



# The Evaluation of Genetic Profiles of *UGT1A4* and *UGT1A6* in the Turkish Population

## Türk Popülasyonunda *UGT1A4* ve *UGT1A6* Genetik Profillerinin Değerlendirilmesi

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### Abstract

**Aim:** Uridine diphosphate glucuronosyltransferases (UGTs) are a superfamily of conjugation phase II enzymes and is responsible for catalyzing the glucuronidation of many endobiotic or xenobiotic substrates. The present study aimed to determine allele and genotype frequencies of *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and *UGT1A6* c.19T>G polymorphisms in the healthy Turkish population and also to compare them with different population data.

**Material and Method:** *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G polymorphisms were determined in DNA samples of 114 healthy Turkish volunteers using polymerase chain reaction and restriction fragment length polymorphism methods.

**Results:** The frequencies of variant alleles were 12.7% for *UGT1A4* c.142T>G, 39.9% for *UGT1A6* c.541A>G and 44.7% for *UGT1A6* c.19T>G. The frequencies of the *UGT1A4* and *UGT1A6* variant alleles determined were observed to be similar to those of the majority of European populations. However, the *UGT1A6* frequencies in the Turkish population differed significantly from those reported specifically for the Thai and East Asian populations.

**Conclusion:** This study introduces the frequencies of *UGT1A4* and *UGT1A6* polymorphisms in the Turkish population. As a result of our literature reviews, this study is the first report that investigated the frequencies of *UGT1A6* c.541A>G and c.19T>G polymorphisms in the healthy Turkish population. A study of the *UGT1A4*\*3 polymorphism was found in Turkish epilepsy patients in the literature search, but not in healthy individuals. Therefore, it can be stated that this study is also the first report investigating the *UGT1A4*\*3 polymorphism in the healthy Turkish individuals. This study could ensure clinically beneficial information about drug metabolism by *UGT1A4* and *UGT1A6* in the Turkish population.

**Keywords:** *UGT1A4*, *UGT1A6*, glucuronidation, polymorphism, Turkish population

### Öz

**Amaç:** Üridin difosfat glukuronosiltransferazlar (UGT'ler), konjugasyon faz II enzimlerinin bir süper ailesidir ve birçok endobiyotik veya ksenobiyotik substratın glukuronidasyonunu katalize etmekten sorumludur. Bu çalışmada, sağlıklı Türk popülasyonunda *UGT1A4* c.142T>G, *UGT1A6* c.541A>G ve *UGT1A6* c.19T>G polimorfizmlerinin allel ve genotip frekanslarının belirlenmesi ve farklı popülasyon verileriyle karşılaştırılması amaçlanmıştır.

**Gereç ve Yöntem:** *UGT1A4* c.142T>G, *UGT1A6* c.541A>G ve c.19T>G polimorfizmleri, polimeraz zincir reaksiyonu ve restriksiyon fragman uzunluğu polimorfizmi yöntemleri kullanılarak 114 sağlıklı Türk gönüllülerinin DNA örneklerinde belirlendi.

**Bulgular:** Varyant allel frekansları *UGT1A4* c.142T>G için % 12.7, *UGT1A6* c.541A>G için % 39.9 ve *UGT1A6* c.19T>G için % 44.7 idi. Belirlenen *UGT1A4* ve *UGT1A6* varyant allel frekanslarının, Avrupa popülasyonlarının çoğunluğuna benzer olduğu gözlemlendi. Ancak, Türk popülasyonundaki *UGT1A6* frekanslarının, özellikle Tayland ve Doğu Asya popülasyonlarının frekanslarından önemli ölçüde farklıydı.

**Sonuç:** Bu çalışma, Türk popülasyonunda *UGT1A4* ve *UGT1A6* polimorfizmlerinin sıklığını sunmaktadır. Literatür incelemelerimizin sonucu olarak, bu çalışma sağlıklı Türk popülasyonunda *UGT1A6* c.541A>G ve c.19T>G polimorfizmlerinin sıklığını araştıran ilk rapordur. Literatür taramasında Türk epilepsi hastalarında *UGT1A4*\*3 polimorfizmi ile ilgili bir çalışma bulunmuştur, ancak sağlıklı bireyler ile ilgili veri bulunmamıştır. Dolayısıyla bu çalışmanın, sağlıklı Türk bireylerinde *UGT1A4*\*3 polimorfizmini araştıran ilk rapor olduğu ifade edilebilir. Bu çalışma, Türk popülasyonunda *UGT1A4* ve *UGT1A6* ile gerçekleşen ilaç metabolizması hakkında klinik olarak faydalı bilgiler sağlayabilir.

