54	3 (3)	(137)
RISE0091	Hawn et al.	2003	Pneumonia	European	Mixed	Adults	CCC	3E	1 (3)	(138)
RISE0092	Hoebee et al.	2003	RSV	European	Mixed	Mixed, infants	CCC	30, 43	2 (3)	(139)
RISE0099	Lopez-	2003	Tuberculosis	European	Mixed	Adults	ACB	21, 30,	2 (2)	(140)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
	Maderuelo et al.							31, 32		
RISE0107	Ozbas-Gerceker et al.	2003	Tuberculosis, pneumonia	Admixed	Mixed	Mixed, adults	CAC	30	1 (1)	(141)
RISE0109	Rossouw et al.	2003	Tuberculosis	Admixed	Mixed	Adults	BBB	30	1 (1)	(142)
RISE0113	Scola et al.	2003	Tuberculosis	European	Mixed	Adults	ACC	30	2 (2)	(143)
RISE0114	Selvaraj et al.	2003	Tuberculosis	Asian	Mixed	Adults	ACC	3E	1 (3)	(144)
RISE0118	Waterer et al.	2003	Pneumonia	Admixed	Mixed	Adults	B0C	53	2 (2)	(145)
RISE0120	Yuan et al.	2003	Pneumonia	Admixed	Mixed	Adults	BBC	30	1 (1)	(146)
RISE0122	Awomoyi et al.	2004	Tuberculosis	African	Males	Adults	ACC	30	1 (5)	(147)
RISE0125	Ben-Ali et al.	2004	Tuberculosis	African	Mixed	Adults	ACC	30	1 (1)	(148)
RISE0126	Bikmaeva et al.	2004	Tuberculosis	European	Mixed	Adults	BCC	30	1 (1)	(149)
RISE0128	Chiu et al.	2004	SARS	Asian	Females	Adults	ACC	30	1 (5)	(150)
RISE0134	Fitness et al.	2004	Tuberculosis	African	Mixed	Adults	ACC	30	9 (21)	(151)
RISE0138	Gomi et al.	2004	Pneumonia	Asian	Mixed	Adults	ACC	30	1 (1)	(152)
RISE0142	Hoebee et al.	2004	RSV	European	Mixed	Mixed, infants	CAC	30, 43	3 (3)	(153)
RISE0143	Hull et al.	2004	RSV	European	Mixed	Infants	ACC	30	8 (18)	(154)
RISE0144	Itoyama et al.	2004	SARS	Asian	Mixed	Adults	BCC	30, 3E, 43	1 (1)	(155)
RISE0148	Liu et al.	2004	Tuberculosis	Asian	Males	Adults	ACB	30	2 (5)	(156)
RISE0152	Newport et al.	2004	Tuberculosis	African	Males	Adults	BCC	30	1 (1)	(157)
RISE0155	Ogus et al.	2004	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (1)	(158)
RISE0158	Pacheco et al.	2004	Tuberculosis	Admixed	Mixed	Adults	BBC	32	1 (1)	(159)
RISE0160	Quasney et al.	2004	Pneumonia	Admixed	Mixed	Adults	B0C	43, 53	1 (1)	(160)
RISE0163	Roth et al.	2004	Tuberculosis	Admixed	Mixed	Adults	BAB	31/2	1 (2)	(161)
RISE0165	Selvaraj et al.	2004	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (4)	(162)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0168	Tal et al.	2004	RSV	European	Mixed	Mixed, infants	CCC	30, 43	1 (1)	(163)
RISE0169	Tso et al.	2004	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (2)	(164)
RISE0175	Awomoyi et al.	2005	Tuberculosis	African	Mixed	Adults	ACC	30	1 (2)	(165)
RISE0179	Chan et al.	2005	SARS	Asian	Mixed	Adults	ABC	30, 43	1 (1)	(166)
RISE0180	Cipriano et al.	2005	Pneumonia	European	Mixed	Elderly	ACC	30	1 (1)	(167)
RISE0181	Correa et al.	2005	Tuberculosis	Admixed	Mixed	Adults	BCB	30	1 (2)	(168)
RISE0184	Flores-Villanueva et al.	2005	Tuberculosis	Admixed, Asian	Mixed	Adults	BCC	21, 30, 31, 31/2, 32	4 (4)	(169)
RISE0185	Gomez et al.	2005	Tuberculosis	Admixed	Mixed	Adults	BCB	31/2, 32	1 (1)	(170)
RISE0186	Hamano et al.	2005	SARS	Asian	Mixed	Adults	ACC	31, 31/2, 43	3 (5)	(171)
RISE0188	Ip et al.	2005	SARS	Asian	Mixed	Adults	CCC	30	1 (1)	(172)
RISE0189	Itoyama et al.	2005	SARS	Asian	Females, males	Adults	ACC	21, 31, 31/2, 32	1 (3)	(173)
RISE0192	Korytina et al.	2005	Pneumonia	European	Mixed	Children	ACC	30	4 (5)	(174)
RISE0197	Schaaf et al.	2005	Pneumonia	European	Mixed	Adults	ACC	30	1 (1)	(175)
RISE0199	Shin et al.	2005	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (3)	(176)
RISE0206	Yuan et al.	2005	SARS	Asian	Mixed	Adults	ACC	30, 43, 54	2 (3)	(177)
RISE0207	Zhang et al.	2005	Tuberculosis	Asian	Mixed	Adults	ACC	30, 43	1 (2)	(178)
RISE0208	Zhang et al.	2005	SARS	Asian	Mixed	Adults	BCC	30, 43	1 (3)	(179)
RISE0210	Amirzargar et al.	2006	Tuberculosis	Asian	Mixed	Adults	ACC	30	12 (21)	(180)
RISE0213	Barreiro et al.	2006	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (8)	(181)
RISE0220	Chapman et al.	2006	Pneumonia	European	Mixed	Mixed	CCC	30	1 (1)	(182)
RISE0223	Chen et al.	2006	SARS	Asian	Mixed	Adults	AAC	30	4 (4)	(183)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0225	Chong et al.	2006	SARS	Asian	Mixed	Adults	CCC	30, 53	3 (4)	(184)
RISE0230	Druszczynska et al.	2006	Tuberculosis	European	Mixed	Adults	ACC	30	2 (2)	(185)
RISE0233	Etokebe et al.	2006	Tuberculosis	European	Mixed, males	Adults	ACC	30, 43	1 (2)	(186)
RISE0239	Gomez et al.	2006	Tuberculosis	Admixed	Mixed	Adults	BCB	30	2 (3)	(187)
RISE0240	Hawn et al.	2006	Tuberculosis	Asian	Mixed	Mixed	CCC	30	1 (4)	(188)
RISE0241	He et al.	2006	SARS	Asian	Mixed	Adults	ACC	31	2 (2)	(189)
RISE0242	Henao et al.	2006	Tuberculosis	Admixed	Mixed	Adults	BCC	21, 31/2, 32	5 (8)	(190)
RISE0243	Hsu et al.	2006	Tuberculosis	Asian	Mixed	Adults	BCB	30	1 (3)	(191)
RISE0247	Krueger et al.	2006	RSV	European	Mixed	Mixed	CCC	30	3 (5)	(192)
RISE0252	Liu et al.	2006	Tuberculosis	Asian	Males	Adults	ACC	30	1 (4)	(193)
RISE0263	Ozturk et al.	2006	Pneumonia	Admixed	Mixed	Children	BCC	30	2 (2)	(194)
RISE0267	Puthothu et al.	2006	RSV	European	Mixed	Mixed	CCC	30	2 (4)	(195)
RISE0268	Puthothu et al.	2006	RSV	European	Mixed	Mixed	CCC	30	2 (3)	(196)
RISE0269	Puthothu et al.	2006	RSV	European	Mixed	Mixed	CCC	30	2 (4)	(197)
RISE0270	Puthothu et al.	2006	RSV	European	Mixed	Mixed	CCC	30	1 (2)	(198)
RISE0280	Selvaraj et al.	2006	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (1)	(199)
RISE0283	Taype et al.	2006	Tuberculosis	Admixed	Males	Adults	BCC	30	1 (3)	(200)
RISE0284	Thye et al.	2006	Tuberculosis	African	Mixed	Adults	BCB	31/2	1 (6)	(201)
RISE0290	Vaid et al.	2006	Tuberculosis	Asian	Mixed	Adults	ACC	31	3 (4)	(202)
RISE0291	Vidyarani et al.	2006	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (2)	(203)
RISE0298	Alagarasu et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(204)
RISE0300	Awomoyi et al.	2007	RSV	Admixed	Mixed	Mixed	CCC	30	1 (2)	(205)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0302	Babb et al.	2007	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (7)	(206)
RISE0303	Babb et al.	2007	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (3)	(207)
RISE0305	Ben-Ali et al.	2007	Tuberculosis	African	Mixed	Adults	ACC	30	1 (4)	(208)
RISE0308	Chan et al.	2007	SARS	Asian	Mixed	Adults	CCB	31, 43	2 (6)	(209)
RISE0311	Chu et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACC	30	3 (5)	(210)
RISE0314	Emonts et al.	2007	Pneumonia	European	Mixed	Mixed, children	CCC	30, 43	1 (1)	(211)
RISE0317	Fernando et al.	2007	Tuberculosis	Admixed	Mixed	Adults	BCC	32	1 (1)	(212)
RISE0321	Gomez et al.	2007	Tuberculosis	Admixed	Mixed	Adults	BCB	31/2	1 (1)	(213)
RISE0324	Harishankar et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (2)	(214)
RISE0327	Hwang et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (5)	(215)
RISE0328	Inoue et al.	2007	RSV	Asian	Mixed	Children	BBC	30	2 (4)	(216)
RISE0329	Janssen et al.	2007	RSV	European	Mixed	Mixed	CCC	30	50 (68)	(217)
RISE0335	Kusuhara et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACC	30, 43	1 (4)	(218)
RISE0337	Lee et al.	2007	Pneumonia	Asian	Mixed	Adults	ACC	30	1 (1)	(219)
RISE0338	Leung et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (3)	(220)
RISE0342	Mak et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (2)	(221)
RISE0344	Moller et al.	2007	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (3)	(222)
RISE0345	Moller et al.	2007	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (18)	(223)
RISE0347	Moran et al.	2007	Tuberculosis	Admixed, African, European	Mixed	Adults	BCC	30	1 (1)	(224)
RISE0348	Ng et al.	2007	SARS	Asian	Mixed	Adults	CCC	30, 43, 53	3 (6)	(225)
RISE0349	Nino-Moreno et al.	2007	Tuberculosis	Admixed	Mixed	Adults	BCC	30	2 (4)	(226)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0351	Oh et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACB	30, 33	2 (2)	(227)
RISE0353	Paulus et al.	2007	RSV	Admixed	Mixed	Children	BBC	30, 43	1 (1)	(228)
RISE0356	Prabhu Anand et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (2)	(229)
RISE0358	Puthothu et al.	2007	RSV	European	Mixed	Mixed	CCC	30	1 (3)	(230)
RISE0361	Rosas-Taraco et al.	2007	Tuberculosis	Admixed	Mixed	Adults	CCB	31/2, 32	2 (2)	(231)
RISE0362	Sahiratmadja et al.	2007	Tuberculosis	Asian	Mixed	Adults	BCC	30	2 (7)	(232)
RISE0363	Sahiratmadja et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (3)	(233)
RISE0366	Sallakci et al.	2007	Tuberculosis	Admixed	Mixed	Mixed	CCC	30	1 (1)	(234)
RISE0368	Soborg et al.	2007	Tuberculosis	African	Mixed	Adults	ABC	30	1 (3)	(235)
RISE0370	Szeszko et al.	2007	Tuberculosis	European	Mixed	Adults	BCC	30	1 (29)	(236)
RISE0373	Thuong et al.	2007	Tuberculosis	Asian	Mixed	Adults	CBC	30	1 (3)	(237)
RISE0377	Vejbaesya et al.	2007	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (5)	(238)
RISE0379	Wilbur et al.	2007	Tuberculosis	South_American	Mixed	Adults	BCC	21, 31	1 (2)	(239)
RISE0380	Yende et al.	2007	Pneumonia	African, European	Mixed	Elderly	BCC	30	2 (7)	(240)
RISE0381	Yuan et al.	2007	SARS	Asian	Mixed	Adults	ACC	30, 43	1 (1)	(241)
RISE0384	Amanatidou et al.	2008	RSV	European	Mixed	Mixed	CCC	30	1 (3)	(242)
RISE0387	Asai et al.	2008	Tuberculosis	Asian	Mixed	Adults	ACC	32	1 (3)	(243)
RISE0393	Castiblanco et al.	2008	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (1)	(244)
RISE0397	Cosar et al.	2008	Tuberculosis	Admixed	Mixed	Children	BBC	30	1 (1)	(245)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0399	Ding et al.	2008	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(246)
RISE0402	Farnia et al.	2008	Tuberculosis	Asian	Mixed	Adults	ACC	31/2	1 (3)	(247)
RISE0403	Garcia-Laorden et al.	2008	Pneumonia	European	Mixed	Adults, elderly	BCC	30	2 (2)	(248)
RISE0406	Helminen et al.	2008	RSV	European	Mixed	Mixed	CCB	30	4 (4)	(249)
RISE0408	Herb et al.	2008	Tuberculosis	African	Mixed	Adults	BCC	30	1 (1)	(250)
RISE0413	Kumar et al.	2008	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (1)	(251)
RISE0418	Li et al.	2008	SARS	Asian	Mixed	Adults	CCC	30, 43	4 (23)	(252)
RISE0423	Mailaparambil et al.	2008	RSV	European	Mixed	Mixed	CCC	30	7 (18)	(253)
RISE0427	Mokrousov et al.	2008	Tuberculosis	European	Mixed	Adults	ACC	30	1 (2)	(254)
RISE0429	Nejentsev et al.	2008	Tuberculosis	Asian, African, European	Mixed	Adults	BCB	30	1 (1)	(255)
RISE0438	Roth et al.	2008	Pneumonia	Admixed	Mixed	Children	BCB	30	1 (2)	(256)
RISE0443	Selvaraj et al.	2008	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (6)	(257)
RISE0444	Selvaraj et al.	2008	Tuberculosis	Asian	Mixed	Adults	ACC	30	5 (8)	(258)
RISE0446	Selvaraj et al.	2008	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (2)	(259)
RISE0449	Shin et al.	2008	Tuberculosis	Asian	Males	Adults	ABC	30	1 (1)	(260)
RISE0456	Tang et al.	2008	SARS	Asian	Mixed	Adults	BCB	31	1 (4)	(261)
RISE0458	Thuong et al.	2008	Tuberculosis	Asian	Mixed	Mixed	CCC	30	1 (9)	(262)
RISE0461	van de Garde et al.	2008	Pneumonia	European	Mixed	Adults	BCB	30, 43, 53	1 (1)	(263)
RISE0464	Wang et al.	2008	SARS	Asian	Mixed	Adults	CCC	31, 43	1 (8)	(264)
RISE0468	Yuan et al.	2008	Pneumonia	Admixed	Mixed	Mixed	CCC	30	4 (5)	(265)
RISE0472	Alagarasu et al.	2009	Tuberculosis	Asian	Mixed	Adults	ACC	30	3 (3)	(266)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0473	Alagarasu et al.	2009	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (6)	(267)
RISE0476	Ansari et al.	2009	Tuberculosis	Asian	Mixed	Mixed, adults	CCB	31/2, 43	2 (2)	(268)
RISE0488	Chen et al.	2009	Pneumonia	Asian	Mixed	Children	ACC	30	1 (4)	(269)
RISE0494	Endeman et al.	2009	Pneumonia	European	Mixed	Adults	ACC	30, 43, 53	1 (1)	(270)
RISE0495	Forton et al.	2009	RSV	European	Mixed	Infants	ABC	30	5 (13)	(271)
RISE0498	Intemann et al.	2009	Tuberculosis	African	Mixed	Adults	BCC	31/2	1 (6)	(272)
RISE0505	Lamsyah et al.	2009	Tuberculosis	African	Mixed	Adults	ACC	30	1 (2)	(273)
RISE0508	Lee et al.	2009	Tuberculosis	Asian	Mixed	Adults	BCB	30	1 (1)	(274)
RISE0511	Merza et al.	2009	Tuberculosis	Asian	Mixed	Adults	ACC	31	3 (10)	(275)
RISE0513	Moller et al.	2009	Tuberculosis	Admixed	Mixed	Adults	BCC	30	2 (10)	(276)
RISE0514	Naslednikova et al.	2009	Tuberculosis	European	Mixed	Adults	ACC	30	4 (4)	(277)
RISE0517	Payton et al.	2009	Pneumonia	African	Mixed	Children	ACB	50	1 (10)	(278)
RISE0518	Puthothu et al.	2009	RSV	European	Mixed	Mixed	CCC	30	2 (4)	(279)
RISE0522	Sadki et al.	2009	Tuberculosis	African	Mixed	Adults	ACC	30	1 (1)	(280)
RISE0523	Sanchez-Castanon et al.	2009	Tuberculosis	European	Mixed	Adults	ACC	30	1 (2)	(281)
RISE0524	Sapru et al.	2009	Pneumonia	Admixed	Mixed	Adults	B0B	54	1 (1)	(282)
RISE0525	Selvaraj et al.	2009	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (4)	(283)
RISE0531	Tang et al.	2009	Tuberculosis	Asian	Mixed	Mixed	CBC	30	1 (3)	(284)
RISE0533	Thye et al.	2009	Tuberculosis	African, European	Mixed	Adults	BCC	30	1 (9)	(285)
RISE0534	Thye et al.	2009	Tuberculosis	African	Mixed	Adults	BCC	21, 31, 31/2, 32	1 (4)	(286)
RISE0535	Thye et al.	2009	Tuberculosis	African	Mixed	Adults	BCC	31/2	1 (7)	(287)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0536	Tian et al.	2009	RSV	Asian	Mixed	Infants	ABC	30	1 (1)	(288)
RISE0537	Trajkov et al.	2009	Tuberculosis	European	Mixed	Adults	ACC	30	13 (22)	(289)
RISE0543	Vidyarani et al.	2009	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (4)	(290)
RISE0545	Vollstedt et al.	2009	Tuberculosis	Asian	Mixed	Adults	BCC	30	1 (17)	(291)
RISE0546	Wang et al.	2009	SARS	Asian	Mixed	Adults	ACB	30	1 (4)	(292)
RISE0547	Xiao et al.	2009	Tuberculosis	Asian	Mixed	Children	ACC	30	1 (2)	(293)
RISE0550	Yende et al.	2009	Pneumonia	European	Mixed	Elderly	ACC	30	1 (1)	(294)
RISE0555	Anggraini	2010	Tuberculosis	Asian	Mixed	Adults	ACC	32	1 (4)	(295)
RISE0556	Banoei et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(296)
RISE0561	Chan et al.	2010	SARS	Asian	Mixed	Adults	A0B	43	1 (1)	(297)
RISE0563	Chapman et al.	2010	Pneumonia	European	Mixed	Mixed	CBC	30	1 (2)	(298)
RISE0565	Che et al.	2010	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (3)	(299)
RISE0566	Chen et al.	2010	Pneumonia	Asian	Mixed	Children	BCC	30, 43	1 (1)	(300)
RISE0568	Ching et al.	2010	SARS	Asian	Mixed	Adults	ACB	30	1 (2)	(301)
RISE0578	Ganachari et al.	2010	Tuberculosis	Admixed	Mixed	Adults	BCB	32	2 (2)	(302)
RISE0580	Garcia-Elorriaga et al.	2010	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (1)	(303)
RISE0584	Hatta et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(304)
RISE0596	Lian et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (6)	(305)
RISE0597	Lofgren et al.	2010	RSV	European	Mixed	Infants	ACC	30	1 (1)	(306)
RISE0598	Lu et al.	2010	RSV	Asian	Mixed	Infants	A0C	30	1 (1)	(307)
RISE0600	Ma et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACB	30, 43	4 (5)	(308)
RISE0601	Madach et al.	2010	Pneumonia	European	Mixed	Adults	C0C	43, 54	1 (1)	(309)
RISE0602	Marashian et al.	2010	Tuberculosis	Asian	Mixed	Adults	A0C	30	1 (4)	(310)
RISE0606	Moller et al.	2010	Tuberculosis	Admixed,	Mixed,	Mixed,	CCB	30, 3E	1 (4)	(311)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
				African	females	adults				
RISE0607	Moller et al.	2010	Tuberculosis	Admixed	Mixed	Adults	BCC	30	8 (53)	(312)
RISE0608	Mosaad et al.	2010	Tuberculosis	African	Mixed	Children	ACB	30	2 (2)	(313)
RISE0611	Najmi et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACB	30, 43	1 (2)	(314)
RISE0616	Prabhu Anand et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(315)
RISE0618	Russell et al.	2010	Pneumonia	African, European	Mixed	Children, adults	B0B	43	1 (8)	(316)
RISE0619	Sadki et al.	2010	Tuberculosis	African	Mixed	Adults	ACC	30	3 (3)	(317)
RISE0622	Sambasivan et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(318)
RISE0624	Selvaraj et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACC	30	7 (8)	(319)
RISE0625	Sharma et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(320)
RISE0628	Sole-Violan et al.	2010	Pneumonia	European	Mixed	Adults	BCB	30, 43, 53	4 (5)	(321)
RISE0631	Taype et al.	2010	Tuberculosis	Admixed	Males	Adults	BCC	30	7 (8)	(322)
RISE0637	Vallinoto et al.	2010	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (1)	(323)
RISE0639	Wang et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACB	30	3 (3)	(324)
RISE0640	Wang et al.	2010	Tuberculosis	Asian	Mixed	Adults	ABB	30	3 (4)	(325)
RISE0642	Wang et al.	2010	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (2)	(326)
RISE0647	Xue et al.	2010	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (4)	(327)
RISE0652	Zembrzuski et al.	2010	Tuberculosis	South_American	Mixed	Mixed	CCC	21	15 (19)	(328)
RISE0654	Abhimanyu et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (13)	(329)
RISE0655	Abhimanyu et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	6 (12)	(330)
RISE0656	Adams et al.	2011	Tuberculosis	Admixed	Mixed	Adults	BCB	31/2	2 (11)	(331)
RISE0657	Afzal et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(332)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0660	Akgunes et al.	2011	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (3)	(333)
RISE0661	Ampuero et al.	2011	RSV	Admixed	Mixed	Mixed, infants	CCC	30, 43	3 (12)	(334)
RISE0663	Anoosheh et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (5)	(335)
RISE0664	Ansari et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACB	31/2, 43	4 (4)	(336)
RISE0668	Aydin et al.	2011	Pneumonia	Admixed	Mixed	Children	BCC	30	1 (3)	(337)
RISE0671	Ben-Selma et al.	2011	Tuberculosis	African	Mixed	Adults	ACC	30	1 (1)	(338)
RISE0673	Ben-Selma et al.	2011	Tuberculosis	African	Mixed	Adults	ACC	30	1 (1)	(339)
RISE0674	Ben-Selma et al.	2011	Tuberculosis	African	Mixed	Adults	ACC	30	2 (4)	(340)
RISE0675	Ben-Selma et al.	2011	Tuberculosis	African	Mixed	Adults	ACC	30	1 (2)	(341)
RISE0676	Ben-Selma et al.	2011	Tuberculosis	African	Mixed	Adults	ACC	30	1 (2)	(342)
RISE0685	Curtis et al.	2011	Tuberculosis	European	Mixed	Adults	ACC	30	1 (6)	(343)
RISE0686	Dai et al.	2011	Tuberculosis	Asian	Mixed	Adults	ABB	30	1 (6)	(344)
RISE0687	Dalgic et al.	2011	Tuberculosis	Admixed	Mixed	Children	BCC	32	1 (1)	(345)
RISE0688	Dalgic et al.	2011	Tuberculosis	Admixed	Mixed	Children	BCC	30	1 (2)	(346)
RISE0689	de Wit et al.	2011	Tuberculosis	Admixed	Mixed	Adults	BCC	3E	6 (6)	(347)
RISE0695	Endeman et al.	2011	Pneumonia	European	Mixed	Adults	ACC	30	6 (9)	(348)
RISE0697	Feng et al.	2011	Tuberculosis	Asian	Mixed	Children	ABC	30	1 (1)	(349)
RISE0702	Garcia-Laorden et al.	2011	Pneumonia	European	Mixed	Adults	BCC	30	3 (7)	(350)
RISE0705	Han et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(351)
RISE0706	Hashemi et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(352)
RISE0707	Hashimoto et al.	2011	RSV	Asian	Mixed	Mixed	CCC	30	1 (1)	(353)
RISE0708	Hattori et al.	2011	RSV	Asian	Mixed	Children	BBC	30	1 (3)	(354)
RISE0711	Hussain et al.	2011	Tuberculosis	Asian	Mixed	Adults	A0C	21	1 (1)	(86)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0712	Intemann et al.	2011	Tuberculosis	African	Mixed	Adults	BCC	31/2	1 (7)	(355)
RISE0715	Kang et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(356)
RISE0718	Kobayashi et al.	2011	Tuberculosis	Asian	Mixed	Adults	BCC	30	1 (9)	(357)
RISE0719	Kresfelder et al.	2011	RSV	African	Mixed	Infants	ABC	30	3 (4)	(358)
RISE0722	Li et al.	2011	Tuberculosis	Asian	Mixed	Adults	ABC	30	2 (2)	(359)
RISE0725	Liang et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (6)	(360)
RISE0726	Liang et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(361)
RISE0730	Ma et al.	2011	Tuberculosis	Asian	Mixed	Adults	ABB	30	1 (17)	(362)
RISE0740	Naderi et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(363)
RISE0742	Noumsi et al.	2011	Tuberculosis	African	Mixed	Adults	ACC	30	1 (2)	(364)
RISE0757	Selvaraj et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(365)
RISE0761	Singh et al.	2011	Tuberculosis	Asian	Mixed	Adults	ACC	30, 43	2 (8)	(366)
RISE0762	Sole-Violan et al.	2011	Pneumonia	European	Mixed	Adults	BCB	30	1 (1)	(367)
RISE0763	Solgun et al.	2011	Tuberculosis	Admixed	Mixed	Children	BCC	30	2 (4)	(368)
RISE0764	Stagas et al.	2011	Tuberculosis	European	Mixed	Adults	ABC	32	1 (3)	(369)
RISE0768	Thye et al.	2011	Tuberculosis	African	Mixed	Adults	BCC	30	1 (4)	(370)
RISE0770	Uciechowski et al.	2011	Tuberculosis	African, European	Mixed	Adults	ACC	30, 31/2	1 (2)	(371)
RISE0780	Zheng et al.	2011	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (2)	(372)
RISE0781	Zhu et al.	2011	SARS	Asian	Mixed	Adults	ACC	30	2 (10)	(373)
RISE0784	Alavi-Naini et al.	2012	Tuberculosis	Asian	Mixed	Adults	BBB	30	1 (1)	(374)
RISE0785	Antonopoulou et al.	2012	Influenza	European	Mixed	Adults	ACC	30, 43	1 (3)	(375)
RISE0787	Arji et al.	2012	Tuberculosis	African	Mixed	Adults	BCC	30	2 (2)	(376)
RISE0790	Bahari et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(377)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0791	Baker et al.	2012	Tuberculosis	African	Mixed	Adults	ACB	30	1 (24)	(378)
RISE0792	Ben-Selma and Boukadida	2012	Tuberculosis	African	Mixed	Adults	ACC	30, 43	1 (1)	(379)
RISE0793	Ben-Selma et al.	2012	Tuberculosis	African	Mixed	Adults	ACC	30	1 (1)	(380)
RISE0794	Ben-Selma et al.	2012	Tuberculosis	African	Mixed, females, males	Adults	BBC	30	1 (2)	(381)
RISE0799	Carroll et al.	2012	Pneumonia	Admixed	Mixed	Children	BBC	30	4 (6)	(382)
RISE0810	Esposito et al.	2012	Influenza	European	Mixed	Children	ABB	30, 43	3 (5)	(383)
RISE0812	Everitt et al.	2012	Influenza	European	Mixed	Adults	ACC	30	1 (1)	(384)
RISE0813	Faber et al.	2012	RSV	European	Mixed	Infants, children	BAC	30, 43	1 (3)	(385)
RISE0817	Gurbuzler et al.	2012	Pneumonia	Admixed	Mixed	Children	BCC	30	2 (2)	(386)
RISE0822	Hijikata et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	9 (32)	(387)
RISE0825	Horne et al.	2012	Tuberculosis	Asian	Mixed	Mixed	CBC	30	1 (3)	(388)
RISE0831	Kobayashi et al.	2012	Tuberculosis	Asian	Mixed	Adults	BCC	30	1 (1)	(389)
RISE0834	Kouhpayeh et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(390)
RISE0839	Li et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(391)
RISE0842	Liu et al.	2012	Pneumonia	Asian	Mixed	Adults	BCC	30	1 (2)	(392)
RISE0847	Martin-Loeches et al.	2012	Pneumonia	European	Mixed	Adults	CCC	30, 43, 53	1 (3)	(393)
RISE0850	Mishra et al.	2012	Tuberculosis	Asian	Mixed, females, males	Adults	ACC	30	4 (6)	(394)
RISE0851	Morales-Garcia et al.	2012	Influenza	Admixed	Mixed	Adults	BCC	31/2	6 (8)	(395)
RISE0855	Nuolivirta et al.	2012	RSV	European	Mixed	Infants	A0A	43	1 (1)	(396)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0858	Ogarkov et al.	2012	Tuberculosis	European	Mixed	Adults	ACC	30, 53	1 (1)	(397)
RISE0859	Overodder and Naver	2012	RSV	Admixed	Mixed	Children	BCC	30	1 (1)	(398)
RISE0861	Pakasi et al.	2012	Tuberculosis	Asian	Mixed	Adults	AAC	30	1 (1)	(399)
RISE0862	Pan et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (4)	(400)
RISE0864	Png et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (15)	(401)
RISE0871	Rathored et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(402)
RISE0875	Sanchez et al.	2012	Tuberculosis	Admixed	Mixed	Adults	BCC	30	5 (16)	(403)
RISE0878	Schuurhof et al.	2012	RSV	European	Mixed, females, males	Mixed, infants	CAC	30, 43	2 (3)	(404)
RISE0880	Selvaraj et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (4)	(405)
RISE0881	Shah et al.	2012	Tuberculosis	Asian	Mixed	Mixed	CCC	30	1 (2)	(406)
RISE0884	Singh et al.	2012	Tuberculosis	Asian	Mixed	Adults	CCB	30	1 (3)	(407)
RISE0885	Singla et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(408)
RISE0886	Singla et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (2)	(409)
RISE0887	Songane et al.	2012	Tuberculosis	Asian	Mixed	Adults	BCB	30	12 (16)	(410)
RISE0888	Souza et al.	2012	Tuberculosis	Admixed	Mixed	Adults	BBC	30	1 (1)	(411)
RISE0890	Taheri et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(412)
RISE0893	Thuong et al.	2012	Tuberculosis	Asian	Mixed	Mixed	CCC	30	1 (13)	(413)
RISE0895	Velez Edwards et al.	2012	Tuberculosis	African, European	Mixed	Adults	BCC	30, 3E	1 (8)	(414)
RISE0896	Verma et al.	2012	Tuberculosis	Asian	Mixed	Adults	CCC	30	1 (1)	(415)
RISE0898	Wang et al.	2012	Tuberculosis	Asian	Mixed	Adults	BCB	30	4 (4)	(416)
RISE0899	Wang et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(417)
RISE0904	Xue et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (8)	(418)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0905	Zaki et al.	2012	Tuberculosis	African	Mixed	Adults	ACB	30	1 (10)	(419)
RISE0908	Zhang et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (11)	(420)
RISE0911	Zhang et al.	2012	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (6)	(421)
RISE0912	Zhao et al.	2012	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(422)
RISE0914	Zhou et al.	2012	Influenza	Asian	Mixed	Adults	C0C	43	1 (1)	(423)
RISE0916	Zuniga et al.	2012	Influenza	Admixed	Mixed	Adults	BCB	41/2	4 (4)	(424)
RISE0917	Abhimanyu et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACB	30	2 (2)	(425)
RISE0919	Alexandra et al.	2013	Tuberculosis	European	Mixed, females, males	Adults	ACC	30	1 (2)	(426)
RISE0920	Ali et al.	2013	RSV	Admixed	Mixed	Infants	BBC	30	1 (2)	(427)
RISE0930	Bahari et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (2)	(428)
RISE0932	Boechat et al.	2013	Tuberculosis	Admixed	Mixed	Adults	BAC	30	1 (1)	(429)
RISE0935	Bowdish et al.	2013	Tuberculosis	African	Mixed	Adults	CBC	30	1 (1)	(430)
RISE0937	Cai et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACB	30	3 (19)	(431)
RISE0938	Capparelli et al.	2013	Tuberculosis	European	Mixed	Adults	ACC	31	2 (2)	(432)
RISE0947	da Cruz et al.	2013	Tuberculosis	Admixed	Mixed	Adults	BCC	31	1 (4)	(433)
RISE0951	Garcia-Elorriaga et al.	2013	Tuberculosis	Admixed	Mixed	Adults	BCB	30, 32, 33	1 (2)	(434)
RISE0957	Hashemi et al.	2013	Tuberculosis	Asian	Mixed	Adults	BCB	30	2 (2)	(435)
RISE0963	Jahantigh et al.	2013	Tuberculosis	Asian	Mixed	Adults	BCC	30	2 (3)	(436)
RISE0964	Ji et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (2)	(437)
RISE0967	Kortyna et al.	2013	Pneumonia	European	Mixed	Children	ACC	30	8 (10)	(438)
RISE0969	Leandro et al.	2013	Tuberculosis	Admixed	Mixed	Adults	BCC	31/2, 32	2 (2)	(439)
RISE0970	Lee et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (6)	(440)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE0977	Liu et al.	2013	Influenza	Asian	Mixed	Adults	ACC	30	2 (5)	(441)
RISE0979	Lopes et al.	2013	Tuberculosis	Admixed	Mixed	Adults	BCC	32	1 (7)	(442)
RISE0981	Martinez-Ocana et al.	2013	Influenza	Admixed	Mixed	Adults	BCC	30	3 (6)	(443)
RISE0984	Meenakshi et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACC	31/2	2 (2)	(444)
RISE0985	Metanat et al.	2013	Tuberculosis	Asian	Mixed	Adults	BCC	30	2 (5)	(445)
RISE0986	Mhmoud et al.	2013	Tuberculosis	African	Mixed	Adults	ACC	30	2 (5)	(446)
RISE0987	Misch et al.	2013	Pneumonia	European	Mixed	Adults	BCB	21, 3E, 32, 43	3 (14)	(447)
RISE0990	Naderi et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (2)	(448)
RISE0993	Nuolivirta et al.	2013	Pneumonia	European	Mixed	Infants	ACC	30	3 (3)	(449)
RISE0994	Ocejo-Vinyals et al.	2013	Tuberculosis	European	Mixed	Adults	ACB	30	1 (1)	(450)
RISE0998	Peng et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (3)	(451)
RISE1005	Salnikova et al.	2013	Pneumonia	European	Mixed	Adults	CCB	30, 43	12 (14)	(452)
RISE1007	Salnikova et al.	2013	Pneumonia	European	Mixed	Adults	BCB	30	3 (3)	(453)
RISE1008	Sanchez et al.	2013	Tuberculosis	Admixed	Mixed	Adults	BCB	3E	1 (1)	(454)
RISE1014	Song et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACB	30	4 (4)	(455)
RISE1017	Taheri et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(456)
RISE1019	Tapia et al.	2013	RSV	Admixed	Mixed	Infants	B0C	43	3 (6)	(457)
RISE1027	Velayati et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACC	32	2 (6)	(458)
RISE1028	Wang et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (2)	(459)
RISE1032	Wu et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACB	30	2 (3)	(460)
RISE1034	Yang et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACB	31/2, 32	25 (30)	(461)
RISE1036	Zhang et al.	2013	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (6)	(462)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE1038	Zhang et al.	2013	Influenza	Asian	Mixed	Adults	CCC	30, 43	1 (1)	(463)
RISE1044	Arji et al.	2014	Tuberculosis	African	Mixed	Adults	BCB	30	3 (8)	(464)
RISE1046	Carpenter et al.	2014	Tuberculosis	Admixed	Mixed	Adults	BAC	30	1 (1)	(465)
RISE1047	Chen et al.	2014	Pneumonia	African	Mixed	Mixed	CCC	30, 43, 53	1 (1)	(466)
RISE1049	Ciencewicki et al.	2014	RSV	Admixed	Mixed	Infants	B0B	43	1 (1)	(467)
RISE1050	da Silva et al.	2014	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (4)	(468)
RISE1053	Drysdale et al.	2014	RSV	Admixed	Mixed	Infants	B0C	30, 43	10 (11)	(469)
RISE1056	Etokebe et al.	2014	Tuberculosis	European	Mixed	Adults	ACC	30	1 (1)	(470)
RISE1057	Feng et al.	2014	Tuberculosis	Asian	Mixed	Adults	ABB	30, 43	1 (2)	(471)
RISE1059	Goutaki et al.	2014	RSV	European	Mixed	Children	BCC	30	2 (4)	(472)
RISE1062	Herrera-Ramos et al.	2014	Influenza	European	Mixed	Adults	ACC	30	3 (15)	(473)
RISE1063	Hu et al.	2014	Tuberculosis	Asian	Mixed	Adults	ACB	30	3 (3)	(474)
RISE1067	Joshi et al.	2014	Tuberculosis	Asian	Mixed	Adults	CCC	31/2	1 (2)	(475)
RISE1069	Khan et al.	2014	Tuberculosis	Asian	Mixed	Mixed	CCC	30	1 (1)	(476)
RISE1074	Lopez Campos et al.	2014	Tuberculosis	Admixed	Mixed	Adults	BCC	30	2 (2)	(477)
RISE1075	Lu et al.	2014	Tuberculosis	Asian	Mixed	Adults	ACC	30	2 (6)	(478)
RISE1078	Mahmoud et al.	2014	Tuberculosis	African	Mixed	Adults	ACC	30	1 (1)	(479)
RISE1079	Marr et al.	2014	RSV	Admixed	Mixed	Infants, children	BCC	30, 43	5 (8)	(480)
RISE1082	Mills et al.	2014	Influenza	European	Mixed	Adults	BBC	30	1 (1)	(481)
RISE1087	Naderi et al.	2014	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(482)
RISE1090	Park et al.	2014	Tuberculosis	Asian	Males	Adults	ABC	30	2 (2)	(483)
RISE1093	Qrafli et al.	2014	Tuberculosis	African	Mixed	Adults	BCC	30	1 (3)	(484)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE1094	Randolph et al.	2014	RSV	European	Mixed	Infants, children	BAC	30, 43	1 (2)	(485)
RISE1095	Rangel-Ramirez et al.	2014	RSV, influenza	Admixed	Mixed	Mixed, adults	CCC	30	1 (1)	(486)
RISE1097	Sabri et al.	2014	Tuberculosis	African	Mixed	Adults	ACB	30	1 (5)	(487)
RISE1100	Sanchez et al.	2014	Tuberculosis	Admixed	Mixed	Adults	BCC	30	28 (31)	(488)
RISE1102	Seshadri et al.	2014	Tuberculosis	Asian	Mixed	Mixed	CBC	30	1 (2)	(489)
RISE1105	Shen et al.	2014	Tuberculosis	Asian	Mixed	Children	ABC	30	1 (1)	(490)
RISE1107	Singh et al.	2014	Tuberculosis	Asian	Mixed	Adults	ACC	30	3 (5)	(491)
RISE1109	Sivangala et al.	2014	Tuberculosis	Asian	Mixed	Adults	CCC	3E, 31/2	3 (3)	(492)
RISE1113	Sulaja and Chauhan	2014	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (1)	(493)
RISE1115	To et al.	2014	Influenza	Asian	Mixed	Adults	ACC	30, 43	1 (1)	(494)
RISE1116	Varahram et al.	2014	Tuberculosis	Asian	Mixed	Adults	BCC	30	3 (5)	(495)
RISE1119	Yang et al.	2014	Tuberculosis	Asian	Mixed	Adults	ABC	3E	2 (9)	(496)
RISE1127	Zhang et al.	2014	Tuberculosis	Asian	Mixed	Adults	ABB	30	1 (1)	(497)
RISE1128	Zhao et al.	2014	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (4)	(498)
RISE1129	Zidan et al.	2014	Pneumonia	European	Mixed	Children	ACC	30, 43, 53	1 (1)	(499)
RISE1140	Campo et al.	2015	Tuberculosis	Asian	Mixed	Mixed	CBC	30	1 (3)	(500)
RISE1145	Cheng et al.	2015	Influenza	Asian	Mixed	Adults	ACC	30, 43	1 (2)	(501)
RISE1157	Jiang et al.	2015	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (6)	(502)
RISE1159	Li et al.	2015	Pneumonia	Asian	Mixed	Children	AAC	30	1 (1)	(503)
RISE1163	Liu et al.	2015	RSV	Asian	Mixed	Children	ACC	30, 43	1 (3)	(504)
RISE1164	Liu et al.	2015	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (2)	(505)
RISE1180	Trifunovic et al.	2015	Tuberculosis	European	Mixed	Adults	ACC	30	2 (4)	(506)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE1183	Wu et al.	2015	Tuberculosis	Asian	Mixed	Adults	BCC	30	1 (2)	(507)
RISE1189	Zhao et al.	2015	Tuberculosis	Asian	Mixed, females, males	Adults	BBB	30	2 (2)	(508)
RISE1192	Azab et al.	2016	Pneumonia	European	Mixed	Children	ABC	30	1 (1)	(509)
RISE1194	Chou et al.	2016	Pneumonia	Asian	Mixed	Adults	ACC	30, 43	3 (6)	(510)
RISE1196	da Silva et al.	2016	Tuberculosis	Admixed	Mixed	Adults	BCC	30	1 (3)	(511)
RISE1198	de Lima et al.	2016	Tuberculosis	Admixed	Mixed	Adults	BCC	31/2	9 (14)	(512)
RISE1200	Gaio et al.	2016	Influenza	European	Mixed	Mixed	C0C	43	1 (1)	(513)
RISE1201	Georgitsi et al.	2016	Pneumonia	European	Mixed	Adults	ACC	30	1 (1)	(514)
RISE1204	High et al.	2016	RSV	Admixed	Mixed	Infants	B0A	43	1 (1)	(515)
RISE1205	Holscher et al.	2016	Tuberculosis	African	Mixed, females	Adults	BCB	31, 43	5 (5)	(516)
RISE1208	Jafari et al.	2016	Tuberculosis	Asian	Mixed	Adults	ACC	30	6 (14)	(517)
RISE1211	Lee et al.	2016	Tuberculosis	Asian	Mixed	Adults	CCC	30	2 (7)	(518)
RISE1214	Liu et al.	2016	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (4)	(519)
RISE1215	Liu et al.	2016	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (1)	(520)
RISE1218	Lopez-Rodriguez et al.	2016	Influenza	European	Mixed	Adults	ACC	30	1 (1)	(521)
RISE1219	Lu et al.	2016	Tuberculosis	Asian	Mixed	Adults	AAC	30	1 (1)	(522)
RISE1220	Meyer et al.	2016	Tuberculosis	African	Mixed	Adults	BCB	30	4 (15)	(523)
RISE1222	Ren et al.	2016	Tuberculosis	Asian	Mixed	Adults	CBC	30	2 (7)	(524)
RISE1224	Smelaya et al.	2016	Pneumonia	European	Mixed	Adults	BCB	30	8 (11)	(525)
RISE1229	Thuong et al.	2016	Tuberculosis	Asian	Mixed	Mixed, adults	CBC	30, 43	1 (12)	(526)
RISE1236	Yuan et al.	2016	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (3)	(527)

