REVIEW

The genetics of strabismus

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Strabismus (misalignment of the eyes; also known as "squint") comprises a common heterogeneous group of disorders characterised by a constant or intermittent ocular deviation often associated with amblyopia (unilateral failure of normal visual development) and reduced or absent binocular vision. The associated poor cosmetic appearance may also interfere with social and psychological development. Extensive twin and family studies suggest a significant genetic component to the aetiology of strabismus. The complexity of the molecular basis of strabismus is now beginning to be elucidated with the identification of genetic loci and disease causing genes. Currently greater insights have been gained into the incomitant subtype (differing magnitude of ocular misalignment according to direction of gaze), whereas less is known about the pathogenesis of the more common childhood concomitant strabismus. It is hoped that a greater understanding of the molecular genetics of these disorders will lead to improved knowledge of disease mechanisms and ultimately to more effective treatment. The aim of this paper is to review current knowledge of the molecular genetics of both incomitant and concomitant strabismus.

disorders such as the various forms of concomitant strabismus.

INCOMITANT STRABISMUS

Incomitant strabismus is characterised by a degree of ocular misalignment which differs depending upon the direction of gaze or according to which eye is fixing an object, and is associated with defective ocular movement.

Some forms of incomitant strabismus show a strong familial component; both autosomal recessive and autosomal dominant modes of inheritance are described. Rare forms of ocular myopathy, particularly chronic progressive external ophthalmoplegia (CPEO), may be associated with mitochondrial DNA (mtDNA) mutations.

Strabismus associated with mitochondrial cytopathies

The mitochondrial cytopathies are an uncommon group of multi-system disorders in which there is biochemical, histopathological, or genetic evidence of mitochondrial dysfunction. Skeletal muscle biopsy is characterised histologically by ragged red fibres and abnormal mitochondria.

Clinical abnormalities often begin in childhood and may include lactic acidosis, anaemia, myopathy, neurological abnormalities, endocrine disturbance, renal disease, sensorineural hearing loss, and a retinal dystrophy. Cardiac conduction defects are a major cause of premature death.

A number of clinical phenotypes with strabismus and abnormal eye movements are recognised including chronic progressive external ophthalmoplegia¹ and Kearns-Sayre syndrome (KSS).²

Chronic progressive external ophthalmoplegia (CPEO)**Ocular and histopathological features**

CPEO is characterised by the gradual onset of acquired strabismus and ptosis with limitation of ocular movements due to a progressive myopathy of the extraocular muscles. Ragged red fibres are often present on skeletal muscle biopsy.

CPEO may be seen in isolation or associated with other systemic abnormalities including hypogonadism and cardiomyopathy. It may be seen in association with mtDNA deletions or with point mutations in mtDNA. In CPEO

Molecular biology has made a major contribution to the understanding of disease mechanisms in many areas of ophthalmology and promises to revolutionise our understanding of the aetiology of strabismus. The pathogenesis of the various forms of strabismus is poorly understood; it is known, however, that there is a significant genetic contribution and the identification of the causative genetic mutations will open new areas of research into disease mechanisms. Comparatively little is known about the biochemistry of the processes involved in ocular alignment or the control of eye movement; there are therefore few obvious candidate genes. Identification of the causative genetic mutations will depend therefore upon traditional linkage analysis to identify chromosomal loci involved, followed by screening of genes mapping to the region of interest. To date most progress has been made in incomitant strabismus, but improved techniques for high throughput genotyping and the development of statistical methods for the study of non-mendelian disorders has meant that it is now possible to dissect the molecular mechanisms of complex

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Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CFEO, congenital fibrosis of the extraocular muscles; CPEO, chronic progressive external ophthalmoplegia; DS, Duane syndrome; KSS, Kearns-Sayre syndrome; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MIDD, maternally inherited diabetes and deafness; mtDNA, mitochondrial DNA

without systemic abnormalities the mtDNA deletions are usually confined to muscle but in syndromic forms such as KSS the deletions are present in a variety of tissues. Patients harbouring mtDNA deletions are usually sporadic, whilst maternally inherited forms of CPEO are usually associated with point mutations of mtDNA. Autosomal inheritance patterns may also be seen.

