

# Blended Phenotype of Prader-Willi Syndrome and HSP-*SPG11* Caused by Maternal Uniparental Isodisomy

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## Abstract

### Objective

Uniparental isodisomy can lead to blended phenotypes of imprinting disorders and autosomal recessive diseases. To determine whether a presentation of Prader-Willi syndrome (PWS) and progressive neurologic symptoms was caused by uniparental isodisomy, a detailed clinical and molecular characterization was performed.

### Methods

A combination of clinical, molecular, and imaging data was included in this study.

### Results

We present the case of a 12-year-old boy with a blended phenotype of PWS and hereditary spastic paraplegia type 11 (HSP-*SPG11*) caused by maternal uniparental isodisomy of chromosome 15 (UPiD(15)mat) covering a loss-of-function variant in *SPG11* (NM\_025137.4: c.733\_734del; p.Met245ValfsTer2). Although symptoms in early childhood including hypotonia, global developmental delay, hyperphagia, obesity, and seizures were consistent with PWS, additional features of progressive spastic paraparesis, parkinsonism, and cognitive decline in later childhood were atypical. Brain MR imaging showed thinning of the corpus callosum and signal abnormalities of the forceps minor, consistent with a “ears of the lynx” sign. Exome sequencing confirmed a frameshift variant in *SPG11* located in the PWS imprinting region on chromosome 15.

### Discussion

This case highlights that atypical clinical features in patients with well-described imprinting disorders should lead to investigations for recessive conditions caused by variants in genes that localize to the region of homozygosity, including autosomal recessive forms of HSP.

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## Glossary

HSP = hereditary spastic paraplegia; PWS = Prader-Willi syndrome; SPG11 = spastic paraplegia type 11; UPD = uniparental disomy.

Prader-Willi syndrome (PWS) is a rare genetic disease that typically presents with severe hypotonia and feeding difficulties in early infancy, followed by hyperphagia and obesity in early childhood. Global developmental delay/intellectual disability and behavioral symptoms are common, but severity is variable. Endocrinological features include hypothalamic hypogonadism and short stature.<sup>1</sup>

While most cases with PWS result from the absence of paternally expressed imprinted genes on chromosome 15 through paternal deletion, less is known about PWS arising from maternal uniparental isodisomy (UPiD(15)mat). In addition to the disruption of parent-specific imprinting, uniparental disomy (UPD) also creates homozygous genomic regions and may therefore unmask recessive phenotypes. Hereditary Spastic paraplegia type 11 (HSP-SPG11)<sup>2</sup> is an autosomal recessive, early-onset, and complex form of HSP caused by variants in *SPG11*, which is located on chromosome 15 in the PWS imprinting region.<sup>3</sup> In this study, we report a blended phenotype of PWS and HSP-SPG11, caused by UPiD(15)mat.

## Methods

This study was approved at Boston Children's Hospital (IRB-P00033016).

## Case History

The patient was born at term without prenatal or perinatal complications to nonconsanguineous African American parents. There was no significant family history. The first concerns arose in infancy when he presented with axial hypotonia, delayed motor milestones (unsupported sitting at 11 months; standing at 18 months; and walking at 25 months), and motor stereotypies. Speech development was delayed, but he made steady progress

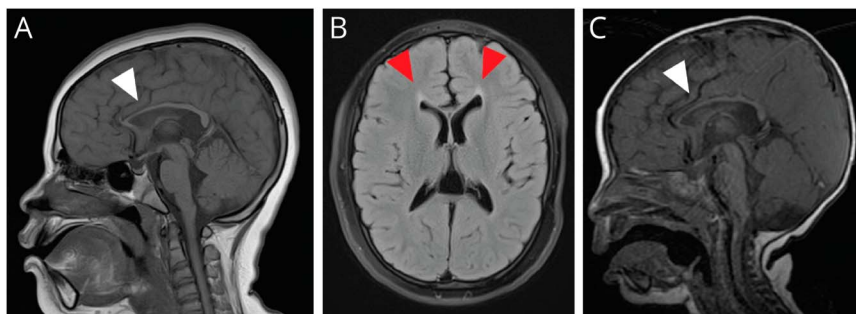
without evidence of regression. At the age of 7 months, he presented with focal impaired awareness seizures, treated with oxcarbazepine and later topiramate. Approximately at the age of 2 years, he developed hyperphagia and obesity, gaining 13 pounds in 5 months. Given the combination of hypotonia, developmental delay, hyperphagia and obesity, he was suspected to have PWS. Chromosomal microarray and DNA methylation testing confirmed PWS due to maternal UPD (UPiD(15)mat).

