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Clinical features associated with an I126M α2-chimaerin mutation in a family with autosomal dominant Duane retraction syndrome

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Abstract

Purpose—We describe the clinical phenotype of a Mexican family segregating Duane syndrome as an autosomal dominant trait linked to chromosome 2q31 (DURS2) and previously reported to harbor a heterozygous α2-chimaerinmissense mutation.

Methods—A five-generation Mexican family was analyzed. Ten affected subjects were available for clinical examination. Participating subjects were tested for visual acuity, ocular alignment by prism cover testing, ocular ductions and versions, and globe retraction. In children, alignment was measured with the Krimsky test in cardinal positions of gaze.

Results—Ten cases were included, 6 females and 4 males. Five cases presented with bilateral and 5 with unilateral Duane syndrome. Right side was the most commonly affected side on unilateral cases. Five cases exhibited exotropia, 4 esotropia, and 1 hypotropia. Seven patients had important limitation of abduction; two, moderate limitation. Four patients had mild adduction limitation and 4 had moderate limitation. No additional anomalies such as fourth (trochlear) nerve palsy, blepharoptosis, or dense amblyopia, reported in previous Duane syndrome families, were observed. All 3 cases that exhibited vertical dysfunction had upgaze limitation. One instance of nonpenetrance was recorded.

Conclusions—Considerable intrafamilial clinical variability was observed in this Duane syndrome pedigree carrying a α2-chimaerin mutation. The presence of bilateral involvement and associated vertical movements, commonly observed in this and others DURS2 families, could suggest the occurrence of *CHN1* mutations as the source of the disease in isolated or familial DURS cases.

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Introduction

Duane retraction syndrome is a congenital ocular motility disorder that accounts for up to 4% of all strabismus cases. It is considered the most common type of congenital aberrant ocular innervation.[1,2] Duane syndrome can be caused by absence or hypoplasia of both the abducens nucleus and nerve with anomalous innervation of its target, the lateral rectus muscle, by a branch of the oculomotor nerve. This in turn leads to absent abduction or adduction and narrowing of the palpebral fissure, with retraction of the globe on attempted adduction.[3–5] Associated ocular anomalies in subjects with Duane syndrome can include nystagmus, anisocoria, ptosis, optic nerve colobomas, epibulbar dermoids, crocodile tears, and aniridia.[6–11] Systemic malformations can be found in Duane syndrome patients, particularly skeletal (limb hypoplasia, polydactyly, hypoplastic or absent radius and/or thumb), vertebral (scoliosis, spina bifida, “butterfly” vertebrae, Klippel-Feil anomaly), genitourinary (renal agenesis, vesicoureteral reflux), and cardiac (patent ductus arteriosus, auricular septal defect) defects.[7,9,12–14] However, a distinction should be made between true etiologic associations and coincidental findings. Well-known syndromic entities associating Duane syndrome include Okihiro (Duane syndrome and radial ray defects), Wildervanck (Duane syndrome, Klippel-Feil anomaly, and deafness), Moebius (congenital paresis of facial and abducens cranial nerves) and Townes-Brocks (ear, limb, anal, renal and heart anomalies) syndromes, among others. Approximately 90% of nonsyndromic Duane syndrome cases occur sporadically,[15,16] with predominant affectation for females and the left eye.[7,17] The remaining 10% of Duane syndrome subjects have familial antecedents of the disorder and these inherited cases are commonly bilateral and have associated vertical movement abnormalities.[18–20] Previously, genetic linkage studies in several of these pedigrees allowed the assignment of a locus for autosomal dominant Duane syndrome, named DURS2, at chromosome 2q31.[20–22] Recently, Miyake and colleagues[23] provided genetic, *in vitro*, and *in vivo* evidence that mutations in the *CHN1* gene, encoding α2-chimaerin, are responsible for the 2q31-linked form of Duane syndrome. Alpha-2-chimaerin is a Rac guanosine triphosphatase-activating protein (RacGAP) signaling protein implicated in the pathfinding of corticospinal axons.

The purpose of this study is to describe the clinical phenotype resulting from a mutation in the α2-chimaerin gene in a Mexican family that segregates DURS2 as an autosomal dominant trait.[23] This is the first detailed report regarding phenotypic features in Duane syndrome subjects carrying an α2-chimaerin mutation.

