Advances in the Genetics of Congenital Ptosis

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Abstract

Congenital ptosis, a birth defects presents at birth or by 1 year of age, is characterized by the drooping of the upper eyelid. Either in isolation (nonsyndromic) or with many different systemic disorders (syndromic). The estimated prevalence of ptosis (congenital and acquired) ranges from 0.79 to 1.99 per 10,000 people in different populations, and it is more prevalent in males. The underlying pathogenesis of congenital ptosis is myogenic and neurogenic, related to the development of muscles and nerves. Although most cases are sporadic, there are familial transmission characteristics, including autosomal dominant, recessive mode, and X-linked inheritance patterns. Moreover, some forms are due to chromosomal aberrations and mutations and deletions in mitochondrial DNA. Genes involved in simple congenital ptosis (SCP) are ZFHX4 and COL25A1. The clinical aspects of various syndromes involving congenital ptosis are partly caused by single-gene mutations. However, the pathogenesis of congenital ptosis is not fully understood. We review the reported epidemiology, genetics, and clinical features of congenital ptosis and associated syndromes here.

Introduction

Blepharoptosis, abbreviated as ptosis, includes both congenital and acquired conditions. Congenital ptosis (OMIM %178300, OMIM %300245), a birth defect defined as ptosis present at birth or by 1 year of age, is characterized by the drooping of the upper eyelid. It is generally due to myogenic factors or innervation abnormalities, resulting in narrowing of the vertical dimension of the palpebral fissure and even partial or complete occlusion of vision [1–3]. Congenital ptosis is the most common type of ptosis in childhood and seems to be more prevalent in males. The estimated prevalence of ptosis (congenital and acquired) varies between 0.79 and 1.99 per 10,000 people in different populations (Table 1) [4, 5]. The prevalence of congenital ptosis in China was found to be 0.18%, based on mass screening of 247,389 people [6]. Although most congenital cases internationally and in China are sporadic (nonhereditary), related to environmental factors affecting the embryo, there are familial transmission characteristics (11.7–19.4%). Ptosis (congenital and acquired) can occur unilaterally or bilaterally. The unilateral form is much more common, occurring in 63–91.5% of cases. In unilateral cases, the left side is more often affected. The general characteristics of ptosis in various populations are summarized in Table 1 [7–10].

The normal adult upper lid margin is 0.5–2 mm below the superior corneal limbus and the levator func-
tion is usually normal (12–15 mm). According to its severity, upper eyelid ptosis can be mild (upper eyelid droop 1–2 mm), moderate (3–4 mm), or severe (>4 mm). Generally, mild ptosis is associated with good levator function (measured by upper eyelid excursion as a patient looks from downgaze to upgaze, >8 mm), moderate ptosis with fair levator function (5–7 mm), and severe ptosis with poor levator function (1–4 mm) [11, 12].

In some cases, congenital ptosis occurs as an isolated condition (nonsyndromic congenital ptosis [NSCP]) that makes patients a tired appearance without affecting their health. Familial inheritance patterns of NSCP include autosomal dominant inheritance, autosomal recessive inheritance, and X-linked dominant inheritance. Generally, but not in all cases, patients may have strabismus and eyestrain may be secondary to visual occlusion and disruption by the ptotic eyelid [13]. Other ocular symptoms include astigmatism due to eyelid tension and changes in the corneal curvature [14], amblyopia due to astigmatic anisometropia or deprivation [1], and headaches due to forced brow elevation to increase the visual field. The prevalence (14.9%) of amblyopia in patients with congenital ptosis is higher than that in the general population [15, 16]. In other cases, congenital ptosis may occur in conjunction with various other conditions in syndromic form (syndromic congenital ptosis [SCP]). In addition to causing visual impairment, SCP also warns of a more severe condition in other systems of the body, such as myasthenia gravis, myotonia congenita, mitochondrial myopathies, and so on [12, 17]. In addition to this, ptosis can cause cosmetic disfigurement, resulting in psychological disorders in patients. Most cases of SCP with familial transmission characteristics are caused by mutations of a single-gene resulting in deficient function of muscle and nerve. The focus of this review is to discuss the genetic aspects of congenital ptosis and associated syndromes.

