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Anophthalmia and Microphthalmia in Pakistan: Current Genetic Insights and Future Perspectives

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ABSTRACT

Anophthalmia and microphthalmia (A/M) are genetic disorders characterized by the absence or reduced size of the ocular globe, as compared to the globe size of the normal population. These disorders can be inherited in both autosomal recessive and dominant patterns. Certain genes have been reported to contribute significantly to the emergence of diseased phenotypes. Mutation in Forkhead Box E3 gene has been reported in different studies involving the Pakistani population, where the pattern of inheritance is autosomal recessive. Moreover, ALDH1A3 and VSX2 have been associated as well with severe phenotypes of A/M. SOX2 has been reported in the cases of de novo mutations and syndromic microphthalmia. The current review summarizes the most recurrent mutations in these genes in patients suffering from A/M in Pakistan. It showcases the importance of variant studies and how the demographic location of individuals may make them susceptible to a particular type of mutation. It also compares mutation profiles between the Pakistani population and global cohorts, emphasizing the impact of consanguineous marriages on the high prevalence of these conditions in the country. More studies may prove helpful in formulating a diagnostic kit for this disease so that a genotype-phenotype correlation can be established.

Keywords: anophthalmia, genetic diseases, genotype-phenotype correlation, microphthalmia, ocular disorders

1. INTRODUCTION

Rare genetic disorders comprise a group of diseased phenotypes that appear among 1 in 2000 individuals or even fewer [1]. These disorders affect people of all ages and demographic locations. Ocular genetic disorders are such disorders which cause mild to chronic blindness from birth to late 50s. These disorders can be categorized into three groups based on the malformation they cause: i) structural disorders, ii) photoreceptor

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disorders, and iii) nervous system disorders. These include anophthalmia, microphthalmia, primary congenital glaucoma, Usher's syndrome, age-related macular degeneration, Leber congenital amaurosis, and stationary night blindness. People from developing countries, especially from South Asia, are majorly affected by these disorders because of consanguineous marriages and the lack of diagnosis and management. This review discusses the prevalence of anophthalmia and microphthalmia, the genes associated with these diseases, and the most common mutations of these genes in the Pakistani population.

2. STRUCTURAL DISORDERS: ANOPHTHALMIA AND MICROPHTHALMIA

Anophthalmia and microphthalmia (A/M) comprise the absence or the small size of the ocular globe (as compared to the globe size of the normal population of the same age), respectively (shown in Figure 1) [2, 3]. Both share the same clinical features, hence they are difficult to distinguish in multiple cases [4, 5]. Anophthalmia and microphthalmia are expected to affect 1 in 30000 and 1 in 7,000 children, respectively [6]. These defects can be unilateral or bilateral and can also be a part of a syndromic disease [7]. The impact on vision is determined by the degree, size, and presence of ocular abnormalities [6, 8]. A/M is related to ocular coloboma, a structural abnormality which occurs when the optic fissure is not completely fused. Both of these conditions are believed to have the same genetic foundation [7, 9–11]. Even though microphthalmia causes 3.2% to 11.2% of blindness in children, yet there are no therapies available to improve visual performance in these individuals, with the current treatment emphasizing increasing the remaining eyesight and enhancing aesthetics [6–8].

A/M are highly heterogeneous disorders with a high degree of clinical heterogeneity. They are frequently coupled with additional visual abnormalities in the contralateral eye (complex) or microphthalmic eye, such as ocular coloboma, anterior segment dysgenesis (ASD), vitreoretinal dysplasia, and cataracts [6]. Additionally, 33-95% of A/M patients have other non-ocular abnormalities, while 20-45% of these patients are diagnosed with a syndrome [2, 12–15]. Its variability may stem from genetic modifiers or environmental factors, such as the lack of vitamin A and alcohol addiction in mothers [2, 12, 16–18].