Report of Cases

A five-generation Mexican family (Figure 1) segregating Duane syndrome as an autosomal dominant trait was analyzed. All subjects were of Mexican Mestizo origin and without history of additional genetic or inherited diseases. Of a total of 15 affected subjects identified, 10 were available for clinical examination. A number of unaffected relatives were also examined. Participating subjects were tested for visual acuity, ocular alignment, ocular ductions and versions, and globe retraction. Ductions were assessed by two independent examiners (CM-C and VK-J). Ocular alignment was measured by prism cover testing with the subject viewing a distant object in the seven cardinal positions of gaze. In children, alignment was measured with the Krimsky test in cardinal positions of gaze. When possible, Titmus stereo test was performed to evaluate binocular visual function. None of the subjects exhibited biomicroscopic or fundoscopic anomalies. Significant ametropia was not observed in any case. Table 1 summarizes the clinical findings in affected subjects. The detailed results of clinical examination in each subject are listed in e-Supplement 1 (available at jaapos.org).

Previous molecular analysis in affected subjects from this family reported a 378 T>G transversion in exon 6 of the *CHN1* gene, predicting an I126M (isoleucine to methionine) missense mutation at residue 126 of α2-chimaerin (Pedigree RF in reference [23]).

Discussion

Duane syndrome has an estimated prevalence of about 1 in 1000 in the general population. Earlier electrophysiologic,[24] post mortem,[4,25] and magnetic resonance imaging (MRI)[26–28] data have established that the disorder can be caused by deficient abducens (sixth) nerve innervation of the lateral rectus muscle. In addition, however, recent studies using high-resolution, multipositional MRI showed that some 2q31-linked Duane syndrome subjects (DURS2), subsequently found to harbor *CHN1* mutations, also have hypoplastic oculomotor nerves and small oculomotor-innervated muscles,[19–23] indicating that, at least in some cases, Duane syndrome is a diffuse congenital cranial dysinnervation anomaly not limited to the abducens cranial nerve.[19] Several genes have been associated to syndromic forms of Duane syndrome, including SALL4,[29] and HOXA1.[30]

Recently, Miyake and colleagues[23] identified heterozygous gain of function mutations in the *CHN1* gene as the cause of the 2q31-linked Duane syndrome in 7 families from different ethnic backgrounds. *In vitro* and *in vivo* analysis indicated that these mutations hyperactivate α2-chimaerin RacGAP activity or enhance α2-chimaerin membrane translocation.[23] Furthermore, *in ovo* expression of mutant *CHN1* alters the development of ocular motor axons demonstrating that hyperactivated α2-chimaerin results in aberrant cranial motor neuron development.[23]

Here, we have described the clinical characteristics of a Duane syndrome Mexican family carrying a α2-chimaerin I126M amino acid substitution.[23] In this family, five generations were known to be affected, with a total of 18 diseased individuals, of whom 15 were alive and 10 were available for clinical examination. Individual III-9 carries the I126M *CHN1* mutation but detailed ocular movement examination failed to demonstrate any abnormality of ocular motility. Consistent with this observation, lack of penetrance has been reported in other DURS2 pedigrees harboring *CHN1* mutations.[19,23]

Remarkably, of the seven original DURS2 pedigrees reported to harbor *CHN1* mutations, three were of Mexican descent. The other two pedigrees, FY and IJ,[23] harbor different α2-chimaerin mutations resulting in L20F and P252Q amino acid substitutions, respectively. The occurrence of distinct *CHN1* mutations in three DURS2 Mexican pedigrees argues against a founder mutation in this ethnic group. In this sense, no *CHN1* mutational hot-spots have been recognized in DURS2.[23]

A common finding in these three Mexican DURS2 pedigrees is the cosegregation of Duane syndrome types 1 and 3 but not type 2 (isolated limitation of adduction). Interestingly, we found a 50% incidence of unilateral Duane syndrome (5 of 10) in affected members of pedigree RF, and four of these involved the right side. All but one of the unilateral cases had history of previous ocular surgeries and this factor could be related to the high proportion of unilateral Duane syndrome. However, as most surgeries were performed during childhood and in other institutions, this probability cannot be addressed. In contrast to the high proportion of unilateral cases in the present family, only 1 of 4 affected subjects of pedigree FY had unilateral (left) Duane syndrome[19] and only 1 of 25 affected subjects of pedigree IJ exhibited unilateral (left) Duane syndrome.[18]

