Symposium 3: Future perspecitves in AR and CRS

Genomics in allergic rhinitis

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Allergic rhinitis (AR) is believed to be a complex disease which both genetic and environmental factors contribute to its pathogenesis and genetic factors determine the susceptibility of AR occurrence. Developing atopy to a particular allergen requires appropriate exposure and the subsequent development of a specific IgE antibody response in a genetically susceptible host.

Throughout the history of genetics of allergic diseases, the research strategy has gone through three stages, i.e. genome-wide linkage studies, candidate-gene association studies and genome wide association studies (GWASs). The year 2007 has witnessed a quantum leap in genotype and phenotype association analyses with the publication of the first GWASs for an asthma trait. The last decade has been marked by the publication of more than 20 GWASs of AR and the associated allergic phenotypes. Allergic diseases and traits have been shown to share a large number of genetic susceptibility loci, of which IL33/IL1RL1, IL-13-RAD50 and C11orf30/LRRC32 appear to be important for more than two allergic phenotypes. Correspondingly, the first and the only one GWAS till now regarding AR was employed in a Singapore Chinese Population and this study reported MRPL4 and BCAP were two novel candidate genes for atopy and AR. In addition, recently, a relatively large meta-analysis of GWASs among 4 large European adult cohorts identified HLA-DRB4, C11orf30/LRRC32 three loci reached genome-wide significance for either phenotype of AR and grass sensitization.

Although GWASs have provided valuable insights into the genetic architecture of allergic disease, scientists recognized increasingly that most variants identified so far conferred relatively small increments in risk, and explained only a small proportion of familial clustering, leading not uncovering the full profile of the genetic characteristics of the disease, i.e. 'missing' heritability. Many explanations for this missing heritability have been suggested. To begin with, the fact that GWAS is reliance on common haplotype

blocks and genotyping of common variants restricts its ability to detect rare risk alleles that might be contributing to the disease. Secondly, copy number variations which are segmentally duplicated sequences in the genome that contribute a sizeable effect on the variability of gene expression could not be identified with the GWAS approach. Besides, another potential mechanism is the existence of epigenetics which refers the heritable changes in gene expression that occur in the absence of changes to the DNA sequence itself and might be induced by environmental factors and transmitted through generations.

The challenge now is to identify robust susceptibility loci for allergy and then translate statistical significance from genetic and genomic studies to biological and clinical effect. Understanding the genetic discoveries in allergic disease will potentially lead to better molecular phenotyping, prognostication, prediction of treatment response, and insights into molecular pathways to develop more targeted therapies.