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ORIGINAL PAPER

The CYP4502D6 *4 and *6 alleles are the molecular genetic markers for drug response: implications in colchicine non-responder FMF patients

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Abstract The cytochrome P450 2D6 (CYP2D6) is a cytochrome P450 enzyme involved in the oxidative biotransformation of the xenobiotics, carcinogens and various clinically important drugs. Patients are evaluated in three sub-groups of extensive (EM), intermediate (IM) and poor metabolizer (PM) phenotypes due to their drug-metabolising ability for the target CYP2D6 gene. Colchicine non-responsive FMF patients were prospectively genotyped for the major CYP2D6 alleles in the current study. Major CYP2D6 alleles of *1, *3, *4, *5, and *6 were genotyped for 30 responsive and 60 non-responsive FMF patients by multiplex PCR-based reverse-hybridization StripAssay and real-time PCR methods. DNA banks isolated from blood–EDTA were retrospectively used in the current patients and results were compared statistically. Increased *CYP2D6* *4 and *6 allele frequencies were highly detected in the colchicine non-responsive FMF patients when compared to the responsive group. Results showed the frequencies of major CYP2D6 *1(wild), *3(*2637A* > delA), *4(*G1934A*), *5(total gene deletion) and *6(*1707T* del) alleles in 0.550, 0.042, 0.158, 0.025 and 0.225 for non-responder and 0.880 and 0.120 (CYP2D6*1 and *4) for the responder groups, respectively. Despite small sample size, this study suggests that there is an association between CYP2D6*4 and CYP2D6*6 alleles and drug intoxicants in colchicine non-responder FMF patients.

Keywords CYP2D6 polymorphism · Colchicine resistance · FMF · Pharmacogenetics

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1 Introduction

The cytochrome P450 2D6 (CYP2D6) is the highly polymorphic isoenzyme of the cytochrome P450 system involved in the metabolising of 25 % of the commonly prescribed drugs. Inter-individual genetic differences in the pharmacokinetics of commonly prescribed drugs may represent a problem in some clinical applications (Lu et al. 2014; Zalata et al. 2014). Pharmacogenomic studies aim to report the association between inter-individual genetic differences and drug responses. These differences result in the poor prediction of plasma levels of drugs, leading to unexpected toxicities or undertreatment (Ivanov

et al. 2014; Ingelman-Sundberg and Rodriguez-Antona 2005; Pirmohamed et al. 2004). It is well known that much of the observed variation in drug efficacy and safety has a hereditary basis, arising from polymorphisms in genes, encoding drug-metabolising enzymes (Ingelman-Sundberg 2005). The activity of many drugs depends on their interaction with enzymes of the CYP450 system (Evans and Relling 2004; Landino et al. 2011). CYP2D6 is the best-characterised polymorphic CYP gene, with more than 80 relevant alleles identified on the chromosome 22q13.1 (Pratt et al. 2010). Polymorphisms in CYP2D6 result in poor metabolism (PM), intermediate metabolism (IM), extensive metabolism (EM) and ultra-rapid metabolism (UM) of drugs (Zanger et al. 2001). The PM phenotype is not attributed to any functional allele of CYP2D6; in contrast, the UM phenotype is partially attributed to three or more functional alleles of CYP2D6. The IM carries two alleles, which encode enzymes with decreased activity, whereas the EM carries two functional alleles (Zanger et al. 2004; Ingelman-Sundberg 2005; Lundqvist et al. 1999). However, the presence of only one functional allele may decrease the activity of the polymorphic enzyme (Koski et al. 2006; Janetto et al. 2002). The PM or the IM phenotype can increase the risk of adverse effects because of the inability of individuals with these phenotypes to metabolise a drug effectively. In contrast, individuals with the UM phenotype have an increased risk of therapeutic failure or side effects because of the formation of toxic metabolites. Adverse drug reactions or undertreatment may be avoided by modifying drug selection or dosage in patients with a PM, IM, or UM phenotype (Phillips et al. 2001; Kirchheiner et al. 2005).