In the present pedigree, RF, no affected individuals had fourth (trochlear) nerve palsy, blepharoptosis, or dense amblyopia. However, 2 bilateral cases (3 and 4) exhibited amblyopia (ie, difference of vision between both eyes of≥2 lines of visual acuity). In contrast, in pedigree FY, one subject with bilateral Duane syndrome had no right eye retraction, three had limitation

of vertical gaze, and one had blepharoptosis. No instance of dense amblyopia was observed in this pedigree.[19] In pedigree IJ, there was a high incidence of strabismus and amblyopia, which are uncommon in unilateral Duane syndrome, as well as a striking degree of variability in the amount of restriction and vertical dysfunction.[18] Additional neuro-ophthalmologic anomalies were observed in a number of subjects including trochlear nerve palsy and ptosis. No instances of hypotropia were recorded in pedigrees IJ and FY.[18,19] Interestingly, if compared with cases from the literature, the degree of strabismus in bilateral cases in the pedigree RF, reported here, is small.[31]

DURS2 interfamilial phenotypic differences could be explained by distinct effects of a given *CHN1* mutation, with some mutations affecting the development of the trochlear and oculomotor nerves more than others. The marked intrafamilial phenotypic differences among subjects carrying the same α2-chimaerin mutation, however, favor genetic or environmental modifiers.

In conclusion, we present the clinical description of individuals affected with Duane syndrome in a Mexican family in which a α2-chimaerin mutation was identified as the source of the disease. Overall, the clinical features of this family were similar to those described in other familial Duane syndrome cases that have been shown recently to be caused by mutations in α2-chimaerin, including a subset of affected family members with bilateral involvement and vertical movement abnormalities.[18–20] Considerable intrafamilial clinical variability and one case of non-penetrance were recorded. Although more studies are needed to establish if a genotype-phenotype correlation exists, we suggest that the presence of bilateral involvement and associated vertical movements in isolated or familial Duane syndrome cases could suggest the occurrence of *CHN1* mutations as the source of the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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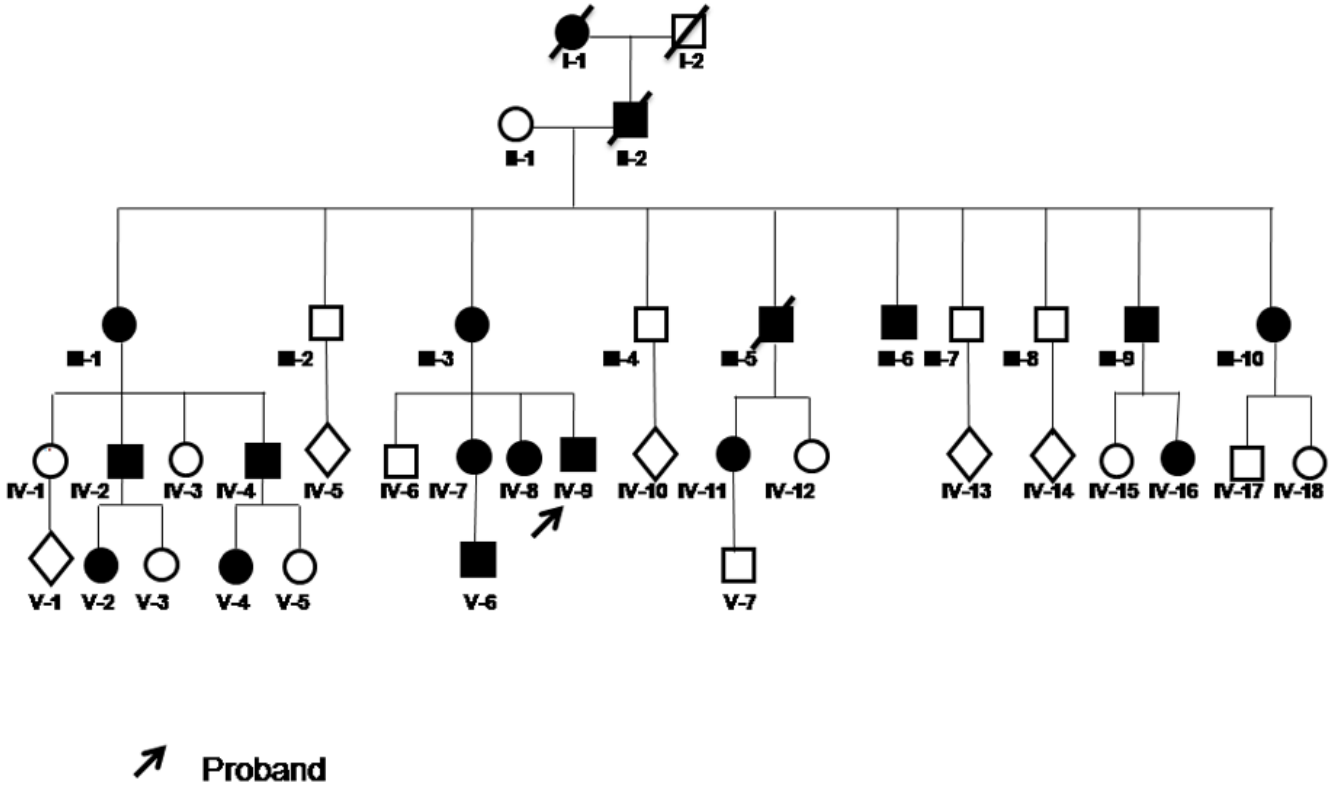