**Anahtar Kelimeler:** *UGT1A4*, *UGT1A6*, glukuronidasyon, polimorfizm, Türk popülasyonu



## INTRODUCTION

Glucuronidation is one of the most important phase II metabolic pathways in human. It is catalyzed by the family of UDP-glucuronosyl transferase (UGTs) enzymes which are a superfamily of membrane attached proteins in the endoplasmic reticulum.<sup>[1]</sup> UGTs (EC 2.4.1.17) catalyze the conjugation of endobiotic or xenobiotic compounds with glucuronic acid from the cofactor UDP- $\alpha$ -D-glucuronic acid (UDPGA).<sup>[2]</sup> Glucuronidation is responsible for about about 40 to 70% of xenobiotic elimination<sup>[3]</sup> and commonly makes compounds biologically inactive and increases excretion of compounds through urine or bile.<sup>[2]</sup> Some of the UGT substrates are bile acids, bilirubin, thyroid hormones, fatty acids, environmental toxins and pollutants, dietary components, tobacco smoke carcinogens, and various prescribed medications including acetaminophen, morphine, tamoxifen, mycophenolic acid, ciprofibrate, SN-38, aromatase inhibitors (letrozole, exemestane and anastrozole), vorinostat, steroid hormones, lamotrigine, some tricyclic antidepressants, and antipsychotics such as olanzapine and clozapine.<sup>[4-6]</sup> UGTs are expressed in various tissues and organs, primarily in the liver as well as in lungs, placenta, uterus, brain and intestinal mucosa.<sup>[6]</sup>

The superfamily of UGT consist of four families; which are UGT1, UGT2, UGT3 and UGT8.<sup>[7]</sup> The enzymes UGT1 and UGT2 have significant roles in toxicology and pharmacology, but the contribution of the UGT3 and UGT8 enzymes to drug metabolism has been determined to be relatively small.<sup>[7]</sup> The *UGT1A* gene is located on chromosome 2q37 and encodes nine functional proteins (*UGT1A4* and *UGT1A3-1A10*), which are produced by the splicing of a unique first exon to the common exons 2–5.<sup>[8]</sup>

Many variants have been identified in the superfamily of UGT.<sup>[9]</sup> Genetic polymorphisms in genes encoding UGT enzymes have toxicological, physiological and pharmacological significance.<sup>[10]</sup> In the *UGT1A4* gene, more than 100 single nucleotide polymorphisms (SNPs) have been identified, and one of the best studied allele among them was *UGT1A4\*3* which encodes a Leu48Val amino acid change (L48V; c.142T>G; rs2011425) in the corresponding enzyme.<sup>[6]</sup> The *UGT1A4\*3* was associated with twice as high much glucuronidation activity *in vitro*.<sup>[11]</sup> Furthermore, L48V was suggested to associated with lower mean plasma concentrations of olanzapine in patients with schizophrenia.<sup>[5,12]</sup> Alterations in glucuronidation activities due to *UGT1A4* alleles have been reported to be substrate-dependent.<sup>[9]</sup>

In the *UGT1A6* gene, the three most common nonsynonymous polymorphisms were Thr181Ala (541 A>G), Arg184Ser (552 A>C) and Ser7Ala (19 T>G).<sup>[13]</sup> Both Thr181Ala and Arg184Ser variants are mostly (>98%) in complete linkage disequilibrium.<sup>[14]</sup> These two variants result in a 30–50% decline in enzyme activity as opposed to the wild type allele.<sup>[14,15]</sup> It has been suggested that *UGT1A6* polymorphism affect the glucuronidation rate of its substrates in *in vitro* studies, and also that the A541G, A552C and T19G SNPs in the coding sequence of *UGT1A6* gene may affect the pharmacokinetics of valproic acid, by that means, changing the adverse effect profiles and efficacy of the drug.<sup>[16]</sup> Alterations in the enzyme function of UGTs may influence the clearance of and thus, systemic exposure to their substrates.<sup>[17]</sup>

The frequencies of the SNPs of *UGT1A4* and *UGT1A6* included in the study may vary among diverse populations. Differences in the frequencies of these SNPs can cause individual and ethnic differences in glucuronidation capacity, leading to differences in drug response, drug efficacy, toxicity of drugs and other xenobiotics, predisposition to various diseases.

