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Genetic polymorphisms of the drug-metabolizing enzyme CYP2J2 in a Tibetan population

Peilong Cao, MD[a], Qian Zhao, MD[b], Yuan Shao, MD, PhD[b], Hua Yang, MD[c], Tianbo Jin, MD, PhD[c,d], Baiya Li, MD, PhD[b,*], Honghui Li, MD, PhD[b,*]

Abstract

As an important metabolic enzyme, it is necessary to investigate the genetic polymorphisms of *CYP2J2* among healthy Tibetan individuals. Genetic polymorphisms of *CYP2J2* could affect enzyme activity and lead to differences among individual responses to drugs.

We sequenced the whole gene of *CYP2J2* in 100 unrelated, healthy Tibetan volunteers from the Tibet Autonomous Region and screened for genetic variants in the promoters, introns, exons, and the 3′-UTR regions.

We detected 4 novel genetic polymorphisms of the *CYP2J2* gene. The allelic frequencies of CYP2D6*1 and *7 were 0.955 and 0.045, respectively. CYP2D6*1/*7 decreased the activity of CYP2J2 and was expressed in 9% of the sample population.

Our results provided basic data about CYP2J2 polymorphisms in a Tibetan population, suggested that the enzymatic activities of CYP2J2 might be different within the ethnic group, and offered a theoretical basis for individualized medical treatment and drug genomics studies.

Abbreviations: AA = arachidonic acid, CAD = coronary artery disease, CYP = cytochrome P450, EET = epoxyeicosatrienoic acid, LD = linkage disequilibrium, PCR = polymerase chain reaction, SIFT = Sorting Intolerant From Tolerant, SNP = single nucleotide polymorphism.

Keywords: CYP2J2, drug metabolism, gene polymorphism, Tibetan

1. Introduction

As one of the most important metabolic enzyme systems in humans, cytochrome P450 (CYP) enzymes are a central part in the metabolism of numerous drugs, especially in drug biotransformation processes.[1] CYP2J2 is the only member of CYP450 II J subfamily which transforms arachidonic acid (AA) to regioselective epoxyeicosatrienoic acids (EETs).[2] CYP2J2 plays important roles in maintaining homeostasis including the regulation of inflammation, relaxation of smooth muscles, angiogenesis, and vasodilatation. CYP2J2 is mainly expressed in the cardiovascular system[3] and is also found in the intestines, stomach, and other tissues.[4,5] CYP2J2 metabolizes many therapeutic agents, including ebastine, astemizole, perphenazine, diclofenac, and bufurarol.[6] Previous in vitro and in vivo studies have reported that AA which is a CYP2J2 substrate and ebastine strongly inhibited astemizole O-demethylation.[7] CYP2J2 catalyzes the metabolic conversion of AA to EETs, which are active drug compounds employed in the protection of the heart after ischemia.[8]

Tibetans are the 9th-largest minority group in China and inhabit the Tibetan plateau, which is geographically separated from other ethnic groups in the region. Tibet, known as the "world's third pole," is located in Southwest China at an average altitude of 4268 m.[9] Studies have shown that the Tibetans originated from east and central Asia.[10] Idiographic cold climates and hypoxia in Tibet make it an enriching natural laboratory to investigate human natural selection. The Tibetan people, with a population of 6,282,182 (according to the Chinese population survey 2010), are a well-known successful case of adaptation to high altitude. The Tibetans have a long history and have a lasting influence on the culture and traditions of Tibet. One study focusing on genomic variations of Tibetans reported that a considerable part of the Tibetan gene pool diverged from the Han ethnic group about 3000 years ago.[11]

Exome sequencing, genome-wide sequence variation analysis, and whole-genome genotyping have been used to reveal the important functional loci in the genetic adaptation to high altitude in Tibetans,[11–13] but studies have not focused on the polymorphisms of drug-metabolizing enzyme *CYP2J2* in Tibetans. In this study, we systematically screened the whole *CYP2J2* genes of 100 healthy, unrelated Tibetans to identify their polymorphisms, predict the enzyme function, and compare their frequencies with previous observations in other populations. Our results serve to provide a better knowledge of CYP2J2 variants and an available database to develop personalized medicine which will help devise new strategies for optimization of drug therapy in the Tibetan ethnic group.

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PC and QZ have equally contributed to this work.

