

RESEARCH ARTICLE

Association between Variants in Atopy-Related Immunologic Candidate Genes and Pancreatic Cancer Risk

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Abstract

Background

Many epidemiology studies report that atopic conditions such as allergies are associated with reduced pancreas cancer risk. The reason for this relationship is not yet understood. This is the first study to comprehensively evaluate the association between variants in atopy-related candidate genes and pancreatic cancer risk.

Methods

A population-based case-control study of pancreas cancer cases diagnosed during 2011–2012 (via Ontario Cancer Registry), and controls recruited using random digit dialing utilized DNA from 179 cases and 566 controls. Following an exhaustive literature review, SNPs in 180 candidate genes were pre-screened using dbGaP pancreas cancer GWAS data; 147 SNPs in 56 allergy-related immunologic genes were retained and genotyped. Logistic regression was used to estimate age-adjusted odd ratio (AOR) for each variant and false discovery rate was used to adjust Wald p-values for multiple testing. Subsequently, a risk allele score was derived based on statistically significant variants.

Results

18 SNPs in 14 candidate genes (*CSF2*, *DENND1B*, *DPP10*, *FLG*, *IL13*, *IL13RA2*, *LRP1B*, *NOD1*, *NPSR1*, *ORMDL3*, *RORA*, *STAT4*, *TLR6*, *TRA*) were significantly associated with pancreas cancer risk. After adjustment for multiple comparisons, two *LRP1B* SNPs remained statistically significant; for example, *LRP1B* rs1449477 (AA vs. CC: AOR=0.37, 95% CI: 0.22–0.62; p (adjusted)=0.04). Furthermore, the risk allele score was associated with a significant reduction in pancreas cancer risk (p=0.0007).

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Conclusions

Preliminary findings suggest certain atopy-related variants may be associated with pancreas cancer risk. Further studies are needed to replicate this, and to elucidate the biology behind the growing body of epidemiologic evidence suggesting allergies may reduce pancreatic cancer risk.

Introduction

Pancreatic cancer is usually fatal, with fewer than 10% of cases surviving five years [1]. While its etiology is not well understood, smoking [2,3], pancreatitis [4,5], obesity [6] and family history of pancreas cancer [7] are long established pancreatic cancer risk factors, together with the more recently identified ABO blood group [8,9]. There is a growing body of evidence, including meta- and pooled-analyses, that suggests atopic diseases such as allergies and hay fever, are associated with reduced pancreatic cancer risk [10–13]. While there is no accepted understanding of how allergies may reduce pancreatic cancer risk, enhanced cancer immune surveillance has been suggested [10]. In light of the association between atopy and pancreas cancer risk [10–13], and the known inherited component to both atopic conditions [14], and pancreatic cancer [7], it is possible these two diseases may share a common genetic link, and evaluation of the association between atopy-related immunologic genetic variants and pancreatic cancer risk is warranted.

We investigated the association between pancreatic cancer risk and a comprehensive selection of variants in atopy-related immunologic candidate genes to help better understand the observed relationship between allergies and pancreas cancer risk, and to determine whether it may be explained by shared genetic factors.

Materials and Methods

A population-based case-control study was conducted to investigate the association between variants in atopy-related genes and pancreatic cancer risk. Ethics approval was obtained from the local research ethics boards (REB) (Mount Sinai Hospital REB, Toronto, Canada and University of Toronto REB, Toronto, Canada). Written informed consent was obtained for collection of biologic samples, and each participant had the freedom to decline or withdraw from this study at any given point in time.

Recruitment of Pancreas Cancer Cases and Controls

Pancreatic cancer cases were recent participants in the Ontario Pancreas Cancer Study, which identified cases through the Ontario Cancer Registry. As described previously [13], the Ontario Pancreas Cancer Study recruited residents of Ontario, Canada with a pathology report confirmed adenocarcinoma of the pancreas, or adenocarcinoma metastasis (confirmed as pancreas cancer by treating physician). Cases diagnosed between February 2011 and August 2012 were eligible for the current study, and of the 1095 pancreatic cancer cases identified, 327 (30%) were deceased or ineligible, and 130 (12%) could not be contacted. Of the 638 cases who were mailed a study package (with consent forms, 4 questionnaires, blood collection form, blood kit), 248 (39%) provided a blood or saliva sample (for DNA extraction) in addition to questionnaires, while 375 completed questionnaires only. Cases took a blood kit to a medical laboratory for their blood draw, and in some instances home blood draws were arranged. Cases that

preferred to give a saliva sample were mailed an Oragene DNA Self Collection Kit (DNA Genotek, Kanata, ON) including instructions, consent form, and a pre-paid reply envelope. Participants ranged in age from 30–88 years.

Controls residing in Ontario were recruited during 2011 using a modified random digit dialing procedure and frequency matched to the expected case distribution by sex and 5-year age groups (previously described [13]). Of the 1734 controls who agreed to participate and were mailed study packages, 1285 (74%) returned the questionnaire and blood/saliva request form. Subjects who chose to give a saliva sample were mailed an Oragene DNA Self Collection Kit (DNA Genotek, Kanata, ON) (with instructions, consent forms, and a pre-paid reply envelope). Subjects who chose to give a blood sample were mailed a blood kit which they took to a laboratory under contract with the study for their blood draw. While 1285 controls completed questionnaires, only 608 (47%) provided a blood sample at a laboratory or mailed back a saliva sample (for DNA extraction).