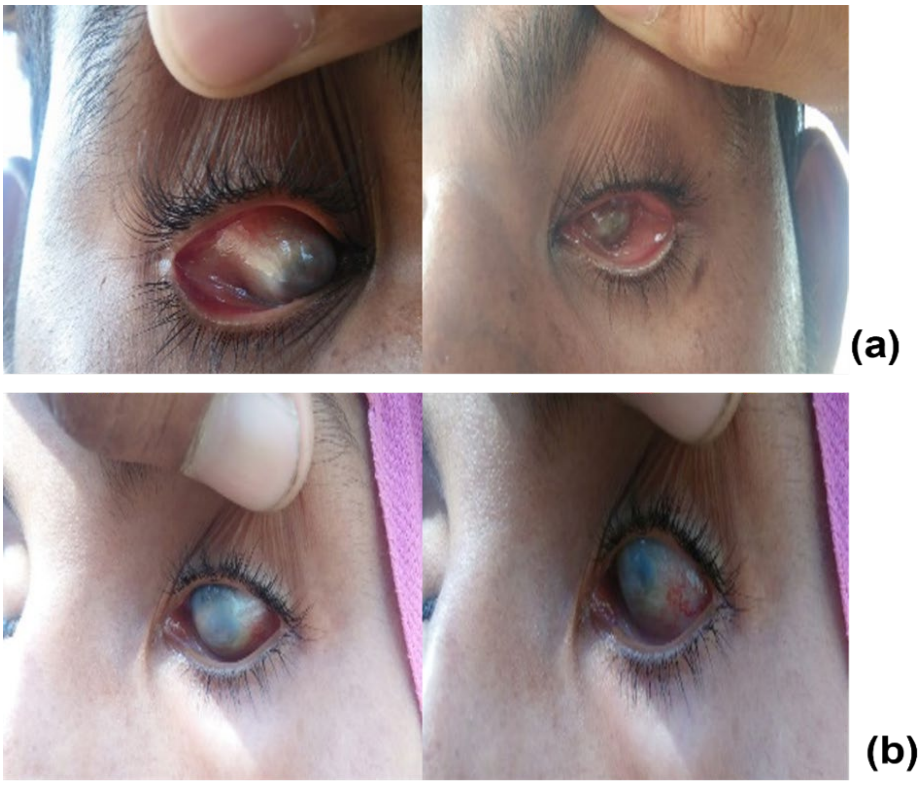


Figure 1. The Patients of (a) Anophthalmia Lacking Ocular Socket and (b) Microphthalmia with Smaller Eye Sockets.

Both patients in Figure 1 have corneal opacity in both eyes with vision loss. Ethical approval to use these images was taken from the Bioethics committee of the Department of Biochemistry, Quaid-I-Azam University, Islamabad.

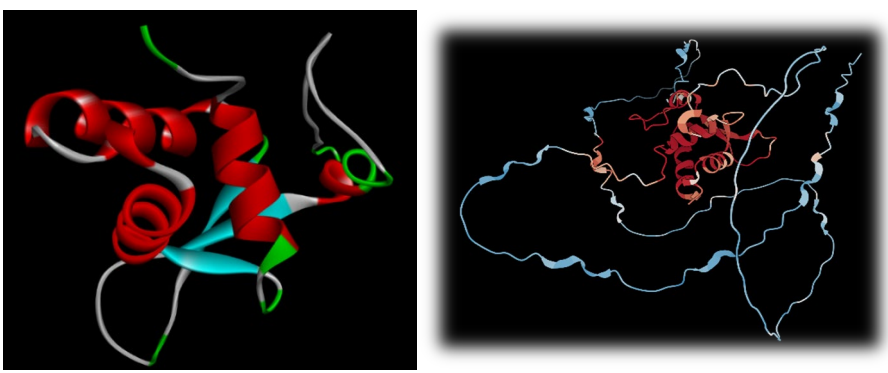
3. GENES ASSOCIATED WITH ANOPHTHALMIA AND MICROPHTHALMIA

Approximately 60 genes reportedly have an association with the A/M phenotype. In the Pakistani population, some genes more commonly mutate than others. These genes include Forkhead box E3 (FOXE3), SOX2, STRA6, and AlDH1A3.

3.1.3.1 FOXE3

Forkhead box E3 (FOXE3) is a transcription factor that belongs to the Forkhead box (FOX) family. It is important in the development of lenses in vertebrates [19–21]. Proteins that belong to the FOX family have a structural feature, that is, a highly conserved winged-helix DNA-binding domain (Forkhead domain, FHD). Based on the similarity in sequence within and outside FHD, these proteins are divided into subgroups (A-S). Phylogenetically, FOXE proteins most closely resemble the FOXD proteins. The FOXE family consists of FOXE1 and FOXE3. The former is associated with thyroid and palatal development, while the latter is associated with lens development. Although FOXE3 is only expressed in the eye lens in mouse embryos [19, 20], both mice and humans carrying FOXE3 variants demonstrate complex ocular phenotypes, such as A/M and anterior segment anomalies, in addition to lens anomalies [19, 20, 22, 23]. Importantly, the FOXE3 gene has only one exon and its mRNA remains unspliced. Therefore, truncating variations are unlikely to cause nonsense-mediated decay (NMD), which results in the normal production of the mutant mRNA and protein [23–26].