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[a] Department of Pathology, [b] Department of Otorhinolaryngology, The First Affiliated Hospital of Xi'an Jiaotong University, [c] Key Laboratory of Resource Biology and Biotechnology in Western China (Northwest University), Ministry of Education, College of Life Sciences, Northwest University, Xi'an, [d] School of Medicine, Xizang Minzu University, Xianyang, Shaanxi, China.

[*] Correspondence: Honghui Li and Baiya Li, No. 277, Yanta West Road, Xi'an, Shaanxi, China 710061 (e-mails: lihonghui127076@163.com, lby0929@163.com).

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2. Materials and methods

2.1. Subjects

Through a very detailed exclusion and recruitment criteria, a total of 100 healthy, unrelated native Tibetan individuals (50 males and 50 females) were sampled for the population genetic research from the Tibet Autonomous Region. All the chosen subjects were judged to be Tibetans based on at least the past 3 generations of paternal ancestry. Individuals with chronic diseases involving vital organs (heart, brain, kidney, liver, and lung), and severe endocrinological, metabolic and nutritional diseases were excluded. The exclusion process aimed to minimize the known factors including environmental and therapeutics that interfere with genetic variation in the genes of interest.

Signed informed consents detailing the experimental procedures and the purpose of the study was obtained from the participants. The Human Research Committee of Xizang Minzu University for Approval of Research Involving Human Subjects approved the study protocol.

2.2. DNA sequencing

Peripheral blood samples were collected from each individual. Genomic DNA was extracted using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Ltd, Xi'an, China) according to the manufacturer's protocol. Polymerase chain reaction (PCR) primers were designed to amplify 2000 bp of the promoter and all exons of the CYP2J2 (Table 1). PCR was performed with 10 μL reactions, 1 μL template DNA and 5 μL HotStar Taq Master Mix (Qiagen, Germantown, MD), 0.5 μL primer (5 μM), and 3 μL deionized water. The thermal cycling conditions were initial denaturation for 15 minutes at 95°C followed by 35 cycles of denaturation at 95°C for 30 seconds, 55 to 64°C for 30 seconds, and 72°C for 1 minute, and a final extension step at 72°C for 3 minutes. PCR products were incubated with 0.5 μL shrimp alkaline phosphatase (Roche Diagnostics, Basel, Switzerland), 8 μL HotStar PCR product, and 1.5 μL deionized water (to a total volume of 10 μL), at 37°C for 30 minutes, followed by heat inactivation at 80°C for 15 minutes. Purified PCR products were directly sequenced using the ABI Prism BigDye Terminator Cycle Sequencing Kit version 3.1 (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA) using an ABI Prism 3100 sequencer (Applied Biosystems, Thermo Fisher Scientific, Inc.).

2.3. Statistical analysis

Sequencher 4.10.1 (http://www.genecodes.com/) was used to analyze sequences and SPSS 17.0 statistical packages (SPSS, Chicago, IL) were used to perform statistical calculations. *CYP2J2* variants were analyzed based on the nucleotide reference sequence AF272142 (http://www.cypalleles.ki.se/) and the protein reference sequence P51589 (http://www.uniprot.org/). Allelic and genotypic frequencies were calculated through statistical methods. Comparisons of allelic frequencies among different ethnic populations were done using chi-squared tests with the significance level set at 0.05. Haploview 4.2 was used to calculate linkage disequilibrium (LD) and Hardy–Weinberg equilibrium. Haplotypes were constructed from the selected tag single nucleotide polymorphisms (SNPs) and haplotype frequencies were derived for the study population.

2.4. Translational prediction

We adopted the 2 online tools PolyPhen-2 (Polymorphism Phenotyping v2, http://genetics.bwh.harvard.edu/pph2/) and Sorting Intolerant From Tolerant (SIFT, http://sift.bii.astar.edu.sg/) to analyze variants in the exon regions of CYP2J2 and predict the enzyme function of novel nonsynonymous SNPs. Each variant was given a score based on the extent of influence on enzyme function. The SIFT based on the score divided the results into 4 categories including tolerant (0.201–1.00), borderline (0.101–0.20), potentially intolerant (0.051–0.10), and intolerant (0.00–0.05). PolyPhen-2 results were divided into 5 categories: probably benign (0.000–0.999), borderline (1.000–1.249), potentially damaging (1.250–1.449), possibly damaging (1.500–1.999), and probably damaging (≥2.000).