A study of the *UGT1A4\*3* polymorphism in the Turkish population was found in the literature survey. Gulcebi et al.<sup>[10]</sup> investigated the relationship between *UGT1A4\*2* and *UGT1A4\*3* polymorphisms and lamotrigine serum concentration in epilepsy patients. On the other hand, in the Turkish population, no studies of the polymorphism mentioned in *UGT1A4* gene in healthy individuals and data on the polymorphisms commonly found in *UGT1A6* gene were found. Therefore, the aim of this study is to determine allele and genotype frequencies of *UGT1A4\*3* and *UGT1A6* A541G and *UGT1A6* T19G polymorphisms in the healthy Turkish population and also to compare them with different population data.

## MATERIAL AND METHOD

### Samples

The DNA samples extracted in the previous study (22/10/2015, protocol no: 2015/317) were included in the present survey. Additionally, the ethical approval of the current study was also obtained from Mersin University Ethics Committee (08/07/2020, protocol no: 2020/490). The genomic DNA samples isolated from whole blood were stored at -80°C until analysis. This study was carried out using DNA samples of 114 healthy, unrelated Turkish volunteers aged 18-65 and was conducted according to the Good Clinical Practices and the Declaration of Helsinki.

### Genotyping

*UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs were analyzed using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods. PCR-RFLP methods were carried out in a MiniAmp Plus Thermal Cycler (Thermo Fisher, USA).

#### ***UGT1A4* c.142T>G, p.L48V, rs2011425**

*UGT1A4* c.142T>G SNP was identified according to Hakooz et al.<sup>[9]</sup> with slight modifications. The forward (F): 5'-GCCATAACGAAAGGCAGT-3' and reverse (R): 5'-CACACAACACCTATGAAGGG-3' primers were used to amplify 567 bp of the *UGT1A4* gene that contain the polymorphic region. PCR products were digested at 37°C for 15 minutes using Fast Digest StuI restriction enzyme (Thermo Fisher Scientific). The genotypes of the wild type (319, 248 bp), mutant (567 bp) and heterozygous (567, 319 and 248 bp) were determined using 2% agarose gel with ethidium bromide (**Figure 1A**).

#### ***UGT1A6* c.541A>G, p.T181A, rs2070959**

Analysis of the *UGT1A6* c.541A>G SNP was performed using primers set; F: 5'-GGAAATACCTAGGAGCCCT GTGA-3' and R: 5'-AGGAGCCAAATGAGTGAGGGAG-3'.<sup>[13]</sup> The primers were used to amplify the 992 bp fragment of the gene. PCR products were digested at 37°C for 15 minutes using Fast Digest NsiI restriction enzyme (Thermo Fisher Scientific). The genotypes of the wild

type (992 bp), mutant (616 and 376 bp) and heterozygous (992, 616 and 376 bp) were identified using 2% agarose gel with ethidium bromide (**Figure 1B**).

#### UGT1A6 c.19T>G, p.Ser7Ala, rs6759892

The 19T>G polymorphism in the *UGT1A6* gene was analysed using primer set; F: 5'-GATTTGGAGAGTGAAAACCTCTTT-3' and R: 5'-CAGGCACCACCCTACAATCTC-3'.<sup>[13]</sup> The primers were used to amplify the 237 bp fragment of the gene. PCR products were digested in 15 minutes at 37°C using Fast Digest HhaI restriction enzyme (Thermo Fisher Scientific). The genotypes of the wild type (237 bp), mutant (165 and 72 bp) and heterozygous (237, 165 and 72 bp) were detected using 2.5% agarose gel with ethidium bromide (**Figure 1C**).

