



# Making progress toward understanding the genetic architecture of asthma in the most affected US ethnic group

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**Asthma GWAS of Puerto Rican individuals finds strongest association within the 17q21 ORMDL3/GSDMB locus** <http://ow.ly/M23930ayVbG>

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Asthma is a common airway disease that results from complex interactions among genetic and environmental factors. In the USA, asthma disparities by race and ethnicity are a well-known problem [1]: prevalence is highest among Puerto Ricans (16.1%), followed by non-Hispanic blacks (11.2%), non-Hispanic whites (7.7%) and Mexicans (5.4%) [2]. These disparities extend to asthma morbidity and mortality, which are highest in Puerto Ricans and African Americans compared to members of other racial/ethnic groups in the USA [3, 4]. Previous studies suggest that inter-ethnic differences in asthma risk and severity are related to differences in genetic ancestry, reflected by racial/ethnic categories [5]; however, the study of genetics in minority groups who share the largest asthma burden has lagged, compared to the study of the genetics of asthma in subjects of European ancestry [6].

With the advent of genome-wide genotyping technologies in the mid 2000s, asthma association studies have adopted the unbiased genome-wide association study (GWAS) approach, with over 30 such studies published to date [7]. Although some of the initial GWAS were based on relatively small numbers of individuals, and identified associations that were not widely replicated, results from large multi-centre, multi-cohort GWAS have provided consistent results [7]. Among the most prominent published asthma GWAS are: 1) a GABRIEL consortium study based on 10365 European persons with physician-diagnosed asthma and 16110 European controls [8]; and 2) an EVE consortium study based on 3246 cases with asthma, 3385 non-asthmatic controls, 1702 asthma case-parent trios, and 355 family-based cases and 468 family-based controls, comprising European American, African American and African Caribbean, and Latino subjects [9]. These and other studies have identified loci (e.g. the 17q21 locus, *HLA-DQ*, *IL1RL1*, *IL18RL1*, *IL33*, *TSLP*, *SLC22A5*, *SMAD3* and *RORA*) that are consistently associated with asthma at strict statistical thresholds in various independent cohorts, leaving little doubt that the results are truly significant. Some of the loci identified are population-specific, such as *PYHIN1* single nucleotide polymorphism (SNP) associations, observed only in subjects of African descent.

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In this issue of the *European Respiratory Journal*, YAN *et al.* [10] present the first GWAS of asthma that focuses on Puerto Ricans, the group with the highest asthma prevalence, morbidity, and mortality in the USA [2]. The most significant association identified in this new study of 2144 Puerto Rican individuals with asthma and 2893 controls was within the 17q21 locus, the region that contains the most well known and highly replicated asthma association signal [11]. Specifically, 89 SNPs in this region were significant, based on a GWAS p-value threshold of  $5 \times 10^{-8}$ , of which rs907092 was the most significantly associated with asthma, with a p-value of  $1.2 \times 10^{-12}$ . Furthermore, according to conditional analyses, the SNP associations in this region were due to a single signal. Previous GWAS meta-analyses also found that the SNP rs907092 was significantly associated with asthma; among Europeans in the GABRIEL study it had a p-value of  $3.6 \times 10^{-17}$  [8], whereas among North American populations in the EVE study it had an overall p-value of  $3.2 \times 10^{-12}$ , and p-values of  $1.3 \times 10^{-6}$ ,  $1.7 \times 10^{-6}$  and 0.02 among European Americans, Latino Americans and African Americans, respectively [9]. In these previous studies, however, the top 17q21 locus associations were different: the top SNP reported by GABRIEL was rs2305480 (p-value of  $6.4 \times 10^{-23}$  for childhood asthma); the top SNP reported by EVE was rs11078927 (p-value of  $1.2 \times 10^{-14}$ ; European American p-value  $8.6 \times 10^{-7}$ , Latino American p-value  $3.1 \times 10^{-7}$ , and African American p-value  $1.2 \times 10^{-3}$ ). Although different top 17q21 SNPs have been reported, they represent the same signal, as rs2305480 and rs11078927 are in strong linkage disequilibrium ( $r^2=1$  for Europeans according to SNP Annotation and Proxy Search using CEU HapMap3 or 1000 Genome Project Phase I data). In addition, rs907092 is in strong linkage disequilibrium with the top EVE and GABRIEL SNPs, with  $r^2$  values of 0.84–0.85. Overall, these data suggest that there is a single 17q21 association signal among Europeans, Latino Americans and Puerto Ricans that is weakly observed among African Americans. YAN *et al.* [10] also replicated (p-value <0.05) the EVE associations of top *IL1RL1* and *TSLP* SNPs, and the top GABRIEL association of an *IL18R1* SNP.

In addition to looking at association results for single SNPs, YAN *et al.* [10] took advantage of the family-based design of some of their cohorts to compare the linkage disequilibrium pattern in the 17q21 region among different populations. They found that linkage disequilibrium between SNPs in this region was similar between Puerto Rican cohorts, but different between Puerto Ricans, when compared to Mexicans or white Europeans. This finding raises the question of whether inter-ethnic differences due to genetic ancestry in this region confer a differential risk of asthma in Puerto Ricans. The results of this current GWAS and family-based analysis suggest that this is not the case, as a single peak with SNPs in high linkage disequilibrium was observed among these populations. However, more detailed studies of linkage disequilibrium in this region in larger multi-ethnic cohorts with more detailed genotyping or sequencing data could shed more light on this question. Because Yorubans (YRI) from HapMap3 have a strikingly different linkage disequilibrium pattern in this region from Europeans (CEU), even among the top 17q21 SNPs reported in EVE and GABRIEL, and by YAN *et al.* [10] (e.g.  $r^2$  between rs2305480 and rs11078927 is 0.79;  $r^2$  between rs907092 and rs11078927 is 0.55;  $r^2$  between rs907092 and rs2305480 is 0.50), it will be important to include individuals of predominantly African ancestry in future studies that dissect associations in this region.

