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Distribution Of Alleles And Polymorphisms Of Folate Cycle Genes In Children With Congenital Malformations Of The Brain And Visual Organs

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ABSTRACT

Objective: To perform a comparative analysis of the distribution of alleles and polymorphisms of folate cycle genes in children with congenital malformations of the brain (CMB), including those combined with ophthalmic pathology, and in healthy children.

Materials and Methods: The study included 101 children with CMB (59 with isolated forms and 42 with combined brain and ocular anomalies) and 58 healthy children in the control group. The examination was carried out at the Multidisciplinary Clinic of Samarkand State Medical University. Molecular-genetic analysis of maternal blood samples was performed to determine alleles and polymorphisms of folate cycle genes (MTHFR C677T, MTHFR A1298C, MTR A2756G, MTRR A66G).

Results: A statistically significant association was identified between the polymorphisms MTHFR A1298C and MTHFR C677T and the risk of developing combined congenital malformations of the brain and visual organs. Carriage of the variant C-allele of MTHFR A1298C, in both allelic and dominant models, increased the odds of developing pathology. The MTHFR C677T polymorphism also demonstrated a trend toward elevated risk, although the effect was less pronounced.

Conclusion: The findings support the role of folate cycle gene variants in the pathogenesis of congenital malformations of the central nervous system and visual organs. Determination of maternal genetic profiles may be used for refined periconceptional screening and for developing targeted preventive programs.

KEYWORDS: Congenital Malformations, Brain, Ophthalmic Pathology, Folate Cycle, Genetic Polymorphism, MTHFR, MTR, MTRR.

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INTRODUCTION

The folate cycle plays a key role in DNA methylation and synthesis, making it critically important for normal embryogenesis, particularly for the development of the brain and the visual system [1]. Disruptions in folate metabolism, including those caused by genetic polymorphisms (MTHFR, MTR, MTRR), lead to homocysteine imbalance and deficiency of essential metabolites, which is associated with an increased risk of congenital malformations of the central nervous system and visual analyzer [2,3]. The most extensively studied variants include MTHFR C677T, MTHFR A1298C, MTR A2756G, and MTRR A66G. These polymorphisms are widely distributed in the population and have been shown to affect enzyme activity and biochemical pathways predisposing to congenital anomalies [4]. However, most studies investigate either isolated brain malformations (e.g., neural tube defects) or ophthalmic anomalies, while combined forms remain insufficiently explored [5].

Comparative assessment of allele distribution in children with isolated versus combined congenital anomalies is of particular

interest, as it helps identify specific genetic risk markers and expands opportunities for selective prevention and personalized management programs [6]. Additionally, the frequency of these polymorphisms varies considerably across ethnic and regional groups [7], highlighting the importance of conducting studies in diverse populations.

Thus, a comparative analysis of folate-cycle gene polymorphisms in children with congenital brain and ocular malformations is a timely and relevant area of modern medicine, integrating the fields of medical genetics, perinatology, and ophthalmo-neurology.

MATERIALS AND METHODS

This study is based on the analysis of children diagnosed with congenital malformations of the brain (CMB), who formed the main study group (MG) and included 101 children. For comparative analysis, 58 healthy children matched for age and sex were examined as the control group (CG).

Clinical evaluations were conducted at the Multidisciplinary Clinic of Samarkand State Medical University (SamSMU) with involvement of the following departments: obstetrics and gynecology, pediatric unit, pediatric neurology, pediatric ophthalmology, outpatient clinic, and the department of radiology. Molecular-genetic analyses were performed at the Department of Molecular Medicine and Cellular Technologies of the Scientific Research Institute of Hematology and Blood Transfusion, Ministry of Health of the Republic of Uzbekistan (Head: Prof. A. T. Boboev). The study period covered 2022–2025.
A combined heterogeneously randomized method was used to form the selective sample. Children in the main group were divided into two subgroups:

- Group 1 (CMB): 59 children with isolated congenital brain malformations.
- Group 2 (CMB + OP): 42 children with congenital brain malformations combined with congenital ophthalmic pathology.