### Anatomy

The upper eyelids are composed of several structures. Commonly, these structures are divided into anterior, middle, and posterior lamellae [18].

The anterior lamella refers to the skin and orbicularis oculi muscle of the eyelid. Below the skin of the upper eyelid lies the orbicularis oculi muscle which is divided into orbital and palpebral portions. The former consists of concentric muscle fibers and it functions to close the eyes tightly. The latter consists of semilunar muscle fibers. The posterior lamella refers to the retractors, superior tarsal muscle, tarsus, and the conjunctiva. The levator palpebrae superioris (LPS) and Müller’s muscle are the retractor muscles of the upper eyelid. The LPS, a striated muscle, is innervated by the superior division of the oculomotor nerve (cranial nerve III) and controls lid opening [12]. The superior tarsal muscle, or Müller’s muscle, lies deep in the levator aponeurosis. This smooth muscle contributes to the resting tone of the upper eyelid, providing about 2–3 mm of upper eyelid elevation, and is innervated by sympathetic fibers [12]. Some researchers also reference the orbital septum as the middle lamella. Deep in the orbital septum lie the postseptal orbital fat pads which are traditionally divided into the central (preaponeurotic) and medial (nasal) fat pads. The former serves as a gliding surface for thelevator muscle and aponeurosis [18].

### Histopathology

The LPS is the major elevator of the upper eyelid. Normal muscle fibers of LPS are elongated and arranged in parallel bundles, and the nuclei are at the periphery. The nuclear membrane is clear and complete with homoge-

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### Table 1. Characteristics of ptosis (congenital and acquired) in various populations

| Patients, n | Prevalence | Congenital, % | Nonsyndromic, % | Unilateral, % | Laterality, % | Sex ratio, % | Familial, % | Origin of patients | Ref |
|-------------|------------|---------------|-----------------|---------------|---------------|--------------|--------------|-----------------|-----|
| 2,408       | 19.9/100,000 | –             | –               | –             | –             | 54, M        | –            | Israel          | [5] |
| 2,328       | –          | 78            | 73.7            | 63            | 52.2, L       | 57.4, M      | –            | Korea           | [7] |
| 336         | –          | 68.9          | –               | 64.7          | 74, L         | M > F        | 19.4         | Egypt           | [8] |
| 155         | –          | –             | 65.2            | 47.7          | –             | 68.4, M      | 32.9         | China           | –   |
| 155         | –          | –             | 49              | 80            | 54.2, R       | 60, M        | 16.77        | Birmingham, UK  | [9] |
| 107         | 7.9/100,000 | 89.7          | 75.7            | 91.5          | 68.4, L       | 55, M        | 11.7          | Minnesota, USA  | [4] |

M, male; F, female; L, left; R, right; Ref, reference.
neous chromatin. However, LPS from NSCP individuals has contained a primary defect in the muscle, with fibrosis, a reduction or disruption of myofibers, fat infiltration, and internalization of nuclei. Some authors have noted an inverse correlation between the degree of ptosis and the number of residual striated muscle fibers. Scanty and atrophic remaining striated muscles [19], inflammatory cells, abnormal mitochondria (megamitochondria, mitochondrial matrix alterations, and abnormal cristae) [20], and amorphous extracellular material [21] have also been reported. At present, there are two opinions concerning the pathological change in the LPS in congenital ptosis, dystrophic (an inherited disease with progressive muscle weakness and wasting), and dysgenesis (a defect in the development of the muscle) [22]. However, the specific pathological description is still insufficiently clear, leading to considerable confusion regarding the basic pathogenesis of congenital ptosis.

The prominent features of Müller’s muscle (the superior tarsal muscle) specimens with congenital ptosis are the reduction of the muscle fibers, cytoplasmic vacuoles containing flocculent material, degraded nuclear chromatin, and indistinct nuclear membranes in myocytes. All of this demonstrated a widespread atrophic pattern in the Müller’s muscle [23].

