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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).

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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

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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).

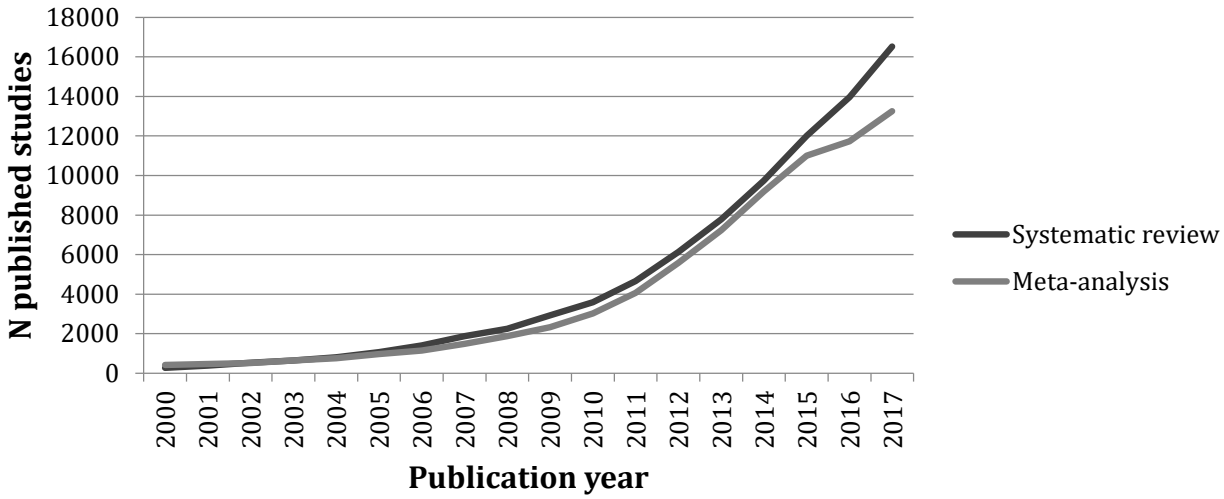


Figure 1 Number of published studies using keywords „systematic review“ and „meta-analysis“ (Medline search performed on December 17, 2018 (48))

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.

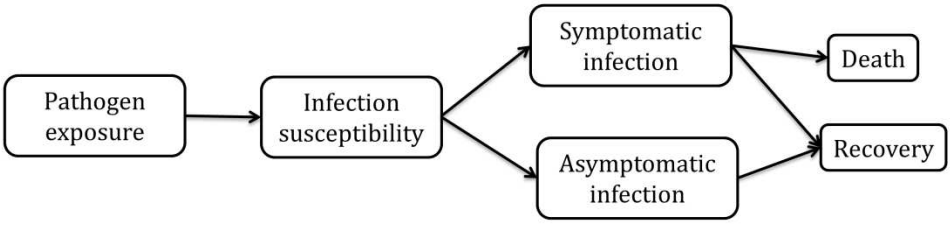


Figure 2 Simplified scheme of disease model

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.

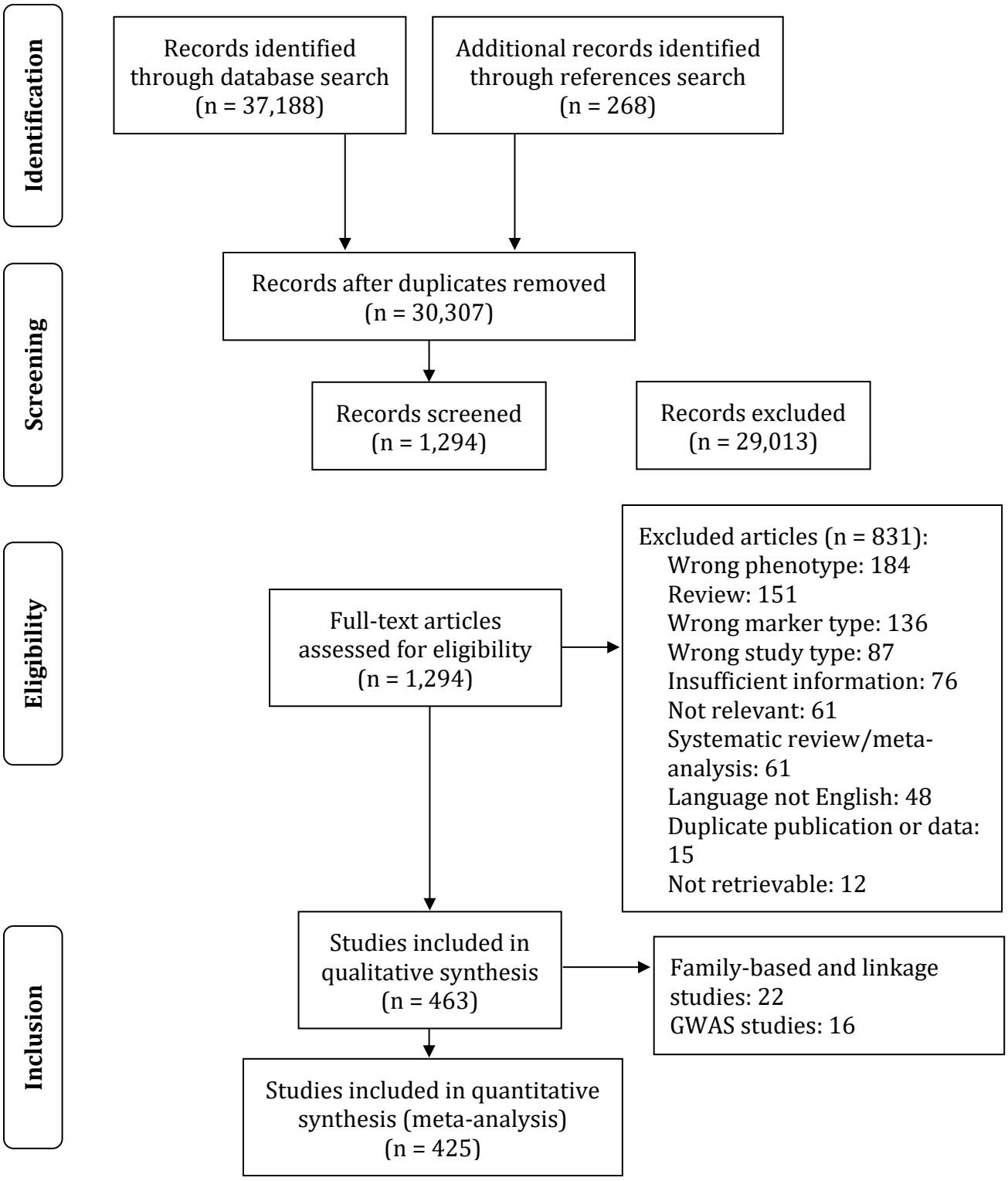


Figure 3 PRISMA guidelines study flowchart and data extraction process scheme

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.

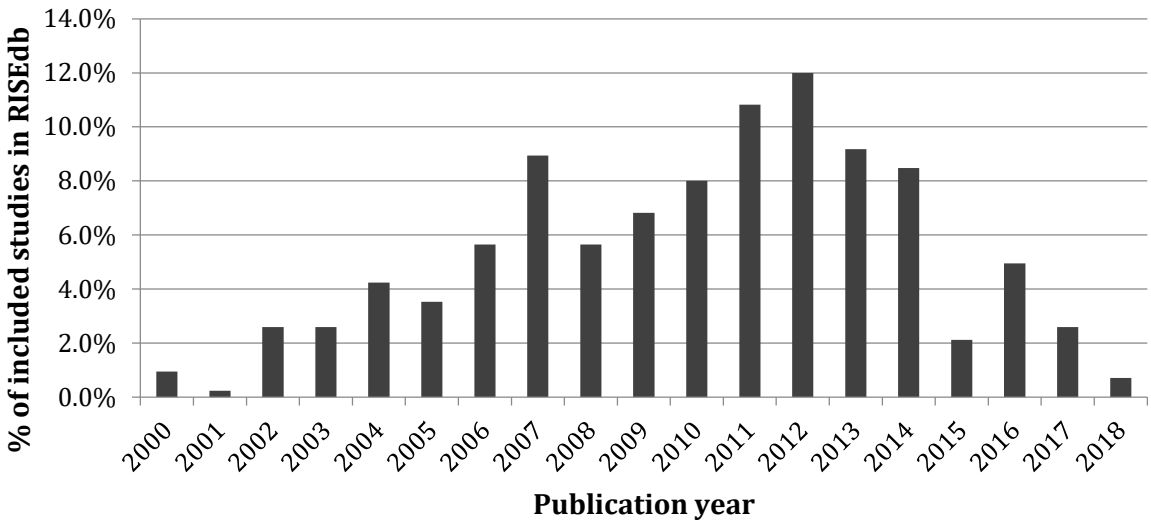


Figure 4 Distribution of included studies in RISEdb according to publication year

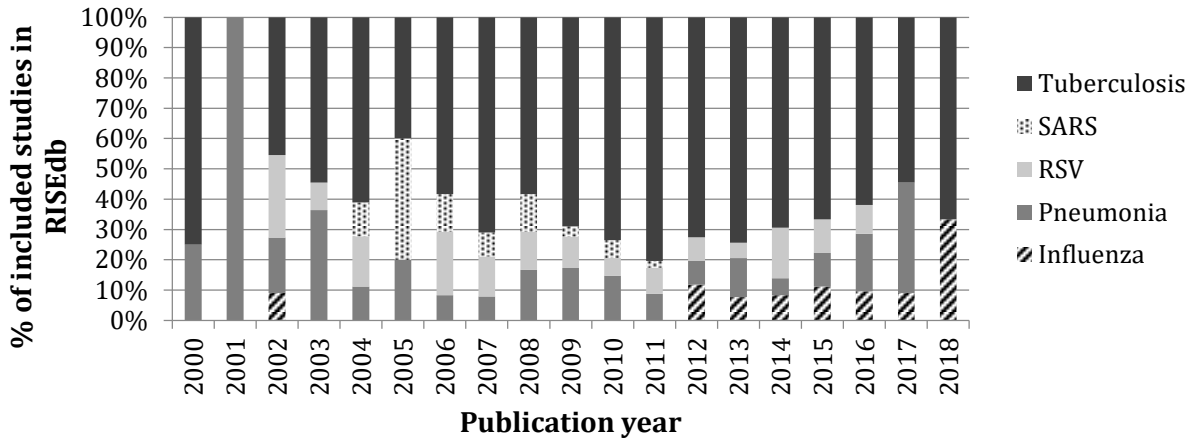


Figure 5 Distribution of included studies in RISEdb according to the publication year and stratified per disease

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.

