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Review Article

Role of the CYP1A2 Gene Polymorphisms and the Risk of Fetal Congenital Anomalies of the Uzbek Population

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Abstract

This article presents the results of molecular genetic studies of the CYP1A2 gene in 55 patients with fetal congenital anomalies from the Uzbek population. The results of the study showed that the T allele and heterozygous and mutant homozygous genotypes of the CYP1A2 gene polymorphism are significant markers of an increased risk of fetal anomalies in patients from the Uzbek population. (x2= 39.77; p < 0.005; OR = 32.89; 95% CI 88.81-122.84).

Keywords: Fetal Anomaly, Genetics, Xenobiotic Genes, CYP1A2 Gene

Introduction

Congenital malformations are becoming an increasingly significant factor in the patterns of childhood morbidity, disability, and infant mortality. According to recent studies, congenital malformations occur in 10-12% of newborns, and they account for more than 36.6% of infant mortality [1-12]. The worldwide increase in fetal abnormalities is primarily associated with the immunosuppressive effects of modern civilization on the human body. Environmental pollution and increased background radiation-these are by no means an exhaustive list of factors that weaken the human body's natural defense mechanisms and contribute to the development of a range of diseases, including those affecting reproductive health. [1,12, 10].

In ecologically disadvantaged regions, the development of fetal abnormalities is largely associated with the exposure of the mother and fetus to reproductive toxins that possess teratogenic and mutagenic properties [1,3,5,7,9,11].

Studies have established that the first phase of the metabolism of these xenobiotics is carried out by cytochromes P450 (CYP1A1 and CYP1A2). Polymorphisms in the genes encoding these enzymes have been identified, which determine the level of their oxidative activity. There is a view that congenital anomalies, fetal loss, and fetal growth restriction are associated with specific alleles and genotypes of CYP1A1 and CYP1A2, which determine individual characteristics of xenobiotic biotransformation. [2,3,4,6,10].

Uzbek scientists Karimov HY, Mavlyanova NN, and Boboev KT (2018) identified the role of xenobiotic biotransformation enzymes in pregnant women with recurrent pregnancy loss (RPL). The study results showed that pregnant women with FLS had a higher frequency of combined null genotypes (GSTM10/0 + GSTT10/0) compared to the population sample (25.4% vs. 4.1%, respectively). The data obtained indicate that female individuals in the Uzbek population with combined null genotypes of the xenobiotic enzyme genes GSTM1 and GSTT1 have a tendency toward an increased risk of developing fetal loss syndrome [2,3]. Given the above, we were very interested in studying the polymorphism of the CYP1A2

genetic marker, which determines the activity of the liver enzyme responsible for the breakdown of caffeine and a number of drugs, as well as its immunosuppressive effect on the body.

The aim of our study was to assess the detection rate of allelic variants and the association of CYP1A2 gene polymorphisms in women from the Uzbek population with fetal developmental anomalies.

Materials and Methods

We examined 95 pregnant women with fetal anomalies. The patients' ages ranged from 20 to 43 years. All patients underwent general clinical, instrumental, functional (ultrasound screening), and genetic PCR (REAL TIME) testing. All examined women received consultations from related specialists (geneticist, internist, neurologist, infectious disease specialist, dermatologist, endocrinologist, etc.). The control group consisted of 40 pregnant women with a normal course of pregnancy without fetal developmental abnormalities.

Molecular genetic testing of biomaterials (DNA) was performed at the laboratory of the Republican Scientific and Practical Medical Center for Reproductive Medicine and Reproductive Health (RSNPMCRMH) of the Ministry of Health of the Republic of Uzbekistan. e DNA/RNA was isolated from all biological blood samples using the "Ribo-Prep" kit (Interlabservice, Russia).

