# 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-
EBSCO CINAHL Plus	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
Web of Science	"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] OK Demographic*[tiab] OK Lifestyle*[tiab] OK Fruit*[tiab] OK
Wiley Cochrane Library	Vegetable*[tiab] OR Sex[tiab] OR Race[tiab] OR Education[tiab] OR Income[tiab] OR
Whey Cochrane Library	Living area[tiab] OK Physical activity[tiab] OK Socioeconomic[tiab] OK Socio
	economic[tiab] OK "tobacco use"[mn] OK Tobacco[tiab] OK Shisha[tiab] OK
	Disorders"[MaSHinoovn] OP "illigit drugs"[MaSHinoovn] OP illigit drugs[tiab] OP
	Usorders [mesin:noexp] OK IIICIt drugs [mesin:noexp] OK IIICIt drug*[tiab] OK
	I mich substance use[tiab] OK blood pressure [MeSH] OK blood pressure [tiab])

Author	Country	Characteristics	Study	ATS/ERS	SNPs Studied	Genotyping	Statistic
Name	,		Design	Criteria		Method	
Ahn, 2011	South	Sample Size:	Case-	2000	IL-8 rs4073	TagMan	Linear
	Korea	Cases=237	control		IL-8 rs2227307		regressio
		Controls=456			IL-8 rs2227306		n model
							Odds
		Population:					ratio
		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%)					

# Supplementary Table 2. Characteristics of the included studies.

Aquino-	Mexico	Sample Size:	Case-	2000	MICA exons 2–3	RSCA	Chi-
Galvez,		Cases=80	control		MICA exons 4–5		square
2009		Controls=201					Fisher's
							exact
		Population:					Odds
		Mixed					ratio
							rutio
		Δσε·					
		$C_{359}(64.77+11.02)$					
		Control $(53.4 \pm 11.2)$					
		Condor:					
		Mala (Casa-42, Control-72)					
		$\frac{1}{100}$					
· ·		remaie (Case=38, Control=129)	6	2011		T 14	D
Aquino-	Mexico	Sample Size:	Case-	2011	HSPAIL	TaqMan	Pearson
Galvez,		Cases=168	control		rs20/5800		$\chi^2$
2015		Controls=205			HSPA1L		Odds
					rs2227956		ratio
		Population:			HSPA1A		
		Mixed			rs1043618		
					HSPA1B		
		Age:			rs1061581		
		Case (64.5±11)					
		Control $(47+5,4)$					
		Gender:					
		Male (Case=103, Control=36)					
		Female (Case=65, Control=169)					

Bonella.	Germany	Sample Size:	Case-	2011.2018	MUC.5B	TagMan	Spearma
2021		Cases=62	control		rs35705950		n or
2021		Controls=50	control		TOLLIP rs 5743890		Pearson
		2011/013-50			$T \cap I I I P rc 3750920$		Correlati
		Donulation			TOLLII 1357 50920		contelati
		Coursesien					On
		Caucasian					Coefficie
							nt
		Age:					Fisher's
		Case (63.5±11)					exact
		Control $(42\pm2)$					Cox
							regressio
		Gender:					n
		Male (Case=43, Control= $37$ )					
		Female (Case=8 Control=13)					
		Ternale (ease=0, control=13)					
		Smalling					
		Sinoking:					
		Non-smoker (Case=9, Control=33)					
		Ex-smoker (Case=40, Control=7)					
		Current Smoker (Case=4, Control=10)					
Borie, 2013	France	Sample Size:	Case-	2001	MUC5B	TaqMan	Chi-
		Cases=142	control		rs35705950		square
		Controls=1383					Fisher's
							exact
		Population:					Odds
		Caucasian					ratio
							latio
		Δσο:					
		(60.8+8.0)					
		Case (09.0±0.9)					
		Condow					
		$Male\left(Case=82\%\right)$					
		remaie (Case=18%)					
		Smoking:					
		Yes (Case=68%, Active=4%)					
		No (Case=32%)					

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=221Population: CaucasianAge: Case ( $70\pm8.8$ ) Control ( $71.4\pm8$ 10.2)Gender: Male (Case=47) Female (Case=95)	Case- control	2001	<i>FCGR3B</i> copy number	Quantitative polymerase chain reaction	Chi- square Fisher's exact Odds ratio

Checa, 2008	Mexico	Sample Size: Cases=130 Controls=305 Population:	Case- control	2000	MMP-1 -755 MMP-1 -1607	Polymerase chain reaction restriction fragment length	Fisher's exact Odds ratio
		Mixed Age: Case (62.5±9.6) Control (40.6±12.4)				polymorphis m	
		Gender: Male (Case=67, Control=189) Female (Case=63, Control=116) Smoking:					
		Current or former smoker (Case=49, Control=107)					
Helling,	United	Sample Size:	Case-	2013	MUC5B	TaqMan	Odds
2017	States	Cases=203 Controls=139	control		rs35705950		ratio
		<b>Population:</b> Mixed					
		<b>Age:</b> Case (64±8.3) Control (57±14.5)					
		<b>Gender:</b> 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)					
Horimasu, 2015	Germany	Sample Size: Cases=44 Controls=310	Case- control	2002	MUC5B rs35705950	TaqMan	Chi- square

		Population: Asian Age: Case $(67.5\pm1.6)$ Control $(50.6\pm0.4)$ Gender: Male (Case=35, Control=255) Female (Case=9, Control=55)					Fisher's exact Odds ratio
		Smoking: Yes (Case=32, Control=166) No (Case=11, Control=139) No data (Case=0, Control=5)					
Horimasu, Ger 2015	ermany	Sample Size: Cases=71 Controls=35 Population: Caucasian Age: Case $(67.6\pm1.2)$ Control $(44.3\pm2.3)$ 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:	Case-	2011	MUC5B	TaqMan	Chi-
Ũ		Cases=187	control		rs35705950	•	square
		Controls=250					Ödds
							ratio
		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)					

