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The promise and obstacles of asthma genetics research

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After two decades of major initiatives to define the genetic basis for asthma, it seems reasonable to reflect on what has (and has not!) been accomplished. In the current issue of *The Journal*, Marinho et al¹ confirm the presence of an important asthma risk locus on chromosome 17. Aspects of this study point out and often address many of the limitations and strengths of asthma genetics research and the obstacles to realizing the promises of this line of research, which we highlight in the following point-by-point discussion²:

1. Insufficient Power

The asthma genetics literature has been “polluted” with studies that were so manifestly underpowered as to dismiss any realistic likelihood regarding their utility and conclusions. A positive aspect of the current study is that it comprised 983 subjects. This problem can be appreciated by the power analysis performed here in that with 983 subjects and a gene with an estimated allele frequency of 45%, this study had a 99% power to detect an effect size of 2. Clearly then, published studies involving 20 to 30 or fewer subjects had no likelihood of identifying a true asthma linkage. And even this study is likely underpowered for identifying other asthma genes, because the effect size of “2” signifies an assumption that the relevant gene doubles the subject's chance of developing asthma. Dozens of genes are suspected of being involved in asthma risk, and each only provides a modest additional risk, so that to identify these genes, studies will have to involve many-fold more subjects (eg, 5–10,000). This study succeeded with its “modest” enrollment because they ultimately identified odds ratios of risk for their genetic markers that ranged from 1.6 to 2.1.

2. Cherry-picking

How could so many asthma genetics studies be published with group sizes much too small to be realistic? Examining too many genes, linking them to too many phenotypes, and failing to properly address multiple comparison statistical error results in some linkages always appearing to be positive. In retrospect, it becomes obvious why the literature is rampant with “asthma genes” that studies variously link to total immunoglobulin E, specific immunoglobulin E, airway hyperreactivity, lung function, whatever, because—if enough phenotyping is done—eventually something links. This study performed proper multiple testing corrections. When these studies are executed on sufficiently powered populations, the resultant *P* values are in the order of .000006, even after this correction (see Table 4 in Marinho et al) and not merely .05.

3. Population Stratification

Simply put, certain genes are overexpressed in local populations and, similarly, asthma is overexpressed in certain locations. When both these events occur in the same region, an apparent but false linkage of those genes to asthma will be reported. Replicating these studies across ethnically diverse populations is essential. One achievement of this study is that it confirms associations that have been previously reported in approximately 20 publications, while using a distinct population (see Table 1 in Marinho et al). While reducing enthusiasm for the originality of this work, this is one area where the “piling on” of studies is to be encouraged.

4. Asthma as a Syndrome

What we call “asthma” is a physiological phenomenon that represents the final common lung response to numerous insults. Consider such presentations as those with allergies and eosinophilia, no allergies but hypereosinophilia, or agranulocytosis.^{3,4} Each of these—and many others—almost certainly represents distinct diseases with distinct genetic profiles.

5. Incomplete Penetrance

Genetic studies have to deal with subjects who inherit the asthma “gene” of interest but who, in the absence of additional genetic and environmental risk factors, have not yet developed asthma.

6. Gene × Environment Interactions

Although little is known regarding all the environmental interactions driving asthma, one unambiguous insult is smoking. Smoking might define a unique asthma phenotype, but it also helps ensure that those with the relevant gene express the phenotype.⁵

7. Gene × Gene Interactions (epistasis)

Aside from environmental insults, it is equally likely that a given gene may not achieve full expression in the absence of complementary genes. It is easy to imagine that asthma requires the convergence of sets of genes driving disordered function of the lung with genes involved in driving development of atopy. Examples of synergy include interactions between a gene driving interleukin-4 overexpression^{6,7} and one driving interleukin-4 overresponsiveness.⁸

8. Functional Genomics

This study addressed single nucleotide polymorphisms (SNPs) scattered across several genes in Chr17q12-21. By definition “linkages” are associations with genes, not necessarily the actual genes. These studies work because to drive the statistical “hit” the SNP does not have to be the actual gene, but merely has to be in linkage disequilibrium with the actual gene. One of the more esoteric aspects of this study was their reporting of “haplotype blocks”—which simplistically means that within Chr17q12-21 there is, in fact, a lot of linkage disequilibrium. The next step is functional genomics; that is, proving that these SNPs actually mediate relevant biological function. None of the genes identified in this study were obvious candidate genes likely to drive asthma. Conversely, that is exactly why these genetic studies have to be done. *ORMDL3* is expressed on endoplasmic reticulum and regulates sphingolipid synthesis,⁹ suggesting it might have a role in lymphocyte trafficking. *GSDMB* has a role in stem cell proliferation.¹⁰ Many of these variants were located within the coding regions or in regions likely to influence promoter strength and therefore extent of expression of the gene.

In summary, this study primarily replicated previously reported associations between 17q12-21 polymorphisms and asthma. This is not trivial, because this confirmation in an unrelated population in a properly powered and statistically analyzed study categorically defines 17q12-21 as an important asthma susceptibility locus. One (or more!) of the genes in this locus is an asthma gene, and none would have been entertained as asthma genes in the absence of genetic association studies. Likely the impact of these variants is substantial, considering their high frequency in the population (42%–49.8%) and the 1.6- to 2.1-fold increased risk these variants provide. It is now imperative to take these studies to the next level and functionally define the actual gene(s) in this locus and, hopefully, find a useful pharmacologic target.

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