The FOXE3 gene produces a 319 amino acid long transcription factor, with a DNA-binding domain called the Forkhead domain (shown in Figure 2) found between amino acids 71 and 165 [19, 22]. In humans, mice, and zebrafish, FOXE3 is preferentially expressed during the formation of the lens [19, 21, 27].



(a) **(b)**

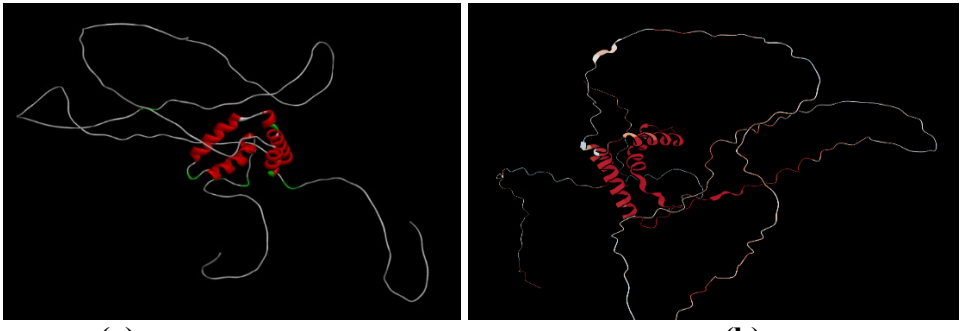
Figure 2. Forkhead Domain of FOXE3 (a) The Dark Red Color of the FOXE3 Protein Structure Shows the DNA Binding Domain Which is also called the Forkhead Domain. This Structure of FOXE3 is Predicted by

AlphaFold [28] and Then Reconstructed with Biovia Discovery studio®, (b) FOXE3 Gene Structure with Susceptible Mutation Areas. Brown Color Shows the Area Where Mutation Occurs Most of the Time.

3.2. SOX2

Heterozygous mutations in SOX2 account for 15-40% of cases. These variations are the most known reason for severe microphthalmia and bilateral anophthalmia [3, 6, 7]. Mutations in SOX2 can lead to simple or complex A/M, including unilateral or bilateral A/M and Syndromic Microphthalmia 3 (MCOPS3), respectively. MCOPS3 is mainly characterized by seizures, sensorineural hearing loss, brain malformation, neurocognitive delays, microcephaly, and genital anomalies [3, 7, 29]. SOX2 has over 76 disease-associated variations [2, 3, 6]. The majority (60%) of A/M-causing SOX2 mutations are de novo, however, it can also result from SOX2 haploinsufficiency, when alleles are inherited in an autosomal dominant fashion [2, 3, 6, 29]. Due to germinal mosaicism, SOX2 mutations that cause the disorder can pass down from asymptomatic parents, as in the case of a lady who had no ocular abnormalities but gave birth to a daughter who had bilateral anophthalmia and extraocular SOX2 syndrome characteristics [30, 31]. In light of this fact, it is crucial to assess parents for future family planning and appropriate genetic counseling [4, 6, 14, 15].

Substitutional mutations in DNA-binding or transactivation domains (Figure 3) may cause postnatal growth retardation and non-penetrance, or a milder form of the disease with ocular symptoms, such as ocular coloboma [3, 7, 14].