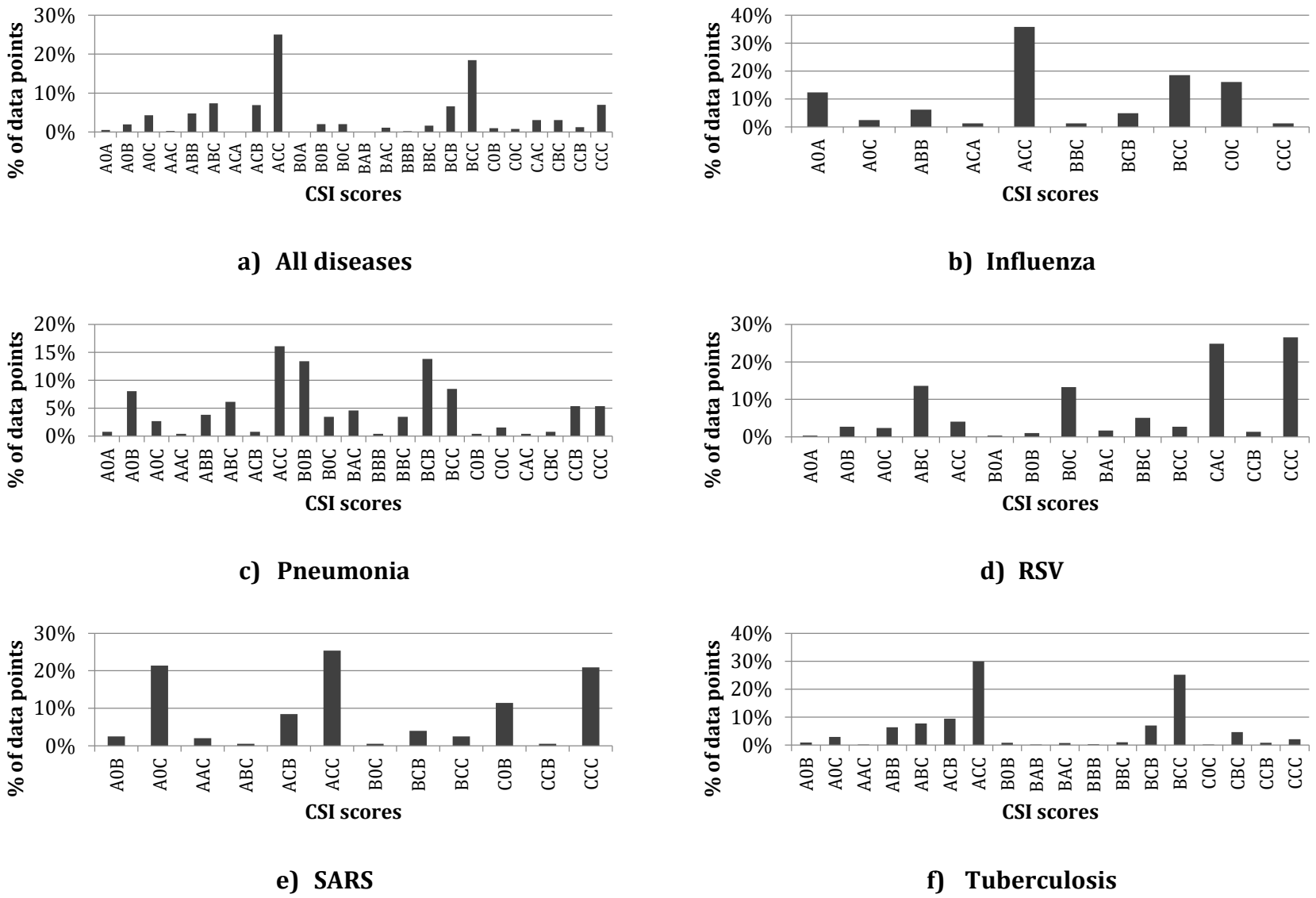


Figure 6 CSI scores for pooled and per each disease category (Confounding-Selection-Information risk of bias scale; grades of credibility: A – high, B – intermediate, C – weak, 0 – *post-hoc* stratification of cases in disease severity models)

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.

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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

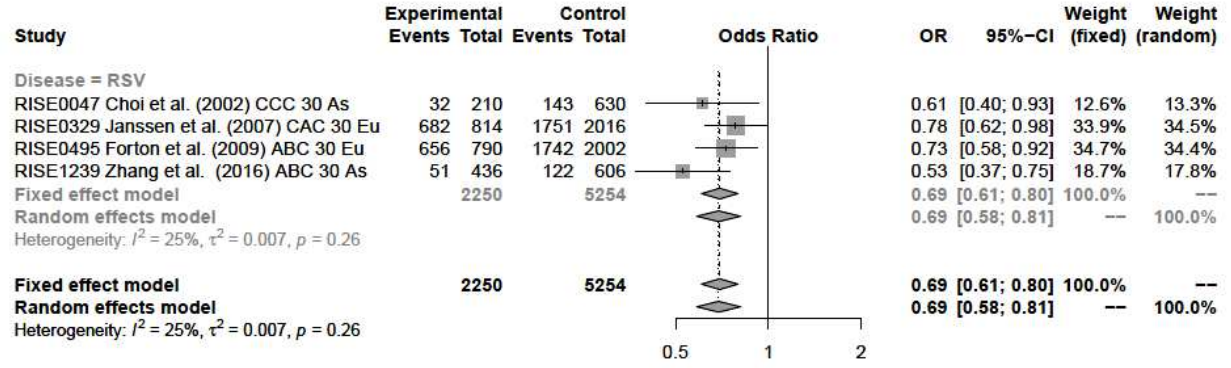
Gene	SNP	Alleles*	N studies	N cases	N controls	Stratification	P	OR [95% CI]	BFDP med/low (very low)	I^2, %	Venice score
Pooled diseases											
CCL2	rs1024611	A/G	23	9342	10215	-	0.022	0.89 [0.81, 0.98]	0.852 (0.997)	52.8	BCC
CCL2	**rs1024611**	**A/G**	**5**	**2195**	**2031**	**Admixed**	**<0.001**	**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

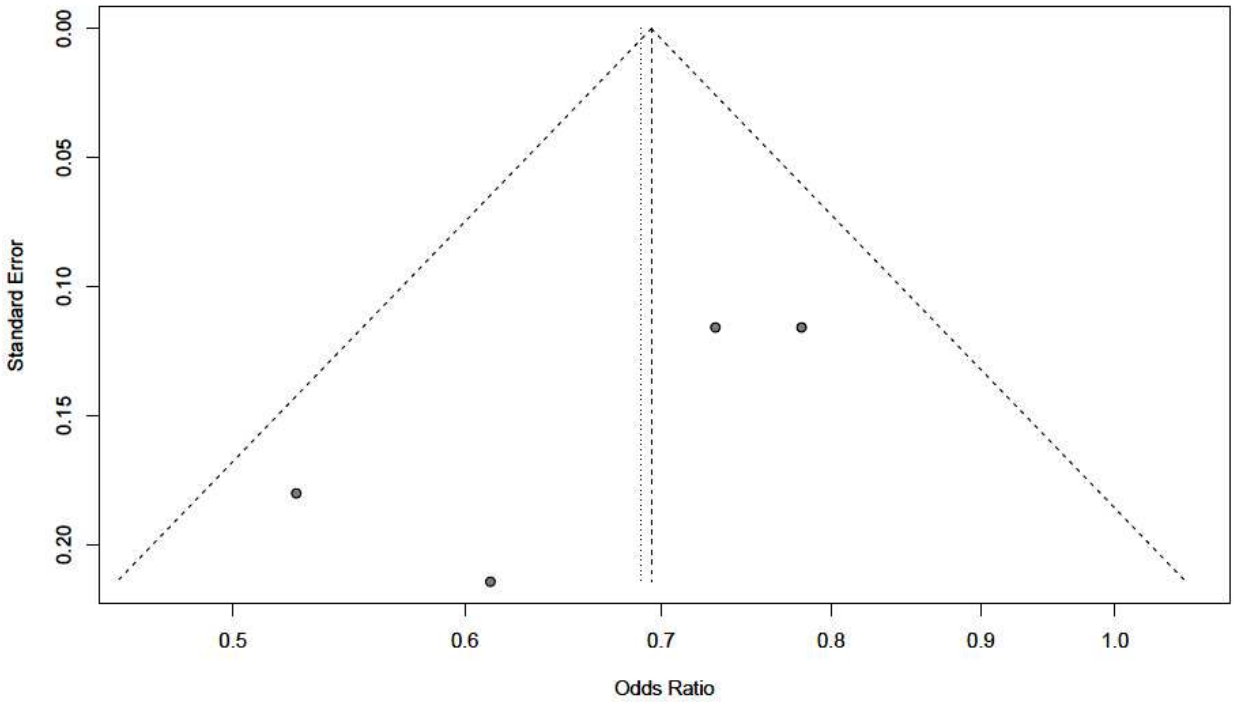
Table A.7 Random-effects meta-analyses results, various models, subset analysis (exposed controls: 31/2 and 32 disease models) and disease severity (43 disease model) [nominally significant results only, significant results for the mid/low BFDP level shown in bold]