3. Results

3.1. Genetic variants

From the sequences, we identified a total of 24 CYP2J2 polymorphisms in the current Tibetan group that contained 4 novel SNPs. Among these polymorphisms, 4 synonymous mutations and 1 nonsynonymous mutation were identified. These mutants included 148C>T, 183C>T, 10782A>C, 15072T>C, and 18919C>A (Table 2).

3.2. Allelic and genotypic frequencies

We identified 2 alleles of CYP2J2 in Tibetans—CYP2J2*1 represented the wild allele and had the highest frequency (95.5%) and CYP2J2*7 with a frequency of 4.5%.

We detected 2 genotypes in the population. The homozygous CYP2J2*1/*1 is the wild one (91%). The heterozygous genotype *1/*7 (9%) resulted in a decreased enzyme activity. The allelic

Table 1

The primers used to amplify regions of CYP2J2.

Primer name	Primer sequence (5′–3′)	DNA size for PCR, bp	Primer sequence (3′–5′)
UTR and Exon 1	ACAGCAAGATGAGACTACCGAG	783	CCAGGTTACCAGCGTTAGCC
Exon 2	CTCATGCCTTGCTCTAGGGAC	779	CACGTTCCTCTGCTATAAATGGGT
Exon 3	GTGCATTCCTAGTGTTTACCATAC	788	TGCCCATCTTTGTGTATTTACTTCT
Exon 4	AGCATTGCATATGACAGAGGTGG	856	AGACTCAAGGGCAACAGCAAT
Exon 5	AACACTCAACCAGTGCTCAGAT	776	GAGAAGATGCTGTGCTTCTGG
Exon 6	CAAATCTGTCTCGTTCACATCC	827	ATACCAGACTAAAGTGCTTGAAC
Exon 7	GAGCTGCCTCACTCCTTCTAC	850	CTGACCTAGAACTGCTGCCTG
Exon 8	CCAAGCCCTACTGAAACTGACC	688	TTTCCAGAGGACAGAACACAGG
Exon 9	CTTCTATGGTCCTACACCCTGC	869	ACCACTTTGACTTGAGCTTCTC
Exon 9 and UTR	CCCAGCTCTACTGTCTCGTC	778	GCAACGGAGCAAGACACTAC

PCR = polymerase chain reaction.

Table 2

The frequencies and positions of CYP2J2 genetic variants in the Tibetans.

SNP	Position	Nucleotide change	Allele	Frequencies	Amino-acid effect	Region
rs890293	−76	G>T	*7	0.09	Decreased	Promoter
rs11572191	148	C>T		0.01	Leu50=	Exon 1
rs2229189	183	C>T		0.08	Phe61=	Exon 1
rs3820538	10522	C>T		0.05	No translated	Intron 1
rs537207272	10782	A>C		0.01	M116V	Exon 2
/	10814	G>A	Novel	0.02	No translated	Intron2
rs3738474	10835	G>A		0.09	No translated	Intron 2
rs11572245	10982	G>C		0.18	No translated	Intron 2
rs149199403	10984	G>A		0.1	No translated	Intron 2
/	14113	C>T	Novel	0.01	No translated	Intron 2
/	14705	C>G	Novel	0.02	No translated	Intron 3
rs774418459	15072	T>C		0.02	Ser206=	Exon 4
rs1570693	15285	A>C		0.33	No translated	Intron 4
rs1155002	18644	G>A		0.52	No translated	Intron 5
/	18740	G>A	Novel	0.02	No translated	Intron 5
rs2271800	18753	T>G		0.31	No translated	Intron 5
rs2229191	18919	C>A		0.07	Arg321=	Exon 6
rs2271798	19114	T>C		0.31	No translated	Intron 6
rs79222846	19228	A>G		0.02	No translated	Intron 6
rs540658803	21581	C>A		0.01	No translated	Intron 6
rs141264114	32899	G>A		0.01	No translated	Intron 8
rs4388726	33266	C>T		0.19	No translated	3′-UTR
rs2280273	33440	A>G		0.23	No translated	3′-UTR
rs11572327	33472	A>G		0.05	No translated	3′-UTR

SNP = single nucleotide polymorphism.

and genotypic frequencies of CYP2J2 in Tibetan are shown in Table 3.

