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Letter to the Editor

How important is allergic sensitization as a cause of atopic asthma?

Dear Editor:

Atopy, the excessive production of specific IgE in response to common environmental allergens, is believed to be an important causative factor for asthma, irrespective of age at onset. A theoretical paradigm has evolved in which allergen exposure produces allergic sensitization and continued exposure leads to clinical asthma through the development of airway inflammation, bronchial hyperresponsiveness, and reversible airflow obstruction. In general, however, the genes controlling IgE levels have surprisingly little overlap with the genes mediating asthma susceptibility; some people insist that atopy is secondary to asthma, not a primary driver of the disease.[1] Genetic studies of children with atopic dermatitis have shown that defects in barrier proteins such as Filaggrin commonly predispose individuals to the disease, indicating that increases in IgE responsiveness may be secondary to barrier failure. Analogically, the integrity of the airway epithelium in patients with asthma is often disrupted with loss of epithelial cell–cell contact. Because many of the recently identified susceptibility genes for asthma are expressed in airway epithelium, changes at the airway epithelial barrier may play a central role in secondary sensitization to allergens.

We recently found that the CDHR3 variant (Cys529→Tyr), that supports efficient human rhinovirus C entry and replication, was associated specifically with a phenotype of adult asthma characterized by atopy, early-onset, and airflow obstruction.[2] We also constructed a multi-SNP genetic risk score (GRS) for airflow obstruction using genotype information for 16 genes associated with lower FEV_1/FVC in a genome-wide association study (GWAS) of Japanese populations as well as in previous GWASs of non-Japanese populations[3,4]; an increased GRS, which may reflect deregulated lung growth or development, was strongly associated with a particular phenotype of asthma characterized by atopy, early-onset, and airflow obstruction. Interestingly, both genetic factors, the CDHR3 variant and the GRS for airflow obstruction, were not associated with atopy. Meanwhile, our previous study showed that loci showing strong association to IgE had minimal effects on asthma.[5]

Given that these findings suggest that allergic sensitization in asthma may be an inconstant secondary effect of asthma instead of its cause, we used a Mendelian randomization strategy to examine whether atopy is a cause of asthma, or a consequence of it. Alleles for genetic variants are randomly inherited at meiosis. Mendelian randomization analysis uses these genetic variants to test whether a particular risk factor is causal for a disease outcome. Multiple genetic variants based on GWAS data increases the power of Mendelian randomization.[6] Here, we initially conducted a GWAS for atopy using 967 healthy adults (541 were atopic).[2,3] We defined atopy as a positive IgE response to at least 1 of 14 common inhaled allergens (Supplementary Table 1). We tested for gene-level replications across 25 genes that were identified in 2 previous non-Japanese GWASs[7,8] as being associated with atopy and with *P*-values less than 5.0×10^{-8}.[4] When we selected the top SNPs with the strongest statistical evidence of association with atopy in each region extending ±100 kb from each candidate gene, 20 out of the 25 genes were nominally associated ($P < 0.05$) with atopy in our GWAS (Supplementary Table 1).

In addition to the 967 healthy adults and 216 patients with asthma for whom we already had GWAS genotyping, we used the TaqMan allele-specific amplification method to genotype a further 533 healthy adults and 325 adults with asthma for these 20 SNPs.[2] They were all recruited in the Tsukuba area, Japan.[2,3] For 1 of the SNPs, *PVT1-MYC* (rs6470586), we were unable to obtain reliable genotype information due to insufficient amplification and, therefore, we calculated the atopy GRS using the genotype information of the remaining 19 SNPs in a total of 1500 healthy adults (883 were atopic) and 541 adults with asthma (391 were atopic) (Supplementary Table 2). The GRS, which combines the modest effects of multiple SNPs into a single variable, is calculated as the weighted sum of the product of the OR for risk alleles using the formula

$$\mathrm{GRS}i = \sum_{k=1}^{19} ORk^{RAk}$$

where GRS*i* is the atopy GRS for individual *i*; OR*k* is the OR of SNP*k* as the weight of each risk allele derived from our GWAS for atopy; and RA*k* is the number of risk alleles for SNP*k* (0, 1, or 2).

In this population, atopy was strongly associated with asthma (OR = 1.82, $P = 3.40 \times 10^{-8}$). In non-asthmatic healthy adults, GRS was highly associated with atopy (GRS [SD] 26.9 [113] and 26.4 [1.05] for 883 atopic and 617 non-atopic individuals, respectively, $P = 2.64 \times 10^{-16}$). However, despite the strong association of GRS with atopy, GRS was not associated with asthma ($P = 0.31$). Furthermore, the extent of the association between atopy and asthma did not change after adjustment for GRS (OR = 1.89, $P = 1.07 \times 10^{-8}$) and GRS levels in patients with atopic asthma were similar to those of non-atopic asthma, and were significantly lower than those of atopic healthy adults (Fig. 1), suggesting that the significant association between atopy and asthma was not entirely mediated by the GRS effect. These results indicated that the Mendelian randomization technique revealed no evidence of a causal link between atopy and asthma, which is consistent with

