Strabismus is misalignment of one eye in relation to the other, resulting in failure of the 2 eyes to simultaneously focus on the same image and loss of binocular vision. Strabismus affects 2% to 4% of the population and can result in amblyopia, which is often not discovered in time to initiate effective treatment. Thus, an understanding of the genetic underpinnings of strabismus may help identify patients at risk early enough to prevent disability and may lead to new preventive or therapeutic approaches.

Strabismus has both concomitant and incomitant forms. Concomitant strabismus occurs when the angle of deviation of the eyes remains constant, independent of the direction of gaze, and includes the common forms of strabismus, such as esotropia, exotropia, hyperopia, microstrabismus, and monofixation syndrome. The pathogenesis of concomitant strabismus in the absence of obvious structural abnormalities of the eye or brain remains poorly understood. Concomitant strabismus can be inherited as a complex genetic trait, however, and it is likely that both genes and the environment contribute to its occurrence. Incomitant strabismus, also referred to as paralytic or complex strabismus, occurs when the misalignment or the angle of deviation varies with gaze direction. Incomitant strabismus accounts for approximately 5% of strabismus cases and includes the various forms of Duane retraction syndrome (DRS), horizontal gaze palsy, and congenital fibrosis of the extraocular muscles (CFEOM). These rare forms of complex strabismus can be inherited as mendelian traits, and the genetic bases of several forms of incomitant strabismus have been defined.

CONCOMITANT STRABISMUS: A COMPLEX GENETIC TRAIT

Population Studies

The heritability of concomitant strabismus is supported by differences in its frequency and type in various ethnic populations. The prevalence of strabismus is 2% to 4% among the white population and 0.6% among African and Asian populations. Esotropia is more common than exotropia in the white population of the United States and Europe, whereas exotropia is more frequent in the Asian population and among black populations of the United States and Africa. In Hawaii, esotropia is more common in white populations, exotropia is more common in Asian populations, and the 2 forms are relatively equal in the mixed ethnic population.

Twin Studies

The heritability of concomitant strabismus is supported by twin studies, which reveal a concordance rate of 73% to 82% among monozygotic twins and 35% to 47% among dizygotic twins. The higher concordance between dizygotic twins than siblings likely reflects the influence of environmental risk factors.

Family Studies

Family studies support the heritability of concomitant strabismus. Examination of a cohort of 7100 strabismic patients from 12 published family studies revealed that 2171 strabismic probands (30.6%) had a close relative with strabismus. Families are usually concordant for either esotropia or exotropia, but families with both forms have been reported. This finding may reflect the presence of 2 relatively common genes or 1 gene with variable expressivity. In addition, the same geno-
The incidence of strabismus was determined among the 39,227 children of mothers enrolled in the Collaborative Perinatal Project.14,17 Strabismus subclassification was limited to esotropia and exotropia, and strabismus was diagnosed by pediatricians and neurologists using the Hirschberg test of corneal light reflexes, a relatively imprecise estimate of strabismus that may inaccurately segregate populations. Therefore, the reported 3% incidence of esotropia and 1.2% incidence of exotropia, with an overall odds ratio for concordant siblings of 3.0 and 2.8, respectively, may have been erroneously low. This finding is supported by the finding of a much higher odds ratio from a smaller study performed by pediatric ophthalmologists who tested for subtle forms of strabismus.12 Overall, the relative risk for first-degree relatives of an affected proband with common strabismus is currently estimated to be between 3 and 5.12,14-16

Environmental Risk Factors

Studies of the children of mothers enrolled in the Collaborative Perinatal Project also revealed that advanced maternal age, cigarette smoking during pregnancy, and low birth weight (<1500 g) each contribute to the risk of strabismus.14 When corrected for these environmental risk factors, however, the odds ratios for heritability of concomitant strabismus remained significant, decreasing to 2.2 for esotropia and 2.0 for exotropia.17