We further compared the distribution of CYP2J2 among different ethnic populations all over the world through literature surveys. We found that the distribution frequency is unique among different populations (Table 4), and identified that the CYP2J2 distribution in the Tibetan population is more similar to the Asian populations than other populations.

3.3. LD analysis

Haploview software was used to perform LD analysis and define blocks. In genetic association studies, LD, as the population-genomic feature, is used to locate the variants that predispose individuals to genetic diseases.[14]Figure 1 shows the extent of LD among the SNPs using the D′ value. One LD block with a very strong linkage among 10984G>A, 15285A>C, 18644G>A, 18753T>G, 19114T>C, 33266C>T, and 33440A>G was identified among the 24 polymorphisms.

3.4. Protein function prediction of nonsynonymous mutations

Figure 2 shows the predicted functional consequence of the novel nonsynonymous mutations by PolyPhen-2 and SIFT. The 10782A>C was predicted by PolyPhen-2 to be benign. SIFT analysis data were consistent with PolyPhen-2 results.

4. Discussion

CYP2J2, as an enzyme responsible for the first-pass metabolism, is mainly expressed predominantly in the vascular endothelial cells and the heart tissue.[15] It is known that AA and linoleic acid are the endogenous substrates of CYP2J2.[16] CYP2J2 converts AA to regioselective EETS, which plays a significant role in maintaining the homeostasis of several human vital organs, such as the heart, lung, and kidney.[17] EETs mediate a number of biological processes including induction of membrane hyperpolarization and vasodilation, and reduction of inflammation by inhibition of transcription factors and increasing fibrinolysis activity.[18] It is quite

Table 3

Allelic and genotypic frequencies of CYP2D6 in the Tibetan population.

Gene	Allele	Number	Phenotype	Frequency, %
CYP2J2	*1	191	Normal	95.5
	*7	9	Decreased	4.5
Total number		200		100.0
	Genotype	**Number**	**Phenotype**	**Frequency, %**
	*1/*1	91	Normal	91.0
	*1/*7	9	Decreased	9.0
Total number		100		100.0

Table 4

Allele frequencies of CYP2J2 in different populations.

Population		Sample size	Allele frequency, %						Reference
			*1	*4	*5	*7	*8	*9	
Tibetan		100	95.50			4.50			Present study
Russian		227	95.16			4.84			[22]
Tatars		178	96.35			3.65			
Bashkirs		102	98.53			1.47			
Ovambos		186	93.28			6.72			[23]
Mongolians		118	96.61			3.39			
Japanese		338	93.79			6.21			
Americans		116	90.09			9.91			[24]
Germans		960	93.54			6.46			[25]
Spanish		89	93.26			6.74			[26]
African-Americans		102	88.73			11.27			[27]
Chinese		384	97.40			2.60			[28]
Taiwanese		200	88			12			[20]
African Ancestry	ACB	96	89.06		0.52	10.42			1000 Genomes Project
	ASW	61	81.97		1.64	16.39			
	ESN	99	81.82			18.18			
	GWD	113	84.52		0.44	15.04			
	LWK	99	85.85	0.51		13.64			
	MSI	85	78.24		1.76	20.00			
	YRI	108	84.26		0.46	15.28			
American	CLM	94	94.68			5.32			
	MXL	64	96.87			3.13			
	PEL	85	99.41			0.59			
	PUR	104	93.75			6.25			
East Asia	CDX	93	98.39			1.61			
	CHB	103	95.63			4.37			
	CHS	105	93.81			6.19			
	JPT	104	96.16			2.40	1.44		
	KHV	99	97.98			2.02			
European	CEU	99	94.95			5.05			
	FIN	99	92.93			7.07			
	GBR	91	95.05			4.95			
	IBS	107	93.93			6.07			
	TSI	107	94.86			5.14			
South Asia	BEB	86	99.24			0.76			
	GIH	103	94.66			5.34			
	ITU	102	93.63			5.88		0.49	
	PJL	96	92.19			6.77		1.04	
	STU	102	90.20			9.80			

meaningful to study the polymorphisms of CYP2J2 in view of the function of the enzyme.