Molecular genetics and pathogenesis

CPEO is associated with deletions or point mutations of mitochondrial DNA; the phenotype may be confined to the extraocular muscles or include other systemic abnormalities. Tissues with a high metabolic demand such as the retina, heart, and skeletal muscle are commonly affected. A number of different phenotypes are recognised and there are several different genetic mechanisms which result in multiple deletions and point mutations of mitochondrial DNA.^{3 4}

CPEO is a clinically heterogeneous disorder showing sporadic, maternal, autosomal dominant or recessive inheritance; it is now evident that nuclear encoded proteins can influence mitochondrial DNA replication or repair. To date, mutations in three autosomal genes have been identified in dominant CPEO (table 1): adenine nucleotide translocator-1 (*ANT1*),⁵ encoding the muscle-specific adenine nucleotide translocase; chromosome 10 open reading frame 2 (*C10orf2*),⁶ encoding Twinkle helicase; and polymerase gamma (*POLG*),⁷ encoding the alpha subunit of polymerase gamma. Mutations in *POLG* have also been shown to cause autosomal recessive CPEO.⁷ Interestingly digenic inheritance has been recently reported in a sporadic case, with recessive mutations in both *POLG* and *C10orf2*,⁸ suggesting that the encoded proteins of these genes may interact with each other, in a similar fashion as has been previously described in digenic inheritance of retinitis pigmentosa attributable to *ROM1* and *RDS* mutations.⁹

All three CPEO associated genes have a role in mtDNA replication and/or repair, which when mutated lead to multiple deletions of mtDNA. The Twinkle protein has been recently characterised as a 5' to 3' DNA helicase which is specifically stimulated by mitochondrial single-stranded DNA-binding protein.¹⁰ Human mitochondrial DNA is replicated by the two-subunit DNA polymerase gamma, with mutations in *POLG* (encoding the alpha subunit) having been shown to cause error prone DNA synthesis.¹¹ The protein product of *ANT1* is a mitochondrial ATP/ADP exchanger. It has been suggested that mutations in *ANT1* result in an imbalance of the mitochondrial deoxynucleotide pool that subsequently affects the accuracy of mtDNA replication, thereby leading to accumulation of mutant mtDNA.⁵

More loci and genes responsible for other autosomal forms of CPEO remain to be identified.

Table 1 Loci and genes identified in the mitochondrial cytopathies				
Disorder	OMIM number	Inheritance	Locus	Gene
CPEO1	157640	AD	10q24	<i>C10orf2</i>
CPEO2/3	157640	AD	4q35	<i>ANT1</i>
CPEO4	157640	AD and AR	15q25	<i>POLG</i>
KSS	530000	Mt	MtDNA	Various MtDNA deletions
CPEO with hypogonadism	603280	AD	–	Not identified
CPEO with severe cardiomyopathy	601779	AR	–	Not identified

AD, autosomal dominant; AR, autosomal recessive; CPEO, chronic progressive external ophthalmoplegia; KSS, Kearns-Sayre syndrome; mt, mitochondrial.

Recently primary mutations in mtDNA have also been identified in CPEO, including the A3243G mtDNA point mutation, in association with severe progressive multi-organ involvement.^{12–14} These numerous point mutations usually show maternal inheritance, although occasionally sporadic inheritance has been reported.¹⁴

Kearns-Sayre syndrome (KSS)

Ocular features

Kearns-Sayre syndrome is characterised by progressive ophthalmoplegia, pigmentary retinopathy, cardiomyopathy, and other, variable systemic features. In contrast to CPEO, inheritance is usually sporadic; autosomal inheritance has not been described in KSS syndrome.

