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Association of The Lys198asn Polymorphism of The Endothelin-1 (Edn1) Gene with Congenital Malformations in Newborns

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Abstract

***Objective**: To evaluate the distribution of alleles and genotypes of the Lys198Asn (rs5370) polymorphism in the EDN1 gene and determine its association with the risk of various pathogenetic variants of congenital anomalies (CAs) in newborns.*

***Materials and Methods**: A molecular genetic study was conducted on 123 newborns with CAs (main group) and 110 healthy infants (control group) using PCR. Statistical analysis included the Chi-squared test (χ^2), Odds Ratio (OR), and 95% Confidence Interval (95% CI).*

***Results**: Accumulation of the mutant Asn allele was identified in the CA group (23.01% vs. 15.91% in controls), reaching a peak in subgroups with chromosomal pathology (26.47%) and folate-independent CAs (26.19%). The total proportion of Lys/Asn and Asn/Asn carrier genotypes in infants with CAs was 39.82% (vs. 28.18% in controls). A statistically significant association was established between the homozygous Asn/Asn genotype and the risk of CAs with chromosomal pathology (17.65% vs. 3.64% in controls; OR = 5.7; 95% CI: 1.34–24.09). For folate-independent CAs, the Asn/Asn genotype increased the risk by 2.8 times (OR = 2.8; 95% CI: 0,51–15,27). Receiver operating characteristic analysis revealed that the Lys/Asn genotype possesses balanced predictive value for primary screening (AUC = 0.55; OR = 1.56), while the Asn/Asn genotype demonstrates high specificity (SP = 0.96).*

***Conclusions**: The Lys198Asn polymorphism of the EDN1 gene is associated with an increased risk of congenital anomalies in newborns, exerting its strongest effect in cases with chromosomal aberrations and folate-independent CAs. The Asn/Asn genotype serves as a highly specific molecular biomarker for stratifying high reproductive risk groups.*

Keywords: Endothelin-1 (EDN1), Lys198Asn polymorphism, gene polymorphism, congenital malformations, newborns, genetic factors, molecular genetics, genetic predisposition, congenital anomalies, neonatology.

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1. Introduction

Congenital malformations (CMs) remain one of the key problems of modern perinatology, pediatrics, and medical genetics, substantially affecting infant mortality and childhood disability rates [2]. The formation of organs and systems during embryogenesis is regulated by a complex interaction of genetic and environmental factors. The endothelin system occupies a special place among the molecular-genetic mechanisms of morphogenesis, providing regulation of vascular tone, cell proliferation, and organogenesis [1, 7].

Endothelin-1 (EDN1), encoded by the gene of the same name, is a potent vasoconstrictor and mitogen that plays a fundamental role in maintaining vascular homeostasis, synaptogenesis, and neural crest cell migration during early embryogenesis [5, 7]. Disturbances in endothelin-dependent regulation lead to endothelial dysfunction, oxidative stress, and local tissue ischemia [4, 6]. In newborns, endothelin-1 imbalance is associated with severe pathological conditions, including persistent pulmonary hypertension and hemodynamic disorders in congenital developmental anomalies [8, 9].

Of particular interest is the functionally significant Lys198Asn (rs5370) polymorphism of the EDN1 gene, in which a nucleotide substitution may affect the level of peptide expression and its biological activity [3]. Changes in endothelin-1 expression may exert a teratogenic effect by disrupting differentiation of embryonic tissues and aggravating the phenotypic manifestations of other pathogenetic factors [7, 8]. Despite available data on the role of this polymorphism in vascular pathology, its contribution to the etiological structure and risk of various pathogenetic variants of CMs, including folate-dependent, folate-independent forms, and anomalies associated with chromosomal pathology, remains insufficiently studied in newborns. The aim of the study was to evaluate the distribution of alleles and genotypes of the Lys198Asn polymorphism of the EDN1 gene and to determine its possible association with the risk of various pathogenetic variants of congenital malformations in newborns.

