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GENETIC FACTORS OF OPHTHALMIC MORBIDITY IN CHILDREN AGED 4-12 YEARS: A RETROSPECTIVE COHORT STUDY

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ABSTRACT
A retrospective study was conducted to analyze the structure of ophthalmic morbidity and the pattern of hereditary burden in children aged 4-12 years based on the review of 1,280 outpatient records of patients under dispensary follow-up by an ophthalmologist. The relevance of the work is determined by the significant prevalence of visual impairments in the pediatric population and the need for early identification of risk groups to prevent the progression of ophthalmic pathology. The frequency of various nosological forms and the presence of hereditary burden through maternal and paternal lines, as well as among grandparents and siblings, were assessed. The dominant nosologies were found to be myopia (38.4%) and refractive and accommodative disorders (31.7%). The frequency of myopia increased from younger to older age groups, rising from 22.1% to 51.2% ($p<0.001$), and was higher in girls (40.8%) compared to boys (36.2%; $p=0.042$). Hereditary burden was documented in 68.9% of patients, with a significant predominance of the maternal line (41.3%) over the paternal line (28.7%; $p<0.001$). Among patients with a positive family history, the proportion of myopia reached 51.2%, and retinal diseases – 16.4%, exceeding the corresponding rates in the overall sample (38.4% and 9.2%, respectively). The frequency of retinal diseases was higher in cases of maternal burden (18.4%) compared to paternal burden (13.8%; $p=0.047$), which may reflect the role of mitochondrial and X-linked inheritance mechanisms. The obtained data confirm the high significance of hereditary factors, particularly through the maternal line, in the formation of ophthalmic morbidity in children.

KEYWORDS: myopia, hereditary burden, retinal diseases, children, family history, ophthalmic morbidity.

INTRODUCTION
Hereditary and genetically determined diseases of the visual organ occupy a significant place in the structure of pediatric ophthalmic pathology and represent one of the leading causes of low vision and blindness in childhood. To date, approximately 500 genes have been identified in which mutations give rise to ocular pathologies, underscoring the profound genetic heterogeneity of ophthalmic diseases [1]. According to population-based epidemiological studies, hereditary etiology is identified in approximately 30% of patients with ocular diseases, while its proportion in the structure of blindness and low vision ranges from 42% to 84% across different populations [2]. Numerous studies confirm that 42.3% of ocular diseases are attributable to hereditary factors [3]. Predisposition to ophthalmic diseases is transmitted across generations; autosomal dominant, autosomal recessive, and X-linked inheritance patterns are distinguished [4, 5]. Of particular interest is mitochondrial inheritance, in which mutations in mitochondrial DNA are transmitted exclusively through the maternal line, since the zygote receives mitochondria solely from the oocyte cytoplasm [6, 7]. A classic example is Leber hereditary optic neuropathy (LHON), with a frequency of 1:30,000-50,000, caused by mutations in the MT-ND1, MT-ND4, MT-ND4L, MT-ND5, and MT-ND6 genes, manifesting at a young age, with males affected 4-5 times more frequently than females [8, 9]. Autosomal dominant optic atrophy, manifesting in the first decade of life, is considered the most common hereditary neuropathy, with a prevalence of 1:10,000-1:50,000 [10, 11].
Inherited retinal diseases (IRDs) constitute a clinically and genetically heterogeneous group. In a Dutch pediatric cohort study (624 patients under 20 years of age), the most frequent phenotypes were retinitis pigmentosa (20%), Leber congenital amaurosis (16%), X-linked retinoschisis (10%), and achromatopsia (10%); a genetic cause was identified in 76% of cases, with the most frequently involved genes being RS1, CEP290, CNGB3, and CRB1 [12, 13]. Stargardt disease (prevalence 1:10,000) is caused by mutations in the ABCA4 gene, inherited in an autosomal recessive manner; over 900 pathogenic variants have been identified to date [14].
High-grade myopia, a multifactorial disease, makes a substantial contribution to ophthalmic pathology. More than 18 susceptibility loci (MYP1-MYP18) with different inheritance patterns have been identified [15, 16]. A novel

potentially pathogenic missense variant in the KDM5C gene on the X chromosome, associated with X-linked high myopia, has recently been described [17]. Data on sex differences in the prevalence of refractive errors highlight the role of X-chromosomal genes [18]. Twin and pedigree studies demonstrate the heritability of myopia at 60-90% [19]. Family aggregation analysis (Beaver Dam Eye Study) revealed significant positive correlations between siblings (0.33), parents and offspring (0.17), and cousins (0.10), confirming the polygenic nature of refractive error inheritance [20].

