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SUPPLEMENTARY MATERIAL

Gene polymorphisms and risk of idiopathic pulmonary fibrosis: a systematic review and meta-analysis

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Key words: idiopathic pulmonary fibrosis, interstitial lung disease, *MUC5B*, *rs35705950*, gene polymorphism.

Supplementary Table 1. Search strategy for systematic review.

Databases	Search Strategy
PubMed	("Idiopathic Pulmonary Fibrosis"[MeSH] OR "lung diseases, interstitial"[MeSH] OR "Idiopathic Pulmonary Fibrosis"[tiab] OR "idiopathic pulmonary fibroses"[tiab] OR "fibrosing alveoliti*"[tiab] OR "fibrocystic pulmonary dysplasia*"[tiab] OR "interstitial pneumonia*"[tiab] OR "interstitial lung disease*"[tiab]) AND (Risk*[tiab] OR Risk Factor[MeSH] OR "risk factor*"[tiab] OR "modifiable*"[tiab] OR "non-modifiable*"[tiab] OR smoking[MeSH] OR Smok*[tiab] OR "Diabetes Mellitus"[MeSH:noexp] OR Diabet*[tiab] OR Obesity[MeSH:noexp] OR obes*[tiab] OR "Alcoholics"[mh] OR alcohol*[tiab] OR "Stress Disorders, Traumatic"[MeSH:noexp] OR "Stress, Psychological"[MeSH:noexp] OR Stress[tiab] OR "diet"[noexp] OR Diet*[tiab] OR "Exercise"[MeSH:noexp] OR Exercis*[tiab] OR "Hypertension"[MeSH:noexp] OR hypertension[tiab] OR "medical history taking"[MeSH] OR Family history[tiab] OR "Body mass index"[MeSH] OR "body mass index"[tiab] OR BMI[tiab] OR Genetic*[tiab] OR Age[tiab] OR Gender[tiab] OR Ethnic*[tiab] OR Demographic*[tiab] OR Lifestyle*[tiab] OR Fruit*[tiab] OR Vegetable*[tiab] OR Sex[tiab] OR Race[tiab] OR Education[tiab] OR Income[tiab] OR Living area[tiab] OR Physical activity[tiab] OR Socioeconomic[tiab] OR Socio economic[tiab] OR "tobacco use"[mh] OR Tobacco[tiab] OR Shisha[tiab] OR Khat[tiab] OR Recreational drug*[tiab] OR "Substance-Related Disorders"[MeSH:noexp] OR "illicit drugs"[MeSH:noexp] OR illicit drug*[tiab] OR Illicit substance use[tiab] OR "blood pressure"[MeSH] OR 'Blood pressure'[tiab])
EBSCO CINAHL Plus	
Web of Science	
Wiley Cochrane Library	

Supplementary Table 2. Characteristics of the included studies.

Author Name	Country	Characteristics	Study Design	ATS/ERS Criteria	SNPs Studied	Genotyping Method	Statistic
Ahn, 2011	South Korea	**Sample Size:** Cases=237 Controls=456 **Population:** Asian **Age:** Case, IPF (58 [41-83]) Case, Clinical IPF (66 [47-83]) Control (62 [50-87]) **Gender:** Male (Case, IPF=112, Case, Clinical IPF=51, Control=278) Female (Case, IPF=50, Case, Clinical IPF=24, Control=178) **Smoking:** Current (Case, IPF=28.4%, Case, Clinical IPF=24%, Control=13.8%) Ex-smoker (Case, IPF=30.2%, Case, Clinical IPF=28%, Control=14.4%)	Case-control	2000	*IL-8 rs4073* *IL-8 rs2227307* *IL-8 rs2227306*	TaqMan	Linear regression model Odds ratio

Aquino-Galvez, 2009	Mexico	**Sample Size:** Cases=80 Controls=201 **Population:** Mixed **Age:** Case (64.77±11.02) Control (53.4±11.2) **Gender:** Male (Case=42, Control=72) Female (Case=38, Control=129)	Case-control	2000	*MICA exons 2–3* *MICA exons 4–5*	RSCA	Chi-square Fisher's exact Odds ratio
Aquino-Galvez, 2015	Mexico	**Sample Size:** Cases=168 Controls=205 **Population:** Mixed **Age:** Case (64.5±11) Control (47±5.4) **Gender:** Male (Case=103, Control=36) Female (Case=65, Control=169)	Case-control	2011	*HSPA1L rs2075800* *HSPA1L rs2227956* *HSPA1A rs1043618* *HSPA1B rs1061581*	TaqMan	Pearson χ^2 Odds ratio

Bonella, 2021	Germany	**Sample Size:** Cases=62 Controls=50 **Population:** Caucasian **Age:** Case (63.5±11) Control (42±2) **Gender:** Male (Case=43, Control=37) Female (Case=8, Control=13) **Smoking:** Non-smoker (Case=9, Control=33) Ex-smoker (Case=40, Control=7) Current Smoker (Case=4, Control=10)	Case-control	2011, 2018	*MUC5B rs35705950* *TOLLIP rs5743890* *TOLLIP rs3750920*	TaqMan	Spearman or Pearson Correlation Coefficient Fisher's exact Cox regression
Borie, 2013	France	**Sample Size:** Cases=142 Controls=1383 **Population:** Caucasian **Age:** Case (69.8±8.9) **Gender:** Male (Case=82%) Female (Case=18%) **Smoking:** Yes (Case=68%, Active=4%) No (Case=32%)	Case-control	2001	*MUC5B rs35705950*	TaqMan	Chi-square Fisher's exact Odds ratio

Bournazos, 2010	United Kingdom	**Sample Size:** Cases=142 Controls=218 **Population:** British Caucasians **Age:** Case (70±8.8) **Gender:** Male (Case=47) Female (Case=95)	Case-control	2001	*FcγRIIIb CD16b*	Allele-specific polymerase chain reaction	Chi-square Fisher's exact Odds ratio
Bournazos, 2011	United Kingdom	**Sample Size:** Cases=142 Controls=221 **Population:** Caucasian **Age:** Case (70±8.8) Control (71.4±8 10.2) **Gender:** Male (Case=47) Female (Case=95)	Case-control	2001	*FCGR3B* copy number	Quantitative polymerase chain reaction	Chi-square Fisher's exact Odds ratio

Checa, 2008	Mexico	**Sample Size:** Cases=130 Controls=305 **Population:** Mixed **Age:** Case (62.5±9.6) Control (40.6±12.4) **Gender:** Male (Case=67, Control=189) Female (Case=63, Control=116) **Smoking:** Current or former smoker (Case=49, Control=107)	Case-control	2000	*MMP-1 -755* *MMP-1 -1607*	Polymerase chain reaction restriction fragment length polymorphism	Fisher's exact Odds ratio
Helling, 2017	United States	**Sample Size:** Cases=203 Controls=139 **Population:** Mixed **Age:** Case (64±8.3) Control (57±14.5) **Gender:** Male (Case=124, Control=69) Female (Case=79, Control=70) **Smoking:** Yes (Case=32, Control=166) No (Case=11, Control=139) No data (Case=0, Control=5)	Case-control	2013	*MUC5B rs35705950*	TaqMan	Odds ratio
Horimasu, 2015	Germany	**Sample Size:** Cases=44 Controls=310	Case-control	2002	*MUC5B rs35705950*	TaqMan	Chi-square

		Population: Asian **Age:** Case (67.5±1.6) Control (50.6±0.4) **Gender:** Male (Case=35, Control=255) Female (Case=9, Control=55) **Smoking:** Yes (Case=32, Control=166) No (Case=11, Control=139) No data (Case=0, Control=5)					Fisher's exact Odds ratio
Horimasu, 2015	Germany	**Sample Size:** Cases=71 Controls=35 **Population:** Caucasian **Age:** Case (67.6±1.2) Control (44.3±2.3) **Gender:** Male (Case=51, Control=15) Female (Case=20, Control=20) **Smoking:** Yes (Case=35, Control=6) No (Case=33, Control=17) No data (Case=3, Control=12)	Case-control	2002	*MUC5B rs35705950*	TaqMan	Chi-square Fisher's exact Odds ratio

Jiang, 2015	China	**Sample Size:** Cases=187 Controls=250 **Population:** Asian **Age:** Case (69.7±4.3) Control (67.7±7.3) **Gender:** Male (Case=138, Control=172) Female (Case=49, Control=178) **Smoking:** Yes (Case=135, Control=147) No (Case=52, Control=103)	Case-control	2011	*MUC5B rs35705950*	TaqMan	Chi-square Odds ratio

Kishore, 2016	Czech Republic	**Sample Size:** Cases=165 Controls=96 **Population:** Caucasian **Age:** Case (67.97 ± 11.60) Control (34.45 ± 8.94) **Gender:** Male (Case=125, Control=45) Female (Case=40, Control=51)	Case-control	2000, 2001, 2011	*IL-1 α rs1800587* *IL-1 β rs16944* *IL-1 β rs1143634* *PRKCE rs628877* *LRRC34 rs6793295* *TF rs1799899* *IL-8 rs4073* *FAM13A rs2609255* *TLR3 rs3775291* *TERT rs2736100* *IL-13 rs1800925* *IL-4 rs2243248* *IL-4 rs2243250* *IL-4 rs2070874* *CDKN1A rs733590* *OBFC1 rs11191865* *MUC2 rs7934606* *MUC5B rs35705950* *ATP11A rs1278769* *IL-4R α rs1801275* *TP53 rs12951053* *TP53 rs12602273* *MAPT rs1981997* *ACE rs4277405* *ACE rs4459609* *DPP9 rs12610495*	Allele-specific MALDI-TOF	Chi-square Fisher's exact Odds ratio
Peljto, 2015	United States	**Sample Size:** Cases=239 Controls=87 **Population:** Asian	Case-control	2011	*LRRC34 rs6793295* *FAM13A rs2609255* *TERT rs2736100* *DSP rs2076295*	-	LRM Odds ratio

