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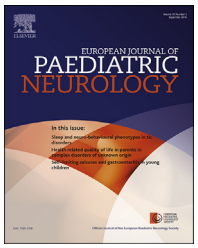

Case Study

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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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 interfamilial variability. 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.

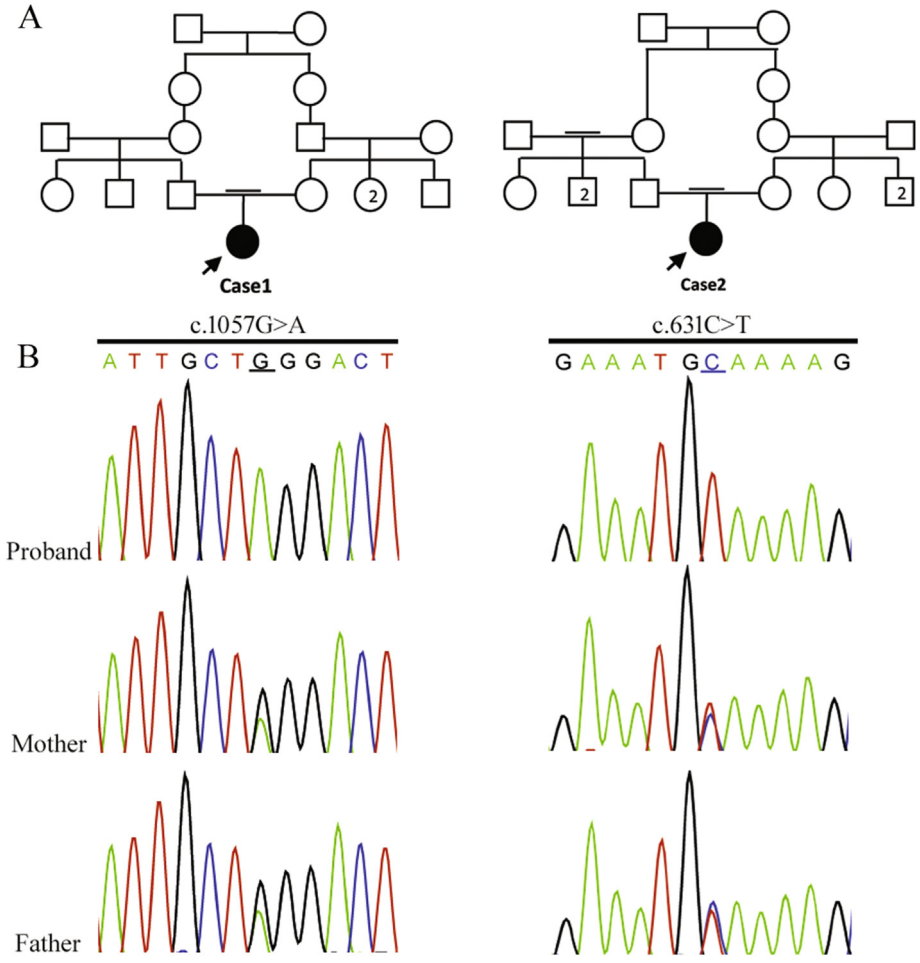

Fig. 1 – Pedigree and electropherogram from case 1 and 2.

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