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UGT2B7 c.-161C>T polymorphism frequency in Croatian population

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Uridine diphosphate glucuronosyltransferase-2B7 (UGT2B7), enzyme responsible for the elimination of a number of xenobiotics through glucuronidation, is expressed in the gut, kidneys, intestines, and brain. However, data on the frequency of *UGT2B7* polymorphisms in the Croatian population are limited. The aim of this study was to assess the frequency of the *UGT2B7 c.-161C>T* (rs7668258) polymorphism in the Croatian population and to compare it with reported frequencies in other populations. This polymorphism is in complete linkage disequilibrium with the *UGT2B7* c.*802C>T* (*UGT2B7*2,* rs7439366) variant, which is important in clinical medicine. The study reports data of 501 participants from University Hospital Centre Zagreb. All data were collected and analysed retrospectively. Genotyping was performed by real-time polymerase chain reaction (PCR) using the TaqMan® Drug Metabolism Genotyping Assay for *UGT2B7 c.-161C>T* (rs7668258). We found that 120 (23.95 %) participants were carriers of the *UGT2B7 c.-161CC* genotype and 255 (50.9 %) were heterozygous carriers (*UGT2B7 c.-161CT*), while 126 (25.15 %) were homozygous carriers of the variant allele (*UGT2B7 c.-161TT*). The frequency of the variant *UGT2B7 c.-161C>T* allele in this study was T=0.506. The frequency of the *UGT2B7 c.-161C>T* allelic variants and genotypes in the Croatian population is similar to other European populations.

KEY WORDS: allelic variants; genotyping; glucuronidation; pharmacogenetics; uridine diphosphate glucuronosyltransferase-2B7

Many pharmaceuticals and other xenobiotics (such as drugs, environmental and industrial chemicals) and endobiotics (such as bilirubin, bile acids, fatty acids, 20-hydroxyeicosatetraenoic acid, thyroid hormones, and steroids) are non-polar, lipid-soluble substances. Their phase II metabolism (also known as conjugation reaction) yields polar and hydrophilic compounds by adding an endogenous polar group (e.g., glucuronic acid, sulphate, glutathione, or acetyl) to a lipophilic substrate. This enhances their clearance with urine and bile and works as a detoxification mechanism (1–3). In humans, the most common conjugation pathway is glucuronidation due to a wide range of potential substrates and high availability of glucuronic acid, an endogenous chemical derived from cofactor uridine diphosphate glucuronic acid (UDP glucuronic acid), which covalently binds to a nucleophilic substrate to form a water-soluble conjugate and uridine diphosphate. Glucuronidation is mediated by uridine diphosphate glucuronosyltransferases (UDP glucuronosyltransferases, UGTs), enzymes present in many tissues (mainly in the liver, gut, and kidneys) and localised in the endoplasmic reticulum, which implies lipophilic properties of their substrates (2–4). Furthermore, glucuronidation is essential for the clearance of drugs such as analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), antineoplastics, antiepileptics, and benzodiazepines (5).

Most glucuronides are less active than their parent substances, but there are exceptions, such as morphine-6-glucuronide, a strong μ-opioid receptor agonist, whose activity is even higher than that of morphine (6). According to their amino acid sequence, UGTs in humans generally belong to four families: UGT1, UGT2, UGT3, and UGT8. The most significant drug-conjugating UGTs are members of the UGT1A and UGT2B subfamilies. Their isoforms are extensively expressed in the intestine and the gut, where they play a crucial role in facilitating the first-pass metabolism of various pharmaceutical and biological phenolic substances. Some like UGT1A1, 1A2, 1A3, 1A6, 1A9, 2B7, and 2B15 are clinically the most important (4).

UGTs have different selectivity for specific substrates, but it occasionally overlaps, as several isoforms can often participate in

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glucuronidation of the same substrate. From a toxicological standpoint, this feature is beneficial, because if one isoform malfunctions, it does not always entail lower clearance and detoxification (7).

