

The frequency of isoenzymes of cytochrome P450 – CYP3A4 in children with drug-resistant epilepsy in Ukraine

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Background: The frequency with which drug-resistant epilepsies occur is unchanged and reaches 30%. It is believed that isoenzymes of cytochrome P450 can significantly affect the metabolism, efficacy and safety of antiepileptic drugs (AEDs). The purpose of our study was to: find out in children with drug-resistant epilepsy the frequency with which polymorphism of isoenzymes of cytochrome P450 – CYP3A4 occurs taking part in biotransformation of most AEDs.

Objectives: Study of the frequency of isoenzymes of cytochrome P450 – CYP3A4 in children with drug-resistant epilepsy in Ukraine

Materials & Methods: We analyzed the results of an examination of 68 patients, 42 (62.69%) boys and 26 (37.31%) girls, aged from 5 months to 18 years. Children suffer from severe, refractory to the treatment forms of epilepsy. All patients that were examined are Ukrainians, Slavs. Genetic studies were carried out using the allelic-specific polymerase chain reaction (PCR) method followed by the visualization of agarose gel amplification products. Due to the allelic-specific primers we identified a single-nucleotide polymorphism of the 392A> G of gene CYP3A4 * 1B (rs2740574).

Results: Before us nobody has conducted such kind of studies in Ukraine. In the study group allele *CYP3A4*1A* dominated in 61 patients (89.71%). This genotype is quite common in many populations and is typical for fast metabolizers. The rate of polymorphism *CYP3A4*1B* – 10,29 %, does not significantly differ ($p>0.05$) from the indicators with which it is recorded in the general population among the Caucasians, where it is 9.00 %. In most cases (57.13 %) was recorded a combination of allelic variants of *CYP3A4*1B* and other genotypes (*CYP2C9*2* and *CYP2C19*2*) that control enzymes and slow down the metabolism of AEDs. In 4 (57.13%) of 7 children, we identified undesirable side-effects on drug and worsening of the disease associated with AED treatment. Undesirable side effects occurred in the form of allergic manifestations and pathological changes from the nervous system. Detection of the *CYP3A4 * 1B* genotype in children with high-quality epilepsy requires a slower titration of AEDs and administration of doses that are less than therapeutic.

