Genome-wide association study for pollinosis identified two novel loci in *interleukin (IL)-1B* in a Japanese population

（日本人集団での GWAS による *IL-1B* 内の
花粉症関連遺伝子多型の同定）

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主論文の要旨

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Ryosuke FUJII

Abstract

Background The number of pollinosis patients in Japan has significantly increased over the past 20 years. The majority of genome-wide wide association studies (GWAS) on pollinosis have been conducted in subjects of European descent with few studies in Japanese populations. The aim of our GWAS was to identify genetic loci associated with self-reported pollinosis in a Japanese population and to understand its molecular background by using a combination of single nucleotide polymorphisms (SNPs) and gene- and pathway-based analyses.

Methods A total of 731 and 560 individuals who were recruited as participants of the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study participated in the discovery and replication phases, respectively. The phenotype of pollinosis was based on the information from a self-administered questionnaire.

Results In the single-SNP analysis, four SNPs (rs11975199, rs11979076, rs11979422, and rs12669708) reached suggestive significance level ($P < 1 \times 10^{-4}$) and had effects in the same direction in both phases of the study. The pathway-based analysis identified two suggestive pathways (nucleotide-binding oligomerization domain -like receptor and tumor necrosis factor signaling pathways). Both rs1143633 and rs3917368 in the *interleukin-1B* gene showed associations in the retrace (from pathway to gene and SNP) analysis.

Conclusion We performed single-SNP, gene, and pathway, analysis, and shed light on the molecular mechanisms underlying pollinosis in a Japanese population.

日本人集団での GWAS による *IL-1B* 内の花粉症関連遺伝子多型の同定

藤井亮輔

要旨

背景：過去 20 年間に、日本の花粉症患者は著しく増加している。花粉症とその遺伝的要因との関連を網羅的に解析するゲノムワイド関連研究（GWAS）は欧米人集団のみで行われており、日本人集団を対象とした研究はこれまで行われていない。そこで、本研究では日本人集団の花粉症と関連する一塩基多型（SNP）を特定することを目的とした。また、さらに花粉症の分子生物学的な背景も明らかにするために、遺伝子およびパスウェイレベルでの解析も実施した。

方法：対象者は日本多施設共同コホート研究（J-MICC Study）の参加者の一部であり、731 名を探索セット（discovery phase）に、560 名を検証セット（validation phase）とした。対象者の花粉症の表現型は、自記式質問票によって評価した。

結果：SNP レベルの解析では、4 つの SNPs（rs11975199 と rs11979076、rs11979422、rs12669708）が suggestive significance level（$P < 1.0\times10^{-4}$）に到達し、探索および検証研究のそれぞれで同方向の効果を示した。パスウェイレベルの解析では 2 つのパスウェイ（NOD-like receptor（NLR）signaling と tumor necrosis factor（TNF）signaling）と関連を示した。2 つのパスウェイ内をさらに遺伝子レベル、SNP レベルと遡って解析すると、インターロイキン 1B（*IL-1B*）中の 2 つの SNPs（rs1143633 と rs3917368）で花粉症と有意な関連を示した。

結論：本研究では SNP レベルの解析に加えて、遺伝子およびパスウェイレベルでの解析を行なった。日本人の花粉症の基礎的な分子生物学的メカニズム解明の一助となり得るだろう。

主論文

Abstract

Background The number of pollinosis patients in Japan has significantly increased over the past 20 years. The majority of genome-wide wide association studies (GWAS) on pollinosis have been conducted in subjects of European descent with few studies in Japanese populations. The aim of our GWAS was to identify genetic loci associated with self-reported pollinosis in a Japanese population and to understand its molecular background by using a combination of single nucleotide polymorphisms (SNPs) and gene- and pathway-based analyses. ***Methods*** A total of 731 and 560 individuals who were recruited as participants of the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study participated in the discovery and replication phases, respectively. The phenotype of pollinosis was based on the information from a self-administered questionnaire. ***Results*** In the single-SNP analysis, 4 SNPs (rs11975199, rs11979076, rs11979422 and rs12669708) reached suggestive significance level ($P < 1\times10^{-4}$) and had effects with the same direction in both phase. The pathway-based analysis identified 2 suggestive pathways (NOD-like receptor (NLR) signaling and tumor necrosis factor (TNF) signaling pathway). rs1143633 and rs3917368 in the *IL-1B* gene showed associations in the retrace (getting back from pathway to gene and SNP) analysis. ***Conclusion*** We performed single-SNP, gene, and pathway, analysis, and shed light on the molecular mechanisms underlying pollinosis in a Japanese population.

Introduction

Allergic rhinitis (AR) is a common disease worldwide, and its prevalence has increased in industrialized countries over the last few decades [1-5]. AR is generally defined as an immunoglobulin E (IgE)-mediated inflammatory response of the nasal mucous membrane. This reaction is induced by exposure to specific allergens such as pollen, dust mites, molds and pets. Pollen is suspected as a major cause of seasonal AR, whereas other allergens are associated with perennial AR. The major allergens for seasonal AR in Japan are pollen from the Japanese cedar (*Cryptomeria japonica*; sugi) and Japanese cypress (*Chamaecyparis obtusa*; hinoki) [6]. The dispersion of Japanese cedar pollen generally peaks between February and April [7], and Japanese cypress pollen is dispersed from April to May. Moreover, 70% of cedar pollinosis patients also experience seasonal AR as a result of cypress pollinosis; thus, the allergic symptoms caused by these types of pollinosis can continue for up to 4 months [8]. Therefore, pollinosis is considered as a common health issue in Japan [9-11].

From an economic standpoint, the medical expenses associated with AR management are considerable [12]. From the patient's perspective, AR has adversely influences quality of life because of widespread symptoms such as sneezing, watery rhinorrhea, nasal congestion and/or itchy nose. Previous studies reported that these symptoms affect daytime activity, work productivity, and sleep quality in patients [8,13,14]. In children, seasonal AR impacts on learning performance, and impairs behavior and

attention [15,16].

To better understand the genetic factors underlying AR, genome-wide association studies (GWAS) have recently been conducted. A genome-wide meta-analysis by Ramasamy et al. identified three single nucleotide polymorphisms (SNPs) with genome-wide significance and 12 loci with suggestive associations of AR and grass sensitization [17]. Hinds et al. found 16 shared loci associated with self-reported cat, dust mite, and pollen allergy [18]. Further, Bønnelykke K et al. reported that 10 loci are significantly associated with allergic sensitization in Caucasian individuals [19]. Combining the findings from previous GWAS together, only four loci (*toll-like receptor (TLR)6-TLR1*, *HLA-DQA2-HLA-DQA1*, *interleukin (IL)2-ADA1*, and *LRRC32-C11orf30*) of all 47 SNPs overlap. Although considerable work has been performed to identify genetic variants associated with allergic traits such as AR, the prior studies have focused almost exclusively on subjects of European descent [17-22]. However, recent work suggests that GWAS in non-European populations are needed to elucidate ethnically different variants [23]. In Japan, although there have been some candidate gene studies on pollinosis [24-29], no GWAS has been conducted. The aim of our study was to conduct a genome-wide agnostic screening for genetic loci associated with self-reported pollinosis, a major cause of seasonal AR, in a Japanese genome cohort study. Furthermore, to augment our single-SNP screen, we also utilized gene- and pathway-based analyses to expand our knowledge on the molecular

factors underlying pollinosis.

Materials and Methods

Study subjects

The present study was nested within the broader Japan Multi-Institutional Collaborative Cohort (J-MICC) Study, a large-scale cohort study performed in Japan. The aim of the J-MICC Study is to examine and detect gene-environmental interactions associated with lifestyle-related diseases, primarily cancer. This cohort study was launched in 2005, and the recruitment of 100,000 participants was completed in March 2014. Participants in the J-MICC Study are individuals aged 35 to 69years who enrolled by responding to study announcements in 14 different areas throughout Japan. The J-MICC Study has been well-described previously [30] and on its website (URL: http://www.jmicc.com/). In our current study, we performed a two-stage GWAS using information from two independent sites. The first stage was for screening (discovery phase), and the second stage for confirming the findings from the first stage (replication phase). In both phases, all research procedures complied with the Ethical Guidelines for Human Genome and Genetic Sequencing Research in Japan.

Discovery phase (Daiko Study)

The discovery phase analysis was carried out using data from the participants of the Daiko Study, one

of the study sites of the J-MICC Study. A total of 766 individuals (231 men and 535 women) with information on pollinosis history were selected for this analysis. At this site, we inquired about three different types of pollinosis (the presence of any pollinosis, Japanese cedar pollinosis, and Japanese cypress pollinosis) using a self-administered questionnaire. Written informed consent was obtained from all participants. The protocol of this study was approved by the Ethics Review Committee of the Nagoya University Graduate School of Medicine (No. 2015-0274).

