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CYP2U1 mutations in two Iranian patients with activity induced dystonia, motor regression and spastic paraplegia

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Abstract

Hereditary spastic paraplegia (HSP) is a heterogeneous condition characterized by progressive spasticity and weakness in the lower limbs. It is divided into two major groups, complicated and uncomplicated, based on the presence of additional features such as intellectual disability, ataxia, seizures, peripheral neuropathy and visual problems. SPG56 is an autosomal recessive form of HSP with complicated and uncomplicated manifestations, complicated being more common. *CYP2U1* gene mutations have been identified as responsible for SPG56. Intellectual disability, dystonia, subclinical sensory motor neuropathy, pigmentary degenerative maculopathy, thin corpus callosum and periventricular white-matter hyperintensities were additional features noted in previous cases of SPG56.

Here we identified two novel mutations in *CYP2U1* in two unrelated patients by whole exome sequencing. Both patients had complicated HSP with activity-induced dystonia, suggesting dystonia as an additional finding in SPG56. Two out of 14 previously reported patients had dystonia, and the addition of our patients suggests dystonia in a quarter of SPG56 patients. Developmental regression has not been reported in SPG56 patients so far but both of our patients developed motor regression in infancy.

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Keywords

Hereditary spastic paraplegia; *CYP2U1*; SPG56; Complicated; Dystonia; Regression

1. Introduction

Hereditary spastic paraplegia (HSP) is a heterogeneous condition characterized by progressive spasticity and weakness in the lower limbs. Based on the presence of other neurological and extra-neurological signs and symptoms, it is divided into two broad categories, complicated and uncomplicated HSP.[8,5,9] Additional findings can include intellectual disability, ataxia, seizures, peripheral neuropathy and visual problems.[16,17] While some genetic types are associated with either complicated or uncomplicated HSP, other genetic types can be associated with both.[10] The prevalence is between 3 and 10 in 100,000 depending on the ethnic group.[1] The most common form of inheritance of uncomplicated HSP is dominant, while autosomal recessive inheritance is more common for complicated forms. Countries with high rate of consanguineous marriages have higher rates of autosomal recessive inheritance.[4,2]

CYP2U1 mutations have been reported in families with complicated HSP.[18,3,14,15] Tesson et al.[18] reported 11 patients from five families, with complicated HSP and *CYP2U1* mutations. They all had spasticity in the lower limbs, three of them had intellectual disability and two had dystonia in the upper limbs. Onset of disease ranged from 8 months to 5 years. There was a high degree of intra- and interfamilialvariability. In the same family, there were cases with mild disability (unable to run) and others with severe disability (wheelchair bound).

Citterio et al.[3] evaluated 150 patients with complicated HSP for mutations in *CYP2U1*/SPG56, *DDHD2*/SPG54 and *GBA2*/SPG46. For each gene, they found a mutation in a single family within the cohort. The patient with *CYP2U1* mutation had onset of disease at 18 months. He had spasticity, weakness, intellectual disability, thin corpus callosum and periventricular white-matter hyperintensities. Leonardi et al.[14] reported a family with three affected members carrying a homozygous mutation in *CYP2U1* with onset of visual impairment and spastic paraplegia in their twenties or thirties. Opthalmological investigation revealed pigmentary degenerative maculopathy in all three patients.

Masciullo et al.[15] reported an isolated case of SPG56 in a 6-year-old girl with early onset spastic paraplegia and mild mental retardation. Spinal MRI revealed hydromyelia and the authors suggested that the case fell within the complicated phenotype of SPG56.

1.1. Patients and methods

A cohort of patients with a diagnosis of HSP have been ascertained at Kariminejad-Najmabadi Pathology & Genetics Center, Tehran Iran. The unique inclusion criterion for HSP was progressive spasticity and weakness in the lower limbs. Detailed clinical data were obtained by standardized questionnaire. All families provided written informed consent according to institutional guidelines. Ethics approval has been obtained by the local and University of California, San Diego's Ethics Committees.