The development of hereditary eye diseases may be triggered by external factors during pregnancy: viral infections, intoxications, ionizing radiation, hormonal disturbances, Rh incompatibility, and parental age [21]. It is important to note that it is the predisposition, rather than the disease itself, that is inherited; for example, a mutation in the RASGRF1 gene increases the risk of myopia, but its realization depends on the child's growth and developmental conditions [22].

The study of hereditary factors in pediatric ophthalmology has diagnostic, prognostic, and therapeutic significance. Identification of the genetic variant is necessary for determining the inheritance pattern, calculating risk in affected families, and planning preventive measures [23]. Medical-genetic counseling is becoming an integral part of care, and in the era of gene therapy, early diagnosis opens up possibilities for pathogenetic treatment [24, 25].

The aim of this study was to evaluate the structure of ophthalmic morbidity and characterize the pattern of hereditary burden across different lines of kinship (maternal, paternal, grandparents, and siblings) based on a retrospective analysis of outpatient records of children aged 4-12 years under ophthalmological dispensary follow-up.

MATERIALS AND METHODS

A retrospective analytical study was conducted based on the review of medical documentation of patients in the pediatric ophthalmology department. The study objects were outpatient records of children aged 4 to 12 years inclusive under dispensary follow-up by an ophthalmologist. The total sample size comprised 1,280 records. Inclusion criteria were the presence of a confirmed ophthalmic diagnosis, regularity of dispensary follow-up (at least once per year), and completeness of the family history section. Records lacking data on hereditary burden, as well as those with unspecified or presumptive diagnoses, were excluded. The review of documentation was carried out in compliance with ethical principles and personal data protection requirements; identifying information was not recorded.

For each record, the patient's sex and age at the time of the last examination were documented, along with the primary clinical diagnosis coded according to ICD-10. For statistical analysis, all nosological forms were grouped into five categories: myopia; refractive and accommodative disorders (accommodative spasm, hypermetropia, astigmatism, anisometropia); retinal and optic nerve diseases (dystrophic changes, optic nerve atrophy, retinopathy); inflammatory diseases (conjunctivitis, keratitis, uveitis, blepharitis with chronic or recurrent course); and other conditions (congenital cataract, strabismus, nystagmus, ptosis, dacryocystitis).

Data on hereditary burden were extracted from the "Family History" section. The presence of ophthalmic diseases in relatives was assessed separately across four categories: maternal line (mother, maternal grandmother); paternal line (father, paternal grandmother); grandparents without lineage specification; and siblings. For each patient, the presence or absence of a positive family history was recorded for each category.

Statistical analysis was performed using Microsoft Excel and statistical software packages. For categorical variables, absolute frequencies and percentages were calculated; for quantitative variables, arithmetic means and standard deviations were determined. Comparison of frequencies between groups was performed using the Pearson chi-square test with Yates' continuity correction. Differences were considered statistically significant at $p<0.05$. Results are presented as tables and charts.

The study was conducted as part of the student research work at Stavropol State Medical University. No additional intervention was performed in the diagnostic or treatment process; data collection was limited to the analysis of existing documentation, consistent with the criteria for retrospective studies.

RESULTS

A total of 1,280 outpatient records of children under ophthalmological dispensary follow-up were reviewed. All records met the inclusion criteria.

Males predominated in the sample, accounting for 52.3% (n=669), while females comprised 47.7% (n=611). Patient age ranged from 4 to 12 years, with a mean of 7.8±2.4 years. The largest number of observations fell within the 7-9 years (39.5%, n=506) and 10-12 years (36.3%, n=465) age groups; children aged 4-6 years accounted for 24.2% (n=309). Age and sex distribution is presented in Figure 1.