RISE ID	Author(s)	Year	Disease	Ethnicity	Gender	Age	CSI	Disease model	Number of genes (SNPs)	Ref.
RISE1239	Zhang et al.	2016	RSV	Asian	Mixed	Infants	ABC	30	1 (2)	(528)
RISE1241	Zhu et al.	2016	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (3)	(529)
RISE1243	Abouzeid et al.	2017	Pneumonia	European	Mixed	Children	ABC	30, 43	1 (1)	(530)
RISE1245	Amiri et al.	2017	Tuberculosis	Asian	Mixed	Adults	ACB	30	1 (4)	(531)
RISE1247	Azar et al.	2017	Tuberculosis	Asian	Mixed	Adults	ACC	3E	1 (2)	(532)
RISE1256	Mao et al.	2017	Pneumonia	Asian	Mixed	Adults	ACC	30	2 (4)	(533)
RISE1257	Mehrbod et al.	2017	Influenza	Asian	Mixed	Adults	ACC	30	1 (1)	(534)
RISE1260	Qrafli et al.	2017	Tuberculosis	African	Mixed, females, males	Adults	ACC	30	1 (3)	(535)
RISE1261	Rolandelli et al.	2017	Tuberculosis	Admixed	Mixed	Adults	BCB	3E, 43	1 (1)	(536)
RISE1262	Seshadri et al.	2017	Tuberculosis	Asian	Mixed	Mixed	CBC	30	1 (1)	(537)
RISE1264	van Kempen et al.	2017	Pneumonia	European	Mixed	Adults	ACC	30	1 (2)	(538)
RISE1266	Zhao et al.	2017	Pneumonia	Asian	Mixed	Children	ACC	30	4 (4)	(539)
RISE1267	Zheng et al.	2017	Tuberculosis	Asian	Mixed	Adults	ABC	30	1 (5)	(540)
RISE1276	Garcia et al.	2018	Influenza	Admixed	Mixed	Adults	C0C	43, 53, 54	1 (3)	(541)
RISE1278	Hsieh et al.	2018	Tuberculosis	Asian	Mixed	Adults	ACC	30	1 (2)	(542)
RISE1288	Roodposhti et al.	2018	Tuberculosis	Asian	Mixed, females, males	Adults	ACC	30	1 (1)	(543)

