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Duane Syndrome

Synonyms: Duane Anomaly, Isolated; Duane Retraction Syndrome; Stilling-Turk-Duane Syndrome

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Summary

Clinical characteristics

Duane syndrome is a strabismus condition clinically characterized by congenital non-progressive limited horizontal eye movement accompanied by globe retraction which results in narrowing of the palpebral fissure. The lateral movement anomaly results from failure of the abducens nucleus and nerve (cranial nerve VI) to fully innervate the lateral rectus muscle; globe retraction occurs as a result of abnormal innervation of the lateral rectus muscle by the oculomotor nerve (cranial nerve III). At birth, affected infants have restricted ability to move the affected eye(s) outward (abduction) and/or inward (adduction), though the limitations may not be recognized in early infancy. In addition, the globe retracts into the orbit with attempted adduction, accompanied by narrowing of the palpebral fissure. Many individuals with Duane syndrome have strabismus in primary gaze but can use a compensatory head turn to align the eyes, and thus can preserve binocular vision and avoid diplopia. Individuals with Duane syndrome who lack binocular vision are at risk for amblyopia. The majority of affected individuals with Duane syndrome have isolated Duane syndrome (i.e., they do not have other detected congenital anomalies). Other individuals with Duane syndrome fall into well-defined syndromic diagnoses. However, many individuals with Duane syndrome have non-ocular findings that do not fit a known syndrome; these individuals are included as part of the discussion of nonsyndromic Duane syndrome.

Diagnosis/testing

The diagnosis of Duane syndrome is usually made by an ophthalmologist based on clinical findings. More than 98% of individuals with isolated Duane syndrome and no family history lack an identified genetic etiology.

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Molecular genetic testing for a pathogenic variant in *CHN1*, *MAFB*, or *SALL4* is most appropriate for those with a positive family history of isolated Duane syndrome (although *de novo* pathogenic variants in these genes have been detected in some simplex cases) and for those with clinical ocular findings designated as type I or type III 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 individuals with mild involvement) to improve the compensatory head position; extraocular muscle surgery to address alignment in primary gaze, compensatory head posture, and upshoot or downshoot.

Prevention of secondary complications: Amblyopia therapy to prevent vision loss in the less preferred eye; extraocular muscle surgery to prevent loss of binocular vision in individuals who abandon the compensatory head posture and allow strabismus to become manifest, and to prevent neck muscle problems in those with large compensatory head postures.

Surveillance: Ophthalmologic visits every three to six months during the first years of life to prevent, detect, and treat amblyopia; annual or biannual examinations once the presence of binocular vision and reduced risk for amblyopia is confirmed, and in all individuals older than age seven to 12; no surveillance in adulthood beyond public health guidelines.

Evaluation of relatives at risk: Eye examination within the first year of life so that early diagnosis and treatment can prevent secondary complications.

Genetic counseling

The majority of individuals with isolated Duane syndrome represent simplex cases (i.e., a single occurrence in a family), with a positive family history apparent for only approximately 10% of affected individuals. Duane syndrome resulting from a *CHN1, MAFB,* or *SALL4* pathogenic variant is inherited in an autosomal dominant manner. Most individuals with isolated *CHN1*-, *MAFB*-, or *SALL4*-related Duane syndrome have the disorder as the result of a pathogenic variant inherited from an affected parent. Each child of an individual with Duane syndrome resulting from an identified pathogenic variant has a 50% chance of inheriting the variant. Prenatal and preimplantation genetic testing are possible once the causative pathogenic variant has been identified in an affected family member.

Diagnosis

Duane syndrome is a strabismus condition clinically characterized by congenital non-progressive limited horizontal eye movement accompanied by globe retraction which results in narrowing of the palpebral fissure. The diagnosis of Duane syndrome is based on clinical findings and classified into three types (see Table 1).

Most affected individuals with Duane syndrome have isolated Duane syndrome (i.e., they do not have other detected congenital anomalies). Other individuals fall into well-defined syndromic diagnoses (see Genetically Related Disorders and Differential Diagnosis). However, many individuals with Duane syndrome have non-ocular findings that are not classified as a particular syndrome; they are included in this review for completeness.

The vast majority of individuals with isolated Duane syndrome represent simplex cases (i.e., a single occurrence in a family). A positive family history showing autosomal dominant inheritance is apparent for approximately 10% of affected individuals [Gutowski & Chilton 2015].