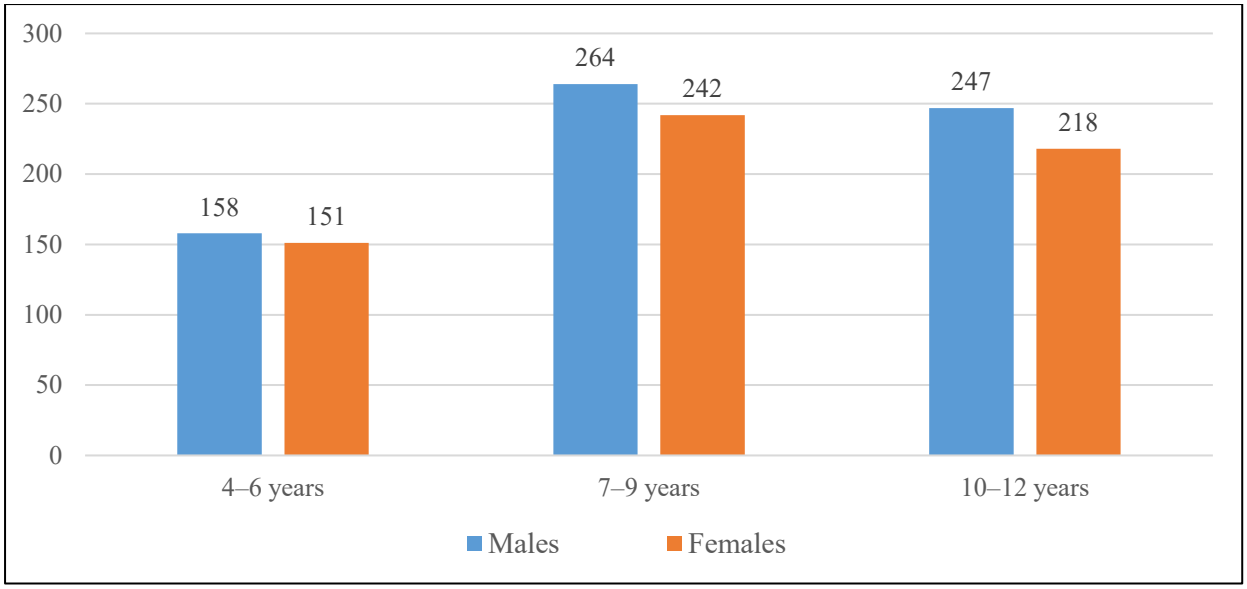

Figure 1. Distribution of patients by age and sex.

The most common pathology was myopia, observed in 38.4% of patients (n=491), among which low-grade myopia (up to 3.0 D) predominated (58.0%, n=285), moderate myopia (3.25-6.0 D) accounted for 31.2% (n=153), and high-grade myopia (over 6.0 D) for 10.8% (n=53). Refractive and accommodative disorders were recorded in 31.7% (n=406), with accommodative spasm being the leading diagnosis (41.9%, n=170), hypermetropia in 33.0% (n=134), astigmatism in 19.5% (n=79), and anisometropia in 5.6% (n=23).

Retinal and optic nerve diseases were diagnosed in 9.2% (n=118), including retinal dystrophic changes (48.3%, n=57), partial optic nerve atrophy (27.1%, n=32), and retinopathy (16.1%, n=19). Inflammatory diseases were noted in 12.5% (n=160), predominantly chronic conjunctivitis (44.4%, n=71) and recurrent blepharitis (30.6%, n=49). Other conditions accounted for 8.2% (n=105): strabismus (38.1%, n=40), congenital cataract (19.0%, n=20), nystagmus (14.3%, n=15), ptosis (9.5%, n=10), and other rare pathologies (19.1%, n=20). The distribution of nosological groups by sex is presented in Table 1.

Table 1. Distribution of nosological forms by patient sex

Nosological group	Males (n=669)	Females (n=611)	Total (n=1,280)	χ^2, p
Myopia	36.2% (242)	40.8% (249)	38.4% (491)	χ^2=4.12; p=0.042*
Refractive and accommodative disorders	32.1% (215)	31.3% (191)	31.7% (406)	χ^2=0.08; p=0.779
Retinal and optic nerve diseases	9.7% (65)	8.7% (53)	9.2% (118)	χ^2=0.44; p=0.507
Inflammatory diseases	13.0% (87)	11.9% (73)	12.5% (160)	χ^2=0.35; p=0.555
Other conditions	9.0% (60)	7.3% (45)	8.2% (105)	χ^2=1.18; p=0.277

Note: * – p<0.05.

Statistically significant sex differences were observed only for myopia, with a higher frequency in girls than in boys (χ^2=4.12; p=0.042). No significant differences were found for the remaining groups.

Age-related dynamics are presented in Table 2. The frequency of myopia increased from younger to older age groups: 22.1%, 39.6%, 51.2% (χ^2=65.5; p<0.001). Refractive and accommodative disorders, conversely, decreased: 42.6%, 32.0%, 23.7% (χ^2=35.1; p<0.001). No significant age-related differences were observed for the remaining groups.