Linkage Analysis

Large families that segregate concomitant strabismus as a mendelian trait would provide the greatest power to identify strabismus disease genes, but such families are rare. Data from smaller families with sibpairs or from trios (parents and affected child) who are concordant or discordant for strabismus can also be pooled and analyzed by linkage and/or association studies. Two approximately 10-centimorgan (cM) genome-wide linkage studies of concomitant strabismus have been published.16,18 The first analyzed 7 large pedigrees cosegregating strabismus and obtained a significant lod score to markers on chromosome 7p22.1 in 1 family (STBMS1, Online Mendelian Inheritance in Man [OMIM]: 185100).16 Although this pedigree appears to segregate strabismus as a dominant trait, analysis assumes recessive inheritance with incomplete penetrance and a high carrier frequency. It remains possible that the observed segregation results from complex interactions of several genes. The remaining 6 families were smaller and none mapped to this locus. In the second study, 30 sibpairs concordant for strabismus were analyzed, combining both esotropic and exotropic probands.18 This study was underpowered and yielded an insignificant lod score. Therefore, although disease or susceptibility genes for common strabismus have yet to be identified, myriad population, twin, and family studies support concomitant strabismus as a complex genetic trait.

INCOMITANT STRABISMUS: CONGENITAL CRANIAL DYSINNERVATION DISORDERS

The various forms of incomitant strabismus share a common presentation as congenital, nonprogressive restrictive ophthalmoplegias.19 Positron forced duction testing, a tight feel to the extraocular muscles at the time of strabismus surgery, and connective tissue apparent on extraocular muscle biopsy specimens led to the hypothesis that these disorders result from primary fibrosis of the extraocular muscles and to the name congenital fibrosis syndromes. Autopsies of patients with DRS20,21 and CFEOM,22 however, revealed absence of the abducens nerve and superior branch of the oculomotor nerve, respectively, supporting the hypothesis that these disorders result instead from aberrant innervation. Studies of mendelian forms of incomitant strabismus have now demonstrated that these disorders can result from mutations in genes critical to the development of ocular motoneurons and their axonal connections and led to their renaming as the congenital cranial dysinnervation disorders (CCDDs).23

CONGENITAL FIBROSIS OF THE EXTRACOULAR MUSCLES

Congenital fibrosis of the extraocular muscles has been referred to by more than 20 different names in the English literature alone, reflecting, to some degree, the varying opinions as to its pathogenesis.24 It is now most commonly referred to as CFEOM, which remains a misnomer. Congenital fibrosis of the extraocular muscles has been reported in families of many different ethnic backgrounds. Although most families demonstrate autosomal dominant inheritance with full penetrance, partial penetrance or recessive inheritance are also reported; genetic analysis of CFEOM pedigrees has led to the identification of several different syndromes that account for this variability. An individual is now diagnosed as having CFEOM based on the presence of congenital restrictive ophthalmoplegia that primarily affects extraocular muscles in the oculomotor distribution. He or she is diagnosed as having a specific form of CFEOM based on both phenotype and genotype.

CFEOM1 (OMIM: 135700) as a Result of KIF21A Mutations

An individual with CFEOM1 has (1) congenital nonprogressive bilateral external ophthalmoplegia and congenital bilateral ptosis, (2) an inftraducted primary position of each eye, and (3) inability to raise either eye above the horizontal midline. The horizontal position of each eye can be midline, esotropic, or exotropic, and horizontal movements can be full to none. Residual eye movements can be remarkably abnormal, including synergistic convergence and divergence, Marcus Gunn jaw-winking phenomenon,25 or lid elevation while tooth brushing.26 Misinnervation is also supported by electromyographic studies that show aberrant extraocular muscle firing and co-contraction in individuals later determined to harbor KIF21A mutations.27,28
Autopsy findings of an affected member of a CFEOM1 pedigree subsequently found to harbor the most common KIF21A mutation support a neurogenic origin for CFEOM1. The autopsy revealed absence of the superior division of the oculomotor nerve and profound hypoplasia of the 2 muscles normally innervated by this nerve, the levator palpebrae superioris and superior rectus. In addition, the caudal central motoneurons that normally innervate the levator were absent. There was a qualitative decrease in the number of motoneurons in all oculomotor subnuclei and the abducens nucleus, a decreased diameter of inferior division of the oculomotor nerve, and an increase in central nuclei within myofibers of all extraocular muscles examined.