		Age at diagnosis: Case (65.1±7.7) **Gender:** Male (Case=179) Female (Case=60) **Smoking:** Yes (Case=161)			*Intergenic rs4727443 OBFC1 rs11191865 MUC5B rs35705950 TOLLIP rs5743890 TOLLIP rs111521887 ATP11A rs1278769 IVD rs2034650 DPP9 rs1260495*		
Peljto, 2015	United States	**Sample Size:** Cases=83 Controls=111 **Population:** Mixed **Age at diagnosis:** Case (66.0±7.7) **Gender:** Male (Case=59) Female (Case=24) **Smoking:** Yes (Case=41)	Case-control	2011	*LRRC34 rs6793295 FAM13A rs2609255 TERT rs2736100 DSP rs2076295 Intergenic rs4727443 OBFC1 rs11191865 MUC5B rs35705950 TOLLIP rs5743890 TOLLIP rs111521887 ATP11A rs1278769 IVD rs2034650 DPP9 rs1260495*	-	LRM Odds ratio

Riha, 2004	Australia	**Sample Size:** Cases=22 Controls=140 **Population:** Caucasian **Age:** 60±14 **Gender:** Male to female ratio (17:5) **Smoking:** Current or ex-smokers (95%)	Case-control	2000	*TGF-β1 exon 1* *IL-6 –174* *TNF-α –308* *IL-1Ra intron 2*	Restriction fragment length polymorphism	Chi-square LRM Odds ratio
Selman, 2003	Mexico	**Sample Size:** Cases=84 Controls=194 **Population:** Mixed **Age:** Case (62.3±10.9) Control (41±14.5) **Gender:** Male (Case=59, Control=124) Female (Case=25, Control=70) **Smoking:** Yes (Case=30, Control=91) No (Case=54, Control=103)	Case-control	2000	*SP-A SP-A1_6A* *SP-A AA219_T* *SP-A AA50_C* *SP-A AA62_G* *SP-B B1580_C* *SP-C CA138* *SP-C CA136* *SP-D* (not mentioned)	Polymerase chain reaction restriction fragment length polymorphism	Fisher's exact LRM Odds ratio

Son, 2013	South Korea	**Sample Size:** Cases=85 Controls=85 **Population:** Asian **Age:** Case (61±8) Control (59±8) **Gender:** Male (Case=55, Control=55) Female (Case=30, Control=30) **Smoking:** Yes (Case=51, Control=43) No (Case=34, Control=41)	Case-control	2001	*TGF-b_1 T869C*	DNA sequencing	Chi-square LRM Odds ratio
Stock, 2013	United Kingdom	**Sample Size:** Cases=110 Controls=416 **Population:** Caucasian **Age:** Case (64.6 [45–85]) **Gender:** Male (Case=79) Female (Case=31)	Case-control	2000, 2001	*MUC5B rs35705950*	TaqMan	Chi-square Fisher's exact Odds ratio
Stock, 2020	United Kingdom	**Sample Size:** Cases=23 Controls=20 **Population:** Caucasian	Case-control	2000, 2001	*MUC5B rs35705950*	TaqMan	Odds ratio

Uh, 2013	South Korea	**Sample Size:** Cases=220 Controls=456 **Population:** Asian **Age:** Case (62 [50–83]) Control (63 [50–87]) **Gender:** Male (Case=153, Control=278) Female (Case=67, Control=178) **Smoking:** Current (Case=26%, Control=14%) Ex-smoker (Case=30%, Control=15%)	Case-control	2001	*ACE -5538* *ACE -5508* *ACE -3927* *ACE -262* *ACE -115* *ACE +5467* *ACE +6307* *ACE +11575* *ACE +15276* *ACE +21181* *ACE +21288*	Single base extension and electrophoresis	Fisher's exact LRM Odds ratio
Uh, 2014	South Korea	**Sample Size:** Cases=237 Controls=183 **Population:** Asian **Age:** Case (62[31–83]) Control (61 [50–81]) **Gender:** Male (Case=163, Control=55) Female (Case= 74 Control=128) **Smoking:** Current (Case=27%, Control=9.3%) Ex-smoker (Case=29.5%, Control=12.6%)	Case-control	2001	*ADAM33 rs3918392* *ADAM33 rs511898* *ADAM33 rs2485700* *ADAM33 rs2271511* *ADAM33 rs528557* *ADAM33 rs2853209* *ADAM33 rs2280089* *ADAM33 rs628977* *ADAM33 rs677044*	Single base extension and electrophoresis	Chi-square Fisher's exact LRM Odds ratio

Van Der Vis, 2016	Netherlands	**Sample Size:** Cases=115 Controls=249 **Population:** Caucasian **Age at diagnosis:** Case (63.5±11.0) **Gender:** Male (Case=97) Female (Case=28) **Smoking:** Yes (Case=77) No (Case=38)	Case-control	2001, 2011, 2013	*MUC5B rs35705950*	TaqMan	Pearson Chi-square Fisher's exact Odds ratio
Vasakova, 2006	Czech Republic	**Sample Size:** Cases=30 Controls=103 **Population:** Caucasian **Age:** Case (65.4 [36–85]) Control (53 [24–71]) **Gender:** Male (Case=10, Control=24) Female (Case=20, Control=79)	Case-control	2000	*IL-1α -889* *IL-1β -511* *IL-1β +3962* *IL-1R pst 1970* *IL-1RA mspa 11100* *IL-4RA þ1902* *IL-12 -1188* *INF-γ UTR 5644* *TGF-β1 codon 10* *TGF-β1 codon 25* *TNF-α -308* *TNF-α -238* *IL-2 -330* *IL-2 +166* *IL-4 -1098* *IL-4 -590* *IL-4 -33* *IL-6 -174* *IL-6 +565* *IL-10 -1082*	Polymerase chain reaction	Chi-square

					IL-10 -819 *IL-10 -592*		
Wang, 2014	China	**Sample Size:** Cases=165 Controls=1013 **Population:** Asian **Age:** Case (61.78±12.72) Control (58.61±12.72) **Gender:** Male (Case=55, Control=360) Female (Case=29, Control=329) **Smoking:** Smokers (Case=58%)	Case-control	2011	*MUC5B rs35705950*	TaqMan Polymerase chain reaction restriction fragment length polymorphism	Chi-square Student's *t* test Odds ratio

Wei, 2014	United States	**Sample Size:** Cases=84 Controls=689 **Population:** Caucasian **Age:** Case (64.4±7.7) Control (55.7±13.2) **Gender:** Male (Case=55, Control=360) Female (Case=29, Control=329) **Smoking:** Current (Case=1) Ever (Case=52) Never (Case=31)	Case-control	2001	*MUC5B rs35705950* *TERT rs2736100*	TaqMan Polymerase chain reaction	Chi-square Fisher's exact Odds ratio
Xaubet, 2010	Spain	**Sample Size:** Cases=174 Controls=121 **Population:** Caucasian **Age:** Case (67.8±0.78) Control (36.7±0.90) **Gender:** Male (Case=108, Control=72) Female (Case=66, Control=153)	Case-control	2000	*COX2.3050* *COX2.8473* *COX2.926*	TaqMan	Chi-square LRM Odds ratio

Zhang, 2011	United States	**Sample Size:** Cases=341 Controls=802 **Population:** Caucasian **Age:** Case (67.9±8.8) Control (52.7±14.7) **Gender:** Male (Case=238, Control=436) Female (Case=103, Control=366)	Case-control	2001	*MUC5B rs35705950*	TaqMan	Odds ratio
Zhang, 2012	China	**Sample Size:** Cases=36 Controls=11955 **Population:** Asian **Age:** Case (63.4±5.1) Control (48.3±12.1) **Gender:** Male (Case=24, Control=8129) Female (Case=12, Control=3826)	Case-control	2000	*HLA-A-B A2B8* *HLA-A-B A2B13* *HLA-A-B A2B15* *HLA-A-B A2B27* *HLA-A-B A2B35* *HLA-A-B A2B40* *HLA-A-B A2B46* *HLA-A-B A2B51* *HLA-A-B A2B55* *HLA-A-B A3B35* *HLA-A-B A11B13* *HLA-A-B A11B15* *HLA-A-B A11B27* *HLA-A-B A11B54* *HLA-A-B A24B27* *HLA-A-B A24B40* *HLA-A-B A24B58* *HLA-A-B A30B13* *HLA-A-B A30B40* *HLA-A-B A33B58*	Polymerase chain reaction sequence-specific amplification	Chi-square Fisher's exact Relative risk

Zhang, 2015	China	**Sample Size:** Cases=102 Controls=266 **Population:** Asian **Age:** Case (59.34±9.87) Control (56.70±12.80) **Gender:** Male (Case=45, Control=137) Female (Case=57, Control=129) **Smoking:** Current (Case=0) Ex-smoker (Case=26) Non-smoker (Case=76)	Case-control	2011	*TNF-α -308* *TGF-β1 -869* *IL-10 -592* *IL-10 -819* *IL-10 -1082* *IFN-γ -874* *HLA A*01* *HLA A*02* *HLA A*11* *HLA A*24* *HLA A*26* *HLA A*30* *HLA A*33* *HLA B*07* *HLA B*13* *HLA B*15* *HLA B*27* *HLA B*35* *HLA B*38* *HLA B*40* *HLA B*44* *HLA B*46* *HLA B*51* *HLA B*52* *HLA B*54* *HLA B*55* *HLA B*58* *DRB1*01* *DRB1*03* *DRB1*04* *DRB1*07* *DRB1*08* *DRB1*09* *DRB1*11* *DRB1*12* *DRB1*13* *DRB1*14* *DRB1*15*	High resolution melting assay	Chi-square Fisher's exact Odds ratio

Zorzetto, 2003	Italy	**Sample Size:** Cases=74 Controls=166 **Population:** Caucasian **Age:** Case (66.5±10.88) Control (61.7±8.4) **Gender:** Male (Case=51, Control=105) Female (Case=23, Control=61) **Smoking:** Yes (Case=37) No (Case=37)	Case-control	2001	*CR1 -3650 e22* *CR1 -520 i27* *CR1 -5507 e33*	Polymerase chain reaction restriction fragment length polymorphism	Chi-square Odds ratio

Abbreviation: ATS/ERS, American Thoracic Society/European Respiratory Society; IPF, Idiopathic Pulmonary Fibrosis; UCSF, University of California San Francisco; UTSW, University of Texas Southwest.