Replication phase (Shizuoka–Sakuragaoka Study)

We used data from the baseline survey of the Shizuoka–Sakuragaoka Study, another site of the J-MICC Study, to validate the findings from the discovery phase. In this phase, 581 participants (360 men and 221 women) were included. Participants at this site were asked only whether they had a pollen allergy or not. We obtained written informed consent from all participants. The protocol of this study was approved by the Ethics Committee of the University of Shizuoka (No. 22-39).

Genotyping and quality control

DNA samples were automatically extracted from all buffy-coat fractions using the BioRobot M48 Workstation (QIAGEN Group, Tokyo, Japan). For both the discovery and replication phases, 964,193

SNPs were genotyped using the Illumina HumanOmniExpressExome ver1.2 platform (Illumina, San Diego, CA) at the RIKEN Center for Integrative Medical Sciences (Yokohama, Japan). At the phase of quality control (QC) phase, we excluded SNPs matching any one of the following five criteria: (1) call rate < 98%, (2) Hardy–Weinberg equilibrium (HWE) $P < 1 \times 10^{-6}$, (3) minor allele frequency < 0.01, (4) insertion and deletion, and (5) non-autosomal SNP (X, Y, mitochondrial chromosome), and linkage disequilibrium (LD) pruning. After the QC for SNPs, participants who had a proportion of identity by descent (IBD) > 0.1875 and outliers in a principal component analysis (PCA) were excluded. Following QC, a total of 570,398 SNPs were finally available for the analysis of 731 and 560 individuals in the discovery and replication phases, respectively.

Single-SNP analysis

All statistical analyses were performed using software R ver3.3.1 and PLINK ver1.07. Principal components (PCs) were calculated by EIGENSOFT ver6.1.4 to remove the influence of population stratification [31]. We carried out a logistic regression to screen the associations between pollinosis and each individual SNP. SNPs were coded under an additive genetic model, and a logistic regression analysis with adjustment for age, sex and the top five PCs was conducted. *P*-values $< 5 \times 10^{-8}$ and *P*-values $< 1 \times 10^{-4}$ was considered to signify genome-wide significance and suggestive significance,

respectively. A combined *P*-value in both phases was calculated using Fisher's method [32].

Gene- and pathway-based analyses

To augment our single-SNP analysis, we then performed gene- and pathway-based analyses to identify particular genes and pathways associated with pollinosis. We used the sequence kernel association test (SKAT) [33,34], which allows us to test for associations between a group of genetic variants in a gene or pathway and outcomes with adjustment for covariates. Briefly, the approach works by comparing pairwise similarity in phenotypes to pairwise similarity in genotypes as measured through a kernel function. Different kernel functions capture different underlying models. Gene-based SNP sets for each study were created by matching SNPs to gene locations, which were determined using the UCSC Genome Browser (GRCh37) database. We analyzed a total of 24,756 genes (447,224 SNPs) in the discovery phase and 24,717 genes (427,203 SNPs) in the replication phase. Pathway-based SNP sets were subsequently generated by aggregating the SNPs within genes comprising pathways. Gene–pathway membership was confirmed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Database. In the pathway-based approach, we selected 10 biologically plausible pathways associated with pollinosis: (1) asthma, (2) B cell receptor signaling, (3) cytokine receptors, (4) Fc gamma R-mediated phagocytosis, (5) nuclear factor-kappa B signaling, (6) natural killer cell-mediated

cytoxicity, (7) nucleotide-binding oligomerization domain-like receptor (NLR) signaling, (8) T cell receptor signaling, (9) Toll-like receptor (TLR) signaling, and (10) tumor necrosis factor (TNF) signaling. *P*-values in the discovery phase were corrected for the false discovery rate (FDR) using the Benjamini–Hochberg method [35]. The significance threshold after FDR correction was set at $P < 0.25$ in the present study. The genes and pathways passing the threshold in the discovery phase were analyzed in the replication phase. All *P*-values in the replication phase were reported.

Results

Single-SNP analysis

The demographic data of the participants in the discovery and replication phases are summarized in Table 1. Manhattan plots for all pollinosis, cedar and cypress pollinosis in the discovery phase are shown in Supplementary Fig. 1-3. We identified no SNPs meeting the genome-wide significance level ($P < 5 \times 10^{-8}$) when comparing those with each of the allergen-specific types of pollinosis (cedar and cypress pollinosis) and those without. However, 58 SNPs showed associations with both types of pollinosis at the suggestive significance level ($P < 1 \times 10^{-4}$) (see Supplementary Table S1). The GWAS for cedar and cypress pollinosis identified 42 and 54 SNPs that reached the suggestive threshold, respectively (see Supplementary Table S2,3). Consequently, 123 unique SNPs passed into the replication phase in the 560 unrelated samples. Our replication study identified six significant SNPs out of these 123 SNPs. However, when comparing the results of the discovery phase with those of the replication phase, two of the six significant SNPs were inconsistent in their direction of effects across the phases (Table 2). The four remaining SNPs at rs11975199 between *LOC100631260* and *MARK2P7* (OR = 0.76 [95% CI = 0.59–0.96], $P = 0.024$), rs11979076 between *LOC100631260* and *MARK2P7* (OR = 0.75 [95% CI = 0.59–0.96], $P = 0.021$), rs11979422 between *LOC100631260* and *MARK2P7* (OR = 0.76 [95% CI = 0.59–0.96], $P = 0.024$), and rs12669708 in *MARK2P7* (OR = 0.77

[95% CI = 0.60–0.98], $P = 0.034$) showed consistent effects in the two phases. When we combined the *P*-values in the discovery and replication phases, no SNPs reached genome-wide significance levels (see Supplementary Table S4).

Gene-based analysis

In the discovery phase, the gene-based analysis identified no significant or suggestive genes for the risk of all pollinosis and cedar pollinosis. For cypress pollinosis, we identified two suggestive genes that passed the criteria into the replication phase: *PHF13* (chromosome 1, $Q_{linear} = 0.244$), and *KLHL21* (chromosome 1, $Q_{linear} = 0.244$) (Table 3). In the replication phase, however, neither *PHF13* nor *KLHL21* was significantly associated with pollinosis ($P_{linear} = 0.489$ and 0.459, respectively). Integrated analysis also showed no significant genes (see Supplementary Table S5).

Pathway-based analysis

In the discovery phase, pathway-based analysis identified one significant and one suggestive pathway related to pollinosis (Table 4). The NLR signaling pathway showed a significant relationship with cypress pollinosis when we applied linear and identity-by-state (IBS) kernel function ($Q_{linear} = 0.025$ and $Q_{IBS} = 0.045$, respectively). The TNF signaling pathway reached a suggestive significance level of

association with cedar pollinosis (Q = 0.231). The SKAT results in the replication phase are shown in Table 5. The NLR signaling and TNF signaling pathways reached a suggestive significance level (P = 0.094 and 0.095 in linear kernel function, repsectively). Thus, the NLR signaling and TNF signaling pathways seem to be a candidate pathways for association with pollinosis.

Retrace (pathway–gene–SNP) analysis

We again performed gene-based tests by focusing on genes in the TNF and NLR signaling pathways that reached suggestive significance levels in the pathway analysis. No significant genes were observed in the TNF signaling pathway, although six genes in the NLR signaling pathway passed the threshold of Q-value < 0.25 in the discovery phase (Table 6). Of these genes, only the *interleukin (IL)-1B* gene was found to be associated with pollinosis in the replication phase (P_{linear} = 0.022 and P_{IBS} = 0.027) (Table 7). Thus, we traced back the results of the single-SNP test to find unique loci associated with pollinosis. As shown in Table 8, two SNPs (rs1143633 and rs3917368) in the *IL-1B* were significantly associated with pollinosis in both phases without correction for multiple comparisons.

Discussion

We performed a GWAS with single-SNP as well as gene- and pathway-based approaches to investigate the genetic etiology of pollinosis, including cedar and cypress pollinosis in Japan. We identified two possible loci associated with self-reported pollinosis in two independent studies that is, the discovery phase (311 cases and 420 controls) and the replication phase (277 cases and 283 controls).

The present GWAS has three distinctive features. First, we believe that this is the first GWAS on pollinosis in a Japanese population. Earlier studies utilized candidate gene or pathway approaches. As for Asian populations, to the best of our knowledge, the only GWAS on allergic traits was conducted in a Chinese population from Singapore [36,37]. Second, our results focused specifically on cedar and cypress pollen, which are major allergens of seasonal AR in Japan. This enabled us to gain an insight into allergen-specific mechanisms and enhance the study power, even with small sample sizes. Third, we attempted to use powerful gene- and pathway-based approaches to augment the standard GWAS analysis. Although little has been reported on the genes and pathways associated with pollinosis, a recent review by Bønnelykke K, et al. suggested the importance of grouped analysis [23]. In the present study, we used SKAT for the gene, and pathway, analysis, and found some plausible variants after identifying suggestive genes and pathways.