Kishore.	Czech	Sample Size:	Case-	2000, 2001,	II-1 α rs1800587	Allele-	Chi-
2016	Republic	Cases=165	control	2011	II = 1 R rc 16044	specific	square
2010	nopusite	Controls=96	control	2011	$IL^{-1} \rho IST0344$	MAI DI-TOF	Fisher's
					$IL-1 \beta rs 1 143634$		exact
		Population:			PRKCE IS6288//		Odds
		Caucasian			LKRC34		ratio
		Cadeasian			rs6/93295		Tutto
		Δ.σ.ο.			IF rs1/99899		
		Agc.			IL-8 rs40/3		
		Case $(07.97 \pm 11.00)$			FAM13A		
		Control $(34.45 \pm 8.94)$			rs2609255		
					TLR3 rs3775291		
		Gender:			<i>TERT rs2736100</i>		
		Male (Case=125, Control=45)			IL-13 rs1800925		
		Female (Case=40, Control=51)			IL-4 rs2243248		
					IL-4 rs2243250		
					IL-4 rs2070874		
					CDKN1A		
					rs733590		
					OBFC1		
					rs11191865		
					MUC2 rs7934606		
					MUC5B		
					rs35705950		
					ATP11A		
					rs1278769		
					$II - 4R \alpha rs 1801275$		
					TP53 rs12951053		
					TP53 rs12602273		
					MΔPT rs 1981997		
					$\Delta CE rc A 277A05$		
					ACE rs 4450600		
					DDD0 rc 12610/05		
Polito 2015	United	Sampla Siza	Casa	2011	DFF91512010495		1 D 1 4
1 eijio, 2015	Statos	$\int \frac{d^2}{dt} = \int \frac{dt}{dt} =$	Case-	2011	$r_{c}6702205$	-	Odda
	States	Casco = 2.55 Controls = 87	CONTO		ΓΔΛΛ13Δ		ratio
		COHUOIS-07			171111377 rc2600255		Tatio
		Population			152009233 TEDT #c2726100		
		ropulation:			1EKT 152/30100		
		Asian			DSP 1520/6295		

		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	Case- control	2000	TGF-β1 exon 1 IL-6 –174 TNF-α –308 IL-1Ra intron 2	Restriction fragment length polymorphis m	Chi- square LRM Odds ratio
		Gender: Male to female ratio (17:5) Smoking: Current or ex-smokers (95%)					
Selman, 2003	Mexico	Sample Size: Cases=84 Controls=194Population: MixedAge: Case ( $62.3\pm10.9$ ) Control ( $41\pm14.5$ )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	<i>SP-A SP-A1_6A</i> <i>SP-A AA219_T</i> <i>SP-A AA50_C</i> <i>SP-A AA62_G</i> <i>SP-B B1580_C</i> <i>SP-C CA138</i> <i>SP-C CA136</i> <i>SP-D</i> (not mentioned)	Polymerase chain reaction restriction fragment length polymorphis m	Fisher's exact LRM Odds ratio

Son. 2013	South	Sample Size:	Case-	2001	TGF-b1 T869C	DNA	Chi-
,	Korea	Cases=85	control			sequencing	square
	norea	Controls=85	00110101			sequence8	IRM
							Odds
		Population:					ratio
		Asian					rutio
		/ totall					
		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)					
Stock, 2013	United	Sample Size:	Case-	2000, 2001	MUC5B	TaqMan	Chi-
	Kingdom	Cases=110	control		rs35705950		square
		Controls=416					Fisher's
							exact
		Population:					Odds
		Caucasian					ratio
		Age:					
		Case (64.6 [45–85])					
		Caralan					
		Gender:					
		Male (Case=79)					
Staal 2020	United	Female (Case=31)	Casa	2000 2001	MUCED	Taghtan	Odda
SIOCK, 2020	Vingdom	Sample Size:	Case-	2000, 2001	WUUUSD	rayman	ratio
	Kingdom	Cases=25	control		1555705950		ratio
		CONTROLS=20					
		Population:					
		Caucasian					
		Cudeusian					

Uh. 2013	South	Sample Size:	Case-	2001	ACE - 5538	Single base	Fisher's
011, 2013	Korea	Cases=220	control	2001	ACE -5508	extension and	exact
	Rorea	Controls-456	control		ACF - 3927	electrophores	IRM
		Control3-430			ACE -262	ic	Odds
		Bonulation			ACL = 202	15	ratio
		Asian			ACE = FIGT		Tatio
		Asian			ACE + 5407		
		•			ACE + 6307		
		Age:			ACE + 115/5		
		Case (62 [50–83])			ACE +15276		
		Control (63 [50–87])			ACE +21181		
					ACE +21288		
		Gender:					
		Male (Case=153, Control=278)					
		Female (Case=67, Control=178)					
		Smoking:					
		Current (Case=26%, Control=14%)					
		Ex-smoker (Case=30%, Control=15%)					
Uh, 2014	South	Sample Size:	Case-	2001	ADAM33	Single base	Chi-
,	Korea	Cases=237	control		rs3918392	extension and	square
		Controls=183			ADAM33	electrophores	Fisher's
					rs511898	is	exact
		Population:			ADAM33		LRM
		Asian			rs2485700		Odds
					ADAM33		ratio
		Age:			rs2271511		ratio
		Case (62[31-83])			ADAM33		
		Control $(61 [50-81])$			rs528557		
					ADAM33		
		Gender			rs2853209		
		Male (Case $-163$ , Control $-55$ )			ADAM33		
		Female (Case $74$ Control $128$ )			rs2280089		
					ADAM33		
		Smoking			rs628977		
					15020577	1	
		(urrent)(ase=2/%)(ontrol=9.3%)			ADAM33		
		Current (Case=2/%, Control=9.3%)			ADAM33		