Supplementary Table 3. Association between SNPs and IPF mentioned in the included studies.

Study	Gene SNPs	Main findings
Ahn, 2011	*IL-8 rs4073*	Significant association between *IL-8 rs4073* and increased risk of IPF. ***Multivariate analysis:*** Adjusted for age, gender and smoking
Aquino-Galvez, 2009	*MICA*	Significant association between *MICA*001* allele and *MICA*001/*00201* genotype and increased risk of IPF.
Aquino-Galvez, 2015	*HSPA1B rs1061581* *HSPA1L rs2227956* *HSPA1 rs1043618*	Significant association between *HSPA1B rs1061581*, *HSPA1L rs2227956* and *HSPA1 rs1043618* and decreased risk of IPF.
Bonella, 2021	*MUC5B rs35705950* *TOLLIP rs5743890* *TOLLIP rs3750920*	Significant association between *MUC5B rs35705950* minor allele and increased risk of IPF.
Borie, 2013	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* and increased risk of IPF.
Bournazos, 2010	*FcγRIIIb CD16b*	Significant association between NA1 allele and NA1/NA1 genotype and increased risk of IPF. Significant association between NA1 allele heterozygotes and homozygotes and increased risk of IPF. Significant association between NA2 allele and decreased risk of IPF.
Bournazos, 2011	*FCGR3B* copy number	Significant association between *FCGR3B* copy number and increased risk of IPF.
Checa, 2008	*MMP-1 -755*	Significant association between *MMP-1 -755 T/T* genotype and increased risk of IPF (among IPF smokers). ***Multivariate analysis:*** Adjusted for smoking
Helling, 2017	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* and increased risk of IPF.
Horimasu, 2015 (Asian)	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* and increased risk of IPF.
Horimasu, 2015 (Caucasian)	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* and increased risk of IPF.
Jiang, 2015	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* and increased risk of IPF.
Kishore, 2016	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* and increased risk of IPF.
Peljto, 2015 (Asian)	*MUC5B rs35705950* *IVD rs2034650*	Significant association between *IVD rs2034650* and increased risk of IPF. ***Multivariate analysis:*** Adjusted for age and gender Adjusted for age, gender and MUC5B rs35705950

Peljto, 2015 (Mixed)	*MUC5B rs35705950* *IVD rs2034650*	Significant association between *MUC5B rs35705950* and increased risk of IPF. Significant association between *IVD rs2034650* and increased risk of IPF. ***Multivariate analysis:*** Adjusted for age and gender Adjusted for age, gender and MUC5B rs35705950
Riha, 2004	*TNF-α –308*	Significant association between *TNF-α (-308 A)* allele and increased risk of IPF.
Selman, 2003	*SP-B B1580_C*	Significant association between *SP-B B1580_C* and increased risk of IPF (among IPF smokers). ***Multivariate analysis:*** Adjusted for gender and smoking
Son, 2013	*TGF-b_1 T869C*	Significant association between *TGF-b_1 T869C* and increased risk of IPF. ***Multivariate analysis:*** Adjusted for age, gender and smoking
Stock, 2013	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* and increased risk of IPF. ***Multivariate analysis:*** Adjusted for age, gender, smoking and composite physiological index (CPI)
Stock, 2020	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* minor allele and increased risk of IPF.
Uh, 2013	*ACE -5538*	Significant association between *ACE -5538T>C* and *-5508A>C* and increased risk of IPF. ***Multivariate analysis:*** Adjusted for age, gender and smoking
Uh, 2014	*ADAM33 rs628977*	Significant association between *ADAM33 rs628977* in a recessive model and decreased risk of IPF. ***Multivariate analysis:*** Adjusted for age, gender and smoking
Van Der Vis, 2016	*MUC5B rs35705950*	Significant association between *MUC5B* minor allele and increased risk of IPF.
Vasakova, 2006	*IL-4 -590* *IL-4 -33*	Significant association between CT genotypes of *IL-4 -590* and *-33* and increased risk of IPF.
Wang, 2014	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* minor allele and increased risk of IPF.
Wei, 2014	*MUC5B rs35705950* *TERT rs2736100*	Significant association between *MUC5B rs35705950* minor allele and increased risk of IPF. ***Multivariate analysis:*** Adjusted for age, gender, smoking status, disease status and/or body mass index (BMI) when appropriate

Xaubet, 2010	*COX2.3050* *COX2.8473*	Significant association between GG/CC double homozygote of *COX2.3050* and *COX2.8473* and increased risk of IPF. ***Multivariate analysis:*** Adjusted for age and gender
Zhang, 2011	*MUC5B rs35705950*	Significant association between *MUC5B rs35705950* and increased risk of IPF.
Zhang, 2012	*HLA-A*3* *HLA-B*14* *HLA-B*15* *HLA-B*40* *HLA-A2B15* *HLA-A2B40* *HLA-A11B15* *HLA-A24B58* *HLA-A30B40*	Significant association between *HLA-A*3*, *HLA-B*14*, *HLA-B*15*, *HLA-B*40*, *HLA-A2B15*, *HLA-A2B40*, *HLA-A11B15*, *HLA-A24B58* and *HLA-A30B40* and increased risk of IPF.
Zhang, 2015	*HLA-A*02-DRB1*04*	Significant association between *HLA-A*02-DRB1*04* and increased risk of IPF.
Zorzetto, 2003	*CR1 -5507 e33*	Significant association between *C5507G exon 33* GG genotype and increased risk of IPF.

Supplementary Table 4. Quality assessment of studies using Newcastle-Ottawa scale.

Author and year	Selection				Comparability	Exposure			Total stars
	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method for ascertainment of cases and controls	Non-response rate	
Ahn, 2011	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Aquino-Galvez, 2009	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Aquino-Galvez, 2015	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Bonella, 2021	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Borie, 2013	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Bournazos, 2010	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Bournazos, 2011	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Checa, 2008	⋆	⋆	⋆	⋆	⋆-	⋆	⋆	-	7
Helling, 2017	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Horimasu, 2015	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Horimasu, 2015	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Jiang, 2015	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Kishore, 2016	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Peljto, 2015	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Peljto, 2015	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Riha, 2004	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6
Selman, 2003	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Son, 2013	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Stock, 2013	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Stock, 2020	⋆	⋆	⋆	⋆	--	⋆	⋆	-	6

Uh, 2013	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Uh, 2014	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Van Der Vis, 2016	⋆	⋆	⋆	⋆	- -	⋆	⋆	-	6
Vasakova, 2006	⋆	⋆	⋆	⋆	- -	⋆	⋆	-	6
Wang, 2014	⋆	⋆	-	⋆	- -	⋆	⋆	-	5
Wei, 2014	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Xaubet, 2010	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	-	8
Zhang, 2011	⋆	⋆	⋆	⋆	- -	⋆	⋆	-	6
Zhang, 2012	⋆	⋆	⋆	⋆	- -	⋆	⋆	-	6
Zhang, 2015	⋆	⋆	⋆	⋆	- -	⋆	⋆	-	6
Zorzetto, 2003	⋆	⋆	⋆	⋆	- -	⋆	⋆	-	6

Note: Comparability was examined as following: one star awarded if study adjusted for smoking, another star awarded if study adjusted for age and gender

Supplementary Table 5. Genotypic distribution and HWE of IPF and non-IPF subjects for a) *MUC5B rs35705950*, b) *IL-4 rs2243250*, c) *IL-4 rs2070874*, and d) *TNFa -308*

a) MUC*5B rs35705950*

Author and Year	GG (Cases)	GT (Cases)	TT (Cases)	GG (Controls)	GT (Controls)	TT (Controls)	HWE (*P* Value)	HWE (Adjusted *P* Value)
Bonella 2021	23	35	4	42	7	1	0.3042	0.646
Borie 2013	49	76	17	1103	259	29	0.0037	**0.0481**
Helling 2017	101	87	15	107	32	0	0.1251	0.4066
Horimasu 2015	41	3	0	305	5	0	0.8862	0.8862
Horimasu 2015	32	31	8	32	3	0	0.7911	0.8667
Jiang 2015	134	34	19	202	41	7	0.0102	0.0663
Kishore 2016	67	75	9	80	14	2	0.1648	0.4285
Stock 2013	42	58	10	337	71	8	0.0707	0.3064
Stock 2020	8	13	2	14	6	0	0.43	0.646
Van Der Vis 2016	59	51	5	205	43	1	0.4257	0.646
Wang 2014	154	11	0	997	16	0	0.8	0.8667
Wei 2014	37	44	3	539	139	11	0.556	0.7228
Zhang 2011	131	186	24	636	154	12	0.4472	0.646

a) MUC*5B rs35705950*, Asian

Author and Year	GG (Cases)	GT (Cases)	TT (Cases)	GG (Controls)	GT (Controls)	TT (Controls)	HWE (*P* Value)	HWE (Adjusted *P* Value)
Horimasu 2015	41	3	0	305	5	0	0.8862	0.8862
Jiang 2015	134	34	19	202	41	7	0.0102	**0.0306**
Wang 2014	154	11	0	997	16	0	0.8	0.8862

a) MUC*5B rs35705950*, Caucasian

Author and Year	GG (Cases)	GT (Cases)	TT (Cases)	GG (Controls)	GT (Controls)	TT (Controls)	HWE (*P* Value)	HWE (Adjusted *P* Value)

