# HEREDITARY SPASTIC PARAPLEGIA: NOVEL MUTATIONS AND EXPANSION OF THE PHENOTYPE VARIABILITY IN SPG56

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## Introduction

*We describe a novel sporadic case of SPG56, a rare complicated form of HSP, that expands the clinical and molecular spectrum of the disease, being associated to novel mutantions in CYP2U1 and showing as novel feature dorsal hydromyelia at spinal cord MRI*

## Methods

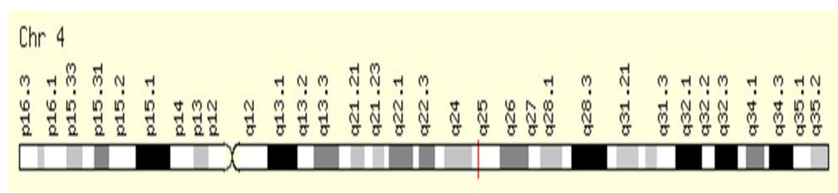
*Neurological assesments included the Spastic Paraplegia Rating Scale (SPRS), and Wechsler Adult Intelligence Scale (WAIS), neurophysiological and neuroimaging studies. Targeted next-generation sequencing panels for the whole set of genes associated with HSP were performed in the probands and her relatives*

## Results

*The patient presented an early-onset, slowly progressive paraparesis associated with mild mental retardation. Neuroimaging studies showed dorsal hydromyelia but no brain MRI abnormalities. Targeted next-generation identified two novel mutations: the c.5C>A/p.S2* on the maternal allele in compound heterozygosity with the paternally-inherited c.1288+5G>C in CYP2U1. Both mutations predict early protein truncation and a loss of function and were absent in publically available large exome databases including ESV6500 (evs.gs.washington.edu) and ExAC (exac.broadinstitute.org).*
*Until now, a very few patients affected by SPG56 have been described. In our SPG56 patient we detected two novel mutations in CYP2U1, both of which are predicted to be deleterious for gene expression.*
*Regarding the phenotype, our patient shared features reported in SPG56 patients, in particular the early-onset of symptoms and the cognitive involvement, whereas she did not show any peripheral nerve involvement and brain MRI was completely normal.*
*Interestingly, as novel associated neuroimaging finding, she manifested a condition of hydromyelia at spinal cord MRI. We propose that the presence of hydromielia would not be a casual association but rather it may be part of the complicated phenotype of SPG56 in our patient: in fact, CYP2U1 encodes an enzyme involved in phospholipid metabolism, whose integrity appears critical for mitochondrial structure and dynamics. Interestingly , the diagnosis of hereditary HSP was delayed in our patient, as dorsal hydromielia was initially thought to be the cause of spastic paraparesis: however she suffered of a progressive spastic paraparesis with associated abnormal MEP not associated to an evolving dilation of the central canal over time, thus supporting that hydromyelia is not the cause of spastic paraplegia in such case.*

**Exon Structure for CYP2U1**

| Id | Chromosome | Contig | Strand | Exon Start | Exon End |
|---|---|---|---|---|---|
| 113612 | 4 | HuRef | + | 104584305 | 104584387 |
| 113612 | 4 | HuRef | + | 104584388 | 104584877 |
| 113612 | 4 | HuRef | + | 104597714 | 104598349 |
| 113612 | 4 | HuRef | + | 104600120 | 104600281 |
| 113612 | 4 | HuRef | + | 104602094 | 104602261 |
| 113612 | 4 | HuRef | + | 104602989 | 104603167 |
| 113612 | 4 | HuRef | + | 104603168 | 104606201 |
| 113612 | 4 | | + | 107931561 | 107931643 |
| 113612 | 4 | | + | 107931573 | 107931643 |
| 113612 | 4 | | + | 107931644 | 107932133 |
| 113612 | 4 | | + | 107931644 | 107932187 |
| 113612 | 4 | | + | 107944970 | 107945605 |
| 113612 | 4 | | + | 107947376 | 107947537 |
| 113612 | 4 | | + | 107949350 | 107949517 |
| 113612 | 4 | | + | 107950245 | 107950423 |
| 113612 | 4 | | + | 107950424 | 107953457 |
| 113612 | 4 | | + | 107950424 | 107953461 |
| 113612 | 4 | CHM1_1.1 | + | 108829176 | 108829258 |
| 113612 | 4 | CHM1_1.1 | + | 108829259 | 108829748 |
| 113612 | 4 | CHM1_1.1 | + | 108842600 | 108843235 |
| 113612 | 4 | CHM1_1.1 | + | 108845006 | 108845167 |
| 113612 | 4 | CHM1_1.1 | + | 108846980 | 108847147 |
| 113612 | 4 | CHM1_1.1 | + | 108847875 | 108848053 |
| 113612 | 4 | CHM1_1.1 | + | 108848054 | 108851087 |




## Conclusions

*This case, expands and further characterizes the clinical and molecular spectrum of SPG56. In this regard, in consideration of the putative gene function in neurodevelopment, we suggest a causal association between CYP2U1 mutations and hydromyelia in our patient.*

## Bibliography

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