Familial Mediterranean fever (FMF), an inherited disorder of Mediterranean origin, is characterised by recurrent self-limiting attacks of joint, chest and abdominal pain associated with fever (Sohar et al. 1967). Colchicine is the mainstay of FMF treatment because it reduces the attack frequency and duration in most patients (Eisenstein et al. 2013; Zemer et al. 1974; Dalbeth et al. 2014). Regular colchicine is quite effective in controlling FMF attacks. Approximately 65 % patients receiving colchicines show complete remission of FMF, while 20–30 % patients exhibit a partial response. However, 10–20 % patients are resistant to colchicine therapy (Drenth and Van Der Meer 2001). Some patients exhibit diminished response to colchicine therapy when compared to the well-treated FMF patients.

The isoenzyme CYP2D6 metabolises around 25 % of the prescribed drugs used as general therapeutics and polymorphic major CYP2D6 alleles have been reported in different populations and sub-populations. The present study aimed to determine the prevalence of genotypes and allele frequencies of CYP2D6 and their associations with colchicine non-responder FMF patients.

2 Materials and methods

2.1 Patients, clinical diagnosis and laboratory assessment

A total of 60 colchicine non-responder FMF patients (32 male and 28 female) and 30 colchicine responder FMF patients (15 male and 15 female) were included in the current case control study. The informed consents were obtained from all patients. The patients expressing at least 2 attacks per month, despite regular colchicine administration (0.5–2 mg/per day) and with minor and/or major acute phase reactants after colchicine treatment were diagnosed as non-responder group in the current study. Results were compared to the well-treated FMF group (responder) diagnosed as FMF and had colchicine treatment for at least one year and had no attack during a year.

2.2 Genotyping

DNA bank isolated from peripheral blood–EDTA was used retrospectively in the current study. The total genomic DNA was extracted from 100 µl peripheral blood samples from patients by the Invitek kit extraction technique (Invitek, Invisorb spin blood, Germany) for genotyping and stored at −20 °C until genetic analysis was performed. Genotyping of target genes were performed by StripAssay technique (Vienna Lab, PGX-HIV StripAssay GmbH, Austria) which is based on the reverse-hybridization principle automatically and real-time PCR methods (Light-Cycler 2.0, Roche). The MEFV and CYP2D6 (Fig. 1) genes were simultaneously amplified and genotyped by biotin labelling in a single multiplex amplification reaction (Viennelab, PGX-HIV StripAssay, Austria). The exons 2, 5 and 10 for MEFV and alleles *1, *3, *4, *5 and *6 for CYP2D6 genes were genotyped. MEFV gene analysis was performed in a Perkin Elmer 9600 and CYP2D6 gene analysis was performed in a light-cycler 2.0 protocol (Roche).

3 Results

A total of 60 colchicine non-responder FMF patients and 30 well-treated FMF patients with colchicine (responder) were evaluated for MEFV and CYP450 2D6 genes in the presented results. The current responder and non-responder FMF cohort have one or combined heterozygous and/or homozygous point mutations in target MEFV gene