Molecular genetics and pathogenesis

Mitochondrial DNA deletions are the underlying cause of KSS.^{3 4 14} These deletions are very variable and different amounts of deleted mtDNA have been shown to be present in different tissues compatible with the multi-system nature of the disorder.^{15 16} In addition to mtDNA deletions, point mutations have also been recently identified in a minority of patients, including the adenine-to-guanine transition at position 3243 of mitochondrial DNA (A3243G), in a transfer RNA leucine (tRNA^{Leu} [UUR]) encoding region.^{13 17} This is the same mutation found commonly in the syndrome of maternally inherited diabetes and deafness (MIDD)^{18 19} and severe encephalopathy with death at a young age (MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes).²⁰

Strabismus associated with cranial nerve misrouting

Some forms of incomitant strabismus, for example Duane syndrome (DS) and congenital fibrosis of the extraocular muscles (CFEOM), originally thought to be due to extraocular muscle fibrosis, have now been demonstrated to be due to abnormal innervation of the extraocular muscles (table 2).

Duane Syndrome (DS)

Ocular and histopathological features

DS accounts for about 5% of patients presenting with strabismus.²¹ In the typical form there is limitation of abduction and narrowing of the palpebral fissure and retraction of the globe on adduction. The latter features are thought to be due to co-contraction of the medial and lateral recti. Atypical forms may show other combinations of horizontal muscle restrictions and “upshoots” and “downshoots” of the affected eyes are common.

Postmortem studies of two patients with DS have demonstrated hypoplasia of the sixth nerve nucleus and absence of

Table 2 Loci and genes identified in the cranial nerve misrouting syndromes				
Disorder	OMIM number	Inheritance	Locus	Gene
DS	126800	AD	2q31	Not identified
DS	126800	Chromosomal anomalies	8q13*	? CPAH
DS (Okishiro syndrome)	126800	AD	20q13	<i>SALL4</i>
MBS1	157900		13q12.2–q13	Not identified
MBS2	601471	AD	3q21–q22	Not identified
MBS3	604185	AD	10q21.3–q22.1	Not identified
CFEOM1	135700	AD	12p11.2–q12	<i>KIF21A</i>
CFEOM2	602078	AR	11q13.1	<i>ARX</i> (<i>PHOX2A</i>)
CFEOM3	600638	AD	16q24.2–q24.3	Not identified

*Cytogenetic abnormality.

the sixth nerve on the affected side, the ipsilateral lateral rectus being innervated by branches of the third nerve.²² Other cranial nerve misroutings, for example Marcus-Gunn jaw winking ptosis and crocodile tears, have also been reported in DS suggesting that in some cases there is more widespread cranial nerve miswiring.^{23–24} A variety of other systemic abnormalities have been reported in association with DS.^{25–26}

Molecular genetics and pathogenesis

Although most patients with DS have no family history of the disorder, familial cases are seen. This suggests that DS may have a genetic component and such families are an extremely good resource for mapping the causative genes. Autosomal dominant DS has been mapped to chromosome 2q31,^{21–27} and the finding of cytogenetic abnormalities in patients with DS suggests that there may be another locus on chromosome 8q13.^{28–29} It has recently been demonstrated that a carboxypeptidase gene (*CPAH*) was directly interrupted, between the first and second exons, in a patient with DS carrying a translocation break point in the *DURS1* region on chromosome 8q13.³⁰ However screening of a panel of patients with sporadic DS failed to identify any causative mutations in this gene.³⁰ Two further potential loci on chromosomes 4q and 22q have been identified from the study of patients with chromosomal rearrangements.^{31–33}

DS associated with cervical spine and radial ray abnormalities and deafness, with an autosomal dominant mode of inheritance, is known as Okihiro syndrome or Duane radial ray syndrome. This disorder has been mapped to chromosome 20q13, with truncating mutations identified in *SALL4*, encoding a zinc finger transcription factor.^{34–35} *SALL4* represents the first definitively identified Duane syndrome causative gene, which to date has not been screened in a wider DS population, although mutations in *SALL4* have been found in other related developmental disorders.³⁵

A further syndromic form of DS is Wildervanck syndrome which consists of congenital sensorineural deafness, Klippel-Feil anomaly (fused cervical vertebrae), and DS. The disorder is almost completely limited to females, suggestive of X linked dominant inheritance.