In the study, we systematically sequenced *CYP2J2* using Sequencher 4.10.1 and analyzed the polymorphism distribution and allele frequencies of *CYP2J2*. From the 24 SNPs, we identified 4 novel all-intron polymorphisms. We found the 10782A>C was a nonsynonymous mutation with no effect on the function of the enzyme. Nonsynonymous mutations directly change the sequence and structure of the protein and have a direct impact on its function. Increasing evidence suggests that nonsynonymous mutations occur after translation and could influence the protein function or even damage it. We explored the distribution of CYP2J2 in the different population and identified a diverse frequency distribution. Our results provide the basic information about CYP2J2 polymorphisms in the Tibetan population and contribute to the development of individualized medication.

Owing to its important function, CYP2J2 has been comprehensively studied. Earlier studies have identified polymorphisms of the CYP2J2 gene in different populations and have focused on the association between CYP2J2 polymorphisms (rs890293) and cardiovascular risk, but this has provided inconsistent results. Zhu et al reported that rs890293 does not have a significant association with coronary artery disease (CAD).[19] Spiecker et al[16] and Liu et al[20] showed that the functionally relevant polymorphism rs890293 was independently associated with an increased risk of CAD in younger groups in Tainan. A decreased risk of CAD was associated with rs890293 in African-Americans by Lee while no significant association was found in Caucasians.[21] The above differences could be due to different dietary habits and geographical factors between different populations. Other studies have demonstrated that CYP2J2 is the major enzyme responsible for the metabolism of many different drugs. Wu et al proved that CYP2J2 is an important enzyme for the pharmacokinetics of anthelmintics in human liver. Christina Westphal demonstrated that the overexpression of CYP2J2 is a protective factor against arrhythmia susceptibility in a mouse model of cardiac hypertrophy.

Our study revealed that 9% of the sampled Tibetans carried the mutant CYP2J2 with decreased activity. We also identified

