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Polymorphisms of ABCG2 and its impact on clinical relevance

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ABSTRACT

Human ABCG2 is one of the most important ATP-binding cassette (ABC) transporters. This protein functions as a xenobiotic transporter of large, hydrophobic, positively or negatively charged molecules, a wide variety anticancer drugs, fluorescent dyes, and different toxic compounds found in normal food. SNPs in ABCG2 may affect absorption and distribution of these substrates, altering the accumulation, effectiveness and toxicity of compounds or drugs in large populations. Its transport properties have been implicated clinically and ABCG2 expression is linked with different disease states. We reviewed the SNPs of ABCG2 in clinical relevance about gout, acute myeloid leukemia, solid tumors, and other diseases.

1. Introduction

ABCG2 (breast cancer resistance protein, BCRP) belongs to the ATP-binding cassette (ABC) superfamily which is one of the most important members of active transport molecules [1,2]. It is a 72-kDa protein composed of 665 amino acids, and has an N-terminal ATP binding domain (NBD) and a C-terminal transmembrane domain (TMD) that consist of six helices, a structure half the size and in reverse configuration to most other ABC proteins comprising two NBDs and two TMDs [3]. Since ABCG2 is a half-transporter, it is believed to dimerize or possibly oligomerize in order to function [4–6]. A GXXXG motif (residues 406 to 410), involved in the dimerization of other membrane proteins such as glycophorin A [7], was found in the ABCG2 protein and the subsequent mutation of glycines to leucines resulted in impaired function rather than the expression of ABCG2 [8]. However a new report about ABCG2 structure using cryo-electron microscopy shows that these two motifs do not contact each other since they are located on opposite sides of the protein [9]. A disulfide bridge at C603 is thought to contribute to homodimer formation [10].

ABCG2 is widely expressed in organisms and mainly in the gastrointestinal tract, liver, kidney and brain endothelium. It plays an important role in efflux to expel xenobiotics from cells, including chemotherapeutics [2,11–13]. So, it is important to analyze the activities of ABCG2 and its nonsynonymous single-nucleotide polymorphisms (SNPs) in the patients.

SNPs introduce an amino acid change in the peptide sequence, which can alter the expression, function or localization of the proteins they encode. Primary structural variations of ABCG2 are associated with its substrate-transporter function. Numerous SNPs in the ABCG2 gene have been found in ethnically diverse populations [14–17]. Genotyping studies revealed several hundred naturally occurring nonsynonymous SNPs (424 variants listed in the Ensembl GRCh37 database, release Oct 2016). Of these, SNPs 421 C > A, 376 C > T, 623C > T and 1322 G > A SNPs have been studied most extensively.

2. Major ABCG2 genetic variants

The 421 C > A (Q141K) SNP appears to be very common in Asian populations, with reported allelic frequencies between 27% and 34% [18–20], whereas this SNP is rare in sub-Saharan African and

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African-American populations, with frequencies of 5% [21]. Its frequency in Caucasian populations is approximately 10% [22]. Drug accumulation was higher in PA/Q141K cells than that in other ABCG2 transfectants, suggesting that the SNP 421 C > A reduces ABCG2 function. These observations from laboratory and clinical studies suggest that the levels and functions of ABCG2 expressed from the 421 C > A ABCG2 allele are reduced compared with those of the wild-type protein. The 421 C > A mutation is located within the functionally important ATP-binding region between the Walker A and B motifs of ABCG2 and thus is likely to affect the ATPase activity of the protein [18,23]. The Q141K change has been shown to result in decreased plasma membrane expression, decreased or reduced ATPase activity compared to wild-type ABCG2 [19,23,24].

Another ABCG2 SNP, 376 C > T, substitutes a stop codon for Gln-126 (Q126stop). It is present at low frequencies in healthy Japanese samples as a heterozygosity (reported frequencies of 3/124 and 2/120 in two studies) [19,21]. The frequency of the T376 allele of ABCG2 is low and not observed in Caucasian or African-American groups. A combination of the 376 C > T and 421 C > A SNPs would be expected to occur in a considerable proportion of the Japanese population. Because these SNPs would have negative effects on ABCG2 activity, the combined 376 C > T and 421 C > A variant are expected to show severely reduced ABCG2 activity [25].

Other non-synonymous SNPs, 623 T > C and 1322 G > A (F208S and S441 N) have been shown to affect ABCG2 protein levels at the plasma membrane, indicating that these non-synonymous SNPs reduce the stability of ABCG2 by enhancing its ubiquitin-mediated proteasome proteolysis, resulting in reduced ABCG2 function [26].

Overall the net effect of SNPs in ABCG2 is to reduce the transport of substrates due to a decreased plasma membrane protein expression or impaired function of properly localized transporter [27]. Based on laboratory data, we will review the clinical feature of ABCG2 SNPs.

3. The challenge of exploiting ABCG2 in the clinic

At present, the relationship between ABCG2 polymorphisms and clinical response is mainly an area of focus on gout and tumor resistance. We will show the overall developments mainly in these diseases.

3.1. ABCG2 SNPs in gout

In gout, a most common inflammatory arthropathy, ABCG2 SNPs dysfunction mainly impairs uric acid transport and leads to higher plasma concentrations [28].

