SNP Communication

Ethnic Differences in ATP-binding Cassette Transporter, Sub-family G, Member 2 (ABCG2/BCRP): Genotype Combinations and Estimated Functions

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Summary: ATP-binding cassette transporter, sub-family G, member 2 (ABCG2/BCRP) is a xenobiotic transporter and also regulates serum uric acid levels as a urate transporter. We have shown that the severity of ABCG2 dysfunction can be estimated by simple genotyping of two dysfunctional variants, Q126X (rs72552713) and Q141K (rs2231142). This genotyping method is widely accepted for the risk analysis of hyperuricemia/gout, but there is no report on ethnic differences in ABCG2 dysfunctions. Here, we estimated ABCG2 dysfunctions by its genotype combination (Q126X and Q141K) and compared them in three different ethnic groups (500 Japanese, 200 Caucasians and 100 African-Americans). The minor allele frequencies of Q126X and Q141K in Japanese (0.025 and 0.275, respectively) were significantly higher than those in Caucasians (0.005 and 0.085, respectively) and African-Americans (0 and 0.090, respectively). Additionally, the rates of mild, moderate and severe ABCG2 dysfunctions in Japanese (35.4%, 12.4% and 1.6%, respectively) were higher than those in Caucasians (14.0%, 2.5% and 0%, respectively) and African-Americans (14.0%, 2.0% and 0%, respectively). Because ABCG2 dysfunctional diplotypes were commonly observed in both Caucasians (16.5%) and African-Americans (16.0%), the genotyping of the two ABCG2 dysfunctional variants is useful for evaluating individual differences in the ABCG2 dysfunction which affect the pharmacokinetics of substrate drugs and hyperuricemia risk in all three ethnic groups.

Keywords: ABC transporters; urate excretion; gouty arthritis; single nucleotide polymorphism; nonsynonymous mutation

ATP-binding cassette (ABC) transporter, sub-family G, member 2 (ABCG2, also known as BCRP) is a xenobiotic transporter. Previous clinical studies on ABCG2 polymorphisms have shown that they affect the pharmacokinetics of important clinical drugs.
such as gefinitin\(^1\) and rosuvastatin,\(^2\) ABCG2 also regulates serum uric acid (SUA) levels as a urate transporter by mediating urate excretion.\(^3,4\) Moreover, several genetic analyses in humans and animal model studies have demonstrated that ABCG2 dysfunctions play a key role in the pathogenesis of hyperuricemia,\(^5,7\) which increases the risk of gouty arthritis and could lead to renal failure,\(^6\) cardiovascular diseases,\(^7\) cerebrovascular diseases\(^10\) or hypertension.\(^11,12\) We have shown that the severity of ABCG2 dysfunction can be estimated by genotyping only two dysfunctional variants, Q126X (rs72552713) and Q141K (rs2231142).\(^3\) These two variants are commonly observed in Japanese populations;\(^13\) thus, ABCG2 dysfunctions due to these variants are also common in Japanese populations.\(^3\) However, there have been no reports comparing the distribution of ABCG2 dysfunction estimated from its genotype combinations in different ethnic populations. Thus, in this study, we investigated ethnic differences in ABCG2 dysfunction estimated by genotype combinations among Japanese, Caucasian and African-American population groups.

This study was approved by each institutional ethical committee, and all procedures involved in it were performed in accordance with the Declaration of Helsinki. After obtaining written informed consent, DNA samples of 500 Japanese individuals were collected from the Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study).\(^14\) DNA samples of the other population groups were obtained from the racially-defined Human Variation Panels available from the Coriell Institute Cell Repository (Camden, NJ). Samples were from 200 Caucasians (HD200CAU) and 100 African-Americans (HD100AA).

Genomic DNA of Japanese samples was extracted from whole peripheral blood cells.\(^15\) Genotyping of Q126X and Q141K was performed using TaqMan methode (Life Technologies Corporation).\(^17\) The association analyses were performed using a Fisher's exact test. For all calculations in the statistical analysis, the software R (version 3.0.3) (http://www.r-project.org/) and SPSS v.22.0J (IBM Japan Inc., Tokyo, Japan) were used.

The genotyping results of ABCG2 for 500 Japanese, 200 Caucasians and 100 African-Americans are shown in Supplementary Tables 1 and 2. These two single nucleotide polymorphisms (SNPs) were found to be in Hardy-Weinberg equilibrium in all three population groups (p > 0.05). As compared with the Caucasian and African-American population groups, the genotype distribution of Q126X (C/C, C/T or T/T) in the Japanese population group was significantly different (p = 0.015 and 0.013, respectively; Supplementary Table 1). Similarly, genotype distribution of Q141K (C/C, C/A or A/A) in the Japanese population group was also significantly different from the two other groups (p = 1.74 × 10\(^{-14}\) and 4.73 × 10\(^{-8}\), respectively; Supplementary Table 2). In contrast, there was no significant difference in the genotype distribution of either Q126X or Q141K between the Caucasian and African-American population groups (p = 0.55 and 1.00, respectively). In addition, the minor allele frequencies (MAFs) of Q126X (allele T) and Q141K (allele A) in the Japanese population group (0.025 and 0.275, respectively) were significantly higher than those in the Caucasians (MAF = 0.005 and 0.085; p = 0.016 and 1.57 × 10\(^{-16}\), respectively) and the African-Americans (MAF = 0 and 0.09; p = 0.014 and 2.66 × 10\(^{-9}\), respectively). These results indicate that the dysfunctional ABCG2 genotypes are more common in the Japanese population group than in the other population groups.