(a) **(b)**

Figure 3. (a) The Structure of SOX2 Protein is Predicted by PDB and Modified with Biovia Discovery Studio® [28], (b) SOX2 Gene Structure

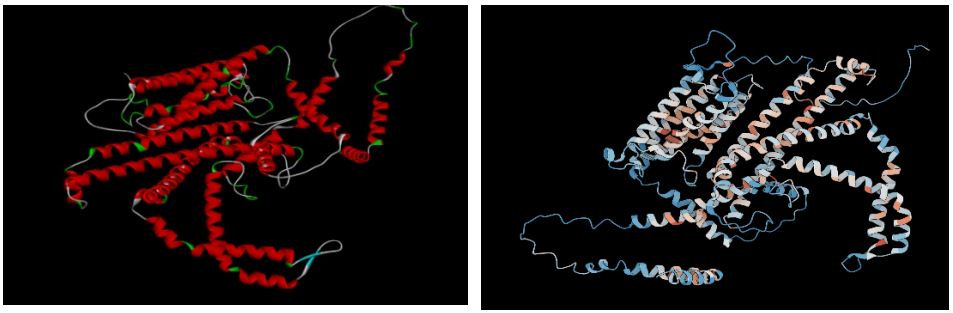
(With Susceptible to Mutation Areas) Highlighted. The Structure is Determined by AlphaFold for the Most Vulnerable Positions for Mutations According to Literature. Brown Color Shows the Area Where Mutation Occurs Most of the Time.

3.3. STRA6

STRA6 can lead to A/M when both alleles are mutated. This mutation may include missense, frameshift, nonsense, indel, and whole gene deletion. MCOPS9 is frequently caused by pathogenic recessive STRA6 mutations and further causes pulmonary, diaphragmatic, and cardiac problems. These are syndromic traits and mortality occurs during the first two years of life [7, 32, 33]. Moreover, patients with homozygous missense STRA6 mutations may also show isolated A/M and milder symptoms, such as a patient with bilateral anophthalmia and moderate syndromic characteristics [12]. However, no connection between genetics and phenotype has been discovered yet [3, 33, 34].

STRA6 is a retinol-binding protein transmembrane receptor that mediates the absorption of vitamin A into cells [3, 12, 35–38]. A missense mutation in STRA6 causes the malabsorption of vitamin A, according to cellular research [12]. Additionally, zebrafish models replicate the clinical phenotype, with the suppression of retinoic acid causing microphthalmia and other developmental abnormalities [12]. Individuals affected with STRA6 mutations show diverse phenotypes, as seen in one family which showed a spectrum of phenotypes, including anophthalmia and microphthalmia with contralateral ocular coloboma. This implies that phenotypic diversity may be impacted by both genetic and environmental influences, such as the variability in vitamin A intake [34].

The severity of the abnormalities brought on by STRA6 mutations (Figure 4) shows how crucial retinoic acid signaling is for development [35]. By regulating the expression of genes involved in development, retinoids can control how an individual develops [12, 37, 38]. STRA6 deficiency in zebrafish affects gene regulation and retinoic acid receptor signaling, leading to abnormalities in the development of craniofacial and cardiac structures, as well as microphthalmia [37]. Animal and cellular models show that STRA6 mediates the intake of vitamin A and its discontinuity causes A/M by disrupting the retinoic acid signaling pathway, reducing the gene expression essential for eye development [38].



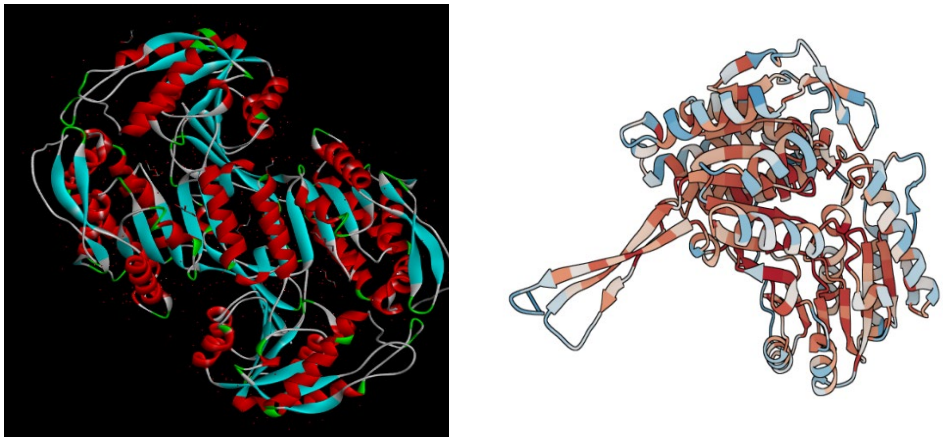
(a) **(b)**

Figure 4. Structure of STRA6 and Position of Mostly Reported Mutations. (a) PDB Structure of STRA6 Determined by X-ray Crystallography and (b) The Structure Determined by AlphaFold for the Most Vulnerable Positions for Mutations According to Literature. Brown Color Shows the Area Where Mutation Occurs Most of the Time.