Van Der Vis, 2016	Netherlan ds	Sample Size: Cases=115 Controls=249 Population: Caucasian Age at diagnosis: Case (63.5±11.0) Gender: Male (Case=97) Female (Case=28)	Case- control	2001, 2011, 2013	MUC5B rs35705950	TaqMan	Pearson Chi- square Fisher's exact Odds ratio
Vasakova,	Czech	Smoking: Yes (Case=77) No (Case=38) Sample Size:	Case-	2000	1L-1α-889	Polymerase	Chi-
2006	Republic	Cases=30 Controls=103 <b>Population:</b> Caucasian <b>Age:</b> Case (65.4 [36–85]) Control (53 [24–71]) <b>Gender:</b> Male (Case=10, Control=24) Female (Case=20, Control=79)	control	2000	IL-1β -511 IL-1β -511 IL-1R pst 1970 IL-1RA mspa 11100 IL-4RA $\beta$ 1902 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 -590 IL-4 -55 IL-6 -174 IL-6 +565 IL-10 -1082	chain reaction	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 polymorphis m	Chi- square Student's <i>t</i> test Odds ratio

Wei, 2014	United	Sample Size:	Case-	2001	MUC5B	TagMan	Chi-
,	States	Cases=84	control		rs35705950	Polymerase	square
		Controls=689			TERT rs2736100	chain reaction	Fisher's
							exact
		Population:					Odds
		Caucasian					ratio
		Cadeasian					ratio
		Δσε					
		Agc.					
		Case $(04.4\pm7.7)$					
		$COIIIIOI (33.7 \pm 13.2)$					
		Conder:					
		Mala (Casa-EE, Control-260)					
		$F_{\text{amale}} (Case=33, Control=300)$					
		remaie (Case=29, Control=329)					
		Smoking					
		Since $(C_{2}, C_{2}, $					
		Current (Case = 1)					
		Ever (Case=52)					
V. L. t	C	Never (Case=31)	C	2000	COV2 2050	TINAL	
Xaubet,	Spain	Sample Size:	Case-	2000	COX2.3050	TaqMan	Chi-
2010		Cases=1/4	control		COX2.84/3		square
		Controls=121			COX2.926		
							Odds
		Population:					ratio
		Caucasian					
		Age:					
		Case $(6/.8\pm0./8)$					
		Control (36.7±0.90)					
		Male (Case=108, Control=72)					
		Female (Case=66, Control=153)					

Zhang, 2011	United	Sample Size:	Case-	2001	MUC5B	TaqMan	Odds
0	States	Cases=341	control		rs35705950		ratio
		Controls=802					
		Population:					
		Caucasian					
		Age:					
		Case (67.9±8.8)					
		Control (52.7±14.7)					
		Condor					
		$\frac{1}{1}$					
		Fomalo (Caso-103, Control-366)					
Zhang 2012	China	Sample Size:	Caso	2000	$HI \Delta_{-} \Delta_{-} B \Delta_{2} B B$	Polymoraso	Chi
Zhang, 2012	China	Casor=36	control	2000	HIA - A - B A 2 B 12	chain reaction	CIII-
		Cases=30 Controls=11055	Control		HIA - A - B A 2 B 15	chainteaction	Square Fishor's
		Controis=11555			$HI \Delta_{-} \Delta_{-} R \Delta_{$	specific	evact
		Population			HIA - A - B A 2 B 25	amplification	Rolativo
		Asian			$HIA_A = B A 2 B 40$	amprincation	rick
					HIA-A-R A2R46		TISK
		Ασε·			HIA-A-BA2B51		
		Case $(63.4+5.1)$			HIA-A-B A2B55		
		Control $(48.3+12.1)$			HIA- $A$ - $BA$ 3 $B$ 35		
					HLA-A-B A11B13		
		Gender:			HLA-A-B A11B15		
		Male (Case=24, Control=8129)			HLA-A-B A11B27		
		Female (Case=12, Control=3826)			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		

Zhang, 2015	China	Sample Size:	Case-	2011	TNF-α - 308	High	Chi-
0/		Cases=102	control		TCF-R1 -869	resolution	square
		Controls=266			II_10_592	melting assav	Fisher's
					II-10-819	0 /	exact
		Population:			II-10-1082		Odds
		Asian			IEN y 874		ratio
					ΠΠ-γ-074 ΗΙΔΔ*01		
		Age:			HIA A*02		
		Case (59.34±9.87)			HIA A*11		
		Control (56.70±12.80)			HIA A*24		
					HIA A*26		
		Gender:			HIA A*30		
		Male (Case=45, Control=137)			HIA A*33		
		Female (Case=57, Control=129)			HIA B*07		
					HIA B*13		
		Smoking:			HIA B*15		
		Current (Case=0)			HIA B*27		
		Ex-smoker (Case=26)			HIA B*35		
		Non-smoker (Case=76)			HIA B*38		
					HIA 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		

Zorzetto,	Italy	Sample Size:	Case-	2001	CR1 -3650 e22	Polymerase	Chi-
2003		Cases=74	control		CR1 -520 i27	chain reaction	square
		Controls=166			CR1 -5507 e33	restriction	Ödds
						fragment	ratio
		Population:				length	
		Caucasian				polymorphis	
						m	
		Age:					
		Case $(66.5 \pm 10.88)$					
		Control $(61.7\pm8.4)$					
		Gender:					
		Male (Case=51, Control=105)					
		Female (Case=23, Control=61)					
		Smoking:					
		Yes (Case=37)					
		No (Case=37)					