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

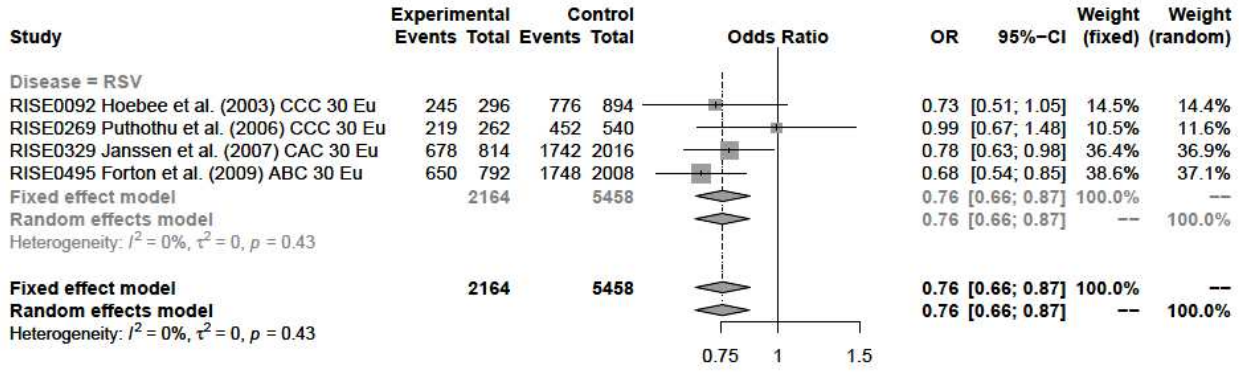


a)

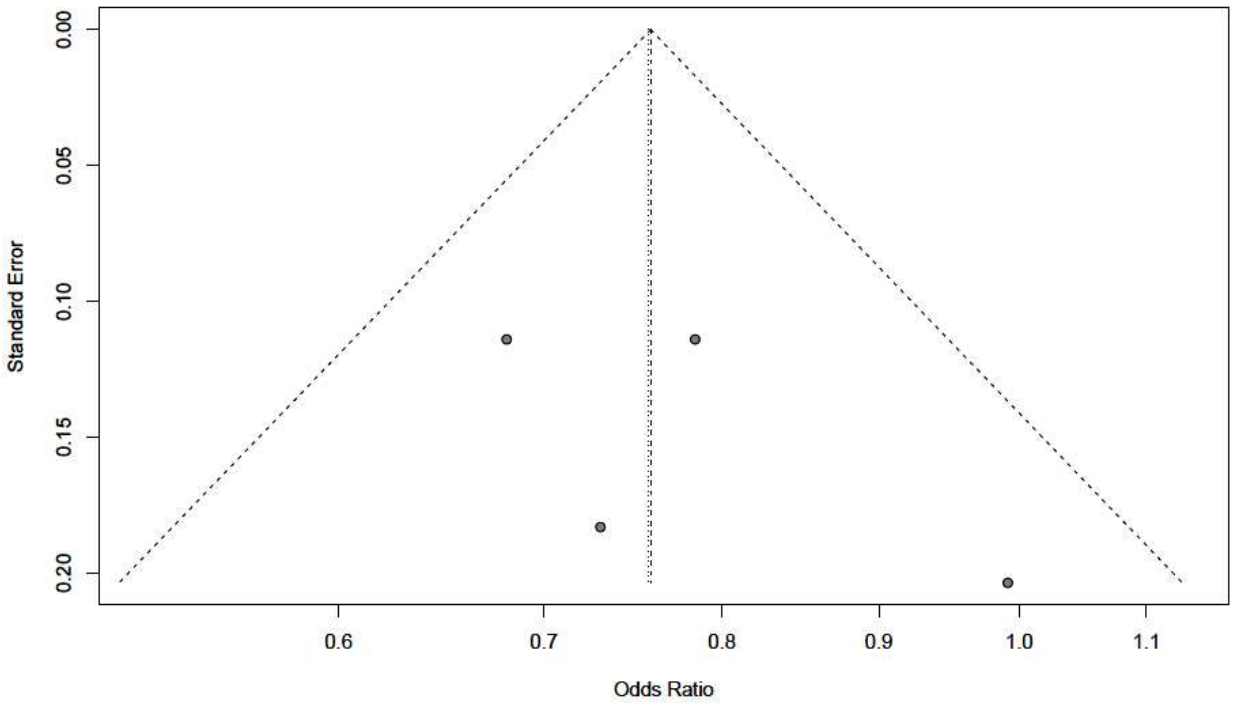


b)

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]

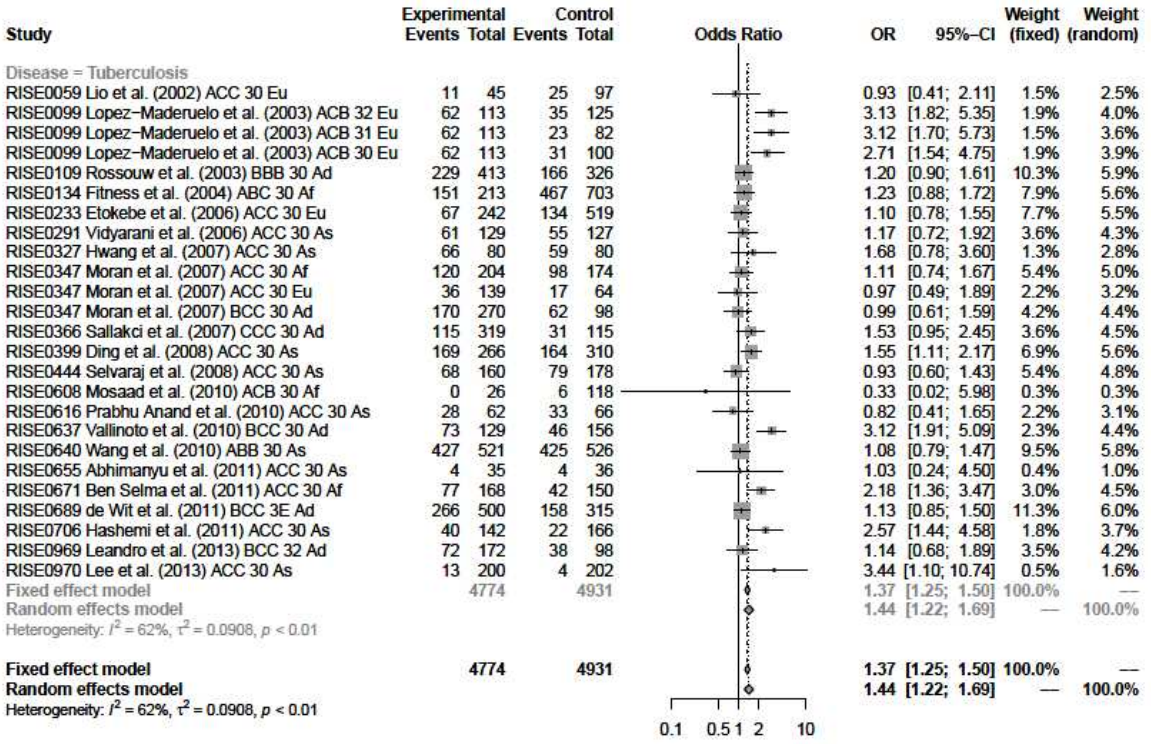


a)

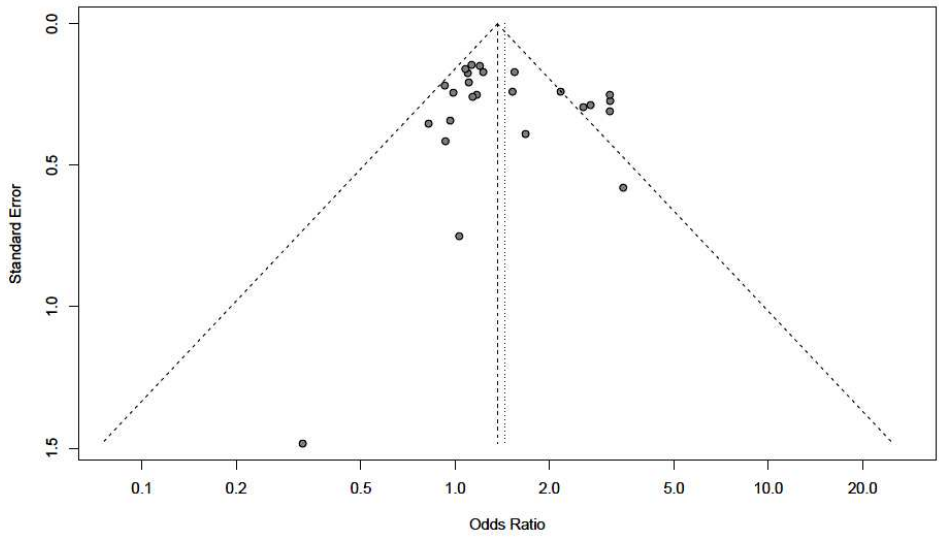


b)

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]

