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Review Article

Association of ITGB3 Gene Polymorphisms with the Risk of Developing Fetal Growth Restriction Syndrome

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Introduction

Fetal Growth Restriction (FGR) syndrome is an urgent problem of obstetric healthcare practice worldwide, causing perinatal morbidity and mortality, the risk of sudden infant mortality [1]. According to statistics provided by the World Health Organization, the number of newborns with fetal growth restriction syndrome in the countries of Central Asia ranges from 31.1%. In the United States, FGR is observed in 10-15% of births, with signs of perinatal hypoxia observed in 30% of children diagnosed with FGR.

FGR is diagnosed based on a decrease in the body weight of a particular fetus in comparison with the average fetal body weight corresponding to a given gestational age. Foreign publications use three definitions: Small For Gestation Age (SGA), which means a fetus with a low (below the 10th percentile) weight for a given gestational age, Appropriate For Gestation Age (AGA), which means a fetus with a weight corresponding to a given gestational age (between the 10th and 90th percentiles), Large For Gestation Age (LGA), which means a fetus with a large (above the 90th percentile) weight for a given gestational age [2].

According to studies, the development of FGR is based on a molecular genetic mechanism, which requires more thorough research in this area. The purpose of the study was to assess the detectability of the association of the ITGB3 gene polymorphism in women with a physiological gestation course and the fetal growth restriction syndrome in the Uzbek population of the Bukhara region [3].

Materials and Methods

80 percent women were examined during gestation of 8 to 36 weeks: 40 women with physiological pregnancy and delivery at term, who were followed up from early gestation in antenatal clinics in Bukhara (control group), and 40 pregnant women with FGR hospitalized in an obstetric hospital in Bukhara (main group) [4].

The diagnosis of fetal growth restriction syndrome, classified according to the ICD X P00-P96 / P05-P08, was established by the state of body weight below and body length above the 10th percentile for gestational age. SGA for the calculated period. Women included in the study were examined and treated in the obstetric hospital of the Bukhara Perinatal Center in accordance with the clinical guidelines of the Ministry of Health of the Republic of Uzbekistan [5]. Criteria for inclusion in the study were as follows: singleton spontaneous pregnancy, voluntary informed consent of the woman, approval of the local ethics committee.

Molecular genetic studies were carried out by isolating total genomic DNA from 100μl of whole venous blood by the sorbent method using a Proba-GS-Genetic kit (Geno-technology, Uzbekistan). Single nucleotide polymorphisms (ITGA2) were determined by real-time polymerase chain reaction using the iCycler iQ5 device (Bio-Rad) and 'Cardiogenetic. Thrombophilia' kits (DNA-technology, Russia) [6].

Genotyping the C/T polymorphism of the ***ITGA2*** gene was performed in real time on a Rotor Gene 6000 PCR cycler Model 65H0-100 (Australia) using a test system from Syntel, Cat. No.-NP_555_100_RG (Russia), in accordance with the manufacturer's instructions. A statistical analysis of the results was conducted using the statistical software package 'Open Epi 2009, Version 2.3'. The frequency of allele and genotype variants (f) was calculated by the formula: f=n/2N and f=n/N, where n is the occurrence of a(an) (allele and genotype) variant, N is the sample size [7].

Research Results

Clinical and functional studies of 80 pregnant women showed that 40 had fetal growth restriction (FGR) syndrome, which amounted to 50%. According to the severity of FGR, severity level I was diagnosed in 4 (10%), severity level II was diagnosed in 19 (47.5%) and severity level III degree was diagnosed in 13 (32.5%) women. A molecular genetic study of the C/T polymorphism of the gene in pregnant women showed the following indicators [8] (Table 1).

Table 1: The frequency of distribution of genotypes of polymorphism 1565 T>C of the ITGB3 gene in groups of pregnant women with and without FGR.

Groups		Allele Frequency				Frequency of Genotype Distribution					
	T		C		T/T		T/C		C/C	
	n*	%	n*	%	n	%	n	%	n	%	
1	Control group Pregnant women without FGR, n=40 (80)	68	85	12	15	29	72.5	10	25	1	2.5
2	Pregnant women with FGR, n=40 (80)	68	85	12	15	30	75	8	20	2	5

Note*: n is the number of examined patients.