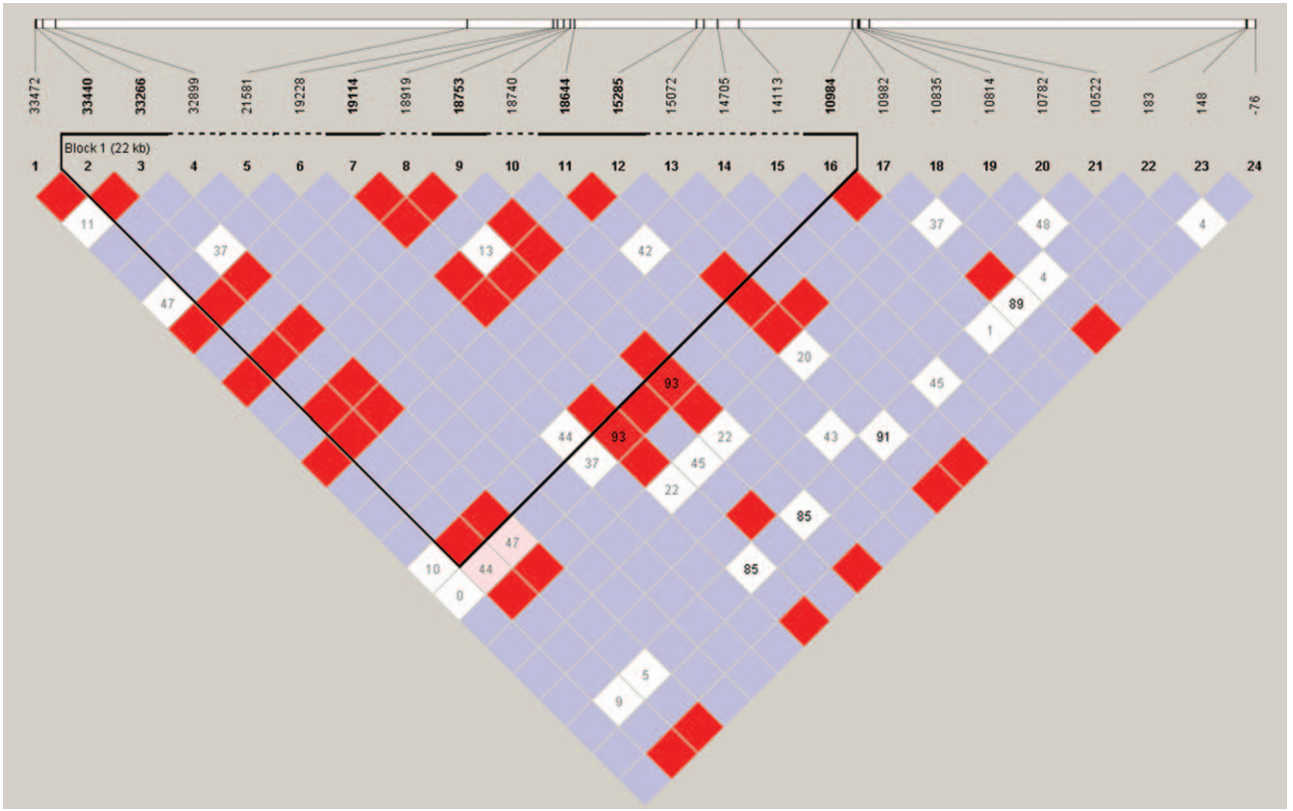

Figure 1. Linkage disequilibrium and analysis of CYP2J2 genetic polymorphisms. Strong LD is displayed by bright red (very strong: LOD > 2, D′ = 1) or pink red (moderately strong: LOD > 2, D′ < 1), intermediate LD is displayed by blue (LOD < 2, D′ = 1), and absence of LD is displayed by white (LOD < 2, D′ < 1). LD = linkage disequilibrium, LOD = logoddsscore.

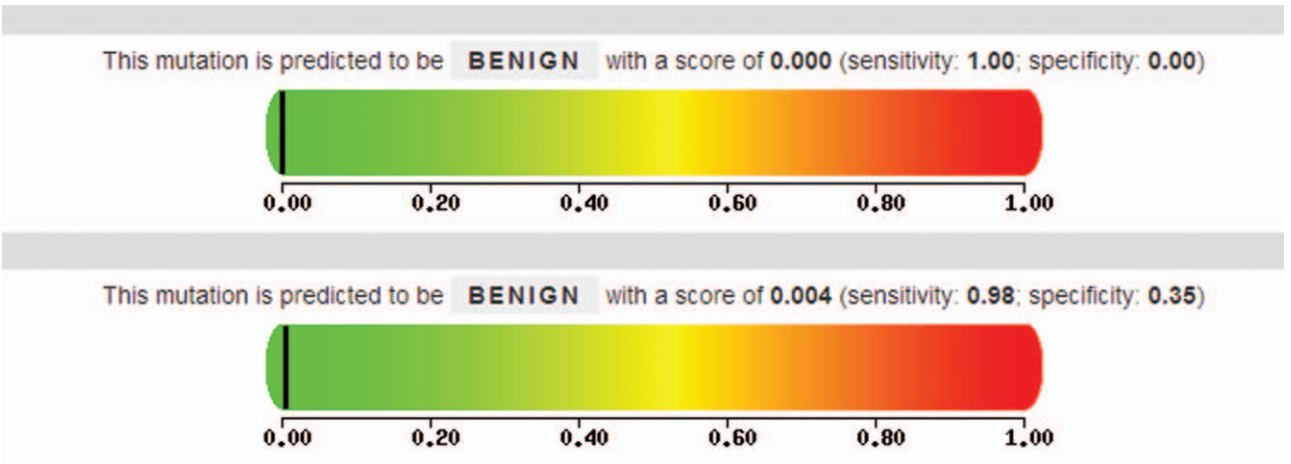

Figure 2. Predicted protein function of all the CYP2J2 nonsynonymous mutations (M116V).

the polymorphisms of CYP2J2 and their genetic frequencies in a Tibetan population. It is necessary to carry a more in-depth study for exploring the distribution of the polymorphisms and their effect on drug clearance rates and adverse drug reactions.

5. Conclusion

In conclusion, we systematically analyzed the variants of CYP2J2 by directly sequencing the gene in a Tibetan population and compared its distribution in other ethnic groups. The study offers some useful information for the establishment of a database of Tibetan population CYP2J2 genetic polymorphisms, which would offer a theoretical basis for individualized medical treatment and drug genomics studies in Tibet. We need a larger sample size for validating our study, which would be useful for the advancement of personalized medicine.

Author contributions

Conceptualization: Peilong Cao.

Data curation: Qian Zhao.
Formal analysis: Yuan Shao.
Methodology: Qian Zhao, Hua Yang.
Project administration: Baiya Li.
Resources: Yuan Shao, Honghui Li.
Software: Tianbo Jin.
Validation: Baiya Li.
Writing – original draft: Peilong Cao.
Writing – review & editing: Honghui Li.

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