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 <i>IL-8 rs4073</i> and increased risk of IPF.
		Multivariate analysis:
Aguina Calvaz 2000		Adjusted for age, gender and smoking
Aquino-Gaivez, 2009	MICA	risk of IPF.
Aquino-Galvez, 2015	HSPA1B rs1061581	Significant association between HSPA1B rs1061581, HSPA1L rs2227956 and HSPA1 rs1043618 and
	HSPA1L rs222/956	decreased risk of IPF.
	HSPA1 rs1043618	
Bonella, 2021	MUC5B rs35/05950	Significant association between MUC5B rs35705950 minor allele and increased risk of IPF.
	TOLLIP rs5/43890	
Davia 2012	TOLLIP 153750920	Circuition at an a sintian between MUCED == 25705050 and in an and side of IDE
Borie, 2013	MUC3B 7835705950	Significant association between MUC5B rs35705950 and increased risk of IPF.
Bournazos, 2010	FcyRIIIb CD16b	Significant association between NAT allele and NAT/NAT genotype and increased risk of IPF.
		IPF.
		Significant association between NA2 allele and decreased risk of IPF.
Bournazos, 2011	FCGR3B copy	Significant association between FCGR3B copy number and increased risk of IPF.
	number	
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 <i>MUC5B rs35705950</i> and increased risk of IPF.
Horimasu, 2015 (Asian)	MUC5B rs35705950	Significant association between <i>MUC5B rs35705950</i> and increased risk of IPF.
Horimasu, 2015	<i>MUC5B rs35705950</i>	Significant association between <i>MUC5B</i> rs35705950 and increased risk of IPF.
(Caucasian)		
Jiang, 2015	MUC5B rs35705950	Significant association between <i>MUC5B rs35705950</i> and increased risk of IPF.
Kishore, 2016	MUC5B rs35705950	Significant association between MUC5B rs35705950 and increased risk of IPF.
Peljto, 2015 (Asian)	MUC5B rs35705950	Significant association between <i>IVD rs2034650</i> and increased risk of IPF.
	IVD rs2034650	
		Multivariate analysis:
		Adjusted for age and gender
		Adjusted for age, gender and MUC5B rs35705950

Peljto, 2015 (Mixed)	MUC5B rs35705950	Significant association between MUC5B rs35705950 and increased risk of IPF.
	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
Riha, 2004	TNF-α –308	Significant association between <i>TNF-</i> $\alpha$ (-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	<i>TGF-b</i> ₁ <i>T869C</i>	Significant association between TGF-b <sub>1</sub> T869C and increased risk of IPF.
		Multivariate analysis:
		Adjusted for age, gender and smoking
Stock, 2013	MUC5B rs35/05950	Significant association between MUC5B rs35/05950 and increased risk of IPF.
		Multivariate analysis:
<u>Cr. 1. 2020</u>		Adjusted for age, gender, smoking and composite physiological index (CPI)
Stock, 2020	MUC5B rs35/05950	Significant association between MUC5B rs35/05950 minor allele and increased risk of IPF.
Uh, 2013	ACE -5538	Significant association between ACE -55381>C and -5508A>C and increased risk of IPF.
		Multivariate analysis
		Adjusted for age, gender and smoking
Lib 2014		Aujusted for age, genuer and smoking
01, 2014	ADAWISS 15626977	Significant association between ADAM55 18626977 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 ML/C5B minor allele and increased risk of IPE
Vasakova 2006	<i>II-4 - 590</i>	Significant association between CT genotypes of <i>II-4</i> -590 and -33 and increased risk of IPE
Vusukovu, 2000	11-4 - 33	significant association between er genotypes of <i>L</i> 7 550 and 55 and mereased lisk of it 1.
Wang, 2014	MUC5B rs35705950	Significant association between MUC5B rs35705950 minor allele and increased risk of IPE.
Wei, 2014	MUC5B rs35705950	Significant association between MUC5B rs35705950 minor allele and increased risk of IPF
	TERT rs2736100	
		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 <i>MUC5B</i> rs35705950 and increased risk of IPF.
Zhang, 2012	HLA-A*3	Significant association between HLA-A*3, HLA-B*14, HLA-B*15, HLA-B*40, HLA-A2B15, HLA-
	HLA-B*14	A2B40, HLA-A11B15, HLA-A24B58 and HLA-A30B40 and increased risk of IPF.
	HLA-B*15	
	HLA-B*40	
	HLA-A2B15	
	HLA-A2B40	
	HLA-A11B15	
	HLA-A24B58	
	HLA-A30B40	
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.

Supplement	ary Table 4. C	Quality assessment of s	tudies using	Newcastle-O	ttawa scale.				
Author and year		Selection			Comparability		Exposure		Total
	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	stars
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) MUC5B rs35705950

Author and Year	GG	GT	TT	GG	GT	TT	HWE	HWE
	(Cases)	(Cases)	(Cases	(Controls)	(Controls)	(Controls)	(P Value)	(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) MUC5B rs35705950, Asian

Author and Year	GG (Cases)	GT (Cases)	TT (Cases )	GG (Controls)	GT (Controls)	TT (Controls)	HWE (P Value)	HWE (Adjusted <i>P</i> 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) MUC5B rs35705950, Caucasian

