GENEReviews

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Duane Syndrome

[*Duane Retraction Syndrome; Stilling-Turk-Duane Syndrome; Duane Anomaly, Isolated. Includes: Duane Retraction Syndrome 2*]

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Summary

Disease characteristics. Duane syndrome is a strabismus syndrome characterized by congenital non-progressive horizontal ophthalmoplegia (inability to move the eyes) primarily affecting the abducens nucleus and nerve and its innervated extraocular muscle, the lateral rectus muscle. At birth, affected individuals have restricted ability to move the affected eye(s) outward (abduction) and/or inward (adduction). In addition, the globe retracts into the orbit with attempted adduction, accompanied by narrowing of the palpebral fissure. Most individuals with Duane syndrome have strabismus in primary gaze but can use a compensatory head to align the eyes, and thus can preserve single binocular vision and avoid diplopia. Individuals with Duane syndrome who lack binocular vision are at risk for amblyopia. Approximately 70% of individuals with Duane syndrome have isolated Duane syndrome; i.e., they do not have other detected congenital anomalies.

Diagnosis/testing. The diagnosis of Duane syndrome is based on clinical findings. No gene defect has been identified for isolated Duane syndrome. One locus (DURS2 at chromosome 2q31) has been mapped in four families with autosomal dominant Duane syndrome.

Management. *Treatment of manifestations:* spectacles or contact lenses for refractive error; occlusion or penalization of the better-seeing eye for treatment of amblyopia; prism glasses, usually in older mild cases, to improve the compensatory head position; extraocular muscle surgery to correct or improve compensatory head posture, improve alignment in primary gaze position, improve upshoot or downshoot. *Prevention of secondary complications:* specialist examination early in life to detect refractive errors to prevent amblyopia and avoid compounding the motility problem; amblyopia therapy to prevent vision loss in the less-preferred eye; surgery to prevent loss of binocular vision in individuals who abandon the compensatory head posture and allow strabismus to become manifest. *Surveillance:* ophthalmologic visits every 3-6 months during the first years of life to prevent and treat amblyopia; annual or biannual eye examinations when no longer at risk for amblyopia (after

age 7-12 years). *Testing of relatives at risk:* eye examination within the first months of life so that early diagnosis and treatment can prevent secondary complications.

Genetic counseling. Most individuals with isolated Duane syndrome are simplex cases (i.e., a single occurrence in a family) of unknown cause. Isolated Duane syndrome mapping to the DURS2 locus is inherited in an autosomal dominant manner with incomplete penetrance.

Diagnosis

Clinical Diagnosis

Duane syndrome, a congenital, non-progressive eye movement disorder, is characterized by the following:

- Congenital limitation of abduction and/or adduction
- Globe retraction (co-contraction) on adduction
- Palpebral fissure (i.e., the separation between the upper and lower eyelids) narrowing on adduction.

Note: Adduction is movement of the globe toward the midline (the nose); abduction is movement of the globe away from the midline (toward the ear).

Isolated Duane syndrome. Most individuals with Duane syndrome have isolated Duane syndrome, i.e., they do not have other detected congenital anomalies. The vast majority of individuals with isolated Duane syndrome are simplex cases (i.e., single occurrence in a family). This *GeneReview* focuses on isolated Duane syndrome. (See Differential Diagnosis for a discussion of Duane syndrome with associated congenital anomalies.)

Duane syndrome can be clinically subdivided into three types:

Type 1 (~75%-80% of all Duane syndrome) is characterized by the following:

- Absent to markedly restricted abduction
- Normal to mildly restricted adduction
- Retraction of the globe and narrowing of the palpebral fissure on adduction
- Upshoot and downshoot of affected globe on attempted adduction
- Esotropia in primary gaze (variably present)
- Head turn toward involved side (variably present)
- Unilateral or bilateral involvement

Type 2 (~5%-10% of all Duane syndrome) is characterized by the following:

- Absent to markedly restricted adduction
- Normal to mildly restricted abduction
- Retraction of the globe and narrowing of the palpebral fissure (the separation between the upper and lower eyelids) on adduction
- Upshoot and downshoot of affected globe on attempted adduction (variably present)
- Exotropia in primary gaze (variably present)
- Head turn toward uninvolved side (variably present)
- Unilateral or bilateral involvement

Type 3 (~10%-20% of all Duane syndrome) is characterized by the following:

- Absent to markedly restricted abduction
- Absent to markedly restricted adduction
- Retraction of the globe and narrowing of the palpebral fissure on attempted adduction
- Upshoot and downshoot of affected globe on attempted adduction (more common than in types 1 or 2)
- Esotropia or exotropia in primary gaze (variably present)
- Head turn toward involved side (variably present)
- Unilateral or bilateral involvement

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. No gene defect has been identified for isolated Duane syndrome.