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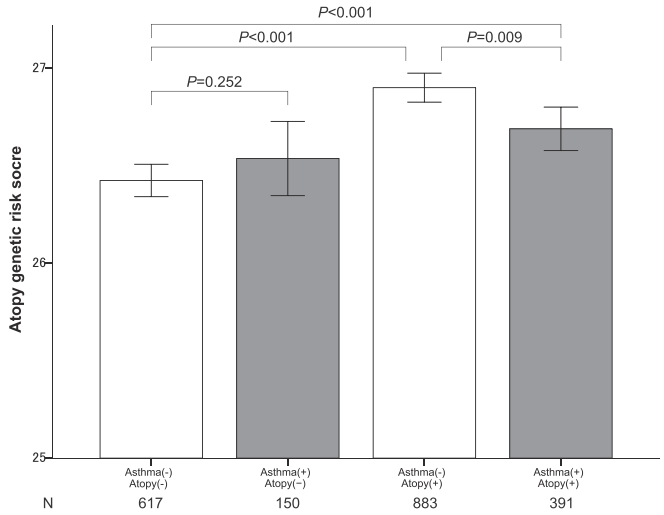

Fig. 1. The GRS levels according to the presence or absence of atopy and asthma. When we compared the levels of GRS according to the 4 groups (atopic and non-atopic healthy adults, adults with atopic and non-atopic asthma), the highest levels of GRS was found in atopic healthy adults. Error bars indicate 95% confidence intervals.

the contention that atopy is a result of, rather than a cause of, asthma in this population. Allergen-specific IgE responsiveness is a phenotypically heterogeneous condition and IgE sensitization to Japanese cedar is less related to asthma[9]; however, we did not see any difference in the results after we repeated the analyses by excluding a Japanese cedar-specific IgE response from the definition of atopy.

As the levels of GRS for the 391 patients with atopic asthma were significantly higher than those for the 617 non-atopic, non-asthmatic healthy individuals (Fig. 1), we calculated the population attributable risk fraction (PARF) using the formula

$$\mathrm{PARF} = P(E)(\mathrm{OR}-1)/[1+P(E)(\mathrm{OR}-1)]$$

where $P(E)$ is the probability of having the highest GRS than individuals in the lower quintile of the risk score distribution

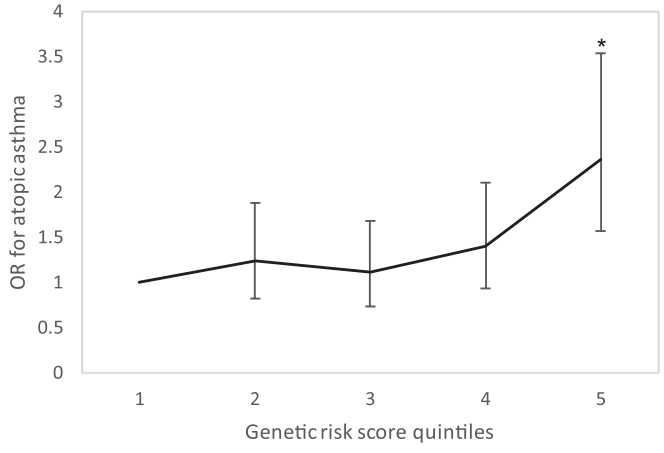

Fig. 2. Odds ratios for association between the atopy GRS and atopic asthma across the GRS quintiles. For each atopy GRS quintile, odds ratios for the development of atopic asthma were obtained using 391 patients with atopic asthma and 617 non-atopic non asthmatic healthy individuals. The odds ratio for comparison between the 5th and 1st quintiles was 2.36 (95% CI = 1.57–3.54, $^{*}P = 2.9 \times 10^{-5}$). The odds ratio for comparison between the 5th and 1st to 4th quintiles was 1.99 (95% CI = 1.46–2.72, $P = 1.2 \times 10^{-5}$), which was used for the estimation of proportion of atopic asthma cases attributable to the GRS.

($P(E) = 0.2$), and OR refers to the odds of having atopic asthma for individuals in quintiles 5 of the GRS distribution as compared to the odds of having atopic asthma for individuals in the lower quintile (quintiles 1 to 4) of the GRS distribution (Fig. 2). The estimated proportion of atopic asthma cases attributable to genetic susceptibility to atopy or GRS in the highest quintile was 16.6%.

In this study, we do not intend to argue that atopy does not play an important role in the pathobiology of atopic asthma; acquired allergic sensitization could play a role in maintaining chronic asthma by setting off the allergic inflammatory cascade and subsequent disease progression. Nevertheless, the danger is that overemphasis on a particular theoretical paradigm for which the evidence is less substantial than is commonly assumed may have led to an under-recognition of, and insufficient research into, other potential novel causal pathways, such as the susceptibility to viral infection or impaired lung growth that underlie atopic asthma.[10]

Acknowledgment

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.alit.2017.10.005.

Conflict of interest

NH has received lecture fees from AstraZeneca, Astellas Pharma, MSD and Boehringer Ingelheim. The rest of the authors have no conflict of interest.

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