Author and Year	GG	GT	TT	GG	GT	TT	HWE	HWE
	(Cases)	(Cases)	(Cases	(Controls)	(Controls)	(Controls)	(P Value)	(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 <i>P</i> 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 <i>P</i> 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 ( <i>P</i> Value)	HWE (Adjusted <i>P</i> 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 <i>P</i> Value	l <sup>2</sup>
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 <i>P</i> Value	<sup>2</sup>
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 <i>P</i> Value	l <sup>2</sup>
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% Cl	Adjusted <i>P</i> Value	l <sup>2</sup>
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% Cl	Adjusted <i>P</i> Value	l <sup>2</sup>
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 <i>P</i> Value	l <sup>2</sup>
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)

Study	Experim Events	ental Total	Co Events	ontrol Total	Odds Ratio	OR	95%-CI	Weight
Bonella 2021	4	62	1	50		3.38	[0.37; 31.24]	2.3%
Borie 2013	17	142	29	1391		6.39	[3.42; 11.95]	29.3%
Helling 2017	15	203	0	139		22.94	[1.36; 386.68]	1.4%
Horimasu 2015 (Asian)	\ 0	44	0	310		0 50	[0 52, 160 59]	0.0%
liang 2015	) 0 10	187	7	250		3.20	[0.55, 109.56]	14%
Kishore 2016	9	151	2	250		2.98	[0.63: 14.09]	4.8%
Stock 2013	10	110	8	416		5.10	[1.96; 13.25]	12.6%
Stock 2020	2	23	0	20		4.77	[0.22; 105.41]	1.2%
Van Der Vis 2016	5	115	1	249		11.27	[1.30; 97.62]	2.5%
Wang 2014	0	165	0	1013				0.0%
Wei 2014	3	84	11	689	+=	2.28	[0.62; 8.35]	6.8%
Zhang 2011	24	341	12	802		4.98	[2.46; 10.09]	23.1%
<b>Random effects model</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$	0, <i>p</i> = 0.9	<b>1698</b> 1		5460		5.01	[3.57; 7.03]	100.0%
					0.01 0.1 1 10 100			

Dominant model (TT+TG vs. GG)

	Experimental Contro							
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-Cl	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%
<b>Random effects model</b> Heterogeneity: $I^2 = 69\%$ , $\tau^2 =$	: 0.1584, µ	<b>1698</b>	1	5460		4.99	[3.77; 6.61]	100.0%
					0.1 0.51 2 10			

# Overdominant model (TG vs. TT+GG)

	Experim	ental	Co	ontrol					
Study	Events	Total	Events	Total		Odds Ratio	OR	95%-Cl	Weight
Bonella 2021	35	62	7	50			7.96	[3.10; 20.46]	5.4%
Borie 2013	76	142	259	1391			5.03	[3.52; 7.19]	10.8%
Helling 2017	87	203	32	139			2.51	[1.55; 4.06]	9.5%
Horimasu 2015 (Asian)	3	44	5	310		<u> </u>	4.46	[1.03; 19.37]	2.9%
Horimasu 2015 (Caucasian	) 31	71	3	35			- 8.27	[2.31; 29.52]	3.6%
Jiang 2015	34	187	41	250			1.13	[0.69; 1.87]	9.3%
Kishore 2016	75	151	14	96		<u> </u>	5.78	[3.02; 11.08]	7.8%
Stock 2013	58	110	71	416			5.42	[3.44; 8.53]	9.8%
Stock 2020	13	23	6	20			3.03	[0.86; 10.72]	3.7%
Van Der Vis 2016	51	115	43	249			3.82	[2.33; 6.25]	9.4%
Wang 2014	11	165	16	1013			4.45	[2.03; 9.77]	6.6%
Wei 2014	44	84	139	689			4.35	[2.73; 6.94]	9.7%
Zhang 2011	186	341	154	802		-	5.05	[3.83; 6.66]	11.6%
<b>Random effects model</b> Heterogeneity: $I^2 = 69\%$ , $\tau^2 =$	= 0.1633, µ	<b>1698</b>	1	5460	<b></b>		4.06	[3.05; 5.41]	100.0%
5 ,	/				0.1	0.5 1 2 10			

Homozygote codominant model (TT vs. GG)

	Experim	ental	Co	ontrol					
Study	Events	Total	Events	Total	Odd	s Ratio	OR	95%-Cl	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		<b></b>	8.78	[6.19; 12.43]	100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$	0, p = 0.6	7			1 1				
					0.01 0.1	1 10 100			

# Heterozygote codominant model (TT vs. TG)

Study	Experime Events	ental Total	Co Events	ntrol Total		Ode	ds Rat	tio		OR	g	5%-CI	Weight
Bonella 2021	4	39	1	8						0.80	[0.08;	8.28]	2.3%
Borie 2013	17	93	29	288						2.00	[1.04;	3.83]	29.5%
Helling 2017	15	102	0	32			+			11.51	[0.67; 1	98.02]	1.5%
Horimasu 2015 (Asian)	0	3	0	5									0.0%
Horimasu 2015 (Caucasian	) 8	39	0	3					-	1.89	[0.09;	40.22]	1.3%
Jiang 2015	19	53	7	48				-		3.27	[1.23;	8.71]	13.1%
Kishore 2016	9	84	2	16				-		0.84	[0.16;	4.31]	4.7%
Stock 2013	10	68	8	79			-			1.53	[0.57;	4.13]	12.7%
Stock 2020	2	15	0	6			++		_	2.41	[0.10;	57.73]	1.2%
Van Der Vis 2016	5	56	1	44			+		-	4.22	[0.47;	37.48]	2.6%
Wang 2014	0	11	0	16									0.0%
Wei 2014	3	47	11	150		_				0.86	[0.23;	3.23]	7.2%
Zhang 2011	24	210	12	166						1.66	[0.80;	3.42]	23.8%
<b>Random effects model</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$	0, p = 0.78	<b>820</b>		861		1	<b>\</b>	1		1.83	[1.28;	2.61]	<b>100.0</b> %
				(	0.01	0.1	1	10	100				