Table A.3 Random-effects meta-analyses results, allelic model, disease susceptibility (expanded 30 disease model) [nominally significant results only, significant results for the mid/low BFDP level shown in bold]

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
Influenza											
IFITM3	rs12252	C/T	5	592	3551	-	<0.001	1.94 [1.37, 2.75]	0.352 (0.966)	43.7	CBC
Pneumonia											
FCGR2A	rs1801274	A/G	4	241	674	Admixed	0.003	0.67 [0.52, 0.87]	0.591 (0.987)	26.3	CBC
RSV											
IL4	**rs2070874**	**C/T**	**4**	**1125**	**2627**	**-**	**<0.001**	**0.69 [0.58, 0.81]**	**0.007 (0.271)**	**24.7**	**BAC**
IL4	rs2243250	C/T	7	1641	3631	-	0.002	0.77 [0.65, 0.91]	0.473 (0.979)	51.5	BCC
IL4	**rs2243250**	**C/T**	**4**	**1082**	**2729**	**European**	**<0.001**	**0.76 [0.66, 0.87]**	**0.046 (0.718)**	**0**	**BAC**
Tuberculosis											
CCL2	rs1024611	A/G	23	9166	9358	-	0.028	0.85 [0.73, 0.98]	0.860 (0.997)	88.8	BCC
CCL2	rs1024611	A/G	6	2426	2182	Admixed	0.035	0.68 [0.47, 0.97]	0.889 (0.998)	93.6	BCC
CCL2	rs2857656	C/G	4	2810	3074	African	0.001	0.87 [0.80, 0.95]	0.475 (0.979)	7.0	BAC
CCL2	rs3917891	C/T	4	2826	3080	African	0.006	1.14 [1.04, 1.25]	0.680 (0.991)	0	BAC
CCL2	rs3917891	C/T	5	3056	3222	-	0.006	1.14 [1.04, 1.25]	0.680 (0.991)	0	BAC
CCL2	rs41416652	C/T	3	1081	923	-	0.001	2.28 [1.39, 3.72]	0.729 (0.993)	0	BAC
CCL2	rs4586	C/T	4	2814	3082	African	0.013	0.90 [0.83, 0.98]	0.847 (0.997)	0	BAC
CD209	rs735239	A/G	5	1344	1460	-	0.027	1.32 [1.03, 1.69]	0.862 (0.997)	63.6	BCC
IFNG	**rs2430561**	**A/T**	**26**	**4914**	**5012**	**-**	**<0.001**	**1.31 [1.19, 1.46]**	**0.001 (0.054)**	**54.2**	**BCC**
IFNG	rs2430561	A/T	4	611	1145	African	0.022	1.23 [1.03, 1.47]	0.843 (0.996)	0	CAC
IFNG	rs2430561	A/T	6	765	987	European	0.009	1.62 [1.13, 2.31]	0.794 (0.995)	81.9	CCC
IFNG	rs2430561	A/T	7	1943	1189	Admixed	0.002	1.30 [1.10, 1.53]	0.411 (0.973)	50.2	BCC
IFNG	rs2430561	A/T	9	1595	1691	Asian	0.003	1.23 [1.07, 1.42]	0.622 (0.989)	21.4	BAC
IL10	rs1800872	A/C	6	1197.5	1179	Admixed	0.003	0.75 [0.62, 0.91]	0.580 (0.986)	39.0	BBC

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
IL1B	rs16944	C/T	7	1565	1574.5	-	0.027	0.87 [0.78, 0.98]	0.857 (0.997)	9.6	BAC
IL2	rs2069762	G/T	6	730	1026	-	0.042	1.18 [1.01, 1.39]	0.904 (0.998)	17.2	CAC
P2RX7	rs3751143	A/C	16	5037	5894	-	0.015	0.84 [0.73, 0.97]	0.823 (0.996)	68.5	-
P2RX7	rs3751143	A/C	9	3659	4429	Asian	0.032	0.81 [0.67, 0.98]	0.867 (0.997)	75.0	-
SLC11A1	rs17235409	A/G	30	4265	4421	-	0.010	1.22 [1.05, 1.41]	0.694 (0.992)	53.0	BCC
SLC11A1	rs17235409	A/G	4	587	644	African	0.025	1.43 [1.05, 1.96]	0.869 (0.997)	35.1	CBC
SLC11A1	rs17235416	+/-	15	2168	2400	Asian	0.011	0.77 [0.63, 0.94]	0.752 (0.994)	61.0	BCC
SLC11A1	rs17235416	+/-	27	4731	5304	-	0.001	0.81 [0.72, 0.92]	0.346 (0.965)	49.9	BBC
SLC11A1	rs17235416	+/-	4	1121	958	Admixed	0.019	0.81 [0.67, 0.96]	0.799 (0.995)	0	BAC
SLC11A1	rs3731865	C/G	19	2889	3336	-	0.008	1.38 [1.09, 1.75]	0.731 (0.993)	74.1	BCC
TLR2	rs3804099	C/T	8	1821	2025	-	0.030	1.11 [1.01, 1.23]	0.923 (0.998)	0	BAC
TLR2	**rs5743708**	**A/G**	**6**	**1727**	**1684**	**-**	**<0.001**	**3.21 [2.05, 5.02]**	**0.066 (0.788)**	**0**	**BAC**
TNFA	rs1800629	A/G	12	1346	1553	Asian	0.017	1.35 [1.05, 1.72]	0.808 (0.996)	35.5	BBC
VDR	rs7975232	A/C	14	1596	2059	-	0.030	1.15 [1.01, 1.31]	0.893 (0.998)	31.6	BBC
Pooled diseases											
CCL2	rs1024611	A/G	24	9573	10366	-	0.027	0.86 [0.74, 0.98]	0.859 (0.997)	88.4	BCC
CCL2	rs1024611	A/G	6	2426	2182	Admixed	0.035	0.68 [0.47, 0.97]	0.889 (0.998)	93.6	BCC
CCL2	rs2857656	C/G	4	2810	3074	African	0.001	0.87 [0.80, 0.95]	0.475 (0.979)	7	BAC
CCL2	rs3917891	C/T	5	3056	3222	-	0.006	1.14 [1.04, 1.25]	0.680 (0.991)	0	BAC
CCL2	rs3917891	C/T	4	2826	3080	African	0.006	1.14 [1.04, 1.25]	0.680 (0.991)	0	BAC
CCL2	rs41416652	C/T	3	1081	923	-	0.001	2.28 [1.39, 3.72]	0.729 (0.993)	0	BAC
CCL2	rs4586	C/T	4	2814	3082	African	0.013	0.90 [0.83, 0.98]	0.847 (0.997)	0	BAC
CD209	rs735239	A/G	5	1344	1460	-	0.027	1.32 [1.03, 1.69]	0.862 (0.997)	63.6	BCC
IFITM3	rs12252	C/T	5	592	3551	-	<0.001	1.94 [1.37, 2.75]	0.352 (0.966)	43.7	CBC
IFNG	**rs2430561**	**A/T**	**28**	**5487**	**5878**	**-**	**<0.001**	**1.34 [1.19, 1.51]**	**0.002 (0.080)**	**70.8**	**BCC**
IFNG	rs2430561	A/T	7	1943	1189	Admixed	0.002	1.30 [1.10, 1.53]	0.411 (0.973)	50.2	BCC
IFNG	rs2430561	A/T	4	611	1145	African	0.022	1.23 [1.03, 1.47]	0.843 (0.996)	0	CAC

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
IFNG	rs2430561	A/T	6	765	987	European	0.009	1.62 [1.13, 2.31]	0.794 (0.995)	81.9	CCC
IFNG	rs2430561	A/T	10	2071	2140	Asian	0.017	1.34 [1.05, 1.70]	0.812 (0.996)	78.0	BCC
IL10	rs1800872	A/C	8	1290.5	1340	Admixed	0.021	0.71 [0.54, 0.95]	0.849 (0.997)	75.4	BCC
IL1B	rs16944	C/T	9	2355	2781.5	-	0.043	0.91 [0.83, 1.00]	0.931 (0.999)	6.6	BAC
IL4	**rs2070874**	**C/T**	**7**	**1672**	**3514**	**-**	**<0.001**	**0.75 [0.65, 0.87]**	**0.087 (0.834)**	**40.0**	**BBC**
IL6	rs1800796	C/G	4	2357	1974	-	0.018	1.21 [1.03, 1.41]	0.798 (0.995)	34.0	BBC
MBL2	rs7095891	C/T	5	1680	1844	Asian	0.016	1.20 [1.03, 1.38]	0.758 (0.994)	0	BAC
P2RX7	rs3751143	A/C	16	5037	5894	-	0.015	0.84 [0.73, 0.97]	0.823 (0.996)	68.5	-
P2RX7	rs3751143	A/C	9	3659	4429	Asian	0.032	0.81 [0.67, 0.98]	0.867 (0.997)	75.0	-
SFTPA2	rs1059046	A/C	5	1227	1861	-	0.001	0.82 [0.73, 0.92]	0.260 (0.949)	0	BAC
SFTPA2	rs1965708	A/C	5	1227	1861	-	0.041	1.21 [1.01, 1.45]	0.887 (0.998)	21.4	BAC
SLC11A1	rs17235409	A/G	30	4265	4421	-	0.010	1.22 [1.05, 1.41]	0.694 (0.992)	53.0	BCC
SLC11A1	rs17235409	A/G	4	587	644	African	0.025	1.43 [1.05, 1.96]	0.869 (0.997)	35.1	CBC
SLC11A1	rs17235416	+/-	27	4731	5304	-	0.001	0.81 [0.72, 0.92]	0.346 (0.965)	49.9	BBC
SLC11A1	rs17235416	+/-	4	1121	958	Admixed	0.019	0.81 [0.67, 0.96]	0.799 (0.995)	0	BAC
SLC11A1	rs17235416	+/-	15	2168	2400	Asian	0.011	0.77 [0.63, 0.94]	0.752 (0.994)	61.0	BCC
SLC11A1	rs3731865	C/G	19	2889	3336	-	0.008	1.38 [1.09, 1.75]	0.731 (0.993)	74.1	BCC
TLR2	rs3804099	C/T	10	2062	2555	-	0.011	1.12 [1.03, 1.23]	0.854 (0.997)	0	BAC
TLR6	rs5743810	C/T	5	978	2058	-	0.040	0.86 [0.74, 0.99]	0.890 (0.998)	20.4	CAC
TLR9	rs352139	A/G	4	1394	1408	-	0.028	0.88 [0.79, 0.99]	0.894 (0.998)	0	BAC
TNFA	rs1800629	A/G	31	5583	7435	-	0.023	1.17 [1.02, 1.33]	0.821 (0.996)	45.8	BBC
TNFA	rs1800629	A/G	15	1972	2176	Asian	0.011	1.34 [1.07, 1.68]	0.770 (0.994)	39.0	BBC
TNFA	rs361525	A/G	18	3254	4943	-	0.032	1.53 [1.04, 2.26]	0.893 (0.998)	85.0	BCC
VDR	rs7975232	A/C	15	1692	2160	-	0.043	1.14 [1.00, 1.29]	0.900 (0.998)	29.9	BBC

* reference/alternate allele

Table A.4 Random-effects meta-analyses results, dominant model, disease susceptibility (expanded 30 disease model) [nominally significant results only, significant results for the mid/low BFDP level shown in bold]

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
Influenza											
IFITM3	rs12252	C/T	5	592	3551	-	0.001	3.52 [1.66, 7.46]	0.865 (0.997)	19.1	CAC
Tuberculosis											
CCL2	rs1024611	A/G	22	8935	9207	-	0.044	0.84 [0.71, 1.00]	0.905 (0.998)	82.3	-
CCL2	rs2857656	C/G	4	2810	3074	African	0.008	0.84 [0.74, 0.96]	0.760 (0.994)	0	BAC
CCL2	rs3917891	C/T	4	2826	3080	African	0.003	1.18 [1.06, 1.32]	0.593 (0.987)	0	BAC
CCL2	rs3917891	C/T	5	3056	3222	-	0.002	1.18 [1.06, 1.32]	0.593 (0.987)	0	BAC
CCL2	rs4586	C/T	4	2814	3082	African	0.018	0.88 [0.80, 0.98]	0.855 (0.997)	0	BAC
CCL2	rs4586	C/T	8	3882	4338	-	0.026	0.90 [0.82, 0.99]	0.900 (0.998)	0	BAC
CCL5	rs2107538	A/G	10	2232	2127	-	0.007	1.60 [1.14, 2.25]	0.777 (0.995)	66.3	BCC
CD209	rs735239	A/G	4	1206	1320	-	0.010	1.64 [1.13, 2.38]	0.817 (0.996)	74.2	BCC
IFNG	rs2430561	A/T	9	1595	1691	Asian	0.028	1.33 [1.03, 1.71]	0.858 (0.997)	47.6	BBC
IFNG	rs2430561	A/T	6	1803	1108	Admixed	0.035	1.36 [1.02, 1.82]	0.888 (0.998)	67.7	BCC
IFNG	**rs2430561**	**A/T**	**25**	**4774**	**4931**	**-**	**<0.001**	**1.44 [1.22, 1.69]**	**0.009 (0.329)**	**61.9**	**BCC**
IFNG	rs2430561	A/T	6	765	987	European	0.023	1.75 [1.08, 2.84]	0.896 (0.998)	77.5	CCC
MBL2	rs7095891	C/T	4	2294	3562	-	0.024	1.17 [1.02, 1.34]	0.856 (0.997)	0	BAC
P2RX7	rs3751143	A/C	9	3659	4429	Asian	0.010	0.73 [0.57, 0.93]	0.772 (0.994)	77.8	-
P2RX7	rs3751143	A/C	16	5037	5894	-	0.008	0.79 [0.66, 0.94]	0.709 (0.992)	69.8	-
PTPN22	rs2476601	C/T	4	616	639	-	0.037	2.57 [1.06, 6.23]	0.935 (0.999)	44.5	CBC
SLC11A1	rs17235409	A/G	4	587	644	African	0.024	4.00 [1.20, 13.36]	0.939 (0.999)	6.7	CAC
SLC11A1	rs17235416	+/-	15	2168	2400	Asian	0.016	0.77 [0.62, 0.95]	0.798 (0.995)	54.2	BCC
SLC11A1	rs17235416	+/-	27	4731	5304	-	0.001	0.79 [0.69, 0.91]	0.331 (0.963)	40.7	BBC

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
SLC11A1	rs17235416	+/-	4	1121	958	Admixed	0.031	0.80 [0.65, 0.98]	0.869 (0.997)	0	BAC
SLC11A1	rs3731865	C/G	12	2678	2976	-	0.003	2.50 [1.37, 4.54]	0.846 (0.997)	40.8	BBC
SLC11A1	rs3731865	C/G	6	1107	1362	Asian	0.016	4.32 [1.32, 14.21]	0.937 (0.999)	46.8	BBC
TLR2	rs3804099	C/T	8	1821	2025	-	0.001	1.38 [1.14, 1.66]	0.267 (0.950)	0	BAC
TLR2	rs3804099	C/T	6	1013	1523	Asian	0.015	1.41 [1.07, 1.87]	0.830 (0.996)	0	BAC
TLR2	rs5743708	A/G	3	1727	1684	-	0.018	3.37 [1.23, 9.28]	0.933 (0.999)	0	BAC
VDR	rs731236	T/C	22	3050	3726	-	0.034	0.81 [0.66, 0.98]	0.867 (0.997)	59.8	-
Pooled diseases											
CCL2	rs1024611	A/G	23	9342	10215	-	0.048	0.85 [0.73, 1.00]	0.907 (0.998)	81.6	-
CCL2	rs2857656	C/G	4	2810	3074	African	0.008	0.84 [0.74, 0.96]	0.760 (0.994)	0	BAC
CCL2	rs3917891	C/T	4	2826	3080	African	0.003	1.18 [1.06, 1.32]	0.593 (0.987)	0	BAC
CCL2	rs3917891	C/T	5	3056	3222	-	0.002	1.18 [1.06, 1.32]	0.593 (0.987)	0	BAC
CCL2	rs4586	C/T	4	2814	3082	African	0.018	0.88 [0.80, 0.98]	0.855 (0.997)	0	BAC
CCL2	rs4586	C/T	8	3882	4338	-	0.026	0.90 [0.82, 0.99]	0.900 (0.998)	0	BAC
CCL5	rs2107538	A/G	16	3975	4673	-	0.041	1.27 [1.01, 1.60]	0.890 (0.998)	59.0	BCC
CD209	rs735239	A/G	4	1206	1320	-	0.010	1.64 [1.13, 2.38]	0.817 (0.996)	74.2	BCC
IFITM3	rs12252	C/T	5	592	3551	-	0.001	3.52 [1.66, 7.46]	0.865 (0.997)	19.1	CAC
IFNG	rs2430561	A/T	6	1803	1108	Admixed	0.035	1.36 [1.02, 1.82]	0.888 (0.998)	67.7	BCC
IFNG	**rs2430561**	**A/T**	**27**	**5347**	**5797**	**-**	**<0.001**	**1.46 [1.23, 1.74]**	**0.025 (0.575)**	**71.8**	**BCC**
IFNG	rs2430561	A/T	6	765	987	European	0.023	1.75 [1.08, 2.84]	0.896 (0.998)	77.5	CCC
IFNG	rs2430561	A/T	10	2071	2140	Asian	0.015	1.50 [1.08, 2.08]	0.835 (0.996)	76.6	BCC
IL10	rs1800872	A/C	8	1645	2140	Asian	0.007	1.23 [1.06, 1.44]	0.747 (0.994)	8.4	BAC
IL17	rs2275913	A/G	4	1117	2443	-	0.048	1.85 [1.01, 3.40]	0.926 (0.998)	87.2	BCC
IL2	rs2069762	G/T	7	1137	2034	-	0.018	1.34 [1.05, 1.71]	0.828 (0.996)	0	BAC
IL4	rs2243250	C/T	6	869	1218	Asian	0.006	0.65 [0.48, 0.89]	0.765 (0.994)	0	CAC