For each SNP analysis, 10% of the samples were randomly reanalyzed for quality assurance, which ensured 100% concordance.

#### Statistical analysis

Genotype and allele frequencies were calculated by genotype counting method. The observed frequencies of *UGT1A4* and *UGT1A6* SNPs were compared with the expected frequencies using the chi-square ( $\chi^2$ ) test based on Hardy-Weinberg equilibrium. The obtained data of the present study were compared with previously reported data of various populations. Differences in the frequencies between populations were tested by  $\chi^2$  test. Statistical analyzes were

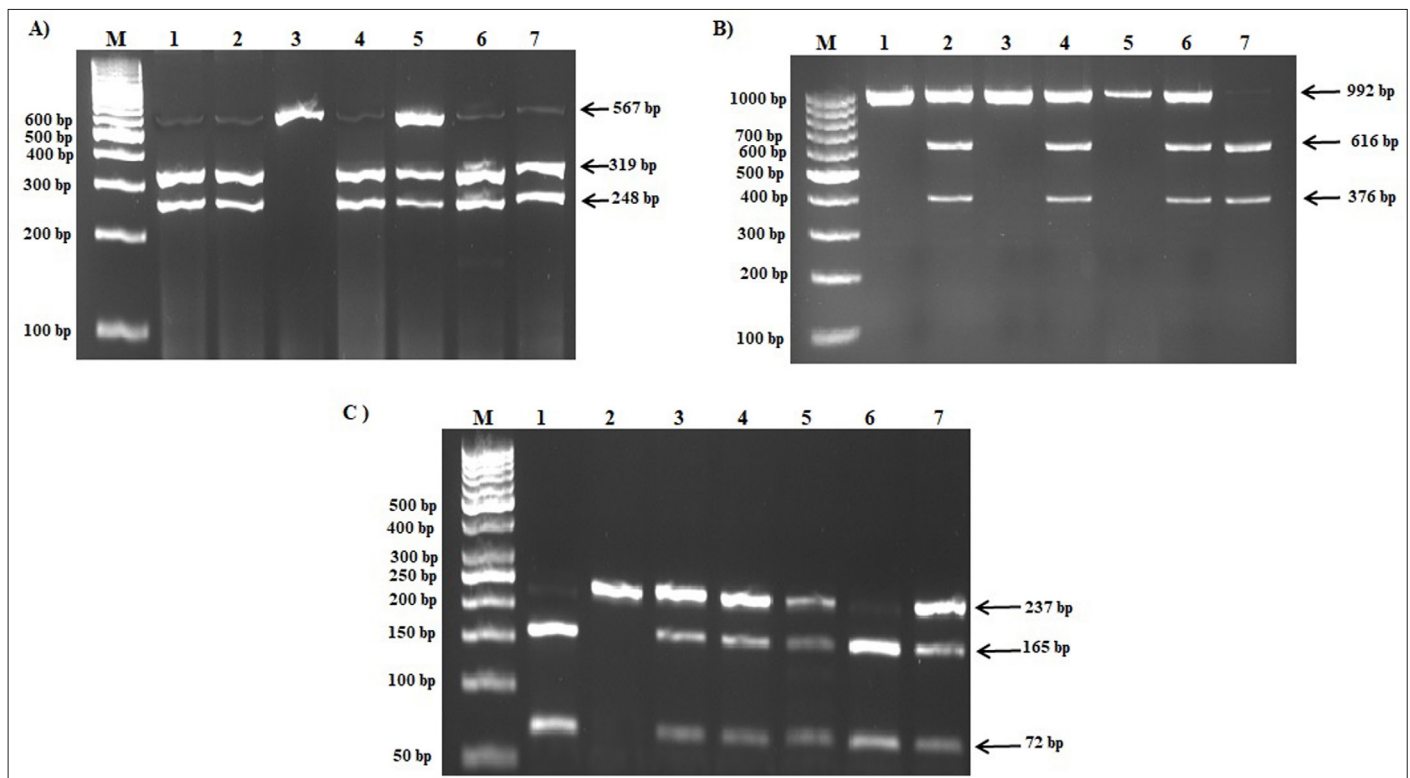
conducted with IBM SPSS 25.0 computer software for Windows.  $p < 0.05$ ,  $< 0.01$  and  $< 0.001$  were accepted statistically significant.