Bonella 2021	23	35	4	42	7	1	0.3042	0.5963
Horimasu 2015	32	31	8	32	3	0	0.7911	0.7911
Kishore 2016	67	75	9	80	14	2	0.1648	0.5963
Stock 2013	42	58	10	337	71	8	0.0707	0.5656
Stock 2020	8	13	2	14	6	0	0.43	0.5963
Van Der Vis 2016	59	51	5	205	43	1	0.4257	0.5963
Wei 2014	37	44	3	539	139	11	0.556	0.6354
Zhang 2011	131	186	24	636	154	12	0.4472	0.5963

b) *IL-4 rs2243250*

Author and Year	CC (Cases)	CT (Cases)	TT (Cases)	CC (Controls)	CT (Controls)	TT (Controls)	HWE (*P* Value)	HWE (Adjusted *P* Value)
Kishore 2016	128	26	10	64	25	5	0.2357	0.2357
Vasakova 2006	3	26	1	77	20	5	0.0274	0.0548

c) *IL-4 rs2070874*

Author and Year	CC (Cases)	CT (Cases)	TT (Cases)	CC (Controls)	CT (Controls)	TT (Controls)	HWE (*P* Value)	HWE (Adjusted *P* Value)
Kishore 2016	122	38	5	66	27	3	0.9064	0.9064
Vasakova 2006	9	20	1	77	20	5	0.0274	0.0548

d) *TNFa -308*

Author and Year	GG (Cases)	AG (Cases)	AA (Cases)	GG (Controls)	AG (Controls)	AA (Controls)	HWE (*P* Value)	HWE (Adjusted *P* Value)
Riha 2004	9	11	2	103	36	1	0.2554	0.2554
Zhang 2015	84	18	0	225	41	0	0.1732	0.2554

Supplementary Table 6. Association findings of a) *MUC5B rs35705950*, b) *IL-4 rs2243250*, c) *IL-4 rs2070874*, and d) *TNFa* -308 and IPF using random effects model.

a) *MUC5B rs35705950*

Allelic and Genotypic Model	Odds Ratio	95% CI	Adjusted *P* Value	I^2
Allele Contrast	3.84	3.20 – 4.61	<0.0001	49%
Recessive	5.01	3.57 – 7.03	<0.0001	0%
Dominant	4.99	3.77 – 6.61	<0.0001	69%
Overdominant	4.06	3.05 – 5.41	<0.0001	69%
Homozygote Codominant	8.78	6.19 – 12.43	<0.0001	0%
Heterozygote Codominant	1.83	1.28 – 2.61	0.006	0%
Heterozygote Codominant	4.64	3.42 – 6.29	<0.0001	72%

b) *MUC5B rs35705950*, Asian

Allelic and Genotypic Model	Odds Ratio	95% CI	Adjusted *P* Value	I^2
Allele Contrast	2.83	1.51 – 5.32	0.009	51%
Recessive	3.93	1.61 – 9.55	0.018	NA
Dominant	2.82	1.30 – 6.14	0.062	63%
Overdominant	2.57	0.88 – 7.54	0.599	80%
Homozygote Codominant	4.09	1.67 – 10.00	0.014	NA
Heterozygote Codominant	3.27	1.23 – 8.71	0.123	NA
Heterozygote Codominant	2.64	0.97 – 7.17	0.396	76%

c) *MUC5B rs35705950*, Caucasian

Allelic and Genotypic Model	Odds Ratio	95% CI	Adjusted *P* Value	I^2
Allele Contrast	4.11	3.56 – 4.75	<0.0001	0%
Recessive	4.50	2.85 – 7.12	<0.0001	0%
Dominant	5.87	4.92 – 7.02	<0.0001	0%
Overdominant	4.94	4.14 – 5.91	<0.0001	0%

Homozygote Codominant	8.52	5.34 – 13.59	<0.0001	0%
Heterozygote Codominant	1.45	0.90 – 2.33	0.871	0%
Heterozygote Codominant	5.63	4.69 – 6.76	<0.0001	0%

d) *IL-4 rs2243250*

Allelic and Genotypic Model	Odds Ratio	95% CI	Adjusted *P* Value	I^2
Allele Contrast	1.88	0.27 – 12.87	1.000	96%
Recessive	1.03	0.39 – 2.77	1.000	0%
Dominant	3.90	0.09 – 166.79	1.000	97%
Overdominant	3.61	0.08 – 170.72	1.000	97%
Homozygote Codominant	1.56	0.38 – 6.49	1.000	30%
Heterozygote Codominant	0.65	0.06 – 7.55	1.000	74%
Heterozygote Codominant	4.00	0.07 – 236.10	1.000	97%

e) *IL-4 rs2070874*

Allelic and Genotypic Model	Odds Ratio	95% CI	Adjusted *P* Value	I^2
Allele Contrast	1.63	0.41 – 6.49	1.000	91%
Recessive	0.86	0.26 – 2.90	1.000	0%
Dominant	2.29	0.26 – 20.30	1.000	94%
Overdominant	2.44	0.24 – 24.92	1.000	95%
Homozygote Codominant	1.09	0.32 – 3.72	1.000	0%
Heterozygote Codominant	0.59	0.11 – 3.24	1.000	40%
Heterozygote Codominant	2.48	0.23 – 26.54	1.000	95%

f) *TNFa -308*

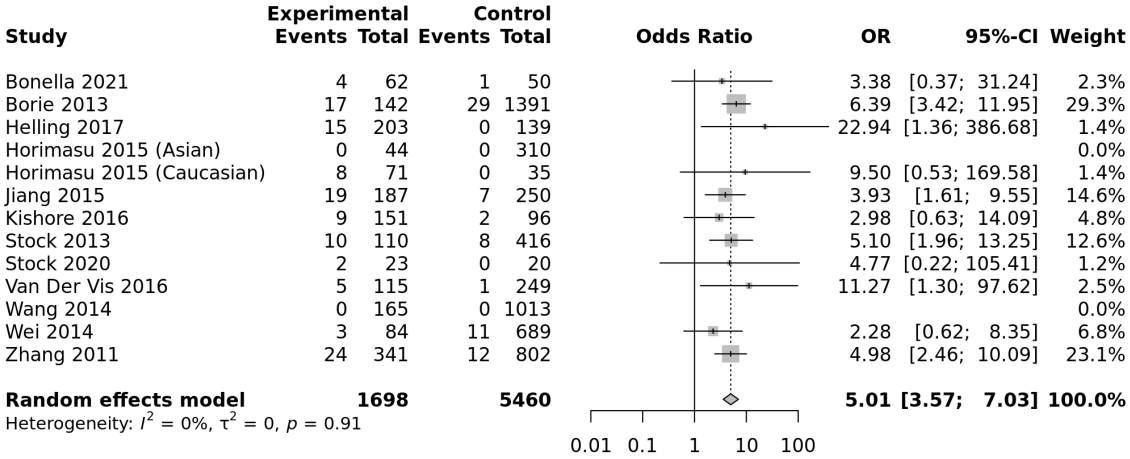
Allelic and Genotypic Model	Odds Ratio	95% CI	Adjusted *P* Value	I^2
Allele Contrast	1.91	0.69 – 5.32	1.000	80%
Recessive	13.90	1.20 – 160.40	0.245	NA

Dominant	2.06	0.62 – 6.86	1.000	79%
Overdominant	1.72	0.72 – 4.11	1.000	61%
Homozygote Codominant	22.89	1.89 – 277.52	0.098	NA
Heterozygote Codominant	6.55	0.54 – 79.23	0.978	NA
Heterozygote Codominant	1.90	0.66 – 5.48	1.000	72%

Supplementary Figure 1. Forest Plot demonstrating association between risk of IPF genotypic models of a) *MUC5B rs35705950*, b) *IL-4 rs2243250*, c) *IL-4 rs2070874*, and d) *TNFa -308*.

a) *MUC5B rs35705950*

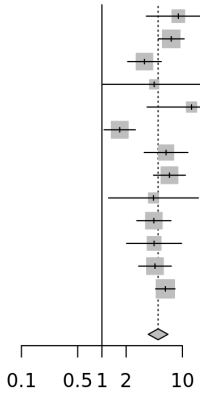
Recessive model (TT vs. TG+GG)



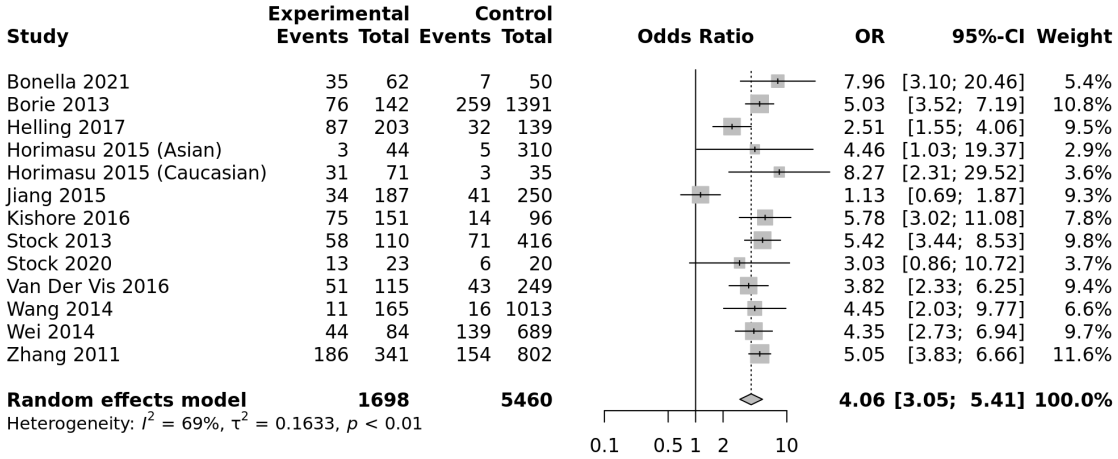
Dominant model (TT+TG vs. GG)

Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	Weight
Bonella 2021	39	62	8	50	8.90	[3.57; 22.23]	5.5%
Borie 2013	93	142	288	1391	7.27	[5.02; 10.52]	10.7%
Helling 2017	102	203	32	139	3.38	[2.09; 5.46]	9.4%
Horimasu 2015 (Asian)	3	44	5	310	4.46	[1.03; 19.37]	2.9%
Horimasu 2015 (Caucasian)	39	71	3	35	13.00	[3.64; 46.40]	3.6%
Jiang 2015	53	187	48	250	1.66	[1.06; 2.60]	9.8%
Kishore 2016	84	151	16	96	6.27	[3.35; 11.72]	7.9%
Stock 2013	68	110	79	416	6.91	[4.38; 10.90]	9.7%
Stock 2020	15	23	6	20	4.38	[1.21; 15.81]	3.5%
Van Der Vis 2016	56	115	44	249	4.42	[2.71; 7.22]	9.4%
Wang 2014	11	165	16	1013	4.45	[2.03; 9.77]	6.5%
Wei 2014	47	84	150	689	4.56	[2.86; 7.28]	9.6%
Zhang 2011	210	341	166	802	6.14	[4.66; 8.10]	11.6%
Random effects model		**1698**		**5460**	**4.99**	**[3.77; 6.61]**	**100.0%**

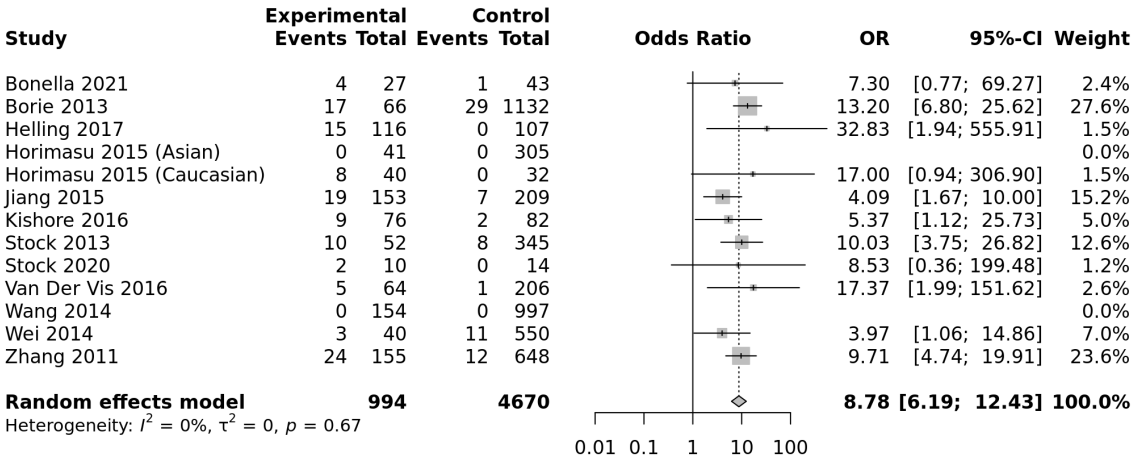
Heterogeneity: I^2 = 69%, τ^2 = 0.1584, p < 0.01



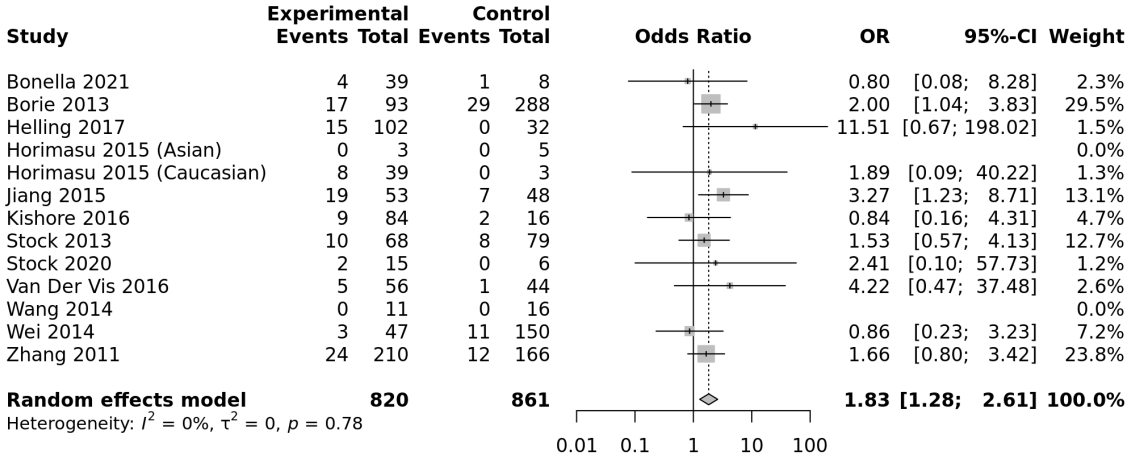
Overdominant model (TG vs. TT+GG)



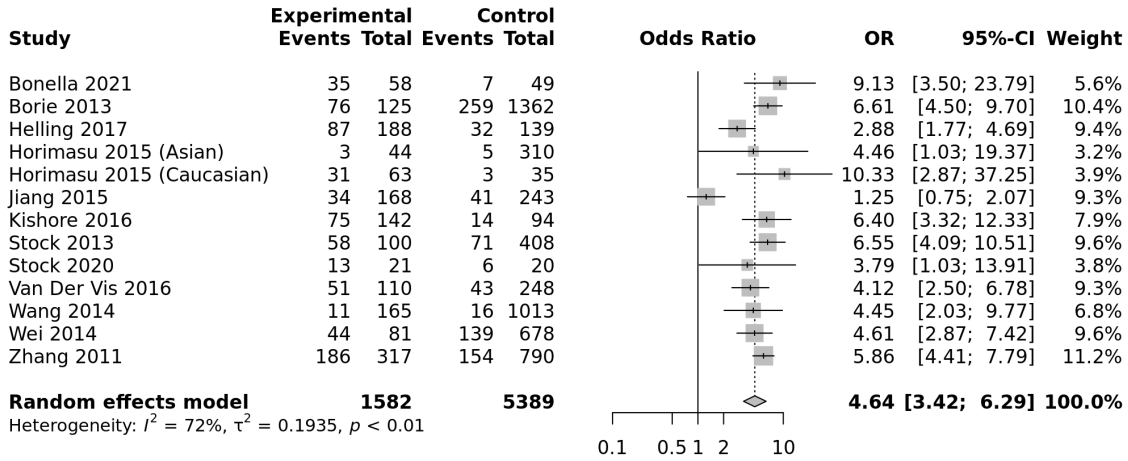
Homozygote codominant model (TT vs. GG)


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR
95%-CI
Weight
Bonella 2021 4 27 1 43 7.30 [0.77; 69.27] 2.4%
Borie 2013 17 66 29 1132 13.20 [6.80; 25.62] 27.6%
Helling 2017 15 116 0 107 32.83 [1.94; 555.91] 1.5%
Horimasu 2015 (Asian) 0 41 0 305 0.0%
Horimasu 2015 (Caucasian) 8 40 0 32 17.00 [0.94; 306.90] 1.5%
Jiang 2015 19 153 7 209 4.09 [1.67; 10.00] 15.2%
Kishore 2016 9 76 2 82 5.37 [1.12; 25.73] 5.0%
Stock 2013 10 52 8 345 10.03 [3.75; 26.82] 12.6%
Stock 2020 2 10 0 14 8.53 [0.36; 199.48] 1.2%
Van Der Vis 2016 5 64 1 206 17.37 [1.99; 151.62] 2.6%
Wang 2014 0 154 0 997 0.0%
Wei 2014 3 40 11 550 3.97 [1.06; 14.86] 7.0%
Zhang 2011 24 155 12 648 9.71 [4.74; 19.91] 23.6%
Random effects model 994 4670 8.78 [6.19; 12.43] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.67
0.01 0.1 1 10 100

Heterozygote codominant model (TT vs. TG)

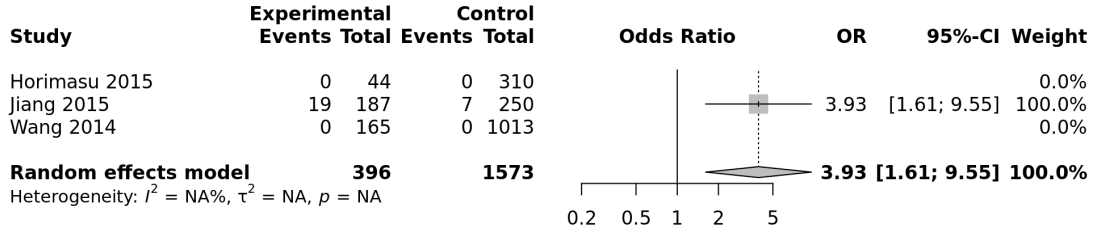


Heterozygote codominant model (TG vs. GG)