Moebius syndrome

Ocular and histopathological features

Moebius syndrome consists of bilateral congenital facial nerve paresis and bilateral failure of abduction due to sixth nerve palsy. Other cranial nerve palsies are often present and a variety of other features including limb malformations and dental anomalies. Postmortem studies have demonstrated brainstem abnormalities including hypoplasia of the sixth, seventh, and twelfth cranial nerve nuclei or nerve fibres.^{36–38}

Molecular genetics and pathogenesis

Although most cases are sporadic, Moebius syndrome may be familial, with autosomal dominant, autosomal recessive, and X linked modes of inheritance reported. Kremer *et al* have demonstrated linkage to chromosome 3q21–q22 in a Dutch family with dominantly inherited Moebius syndrome.³⁹ The gene *SOX14* has been suggested as a possible candidate gene in Moebius syndrome,⁴⁰ due to its chromosomal localisation to 3q23 and its expression in the apical ectodermal ridge, a structure that directs outgrowth of the embryonic limb bud. *SOX14* is also expressed in the neural tube and is therefore likely to be involved in other features of the syndrome. No mutations have been identified in this gene to date.

A second locus, 10q21.3–q22.1, has been identified in a large Dutch family, indicating further genetic heterogeneity.⁴¹ Recent mutation analysis of the Moebius candidate genes *POT1* and *GATA2* on chromosome 3 and *EGR2* on chromosome 10 failed to identify any disease associated mutations.⁴²

In addition, a number of chromosomal abnormalities have been identified in patients who show features of Moebius syndrome, suggesting further possible candidate loci on 13q12.2–q13 and 1p22.^{43–46}

Congenital fibrosis of the extraocular muscles (CFEOM)

Ocular and histopathological features

CFEOM is a rare inherited disorder in which there is ptosis, strabismus, and severe limitation of extraocular movement. Both autosomal dominant and recessive modes of inheritance have been reported. High refractive errors, particularly astigmatism, and amblyopia are common, with most patients lacking binocular function. As its name suggests the disorder was initially thought to be due to a congenital abnormality of the extraocular muscles leading to fibrosis, but more recent evidence suggests that the primary abnormality is likely to be maldevelopment of the nuclei of cranial nerves III, IV, and VI with associated cranial nerve miswiring.⁴⁷ Currently, three CFEOM phenotypes have been defined.⁴⁷

The commonest phenotype, CFEOM1 or classic CFEOM, is characterised by non-progressive bilateral congenital ptosis and ophthalmoplegia. The eyes are infraducted in the primary position and there is restricted ocular elevation. Horizontal strabismus, esotropia, or exotropia, is common. The horizontal ductions are variably affected and there may be aberrant ocular movements. At surgery forced duction testing is positive. Inheritance is autosomal dominant.

In CFEOM2, patients have bilateral ptosis, large angle exotropia with severely limited horizontal and vertical eye movements, and inheritance is autosomal recessive. CFEOM3 is characterised by a variable phenotype and atypical features including unilateral disease, absent or unilateral ptosis, and relatively normal ocular elevation. Inheritance is autosomal dominant with incomplete penetrance.

Molecular genetics and pathogenesis

CFEOM1 has been mapped to 12p11.2–q12 (FEOM1 locus).⁴⁸ Engle *et al*⁴⁹ have reported the results of a postmortem study of an affected individual from a family that mapped to the FEOM1 locus which demonstrated absence of the superior division of the oculomotor nerve and atrophy and fibrosis of the levator palpebrae superioris and superior rectus (the muscles the absent division would normally supply). It would appear that in CFEOM1 the primary event is a failure of development or loss, in prenatal life, of the alpha motor neurons of the superior division of the oculomotor nerve leading to secondary muscle fibrosis. This may lead to horizontal as well as vertical restrictions of extraocular movement. Recently Yamada *et al* have identified mutations of kinesin KIF21A in their families with CFEOM1.⁵⁰ Six different mutations were identified in 44 of 45 probands with the CFEOM1 phenotype. Kinesins are a family of proteins that play a key role in axonal transport, but it is yet unclear how reduced function of KIF21A results in abnormal cranial nerve development.