1.2. Whole exome sequencing (WES)

Exome capture was performed using the SureSelect Human All Exome 50 Mb Kit (Agilent Technologies, Santa Clara, CA) with 150-bp paired-end read sequences generated on a HiSeq2000 (Illumina, San Diego, CA). Sequences were aligned to hg19 and variants identified through the GATK pipeline. Variations were annotated with in house software and the SeattleSeq server. Identified variants were checked against public databases dbSNP ver. 144 (http://www.ncbi.nlm.nih.gov/SNP/), Exome Variant Server (http://evs.gs.washington.edu/EVS/) and ExAC (http://exac.broadinstitute.org/). Sanger sequencing was applied to confirm co-segregation of variants in parents.

1.3. Case 1

Case 1 is the only child of first cousin parents (Fig. 1a, Table 1). Pregnancy and delivery were uneventful. She sat at 6 months, crawled at 8 months and walked with support at 11 months. At that point, her motor skills began to deteriorate, evidenced by repeated falling from an upright position and development of tip-toe gait, followed by loss of ability to walk and crawl. Her muscle tone was spastic. At the age of two years, physical therapy was started and she slowly regained the ability to walk a few meters with a walker. Upperlimbs were weak with impaired fine motor movements in both hands. She was able to understand speech according to her age but only started to speak at the age of 5 years. Cognition was normal and she attended a special school for physically handicapped children. She could read and calculate. Suspecting a form of dopa-responsive dystonia, her physicians prescribed levodopa + benserazide combination daily at the age of 10 years for about one year. According to the parents there was a dramatic improvement for a short time, but no improvement thereafter. The dose was increased however no effective improvement was noticed. The treatment was discontinued after one year with no notable worsening. Trihexiphenidyl was prescribed at the same time without notable effect so was discontinued.

Neurological examination at the age of 11 years showed moderator pseudobulbar dysarthria with reduced and markedly slow tongue mobility. There were intermittent involuntary movements of the perioral muscles and the tongue, especially when concentrating on difficult tasks. Generalized, left > right and distal > proximal weakness of the upper limbs (proximal 4/5, distal 3-4/5) and reducedfine motor movements of both hands were present. Generalized bilateral distal > proximal weakness of the lower limbs (proximal 3/5, distal 1-2/5) were also present. Spastic tone in all extremities was noted. Tendon reflexes were brisk. Babinski sign was negative. Activity-induced dystonic posturing in both arms and neck (upon motor activation in the legs) and legs (upon motor activation in the arms) was noted (Supplementary Videos 1 and 2). There was pronounced clonus in both legs especially with exertion. Weakness of truncal muscles was noted. Sense of touch and position were intact. There was malposition of the thumbs in adduction that could be corrected passively. There was atrophy of intrinsic foot muscles. Aided walking was possible, being predominantly spastic. The gait base was narrow, knees touching each other due to adductor spasticity, with marked instability in the ankle joints with eversion malposition. Lumbar puncture at 18 months was unremarkable. EMG/NCV studies showed reduced amplitude and nerve conduction velocity. Evoked potentials, AEP and VEPs were both normal. Routine ophthalmological examination was unremarkable.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.ejpn.2016.05.013.

1.4. Case 2

Case 2 is the only child of first cousin parents (Fig. 1b). Pregnancy and delivery were uneventful. There were two distant cousins who died at the ages of 16 and 18 years with a neurodegenerative disease as well as two other cousins aged 24 and 27 years reported to have a neurodegenerative disease, all with unknown etiology. Motor milestones, such as holding head, sitting, standing and crawling were achieved on time. She had just achieved the ability to walk with support at 11 months, but started regressing after an upper respiratory infection. She started walking on tiptoes and her tone became spastic. Within a few months she lost motor function to the point that she had difficulty holding her head upright and swallowing food. Physical therapy introduced at the age of 26 months offered slight improvement but did not restore her ability to walk. At 2.5 years levodopa + benserazide combination was prescribed for a week but was discontinued as there was no improvement. Baclofen was administered daily from 2 to 4 years but was also discontinued.