Locus. DURS2 (chromosome 2q31)

- Mode of inheritance is autosomal dominant.
- Duane syndrome phenotype in four pedigrees has mapped to DURS2 locus [Appukuttan et al 1999, Chung et al 2000, Evans et al 2000, Engle et al 2007].
- Of the 45 affected members examined in the four pedigrees, 41 had bilateral Duane syndrome (91%). Two-thirds had type 1 Duane syndrome; one-third had type 3 Duane syndrome; none had type 2 Duane syndrome.
- The incidence of strabismus, amblyopia, and vertical movement abnormalities with DURS2-linked Duane syndrome appears to be higher than that found in individuals with Duane syndrome not linked to DURS2 [Chung et al 2000, Demer et al 2007, Engle et al 2007].
- Magnetic resonance imaging (MRI) of the brain and orbit of affected family members often revealed nondetectable abducens nerve(s) but also small oculomotor nerve with hypoplasia of oculomotor and trochlear innervated muscles. These data suggest that DURS2-linked Duane syndrome is a diffuse ocular congenital cranial dysinnervation disorder not limited to maldevelopment of the abducens nerve [Demer et al 2007].

Clinical Description

Natural History

Duane syndrome is a strabismus syndrome characterized by congenital non-progressive horizontal ophthalmoplegia (inability to move the eyes) without ptosis (droopy eyelids) primarily affecting the abducens nucleus and nerve and its innervated extraocular muscle, the lateral rectus muscle. At birth, affected individuals have restricted ability to move the affected eye(s) outward (abduction) and/or inward (adduction). In addition, the globe retracts into the orbit with attempted adduction, accompanied by narrowing of the palpebral fissure. The left side is more commonly affected in most studies.

The female-to-male ratio for simplex cases is 3:2.

Strabismus. Strabismus is the deviation of the position of one eye relative to the other, resulting in misalignment of the line of sight of the two eyes. Many individuals with Duane syndrome have strabismus in primary gaze; esotropia is more common in Duane syndrome type 1 and exotropia in Duane syndrome type 2. The impaired movement of one eye with respect to the other allows individuals with strabismus in primary gaze to utilize a compensatory head turn in order to align the eyes, thus avoiding diplopia and preserving single binocular vision.

Amblyopia. Amblyopia occurs in approximately 10% of individuals with Duane syndrome; these persons are typically a subset of those with Duane syndrome who lack binocular vision. The amblyopia in Duane syndrome responds to standard therapy if detected early; if not treated promptly, the vision loss from amblyopia is irreversible.

Visual acuity. Visual acuity is good except in those individuals with amblyopia.

Marcus Gunn jaw-winking phenomenon. An individual with Duane syndrome and Marcus Gunn jaw-winking phenomenon has been reported, lending support to the idea that the two syndromes are primarily neurogenic in origin [Isenberg & Blechman 1983].

Pathophysiology. It is generally believed that Duane syndrome results from maldevelopment of motor neurons in the abducens nucleus and aberrant innervation of the lateral rectus muscle. Early studies of Duane syndrome reported fibrosis of the lateral rectus or medial rectus muscles, and suggested a primary myopathic etiology for this disorder. Subsequently, several postmortem examinations of patients with simplex Duane syndrome revealed absence of the abducens motor neurons and ipsilateral cranial nerve VI, and partial innervation of the lateral rectus muscle(s) by branches from the oculomotor nerve. Electromyography revealed simultaneous activation of the medial and lateral rectus muscles, supporting co-contraction of these two horizontal muscles as the cause of the globe retraction.

Magnetic resonance imaging (MRI) in simplex cases has verified the absence of cranial nerve VI [Parsa et al 1998] and co-contraction of the horizontal rectus muscles on attempted adduction.