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
IL6	rs1800795	C/G	3	1272	1160	Asian	0.018	1.69 [1.09, 2.63]	0.882 (0.997)	0	BAC
IL6	rs1800796	C/G	4	2357	1974	-	0.006	1.25 [1.07, 1.47]	0.690 (0.992)	13.8	BAC
MBL2	rs7095891	C/T	8	3277	5295	-	0.004	1.17 [1.05, 1.30]	0.582 (0.987)	0	BAC
MBL2	rs7095891	C/T	5	1680	1844	Asian	0.013	1.22 [1.04, 1.44]	0.825 (0.996)	0	BAC
P2RX7	rs3751143	A/C	9	3659	4429	Asian	0.010	0.73 [0.57, 0.93]	0.772 (0.994)	77.8	-
P2RX7	rs3751143	A/C	16	5037	5894	-	0.008	0.79 [0.66, 0.94]	0.709 (0.992)	69.8	-
SFTPA2	rs1059046	A/C	4	1141	1766	-	0.009	0.80 [0.68, 0.95]	0.758 (0.994)	0	BAC
SLC11A1	rs17235409	A/G	4	587	644	African	0.024	4.00 [1.20, 13.36]	0.939 (0.999)	6.7	CAC
SLC11A1	rs17235416	+/-	15	2168	2400	Asian	0.016	0.77 [0.62, 0.95]	0.798 (0.995)	54.2	BCC
SLC11A1	rs17235416	+/-	27	4731	5304	-	0.001	0.79 [0.69, 0.91]	0.331 (0.963)	40.7	BBC
SLC11A1	rs17235416	+/-	4	1121	958	Admixed	0.031	0.80 [0.65, 0.98]	0.869 (0.997)	0	BAC
SLC11A1	rs3731865	C/G	12	2678	2976	-	0.003	2.50 [1.37, 4.54]	0.846 (0.997)	40.8	BBC
SLC11A1	rs3731865	C/G	6	1107	1362	Asian	0.016	4.32 [1.32, 14.21]	0.937 (0.999)	46.8	BBC
TLR2	**rs3804099**	**C/T**	**10**	**2062**	**2555**	**-**	**<0.001**	**1.40 [1.18, 1.65]**	**0.048 (0.724)**	**0**	**BAC**
TLR2	rs3804099	C/T	6	1013	1523	Asian	0.015	1.41 [1.07, 1.87]	0.830 (0.996)	0	BAC
TLR2	rs5743708	A/G	4	3166	4112	-	0.027	2.97 [1.13, 7.79]	0.935 (0.999)	0	BAC
TLR2	rs5743708	A/G	2	845	1095	Admixed	0.029	3.30 [1.13, 9.65]	0.938 (0.999)	0	CAC
TLR9	rs352139	A/G	4	1394	1408	-	0.011	0.80 [0.67, 0.95]	0.758 (0.994)	16.8	BAC
TNFA	rs1800630	A/C	6	1068	1295	-	0.007	2.10 [1.22, 3.61]	0.867 (0.997)	0	BAC
TNFA	rs1800630	A/C	5	903	878	Asian	0.004	2.37 [1.32, 4.29]	0.863 (0.997)	0	CAC
TNFA	rs361525	A/G	10	3254	4943	-	0.025	2.12 [1.10, 4.09]	0.918 (0.998)	46.0	BBC
VDR	rs731236	T/C	25	3609	4901	-	0.026	0.83 [0.70, 0.98]	0.864 (0.997)	54.3	BCC

* reference/alternate allele

Table A.5 Random-effects meta-analyses results, recessive model, disease susceptibility (expanded 30 disease model) [nominally significant results only, significant results for the mid/low BFDP level shown in bold]

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
Influenza											
IFITM3	rs12252	C/T	5	592	3551	-	0.003	0.52 [0.33, 0.8]	0.765 (0.994)	41.7	CBC
Pneumonia											
FCGR2A	rs1801274	A/G	6	1704	2211	-	0.031	1.65 [1.05, 2.59]	0.899 (0.998)	79.4	-
FCGR2A	rs1801274	A/G	4	241	674	Admixed	<0.001	2.32 [1.48, 3.64]	0.560 (0.985)	31.9	CBC
RSV											
IL4	rs2243250	C/T	5	1114	2357	-	0.005	1.48 [1.13, 1.94]	0.678 (0.991)	19.7	BAC
Tuberculosis											
CCL2	rs1024611	A/G	22	8935	9207	-	0.021	1.32 [1.04, 1.66]	0.820 (0.996)	82.1	BCC
CCL2	rs1024611	A/G	5	2195	2031	Admixed	0.004	1.92 [1.23, 2.98]	0.787 (0.995)	88.3	BCC
CCL2	rs2857656	C/G	4	2810	3074	African	0.047	1.17 [1.00, 1.37]	0.909 (0.998)	25.6	BBC
CCL2	rs41416652	C/T	3	1081	923	-	0.004	0.45 [0.26, 0.78]	0.850 (0.997)	0	BAC
IFNG	**rs2430561**	**A/T**	**25**	**4774**	**4931**	**-**	**<0.001**	**0.71 [0.61, 0.83]**	**0.017 (0.471)**	**15.2**	**BAC**
IFNG	rs2430561	A/T	6	1803	1108	Admixed	0.002	0.68 [0.53, 0.87]	0.541 (0.984)	0	BAC
IFNG	rs2430561	A/T	6	765	987	European	0.012	0.51 [0.31, 0.86]	0.879 (0.997)	68.4	CCC
IFNG	rs2430561	A/T	9	1595	1691	Asian	0.025	0.77 [0.61, 0.97]	0.857 (0.997)	0	BAC
IL10	rs1800872	A/C	5	1057	1098	Admixed	0.014	1.41 [1.07, 1.86]	0.818 (0.996)	38.2	BBC
IL10	rs1800896	A/G	24	6536	6584	-	0.048	1.29 [1.00, 1.67]	0.903 (0.998)	55.8	-
SLC11A1	rs17235409	A/G	30	4265	4421	-	0.038	0.83 [0.69, 0.99]	0.887 (0.998)	58.4	BCC
SLC11A1	rs3731865	C/G	18	2678	2976	-	0.004	0.71 [0.56, 0.90]	0.655 (0.990)	65.5	BCC
TIRAP	rs8177374	C/T	3	1191	1475	Asian	0.030	2.86 [1.11, 7.42]	0.935 (0.999)	0	BAC
TLR2	rs5743708	A/G	4	1727	1684	-	<0.001	0.30 [0.18, 0.50]	0.282 (0.954)	0	BAC

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
TNFA	rs1799724	C/T	5	983	840	Asian	0.019	0.33 [0.13, 0.83]	0.930 (0.999)	36.4	CBC
TNFA	rs1800629	A/G	12	1346	1553	Asian	0.014	0.73 [0.57, 0.94]	0.808 (0.996)	29.3	BBC
VDR	rs2228570	C/T	16	2006	2003	Asian	0.020	1.53 [1.07, 2.19]	0.863 (0.997)	51.3	BCC
VDR	rs2228570	C/T	21	2415	2613	-	0.010	1.51 [1.10, 2.08]	0.812 (0.996)	46.0	BBC
VDR	rs731236	T/C	14	2037	1804	Asian	0.024	1.52 [1.06, 2.19]	0.876 (0.997)	29.3	BBC
Pooled diseases											
CCL2	rs1024611	A/G	23	9342	10215	-	0.017	1.31 [1.05, 1.63]	0.805 (0.995)	81.3	BCC
CCL2	rs1024611	A/G	5	2195	2031	Admixed	0.004	1.92 [1.23, 2.98]	0.787 (0.995)	88.3	BCC
CCL2	rs2857656	C/G	4	2810	3074	African	0.047	1.17 [1.00, 1.37]	0.909 (0.998)	25.6	BBC
CCL2	rs41416652	C/T	3	1081	923	-	0.004	0.45 [0.26, 0.78]	0.850 (0.997)	0	BAC
FCGR2A	rs1801274	A/G	4	241	674	Admixed	<0.001	2.32 [1.48, 3.64]	0.560 (0.985)	31.9	CBC
IFITM3	rs12252	C/T	5	592	3551	-	0.003	0.52 [0.33, 0.80]	0.765 (0.994)	41.7	CBC
IFNG	**rs2430561**	**A/T**	**27**	**5347**	**5797**	**-**	**<0.001**	**0.68 [0.57, 0.81]**	**0.018 (0.491)**	**39.6**	**BBC**
IFNG	rs2430561	A/T	6	1803	1108	Admixed	0.002	0.68 [0.53, 0.87]	0.541 (0.984)	0	BAC
IFNG	rs2430561	A/T	6	765	987	European	0.012	0.51 [0.31, 0.86]	0.879 (0.997)	68.4	CCC
IFNG	rs2430561	A/T	10	2071	2140	Asian	0.021	0.68 [0.49, 0.94]	0.852 (0.997)	50.7	BCC
IL10	rs1800896	A/G	7	1043	1232	European	0.021	1.30 [1.04, 1.62]	0.829 (0.996)	10.9	BAC
IL4	**rs2070874**	**C/T**	**5**	**1277**	**2513**	**-**	**<0.001**	**1.800 [1.45, 2.22]**	**0.000 (0.014)**	**0**	**BAC**
IL4	rs2243250	C/T	14	4545	6291	-	0.030	1.22 [1.02, 1.47]	0.882 (0.997)	43.0	-
IL4	rs2243250	C/T	6	869	1218	Asian	0.048	1.41 [1.00, 1.98]	0.903 (0.998)	51.9	CCC
SFTPA1	rs1136450	C/G	4	1141	1766	-	0.005	0.78 [0.65, 0.92]	0.547 (0.984)	0	BAC
SFTPA2	rs1059046	A/C	4	1141	1766	-	0.010	1.36 [1.08, 1.72]	0.763 (0.994)	0	BAC
SLC11A1	rs17235409	A/G	30	4265	4421	-	0.038	0.83 [0.69, 0.99]	0.887 (0.998)	58.4	BCC
SLC11A1	rs3731865	C/G	18	2678	2976	-	0.004	0.71 [0.56, 0.90]	0.655 (0.990)	65.5	BCC
TIRAP	rs8177374	C/T	3	1191	1475	Asian	0.030	2.86 [1.11, 7.42]	0.935 (0.999)	0	BAC

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
TLR6	rs5743810	C/T	5	978	2058	-	0.007	1.32 [1.08, 1.62]	0.717 (0.993)	0	CAC
TNFA	rs1799724	C/T	8	1540	2019	-	0.039	0.44 [0.21, 0.96]	0.932 (0.999)	37.3	BBC
TNFA	rs1799724	C/T	7	1133	1011	Asian	0.001	0.31 [0.16, 0.63]	0.858 (0.997)	8.3	BAC
TNFA	rs1800629	A/G	15	1972	2176	Asian	0.011	0.75 [0.59, 0.94]	0.783 (0.995)	32.8	BBC
TNFA	rs361525	A/G	17	3254	4943	-	0.012	0.59 [0.39, 0.89]	0.849 (0.997)	83.4	BCC
VDR	rs2228570	C/T	16	2006	2003	Asian	0.020	1.53 [1.07, 2.19]	0.863 (0.997)	51.3	BCC
VDR	rs2228570	C/T	23	2572	2778	-	0.007	1.55 [1.13, 2.12]	0.747 (0.994)	48.9	BBC
VDR	rs731236	T/C	14	2037	1804	Asian	0.024	1.52 [1.06, 2.19]	0.876 (0.997)	29.3	BBC

* reference/alternate allele

Table A.6 Random-effects meta-analyses results, heterozygote advantage model, disease susceptibility (expanded 30 disease model) [nominally significant results only, significant results for the mid/low BFDP level shown in bold]

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
Pneumonia											
FCGR2A	rs1801274	A/G	6	1704	2211	-	0.031	0.74 [0.56, 0.97]	0.869 (0.997)	57.6	BCC
FCGR2A	rs1801274	A/G	4	241	674	Admixed	0.002	0.59 [0.42, 0.82]	0.606 (0.988)	11.5	CAC
Tuberculosis											
CCL2	rs1024611	A/G	22	8935	9207	-	0.032	0.90 [0.81, 0.99]	0.900 (0.998)	55.0	BCC
CCL2	**rs1024611**	**A/G**	**5**	**2195**	**2031**	**Admixed**	**<0.001**	**0.72 [0.63, 0.81]**	**0.000 (0.004)**	**0**	**BAC**
CCL2	rs3917891	C/T	5	3056	3222	-	0.004	0.85 [0.76, 0.95]	0.613 (0.988)	0	BAC
CCL2	rs41416652	C/T	3	1081	923	-	0.030	1.88 [1.06, 3.32]	0.913 (0.998)	0	BAC
CCL2	rs4586	C/T	8	3882	4338	-	0.019	1.11 [1.02, 1.22]	0.901 (0.998)	0	BAC
CCL5	rs2107538	A/G	6	1304	1305	Asian	0.003	0.79 [0.67, 0.92]	0.490 (0.981)	0	BAC
CD209	rs735239	A/G	4	1206	1320	-	0.006	0.62 [0.44, 0.87]	0.757 (0.994)	66.9	BCC
IFNG	rs2430561	A/T	25	4774	4931	-	0.013	0.86 [0.76, 0.97]	0.807 (0.995)	40.9	BBC
IL10	rs1800872	A/C	5	1057	1098	Admixed	0.009	0.77 [0.63, 0.94]	0.752 (0.994)	8.4	BAC
IL10	rs1800896	A/G	25	6536	6584	-	0.046	0.87 [0.76, 1.00]	0.913 (0.998)	50.1	-
IL10	rs1800896	A/G	5	459	720	European	0.004	0.69 [0.53, 0.88]	0.580 (0.986)	0	CAC
MBL2	rs7095891	C/T	4	2294	3562	-	0.024	0.87 [0.78, 0.98]	0.857 (0.997)	0	BAC
P2RX7	rs3751143	A/C	16	5037	5894	-	0.009	1.24 [1.05, 1.46]	0.743 (0.993)	62.6	-
P2RX7	rs3751143	A/C	9	3659	4429	Asian	0.006	1.37 [1.09, 1.71]	0.667 (0.991)	72.1	-
PTPN22	rs2476601	C/T	4	616	639	-	0.037	0.39 [0.16, 0.95]	0.935 (0.999)	44.5	CBC
SLC11A1	rs17235416	+/-	27	4731	5304	-	0.024	1.17 [1.02, 1.34]	0.856 (0.997)	42.0	BBC
SLC11A1	rs3731865	C/G	18	2678	2976	-	0.024	1.25 [1.03, 1.51]	0.833 (0.996)	46.3	BBC
TNFA	rs1800629	A/G	12	1346	1553	Asian	0.011	1.34 [1.07, 1.69]	0.793 (0.995)	14.3	BAC

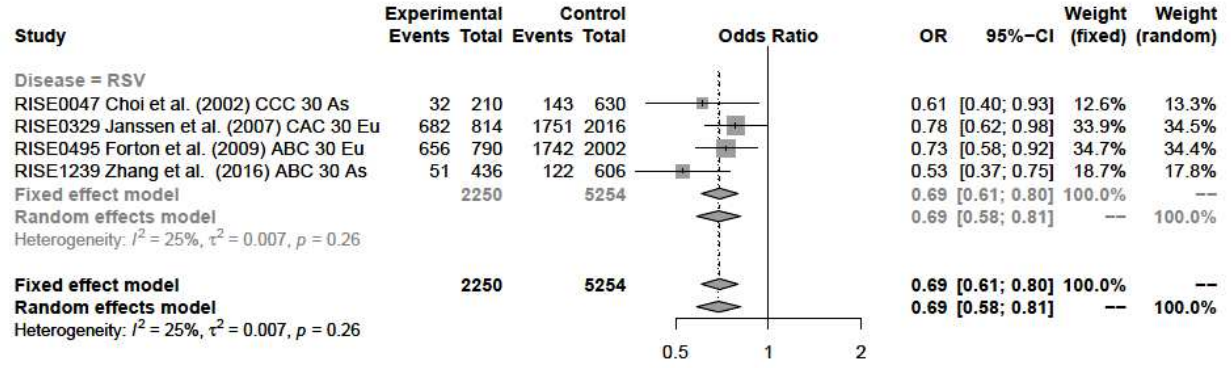
Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
Pooled diseases											
CCL2	rs1024611	A/G	23	9342	10215	-	0.022	0.89 [0.81, 0.98]	0.852 (0.997)	52.8	BCC
CCL2	**rs1024611**	**A/G**	**5**	**2195**	**2031**	**Admixed**	**<0.001**	**0.72 [0.63, 0.81]**	**0.000 (0.004)**	**0**	**BAC**
CCL2	rs3917891	C/T	5	3056	3222	-	0.004	0.85 [0.76, 0.95]	0.613 (0.988)	0	BAC
CCL2	rs41416652	C/T	3	1081	923	-	0.030	1.88 [1.06, 3.32]	0.913 (0.998)	0	BAC
CCL2	rs4586	C/T	8	3882	4338	-	0.019	1.11 [1.02, 1.22]	0.901 (0.998)	0	BAC
CD209	rs735239	A/G	4	1206	1320	-	0.006	0.62 [0.44, 0.87]	0.757 (0.994)	66.9	BCC
FCGR2A	rs1801274	A/G	4	241	674	Admixed	0.002	0.59 [0.42, 0.82]	0.606 (0.988)	11.5	CAC
IFNG	rs2430561	A/T	27	5347	5797	-	0.012	0.85 [0.75, 0.96]	0.741 (0.993)	54.7	BCC
IL10	rs1800872	A/C	7	1150	1259	Admixed	0.001	0.76 [0.64, 0.89]	0.254 (0.947)	0	BAC
IL10	rs1800896	A/G	34	8706	9473	-	0.006	0.85 [0.76, 0.95]	0.613 (0.988)	52.3	BCC
IL10	rs1800896	A/G	7	1043	1232	European	0.012	0.77 [0.63, 0.94]	0.752 (0.994)	22.0	BAC
IL6	rs1800796	C/G	4	2357	1974	-	0.028	0.86 [0.75, 0.98]	0.859 (0.997)	0	BAC
MBL2	rs11003125	C/G	6	1855	2044	Asian	0.028	0.87 [0.76, 0.98]	0.857 (0.997)	0	BAC
MBL2	rs7095891	C/T	5	1680	1844	Asian	0.019	0.82 [0.70, 0.97]	0.834 (0.996)	0	BAC
MBL2	rs7095891	C/T	8	3277	5295	-	0.005	0.87 [0.79, 0.96]	0.681 (0.991)	0	BAC
P2RX7	rs3751143	A/C	16	5037	5894	-	0.009	1.24 [1.05, 1.46]	0.743 (0.993)	62.6	-
P2RX7	rs3751143	A/C	9	3659	4429	Asian	0.006	1.37 [1.09, 1.71]	0.667 (0.991)	72.1	-
SFTPA1	rs1136450	C/G	4	1141	1766	-	0.042	1.19 [1.01, 1.40]	0.885 (0.998)	0	BAC
SFTPA2	rs17886395	C/G	4	1141	1766	-	0.012	1.31 [1.06, 1.61]	0.754 (0.994)	8.5	BAC
SLC11A1	rs17235416	+/-	27	4731	5304	-	0.024	1.17 [1.02, 1.34]	0.856 (0.997)	42.0	BBC
SLC11A1	rs3731865	C/G	18	2678	2976	-	0.024	1.25 [1.03, 1.51]	0.833 (0.996)	46.3	BBC
TNFA	rs1800629	A/G	15	1972	2176	Asian	0.016	1.29 [1.05, 1.58]	0.790 (0.995)	18.2	BAC
TNFA	rs361525	A/G	18	3254	4943	-	0.042	1.39 [1.01, 1.91]	0.896 (0.998)	66.8	BCC

* reference/alternate allele

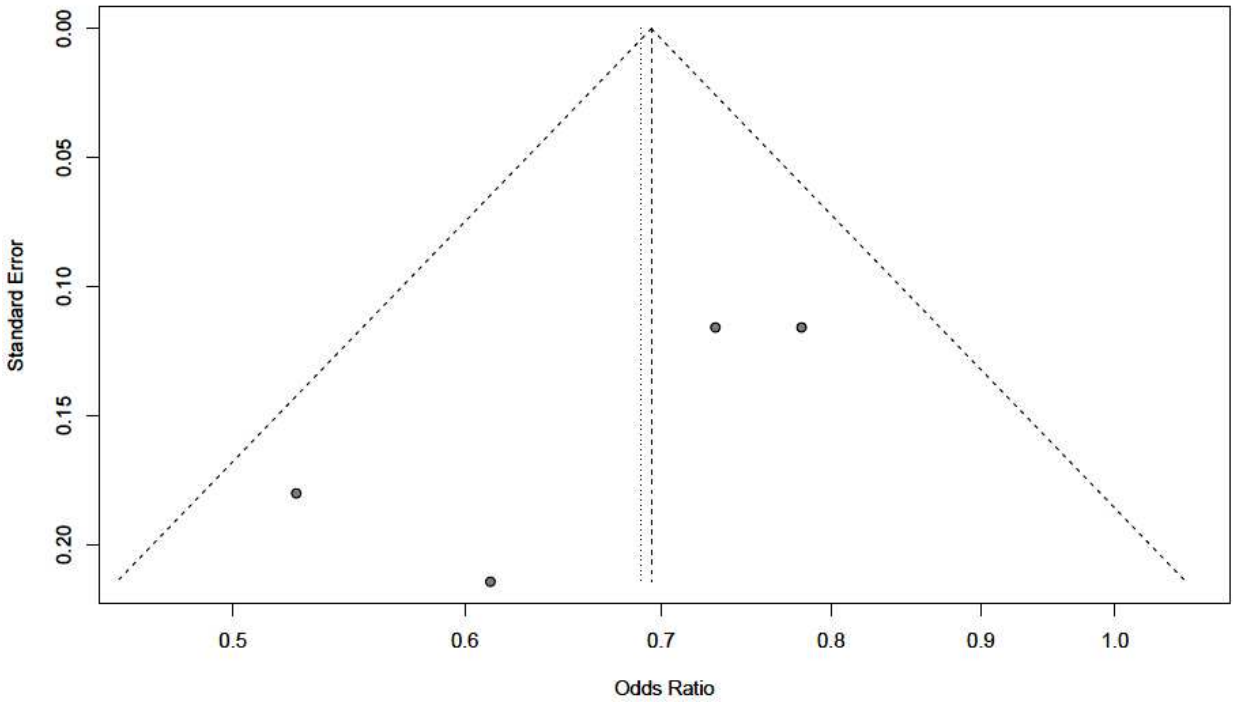
Table A.7 Random-effects meta-analyses results, various models, subset analysis (exposed controls: 31/2 and 32 disease models) and disease severity (43 disease model) [nominally significant results only, significant results for the mid/low BFDP level shown in bold]

Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
Disease model: 31/2											
Pooled diseases											
Dominant model											
IL10	rs1800896	A/G	4	513	847	Asians	0.016	1.46 [1.07, 1.99]	0.836 (0.996)	0	CAC
Heterozygote advantage model											
IL10	rs1800896	A/G	4	513	847	Asians	0.002	0.65 [0.49, 0.86]	0.606 (0.988)	0	CAC
Disease model: 32											
Tuberculosis											
Allelic model											
CCL2	rs1024611	A/G	4	1529	1570	-	0.019	0.65 [0.45, 0.93]	0.858 (0.997)	90.5	BCC
Recessive model											
CCL2	rs1024611	A/G	4	1529	1570	-	0.004	1.84 [1.22, 2.78]	0.773 (0.994)	85.2	BCC
Heterozygote advantage model											
CCL2	**rs1024611**	**A/G**	**4**	**1529**	**1570**	**-**	**0.000**	**0.71 [0.62, 0.82]**	**0.004 (0.162)**	**0**	**BAC**
Disease model: 43											
Pooled diseases											
Recessive model											
IL10	rs1800896	A/G	4	273	307	-	0.019	1.88 [1.11, 3.17]	0.893 (0.998)	0	CAC

* reference/alternate allele

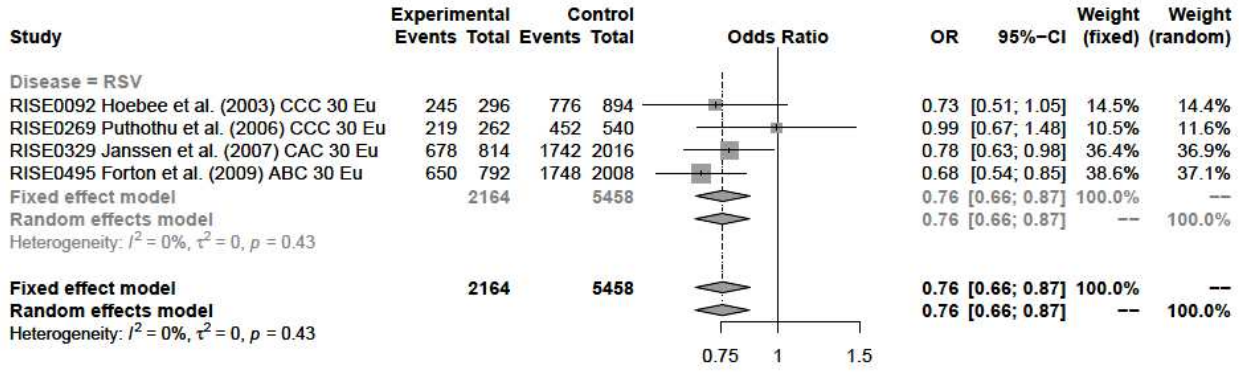


a)

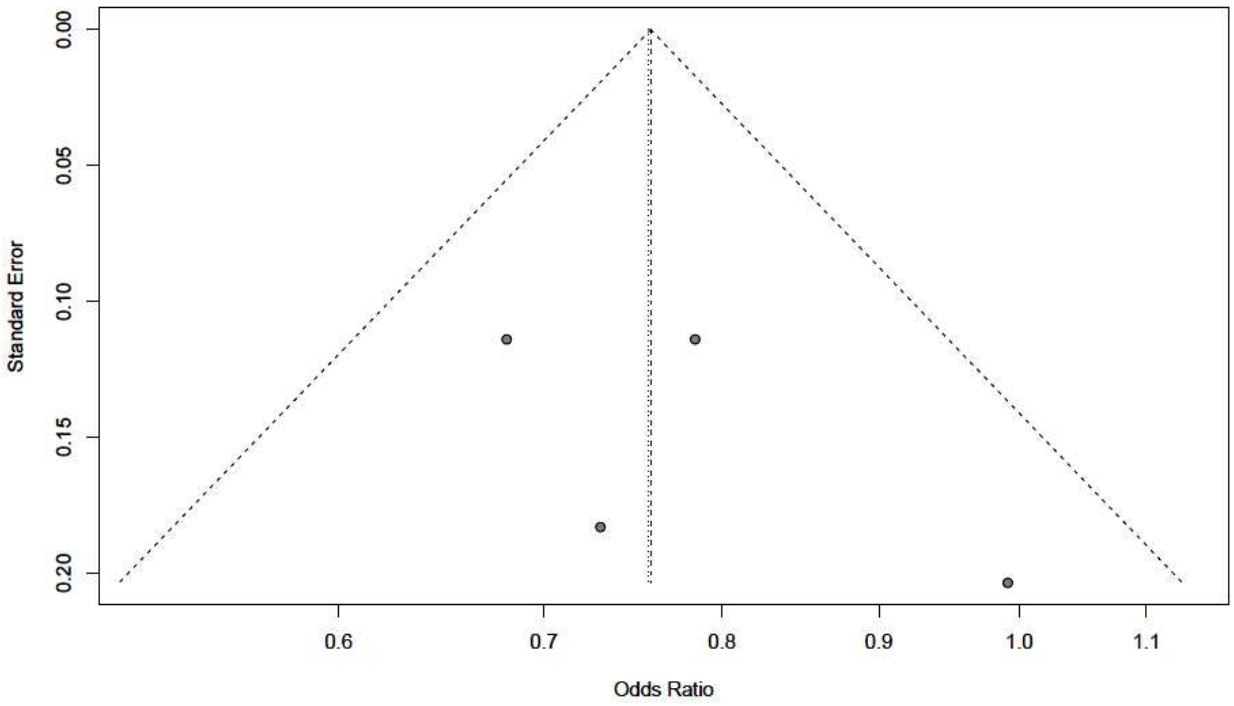


b)

Figure A.1 Forest (a) and funnel (b) plot for *IL4* (rs2070874) in allelic model of RSV meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

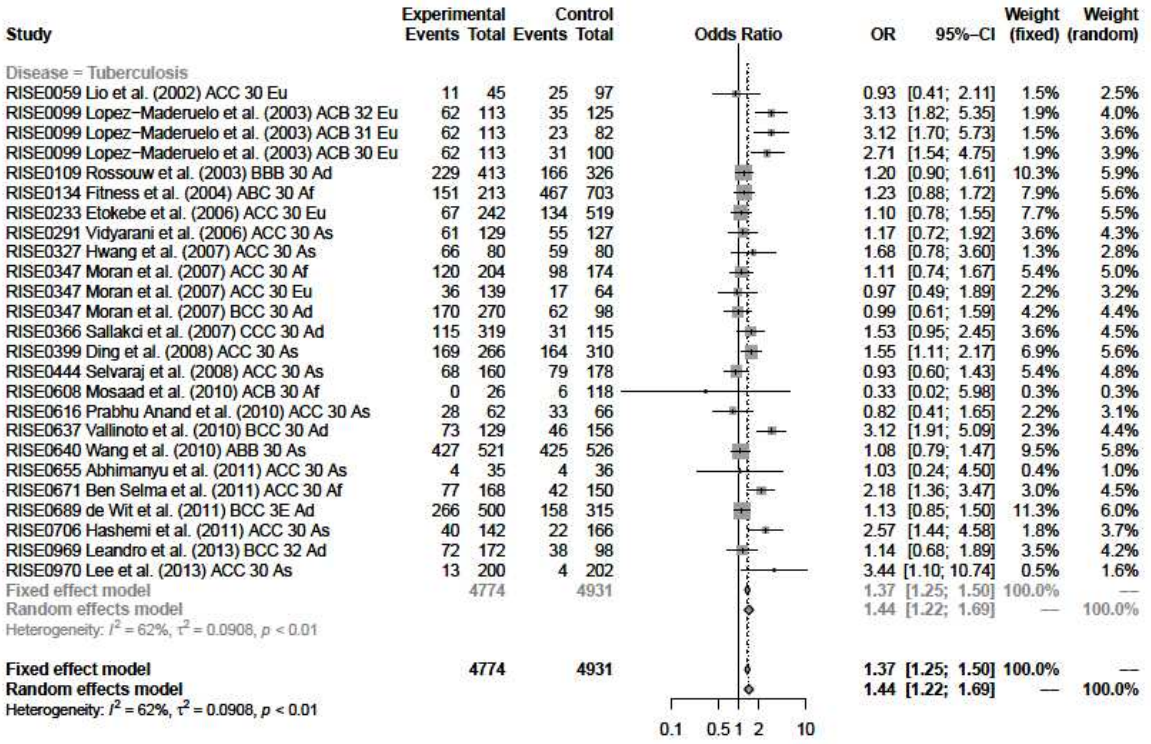


a)

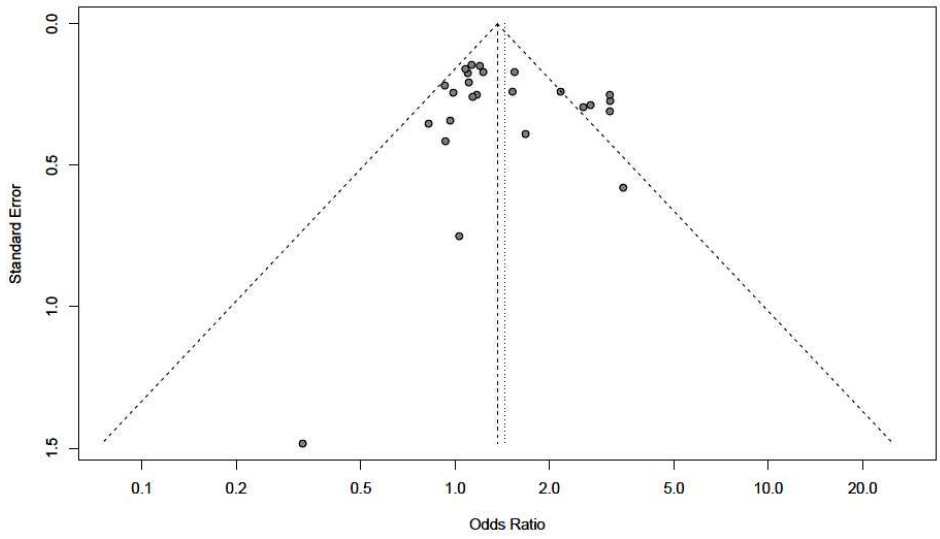


b)

Figure A.2 Forest (a) and funnel (b) plot for *IL4* (rs2243250) in allelic model of RSV meta-analysis, stratified on European ethnicity (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

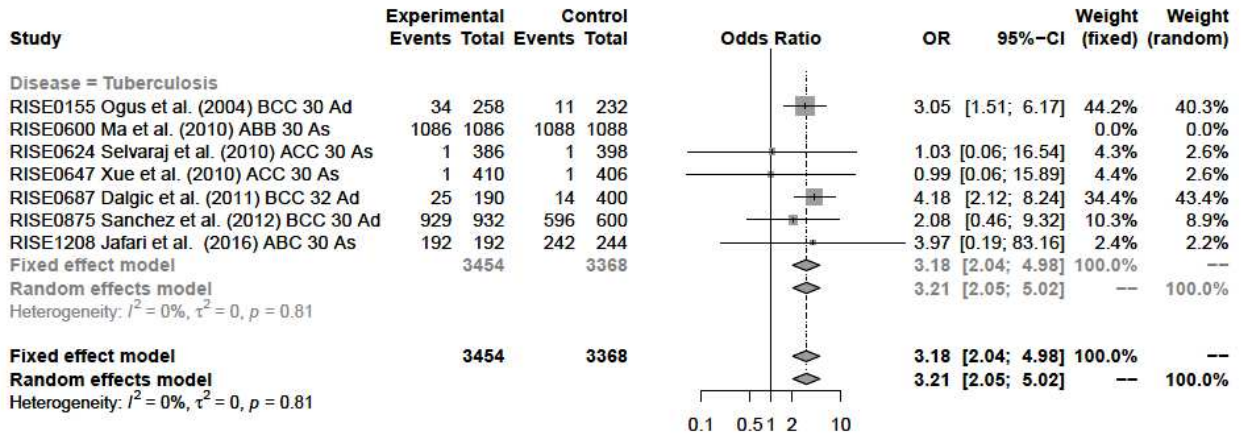


a)

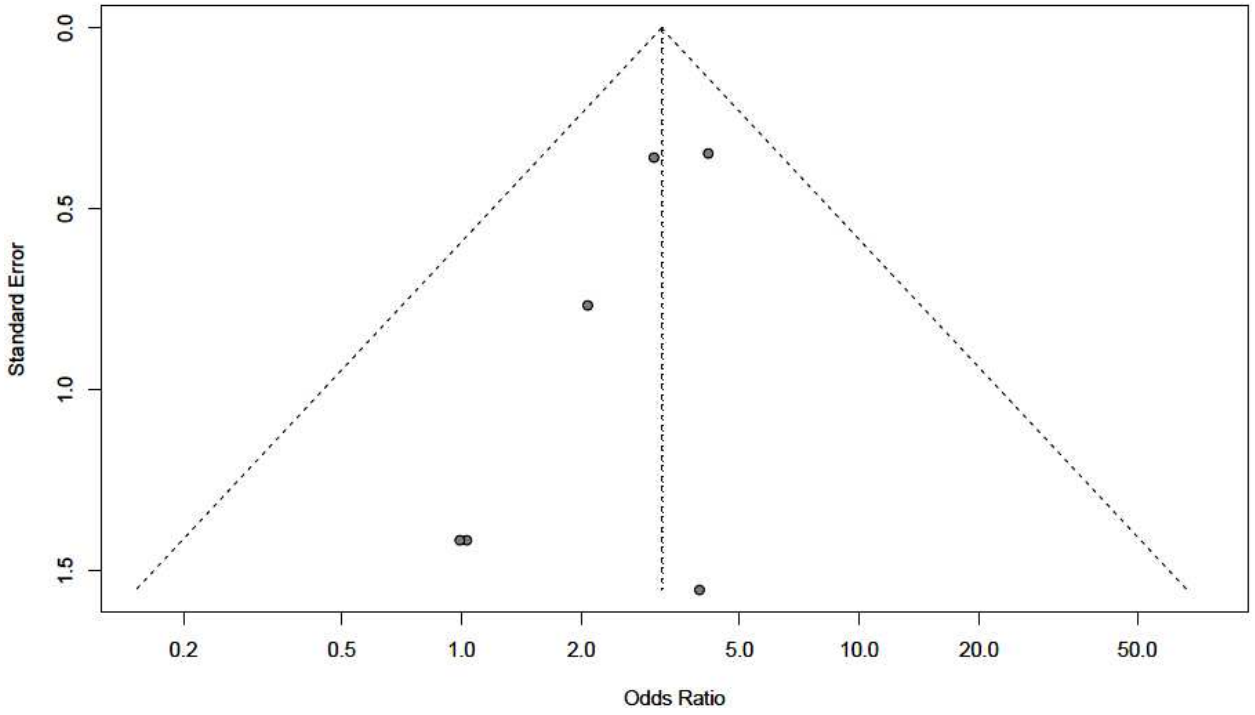


b)

Figure A.3 Forest (a) and funnel (b) plot for *IFNG* (rs2430561) in allelic model of tuberculosis meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

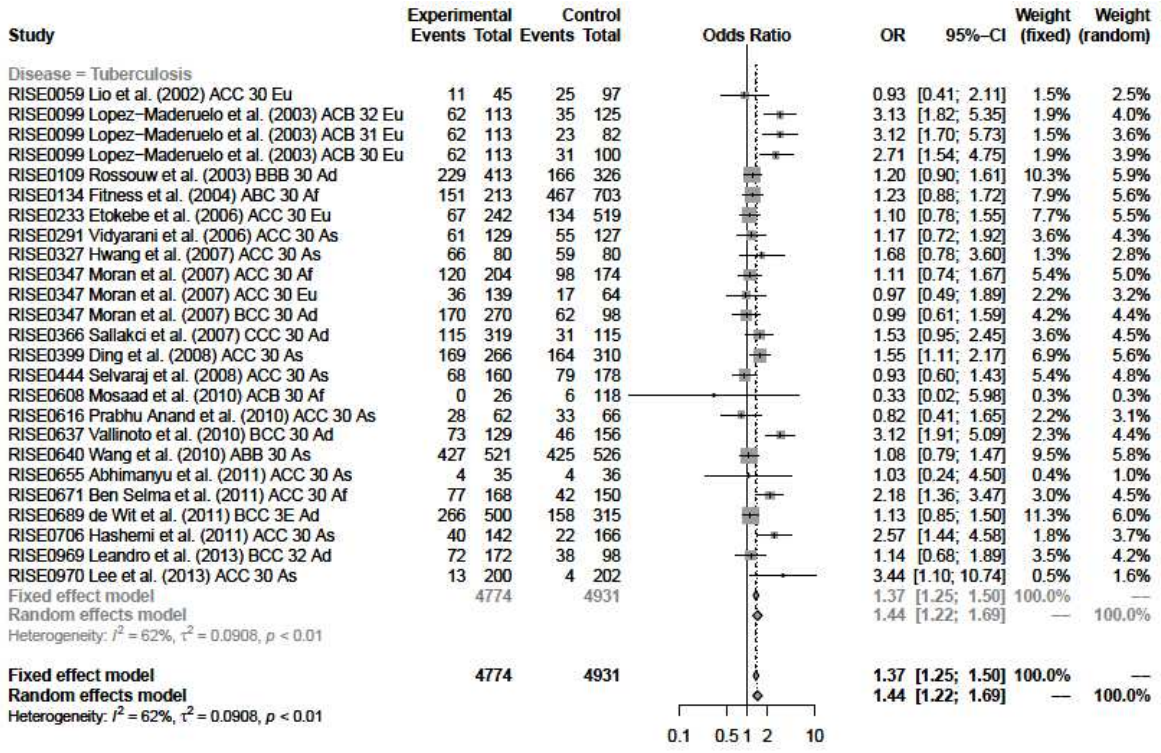


a)

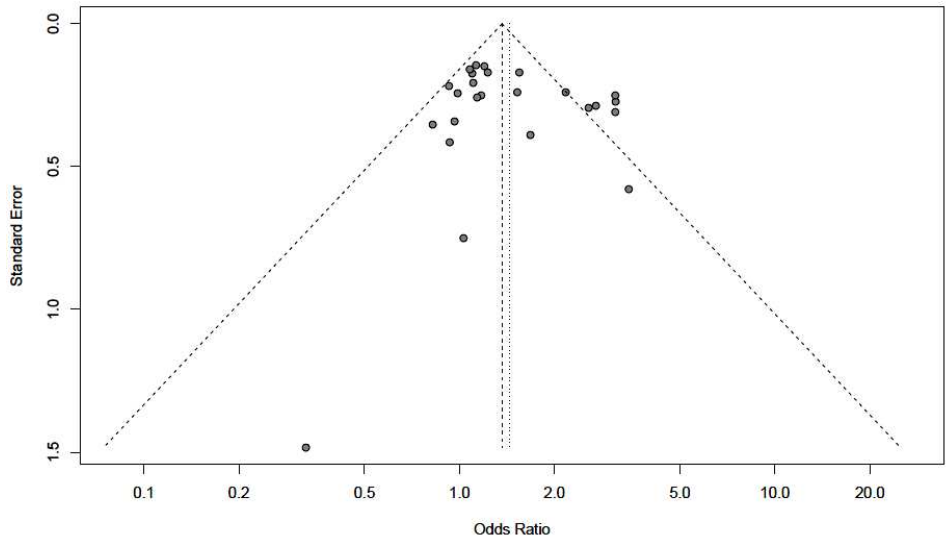


b)

Figure A.4 Forest (a) and funnel (b) plot for *TLR2* (rs5743708) in allelic model of tuberculosis meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