At examination she had spasticity in all limbs. Muscle force was normal and there was no muscle atrophy. She had activity induced dystonic posturing in both arms and neck (upon motor activation in the legs) and activity induced dystonic posturing in legs (upon motor activation of arms). She understood speech but could not yet speak. Hand movements and fine motor skills were impaired. Plantar reflex was extensor, knee reflex was brisk. There were contractures in knee extension and ankle flexion. Brain MRI showed slight signal abnormality in bilateral periventricular regions which could be due to delayed myelination. Ophthalmological examination has not been performed. Auditory evoked potential (AEP) and Otoacoustic Emissions (OAE) were normal. Oligonucleotide Array Comparative Genomic Hybridization (OaCGH) did not show any chromosomal abnormality.

2. Results

Exome sequencing revealed homozygous missense and nonsense mutations (c.1057 G > A, p.Gly353Arg and c.631C> T, p.Gln211X) in the affected from family 8 and family 9 respectively. These variants were not seen in our in house exome database containing more than 1800 individuals (1000 of which are of matching Arab/Middle East descent), nor were they recorded in the NHLBI Exome Variant server, the ExAC database (http://exac.broadinstitute.org/) or in any public SNP database. The mutations were confirmed by Sanger sequencing of all samples from the families to both validate the variant and verify that the mutations segregated according to a strictly recessive model with full penetrance. Tested parents were confirmed to be heterozygous carriers.

3. Discussion

Dystonia is seen only in a few HSPs including SPG35, SPG3A, and SPG56.[11,7,12,6,13] From the fourteen reported cases of SPG56, only two had dystonia without further specification. Here we report two unrelated families with SPG56 in which dystonia is associated with HSP.

Both of our patients developed normally until the age of 11 months and had begun to walk with support until they both regressed rapidly with walking on tip-toe as the initial sign. Both eventually lost almost all of their motor skills. This severe type of motor regression exceeds the phenotype in previously reported cases.

For both cases, brain MRIs showed delayed myelination at age four and three years and so SPG56 is similar to SPG44 and Pelizaeus-Merzbacher disease. MRI abnormalities reported in previous cases included white matter lesions and globus pallidus hypointensities without further specification on myelination.

Intellectual disability is a variable feature in SPG56. Three out of twelve previously reported cases had intellectual disability. In our patients, Case 1 has normal intelligence, while Case 2 is still not able to speak at age four, hindering a detailed analysis of intellectual ability.