Studies in Xenopus oocytes injected with ABCG2 mRNA confirmed ABCG2 was a transporter of uric acid, as uric acid transport rates in oocytes injected with ABCG2 encoding the Q141K SNP were over 50% lower than rates in oocytes expressing wild-type ABCG2 [29]. Clinical research data are consistent with those in vitro. In a study of 104 patients with primary gout and in 300 control subjects, the 421C > A of ABCG2 in normoexcretors was 10 times higher than that in underexcretors [30].

In 90 Japanese patients with hyperuricemia Q141K SNPs were frequently seen in patients and ATP-dependent urate transport was reduced or eliminated. An association study with 161 male gout patients and 865 male controls showed that all of those with dysfunctional ABCG2 had an increased risk of gout, and that the risk was even greater in patients with≤1/4 function. In 2150 Japanese individuals, the frequency of those with dysfunctional ABCG2 was more than 50% [31]. In other East Asian, similar research of 352 male patients with gout and 350 gout-free normal male controls found that the A allele frequency was 49.6% in the gout patients and 30.9% in the controls. Patients with mild to severe ABCG2 dysfunction accounted for 78.4% of gout cases indicating that the Q141K SNP is associated with an increased risk of gout [32]. In Korea, a research of 109 patients with gout and 102 healthy controls showed that patients had significantly higher A/A genotype (29.3% vs. 4.9%, respectively) and A allele (52.8% vs. 26.5%, respectively) frequency of Q141K SNP. These data demonstrated a significant association between Q141K SNP in the ABCG2 gene and gout [33]. A meta-analysis in 2015 also demonstrated that Q141K variant would significantly increase the risk of gout in Asians [34]. Similar results were found in a Population Architecture using Genomics and Epidemiology (PAGE) study of 22,734 European Americans, 9720 African Americans, 3849 Mexican Americans, and 3550 American Indians. Q141K SNP was significantly associated with serum uric acid levels and gout. The T allele was associated with a 0.24-mg/dL increase in serum uric acid level ($p = 1.37 \times 10^{-80}$) and a 1.75-fold increase in the odds of gout ($p = 1.09 \times 10^{-12}$) [35].

The Q141K SNP also affects the therapeutic response of gout. Researchers found that Q141K SNP conferred a significantly increased risk of poor response to allopurinol (odds ratio (OR)= 2.71 (1.70–4.48), $p = 6.0 \times 10^{-5}$) in 264 gout patients. This association remained significant after adjustment for age, sex, body mass index, ethnicity, estimated glomerular filtration rate, diuretic use and SU off urate-lowering therapy [36]. Fadieieva's team believe that Q141K variants can be predictors of poor gout response. It has been established that Q141K polymorphism can directly modulate ABCG2-mediated allopurinol and oxypurinol efflux. The K allele is associated with a lower reduction in serum uric acid in response to allopurinol treatment [37]. It was also found that alcohol consumption and ABCG2 Q141K, independently and jointly, associated with the risk of chronic tophaceous gout development [38].

In addition to Q141K, Q126X SNP is also indicated as risk factor in gout [32,36]. But 34G > A (V12 M) SNP was found to have a protective effect on gout susceptibility in the Han Chinese population [32]. Several new SNPs are potentially associated with gout. Researchers conducted 143 cases and 310 controls. Four susceptibility SNPs were identified to potentially associate with occurrence of gout. Rs2622621 and rs3114018 in ABCG2 can increase the risk of gout in log-additive model (rs2622621,OR = 1.90, 95% confidence interval (CI) 1.39–2.61, $p < 0.001$; rs3114018, OR = 1.55, 95% CI 1.13–2.13, $p = 0.006$). They also found that rs17731799G/T-G/G and rs3114020 T/C-T/T in ABCG2 can increase the risk of gout in a dominant model (rs17731799, OR = 1.67, 95% CI 1.05–2.66, $p = 0.028$; rs3114020, OR = 1.58, 95% CI 1.00–2.51, $p = 0.048$) [39].

3.2. ABCG2 SNPs in chronic myeloid leukemia (CML) treatment

ABCG2 SNPs are closely related to the resistance of Imatinib, the first-choice treatment for patients with chronic phase CML. Using K562 cells overexpressing ABCG2 SNPs 34G > A, 421C > A, 623T > C, 886G > C, 1574T > G, and 1582G > A and wild-type, it was found that ABCG2 421C > A, 623T > C, 886G > C, and 1574T > G reduced cell membrane expression of ABCG2 and the protective effect of ABCG2 against imatinib, CGP74588, dasatinib, and nilotinib cytotoxicity compared with wild-type [40].

SNPs in ABCG2 are also associated with pharmacogenetics of imatinib mesylate(IM). In 229 patients, researchers found that Q141K SNP were significantly associated with poor response to IM especially for major or complete cytogenetic response [41]. In 67 Japanese chronic phase CML patients, associations between IM trough concentration, clinical response, and ABCG2 SNPs were investigated. The dose-adjusted IM was significantly higher in patients with ABCG2 421C > A than in those with 421 CC ($p = 0.015$) [42]. In 82 patients with CML who had been administered 400 mg IM daily for over 6 months, the trough imatinib concentration and

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