Two SNPs (rs1143633 and rs3917368) in the *IL1B* region on chromosome 2q14 were potentially associated with pollinosis in both the discovery and replication phases. IL-1 is a well-known pro-imflammatory cytokine involved in host defense and autoimmune disease [38]. Additionally, a previous *in vitro* study demonstrated that IL releases histamine from basophils and mast cells, which implies an association between IL and human allergy reaction [39]. In fact, genetic variants in *IL-1B*, a subtype of IL, have been related to the severity of chronic inflammation and autoimmune diseases such as asthma and atopic dermatitis [40-42]. Regarding rs1143633, a previous study has suggested an association between rs1143634 in *IL1B*, a SNP located in 77 kb upstream of rs11343633, with AR [43]. Furthermore, rs1143634 is reportedly linked to increased IL1B secretion [44]. Additionally, rs1143634 has strong linkage disequilibrium (LD) with rs1143627, a variant that alters transcription efficacy of *IL1B* [45], although we could not confirm the LD between rs1143633 and rs1143627. Taken together, we can presume that rs1143634, a nearby SNP of rs1143633, could potentially change the amount of IL-1B secretion. Another inference is that the association between rs1143627 and rs1143634 may modify *IL-1B* transcription. Moreover, the results of a previous study on a Chinese population in Taiwan has suggested an association between rs3917368 in *IL1B* and Graves' ophthalmopathy, the most common symptom of Graves' disease [46]. In a study on hand osteoarthritis, Moxley et al.

observed strong LD of rs3917368 with rs16944, a well-known SNP in *IL1B* that can alters *IL-1B* transcription [47]. Indeed, we confirmed moderate LD of rs3917368 and rs16944 in both phases (r^2 = 0.435 and 0.361, respectively). In consideration of these findings, because rs3917368 has strong LD with rs16944, the former may be associated with immune systems through regulation of *IL-1B* gene expression.

Our study has several limitations. First, the phenotype definition of pollinosis was based on self-reported history, not on a blood test (*e.g.* IgE level) or skin prick test, which are routinely used for clinical diagnosis. However, consistency of the results between questionnaire-based pollinosis and diagnosis-based pollinosis was shown in a previous study of AR [24]. Second, the sample sizes in both phases (731 and 560, respectively) were smaller than those in typical GWAS, which might have made it difficult to find significant associations of SNPs found in previous studies on pollinosis. Nevertheless, we believe that our approaches provide a useful scientific basis for future studies on the genetic etiology underlying pollinosis.

In conclusion, we identified two variants in *IL-1B* associated with pollinosis in a Japanese population. Our gene- and pathway-based analyses may shed light on the molecular mechanisms of pollinosis.

Further studies are expected to identify functionally related variants and shared loci for several allergic phenotypes.

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Competing financial interests

The author declares no competing financial interests.

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Table 1. The characteristics of the participants in the discovery and replication phases

	Discovery phase			Replication phase
	All pollinosis	Cedar	Cypress	All pollinosis
N	731	649	554	560
Age (Mean, SD)	53.1 (10.6)	53.2 (10.5)	53.3 (10.7)	50.2 (9.4)
Sex (Male)	222 (30.4%)	195 (30.0%)	164 (29.6%)	344 (61.4%)
Pollinosis (Yes)	311 (42.5%)	229 (35.3%)	134 (24.2%)	277 (49.5%)

Table 2. Summary of results in the single-SNP association test

				Discovery phase			Replication phase	
SNP	CHR	Major allele	MAF	OR (95% CI)	P	Pollinosis	OR (95% CI)	P
rs11617981	13	C	0.45	1.60 (1.26–2.02)	9.83×10^{-5}	Cedar	0.77 (0.61–0.98)	0.036
rs540607	19	T	0.21	1.98 (1.42–2.76)	5.55×10^{-5}	Cypress	0.73 (0.54–0.99)	0.045
rs11975199	7	A	0.43	0.54 (0.40–0.73)	7.30×10^{-5}	Cypress	0.76 (0.59–0.96)	0.024
rs11979076	7	T	0.43	0.54 (0.40–0.73)	7.30×10^{-5}	Cypress	0.75 (0.59–0.96)	0.021
rs11979422	7	A	0.43	0.54 (0.40–0.73)	7.30×10^{-5}	Cypress	0.76 (0.59–0.96)	0.024
rs12669708	7	G	0.44	0.55 (0.40–0.74)	8.41×10^{-5}	Cypress	0.77 (0.60–0.98)	0.034

CHR: chromosome; MAF: minor allele frequency; OR: odds ratio; 95%CI: 95% confidence interval.

Table 3. The results of gene-based analysis in the discovery and the replication phases (in linear kernel function)

Gene	Discovery phase[a)]			Replication phase[b)]
	All	Cedar	Cypress	All
PHF13	0.945	0.814	0.244	0.489
KLHL21	0.945	0.814	0.244	0.459

[a)]: *Q*-values (Benjamini–Hochberg method–corrected *P*-values) are shown.

[b)]: *P*-values are not corrected in the replication phase.

Table 4. The results of the pathway-based analysis in the discovery phase (*Q*-value)

Pathway	All pollinosis				Cedar				Cypress			
	Linear	W. linear	IBS	W. IBS	Linear	W. linear	IBS	W. IBS	Linear	W. linear	IBS	W. IBS
Asthma	0.861	0.741	0.808	0.808	0.888	0.549	0.873	0.487	0.642	0.859	0.582	0.885
B cell receptor signaling	0.861	0.741	0.808	0.808	0.888	0.904	0.873	0.905	0.730	0.877	0.582	0.885
Cytokine receptors	0.888	0.808	0.912	0.822	0.888	0.549	0.873	0.487	0.783	0.859	0.582	0.885
Fc gamma R-mediated phagocytosis	0.861	0.808	0.808	0.822	0.888	0.904	0.873	0.905	0.959	0.877	0.915	0.885
Nuclear factor (NF)-kappa B signaling	0.861	0.741	0.808	0.808	0.888	0.549	0.873	0.529	0.642	0.877	0.582	0.885
Natural killer cell-mediated cytotoxicity	0.861	0.808	0.808	0.838	0.801	0.904	0.873	0.905	0.619	0.859	0.582	0.885
NOD-like receptor signaling	0.861	0.808	0.808	0.822	0.888	0.549	0.873	0.487	0.025**	0.859	0.045**	0.885
T cell receptor signaling	0.861	0.741	0.808	0.808	0.888	0.498	0.873	0.487	0.866	0.859	0.760	0.885
Toll-like receptor signaling	0.888	0.741	0.916	0.822	0.888	0.549	0.873	0.487	0.647	0.859	0.582	0.885
Tumor necrosis factor (TNF) signaling	0.861	0.741	0.808	0.808	0.888	0.231*	0.873	0.408	0.959	0.877	0.930	0.885

Linear: linear kernel; W.linear: weighted linear kernel; IBS: IBS kernel; W.IBS: weighted IBS kernel.

**: *Q*-value < 0.1, *: *Q*-value < 0.25.

Table 5. The results of the pathway-based analysis in the replication phase (*P*-value)

	Linear	W.linear	IBS	W.IBS
NLR signaling	0.094*	0.427	0.223	0.269
TNF signaling	0.095*	0.987	0.171	0.961

NLR: NOD-like receptor; TNF: Tumor necrosis factor; Linear: linear kernel; W.linear: weighted linear kernel; IBS: IBS kernel; W.IBS: weighted IBS kernel.

*: *P*-value < 0.1.

Table 6. The results of the gene-based analysis in the NOD-like receptor (NLR) signaling pathway in the discovery phase (*Q*-value)

	All pollinosis				Cedar				Cypress			
	Linear	W.linear	IBS	W. IBS	Linear	W. linear	IBS	W. IBS	Linear	W. linear	IBS	W. IBS
TAB2	0.464	0.513	0.635	0.557	0.447	0.388	0.611	0.524	0.065**	0.070**	0.130*	0.139*
MAPK9	0.715	0.681	0.635	0.557	0.447	0.428	0.113*	0.158*	0.533	0.541	0.626	0.669
CARD9	0.464	0.513	0.661	0.557	0.441	0.305	0.611	0.524	0.056**	0.070**	0.626	0.698
CARD6	0.715	0.642	0.635	0.557	0.511	0.388	0.203*	0.267	0.540	0.507	0.626	0.669
CARD8	0.949	0.910	0.950	0.838	0.867	0.869	0.878	0.557	0.204*	0.128*	0.626	0.669
IL1B	**0.464**	**0.513**	**0.961**	**1.000**	**0.441**	**0.198***	**0.878**	**0.801**	**0.540**	**0.507**	**0.874**	**0.892**

Linear: linear kernel; W.linear: weighted linear kernel; IBS: IBS kernel; W.IBS: weighted IBS kernel.