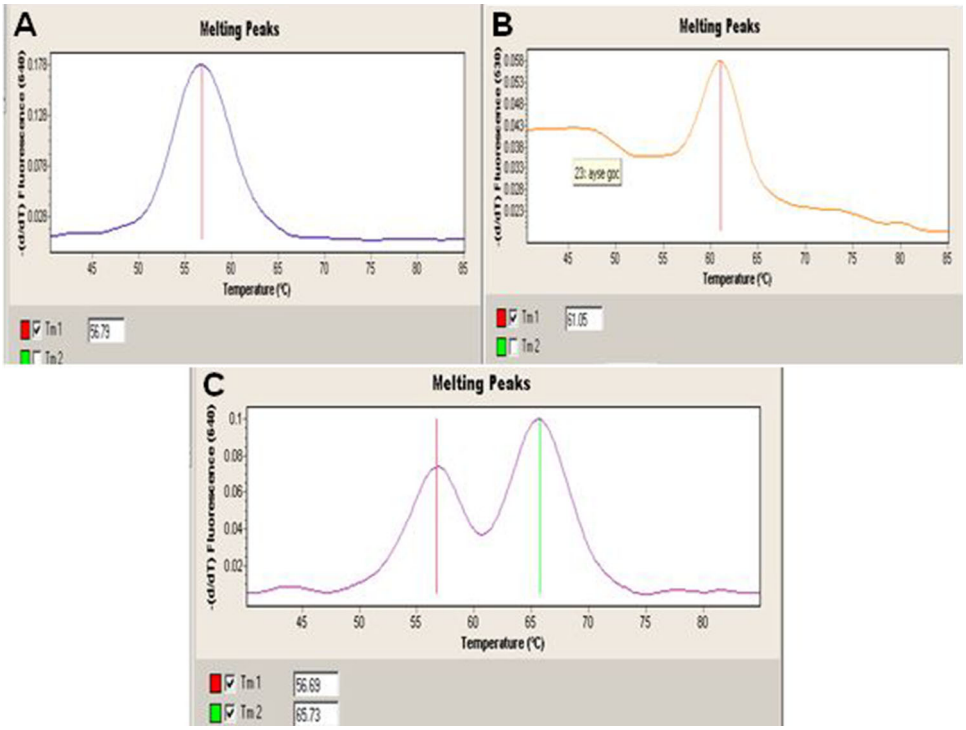

Fig. 1 Real-time PCR images of CYP2D6*1*1 (**a, b**) and CYP2D6*1*4 (**a, c**) genotypes

Table 1 The mutation-type distribution of the MEFV gene in current colchicine responder and non-responder FMF patients

Mutation type	Genotype	NR *n* (%)	*R* *n* (%)
Heterozygous	M694 V	27 (45.0)	12 (40.0)
	M680I(G > C)	3 (5.0)	3 (10.0)
	E148Q	11 (18.3)	2 (6.6)
	P369S	1 (1.6)	–
	K695R	–	3 (10.0)
	A744S	–	1 (3.3)
Homozygous	M694 V	12 (20.0)	–
	E148Q	1 (1.6)	–
	M680I(G > C)	–	1 (3.3)
Combined	E148Q/M694 V	3 (5.0)	–
	M694 V/V726A	2 (3.3)	3 (10.0)
	E148Q/M680I(G > C)	–	1 (3.3)
	V726A/R761H	–	1 (3.3)
	M680I/M694 V	–	3 (10.0)

NR colchicine non-responder, *R* colchicine responder

(Table 1). The M694 V was the most frequent missense point mutation detected in both groups (Table 1). For CYP2D6 gene, low extensive metabolizer genotypes and increased *4 and *6 allele frequencies were detected in the current colchicine non-responder FMF cohort. The eighteen patients (30 %) were extensive metabolizer, thirty patients (50 %) were intermediate and twelve patients (20 %) were poor metabolizer for CYP2D6 gene in the current non-responder cohort (Table 2). The allele frequencies of CYP2D6 *1 (wild), *3(2637A > delA), *4(G1934A), *5(total gene deletion) and *6(1707T del) were 0.550, 0.042, 0.158, 0.025 and 0.225 respectively (Table 2). Two patients were homozygous for *3/*3 and other two were homozygous for the *4/*4 genotypes in non-responder group (Table 2). These patients were evaluated as homozygous mutated poor metabolizer patients for the same major allele. The intermediate metabolizer patients were 21 patients in *1/*6, 8 patients in *1/*4 and 1 patient in*1/*5 genotypes for the same group (Tables 2, 3). The heterozygous poor metabolizer patients were 5 patients in *4/*6, 2 patients in *4/*5 and 1 patient in *3/*6 genotypes, respectively (Table 2). The remaining 18 non-responder FMF patients were in homozygous genotypes for the wild-type allele (CYP2D6*1) in the current FMF cohort (Table 2). Twenty-four (80 %) colchicine responder FMF patients showed extensive (*1/*1 genotype), 5 patients (17 %) intermediate (*1/*4 genotype) and 1 patient (3 %) showed poor metabolizer phenotype (*4/*4 genotype) for the target CYP2D6 in the presented results (Table 2).