FIG 1.

Genealogical tree of a five-generation Mexican family segregating DURS as an autosomal dominant trait. Black symbols denote affected individuals. Arrowed subject is the propositus.

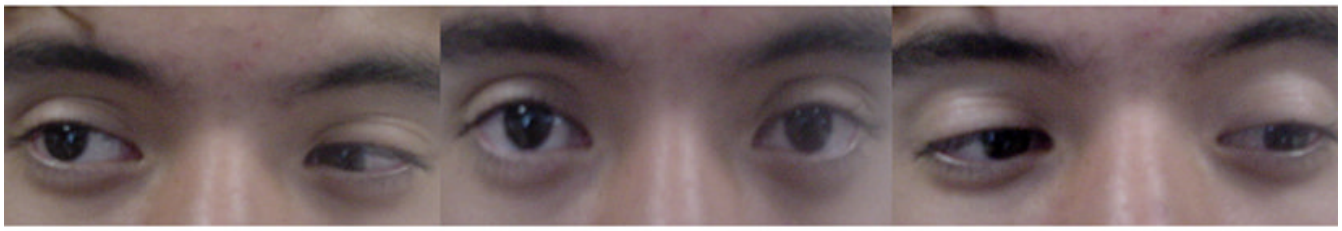

FIG 2.
Bilateral Duane's syndrome. Index case (IV-9 in Figure 1): left panel: right version; center panel: primary position of gaze; right panel: left version. Note palpebral narrowing, eye retraction, and mild limitation during abduction in both eyes.

Table 1

Subjects and clinical examination

Case	Gender	Age(years)	Deviation	Limitation		Previous surgery	Affected side
				ABD	ADD		
1	M	15	XT	++ (RE) + (LE)	++ (RE) ++ (LE)	No	Bilateral
2	F	28	HT	++		Yes	Right
3	F	30	XT	++ (RE) ++ (LE)	+ (RE)	No	Bilateral
4	F	26	ET	+++ (RE) +++ (LE)	++ (RE) + (LE)	No	Bilateral
5	F	39	XT	+ (RE)	+ (RE) + (LE)	Yes	Bilateral
6	M	45	ET	++	+	Yes	Right
7	F	59	XT	++	++	Yes	Right
8	F	50	ET	++		No	Right
9	M	4	XT	++ (RE) ++ (LE)	+ (RE) + (LE)	No	Bilateral
10	M	5	ET	++	+	Yes	Left

ET, esotropia; *XT*, exotropia; *HT*, hypotropia; *RE*, right eye; *LE*, left eye; *ABD*, abduction; *ADD*, adduction