To detect genotype polymorphism consisting of CYP1A2 gene alleles, allele-specific primers from the manufacturer were selected from the DNA samples. To genotype DNA samples using the Polymerase Chain Reaction (PCR) method, 200 DNA samples were analyzed. For this purpose, the 96-well automated amplifier "Applied Biosystems Veriti" was optimized according to the following program: initial denaturation once at 94°C for 180 seconds, 94°C for 10 seconds, 64°C for 10 seconds, and 72°C for 20 seconds. We repeated these steps 40 times in the program to initiate the polymerase chain reaction. Statistical analysis of the results was performed using the "OpenEpi 2009, Version 2.3" statistical software package.

We studied 95 women; the main group consisted of 55 pregnant women with fetal developmental abnormalities, accounting for 57.8% of cases. Diagram 1The main group included pregnant women with fetal developmental anomalies at 16-21 weeks of gestation-of the 55 women, 31 were diagnosed with fetal hydrocephalus (56%), 15 were diagnosed with fetal spina bifida (27.3%), and the remaining 9 patients were diagnosed with fetal microcephaly, accounting for 16% of the group. The control group consisted of 40 pregnant women without fetal anomalies and with a normal course of pregnancy. Diagram 2.

Study Results

The results of molecular genetic studies of the CYP1A2 gene are presented in (Table 1).

Table 1: Frequency distribution of allelic variants and polymorphism of the CYP1A2 gene in patients with fetal anomalies and a control group of healthy pregnant women.

No	Group	Allele Frequency				Genotype Distribution Frequency					
		C		T		C/C		C/T		T/T	
		n	%	n	%	n	%	n	%	n	%
1	Main group n=55 (110)	55	50	55	50	15	27.3*	25	45.5*	15	27.3*
2	Control group n=40 (80)	77	96.3	3	3.7	37	92.5	3	7.5	0	0

Note*: n - number of patients examined; *n - number of alleles examined

Analysis of the detection rate of allelic variants of the CYP1A2 gene in 55 patients in the group with anomalies showed that among 110 DNA samples, 50% (55/110) cases revealed the presence of the normal C allele, while in the control group with normal pregnancies - 96.3% (77/80), respectively, which was 1.9 times higher than the rate in the main group. The non-functional T allele of the CYP1A2 gene in the control group accounted for 3.7% (3/80), whereas in the main group of patients this T allele accounted for 50% (55/110), respectively, which was 13.5 times higher than the control group's figures. 0= 44.56; p < 0.005; OR = 25.67; 95% CI 7.63¬86.29).

Genotyping analysis of the CYP1A2 gene polymorphism showed that in the control group of healthy patients, the functional C/C genotype was identified in 37, accounting for 92.5% of cases (37/40), while in the main group of patients, the functional C/C genotype was identified in 15 out of 55, accounting for 27.3% of cases (15/55), respectively, which was 3.4 times lower compared to the control subjects. (x= 40.23; p < 0.005; OR = 25.67; 95% CI 8.91-122.84).

The C/T heterozygous variant of the CYP1A2 gene was detected in 7.5% of cases (3/40) in the control group, whereas in the main group of patients with fetal anomalies, it was detected in 45.5% of cases (25/55), which was 6.1 times higher than the rate observed in healthy patients. (x2= 39.77; p < 0.005; OR = 32.89; 95% CI 88.81-122.84). The homozygous mutant T/T variant of the CYP1A2 gene was identified in 15 of 55 patients with fetal anomalies, accounting for 27.3% (15/55), whereas this genotype was not detected in the

group of healthy patients. (x2= 32.89; p < 0.24; OR = 32.89; 95% CI 8.81-122.84).

Analysis of the results indicates that the heterozygous C/T and non-functional homozygous T/T genotype variants of the CYP1A2 gene polymorphism are a genetic determinant involved in the development of reproductive dysfunction, consisting of its role in the metabolism of xenobiotics (foreign substances) and endogenous steroids, and its carriage is a predisposing factor for the development of fetal anomalies, increasing the risk by 13.5 times (OR=32.89).

It should be noted that an important step in the study of polymorphic genes potentially associated with the mechanism of fetal anomaly development is the analysis of the expected and observed frequencies of genotypes for the polymorphisms under study and the conformity of the frequency distribution to Hardy-Weinberg (HW) equilibrium. (Table 2).