Suggestive Findings

Duane syndrome, a congenital, non-progressive eye movement disorder, **should be suspected** in individuals who present with the following features:

- Congenital limited horizontal eye movement with impairment of abduction and/or adduction
- Globe retraction (co-contraction) accompanied by narrowing of the palpebral fissure (i.e., reduced distance between the upper and lower eyelids) on adduction.

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

Establishing the Diagnosis

Clinical findings. The diagnosis of Duane syndrome **is established in** a proband typically by an ophthalmologist by detection of the specific clinical findings of limited abduction and/or adduction in association with globe retraction on adduction. Individuals can usually be categorized within the three types detailed below, though there may be some overlap among these categories.

Table 1. Clinical Findings: Comparison of Duane Syndrome Types I-III

Clinical Finding	Type I (~75%-80% of cases)	Type II (~1%-5%)	Type III (~10%-20%)
Abduction	Absent to markedly restricted	Normal to mildly restricted	Absent to markedly restricted
Adduction	Normal to mildly restricted	Absent to markedly restricted	Absent to markedly restricted
Globe retraction & palpebral fissure narrowing	Present on adduction	Present on adduction	Present on adduction or attempted adduction
Upshoot & downshoot of affected globe on adduction	Variably present	Variably present	Variably present; more common than in types I or II
Primary gaze	Esotropia, variably present	Exotropia, variably present	Esotropia more common than exotropia, variably present
Anomalous head posture / head turn	Turn towards involved side, variably present	Turn towards uninvolved side, variably present	Turn towards involved side, variably present
Laterality [1]	Unilateral or bilateral	Unilateral or bilateral	Unilateral or bilateral

Note: An alternative simpler classification is to note the deviation in primary gaze (esotropic or exotropic Duane syndrome) and specify whether there is limitation of adduction, abduction, or both.
1. The eye findings are more likely to be bilateral in familial cases and in those in whom a pathogenic variant is identified in one of the known associated genes [Engle et al 2007, Gutowski & Chilton 2015].

Molecular genetic testing (see Table 2) is most appropriate for those individuals with:

- A positive family history of Duane syndrome.
  - After finding a *CHN1* pathogenic variant in seven of 20 families with Duane syndrome, Miyake et al [2010] screened 140 individuals with Duane syndrome with a negative family history and failed to identify a *CHN1* pathogenic variant in any individual. Of note, a suspected disease-causing *CHN1* variant was identified in an affected individual lacking a positive family history [Biler et al 2017], but such reports are rare.
  - Park et al [2016] studied 401 individuals with Duane syndrome and found a pathogenic variant in *MAFB* in four probands. Three of the probands had a positive family history; in the fourth the pathogenic variant was *de novo*. Also, in one of the familial pedigrees, the *de novo* nature of the pathogenic variant was determined for the original proband, who had unaffected parents.

  - Due to variable expressivity, individuals with a *SALL4* pathogenic variant may present with apparently isolated Duane syndrome themselves [Al-Baradie et al 2002, Yang et al 2013], though they may have a positive family history of syndromic Duane syndrome.
- Bilateral Duane syndrome. The eye findings are more likely to be bilateral in familial cases and in those in whom a pathogenic variant is identified in one of the known associated genes [Engle et al 2007, Gutowski & Chilton 2015].
- Duane syndrome type I or type III or a combination of those types. Duane syndrome type II has not been observed in those with a positive family history or in individuals with pathogenic variants in the identified genes, suggesting a distinct etiology [Engle et al 2007, Gutowski & Chilton 2015].

Molecular genetic testing approaches can include **concurrent or serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Concurrent single-gene testing.** Sequence analysis of *CHN1*, *MAFB*, and *SALL4* is performed first, and followed by gene-targeted deletion/duplication analysis of *MAFB* and *SALL4* if no pathogenic variant is found.

  Note: (1) If serial gene analysis is to be performed for isolated Duane syndrome, sequence analysis *CHN1* is performed first, followed by sequence analysis of *MAFB* and gene-targeted deletion/duplication analysis if no pathogenic variant is found. The exception to this would be if there was evidence of hearing loss in addition to Duane syndrome, in which case *MAFB* followed by *CHN1* would be more appropriate. If the causative variant is not identified, *SALL4* sequencing and gene-targeted deletion/duplication analysis should be considered. (2) Since *CHN1*-related disease occurs through a gain-of-function mechanism and large intragenic deletion or duplication has not been reported, testing for *CHN1* intragenic deletions or duplication is unlikely to identify a disease-causing variant.

