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Clinical Short Communication

Phenotypical features of two patients diagnosed with PHARC syndrome and carriers of a new homozygous mutation in the *ABHD12* gene

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ABSTRACT

PHARC (Polyneuropathy, Hearing loss, Ataxia, Retinitis pigmentosa and Cataracts) (MIM# 612674) is an autosomal recessive neurodegenerative disease caused by mutations in the *ABHD12* gene. We evaluated two Spanish siblings affected with pes cavus, sensorimotor neuropathy, hearing loss, retinitis pigmentosa and juvenile cataracts in whom the genetic test of *ABHD12* revealed a novel homozygous frameshift mutation, c.211_223del (p.Arg71Tyrfs*26). The earliest clinical manifestation in these patients was a demyelinating neuropathy manifested with a Charcot-Marie-Tooth phenotype over three decades. Progressive hearing loss, cataracts and retinitis pigmentosa appeared after the age of 30. We herein describe the complete clinical picture of these two patients, and focus particularly on neuropathy characteristics. This study supports the fact that although PHARC is rare, its phenotype is very characteristic and we should include its study in patients affected with demyelinating polyneuropathy, hearing loss and retinopathy.

1. Introduction

PHARC syndrome (MIM# 612674) is an autosomal recessive entity characterized by polyneuropathy, hearing loss, ataxia, retinitis pigmentosa and cataracts. Some patients diagnosed with PHARC also show pyramidal tract signs or cerebellar signs, such as dysarthria, dysmetria or nystagmus. PHARC was first described by Fiskerstrand et al. [1] and it is caused by mutations in the *ABHD12* gene, which encodes the enzyme α/β hydrolase domain containing 12 [2]. By means of new generation sequencing technologies, some PHARC cases have been found among families previously diagnosed with syndromic and non-syndromic retinitis pigmentosa [3] and deaf-blindness (Usher syndrome) [4,5].

We describe the phenotype of two Spanish patients with PHARC syndrome who harbour a novel homozygous frameshift mutation, c.211_223del (p.Arg71Tyrfs*26), in the *ABHD12* gene. The description of this new family extends the spectrum of mutations in the *ABHD12* gene associated with PHARC and aims to better define the neuropathy that forms part of this entity.

2. Material and methods

Patients were assessed in the Neuromuscular Unit of a tertiary referral centre in Valencia, Spain. The studied individuals comprised two affected siblings (II-1,II-3), their healthy parents and a healthy brother (II-5) (Fig. 1). All of them were clinically evaluated and underwent electrophysiological studies with standard techniques. The affected individuals were thoroughly investigated and they had two different electrophysiological studies separated by an interval of 30 years. In the proband (II-3) the diagnosis was established by medical history and detailed evaluation of polyneuropathy and audiologic and ophtalmological assessment. Peripheral neuropathy was classified as demyelinating Charcot-Marie-Tooth (CMT) phenotype according to motor nerve conduction velocities (MNCVs). Ophthalmological examination consisted of fundoscopy, standard electroretinogram (ERG), perimetry, and determination of visual acuity. Audiological study included: otoscopic examination, otoacoustic emissions (OAEs), cochlear microphonics (CM), pure tone audiometry (PTA) and auditory brainstem response (ABR). DNA was obtained from the two affected siblings, their

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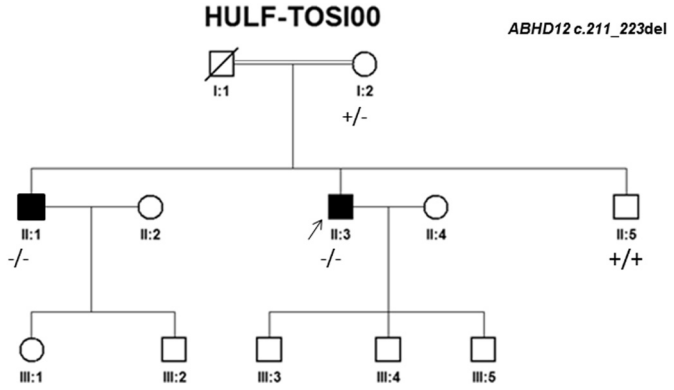

Fig. 1. Pedigree of the family identified with the c.211_223del *ABHD12* mutation. Patients II-1 and II-3 were homozygous for the c.211_223del change (−/−), the mother (I-2) was heterozygous (+/−) and the clinically unaffected brother (II-5) was normal homozygous (+/+).

healthy brother and mother. Genetic diagnosis was reached by Sanger sequencing of the *ABHD12* gene that was oriented based on the patients phenotype. All exons and their intronic flanking sequences of the *ABHD12* gene were studied.

The research protocols were approved by the Institutional Board of the Ethics Committee of the Hospital Universitari i Politècnic La Fe (Valencia, Spain). Written informed consents were obtained from all the studied individuals.

3. Results

Pedigree information is illustrated in Fig. 1. There was consanguinity between the parents.