Table 2. Distribution of nosological forms by patient age

Nosological group	4-6 years (n=309)	7-9 years (n=506)	10-12 years (n=465)	χ^2, p
Myopia	22.1% (68)	39.6% (200)	51.2% (238)	χ^2=65.5; p<0.001*
Refractive and accommodative disorders	42.6% (132)	32.0% (162)	23.7% (110)	χ^2=35.1; p<0.001*
Retinal and optic nerve diseases	8.7% (27)	9.9% (50)	8.8% (41)	χ^2=0.48; p=0.787
Inflammatory diseases	14.2% (44)	11.3% (57)	12.7% (59)	χ^2=2.92; p=0.232
Other conditions	10.4% (32)	7.3% (37)	7.7% (36)	χ^2=2.82; p=0.244

*Note: * – p<0.001.*

Hereditary burden was documented in 68.9% of records (n=882); in 31.1% (n=398), no information was available. The distribution by line of kinship is presented in Table 3. Burden was most frequently recorded through the maternal line – 41.3% (n=364), and significantly less frequently through the paternal line – 28.7% (n=253) (χ^2=12.31; p<0.001). Through grandparents – 18.5% (n=163), and through siblings – 12.4% (n=109).

Table 3. Frequency of hereditary burden by line of kinship

Line of kinship	Proportion of patients	Absolute number
Maternal line	41.3%	364
Paternal line	28.7%	253
Grandparents	18.5%	163
Siblings	12.4%	109

In 15.6% (n=138), burden was noted simultaneously through both maternal and paternal lines; combination with siblings – in 8.3% (n=73) through the maternal line and 5.7% (n=50) through the paternal line; triple combination – in 3.1% (n=27).

Comparative analysis of the nosological profile according to hereditary burden (Table 4) showed that patients with a positive family history had higher proportions of myopia (51.2% vs. 38.4%; χ^2=20.80; p<0.001) and retinal diseases (16.4% vs. 9.2%; χ^2=10.52; p=0.001). The frequency of refractive and accommodative disorders, conversely, was lower (25.8% vs. 31.7%).

Table 4. Nosological structure in patients with and without hereditary burden

Nosological group	Positive history (n=882)	Negative history (n=398)	χ^2, p
Myopia	51.2% (452)	9.8% (39)	χ^2=20.80; p<0.001***
Refractive and accommodative disorders	25.8% (228)	44.7% (178)	χ^2=17.92; p<0.001***
Retinal and optic nerve diseases	16.4% (145)	6.0% (24)	χ^2=10.52; p=0.001**
Inflammatory diseases	11.6% (102)	14.5% (58)	χ^2=2.31; p=0.129
Other conditions	5.8% (51)	13.6% (54)	χ^2=4.57; p=0.032*

Note: * p<0.05; ** p<0.01; *** p<0.001. Percentages of the group total are shown in parentheses

Analysis of the nosological structure according to the line of kinship (Table 5) revealed that with maternal burden, the frequency of retinal diseases was higher than with paternal burden (18.4% vs. 13.8%; χ^2=3.95; p=0.047). With burden through siblings, myopia (58.7%) and retinal diseases (21.1%) were most frequently recorded.

Table 5. Nosological structure according to the line of hereditary burden

Nosological group	Maternal (n=364)	Paternal (n=253)	Siblings (n=109)	Grandparents (n=163)
Myopia	52.7% (192)	48.6% (123)	58.7% (64)	50.3% (82)
Refractive and accommodative disorders	24.2% (88)	28.1% (71)	20.2% (22)	26.4% (43)
Retinal and optic nerve diseases	18.4% (67)	13.8% (35)	21.1% (23)	16.6% (27)
Inflammatory diseases	10.2% (37)	12.6% (32)	6.4% (7)	11.0% (18)
Other conditions	4.5% (16)	6.7% (17)	3.7% (4)	6.1% (10)

The frequency of hereditary burden by age is presented in Figure 2: 62.8% in children aged 4-6 years, 70.9% in 7-9 years, and 71.0% in 10-12 years; differences were not statistically significant (χ^2=3.26; p=0.196).

