Genetic Polymorphisms Associated with Valproic Acid Therapy: Review article

Reham A.M.Ellisy[a*], Ali Helmi Bakri[b], Safwat A. Mangoura[c], Mahmoud H. Abdelraheem[c], Hanan S.M. Farghaly[c]

[a]Medical Pharmacology Department, Faculty of Medicine, South Valley University, Qena, Egypt.
[b]Pediatric Department , Faculty of Medicine, South Valley University, Qena, Egypt.
[c]Medical Pharmacology Department, Faculty of Medicine, Assiut University, Assiut, Egypt.

Abstract

Background: Valproic acid is an important anticonvulsant and mood-stabilizing drug. It is also used in the therapy of bipolar disorders, migraine, cancer and neurodegenerative disorders. The use of valproate in epileptic disorders depends on trial and error with fluctuation of the prescribed dose until the patient is controlled with the least effective dose without side effects. With the emergence of pharmacogenomics, it is important to know the genes regulating valproic acid signaling pathways, related transporters, receptor mutations, pharmacokinetics, pharmacodynamics and adverse drug reactions. Thereafter, we can use valproic acid with more efficacy and tolerability. Highlight the genetic variations associated with valproic acid mechanism of action, pharmacokinetics, pharmacodynamics and side effects. We have searched literatures in PubMed, google scholar,Egyptian bank of knowledge and science direct.

Conclusion: There are several candidate genes affecting valproic acid efficacy, tolerability and safety. Therefore, we can prescribe the right valproic dose to the right patient at the right time, thus, allowing optimization of valproic acid therapy.

Keywords: Genetic variants; pharmacogenetics; polymorphism; valproic acid.

DOI: 10.21608/svuijm.2021.60196.1070
***Correspondence: reham.abdelrazek@med.svu.edu.eg.com**
Received: 27 January,2021.
Revised: 9 February, 2021.
Accepted: 9 February, 2021.
Cite this article as: Reham A.M.Ellisy, Ali Helmi Bakri, Safwat A. Mangoura, Mahmoud H. Abdelraheem, Hanan S.M. Farghaly. (2022). Genetic Polymorphisms Associated with Valproic Acid Therapy: Review article. *SVU-International Journal of Medical Sciences*. Vol.5, Issue 2, pp: 355-361.

Copyright: © Ellisy et al (2022) Immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge. Users have the right to Read, download, copy, distribute, print or share link to the full texts under a Creative Commons BY-NC-SA 4.0 International License.

1. Genetic polymorphism in valproic acid pharmacokinetics

The metabolizing system highly influences the response to a drug; thus, genetic variations in the expression and activities of drug metabolizing enzymes can greatly alter the pharmacokinetics of a drug and ultimately its response or side effects. Liver is the main site of valproic acid (VPA) metabolism apart of small percentage excreted unchanged by the kidney **(Zhu et al., 2017).**

In human, there are three metabolic pathways including the uridine 5-diphospho glucuronosyl transferase(UGT)-mediated pathway which account for 50%of VPA metabolism, while, mitochondrial B-oxidation pathway comprised 40%,and CYP-mediated oxidation pathway considered the least metabolic pathway representing the remaining 10% **(Zhu et al., 2017).**

Numerous studies have confirmed that genetic variants may influence VPA pharmacokinetics.

1.1. UGT Variants in VPA pharmacokinetics

Glucuronidation pathway is the major route of VPA elimination.

Currently, a wide genetic association studies have focused on the role of the most important UGT genetic variants on VPA metabolism,including UGT1A4, UGT1A6, UGT1A3 and UGT2B7 (Table 1) **(Zhang et al., 2013).**

Table 1. UGT genetic variants encoding VPA acid pharmacokinetics

Metabolic enzyme	Locus	Effect	References
UGT1A4	UGT1A4*2 70(C>A)	The carriers of the variant UGT1A4*270(C>A),tend to require large dosesof VPA due to increased activity of the enzyme.	**(Chatzistefanidis et al., 2012)**
UGT1A6	UGT1A6 19T>G; 541A>G; 552A>C	The carriers of the variant UGT1A6 19T>G, 541A>G and 552A>C allele tended to require higher VPA dosages and lower adjusted plasma VPA concentrations than non carriers.	**(Hung et al., 2011)**
UGT2B7	UGT2B7 161C>T; 802C>T	- The UGT2B7 -161C>T CC genotype has lower adjusted plasma VPA concentration thanthose with CT or TT genotype -The UGT2B7 802C>T genotype has tremendously higher adjusted VPA concentrations than those without variant alleles in Chinese epilepsy patients.	**(Hung et al., 2011)**
UGT1A3	UGT1A3*5	UGT1A3*5 carriers need a higher VPA dose to ensure its therapeutic range of 50–100 μg ml	**(Sun et al., 2015)**