**: *Q*-value < 0.1, *: *Q*-value < 0.25.

Table 7. The results of the gene-based analysis in the NOD-like receptor (NLR) signaling pathway in the replication phase (*P*-value)

	Linear	W.linear	IBS	W.IBS
TAB2	0.503	0.503	0.496	0.496
MAPK9	0.525	0.339	0.665	0.206
CARD9	0.445	0.18	0.602	0.228
CARD6	0.586	0.196	0.736	0.241
CARD8	0.284	0.326	0.391	0.417
IL1B	**0.022***	**0.179**	**0.027***	**0.155**

Linear: linear kernel; W.linear: weighted linear kernel; IBS: IBS kernel; W.IBS: weighted IBS kernel.

*: *P*-value < 0.05.

Table 8. Results of the single-SNP association test in the *IL1B* region (no correction for multiple comparison)

		Discovery phase						Replication phase	
		All		Cedar		Cypress		All	
SNP	Major allele	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
exm2265188	*G*	1.23 (0.99–1.52)	0.062	1.22 (0.96–1.55)	0.102	1.24 (0.93–1.66)	0.144	1.05 (0.82–1.35)	0.697
rs10169916	*T*	1.24 (0.99–1.53)	0.053	1.22 (0.96–1.55)	0.101	1.24 (0.93–1.66)	0.144	1.04 (0.81–1.33)	0.762
rs1071676	*G*	0.97 (0.58–1.62)	0.912	1.22 (0.72–2.06)	0.465	1.13 (0.60–2.12)	0.716	1.44 (0.82–2.51)	0.204
rs1143633	***C***	1.29 (1.04–1.60)	**0.018***	1.35 (1.07–1.72)	**0.012***	1.32 (0.99–1.75)	**0.056**	1.34 (1.04–1.72)	**0.023***
rs1143634	*A*	0.97 (0.58–1.62)	0.912	1.22 (0.72–2.06)	0.465	1.13 (0.60–2.12)	0.716	1.44 (0.82–2.51)	0.204
rs12621220	*T*	1.17 (0.93–1.48)	0.170	1.18 (0.92–1.52)	0.195	1.07 (0.78–1.48)	0.660	1.04 (0.81–1.35)	0.739
rs16944	*A*	1.24 (0.99–1.53)	0.051	1.23 (0.97–1.56)	0.089	1.26 (0.94–1.69)	0.116	1.06 (0.83–1.36)	0.641
rs2853550	*A*	1.02 (0.75–1.39)	0.892	0.94 (0.66–1.33)	0.722	1.12 (0.75–1.67)	0.574	0.82 (0.55–1.25)	0.360
rs3136558	*G*	0.86 (0.69–1.06)	0.153	0.87 (0.69–1.10)	0.241	0.88 (0.67–1.17)	0.377	1.20 (0.94–1.52)	0.145
rs3917366	*A*	0.97 (0.58–1.62)	0.912	1.22 (0.72–2.06)	0.465	1.13 (0.60–2.12)	0.716	1.44 (0.82–2.51)	0.204
rs3917368	***C***	1.26 (1.02–1.55)	**0.034***	1.32 (1.04–1.68)	**0.020***	1.33 (1.00–1.76)	**0.049***	1.35 (1.05–1.73)	**0.018***
rs7596684	*C*	1.05 (0.71–1.55)	0.806	1.13 (0.74–1.72)	0.565	1.16 (0.71–1.90)	0.561	1.32 (0.87–2.02)	0.194

SNP: single nucleotide polymorphism; OR: odds ratio; 95%CI: 95% confidence interval.

*: $P < 0.05$.

Supplementary Table S1. The list of suggestive SNPs in the discovery phase (all pollinosis)

Chromosome	SNP	Position	Major allele	N[a]	OR	*P*
12	rs6489966	115079592	T	731	0.589	1.70×10^{-6}
9	rs7860104	16661210	A	731	1.733	2.23×10^{-6}
18	rs1833356	7267670	A	731	1.620	1.43×10^{-5}
3	exm338214	113015660	A	731	1.608	1.48×10^{-5}
3	rs2270781	113015660	A	731	1.608	1.48×10^{-5}
2	rs7562836	38002507	G	731	0.576	1.83×10^{-5}
1	rs11165065	94491468	A	731	0.515	2.24×10^{-5}
18	rs6508093	49344684	A	729	0.630	2.90×10^{-5}
19	rs8110935	57548289	C	731	2.616	2.97×10^{-5}
9	rs1544161	23307377	A	729	1.755	3.29×10^{-5}
3	rs1456095	157216017	T	731	0.610	3.47×10^{-5}
1	rs2273344	11105122	C	731	2.002	3.59×10^{-5}
2	rs2083246	216449837	G	731	0.602	3.67×10^{-5}
5	rs1707062	22869771	T	731	1.630	3.91×10^{-5}
18	rs1009685	23041828	A	731	1.814	3.99×10^{-5}
6	rs3850223	140780824	G	731	0.629	4.03×10^{-5}
4	rs4862031	183068987	G	730	0.628	4.12×10^{-5}
18	rs883746	49360609	C	731	0.642	4.83×10^{-5}
8	rs16889881	118571202	T	731	1.870	4.88×10^{-5}
17	rs28364644	52977353	G	731	2.039	5.12×10^{-5}
18	exm2272650	23178593	G	730	1.557	5.46×10^{-5}
4	rs9312290	183067139	A	731	0.632	5.47×10^{-5}
4	rs6824735	175740569	C	728	1.545	5.49×10^{-5}
3	rs4682485	113076730	T	728	1.556	5.61×10^{-5}
16	rs2542674	54206026	T	729	1.633	5.85×10^{-5}
1	rs12047092	191618129	A	731	2.288	5.89×10^{-5}
3	rs4682133	113062986	A	731	1.554	5.90×10^{-5}
3	rs9863193	113064142	G	729	1.554	5.91×10^{-5}
1	rs2814580	191610760	C	730	2.281	6.27×10^{-5}
1	rs871644	18297688	A	731	0.520	7.03×10^{-5}
1	rs1336855	191604694	G	726	2.431	7.03×10^{-5}
6	exm–rs2071537	32818991	A	731	2.025	7.15×10^{-5}
6	rs2071537	32818991	A	731	2.025	7.15×10^{-5}
20	rs2142139	15237052	A	731	0.499	7.19×10^{-5}

2	rs1465630	109881236	T	731	2.124	7.26×10^{-5}
11	rs4938184	115053808	T	731	1.559	7.26×10^{-5}
11	rs4937357	128467510	T	731	0.459	7.49×10^{-5}
15	rs2684777	99396694	C	731	1.573	7.61×10^{-5}
9	rs2482709	94199559	T	726	1.506	7.62×10^{-5}
2	rs4670214	38005048	G	730	0.629	7.71×10^{-5}
7	rs1581515	54238625	G	731	1.696	7.80×10^{-5}
7	rs1996991	54250014	C	731	1.696	7.80×10^{-5}
7	rs2049409	54249748	G	731	1.696	7.80×10^{-5}
7	rs7799840	54247600	C	731	1.696	7.80×10^{-5}
7	rs885234	54234447	A	731	1.696	7.80×10^{-5}
5	rs895298	123734441	C	731	1.696	8.30×10^{-5}
8	rs1497630	109680768	A	731	1.621	8.42×10^{-5}
12	rs1587458	33252638	A	731	1.838	8.62×10^{-5}
1	rs1338035	191627004	T	731	2.233	8.85×10^{-5}
2	rs34058885	49563508	G	731	0.631	9.16×10^{-5}
2	rs17425341	44324287	G	730	1.558	9.26×10^{-5}
3	rs347322	140142144	T	731	0.615	9.27×10^{-5}
3	rs3828401	140171785	A	731	1.741	9.35×10^{-5}
10	rs7085583	30817129	G	731	2.140	9.37×10^{-5}
17	rs7225744	10016398	C	731	0.646	9.39×10^{-5}
3	rs1456113	157188045	A	731	0.622	9.50×10^{-5}
6	rs3003921	152279514	T	729	1.528	9.58×10^{-5}
18	rs9948281	23057181	C	731	1.571	9.86×10^{-5}

[a]: number of people genotyped.

OR: odds ratio; SNP: single nucleotide polymorphism.