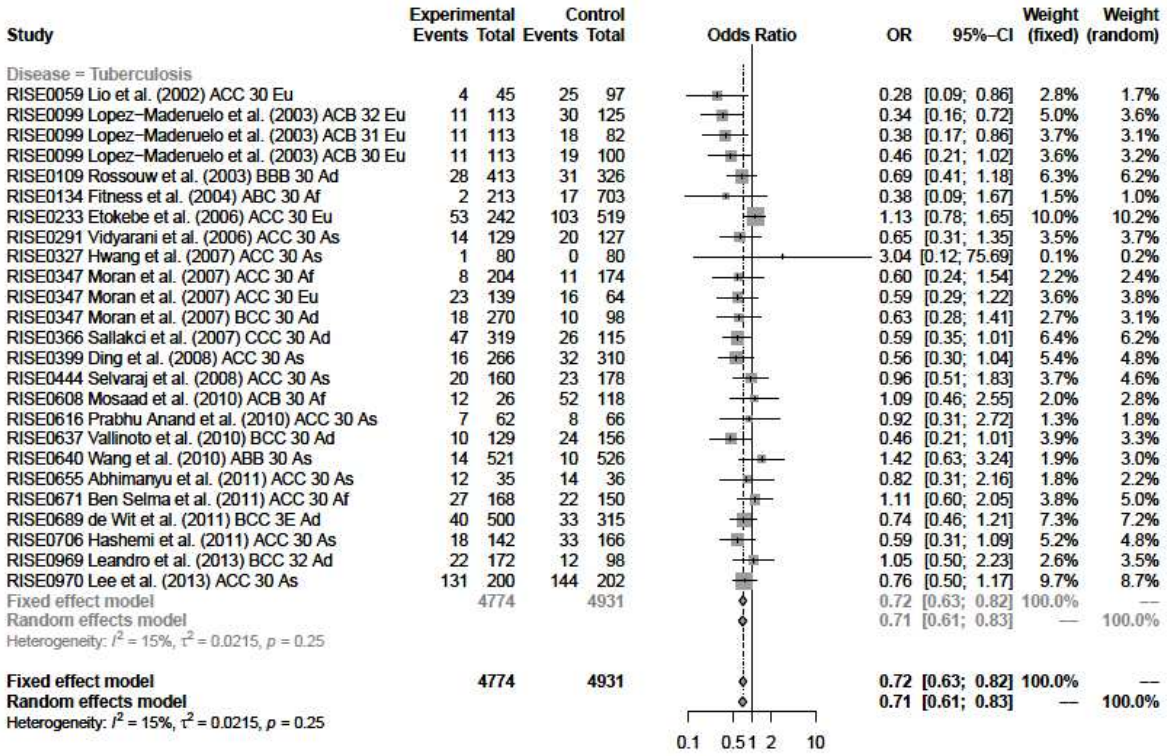


a)

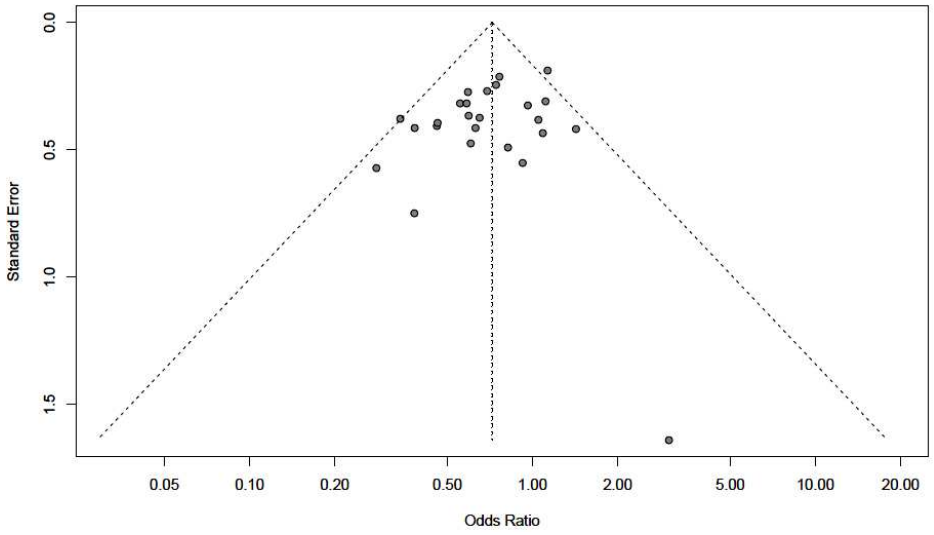


b)

Figure A.5 Forest (a) and funnel (b) plot for *IFNG* (rs2430561) in dominant model of tuberculosis meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

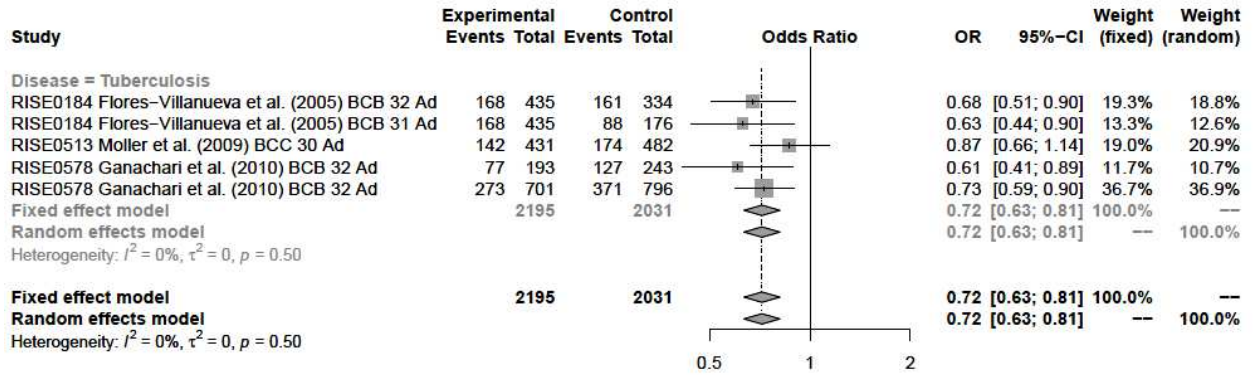


a)

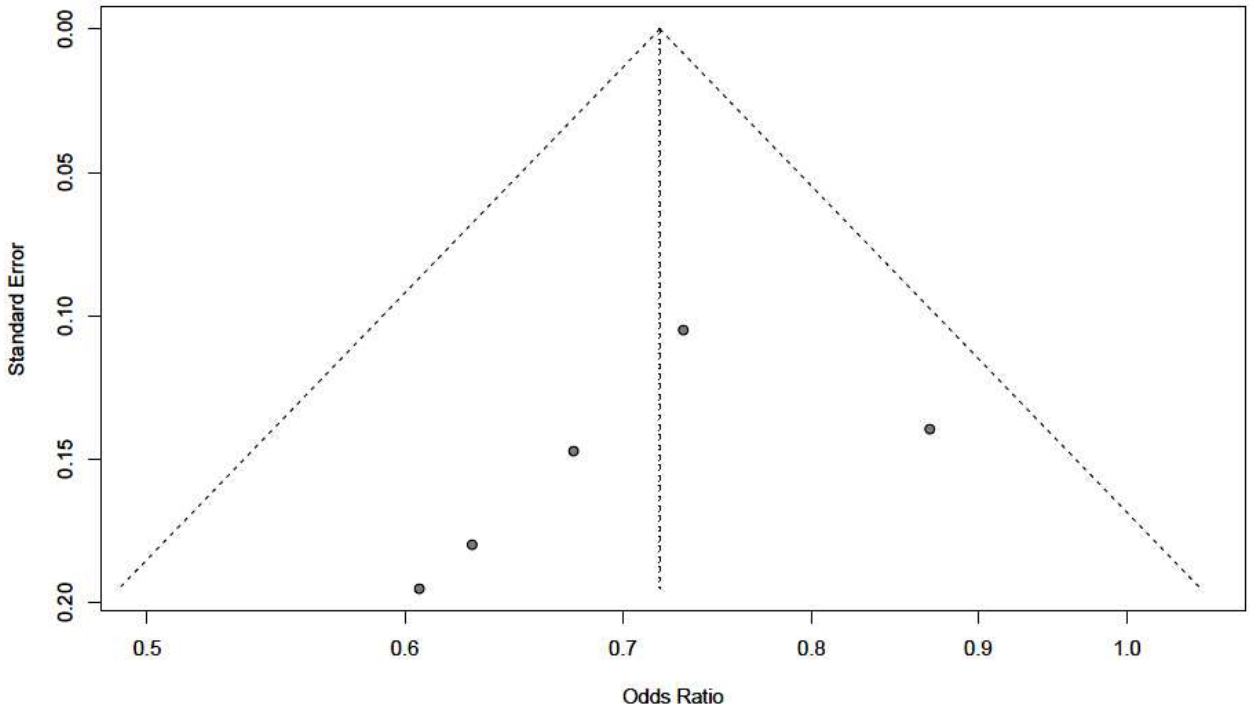


b)

Figure A.6 Forest (a) and funnel (b) plot for *IFNG* (rs2430561) in recessive model of tuberculosis meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

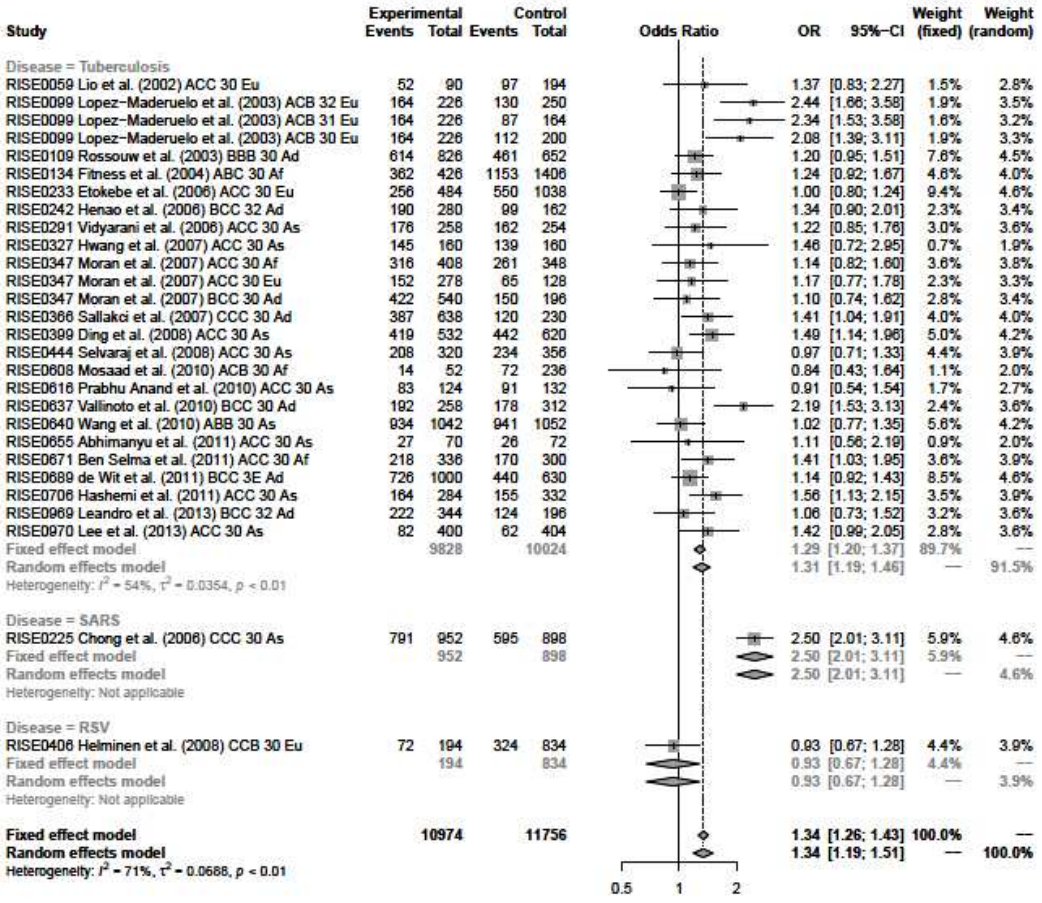


a)

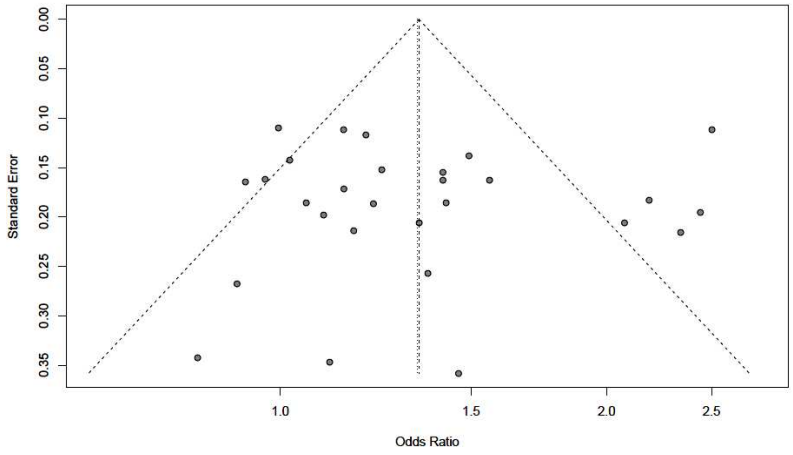


b)

Figure A.7 Forest (a) and funnel (b) plot for *CCL2* (rs1024611) in heterozygote advantage model of tuberculosis meta-analysis, stratified on admixed populations (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

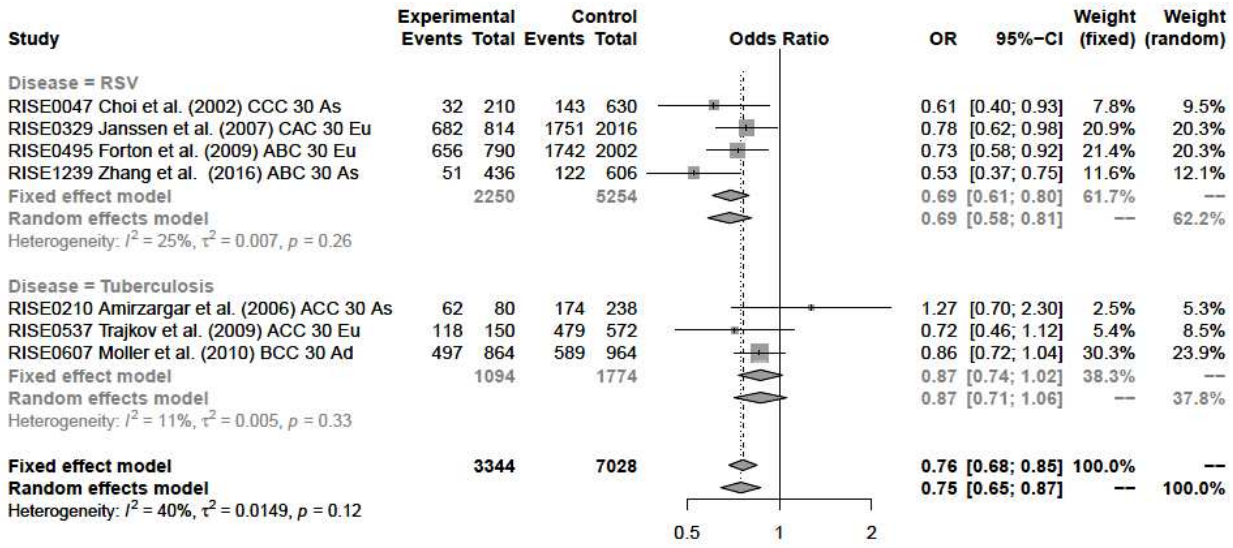


a)

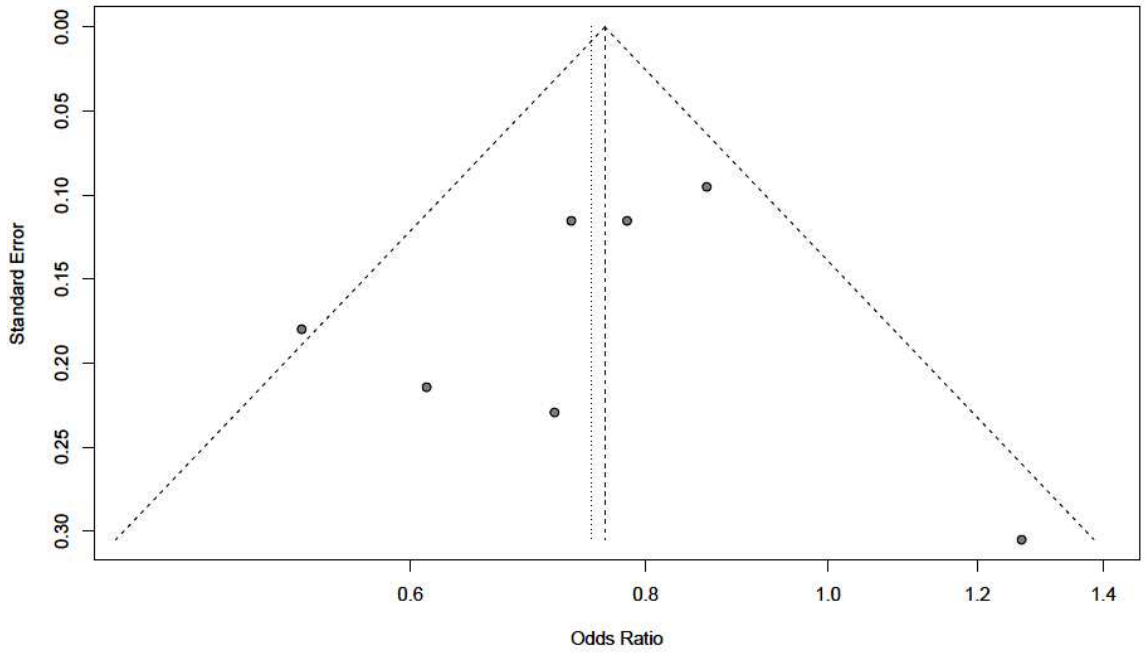


b)

Figure A.8 Forest (a) and funnel (b) plot for *IFNG* (rs2430561) in allelic model of pooled diseases meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

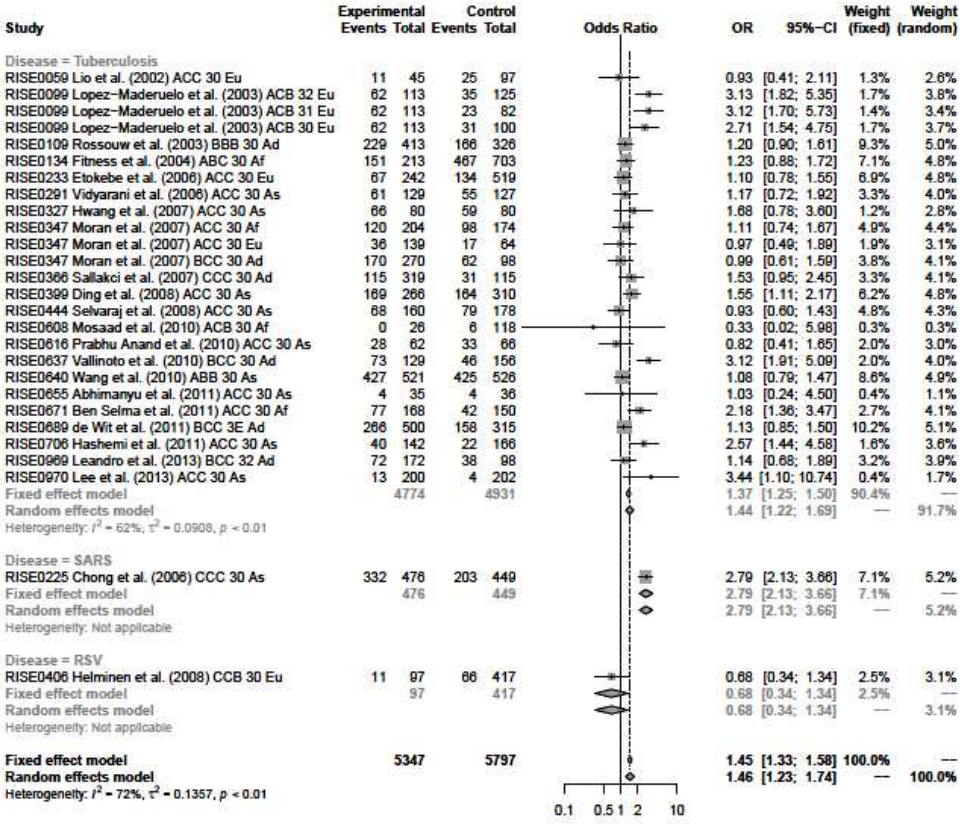


a)

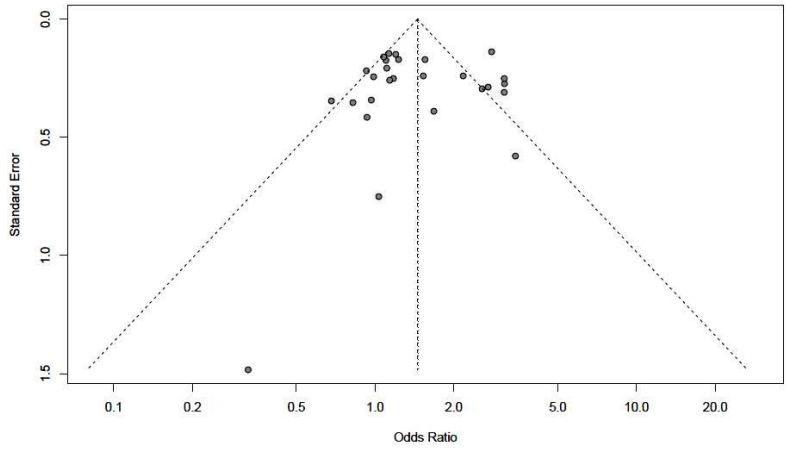


b)

Figure A.9 Forest (a) and funnel (b) plot for *IL4* (rs2070874) in allelic model of pooled diseases meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