## RESULTS

*UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs were detected with DNA samples of 114 healthy Turkish individuals using the PCR-RFLP methods. Of the 114 individuals included in the study, 52 (46%) were male, 62 (54%) were female. The mean age with standard deviation of the study population was  $28.55 \pm 9.33$  years ( $26.15 \pm 8.50$  years for female and  $31.42 \pm 9.55$  years for male).

As shown in **Table 1**, distributions of the genotypes frequencies obtained were consistent with Hardy-Weinberg equilibrium. The frequencies of TT, TG and GG genotypes of *UGT1A4* polymorphism were 75.4%, 23.7% and 0.9%, respectively, and thus, the frequencies of T and G alleles were identified as 87.3% and 12.7%, respectively. The frequencies of AA, AG and GG genotypes of *UGT1A6* A541G SNP were 33.3%, 53.5% and 13.2%, respectively, and the frequencies of A and G alleles were found as 60.1% and 39.9%. The frequencies of TT, TG and GG genotypes of *UGT1A6* T19G SNP were 27.2%, 56.1% and 16.7%, respectively, and therefore, the frequencies of T and G alleles were detected as 52.3% and 44.7%, respectively.

**Figure 1** shows agarose gel images of RFLPs of *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs determined by electrophoresis.



**Figure 1.** Agarose gel images of restriction fragment length polymorphisms of *UGT1A4* T142G, *UGT1A6* A541G and *UGT1A6* T19G single nucleotide polymorphisms (SNPs) determined by electrophoresis. For *UGT1A4* T142G SNP (**A part**); M: Marker (100 bp), Lane 1, 2, 4, 6 and 7: wild type genotype (319, 248 bp), Lane 3: mutant genotype (567 bp), Lane 5: heterozygous genotype (567, 319, 248 bp). For *UGT1A6* A541G SNP (**B part**); M: Marker (100 bp), Lane 1, 3 and 5: wild type genotype (992 bp), Lane 2, 4 and 6: heterozygous genotype (992, 616, 376 bp), Lane 7: mutant genotype (616, 376 bp). For *UGT1A6* T19G SNP (**C part**); M: Marker (50 bp), Lane 2: wild type genotype (237 bp), Lane 3-5 and 7: heterozygous genotype (237, 165, 72 bp), Lane 1 and 6: mutant genotype (165, 72 bp).

**Table 1.** Genotype and allele frequencies of *UGT1A4* and *UGT1A6* SNPs observed in this study (n=114)

Variants	Genotype	Observed genotype frequency, n (%)	Expected genotype frequency, n	HWE	Allele frequency, n (%)
<i>UGT1A4</i> *3					
c.142T>G rs2011425	TT	86 (75.4)	86.8	$\chi^2=0.507$ p=0.476	T=199 (87.3) G=29 (12.7)
	TG	27 (23.7)	25.3		
	GG	1 (0.9)	1.8		
<i>UGT1A6</i>					
c.541A>G rs2070959	AA	38 (33.3)	41.2	$\chi^2=1.523$ p=0.217	A=137 (60.1) G=91 (39.9)
	AG	61 (53.5)	54.7		
	GG	15 (13.2)	18.2		
c.19T>G rs6759892	TT	31 (27.2)	34.8	$\chi^2=2.089$ p=0.148	T=126 (52.3) G=102 (44.7)
	TG	64 (56.1)	56.4		
	GG	19 (16.7)	22.8		

## DISCUSSION

To our knowledge, this is the first report that investigated the allele and genotype frequencies of *UGT1A6* c.541A>G and c.19T>G in a healthy Turkish population. A study of the *UGT1A4*\*3 polymorphism in the Turkish population was found in the literature survey. However, the study conducted by Gulcebi et al.<sup>[10]</sup> on the *UGT1A4*\*3 polymorphism was conducted in epilepsy patients in the Turkish population, not healthy individuals. Therefore, it can be stated that this study is the first report investigating the *UGT1A4*\*3 polymorphism in the healthy Turkish individuals. The frequency found by Gulcebi et al.<sup>[10]</sup> was similar to the frequency of *UGT1A4*\*3 polymorphism observed in healthy individuals in the present study.