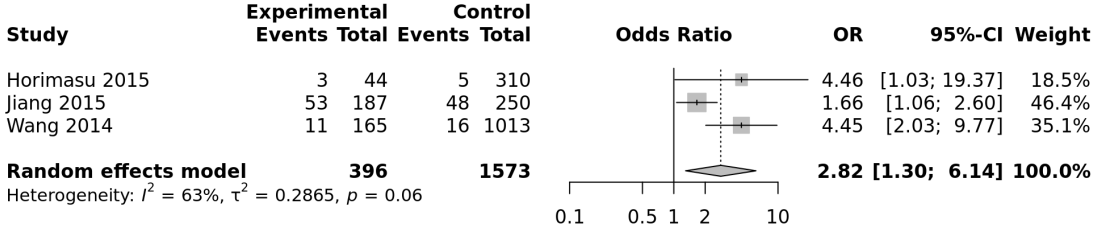

Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Bonella 2021 35 58 7 49 9.13 [3.50; 23.79] 5.6%
Borie 2013 76 125 259 1362 6.61 [4.50; 9.70] 10.4%
Helling 2017 87 188 32 139 2.88 [1.77; 4.69] 9.4%
Horimasu 2015 (Asian) 3 44 5 310 4.46 [1.03; 19.37] 3.2%
Horimasu 2015 (Caucasian) 31 63 3 35 10.33 [2.87; 37.25] 3.9%
Jiang 2015 34 168 41 243 1.25 [0.75; 2.07] 9.3%
Kishore 2016 75 142 14 94 6.40 [3.32; 12.33] 7.9%
Stock 2013 58 100 71 408 6.55 [4.09; 10.51] 9.6%
Stock 2020 13 21 6 20 3.79 [1.03; 13.91] 3.8%
Van Der Vis 2016 51 110 43 248 4.12 [2.50; 6.78] 9.3%
Wang 2014 11 165 16 1013 4.45 [2.03; 9.77] 6.8%
Wei 2014 44 81 139 678 4.61 [2.87; 7.42] 9.6%
Zhang 2011 186 317 154 790 5.86 [4.41; 7.79] 11.2%
Random effects model 1582 5389 4.64 [3.42; 6.29] 100.0%
Heterogeneity: I^2 = 72%, τ^2 = 0.1935, p < 0.01
0.1
0.5
1
2
10

b) *MUC5B rs35705950*, Asian

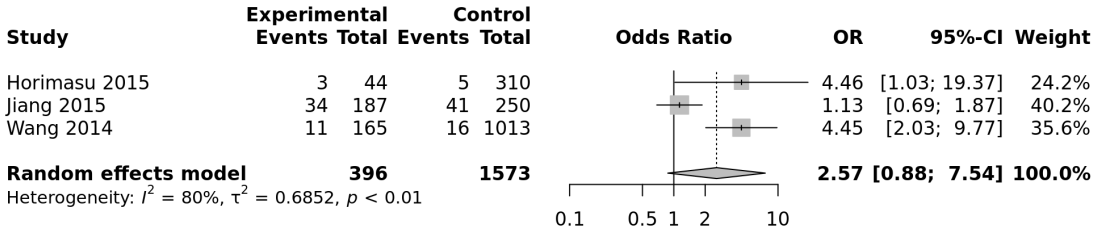
Recessive model (TT vs. TG+GG)



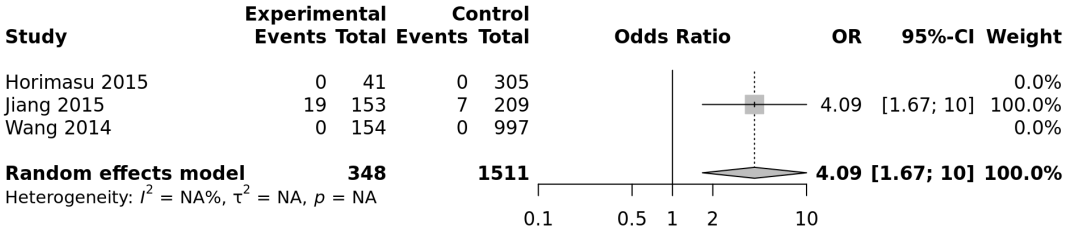
Dominant model (TT+TG vs. GG)



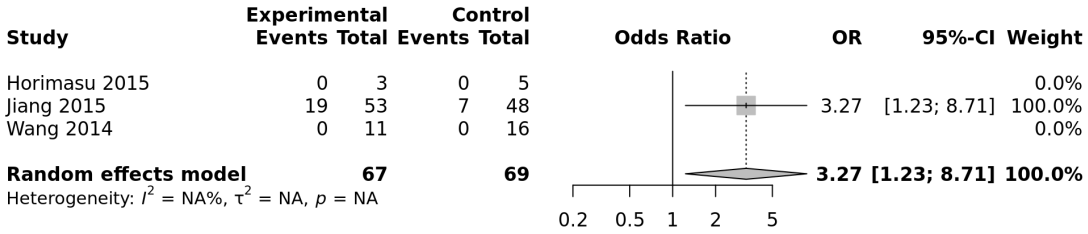
Overdominant model (TG vs. TT+GG)



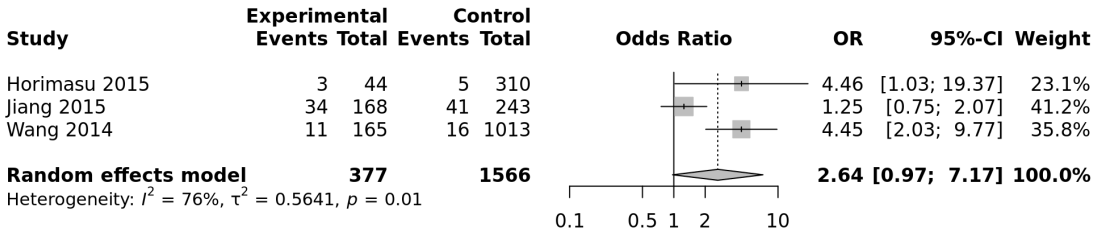
Homozygote codominant model (TT vs. GG)



Heterozygote codominant model (TT vs. TG)

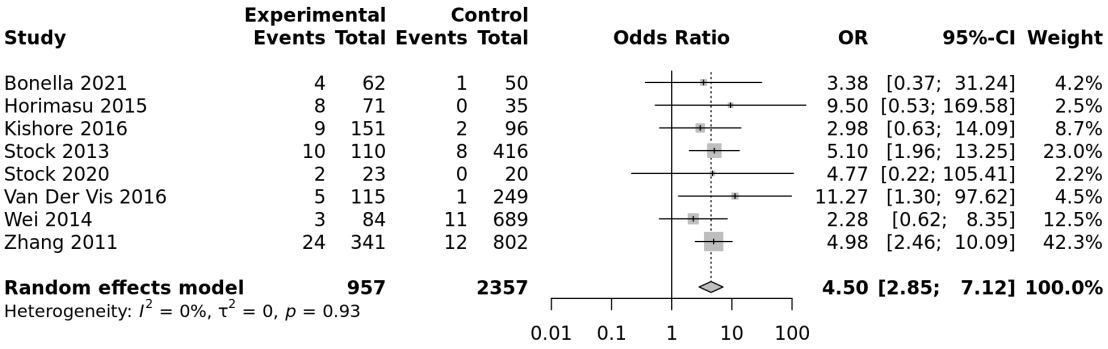

Study
Experimental Events Total
Control Events Total
Odds Ratio
OR
95%-CI
Weight
Horimasu 2015 0 3 0 5 0.0%
Jiang 2015 19 53 7 48 3.27 [1.23; 8.71] 100.0%
Wang 2014 0 11 0 16 0.0%
Random effects model 67 69 3.27 [1.23; 8.71] 100.0%
Heterogeneity: I^2 = NA%, τ^2 = NA, p = NA
0.2
0.5
1
2
5

Heterozygote codominant model (TG vs. GG)

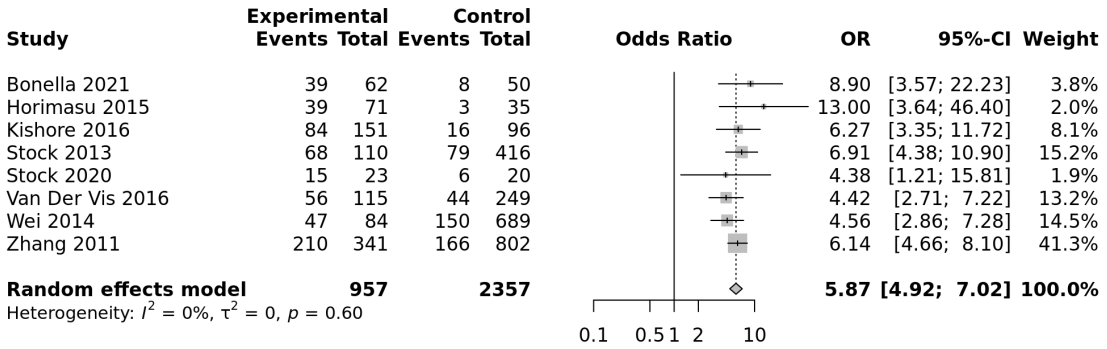


c) *MUC5B rs35705950*, Caucasian

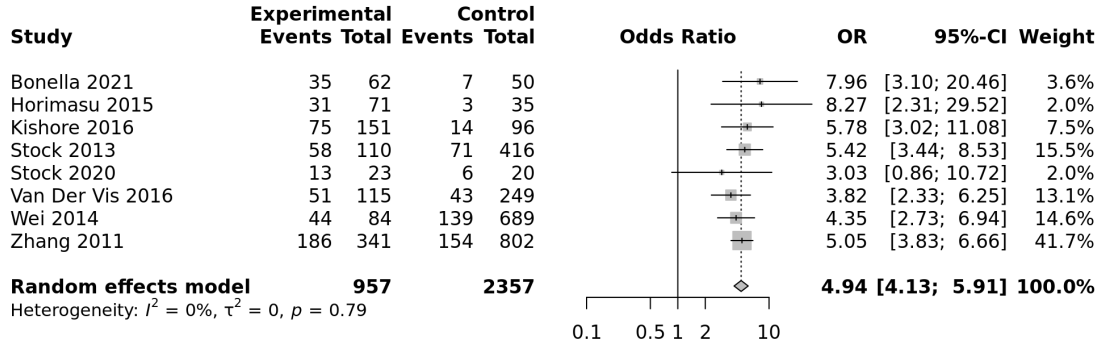
Recessive model (TT vs. TG+GG)