Considering that there are many drug substrates (Table 1) (3, 8), UGTs are involved in various drug-drug interactions of which the inhibitory ones are a key source of adverse reactions to drugs. A number of medicines inhibit UGTs *in vitro*, but not many are considered clinically relevant (3). Those that are, most often affect uridine diphosphate glucuronosyltransferase-2B7 (UGT2B7) (9). Immunosuppressants tacrolimus and cyclosporine are an example of highly effective UGT inhibitors (10). By engaging UGTs, valproic acid inhibits the metabolism of lamotrigine, lorazepam, and zidovudine, while probenecid inhibits the metabolism of acetaminophen, clofibrate, lorazepam, and zidovudine (3). Zidovudine pharmacokinetics is also significantly altered in HIV patients receiving fluconazole, which inhibits glucuronidation (3).

The UGT2B7 enzyme is encoded by *UGT2B7,* a 16 Kb, six-exon gene located on chromosome 4q13. This gene is highly polymorphic and has a number of non-synonymous, synonymous, intron and promoter single nucleotide polymorphisms (SNPs) (11). Structurally, the *N*-terminal substrate-binding domain of the gene product UGT2B7 is encoded by the first and second exon, while the highly conserved C-terminal UDP-glucuronic acid cofactor-binding domain is encoded by the area between the third and sixth exon. Furthermore, *UGT2B7* genetic variations reveal ethnic diversity and have a wide range of inter-individual differences in glucuronidation activity (12). Reports on how *UGT2B7* polymorphisms influence its enzyme activity are still contradictory. Some studies report higher and others lower activity, which suggests that the activity of UGT2B7 may be substrate- dependent (13–18).

Genetic association studies indicate that the *UGT2B7*2* polymorphism has an important role in moderating both pharmacokinetic and pharmacodynamic properties of substrate drugs due to lower enzyme activity and glucuronidation rate. In addition, this polymorphism moderates toxic and/or carcinogenic effects of other endogenous and exogenous substrate metabolites and may have a part in disease pathogenesis (19), including vasoconstriction, hypertension, atherosclerosis, and renal injury through lower glucuronidation of 20-hydroxyeicosatetraenoic acid (20-HETE) (20, 21).

Considering that *UGT2B7* polymorphisms may up (22–24) or lower (25, 26) glucuronidation and excretion of a number of substrates, it is clinically important to predict metaboliser phenotypes of specific *UGT2B7* polymorphisms and personalise treatment.

For this reason, several studies have investigated the distribution of different polymorphisms of this gene in different populations, but no such study has been carried out in Croatia, save for a very limited study on *UGT2B7 c.-161C>T* frequency in adult patients with epilepsy (27).

The aim of this study was to complement our earlier genotyping research of the *UGT2B7 c.-161C>T* (rs7668258) polymorphism (and consequently of the rs7439366 variant) in the Croatian population as this specific polymorphism is in strong linkage disequilibrium (LD) with *UGT2B7*2* (rs7439366)variant (21, 28) and has a considerable impact on the pharmacokinetics of lamotrigine (29–32). In view of the cases in clinical practice, we believe its genotypes may result in variable kinetics and predisposition to side effects of several substrate drugs (21, 32). Our secondary aim was to compare its genotype frequencies with other ethnicities in Europe and worldwide.

PARTICIPANTS AND METHODS

Study population

The study included 501 Caucasian participants from different parts of Croatia, 252 men and 249 women (median age 34 years; range 2–77 years), who make a good sample of mixed Croatian population. All participants were recruited at the University Hospital Centre Zagreb to which they were referred for regular pharmacogenetic testing with different diagnoses and pharmacotherapy. The study includes pharmacogenetic data collected from 2016 to 2022.

For comparison, we relied on the Genome Aggregation Database (gnomAD) v.2.1.1 (33, 34) and 1000 Genomes database (35, 36) as sources of allele population frequencies worldwide.