DNA extraction was conducted at the Biospecimen Repository at Mount Sinai Hospital (Toronto, Canada). DNA extraction from blood was conducted using the MaXtract procedure (Qiagen, Valencia, CA), and DNA from saliva was extracted using the Oragene kit methods (DNA Genotek, Kanata, ON). All extracted DNA was stored at 4°C.

Atopy-Related Immunologic Candidate Gene and SNP Selection

Initially, 183 atopy-related immunologic candidate genes were identified through an extensive literature review of the genetics of atopic diseases, including many observational studies assessing the association between genetic variants and allergy/atopy risk, and many genome-wide association studies (GWAS) of atopy-related traits, plus several cancer studies that assessed immunologic variants, and a few papers about the pathophysiology of atopy (listed in [S1 Table](#)). In order to narrow down this list of ~180 candidate genes and select single nucleotide polymorphisms (SNPs) for genotyping, the following screening was undertaken. GWAS datasets from the Pancreatic Cancer Cohort and Case-Control Consortium (PanScan) were downloaded from the Database of Genotypes and Phenotypes (dbGaP) via the National Institute of Health website (phs000206.v3.p2) [15–18]. All SNPs on the Illumina HumanHap550v3.0 array (used in PanScan) that tagged any of our ~180 a priori candidate genes were identified [SNPs within genes of interest (± 1 kb), or SNPs in high linkage disequilibrium (LD) ($R^2 > 0.8$)]. PLINK v.1.07 [19], the whole genome analysis toolset, was used to estimate associations between pancreatic cancer risk and each tagging SNP. SNPs were sorted according to ascending magnitude of p-value. The most significant SNPs ($P < 0.01$) were selected (retained) for genotyping regardless of minor allele homozygote frequency as reported in HapMap CEU population. SNPs with $P > 0.01$ were not selected for genotyping if the minor allele homozygote frequency was $< 5\%$. In cases where SNPs were in high LD ($R^2 > 0.8$), only the most significant SNPs were retained. The initial 183 genes were pared down to 59 genes. In total, 152 SNPs in 59 immunologic candidate genes were selected to be in the final list for genotyping by the current study (listed in [S2 Table](#)).

DNA Genotyping

Genotyping of DNA from the Ontario cases and controls for the selected SNPs (in 59 genes) was conducted by the Clinical Genomics Centre at Mount Sinai Hospital (Toronto, Canada) using the MassARRAY iPLEX Sequenom Platform (Sequenom, San Diego, CA). Sequenom assay design software was used to design the reaction panels for genotyping the selected SNPs. The software was unable to identify unique optimal primer binding sites for 7 of the 152 SNPs selected, and we identified alternative SNPs in high LD ($R^2 > 0.85$) for 2 of these 7 SNPs.

Therefore, 147 SNPs in 56 genes were included in the final reaction panels for genotyping. There were 10 negative controls and 10 replicates included in the reaction plates. The genotyping success rate was 99%. Call rates were <90% for 16 SNPs, therefore statistical data analyses were restricted to 131 SNPs. Of the 852 samples, 12 failed genotyping (e.g., <60% of SNPs were successfully genotyped). In total, genotype data for 238 cases and 602 controls were available for statistical data analyses.

Genotypes were assessed for significant deviation from Hardy-Weinberg equilibrium using the Online Encyclopedia for Genetic Epidemiology studies calculator [20]; SNP rs3126085 in the *FLG* gene (and 4 other non-significant SNPs) were found to deviate from Hardy-Weinberg equilibrium (at $p = 0.01$ level of significance).

Statistical Analysis

Due to concerns of confounding by ethnicity, we restricted all analyses to white persons (results for non-whites ($n = 74$) are not presented due to small sample size). There were 179 white cases (95 female, 84 male) and 566 white controls (278 female, 288 male) with genotyped DNA that comprise the dataset used for this paper. Odds Ratios (ORs), age group adjusted odds ratios (AORs) and 95% confidence intervals (CI) were estimated using logistic regression. Rare homozygous and heterozygous genotypes were combined when minor allele homozygotes had <5% prevalence among controls and ORs were in the same direction. P-values (Wald test) and p-values adjusted for multiple comparisons were both computed; false discovery rate was used to adjust for multiple comparisons [21]. Analyses were restricted to females for the 8 SNPs in 2 genes on the X chromosome. A risk allele score was derived by summing the total number of risk allele counts for each of the 17 statistically significant SNPs for each person (X chromosome SNP was excluded). Each SNP was scored as 0 or 1 (1 was assigned to individuals carrying 1 or 2 copies of the protective allele), and this was summed up across all 17 SNPs to create the risk allele score. All analyses were conducted using SAS version 9.2 (SAS Institute Inc.).