The disorder CFEOM1 is inherited as an autosomal dominant trait, and if all affected members of a CFEOM family meet CFEOM1 criteria, the family is classified as a CFEOM1 pedigree. In most pedigrees, CFEOM1 maps to the FEOM1 locus at the centromeric region of chromosome 12 and results from heterozygous mutations in KIF21A. In addition, rare CFEOM1 probands likely harbor mutations in the FEOM3 gene. KIF21A has 3 domains and is a member of the kinesin family of molecular motors that transport cargo along microtubules and, in neurons, are responsible for anterograde axonal transport. The motor domain contains the microtubule binding site. The tail domain is where cargo is loaded and carried, often via an adaptor or scaffolding protein or protein complex. The stalk domain is a flexible connector between the motor and tail that typically contains α-helical coiled-coil repeats through which kinesin can homodimerize or heterodimerize, permitting 2 kinesin motors to “walk” down the microtubule. In some instances, the distal stalk also interacts with cargo. Mouse Kif21a is expressed abundantly in the brain, including neuronal cell bodies, axons, and dendrites; its cargo is not known. Other kinesin family members regulate many aspects of neuronal differentiation, including neurite extension, collateral branching, and growth cone and cytoskeleton dynamics, supporting the hypothesis that CFEOM1 results from a defect in neuronal differentiation.

Remarkably, mutations that affect only 5 KIF21A amino acid residues have been reported among the more than 50 unrelated CFEOM1 probands harboring KIF21A mutations. Three of these altered residues, including the most common, R954W (c2860C→T), which is found in more than 80% of probands, are located in the α position, whereas a fourth is located in the adjacent e position of heptad repeats within the same coiled-coil region of the KIF21A stalk. The α-helical heptad coiled-coil regions are critical for the association and stability of kinesin interactions, with the intertwined molecules touching at the a and d positions. Therefore, these mutations may interfere with KIF21A’s interaction with its unidentified partner(s) and/or its unidentified cargo. The fifth altered amino acid residue is located at the end of the motor domain.

Magnetic resonance imaging of the orbit and brainstem of participants from 6 unrelated CFEOM1 pedigrees revealed no imaging features that distinguished among the 3 amino acid substitutions represented among these individuals. This finding suggests that these different recurrent mutations produce the same protein dysfunction, likely resulting in absent or aberrant cargo delivery to the growth cone of the developing ocular motoneuron.

CFEOM2 (OMIM: 602078) as a Result of PHOX2A Mutations

Individuals with this recessive phenotype are born with bilateral ptosis with their eyes primarily fixed in an exotropic position. This eye position suggests that the only normally functioning extraocular muscle is the abducens innervated lateral rectus, which succeeds in pulling each eye outward. Central ocular motility reflexes are intact except for convergence. Interestingly, pupilary light and near reflexes are not present, but irises are anatomically normal and respond to pupillary pharmacologic treatment. The disorder CFEOM2 maps to the FEOM2 locus on chromosome 11q13 and results from recessive mutations in the homeodomain transcription factor PHOX2A (ARIX). One nonsense, 1 missense, and 2 splice site homozygous mutations have been reported, suggesting that CFEOM2 results from complete loss of function of PHOX2A.

Phox2a encodes a pairedlike transcription factor homeodomain protein with expression restricted to several classes of differentiating neurons in the central and peripheral nervous system. Mouse Phox2a null mutants and zebrafish with homozygous point mutations in the Phox2a homeodomain die soon after birth. In both mutants, the oculomotor and trochlear nuclei are absent, consistent with Phox2a expression in the proliferating oculomotor and trochlear motoneuron precursors. These animals also have absence of the locus coeruleus, atrophy of cranial sensory ganglia, and absence of parasympathetic ganglia of the head, phenotypes not detected in patients with CFEOM2.

Magnetic resonance imaging studies of brain and brainstem of 9 individuals with CFEOM2 have revealed the anatomical absence of the oculomotor and probably the trochlear nerves bilaterally. Therefore, clinical presentation, neuroimaging, and Phox2a animal models all support the concept that CFEOM2 is a primary neurogenic abnormality of oculomotor and trochlear motoneuron development with secondary myopathic changes.

