

EDITORIAL

Clinical & Experimental Allergy

Body mass index, asthma, and genetic variation

This editorial discusses the findings of the paper in this issue by E. Melén et al. [2] pp. 463–474.

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Observational studies show that body mass index and asthma are associated [1]. In this issue, Melen et al. [2] describe the study of genetic determinants of body mass index (BMI) in individuals with and without asthma. In a discovery set of children with asthma, Melen et al. report association of genetic variants in *DENND1B* with BMI, albeit with heterogeneous effects that did not consistently replicate. Intriguingly, variants in the same region have been reported to be associated with childhood asthma [3]. The strongest signal described by Melen et al. was for variant rs4915551. As no association between rs4915551 and BMI was seen in a previous large study of BMI [4], the effects on BMI reported by Melen et al. may have been driven by an interaction between the genetic variant and asthma status. Melen and colleagues have been able to bring together data from multiple cohorts and case-control studies to improve power to address these study questions, and although the study is large, the authors acknowledge that unanswered questions remain. The interpretational caveats of this study highlight the challenges of studying 'gene-environment' interactions more generally.

Genome-wide association studies (GWAS) have rapidly improved our understanding of the genetic determinants of complex traits and diseases. In contrast with candidate gene association studies which rely on a good choice of the genomic region to study and unbiased publication of findings, GWAS provide a hypothesis free approach which has the potential to highlight the role of proteins and pathways previously unsuspected

to contribute to disease risk. Variants associated with asthma have implicated a number of genes/regions, including *IL1RI/IL18R1*, *HLA-DQB1*, *IL33*, *SMAD3*, *IL2RB* [5], *IL6R* [6] and specifically in childhood asthma, *ORMDL3/GSDMB* [5, 7] as well a reported association with *DENND1B* variants mentioned above [3]. A recent GWAS of BMI in almost 250 000 individuals identified 32 loci for BMI, none of which overlapped with the reported asthma GWAS loci with the possible exception of signals in the chromosome six major histocompatibility complex [4]. A more comprehensive assessment of overlapping genetic determinants is probably warranted given a previous estimate that 8% of the genetic component of obesity is shared with asthma [8].

Clinical translation of findings, or at least further insight into the pathways that cause asthma and obesity, might be realized if we can identify genetic mechanisms that are common to both disorders or genetic mechanisms which exert their effects in identifiable subgroups of individuals. Observational studies have suggested that obesity precedes asthma in children, but the evidence is far from clear-cut [1] and could be complicated if ascertainment of asthma were related to BMI. A study design called Mendelian randomisation [9] can help support or refute evidence from observational studies, but the method assumes rather more complete understanding of the pathways than is currently available. In this issue, Melen et al. focus on genetic associations with BMI in study participants with and without asthma. Given the possible temporal relationship between early obesity and subsequent childhood asthma, one could also usefully study genetic associations with asthma in individuals with and without obesity. In either case, a gene-environment interaction might be postulated to be driving the association within a particular subgroup.

The study of gene-environment interactions is very challenging [10, 11], and perhaps even more difficult to interpret when the 'environmental' factor studied is an intermediate phenotype such as BMI [12]. In particular,

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researchers studying gene-environment interactions, or studying genetic associations in subgroups (e.g. defined by environmental exposure), require studies with large sample sizes [11, 13], particularly if appropriate account is taken of multiple testing in genome-wide analyses.

With the study of hundreds of thousands of directly measured single nucleotide polymorphisms (SNPs) and imputation of genotypes at many more SNPs, GWAS generally employ very strict *P*-value thresholds for declaring genome-wide significant association [14]. The effect size of common variants tends to be modest for almost all traits – for example, most reported asthma GWAS risk variants show odds ratios in the region of 1.1 to 1.2. Therefore, to achieve adequate power to detect associations, GWAS have utilized very much larger sample sizes than were previously employed in candidate gene association studies and this has been shown to be a highly successful strategy for detecting the overall (marginal) effects of genetic variants without explicitly modelling interactions.

In contrast, few gene-environment studies to date have shown convincing, replicated associations. This may simply be due to the larger sample size required to study interactions. Melen et al. studied a discovery set of 2691 children with asthma and attempted replication in 2014 children with asthma. Overall, the association between rs4915551 and BMI in children with asthma did not replicate. In this particular instance, there was convincing evidence of heterogeneity of the effect of the

SNP across different populations that may explain why the signal could not be convincingly replicated when meta-analysing data from all populations. Unambiguous evidence would likely require even larger sample sizes. Indeed, if measurement errors (including misclassified asthma diagnoses) are taken account of, tens of thousands of cases may be required to have adequate power to detect gene-environment interactions [13].

The previously reported association between childhood asthma and variants in the chromosome 1q31 region including *DENND1B* [3] was not replicated by two other recent studies [6, 15] and was also not replicated by Melen et al. [2]. The finding of striking heterogeneity of effects offers a possible explanation for the divergent findings between studies and highlights that perhaps not all GWAS findings will prove to be equally straightforward to interpret. Gene-environment interactions may well explain heterogeneous genetic effects. The maturation of even larger genetic studies, including large biobanks, will provide unrivalled tools for understanding these effects.

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