At the age of 8 years, the patient developed lower extremity weakness and spasticity, initially asymmetric, followed by progressive gait difficulties, dysarthria, bradykinesia, and cognitive deterioration over the course of several months. There was no clear trigger, though there was a mild febrile illness at the onset of this decline. Laboratory studies (including creatine kinase, vitamin B<sub>12</sub> levels, thyroid function tests, c-reactive protein, erythrocyte sedimentation rate, routine CSF studies, serum, and CSF autoimmune encephalitis panels) were normal. Brain MR imaging showed thinning of the anterior corpus callosum (Figure, A) and periventricular white matter, as well as fluid-attenuated inversion recovery hyperintensity in the forceps minor, characteristic of the ears of the lynx sign (Figure, B).

A retrospective review confirmed that a thin corpus callosum was already present on MRI scans obtained at the ages of 8 months and 2 years (Figure, C). Spine MR imaging was unremarkable. EEG showed rare right frontal sharp waves but no other epileptiform discharges or seizures.

Because these symptoms were atypical of PWS (Table), exome sequencing was pursued, showing a maternally inherited pathogenic variant (American College of Medical Genetics and Genomics criteria: PP5, PSV1, and PM2) in *SPG11* (NM\_025137.4: c.733\_734del; p.Met245ValfsTer2). This variant was present in a homozygous state due to UPiD(15)mat.

## Figure Neuroimaging Findings



(A) Sagittal T1-weighted image at the age of 12 years showing a thin corpus callosum with predominant thinning of the anterior parts (white arrowhead). (B) Axial T2-fluid-attenuated inversion recovery image at the age of 12 years showing hyperintense signal in the forceps minor (red arrowheads). These signal changes resemble the shape of the ears of a lynx with their characteristic apical hair tuft and have been designated the "ears of the lynx" sign. (C) Sagittal T1-weighted image at the age of 8 months shows that thinning of the corpus callosum (white arrowhead) was present even at this early age

**Table** Blended Phenotype Caused by UPiD(15)mat and a Loss-of-Function Variant in *SPG11* (NM\_025137.4: c.733\_734del; p.Met245ValfsTer2)

| Prader-Willi syndrome  | Hereditary spastic paraplegia type 11 (HSP-SPG11)         |
|--|---|
| Axial hypotonia  |   |
| Developmental delay/intellectual disability (progressive cognitive decline in HSP-SPG11) |   |
| Seizures (infrequent)  |   |
| Behavioral problems  | Progressive spasticity                                    |
| Hyperphagia and obesity in early childhood   | Parkinsonism  |
| Hypogonadism   | Dysarthria and dysphagia                                  |
| Short stature/growth hormone deficiency  | Brain MRI: thin corpus callosum and ears of the lynx sign |

Between the ages of 8 and 12 years, there was a steady, though slower, progression of symptoms. Now at the age of 12 years, the patient experiences spastic diplegia, moderate to severe dysarthria, dysphagia, and urinary urgency and incontinency. He is able to ambulate short distances with assistance but requires a wheelchair outside the home. Examination is notable for weakness and spasticity in both legs (Modified Ashworth Scale of 2–3), fixed contractures of the ankles, as well as parkinsonism with hypophonia, hypomimia, bradykinesia, a rest and postural tremor of the hands, and asymmetric rigidity in the upper extremities. The Spastic Paraplegia Rating Scale score is 41. Baclofen and levodopa-carbidopa led to moderate symptomatic improvement.

## Discussion

This report highlights that atypical clinical features in patients with imprinting disorders due to isodisomy may be related to the unmasking of autosomal recessive disorders caused by genes localized to the region of homozygosity, including HSP.<sup>4,5</sup> Our report adds to the list of blended phenotypes of PWS and recessive disorders, which thus far includes Tay-Sachs disease,<sup>6</sup> Bloom syndrome,<sup>7</sup> and congenital ichthyosis.<sup>8</sup> Progressive spastic diplegia, dysarthria, parkinsonism, and cognitive regression are not part of the typical spectrum of neurologic symptoms seen in PWS, but they are features of autosomal recessive complex HSP, including HSP-SPG11. A thin corpus callosum and ears of the lynx sign, while not entirely specific to SPG11 (because also found in HSP-ZFYVE26<sup>9</sup> and the AP-4-associated HSPs<sup>10</sup>), provided an early diagnostic clue in this case. Of interest the rate of neurologic decline in this patient was faster compared with what is typically seen in SPG11, which may be part of this unique blended phenotype. Taken together, these clinical observations highlight the importance of pursuing additional genetic testing for recessive diseases in patients with imprinting disorders when presenting with features outside of well-described syndromes. Our report adds to the growing recognition of diseases resulting from multilocus genomic variation.<sup>11</sup>

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## Disclosure

A.R. Kunta, J. Jueng, C. Jordan, J. Kojic, A. Mo, and D. Ebrahimi-Fakhari report no disclosures relevant to the manuscript. Go to [Neurology.org/NG](http://Neurology.org/NG) for full disclosures.

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