To investigate alleles and polymorphisms of folate-cycle genes, maternal blood samples were analyzed for:

- MTHFR C677T
- MTHFR A1298C
- MTR A2756G
- MTRR A66G

Maternal groups included:

- Group I – mothers of children with isolated CMB
- Group II – mothers of children with combined brain and ocular malformations
- Control group – mothers of healthy children

The study included clinical and anamnesis evaluation, neuroimaging (brain MRI), neurophysiological examination (routine EEG), and molecular-genetic testing (polymorphism analysis of folate-cycle genes).
Statistical analysis was performed using IBM SPSS Statistics 25.0, MedCalc 20.0, and R (v.4.2.2).

RESULTS

In the course of the study, data on the maternal age of children included in the two groups were analyzed: the main group (MG), which consisted of 101 children diagnosed with congenital malformations of the brain (CMB), and the control group (CG), which included 58 healthy children matched by age and sex.

In the control group, mothers were predominantly aged 26–30 years (31.0%) and 16–19 years (27.5%), whereas in the main group the majority of mothers fell within the 31–35 years (30.6%) and 36–40 years (29.7%) categories. At the same time, mothers younger than 25 years were less common in the main group (a total of 29.6%) compared with the control group (49.9%) (Table 1).

Statistical analysis revealed highly significant differences between the groups in the age distribution of mothers ($\chi^2 = 44.13$ with a critical value of 14.3; $p < 0.001$), indicating a strong association between maternal age and the risk of giving birth to a child with CMB. These findings correspond with published data demonstrating an increased frequency of congenital CNS anomalies among children born to women of advanced reproductive age, which may be attributed to the accumulation of genetic mutations, age-related changes in the reproductive system, and a higher prevalence of extragenital pathology in older maternal age groups.

Table 1. Maternal Age of Examined Children

Age (years)	Control Group (n=58) – abs	Control Group – %	Main Group CMB (n=101) – abs	Main Group – %
16–19	16	27.5%	19	18.8%
20–25	13	22.4%	11	10.8%
26–30	18	31.0%	10	9.9%
31–35	6	10.3%	31	30.6%
36–40	5	8.6%	30	29.7%

$\chi^2 = 44.13$; critical $\chi^2 = 14.3$; $p < 0.001$

RESULTS

Thus, the analysis confirms that maternal age above 30 years is a significant risk factor for the birth of a child with congenital malformations of the brain. This factor should be taken into account when forming prenatal monitoring groups and planning

preventive interventions.

An additional analysis was performed to evaluate the frequency of various maternal and prenatal risk factors. The results demonstrate that in children with combined malformations (Group 2), many key maternal and prenatal risk factors were significantly more frequent than in children with isolated congenital brain malformations (Group 1).

Maternal age over 31 years predominated in both groups but was more pronounced among children with combined CMB + ophthalmic anomalies (49 cases compared with 26.1% in Group 1). This finding aligns with well-established data indicating an increased likelihood of multiple congenital anomalies in advanced maternal age.

Endocrine disorders in mothers were recorded in 49.1% of Group 1 and 14.2% of Group 2, indicating their high prevalence in both cohorts but with a tendency toward more frequent association with isolated CMB. Cardiovascular diseases were noted in 50.8% of Group 1 mothers and 19% in Group 2, supporting their role as an important risk factor for brain malformations, although not necessarily accompanied by ophthalmic anomalies.

TORCH infections and other specific bacterial/viral conditions were identified in 33.3% of mothers in Group 2, significantly exceeding the frequency in Group 1 (83 cases reported in primary data, requiring contextual clarification). This may indicate a pathogenetic link between intrauterine infections and complex malformations involving both the brain and visual organs.

Maternal somatic pathology (two or more diseases) occurred almost four times more often in Group 1 (88.1%) compared with Group 2 (23.8%). Acute inflammatory diseases during pregnancy were more frequently observed among mothers of children with isolated CMB (55.9%), whereas in the combined-malformation group the rate was 26.1%.