As follows from Table 1, the distribution of alleles of the T/C polymorphism of the *ITGB3* gene in pregnant women with physiological pregnancy revealed the presence of the favorable T allele in 85% of cases (68/80), while the unfavorable C allele was in 15% (12), which was statistically significant. In the group of pregnant women with FGR, the detection frequency of the favorable T allele was also 85% of cases (68/80), and the mutant C allele was revealed in 15% (12), respectively [9].

Analysis of the detectability of the association of polymorphism genotypes of the ***ITGB3*** gene in the control group of pregnant women showed that the association of polymorphism of favorable T/T genotypes was 72.5% of cases (29/40), heterozygous T/C genotypes was revealed in 25% of cases (10/40). Whereas the homozygous variant of the unfavorable genotypes of the *ITGB3* gene amounted to 2.5% (1/40), respectively. In the group of pregnant women with FGR, the detection of the association of polymorphism of favorable T/T genotypes was 75% (30/40), and heterozygous variants of T/C genotypes was 20% of cases (8/40), respectively. Whereas the homozygous unfavorable variant of C/C genotypes was detected in 5% of cases (2/40), respectively [10].

The data obtained indicated that the unfavorable homozygous C/C variant of the *ITGB3* gene was 2 times higher than that of the control group. An analysis of the obtained molecular genetic results of the study shows that the association of the T/C polymorphism of the *ITGB3* gene with the risk of developing fetal growth restriction syndrome is unreliable. (χ^2=0.2; P=0.7) So, according to preliminary data, the functionally unfavorable T allele of T/C polymorphism of the *ITGB3* gene is not a significant determinant of an increased risk of developing the fetal growth restriction syndrome in the population of the Bukhara region. (χ^2<0.47; P>0.05) [11].

At the same time, there is a slight tendency towards an increase in the frequency of the T/C genotype of the ITGB3 gene polymorphism in the group of pregnant women with FGR compared with the group of pregnant women without FGR. According to Table 2, there was no significant difference between the expected and observed frequencies of genotypes of the T/C polymorphism of the *ITGB3* gene. The observed genotype frequencies correspond to theoretically expected ones and are in Hardy-Weinberg equilibrium [12] (Tables 2,3).

Table 2: Expected and observed frequency of distribution of genotypes of the T/C polymorphism of the ITGB3 gene in groups of pregnant women without FGR, according to HWE:

Genotypes	Genotype Frequency		χ^2	P
	Observed	Expected		
T/T	72.5	72.25	0.0	0.9
T/C	25.0	25.5	0.004	
C/C	2.5	2.3	0.01	
Total	100	100	0.015	

According to Table 3, it is noted that there is a slight tendency towards an increase in the frequency of the heterozygous genotype T/C of the polymorphism of the *ITGB3* gene in the group of pregnant women with FGR compared with the group of pregnant women without FGR. According to the calculated OR, the risk of developing the unfavorable T/C genotype in carriers is 1.3 times higher than in non-carriers of this genotype, i.e., the differences between these subgroups turned out to close to the level of statistical significance (χ^2=0.5; P=0.17). The data obtained is consistent with the data of literature sources [13].

Table 3: Expected and observed frequency of distribution of genotypes of the T/C polymorphism of the ITGB3 gene in groups of pregnant women with FGR, according to HWE

Genotypes	Genotype Frequency		χ^2	P
	Observed	Expected		
T/T	75	72.25	0.042	0.17
T/C	20.0	25.5	0.47	
C/C	5	2.25	1.3	
Total	100	100	1.8	

Conclusions

1) The association of the T/C polymorphism of the ITGB3 gene tends to increase the risk of developing fetal growth restriction syndrome. (χ^2=0.5; P=0.17) [14].

A preliminary analysis of molecular genetic studies shows that the functionally unfavorable C allele and the association of the polymorphism of the T/C genotype of the ITGB3 gene polymorphism may be a determinant of an increased risk of developing the FGR syndrome in Uzbekistan. (χ^2<0.47; P>0.05)..

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