**Genetics of NSCP**

NSCP is the most prevalent form of congenital ptosis. Its pathogenesis is presumably multifactorial. Vestal et al. [24], using all available twin data including monozygotic and dizygotic twins with unilateral or bilateral congenital ptosis, found a heritability index of 0.75, indicating that 75% of the phenotype is attributable to genetic factors. In addition to this, clinical heterogeneity is a major feature of hereditary congenital ptosis. One case study reported 4-year-old monozygotic twins with incomplete concordance for NSCP (one unilateral, one bilateral) [25]. Another case reported a large family affected by autosomal dominant NSCP with 70–90% penetrance. These patients display NSCP which in some patients is unilateral and in some bilateral, some symmetric and some asymmetric, some with levator-abducens and medial rectus-ocularis synkinetic activation and some with no such activation. The author suggests the possibility of a modifier gene determining laterality of ptosis [26]. The presence of occasional discordance in twins and variable penetrance in familial cases may also suggest a more complicated, possibly multifactorial, genetic defect, or an environmental influence.

The candidate gene of NSCP that has been identified is rare. The ZFHX4/ZFH-4 gene, located at chromosome 8q21.13, encodes a 3,567-amino acid protein with a zinc-finger homeodomain that acts as a transcription factor, one of the important gene types that cause developmental diseases. ZFHX4 was found to be a candidate gene following DNA analysis of a child with bilateral NSCP who has a balanced translocation of chromosomes t(1;8) (p34.3;q21.12). The breakpoint in chromosome 8 was found to disrupt the ZFHX4 gene located at 8q21.12 [27].

The missense alteration G1241T and L4137F in ZFHX4 gene in children can cause the occurrence of congenital ptosis [28]. Study has also shown that ZFHX4 is involved in muscle and neural differentiation (affecting the structure and function of the oculomotor cranial nerve nuclei) [29]. Mouse Zfhx4 expression is prominent in developing muscle and brain (especially in the midbrain, in which the oculomotor nuclei are situated). In both tissues, Zfhx4 RNA levels are highest embryonically, then decrease gradually to barely detectable levels in adults [30]. Future work is required to look at the ZFHX4 gene in other patients with NSCP to find mutations that would indicate causality.

COL25A1, located at chromosome 4q25, encodes a 654-amino acid brain-specific membrane-bound collagen expressed in the oculomotor and abducens nerves. Studies have shown that a COL25A1 recessive mutation is the pathogenic factor in two children with NSCP (one unilateral, one bilateral) [31]. Recessive COL25A1 mutations lead to not only decreased levels of COL25A1 expression but also, apparently, decreased levels of certain molecules involved in developmental axonal guidance. Therefore, the lack of COL25A1 expression might interfere with molecular pathways involved in oculomotor neuron development, leading to congenital cranial dysinnervation disorders phenotypes [32]. In experimental animals, Col25a1 is involved in early myogenesis and plays a key role in myoblast fusion. Col25a1−/− mice exhibit a delay in the fusion and organization of myofibers during primary myogenesis [33]. However, the associated ophthalmic phenotype has not been specified. Further study is needed to understand how frequently recessive COL25A1 mutations underlie these specific ocular phenotypes.