Heterozygote codominant model (TG vs. GG)

	Experim	ental	Co	ontrol					
Study	Events	Total	Events	Total	0	dds Ratio	OR	95%-Cl	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		<u> </u>	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		<u></u>	5.86	[4.41; 7.79]	11.2%
Random effects model	0 1025	1582	1	5389	<b></b>	&	4.64	[3.42; 6.29]	100.0%
Heterogeneity: $I = I2\%$ , t =	- 0.1955, J	. < 0.0	T		0 1	0512 10			
<b>Random effects model</b> Heterogeneity: $I^2 = 72\%$ , $\tau^2 =$	= 0.1935, µ	<b>1582</b> 0 < 0.0	1	5389	0.1	0.51210	4.64	[3.42; 6.29]	100.0%

#### b) MUC5B rs35705950, Asian

#### **Recessive model (TT vs. TG+GG)**

Experimental Control Odds Ratio Study **Events Total Events Total** OR 95%-CI Weight Horimasu 2015 0 44 0 310 0.0% Jiang 2015 Wang 2014 19 187 7 250 3.93 [1.61; 9.55] 100.0% 0 165 0 1013 0.0% Random effects model 396 1573 - 3.93 [1.61; 9.55] 100.0% Heterogeneity:  $I^2 = NA\%$ ,  $\tau^2 = NA$ , p = NA0.2 0.5 1 2 5

### Dominant model (TT+TG vs. GG)

Study	Experimental Events Total Ev	Control ents Total	Odds Ratio	OR	95%-Cl Weight	
Horimasu 2015 Jiang 2015 Wang 2014	3 44 53 187 11 165	5 310 48 250 16 1013		- 4.46 1.66 4.45	[1.03; 19.37] 18.5% [1.06; 2.60] 46.4% [2.03; 9.77] 35.1%	
<b>Random effects mode</b> Heterogeneity: $I^2 = 63\%$ , $\tau$	<b>1 396</b> ${}^{2} = 0.2865, p = 0.00$	<b>1573</b>	0.1 0.5 1 2 10	2.82	[1.30; 6.14] 100.0%	

#### Overdominant model (TG vs. TT+GG)



#### Homozygote codominant model (TT vs. GG)

Study	Experime Events 1	ental Fotal	Co Events	ontrol Total	Od	ds R	atio	OR	95%-CI	Weight
Horimasu 2015 Jiang 2015 Wang 2014	0 19 0	41 153 154	0 7 0	305 209 997				— 4.09	[1.67; 10]	0.0% 100.0% 0.0%
<b>Random effects mode</b> Heterogeneity: $I^2 = NA\%$ ,	$\tau^2 = NA, p =$	<b>348</b> = NA		<b>1511</b> 0.	1 0.5	1	2	<b>4.09</b>	[1.67; 10]	100.0%

Heterozygote codominant model (TT vs. TG)

Study	Experime Events 1	ntal otal	Co Events	ntrol Total		Odd	s Ra	atio		OR	95%-CI	Weight
Horimasu 2015 Jiang 2015 Wang 2014	0 19 0	3 53 11	0 7 0	5 48 16			-		-	3.27	[1.23; 8.71]	0.0% 100.0% 0.0%
<b>Random effects mode</b> Heterogeneity: $I^2 = NA\%$ , $\tau$	$h^{2} = NA, p =$	<b>67</b> NA		69	0.2	0.5	- 1	2	5	3.27	[1.23; 8.71]	100.0%

# Heterozygote codominant model (TG vs. GG)



#### c) MUC5B rs35705950, Caucasian

#### **Recessive model (TT vs. TG+GG)**



#### Dominant model (TT+TG vs. GG)

Study	Experime Events	ental Total	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	Weight
Bonella 2021	39	62	8	50		8.90	[3.57; 22.23]	3.8%
Horimasu 2015	39	71	3	35	<del>  .</del>	- 13.00	[3.64; 46.40]	2.0%
Kishore 2016	84	151	16	96		6.27	[3.35; 11.72]	8.1%
Stock 2013	68	110	79	416	<u> </u>	6.91	[4.38; 10.90]	15.2%
Stock 2020	15	23	6	20		4.38	[1.21; 15.81]	1.9%
Van Der Vis 2016	56	115	44	249		4.42	[2.71; 7.22]	13.2%
Wei 2014	47	84	150	689		4.56	[2.86; 7.28]	14.5%
Zhang 2011	210	341	166	802	-	6.14	[4.66; 8.10]	41.3%
Random effects mode Heterogeneity: $I^2 = 0\%$ , $\tau^2$	$p^2 = 0, p = 0$	<b>957</b>		2357		5.87	[4.92; 7.02]	100.0%
5 7 7					0.1 0.51 2 10			

# Overdominant model (TG vs. TT+GG)

	Experime	ental	Co	ntrol					
Study	Events	Total	Events	Total		Odds Ratio	OR	95%-Cl	Weight
Bonella 2021	35	62	7	50			- 7.96	[3.10; 20.46]	3.6%
Horimasu 2015	31	71	3	35			— 8.27	[2.31; 29.52]	2.0%
Kishore 2016	75	151	14	96		<u> </u>	5.78	[3.02; 11.08]	7.5%
Stock 2013	58	110	71	416		- <u>i</u> -	5.42	[3.44; 8.53]	15.5%
Stock 2020	13	23	6	20			3.03	[0.86; 10.72]	2.0%
Van Der Vis 2016	51	115	43	249			3.82	[2.33; 6.25]	13.1%
Wei 2014	44	84	139	689			4.35	[2.73; 6.94]	14.6%
Zhang 2011	186	341	154	802		-	5.05	[3.83; 6.66]	41.7%
<b>Random effects mode</b> Heterogeneity: $l^2 = 0\%$ , $\tau^2$	p = 0, p = 0	<b>957</b> .79		2357	<b></b>		4.94	[4.13; 5.91]	100.0%
	-, p 0				0.1	0.512 10			