Supplementary Table S2. The list of suggestive SNPs in the discovery phase (cedar pollinosis)

Chromosome	SNP	Position	Major allele	N[a]	OR	*P*
12	rs6489966	115079592	T	649	0.583	1.02×10^{-5}
9	rs12346450	132850277	A	649	1.947	1.09×10^{-5}
9	rs1544161	23307377	A	647	1.893	1.12×10^{-5}
18	rs1833356	7267670	A	649	1.721	1.12×10^{-5}
9	rs1929171	23343995	C	649	1.877	1.15×10^{-5}
8	rs1497630	109680768	A	649	1.788	1.33×10^{-5}
9	rs7851530	132882141	A	648	1.932	1.43×10^{-5}
1	rs1336855	191604694	G	644	2.747	1.87×10^{-5}
9	rs7029374	23358448	A	649	1.812	1.92×10^{-5}
4	rs6824735	175740569	C	646	1.651	2.22×10^{-5}
9	rs7860104	16661210	A	649	1.711	2.57×10^{-5}
9	rs6475727	23285981	C	648	1.906	2.61×10^{-5}
1	rs12047092	191618129	A	649	2.496	2.81×10^{-5}
13	rs4773843	95839495	T	649	0.314	2.91×10^{-5}
1	rs2814580	191610760	C	648	2.487	3.00×10^{-5}
18	rs11081311	7268039	G	647	0.572	3.21×10^{-5}
21	rs233231	45966733	G	649	1.641	3.27×10^{-5}
17	rs28364644	52977353	G	649	2.180	3.70×10^{-5}
8	rs2935755	109664109	A	649	1.726	3.94×10^{-5}
1	rs1338035	191627004	T	649	2.436	4.15×10^{-5}
1	rs2273344	11105122	C	649	2.097	4.29×10^{-5}
3	rs802792	9224175	A	649	0.607	4.47×10^{-5}
12	rs1587458	33252638	A	649	1.983	4.93×10^{-5}
3	rs12639182	38736230	T	649	0.612	5.30×10^{-5}
10	rs7085583	30817129	G	649	2.353	5.43×10^{-5}
9	rs10757418	23354494	G	649	1.723	5.50×10^{-5}
11	rs11215424	115087421	G	649	1.864	5.53×10^{-5}
1	rs731024	6644723	A	649	0.597	6.03×10^{-5}
7	rs1581515	54238625	G	649	1.792	6.35×10^{-5}
7	rs1996991	54250014	C	649	1.792	6.35×10^{-5}
7	rs2049409	54249748	G	649	1.792	6.35×10^{-5}
7	rs7799840	54247600	C	649	1.792	6.35×10^{-5}
7	rs885234	54234447	A	649	1.792	6.35×10^{-5}
1	rs9628688	89730723	T	649	1.725	6.60×10^{-5}

3	rs13073891	140140442	C	649	0.570	6.61×10^{-5}
3	rs347322	140142144	T	649	0.570	6.61×10^{-5}
5	rs1707062	22869771	T	649	1.674	7.84×10^{-5}
2	rs7562836	38002507	G	649	0.571	8.63×10^{-5}
9	rs7864583	23277704	A	649	3.024	9.24×10^{-5}
20	rs1276434	55479307	T	649	1.588	9.43×10^{-5}
20	rs6139981	6411203	C	648	1.598	9.72×10^{-5}
13	rs11617981	105795017	C	649	1.595	9.83×10^{-5}

[a]: number of people genotyped.

OR: odds ratio; SNP: single nucleotide polymorphism.

Supplementary Table S3. The list of suggestive SNPs in the discovery phase (hinoki pollinosis)

Chromosome	SNP	Position	Major allele	N[a]	OR	*P*
12	rs6489966	115079592	T	731	0.589	1.70×10^{-5}
9	rs7860104	16661210	A	731	1.733	2.23×10^{-5}
18	rs1833356	7267670	A	731	1.620	1.43×10^{-5}
3	exm338214	113015660	A	731	1.608	1.48×10^{-5}
3	rs2270781	113015660	A	731	1.608	1.48×10^{-5}
2	rs7562836	38002507	G	731	0.576	1.83×10^{-5}
1	rs11165065	94491468	A	731	0.515	2.24×10^{-5}
18	rs6508093	49344684	A	729	0.630	2.90×10^{-5}
19	rs8110935	57548289	C	731	2.616	2.97×10^{-5}
9	rs1544161	23307377	A	729	1.755	3.29×10^{-5}
3	rs1456095	157216017	T	731	0.610	3.47×10^{-5}
1	rs2273344	11105122	C	731	2.002	3.59×10^{-5}
2	rs2083246	216449837	G	731	0.602	3.67×10^{-5}
5	rs1707062	22869771	T	731	1.630	3.91×10^{-5}
18	rs1009685	23041828	A	731	1.814	3.99×10^{-5}
6	rs3850223	140780824	G	731	0.629	4.03×10^{-5}
4	rs4862031	183068987	G	730	0.628	4.12×10^{-5}
18	rs883746	49360609	C	731	0.642	4.83×10^{-5}
8	rs16889881	118571202	T	731	1.870	4.88×10^{-5}
17	rs28364644	52977353	G	731	2.039	5.12×10^{-5}
18	exm2272650	23178593	G	730	1.557	5.46×10^{-5}
4	rs9312290	183067139	A	731	0.632	5.47×10^{-5}
4	rs6824735	175740569	C	728	1.545	5.49×10^{-5}
3	rs4682485	113076730	T	728	1.556	5.61×10^{-5}
16	rs2542674	54206026	T	729	1.633	5.85×10^{-5}
1	rs12047092	191618129	A	731	2.288	5.89×10^{-5}
3	rs4682133	113062986	A	731	1.554	5.90×10^{-5}
3	rs9863193	113064142	G	729	1.554	5.91×10^{-5}
1	rs2814580	191610760	C	730	2.281	6.27×10^{-5}
1	rs871644	18297688	A	731	0.520	7.03×10^{-5}
1	rs1336855	191604694	G	726	2.431	7.03×10^{-5}
6	exm-rs2071537	32818991	A	731	2.025	7.15×10^{-5}
6	rs2071537	32818991	A	731	2.025	7.15×10^{-5}
20	rs2142139	15237052	A	731	0.499	7.19×10^{-5}

2	rs1465630	109881236	T	731	2.124	7.26×10^{-5}
11	rs4938184	115053808	T	731	1.559	7.26×10^{-5}
11	rs4937357	128467510	T	731	0.459	7.49×10^{-5}
15	rs2684777	99396694	C	731	1.573	7.61×10^{-5}
9	rs2482709	94199559	T	726	1.506	7.62×10^{-5}
2	rs4670214	38005048	G	730	0.629	7.71×10^{-5}
7	rs1581515	54238625	G	731	1.696	7.80×10^{-5}
7	rs1996991	54250014	C	731	1.696	7.80×10^{-5}
7	rs2049409	54249748	G	731	1.696	7.80×10^{-5}
7	rs7799840	54247600	C	731	1.696	7.80×10^{-5}
7	rs885234	54234447	A	731	1.696	7.80×10^{-5}
5	rs895298	123734441	C	731	1.696	8.30×10^{-5}
8	rs1497630	109680768	A	731	1.621	8.42×10^{-5}
12	rs1587458	33252638	A	731	1.838	8.62×10^{-5}
1	rs1338035	191627004	T	731	2.233	8.85×10^{-5}
2	rs34058885	49563508	G	731	0.631	9.16×10^{-5}
2	rs17425341	44324287	G	730	1.558	9.26×10^{-5}
3	rs347322	140142144	T	731	0.615	9.27×10^{-5}
3	rs3828401	140171785	A	731	1.741	9.35×10^{-5}
10	rs7085583	30817129	G	731	2.140	9.37×10^{-5}
17	rs7225744	10016398	C	731	0.646	9.39×10^{-5}
3	rs1456113	157188045	A	731	0.622	9.50×10^{-5}
6	rs3003921	152279514	T	729	1.528	9.58×10^{-5}
18	rs9948281	23057181	C	731	1.571	9.86×10^{-5}

[a]: number of people genotyped.

OR: odds ratio; SNP: single nucleotide polymorphism.

Supplementary Table S4. The *P*-values of top 100 SNPs in the integrated genome-wide association study

SNP	Chromosome	Position	*P*
rs4635643	3	73010544	1.65×10^{-5}
rs2095108	9	114078716	1.72×10^{-5}
rs8019026	14	21206023	3.14×10^{-5}
rs6489966	12	115079592	1.54×10^{-5}
rs7860104	9	16661210	1.59×10^{-5}
rs6466365	7	110577992	2.49×10^{-5}
rs12439499	15	35117336	3.06×10^{-5}
rs7714832	5	149675169	3.12×10^{-5}
exm2261531	3	6764063	3.14×10^{-5}
rs2109863	7	110611438	3.75×10^{-5}
rs2084073	14	48564424	3.77×10^{-5}
rs7795011	7	110602792	3.82×10^{-5}
rs7562836	2	38002507	3.83×10^{-5}
rs1518364	2	198809975	3.91×10^{-5}
rs758953	7	110613685	4.27×10^{-5}
rs2542674	16	54206026	4.46×10^{-5}
exm-rs6738825	2	198896895	5.05×10^{-5}
rs1579695	2	198900363	5.05×10^{-5}
rs4410288	2	198819824	5.15×10^{-5}
rs700679	2	198706916	5.39×10^{-5}
rs1065953	2	198614612	5.52×10^{-5}
rs34608683	2	198735712	5.65×10^{-5}
rs700655	2	198643631	6.34×10^{-5}
exm338214	3	113015660	6.56×10^{-5}
rs4677213	3	72994594	6.70×10^{-5}
rs4866716	5	3105242	7.07×10^{-5}
rs1595823	2	198891799	7.36×10^{-5}
rs3794338	13	24433291	7.45×10^{-5}
exm255662	2	198950240	7.66×10^{-5}
rs2684788	15	99504437	7.74×10^{-5}
rs218268	4	55411087	7.83×10^{-5}
exm2267689	14	101668606	8.77×10^{-5}
rs775214	3	113010950	8.92×10^{-5}
rs3850223	6	140780824	9.22×10^{-5}