Genetic research can provide an important basis for the diagnosis and treatment of congenital ptosis. However, the relative roles of environmental and genetic influences during embryonic development are not known. The contributions to pathogenesis remain to be completely elucidated.
| Syndrome                          | Prevalence                        | Main clinical features                                                                 | Inheritance | Gene/locus            | Ref.   |
|----------------------------------|-----------------------------------|----------------------------------------------------------------------------------------|-------------|-----------------------|--------|
| CFEOM                            | 1/230,000 in England              | CFEOM1: paralytic strabismus, ophthalmoplegia, ptosis                                  | AD          | KIF21A                | [34]   |
|                                  |                                   | CFEOM2: miosis, ptosis, exotropia ophthalmoplegia                                      | AR          | ARIX/PHOX2A           |        |
|                                  |                                   | CFEOM3: ptosis, ophthalmoplegia, cognitive impairment, facial dysmorhia, digital anomalies | AD          | TUBB3, KIF21A, and a locus on chromosome 13q |        |
|                                  |                                   | CFEOM4: ptosis, ophthalmoplegia, oligoactly                                            | AR          | Locus on chromosome 21q  |        |
| Horner’s syndrome                | 1/6,250 for those with a congenital onset | Ptosis, miosis, anhidrosis, cervical sympathetic paralysis, enophalamos, small pupil, heterochromia iridis | AD          | –                     | [42, 43] |
| BPES                             | 1/50,000 births                   | BPES type I: blepharophimosis, ptosis, epicanthus inversus, telecanthus, lacrimal puncta anomalies | AD          | FOXL2                 | [45, 48] |
|                                  |                                   | BPES type II: above phenotype plus premature ovarian failure                             |             |                       |        |
| Myotonic dystrophy type 1 or Steinert disease (DM1) | 0.5–18.1/100,000 | Ptosis, weakness of eyelid closure, and limitation of extraocular movements, cataract, distal muscle weakness, myotonia, muscular dystrophy, dysarthria, dysphagia, cardiac involvement, respiratory involvement, cerebral involvement, endocrine disorders | AD          | DMPK                  | [39, 49] |
| Congenital cranial nerve III/ ONP | –                                | Ptosis, ophthalmoplegia, diplopia                                                      | –           |                       | [52]   |
| Chronic Progressive External Ophthalmoplegia (CPEO) | 12/1,060 | Ptosis, ocular dyskinesia, ophthalmoplegia, limb weakness | AR, AD, MT | ANT1, POLG, POLG2, TWNK, RNASEH1 | [54]   |
| 3MC syndrome                     | –                                 | High-arched eyebrows, cleft lip/palate, hearing loss, ptosis, umbilical hernias/omphalocele, urogenital abnormalities, intellectual disability, developmental delay | AR          | MASP1, COLEC10, COLEC11 | [57]   |
| Turner syndrome                  | 3.3–4/10,000 in live-born girls   | Short stature, infertility, hypergonadotrophic hypogonadism, type 2 diabetes mellitus, autoimmunity, neurocognitive problems, congenital heart malformations, intrauterine lethality, skeletal anomalies | NA          | –                     | [58]   |
| Noonan’s Syndrome (NS)           | 4–10/10,000                      | Growth and endocrine involvement, cardiac involvement, renal and genitourinary involvement, abnormal pigmentation, gastrointestinal involvement, hematologic involvement, neurological, cognitive, and behavioral involvement, eye and ear involvement, orthopedic and dental, lymphatic involvement | AD, AR     | PTPN11, SOS1, RAF1, KRAS, NRAS, BRAF, SHOC2, CBL, LZTR1 | [59]   |
| Baraitser–Winter cerebrofrontofacial syndrome (BWCFF) | 0.5–18.1/100,000 | Facial features (metopic ridging/trigonocephaly, ptosis, hypertelorism), cortical malformations (pachygyria/lissencephaly), short neck, short stature, intellectual disability, cardiac defects, genitourinary anomalies, skeletal anomalies | AD          | ACTB, ACTG1            | [60]   |
| Kabuki syndrome (KS)             | 1/32,000 live births             | Facial features, ophthalmologic anomalies, auditory dysfunction, skeletal abnormalities, postnatal growth retardation, mental retardation, cardiac defects, dermatoglyphic abnormalities, genitourinary anomalies | AD, XLD    | KMT2D, KDM6A           | [61]   |
Syndromic Congenital Ptosis

Around 25–51% of patients with ptosis have additional abnormalities. According to the incidence rate, the following syndromes were selected for discussion (Table 2).

**Congenital Fibrosis of the Extraocular Muscles**

Congenital fibrosis of the extraocular muscles (CFEOM) is a group of conditions characterized by congenital paralytic strabismus secondary to restrictive ophthalmoplegia with accompanying congenital ptosis, also known as a subset of a group of disorders called the congenital cranial dysinnervation disorders, which primarily affects ocular motility. These disorders are caused by abnormal development of the innervation of extraocular muscles [34]. The reported prevalence of CFEOM in England is 1/230,000. CFEOM is relatively commonly associated with a genetic defect, and genotypic heterogeneity exists. According to ophthalmic findings and genetic differences, the subtypes of CFEOM are described as follows.