Orbital and brainstem MRI of affected members of two pedigrees in which Duane syndrome maps to the DURS2 locus did not visualize the abducens nerve in most patients and revealed structurally abnormal lateral rectus muscles. The oculomotor and optic nerves were also small [Demer et al 2007]. Together, these studies suggest the following:

- At least a subset of Duane syndrome likely results from maldevelopment of abducens motoneurons with varying amounts of anomalous innervation of the lateral rectus.
- Duane syndrome resulting from mutations in the gene at the DURS2 locus may represent a diffuse congenital cranial dysinnervation disorder that also affects the development of additional cranial nerves.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known, as the gene(s) causing isolated Duane syndrome has/have not been identified.

Penetrance

DURS2-linked Duane syndrome may have reduced penetrance [Engle et al 2007].

Nomenclature

Historically, Duane syndrome was initially proposed to be myogenic in origin. Electromyelography (EMG) of the EOM's, postmortem examinations, and MRI, however, now support a neurogenic etiology [Demer et al 2007]. This has led to the renaming of Duane syndrome as the "co-contractive retraction syndrome" (CCRS, types 1-3) [Hertle et al 2002] and classifying it as one of the ocular congenital cranial dysinnervation disorders (CCDD) [Gutowski et al 2003, Engle 2006].

Duane syndrome is named for the ophthalmologist Alexander Duane (1858-1926).

Prevalence

Duane syndrome accounts for 1%-5% of all cases of strabismus.

Isolated Duane syndrome in familial and simplex cases has been identified worldwide. The prevalence of Duane syndrome is estimated to be 1:1000 in the general population.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Duane syndrome with associated congenital anomalies. Approximately 30% of individuals with Duane syndrome have other congenital anomalies, particularly of the ear, kidney, heart, upper limbs, and skeleton. These associated anomalies are typically reported in simplex cases, but also occur together with Duane syndrome as familial malformation or genetic syndromes.

- ***SALL4*-related disorders**. The *SALL4*-related syndromes include Okihiro syndrome, Duane-radial ray syndrome, acro-renal-ocular syndrome, and IVIC syndrome. These overlapping syndromes are characterized by unilateral or bilateral Duane syndrome and radial ray malformations that can include thenar hypoplasia and/or hypoplasia or aplasia of the thumbs; hypoplasia or aplasia of the radii; shortening and radial deviation of the forearms; triphalangeal thumbs; and duplication of the thumb (preaxial polydactyly). Deafness, renal anomalies, and imperforate anus can be co-inherited. Inheritance is autosomal dominant.

  Heterozygous *SALL4* mutations are associated with most familial cases of these syndromes [Al-Baradie et al 2002, Kohlhase et al 2002, Kohlhase et al 2003, Kohlhase et al 2005, Paradisi & Arias 2007]. Individuals with simplex isolated Duane syndrome have not been found to harbor mutations in *SALL4* [Wabbels et al 2004].

- ***HOXA1*-related syndromes.** The *HOXA1*-related syndromes include the overlapping Bosley-Salih-Alorainy syndrome (BSAS, MIM 601536) [Tischfield et al 2005] and Athabaskan brainstem dysgenesis syndrome (ABDS) [Holve et al 2003]. They are characterized by Duane syndrome type 3 or horizontal gaze palsy and, in most individuals, bilateral sensorineural hearing loss caused by an absent cochlea and rudimentary inner-ear development. Subsets of individuals manifest mental retardation, autism, moderate-to-severe central hypoventilation, facial weakness, swallowing difficulties, vocal cord paresis, conotruncal heart defects, and skull and craniofacial abnormalities.

  These disorders result from truncating mutations in *HOXA1* [Tischfield et al 2005]. Inheritance is autosomal recessive. Individuals with simplex isolated Duane syndrome have not been found to harbor mutations in *HOXA1* [Tischfield et al 2006].

- **Wildervanck syndrome** (cervicooculoacoustic syndrome, MIM 314600) is characterized by Duane syndrome, deafness, and Klippel-Feil anomaly (fused cervical vertebrae). The perceptive deafness results from a bony malformation of the inner ear. Most Wildervanck syndrome is sporadic and limited to females.
- **Goldenhar syndrome** (hemifacial microsomia, oculoauriculovertebral spectrum, MIM 164210) is characterized by craniofacial, ocular, cardiac, vertebral, and central nervous system defects, consistent with maldevelopment of the first and second branchial arches. Duane syndrome can be associated with this disorder [Tillman et al 2002, Caca et al 2006]. The majority of cases are sporadic, but there are a few reports of both autosomal dominant and recessive inheritance.

