

Research Advances in Genetic Diagnosis of Systemic Diseases Associated with Early-Onset High Myopia

Linhong Lei¹, Dan Tao^{2*}

¹Department of Ophthalmology & Otorhinolaryngology, Qilin District People's Hospital, Qujing, Yunnan, 655000, China

²Department of Ophthalmology, Yunnan Provincial Maternal and Child Health Hospital, Kunming, Yunnan, 650051, China

ABSTRACT

In recent years, as myopia has shown a trend towards onset at younger ages, ophthalmologists have begun to pay high attention to early-onset high myopia (eoHM) in children. Childhood high myopia is a condition closely associated with ocular and systemic diseases. Studies have found that approximately 54% of children with high myopia have accompanying systemic diseases. eoHM is typically closely related to genetic factors and is often comorbid with syndromes. Often, before high myopia is diagnosed, the underlying systemic disease may remain undiagnosed. Therefore, eoHM also serves as an important clue for the early clinical identification of potential systemic diseases. With the rapid development of genetic testing technologies, ophthalmologists have gained a deeper understanding of genes related to systemic diseases associated with eoHM. Strengthening its genetic diagnosis and research is crucial for the early prevention, early diagnosis, timely treatment, and long-term management of both vision and systemic diseases in children with eoHM. Furthermore, for children with eoHM, the collaboration of multidisciplinary teams is necessary to ensure the timely detection and treatment of possible syndrome-associated disorders caused by genetic factors, jointly completing the diagnostic and therapeutic work, and improving the management system for blinding complications of eoHM. This will ultimately provide children with reasonable and precise treatment, enhancing their visual quality and quality of life.

KEYWORDS

Early-onset high myopia; Syndromic hereditary ocular disease; Systemic disease; Multidisciplinary collaborative diagnosis; Stickler syndrome; Marfan syndrome; Down syndrome; Crouzon syndrome; Oculocutaneous albinism

1 Introduction

In recent years, the global prevalence of high myopia has increased significantly, especially in Asia ^[1]. High myopia is associated with a high risk of blindness and visual impairment complications ^[2], which can lead to various vision-threatening complications. Improper management may result in irreversible visual damage and even blindness in severe cases. High myopia is defined as a spherical equivalent refractive error of ≥ 6.00 diopters (D). Among them, those with an onset age before school age (<7 years old) are referred to as early-onset high myopia (eoHM). eoHM can be further divided into the simple type, which only presents as high myopia, and the syndromic type, which is combined with other ocular diseases or abnormalities of other systemic systems. Childhood high myopia is a disease closely related to ocular and systemic diseases ^[3]. Studies have found that approximately 54% of children with high myopia are accompanied by systemic diseases ^[4]. eoHM is usually closely related to genetic factors and is often associated with syndromes; in many cases, the systemic diseases may not have been diagnosed before the diagnosis of high myopia ^[5]. Therefore, it is also an important clue for the early clinical identification of potential systemic diseases. With the rapid development of gene detection technology and ophthalmologists' in-depth understanding of the genes related to systemic diseases associated with eoHM, this article reviews the research progress in genetic diagnosis of systemic diseases associated with eoHM as follows:

2 EoHM and Related Systemic Diseases

Children with high myopia have a high incidence of combined systemic diseases. Studies on the association patterns and incidence rates between childhood high myopia and systemic diseases have found that approximately 54% of children with high myopia have abnormalities in other systemic systems and organs, such as Stickler syndrome, Down syndrome, Marfan syndrome, Crouzon syndrome, Donnai-Barrow syndrome, renal-coloboma syndrome, Knobloch syndrome, oculocutaneous albinism, severe developmental delay, and extreme prematurity. These systemic diseases may or may not be combined with other ocular abnormalities except high myopia. Among them, the incidence of syndromic genetic eye diseases (GED) is 26.9%, the most common being Stickler syndrome (accounting for 8%), followed by Down syndrome and Marfan syndrome (each accounting for 5%), Crouzon syndrome and oculocutaneous albinism (each

* **Corresponding Author:** Dan Tao, 395019586@qq.com

accounting for 0.9%). The incidence of other types of systemic diseases is 27.1%, among which the most common is severe developmental delay (accounting for 11.6%), followed by extreme prematurity (accounting for 9.8%)^[6]. Compared with adults, children are still in the developmental stage. Complications of various systemic diseases not only damage visual function but also may delay the development of children's motor, cognitive, language, and social-emotional abilities, bringing lifelong adverse effects. Therefore, strengthening the genetic diagnosis and research of systemic diseases associated with eoHM is crucial for the early prevention, early diagnosis, timely treatment, and long-term management of visual development and overall development in children with eoHM^[7].