Table 1 UGT enzymes and their drug substrates (3, 8)

Enzymes	Substrates
UGT1A1	atazanavir, R-carvedilol, etoposide, β-oestradiol, ezetimibe, SN-38 (active metabolite of irinotecan)
UGT1A3	ezetimibe, telmisartan
UGT1A4	amitriptyline, lamotrigine, 1-OH midazolam, olanzapine, trifluoperazine
UGT1A6	deferiprone, paracetamol, serotonin
UGT1A9	edaravone, entacapone, indomethacin, mycophenolic acid, R-oxazepam, paracetamol, propofol, sorafenib
UGT2B7	aldosterone, chloramphenicol, codeine, diclofenac, efavirenz, epirubicin, fenofibrate, flurbiprofen, morphine, naloxone, naproxen, zidovudine
UGT2B15	dabigatran, lorazepam, R-methadone, S-oxazepam
UGT2B17	testosterone, vorinostat

Genotyping

For genotyping, 3 mL of blood samples were collected into BD Vacutainer™ K_3EDTA tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Genomic DNA was extracted from whole blood using the QIAamp® kit (Qiagen, Hilden, Germany). For genotyping we relied on the TaqMan® Drug Metabolism Genotyping Assay for *UGT2B7 c.-161C>T* (rs7668258; assay ID: C__27827970_40) (Applied Biosystems, Carlsbad, CA, USA) and ran it on a 7500 Real-Time PCR System (Applied Biosystems, Carlsbad, CA, USA) according to the manufacturer's instructions.

Data analysis

Allele and genotype frequencies were counted directly and data entered into Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA). Testing for Hardy-Weinberg equilibrium (HWE) was performed with online HWE calculator Gene Calc (37).

RESULTS AND DISCUSSION

The distribution of *UGT2B7 c.-161C>T* is consistent with HWE (p=0.92113). Our Croatian population had almost identical distribution of participants homozygous for the *UGT2B7 c.-161C* (23.95 %, 120 participants) and *UGT2B7 c.-161T* (25.15 %, 126 participants) allele. The number of participants heterozygous for the *UGT2B7 c.-161CT* was 255 (50.9 %). The frequency of the variant *UGT2B7 c.-161C>T* allele was 0.506, and in this respect the Croatian population does not differ from the bulk of Europe (Table 2) with the exception of the Finnish population. It turns out to be somewhat more common in Croatian than in African/African American, East and South Asian, Latino/Admixed American, and Ashkenazi Jewish populations (Table 3).

Our results in 500 participants are in line with the Croatian study in adult epilepsy patients reporting of *UGT2B7 c.-161C>T* genotype frequencies of *CC* (24.9 %), *CT* (47.8 %), and *TT* (27.3 %), and overall variant *T* allele frequency of 51.2 % (27). They are also in line with reports for other European populations, with the exception of the Finnish (33–36). Considering other races, the polymorphism at locus *UGT2B7 c.-161C>T* (rs7668258) notably varies from African/African Americans, East and South Asians, and Latino/Admixed Americans.

Considering that this is not a genetic association study, our study is limited to genotyping only one rs7668258 variant and to determining the *c.-161C>T* frequency in the Croatian population. Future studies should examine the frequency of different haplotypes that include the *UGT2B7 -c.161 C>T* or *c.802C>T* (*2) variant and their role in glucuronidation variability of different substrates. Future research should also put more focus on the association between substrate metabolism and the *UGT2B7 c.-161C>T* polymorphism and its genotype distribution in different conditions associated with this variant (e.g. oxidative stress, hypertension, atherosclerosis, renal disease, cancer) (20, 21, 35, 38–41). As the activity of UGT2B7 encoded by the *c.-161C>T* variant allele carriers is substrate-specific and confirmed for different drugs, further research should also focus on examining the clinical relevance of this polymorphism for other substrate drugs such as fenofibrates. The relevance of *UGT2B7* variants may be particularly important in combined therapy with drugs having the same UGT2B7 metabolic pathway (e.g. diclofenac, morphine, fenofibrate). In patients receiving such therapy it would be important to understand drug-drug-gene interactions that influence drug effectiveness and side effects, especially in terms of different UGT2B7 genotype/phenotype groups.