3.4. ALDH1A3

An estimated 10% of A/M cases are presumably caused by mutations in the retinaldehyde dehydrogenase gene ALDH1A3 [18, 39]. Missense, nonsense, and exon-skipping variants are all its disease-associated variations (Figure 5) [39–42]. Bilateral A/M is frequently accompanied by biallelic ALDH1A3 mutations, which can be isolated or complex [7]. Neurocognitive phenotypes are frequently linked to biallelic pathogenic A/M ALDH1A3 alleles, although other extraocular symptoms are relatively rare [3, 7, 39]. In an instance of autosomal recessive ALDH1A3 variations, a sister without symptoms had the same homozygous mutation as her two siblings who had bilateral A/M. This is one example of non-penetrance with ALDH1A3 disease-associated variations [41, 43]. ALDH1A3 oxidizes retinaldehyde to retinoic acid [3, 39, 44]. One of the three retinaldehyde dehydrogenases found in humans, ALDH1A3 has distinct spatial and temporal expression patterns [44–46]. Pax6 regulates the expression of ALDH1A3, as demonstrated by mice model studies [44, 47]. The periocular mesenchyme expresses the mouse retinaldehyde dehydrogenase gene Raldh2 (human ALDH1A2) [45, 46]. Optic cup invagination is prevented by Raldh2 loss-of-function mutations [45]. Raldh3-/- mouse mutant embryos start the development of the optic cup, however, because the ventral optic cup lacks retinoic acid, the ventral retina shortens [46, 47]. As a result, ALDH1A3 seemingly plays a conserved function in retinoic acid

synthesis in developing the ventral optic cup. These variations cause abnormalities in optic cup development, such as invagination [44, 46].



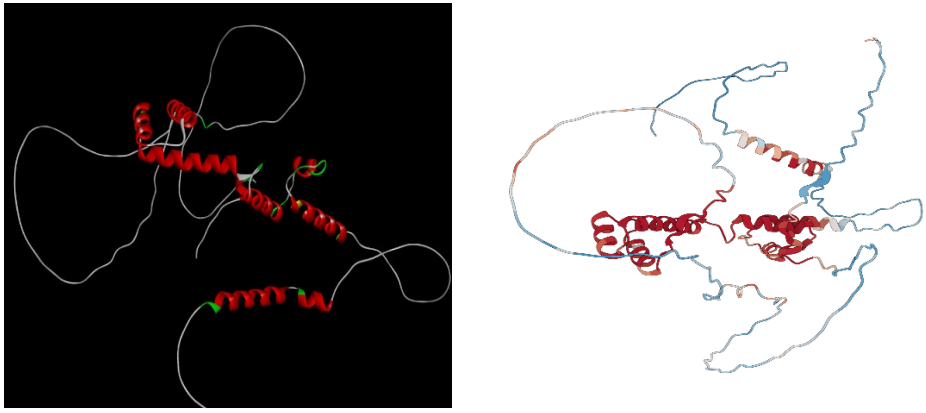
(a) **(b)**

Figure 5. Structure of ALDH1A3 and Positions of Mostly Reported Mutations. (a) PDB Structure of ALDH1A3 Determined by X-ray Crystallography and (b) Structure Determined by AlphaFold for the Most Vulnerable Positions for Mutations According to Literature. Brown Color Shows the Area Where Mutation Occurs Most of the Time.

3.5. VSX2

Visual System Homeobox 2 (VSX2) is a homeodomain-containing transcription factor expressed in the retina in humans, mice, and zebrafish embryo development [48]. VSX2 deficiency leads to microphthalmia with ocular anomalies across species, indicating its evolutionary conservation [49, 50].

Homozygous mutations in VSX2 result in 2% non-syndromic microphthalmia. Pathogenic variants of VSX2 include substitution, pre-termination condon, exon skipping, and splice-site variations [51]. In most cases, VSX2 follows a recessive mode of inheritance [7]. The structure of VSX2 is shown in Figure 6.