- **A multigene panel** that includes *CHN1*, *MAFB*, *SALL4*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing (which does not require the clinician to determine which gene[s] are likely involved) may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in Duane Syndrome

Gene [1, 2]	Proportion of Duane Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
CHN1	Familial: up to 15% [6] Simplex: rare [7]	>99% [6, 7]	Unknown [8]
MAFB	Familial: 4% [9, 10] Simplex: rare [9]	3/4 [9]	1/4 [9]
SALL4	Familial: very rare [11] Simplex: not reported [11]	≤80% [11, 12]	10%-15% [13]
Unknown	Familial: ~80% [14] Simplex: >90% [14]	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Probands with familial Duane syndrome described in: Miyake et al [2008], Volk et al [2010], Chan et al [2011], Miyake et al [2011], Biler et al [2017]
7. Probands with a family history negative for Duane syndrome described in Miyake et al [2010], Volk et al [2010], and Biler et al [2017]; however, pathogenicity of disease-associated variants was not proven for all variants.
8. No data on detection rate of gene-targeted deletion/duplication analysis are available; however, since *CHN1* pathogenic variants act through a gain-of-function mechanism, detection of large deletions or duplication is unlikely.
9. Park et al [2016] studied 401 probands with Duane syndrome and found a pathogenic variant in *MAFB* in four probands with Duane syndrome; in three individuals the condition was familial and in the fourth the pathogenic variant was *de novo*. In one of the familial cases, hearing loss was present with the Duane syndrome in three of the four affected family members in three generations. In an additional ten simplex cases with Duane syndrome and hearing loss, no pathogenic variant in *MAFB* was identified.
10. Three of 77 individuals with familial Duane syndrome had a pathogenic variant in *MAFB* [Authors, personal observation].
11. Isolated Duane syndrome was observed in one of eight and one of four affected individuals in two families with a pathogenic variant in *SALL4* detected on sequence analysis [Al-Baradie et al 2002, Yang et al 2013]. A study of 25 individuals with nonfamilial isolated Duane syndrome did not identify pathogenic variants on sequence analysis of *SALL4* [Wabbels et al 2004].
12. Al-Baradie et al [2002], Kohlhase et al [2002], Kohlhase et al [2003], Borozdin et al [2004b], Kohlhase et al [2005]
13. Borozdin et al [2004a], Borozdin et al [2007]
14. Miyake et al [2008], Volk et al [2010], Chan et al [2011], Miyake et al [2011], Park et al [2016], Biler et al [2017]. In the cohort described by the authors, 98% of simplex, isolated Duane syndrome lacked an identified genetic etiology.

Note: The testing recommendations in this section are for individuals with Duane syndrome, either isolated or with one or more non-ocular anomalies that do not constitute an established or recognizable syndrome. If an individual presents with Duane syndrome plus significant anomalies that suggest the possibility of a chromosome abnormality, testing with chromosome microarray analysis (CMA) can be considered.

Clinical Characteristics

Clinical Description

Duane syndrome is a strabismus condition clinically characterized by congenital non-progressive limited horizontal eye movement accompanied by globe retraction which results in narrowing of the palpebral fissure. The lateral movement anomaly is due to failure of the abducens nucleus and nerve (cranial nerve VI) to fully innervate the lateral rectus muscle, with globe retraction occurring due to abnormal innervation of the lateral

rectus muscle by the oculomotor nerve (cranial nerve III). At birth, affected infants have restricted ability to move the affected eye(s) outward (abduction) and/or inward (adduction), though the limitations may not be recognized in early infancy. In addition, the globe retracts into the orbit with attempted adduction, accompanied by narrowing of the palpebral fissure. Affected individuals may also have upshoot or downshoot of the affected eye on attempted adduction. For reasons yet to be determined, the left side is more commonly affected; this is supported by the authors' internal data showing that the left side is affected in 70% of unilateral cases [Gutowski & Chilton 2015; Kekunnaya et al 2012; Authors, unpublished observation].

Duane syndrome is often reported as more common in females than in males, particularly in unilateral and simplex cases [Kekunnaya et al 2012, Graeber et al 2013, Kekunnaya & Negalur 2017]. Internal data reveal that 56% of individuals with unilateral Duane syndrome are female and 51% of simplex cases are female [Authors, unpublished observation].