Table 2: Expected and observed genotype frequencies according to the HW equilibrium for the CYP1A2 gene polymorphism in the main group of patients.

Genotypes	Genotype Frequency		X^2	P
	Observed	Expected		
C/ C	15	13.75	0.114	0.5
S/T	25	27.5	0.227	
T/T	15	13.75	0.113	
Total	100	100	0.45	

As shown in Table 2, the genotype frequency distribution for the CYP1A2 polymorphism in the main group of patients revealed that the expected frequency of functional homozygous C/C genotypes was 13.7%, the heterozygous C/T genotype was 27.5%, which was 1.1 times higher than the observed frequencies. The expected frequency of the homozygous unfavorable genotype variant-T/T- of the CYP1A2 gene was 13.75%, respectively. The results obtained are important indicators serving as criteria for predicting the risk of disease development.

In contrast, in the control group, the expected frequency of the favorable C/C genotype of the CYP1A2 gene was 37.06%, the frequency of the heterozygous C/T variant was 2.89%, and that of the mutant T/T genotype was 0.06%, respectively (Table 3).

Table 3: Expected and observed frequencies of genotypes for the fetal anomaly development polymorphism of the CYP1A2 gene.

Genotype	Genotype Frequency		x^2	P
	Observed	Expected		
C/ C	37	37.06	0.0001	0.8
C/T	3	2.89	0.0042	
T/T		0.06	0.0563	
Total	100	100	0.06	

A comparative analysis of the expected and observed genotype frequencies for the CYP1A2 gene polymorphism revealed statistically significant differences (P < 0.05) in all study groups and subgroups, indicating that the observed genotype frequencies in the study samples conform to Hardy-Weinberg equilibrium.

Analysis of the results showed that in both the control group and the main group with fetal anomalies, the expected and observed heterozygosity rates for the studied polymorphism were statistically significant, characterized by a 1.1-fold increase in the frequency of the expected C/T heterozygosity in the CYP1A2 gene polymorphism, which is of significant importance in predicting the risk of fetal anomalies. It should be noted that CYP1A2 is involved in the detoxification of aflatoxins, nitrosamines, and polycyclic aromatic hydrocarbons. If the enzyme functions improperly due to a mutation, toxic substances may accumulate and exert a teratogenic (development-disrupting) effect on the fetus.

Thus, the T allele and heterozygous and mutant homozygous genotypes of the CYP1A2 gene polymorphism are significant markers of an increased risk of fetal abnormalities in the Uzbek population. (z-2 39.77; p < 0.005; OR = 32.89; 95% CI88.81-122.84).

a) The results of genetic studies of the CYP1A2 gene in 55 patients in the group with anomalies revealed carriage of the non-functional T allelic variant in 50% (55/110) of cases versus 3.7% (3/80) in patients with normal pregnancies. 0= 44.56; p < 0.005; OR = 25.67; 95% CI 7.63-86.29)

b) Genotyping analysis of the CYP1A2 gene polymorphism revealed that functional C/C genotypes were present in 27.3% of cases, and heterozygous C/T genotypes in 45.5% of cases, which was 6.1 times higher than the rates observed in healthy patients ( ). (x2= 39.77; p < 0.005; OR = 32.89; 95% CI 88.81-122.84).

c) The homozygous mutant T/T variant of the CYP1A2 gene was identified in 15 of 55 patients with fetal anomalies, accounting for 27.3% (15/55), whereas this genotype was not detected in the group of healthy patients. (x2= 32.89; p < 0.24; OR = 32.89; 95% CI 8.81; 122.84).

d) The T allele and heterozygous and mutant homozygous genotypes of the CYP1A2 gene polymorphism are significant markers of an increased risk of fetal anomalies in patients from the Uzbek population. (x2= 39.77; p < 0.005; OR = 32.89; 95% CI 88.81-122.84).

Acknowledgement

None.

Conflict of Interest

None.

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