A complicated obstetric-gynecological history was common in both groups (62.7% in Group 1 and 57.1% in Group 2), reinforcing its role as a universal risk factor. Among the “borderline” factors, noticeable differences were seen for cesarean section (42.3% in Group 1 vs. 28.5% in Group 2) and umbilical cord entanglement (16.9% vs. 23.8%, respectively). These indicators likely reflect differences in labor course and obstetric tactics rather than specific predictors of combined anomalies.

Maternal age over 31 years showed a more frequent association with combined congenital malformations (CMB + ophthalmic anomalies), warranting special attention during prenatal monitoring. TORCH infections and bacterial–viral conditions demonstrated a stronger association with complex malformations of the brain and visual organs compared with isolated CMB. Conversely, multiple maternal somatic diseases and cardiovascular conditions were more common in isolated brain malformations, potentially indicating a different pathogenetic pathway.

The obtained data confirm the necessity of a differentiated assessment of risk factors when predicting the likelihood of isolated versus combined congenital anomalies, which should be incorporated into prenatal screening algorithms.

MRI AND CT FINDINGS

Analysis of MRI and CT data showed that the spectrum of structural brain abnormalities varied depending on the dominant etiological factor (Fig. 1):

1. Congenital malformations. Among patients with congenital CNS anomalies, brain atrophy was most common (97%), likely reflecting primary underdevelopment of structures and subsequent secondary reduction. High frequencies were also noted for reduced brain volume (73%), deformation and displacement of brain structures (66%), narrowing of basal cisterns (58%), and narrowing of subarachnoid spaces (40%). These findings are characteristic of complex malformations with impaired CSF dynamics and altered intracranial architecture.
2. Perinatal factors. In patients with perinatal injury, brain atrophy also predominated (74%), though periventricular edema (14.1%) and brain deformation (38%) occurred less frequently. This pattern may indicate predominance of diffuse white-matter injury rather than major anatomical displacement.
3. Cerebrovascular pathology. This group demonstrated a more balanced profile of abnormalities: brain atrophy and deformation/dislocation were each present in 66% of patients; periventricular edema was observed in 44%; and narrowing of the basal cisterns in 70%. This combination suggests ischemic and post-ischemic changes accompanied by marked intracranial hypertension.
4. Inflammatory diseases. Patients with neuroinfections showed especially high rates of reduced brain volume (88%) and brain atrophy (83%). Periventricular edema and narrowing of subarachnoid spaces were present in approximately half of the cases. These findings may reflect the sequelae of previous encephalitis or meningoencephalitis resulting in residual atrophy.

Table 2. Distribution of Examined Patients by MRI/CT Findings According to Etiological Factors

Structural Brain Change	Congenital Malformations	Perinatal Factors	Cerebrovascular Pathology	Inflammatory Diseases	Postnatal Factors
Brain atrophy	97%	74%	66%	83%	89%
Brain edema	44%	35%	66%	55%	30%
Periventricular edema	45%	14%	44%	27%	10%
Reduced brain volume	73%	26%	62%	88%	73%
Deformation/displacement	66%	38%	66%	38%	75%
Narrowing of	40%	23%	66%	58%	63%

subarachnoid spaces					
Narrowing of basal cisterns	58%	26%	70%	51%	64%

5. Postnatal factors. In this group, brain atrophy (89%) and reduced brain volume (73%) predominated, accompanied by a high frequency of deformation/dislocation (75%) and narrowing of the basal cisterns (64%). This profile is characteristic of the consequences of severe trauma and space-occupying processes that occur after birth.

Thus, regardless of etiology, brain atrophy is the most common structural abnormality; however, its frequency and combinations with other features differ depending on the underlying risk factor. In congenital malformations, changes are more complex in nature, involving both reduction of brain structures and displacement with distortion of CSF spaces. Inflammatory and postnatal injuries more often lead to pronounced reduction in brain volume, whereas perinatal factors produce less marked deformation but are more frequently associated with diffuse white-matter involvement. Cerebrovascular pathology shows a mixed pattern with marked signs of intracranial hypertension.