Restriction in vertical movement of the eyes may also be found in some individuals with Duane syndrome, depending on the associated gene (see Genotype-Phenotype Correlations).

Strabismus is the 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 I and exotropia in Duane syndrome type II.

- Although esotropia is more common in most studies, a recent report found that nearly a third of individuals with Duane syndrome seen at a tertiary care center in south India had exotropia [Bhate et al 2017].
- While movement of the affected eye is impaired, when the contralateral eye is able to move freely, it allows individuals with strabismus in primary gaze to use a compensatory head turn in order to align the eyes, thus avoiding diplopia and preserving single binocular vision.

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 early in life, the vision loss from amblyopia is irreversible.

Visual acuity is good except in those individuals with amblyopia.

Other dysinnervation phenomena may occur in individuals with Duane syndrome**.** These include:

- Infraduction of the affected eye in attempted lateral gaze; this occurs in the majority of cases [Rhiu et al 2018.] The phenomenon is more likely to be observed in more severely affected individuals.
- Marcus Gunn jaw-winking phenomenon (upper eyelid movement/fluttering each time the jaw opens and closes) [Isenberg & Blechman 1983, Oltmanns & Khuddus 2010, Gupta et al 2014].
- An exaggerated oculo-auricular phenomenon (coactivation of external ear muscles during lateral gaze) [Gilbert & Hunter 2017].
- Crocodile tears (tearing with chewing due to aberrant facial salivary fibers innervating the lacrimal gland) [Gutowski & Chilton 2015].

Neuroimaging. Orbital and brain stem MRI of affected members of two pedigrees with *CHN1* pathogenic variants did not visualize the abducens nerve in most affected individuals and revealed structurally abnormal lateral rectus muscles in some. The oculomotor and optic nerves were also small [Demer et al 2007]. Decreased superior oblique muscle volume has also been observed on MRI in individuals with *CHN1* pathogenic variants, supporting trochlear nerve hypoplasia [Miyake et al 2011].

Magnetic resonance imaging (MRI) in simplex cases (without a pathogenic variant identified in any known gene) has verified the absence or severe hypoplasia of the abducens nerve, often with normal appearance of the lateral rectus muscle [Demer et al 2006].

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 [Yüksel et al 2010]. Early studies of Duane syndrome reported fibrosis of the lateral rectus or medial rectus muscles, and suggested a primary myopathic etiology for this disorder [Matteucci 1946]. Subsequently, several postmortem examinations of individuals 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 [Hotchkiss et al 1980, Miller et al 1982]. 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 [Scott & Wong 1972].

The decreased superior oblique muscle volume observed on MRI, supporting trochlear nerve hypoplasia, leads to the suggestion that Duane syndrome resulting from pathogenic variants in *CHN1* represents a congenital cranial dysinnervation disorder that results from errors not only in abducens, but also trochlear and oculomotor axon pathfinding [Miyake et al 2011].

Animal models of both *CHN1* and *MAFB* pathogenic variants support a neurogenic cause of Duane syndrome. In *CHN1*-related mouse models, axons of the abducens nerve stall, then retract and die, and the lateral rectus is subsequently innervated by branches from the oculomotor nerve [Nugent et al 2017]. In *Mafb*-knockout mice, the abducens nucleus does not form, and the lateral rectus muscle is innervated by branches from the oculomotor nerve [Park et al 2016].

Other Anomalies

Most affected individuals with Duane syndrome have isolated Duane syndrome without other congenital anomalies. Published estimates of individuals with other systemic findings range from lows of under 10% [Kekunnaya et al 2012] to just over 50% [Marshman et al 2000]. Far fewer individuals have a constellation of anomalies that falls within recognizable syndromic patterns which are often inherited in an autosomal dominant pattern. In the authors' cohort, approximately 30% of all individuals with a diagnosis of Duane syndrome have non-ocular systemic findings. When individuals who fall within the spectrum of *SALL-4* related disorders are removed, 25% of individuals have syndromic findings [Authors, unpublished data].

From the authors' unpublished data, 26.7% of individuals with Duane syndrome who do not have a pathogenic variant in any of the currently known associated genes have non-ocular findings, ranging from minor anomalies such as preauricular tags to more severe conditions such as Hirschsprung disease.