# Homozygote codominant model (TT vs. GG)

Study	Experime Events	ental Total E	Co vents	ntrol Total	Odds Ratio	OR	95%-CI	Weight
Bonella 2021	4	27	1	43	+	7.30	[0.77: 69.27]	4.3%
Horimasu 2015	8	40	0	32		17.00	[0.94; 306.90]	2.6%
Kishore 2016	9	76	2	82		5.37	[1.12; 25.73]	8.9%
Stock 2013	10	52	8	345		10.03	[3.75; 26.82]	22.5%
Stock 2020	2	10	0	14		8.53	[0.36; 199.48]	2.2%
Van Der Vis 2016	5	64	1	206		17.37	[1.99; 151.62]	4.6%
Wei 2014	3	40	11	550		3.97	[1.06; 14.86]	12.5%
Zhang 2011	24	155	12	648		9.71	[4.74; 19.91]	42.3%
<b>Random effects mode</b> Heterogeneity: $l^2 = 0\%$ , $\tau^2$	$e^2 = 0, p = 0$	<b>464</b> .93		1920		8.52	[5.34; 13.59]	100.0%
					0.01 0.1 1 10 100			

Heterozygote codominant model (TT vs. TG)

	Experime	ental	Co	ntrol				
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-Cl	Weight
Bonella 2021	4	39	1	8		0.80	[0.08; 8.28]	4.1%
Horimasu 2015	8	39	0	3		1.89	[0.09; 40.22]	2.4%
Kishore 2016	9	84	2	16		0.84	[0.16; 4.31]	8.4%
Stock 2013	10	68	8	79		1.53	[0.57; 4.13]	22.8%
Stock 2020	2	15	0	6		- 2.41	[0.10; 57.73]	2.2%
Van Der Vis 2016	5	56	1	44		4.22	[0.47; 37.48]	4.7%
Wei 2014	3	47	11	150		0.86	[0.23; 3.23]	12.8%
Zhang 2011	24	210	12	166	+	1.66	[0.80; 3.42]	42.6%
<b>Random effects mod</b> Heterogeneity: $l^2 = 0\%$ , $\tau$	ell = 0, p = 0	<b>558</b> .93		472		1.45	[0.90; 2.33]	100.0%
5 7 .					0.1 0.51 2 10			

# Heterozygote codominant model (TG vs. GG)

C to a la c	Experim	ental Total	Co	ntrol		Odda Batia	0.0	05% CI	Wainht
Study	Events	IOLAI	Events	Ισται		Juds Kallo	UK	95%-CI	weight
Bonella 2021	35	58	7	49			9.13	[3.50; 23.79]	3.6%
Horimasu 2015	31	63	3	35			- 10.33	[2.87; 37.25]	2.0%
Kishore 2016	75	142	14	94			6.40	[3.32; 12.33]	7.8%
Stock 2013	58	100	71	408		- <u>-</u>	6.55	[4.09; 10.51]	15.0%
Stock 2020	13	21	6	20			3.79	[1.03; 13.91]	2.0%
Van Der Vis 2016	51	110	43	248			4.12	[2.50; 6.78]	13.5%
Wei 2014	44	81	139	678			4.61	[2.87; 7.42]	14.8%
Zhang 2011	186	317	154	790		-	5.86	[4.41; 7.79]	41.3%
<b>Random effects mode</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2$	$e^{\mathbf{I}} = 0, p = 0$	<b>892</b>		2322	Г <u> </u>		5.63	[4.69; 6.76]	100.0%
	-, p 0				0.1	0.512 10			

# d) *IL-4 rs2243250*

# Recessive model (TT vs. TC+CC)

Study	Experiment Events Tot	tal Co tal Events	ontrol Total	Odds Ratio	OR	95%-Cl Weight
Kishore 2016 Vasakova 2006	10 1 1	64 5 30 5	94 102		1.16 0.67	[0.38; 3.49] 79.7% [0.08; 5.96] 20.3%
<b>Random effects mod</b> Heterogeneity: $l^2 = 0\%$ ,	<b>el 1</b> $t^2 = 0, p = 0.66$	94	196	0.1 0.5 1 2 10	<b>1.03</b>	[0.39; 2.77] 100.0%

# Dominant model (TT+TC vs. CC)

Study	Experime Events T	ntal Total Ev	Co vents	ntrol Total	Odds Ratio	OR	95%-Cl	Weight
Kishore 2016 Vasakova 2006	36 27	164 30	30 25	94 102	* -	0.60 — 27.72	[0.34; 1.06] [7.74; 99.23]	51.2% 48.8%
<b>Random effects mode</b> Heterogeneity: $I^2 = 97\%$ ,	ε <b>ί</b> τ <sup>2</sup> = 7.0919,	<b>194</b> p < 0.0	1	196	0.1 0.5 2 10	<u> </u>	[0.09; 166.79] :	100.0%

### Overdominant model (TC vs. TT+CC)



#### Homozygote codominant model (TT vs. CC)

Study	Experime Events	ental Total	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	Weight
Kishore 2016 Vasakova 2006	10 1	138 4	5 5	69 82		1.00 — 5.13	[0.33; 3.05] [0.45; 58.73]	72.9% 27.1%
<b>Random effects mode</b> Heterogeneity: $I^2 = 30\%$ ,	$\tau^2 = 0.4030$	<b>142</b> , p = 0	).23	151	0.1 0.51 2 10	1.56	[0.37; 6.49]	100.0%