The proband (II-3, male, 42 years) started walking at the age of 14 months; he was diagnosed with pes cavus and required corrective shoes during infancy and childhood. At the age of 12 he was assessed in the orthopaedics department for cavo-varus feet and tendoachilles contracture. An electrophysiological study was performed and showed motor conduction velocities compatible with a demyelinating CMT neuropathy (Table 1). The patient had two siblings, and his older brother (II-1) had similar clinical symptoms. The electrophysiological study was extended to his parents and his two brothers. It was normal in the parents and in the asymptomatic brother, and showed results compatible with a demyelinating polyneuropathy in the symptomatic brother (II-1) (Table 1). At the age of 14–16 years, the proband had two recurrent dislocations of the right kneecap, which were surgically treated. He underwent a triple arthrodesis of his right foot and his left foot at the age of 13 and 14, respectively. Aged 30 years, he complained of hearing loss and underwent an audiological assessment: PTA showed hearing loss that was severe in his right ear (80 dB) and profound in his left (> 95 dB). OAEs and ABR were absent. He was diagnosed with sensorineural hearing impairment and sequential cochlear implant surgery of each ear was performed at the age 42 and 43, respectively. He underwent surgery for cataracts in both eyes at age 38. Notwithstanding visual acuity loss was progressive in them both, although its cause had not been studied.

We evaluated the proband (II-3) in our unit when he was 41 years old. Upon examination the patient had pes cavus and hammertoes with ankle tendon retractions; there was mild muscular weakness in the toes and in ankle dorsiflexor muscles. Tendon reflexes could not be elicited and no muscle atrophy was observed. Light touch and pinprick sensations were reduced in lower limbs up to ankle level. Vibratory sensation (tested using a Rydel-Seiffer tuning fork) was absent at the toes and scored 4 at the ankles. In upper limbs it scored 4 at the dorsum of the distal interphalangeal joint of the index finger; position sense was intact. There was a wide-base gait, action tremor in the upper limbs and a positive Romberg test. Cerebellar signs like dysarthria, appendicular dysmetria, nystagmus and ocular movement abnormalities were absent. Nerve conduction studies showed reduced MNCVs and absent sensory nerve potentials (SNP) (Table 1). The genetic study of the duplication of the *PMP22* gene associated with CMT1A was negative. Analyses of plasma phytanic and pristanic acid to rule out Refsum disease and concentration in serum were normal (data not shown). Diagnosis was oriented as an autosomal recessive inherited syndrome that combined a demyelinating polyneuropathy with sensorineural deafness, early cataracts and visual acuity loss. Once Refsum disease had been excluded, the diagnosis of Refsum-like syndrome was made. *ABHD12* gene analysis was performed by Sanger sequencing, and revealed that the proband carried the novel homozygous frameshift c.211_223del (p.Arg71Tyrfs*26) mutation in the *ABHD12* gene, resulting in a premature stop codon. This variant was not present in any database (gnomAD, HGMD, NCBI ClinVar).

At the same time, clinical assessment was completed. Visual evoked potentials (VEP) and ERG confirmed the existence of alteration in rod and cone function in the retina. Further ophthalmological assessment led to the diagnosis of pauci-pigmentary retinopathy with severe visual loss in both eyes. Brain MRI showed very mild cerebellar atrophy and muscle MRI revealed mild fatty infiltration in the intrinsic muscles of both feet and the anterior compartment of the left leg (Fig. 2).

The proband's siblings (II-1 and II-5) and mother (I-2) were assessed (Fig. 1). Patients I-2 and II-5 had no symptoms and their examinations

Table 1
Electrophysiological data in patients with the homozygous c.211_223del change and their relatives.

		Median nerve					Ulnar nerve										
		Motor			Sensory		Motor			Sensory		Peroneal motor			Sural nerve		EMG
Patient	Age	Amp	CV	DL	Amp	CV	Amp	CV	DL	Amp	CV	Amp	CV	DL	Amp	CV	
II-3	11	17	25	4.60	12	31	ND	-	-	ND	-	1.5	20	9.90	NR	-	Chronic denervation in distal muscles of lower and upper limbs
II-3	40	13.4	23.2	6.30	NR	-	10.2	22.8	5.55	NR	-	2.6	16.5	7.60	ND	-	ND
II-1	13	8	30	4.5	ND	-	ND	-	-	ND	-	2.4	19	9.70	6.5	25	Chronic denervation in distal muscles of lower limbs
II-1	45	7.9	29.6	6.3	2.1	25.3	11.5	30.3	4.2	2.5	35.2	0.1	-	9.2	1.2	34.0	Chronic denervation in distal musclesof lower limbs
I-1	42	12	50	4.1	20	43	12	49	2	ND	-	18	49	5.6	20	35	Normal
I-2	38	ND	-	-	ND	-	ND	-	-	ND	-	15.5	50.2	2.25	24	55.5	Normal
II-5	10	16	53.2	2.5	27	58.2	15	58	1.7	9	67.7	10	54	2.25	28	43	Normal

Two electrophysiological studies were performed in both affected patients (II-1 and II-3) at different ages. An electrophysiological study was also performed in the patients' father, mother and brother (I-1, I-2 and II-5).
Motor Amp: amplitude (mV); Sensory Amp: amplitude (microV); CV: conduction velocity (m/s); DL: distal motor latency.
ND: not done. NR: no response. -: not calculated.
Patient II-3 F-wave: Ulnar-ADM 67.00 ms; Tibial (Knee)- AH 112.20 ms.