The rare recessive form CFEOM2, in which affected individuals have bilateral ptosis and a fixed exotropia, has been mapped to 11q13 (FEOM2), with mutations in the *ARLX* (*PHOX2A*) gene having been demonstrated in four families with this phenotype.^{51–52} The *ARLX* gene encoding a transcription factor protein has been identified as playing a key role in the development of the alpha motor neurons of cranial nerve III and VI in mice and this lends credence to the hypothesis that CFEOM is primarily a failure of cranial nerve development.⁵²

A third locus for CFEOM on chromosome 16q (FEOM3) has been identified, with linkage analysis performed in a large Canadian family with atypical CFEOM, also known as CFEOM3.⁵³ In this family there was a wide variation of

clinical expression. Severely affected individuals had eyes fixed in a hypotropic and exotropic position, whereas other affected members were found to have only mild limitation of vertical eye movements. A second large CFEOM3 family has also been mapped to this 16q locus.⁵⁴ Rarely CFEOM1 families map to the FEOM3 locus.⁵⁵

It seems probable that other genes involved in the development of cranial nerve nuclei and guidance of the nerve axons to their extraocular muscle targets will be implicated in this group of disorders.

Other forms of incomitant strabismus

Other forms of incomitant strabismus are also occasionally reported in families. Brown (superior oblique tendon sheath) syndrome has been reported in families, including several concordant monozygotic twins.^{56–58} Familial cases of superior oblique muscle palsies have also been reported, usually with autosomal dominant inheritance.^{59–62} Familial ocular motor palsies including third and sixth cranial nerve paralysis often in association with Bell's palsy (seventh cranial nerve) have also been infrequently reported.^{63–65}

CONCOMITANT STRABISMUS

Concomitant strabismus is characterised by an angle of deviation (magnitude of ocular misalignment) which remains the same in all directions of gaze, whichever eye is fixing. Concomitant strabismus is one of the commonest problems in paediatric ophthalmology affecting 3–5% of the childhood population. Overall esotropia is more common than exotropia, with eso-deviations being three times more prevalent than exo-deviations in the UK population.⁶⁶ There are however significant variations in different racial groups; exotropia is relatively more common in both Asians and Afro-Caribbeans, whereas the majority of Caucasians are esotropes.^{66–68}

Less is known about the pathogenesis of concomitant than incomitant strabismus, but it is evident that both environmental and genetic factors are important. Risk factors for the development of childhood strabismus include family history, hypermetropic refractive errors, racial origin, low birth weight, and maternal smoking in pregnancy.^{68–73} Concomitant squint is also seen more commonly in children with neurodevelopmental disorders such as Trisomy 21, cerebral palsy, and hydrocephalus.

Genetic factors in the aetiology of concomitant strabismus

Family studies suggest that there is a strong genetic component to the aetiology of concomitant strabismus, with approximately 30% of probands with strabismus having a family member or close relative with strabismus.⁷⁴ This is supported by twin studies which have shown a 70–80% concordance in monozygotic twins compared to 30–40% in dizygotic twins.^{74–76} The relative risk for first degree relatives of an affected individual with strabismus is estimated to be between 3 and 5.^{77–79}

The genetic component varies with the different forms of strabismus, being most important in convergent squint associated with long-sighted refractive error.^{74 80 81} Even amongst specific forms of concomitant strabismus there is likely to be considerable genetic heterogeneity.

Molecular genetics

Since strabismus is common in the population, is of early onset, and has a strong genetic component it should be possible to identify families with many affected members, suitable for genetic linkage studies. Recently Parikh *et al* have reported the results of linkage analysis in a large family with non-syndromic strabismus with presumed autosomal recessive inheritance which has identified the first susceptibility

locus on chromosome 7p22.1.⁸² Linkage to 7p was excluded in six other multiplex families confirming genetic heterogeneity in this disorder. Further genome wide linkage studies of appropriate families are required.⁸³

CONCLUSIONS

To date greater advances have been made in the understanding of the underlying molecular genetics of monogenic incomitant strabismus. However, concomitant strabismus is far commoner and represents a significant health burden. It is hoped that the identification of the genetic mutations underlying concomitant strabismus will improve understanding of its aetiology and allow earlier identification of individuals at risk. Early interventions such as correction of high refractive errors and occlusion therapy should lead to a significant reduction in visual morbidity associated with childhood strabismus.

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