1.2. Cytochrome p450 isozymes variants in VPA pharmacokinetics

Undoubtedly, the cytochrome p450 play an important role in VPA metabolism, the metabolite4-en-VPA which is associated with VPA induced hepatotoxicity is produced by CYP2C9,CYP2B6,CYP2A6,CYP2C19metab olic pathway (Table 2)**(Ferraro et al., 2020).**

Table 2.CYP genetic variants affecting VPA pharmacokinetics

Gene	Locus	Effect	References
CYP2A6	CYP2A6*4	One or two variants CYP2A6*4 alleles showed higher VPA concentration than non-alleles.	**(Yoon et al., 2020)**
CYP2B6	CYP2B6*6	Plasma concentration of CYP2B6*6 alleles higher than non-alleles.	**(Tan et al., 2010)**
CYP2C9	CYP2C9*2 CYP2C9*3	Heterozygousgeno-type CYP2C9*2, CYP2C9*3 has higher VPA concentration than wild type.	**(Tan et al., 2010)**
CYP2C19	CYP2C19*2	CYP2C19*2 variant requires higher VPA doses to achieve target plasma concentration.	**(Smith et al.,2016)**

1.3. Drug transporters variants in VPA pharmacokinetics

ABCC2 is a member of multidrug resistance associated proteins (MRP2.ABCCs) [belongs to the adenosine triphosphate - binding cassette (ABC) transporter super-family] mediates the transport of VPA across the blood brain barrier. ABCC2 rs3740066 CC has been correlated with VPA resistance.

MCT1 (SLC16A) (mono carboxylate transporter belongs to the solute-linked carrier (SLC) superfamily) mediates the endogenous short chain monocarboxylates and VPA acid transport across endothelial cells.

MCT1 rs60844753CC genotype has higher resistance compared to CG genotype**(Chen et al., 2019).**

2.Genetic polymorphism in valproic acid pharmacodynamics

Valproic acid executes its action by different mechanisms, increasing gamma amino butyric acid level (GABA) which acting on GABA receptor (GABR) by inhibiting both key enzymes responsible for GABA breakdown, 4-aminobutyrate aminotransferase (ABAT)and succinic semialdehyde dehydrogenase (encoded by ALDH5A1).

Also, VPA act by blocking voltage gated sodium channels encoded by (SCN) gene, blocking calcium channels encoded by (CACN)gene family and histone deacetylase inhibitor(HDAC) which has a role in gene transcription**(Liu et al., 2020).**

Liu and his coworker,(2020)added that in all epileptic patients, SCN2A rs2304016 (A >G), and in patients with focal seizure, SCN1A rs2298771 (A>G) were associated

with therapeutic responsiveness to VPA monotherapy in Chinese epileptic children.

Two SNPs were found to correlate with VPA responses in patients with epilepsy.SNPs located on the following genes GABRA1, GABRG2, GABRA6, ALDH5A1 and ABAT were genotyped. The polymorphisms of ABATrs1731017, ALDH5A1 rs1054899 were found significantly associated with the efficacy of VPA**(Li et al., 2016)**.

However, pharmacodynamics genetic variants need more research on sufficient number of patients to ensure sufficient heterogenicity.

3.Role of genetic variants affecting VPA toxicity

Valproic acid is considered one of the most commonly prescribed antiepileptic drugs in the world, but, adverse effects may limit its use. Some of these adverse effects may be serious as hepatotoxicity, mitochondrial toxicity, encephalopathy due to hyperammonemia and other adverse effects **(Nanau and Neuman, 2013).**

Reactive oxygen species from VPA metabolism is produced by CYP2E1 which is the most powerful oxidative stress inducers in cells. Thus, genetic variants in CYP2E1 can affect patient liability for adverse effects and CYP2E1 inhibitors have protective role**(Zhu et al., 2017).**

Urea cycle disorders (UCDS) patients have exaggerated hyperammonemia when using VPA. So, FDA warning to use VPA in these patients should be put in mind.There are several regulatory enzymes in urea cycle, carbamoyl phosphate synthetase 1(CPS1), ornithine transcarbamoylase(OTC), argininosuccinate synthase (ASS1), argininosuccinatelyase (ASL), and arginase 1(ARG1)could be involved in this toxicity**(Makris et al., 2020).**