Among previously published families, only one of several affected siblings developed dystonia despite sharing an identical *CYP2U1* genotype. However, both of our cases had activity induced dystonia in the face as well as upper and lower limbs. Thus, we suggest that dystonia is more common in SPG56 than previously recognized with about a quarter of patients with *CYP2U1* mutations showing dystonia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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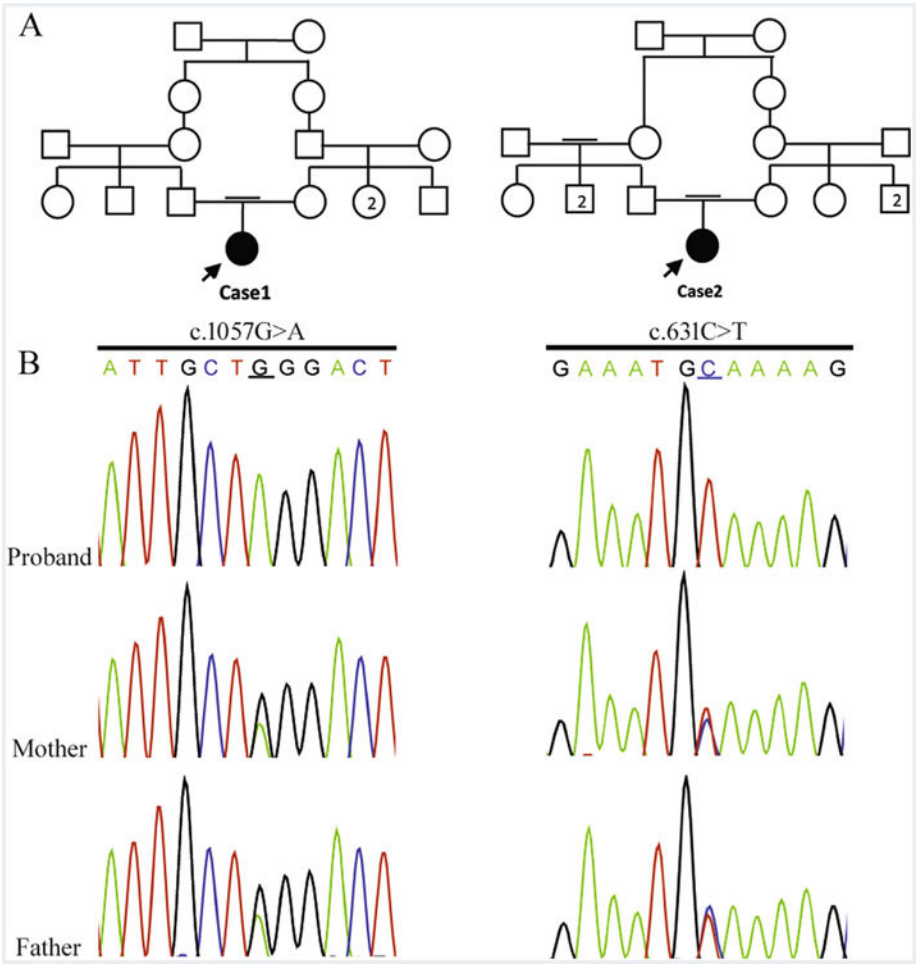