Chromosome disorders. The DURS1 locus (chromosome 8q13) (MIM 126800) was defined by the presence of cytogenetic abnormalities in three simplex cases. No family with isolated Duane syndrome to date has been reported to map to this locus by linkage analysis.

- Patient 1: presumed contiguous gene deletion syndrome with Duane syndrome, branchiootorenal (BOR) syndrome, hydrocephalus, trapezius muscle aplasia, *de novo* 8q12.2-q21.2 deletion [Vincent et al 1994]
- Patient 2: Duane syndrome type 1, microcephaly, mental retardation, dysmorphic features, and an insertion of chromosome region 8q13-q21.2 on to band 6q25 with a complex concurrent deletion within the 8q rearranged region [Calabrese et al 1998]
- Patient 3: Duane syndrome, hypoplastic external genitalia, reciprocal translocation of t(6;8)(q26;q13). The chromosome 8 breakpoint was mapped to the intron between exons 1 and 2 of the carboxypeptidase gene, *CPA6* [Calabrese et al 2000, Pizzuti et al 2002]. Note: No *CPA6* point mutations were identified in 18 simplex cases of Duane syndrome [Pizzuti et al 2002].

Note: It remains to be determined whether *CPA6* is the DURS1 gene, or whether the breakpoint within *CPA6* resulted in Duane syndrome secondary to the disruption of an embedded gene or a position effect, or was incidental.

22q11.2 deletion syndrome (velocardiofacial syndrome, MIM 192430, DiGeorge syndrome, MIM 188400, Cayler cardiofacial syndrome, conotruncal anomaly face syndrome) encompasses a range of findings that includes learning disabilities, characteristic facial features, velopharyngeal insufficiency, hypernasal speech, occult cleft palate and congenital heart disease. Duane syndrome has been reported in association with this syndrome [Versteegh et al 2000].

A *de novo* 1q42.13-q43 deletion was identified in an individual presenting with Duane syndrome type 1, ptosis, mental retardation, rounded face, mid-face hypoplasia, low-set ears, tapering fingers, and brain hypoplasia [Kato et al 2006].

A *de novo* 4q27-q31 deletion was identified in an individual with bilateral Duane syndrome type 1, bilateral ptosis, and mild learning difficulties [Chew et al 1995].

Ocular congenital cranial dysinnervation disorders. The term congenital cranial dysinnervation disorders (CCDDs) refers to disorders of innervation of cranial musculature [Gutowski et al 2003]. The ocular CCDDs are also included in the category of complex or incomitant strabismus, in which the degree of misalignment of the eyes varies with the direction of gaze.

Duane syndrome is the most common of the ocular CCDDs. Other ocular CCDDs include the following:

- **Congenital fibrosis of the extraocular muscles (CFEOM).** CFEOM refers to at least four strabismus syndromes: CFEOM1 (MIM 135700), CFEOM2 (MIM 602078), CFEOM3 (MIM 600638), and Tukel syndrome (MIM 609428), which are characterized by congenital non-progressive ophthalmoplegia (inability to move the eyes) with or without ptosis (droopy eyelids) affecting part or all of the oculomotor nucleus and nerve (cranial nerve III) and its innervated muscles (superior, medial, and inferior recti, inferior oblique, and levator palpebrae superioris) and/or the trochlear nucleus and nerve (cranial nerve IV) and its innervated muscle (the superior oblique). In general, affected individuals have severe limitation of vertical gaze and variable limitation of horizontal gaze. Individuals with CFEOM frequently compensate for the ophthalmoplegia by maintaining abnormal head positions at rest and by moving their heads rather than their eyes to track objects. Individuals with Tukel syndrome also have postaxial oligodactyly or oligosyndactyly of the hands.
- **Moebius syndrome (MBS)** (MIM 157900) is characterized by sixth and seventh nerve palsies, resulting in abduction defect and facial weakness. The vast majority of individuals with Moebius syndrome are simplex cases (i.e., single occurrence in a family) and many are associated with additional developmental defects of lower cranial nerves and distal extremities.
- **Horizontal gaze palsy with progressive scoliosis (HGPPS)** (MIM 607313) is characterized by congenital horizontal gaze palsy (no horizontal eye movements) accompanied by progressive scoliosis. HGPPS is inherited in an autosomal recessive manner and is caused by mutations in *ROBO3* [Jen et al 2004]. Compound heterozygous *ROBO3* mutations have also been identified in children of non-consanguineous parents [Chan et al 2006]. Neuroimaging and neurophysiology studies of individuals with HGPPS found that the axons that make up the major motor and sensory pathways for communication between the brain and the spinal cord fail to cross the midline in the hindbrain [Jen et al 2004, Bosley et al 2005].

