
Response

Genetic admixture in sickle cell disease

Genetic studies require careful thought about ancestry in the study design and analysis to avoid population stratification bias and to maximize the power of finding novel variants. If both the genetic marker and the phenotype vary with respect to ancestry, then a spurious association will occur between the genetic marker and phenotype if one does not adjust properly for ancestry. In this issue of Blood, Silva et al examine the level of admixture in a cohort of Brazilian sickle cell patients and find that patients with sickle cell disease have a wide range of African admixture (15%-85%). They correctly acknowledge that one must appropriately adjust for admixture to avoid false positive findings and that this population may be useful for admixture mapping. However, admixture mapping is only useful if the phenotype of interest also varies with admixture and further research is required to establish this relation in this population. In a cohort of African Americans with sickle cell disease we did not find a significant association between admixture (measured by the first principal component from a principal component analysis) and fetal hemoglobin. However, one should note that the African Americans in this study on average did not have high levels of Caucasian admixture. Admixture mapping has been successfully used to find novel genetic variants and regions for other phenotypes that were related to admixture such as white cell counts and prostate cancer. Furthermore, examining ancestry in genetic studies of sickle cell disease could lead to novel loci that are either more prevalent or specific to certain ethnic groups. For example, sickle cell patients from the Southwestern Province of Saudi Arabia have fetal hemoglobin (HbF) levels twice as high as African Americans despite having similar HBB haplotypes. Furthermore, sickle cell patients from the Eastern Province have even higher levels of HbF (mean [SD] 30.4 ± 6.9). These findings suggest that there are HbF-associated variants that are more prevalent or specific to the Saudi population and that leveraging on ancestry in the genetic analysis can help identify novel variants.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References


To the editor:

Prothrombin 20210G>A genotype and C-reactive protein level

Thrombin is central not only in procoagulatory processes like fibrinogen or platelet activation but also in other systems that are related to inflammation control. Recently, Flick et al characterized inflammatory responses of transgenic prothrombin mutant (F2W1E) mice in a collagen-induced arthritis (CIA) model. Mice carrying the F2W1E transgene that has dramatically reduced procoagulatory effects on fibrinogen and protease-activated receptor 1 exhibited a significantly attenuated inflammatory joint disease in CIA. Prothrombin 20210G>A (F20210G>A) is a gain-of-function variant resulting in increased prothrombin expression and elevated

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of Flick et al.2 We hypothesized that F2 20210G is involved in inflammatory processes and that (pro)thrombin 20210A variant exhibited significantly more frequently CRP elevations in carriers of F2 20210A (0.75 mg/L [0.63-0.87]) than in F2 20210GG wild-type individuals (0.54 mg/L [0.52-0.57]; Mann-Whitney U test, P < .0001, P adj < .05).

The F2 20210G>A genotype is known to influence prothrombin expression.3 In our study population prothrombin levels (mean prothrombin activity [95% CI]) were assessed in 122 patients and were significantly increased in F2 20210A carriers compared with F2 20210GG wild-types F2 20210GG, 112% [109-115], F2 20210A, 138% [111-166], t test, P = .0005). Thus, our finding that the gain-of-function variant F2 20210A is associated with increased CRP levels further corroborates the assumption of Flick et al that (pro)thrombin is positively involved in inflammatory processes and that targeting (pro)thrombin activity could have the potential to modulate inflammatory disease processes.2

Table 1. Association of F2 20210G>A genotype with CRP levels

<table>
<thead>
<tr>
<th>CRP</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI (P)</td>
<td>OR</td>
</tr>
<tr>
<td>≥5 mg/L</td>
<td>2.04</td>
<td>1.44-2.89 (&lt;.0001)</td>
</tr>
<tr>
<td>≥10 mg/L</td>
<td>2.99</td>
<td>1.98-4.89 (&lt;10−5)</td>
</tr>
<tr>
<td>≥15 mg/L</td>
<td>2.64</td>
<td>1.51-4.82 (&lt;0.001)</td>
</tr>
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</table>

Analyses based on 565 patients and 2258 observations. Multivariate analyses were adjusted for weeks of gestation, age and ethnicity. F2 20210A indicates carriage of prothrombin 20210A variant; F2 20210GG, prothrombin 20210GG wild-type; OR, odds ratio; and CI, confidence interval. *95% CI and P value after adjustment for nonindependent observations within clusters.

References
Prothrombin 20210G>A genotype and C-reactive protein level

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