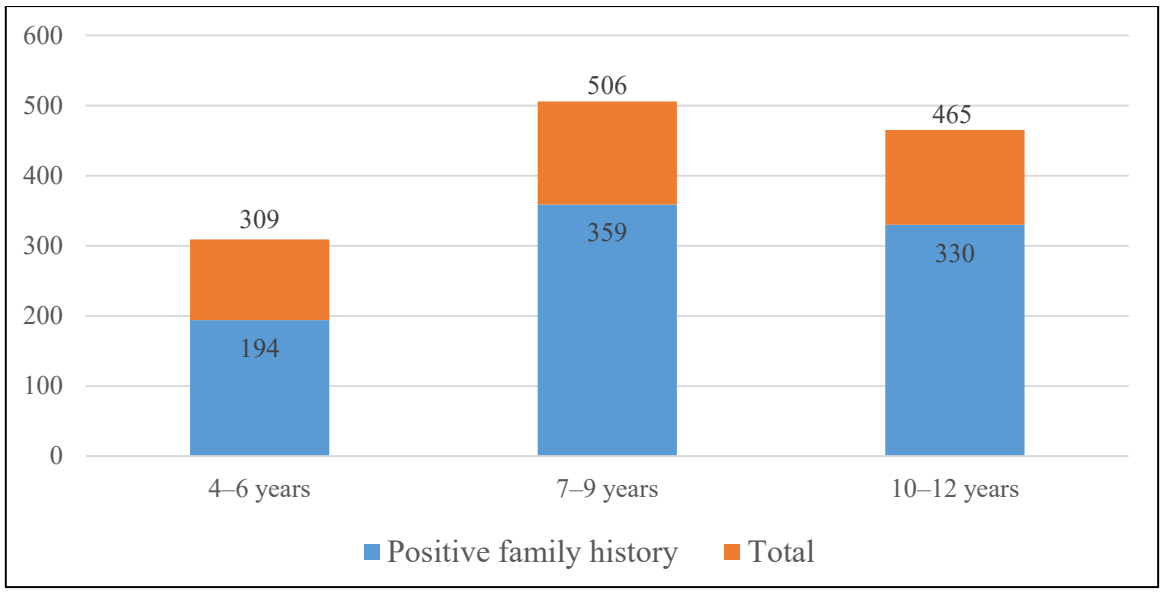

Figure 2. Frequency of hereditary burden by age.

Thus, the analysis allowed us to establish the structure of ophthalmic morbidity in the studied pediatric population, identify significant sex and age differences, and quantitatively characterize hereditary burden across different lines of kinship.

DISCUSSION

This retrospective study of 1,280 outpatient records of children under ophthalmological follow-up provided data on the structure of ophthalmic morbidity and the pattern of hereditary burden in the pediatric population.

The predominance of myopia (38.4%) in the structure of pediatric ophthalmic pathology is consistent with epidemiological data demonstrating a steady increase in the prevalence of refractive errors in the pediatric population [26]. The age-related dynamics (an increase in myopia from 22.1% in the 4-6 years group to 51.2% in the 10-12 years group) reflects the natural progression of refractogenesis, most intense at primary school age, which corresponds to data from large epidemiological studies showing the peak of myopia progression at 7-12 years [27]. The concomitant decrease in the frequency of refractive and accommodative disorders (from 42.6% to 23.7%) is explained by the transformation of accommodative spasm into true myopia [28].

The predominance of myopia in girls (40.8%) compared to boys (36.2%) is consistent with data on the role of X-chromosomal genes in the development of refractive errors [29], as well as with differences in the rates of puberty and eyeball growth [30, 31]. The influence of behavioral factors, including characteristics of visual load at school age, which may differ between boys and girls, cannot be excluded [32].

The high frequency of positive family history (68.9%) indicates a significant genetic component in the etiology of pediatric ophthalmic diseases. This indicator is comparable with the results of large family studies showing a 2- to 8-fold increase in the risk of myopia in the presence of parental disease [33]. Heritability of refractive errors according to twin studies is estimated at 60-90% [34].

The most significant finding is the reliable predominance of hereditary burden through the maternal line (41.3%) compared to the paternal line (28.7%). This phenomenon may be explained by mitochondrial inheritance of certain ophthalmic diseases, in which pathogenic mitochondrial DNA mutations are transmitted exclusively through the maternal line (classic example – LHON) [35]. Other mitochondrial syndromes with ophthalmic manifestations (MIDD, MELAS), also demonstrating maternal inheritance, have been described [36]. Furthermore, mothers are generally better informed about the health status of their relatives, which may lead to more complete history collection through the maternal line (the "maternal memory effect") [37]. The influence of genomic imprinting, in which mutations inherited from the mother may have a more pronounced phenotypic effect, cannot be excluded [38].