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Table 2 *UGT2B7 c.-161C>T* genotype frequencies in the Croatian population and data on European populations (35, 36)

Gene - allele	Genotype	Croatian population[a]	European population	CEU[b]	FIN[b]	GBR[b]	IB[S]b	TSI[b]
UGT2B7 c.-161C>T (rs7668258)	*C/C*	**0.240**	0.250	0.232	0.333	0.220	0.271	0.196
	C/T	**0.509**	0.529	0.576	0.434	0.505	0.551	0.570
	T/T	**0.251**	0.221	0.192	0.232	0.275	0.178	0.234

[a] Frequencies determined in this study. [b] Allele frequencies from the 1000 Genomes database: CEU – Utah residents with Northern and Western European ancestry from the CEPH collection; FIN – Finnish in Finland; GBR – British in England; IBS – Iberian population; TSI – Tuscans in Italy

Table 3 *UGT2B7 c.-161C>T* allele frequencies in the Croatian population and data on worldwide populations (33–36)

NCBI dbSNP ID	Alleles	Croatian population[a]	EUR[b]	FIN[b]	AFR[b]	EAS[b]	SAS[c]	AMR[b]	AJ[b]	Other[b]
UGT2B7 c.-161C>T rs7668258	*C*	**0.4940**	0.4624	0.5599	0.7078	0.7057	0.6010	0.6896	0.5625	0.5221
	T	**0.5060**	0.5376	0.4401	0.2922	0.2943	0.3990	0.3104	0.4375	0.4779

[a] Frequencies determined in this study. [b] Data from the Genome Aggregation Database (gnomAD): EUR – non-Finnish Europeans; FIN – Finnish; AFR – African/African American; EAS – East Asian; AMR – Latino/Admixed American; AJ – Ashkenazi Jewish. [c] Data from the 1000 Genomes database: SAS – South Asia

Conflict of interests

None to declare.

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Učestalost polimorfizma *UGT2B7 c.-161C>T* u hrvatskoj populaciji

Najčešći metabolički put konjugacije u ljudi je glukuronidacija zbog svojih različitih i brojnih potencijalnih supstrata. Enzim UGT2B7, kodiran genom *UGT2B7*, eksprimiran je u bubrezima i crijevima, a aktivan je i u mozgu. Podatci o učestalosti polimorfizma *UGT2B7* u hrvatskoj populaciji vrlo su ograničeni. Cilj ovog istraživanja bio je procijeniti učestalost polimorfizma *UGT2B7 c.-161C>T* (rs7668258), povezanoga s promijenjenom aktivnošću enzima, u hrvatskoj populaciji te ga usporediti s učestalošću u drugim etničkim skupinama. Ovaj je polimorfizam u potpunoj neravnoteži vezanosti s potvrđenom važnom varijantom *UGT2B7 c.802C>T* (*UGT2B7*2*, rs7439366) u kliničkoj medicini. Svi ispitanici redovito su upućivani na farmakogenetičko ispitivanje u KBC Zagreb, a svi podatci prikupljani su nekoliko godina i retrospektivno analizirani. Genotipizacija je provedena lančanom reakcijom polimeraze u stvarnom vremenu (PCR) korištenjem TaqMan® testa genotipizacije metabolizma lijekova za *UGT2B7 c.-161C>T* (rs7668258). Ukupno je bio uključen 501 pacijent: njih 120 (23,95 %) bili su nositelji genotipa *UGT2B7 c.-161CC*, njih 255 (50,9 %) bili su heterozigotni nositelji (*UGT2B7 c.-161CT*), a 126 (25,15 %) ispitanika homozigotni nositelji *UG2TB7 c.-161TT*. Učestalost alela varijante *UGT2B7 c.-161C>T* u ovom istraživanju bila je T=0,506. Kao zaključak, učestalost alelnih varijanti i genotipova *UGT2B7 c.-161C>T* u hrvatskoj populaciji u skladu je s ostalim europskim populacijama.

KLJUČNE RIJEČI: hrvatsko stanovništvo; glukuronidacija; farmakogenetika; polimorfizmi, UGT2B7