2. Methods

In the present study, molecular genetic testing was conducted in 123 newborns divided into the following groups: the main group consisted of 113 newborns diagnosed with CAs; the comparison group comprised allele and genotype frequency distribution data from 110 children without CAs, genotyped at the Laboratory of Molecular Medicine and Cellular Technologies of the Republican Specialized Scientific and Practical Medical Center of Hematology of the Ministry of Health of the Republic of Uzbekistan. For in-depth analysis, patients in the main group were stratified into the following subgroups: Subgroup I.1 — 96 newborns with isolated and systemic CAs; Subgroup I.2 — 17 newborns with CAs caused by chromosomal abnormalities. In turn, subgroup I.1 was differentiated into two cohorts: I.1.a — 75 children with folate-dependent forms of CAs; I.1.b — 21 children with folate-independent CAs.

To determine the Lys198Asn (rs5370) polymorphism of the endothelin-1 (EDN1) gene, a molecular genetic method based on polymerase chain reaction (PCR) was used. Peripheral venous blood of newborns served as the research material. Genomic DNA was extracted from peripheral blood lymphocytes with subsequent control of its quality and suitability for amplification. The obtained data were subjected to statistical processing using software developed in the EXCEL package, utilizing statistical functions, Student's t-test (t), with calculation of error probability (P). Differences were considered statistically significant at an achieved significance level of $p < 0.05$. For analyzing contingency tables containing information on outcome frequency depending on the presence of a risk factor, Pearson's χ^2 test and Odds Ratio (OR) (Cornfield J.A., 1951) with calculation of 95% confidence intervals (CI) were used.

3. Results

Endothelin-1, expressed by the EDN1 gene, plays a

fundamental role in maintaining vascular homeostasis. Possessing a potent vasopressor effect (similar to angiotensin II), it stimulates the proliferative activity of fibroblasts and myofibroblasts, and accelerates collagenogenesis.

As part of the study, a comparative analysis of the distribution of allele and genotype frequencies of the Lys198Asn polymorphism of the EDN1 gene in the studied groups was also conducted. An important stage of the research work was studying the distribution of genetic variants of the Lys198Asn polymorphism of the EDN1 gene, which is involved in regulating vascular tone and neural crest cell migration.

Data on allele and genotype frequencies in the main group, subgroups, and control group are presented in Table 1.

Table 1.

Distribution frequency of alleles and genotypes of the Lys198Asn polymorphism in the EDN1 gene in newborns of the main and control groups

No.	Group	Allele frequency				Genotype distribution frequency					
		Lys		Asn		Lys/ Lys		Lys/Asn		Asn/Asn	
		n	%	n	%	n	%	n	%	n	%
1	Основная группа (n = 113)	174	76,99	52	23,01	68	60,18	38	33,63	7	6,19
2	Фолат-зависимые ВПР (n = 75)	118	78,67	32	21,33	45	60	28	37,33	2	2,67
3	Фолат не зависимые ВПР (n = 21)	31	73,81	11	26,19	12	57,14	7	33,33	2	9,52
4	ВПР с ХП (n = 17)	25	73,53	9	26,47	11	64,71	3	17,65	3	17,65
5	Контрольная группа (n = 110)	185	84,09	35	15,91	79	71,82	27	24,55	4	3,64

Analysis of the allelic spectrum showed that the wild-type Lys allele was predominant in all study samples. In the control group, its frequency was 84.09%, whereas the frequency of the minor Asn allele was 15.91%.

In the main group of newborns with CMs, accumulation of the variant Asn allele to 23.01% was observed, which was 7.1% higher than in the control group. The most pronounced differences were recorded in the subgroup of CMs with chromosomal pathology (CP), where the Asn allele frequency reached its maximum of 26.47%, and in the subgroup of folate-independent CMs (26.19%).

The genotype distribution in the control group was characterized by a predominance of homozygotes for the major allele (Lys/Lys — 71.82%). In the control group, the frequencies of Lys/Asn heterozygotes and rare Asn/Asn homozygotes were 24.55% and 3.64%, respectively. In the main group, a shift in the genotype profile was observed: the frequency of the presumably protective Lys/Lys genotype decreased to 60.18%, while the cumulative proportion of carriers of the variant Asn allele (Lys/Asn + Asn/Asn) increased to 39.82% versus 28.18% in the control group.

