Genome-wide association analysis identifies 11 risk variants associated with the asthma with hay fever phenotype

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Background: To date, no genome-wide association study (GWAS) has considered the combined phenotype of asthma with hay fever. Previous analyses of family data from the Tasmanian Longitudinal Health Study provide evidence that this phenotype has a stronger genetic cause than asthma without hay fever.

Objective: We sought to perform a GWAS of asthma with hay fever to identify variants associated with having both diseases.

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Methods: We performed a meta-analysis of GWASs comparing persons with both physician-diagnosed asthma and hay fever (n = 6,685) with persons with neither disease (n = 14,091). Results: At genome-wide significance, we identified 11 independent variants associated with the risk of having asthma with hay fever, including 2 associations reaching this level of significance with allergic disease for the first time: *ZBTB10* (rs7009110; odds ratio [OR], 1.14; $P = 4 \times 10^{-9}$) and *CLEC16A* (rs62026376; OR, 1.17; $P = 1 \times 10^{-8}$). The rs62026376:C allele associated with increased asthma with hay fever risk has been found to be associated also with decreased expression of the nearby *DEXI* gene in monocytes. The 11 variants were associated with the risk of asthma and hay fever separately, but the estimated associations with the individual phenotypes were weaker than with the combined asthma with hay fever phenotype. A variant near *LRRC32* was a stronger risk factor for hay fever than for asthma, whereas the reverse was observed for variants in/near *GSDMA* and *TSLP*. Single nucleotide polymorphisms with suggestive evidence for association with asthma with hay fever risk included rs41295115 near *IL2RA* (OR, 1.28; $P = 5 \times 10^{-7}$) and rs76043829 in *TNS1* (OR, 1.23; $P = 2 \times 10^{-6}$).

Conclusion: By focusing on the combined phenotype of asthma with hay fever, variants associated with the risk of allergic disease can be identified with greater efficiency. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: *Rhinitis, atopy, selection, genetic correlation, bivariate, single nucleotide polymorphism*

The comorbidity between asthma and rhinitis (or hay fever) is well established[1,2] and might be a consequence of a causal relationship[3,4] or a shared cause.[5,6] Consistent with the latter hypothesis, results from twin and family studies have estimated that both diseases share 50% to 90% of their genetic susceptibility and 20% to 50% of their environmental susceptibility.[7,8]

Genome-wide association studies (GWASs) are a proved approach to discover genetic variants associated with asthma and hay fever. To date, GWASs have identified variants in 18 loci for which there are genome-wide significant associations with asthma,[9] including *ORMDL3*,[10-15] *PDE4D*,[16] *DENND1B*,[17] *HLA*,[11,15,18-21] *IL33*,[11,12,15] *IL1RL1*,[11,12,15,20] *SMAD3*,[11,15] *IL2RB*,[11] *SLC30A8*,[18] *PYHIN1*,[12] *TSLP*,[12,15] *GAB1*,[19] *IKZF4*,[19] 10p14,[19] *LRRC32*,[14,15] *IL6R*,[14] *RORA*,[20] and *TLR1*.[15] Two GWASs of hay fever have been published recently,[22,23] with one variant in the *LRRC32* region being genome-wide significant.[22] In addition, Hinds et al[15] reported that 11 of 23 variants discovered in a GWAS of self-reported allergy were also associated with hay fever risk at the genome-wide significance level, including those in or near *TLR1*, *TSLP*, *LRRC32*, *IL1RL1*, *HLA-DQA1*, *HLA-C*, *PLCL1*, *LPP*, *IL33*, *SMAD3*, and *ETS1*. Therefore, to date, variants in 7 loci (*TLR1*, *TSLP*, *LRRC32*, *IL1RL1*, *HLA*, *IL33*, and *SMAD3*) have been established as risk factors for both diseases, but many more shared risk variants remain to be identified. On the basis of analyses of family data from the population-based Tasmanian Longitudinal Health Study,[24] we hypothesized that by performing a GWAS that explicitly considers the combined phenotype of asthma with hay fever we can substantially improve power to detect genetic risk factors shared between both diseases.

Abbreviations used

A+H+:	Subjects with asthma and hay fever
A+H−:	Subjects with asthma but not hay fever
A−H+:	Subjects with hay fever but not asthma
A−H−:	Subjects without asthma and without hay fever
A+:	Subjects with asthma, with or without hay fever
H+:	Subjects with hay fever, with or without asthma
A−:	Subjects without asthma, with or without hay fever
H−:	Subjects without hay fever, with or without asthma
AAGC:	Australian Asthma Genetics Consortium
AD:	Atopic dermatitis
ALSPAC:	Avon Longitudinal Study of Parents and Their Children
GWAS:	Genome-wide association study
LD:	Linkage disequilibrium
MAF:	Minor allele frequency
OR:	Odds ratio
QC:	Quality control
SNP:	Single nucleotide polymorphism

We found that considering asthma and hay fever as 3 mutually exclusive phenotypes was informative; the strengths and the familial aspects of their relationship with eczema in infancy differed across the 3 outcomes.[24] Specifically, the childhood disease associations with infantile eczema were more pronounced and more likely to have a causal component for asthma with hay fever (A+H+) than for hay fever without asthma (A−H+) and asthma without hay fever (A+H−).

Therefore we estimated familial associations separately for the 3 phenotypes. For phenotype A+H+, we found strong associations between first-degree relatives, with odds ratios (ORs) for sibling, mother-offspring, and father-offspring pairs of approximately 6, 5, and 3, respectively (all $P < .0001$). For phenotypes A−H+ and A+H−, the associations between first-degree relatives were also highly statistically significant but attenuated. For A−H+, they were approximately 4.5, 2.5, and 2, respectively, whereas for A+H−, they were approximately 3, 3, and 2, respectively. However, of potentially more importance for informing GWASs of the genetic causes of these phenotypes, there were also spousal associations for phenotypes A−H+ and A+H−, with the ORs for parent pairs being 1.7 and 2.5, respectively (both $P < .001$). For phenotype A+H+, however, the parents were not associated (OR, 1.2; $P = .6$); that is, one cannot exclude at least part of the familial associations for phenotypes A−H+ and A+H− being caused by nongenetic factors, but this cannot be said of phenotype A+H+.

The lack of a spousal correlation for phenotype A+H+ and the strong associations between first-degree relatives for this phenotype led us to focus our efforts on the discovery of genetic causes of asthma and hay fever by studying GWAS data based on the combined phenotype of asthma with hay fever. Specifically, we performed a meta-analysis of GWASs considering persons with both physician-diagnosed asthma and hay fever to be cases and persons with neither disease to be control subjects.

METHODS

Studies included in the GWAS of asthma with hay fever

Participants (n = 20,776) for this study were from 4 studies (see Table E1 in this article's Online Repository at www.jacionline.org), as summarized below.