CFEOM1 (OMIM #135700) is an autosomal dominant condition and results primarily from heterozygous mutations in \textit{KIF21A} located on chromosome 12q12. \textit{KIF21A} encodes a 1,674-amino acids kinesin protein that has high levels of expression in neurons and works as an inhibitor of microtubule growth at the cell cortex [34]. Yamada et al. [35] first identified a p.R954W substitution (the most frequent mutation) in \textit{KIF21A} as the cause of CFEOM1. The mutation of \textit{KIF21A} in axonal growth cones can induce misregulation of MT dynamics, and the associated changes in axonal morphology and guidance may form the basis of CFEOM1 pathogenesis [36]. Affected individuals present atrophy of the levator palpebrae and superior rectus muscle, leading to severely restricted eye elevation (inability to raise the eyes above the midline) and severe bilateral congenital ptosis.

CFEOM2 (OMIM #602078) is an autosomal recessive condition. The homozygous mutation in the \textit{ARIX/PHOX2A} gene was first identified in patients with CFEOM2 [37]. The \textit{ARIX/PHOX2A} gene, located on chromosome 11q13.4, encodes a 284-amino acid transcription factor that plays a central role in development of the autonomic nervous system. Affected individuals present severe bilateral congenital ptosis, exotropia ophthalmoplegia, and occasionally miosis. \textit{ARIX/PHOX2A} has been shown to be essential to the development of the oculomotor and trochlear nuclei in mice and zebrafish [38].
CFEOM3 is an autosomal dominant condition with incomplete penetrance that can lead to a heterogeneous phenotype characterized by congenital ptosis, ranging from mild to severe, ophthalmoplegia, cognitive impairment, facial dysmorphism, and/or digital anomalies [34, 39]. The causative mutation has been found in the TUBB3 gene located on chromosome 13q22.3, which encodes a 376-amino acid forkhead transcription factor localized in the nucleus and transcriptionally modulates genetic programs required for early eyelid development and ovary differentiation and maintenance. Mouse Foxl2 has been shown to be expressed by both cranial neural crest cells (CNCCs) and cranial mesodermal cells (CMCs), and is required for correct periorcular muscle and bone morphogenesis. Using selective inactivation of Foxl2 in CNCCs or in CMCs, CNCCs provide the topological cues needed for the morphogenesis of certain CMC-derived extraocular muscles such as the LPS or the oblique muscles [44]. A collection of more than 100 genetic alterations affecting the FOXL2 locus have been identified in patients with BPES, including frameshifts, insertions, nonsense or missense mutations, microdeletion in a cis-regulatory element [45] and copy number changes [46], with intragenic mutations accounting for the majority (71%). Mice lacking Foxl2 exhibit craniofacial anomalies, including eye-open at birth and ovarian malformations, with high rates of perinatal mortality [47]. Notch1 activation may serve as the upstream control of Foxl2 expression by periorcular mesenchymal cells, which are destined for levator smooth muscle development of the eyelids [48].

Horner’s Syndrome

Horner’s syndrome (OMIM #143000) results from a disruption in the sympathetic nervous system, producing the classic triad of ipsilateral congenital ptosis, miosis, and anhidrosis. The congenital ptosis seen in Horner’s syndrome is mild, typically on the order of 1–2 mm, and is due to dysfunction of the sympathetically innervated Müller’s muscle [1]. It is important as a warning sign that the oculosynaptic pathway has been interrupted, potentially by serious and even life-threatening processes. The prevalence of Horner’s syndrome was reported to be 1.42/100,000 in patients younger than 19 years, with a birth prevalence of 1/6,250 for those with a congenital onset [42]. Autosomal dominant inheritance of congenital Horner’s syndrome has been reported in family cases [43]. However, genetic studies have been very scarce to date.