Phenotypical and Genetic Heterogeneity of CFEOM3

In a CFEOM3 pedigree, at least 1 affected family member does not meet CFEOM1 criteria (and the pedigree is not CFEOM2). The CFEOM3 pedigrees typically express CFEOM as a dominant trait with broader phenotypic variability than found in CFEOM1 and CFEOM2, including individuals with unilateral involvement and/or residual upgaze. In some families all affected individuals have CFEOM3, and in other families some affected individuals...
have CFEOM3 and some have CFEOM1.37

Mapping of CFEOM3 and CFEOM1 to the FEOM3 Locus on Chromosome 16

The first genetic locus established for CFEOM3 was FEOM3 on chromosome 16qter; 2 large pedigrees map to this locus.35,57 Some affected members of CFEOM3-linked pedigrees have CFEOM1, and not surprisingly, 2 small CFEOM1 pedigrees that do not harbor KIF21A mutations were shown to be consistent with linkage to this locus.30,32 Therefore, it is shown to be consistent with link-

KIF21A

In 1 series, the unidentified alterations will also harbor mutations in acids as in CFEOM1.58 In a separate probands, altering the same amino identified in 2 (9%) of 22 CFEOM3 gion of chromosome 21qter.60 an approximately 1.5-megabase re-

anomalies. The syndrome maps to gree with CFEOM and ulnar hand

cently reported in a Turkish pedi-

A new recessive syndrome was re-

script expressed in the brain and

rupted an uncharacterized tran-

chromosome 13 break point inter-

results from heterozygous nons-

frame shift, and deletion muta-

tions in SALL4, a member of the SAL family of proposed C 2H2 zinc

fingers transcription factors.78,79 The SALL4 gene has also been impli-
cated in DRS associated with Holt-Oram and acro-renal ocular syn-
dromes.80 How SALL4 mutations lead to DRS has not been eluci-
dated.

Tukel Syndrome

A new recessive syndrome was re-
cently reported in a Turkish pedi-
gree with CFEOM and ulnar hand anomalies. The syndrome maps to an approximately 1.5-megabase region of chromosome 21qter.80

DUANE SYNDROME

Named for Alexander Duane,61 DRS is the most common of the CCDDs and accounts for 1% to 5% of stra-
bismus cases.82 The affected eyes of individuals with DRS have limited horizontal gaze and retraction of the globe into the orbit on attempted adduction, resulting in secondary narrowing of the palpebral fissure. Although early studies of DRS suggested a primary myopathic origin, several postmortem examinations of patients with isolated DRS revealed absence of the abducens nerve and motoneurons on the affected side and partial innervation of the lateral rectus muscles by branches from the oculomotor nerve.20,21 Aberrant innervation is supported by electromyographic63,64 and magnetic resonance imaging65 studies, suggesting that at least a subset of DRS results from abducens motoneuron or nerve dysfunction with anomalous innervation of the lateral rectus muscle by the oculomo-
tor nerve.

Isolated DRS

Although a positive family history is reported in 2% to 20% of cases of isolated DRS, only 1 genetic locus has been mapped. The DURS2 locus on chromosome 2q31 (OMIM: 604356) was established by linkage analysis of a large dominant DRS pedig-

SALL4, a member of the SAL family of proposed C 2H2 zinc finger transcription factors.78,79 The SALL4 gene has also been impli-
cated in DRS associated with Holt-Oram and acro-renal ocular syn-
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dated. 

Bosley-Salih-Alorainy

and Athabascan Brainstem

Dysgenesis Syndromes as the

Result of Mutations in HOXA1

The Athabascan brainstem dysgenesis syndrome (OMIM 601536) described in Native American children81 and the Bosley-Salih-Alorainy syndrome (OMIM 601536) described in Saudi Arabian and Turkish children82 overlap. Children with Bosley-Salih-Alorainy syn-
drome have bilateral DRS, and sub-
sets have congenital sensorineural deafness secondary to bilateral ab-
sence of the cochlea, semicircular canals, and vestibule; variable malfo-
mations of the internal carotid arteries; delayed motor milestones; and autism spectrum disorder. Simi-
larly, children with Athabascan brain-
stem dysgenesis syndrome have hori-
zontal gaze restriction, sensorineural deafness, delayed motor develop-
ment,81 and internal carotid artery
Horizontal gaze palsy with progressive scoliosis is a rare autosomal recessive disorder reported in consanguineous pedigrees of many different ethnicities and in offspring of unrelated individuals. Affected individuals are born with absent horizontal eye movements and develop severe progressive scoliosis starting in infancy or childhood. The gaze palsy is congenital and nonprogressive. Ocular alignment, congenital nystagmus, and vertical smooth pursuit defects are variable among individuals. Convergence is retained in a subset of patients and can be substituted for conjugate tracking movements. Neuroimaging typically reveals hypoplasia of the pons and cerebellar peduncles with both anterior and posterior midline clefts of the pons and medulla. Unlike other CCDDs, the abducens nerve is present bilaterally and the orbital extraocular muscles are normal in both configuration and size.

