

The Congenital Cranial Dysinnervation Disorders (CCDDs)

The term 'congenital cranial dysinnervation disorders' or CCDDs was derived in 2002 at a European Neuromuscular Centre (ENMC) international workshop for a group of congenital neuromuscular diseases reflecting the belief that these disorders resulted from developmental errors in innervation.¹ The conditions under consideration were characterised by abnormal eye, eyelid, and/or facial movement. The group includes Duane syndrome, congenital fibrosis of the extraocular muscles (CFEOM), congenital ptosis, horizontal gaze palsy, congenital facial palsy and Möbius syndrome, but this is not an exhaustive list. The current list of clinical phenotypes, genetic loci and genes is certainly incomplete. It is envisaged that other congenital dysinnervation disorders such as Marcus Gunn Jaw winking (ptosis accompanied by elevation of the ptotic eyelid on movement of the lower jaw, due to aberrant trigeminal nerve innervation of levator palpebrae superioris) and Crocodile tears (food provokes excessive tearing, due to aberrant facial salivary fibres innervating the lacrimal gland) and disorders of afferent pathways will also be included. The purpose of this classification is to study the genes underlying the CCDDs which should enhance our understanding of human brain stem and cranial nerve development, with common functional pathways likely to emerge, as well considering potential treatments for these disorders.

The concept from muscular fibrosis to dysinnervation

Isolated strabismus is relatively common affecting 1-5% of the general population. A subset of sporadic and familial congenital, non-progressive ophthalmoplegia with restriction of globe movement was initially referred to as the "congenital fibrosis syndromes" because the primary pathologic process was thought to be in the eye muscles. Further data challenged this view. It was suggested that Duane syndrome, the most common of these disorders, may be primarily neuropathic rather than myopathic and at least five autopsy reports of Duane syndrome have documented anatomic absence of the abducens nerve. In addition, electromyography revealed paradoxical innervation of the lateral rectus by the oculomotor nerve that probably occurs in the absence of normal innervation by the abducens nerve (reviewed in reference 1). Duane syndrome also occurs in the setting of other conditions with anomalous axonal guidance.²

Genetic and neuropathologic studies in CFEOM also support a neurogenic cause for these disorders; an autopsy study of one affected member of a large CFEOM type 1 family showed the absence of the superior division of the oculomotor nerves bilaterally.³ Subsequently CFEOM type 2 was shown to result from mutations in the PHOX2A gene,⁴ the absence of which in mouse and zebrafish results in loss of the nuclei of the oculomotor and trochlear nerves in addition to other neuropathologic changes.

Recently familial horizontal gaze palsy with progressive scoliosis (HGPPS) has been shown to be associated with ROBO3 gene mutations. These patients also have uncrossed corticospinal and dorsal column projections due to disruption of axonal hindbrain pathway crossing.⁵

CCDDs current concepts (Figure 1)

- Congenital, non-progressive, sporadic or familial abnormalities that result from developmental abnormalities of one or more cranial nerves/nuclei with primary or secondary dysinnervation.

- Primary dysinnervation - absence of normal innervation.
- Secondary dysinnervation - aberrant innervation during development by branches of other nerves.
- Dysinnervation may be associated with secondary muscle pathology and/or other orbital and bony structural abnormalities.
- Predominantly vertical ocular motility defects result from abnormalities in development of oculomotor and trochlear nerves and/or nuclei (CFEOM variants and congenital ptosis).
- Predominantly horizontal ocular motility defects result from abnormalities in the development of the abducens nerve and/or nucleus (Duane syndrome and HGPPS).
- Predominantly facial weakness resulting from abnormal development of facial nerve and/or nucleus (congenital facial weakness, and with associated ocular motor abnormalities or Möbius syndrome).

Figure 1. CCDDs the main features

- Congenital, non-progressive
- Sporadic or familial
- Developmental abnormalities of one or more cranial nerves/nuclei
- Primary dysinnervation
 - absence of normal innervation
 - neurons do not develop or are misguided
- Secondary dysinnervation
 - aberrant innervation during development by branches of another nerve

A practical approach: genetic loci, genes and phenotypes

See Figures 2 and Table 1, a brief overview is given here.