#### Heterozygote codominant model (TT vs. TC)

Study	Experime Events 1	ntal Iotal E	Con vents T	trol otal	Odds Ratio	OR	95%-CI	Weight
Kishore 2016 Vasakova 2006	10 1	36 27	5 5	30 25 -		1.92 0.15	[0.58; 6.42] [0.02; 1.42]	57.1% 42.9%
<b>Random effects mode</b> Heterogeneity: $I^2 = 74\%$ , T	ε <b>Ι</b> τ <sup>2</sup> = 2.3562,	<b>63</b> p = 0.0	5	55		0.65	[0.06; 7.55]	100.0%

# Heterozygote codominant model (TC vs. CC)



# e) *IL-4 rs2070874*

# Recessive model (TT vs. TC+CC)

Study	Experime Events	ental Total	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	Weight
Kishore 2016 Vasakova 2006	5 1	165 30	3 5	96 102		0.97 — 0.67	[0.23; 4.15] [0.08; 5.96]	69.3% 30.7%
<b>Random effects mode</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2$	$p^2 = 0, p = 0.$	<b>195</b> 78		198		<b>0.86</b>	[0.26; 2.90]	100.0%

# Dominant model (TT+TC vs. CC)

Study	Experime Events	ental Total	Co Events	ntrol Total		Odds Ratio	OR	95%-Cl	Weight
Kishore 2016 Vasakova 2006	43 21	165 30	30 25	96 102			0.78 — 7.19	[0.45; 1.35] [2.92; 17.71]	51.3% 48.7%
<b>Random effects mode</b> Heterogeneity: $I^2 = 94\%$ , $\tau$	<b>1</b> <sup>2</sup> = 2.3330	<b>195</b> , p < 0	.01	198	0.1	0.5 1 2 1	<b>2.29</b>	[0.26; 20.30]	100.0%

#### **Overdominant model (TC vs. TT+CC)**



#### Homozygote codominant model (TT vs. CC)

Study	Experimen Events To	tal tal E	Coi Events	ntrol Fotal		Odds R	latio		OR	95%-CI	Weight
Kishore 2016 Vasakova 2006	5 : 1	.27 10	3 5	69 82	-		-		0.90 1.71	[0.21; 3.89] [0.18; 16.32]	70.4% 29.6%
<b>Random effects mode</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2$	$p^2 = 0, p = 0.64$	37		151	0.1	0.5 1	 2	10	1.09	[0.32; 3.72]	100.0%

# Heterozygote codominant model (TT vs. TC)

Study	Experime Events 1	ental Total	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	Weight
Kishore 2016 Vasakova 2006	5 1	43 21	3 5	30 25 -		1.18 0.20	[0.26; 5.38] [0.02; 1.87]	61.1% 38.9%
<b>Random effects mode</b> Heterogeneity: $l^2 = 40\%$ , $\tau$	= 0.6332,	<b>64</b> p = 0	.20	55	0.1 0.51 2 10	0.59	[0.11; 3.24]	100.0%

# Heterozygote codominant model (TC vs. CC)



#### f) TNFa -308

#### **Recessive model (AA vs. AG+GG)**

Experimental Control Study **Events Total Events Total Odds Ratio** OR 95%-Cl Weight Riha 2004 2 22 1 140 - 13.90 [1.2; 160.4] 100.0% Zhang 2015 0 102 0 266 0.0% Random effects model124Heterogeneity:  $I^2 = NA\%$ ,  $\tau^2 = NA$ , p = NA124 406 - 13.90 [1.2; 160.4] 100.0% 0.01 0.1 1 10 100

#### Dominant model (AA+AG vs. GG)

Study	Experiment Events Tot	al Co al Events	ontrol Total	Odds Ratio	OR	95%-CI	Weight
Riha 2004 Zhang 2015	13 2 18 10	22 37 02 41	140 266		- 4.02 1.18	[1.59; 10.18] [0.64; 2.16]	45.8% 54.2%
<b>Random effects mode</b> Heterogeneity: $I^2 = 79\%$ , t	$12^{2} = 0.5952, p = 0.5952,$	2 <b>4</b> = 0.03	<b>406</b> 	0.5 1 2	<b>2.06</b>	[0.62; 6.86]	100.0%

#### Overdominant model (AG vs. AA+GG)



#### Homozygote codominant model (AA vs. GG)

Study	Experime Events 1	ntal Iotal E	Co Events	ntrol Total	c	Odds F	Ratio	OR	95%-Cl	Weight
Riha 2004 Zhang 2015	2 0	11 84	1 0	104 225				22.89	[1.89; 277.52]	100.0% 0.0%
<b>Random effects mode</b> Heterogeneity: $I^2 = NA\%$ ,	$\tau^2 = NA, p =$	<b>95</b> NA		329	0.01 0.	1 1	10	<b>22.89</b>	[1.89; 277.52]	100.0%

# Heterozygote codominant model (AA vs. AG)

Study	Experime Events T	ntal otal E	Cor vents 1	ntrol Total	Odds Ratio	OR	95%-CI	Weight
Riha 2004 Zhang 2015	2 0	13 18	1 0	37 41		6.55	[0.54; 79.23]	100.0% 0.0%
<b>Random effects mode</b> Heterogeneity: $I^2 = NA\%$ ,	$\tau^2 = NA, p =$	<b>31</b> NA		78	0.1 0.51 2 10	- 6.55	[0.54; 79.23]	100.0%

# Heterozygote codominant model (AG vs. GG)

