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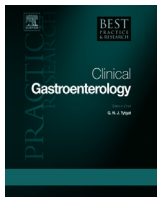

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The genetic basis of eosinophilic esophagitis

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A B S T R A C T

Eosinophilic esophagitis is characterized by destructive responses of the immune system to environmental allergens, including food, on the human esophagus. EoE is now reported as a major cause of upper gastrointestinal morbidity in children and adults and the incidence is reported to be on the increase.

It is known that EoE has a high degree of heritability, with a majority of the phenotypic variation believed to be genetic in origin as shown by genetic epidemiology studies of twins and families.

Prior to 2010, there were no known genetic risk factors for the disease. Three GWAS have since been published identifying 5 loci which influence risk for EoE in both children and adults. The information gained from GWAS has been of value in elucidating the pathways involved, such as IL4/STAT6, and more unexpected pathways such as epithelial apical transport and wound healing.

We will review the results of the EoE GWAS and the known associated genes, concluding with a discussion of some future directions for genetic studies in EoE.

Eosinophilic esophagitis (EoE) is a global health condition now reported on all continents. Reported incidence has risen dramatically over the past ten years [1,2] but varies widely by geographic region,

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with upper estimates at one per 1,000 in the US [4]. EoE is considered a food allergy–related disorder based on the high rate of food allergen sensitization and a higher rate of food anaphylaxis in cases compared with the general population [2,3].

Young Caucasian males are predominantly affected [4] and the rate of co-existing atopic disease (asthma, allergic rhinitis, IgE mediated food allergy) has been reported as high as 70%. Food allergy, in particular, appears to play a large role in pediatric EoE [2,3]. Experimental modeling in mice and humans has demonstrated a key role for innate and adaptive immunity and Th2-cell cytokines (especially *TSLP*, IL-5 and IL-13) in EoE pathogenesis [5–10]. Accumulating evidence suggests that genetics plays a large role in EoE susceptibility [11]. In one pediatric study, nearly 10% of parents of EoE patients had a history of esophageal strictures and ~8% had biopsy proven EoE [11]. Genetic epidemiology of twins and families has shown that eosinophilic esophagitis is highly heritable. Monozygotic twins exhibit high concordance for the trait, estimated at 40% [12,13]. The relative risk for developing EoE is hundreds of times greater compared to the general population for individuals with an affected monozygotic twin [13,14]. Prior to the GWAS era only a few loci had been implicated in EoE by candidate gene studies including eotaxin-3 (CCL26) [15] and filaggrin (FLG) [16].

Unlike candidate gene studies which are based on a prior hypothesis, genome-wide association studies (GWAS) are designed to interrogate the entire genome by tagging linkage disequilibrium blocks using hundreds of thousands of SNPs spread across the genome [17]. There are numerous advantages of GWAS approaches compared with candidate gene studies including: a) interrogation of the entire genome which allows for hypothesis-free testing of all genes compared with candidate gene approaches that rely on a highly subjective process of candidate selection b) dense coverage across genic regions which allow for a better assessment of association in relation to local genetic architecture compared to candidate gene studies that typically report on a few SNPs per gene c) genome-wide data can be used for quality control and estimation of population stratification d) GWAS allow for consistent replication of associations compared with candidate gene studies that frequently report on associations with different SNPs from the same gene e) well established statistical frameworks and benchmarks for statistical significance of discovery and replication signals [18]. The result of which has been the discovery of upwards of 1200 novel associations in over 200 complex and quantitative traits (http://www.genome.gov/gwastudies/) by GWAS that were previously intractable to candidate gene studies or linkage.

The first EoE GWAS published in 2010 included a modest 351 cases combined between the discovery and replication cohorts, yet the study resulted in the identification of multiple genome wide significant variants at a locus on chromosome 5q22 that contained two genes the thymic stromal lymphopoetin (*TSLP*) and *WDR36* [19]. To determine which of the two genes in the region drove the association the authors examined the expression patterns of the both genes in esophageal biopsies demonstrating statistically significant upregulation of *TSLP* expression in EoE cases as well as correlation of *TSLP* expression with the EoE associated variant genotype [19]. The initial expression data was highly suggestive of *TSLP* as the causal gene underlying the association and subsequent work has added to the evidence. The finding that individuals homozygous for the *TSLP* risk allele (AA) have increased *TSLP* expression in the esophageal epithelium compared to heterozygotes and those homozygous (GG) for protective alleles was replicated in an independent sample [20]. *TSLP* genotype has also been shown to correlate with increased basophil response [20] in EoE patients and *TSLP* inhibition prevents the development of EoE in a mouse model [9,20]. Finally, Sherrill et al. have identified a significant association between a *TSLP* receptor (*TSLP*-R) SNP and male EoE subjects [21]. *TSLP* is an IL-7-like cytokine that regulates host adaptive immune responses through dendritic cell and T-cell interactions and may be a promising target for therapeutic intervention.

Following the initial GWAS in 2010, two expanded GWAS were published in 2014 [22,23]. Both studies replicated the association of *TSLP* and reported association at a novel locus on chr2p23.1 that includes the *CAPN14* gene. The Sleiman et al. study also reported genome wide significance at three additional loci, *c11orf30-EMSY, STAT6* and *ANKRD27* [23].

Two of the genes, *c11orf30* and *STAT6*, have previously been associated with allergic/inflammatory disease while *CAPN14* and *ANKRD27* appear specific to EoE. As atopy is a common comorbidity in EoE, Sleiman et al., repeated the logistic regression, conditioning on atopy status to determine if the