Whereas the statistical results for the association between the 17q21 locus and asthma leave little doubt that they are truly significant and specific to childhood asthma, the biological mechanisms by which variation at this locus leads to asthma have not been identified. Four genes, *IKZF3*, *GSDMB*, *ORMDL3* and *ZPBP2*, have been proposed as functional candidates, based on their proximity to the association signal, and expression quantitative trait loci (eQTL) studies, including the current study by YAN *et al.* [10] that reported that the asthma-associated SNPs are also associated with mRNA expression levels of these genes in a tissue-specific fashion [12–14]. Experimental studies that are more detailed support the theory that *ORMDL3* and *GSDMB* are genes that are both associated with asthma: overexpression of either *ORMDL3* or *GSDMB* in the bronchial epithelium in mice leads to increased airway remodelling and responsiveness [15–17]. Future studies are necessary to determine the precise mechanisms *via* which variants in this region modify the risk of asthma through these genes [15–17].

This genetic study by YAN *et al.* [10] is subject to limitations. Of the cohorts used in this meta-analysis, two (GALA I and GALA II) were also part of EVE, and thus, the results of this meta-analysis are not entirely independent of EVE. However, the novelty of this study is the fact that YAN *et al.* [10] focused only on Puerto Rican participants, whereas EVE considered Mexicans and Puerto Ricans as a single group of Latinos. Because asthma prevalence among the Puerto Rican Hispanic subgroup is remarkably higher than that among other Hispanic subgroups, such as Mexican Americans, studies that have analysed combined Hispanic groups could have missed genetic associations for asthma risk and severity. Secondly, the sample size of the study by YAN *et al.* [10] was relatively small for a GWAS, compared to current studies that often look at tens of thousands or more subjects. Despite this limitation, their cohorts remain impressive, as detailed information was gathered for over 4900 Puerto Ricans that required substantial investments in time, personnel, and funds to recruit a fairly under-represented population in genetic studies of asthma. One

reason for the difficulty in studying the genetics of Puerto Ricans is that they are an admixed population, with individuals of heterogeneous genetic ancestry from European, Native American and African populations that have mixed over the past 500 years, resulting in a complex genetic architecture [18]. Traditional case/control GWAS designs are ideally performed in ancestrally similar individuals, to maximise the chances that associations measured are related to disease and not to overall differences in genetic ancestry [19]. Thus, case/control cohorts of Puerto Ricans and other recently admixed ethnic groups, such as African Americans and other Hispanic subgroups, comprise individuals with remarkable differences in Native American, African, and European ancestries resulting in biases that are challenging to account for at the analytical stage. Most of the cohorts used in the study were parent-child trios, an appropriate design chosen specifically to decrease the effects of population stratification, as genetic diversity within families does not vary as much as that between unrelated individuals.

Despite some increased difficulty involved in gathering and analysing genetic data of admixed populations relative to those of a more homogeneous ancestral background, our efforts to understand the genetics of disease should focus on the individuals who are most affected. Whereas some have called for genetic studies to no longer use racial categories (because many racial terms are inadequate, with origins that are often political in nature, rather than biologically based) [20], there are also concerns that if racial/ethnic categories are ignored, then current minority groups will not be adequately included in research and clinical studies [6]. As statistical methods to perform gene association studies in admixed populations continue to improve [9, 21] and an expanded catalogue of variation in diverse populations grows (*via* efforts such as the 1000 Genomes Project and the Consortium on Asthma in African Ancestry Populations (CAAPA) [22, 23]), the need to group subjects into specific racial/ethnic categories for genetic studies will decrease. This is of great importance both to Puerto Ricans and other recently admixed minority groups, as well as the growing number of individuals who are of mixed racial/ethnic backgrounds and are often not included in genetic studies. These groups all represent a growing segment of the US population, the size of which is expected to surpass that of white non-Hispanics by 2060 [24].

Another limitation of the study by YAN *et al.* [10] is one shared by most GWAS: there might have been environmental differences among participants that were not appropriately accounted for. It is difficult to separate health factors that are heritable from those that are socioeconomic and environmental in nature [25]. Whereas genetic ancestry is a risk factor that contributes to asthma disparities, the role of factors that arise from social, economic and environmental disadvantages among minority groups in the USA cannot be ignored. Asthma studies will most effectively serve to reduce disparities if they are able to account for the role of genetics within the context of environmental, stress-related, and healthcare access factors that disproportionately affect some minority groups and are associated with low-income status. Ongoing large-scale whole-genome sequencing projects, such as the National Heart, Lung and Blood Institute Trans-Omics for Precision Medicine (TOPMed) programme, have been very carefully designed to include diverse populations, including those who are most affected by specific diseases. In doing so, these genetics studies would facilitate the development of precision medicine approaches for the treatment of asthma and other complex diseases that would benefit all affected individuals.

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