Genotype-Phenotype Correlations

CHN1. Individuals with pathogenic variants in *CHN1* are more likely to have bilateral involvement, vertical movement abnormalities beyond the upshoot and downshoot often seen in Duane syndrome, and a positive family history when compared to individuals with Duane syndrome who do not have a *CHN1* pathogenic variant [Chung et al 2000, Demer et al 2007, Engle et al 2007, Miyake et al 2008, Miyake et al 2011].

MAFB. Individuals with pathogenic variants in *MAFB* are more likely to have bilateral Duane syndrome and may have mild-to-severe sensorineural hearing loss in addition to the Duane syndrome. Hearing loss was documented in one of four reported pedigrees of otherwise isolated Duane syndrome, and confirmed in three of four individuals in that family [Park et al 2016].

SALL4. Individuals thus far reported with isolated Duane syndrome associated with *SALL4* pathogenic variants have family members with Duane-radial ray syndrome [Al-Baradie et al 2002, Yang et al 2013]. The eye condition tends to be bilateral rather than unilateral in individuals with *SALL4* variants [Kohlhase et al 2005].

Penetrance

Families with Duane syndrome in whom a *CHN1* pathogenic variant has been identified may have reduced penetrance [Engle et al 2007, Miyake et al 2008, Chan et al 2011].

There has been no evidence of reduced penetrance in the limited number of families with isolated Duane syndrome identified with *MAFB* or *SALL4* pathogenic variants [Yang et al 2013, Park et al 2016]

Nomenclature

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

Historically, Duane syndrome was initially proposed to be myogenic in origin. Electromyography of the extraocular muscles, postmortem examinations, and MRI, however, now support a neurogenic etiology [Demer et al 2007]. This is also supported by developmental studies of mouse models [Nugent et al 2017] and has led to the proposed renaming of Duane syndrome as the "co-contractive retraction syndrome" (types 1-3) [Hertle 2002] and classification as one of the congenital cranial dysinnervation disorders [Gutowski et al 2003, Engle 2006].

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 at between 1:1,000 and 1:10,000 in the general population [Yüksel et al 2010, Gutowski & Chilton 2015]

Genetically Related (Allelic) Disorders

CHN1. Pathogenic gain-of-function variants in *CHN1* have also been identified in individuals with vertical strabismus and supraduction deficits in the absence of Duane retraction syndrome [Miyake et al 2011].

MAFB. Missense heterozygous variants in *MAFB* have previously been identified in individuals with multicentric carpotarsal osteolysis [Zankl et al 2012] and noncoding variants have been reported in individuals with cleft lip and/or cleft palate [Beaty et al 2010].

SALL4. *SALL4*-related disorders include a spectrum of phenotypes previously thought to be distinct entities including Duane-radial ray syndrome or Okihiro syndrome, acro-renal-ocular syndrome, and *SALL4*-related Holt-Oram syndrome.

Differential Diagnosis

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.

Table 3. Disorders to Consider in the Differential Diagnosis of Duane Syndrome with Associated Congenital Anomalies

Disorder	Gene(s)	MOI	Clinical Features of the Disorder (in addition to Duane syndrome)
Townes-Brocks syndrome	*SALL1*	AD	• Anal, ear, limb & renal anomalies • Additional ophthalmic findings: coloboma, ptosis, epibulbar dermoid, & crocodile tears
HOXA1-related syndromes (Bosley-Salih-Alorainy syndrome, Athabascan brain stem dysgenesis syndrome; OMIM 601536)	*HOXA1*	AR	• Note: Ocular findings are usually Duane syndrome type III or horizontal gaze palsy • Bilateral sensorineural hearing loss caused by absent cochlea & rudimentary inner-ear development • Subsets of individuals manifest ID, autism, moderate-to-severe central hypoventilation, facial weakness, swallowing difficulties, vocal cord paresis, conotruncal heart defects, & skull & craniofacial abnormalities
Wildervanck syndrome (Cervicooculoacoustic syndrome; OMIM 314600)	Unknown [1]	Unknown [1]	• Deafness • Klippel-Feil anomaly (fused cervical vertebrae)
Goldenhar syndrome (hemifacial microsomia, oculoauriculovertebral spectrum; OMIM 164210)	Unknown	Sporadic AD AR	Craniofacial, ocular, cardiac, vertebral, & CNS defects, consistent w/ maldevelopment of the 1st & 2nd branchial arches
Chromosome 8 anomalies	NA	Sporadic	See footnote 2.
Other chromosome anomalies	NA	Sporadic	See footnotes 3 & 4.