Carbamoyl phosphate synthetase 1 is carbamoyl phosphate producer in liver, CPS1 4217>A polymorphism associated with VPA induced hyperammonemia**(Yagi et al., 2010)**, has been demonstrated in Caucasian epileptic patients**(Janicki et al., 2013).**

Glutamine synthetase enzyme metabolizes ammonia in urea cycle,which is encoded by glutamine synthetase gene (GLUL).GLUL rs107997771 polymorphism can cause serious hyperammonemia in patients using VPA**(Inoue et al., 2015).**

Polymerase γ gene(POLG) variation which is mitochondrial DNA polymerase is associated with fatal VPA hepatotoxicity, POLG1 gene variants as heterozygous p.Q1236H and p.E1143G mutations were associated with VPA-induced hepatic failure**(Bassett et al., 2019).**

Glutathiones-transferase which deactivate endogenous substances by oxidative stress, genetic variants as GSTM1-genotype,GSTM1/GSTT1-genotypes were associated with high gamma glutamyltransferase(GGT) level in patients treated with VPA**(Hynynen et al., 2014)**.

Superoxide dismutase2(SOD2) gene polymorphism largely raise serum transaminases in VPA treated patients.SOD2 Val16Ala Val/Val genotype show raised

alanine aminotransferase levels than Val/Ala and Ala/Ala genotypes(**Saruwatari et al., 2012).**

Valproic acid therapy induced-teratogenicity by down-regulating IGF2R, RGS4, COL6A3,EDNRB and KLF6, which is relevantly related to raising the incidence of neural tubular defect in chicken embryo model(**Hsieh et al., 2013).**

Young epileptic patients taking VPA and having the BsmI polymorphism are at an increased risk of having hyper-cholesterolemia. Hyper-triglyceridemia, increased level of low-density lipoprotein cholesterol and therefore, increased vascular risk factors.BsmI gene is also, a marker for osteoporosis risk(**Phabphal and Geater, 2013**).

Adding three SNPs in the leptin receptor (LEPR), ankyrin repeat kinase domain containing 1 (ANKK1), and α catalytic subunit of adenosine monophosphate-activated protein kinase (AMPK) has demonstrated high associations with VPA-induced weight gain(**Li et al., 2015).**

Valproic acid was also found to downgrade some important oncogens such as up regulated gene4 URG4/up regulator ofcell proliferation (URGCP) and cyclin D1 (CCND1) gene expression, So used to suppress the proliferation of SH-SY5Y neuroblastoma cancer cell line(**Dodurga et al., 2014**).

Conclusion

There are several candidate genes affecting VPA efficacy, tolerability and safety. Therefore, we can prescribe the right VPA dose to the right patient at the right time and allowing VPA therapy optimization.

References

Bassett JT, Rodriguez B, Mulligan L&Fontana RJ.(2019). Acute liver failure in a military recruit treated with valproic acid and harboring a previously unrecognized POLG-1 mutation. Epilepsy & Behavior Reports, 12**,** 100342.

Chatzistefanidis D, Georgiou I, Kyritsis AP&Markoula S. (2012). Functional impact and prevalence of polymorphisms involved in the hepatic glucuronidation of valproic acid. Pharmacogenomics, 13**,** 1055-1071.

Chen J, Su Q, Qin J, Zhou Y, Ruan H, Chen Z,et al.(2019). Correlation of MCT1 and ABCC2 gene polymorphisms with valproic acid resistance in patients with epilepsy on valproic acid monotherapy. Drug Metabolism and Pharmacokinetics, 34**,** 165-171.

Dodurga Y, Gundogdu G, Tekin V, Koc T, Satiroglu-Tufan NL, Bagci G&KucukatayV.(2014). Valproic acid inhibits the proliferation of SHSY5Y neuroblastoma cancer cells by downregulating URG4/URGCP and CCND1 gene expression. Molecular biology reports, 41**,** 4595-4599.

FerraroTN, Fischer BD&Buono RJ.(2020). Genetic Causes of Medication-Resistant Epilepsy. Medication-Resistant Epilepsy: Diagnosis and Treatment**,** 69.

Hsieh CL, Chen KC, Ding CY, Tsai WJ, Wu JF&Peng CC.(2013).Valproic acid substantially downregulated genes folr1, IGF2R, RGS2, COL6A3, EDNRB, KLF6, and pax-3, N-acetylcysteine alleviated most of the induced gene alterations in chicken embryo model. Rom J Morphol Embryol, 54**,** 993-1004.

Hung C-C, HO J-L, Chang W-L, TaiJ J, HsiehT-J, Hsieh Y-W, et al. (2011). Association of genetic variants in six candidate genes with valproic acid therapy optimization. Pharmacogenomics*,* 12**,** 1107-1117.