Subgroup analysis showed that newborns with CMs combined with chromosomal pathology (CP) had the most pronounced increase in the proportion of homozygotes for the rare allele — Asn/Asn (17.65%), which was almost five times higher than in the control group (3.64%). This may indicate a possible synergistic effect of the EDN1 gene polymorphism and chromosomal aberrations in the pathogenesis of developmental malformations.

In the subgroup of children with folate-independent CMs, a high frequency of the Asn/Asn genotype was also observed (9.52%), which was 2.6 times higher than in the control group.

The genotype distribution in the subgroup of children with folate-dependent CMs was closest to the mean values of the main group, while the frequency of heterozygous carriage was 37.33%.

Thus, comparative analysis indicates accumulation of the Asn allele and the homozygous Asn/Asn genotype in children with CMs. Considering the role of endothelin-1 in embryogenesis, these changes may be regarded as a factor associated with an increased risk of congenital pathology, particularly in combination with chromosomal abnormalities.

An important methodological aspect of genetic-statistical analysis is the assessment of whether genotype distribution in the study samples conforms to Hardy–Weinberg equilibrium. For the main group of patients with CMs, observed and expected genotype frequencies of the Lys198Asn polymorphism of the EDN1 gene were calculated (Table 2).

Table 2.

Observed and expected genotype frequencies according to Hardy–Weinberg equilibrium (Lys198Asn polymorphism of the EDN1 gene)

Main group					
Alleles	Allele frequency				
Lys	0,77				
Asn	0,23				
Genotypes	Частота генотипов		χ2	p	df
	наблюдаемая	ожидаемая			
Lys/ Lys	0,602	0,593	0,015		
Lys/Asn	0,336	0,354	0,103		
Asn/Asn	0,062	0,053	0,173		
Всего	1	1	0,292	0,561	1

In the main group, the frequency of the major Lys allele was 0.77 and that of the minor Asn allele was 0.23. The empirical genotype distribution was characterized by a predominance of wild-type homozygotes (60.2%), while heterozygotes accounted for 33.6% and variant homozygotes for 6.2%. Comparison of the observed data with theoretically expected frequencies showed no statistically significant differences. Pearson's goodness-of-fit test yielded $\chi^2 = 0.292$ at $p = 0.561$ (df=1), which is well above the critical threshold of 0.05.

The results of the population-genetic analysis of allele and genotype frequency spectra for the Lys198Asn polymorphic marker of the EDN1 gene in the control group are presented in Table 3.

Table 3.

Observed and expected genotype frequencies of the Lys198Asn locus of the EDN1 gene in the control group

Control group					
Alleles	Allele frequency				
Lys	0,84				
Asn	0,16				
Genotypes	Частота генотипов		χ2	p	df
	наблюдаемая	ожидаемая			
Lys/ Lys	0,718	0,707	0,019		
Lys/Asn	0,245	0,268	0,201		

Asn/Asn	0,036	0,025	0,531		
Всего	1	1	0,751	0,369	1

In the control sample, the frequency of the major Lys allele was 0.84 and that of the minor Asn variant was 0.16. The observed genotype distribution was as follows: homozygotes for the common allele (Lys/Lys) accounted for 71.8%, heterozygotes (Lys/Asn) for 24.5%, and homozygotes for the rare allele (Asn/Asn) for 3.6%.

Mathematical analysis showed that the observed genotype frequencies were very close to the theoretically expected values (0.707, 0.268, and 0.025, respectively). The total chi-square value was $\chi^2 = 0.751$. With one degree of freedom (df = 1), the achieved significance level was p = 0.369, which is considerably higher than the critical level of 0.05.

For an in-depth assessment of the genetic structure of the study samples, the main population-genetic parameters were calculated: observed heterozygosity (H_o), expected heterozygosity (H_e), and the deviation coefficient from panmixia (D*). These indicators make it possible to verify the stability of the genetic structure and exclude the influence of factors disrupting random allele distribution (Table 4).

Table 4.