rs10207433	2	198805930	9.38×10^{-5}
rs1833356	18	7267670	9.68×10^{-5}
rs978658	3	6766178	9.87×10^{-5}
rs1789693	11	74887165	9.93×10^{-5}
rs943659	14	92974354	0.000104434
rs1456095	3	157216017	0.000106417
rs1497630	8	109680768	0.000108663
rs2270782	3	113022996	0.000110084
rs2440119	10	11477584	0.000111906
rs6546619	2	70938472	0.000112939
rs1537759	14	101663335	0.000114565
rs7789182	7	135583537	0.00011554
rs4268783	16	76528976	0.000116831
rs12802926	11	123035936	0.000120314
rs1815009	15	99504671	0.000120922
rs1052278	3	73024350	0.000129966
rs11760145	6	115626947	0.000137123
rs9829514	3	60501861	0.00013885
rs7947358	11	69544508	0.00014012
rs1617377	11	123564532	0.00014078
rs1412038	6	115595273	0.000144623
rs1548305	6	115608842	0.000144623
rs1465630	2	109881236	0.000151635
rs17095701	14	59566125	0.000151686
rs12932943	16	76532392	0.000152327
rs11617981	13	105795017	0.000153779
rs6139981	20	6411203	0.000157938
rs420934	4	104414511	0.00016284
rs7340146	2	70915347	0.000165283
rs2291527	3	73109891	0.000168714
rs17425341	2	44324287	0.000176337
rs17060530	6	100859947	0.000176436
rs11643145	16	76535342	0.000178265
rs3945127	14	101679693	0.000178721
rs5018958	3	174062834	0.000180849
rs13437134	6	115650230	0.000181511

rs830818	5	165753097	0.000185221
rs5024630	13	105797928	0.000185232
rs2550692	16	79069361	0.000185713
rs6869634	5	149616719	0.000193602
rs2441704	8	102133238	0.000198674
rs7699520	4	169049597	0.000198703
rs7597655	2	70936407	0.000204326
rs12892436	14	21203216	0.000208198
rs16985823	2	19184369	0.00021237
rs1875111	3	112978764	0.000212687
rs12773699	10	45455227	0.000213391
rs2071537	6	32818991	0.000216144
rs7654507	4	104528309	0.000224216
rs11165065	1	94491468	0.000224657
rs4821914	22	40091547	0.000224898
rs4676274	2	109948720	0.000225942
rs17069167	8	4016156	0.00022907
rs28364644	17	52977353	0.000230684
rs1587458	12	33252638	0.000231243
rs4403628	1	159753097	0.000231428
rs4682133	3	113062986	0.000232025
rs9863193	3	113064142	0.000232566
rs699526	1	90952184	0.000236484
rs759463	2	70923854	0.000239337
rs6121611	20	61041906	0.000243025
rs4682485	3	113076730	0.000243299
rs16870017	4	20807977	0.000243821
rs895602	8	102132835	0.000248556
rs8101899	19	30224464	0.000250933
rs8012716	14	21202336	0.000251127

SNP: single nucleotide polymorphism.

Supplementary Table S5. The *Q*-values of top 100 genes in the integrated gene-based analysis

	linear kernel					Weighted linear kernel			
Genes	Discovery	Replication	*P*-value	*Q*-value	Genes	Discovery	Replication	*P*-value	*Q*-value
BOLL	0.0170	0.0005	0.0001	0.8150	*CAMK2A*	0.1748	<0.0001	0.0001	0.4950
GRM7-AS3	0.1453	0.0001	0.0002	0.8150	*MIR6812*	0.0017	0.0046	0.0001	0.4950
CFAP44	0.0001	0.3965	0.0003	0.8150	*PIGT*	0.0017	0.0046	0.0001	0.4950
PLCL1	0.0295	0.0008	0.0003	0.8150	*DBNDD2*	0.0017	0.0046	0.0001	0.4950
KLHL5	0.0001	0.2589	0.0003	0.8150	*SYS1-DBNDD2*	0.0019	0.0046	0.0001	0.4950
ADD2	0.0094	0.0028	0.0003	0.8150	*GATA5*	0.0151	0.0006	0.0001	0.4950
EDDM3A	0.1228	0.0002	0.0003	0.8150	*TRIM50*	0.0020	0.0108	0.0003	0.7736
IGF1R	0.0007	0.0414	0.0003	0.8150	*NSUN5*	0.0020	0.0109	0.0003	0.7736
ARSI	0.0189	0.0019	0.0004	0.8150	*MIR4266*	0.0001	0.3001	0.0003	0.7736
LOC90768	0.0001	0.4960	0.0004	0.8150	*CACNA1I*	0.0285	0.0010	0.0003	0.7736
BOC	0.0002	0.2535	0.0005	0.8150	*ZNF414*	0.1473	0.0002	0.0004	0.8372
GBP7	0.0002	0.2373	0.0005	0.8150	*GPATCH1*	0.0001	0.3528	0.0005	0.8372
SCAND1	0.0169	0.0030	0.0006	0.8150	*LINC00462*	0.0208	0.0023	0.0005	0.8372
CABYR	0.3078	0.0002	0.0006	0.8150	*RNASE2*	0.0001	0.5665	0.0005	0.8372
CRX	0.1761	0.0003	0.0006	0.8150	*GTF2I*	0.8031	0.0001	0.0005	0.8372
MIR586	0.1598	0.0003	0.0006	0.8150	*ERGIC3*	0.0975	0.0006	0.0006	0.8372
MARS2	0.0427	0.0014	0.0006	0.8150	*ZBED4*	0.0001	0.5066	0.0006	0.8372
BTBD6	0.1697	0.0004	0.0007	0.8150	*FOXN3*	0.0003	0.2615	0.0007	0.8372
MIR499A	0.0004	0.1949	0.0007	0.8150	*GRIFIN*	0.0021	0.0329	0.0007	0.8372
MIR499B	0.0004	0.1949	0.0007	0.8150	*LOC101928163*	0.2111	0.0004	0.0008	0.8372
KCNS1	0.0003	0.2689	0.0007	0.8150	*LOC100422212*	0.1258	0.0007	0.0009	0.8372
PGPEP1L	0.0028	0.0257	0.0007	0.8150	*TBC1D5*	0.1630	0.0006	0.0009	0.8372
GXYLT2	0.0192	0.0038	0.0008	0.8150	*SLC7A1*	0.1117	0.0008	0.0010	0.8372
ZYG11B	0.1315	0.0007	0.0009	0.9054	*SLCO6A1*	0.0596	0.0017	0.0010	0.8372
ACTA1	0.2522	0.0004	0.0009	0.9054	*HIP1R*	0.0019	0.0547	0.0010	0.8372
ZNF414	0.0719	0.0013	0.0010	0.9054	*VPS37B*	0.0019	0.0565	0.0011	0.8372
TRPC6	0.0335	0.0030	0.0010	0.9054	*ZRANB1*	0.0034	0.0326	0.0011	0.8372
SIM1	0.0936	0.0011	0.0010	0.9054	*LOC100131315*	0.6267	0.0002	0.0012	0.8372
LOC100507477	0.0010	0.1041	0.0011	0.9054	*MIR592*	0.0038	0.0343	0.0013	0.8372
BRF1	0.1912	0.0006	0.0012	0.9599	*MIR499A*	0.0009	0.1572	0.0014	0.8372
PARD3B	0.0046	0.0282	0.0013	0.9599	*MIR499B*	0.0009	0.1572	0.0014	0.8372
TMEM72-AS1	0.1389	0.0009	0.0013	0.9599	*LOC101926943*	0.7734	0.0002	0.0014	0.8372
ASB9P1	0.0042	0.0317	0.0013	0.9599	*ACVR1*	0.0069	0.0211	0.0014	0.8372