Fig. 1. Pedigree and electropherogram from case 1 and 2

Table. 1

Clinical findings in patients with confirmed CYP2U1 mutations

	Family 1 Tesson et al.						Family 2 Tesson et al.		Family 3 Tesson et al.	Family 4 Tesson et al.		Family 5 Citterio et al.	Family 6 Leonardi et al.			Family 7 Masciullo et al.	Family 8 Present case	Family 9 Present case
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**	**Case 9**	**Case 10**	**Case 11**	**Case 12**	**Case 13**	**Case 14**	**Case 15**	**Case 16**	**Case 17**	**Case 18**
Ethnicity	Saudi Arabia	Saudi Arabia	Saudi Arabia	Saudi Arabia	Saudi Arabia	Saudi Arabia	Egypt	Egypt	Italy	Spain and Vietnam	Spain and Vietnam	NR	Italy	Italy	Italy	Italy	Iran	Iran
Sex	M	F	F	F	F	M	M	M	M	F	M	NR	M	F	M	F	F	F
Age	33 y	21 y	18 y	11 y	25 y	21 y	12 y	5y	31 y	29 y	27 y	NR	50 y	46 y	42 y	16 y	15 y	4y
Onset	3y	5y	1.5 y	8 m	Birth	5 y	1.5 y	Birth	8 y	13 m	16 m	18 m	25 y	30 y	30 y	15 m	11 m	11 m
First symptom	Delayed walking, spastic gait	Unsteadiness, Spastic gait	Delayed walking, Unsteadiness	Delayed walking, spasticity	Delayed walking, toe walking	Toe walking	Unsteady gait, tip-toe walking	Spasticity since birth	Cannot run, frequent falls	Delayed walking, spastic gait	Spastic gait	Developmental delay	Visual impairment	Visual Impairment	Visual Impairment	Delayed motor development	Regression, loss of acquired skills	Regression, loss of acquired skills
Age at walking	3y	1.5 y	1,5 y	Never walked	6y (after surgery)	1 y	2 y	Never walked	2 y	Delayed	Normal	NR	Normal	Normal	Normal	2 y	5 y	Not yet
Intellectual Disability	−	−	−	+	−	−	−	No speech	−	+	+	Normal except for expressive language delay	−	−	−	mild	−Speech delay	+
Lower limb hyperreflexia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Babinski	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Lower limb weakness	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	−	−	−	−	+	−
Upper limb hyperreflexia	−	−	−	+	+	+	−	−	+	+	+	−	−	−	−	−	+	+
Upper limb weakness	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Clumsiness in fine movements	−	−	−	−	+	−
Dystonia	−	−	−	+	−	−	−	+	−	−	−	−	−	−	−	−	+	+
Visual impairment	−	−	−	−	−	−	−	−	−	+	−	−	+	+	+	−	−	−
Dysarthria	−	−	−	−	−	−	−	−	−	Yes, mild	Yes, mild	−	+	+	−	−	+	No speech
Drooling	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	−	−	−	−	+	+
Disability Stage (at age)	2 (30 y)	2 (21 y)	2 (18 y)	6 (11 y)	5 (25 y)	2 (21 y)	4	4	2 (28 y)	6 (16 y)	5	5	8/52 (50 y)	7/52 (46 y)	5/52 (42 y)	3	5 (15 y)	5 (4 y)
Brain MRI	ND	Normal	Normal (17 y)	Normal (10 y)	ND	ND	Normal (5 y)	TCC, WMLs, mild cortical changes, (2.5 Y)	Normal (28 y)	Normal (14 y), then WMLs and globus pallidus hypointensities (26 y)	WMLs and globus pallidus hypointensities (26 y)	Normal	Mild brainstem and cerebellar atrophy, thin corpus callosum	NR	Normal	Normal	Delayed myelination (4 y)	Delayed myelination (3 y)
Spinal MRI	ND	Normal	Normal (17 y)	Normal (10 y)	ND	Normal	Normal (4 y)	ND	Normal (28 y)	Normal	Normal	NR	NR	NR	NR	Dorsal hydromyelia	Normal (4Y)	ND
Nerve Conduction Studies (at age)	ND	Subclinical axonal neuropathy (21 y)	Subclinical axonal neuropathy (18 y)	Subclinical axonal neuropathy (10 y)	Subclinical axonal neuropathy (25 y)	Subclinical axonal neuropathy (21 y)	Normal	Normal	Normal (28 y)	ND	ND	Chronic neurogenic signs	Subclinical axonal sensory motor neuropathy	NR	Normal	Normal	Mixed sensory-motor neuropathy (10 y)	ND
Mutation	c.947A > T p.Asp316Val Homozygous	c.947A > T p.Asp316Vals Homozygous	c.947A > T p.Asp316Val Homozygous	c.947A > T p.Asp316Val Homozygous	c.947A > T p.Asp316Val Homozygous	c.947A > T p.Asp316Val Homozygous	c.61_73 p.Leu21Trpfs1 Homozygous	c.61_73 9 p.Leu21Trpfs19 Homozygous	c.1139A > G p.Glu380Gly Homozygous	c.784T > C pCys262Arg c. 1462C > T p.Arg488Trp	c.784T > C pCys262Arg c. 1462C > T p.Arg488Trp	c.1A > C, p.Met1 Homozygous	c.1168C > T p.R390 Homozygous	c.1168C > T p.R390 Homozygous	c.1168C > T p.R390 Homozygous	c.5C > A p.S2 c.1288+5G > C compound heterozygote	c.1057G > A p. Gly353Arg Homozygous	c.631C > T p.Gln211X Homozygous

The following abbreviations are used: F, female; M, male; m, months; ND, not done; NR, not reported; TCC, thin corpus callosum, WML, white matter lesion; y, years.

Disability scale: 1, minimal disability (slight stiffness of the legs); 2, mild disability (unable to run but full autonomy); 3, moderate disability in walking (reduced perimeter and frequent falls); 4, severe disability (unilateral assistance required for walking); 5, bilateral assistance required for walking; 6, wheelchair bound; and 7, bedridden.