Complex and common forms of strabismus that could be confused with Duane syndrome:

- **Common strabismus.** In common or comitant strabismus, the misalignment of the eyes is equal regardless of the direction of gaze. Common strabismus includes esotropia, exotropia, dissociated vertical deviation, microstrabismus, and monofixation syndrome.
- **Sixth nerve palsy** is characterized by impaired abduction of the affected eye in the absence of globe retraction and narrowing of the palpebral fissure. Sixth nerve palsy may be accompanied by esotropia. Sixth nerve palsies are typically acquired. Congenital and/or inherited cases are rare.
- **Crossed fixation.** The signs of Duane syndrome may be difficult to detect in an infant with large-angle esotropia. In such infants, the right eye is used for left gaze and the left eye is used for right gaze. As a result, the child may appear to have an abduction limitation when in fact abduction is found to be full when tested monocularly.
- **Congenital ocular motor apraxia** is a rare disorder of horizontal gaze in which affected individuals are unable to generate horizontal saccades. Horizontal tracking requires head movement, but the head must be thrust past the object of regard in order to overcome the intact doll's head response. Vertical saccades are preserved.
- **Brown syndrome** ('superior oblique tendon sheath syndrome') is characterized by the inability to elevate the adducted eye actively or passively. Forced duction testing is positive for tightness of the superior oblique muscle. The downshoot seen in Duane syndrome can mimic Brown syndrome. Most congenital Brown syndrome is simplex (i.e., single occurrence in a family) and believed to result from anomalies of the tendon

or the trochlear apparatus. Rare familial cases have been reported [Iannaccone et al 2002].

- **Congenital esotropia and exotropia** refer to eye conditions in which the eye(s) is (are) either crossed or deviating outwards. There is evidence of both genetic and environmental components to these disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Duane syndrome, the following evaluations are recommended:

- Family history
- Ophthalmologic examination
  - Determination of primary gaze position, head position with eyes in primary position, and horizontal and vertical gaze restrictions
  - Evaluation for aberrant movements. Globe retraction with narrowing of the palpebral fissure in adduction is the sine qua non of Duane syndrome. Other features sometimes observed include up- and downshoot on attempted adduction, Marcus Gunn jaw wink.
  - Optional forced duction testing.
- Photographic documentation for future comparison
- If surgery is planned: MRI to determine brainstem and orbital anatomy (muscles and nerves)
- General physical examination. Because of association with systemic anomalies, affected children should have a complete physical examination.
- If surgery is performed, forced duction testing to confirm tightness of the horizontal rectus muscles

Treatment of Manifestations

Nonsurgical treatment of ophthalmologic findings

- Refractive errors may be managed with spectacles or contact lenses. Specialist examination is required to detect refractive errors early in life, when affected individuals may be asymptomatic, to prevent amblyopia and avoid compounding the motility problem with a focusing problem.
- Amblyopia can be treated effectively with occlusion or penalization of the better-seeing eye. Early detection (in the first years of life) maximizes the likelihood of a good response to treatment.
- Prism glasses may improve the compensatory head position in mild cases. They are more likely to be tolerated by older persons.

Surgical treatment of ophthalmologic findings (extraocular muscle surgery)

- To correct or improve compensatory head posture
- To improve alignment in primary gaze position
- To improve upshoot or downshoot

Principles of surgical approach

- **Type 1 and type 3.** If head turn is present, consider recession of the medial rectus muscle or horizontal transposition of the vertical rectus muscles. Vertical rectus muscle transposition may be augmented, either with posterior augmentation sutures on the transposed muscles, or with botulinum toxin injections into the medial rectus muscle. If up and/or downshoot occurs in adduction, or if globe retraction is severe and creates a deformity, consider recession of both the medial and lateral rectus muscles. Y-splitting of the lateral rectus muscle may decrease the amount of recession required.
- **Type 2.** If head turn is present, consider recession of the ipsilateral lateral rectus muscle if the patient fixates with the uninvolved eye, and the contralateral lateral rectus if the patient fixates with the involved eye. If upshoot or downshoot occurs in adduction, consider recession of both the medial and lateral rectus muscles.