(a) (b)

Figure 6. Structure of VSX2 and Positions of Mostly Reported Mutations. (a) PDB Structure of VSX2 Determined by X-ray Crystallography and (b) The Structure Determined by AlphaFold for the Most Vulnerable Positions for Mutations According to Literature. Brown Color Shows the Area Where Most of the Time Mutation Occurs.

4. MUTATIONS ASSOCIATED WITH A/M IN THE PAKISTANI POPULATION

Many A/M families have been screened for genetic mutations. The most recurrent mutated gene in autosomal recessive families is the FOXE3 gene. In this gene, DNA binding domain is mutated in most cases, while in some affected individuals a pre-termination codon results in diseased phenotypes. Two mutations located at c.720C>A and c.289A>G are the most common. VSX2 is also associated with bilateral anophthalmia, and its pathogenic variants have been found in some Pakistani families. In some studies, ALDH1A3 and STRA6 have been reported to be pathogenic in autosomal recessive families. In the case of autosomal dominant and sporadic mutations, the SOX2 gene is involved, resulting in syndromic unilateral or bilateral microphthalmia. Table 1 describes the most reported mutations in microphthalmia and anophthalmia.

Table 1. Commonly Mutated Genes in A/M Patients among the Pakistani Population

Gene	Physical Location	Exon Number	DNA Change	c. Position	Amino Acid Change	p. Position	Reference
FOXE3	chr1:47882009	1	Nonsense	c.21_24delGGAT	Frameshift	p.Met7Ilef*216	[52]
FOXE3	chr1:47882231	1	Missense	c.244A>G	M>V	p.M82V	[52]
FOXE3	chr1:47882276	1	Missense	c.289A>G	I>V	p.I97V	[53]
FOXE3	chr1:47882093	1	Nonsense	c.106G>T	PTC	p.E36fs*	[54]
FOXE3	chr1:47882707	1	Nonsense	c.720C>A	PTC	p.C240X	[55]
ALDH1A3	chr15:101425544	2	Insertion	c.172dup	Frameshift	p.E58Gfs*5	[56]
ALDH1A3	chr15:101427837	3	Missense	c.265C > T	C>T	p.R89C	[57]
ALDH1A3	chr15:101440860	9	Missense	c.964G>A	V>M	p.V322M	[53]
ALDH1A3	chr15:101447332	11	Missense	c. 1240G > C	G>C	p.G414R	[56]
ALDH1A3	chr15:101447403	11	Nonsense	c.1310_1311delAT	PTC	p.Y437Wfs*44	[53]
STRA6	chr15:74490127	4	Deletion	c.145_147delC	PTC	p.G50AfsX22	[58]
STRA6	chr15:74488486	6	Missense	c.269C>T	P>L	p.P90L	[58]
STRA6	chr15:74483230	12	Missense	c.878C>T	P>L	p.P293L	[58]
STRA6	chr15:74481585T	13	Missense	c.961A>C	T>P	p.T321P	[58]
STRA6	chr15:74472462	20	Missense	c.1963C>T	R>C	p.R655C	[58]
STRA6	chr15:74472494	20	Missense	c.1931C>T	T>M	p.T644M	[58]
VSX2	chr14:74707928	1	Deletion	c.413_425del	Frameshift	p.S138fs*	[55]
VSX2	chr14:74726393	3	Missense	c.668G>C	G>C	p.G223A	[50]

5. MUTATIONS ASSOCIATED WITH A/M IDENTIFIED GLOBALLY

There have been multiple cases of A/M spectrum, either syndromic or non-syndromic, in different remote regions of Pakistan. Such cases often remain undiagnosed because of a lack of medical records and a proper healthcare system. Properly assigned individual numbers are followed worldwide to identify an individual's medical history. Our country's healthcare system is in developing stages and there are very few facilities for genetic testing. Consequently, the rate of genetic testing is very low. A/M patients are only sequenced for the mutations of the FOXE3 gene, as shown in Table 3.1. There is no mutation reported for syndromic cases in the Pakistani population, although many mutations are available worldwide for other genes, as shown in Table 5.1. There is a need for the screening of other genes reported globally in unsolved A/M cases reported in Pakistan. This would help to better understand the spectrum of A/M in Pakistan. It may also help to set up a diagnostic kit for genome screening to study the large cohort of A/M in different regions of Pakistan. In Europe, multiple cohort studies attempted to establish a genotype-phenotype correlation and found that FOXE3 is majorly mutated in non-syndromic biallelic microphthalmia [59]. Mutations in SOX2 are associated with syndromic anophthalmia, accompanied by Peter's anomaly or autism [2]. Some mutations in ALDH1A3 have been proven to cause monoallelic anophthalmia or biallelic microphthalmia in association with intellectual disability, showcasing the role of retinoic acid in brain development in starting years [40]. STRA6 has not been identified to a significant extent in A/M conditions in Europe. However, its presence in the Pakistani population suggests that a high rate of consanguineous marriages might be the ultimate cause of this diseased condition.