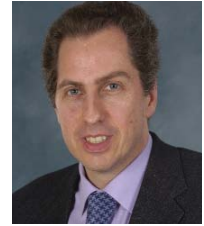
A) Predominantly vertical disorders of ocular motility

Congenital fibrosis of the extraocular muscles (CFEOM) and congenital ptosis result from abnormalities in development of oculomotor and trochlear nerves and/or nuclei (there are several oculomotor sub-nuclei).

1. **CFEOM.** Various forms of CFEOM result from primary dysinnervation of oculomotor and/or trochlear innervated extraocular muscles. The genetic loci for CFEOM phenotypes are referred to as FEOM. Currently, three CFEOM phenotypes (mild facial weakness has been reported to occur sometimes in all phenotypes) and four FEOM loci have been defined.

- KIF21A (FEOM1, 12p11.2-q12)**⁶ The KIF21A gene encodes a kinesin motor protein, with most mutations located within the coiled-coil structure of the stalk. **CFEOM1 phenotype.** Most common CFEOM phenotype: bilateral ptosis, infraducted globes in primary position, limited supraduction, chin-up head posture and variably restricted horizontal gaze. Inheritance is autosomal dominant with full penetrance. Neuropathology shows a primary defect of the superior division of oculomotor nerve. **CFEOM3 phenotype.** See FEOM3 below, rare CFEOM3 families are due to KIF21A mutations which can be non-penetrant.

- PHOX2A (FEOM2, 11q13.2)**⁴ The PHOX2A gene (previously known as ARIX) encodes a homeodomain transcription factor protein.



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CFEOM2 phenotype. Rare form of CFEOM, bilateral ptosis and a large angle exotropia with severely limited horizontal and vertical eye movements. Inheritance is autosomal recessive. There is a primary developmental defect of both oculomotor and trochlear nuclei.

c. **FEOM3 (16q24.2-q24.3)⁷**

CFEOM3 phenotype. A variable phenotype in which at least one affected family member does not meet CFEOM1 criteria. CFEOM3 results from a variable defect in the oculomotor nucleus development. Inheritance is autosomal dominant with incomplete penetrance.

CFEOM1 phenotype. See KIF21A (FEOM1) above, rarely CFEOM1 families map to the FEOM3 locus.⁸

d. **FEOM4**

CFEOM3 phenotype. See FEOM3 above. One family has been identified with a chromosomal translocation, co-inherited in an autosomal dominant pattern.¹

2. **Isolated congenital ptosis.** Some forms of congenital ptosis may result from aberrant development of the unpaired caudal central oculomotor sub-nucleus. Two congenital ptosis loci are reported.

a. **PTOS1 (1p32-p34.1)⁹**

PTOS 1 phenotype. Variable degree congenital unilateral or bilateral ptosis. Inheritance is autosomal dominant with incomplete penetrance of 90%.

b. **PTOS2 (Xp24-27.1)¹⁰**

PTOS2 phenotype. Congenital bilateral symmetrical and severe ptosis almost impinging on the visual axis in the primary position of gaze, with chin-up head posture. Inheritance is X-linked dominant (male and females are equally affected).

Figure 2. The main CCDDs currently recognised and subdivided

Predominantly vertical disorder of ocular motility

- Congenital fibrosis of the extraocular muscles (CFEOM)
- Congenital ptosis

Predominantly horizontal disorder of ocular motility

- Duane syndrome (DS)
- DS + radial ray (DRRS)
- Horizontal gaze palsy with progressive scoliosis (HGPPS)

Disorder of facial motility

- Congenital facial palsy

Disorder of facial motility and ocular abduction deficit

- Möbius syndrome

B) Predominantly horizontal disorders of ocular motility

These disorders include the various forms of Duane syndrome and horizontal gaze palsy and are proposed to result from primary dysinnervation abnormalities in the development of the abducens nerve and/or nucleus.