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; ID = intellectual disability; MOI = mode of inheritance; NA = not applicable

1. Most Wildervanck syndrome is sporadic and limited to females. A case report describes a male with Wildervanck syndrome and a 3-kb deletion at Xq26.3 encompassing one gene, *FGF13,* which encodes a protein that acts intracellularly in neurons throughout brain development [Abu-Amero et al 2014].

2. Several individuals with Duane syndrome have been reported to have chromosome 8 anomalies: anomalies of the 8q13 DURS1 locus (OMIM 126800); mosaic trisomy 8 (2 separate reports); deletion 8q13-q21.2; a *de novo* reciprocal balanced translocation consisting of t(6:8)(q26;q13) disrupting *CPAH*, the gene for carboxypeptidase; and a duplication (or microduplication) of 8q12 [Lehman et al 2009, Amouroux et al 2012, Baroncini et al 2013] and 8p11.2 deletion [Abu-Amero et al 2015]. Three reports suggest that abnormal dosage of *CHD7* may cause the resultant phenotype on 8q12. Individuals described in these case reports manifest Duane syndrome with various associated congenital abnormalities including other cranial nerve deficits, facial dysmorphisms, intellectual disabilities, and cardiac defects.

3. Other chromosome aberrations associated with Duane syndrome have been reported to involve 2q13, 4q27-31, 6p25, 7, 10q24.2q26.3, 12q24.31, 19q13.4, 20q13.12, and 22pter-q13.31. Duane syndrome has been described in one individual with 48,XXYY syndrome and another with atypical Silver-Russell syndrome, Duane syndrome, and maternal uniparental disomy of chromosome 7.

4. Individuals with Duane syndrome and associated congenital defects should be evaluated further for possible underlying chromosomal rearrangements.

Other 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 CCDDs. Other ocular CCDDs include those in Table 4.

Table 4. Other Congenital Cranial Dysinnervation Disorders to Consider in the Differential Diagnosis of Duane Syndrome

Disorder	Gene(s)	MOI	Clinical Features of the Disorder	
			Overlapping w/Duane syndrome	Distinguishing from Duane syndrome
Congenital fibrosis of the extraocular muscles [1]	*KIF21A* *PHOX2A* *TUBB2B* *TUBB3*	AD AR	Often horizontal gaze restrictions	Ptosis, restricted upgaze
Moebius syndrome (OMIM 157900)	Unknown	Various	Horizontal gaze palsy	Facial weakness, no globe retraction
Horizontal gaze palsy with progressive scoliosis (OMIM 607313)	*ROBO3*	AR	Horizontal gaze palsy	No globe retraction, severe, early onset scoliosis

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Congenital fibrosis of the extraocular muscles (CFEOM) refers to at least seven genetically defined syndromes: CFEOM1A, CFEOM1B, CFEOM2, CFEOM3A, CFEOM3B, CFEOM3C, and Tukel syndrome.

Complex and common forms of strabismus that could be confused with Duane syndrome are shown in Table 5.

Table 5. Strabismus-Associated Disorders to Consider in the Differential Diagnosis of Duane Syndrome

Disorder	Clinical Features of the Disorder	
	Overlapping w/Duane syndrome	Distinguishing from Duane syndrome
Common strabismus	Strabismus	Full eye movements
Sixth nerve palsy	Restricted abduction, may be accompanied by esotropia	No globe retraction or fissure narrowing Usually acquired
Comitant esotropia w/crossed fixation	May appear to have abduction limitation	Full abduction can be elicited if tested monocularly.
Congenital ocular motor apraxia	May appear to have abduction limitation	Inability to generate horizontal saccades
Brown syndrome ("superior oblique tendon sheath syndrome")	May appear to have abduction limitation	Inability to elevate the adducted eye actively or passively

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Duane syndrome, the following evaluations are recommended if they have not already been completed:

- Family history
- Ophthalmologic examination
  - Determination of deviation in primary gaze, anomalous head 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. Infraduction of the affected eye in attempted abduction is a common finding. Other features sometimes observed include up- and downshoot on adduction and Marcus Gunn jaw winking.

  - Full ophthalmologic exam to assess for refractive errors, amblyopia, or amblyopia risk factors.
- Optional forced duction testing and/or force generation testing in cooperative individuals
- Photographic documentation to identify changes in the condition and for future review
- If surgery is planned, consideration of brain and orbital MRI to determine brain stem and orbital anatomy (muscles and nerves)
- General physical examination to look for systemic anomalies that can be found in individuals with Duane syndrome
- Hearing evaluation
- Consultation with a clinical geneticist and/or genetic counselor

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 1st 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.
- Correction of hypermetropic refractive error in children may reduce the angle of strabismus and thus decrease the angle of head turn.

