



Letters

Genetic variation and the risk of asthma: does it drive the differences in asthma prevalence among ethnic groups in North America?

Asthma is a complex disease and possibly more than one disease. In North America, asthma prevalence differs among the white population (7.8%; 95% confidence interval [CI], 7.5%–8.1%), the black population (9.5%; 95% CI, 9.0%–10.1%), and the Latino population (14.2%; 95% CI, 12.5%–16.2%).¹ The underlying factors driving the differences in prevalence are yet to be determined.

Population attributable fractions (PAFs) or risks are used in epidemiology to estimate the proportion of risk in a population that can be attributed to a single risk factor or to a group of risk factors that are considered simultaneously.² In the latter case, they are often called summary attributable risks.² PAFs combine how strongly a risk factor is associated with a disease with the distribution of the risk factor within a population. The prevalence of a disease in a population depends on how common a risk factor is, as well as the susceptibility of a population to the risk factor. Hence, by comparing PAFs for the same risk factors in different populations, we can estimate how much a single risk factor or many risk factors contribute to the variation in the disease prevalence among populations.

It has been estimated that 35% to 80% of the current variation in the risk of asthma is attributable to genetic variation.^{3,4} In North America, asthma prevalence has increased during the last decades and differs considerably across North American states and poverty levels.⁵ In fact, when asthma prevalence is examined within poverty levels, the difference between white and black North Americans disappears and the prevalence in Latinos, although still higher than in white or black North Americans, decreases with decreasing poverty.¹ Clearly, the variation is not explained by genetics alone.

Torgerson et al⁶ presented data from a genomewide association study in ethnically diverse North American populations. What is striking about the results is the similarity in the risk of asthma associated with certain single-nucleotide polymorphisms (SNPs) (almost all 95% CIs of odds ratios among the 3 groups overlap) and the moderate variation in risk allele frequencies among the different ethnic groups (Fig 1). We calculated the PAFs for each SNP and ethnicity as $(OR - 1/OR) \times \text{allele frequencies in cases}$ (Fig 1)² and derived their CIs using a substitution method described by Greenland.⁷ We found that the number of asthma cases attributable to each SNP is different for the 3 ethnic groups. As such, when each SNP is considered separately, SNPs could explain different levels of asthma prevalence among different ethnicities. In each population, however, most CIs overlap, and few SNPs explain more than 20% of all asthma cases. Also, SNPs with high PAFs are almost equally frequent in all 3 populations. This finding suggests that it is unlikely

that genetic variation explains much of the current difference in the asthma prevalence among different ethnicities. The bulk of variation is likely to be due to environmental factors.

Assuming that all SNPs in this study are independent risk factors for asthma and not correlated, we calculated the summary attributable risk for all SNPs combined.⁸ The summary attributable risk is 68.5% for Europeans, 70.7% for African/Caribbean Americans, and 70.4% for Latinos. Although our assumption of independence is likely to overestimate the summary attributable risk, this finding confirms that the overall risk of asthma attributable to the genetic variations studied here is similar in the 3 ethnic groups. Again, if most of the variation in asthma prevalence among these ethnicities were explained by the genetic variation studied, one would have expected to see larger differences in the summary attributable risks.

Asthma is a heterogeneous disease, and prevalence can differ considerably even within subpopulations of the same ethnicity.⁹ It is likely that this heterogeneity is caused by complex interaction of genetic and environmental factors. The findings by Torgerson et al show that genetic variations are responsible for different risk patterns in different populations. Nevertheless, our findings suggest that genetic variation alone cannot explain the large differences in asthma prevalence among different North American ethnicities. This finding emphasizes the role of environmental factors in driving the differences in asthma prevalence among ethnic groups.