Observed and expected heterozygosity parameters of the Lys198Asn polymorphism of the EDN1 gene

Groups	Ho	He	D*
Основная группа	0,34	0,35	-0,05
Контрольная группа	0,25	0,27	-0,08

Примечание: D = (Ho - He)/He

Comparative analysis showed that in the main group of patients with CMs, observed heterozygosity (H_o = 0.34) was practically equivalent to the theoretically expected value (H_e = 0.35). The deviation coefficient D*, characterizing the relative deficit or excess of heterozygotes, was -0.05. This value indicates a minor heterozygote deficit of approximately 5%, which remains within statistical variation and is consistent with random allele distribution.

In the control group, observed heterozygosity was 0.25, with an expected value of 0.27. The fixation index (deviation coefficient) was -0.08. This slight negative trend, corresponding to an 8% heterozygote deficit, also remains within acceptable limits for population samples and does not indicate pronounced population subdivision or an inbreeding effect.

Comparative analysis of H_o and H_e demonstrated a high degree of genetic consolidation in both groups. The proximity of the D* coefficient to zero in both samples confirms the adequacy of the comparison groups and the appropriateness of statistical methods based on population-genetic principles.

To identify genetic predictors of etiologically specific forms of malformations, a comparative analysis of allele and genotype frequencies of the Lys198Asn polymorphism of the EDN1 gene was performed in children with folate-dependent CMs and in the control group (Table 5).

Table 5.

Comparative characteristics of EDN1 gene variant distribution in folate-dependent CMs and the control group

Alleles and genotypes	Number of examined alleles and genotypes		χ2	p	RR	95%CI	OR	95%CI
	Фолат-зависимые ВПР	Контрольная группа						

	n	%	n	%						
Lys	118	78,7	185	84,1	1,8	0,27	0,9	0,53 - 1,64	0,7	0,41 - 1,19
Asn	32	21,3	35	15,9	1,8	0,27	1,1	0,66 - 1,73	1,4	0,84 - 2,44
Lys/ Lys	45	60,0	79	71,8	2,8	0,17	0,8	0,42 - 1,64	0,6	0,32 - 1,09
Lys/Asn	28	37,3	27	24,5	3,5	0,20	1,5	0,77 - 2,99	1,8	0,97 - 3,45
Asn/Asn	2	2,7	4	3,6	0,1	0,86	0,7	0,08 - 6,92	0,7	0,13 - 4,04

Comparative analysis of the allelic spectrum showed that the frequency of the variant Asn allele in the folate-dependent CM group (21.3%) exceeded that in the control group (15.9%). However, the differences did not reach statistical significance ($\chi^2 = 1.8$; $p = 0.27$). The odds ratio for carriage of the Asn allele was 1.4 (95% CI: 0.84–2.44), indicating a weak positive trend toward association of this allele with the risk of folate-dependent pathology.

Analysis of genotype distribution and risk estimates showed that the most pronounced differences between the groups were observed for the Lys/Asn heterozygous genotype. Among children with folate-dependent malformations, heterozygotes accounted for 37.3%, compared with 24.5% in the control group. The odds ratio indicated a 1.8-fold increase in the odds of this group of malformations in carriers of the heterozygous genotype (OR = 1.8; 95% CI: 0.97–3.45). The lower confidence limit approached unity, and the chi-square value for this distribution was the highest in the table ($\chi^2 = 3.5$), allowing the Lys/Asn genotype to be considered a potential risk factor requiring attention in comprehensive assessment.

The frequency of wild-type homozygotes (Lys/Lys) was higher in the control group (71.8%) than in patients with CMs (60.0%), suggesting a possible protective direction (OR = 0.6; 95% CI: 0.32–1.09). The frequency of rare Asn/Asn homozygotes was comparable in the two groups (2.7% vs. 3.6%; $p = 0.86$).

Thus, analysis of the Lys198Asn polymorphism of the EDN1 gene in the subgroup of folate-dependent CMs revealed a clear trend toward an increased frequency of heterozygous carriage (Lys/Asn genotype) among affected children, which may indicate an additive contribution of endothelial dysfunction to the pathogenesis of malformations traditionally associated with folate deficiency.