Results

[Table 1](#) shows the statistically significant association between variants in 14 atopy-related immunologic genes and pancreas cancer risk (where SNPs had at least one genotype in which the 95% CI did not include 1, or the p-value was less than 0.05). These 14 genes were: colony stimulating factor 2 (*CSF2*), DENN/MADD domain 1B (*DENND1B*), dipeptidyl-peptidase 10 (*DPP10*), filaggrin (*FLG*), interleukin 13 (*IL13*), interleukin 13 receptor alpha 2 (*IL13RA2*), low density lipoprotein receptor-related protein 1B (*LRP1B*), nucleotide-binding oligomerization domain 1 (*NOD1*), neuropeptide S receptor 1 (*NPSR1*), ORM1-like 3 (*ORMDL3*), RAR-related orphan receptor A (*RORA*), signal transducer and activator of transcription 4 (*STAT4*), toll-like receptor 6 (*TLR6*), and T cell receptor alpha (*TRA*). All other candidate gene variants were not found to be statistically significantly associated with pancreas cancer risk (the complete list of variants assessed are listed in [S2 Table](#)). Eighteen SNPs in 14 genes were significantly associated with pancreas cancer risk: *CSF2* rs17674015 (CA vs. AA: AOR = 0.58, 95% CI: 0.35–0.97), *DENND1B* rs16841842 (CA/AA vs. CC: AOR = 1.43, 95% CI: 1.02–2.02), *DPP10* rs998429 (CC vs. AA: AOR = 1.96, 95% CI: 1.08–3.56), *FLG* rs3126085 (AG/AA vs. GG: AOR = 1.50, 95% CI: 1.03–2.18), *IL13* rs20541 (CT/TT vs. CC: AOR = 1.48, 95% CI: 1.04–2.10), *LRP1B* rs1449477 (AA vs. CC: AOR = 0.37, 95% CI: 0.22–0.62), *LRP1B* rs2029142 (AA vs. GG: AOR = 2.46, 95% CI: 1.49–4.05), *LRP1B* rs1882164 (AA vs. CC: AOR = 0.51, 95% CI: 0.31–0.83), *LRP1B* rs2052910 (AA vs. CC: AOR = 1.90, 95% CI: 1.07–3.36), *LRP1B* rs10496915 (CA/CC vs. AA: AOR = 1.55, 95% CI: 1.08–2.22), *NOD1* rs2907749 (GA vs. AA: AOR = 0.6, 95% CI: 0.44–0.92), *NPSR1* rs1833090 (AA vs. CC: AOR = 2.13, 95% CI: 1.12–4.03), *ORMDL3* rs7216389

Table 1. Age-adjusted odds ratios for statistically significant associations between variants in atopy-related candidate genes and pancreas cancer risk.

Gene	SNP		Cases		Controls		AOR	95% CI	P	P ¹
			N	(%)	N	(%)				
CSF2	rs17674015	AA	29	(16)	70	(12)	1.00		0.03	0.44
		CA	67	(37)	279	(49)	0.58	(0.35–0.97)		
		CC	83	(46)	215	(38)	0.92	(0.56–1.53)		
DENND1B	rs16841842	CC	89	(51)	334	(59)	1.00		0.04	0.46
		CA/AA	86	(49)	229	(41)	1.43	(1.02–2.02)		
DPP10	rs998429	AA	93	(52)	327	(58)	1.00		0.08	0.51
		CA	65	(37)	200	(36)	1.15	(0.80–1.65)		
		CC	20	(11)	36	(6)	1.96	(1.08–3.56)		
FLG	rs3126085 ²	GG	121	(69)	430	(77)	1.00		0.04	0.46
		AG/AA	54	(31)	131	(23)	1.50	(1.03–2.18)		
IL13	rs20541	CC	101	(59)	380	(67)	1.00		0.03	0.44
		CT/TT	71	(41)	184	(33)	1.48	(1.04–2.10)		
IL13RA2 (females) ³	rs638376	AA	18	(19)	86	(31)	1.00		0.04	0.46
		GA	58	(61)	145	(53)	2.09	(1.14–3.81)		
		GG	19	(20)	45	(16)	2.20	(1.04–4.67)		
LRP1B	rs1449477	CC	52	(29)	125	(22)	1.00		0.000	0.04
		CA	100	(56)	270	(48)	0.89	(0.60–1.32)		
		AA	26	(15)	169	(30)	0.37	(0.22–0.62)		
LRP1B	rs2029142	GG	38	(21)	202	(36)	1.00		0.001	0.05
		GA	97	(54)	265	(47)	1.99	(1.31–3.02)		
		AA	44	(25)	97	(17)	2.46	(1.49–4.05)		
LRP1B	rs1882164	CC	51	(29)	119	(21)	1.00		0.02	0.44
		CA	87	(50)	279	(50)	0.71	(0.47–1.06)		
		AA	37	(21)	165	(29)	0.51	(0.31–0.83)		
LRP1B	rs2052910	CC	70	(40)	288	(52)	1.00		0.02	0.44
		CA	81	(47)	212	(38)	1.60	(1.11–2.31)		
		AA	22	(13)	51	(9)	1.90	(1.07–3.36)		
LRP1B	rs10496915	AA	108	(63)	407	(72)	1.00		0.02	0.44
		CA/CC	64	(37)	157	(28)	1.55	(1.08–2.22)		
NOD1	rs2907749	AA	98	(55)	259	(46)	1.00		0.05	0.46
		GA	62	(35)	250	(44)	0.64	(0.44–0.92)		
		GG	19	(11)	54	(10)	0.90	(0.51–1.60)		
NPSR1	rs1833090	CC	88	(51)	297	(53)	1.00		0.05	0.46
		CA	67	(39)	238	(42)	0.96	(0.67–1.38)		
		AA	18	(10)	29	(5)	2.13	(1.12–4.03)		
ORMDL3	rs7216389	TT	55	(31)	136	(24)	1.00		0.11	0.60
		TC	81	(46)	266	(47)	0.76	(0.51–1.13)		
		CC	39	(22)	163	(29)	0.60	(0.38–0.97)		
RORA	rs12913421	GG	102	(59)	280	(50)	1.00		0.05	0.46
		GA	62	(36)	229	(41)	0.76	(0.53–1.09)		
		AA	8	(5)	51	(9)	0.42	(0.19–0.92)		
STAT4	rs6738544	CC	53	(30)	230	(41)	1.00		0.01	0.44
		CA	102	(57)	251	(45)	1.75	(1.20–2.55)		
		AA	24	(13)	82	(15)	1.24	(0.72–2.15)		
TLR6	rs4833095	TT	89	(52)	355	(63)	1.00		0.03	0.44