4 Discussion

Colchicine is the only drug used in the treatment of FMF. Recent literature findings showed that nearly 10–25 % of FMF patients are non-responders for the colchicine treatment. The CYP2D6 is one of the most important enzymes involved in drug metabolism. CYP2D6, which constitutes

Table 2 The genotype and allele frequencies of CYP2D6 gene *1*3*4*5*6 polymorphisms in current colchicine responder and non-responder FMF patients

Gene/genotypes	Metabolizer phenotypes	FMF patients		Allele frequency	
		NR (*n*/%)	*R* (*n*/%)	NR (*n*/%)	*R* (*n*/%)
*1/*1	EM	18 (30)	24(80)	***1:0.550**	*1:0.880
*1/*4	IM	8(13.3)	5(17)	***3:0.042**	*4:0.120
*1/*5	IM	1(1.7)	–	***4:0.158**	
*1/*6	IM	21(35)	–	***5:0.025**	
*3/*6	PM	1(1.7)	–	***6:0.225**	
*4/*6	PM	5(8.4)	–		
*4/*5	PM	2(3.3)	–		
*3/*3	PM	2(3.3)	–		
*4/*4	PM	2(3.3)	1(3)		

All values from allele frequency for NR group are in bold

EM extensive metabolizer, *IM* intermediate metabolizer, *PM* poor metabolizer, *R* colchicine responder, *NR* colchicine non-responder

Table 3 Mutation types and enzyme functions of CYP2D6 *1*3*4*5*6 polymorphisms

Gene/alleles	Exon	Mutation type	Enzyme function
CYP4502D6			
*1		Wild	Normal
*3	5	2637A > delA	Inactive
*4	Intron 3 to exon 4	1934G > A	Inactive
*5	–	Total gene deletion	Inactive
*6	3	1707T > del	Inactive

only 1.5 % of all cytochrome P450 isoforms, metabolises up to one-quarter of all the prescribed drugs. Evaluation of CYP2D6 metabolic status before the initiation of drug therapy may help identify patients who may not respond to the therapy or who are at a risk of developing toxic side effects of the drug. Moreover, evaluation of CYP2D6 metabolic status is important to determine the optimal dosage of a drug (Murphy et al. 2000; Guzey and Spigset 2004).

The polymorphic cytochrome P450 2D6 isoenzyme has varying distribution among populations with diverse ethnic backgrounds and diverse geographical origins. In addition, these populations differ from each other with respect to their diet, cultural habits and primary language. In this manner, a large amount of pharmacogenomic studies aimed to study the association between inter-individual genetic differences and drug responses in clinical practise. The diversity in allele frequencies indicates that genetic composition also varies among populations from different geographical regions (Qin et al. 2008). CYP2D6*4 allele, formed by G1846A substitution that results in a splicing defect, is the most common CYP2D6 allele associated with the PM phenotype and has an allele frequency of 0.14 % in the Chinese, 21 % in Caucasians; 7.8 % in African Americans and 1–3 % in Asians (Scordo et al. 2004; Gaedigk et al. 2005; Gjerde et al. 2008). Furthermore, prevalence of this allele in Caucasian patients with UM, EM, IM and PM phenotypes who were receiving codeine therapy was 1–2, 77–92, 2–11 and 5–10 %, respectively (Crews et al. 2014).There are limited numbers of literature findings on the genetic polymorphisms in CYP2D6 gene and its relation to the commonly prescribed drugs response in the Turkish population. Aydin et al. (2005) reported that the frequency of the defective allele *4 was 0.154 while Bozkurt et al. (1994) showed that the prevalence of CYP2D6-related PM phenotype was 3.4 % in Central Anatolian Turkish population living in Ankara. Another study showed that CYP2D6*4 homozygous mutation rate was 4 % and allele frequency was 0.21 in a Turkish population (Koseler et al. 2007). A recent study found that the allele frequency of CYP2D6*4 (1934 G > A) was 10 % (Serin et al. 2012).