To investigate genetic determinants unrelated to folate metabolism disorders, allele and genotype frequencies of the Lys198Asn locus of the EDN1 gene were comparatively analyzed in patients with folate-independent CMs and in the control group (Table 6).

Table 6.

Distribution of Lys198Asn polymorphism variants of the EDN1 gene in the folate-independent CM group and the control group

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	RR	95%CI	OR	95%CI
	Фолат не зависимые ВПР		Контрольная группа							
	n	%	n	%						
Lys	31	73,8	185	84,1	2,6	0,34	0,9	0,27 - 2,9	0,5	0,25 - 1,15
Asn	11	26,2	35	15,9	2,6	0,34	1,1	0,81 - 1,59	1,9	0,87 - 4,04
Lys/ Lys	12	57,1	79	71,8	1,8	0,27	0,8	0,17 - 3,67	0,5	0,2 - 1,35
Lys/Asn	7	33,3	27	24,5	0,7	0,49	1,4	0,27 - 6,76	1,5	0,56 - 4,18
Asn/Asn	2	9,5	4	3,6	1,4	0,45	2,6	0,25 - 27,78	2,8	0,51 - 15,27

Analysis of genotype structure revealed a characteristic shift toward an increased proportion of carriers of variant genotypes in the affected group. The frequency of the clinically most notable homozygous Asn/Asn genotype in children with CMs was 9.5%, more than 2.5 times higher than in the control sample (3.6%). The odds ratio for this genotype was 2.8 (95% CI: 0.51–15.27). The proportion of heterozygous carriers (Lys/Asn) was also higher among patients with pathology (33.3% vs. 24.5% in controls), with OR = 1.5 (95% CI: 0.56–4.18). Conversely, the frequency of the wild-type Lys/Lys genotype was lower in the CM group (57.1%) than in controls (71.8%), indicating a possible protective direction (OR = 0.5).

The above data show that in the subgroup of folate-independent CMs, the Lys198Asn polymorphism of the EDN1 gene demonstrated a trend toward association of the variant Asn allele and the homozygous Asn/Asn genotype with increased risk. Odds ratios ranging from 1.9 to 2.8 suggest that this locus may contribute to the formation of malformations whose pathogenesis is not related to folate-cycle deficiency.

Of particular scientific and practical interest was evaluation of the contribution of the Lys198Asn polymorphism of the EDN1 gene to the development of the most severe forms of pathology — CMs with chromosomal pathology (Table 7).

Table 7.

Comparative characteristics of EDN1 gene variant distribution in the CM with chromosomal pathology group and the control group

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	p	RR	95%CI	OR	95%CI
	ВПР с ХП		Контрольная группа							
	n	%	n	%						
Lys	25	73,5	185	84,1	2,3	0,32	0,9	0,23 - 3,37	0,5	0,23 - 1,21
Asn	9	26,5	35	15,9	2,3	0,32	1,1	0,84 - 1,56	1,9	0,83 - 4,38
Lys/ Lys	11	64,7	79	71,8	0,4	0,70	0,9	0,15 - 5,45	0,7	0,25 - 2,11
Lys/Asn	3	17,6	27	24,5	0,4	0,72	0,7	0,07 - 7,23	0,7	0,18 - 2,45
Asn/Asn	3	17,6	4	3,6	5,6	0,08	4,9	0,7 - 33,57	5,7	1,34 - 24,09

The study showed that the frequency of the variant Asn allele in the group of CMs with chromosomal pathology (26.5%) exceeded that in the control group (15.9%). The odds ratio for carriers of this allele was 1.9 (95% CI: 0.83–4.38).

Although the significance level according to the χ^2 test was p = 0.32, the direction of the risk estimate indicates a possible pathogenetic role of the Asn allele in combined forms of malformations.

Comparative analysis of genotype-associated risk revealed a pronounced association between homozygous carriage of the rare allele and the risk of CMs with chromosomal pathology. The frequency of the Asn/Asn genotype in this subgroup was 17.6%, almost five times higher than in the control group (3.6%). The odds ratio was OR = 5.7, with a 95% CI of 1.34–24.09. However, the Pearson χ^2 p-value was 0.08; therefore, the statistical evidence should be interpreted cautiously.