Hynynen J, Komulainen T, Tukiainen E, Nordin A, Arola J, Kälviäinen R,et al.(2014). Acute liver failure after valproate exposure in patients with POLG1 mutations and the prognosis after liver transplantation. Liver Transplantation,20**,** 1402-1412.

Inoue K, Takahashi T, Yamamoto Y, Suzuki E, Takahashi Y, ImaiK,et al.(2015) Influence of glutamine synthetase gene polymorphisms on the development of hyperammonemia during valproic acid-based therapy. Seizure*,* 33**,** 76-80.

Janicki PK, Bezinover D, Postula M, Thompson RS, Acharya J, Acharya V,et al.(2013). Increased occurrence of valproic acid-induced hyperammonemia in carriers of T1405N polymorphism in carbamoyl phosphate synthetase 1 gene. International Scholarly Research Notices,2013.

Li H, Wang X, Zhou Y, Ni G, Su Q, Chen Z, Chen Z, et al.(2015). Association of LEPR and ANKK1 Gene Polymorphisms with Weight Gain in Epilepsy Patients Receiving Valproic Acid. International Journal of Neuropsychopharmacology, 18,1461-1457.

Li X, Zhang J, Wu X, Yan H, Zhang Y, He RH,et al.(2016). Polymorphisms of ABAT, SCN2A and ALDH5A1 may affect valproic acid responses in the treatment of epilepsy in Chinese. Pharmacogenomics, 17**,** 2007-2014.

Liu M, Mao J, Xu H, Wang J, Zhao P, Xu Q& Du Z.(2020). Effects of SCN1A and SCN2A polymorphisms on responsivenessto valproic acid monotherapy in epileptic children. Epilepsy Research*,* 168**,** 106485.

Makris G, Lauber M, Rüfenacht V, Gemperle C, Diez-Fernandez C, Caldovic L, et al. (2020). Clinical and structural insights into potential dominant negative triggers of proximal urea cycle disorders. Biochimie,https://doi.org/10.1016/j.biochi.2020.12.003.

Nanau RM&Neuman MG.(2013). Adverse drug reactions induced by valproic acid. Clinical biochemistry*,* 46**,** 1323-1338.

Phabphal K&Geater A.(2013). The association between BsmI polymorphism and risk factors for atherosclerosis in patients with epilepsy taking valproate. Seizure*,* 22**,** 692-697.

Saruwatari J, Deguchi M, Yoshimori Y, Noai M, Yoshida S, Ogusu N, Oniki K, et al.(2012). Superoxide dismutase 2 Val16Ala polymorphism is a risk factor for the valproic acid-related elevation of

serum aminotransferases. Epilepsy Research, 99, 183-186.

Smith R, Haslemo T, Refsum H&Molden E.(2016). Impact of age, gender and CYP2C9/2C19 genotypes on dose-adjusted steady-state serum concentrations of valproic acid-a large-scale study based on naturalistic therapeutic drug monitoring data. European journal of clinical pharmacology, 72, 1099-1104.

Sun YX, Zhuo WY, LinH, Peng ZK, Wang HM, Huang HW,et al.(2015). The influence of UGT2B7 genotype on valproic acid pharmacokinetics in Chinese epilepsy patients. Epilepsy Research, 114, 78-80.

Tan L, Yu JT, Sun YP, Ou JR, Song JH& Yu Y.(2010). The influence of cytochrome oxidase CYP2A6, CYP2B6, and CYP2C9 polymorphisms on the plasma concentrations of valproic acid in epileptic patients. Clinical neurology and neurosurgery, 112, 320-323.

YagiM, Nakamura T, Okizuka Y, Oyazato Y, Kawasaki Y, Tsuneishi S,et al.(2010). Effect of CPS14217C> A genotype on valproic-acid-induced hyperammonemia. Pediatrics International, 52, 744-748.

Yoon HY, Ahn MH, Yee J, Lee N, Han JM&Gwak HS. (2020). Influence of CYP2C9 and CYP2A6 on plasma concentrations of valproic acid: a meta-analysis. Europeanjournal of clinical pharmacology, 76, pp.1053-1058.

Zhang L, Chu X, Wang H, Xie H, Guo C, Cao L,et al. (2013). Dysregulations of UDP-glucuronosyltransferases in rats with valproic acid and high fat diet induced fatty liver. European journal of pharmacology, 721, 277-285.

Zhu MM, Li HL, Shi LH, Chen XP, Luo J & Zhang ZL. (2017). The pharmacogenomics of valproic acid. Journal of human genetics, 62, 1009-1014.