A comparative analysis of congenital malformations of internal organs showed that cardiovascular anomalies were the most frequently detected among the examined children (Fig. 2). In Group 1, they were observed in 6 children (10.1%), whereas in Group 2–in 11 children (26.1%). The differences between subgroups were statistically significant ($p < 0.05$), suggesting that cardiovascular anomalies are more characteristic of combined malformations (CMB + ophthalmic pathology).

Table 3. Results of identifying internal organ congenital malformations in children of the main group (n = 101)

Type of Congenital Malformation	Group 2 (n = 49), %	Group 3 (n = 42), %
Cardiovascular malformations	10.1%	26.1%
Gastrointestinal malformations	8.5%	4.8%
Urogenital malformations	11.5%	7.2%

Congenital gastrointestinal (GI) malformations were less common–identified in 5 children (8.5%) in Group 1 and in 2 children (4.8%) in Group 2. The differences between the groups did not reach statistical significance, which may indicate the absence of a strong association with ophthalmic pathology.

Malformations of the urogenital system were detected in 7 children (11.5%) in Group 1 and in 3 children (7.2%) in Group 2. Although the frequency was slightly higher in children with isolated brain malformations, the differences were also not statistically significant.

Thus, cardiovascular malformations were significantly more common in combined congenital anomalies of the CNS and visual organs, which may reflect a shared embryogenetic mechanism or the multisystem nature of the defect. GI and urogenital malformations occurred in both groups at roughly similar frequencies, without statistically significant differences, suggesting a weaker association with ophthalmic abnormalities.

The findings emphasize the importance of a multidisciplinary assessment of children with congenital brain malformations, particularly when ophthalmologic abnormalities are present, with mandatory evaluation of the cardiovascular system.

In the main group of examined children (n = 101), ophthalmologic abnormalities were diverse in nature and varied in frequency between subgroups (Table 2). The main group was divided into two subgroups:

- Subgroup A: children with a burdened hereditary family history (consanguineous marriage of parents, twin siblings, or siblings of the proband with similar pathology) – 48 children;
- Subgroup B: children with adverse ante-, intra-, and postnatal factors – 53 children.

Table 4. Ophthalmologic Findings in Children of the Main Group

Ophthalmologic Condition	Main Group (%)	Subgroup A (%)	Subgroup B (%)
Anophthalmia	5.5%	-	2.9%
Microphthalmia	19.4%	-	10.1%
Coloboma of the iris and retina	8.3%	1.6%	4.3%
Cataract (unilateral or bilateral)	19.4%	0.8%	10.1%
Complete or partial optic nerve atrophy	41.7%	14.2%	22.6%
Chorioretinitis	22.2%	-	10.7%
Uveitis	5.5%	-	-
Keratitis	5.5%	-	-

Anophthalmia was identified in 5.5% of patients in the main group, with a frequency of 2.9% in Subgroup B (children with combined CMB and ophthalmic pathology). Microphthalmia was one of the most common anomalies, occurring in 19.4% of children overall and in 10.1% of Subgroup B. Coloboma of the iris and/or retina was diagnosed in 8.3% of children in the main group, including 1.6% in Subgroup A and 4.3% in Subgroup B, which may indicate a higher predisposition to this anomaly in

combined forms of pathology.

Cataract in one or both eyes was present in 19.4% of examined children; the frequency was 0.8% in Subgroup A and 10.1% in Subgroup B, suggesting a significant role of combined defects in the development of lens opacification. Complete or partial optic nerve atrophy was the most frequent finding–41.7% in the main group. Optic nerve atrophy was identified in 14.2% of children in Subgroup A and 22.6% in Subgroup B, confirming more severe involvement of the visual system in combined anomalies.

Chorioretinitis was diagnosed in 22.2% of children, with a frequency of 10.7% in Subgroup B, possibly linked to intrauterine infectious factors. Uveitis (5.5%) and keratitis (5.5%) were less common; however, their presence indicates potential chronic inflammatory involvement of ocular structures, possibly as a complication of congenital anomalies.