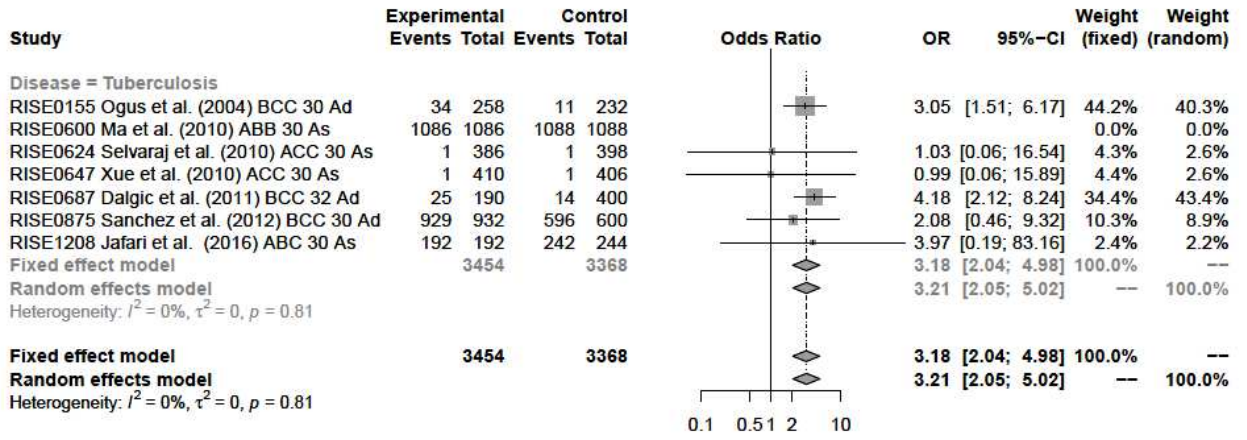


a)

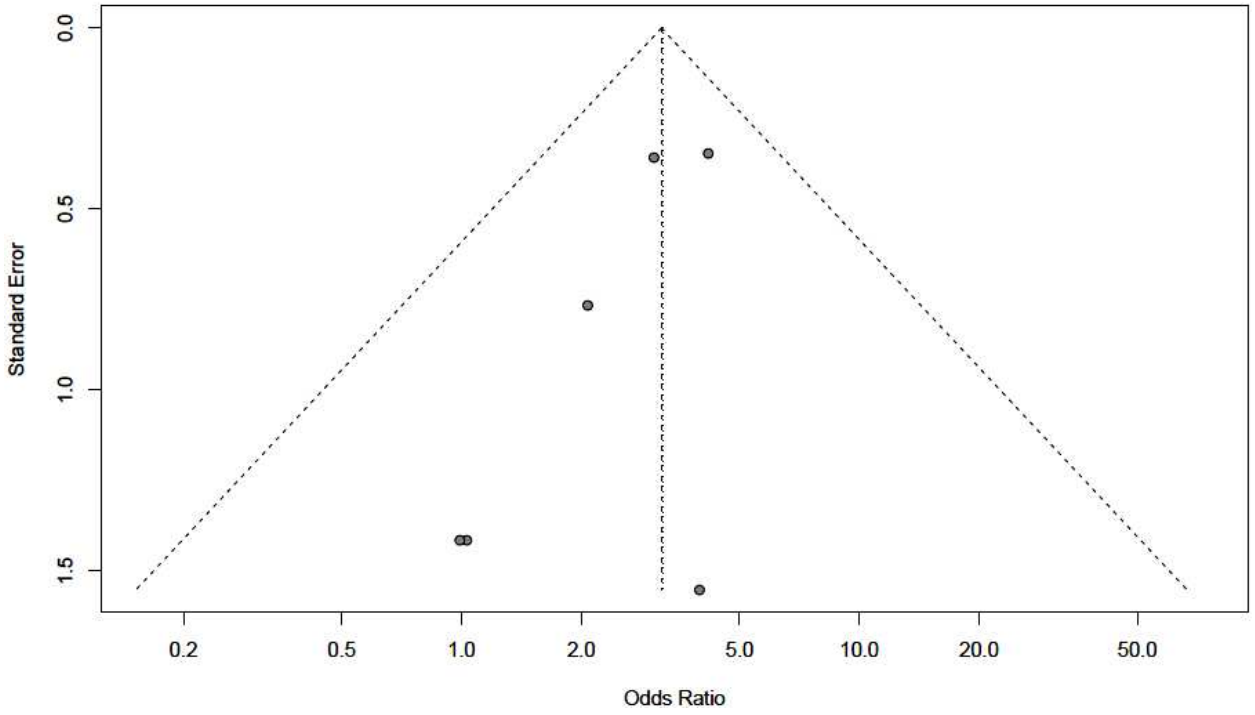


b)

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]

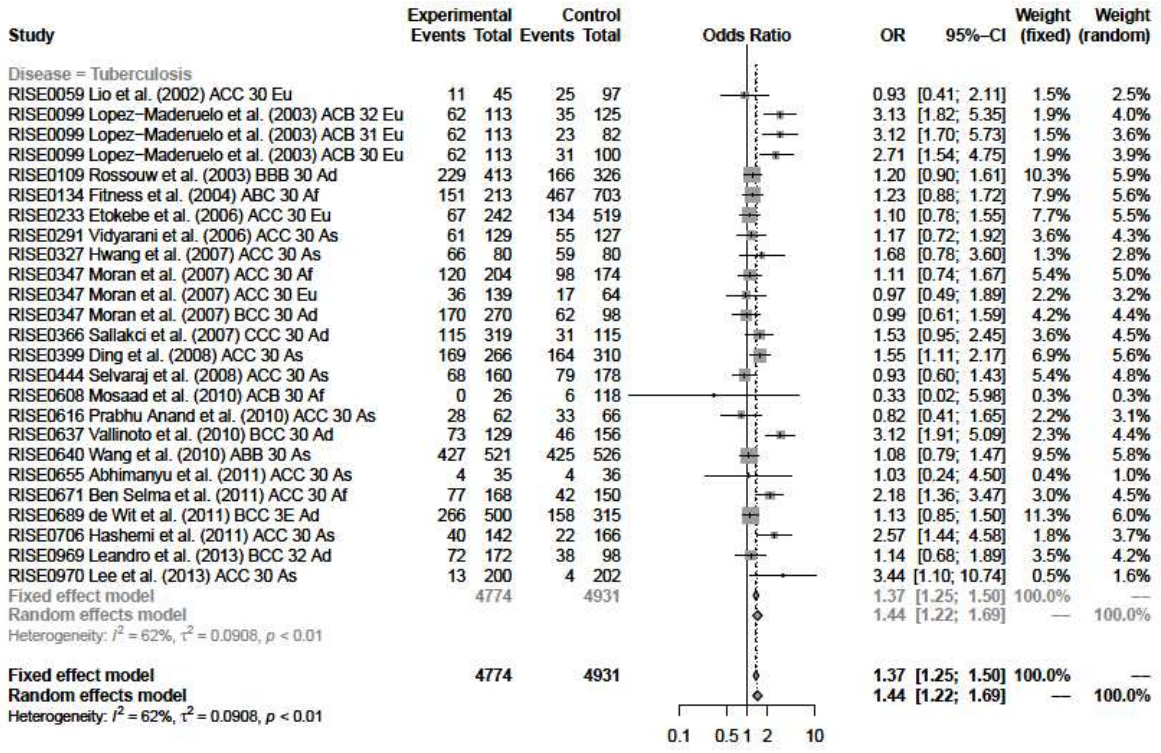


a)

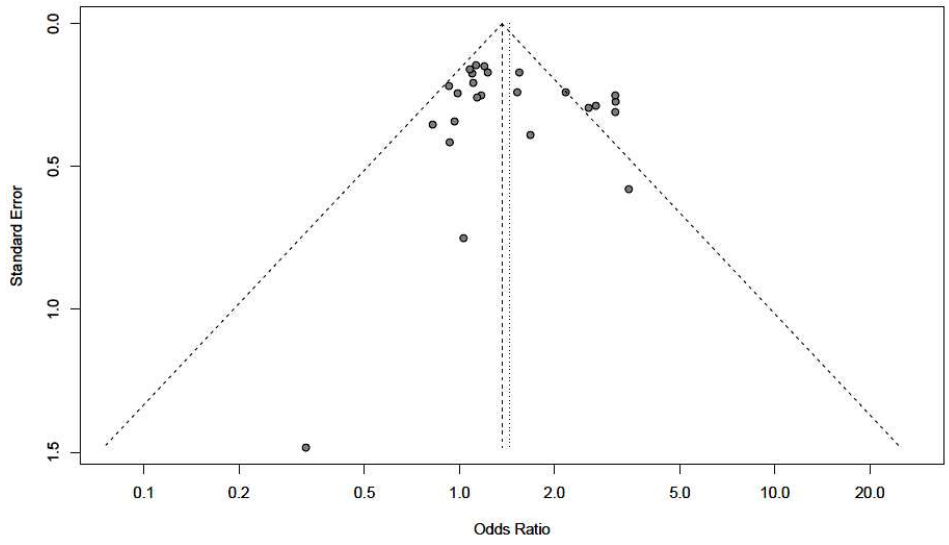


b)

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]