(Continued)

Table 1. (Continued)

Gene	SNP	Cases		Controls		AOR	95% CI	P	P ¹	
		N	(%)	N	(%)					
TRA	rs7146411	CT	67	(39)	174	(31)	1.56	(1.08–2.25)	0.11	0.60
		CC	15	(9)	34	(6)	1.76	(0.91–3.37)		
		GG	58	(33)	147	(26)	1.00			
		AG	76	(43)	289	(51)	0.66	(0.45–0.99)		
		AA	43	(24)	126	(22)	0.87	(0.55–1.38)		
Risk Allele Score ⁴										
	7–13	69	(43)	154	(29)	1.00		0.0007		
	14–15	72	(44)	251	(47)	0.63	(0.43–0.93)			
	16–17	21	(13)	129	(24)	0.36	(0.21–0.62)			

¹Adjusted for multiple comparisons (using false discovery rate)

²SNP rs3126085 not in Hardy-Weinberg equilibrium

³ X chromosome gene, females only

⁴Risk Allele Score: sum of risk allele counts for each of the 17 significant SNPs, each SNP was scored as 1 or 0, and this was summed across SNPs for each person (excluded X chromosome)

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(CC vs. TT: AOR = 0.60, 95% CI: 0.38–0.97), *RORA* rs12913421 (AA vs. GG: AOR = 0.42, 95% CI: 0.19–0.92), *STAT4* rs6738544 (CA vs. CC: AOR = 1.75, 95% CI: 1.20–2.55), *TLR6* rs4833095 (CT vs. TT: AOR = 1.56, 95% CI: 1.08–2.25), *TRA* rs7146411 (AG vs. GG: AOR = 0.66, 95% CI: 0.45–0.99), and *IL13RA2* rs638376 on the X chromosome (GG vs. AA: AOR = 2.20, 95% CI = 1.04–4.67). It is noteworthy that the following 11 SNP associations were in the same direction as found in the PanScan GWAS dataset used to initially screen for variants to retain: rs3126085, rs10496915, rs1449477, rs2052910, rs1882164, rs2029142, rs7216389, rs12913421, rs6738544, rs4833095, rs998429.

After adjustment for multiple comparisons using false discovery rate, two SNPs in the *LRP1B* gene (rs1449477 and rs2029142) remained statistically significant with adjusted p-values <0.05. (These two SNPs have an LD of 0.78, and this is just below our 0.8 cutoff for exclusion). Additionally, the risk allele score was associated with a significant reduction in pancreas cancer risk (score 14–15 vs. 7–13 (referent): AOR = 0.63, 95% CI: 0.43–0.93 and score 16–17 vs. 7–13: AOR = 0.36, 95% CI: 0.21–0.62; p = 0.0007).

Discussion

There is a paucity of literature with which to compare our findings as this is the first study to comprehensively evaluate the association between variants in allergy-related immunologic candidate genes and pancreatic cancer risk. While many studies have examined the association between a history of allergies and pancreas cancer risk, few have evaluated variants in allergy-related genes and pancreatic cancer risk. In 2005, a meta-analysis of ten case-control and four cohort studies reported that allergies, such as hay fever, were associated with a statistically significant reduction in pancreatic cancer risk [10]. In 2014, Cotterchio et al. [13] reported that allergies, such as hay fever, were associated with a significant reduction in pancreatic cancer risk, and this was greatest for those whose skin prick test was positive for allergens. These findings support the growing body of evidence suggesting allergies are associated with reduced pancreatic cancer risk.

One small case-control study evaluated the association between variants in interleukin-4 (*IL-4*) and *IL-4-receptor* genes and pancreatic cancer risk, and no association was observed

[22]; although limitations included insufficient power, and no other genes relevant to allergies were studied. A recent pathway-based analysis of pooled GWAS data reported that T-helper (Th) immune response genes (Th1/Th2), such as transforming growth factor-beta receptor 2 (*TGFB2*), chemokine ligand 18 (*CCL18*), and *IL13RA2*, were associated with pancreatic cancer risk [23].