The current report is the first study that investigates the possible role of CYP2D6 polymorphism on colchicine unresponsiveness in FMF patients. The pharmacogenetic analysis of CYP2D6 polymorphism should be considered in patients with FMF who are unresponsive to colchicine therapy. In our study, we assessed the association between CYP2D6 alleles *1, *3, *4, *5 and *6 and colchicine unresponsiveness in patients with FMF; CYP2D6*4 allele was the most frequent, with an allele frequency of 0.158. Gene amplifications (CYP2D6*1 and CYP2D6*2) are responsible for UM phenotype in approximately 10–30 % patients with FMF (Sachse et al. 1997; Griese et al. 1998; Dahl et al. 1995). Allele frequency of CYP2D6*1 was 0.55 in patients with FMF who did not respond to colchicine therapy. The *1*1 genotype was detected in 80 % colchicine responders and 30 % colchicine non-responders (Table 2), indicating that the EM genotype of CYP2D6 was effective in metabolising colchicine because patients with FMF who had EM genotypes responded to colchicine treatment. CYP2D6*3 has adenine deletion at position 2637, which produces an altered reading frame that encodes an inactive enzyme. CYP2D6*5 has deletion of the entire gene and is present at a similar frequency of approximately 5 % in all populations (Daly et al. 1996; Lovlie et al. 1996). Serin et al. (2012) showed that allele frequencies of CYP2D6*3, CYP2D6*6 and CYP2D6*5 were 1, 2.5 and 3 %, respectively, in the Turkish population. In our study, CYP2D6*6 (after CYP2D6*1-normal form-allele frequency: 0.55) was the most frequent allele, with an allele frequency of 0.225. Allele frequencies of CYP2D6*4, CYP2D6*3 and CYP2D6*5 were 0.158, 0.042 and 0.025 %, respectively, in patients with FMF who did not responded to colchicine therapy. Patients with FMF

who responded to colchicine treatment only had CYP2D6*1 (allele frequency: 0.88) and CYP2D6*4 (allele frequency: 0.12) alleles. The normal allele (CYP2D6*1) was the most frequent allele in colchicine responder group. Alleles CYP2D6*4, CYP2D6*3, CYP2D6*5, which were frequent (associated with poor metabolism) in patients with FMF who did not responded to colchicine therapy, may be responsible for colchicine unresponsiveness. In our study, CYP2D6*6 was the most frequent allele associated with the PM phenotype. CYP2D6*4 allele, with an allele frequency of 0.158, was also frequent in our study. These results indicated that CYP2D6*4 and CYP2D6*6 alleles may be involved in colchicine metabolism and may be responsible for poor metabolism in patients with FMF who receive colchicine therapy. A recent study investigating the effect of colchicine on rat hepatic cytochrome enzymes showed that colchicine inhibited CYP2D6 (Xu et al. 2014).

The M694 V in MEFV gene was the most frequent heterozygous and/or homozygous point mutation in both colchicine responders and non-responders in the current results. The homozygous M694 V gene point mutation was detected in a high portion (20 %) of current colchicine non-responders FMF patients. Ozcakar et al. (2014) have claimed that the M694 V homozygosity may decrease the colchicine response in FMF therapy. The M694 V homozygosity was also frequent in colchicine non-responder patients in the current cohort. Moreover, CYP2D6*4 and CYP2D6*6 alleles were also frequent in colchicine non-responders when compared to the responder patients. Results showed the major CYP2D6 alleles resulting in PM phenotype may be associated with the colchicine unresponsiveness in the presented study.

5 Conclusion

Pharmacogenetical analysis of CYP2D6 polymorphism should be considered in FMF patients who are unresponsive to colchicine treatment and further in vitro and in vivo studies are needed to clarify the interactions between CYP2D6 and FMF patients diagnosed as non-responder for colchicine therapy. The clarifying of CYP2D6 variability may improve the rational drug use in non-responder FMF treatment.

Conflict of interest All authors declare that they have no competing interests.

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