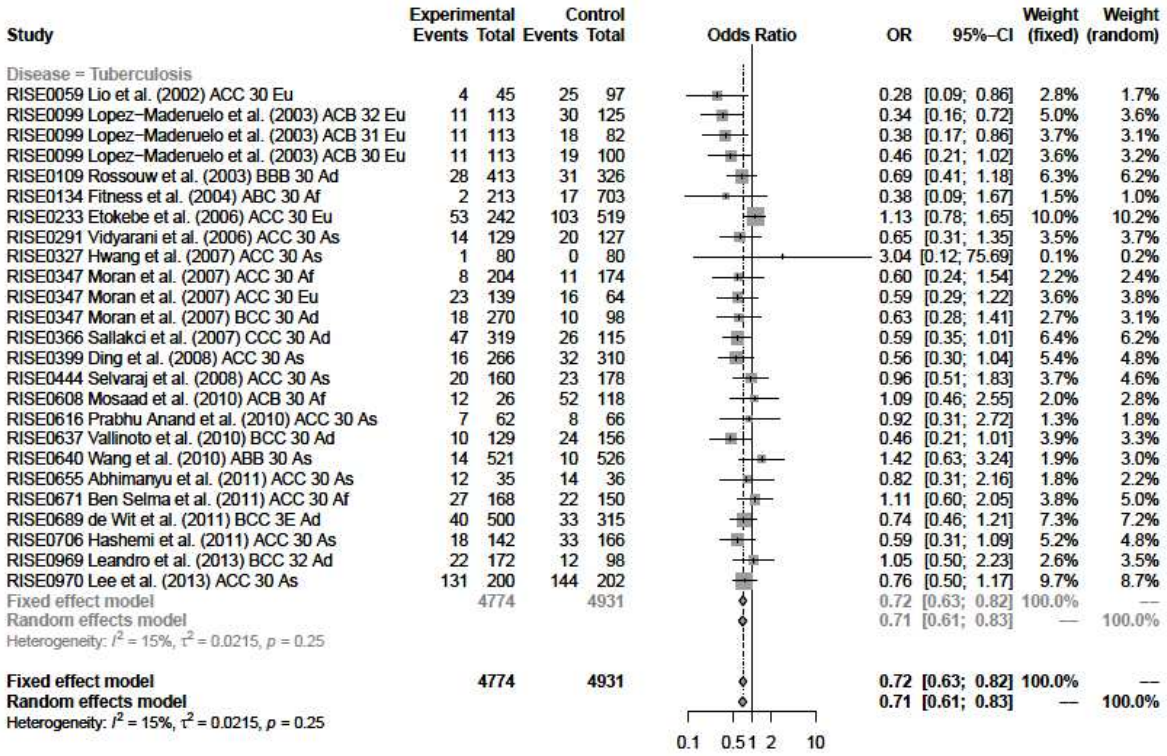


a)

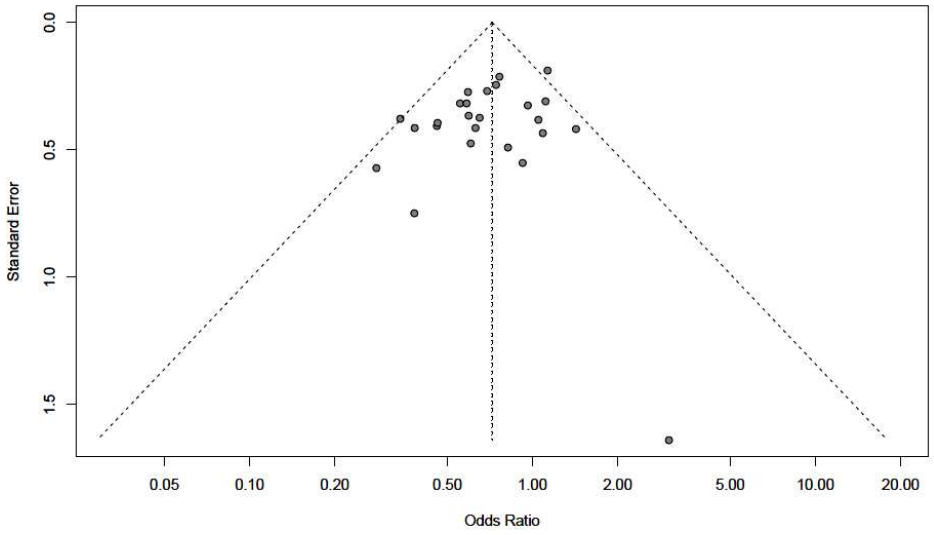


b)

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]

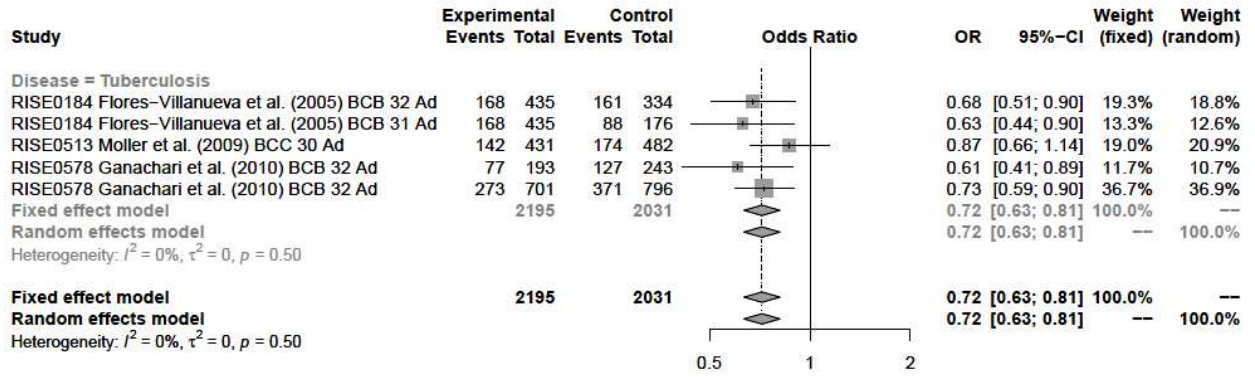


a)

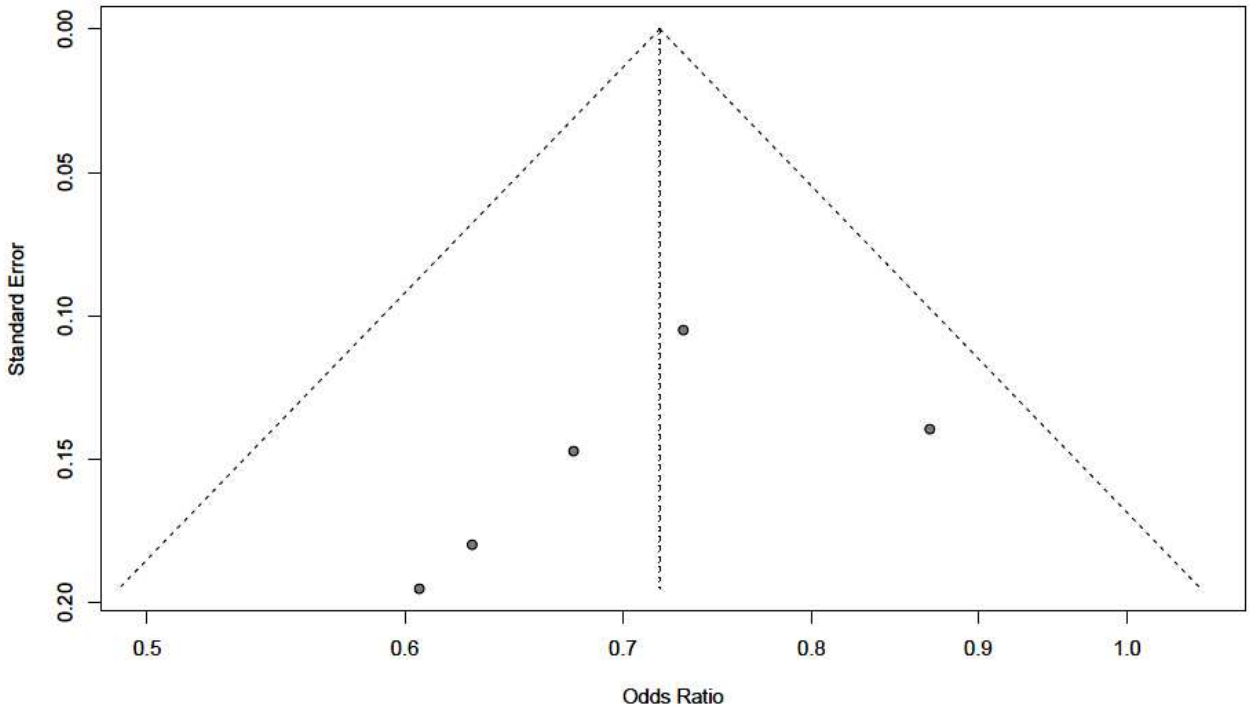


b)

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]

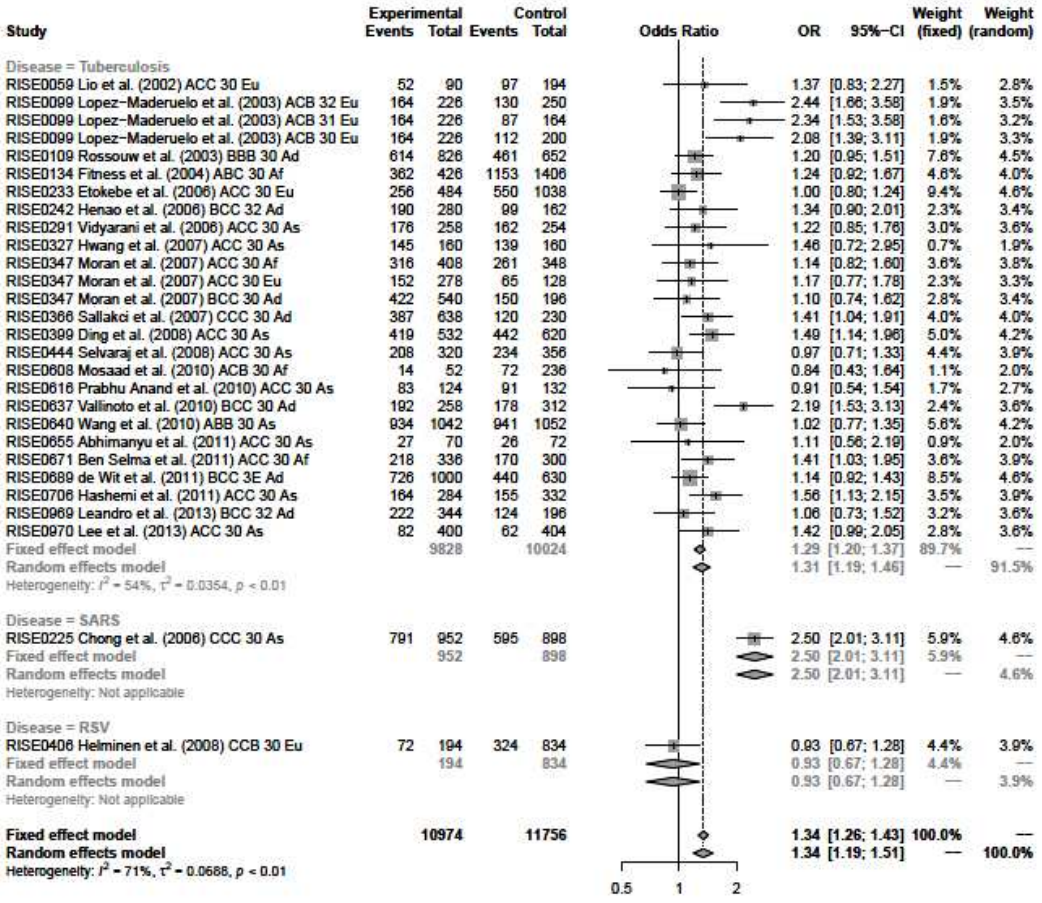


a)