Prevention of Secondary Complications

- Amblyopia therapy to prevent vision loss in the less preferred eye
- Surgery to prevent loss of binocular vision in individuals who abandon the compensatory head posture and allow strabismus to become manifest

Surveillance

Surveillance is important for prevention of amblyopia, and to treat amblyopia if it occurs.

- Routine ophthalmologic visits every three to six months during the first years of life
- Annual or biannual examinations in affected individuals older than age seven to 12 years who have good binocular vision and thus are no longer at risk for amblyopia

Testing of Relatives at Risk

Duane syndrome can often be diagnosed by clinical findings within the first months of life; early diagnosis can result in prevention of secondary complications.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Most individuals with Duane syndrome represent simplex cases (i.e., single occurrence in a family).

Isolated Duane syndrome mapping to the DURS2 locus is inherited in an autosomal dominant manner with incomplete penetrance.

Risk to Family Members — Autosomal Dominant Inheritance (DURS2 Locus for Isolated Duane Syndrome)

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- Some individuals diagnosed with isolated Duane syndrome have an affected parent.
- The DURS2 gene has yet to be elucidated. It is possible that a proband with Duane syndrome may have the disorder as the result of a new gene mutation.
- Recommendations for the evaluation of parents of a proband with isolated Duane syndrome include ophthalmologic examinations. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Sibs of a proband

- The risk to sibs of a proband with isolated Duane syndrome mapping to the DURS2 locus depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to each sibling is 50%.
- When the parents are clinically unaffected, the risk to the siblings of a proband appears to be low.

Offspring of a proband. Each child of an individual with isolated Duane syndrome mapping to the DURS2 locus has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

See Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the gene(s) in which disease-causing mutations occur has/have not been identified. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Because the gene(s) and mutation(s) responsible for isolated Duane syndrome have not been identified, prenatal testing is not available.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Duane Syndrome

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
DURS2	Unknown	2q31	Unknown

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Duane Syndrome

604356	DUANE RETRACTION SYNDROME 2

Table C. Genomic Databases for Duane Syndrome

Locus Name	Entrez Gene
DURS2	27011 (MIM No. 604356)

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

No gene has yet been identified for the locus designated DURS2.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Human Genome Research Institute
Learning About Duane Syndrome

Eye Simulator/Virtual Patient Simulator
This application provides an eye motion and pupil response simulator, animations to demonstrate neurological testing, and quizzes to test comprehension. It also provides a set of patient cases with various neurological pathologies.
http://cim.ucdavis.edu/EyeRelease/Interface/TopFrame.htm

National Eye Institute
2020 Vision Place
Bethesda MD 20892-3655
Phone: 301-496-5248
Email: kcl@nei.nih.gov
www.nei.nih.gov

Prevent Blindness America
211 West Wacker Drive Suite 1700
Chicago IL 60606
Phone: 800-331-2020
Email: info@preventblindness.org
www.preventblindness.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Al-Baradie R, Yamada K, St Hilaire C, Chan WM, Andrews C, McIntosh N, Nakano M, Martonyi EJ, Raymond WR, Okumura S, Okihiro MM, Engle EC. Duane radial ray syndrome (Okihiro syndrome) maps to 20q13 and results from mutations in SALL4, a new member of the SAL family. Am J Hum Genet. 2002;71:1195–9. [PubMed: 12395297]

Appukuttan B, Gillanders E, Juo SH, Freas-Lutz D, Ott S, Sood R, Van Auken A, Bailey-Wilson J, Wang X, Patel RJ, Robbins CM, Chung M, Annett G, Weinberg K, Borchert MS, Trent JM, Brownstein MJ, Stout JT. Localization of a gene for Duane retraction syndrome to chromosome 2q31. Am J Hum Genet. 1999;65:1639–46. [PubMed: 10577917]

Bosley TM, Salih MA, Jen JC, Lin DD, Oystreck D, Abu-Amero KK, MacDonald DB, al Zayed Z, al Dhalaan H, Kansu T, Stigsby B, Baloh RW. Neurologic features of horizontal gaze palsy and progressive scoliosis with mutations in ROBO3. Neurology. 2005;64:1196–203. [PubMed: 15824346]