Blepharophimosis Ptosis Epicanthus Inversus Syndrome

Blepharophimosis ptosis epicanthus inversus syndrome (BPES, OMIM #110100) is a rare inheritable disease that occurs sporadically or in association with autosomal dominant mutations, with an estimated incidence of 1 in 50,000 births. Affected individuals present horizontal narrowing of the eye opening (blepharophimosis), drooping upper eyelids (congenital ptosis), a skin fold arising upwards and inwards from the lower eyelid (epicanthus inversus), telecanthus, and lacrimal puncta anomalies, such as lateral displacement or stenosis. Apart from ophthalmic symptoms, female patients may suffer premature ovarian failure (BPES type I) or not (BPES type II) [39].

At least 88% of patients with BPES types I and II present a mutation or a deletion of FOXL2 coding or regulatory sequences [44]. FOXL2, located on chromosome 3q22.3, encodes a 376-amino acid forkhead transcription factor localized in the nucleus and transcriptionally modulates genetic programs required for early eyelid development and ovary differentiation and maintenance. Mouse Foxl2 has been shown to be expressed by both cranial neural crest cells (CNCCs) and cranial mesodermal cells (CMCs), and is required for correct periorcular muscle and bone morphogenesis. Using selective inactivation of Foxl2 in CNCCs or in CMCs, CNCCs provide the topological cues needed for the morphogenesis of certain CMC-derived extraocular muscles such as the LPS or the oblique muscles [44]. A collection of more than 100 genetic alterations affecting the FOXL2 locus have been identified in patients with BPES, including frameshifts, insertions, nonsense or missense mutations, microdeletion in a cis-regulatory element [45] and copy number changes [46], with intragenic mutations accounting for the majority (71%). Mice lacking Foxl2 exhibit craniofacial anomalies, including eye-open at birth and ovarian malformations, with high rates of perinatal mortality [47]. Notch1 activation may serve as the upstream control of Foxl2 expression by periorcular mesenchymal cells, which are destined for levator smooth muscle development of the eyelids [48].

Myotonic Dystrophy Type 1 or Steinert Disease

Myotonic dystrophy can be divided into two types: type 1 (DM1, OMIM #160900) is congenital. Its prevalence ranges between 0.5 and 18.1 per 100,000 people, making it the most common muscular dystrophy. The clinical condition includes distal muscle weakness, myotonia, muscular dystrophy, dysarthria, dysphagia, facial weakness (congenital ptosis, weakness of eyelid closure, and limitation of extraocular movements), posterior iris descent cataracts, cardiac or respiratory involvement, cerebral involvement, and endocrine disorders [39, 49].

DM1 is a dominantly inherited disorder caused by an expansion of an unstable CTG trinucleotide repeat in the 3’UTR of the DMPK gene located on chromosome 19q13.32, which encodes a 629-amino acid serine-threonine kinase that is necessary for the maintenance of skeletal muscle structure and function. A repeat length exceeding 50 CTG repeats is pathogenic [50]. Most evidence implies that a major pathogenic consequence of expanded CTG repeats in DM1 is the formation of hairpin structures that bind and sequester RNA-binding proteins [51].
Genetics of Congenital Ptosis

Congenital cranial nerve III/oculomotor nerve palsy is a clinical diagnosis, which mostly presents with congenital ptosis and ophthalmoplegia, which may result in diplopia [52]. The superior division cranial nerve 3 (CN3) innervates the ipsilateral superior rectus and LPS muscles. Lesions affecting cranial nerve 3 may occur anywhere along its path between the brainstem and the extraocular muscles and can result in either partial or complete third nerve palsy [53]. Partial third nerve palsies may affect only one of the divisions or only certain nerve fibers. Pupillary response may be intact, poor, or absent, depending on the lesion. In cases in which a mild anisocoria is present, it will be more apparent in brighter light than in the dark. No related genes and loci have been reported.