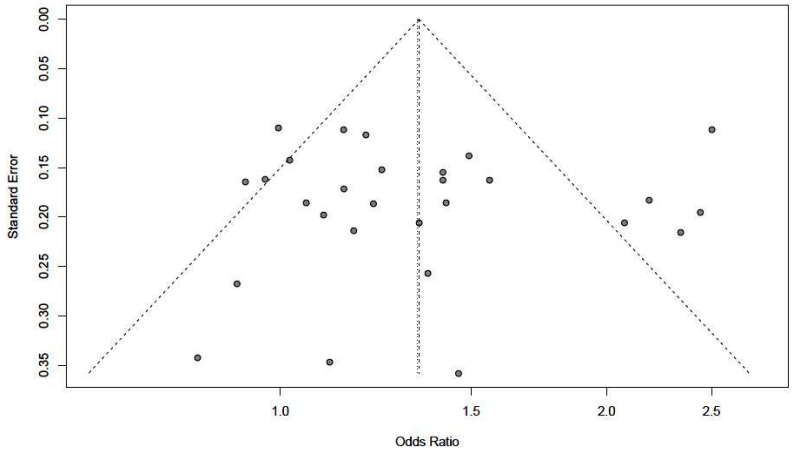


b)

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]

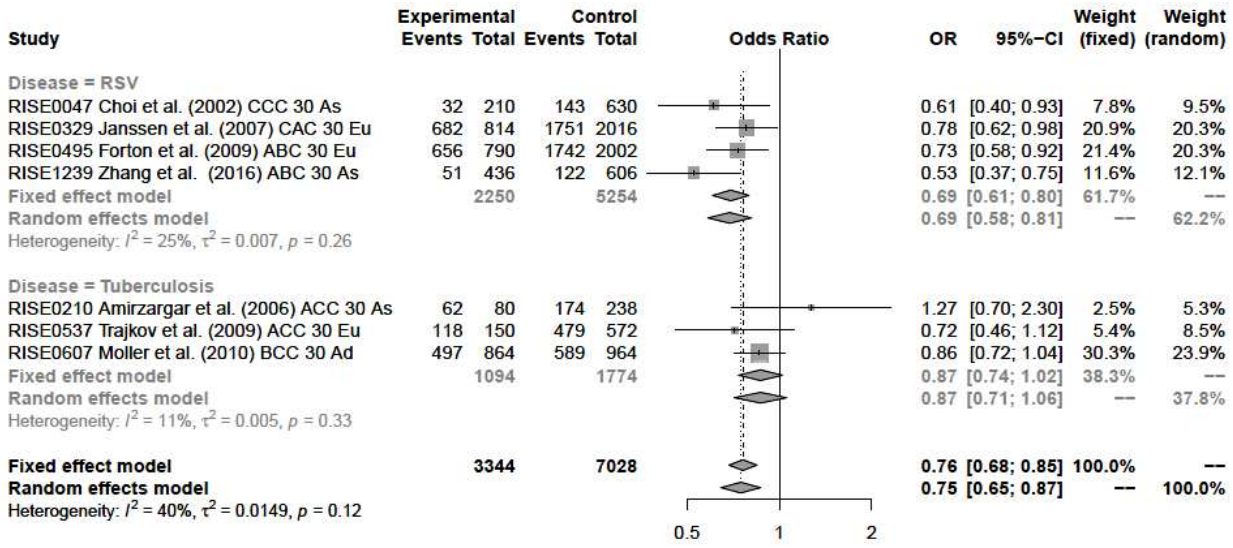


a)

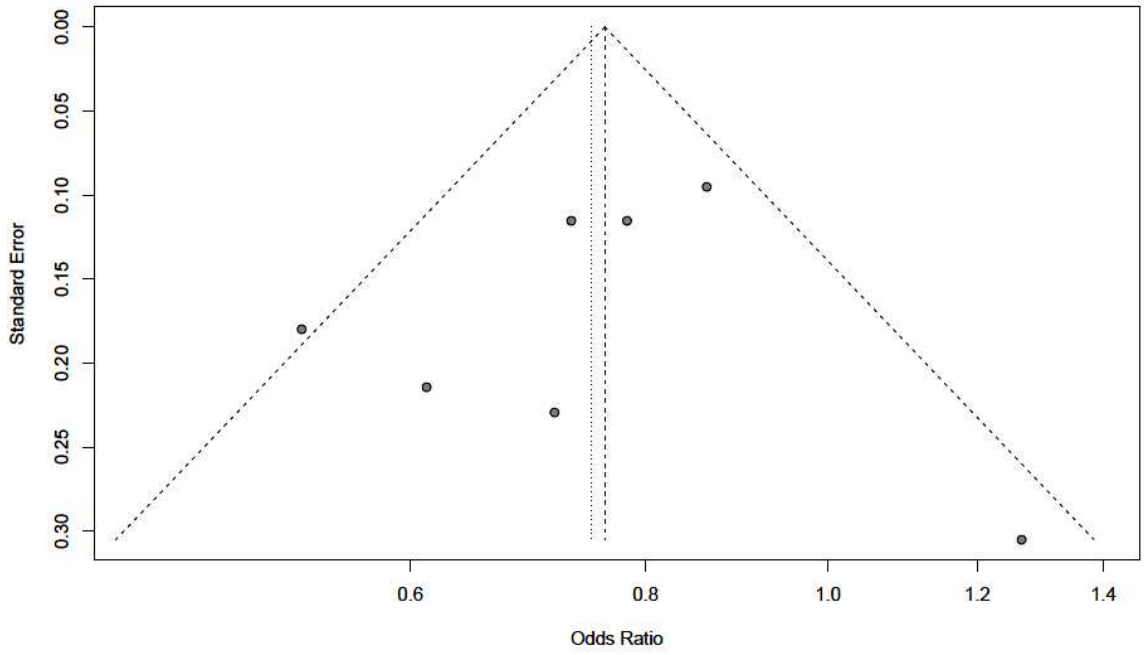


b)

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]

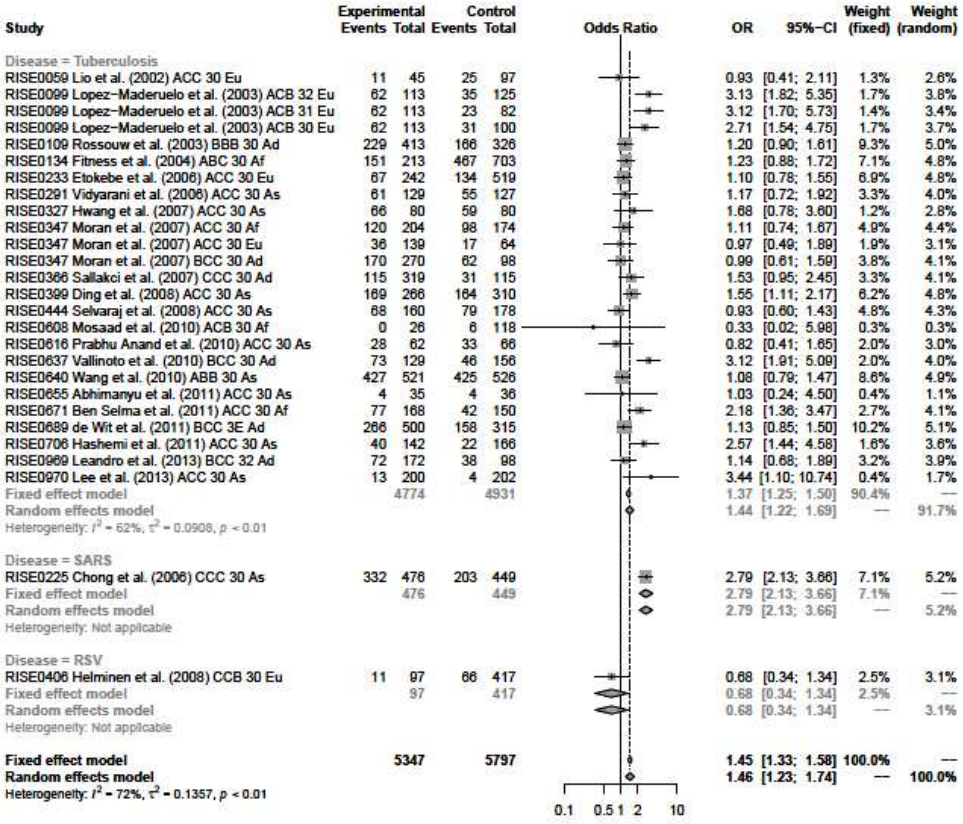


a)

