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Editorial

Joy of Ping-Pong: Genome-Wide and Phenome-Wide Association Studies

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▸ See the article "Phenotypic and Molecular Characterization of Risk Loci Associated With Asthma and Lung Function" in volume 12 on page 806.

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Genomic medicine gives hope for patient-specific therapies. Genome-wide association studies (GWASs) elucidate genetic markers that improve understanding of risks and causes for many diseases and may guide therapy on a patient-specific basis. They will take another approach to identify gene-disease associations. "Reverse GWAS" or phenome-wide association studies (PheWASs) determine which phenotypes are associated with a given genotype. The first PheWAS performed in 2010[1] has provided a systematic approach to analyze many phenotypes potentially associated with a specific genotype and an ability to identify pleiotropy. A recent availability of a large DNA biobank coupled to a de-identified copy of the electronic medical record enable us to integrate genomic data with various phenotypes. Like a ping-pong match, GWASs and PheWASs are complementary, with the ability to replicate and validate others' findings. Denny *et al.*[2] found that PheWASs replicated 210 of the 751 (28%) single-nucleotide polymorphism (SNP)-phenotype associations from the National Human Genome Research Institute's GWAS catalog, including 66% of those associations that were adequately powered to detect the association. They also identified 63 potentially novel SNP-disease associations, demonstrating pleiotropic effects of the variants.

In this issue of the *AAIR*, Karaca *et al.*[3] performed a PheWAS using 16 SNPs associated with asthma and pulmonary function in the previous GWASs. They used the UK Biobank for the initial PheWAS, Genotype-Tissue Expression (GTEx) for expression quantitative trait loci (eQTL) analysis and the International Study of Asthma and Allergies in Childhood Phase II data for validation. The PheWAS identified 206 phenotypic associations with respect to 16 variants. Interestingly, the asthma-related variants were associated with blood levels of immune cells (eosinophils, neutrophils, monocytes, and lymphocytes), and pulmonary function-related variants were associated with body fat-related phenotypes. The GTEx-based analysis showed that the variants tested affect the transcriptomic regulation of multiple surrounding genes across several tissues. As immune mechanisms are implicated in asthma pathogenesis, it is not surprising that asthma risk loci were strongly associated with blood levels of immune cells and, in particular, with eosinophils. However, the significant associations between pulmonary function-related variants and body fat-related phenotypes were of interest. The authors suggested that pulmonary function-related variants would be pleiotropic. Those variants would be related to altered metabolic processes, which led to increased body fat and pulmonary function eventually. This seems reasonable considering

that previous reports showing that accumulated adipose tissue affected pulmonary function in mechanical or immunological ways.[4,5]

It is well known that asthma and pulmonary dysfunction have multi-genetic traits. Karaca *et al.*[3] indicated that the 16 selected variants affected multiple gene expressions in eQTL analysis, which implies that single-risk loci might affect asthma or pulmonary dysfunction predisposition through multi-genetic mechanisms. In addition, the effect of variants on transcriptomic regulation was not tissue-specific, but shared across multiple tissues. This finding suggested that causal mechanisms related to genetic associations would happen simultaneously in multiple tissues.

The threshold for statistical significance is less well established for PheWASs. A Bonferroni correction, which is widely used in PheWASs, is extremely stringent because it assumes unlikely independence across all phenotypes, given that many phenotypes have close relations. In the study conducted by Karaca *et al.*,[3] a unique approach was utilized to exclude spurious associations. They randomly selected test variants matched to the 16 SNPs of interest based on the frequency of minor alleles, number of linkage disequilibrium proxies, distance to nearest gene, and gene density. They then did the same PheWAS and found that the empirical probability to observe that a phenome-wide association surviving multiple testing correction by chance was 0.2%.

This study provided a deep characterization of loci associated with asthma and pulmonary dysfunction using multiple sources. In the new era of big data, the use of PheWASs coupled to GWASs will have the potential to provide novel insights into the pathogenesis of asthma and allergic diseases.

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