Caca I, Unlu K, Ari S. Two cases of Goldenhar syndrome. J Pediatr Ophthalmol Strabismus. 2006;43:107–9. [PubMed: 16598979]

Calabrese G, Stuppia L, Morizio E, Guanciali Franchi P, Pompetti F, Mingarelli R, Marsilio T, Rocchi M, Gallenga PE, Palka G, Dallapiccola B. Detection of an insertion deletion of region 8q13-q21.2 in a patient with Duane syndrome: implications for mapping and cloning a Duane gene. Eur J Hum Genet. 1998;6:187–93. [PubMed: 9781021]

Calabrese G, Telvi L, Capodiferro F, Morizio E, Pizzuti A, Stuppia L, Bordoni R, Ion A, Fantasia D, Mingarelli R, Palka G. Narrowing the Duane syndrome critical region at chromosome 8q13 down to 40 kb. Eur J Hum Genet. 2000;8:319–24. [PubMed: 10854090]

Chan WM, Traboulsi EI, Arthur B, Friedman N, Andrews C, Engle EC. Horizontal gaze palsy with progressive scoliosis can result from compound heterozygous mutations in ROBO3. J Med Genet. 2006;43:e11. [PubMed: 16525029]

Chew CK, Foster P, Hurst JA, Salmon JF. Duane's retraction syndrome associated with chromosome 4q27-31 segment deletion. Am J Ophthalmol. 1995;119:807–9. [PubMed: 7785704]

Chung M, Stout JT, Borchert MS. Clinical diversity of hereditary Duane's retraction syndrome. Ophthalmology. 2000;107:500–3. [PubMed: 10711888]

Demer JL, Clark RA, Lim KH, Engle EC. Magnetic resonance imaging evidence for widespread orbital dysinnervation in dominant Duane's retraction syndrome linked to the DURS2 locus. Invest Ophthalmol Vis Sci. 2007;48:194–202. [PubMed: 17197533]

Engle EC. The genetic basis of complex strabismus. Pediatr Res. 2006;59:343–8. [PubMed: 16492969]

Engle EC, Andrews C, Law K, Demer JL. Two pedigrees segregating Duane's retraction syndrome as a dominant trait map to the DURS2 genetic locus. Invest Ophthalmol Vis Sci. 2007;48:189–93. [PubMed: 17197532]

Evans JC, Frayling TM, Ellard S, Gutowski NJ. Confirmation of linkage of Duane's syndrome and refinement of the disease locus to an 8.8-cM interval on chromosome 2q31. Hum Genet. 2000;106:636–8. [PubMed: 10942112]

Gutowski NJ, Bosley TM, Engle EC. 110th ENMC International Workshop: the congenital cranial dysinnervation disorders (CCDDs). Naarden, The Netherlands, 25-27 October, 2002. Neuromuscul Disord. 2003;13:573–8. [PubMed: 12921795]

Hertle RW. A next step in naming and classification of eye movement disorders and strabismus. J AAPOS. 2002;6:201–2. [PubMed: 12185342]

Holve S, Friedman B, Hoyme HE, Tarby TJ, Johnstone SJ, Erickson RP, Clericuzio CL, Cunniff C. Athabascan brainstem dysgenesis syndrome. Am J Med Genet A. 2003;120:169–73. [PubMed: 12833395]

Iannaccone A, McIntosh N, Ciccarelli ML, Baldi A, Mutolo PA, Tedesco SA, Engle EC. Familial unilateral Brown syndrome. Ophthalmic Genet. 2002;23:175–84. [PubMed: 12324876]

Isenberg S, Blechman B. Marcus Gunn jaw winking and Duane's retraction syndrome. J Pediatr Ophthalmol Strabismus. 1983;20:235–7. [PubMed: 6644485]

Jen JC, Chan WM, Bosley TM, Wan J, Carr JR, Rub U, Shattuck D, Salamon G, Kudo LC, Ou J, Lin DD, Salih MA, Kansu T, Al Dhalaan H, Al Zayed Z, MacDonald DB, Stigsby B, Plaitakis A, Dretakis EK, Gottlob I, Pieh C, Traboulsi EI, Wang Q, Wang L, Andrews C, Yamada K, Demer JL, Karim S, Alger JR, Geschwind DH, Deller T, Sicotte NL, Nelson SF, Baloh RW, Engle EC. Mutations in a human ROBO gene disrupt hindbrain axon pathway crossing and morphogenesis. Science. 2004;304:1509–13. [PubMed: 15105459]