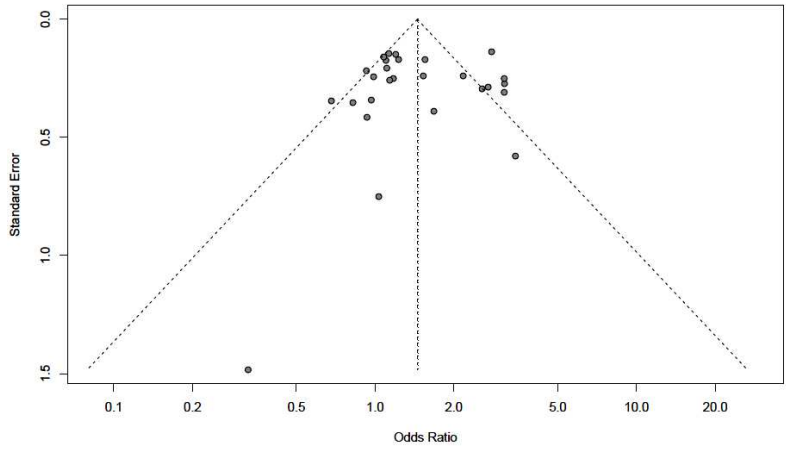


b)

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]

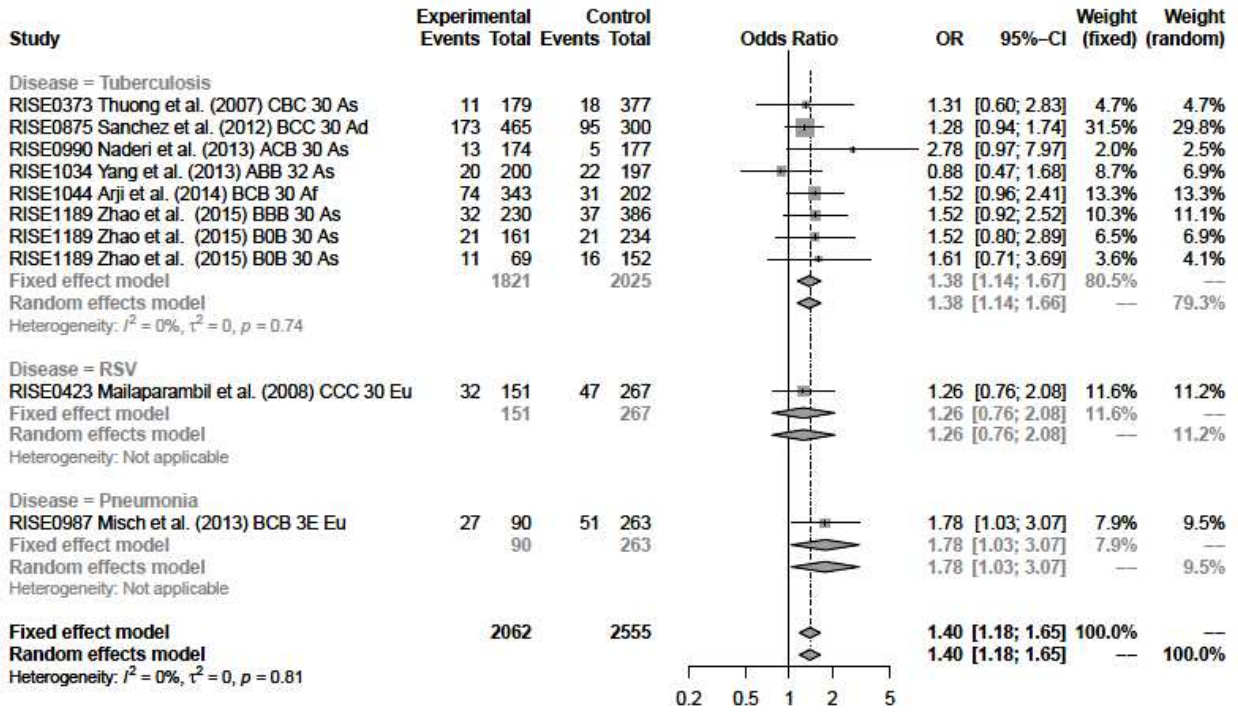


a)

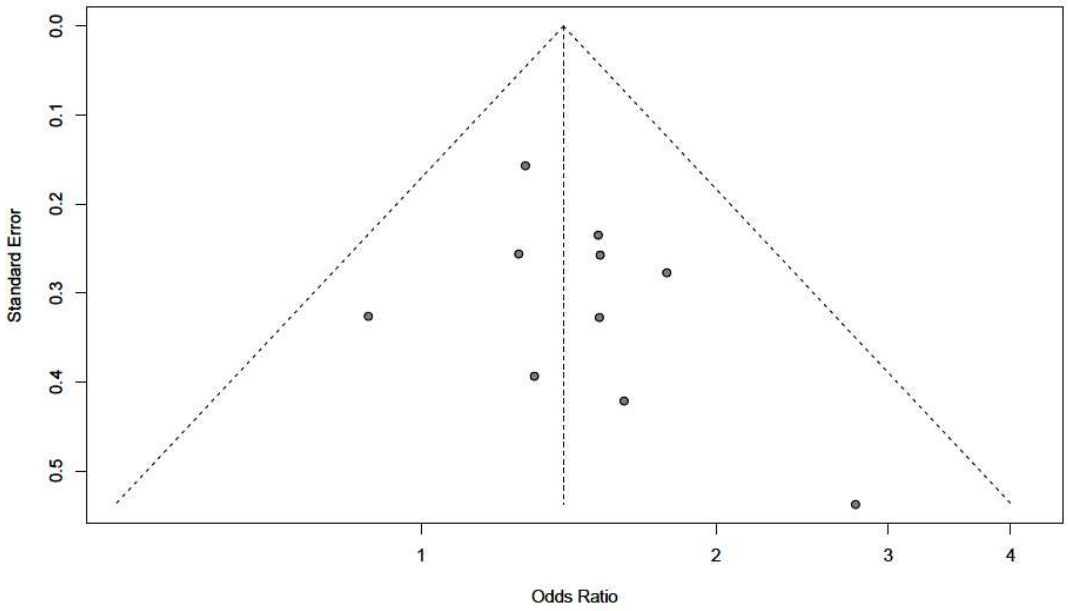


b)

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]

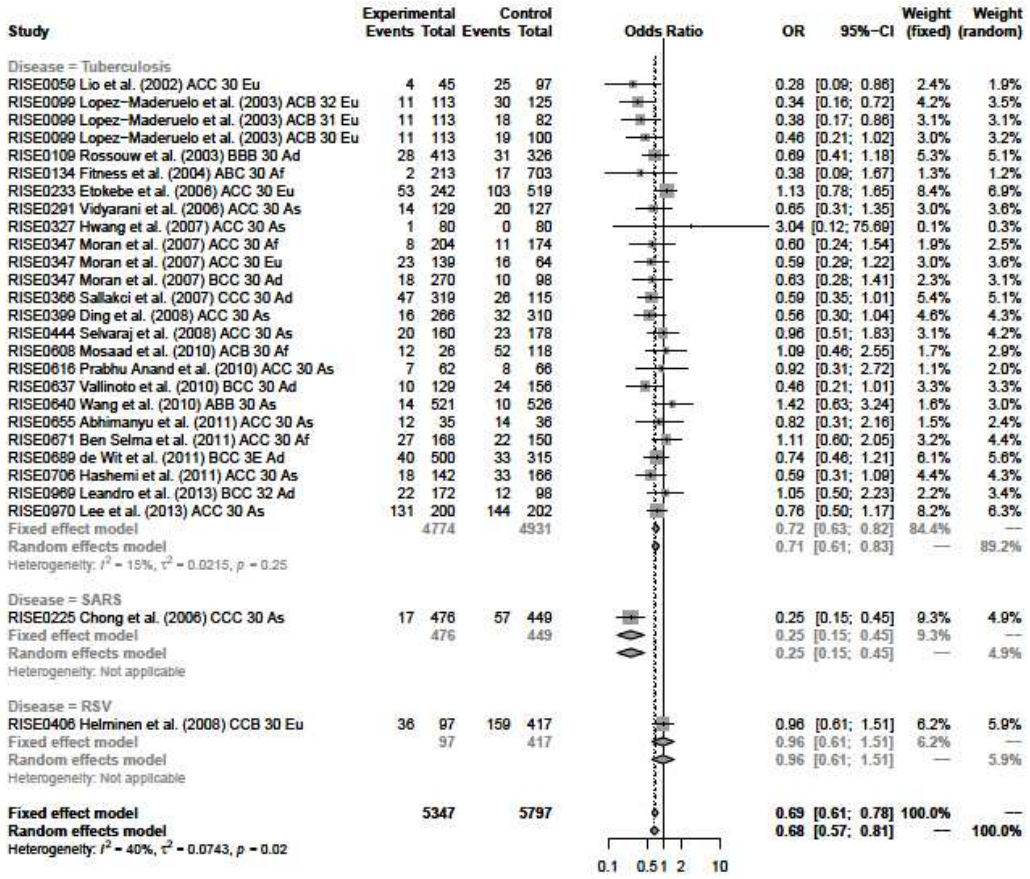


a)