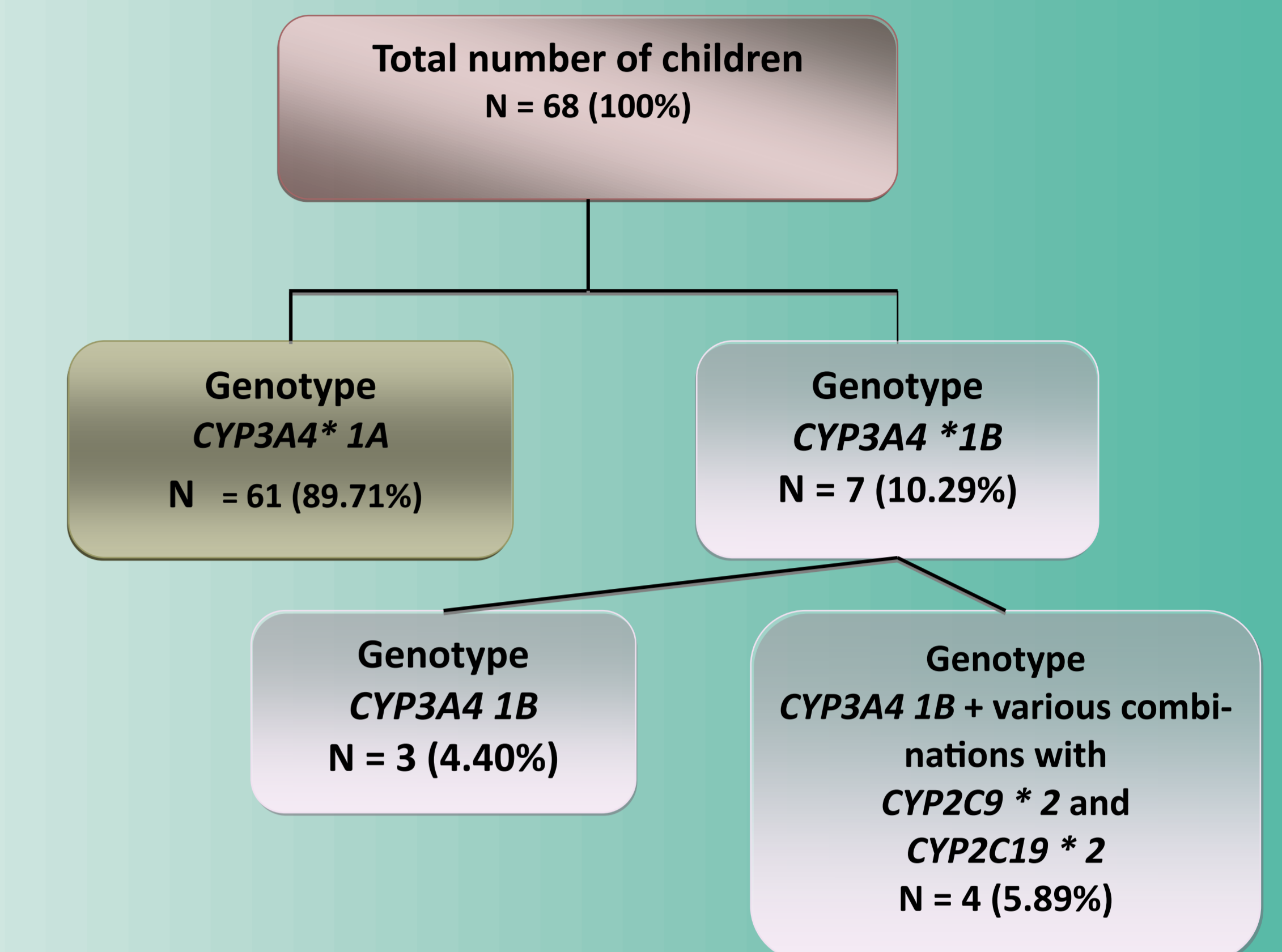


Figure 1. The frequency of genotypes *CYP3A4 * 1A* and *CYP3A4 * 1B* in children with drug-resistant epilepsies in Ukraine

No	Initials	Sex	Age	Polymorphism
1.	S.T.	m	1y. 6m.	<i>CYP3A4*1B</i>
2.	B.S.	m	13y.10m	<i>CYP3A4*1B</i>
3.	V.D.	m	8y. 6m.	<i>CYP3A4*1B</i>
4.	G.A.	m	1y. 3m.	<i>CYP3A4*1B</i> <i>CYP2C9*2</i>
5.	M.D.	m	7y.	<i>CYP3A4*1B</i> <i>CYP2C9*2</i> <i>CYP2C19*2</i>
6.	S.K.	f	10m.	<i>CYP3A4*1B</i> <i>CYP2C9*2</i>
7.	L.A.	f	4y.	<i>CYP3A4*1B</i> <i>CYP2C19*2</i>

Polymorphism of the gene CYP3A4 and its association with other genotypes in children with drug-resistant forms of epilepsy

Conclusion: The carrier of allele variant *CYP3A4*1B* among children with refractory to the treatment epilepsy in 10.29%. Often, these children experienced undesirable side effects – in 57.13% of cases, from the nervous system and allergic manifestations. Pharmacogenetic testing can become an important tool for personalized treatment of pediatric patients with drug-resistant forms of epilepsy and reduce the risks of complications of drug therapy.

Recent publications

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4. Zander U., Turprin M., Klein K., Schwab M. (2008) Functional pharmacogenetic/genomic of human cytochrome P450 involved in drug biotransformation. *Bioanal Chem*. 392: 1093-1108.
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