1. **Duane syndrome.** The prevalence is 1:10000 (1-4% of strabismus cases), 10% are familial.^{2,11} Abducens motorneurons are reduced in number or are absent; there is aberrant innervation of lateral rectus by the oculomotor nerve (Figure 3). Congenital limitation of horizontal globe movement and some globe retraction on attempted adduction is required to make this diagnosis. The balance between the amount of aberrant innervation and the reduction/absence of abducens motor neuron function (and consequent muscle fibrosis) leads to a limitation of horizontal globe movement. Most commonly (~80%) abduction is affected with normal or minimally defective adduction, type 1 Duane syndrome (Figure 4); in type 3 Duane syndrome both abduction and adduction are limited and in type 2 adduction is limited. From case series the left eye (2:1) and females are more frequently affected although the reason for this is not known.^{2,11} At least three Duane syndrome genetic loci have been defined.

a. **DURS1 (8q13)**

DURS1 Phenotype. Duane syndrome is usually bilateral and may be associated with other features such as mental retardation, branchio-oto-renal syndrome and genital tract anomalies in patients

with cytogenetically visible deletions. A peptidase gene, CPAH, has been highlighted as a candidate gene as it is disrupted by a balanced translocation breakpoint at 8q13 in a single patient.¹²

b. **DURS2 (2q31)^{13,14}**

DURS2 Phenotype. Duane syndrome is unilateral or bilateral with decreased abduction with or without decreased adduction (in bilateral cases the left eye tends to be more severely affected). There can be a variety of vertical deviations. Amblyopia is common. Inheritance is autosomal dominant.^{14,15}

c. **SALL4 (DRRS, [Duane radial ray syndrome or Okihiro syndrome], 20q13).^{16,17}** The SALL4 gene encodes a putative zinc finger transcription factor.

DRRS Phenotype. There is Duane syndrome (unilateral or bilateral) and radial dysplasia (unilateral or bilateral) ranging from most commonly thumb hypoplasia to most severely a phocomelic limb (similar to that seen in thalidomide cases). Other features include deafness, renal and ocular manifestations. Inheritance is autosomal dominant. Truncating mutations and SALL4 deletions have been identified in DRRS families.^{16,17} No SALL4 mutations were found in 25 sporadic cases of isolated Duane syndrome.¹⁸

d. **Other potential Duane syndrome genetic loci.** These have been found at 22pter->22q11.2 and at 4q27-31 and are defined cytogenetically (reviewed in reference 1).

Table 1. A summary of the current CCDD classification

CRANIAL NERVE/NUCLEI	SYNDROME	GENETIC LOCUS	PHENOTYPE	GENE LOCATION	GENE
Oculomotor	CFEOM	FEOM1	CFEOM1 (CFEOM3)	12p11.2-q12	KIF21A
		FEOM3	CFEOM3 (CFEOM1)	16q24.2-q24.3	
		FEOM4	CFEOM3		
	Congenital ptosis	PTOS1	PTOS1	1p32-p34.1	
		PTOS2	PTOS2	Xp24-27.1	
Oculomotor & trochlear	CFEOM2	FEOM2	CFEOM2	11q13.2	PHOX2A
Abducens	Duane	DURS1	Duane	8q13	
		DURS2	Duane	2q31	
		Other potential loci	Duane+	22pter->22q11.2	
		DRRS	Duane+	4q27-31	
	HGPPS	HGPPS	HGPPS with absent long-tract crossing	11q23-25	ROBO3
Facial	Congenital facial palsy	FNP1 (MBS2)	FNP1	3q21-22	
		FNP2 (MBS3)	FNP2	10q21.3-22.1	
Facial & abducens	Möbius syndrome	MBS1	MBS1	13q12.2-13	
		MBS4	MBS4	1p22	

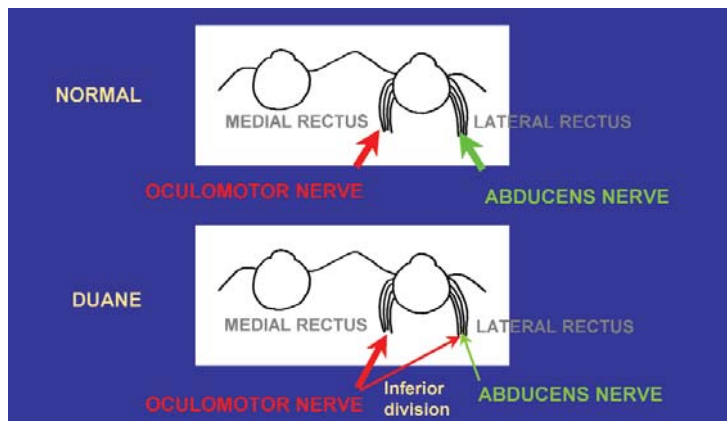


Figure 3: Pathophysiology of Duane Syndrome.