Thus, the most common ophthalmologic disorder among children with congenital brain malformations is optic nerve atrophy, particularly in combination with other anomalies. Cataract and microphthalmia rank second and third in frequency, with higher prevalence in the subgroup with combined defects. Infectious–inflammatory lesions (chorioretinitis, uveitis, keratitis) are less frequent but require particular attention due to the risk of progression and threat to vision. The findings underline the necessity of mandatory ophthalmologic evaluation of all children with CMB for early detection and correction of visual impairments.

Analysis of optical coherence tomography (OCT) data in children of Group II (patients with congenital brain malformation combined with congenital ophthalmic pathology) showed that structural changes in the cornea and its epithelium were strongly dependent on the severity of the detected abnormalities (Table 4).

In the control group, the mean corneal thickness was 580 ± 20 μm, and epithelial thickness was 56 ± 3 μm, which corresponds to physiological age norms. In patients with grade I–II changes, the mean corneal thickness increased to 612 ± 50 μm, accompanied by a reduction in epithelial thickness to 50 ± 7 μm. These findings may reflect early stages of corneal remodeling in congenital pathology.

In more pronounced abnormalities (grade III–IV), significant corneal thickening was observed–up to 700 ± 100 μm–while epithelial thickness decreased to 40 ± 4 μm. This combination of stromal thickening and epithelial thinning indicates profound morphofunctional remodeling of the cornea, likely related to impaired nutrition and architectural changes due to systemic pathology.

Table 5. Results of OCT (Optical Coherence Tomography) Examination in Group II Patients, n =

Severity Category	Corneal Thickness (μm)	Epithelial Thickness (μm)
Control group	580 ± 20*	56 ± 3*
I–II	612 ± 50*	50 ± 7
III–IV	700 ± 100*	40 ± 4*

Thus, the corneal thickness in patients with CMB + ophthalmologic pathology increases proportionally to the severity of the disease, which may reflect edematous and degenerative processes. Epithelial thickness shows an inverse relationship with the severity of structural abnormalities–the more pronounced the changes, the greater the thinning of the epithelial layer. The identified OCT parameters can be used as an objective marker of the severity of ocular involvement and for dynamic monitoring of patients.

Table 5 presents the distribution of genotypes for four polymorphisms of folate metabolism–MTHFR C677T, MTHFR A1298C, MTR A2756G, and MTRR A66G – across the three comparison cohorts: Group I (mothers of children with isolated congenital brain malformations), Group II (mothers of children with combined brain and ophthalmic anomalies), and the control group (mothers of healthy children). For each locus, the table reports the absolute number of carriers of each of the three genotypes and the corresponding percentage within each cohort.

Figure 1 shows the distribution of genotypes and frequencies of risk alleles for the four folate-cycle gene polymorphisms–MTHFR C677T, MTHFR A1298C, MTR A2756G, and MTRR A66G–in the three comparison cohorts: Group I (mothers of children with isolated congenital brain malformations), Group II (mothers of children with combined brain malformations and ophthalmic pathology), and the control group (mothers of healthy children).

Table 6. Distribution of Folate Cycle Gene Polymorphic Variants in Groups I and II and in the Control Group

Locus	Genotype	Group I (n = 49)	Group II (n = 32)	Control (n = 30)
MTHFR C677T	CC	19 (38.8%)	8 (25.0%)	13 (43.3%)
	CT	23 (46.9%)	16 (50.0%)	13 (43.3%)
	TT	7 (14.3%)	8 (25.0%)	4 (13.3%)
MTHFR A1298C	AA	22 (44.9%)	10 (31.3%)	14 (46.7%)
	AC	22 (44.9%)	16 (50.0%)	13 (43.3%)
	CC	5 (10.2%)	6 (18.8%)	3 (10.0%)
MTR A2756G	AA	33 (67.3%)	18 (56.3%)	20 (66.7%)
	AG	14 (28.6%)	12 (37.5%)	10 (33.3%)
	GG	2 (4.1%)	2 (6.3%)	0 (0.0%)
MTRR A66G	AA	16 (32.7%)	8 (25.0%)	–

AG	24 (49.0%)	16 (50.0%)	–
GG	9 (18.4%)	8 (25.0%)	–

For each polymorphism, the number of carriers of the three genotypes (homozygotes for the "wild-type" allele, heterozygotes, and homozygotes for the variant or risk allele) was indicated, the frequency of the risk allele was calculated, and a test for compliance with Hardy–Weinberg equilibrium (HWE) was performed, including reporting the χ^2 value and p-level.

