RESEARCH LETTERS

Population Differences in Genetic Risk for Age-Related Macular Degeneration and Implications for Genetic Testing

The personal genetics revolution has promised patients an account of their individual risks of common, complex diseases based on their DNA sequence. Although under increased scrutiny from the US Food and Drug Administration, several direct-to-consumer genetic testing companies offer such services, and conflicting results for the same disease in the same individual are commonly reported. Even for an unusual case like age-related macular degeneration (AMD) for which a small number of loci with strong effects has consistently been replicated across studies, it is extremely difficult to predict who will or will not develop disease. Furthermore, most genetic association studies have been conducted in European American individuals, and because the frequency of genetic polymorphisms varies across race-ethnicities, the predictive value of any genetic algorithm developed in one population may not translate to another. We have seen an extreme example of this for the ARMS2 (GenBank BC066349) AMD susceptibility locus.

The nonsynonymous coding variant A69S within ARMS2 is one of the strongest genetic risk factors for AMD (in European American individuals: odds ratio [OR] = 2.2 in heterozygotes; OR = 7.1 in homozygotes). This variant (or others in strong linkage disequilibrium with it) has been used in predictive algorithms published in the scientific literature, marketed by direct-to-consumer companies, and used in the Macula Risk test available by physician order.

Methods. As part of the Population Architecture Using Genomics and Epidemiology Study, we characterized ARMS2 A69S in the National Health and Nutrition Examination Survey, a cross-sectional survey of non-Hispanic white individuals, non-Hispanic black individuals, and Mexican American individuals. We assessed AMD according to the Wisconsin Age-Related Maculopathy Grading System using fundus photographs of 1 randomly selected eye in participants aged 60 years and older in the Third National Health and Nutrition Examination Survey. Both early AMD cases (large, soft drusen, pigmentary abnormalities, degeneration of the retinal pigment epithelium) and advanced AMD cases (geographic atrophy, choroidal neovascularization) were included.

Results. The T allele of the ARMS2 variant, which changes the amino acid residue from alanine to serine, was in Hardy-Weinberg equilibrium in all 3 race-ethnicities and of similar frequency across groups (0.22-0.25). As expected, the T allele was associated with AMD in all groups in models adjusted for age, sex, smoking status, and CFH Y402H genotype (P = 0.01 in non-Hispanic white individuals; P = 0.03 in Mexican American individuals; P = 0.05 in non-Hispanic black individuals). However, the direction of the effect was reversed in non-Hispanic black individuals (OR = 0.43) compared with non-Hispanic white individuals (OR = 2.10) and Mexican American individuals (OR = 2.45). In contrast to non-Hispanic white and Mexican American individuals, the T-allele frequency was approximately 13% lower in non-Hispanic black patients compared with non-Hispanic black control subjects.

Comment. There are several possible explanations for our findings. The ARMS2 A69S variant may not be a functional variant, and although it tags a true risk allele in non-Hispanic white and Mexican American individuals, it is not highly correlated with the unknown functional variant(s) in non-Hispanic black individuals. Alternatively, ARMS2 A69S may affect disease risk differently in different race-ethnicities owing to interactions with other genetic or environmental risk factors that vary between the populations. Lastly, other variants in the region such as the complex insertion/deletion in the untranslated region of ARMS2, the nonsense R38X variant, or a promoter polymorphism in the adjacent HTRA1 gene may also affect susceptibility.

Regardless of the reason, if this inverse association in non-Hispanic black individuals is confirmed, genetic tests that naively incorporate ARMS2 A69S without considering ancestry will consistently give incorrect results to non-Hispanic black individuals. Falsely inflated risk estimates may lead to unnecessary follow-up care, increasing both cost and anxiety for these patients, while falsely decreased estimates may decrease vigilance in monitor-

Table. Association of ARMS2 A69S With Age-Related Macular Degeneration in 3 Race-Ethnicities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Hispanic White (n = 2631)</th>
<th>Mexican American (n = 2073)</th>
<th>Non-Hispanic Black (n = 2108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMD cases</td>
<td>190</td>
<td>47</td>
<td>30</td>
</tr>
<tr>
<td>Controls</td>
<td>664</td>
<td>270</td>
<td>209</td>
</tr>
<tr>
<td>MAF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.22</td>
<td>0.25</td>
<td>0.24</td>
</tr>
<tr>
<td>Cases</td>
<td>0.30</td>
<td>0.35</td>
<td>0.13</td>
</tr>
<tr>
<td>Controls</td>
<td>0.19</td>
<td>0.25</td>
<td>0.26</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>1.91 (1.36-2.67)</td>
<td>1.88 (0.89-3.99)</td>
<td>0.41 (0.21-0.83)</td>
</tr>
<tr>
<td>P value</td>
<td>0.01</td>
<td>0.10</td>
<td>0.2</td>
</tr>
<tr>
<td>Adjusted a OR (95% CI)</td>
<td>2.10 (1.43-3.08)</td>
<td>2.45 (1.09-5.51)</td>
<td>0.43 (0.18-1.01)</td>
</tr>
<tr>
<td>P value</td>
<td>.01</td>
<td>.03</td>
<td>.05</td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; MAF, minor allele frequency; OR, odds ratio.