3 Genetic Diagnosis of Systemic Diseases Associated with eoHM

3.1 Stickler Syndrome and COL2A1, COL11A1, COL11A2, COL9A1, COL9A2 Genes

Stickler syndrome is a rare hereditary disease caused by collagen gene mutations, leading to extensive systemic collagen dysfunction, with an incidence of approximately 1:10,000. It is mainly characterized by lesions involving the eyes, orofacial region, joints, and hearing^[8]. Ocular lesions in Stickler syndrome are particularly prominent and severe, mostly presenting as progressive myopia, cataracts, vitreous degeneration, and refractory retinal detachment. The incidence of retinal detachment in patients with Stickler syndrome is 65%, with an average age of 15.2 years, making it a common cause of rhegmatogenous retinal detachment in children. The incidence of myopia is higher than 75%, which is usually congenital high myopia appearing before 6 years old, with stable myopia diopter without progression^[9]. Stickler syndrome is currently classified into six types^[10]. Type I is caused by COL2A1 gene mutation, which has the highest risk of retinal detachment. Type II is caused by COL11A1 gene mutation, including ocular malformations. Type III is caused by COL11A2 gene mutation, without ocular malformations. Types II and III are more likely to present with hearing loss than Type I. Types IV and V are caused by COL9A1 or COL9A2 gene mutations, respectively, and are autosomal recessive types of Stickler syndrome. Type VI is caused by COL9A3 gene mutation^[11]. Clinically, it is difficult to identify Stickler syndrome mainly manifested by ocular abnormalities, which is easily misdiagnosed as simple high myopia and ametropic amblyopia. This suggests that when unexplained high myopia is found in children in the early stage, genetic testing is recommended, and close attention should be paid to ocular and systemic changes during follow-up.

3.2 Down Syndrome (Ds) and Chromosome 21

Ds, also known as trisomy 21 syndrome, is the most common chromosomal aneuploidy disease, with an incidence of 1/600~1/800 in newborns. Its main clinical features are intellectual disability and developmental malformations. The most common malformation is atrial septal defect, followed by gastrointestinal malformations^[12]. In addition, there are some special facial features, epicanthal folds, external ear abnormalities, simian crease, etc., combined with intellectual disability and developmental delay. The most common ocular abnormalities in Down syndrome include high ametropia, strabismus, nystagmus, keratoconus, congenital cataracts, etc.^[13]. Therefore, clinicians should pay close attention to the ocular development of children with Down syndrome during diagnosis and treatment.

3.3 Marfan Syndrome (MFS) and FBN1 Gene

MFS is an autosomal dominant connective tissue disease, estimated to affect at least 1 in 10,000 people, without any racial, geographical, or occupational predilection^[14]. MFS can involve systemic connective tissue, mainly manifested by tall and thin stature, arachnodactyly, spinal deformity, pectus carinatum, pectus excavatum, joint laxity, flat feet, aortic dissection, aortic root dilatation, mitral valve prolapse or insufficiency, etc., especially significant manifestations in the cardiovascular system, skeletal system, and eyes^[15]. The main ocular clinical manifestations are high myopia, ectopia lentis, glaucoma, etc. At present, the most common pathogenic gene of MFS has been confirmed to be the FBN1 gene^[16]. Clinically, sequencing screening for the FBN1 gene can be performed in suspected children for early diagnosis.

3.4 Crouzon Syndrome and Fibroblast Growth Factor Receptor 2 (FGFR2) Gene

Crouzon syndrome is a craniofacial dysostosis caused by premature craniosynostosis, which is an autosomal dominant hereditary disease. Its main clinical manifestations include premature craniosynostosis, craniofacial dysplasia, exophthalmos, shallow orbits, wide interocular distance, exotropia, aquiline nose, short upper lip, maxillary hypoplasia, mandibular prognathism, etc., and patients usually have normal limb development^[17]. Intracranial hypertension occurs in 63% of cases, and with the increase of intracranial pressure, varying degrees of mental retardation may occur^[18]. The incidence of ametropia in patients with Crouzon syndrome is significantly higher than that in healthy people, with 77% of patients having ametropia, especially high ametropia. Crouzon syndrome is mainly caused by mutations in the fibroblast

growth factor receptor 2 (FGFR2) gene ^[19]. The prognosis mainly depends on the severity of the disease. Early correct diagnosis and intervention are very important, focusing on reducing intracranial pressure, preventing intellectual developmental disorders, preserving vision, and improving facial deformities.