Horizontal gaze palsy with progressive scoliosis maps to chromosome 7p15.2, encompassing the HOXA1 gene cluster, and genetic analysis of children with Athabascan brainstem dysgenesis syndrome revealed that their maternal and paternal alleles were identical across the 7p15.2 region, suggesting linkage of a recessive trait to this locus as well. Affected individuals from each of the 3 founder populations (Saudi Arabian, Turkish, and Native American) were found to harbor a unique homozygous truncating HOXA1 mutation that is predicted to result in complete loss of gene function. The phenotypes reported in 2 Hoxa1−/− mouse models are remarkably similar to those in the human HOXA1 syndromes. The mice have grossly abnormal rhomboencephalon development with errors in neural patterning of the hindbrain and associated ganglia, resulting in aberrant abducens and inner ear development. Hoxa1−/− mice die soon after birth, and a subset of them die from hyperventilation. Hence, this CCDD appears to result from an early, diffuse error in hindbrain segmentation.

**Horizontal Gaze Palsy With Progressive Scoliosis as the Result of ROBO3 Mutations**

Horizontal gaze palsy with progressive scoliosis is a rare autosomal recessive disorder reported in consanguineous pedigrees of many different ethnicities and in offspring of unrelated parents. Affected individuals are born with absent horizontal eye movements and develop severe progressive scoliosis starting in infancy or childhood. The gaze palsy is congenital and nonprogressive. Ocular alignment, congenital nystagmus, and vertical smooth pursuit defects are variable among individuals. Convergence is retained in a subset of patients and can be substituted for conjugate tracking movements. Neuroimaging typically reveals hypoplasia of the pons and cerebellar peduncles with both anterior and posterior midline clefts of the pons and medulla. Unlike other CCDDs, the abducens nerve is present bilaterally and the orbital extraocular muscles are normal in both configuration and size.

Horizontal gaze palsy with progressive scoliosis results from the complete loss of ROBO3 function. The ROBO3 gene encodes a transmembrane receptor important in axon guidance and neuronal migration, is expressed in the human fetal hindbrain, and is homologous to mouse Robo3 (Rig1). When Robo3 function is removed in mice, there is failure of hindbrain precerebellar axons and neurons and spinal commissural axons to cross the midline. Consistent with the animal model, electrophysiologic studies in humans provide evidence of ipsilateral corticospinal and dorsal column–medial lemniscus tract innervation.

**RELATED MECHANISMS AND CLINICAL RELEVANCE**

The CCDD genes identified thus far play essential roles in the normal development and/or connectivity of cranial motoneurons. The PHOX2A and KIF21A genes appear to affect development of the midbrain oculomotor and/or trochlear axes, and mutations result in abnormalities of both vertical and horizontal gaze, whereas SALL4, ROBO3, and HOXA1 affect development of the pontine abducens axis, and mutations result in primary abnormalities of horizontal gaze. The underlying gene defects lead to errors at various developmental time points and locations along the developing neuroaxis, including predicted errors in hindbrain segmentation (HOXA1), motoneuron specification (PHOX2A), and axon targeting (CFEOM1, ROBO3). Genetic diagnostic tests are now available for these rare strabismus syndromes.

Future studies are also likely to define the genetic defects that place individuals at risk for the common forms of concomitant strabismus, since these disorders appear to be inherited as complex genetic traits. Insight into the genetic basis of common strabismus should lead to an improved ability to detect and prevent loss of binocular vision and amblyopia.

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8. Bosley-Salih-Alorainy syndrome has been identified as a sporadic trait in Native American children from the American Southwest. Linkage analysis of pedigrees with Bosley-Salih-Alorainy syndrome localized the gene to chromosome 7p15.2, encompassing the HOXA1 gene cluster, and genetic analysis of children with Athabascan brainstem dysgenesis syndrome revealed that their maternal and paternal alleles were identical across the 7p15.2 region, suggesting linkage of a recessive trait to this locus as well. Affected individuals from each of the 3 founder populations (Saudi Arabian, Turkish, and Native American) were found to harbor a unique homozygous truncating HOXA1 mutation that is predicted to result in complete loss of gene function.

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