We found 18 SNPs in 14 atopy-related genes (*CSF2*, *DENND1B*, *DPP10*, *FLG*, *IL13*, *IL13RA2*, *LRP1B*, *NOD1*, *NPSR1*, *ORMDL3*, *RORA*, *STAT4*, *TLR6*, *TRA*) were significantly associated with pancreas cancer risk. After adjustment for multiple comparisons, two SNPs in the *LRP1B* gene remained statistically significant. Furthermore, the derived risk allele score was significantly associated with reduced pancreatic cancer risk.

LRP1B (on chromosome 2) belongs to the low density lipoprotein receptor gene family. *LRP1B* binds with multiple ligands and is involved in the clearance of ligands, and also regulates many processes such as lipid metabolism, and nutrient transport [24–27]. *LRP1B* has been implicated in antigen presentation and as a regulator of inflammation and progression in cancer, with the involvement of LRP1-deficient macrophages (as reviewed in reference [28]). Although most of these *LRP1B* functions have been defined in different studies, it is interesting to see that inflammation, a core process of asthma and cancer, is now also genetically associated with both asthma [29] and pancreatic cancer (this study) at the *LRP1B* locus. It is also possible that the biologic mechanism responsible for the association we observed between *LRP1B* and pancreas cancer risk is unrelated to the immune system. For example, it has been suggested that *LRP1B* may be a tumor suppressor gene implicated in gastric cancer [24], and inactivation of *LRP1B* may enhance thyroid cancer growth by modulating the extracellular environment [30]. Additionally, a large study of somatic copy-number alterations and human cancers identified *LRP1B* deletions as a significant finding [31].

In conclusion, our findings suggest an association between several atopy-related genes and pancreatic cancer risk, and this somewhat supports the possibility that the reduced pancreatic cancer risk associated with allergic diseases may be partly explained by shared genetic factors. Understanding the association between atopic diseases and reduced pancreas cancer risk is of importance and further research is needed to elucidate the biology behind the growing body of epidemiologic evidence suggesting allergies may reduce pancreatic cancer risk. It has been suggested that once the relationship between the immune system and pancreas cancer is better understood then stimulation of the immune system, antibody therapy and vaccines may be possible avenues to explore for pancreas cancer prevention. In addition, larger epidemiologic studies are needed to replicate our findings, and to provide the power to definitely rule out the association between pancreatic cancer risk and the hundreds of other immunologic genes. Lastly, biological studies of the implicated genes and their respective proteins and pathways are needed to understand the role of allergic and immune processes in the development of pancreas cancer.

Supporting Information

S1 Table. Immunologic candidate genes identified in the literature as being involved in atopic diseases such as allergies and asthma (n = 183 genes).

(DOCX)

S2 Table. Atopy-related immunologic candidate genes/SNPs identified in the literature (see S1 Table) and subsequently selected (retained) for genotyping based on preliminary GWAS findings using pancreas cancer dbGaP datasets (n = 59 genes, 152 SNPs).

(DOCX)

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Author Contributions

Conceived and designed the experiments: MC SG TH. Performed the experiments: EL ML. Analyzed the data: EL ZB-C CG. Contributed reagents/materials/analysis tools: MC SG ML CG. Wrote the paper: MC EL ZB-C ML CG SG TH.

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Supporting Information Table S1. Immunologic candidate genes identified in the literature as being involved in atopic diseases such as allergies and asthma (n=183 genes)

Genes associated with atopy in observational epidemiologic studies (+/- GWAS):	
ADAM33	(Blumenthal et al. 2006; Ober and Hoffjan 2006; Su et al. 2008)
ADRB2	(Giubergia et al. 2009; Ober and Hoffjan 2006; Woszczek et al. 2005)
C3	(Barnes et al. 2006; Inoue et al. 2008; Purwar et al. 2009)
C5	(Hasegawa et al. 2004; Ricci et al. 2011)
CCL11	(Batra et al. 2007; Shin et al. 2003; Wang et al. 2007)
CCL26	(Chae et al. 2005; Owczarek et al. 2010)
CCL5	(Fryer et al. 2000; Kim et al. 2004; Leung et al. 2005; Ober and Hoffjan 2006)
CCR2	(Nakamura et al. 2007)
CCR3	(Azazi et al. 2007; Nakamura et al. 2007)
CD14	(Han et al. 2010; Litonjua et al. 2005; Micheal et al. 2011; Ober and Hoffjan 2006)
CHI3L1	(Kwon et al. 2011; Sohn et al. 2009)
CMA1	(Hersberger et al. 2010; Sharma et al. 2005; Weidinger et al. 2005A)
CSF1R	(Andiappan et al. 2011; Shin et al. 2010)
CSF2RB	(Johnson et al. 2011)
CTLA4	(Munthe-Kaas et al. 2004; Ober and Hoffjan 2006; Yang et al. 2004)
DPP10	(Allen et al. 2003; Gao J. et al. 2010; Michel et al. 2010; Zhou et al. 2009)
EDN1	(Immervoll et al. 2001; Michel et al. 2010, Zhu et al. 2008)
EPX	(Hrdlickova and Izakovicova-Holla 2009; Nakamura et al. 2003)
FCER1A	(Granada et al. 2012; Potaczek et al. 2007; Weidinger et al. 2008; Zhou et al. 2012)
FCER2	(Chan et al. 2011; Tantisira et al. 2007)
FCGR2A	(Zeyrek et al. 2008)
FLG	(van den Oord and Sheikh 2009; Poninska et al. 2011; Schuttelaar et al. 2009)
FOXJ1	(Li et al. 2006)
FOXP3	(Fodor et al. 2011; Suttner et al. 2010; Zhang, et al. 2009A)
GATA3	(Arshad et al. 2008; Zhang et al. 2009B)
GSTM1	(Gerbase et al. 2011; Gilliland et al. 2004; Ober and Hoffjan 2006)
GSTP1	(Gerbase et al. 2011; Ober and Hoffjan 2006; Reddy et al. 2010)
GSTT1	(Minelli et al. 2010; Ober and Hoffjan 2006)
HAVCR1	(McIntire et al. 2004; Mou et al. 2010)