a Adjusted for age, sex, smoking, and CFH Y402H genotype.
ing eye health. Furthermore, the relationship between AMD and this variant in other ethnic groups, and thus the possibility for systemic errors in other groups, remains largely unexplored.

As our results highlight, predictive genetic testing for complex diseases faces many challenges. Until we fully understand how a particular genetic variant acts on disease susceptibility, great care must be taken when translating genetic tests from one race-ethnicity to another.

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Financial Disclosure: Drs Spencer and Haines are listed as inventors on patent PCT/US09/034882, “Methods and Compositions for Diagnosis of Age-Related Macular Degeneration,” which covers rights to a particular variant that is used in the calculation of risk in the Macula Risk test and is licensed by ArcticDx Inc, the makers of Macula Risk.

Funding/Support: This work was supported by grant U01HG004798 from the National Institutes of Health (Dr Crawford).

Role of the Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.


β-Blockers and Racial Variation in the Severity of Retinopathy of Prematurity

In the Early Treatment for Retinopathy of Prematurity Study, the incidence of retinopathy of prematurity (ROP) was the same among African American and non–African American infants; however, once ROP was observed, the incidence of progression to severe (prethreshold-old) ROP occurred more commonly among non–African American infants. Herein, we expand on these findings and present a possible cause and research approach focused on prevention of some cases of severe ROP.

Methods. Infants weighing less than 1251 g were logged at each participating center. These infants were followed up for the development of ROP and its progression in severity by study-certified ophthalmologists. We report the incidence of progression from the onset of ROP to type 1 ROP in at least 1 eye by birth weight and race. Type 1 is defined as zone I ROP at any stage with plus disease, as zone I stage 3 ROP, or as zone II stage 2 or 3 ROP with plus disease.

Results. The Table shows the percentage of infants by birth weight (<750, 750-999, and 1000 g) who had any ROP and the percentage who developed type 1 disease. The estimated incidences of ROP for both African American and non–African American infants weighing less than 1251 g at birth were essentially the same, 68%. However, the proportions of consented infants with ROP who ultimately developed type 1 ROP differed significantly. Non–African American infants had a much higher incidence of type 1 ROP in all weight categories and overall compared with African American infants (overall, 20.9% vs 8.6%, respectively; P<.001).

Comment. In this large study of infants weighing less than 1251 g at birth, a striking reduction in type 1 ROP is seen in African American infants. A similar finding for prethreshold ROP has also been reported in the Cryotherapy for Retinopathy of Prematurity Study. One mechanism to explain some of the observed racial differences in ROP invokes β-blocker receptor polymorphisms, which exist in many African American people. The effect of such polymorphisms renders the person “β-blocked.” If this β-blockade state were protective for ROP, then it could be a reason for the relative immunity to severe disease seen in many African American infants. More importantly, it would suggest that treatment with a β-blocker for infants devoid of β-adrenergic receptor polymorphisms could be beneficial.

This polymorphism theory is supported by recent reports indicating an association of cutaneous hemangiomas with ROP and a possible common pathogenesis. Cutaneous hemangiomas show a dramatic reduction with treatment using systemic β-blockers. Cutaneous hemangiomas are far more common in white infants and are very uncommon in African American infants, again suggesting that β-blocker receptor polymorphisms could influence angiogenesis and prevent hemangiomas. β-Adrenergic receptors exist on retinal endothelial cells. However, the exact mechanisms or effects of β-adrenergic receptor blockers on blood vessel growth have not been elucidated.

Prevention is the next frontier in ROP research. It is highly plausible that β-blockers could be effective in preventing ROP. Pharmacokinetic studies indicate that topical betaxolol hydrochloride shows good ocular penetration and reaches the posterior aspect of the eye in good concentrations. By studying the effects of topical betaxolol in infants with birth weight less than 1000 g, we will...