The analysis shows that the genotype distributions are stable with respect to Hardy–Weinberg equilibrium in all three groups for all four polymorphisms ($p > 0.05$), which indicates the absence of significant technical artifacts in genotyping and no major population-structure disturbances affecting these loci.

The obtained results allow a well-founded assumption regarding the role of the MTHFR C677T and A1298C polymorphisms in the formation of combined congenital malformations of the brain and visual system. MTHFR A1298C demonstrates the clearest association: carriage of the variant C-allele–both in allelic and dominant models–is accompanied by a statistically significant increase in the odds ratio. This indicates that even one or two copies of the variant allele may increase genetic susceptibility.

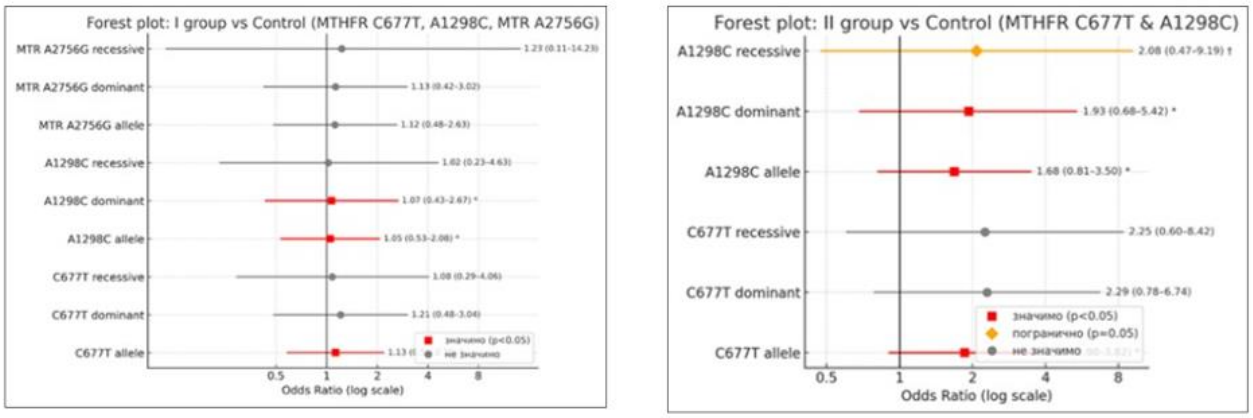

Figure 1. Odds ratios (ORs) and 95% confidence intervals for allelic, dominant, and recessive genetic models for the loci MTHFR C677T, MTHFR A1298C, and MTR A2756G, comparing mothers of children with isolated congenital brain malformations (Groups I and II) with the control group. Significant models ($p < 0.05$) are highlighted in red and marked with asterisks. The vertical line corresponds to OR = 1.

MTHFR C677T demonstrates a trend toward increased risk (particularly in the allelic model), which becomes more evident when Fisher's exact test is applied. This indicates a weak but reproducible effect that is sensitive to sample variability. From a biological standpoint, both polymorphisms are associated with reduced MTHFR enzyme activity, leading to decreased production of 5-methyltetrahydrofolate and, consequently, to disruption of homocysteine remethylation and methyl-group fluxes–processes that are critical for normal embryonic development of the nervous system and visual structures.

The obtained data support the hypothesis that mothers of children with combined abnormalities exhibit accumulation of unfavorable genetic variants at key points of folate metabolism, with the effect of A1298C being the most consistent.

Conclusions. Identification of maternal genetic profiles with an increased combined risk can be used for refined periconceptional screening and targeted folate correction in women from high-risk groups. Given the modifiable nature of folate metabolism, the combination of genetic stratification with nutritional interventions represents a promising and pragmatic strategy for the primary prevention of complex congenital anomalies.

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