Chronic Progressive External Ophthalmoplegia

Chronic Progressive External Ophthalmoplegia (CPEO, OMIM #616479) is a type of mitochondrial myopathy with a low prevalence (12/1,060) [54]. Patients with CPEO may present with bilateral congenital ptosis, usually symmetric ocular motility deficit, complete ophthalmoplegia with no restrictions on forced ductions, and orbicularis oculi weakness. Patients may have onset of this disease at any age. CPEO is characterized by remarkable genetic heterogeneity. The inheritance pattern follows autosomal recessive, autosomal dominant, and maternal transmission pattern. Increasing evidence implicates the role of mitochondrial genetics and most cases of CPEO are the result of mitochondrial DNA (mtDNA) deletions [55], including mtDNA point mutations, a single large-scale mtDNA deletions, duplications or multiple mtDNA deletions, secondary to nuclear mutations to genes including ANT1, POLG, POLG2, TWNK, and RNASEH1. In CPEO medial rectus tissue, there are focal areas of disruption and abnormal mitochondria and selective vacuolization [56].

Ptosis occurs in association with other malformations such as Malpuech Michels Mingarelli Carnevale syndrome [57], Turner syndrome [58], Noonan syndrome [59], Baraitser-Winter cerebrofrontofacial syndrome [60], Kabuki syndrome [61], Kaufman oculocerebrofacial syndrome [62], Duane retraction syndrome [63, 64], Ohdo syndrome [65], and so on. Mutations in the RYR1 [66] and ECEL1 [67] genes can also cause SCP. These are rare conditions that are not discussed in this article. In the clinical assessment of a patient with congenital ptosis, looking for associated anomalies is important because, if they are present, attributing them to a known syndrome could be crucial.

Other Genetic Factors in Congenital Ptosis

There have also been reports of chromosomal structural changes leading to congenital ptosis. A case of de novo 18p deletion syndrome with panhypopituitarism with a feature of congenital ptosis revealed a de novo deletion on the short arm of chromosome 18 [68]. Interstitial duplications of Xq25-q26 exhibit a recognizable microduplication syndrome comprising a remarkable facial appearance with congenital bilateral ptosis, cleft palate and large protruding ears, accompanied by genital and digital defects [69]. Partial trisomies of the short arm of chromosome 6 lead to craniofacial dysmorphism, choanal atresia, congenital ptosis, sensorineural hearing loss, heart defects, developmental delay, and renal dysfunction [70].

In addition, mutations and deletions in mtDNA are a recurrent cause of metabolic and neuromuscular abnormalities. Single large-scale mtDNA deletions are amongst the most frequently diagnosed mtDNA disorders in childhood. The most frequent initial presentation in patients with childhood-onset mitochondrial disease caused by single large-scale mtDNA deletions is congenital ptosis (16/34, 47%) [71].

Epigenetic regulation of gene expression, through covalent modification of histones, is a key process controlling growth and development. H3 acetylation is important for neural, craniofacial, and skeletal morphogenesis, mainly through its ability specifically to regulate the MAPK signaling pathway [72]. Mattioli et al. [73] reported that a frameshift in BRPF1, encoding a protein modifier of two histone acetyltransferases, KAT6A/MOZ/MYST3 and KAT6B/MORF/MYST4, can lead to an intellectual disability syndrome with congenital ptosis. The protein variant shows an aberrant cellular location, loss of certain protein interactions, and decreased histone H3K23 acetylation.

Conclusion

Congenital ptosis is an ophthalmologic condition worldwide that is related to muscle and nerve development. If left untreated, it can have an impact on physical and mental health. More studies with larger families of cases are clearly required, and the establishment of a biobank should be standardized. In addition to this, the etiology of myogenic congenital ptosis needs to be further elucidated. CMCs are at the origin of craniofacial muscles and some posterior skeletal elements of the skull, playing
a key role in craniofacial development. Thus, studies of embryonic development may open new lines of thought. Further study of genetics may be helpful and provide a basis for a classification of congenital ptosis. However, the genetic and epigenetic research progress has been very scarce to date. New genes and loci remain to be identified. Understanding the genetics and epigenetic regulatory modification of congenital ptosis will provide tools for appropriate genetic counseling, and molecular genetic testing can be helpful in confirming an exact diagnosis. Continued research and insight are necessary to advance our understanding to create new and promising treatment modalities.

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