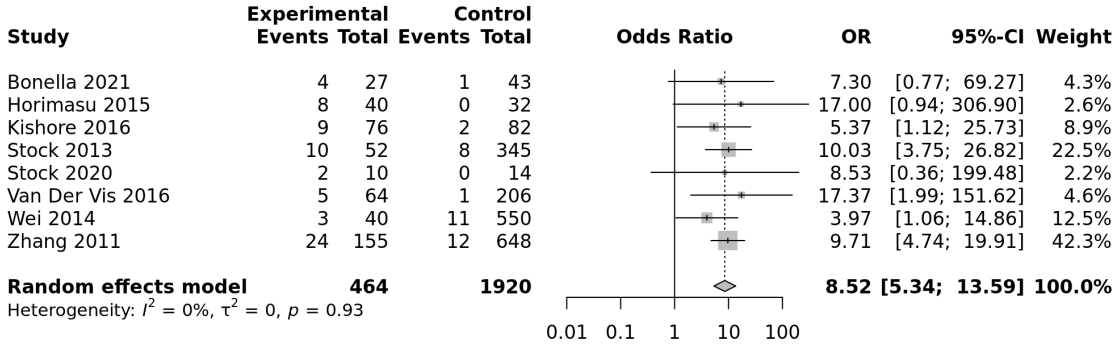
Dominant model (TT+TG vs. GG)



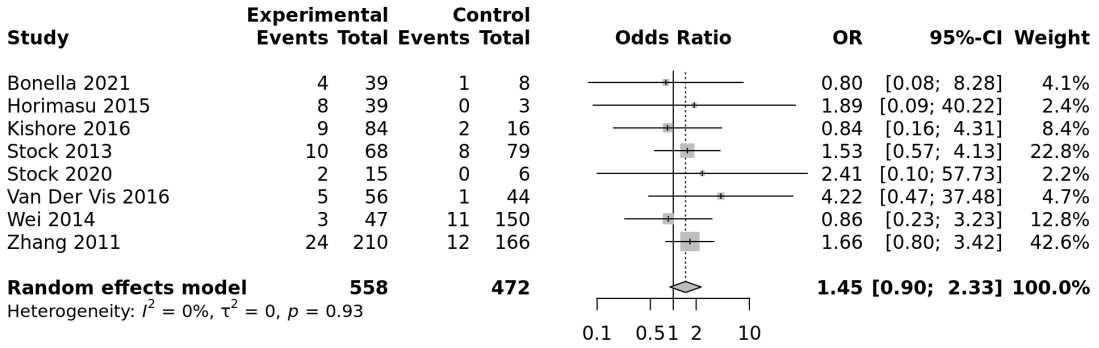
Overdominant model (TG vs. TT+GG)



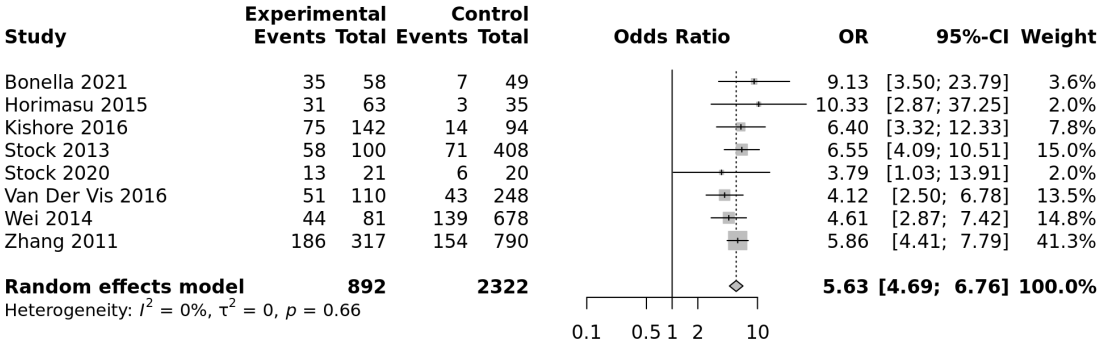
Homozygote codominant model (TT vs. GG)



Heterozygote codominant model (TT vs. TG)

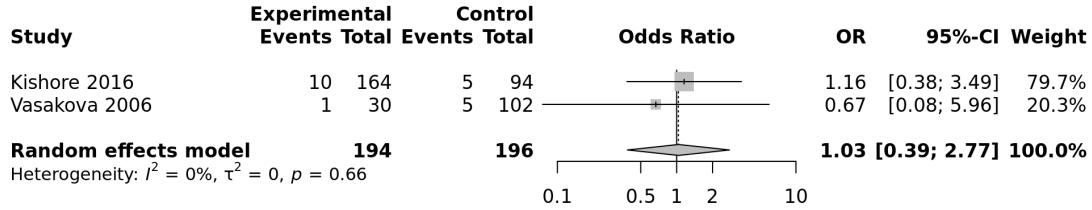


Heterozygote codominant model (TG vs. GG)

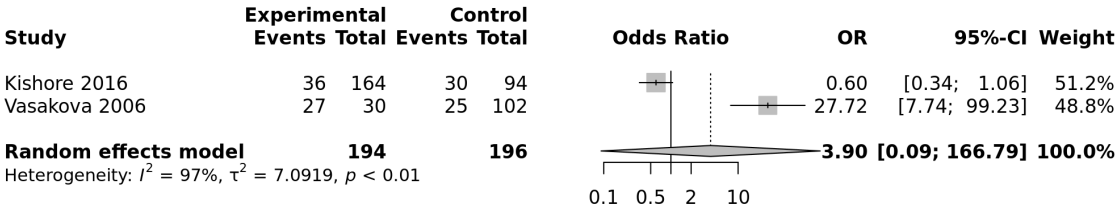


d) *IL-4 rs2243250*

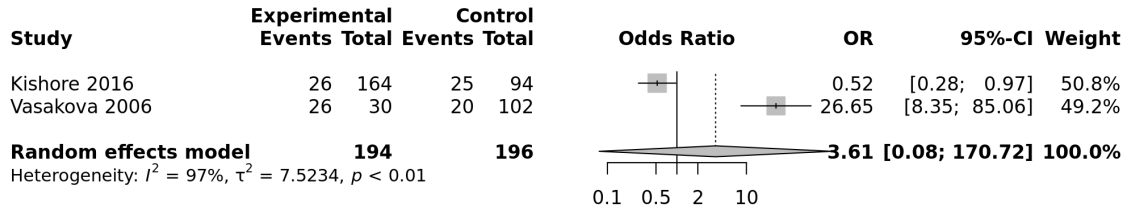
Recessive model (TT vs. TC+CC)



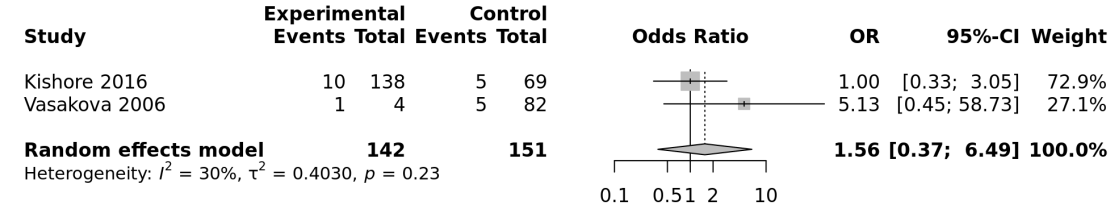
Dominant model (TT+TC vs. CC)



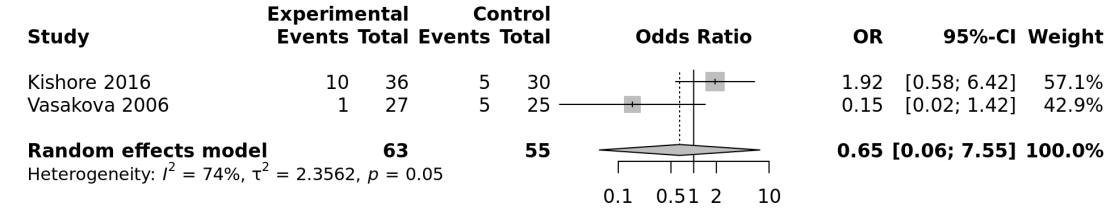
Overdominant model (TC vs. TT+CC)



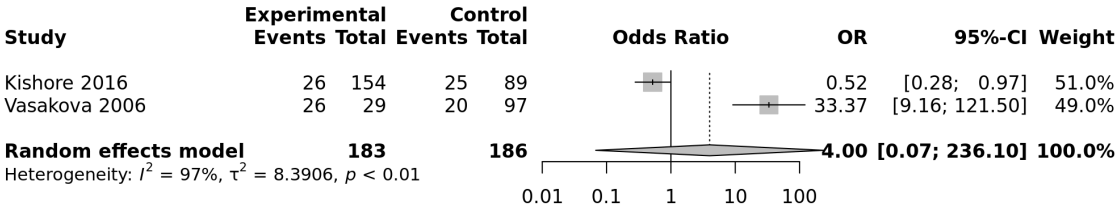
Homozygote codominant model (TT vs. CC)