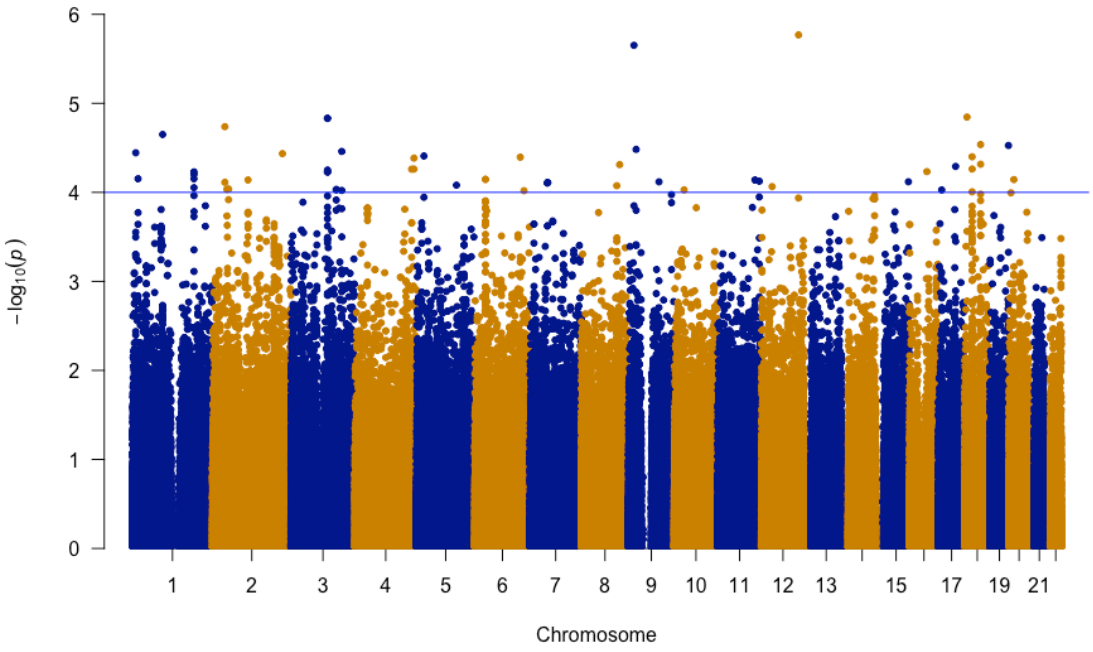
CAMK2A	0.1803	0.0008	0.0014	0.9599	*LIFR-AS1*	0.0010	0.1561	0.0015	0.8372
SPINK6	0.0003	0.5232	0.0014	0.9599	*WNT5B*	0.0003	0.5365	0.0015	0.8372
TMEM72	0.2936	0.0005	0.0015	0.9599	*ANKRD18A*	0.0007	0.2221	0.0015	0.8372
MIR592	0.0045	0.0343	0.0015	0.9599	*FAM201A*	0.0007	0.2222	0.0015	0.8372
MTHFR	0.0269	0.0059	0.0016	0.9599	*LINC00441*	0.0269	0.0057	0.0015	0.8372
ASNSD1	0.0007	0.2210	0.0016	0.9599	*PIP4K2C*	0.0007	0.2296	0.0015	0.8372
PRAM1	0.0794	0.0021	0.0016	0.9599	*RNF144A-AS1*	0.0598	0.0027	0.0015	0.8372
GPR107	0.0003	0.5363	0.0018	0.9599	*IMPA2*	0.0080	0.0203	0.0016	0.8372
NAA50	0.0094	0.0209	0.0019	0.9599	*RIMBP2*	0.0019	0.0898	0.0016	0.8372
C1QTNF9B-AS1	0.0294	0.0068	0.0019	0.9599	*ZBED2*	0.0063	0.0274	0.0017	0.8372
USF3	0.0045	0.0467	0.0020	0.9599	*HOXA10-HOXA9*	0.0273	0.0065	0.0017	0.8372
CLCN6	0.0143	0.0151	0.0020	0.9599	*NRL*	0.1527	0.0012	0.0017	0.8372
LINC01467	0.0241	0.0091	0.0021	0.9599	*LOC101927740*	0.0250	0.0072	0.0017	0.8372
TACR3	0.2490	0.0009	0.0022	0.9599	*CKMT2-AS1*	0.1922	0.0010	0.0019	0.8372
LINC00462	0.0217	0.0108	0.0022	0.9599	*LARS2-AS1*	0.0004	0.5129	0.0019	0.8372
LOC100419170	0.0005	0.5234	0.0023	0.9599	*KRT7*	0.0381	0.0053	0.0019	0.8372
C1QTNF9B	0.0313	0.0080	0.0023	0.9599	*KIF5A*	0.0044	0.0491	0.0020	0.8372
DUSP23	0.0757	0.0034	0.0024	0.9599	*FLJ25758*	0.0732	0.0030	0.0021	0.8372
F2RL1	0.0035	0.0722	0.0024	0.9599	*RNASE4*	0.0791	0.0028	0.0021	0.8372
LOC101927416	0.0088	0.0292	0.0024	0.9599	*ANG*	0.0793	0.0028	0.0021	0.8372
RCBTB2	0.0552	0.0047	0.0024	0.9599	*SLC9C2*	0.0018	0.1220	0.0021	0.8372
TTC39C	0.8988	0.0003	0.0025	0.9599	*LOC101927692*	0.0048	0.0476	0.0021	0.8372
RPUSD1	0.0004	0.7197	0.0025	0.9599	*IRF2BPL*	0.2431	0.0010	0.0022	0.8372
PABPN1L	0.0033	0.0818	0.0025	0.9599	*AKNAD1*	0.1334	0.0018	0.0022	0.8372
ASCC1	0.4540	0.0006	0.0026	0.9599	*LOC101927526*	0.0230	0.0104	0.0022	0.8372
GBP5	0.0006	0.4891	0.0026	0.9599	*VSTM5*	0.0388	0.0065	0.0024	0.8372
SIAH3	0.0046	0.0616	0.0026	0.9599	*RCBTB2*	0.0549	0.0047	0.0024	0.8372
OSBPL10	0.0222	0.0129	0.0026	0.9599	*LOC103352541*	0.0010	0.2710	0.0025	0.8372
ATP6V1A	0.0102	0.0282	0.0026	0.9599	*RNASEH2B*	0.0067	0.0404	0.0025	0.8372
LOC644656	1.0000	0.0003	0.0027	0.9599	*PCK2*	0.3124	0.0009	0.0025	0.8372
HSF5	0.0527	0.0057	0.0027	0.9599	*GGT7*	0.0008	0.3658	0.0025	0.8372
TYRO3P	0.0056	0.0536	0.0027	0.9599	*TYRO3P*	0.0052	0.0529	0.0025	0.8372
LOC103352541	0.0021	0.1438	0.0027	0.9599	*SLC23A1*	0.0322	0.0087	0.0026	0.8372
ANKAR	0.0012	0.2497	0.0028	0.9599	*LOC101927849*	0.0008	0.3699	0.0026	0.8372
LRIG3	0.0874	0.0035	0.0028	0.9599	*ADAMTSL2*	0.0401	0.0071	0.0026	0.8372
DYNC1LI1	0.0018	0.1757	0.0028	0.9599	*MZB1*	0.0326	0.0090	0.0027	0.8372

PDHB	0.4435	0.0007	0.0028	0.9599	*PROB1*	0.0326	0.0090	0.0027	0.8372
ZNF143	1.0000	0.0003	0.0029	0.9599	*SPATA24*	0.0326	0.0090	0.0027	0.8372
CHTF18	0.0004	0.7455	0.0029	0.9599	*FER1L4*	0.1159	0.0025	0.0027	0.8372
SPINK14	0.0010	0.3263	0.0029	0.9599	*SYVN1*	0.4981	0.0006	0.0027	0.8372
GDNF-AS1	0.0006	0.5744	0.0030	0.9599	*MIR6751*	0.4981	0.0006	0.0027	0.8372
ANKRD18A	0.0010	0.3502	0.0031	0.9599	*MTHFR*	0.0060	0.0495	0.0027	0.8372
TRIM37	0.2991	0.0012	0.0031	0.9599	*MIR7855*	0.0004	0.6911	0.0028	0.8372
PLEKHG6	0.1920	0.0018	0.0031	0.9599	*PDHB*	0.4449	0.0007	0.0028	0.8372
COX11	0.0020	0.1757	0.0032	0.9599	*CRELD2*	0.0003	0.9101	0.0028	0.8372
MIR8076	0.0008	0.4435	0.0033	0.9599	*ACTG1*	0.1744	0.0018	0.0028	0.8372
LOC101929380	0.3759	0.0010	0.0033	0.9599	*UGT1A10*	0.5384	0.0006	0.0029	0.8372
MYO19	0.2890	0.0013	0.0033	0.9599	*PARD3B*	0.9992	0.0003	0.0029	0.8372
MIR128-1	0.1212	0.0031	0.0033	0.9599	*LOC101927207*	0.0021	0.1501	0.0029	0.8372
PRKCE	0.0173	0.0218	0.0033	0.9599	*EXOC6*	0.0429	0.0076	0.0030	0.8372
TMEM74	0.0021	0.1800	0.0034	0.9599	*LONRF2*	0.0010	0.3331	0.0030	0.8372
IRF2BPL	0.1511	0.0026	0.0034	0.9599	*FAM46A*	0.0019	0.1793	0.0030	0.8372
DISP3	0.0287	0.0135	0.0034	0.9599	*ZNF727*	0.0045	0.0754	0.0030	0.8372
SNORA23	1.0000	0.0004	0.0035	0.9599	*CD3EAP*	0.2846	0.0012	0.0031	0.8372
ASPM	0.0123	0.0331	0.0036	0.9599	*JAZF1-AS1*	0.0197	0.0176	0.0031	0.8372
RNF43	0.0187	0.0222	0.0036	0.9599	*RLBP1*	0.0010	0.3534	0.0032	0.8372
EDN2	0.8268	0.0005	0.0037	0.9599	*TOP1*	0.0216	0.0165	0.0032	0.8372
PTX3	0.0012	0.3575	0.0037	0.9599	*TMEM178A*	0.0198	0.0194	0.0034	0.8372
ABCA1	0.0191	0.0228	0.0038	0.9599	*CELA3A*	0.0019	0.2039	0.0034	0.8372
LOC101927964	1.0000	0.0004	0.0038	0.9599	*MARVELD1*	0.0032	0.1206	0.0034	0.8372
GNG13	0.0007	0.6769	0.0039	0.9599	*PDIA3*	0.0270	0.0144	0.0034	0.8372
OSGEPL1-AS1	0.0013	0.3533	0.0040	0.9599	*PPP1R13L*	0.6137	0.0006	0.0035	0.8372
PXK	0.3438	0.0013	0.0040	0.9599	*BOD1*	0.0052	0.0762	0.0035	0.8372
ZNHIT3	0.2792	0.0017	0.0040	0.9599	*SNORA23*	1.0000	0.0004	0.0035	0.8372
LOC101928551	0.0010	0.4789	0.0040	0.9599	*SLC6A12*	0.0822	0.0048	0.0035	0.8372
CYSRT1	0.0012	0.3797	0.0040	0.9599	*MSS51*	0.0017	0.2372	0.0035	0.8372
STATH	0.0025	0.1854	0.0041	0.9599	*PPP3CB*	0.0017	0.2372	0.0035	0.8372