HLA-A	(Granada et al. 2012; Lee et al. 2001)
HLA-DQA1	(Ober and Hoffjan 2006; Wang et al. 2004)
HLA-DQA2	(Andiappan et al. 2011; Granada et al. 2012)
HLA-DQB1	(Andiappan et al. 2011; Kalpaklioğlu and Turan 2002; Munthe-Kaas et al. 2007; Ober and Hoffjan 2006)
HLA-DRB1	(Andiappan et al. 2011; Kalpaklioğlu and Turan 2002; Moffatt et al. 2010; Ober and Hoffjan 2006)
HLA-G	(Ciprandi et al. 2009; Granada et al. 2012; Ober and Hoffjan 2006)
IFNG	(Barnes et al. 1999; Hussein et al. 2009; Nakao et al. 2001; Ober and Hoffjan 2006)
IL10	(Hussein et al. 2011; Imboden et al. 2006; Muller et al. 2009; Ober and Hoffjan 2006)
IL13	(Bunyavanich et al. 2011A; Granada et al. 2012; Johnson et al. 2011; Ober and Hoffjan 2006)
IL18	(Imboden et al. 2006; Kruse et al. 2003; Nieters et al. 2004)
IL1A	(Joki-Erkkilä et al. 2003; Karjalainen et al. 2002)
IL1B	(Joki-Erkkilä et al. 2003; Zeyrek et al. 2008)
IL1RL1	(Gudbjartsson et al. 2009; Reijmerink et al. 2010; Shimizu et al. 2005)
IL2	(Christensen et al. 2006; Nieters et al. 2004; Ramasamy et al. 2011)
IL21	(Chatterjee et al. 2009; Hiromura et al. 2007; Kobayashi et al. 2009)
IL21R	(Hecker et al. 2003; Pène et al. 2006)
IL33	(Moffatt et al. 2010; Sakashita et al. 2008)
IL4	(Hersberger et al. 2010; Imboden 2006; Li et al. 2008; Lu et al. 2011; Ober and Hoffjan 2006)
IL4R	(Genuneit et al. 2009; Johnson et al. 2011; Nieters et al. 2004; Ober and Hoffjan 2006)
IL5	(Gudbjartsson et al. 2009; Kabesch et al. 2007)
IL5RA	(Cheong et al. 2005; Namkung et al. 2007)
IL6	(Imboden et al. 2006; Nieters et al. 2004)
LTA	(Ober and Hoffjan 2006; Sharma et al. 2006; Trabetti et al. 1999)
LTC4S	(Eskandari et al. 2006; Moissidis et al. 2005; Ober and Hoffjan 2006)
MS4A2	(Daniels et al. 1996; Nagata et al. 2001; Ober and Hoffjan 2006; Potaczek et al. 2007)
MTHFR	(Husemoen et al. 2006; Thuesen et al. 2010)
NOD1	(Eder et al. 2006; Ober and Hoffjan 2006; Ramasamy et al. 2011; Weidinger et al. 2005 B)
NOS1	(Hollá et al. 2004; Immervoll et al. 2001; Ober and Hoffjan 2006)
NOS2	(Holla et al. 2006; Konno et al. 2001)