**Table 2** shows a comparison of the frequencies *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs (%) observed in this study with those of other populations<sup>[10,12,17,19-28]</sup> and the 1000 Genomes Project.<sup>[18]</sup>

The variant frequencies of *UGT1A4* c.142T>G of the present study were similar to White ancestry, including Swedish, Utah Residents with Northern and Western European Ancestry (CEU), Finnish in Finland (FIN), British in England and Scotland (GBR), Iberian populations in Spain (IBS), Toscani in Italy (TSI), Colombian in Medellin, Colombia (CLM), Mexican Ancestry in Los Angeles, California (MXL), Peruvian in Lima, Peru (PEL), Puerto Rican in Puerto Rico (PUR). The frequencies of the variant allele in White ancestry were between 6.1% and 15.9%. Also, the frequency of *UGT1A4* c.142T>G was not different from frequencies previously found in East Asian populations, including Japanese, Korean, Chinese, Han Chinese, Japanese in Tokyo, Japan (JPT), Han Chinese in Beijing, China (CHB) but was found statistically significant lower than that in Kinh in Ho Chi Minh City, Vietnam (KHV). Among South Asian populations, no significant difference was observed between the frequency in Turkish and those in Gujarati Indian in Houston, Texas (GIH) and Punjabi in Lahore, Pakistan (PJL) populations; however, statistically significant difference was found between the study's findings and those in Sri Lankan Tamil in the UK (STU) and Indian Telugu in the UK (ITU) populations. There was no significant distinction between Turkish and Black ancestry, including Esan in Nigeria (ESN), Luhya in Webuye, Kenya

(LWK), African Caribbeans in Barbados (ACB) and African ancestry in SW USA (ASW) in terms of *UGT1A4* T142G SNP. The frequencies of the variant allele in Black ancestry were between 8.1 and 10.1%.

The *UGT1A6* c.541A>G allele frequency differences between Turkish and White ancestry that include GBR, IBS, CLM, MXL, PEL, PUR were considered to be statistically significant; however, it was not statistically significant when compared to CEU, FIN, TSI populations. The A541G allele frequency in the Turkish population showed significantly difference when compared to South East Asian (Thai) and East Asian populations (Japanese, Korean, Han Chinese, Chinese, JPT, CHB, KHV), but no significant difference was observed in comparison to the South Asian populations (Indian, GIH, PJL, STU, ITU). The A541G variant allele frequencies ranged from 31.9 to 45.1% for South Asian populations. Statistically significant differences were observed between Turkish populations and African populations that include ESN, LWK and ACB except for ASW.

The *UGT1A6* c.19T>G allele frequencies in the Turkish population were similar to those in White ancestry that include CEU, FIN, GBR, TSI, CLM and PUR populations, but was found statistically significant higher than those IBS, MXL and PEL populations. The T19G allele frequency in the Turkish population showed significantly difference when compared to some Asian populations that include Thai, Japanese, Korean, Han Chinese, JPT, CHB, KHV and Indian; but was not significantly distinction when compared to the other Asian populations that include GIH, PJL, STU, ITU. In addition, there was no significantly distinction between Turkish and African populations that include ESN, LWK, ACB and ASW. The T19G variant allele frequencies ranged from 34.3 to 42.2% for African populations.

As seen in **Table 2**, the frequencies of the *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs vary among diverse populations. Differences in the distribution of the frequencies of these alleles may lead to intra- and inter-population differences in glucuronidation capacity, and this may give rise to inter-ethnic and inter-individual differences in response to drug therapy, therapeutic efficacy, toxicity of drugs and other xenobiotics, susceptibility to diverse diseases.