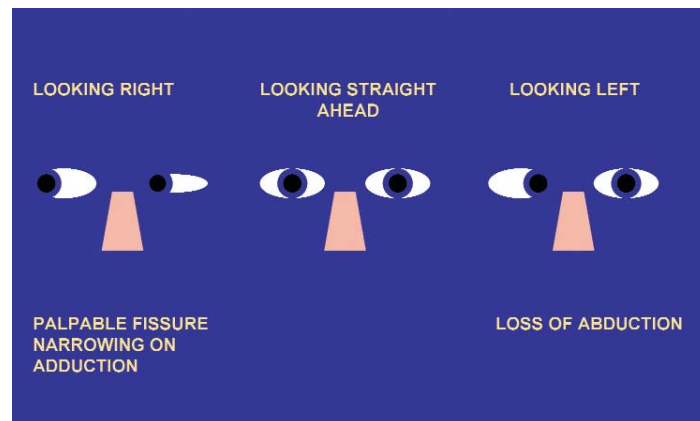


Figure 4: Left eye type 1 Duane Syndrome.

2) **Horizontal gaze palsy.** Horizontal gaze palsy is suggested to result from hypoplasia of the abducens nucleus with interneuron dysinnervation (medial longitudinal fasciculus and pontine paramedian reticular formation). It differs from the other disorders as the extraocular nerves and innervating muscles seem normal.

- a. **ROBO3 [HGPPS]** (Horizontal gaze palsy with progressive scoliosis), 11q23-25. The ROBO3 gene encodes a transmembrane receptor required for hindbrain axon midline crossing.⁵ **HGPPS phenotype.** There is congenital complete absence of conjugate horizontal gaze and childhood onset progressive scoliosis. Inheritance is autosomal recessive.⁵ The uncrossed corticospinal and dorsal column pathways are not associated with an obvious neurological deficit.

C) Disorders with abnormalities of facial motility

This includes congenital non-traumatic facial weakness in isolation or in association with ocular dysmotility.

1. **Facial nerve palsy (FNP).** Isolated congenital facial weakness is usually an autosomal dominant disorder which is proposed to result from facial nuclei and/or nerve maldevelopment. Two genetic loci have been defined.

- a. **FNP1** (previously known as MBS2, 3q21-22)¹⁹ **FNP1 phenotype.** Non-progressive, congenital isolated facial weakness, mostly bilateral, often asymmetrical. Inheritance is autosomal dominant with penetrance of 95%.
- b. **FNP2** (previously known as MBS3, 10q21.3-22.1)²⁰ **FNP2 phenotype.** Non-progressive, congenital isolated facial weakness, unilateral or bilateral, often asymmetrical. There can be hearing loss and rarely congenital deafness. Inheritance is autosomal dominant with penetrance of 60%.

2. **Möbius syndrome.** This is defined as facial weakness combined with an ocular abduction deficit. It is almost always sporadic, fre-

quently accompanied by lingual and/or pharyngeal dysfunction at birth, craniofacial dysmorphisms, and limb malformations.^{1,21} A low recurrence risk of 2% is quoted. In such cases it is thought to be due to a vascular insult in early pregnancy and misoprostol, ergotamine, cocaine and thalidomide have been implicated. Rarely cytogenetic abnormalities have been reported in association with Möbius syndrome, the phenotypes are variable but can additionally include ptosis, two loci are suggested.

- a. **MBS1** (13q12.2-13 defined cytogenetically) reviewed in reference 1.
- b. **MBS4** (1p22 defined cytogenetically) reviewed in reference 1.

Recruitment

We are still actively recruiting CCDD cases, especially Duane syndrome (both familial and sporadic), for genetics studies and would be pleased to hear of cases.

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