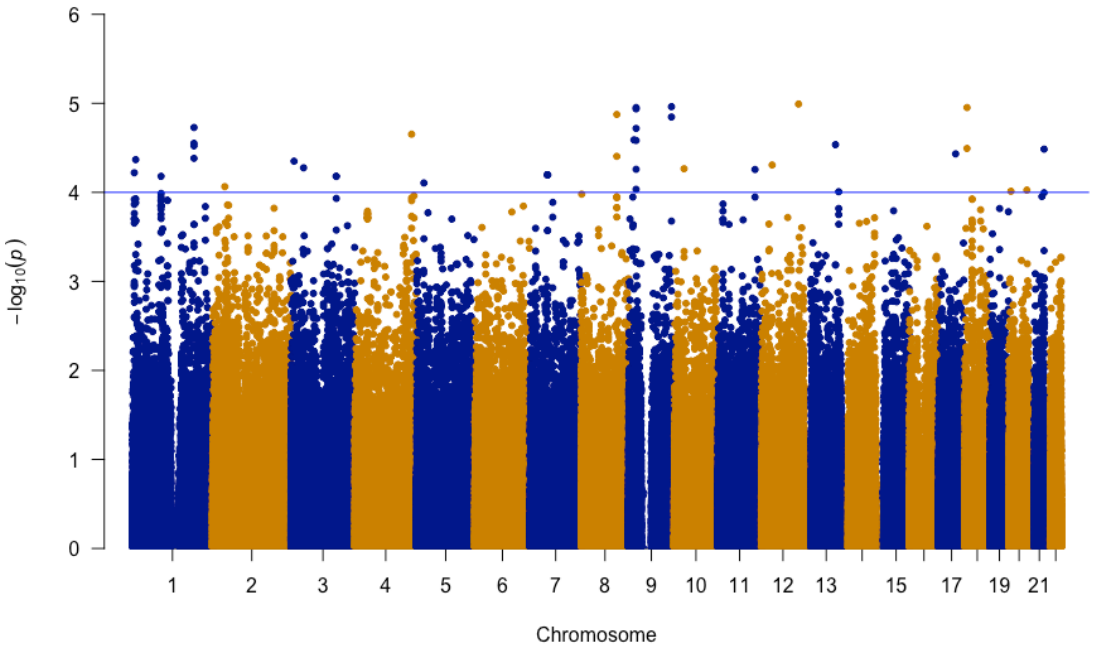
Supplementary Table 6. The *P*-values in the integrated pathway-based analysis

	linear kernel		weighted linear kernel		IBS kernel		weighted IBS kernel	
SetID	P-value	Q-value	P-value	Q-value	P-value	Q-value	P-value	Q-value
Asthma	0.744	0.817	0.290	0.967	0.744	0.762	0.210	0.970
BCR signaling	0.817	0.817	0.634	0.968	0.762	0.762	0.715	0.970
Cytokine-Receptor interaction	0.157	0.522	0.163	0.967	0.279	0.707	0.194	0.970
FCG-R phagocytosis	0.412	0.686	0.914	0.968	0.416	0.707	0.900	0.970
NFKB signaling	0.057	0.522	0.695	0.968	0.118	0.707	0.658	0.970
NK cell cytotoxicity	0.400	0.686	0.968	0.968	0.424	0.707	0.970	0.970
NLR signaling	0.150	0.522	0.691	0.968	0.347	0.707	0.521	0.970
TCR signaling	0.536	0.766	0.260	0.967	0.686	0.762	0.350	0.970
TLR signaling	0.622	0.777	0.794	0.968	0.735	0.762	0.839	0.970
TNF signaling	0.245	0.612	0.590	0.968	0.354	0.707	0.659	0.970

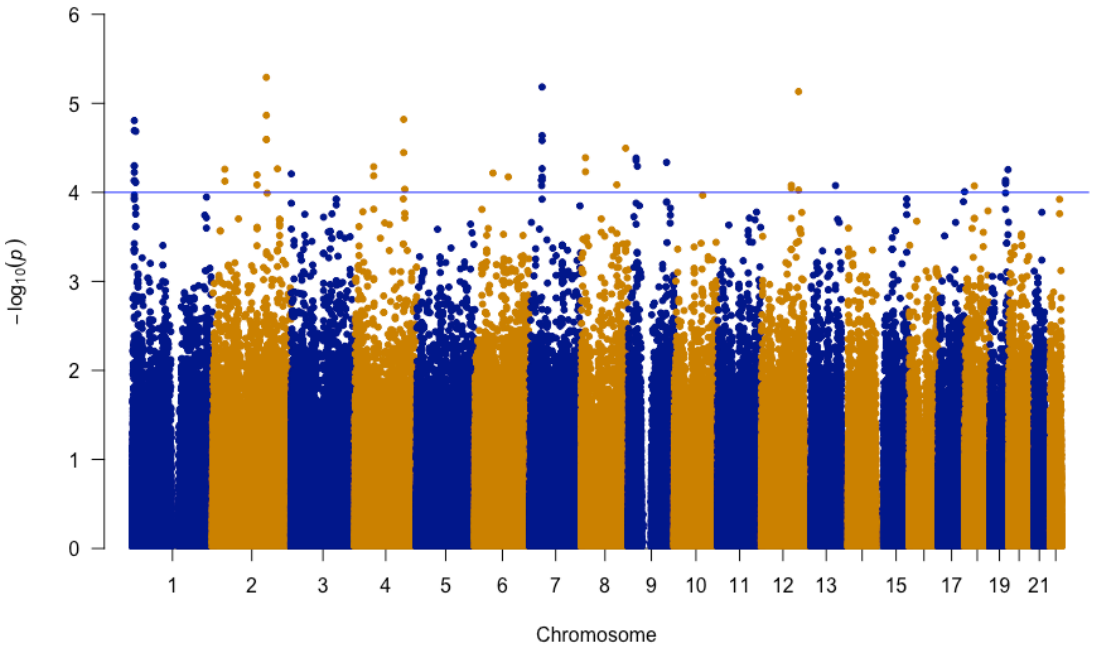
BCR signaling; B-cell receptor signaling: FCG-R phagocytosis; Fc gamma R-mediated phagocytosis: NFKB signaling; Nuclear factor (NF)-kappa B signaling: NK cell cytoxicity; Natural killer cell cytoxicity: NLR signaling; Nucleotide binding oligomerization domain-like receptor signaling: TCR signaling; T cell receptor signaling: TLR signaling; Toll-like receptor signaling: TNF signaling; Tumor necrosis factor signaling.



Supplementary Figure 1: Manhattan plot for the discovery genome-wide association test (all pollinosis). The horizontal blue line indicates the suggestive significant level ($P < 1.0\times10^{-4}$)



Supplementary Figure 2: Manhattan plot for the discovery genome-wide association test (cedar pollinosis). The horizontal blue line indicates the suggestive significant level ($P < 1.0\times10^{-4}$)



Supplementary Figure 3: Manhattan plot for the discovery genome-wide association test (cypress pollinosis). The horizontal blue line indicates the suggestive significant level ($P < 1.0 \times 10^{-4}$)