In patients with a positive family history, the proportion of myopia reaches 51.2%, significantly higher than in the overall sample. This result is consistent with the identification of more than 18 susceptibility loci (MYP1-MYP18) and more than 160 genetic variants associated with myopia, many of which are involved in the regulation of eyeball growth, retinal signal transduction, and scleral metabolism [39, 40]. Myopia represents a classic example of a multifactorial disease in which genetic predisposition is realized through the participation of environmental factors.

The statistically significant increase in the frequency of retinal and optic nerve diseases in patients with hereditary burden (16.4% vs. 9.2%) is expected, given that inherited retinal diseases belong to monogenic disorders with a high risk of inheritance [41]. More than 360 genes associated with IRDs have been described in the literature [42].

The frequency of retinal diseases was higher with maternal burden (18.4%) than with paternal burden (13.8%), which may be attributable not only to mitochondrial mechanisms but also to X-linked inheritance of some forms of retinal dystrophies [43].
The frequency of burden through siblings (12.4%) reflects the risk of involvement in families with an already affected child and has practical significance for medical-genetic counseling, where the risk of recurrence depends on the inheritance pattern and may range from 25% to 50% [44, 45].
Study limitations are associated with the retrospective design and the use of data from outpatient records, where family history was based on parental interview rather than molecular genetic testing, which may have led to an underestimation of hereditary cases [46]. Furthermore, the sample included only children already under dispensary follow-up, limiting extrapolation to the general population. The study did not differentiate between monogenic and multifactorial forms.
Despite these limitations, the results have practical significance. They confirm the need for systematic collection of family history during ophthalmic examination of children. Patients with a positive family history, especially through the maternal line, belong to a high-risk group and require earlier dispensary follow-up and prevention of myopia progression (low-dose atropine, orthokeratology lenses) [47]. The results substantiate the advisability of medical-genetic counseling for families, which, in the era of gene therapy for inherited retinal diseases, is of critical importance [48, 49].
The development of hereditary eye diseases is not limited to genetic factors – periconceptional exposures, infections, and teratogenic factors that may modulate phenotypic expression are also important [50]. A promising direction for further research is the conduct of prospective studies with molecular genetic testing to identify specific genetic variants and assess the interaction of genetic and environmental factors [51].

CONCLUSION

This retrospective study of 1,280 outpatient records of children aged 4-12 years under ophthalmological follow-up allowed us to establish the structure of ophthalmic morbidity and characterize hereditary burden in the pediatric population.
The leading nosological forms are myopia (38.4%) and refractive and accommodative disorders (31.7%), accounting for more than 70% of all ophthalmic pathology. The frequency of myopia increases with age (from 22.1% in the 4-6 years group to 51.2% in the 10-12 years group), while the proportion of refractive and accommodative disorders decreases, reflecting the transformation of accommodative spasm into true myopia. A significant predominance of myopia was found in girls (40.8%) compared to boys (36.2%).
Hereditary burden was documented in 68.9% of patients, with a statistically significant predominance of the maternal line (41.3%) over the paternal line (28.7%). This difference may be due to the mitochondrial inheritance pattern of some ophthalmic diseases, as well as to the characteristics of family history collection. Indications of disease in grandparents were present in 18.5% of patients, and in siblings in 12.4%.
Among patients with a positive family history, the proportion of myopia reaches 51.2%, and retinal and optic nerve diseases – 16.4%, significantly exceeding the corresponding rates in the overall sample (38.4% and 9.2%, respectively). The highest frequency of retinal diseases was observed with maternal burden (18.4%), consistent with the concepts of mitochondrial and X-linked inheritance of retinal dystrophies.
The results substantiate the need for comprehensive family history collection during initial ophthalmic examination of children. Children with a positive family history, particularly through the maternal line, belong to a high-risk group and require earlier dispensary follow-up, more frequent preventive examinations, and the application of modern methods for preventing myopia progression. The identified patterns confirm the advisability of medical-genetic counseling for families with hereditary burden of ophthalmic diseases.

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Ethics Statement: The study was conducted as a retrospective analysis of anonymized outpatient medical records and did not involve any intervention in the diagnostic or treatment process, nor any direct contact with patients. In accordance with the principles of the Declaration of Helsinki and institutional guidelines, ethical approval was not required for this type of study. All data were handled in compliance with personal data protection requirements, and identifying information was not recorded or used at any stage of the analysis.

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