Kato Z, Yamagishi A, Kondo N. Interstitial deletion of 1q42.13-q43 with Duane retraction syndrome. J AAPOS. 2007;11:62–4. [PubMed: 17126050]

Kohlhase J, Chitayat D, Kotzot D, Ceylaner S, Froster UG, Fuchs S, Montgomery T, Rosler B. SALL4 mutations in Okihiro syndrome (Duane-radial ray syndrome), acro-renal-ocular syndrome, and related disorders. Hum Mutat. 2005;26:176–83. [PubMed: 16086360]

Kohlhase J, Heinrich M, Schubert L, Liebers M, Kispert A, Laccone F, Turnpenny P, Winter RM, Reardon W. Okihiro syndrome is caused by SALL4 mutations. Hum Mol Genet. 2002;11:2979–87. [PubMed: 12393809]

Kohlhase J, Schubert L, Liebers M, Rauch A, Becker K, Mohammed SN, Newbury-Ecob R, Reardon W. Mutations at the SALL4 locus on chromosome 20 result in a range of clinically overlapping phenotypes, including Okihiro syndrome, Holt-Oram syndrome, acro-renal-ocular syndrome, and patients previously reported to represent thalidomide embryopathy. J Med Genet. 2003;40:473–8. [PubMed: 12843316]

Paradisi I, Arias S. IVIC syndrome is caused by a c.2607delA mutation in the SALL4 locus. Am J Med Genet A. 2007;143:326–32. [PubMed: 17256792]

Parsa CF, Grant E, Dillon WP Jr, du Lac S, Hoyt WF. Absence of the abducens nerve in Duane syndrome verified by magnetic resonance imaging. Am J Ophthalmol. 1998;125:399–401. [PubMed: 9512165]

Pizzuti A, Calabrese G, Bozzali M, Telvi L, Morizio E, Guida V, Gatta V, Stuppia L, Ion A, Palka G, Dallapiccola B. A peptidase gene in chromosome 8q is disrupted by a balanced translocation in a duane syndrome patient. Invest Ophthalmol Vis Sci. 2002;43:3609–12. [PubMed: 12454025]

Tillman O, Kaiser HJ, Killer HE. Pseudotumor cerebri in a patient with Goldenhar's and Duane's syndromes. Ophthalmologica. 2002;216:296–9. [PubMed: 12207137]

Tischfield MA, Bosley TM, Salih MA, Alorainy IA, Sener EC, Nester MJ, Oystreck DT, Chan WM, Andrews C, Erickson RP, Engle EC. Homozygous HOXA1 mutations disrupt human brainstem, inner ear, cardiovascular and cognitive development. Nat Genet. 2005;37:1035–7. [PubMed: 16155570]

Tischfield MA, Chan WM, Grunert JF, Andrews C, Engle EC. HOXA1 mutations are not a common cause of Duane anomaly. Am J Med Genet A. 2006;140:900–2. [PubMed: 16528738]

Versteegh FG, von Lindern JS, Kemper J, Eichhorn E, Simonsz HJ, Wouters CH. Duane retraction syndrome, a new feature in 22q11 deletion syndrome? Clin Dysmorphol. 2000;9:135–7. [PubMed: 10826628]

Vincent C, Kalatzis V, Compain S, Levilliers J, Slim R, Graia F, Pereira ML, Nivelon A, Croquette MF, Lacombe D, et al. A proposed new contiguous gene syndrome on 8q consists of Branchio-Oto-Renal (BOR) syndrome, Duane syndrome, a dominant form of hydrocephalus and trapeze aplasia; implications for the mapping of the BOR gene. Hum Mol Genet. 1994;3:1859–66. [PubMed: 7849713]

Wabbels BK, Lorenz B, Kohlhase J. No evidence of SALL4-mutations in isolated sporadic duane retraction "syndrome" (DURS). Am J Med Genet A. 2004;131:216–8. [PubMed: 15386473]

Suggested Readings

Engle E. The genetics of strabismus: Duane, Moebius and fibrosis syndromes. In: Traboulsi E (ed) Genetic Diseases of the Eye: a Textbook and Atlas. Mosby, St. Louis, p 477-512. 1998

Chapter Notes

Author Notes

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