3.5 Donnai-Barrow Syndrome (DBS) and LRP2 Gene

DBS is a rare autosomal recessive hereditary disease, mainly characterized by ocular abnormalities, including high myopia, retinal detachment, wide interocular distance, exophthalmos, and iris hypoplasia. Some children have only very mild abnormalities in other systemic organs, but congenital super high myopia is common. Recent studies have found that this disease is caused by LRP2 gene mutation ^[20]. Therefore, when ophthalmologists find children with congenital super high myopia in clinical practice, they should be alert to the genetic diagnosis of Donnai-Barrow syndrome.

3.6 Renal-Coloboma Syndrome (RCS) and PAX2 Gene

RCS is an autosomal dominant genetic disease caused by PAX2 gene mutation, mainly manifested by renal hypoplasia and optic disc dysplasia ^[21]. Ocular lesions mainly include hypoplasia of the optic disc or optic nerve, coloboma of the choroid, retina, and iris, and retinal detachment; some patients have myopia or strabismus. Studies have shown that among patients with confirmed renal-coloboma syndrome, 50% can be detected with PAX2 gene mutation; among confirmed PAX2 mutation cases, approximately 92% have renal lesions and 77% have ocular abnormalities ^[22]. For patients with positive genetic testing results, long-term follow-up observation and lifestyle adjustment are important means to avoid further deterioration of renal function and visual impairment caused by retinal detachment.

3.7 Knobloch Syndrome and COL18A1 Gene

Knobloch syndrome is a triad characterized by occipital closure defects, high myopia, and vitreoretinal degeneration. It is an autosomal recessive genetic disease ^[23]. The main ocular clinical manifestations include flat iris, ectopia lentis, high myopia, vitreoretinal degeneration, nystagmus, etc., which can lead to retinal detachment in severe cases. In 1996, the mutation locus of Knobloch syndrome was mapped to 21q22.3, and COL18A1 was subsequently identified as the pathogenic gene of this disease. Zhang et al. ^[24] once performed whole-exome gene sequencing on 2 Chinese adult patients, which also confirmed that COL18A1 is the pathogenic mutation gene of Knobloch syndrome, and this gene is located on the long arm of chromosome 21.

3.8 Oculocutaneous Albinism (OCA) and OCA2 Gene

OCA is a group of autosomal recessive genetic diseases with genetic heterogeneity, which is related to mutations in genes controlling melanin biosynthesis ^[25]. The eyes are the most severely functionally impaired organs in patients with albinism, with characteristic anatomical abnormalities such as insufficient iris and retinal pigment deposition, foveal hypoplasia, and abnormal projection of optic nerve fibers. Related ocular symptoms include photophobia, nystagmus, high ametropia, diplopia, strabismus, etc. OCA2 caused by OCA2 gene variation is the most common subtype of OCA patients worldwide.

4 Conclusion

In summary, with the increasing trend of myopia onset at a younger age in recent years, ophthalmologists have begun to pay great attention to childhood eoHM. Studies have shown that eoHM is closely related to some systemic diseases. In systemic diseases such as Stickler syndrome, Down syndrome, Marfan syndrome, Crouzon syndrome, Donnai-Barrow syndrome, renal-coloboma syndrome, Knobloch syndrome, and oculocutaneous albinism, most children first visit the ophthalmology department due to eoHM. Children with eoHM are often combined with syndromes and have a genetic tendency. Therefore, in addition to conducting detailed ocular structure and function examinations for children with eoHM, ophthalmologists should also attach great importance to genetic testing for systemic diseases in these children. Combining genetic test results with ophthalmic clinical examination results can avoid misdiagnosis and missed diagnosis of systemic diseases in children with eoHM. At the same time, for children with eoHM, multi-disciplinary personnel, such as ophthalmologists, geneticists, pediatricians, other specialists, and guardians, need to cooperate closely to ensure the timely detection and treatment of syndromes that may be caused by genetic factors, jointly complete the diagnosis and treatment work, strengthen follow-up and intervention, so as to provide reasonable and precise treatment for children, and improve their visual quality and quality of life.

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