Table 2. Most Common Mutations Involved in A/M Worldwide

Gene	Disease Spectrum	Exon Number	DNA Change	c. Position	Amino Acid Change	p. Position	Reference
FOXE3	Non-syndromic	1	Insertion	c.148_170dup	Frameshift	p.G58RfsX174	[23]
FOXE3	Non-syndromic	1	Missense	c.232G>A	A>T	p.A78T	[59]
FOXE3	Non-syndromic	1	Missense	c.269G>T	R>L	p.R90L	[59]
FOXE3	Non-syndromic	1	Missense	c.291C > G	I>M	p.I97M	[23]
FOXE3	Non-syndromic	1	Missense	c.292T>C	Y>H	p.Y98H	[60]
FOXE3	Non-syndromic	1	Missense	c.310C>T	R>C	p.R104C	[59]
FOXE3	Non-syndromic	1	Nonsense	c.345G>A	PTC	p.W115X	[59]
FOXE3	Non-syndromic	1	Missense	c.358C>G	R>G	p.R120G	[61]
FOXE3	Non-syndromic	1	Missense	c.359G > C	R>P	p.R120P	[23]
FOXE3	Non-syndromic	1	Missense	c.371C > T	T>M	p.T124M	[23]
FOXE3	Non-syndromic	1	Missense	c.472G>C	G>R	p.G158R	[59]
FOXE3	Non-syndromic	1	Nonsense	c.557delT	Frameshift	p.F186SfsX38	[62]
FOXE3	Non-syndromic	1	Deletion	c.691_693delGG	Frameshift	p.231delG	[63]
FOXE3	Non-syndromic	1	Nonsense	c.705delC	Frameshift	p.E236SfsX71	[62]
ALDH1A3	Non- Syndromic	3	Missense	c.211G>A	V>M	p.V71M	[64]
ALDH1A3	Non-Syndromic	5	Nonsense	c.521G>A	C>Y	p.C174Y	[65]
ALDH1A3	Syndromic	6	Deletion	c.666G>A	Exon Skipping	p.W180_E222del	[43]
ALDH1A3	Non-Syndromic	6	Nonsense	c.568A>G	PTC	p.K190X	[66]
ALDH1A3	Non-syndromic	9	Nonsense	c.888G>T	PTC	p.E300X	[40]
ALDH1A3	Non-syndromic	9	Missense	c.1064C>G	P>R	p.P355R	[40]

Gene	Disease Spectrum	Exon Number	DNA Change	c. Position	Amino Acid Change	p. Position	Reference
ALDH1A3	Non-syndromic	10	Missense	c.1144G>A	G>R	p.G382R	[40]
Gene	Disease Spectrum	Exon Number	DNA Change	c. Position	Amino Acid Change	p. Position	Reference
ALDH1A3	Non-Syndromic	10	Nonsense	c.1165A>T	PTC	p.K389X	[66]
ALDH1A3	Non-syndromic	10	Missense	c.1231G>A	E>K	p.E411K	[40]
ALDH1A3	Syndromic	12	Missense	c.1398C>A	N>K	p.N466K	[43]
ALDH1A3	Non-Syndromic	13	Missense	c.1477G>C	A>P	p.A493P	[57]
SOX2	Syndromic	1	Deletion	c.(?_-30)_(*220_?)del	Frameshift	SOX2 del	[2]
SOX2	Syndromic	1	Missense	c.151T>C	W>R	p.W51R	[2]
SOX2	Syndromic	1	Missense	c.221G>C	R>P	p.R74P	[2]
SOX2	Syndromic	1	Missense	c.236G>C	W>S	p.W79S	[2]
SOX2	Syndromic	1	Deletion	c.245delT	Frameshift	p.Leu82CysfsX20	[2]
SOX2	Syndromic	1	Nonsense	c.310G>T	PTC	p.E104X	[2]
SOX2	Syndromic	1	Missense	c.434C>T	A>V	p.A145V	[67]
SOX2	Syndromic	1	Nonsense	c.513C>G	PTC	p.Y171X	[2]
SOX2	Syndromic	1	Deletion	c.70_86del	Frameshift	p.A29GfsX66	[2]
SOX2	Syndromic	1	Missense	c.845G>C	G>A	p.G282A	[68]
SOX2	Syndromic	1	Duplication	c.86_95dup	Frameshift	p.N33GfsX66	[2]
VSX2	Non-syndromic	1	Insertion	c.71_72insG	Frameshift	p.A25RfsX101	[2]
VSX2	Non-syndromic	1	Deletion	c.249delG	Frameshift	p.L84SfsX57	[51]
VSX2	Non-syndromic	4	Missense	c.667G>A	G>R	p.G223R	[2]