Surgical treatment of ophthalmologic findings (extraocular muscle surgery)

- Surgical intervention is usually pursued when any of the following criteria are met:
  - Symptomatic compensatory head posture
  - Deviation in primary gaze sufficient to provoke diplopia or amblyopia
  - Disfiguring upshoot or downshoot in adduction

  Note: Surgery does not generally improve abduction of the affected eye, though transposition procedures may provide partial improvement.

- Tightness of the medial rectus muscle can add to the technical difficulty of the surgical procedure.

- Postoperative overcorrection in side gaze, a common occurrence, can create new-onset diplopia.
  - In esotropic Duane syndrome, diplopia occurs due to exotropia in gaze away from the affected side.
  - In exotropic Duane syndrome, diplopia occurs due to an increase in esotropia in gaze toward the affected side.

Principles of surgical approach (reviewed by Kekunnaya et al [2015] and Doyle & Hunter [2019])

- **Esotropic Duane syndrome.** Consider recession of the medial rectus muscle or lateral transposition of one or both vertical rectus muscles (with or without simultaneous weakening of the medial rectus muscle by recession or botulinum toxin injections). Vertical rectus muscle transposition may be augmented by simultaneous resection of the transposed muscles or by placing posterior augmentation sutures on the transposed muscles. When globe retraction is mild, recession of the medial rectus muscle may be combined with a modest resection of the lateral rectus muscle. If globe retraction is severe and creates a deformity, consider recession of both the medial and lateral rectus muscles. Contralateral medial rectus recession may be added for large deviations.
- **Up- and/or downshoot in adduction.** Y-splitting of the lateral rectus muscle reduces upshoot and downshoot in adduction without altering the alignment in primary gaze.

- **Exotropic Duane syndrome.** Consider recession of the ipsilateral lateral rectus muscle in most cases. In more severe cases, a large lateral rectus recession may be combined with lateral transposition of one or both vertical rectus muscles.

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 once the presence of binocular vision and reduced risk for amblyopia is confirmed, and in all individuals older than age seven to 12
- No surveillance in adulthood beyond public health guidelines

Evaluation of Relatives at Risk

Ophthalmologic examination within the first year of life is appropriate in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures. If the pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Typically, Duane syndrome occurs in a single affected family member and the molecular basis of the condition is unknown. Familial Duane syndrome represents about 10% of all Duane syndrome [Gutowski & Chilton 2015].

Duane syndrome resulting from a heterozygous pathogenic variant in *CHN1*, *MAFB*, or *SALL4* is inherited in an autosomal dominant manner.

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- Most individuals with isolated *CHN1*, *MAFB*, or *SALL4*-related Duane syndrome have the disorder as the result of a pathogenic variant inherited from an affected parent.
- Rarely, an individual with *CHN1*, *MAFB*, or *SALL4*-related Duane syndrome represents a simplex case (i.e., a single affected family member) and has the disorder as the result of a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.

- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with Duane syndrome may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance (see Penetrance), or milder phenotype. Therefore, an apparently negative family history cannot be confirmed unless appropriate ophthalmologic evaluation and/or molecular genetic testing have been performed on the parents of the proband.

Sibs of a proband. The risk to sibs of a proband with isolated Duane syndrome depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. There may be phenotypic variability within families regarding unilateral vs bilateral involvement or, in *CHN1*-related Duane syndrome, reduced penetrance [Engle et al 2007, Miyake et al 2008, Chan et al 2011].
- If the proband has a known Duane syndrome-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the Duane syndrome-related pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at an increased risk for Duane syndrome because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with Duane syndrome and an identified pathogenic variant has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for Duane syndrome are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Human Genome Research Institute (NHGRI)**
  Learning About Duane Syndrome
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@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

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Duane Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CHN1	2q31.1	N-chimaerin	CHN1 database	CHN1	CHN1
MAFB	20q12	Transcription factor MafB	MAFB @ LOVD	MAFB	MAFB
SALL4	20q13.2	Sal-like protein 4	SALL4 database	SALL4	SALL4

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Duane Syndrome (View All in OMIM)

118423	CHIMERIN 1; CHN1
604356	DUANE RETRACTION SYNDROME 2; DURS2
607343	SAL-LIKE 4; SALL4

Table B. continued from previous page.