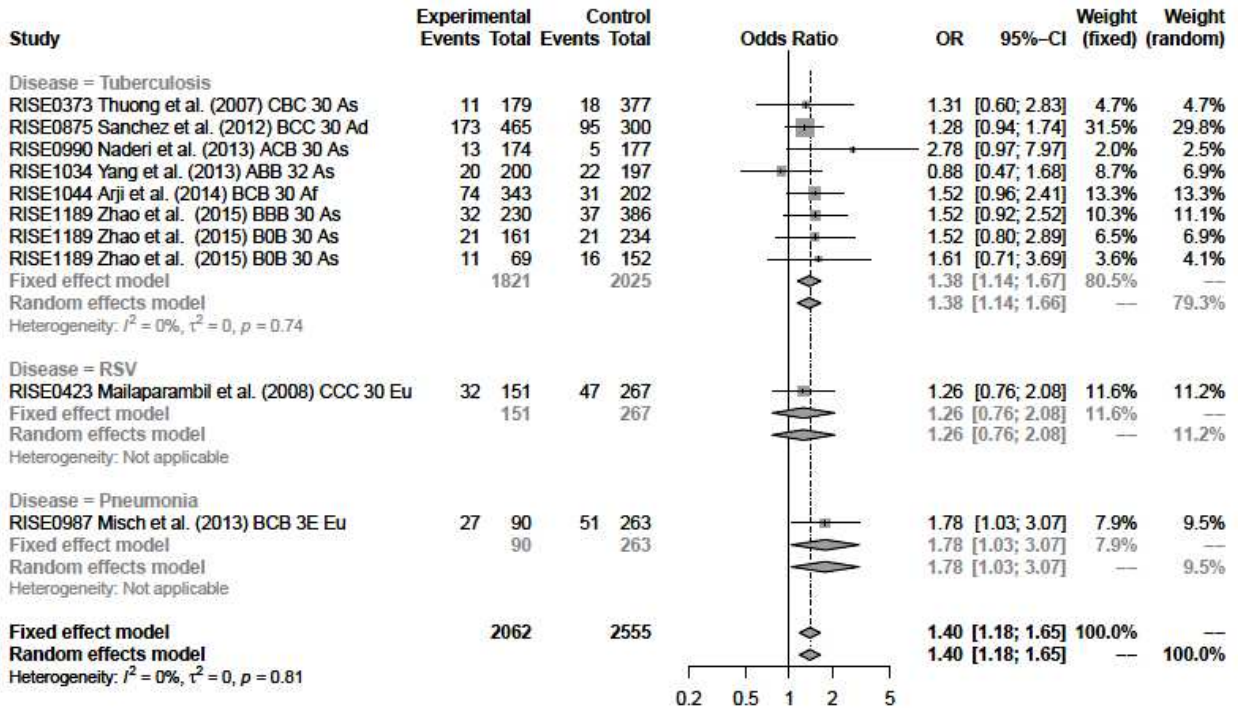


a)

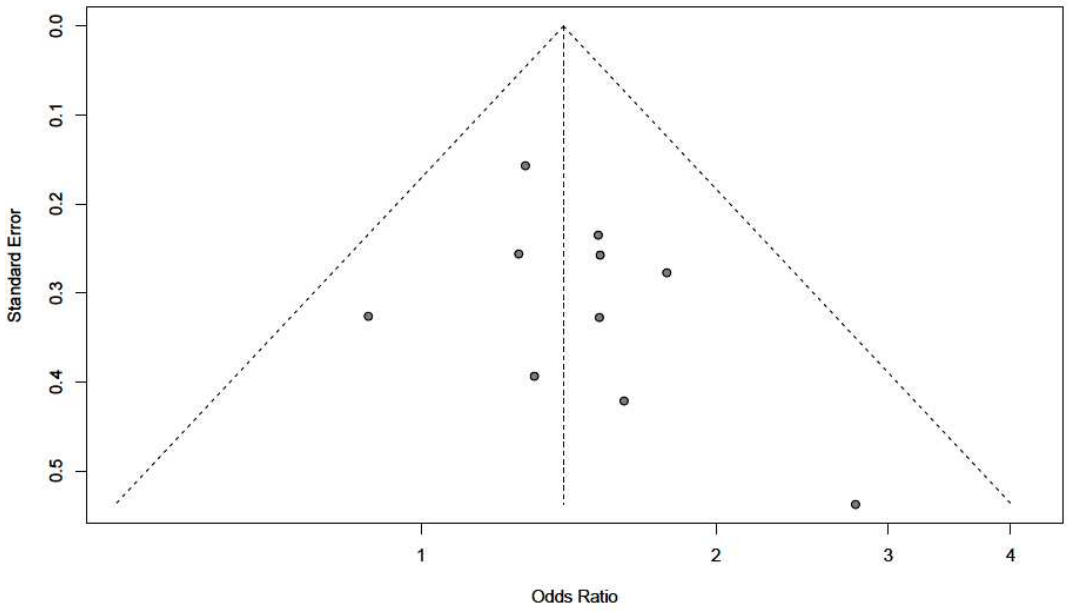


b)

Figure A.10 Forest (a) and funnel (b) plot for *IFNG* (rs2430561) in dominant model of pooled diseases meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

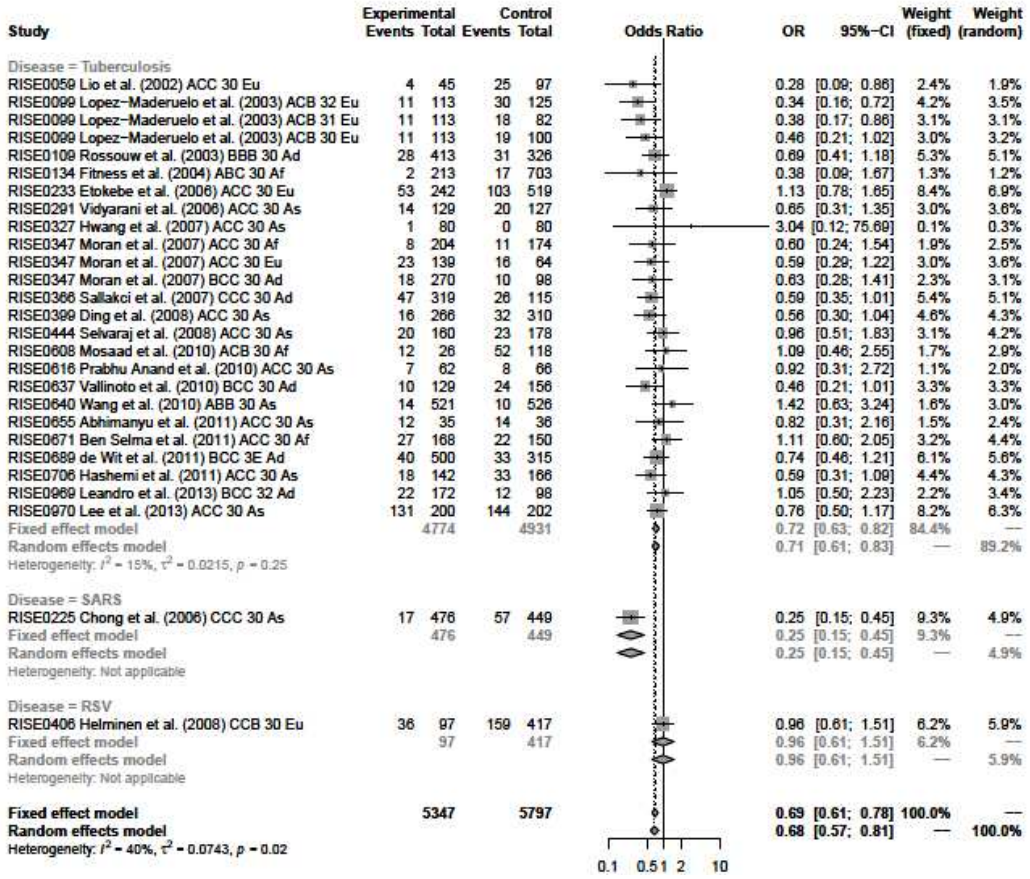


a)

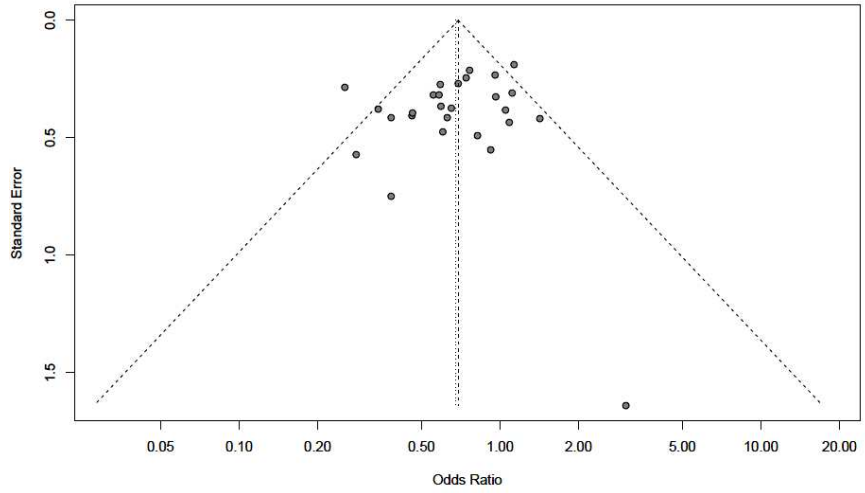


b)

Figure A.11 Forest (a) and funnel (b) plot for *TLR2* (rs3804099) in dominant model of pooled diseases meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

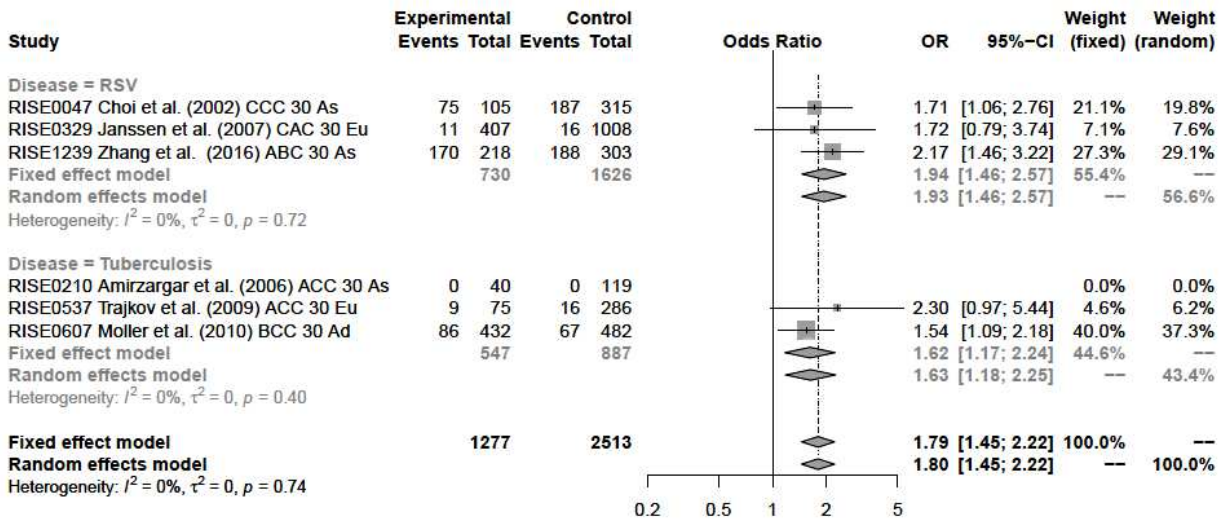


a)

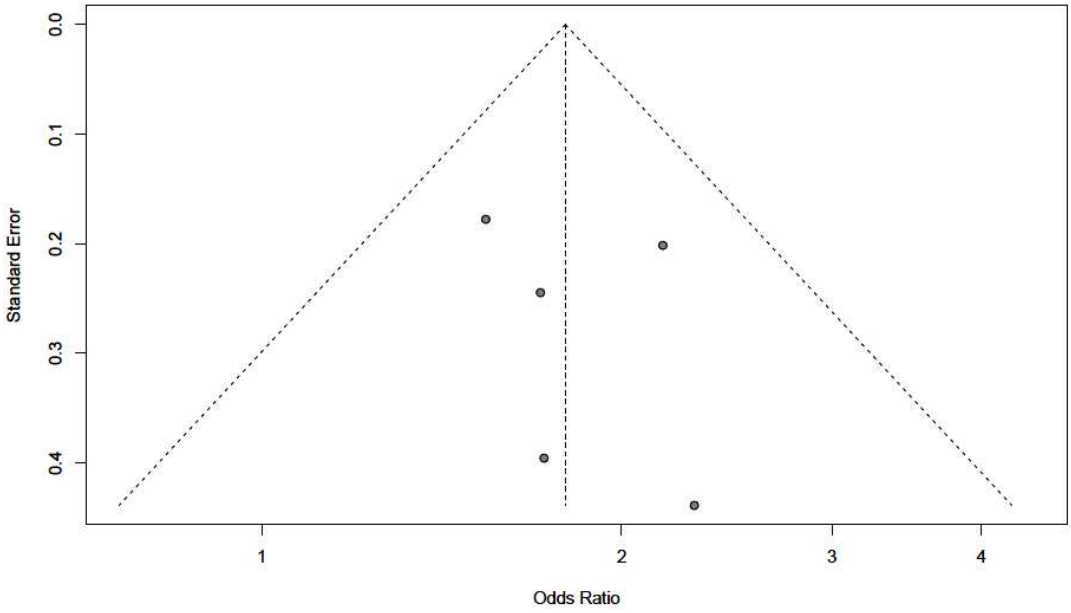


b)

Figure A.12 Forest (a) and funnel (b) plot for *IFNG* (rs2430561) in recessive model of pooled diseases meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

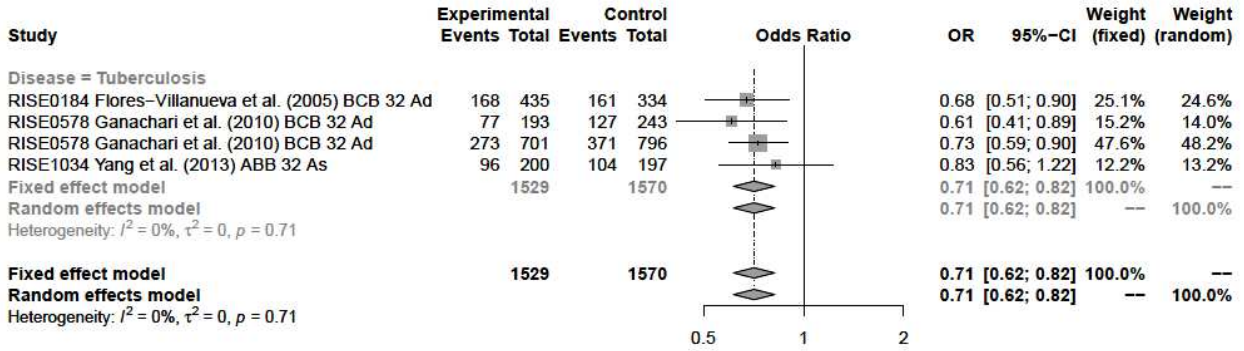


a)

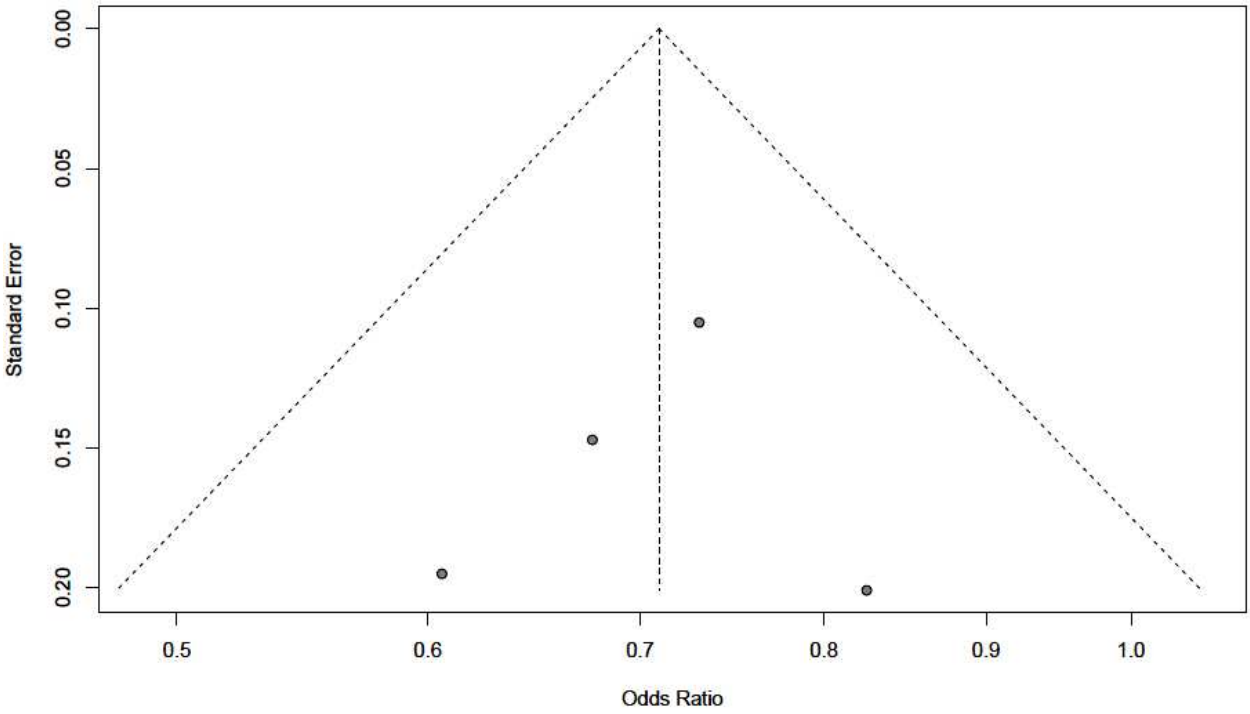


b)

Figure A.13 Forest (a) and funnel (b) plot for *IL4* (rs2070874) in recessive model of pooled diseases meta-analysis (disease susceptibility (expanded 30) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]



a)



b)

Figure A.14 Forest (a) and funnel (b) plot for *CCL2* (rs1024611) in heterozygote advantage model of tuberculosis meta-analysis (exposed healthy seropositive controls (32) model) [each line is represented by a RISE ID, study author and publication year, CSI score, disease model, and ethnicity: As – Asian, Af – African, Eu – European, Ad – Admixed]

Table A.8 Overview of family-based and linkage studies that investigated host genetic factors for respiratory infectious diseases

RISE ID	Author (year)	Disease	Study design	Main results	Ref.
RISE0002	Bellamy et al. (2000)	Tuberculosis	Families with two or more siblings affected by tuberculosis (Gambia and South Africa); first set of 299 markers used in 92 sibpairs, second set of 22 markers from regions with likely positive hits used in 81 sibpairs.	Markers on chromosomes 15q and Xq showed suggestive evidence of linkage (LOD=2.00 and 1.77, respectively), replicated in common ancestry using microsatellite mapping.	(544)
RISE0003	Cervino et al. (2000)	Tuberculosis	Families with at least one affected sib and one parent (Guinea-Conakry); three polymorphisms in the *SLC11A1* gene used in 44 families.	Single base change in intron 4 was nominally significant (P=0.036).	(101)
RISE0009	Greenwood et al. (2000)	Tuberculosis	Members of an extended Aboriginal Canadian family that experienced an outbreak of tuberculosis during 1987–89; 29 markers on chromosome 2q and 8 markers in the promotor region of *TNF.*	Significant linkage observed for tuberculosis-susceptibility locus and D2S424 (distal to *SLC11A1*, LOD=3.81), and a haplotype of 10 *SLC11A1* intragenic variants.	(102)
RISE0010	Hull et al. (2000)	RSV bronchiolitis	117 nuclear families were recruited in which a child had required hospital admission for RSV bronchiolitis (UK); SNPs in the promoter region of the *IL8* gene investigated.	Significant increase of SNP located 251bp upstream of the *IL8* transcriptional start site (P=0.014).	(545)
RISE0030	Hull et al. (2001)	RSV bronchiolitis	77 families identified in the 1998–1999 bronchiolitis season (UK); SNPs in the promoter region of the *IL8* gene investigated.	Nine SNPs in a 7.6-kb segment spanning the *IL8* gene and its promoter region, six of defined the haplotypic structure and show association with bronchiolitis.	(546)
RISE0086	El Baghdadi et al. (2003)	Tuberculosis	116 nuclear families with 211 affected offspring (Morocco); seven	No significant association was found between tuberculosis and any of the *SLC11A*	(547)