NOS3	(Djidjik et al. 2007; Holla et al. 2002)
NPSR1	(Andiappan et al. 2011; Castro-Giner et al. 2010; Ober and Hoffjan 2006)
ORMDL3	(Moffatt et al. 2010; Ober 2011)
PHF11	(Gao J. et al. 2010; Jang et al. 2005; Ober and Hoffjan 2006; Zhang et al. 2003)
PTGDR	(Isidoro-García et al. 2011; Sanz et al. 2006)
PTGS2	(Chan et al. 2007; Ober and Hoffjan 2006; Shi et al. 2008)
RAD50	(Li et al. 2010; Murk et al. 2011; Weidinger et al. 2008)
RNase3	(Jönsson et al. 2010; Kang et al. 2010)
SCGB1A1	(Candelaria et al. 2005; Ku et al. 2011; Ober and Hoffjan 2006)
SOCS1	(Mostecky et al. 2011)
SPINK5	(Hubiche et al. 2007; Ober and Hoffjan 2006; Walley et al. 2001)
STAT1	(Hattori et al. 2007; Pinto et al. 2007)
STAT6	(Amoli et al. 2002; Granada et al. 2012; Ober and Hoffjan 2006; Weidinger et al. 2008)
TAP1	(Ismail et al. 1997; Kim et al. 2007; Ober and Hoffjan 2006)
TBXA2R	(Leung et al. 2002; Ober and Hoffjan 2006; Shin et al. 2003)
TGFB1	(Li et al. 2007; Meng et al. 2005; Ober and Hoffjan 2006)
TGFB2	(Hatsushika et al. 2007; Zhang et al. 2008)
TLR2	(Eder et al. 2004; Kormann et al. 2009; Ober and Hoffjan 2006; Oh et al. 2009; Qian et al. 2010)
TLR4	(Genuneit et al. 2009; Krasznai et al. 2011; Ober and Hoffjan 2006; Senthilselvan et al. 2008)
TLR6	(Miedema et al. 2011; Ober and Hoffjan 2006; Ramasamy et al. 2011)
TNF	(Krasznai et al. 2011; Minhas et al. 2010; Ober and Hoffjan 2006; Sharma et al. 2006)
TSLP	(Bunyavanich et al. 2011B; Harada et al. 2011; Ramasamy et al. 2011)
VDR	(Michel et al. 2010; Poon et al. 2004; Raby et al. 2004)

Genes associated with atopy in GWAS alone:

ABL2	(Ramasamy et al. 2011)
ADRA1B	(Mathias et al. 2010)
ANKRD46	(Wan et al. 2011)
C1orf30 and LRRC32	(Ramasamy et al. 2011)
C16orf72	(Ramasamy et al. 2011)
CA10	(Li et al. 2010)
CLEC16A	(Ramasamy et al. 2011)
DENND1B	(Sleiman et al. 2010)
DNAH5	(Ramasamy et al. 2011)
DNAJC6	(Andiappan et al. 2011)

ENTPD6	(Ramasamy et al. 2011)
EPS15	(Ramasamy et al. 2011)
FNDC3A	(Wan et al. 2011)
GATA2	(Gudbjartsson et al. 2009)
GFRA2	(Gudbjartsson et al. 2009)
GLI3	(Ramasamy et al. 2011)
GNA13	(Mathias et al. 2010)
HLA region	(Ramasamy et al. 2011)
IKZF2	(Gudbjartsson et al. 2009)
IL2RB	(Moffatt et al. 2010)
KCNJ2	(Li et al. 2010)
KIRREL3	(Wan et al. 2011)
LRP1B	(Li et al. 2010)
MRPL4	(Andiappan et al. 2011)
MYB	(Gudbjartsson et al. 2009)
Near CROCC	(Ramasamy et al. 2011)
Near PPM1A and DHRS7	(Ramasamy et al. 2011)
NETO1	(Wan et al. 2011)
OAT	(Wan et al. 2011)
PDE4D	(Himes et al. 2009)
PIK3AP1	(Andiappan et al. 2011)
PRNP	(Mathias et al. 2010)
PYHIN1	(Torgerson et al. 2011)
RORA	(Moffatt et al. 2010; Torgerson et al. 2011)
RTP2	(Torgerson et al. 2011)
SEMA6A	(Ramasamy et al. 2011)
SH2B3	(Gudbjartsson et al. 2009)
SLC22A5	(Moffatt et al. 2010)
SLC25A46	(Ramasamy et al. 2011)
SMAD3	(Moffatt et al. 2010; Torgerson et al. 2011)
SNX10	(Li et al. 2010)
STK35	(Wan et al. 2011)
TLE4	(Hancock et al. 2009)
TMEM108	(Ramasamy et al. 2011)
TMEM232	(Ramasamy et al. 2011)
UBXN2B	(Wan et al. 2011)
WDR36	(Gudbjartsson et al. 2009)

Genes encoding proteins that play a role in atopy, though not yet evaluated in human genetic association studies:

CYSLTR1	(Canonica 2002)
CYSLTR2	(Canonica 2002)
CCL17	(Barnes 2011)
CCL18	(Chang et al. 2010; Hon et al. 2011)
CCL22	(Barnes 2011)

CCL3	(Di Sciascio et al. 2007)
CCL4	(Benson et al. 2006)
CCR4	(Barnes 2011)
CD28	(Barnes 2011)
CD40	(Corry and Kheradmand 1999; Hattori et al. 2007)
CD40LG	(Pawankar et al. 1997)
CD80	(Corry and Kheradmand 1999)
CD86	(Takizawa et al. 2007)
CRLF2	(Yu et al. 2010)
CSF2	(Benson et al. 2009)
FCER1G	(Sääf et al. 2008)
HAVCR2	(Bossé and Hudson 2007)
HRH1	(Shirasaki et al. 2012)
HRH4	(Broide 2010)
ICAM1	(Braunstahl et al. 2001)
ICOS	(Botturi et al. 2011; Shilling et al. 2005)
IL12RB1	(Barnes 2011)
IL12RB2	(Barnes 2011; Yokoe et al. 2001; Kondo et al. 2001)
IL13RA1	(Rothenberg et al. 2011)
IL13RA2	(Hsi et al. 2011)
IL17A	(Wisniewski and Borish 2011)
IL17RB	(Wang and Liu 2009)
IL22	(Souwer et al. 2010)
IL25	(Broide 2010; Wang and Liu 2009)
IL27	(Barnes 2011)
IL7R	(Gao PS et al. 2010; Mobini et al. 2009)
IL9	(Williams et al. 2012)
KIT	(Barnes 2011)
KITLG	(Barnes 2011)
LTB4R	(Barnes 2011)
MAF	(Naito et al. 2011)
NFATC1	(Wisniewski and Borish 2011)
NFATC2	(Wisniewski and Borish 2011)
NFATC3	(Wisniewski and Borish 2011)
NFATC4	(Wisniewski and Borish 2011)
NFKB1	(Corry and Kheradmand 1999)
NFKB2	(Corry and Kheradmand 1999; Martino et al. 2012)
P2RX7	(Barnes 2011)
PRG2	(Pawankar et al. 2011)
PTGDR2	(Barnes 2011; Shirasaki et al. 2009)
STAT4	(Wisniewski and Borish 2011)
TBX21	(Wisniewski and Borish 2011)
TGFB3	(Salib et al. 2004)
TGFBR1	(Salib 2007; Salib et al. 2004)
TGFBR2	(Bottema et al. 2010; Chen et al. 2010; Salib et al. 2004)