**Table 2.** Comparisons of the frequencies of *UGT1A4* c.142T>G and *UGT1A6* c.541A>G, c.19T>G polymorphisms in various population

Ethnicity	Population	n	<i>UGT1A4</i>		<i>UGT1A6</i>		References
			c.142T>G G allele, %	c.541A>G G allele, %	c.19T>G G allele, %		
<b>WHITE</b>							
	Saudi population	182	NA	31.6	NA		Alkharfy et al. <sup>[17]</sup>
	Turkish	114	12.7	39.9	44.7		Present study
	Turkish	129	12.8	NA	NA		Gulcebi et al. <sup>[10]</sup>
	Swedish	112	12.9	NA	NA		Ghotbi et al. <sup>[12]</sup>
European	Utah Residents with Northern and Western European Ancestry (CEU)	99	8.6	32.3	39.9		1000 Genomes project <sup>[18]</sup>
	Finnish in Finland (FIN)	99	6.1	38.4	46.0		1000 Genomes project <sup>[18]</sup>
	British in England and Scotland (GBR)	91	7.1	28.0*	34.6		1000 Genomes project <sup>[18]</sup>
	Iberian populations in Spain (IBS)	107	8.9	26.6**	33.6*		1000 Genomes project <sup>[18]</sup>
	Toscani in Italy (TSI)	107	15.9	29.9	37.4		1000 Genomes project <sup>[18]</sup>
American	Colombian in Medellin, Colombia (CLM)	94	8.0	27.1**	42.0		1000 Genomes project <sup>[18]</sup>
	Mexican Ancestry in Los Angeles, California (MXL)	64	12.5	24.2**	32.0*		1000 Genomes project <sup>[18]</sup>
	Peruvian in Lima, Peru (PEL)	85	13.5	7.6***	25.3***		1000 Genomes project <sup>[18]</sup>
	Puerto Rican in Puerto Rico (PUR)	104	7.7	28.8*	36.5		1000 Genomes project <sup>[18]</sup>
<b>ASIANS</b>							
South East Asian	Thai	84	NA	23.2***	19.0***		Aphichartphunkawee et al. <sup>[19]</sup>
East Asian	Japanese	301	13.0	21.4***	22.6***		Saeki et al. <sup>[20]</sup>
	Korean	40/50 <sup>a</sup>	15.0	16.0***	20.0***		Yea et al. <sup>[21]</sup>
	Korean	132	15.2	NA	NA		Suh et al. <sup>[22]</sup>
	Chinese	214	18.0	NA	NA		Liu et al. <sup>[23]</sup>
	Han Chinese	106	12.3	NA	NA		Chang et al. <sup>[24]</sup>
	Han Chinese	534/531 <sup>b</sup>	NA	22.0***	23.8***		Xing et al. <sup>[25]</sup>
	Chinese	242	NA	18.8***	NA		Chu et al. <sup>[26]</sup>
	Chinese	97	NA	24.2**	NA		Shen et al. <sup>[27]</sup>
	Japanese in Tokyo, Japan (JPT)	104	13.5	21.2***	22.1***		1000 Genomes project <sup>[18]</sup>
	Han Chinese in Beijing, China (CHB)	103	15.5	27.2**	28.6***		1000 Genomes project <sup>[18]</sup>
	Kinh in Ho Chi Minh City, Vietnam (KHV)	99	24.7**	12.1***	15.2***		1000 Genomes project <sup>[18]</sup>
South Asian	Indian	80	NA	31.9	35.6*		Jain et al. <sup>[28]</sup>
	Gujarati Indian in Houston, Texas (GIH)	103	20.4	45.1	48.5		1000 Genomes project <sup>[18]</sup>
	Punjabi in Lahore, Pakistan (PJL)	96	20.8	39.1	48.4		1000 Genomes project <sup>[18]</sup>
	Sri Lankan Tamil in the UK (STU)	102	23.0*	44.1	49.5		1000 Genomes project <sup>[18]</sup>
	Indian Telugu in the UK (ITU)	102	23.5*	42.2	47.5		1000 Genomes project <sup>[18]</sup>
<b>BLACK</b>							
African	Esan in Nigeria (ESN)	99	10.1	23.2***	34.3		1000 Genomes project <sup>[18]</sup>
	Luhya in Webuye, Kenya (LWK)	99	8.1	21.7***	40.4		1000 Genomes project <sup>[18]</sup>
	African Caribbeans in Barbados (ACB)	96	9.4	28.6*	42.2		1000 Genomes project <sup>[18]</sup>
	African ancestry in SW USA (ASW)	61	8.2	28.7	35.2		1000 Genomes project <sup>[18]</sup>

<sup>a</sup>The studied sample sizes were 40 for c.142T>G and 50 for c.541A>G and c.19T>G polymorphisms.