Heterozygote codominant model (TT vs. TC)

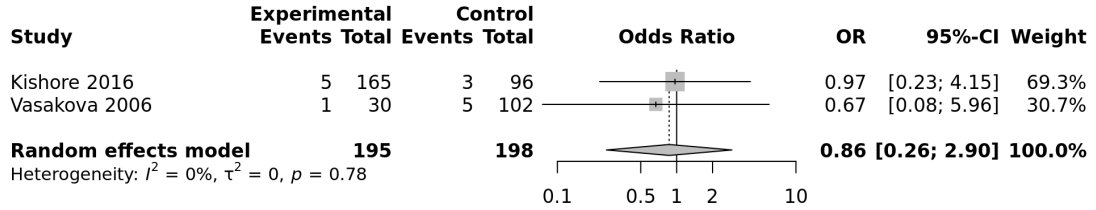


Heterozygote codominant model (TC vs. CC)

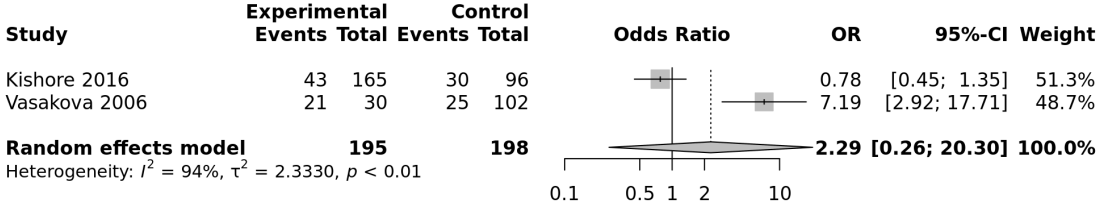


e) *IL-4 rs2070874*

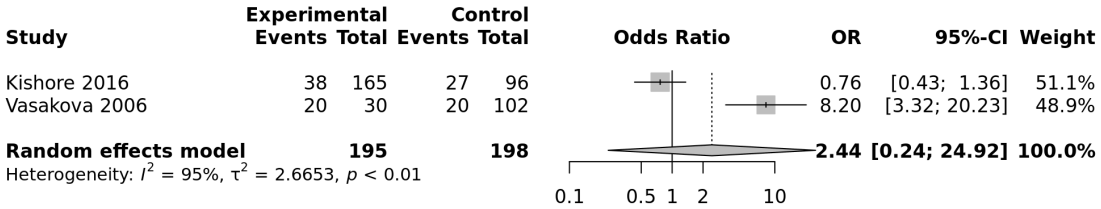
Recessive model (TT vs. TC+CC)



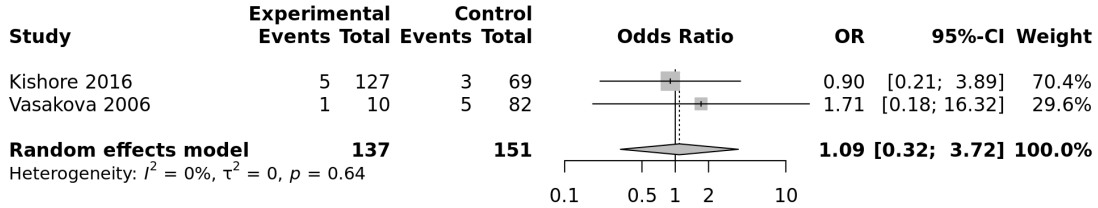
Dominant model (TT+TC vs. CC)



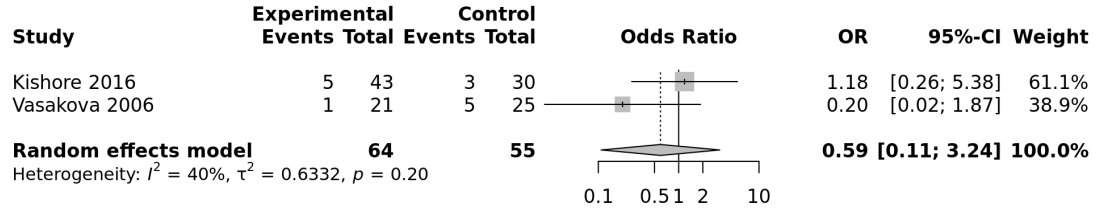
Overdominant model (TC vs. TT+CC)



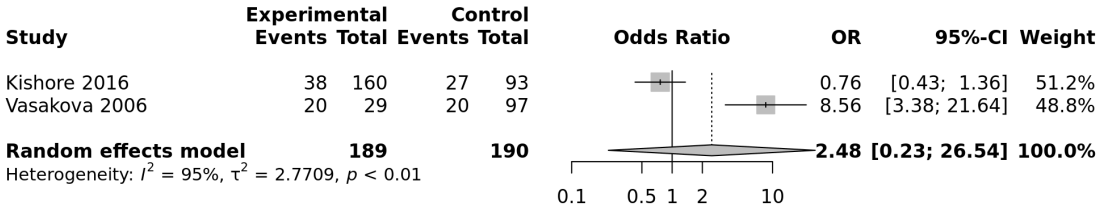
Homozygote codominant model (TT vs. CC)



Heterozygote codominant model (TT vs. TC)

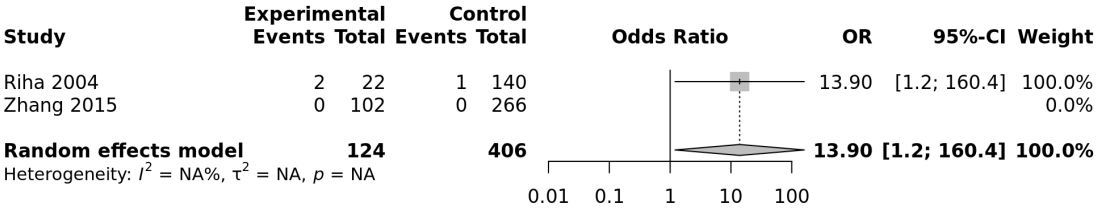


Heterozygote codominant model (TC vs. CC)

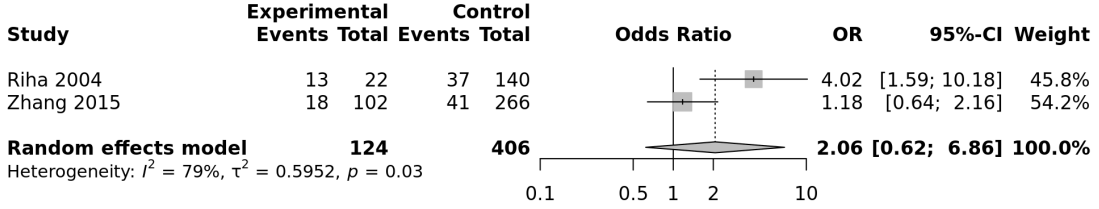


f) *TNFa -308*

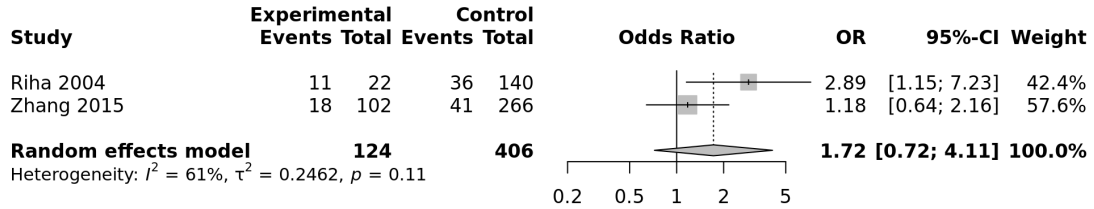
Recessive model (AA vs. AG+GG)



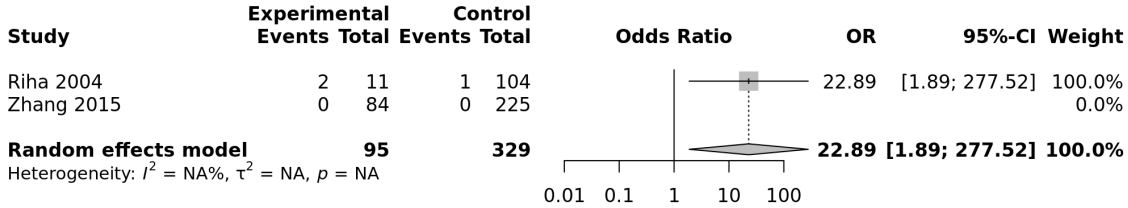
Dominant model (AA+AG vs. GG)



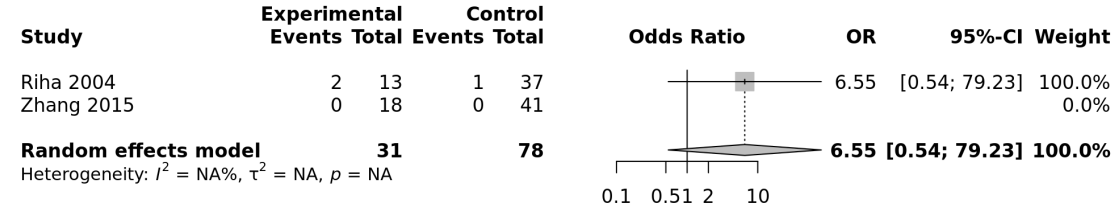
Overdominant model (AG vs. AA+GG)



Homozygote codominant model (AA vs. GG)



Heterozygote codominant model (AA vs. AG)



Heterozygote codominant model (AG vs. GG)