We previously showed that the genotyping of two dysfunctional variants (Q126X and Q141K) is sufficient for estimating the severity of ABCG2 dysfunction.\(^3\) A previous functional analysis showed that Q126X is a nonfunctional variant and that Q141K is a half-functional variant for urate excretion.\(^3,7\) We also showed there was no simultaneous presence of the minor alleles of Q126X and Q141K in one haplotype.\(^5,6\) As shown in Table 1 and our previous report,\(^16\) three haplotypes defined as *1, *2 and *3 could be determined by the genotype combinations of Q126X and Q141K. Thus, all participants can be divided into four functional groups; i.e., full function (*1/*1), 3/4 function (mild dysfunction, *1/*2), 1/2 function (moderate dysfunction, *1/*3 or *2/*2), and ≤1/4 function (severe dysfunction, *2/*3 or *3/*3).\(^18\) In this way, ABCG2 estimated function can be also compared among the three population groups. The distribution of four ABCG2 functional groups in the Japanese population group was significantly different from that in the Caucasian and African-American population groups (p = 1.13 × 10\(^{-15}\), 4.25 × 10\(^{-9}\), respectively; Table 1), while there was no significant difference between the Caucasian and the African-American population groups (p = 1.00). In the Japanese population group, the frequencies of mild, moderate and severe ABCG2 dysfunction (35.4%, 12.4% and 1.6%, respectively) were higher than those of the Caucasian population group (14.0%, 2.5% and 0%, respectively) and the African-American population group (20.8%, 1.4% and 0%, respectively).

Table 1. Ethnic differences in ABCG2 function estimated by its genotype combinations (Q126X and Q141K)

<table>
<thead>
<tr>
<th>Population</th>
<th>ABCG2 estimated function (Diploype of Q126X and Q141K)</th>
<th>p value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full function (*1/*1)</td>
<td>3/4 function (*1/*2)</td>
</tr>
<tr>
<td>Japanese (500)</td>
<td>253 (50.6%)</td>
<td>177 (35.4%)</td>
</tr>
<tr>
<td>Caucasian (200)</td>
<td>167 (83.5%)</td>
<td>28 (14.0%)</td>
</tr>
<tr>
<td>African-American (100)</td>
<td>84 (84.0%)</td>
<td>14 (14.0%)</td>
</tr>
</tbody>
</table>

*p values were obtained by Fisher’s exact test.

*1, *2 and *3 represent haplotypes “Q-Q,” “Q-K” and “X-Q” of two SNPs, Q126X (rs72552713) and Q141K (rs2231142), respectively, as shown in a previous report.\(^16\)
population group (14.0%, 2.0% and 0%, respectively). These results suggest that the Japanese population group could have a higher genetic risk of ABCG2 dysfunction, compared to the other two population groups. Yet, the same ABCG2 dysfunctional diplotypes were still commonly observed in the Caucasian and African-American population groups (16.5% and 16.0%, respectively). Furthermore, the nonfunctional alleles (T) of Q126X were also present in subjects belonging to the Caucasian population group. Therefore, the genotyping of two ABCG2 SNPs, Q126X and Q141K, was helpful for comparing individual differences in ABCG2 dysfunction in all three groups.

Recently, it was reported that Q141K of ABCG2 induces an instability in the nucleotide-binding domain (NBD) in a manner similar to the deletion of F508 (ΔF508) in the cystic fibrosis transmembrane conductance regulator (CFTR, also known as ABCC7) gene.9) Defects of NBD1 in ΔF508 CFTR lead to CFTR domain misassembly.20) It is supposed that the same mechanism occurs in Q141K of ABCG2, and that the multidomain misassembly enhances the susceptibility to ubiquitin-mediated proteasomal degradation of ABCG2 protein.21) This proteasomal degradation causes a 50% reduction in protein expression of the Q141K variant,21) resulting in transporter dysfunction. These reports are consistent with our previous finding that Q141K is a half-functional variant for urate excretion due to its 50% reduction in surface protein expression.3)

In summary, we demonstrated for the first time that differences in the ABCG2 dysfunction were observed among the three population groups (Japanese, Caucasians and African-Americans). Because ABCG2 dysfunctional diplotypes commonly exist not only in the Japanese population group but also in Caucasian and African-American population groups, the genotyping of the two ABCG2 SNPs could be useful for evaluating individual variations in the ABCG2 dysfunction which affect the pharmacokinetics and hyperuricemia/gout risk for all ethnic groups.

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References