RISE ID	Author (year)	Disease	Study design	Main results	Ref.
			SNPs in *SLC11A1* gene investigated.	SNPs.	
RISE0132	Daly et al. (2004)	Otitis media	121 families with at least two children who had received the diagnosis of chronic/recurrent OM (USA); markers at chromosomes 10q and 19q investigated.	Chromosome 10q at marker D10S212 (LOD=3.78) and chromosome 19q at marker D19S254 (LOD=2.61) detected. Conditional analysis revealed significant increase in LOD score support on chromosome 3p (between markers D3S4545 and D3S1259).	(548)
RISE0145	Jamieson et al. (2004)	Tuberculosis	92 (627 individuals) multicase tuberculosis families (Brazil); 16 microsatellites in region 17q11-q21 and 49 informative SNPs in candidate genes.	Single peak for tuberculosis at D17S250 (Z(lr) 2.04; P=0.02) identified. Combined analysis with leprosy confirmed the result at D17S250, equivalent to an allele sharing LOD=2.48. Four loci were implied (*NOS2A, CCL18, CCL4, STAT5B*), supporting hypothesis of a cluster of susceptibility genes across 17q11.2.	(549)
RISE0150	Miller et al. (2004)	Tuberculosis	16 (178 individuals) tuberculosis families (Brazil); first set of 405 markers, second set of 58 markers from positive regions with 22 additional markers.	Three regions (10q26.13, 11q12.3, 20p12.1) retained suggestive evidence (peak LOD scores 1.31, 1.85, 1.78) for linkage to tuberculosis.	(550)
RISE0161	Remus et al. (2004)	Tuberculosis	101 families with tuberculosis and 157 offspring (Morocco); SNPS in *IL12RB1* investigated.	Detection of 19 variants (including 10 novel mutations). Two promoter polymorphisms in strong linkage disequilibrium found to be associated with pulmonary tuberculosis.	(551)
RISE0485	Casselbrant et al. (2009)	Otitis media	403 Caucasian families containing 1,431 genotyped individuals and 377 genotyped affected sib pairs, and 26 African American families containing 75 genotyped individuals and 27 genotyped affected sib pairs; genome-wide linkage scan.	Caucasian-only dataset: significant peaks 17q12 (rs226088), 10q22.3 (rs1878001), 7q33 (rs958408), 6p25.1 (rs554653), 4p15.2 (rs2133507). Combined Caucasian and African American dataset: significant 10q22.3 peak (rs719871). Family-based association testing revealed signals near previously implicated genes: 513 kb from	(552)

RISE ID	Author (year)	Disease	Study design	Main results	Ref.
				SFTPA2 (10q22.3), 48 kb from IFNG (12q14), and 870 kb from TNF (6p21.3). However, no support was detected for previously implied 10q26.3 and 19q13.43. Plausible candidates include AP2B1, CCL5, and a cluster of other CCL genes, and in 10q22.3, SFTPA2.	
RISE0490	Cobat et al. (2009)	Tuberculosis	128 families including 350 siblings from hyperendemic region for tuberculosis (South Africa); genome-wide linkage scan.	Region 11p14 and 5p15 identified as involved in resistance to tuberculosis in endemic areas (fine mapping identified SLC6A3).	(553)
RISE0510	Mahasirimongkol et al. (2009)	Tuberculosis	93 families with multiple siblings out of which 195 individuals affected with tuberculosis (Thailand); genome-wide linkage scan.	Suggestive evidence of region 5q (LOD=2.29), and two candidate regions 17p and 20p (LOD=2.57 and 3.33, respectively).	(554)
RISE0532	Thomas et al. (2009)	RSV	148 children with active RSV disease and one or both parents (USA); several *SP-A* and *SP-D* SNPs.	One *SP-A* and one *SP-D* SNP (and haplotypes) were found to be nominally significant with the development of severe RSV disease.	(555)
RISE0617	Ridruechai et al. (2010)	Tuberculosis	205 trio families (Thailand); SNP within region 5q31.	Significant association with tuberculosis in haplotypes comprising SNPs rs274559, rs274554 and rs274553 of *SLC22A5* gene. Two haplotypes within the *SLC22A4* and *KIF3A* region also associated with tuberculosis.	(556)
RISE0682	Chen et al. (2011)	Otitis media	607 individuals from 139 families, including 159 affected sib pairs and 62 second-degree affected relative pairs (USA); SNPs on region 19q.	Significant evidence of linkage in the region between 61.6 Mb and 63.8 Mb, which contains over 90 known genes.	(557)
RISE0753	Rye et al. (2011)	Otitis media	434 families with 561 affected individuals (Australia); SNPs in *Evi1*,	*FBXO11* SNP associated with severe OM (replicated in case-control study). Neither	(558)

RISE ID	Author (year)	Disease	Study design	Main results	Ref.
			Fbxo11 and four *SMAD* genes.	cohort showed an association with *EVI1* SNPs. Family-based associations at *SMAD2* and *SMAD4* not replicated.	
RISE0942	Cobat et al. (2013)	Tuberculosis	392 children belonging to 135 nuclear families from an area hyperendemic for tuberculosis (South Africa); genome-wide linkage analysis of *TNF.*	A major pleiotropic locus on chromosome region 11p15 identified (*TNF* locus 1).	(559)
RISE1004	Rye et al. (2013)	Otitis media	531 families with 660 affected children (Australia); SNPs in *SLC11A1* gene investigated.	Four polymorphic variants in the human *SLC11A1* gene showed nominal significance with susceptibility to OM. Haplotype analyses support a single genetic effect in the proximal region of *SLC11A1*.	(103)
RISE1096	Rye et al. (2014)	Otitis media	468 individuals from 101 multicase families with 208 OM cases (Australia); fine mapping of the 10q26.3, 19q13.43, and 3p25.3 region.	Reported top SNPs within genes were rs7902734 (P=8.04E-4; ADAM12), rs9418832 (P=7.48E-5; DOCK1) and rs7922424 (P=9.47E-6; intergenic between TCERGIL and PPP2R2D).	(560)
RISE1146	Cobat et al. (2015)	Tuberculosis	97 nuclear families including 237 offspring from an area where endemicity of tuberculosis is low (France); genome-wide linkage analysis of *TNF.*	Significant linkage signal (P < 3 E-05) in close vicinity of *TST1* was identified.	(561)
RISE1173	Rubicz et al. (2015)	Pneumonia Influenza	1,932 members of extended Mexican–American families (various pathogen-specific quantitative antibody levels were analysed); genome-wide linkage scan.	Genome-wide joint linkage and association analysis revealed one significant SNP on chromosome 20 for *C. pneumoniae* (rs4812712, P=5.3E-08).	(562)

Table A.9 Overview of genome-wide association studies that investigated host genetic factors for respiratory infectious diseases

RISE ID	Author (year)	Disease	Study design	Main results	Ref.
RISE0634	Thye et al. (2010)	Tuberculosis	Discovery GWAMA (Ghana and Gambia): 2,237 cases and 3,122 controls (333,754 SNPs); Replication I (Ghana): 1,076 cases and 1,611 controls (top 17 SNPs); Replication II (Ghana and Malawi): 386 cases and 2993 controls (2 top SNPs).	Combined meta-analysis of the discovery and first replication cohort yielded two SNPs with P<5E-7 (rs2335704, rs4331426). Combined meta-analysis of all stages yielded one genome wide significant result (rs4331426, P=6.8x10-9, OR =1.19). Marker is located on chromosome 18 in a gene desert region.	(563)
RISE0846	Mahasirimongkol et al. (2012)	Tuberculosis	Discovery GWAMA (Thailand and Japan): 621 cases and 1,229 controls (533,252 SNPs); Replication GWAMA (Thailand and Japan): 481 cases and 1,138 controls (top 25 SNPs).	No genome wide significant result. Stratification by age meta-analysis yielded one genome wide significant locus in the young (<45 years) dataset (rs6071980, P=2.51E-8, OR=1.73) on chromosome 20 between *MAFB* and *HSEPEP1* genes.	(564)
RISE0865	Png et al. (2012)	Tuberculosis	Discovery (Indonesia): 108 cases and 115 controls (95,207 SNPs); Validation (Indonesia): 600 cases and 540 (top 2,381 SNPs); Replication (Russia): 1,837 cases and 1,779 controls (top 243 SNPs).	Suggestive evidence of association between 8 SNPs, located near or within the genes *JAG1, DYNLRB2, EBF1, TMEFF2, CCL17, HAUS6, PENK*, and *TXNDC4*. Most significant SNP in the overall meta-analysis was rs2273061 (P=0.0004, OR=1.16) on chromosome 20 located in the transcript of *JAG1*.	(565)
RISE0872	Rye et al. (2012)	Otitis media	Discovery (Australia): 416 cases and 1,075 controls (imputed to 2,524,817 SNPs); Replication (Australia): 645 families with 793 affected individuals (7 SNPs).	No genome wide significant result. Adjustment for 2 PCs identified 4 SNPs showing association at $P_{adj\text{-}PCA}<10^{-6}$ and 42 SNPs showing association at $P_{adj\text{-}PCA}<10^{-5}$. Most significant SNP was rs6755194 (P=8.3E-07, OR=1.90) belonging to *CAPN14*.	(566)
RISE0894	Thye et al. (2012)	Tuberculosis	Discovery (Ghana): 1329 cases and 1847 controls (imputed to	One genome-wide significant result was detected in the combined meta-analysis of	(97)

RISE ID	Author (year)	Disease	Study design	Main results	Ref.
			10,921,004 SNPs); Replication (Ghana): 817 cases and 3805 controls (top 11 SNPs); Validation cohorts for top 1 SNP (Gambia): 1,207 cases and 1,349 controls; (Indonesia) 1,025 cases and 983 controls, (Russia) 4,441 cases and 5,874 controls.	the discovery and first stage replication samples (rs2057178, P=2.63E-09, OR=0.77). Replication in three additional cohorts showed consistent effect of the allele, and nominal significance in two out of tree population, with combined meta-analysis p-value from all five datasets reaching P=2.57E-11. This SNP is located in an intergenic region downstream of *WT1* gene.	
RISE0921	Allen et al. (2013)	Otitis media	Discovery (USA): 602 individuals from 143 families with 373 COME/ROM subjects (324,748 SNPs); Replication (USA): 1,584 individuals from 441 families with at least two full siblings who had undergone tympanostomy tube insertion (top 53 SNPs).	No genome wide significant result. Top ranked SNP rs1110060 (P=9.1E-07, OR=0.51) is located on chromosome 15 within the *KIF7* gene. Top 45 SNPs were genotyped in a replication cohort, and one SNP on chromosome 2 reached significance threshold (rs10487394, p=2.9x10-5).	(567)
RISE1048	Chimusa et al. (2014)	Tuberculosis	Discovery (South African Coloureds): 642 cases and 91 controls (390,887 SNPs); Replication of Thye et al. 2010 and 2012 results.	No genome wide significant result. Study did confirm previously reported signals on chromosome 11 for *WT1* gene (rs2057178, P=2.71E-06, OR=0.62).	(568)
RISE1131	Anderson et al. (2015)	Pneumonia	Linear regression to check association with levels of IgG1 to PspC and PspA protein as potential vaccine candidates (Australia): 1,152 individuals (523,060 SNPs).	One genome-wide significant result was observed at *HLA* (rs9275596; P=3.1E-14).	(107)
RISE1142	Chen et al. (2015)	Influenza	Discovery (Hong Kong): 102 A(H7N9) cases and 106 heavily-exposed healthy poultry workers (705,459 SNPs which are imputed).	No genome-wide significant results. Top SNps were intronic variant of *C8B* gene (rs1960384, P=2.07E-06) and 2 kb upstream of *LGALS1 (*rs13057866, P=2.75E-06). The rs4820294/rs2899292 haplotype GG was	(569)

RISE ID	Author (year)	Disease	Study design	Main results	Ref.
				shown to be associated with protection from A(H7N9) infection (OR=0.26, P=5.92E-07).	
RISE1147	Curtis et al. (2015)	Tuberculosis	Discovery (Russia): 5,530 cases and 5,607 controls (imputed to 7.6 million SNPs); Replication from Thye et al. 2010 and 2012 datasets.	Combined meta-analysis showed an association between TB and SNPs located in introns of the *ASAP1* gene on chromosome 8q24 (rs4733781, P=2.6E-11; rs10956514, P=1.0-10).	(570)
RISE1202	Grant et al. (2016)	Tuberculosis	Discovery (Morocco): 252 parents, 239 PTB affected offspring and 67 unaffected offspring; Replication (Morocco): 317 cases and 657 controls (550,352 SNPs).	In the combined meta-analysis four SNPs showed suggestive association (intergenic rs358793 and rs17590261, and intronic *FOXP1* rs6786408 and *AGMO* rs916943). rs916943 showed to be nominally significant for early age-of onset (<25 yers).	(571)
RISE1227	Sveinbjornsson et al. (2016)	Tuberculosis	Discovery (Iceland): 3,686 cases and 277,643 controls (28.3 million SNPs); Replication I (Russia): from Curtis et al. (2015) dataset; Replication II (Croatia): 244 cases and 924 controls (top 3 SNPs).	Replication datasets and combined meta-analysis confirmed significant association of three SNPs in HLA (rs557011, P=2.0E-15; rs9271378, P=3.2E-15; DQA1*03, P= 1.9E-09).	(104)
RISE1252	Hayden et al. (2017)	Pneumonia	Discovery GWAMA (USA): childhood pneumonia (843 cases and 9,091 controls), lifetime pneumonia (3,766 cases and 5,659 controls) (~7M SNPs).	No genome-wide significant results. Regions of interest for childhood pneumonia are *NGR1*, *PAK6*, and near *MATN1,* while for lifetime pneumonia are *RAPGEF2*, *PHACTR1*, near *PRR27*, and near *MCPH1.*	(572)
RISE1259	Qi et al. (2017)	Tuberculosis	Discovery (China): 972 cases and 1,537 controls (691,388 SNPs); Replication I (China): 2,304 cases and 2,108 controls (top 45 SNPs); Replication II (China): 1,156 cases and 2,754 controls (top 9 SNPs).	Combined meta-analysis revealed three significant SNPs with candidate genes *MFN2* (rs4240897 P=1.41E-11), *RGS12* (rs2269497, P=3.37E-08), and *HLA* class II beta chain (rs41553512, P=7.93E-11).	(105)
RISE1263	Tian et al. (2017)	Tuberculosis	23andMe research participants of European ancestry: Positive TB test	One significant SNP for positive TB test (rs2894257, *HLA* gene, P=8.16E-36), and	(106)

RISE ID	Author (year)	Disease	Study design	Main results	Ref.
		Pneumonia	(4,426 cases and 84,290 controls), Pneumonia (40,600 cases and 90,039 controls)	one for pneumonia (rs3131623, *HLA* gene, P=1.99E-15).	
RISE1287	Mekonnen et al. (2018)	Tuberculosis	Discovery (Ethiopia): 153 cases and 139 controls.	Suggestive novel associations were observed between two variants in *NOD1* and TB: rs751770147 [unadjusted $p = 7.28 \times 10^{-5}$] and chr7:30477156(T), a novel variant, [unadjusted $p = 1.04 \times 10^{-4}$]. Two SNPs in *TICAM2* were nominally associated with TB, including rs2288384 [unadjusted p = 0.003].	(573)

11 RESUME

Date (place) of birth: 13/02/1990 (Zagreb, Croatia)
Contact information: +385-98-9887-789; andrea.gelemanovic@gmail.com

Work experience:

01/2015 – 01/2019	**Research associate** University of Split, School of Medicine, Department of Public Health, Split, Croatia
10/2016 – 12/2016	**Visiting researcher** MRC Institute of Genetics & Molecular Medicine, The University of Edinburgh, Edinburgh, United Kingdom
05/2014 – 12/2014	**Scientific research (volunteer)** University of Split, School of Medicine, Department of Public Health, Split , Croatia
01/2013 – 03/2015	**Scientific research (volunteer)** Department for Molecular Biology, Faculty of Science, University of Zagreb, Zagreb, Croatia
04/2011 – 03/2015	**Scientific research (volunteer)** Department of Zoology, Faculty of Science, University of Zagreb, Zagreb, Croatia

Education:

04/2015 – 01/2019	**PhD student** University of Split, School of Medicine, Split, Croatia Translational Research in Biomedicine (TRIBE)
09/2011 – 02/2014	**MSc in Molecular Biology** Division of Biology, Faculty of Science, University of Zagreb, Zagreb, Croatia
09/2013 – 02/2014	**ERASMUS exchange program** Centre for Molecular Biology and Faculty of Life Sciences, University of Vienna, Vienna, Austria
09/2008 – 09/2011	**BSc in Molecular Biology** Division of Biology, Faculty of Science, University of Zagreb, Zagreb, Croatia

Publications:

1. Suri P, Palmer MR, Tsepilov YA, Freidin MB, Boer CG, Yau MS, Evans DS, **Gelemanović A**, Bartz TM, Nethander M, Arbeeva L, Karssen L, Neogi T, Campbell A, Mellstrom D, Ohlsson C, Marshall LM, Orwoll E, Uitterlinden A, Rotter JI, Lauc G, Psaty BM, Karlsson MK, Lane NE, Jarvik GP, Polašek O, Hochberg M, Jordan JM, Van Meurs JBJ, Jackson R, Nielson CM, Mitchell BD, Smith BH, Hayward C, Smith NL,

Aulchenko YS, Williams FMK (2018). Genome-wide meta-analysis of 158,000 individuals of European ancestry identifies three loci associated with chronic back pain. PLoS Genetics 14(9):e1007601.

2. Relja A, Miljković A, **Gelemanović A**, Bošković M, Hayward C, Polašek O, Kolčić I (2017). Nut Consumption and Cardiovascular Risk Factors: A Cross-Sectional Study in a Mediterranean Population. Nutrients 9(12):e1296.
3. Gajšak LR, **Gelemanović** A, Kuzman MR, Puljak L (2017). Impact of stress response in development of first-episode psychosis in schizophrenia: An overview of systematic reviews. Psychiatria Danubina 29(1):14-23.
4. Kolčić I, Relja A, **Gelemanović A**, Miljković A, Boban K, Hayward C, Rudan I, Polašek O (2016). Mediterranean diet in the southern Croatia - does it still exist?. Croatian Medical Journal 57(5):415-24.
5. **Gelemanović A***, Dobberpuhl K*, Krakar G, Patarčić I, Kolčić I, Polašek O (2016). Host genetics and susceptibility to congenital and childhood cytomegalovirus infection: a systematic review. Croatian Medical Journal 57(4):321-30.
6. Previšić A*, **Gelemanović A***, Urbanič G, Ternjej I* (2016). Cryptic diversity in the Western Balkan endemic copepod: four species in one?. Molecular Phylogenetics and Evolution 100:124-134.
7. Patarčić I*, **Gelemanović A***, Kirin M, Kolčić I, Theodoratou E, Baillie K, de Jong M, Rudan I, Campbell H, Polašek O (2015). The role of host genetic factors in respiratory tract infectious diseases: systematic review, meta-analyses and a field synopsis. Scientific Reports 5:16119.

Projects:

1. "PREPARE - Platform foR European Preparedness Against (Re-)emerging Epidemics"; EU FP7; 602525 (2015-2019).
2. "Pleitropy, gene networks and gene pathways in isolated human populations: the 10,001 Dalmatians biobank"; Croatian Science Foundation; 8875 (2015-2018).
3. "BBMRI - Biobanking and Biomolecular Resources Research Infrastructure - Large prospective cohorts"; EU FP7; 313010 (2015-2017).

Conferences:

1. The European Human Genetics Conference 2017, Copenhagen, Denmark, May 2017 (poster presentation: Multiple rare variants in immune genes predict common respiratory infections burden in isolated populations).
2. World Health Summit, Berlin, Germany, October 2016 (poster presentation as part of the New Voices in Global Health initiative: Can existing knowledge help us PREPARE in case of an epidemic crisis? Emergency exercise on Zika virus).
3. Summer Frontiers 2016 – Systems Biology of Innate Immunity, Nijmegen, the Netherlands, September 2016 (oral presentation: Host genetic susceptibility to infectious diseases).
4. The European Human Genetics Conference 2016, Barcelona, Spain, May 2016 (poster presentation: Genetic network as post-GWAS analysis approach for correlated complex phenotypes: example on infectious diseases).
5. 26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Amsterdam, the Netherlands, April 2016 (oral presentation: Genome-wide

association, genetic network and pathway analyses identify novel human genes for susceptibility to common infectious diseases).
6. 10th International Biomedical CROatian Student Summit, Zagreb, Croatia, April 2014 (oral presentation: Molecular and paleopathological analysis of possible cases of rheumatoid arthritis in human archaeological samples from Croatia).
7. 8th ISABS Conference on Forensic, Anthropologic and Medical Genetics and Mayo Clinic Lectures in Translational Medicine, Split, Croatia, June 2013.
8. 5th Croatian Congress of Microbiology with International Participation, Primošten, Croatia, September 2012.

Workshops, seminars, summer schools:

1. 10th International workshop on machine learning in systems biology, The Hague, The Netherlands, September 2016.
2. Research Summer School in Statistical Omics, Split, Croatia, August 2016 (project tutor)
3. 8th Croatian Cochrane Symposium, Split, Croatia, May 2016.
4. Research Summer School in Statistical Omics, Split, Croatia, August 2015 (participant)
5. 7th Croatian Cochrane Symposium, Split, Croatia, May 2015.
6. IntegraLife Workshop on Scientific publishing and intellectual property protection in life sciences, Zagreb, Croatia, November 2014.

Scholarships and awards:

1. British Scholarship Trust scholar 2016/2017 (awarded a scholarship for a two-month research study visit in Edinburgh, UK, October-December 2016).
2. Winner candidate of 2016 New Voices in Global Health initiative (World Health Summit, Berlin, Germany, 2016).
3. First place in Croatian competition in science communication FameLab (Zagreb, Croatia, 2013).
4. Second place in international competition in science communication FameLab (Cheltenham, UK, 2013).
5. Acknowledgement of the Faculty Council of Faculty of Science, University of Zagreb for outstanding achievement in the study (2013).
6. Award of the City of Samobor (2013).
7. Rector's award for manifestation "Night of Biology" at Faculty of Science, University of Zagreb (2012).
8. Scholarship of University of Zagreb for excellence in academic year 2012/2013, 2011/2012.