TNFRSF4	(Wang and Liu 2009)
TNFSF4	(Wang and Liu 2009)
TRA	(Barnes 2011)
TRB	(Barnes 2011)
VCAM1	(Braunstahl et al. 2001)

Note: Literature review conducted during 2012.

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Supporting Information Table S2. Atopy-related immunologic candidate genes/SNPs identified in the literature (see Supplementary Table 1) and subsequently selected (retained) for genotyping based on preliminary GWAS findings using pancreas cancer dbGaP datasets (n=59 genes, 152 SNPs)

Gene (n=59)	SNP (n=152)
CCL18	rs14304
	rs2735835
	rs1719220
CCL3/CCL4	rs1634508
CLEC16A	rs3960630
CSF2	rs17674015
DENND1B	rs12751508
	rs16841842
DPP10	rs6722852
	rs7421482
	rs980317
	rs998429
	rs6726425
	rs17728568
	rs272014
EPX	rs12602891
FCER1A	rs10489849
	rs2494264
FCER1G	rs11421
	rs12094497
FLG	rs10888470
	rs3126085
GLI3	rs3801182
	rs3801189
HAVCR2	rs13182119
HLA-A	rs1611493
	rs2523809
	rs376646
HLA-DQA2	rs7774954
HRH1	rs6778270
ICOS	rs4675377
IKZF2	rs10186029
	rs1871946
IL10	rs1800896
IL13	rs20541

Gene (n=59)	SNP (n=152)
IL13RA1	rs1316954
	rs2495622
	rs2495624
	rs2495626
	rs2997052
IL13RA2	rs5988202
	rs7891628
	rs638376
IL17RB	rs1025690
IL1B	rs1143634
IL1RL1	rs917998
IL25	rs8014568
IL4R	rs1801275
	rs1805015
IL7R	rs6897932
KIRREL3	rs4553380
	rs7113465
KIT	rs1008658
LRP1B	rs10469560
	rs10496860
	rs10496915
	rs10928120
	rs12476507
	rs13016322
	rs13029426
	rs1349223
	rs1449477
	rs2052910
	rs4507038
	rs6719026
	rs1882164
	rs6753877
	rs6758126
	rs10166782
	rs4507039
	rs13415720
	rs4363973
	rs2029142
LTC4S	rs6895902
MYB	rs9321496

Gene (n=59)	SNP (n=152)
NETO1	rs11876415
	rs1484218
	rs1893459
	rs6566663
	rs9958794
	rs10871704
	rs1484217
NFATC1	rs11664153
NFATC2	rs3787189
	rs6021231
	rs6067805
	rs4811174
NOD1	rs10257280
	rs2907749
	rs1558070
NOS3	rs3918227
NPSR1	rs1833090
ORMDL3	rs7216389
PDE4D	rs17721878
	rs11739293
	rs1423473
	rs4394088
	rs6897671
	rs7732908
	rs2938787
	rs13159422
	rs6877743
	rs6869495
PHF11	rs9568227
	rs967163
PIK3AP1	rs1172480
PRNP	rs6084833
RORA	rs11631432
	rs974828
	rs12913421
	rs2433023
	rs12443239
SEMA6A	rs10067680
	rs254227
	rs154576

Gene (n=59)	SNP (n=152)
SH2B3	rs3184504
SPINK5	rs3764930
STAT1	rs12693591
	rs6751855
	rs6758866
	rs3771300
STAT4	rs1031509
	rs6738544
	rs7572482
TAP1	rs2071538
TBX21	rs4141183
TGFB2	rs10482751
TGFB2	rs2043136
	rs3773650
	rs3773656
	rs12495646
	rs3773634
	rs3773644
	rs3773652
	rs5020833
TLR4	rs877572
	rs2737191
TLR6	rs10759930
	rs4833095
TMEM108	rs9854387
	rs1464401
TMEM232	rs7721004
	rs7734243
	rs6891701
TRA	rs1800388
	rs3811259
	rs7146411
	rs741713
	rs7147975
TRB	rs11768792
	rs2040366
	rs4470937

