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Immunology of the Ancestral Differences in Eosinophilic Esophagitis

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Eosinophilic Esophagitis (EoE) is an allergen driven disease characterized by eosinophilic inflammation in the esophagus[1]. Like other atopic disorders such as atopic dermatitis (AD), food allergy (FA), allergic rhinitis (AR), and asthma, EoE has complex etiology with genetic predisposition and environmental factors playing a major role in disease development[2]. The genetic predisposition has been suggested as an important factor by familial and twin studies. Additionally, numerous genetic risk loci have been now described linked to EoE risk confirming that inheritability is associated with genetic predisposition[3].

EoE has now been described in all 5 continents with similar clinical and molecular features, but EoE prevalence and incidence estimates vary across geographical areas[4]. The few studies available addressing EoE prevalence, give us estimates that tend to be on the same order of magnitude in Western Europe, North America and Australia with a range of 10-90 per 100,000 inhabitants (with a meta-analysis indicating a prevalence of 22 /100,000 in kids and 48 /10,000 in adults), but much lower in Japan and China (0.01-0.34 per 100,000)[4]. While EoE has also been described also in South American, Korea, Turkey, and the Middle East, there have been limited reports from sub- Saharan Africa or India[4,5]. This increased in prevalence in European American areas suggest a probable genetic phenotype, as Japan has similar access to care than Western Countries and still lower prevalence.

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Furthermore, a study of 7000 patients with EoE across the United States of America found that 89.3% were European American, 6.1% were African American, and 5.6% were Asian American giving additional evidence for genetic risk factors[6]. These percentages are different from what is found for other atopic diseases such as asthma and atopic dermatitis, where African Americans and people with Hispanic ancestry tend to have higher rates of disease compared to European Americans suggesting that EoE has a unique ancestral risk. In the United States, Western Europe, and Australia for example over 85% known EoE patients are European American and being European American is a major independent risk factor to develop EoE[1,3,4]. Several genetic risk loci have been associated with predisposition to EoE in cohorts of European ancestry with genetic polymorphisms near genes encoding *TSLP, Eotaxin 3, CAPN14, EMSY, DHTKD1, OGDHL, SPNK7, CLEC16A, DEXI, CIITI*, and *LOC283710/KLF13* (reviewed in [3]).

Several studies suggest EoE may be less prevalent in the Hispanic population[4]. In a United States Texas based Hospital serving a largely Hispanic population, a small retrospective study showed that 29 biopsies meeting criteria of EoE selected from 1700 biopsies from patients underwent upper endoscopy for appropriate clinical indications over the 8 years[7]. Esophageal biopsies were reviewed, and twenty-nine patients had esophageal biopsies that met pathologic criteria for EoE for a prevalence of 1.7% in the total population: 13/1350 (0.96%) biopsies from Hispanic patients, 13/179 (7.26%) of biopsies from patients of European ancestry, and 3/171 (1.75%) of biopsies from other races were positive for > 15 eos/hpf[7]. These data are very similar to those obtained in 2 other studies in Hispanic populations.

Regardless of ancestry or country of origin, EoE presents with similar symptoms that vary depending on the age of presentation. Older teenagers and adults have more typically dysphagia, which contrasts with presenting symptoms of children and young adolescents, who have less specific symptoms such as feeding disorder in infants and toddlers and vomiting, gastroesophageal reflux, and abdominal pain in older children[2]. Across ancestral groups, both children and adult patients are typically **males** with a history of allergic disease[2]. Males have 3:1 predominance to EoE indicating the strong genetic link.

Several studies focusing on specific population referring to large third level referral centers of have tried assessed the role of environmental factors in EoE etiology, none of which address differences across ancestries and ethnicities. In 127 neonates, born in one hospital Jensen, *et al.* [8] found a positive association between EoE and several early-life factors such as maternal fever, preterm labor, cesarean delivery, antibiotic and acid suppressant use in infancy in that particular population. The authors also observed an inverse association between having a furry pet in infancy and EoE. The same data have been shown independently by other groups in other atopic diseases. The environment-risk gene interaction has been examined in one study and found an association between breast-feeding and SNP rs6736278 in *CAPN14* and NICU admission and SNP rs17815905 at the LOC283710/KLF13 locus [8].

Conclusion:

To date, the limited epidemiologic study of EoE, which is bereft with methodological issues but nonetheless are the only such data for this field, have been performed on patients with European ancestry. Well controlled multi-ancestral epidemiological studies are lacking. More research is needed to explore these important hypotheses that have been generated by small initial studies. It is critical that we fully explore the molecular and epidemiological differences of EoE etiology across all ancestries across the world. If there are disparities in risk factors or response to therapies, we need to identify them and address them. If there are differences in the optimal treatment plans or disease presentation, we need to train gastroenterologists and allergist to be aware of these differences as they treat patients. Ultimately, we should aim to fully understand how molecular, clinical, and demographic factors contribute to the development of EoE so that we can provide our patients with therapeutic strategies that prevent and cure disease.

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References

1. Spergel JM, Dellon ES, Liacouras CA, et al. Summary of the updated international consensus diagnostic criteria for eosinophilic esophagitis: AGREE conference(). Ann Allergy Asthma Immunol 2018.
2. Cianferoni A, Spergel J. Eosinophilic Esophagitis: A Comprehensive Review. Clin Rev Allergy Immunol 2016;50:159–74. [PubMed: 26194940]
3. Kottyan LC, Rothenberg ME. Genetics of eosinophilic esophagitis. Mucosal Immunol 2017;10:580–8. [PubMed: 28224995]
4. Dellon ES, Hirano I. Epidemiology and Natural History of Eosinophilic Esophagitis. Gastroenterology 2018;154:319–32 e3. [PubMed: 28774845]
5. Baruah B, Kumar T, Das P, et al. Prevalence of eosinophilic esophagitis in patients with gastroesophageal reflux symptoms: A cross-sectional study from a tertiary care hospital in North India. Indian J Gastroenterol 2017;36:353–60. [PubMed: 29022245]
6. Mansoor E, Cooper GS. The 2010-2015 Prevalence of Eosinophilic Esophagitis in the USA: A Population-Based Study. Dig Dis Sci 2016;61:2928–34. [PubMed: 27250980]
7. Yu C, Sterling D, Albayati I, et al. The Prevalence of Biopsy-Proven Eosinophilic Esophagitis in Hispanics Undergoing Endoscopy Is Infrequent Compared to Caucasians: A Cross-Sectional Study. Dig Dis Sci 2017;62:3511–6. [PubMed: 29086329]
8. Jensen ET, Kuhl JT, Martin LJ, Langefeld CD, Dellon ES, Rothenberg ME. Early-life environmental exposures interact with genetic susceptibility variants in pediatric patients with eosinophilic esophagitis. J Allergy Clin Immunol 2018;141:632–7 e5. [PubMed: 29029802]