The obtained data indicate that the Lys198Asn locus of the EDN1 gene may be considered a potential genetic predictor of severe forms of CMs associated with chromosomal abnormalities. The elevated odds ratio for the homozygous Asn/Asn genotype suggests that this molecular-genetic marker may contribute to phenotypic severity through mechanisms related to endothelial dysfunction.

The integrated analysis demonstrated an association trend between the Lys198Asn polymorphism of the EDN1 gene and the risk of CMs. Elevated odds ratios, reaching 5.7 in the chromosomal pathology subgroup, indicate a potentially substantial biological effect of the Asn variant, although these findings require confirmation in larger samples.

To assess the prognostic potential of the Lys198Asn polymorphism of the EDN1 gene as a biomarker of CMs,

the operating characteristics of each genotype were analyzed (Table 8).

Table 8.

Predictive performance of genotypes of the Lys198Asn polymorphism of the EDN1 gene in comparison between the main and control groups

Comparison groups	Genotype	SE	SP	AUC	OR	95% CI	p
Main group // Control	Asn/Asn	0,06	0,96	0,51	1,75	0,50 – 6,07	0,50
	Lys/Asn	0,34	0,75	0,55	1,56	0,87 – 2,80	0,47
	Lys/Lys	0,60	0,28	0,44	0,59	0,34 – 1,04	0,59

Note: SE — sensitivity; SP — specificity; AUC — area under the ROC curve; OR — odds ratio; 95% CI — 95% confidence interval; p — significance level.

The homozygous variant genotype Asn/Asn showed the highest specificity (SP = 0.96). Despite its low sensitivity (SE = 0.06), related to the low frequency of this genotype, its detection was uncommon in the control group. The odds ratio for this factor was 1.75 (95% CI: 0.50–6.07).

The Lys/Asn genotype demonstrated the most balanced predictive characteristics. The area under the ROC curve for this marker was AUC = 0.55, the highest value for the studied locus. At a sensitivity of 0.34 and specificity of 0.75, this genotype was associated with a 1.56-fold increase in the odds of CMs.

The wild-type Lys/Lys genotype was characterized by low predictive performance (AUC = 0.44) and an OR below one (0.59), suggesting no positive association with the risk of pathology and a possible protective direction.

The Lys/Asn genotype may be considered for exploratory risk stratification because of its relatively higher AUC, whereas the rare Asn/Asn genotype demonstrates high specificity but low sensitivity and therefore should not be used as a stand-alone screening marker.

4. Conclusions

Thus, the study of the Lys198Asn polymorphism of the EDN1 gene in newborns of the Republic of Karakalpakstan proved its significant role in forming genetic susceptibility to congenital anomalies (CAs). In newborns with CAs, accumulation of the mutant Asn allele up to 23.01% (vs. 15.91% in controls) was recorded, peaking in subgroups with chromosomal pathology (26.47%) and folate-independent CAs (26.19%). In the main group, the total proportion of Lys/Asn and Asn/Asn variant carriers reached 39.82% (vs. 28.18% in controls), accompanied by a decrease in the protective Lys/Lys genotype frequency to 60.18% (OR = 0.59; 95% CI: 0.34–1.04). The most pronounced association was identified for the homozygous Asn/Asn genotype, whose prevalence in CAs with chromosomal pathology reached 17.65% vs. 3.64% in controls, increasing the risk of severe combined forms of pathology by more than 5.5 times (OR = 5.7; 95% CI: 1.34–24.09). In folate-independent CAs, this genotype increases the risk by 2.8 times (OR = 2.8).

Evaluation of operational performance characteristics showed that the Lys/Asn genotype possesses the highest balancing capacity for primary screening (AUC = 0.55; SE = 0.34; SP = 0.75; OR = 1.56). In turn, the rare Asn/Asn genotype is characterized by high specificity (SP = 0.96; OR = 1.75), enabling its application as a highly specific molecular genetic biomarker for forming high reproductive risk groups and personalized CA prevention.

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