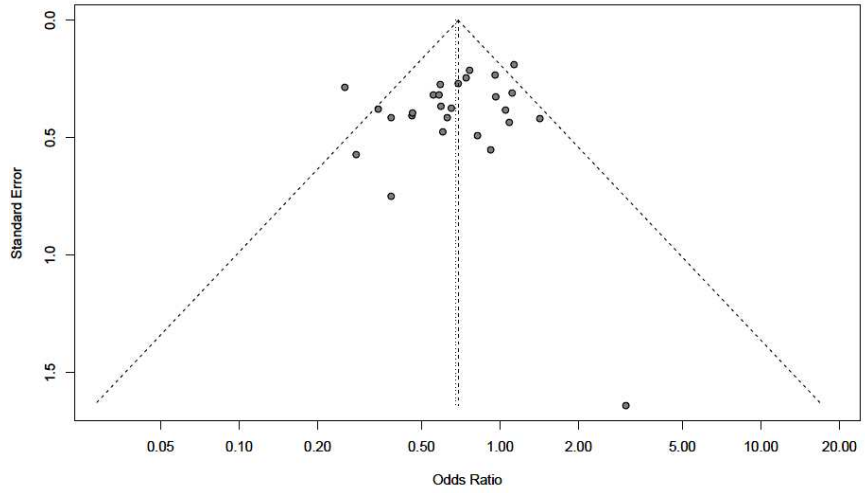


b)

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]

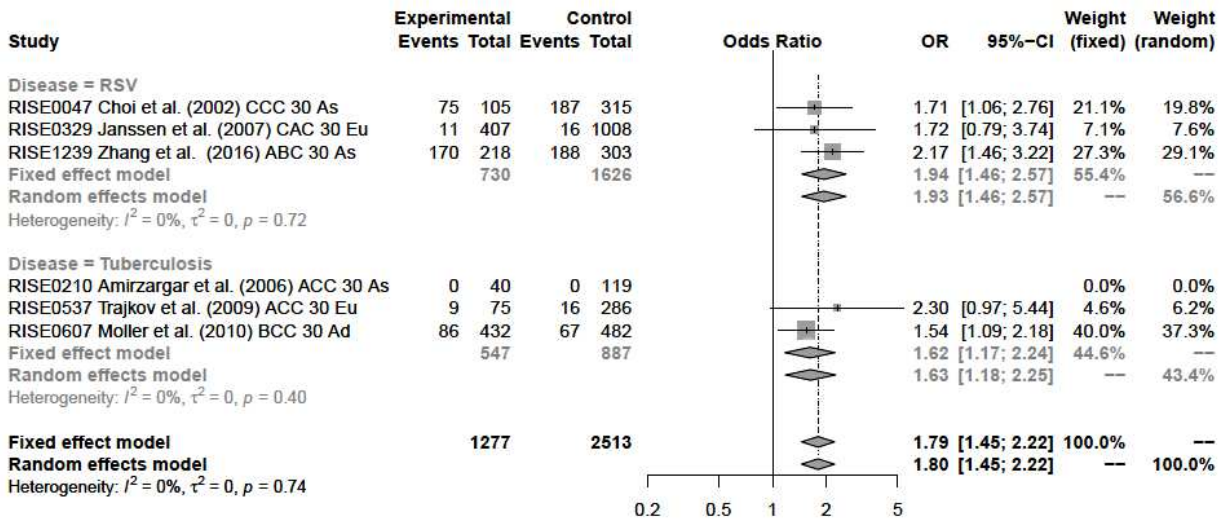


a)

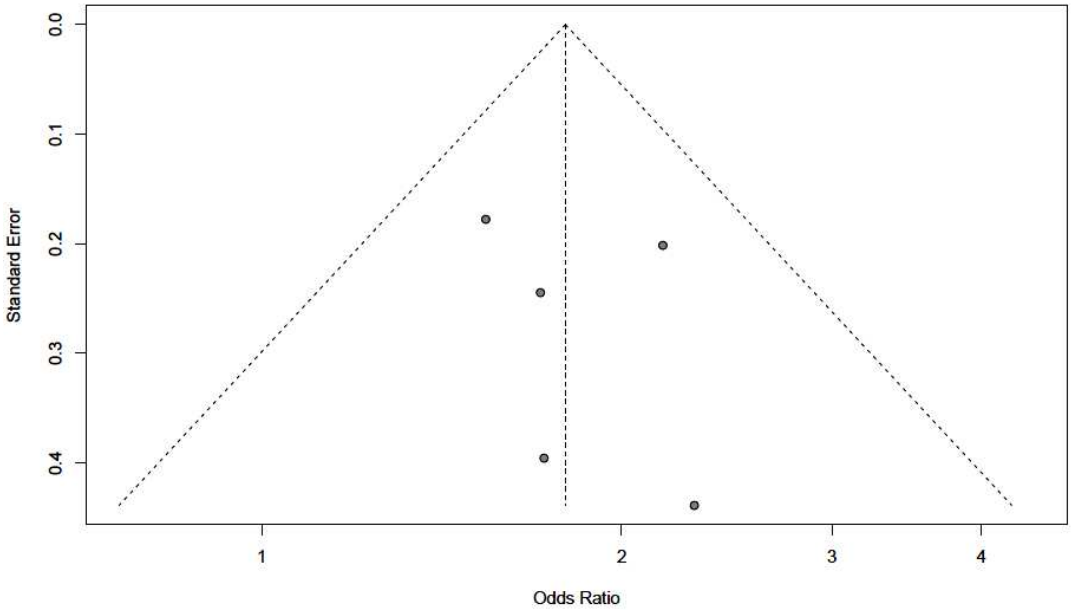


b)

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]

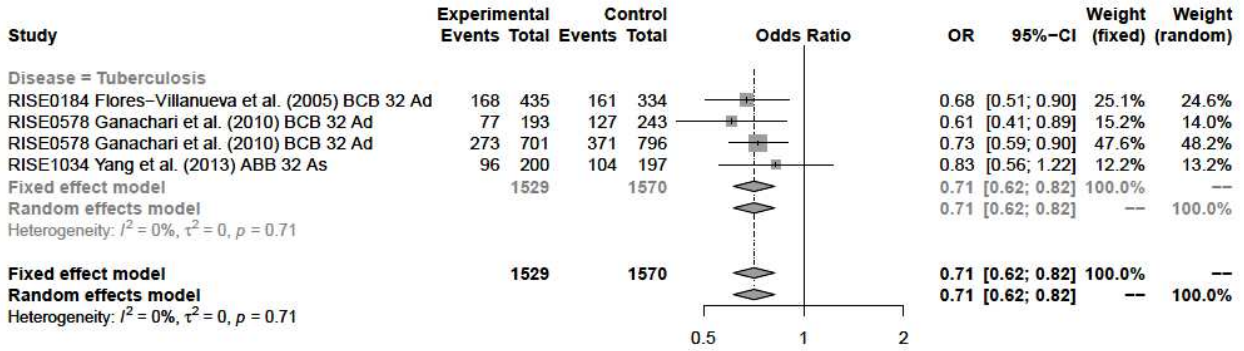


a)

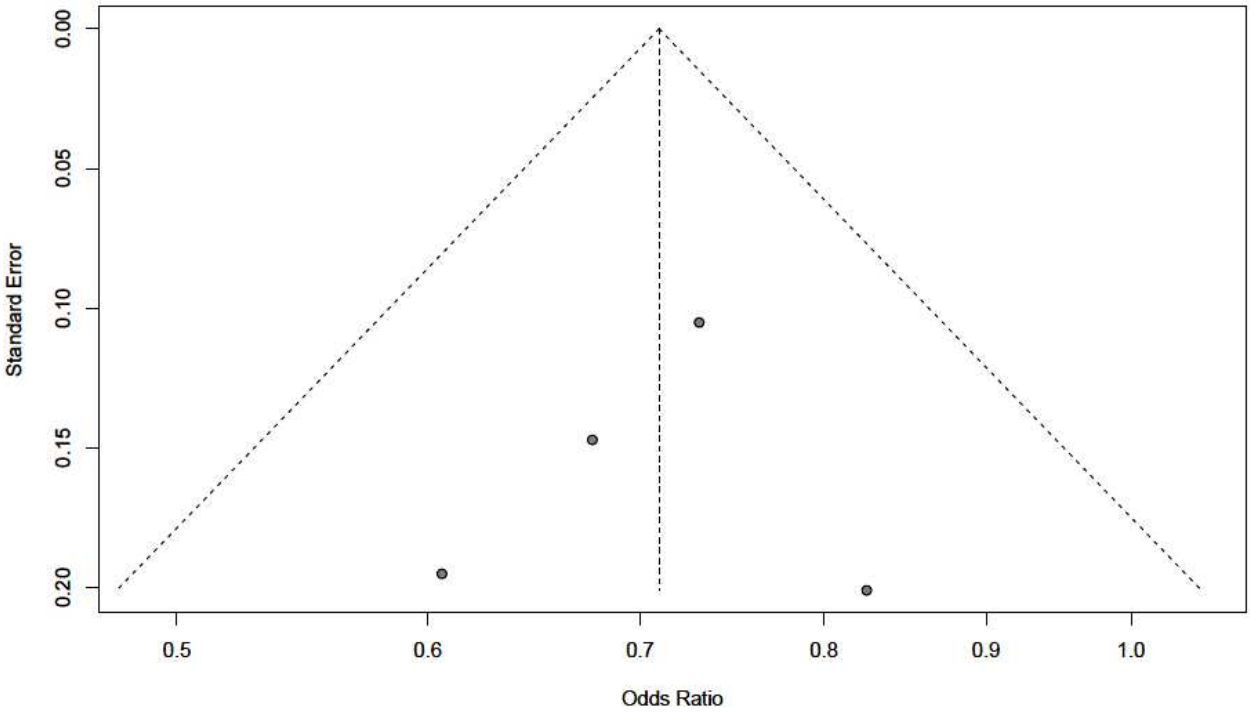


b)

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

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Work experience:

01/2015 – 01/2019	**Research associate** University of Split, School of Medicine, Department of Public Health, Split, Croatia
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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.