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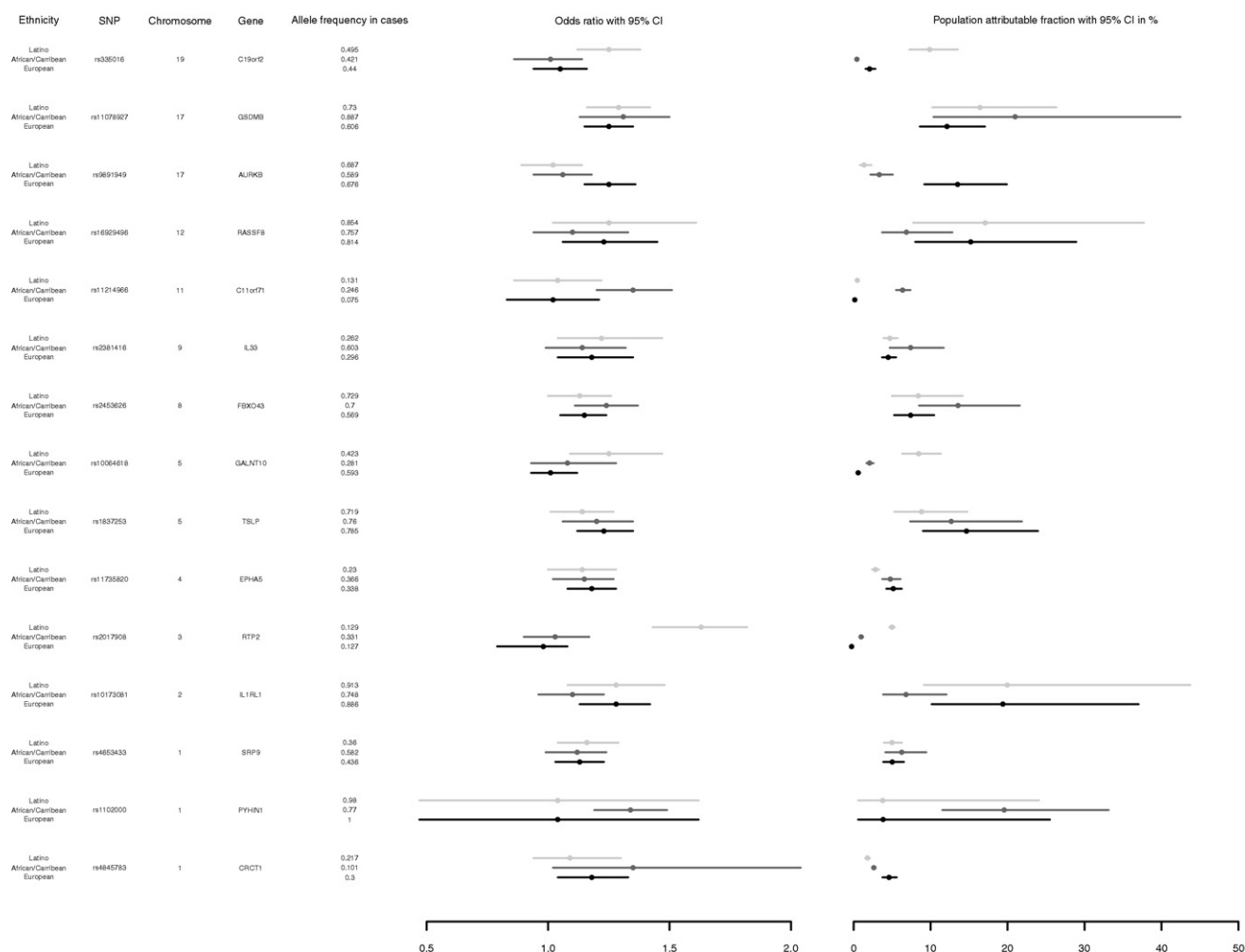


Figure 1. Odds ratios with 95% confidence intervals (CIs) and allele frequencies in cases and corresponding population attributable fractions for the most significant single-nucleotide polymorphisms (SNPs) identified by Torgerson et al.⁶

Anaphylactic reaction to hydroxycobalamin with tolerance to cyanocobalamin

Vitamin B₁₂ (cobalamin) is widely used and generally well tolerated. Two compounds, which are used as intramuscular injections to treat vitamin B₁₂ deficiency, are cyanocobalamin, an artifact formed as a result of use of activated charcoal (which contains cyanide) during purification, and hydroxycobalamin, in which the hydroxyl group replaces the cyano group. Oral B₁₂ supplements in large doses (0.1–2 mg) can also be effective.

Immediate allergic reactions to vitamin B₁₂ are rarely described and may consist of urticaria, angioedema, wheezing, and arterial hypotension.^{1–7} In some reported cases, the patient was allergic to hydroxycobalamin; in other cases, the patient was allergic to cyanocobalamin; and in some cases, the patient was allergic to both compounds.^{1–4,6} The results of skin tests (prick and intradermal) with vitamin B₁₂ were often positive in these cases, suggesting probable IgE-mediated hypersensitivity.^{1,3,6,7} An allergic reaction to benzyl alcohol, which is used as a preservative, is also possible.⁵ Because treatment with vitamin B₁₂ is usually unavoidable and lifelong, in cases of hypersensitivity desensitization with vitamin

B₁₂ is sometimes performed.^{6,7} In some cases, oral or intranasal vitamin B₁₂ is tolerated, although urticaria after taking oral preparations has also been reported.⁴

We present the case of a 37-year-old male patient with multiple sclerosis and a vitamin B₁₂ deficiency who 17 years ago (in 1993) exhibited urticaria approximately 1 hour after receiving intramuscular hydroxycobalamin. Therapy with hydroxycobalamin was at first tolerated for 5 doses before any reaction occurred. In 2010, a neurologist decided to start therapy with vitamin B₁₂ again. However, because the patient's history revealed an aforementioned allergic reaction to vitamin B₁₂, the patient was referred to an allergist. Skin tests (prick and intradermal, 0.01 mg/mL) and a provocation test (Table) were performed with hydroxycobalamin in March 2010 and all the results were negative, so therapy with hydroxycobalamin was started. However, 1 hour after the eighth intramuscular injection of the vitamin, urticaria developed, and the patient was referred again to an allergist in May 2010. This time, the result of the prick test with hydroxycobalamin was negative, and the intradermal test with a dilution of 1:100 (0.01 mg/mL) induced a 5-mm diameter