608968	MAF bZIP TRANSCRIPTION FACTOR B; MAFB
617041	DUANE RETRACTION SYNDROME 3 WITH OR WITHOUT DEAFNESS; DURS3

Molecular Pathogenesis

CHN1 encodes chimaerin. *CHN1* has several alternatively spliced transcript variants encoding multiple N-chimaerin isoforms. N-chimaerin has three domains:

- N-terminal SH2 domain
- C-terminal RhoGAP domain
- Central C1 domain similar to protein kinase C

No pathogenic variants have been identified in the N-terminal SH2 domain. The longest isoform NP_001813.1 has 459 amino acid residues. All identified pathogenic variants are gain-of-function variants that increase N-chimaerin (α2-chimerin RacGAP) activity. Several pathogenic variants appear to enhance N-chimaerin translocation to the cell membrane or enhance its ability to self-associate.

MAFB encodes a 323-amino acid transcription factor of the basic leucine zipper (LZ) family. There are three critical functional domains:

- Extended homology region (EHR)
- Basic region (BR) required for DNA binding
- LZ domain required for dimerization

SALL4 encodes sal-like protein 4 (SALL4), a protein essential to several developmental processes [Elling et al 2006].

Mechanism of disease causation. Several animal models demonstrate that gain-of-function variants in N-chimaerin and partial loss-of-function *MAFB* variants result in Duane syndrome.

N-chimaerin:

- A chick in vivo system was used to demonstrate that N-chimaerin overactivity results in axons terminated prematurely adjacent to the dorsal rectus muscle [Miyake et al 2008].
- Knock-in mice with the p.Leu20Phe *Chn1* substitution have globe retraction, stalling and death of the abducens nerve, and subsequent misinnervation of the lateral rectus by axons from the oculomotor nerve. By contrast, *Chn1* knockout mice show initial defasiculation and wandering of the abducens nerve, but a subset of fibers properly innervates the lateral rectus, supporting the hypothesis that Duane syndrome is caused by gain-of-function variants [Nugent et al 2017].

MAFB:

- Homozygous *Mafb* knockout mice: Duane syndrome and inner ear defects, perinatal lethal [Blanchi et al 2003]
- Heterozygous *Mafb* knockout mice (50% *Mafb* function): Duane syndrome, without hearing deficits
- Homozygous *kreisler* mice (<50% *Mafb* function): Duane syndrome and inner ear defects
- Heterozygous *kreisler* mice (>50% Mafb function): no phenotype.

These allelic series in mice indicate that different tissues have different sensitivity to loss of *MAFB* function. The sensorineural hearing loss results from common cavity deformities of the inner ear. The combined findings of Duane syndrome and inner-ear anomalies pointed to a disruption of early hindbrain development as found in individuals with pathogenic variants in *HOXA1* [Tischfield et al 2005] and in *Mafb* knockout mice [Moriguchi et al 2006, Yu et al 2013]. Loss of 50% of *MAFB* function perturbs abducens nucleus development and causes

Duane syndrome. By contrast, while 50% *MAFB* function is sufficient for inner ear development, greater than 50% loss causes inner ear defects [Park et al 2016].

Table 6. Duane Syndrome: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
CHN1	NM_001822.5 NP_001813.1	c.378T>G	p.Ile126Met	Segregated w/disease but also found at low frequency in the population [Miyake et al 2008, Chan et al 2011]
		c.422C>T	p.Pro141Leu	
		c.443A>T	p.Tyr148Pro	Hyperactivating variant found to expand phenotypic spectrum to vertical strabismus & supraduction deficits in the absence of Duane syndrome [Miyake et al 2011]
MAFB	NM_005461.4 NP_005452.2	c.440delG	p.Gly147AlafsTer78	Isolated Duane syndrome
		c.644delA	p.Gln215ArgfsTer10	
		Whole-gene deletion		
		c.803delA	p.Asn268MetfsTer125	Dominant-negative variant assoc w/Duane syndrome & sensorineural hearing loss in 3 of 4 affected family members [Park et al 2016]
SALL4	NM_020436.4 NP_065169.1	c.1919dupT	p.Met640IlefsTer25	Pathogenic variants in *SALL4* are typically assoc w/other *SALL4*-related disorders.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes from Table 1 in alphabetic order.

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Chapter Notes

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