Higher Prevalence of Risk Alleles for Hyperuricemia Parallels Elevated Incidence of Gout and Growing Risk for Cardiovascular Diseases in a Hmong Population

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Introduction

- Hyperuricemia (HU), (having a Serum Uric Acid [SUA] >6 mg/dL) is a metabolic disorder associated with cardiovascular diseases and gout, and it can be exacerbated by medications and diet (Fig. 1).2
- The Hmong, a unique Asian population >60,000 in MN, have a 2-fold increased risk of gout compared to non-Hmong.3
- 35% of renal stones in Hmong were composed of pure uric acid vs. 2% in non-Hmong.4
- Studies of the genetic bases of HU have identified racial differences in the prevalence of gene variants associated with elevated SUA.5,6

Central Research Question: Does the prevalence of variant alleles associated with elevated SUA differ between Hmong and non-Hmong?

AIM 1: to ascertain risk allele frequencies of 7 Single Nucleotide Polymorphisms (SNPs) within 4 key genes (TABLE 1) associated with SUA homeostasis (Fig. 2).

AIM 2: to compare risk allele frequencies of those SNPs within Hmong subjects with HU versus normal SUA.

Significance: Knowledge of genetic basis for susceptibility to HU could serve as a basis for guiding a clinician’s choice of drug therapy and/or intensive dietary counseling to mitigate this genetic based enhanced risk for HU.

Methods

Salivary DNA of 236 self-identified Hmong, was genotyped by Tagman or Sequenom iPLEX Gold method using Bruker Autoflex II MALDI/TOF mass spectrometer. Frequencies of risk allele associated with elevated SUA in Hmong were compared to (1) Caucasian (CEU) and (2) Han-Chinese (CHB) for four genes documented to be associated with HU using Hap-Map data7. HU vs. genotype was also evaluated within the Hmong using Chi- squared test or Fisher’s exact test when appropriate.

TABLE 1 (Protein Chr Function)

<table>
<thead>
<tr>
<th>Gene (SNP)</th>
<th>Alleles</th>
<th>Hmong (Mean ± SD Min Max)</th>
<th>Han-Chinese (Mean ± SD Min Max)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC2A12</td>
<td>C/T</td>
<td>297 (0.648) 161 (0.352) 204 (0.745) 70 (0.255)</td>
<td>0.0068</td>
<td>62 (0.727) 164 (0.73) 0.0001</td>
</tr>
<tr>
<td>ABCG2</td>
<td>C/T</td>
<td>293 (0.637) 167 (0.366) 194 (0.708) 80 (0.292)</td>
<td>0.059</td>
<td>201 (0.79) 105 (0.11) 0.0001</td>
</tr>
<tr>
<td>PDZK1</td>
<td>C/T</td>
<td>307 (0.673) 149 (0.327) 220 (0.803) 54 (0.197)</td>
<td>0.001</td>
<td>122 (0.54) 104 (0.46) 0.0001</td>
</tr>
</tbody>
</table>

Results

- Mean (±SD) age of participants was 30.2 (15.4), and > 61% either overweight or obese with mean (±SD) SUA 6.3 (1.7) mg/dL (TABLE 2).

- All selected SNPs were in Hardy Weinberg (HW) equilibrium.

- G7 SNPs showed a statistical significance difference in risk allele frequencies vs. Caucasian (CEU) Hap-Map data (TABLE 3).

- G7 SNPs showed a statistical significance difference in risk allele frequencies vs. Han-Chinese (CHB) Hap-Map data (TABLE 3).

- SNP by SNP analysis failed to show association with SUA levels (representative example, see Fig. 4).

Conclusions

- Risk allele frequencies of selected SNPs are not independent of race.

- Significant differences in risk allele frequencies between the Hmong and non-Hmong may partly explain the genetic basis of high prevalence of gout in the Hmong.

- Risk alleles frequencies in Hmong vs. non-Hmong were consistent with the higher prevalence of gout.

- Our sample size precludes a robust assessment of a significant association between genotype and SUA.

Clinical Translation

Our findings contribute to the validation of genetic based biomarkers capable of predicting an individual’s risk for developing HU and/or gout. They may also explain the variability in response to urine lowering drugs thereby optimizing an impact on patient care by:

- Identifying individuals with a genetic predisposition to developing HU and gout

- Optimizing drug selection for patients with known CVD and/or at risk for HU or gout

- Continuing to decrease the economic and social burden of gout

- Addressing the health disparity of gout within the Hmong (or other populations at risk)

Future Directions

Prospective assessment of a larger Hmong cohort is needed to quantify the impact of different genotypes of UA transporters on baseline SUA and differential effectiveness of drugs that act via these same transporters. Prospective assessment of the impact of targeted dietary interventions or drug therapy reviews for genotypically “at risk” populations.

Disclosure

The authors of this paper have declared no conflict of interests

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References


Fig. 1

Fig. 2

Fig. 3

Fig. 4