<sup>b</sup>The studied sample sizes were 534 for c.541A>G and 531 for c.19T>G polymorphisms.

Differences in the frequencies were examined using  $\chi^2$  test.

n: total number of subjects. NA: not available.

Significant at \*p<0.05, \*\*p<0.01 and \*\*\*p<0.001 when compared to the current study.

Lamotrigine, which is widely used as an antiepileptic agent in the treatment of epilepsy, is metabolized by UGT enzymes<sup>[10]</sup>, and its main metabolizing enzyme is *UGT1A4*.<sup>[24]</sup> Gulcebi et al.<sup>[10]</sup> reported that L48V polymorphism decreased the serum concentration of lamotrigine in epilepsy patients in the Turkish population who received monotherapy or polytherapy, and that the levels of lamotrigine were importantly lower for smoking or non smoking polymorphic alleles than for normal. In a study by Chang et al.<sup>[24]</sup> in Han Chinese patients with epilepsy, it was reported that patients with the *UGT1A4* 142TT polymorphism were observed to have a higher blood lamotrigine concentration and better therapeutic efficacy than those with the 142TG or 142GG genotypes. Du et al.<sup>[29]</sup> reported that in Chinese children with epilepsy, the TT genotype of T142G SNP was related to high serum content of lamotrigine and that T142G SNP showed effects on efficacy of lamotrigine. In a study by Ghotbi et al.<sup>[12]</sup> on Swedish patients with schizophrenia, it was reported that the *UGT1A4*\*3 was related with lower average plasma concentrations of olanzapine.

In a study by Dadheech et al.<sup>[13]</sup>, it was conducted to evaluate the association of *UGT1A6* A541G, T19G and A552C SNPs with drug response and adverse drug reactions (ADRs) in  $\beta$ -thalassaemia major patients receiving deferiprone therapy. While a significant difference in the genotypic distribution of the *UGT1A6* Thr181Ala polymorphism has been observed in responders and non-responders, no difference was observed in the genotypic distribution between patients with and without ADR. For genotypic distribution of the *UGT1A6* T19G polymorphism, there was an important distinction between non-responders with and without ADRs and between responders with and without ADRs. Aphichartphunkawee et al.<sup>[19]</sup> declared that *UGT1A6* 541A>G and 552A>C variants were associated with lower valproic acid dose in Thai epileptic patients. Oussallah et al.<sup>[30]</sup> reported that *UGT1A6* A541G, T19G and A552C SNPs were significantly associated with gallstone-related cholecystectomy risk and that the *UGT1A6* A541G SNP was related with the highest risk of gallstone-related cholecystectomy (odds ratio=4.58; 95% confidence interval=1.58–13.28; p=0.00321). Kua et al.<sup>[31]</sup> reported that in Chinese individuals, *UGT1A6* A541G, T19G and A552C SNPs indicated important relationship with increased lung cancer risk and that *UGT1A6* polymorphisms may modify lung cancer risk.

Genetic polymorphisms changing enzyme functions have clinical significance in predicting disease susceptibility and the capability of an individual to respond to particular medications.<sup>[32]</sup> Genetic polymorphisms could aid individualized drug dosage and improved therapeutics.<sup>[33]</sup>

## CONCLUSION

This study introduces the genetic profiles of *UGT1A4* c.142T>G, *UGT1A6* c.541A>G and c.19T>G SNPs in the healthy Turkish population and the comparison of the frequencies obtained with those of various populations. The detection of polymorphisms in the genes encoding the enzymes

mentioned may ensure benefit for dose adjustment of some medications and protection from xenobiotics for precaution and decrease in adverse drug reactions. This study may help to improve toxicogenetic studies and contribute to epidemiological studies..

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was approved by Mersin University Ethics Committee (08/07/2020, protocol no: 2020/490).

**Informed Consent:** The DNA samples used were obtained during the previous study, which was approved by Mersin University Ethics Committee (22/10/2015, protocol no: 2015/317). Informed consent form had been obtained while blood samples were taken from volunteers.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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