6. OTHER FACTORS ASSOCIATED WITH A/M

A/M is mainly caused by genetic dispositions. However, certain factors can trigger or impact the severity of the disease. These factors include maternal vitamin A deficiency, malnutrition, and environmental exposure.

6.1. Maternal Vitamin A Deficiency

Vitamin A is critical for the proper functioning of the eye and its deficiency can impair the visual cycle. Various studies have demonstrated that severe maternal vitamin A deficiency during pregnancy disrupts retinoid signaling pathways, impairing optic vesicle formation and leading to structural anomalies, such as microphthalmia or coloboma [69]. Similarly, a longitudinal study of 91 children with early severe malnutrition revealed persistent visual impairments, including astigmatism, myopia, and retinal pigment epithelium atrophy, underscoring the lifelong consequences of nutritional deprivation during critical developmental windows [70]. These findings highlight the importance of maternal vitamin A levels for the ocular health of newborns. However, no animal model studies have confirmed any correlation between vitamin A deficiency and microphthalmia.

6.2. Macronutrient Deficiency and Epigenetic Modification

Protein-energy malnutrition (PEM) during pregnancy compromises fetal growth through epigenetic mechanisms. Animal models demonstrate that PEM alters DNA methylation patterns in genes regulating eye development, such as *PAX6* and *SOX2*, which are crucial for lens and retinal progenitor cell differentiation [71]. Therefore, maternal malnutrition may result in A/M phenotype. However, no such cases have been reported yet.

6.3. Pharmaceutical Exposure

Prenatal exposure to teratogenic substances significantly elevates the risk of anophthalmia and microphthalmia. Isotretinoin, a vitamin A derivative used for severe acne, disrupts cranial neural crest cell migration, leading to ocular malformations when used during the first trimester [72]. Similarly, thalidomide—a notorious teratogen—interferes with angiogenic processes in the developing eye, resulting in anophthalmia or microphthalmia in up to 40% of exposed fetuses [73]. Maternal smoking and alcohol consumption further exacerbate risks; nicotine constricts

placental blood flow, impairing nutrient delivery, while ethanol metabolites directly damage retinal ganglion cells [74].

7. CONCLUSION

Anophthalmia and microphthalmia are the leading cause of congenital blindness. Environmental factors and maternal health can increase the risk of A/M, but genetic dispositions remain the major role players for the diseased phenotype. In the Pakistani population, mutations in the FOXE3 gene are the leading cause of A/M and the most recurrent pathogenic variant p. C240X has been reported across multiple families. AlphaFold also predicts the pathogenicity of these variants which indicates the future impact this algorithmic model may have on disease-causing variant studies. The role of STRA6, ALDH1A3, and VSX2 genes is critical in better understanding the genetics of A/M. Interestingly, while SOX2 mutations are commonly associated with A/M in European and American populations, no studies to date have reported this association in Pakistan. This discrepancy provides a unique opportunity to explore why SOX2 appears conserved in the Pakistani population but is more mutation-prone in Western cohorts. Unfortunately, due to socioeconomic crises in the country, the A/M phenotype has not been thoroughly studied. Certainly, more studies will yield more information about genes involved in the eye formation pathway. It would also help to form a diagnostic kit for the early detection of A/M in Pakistani families. Moreover, translational research is required to validate these findings and for the identification of drug targets for future therapies.

CONFLICT OF INTEREST

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed during this study.

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