Symptomatic Female Spastic Paraplegia Patient with a Novel Heterozygous Variant of the PLP1 Gene

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Spastic paraplegia (SPG) is a genetically heterogeneous disease entity that comprises more than 70 subtypes based on the causative gene. SPG2 is one such subtype and it is associated with the mutation of the X-linked PLP1 gene that affects men. SPG2 mainly manifests as paraparesis with or without central nervous system (CNS) involvement. However, Pelizaeus–Merzbacher disease (PMD), a severe form of disease associated with the PLP1 gene, manifests with broad-spectrum symptoms, including early-onset nystagmus, hypotonia, cognitive impairment, and shortened life span. Making a final diagnosis of PMD or SPG cannot be based solely on physical symptoms and requires genetic analysis. Here, we examine an unusual case of a female patient with spastic paraplegia and minimal CNS involvement. Using whole-exome sequencing (WES), we identified a novel heterozygous duplication mutation in PLP1, causing the condition.

The proband was a 47-year-old unmarried female. She has nonconsanguineous parents. The proband first visited the department of neurology at the age of 42, presenting gait disturbance and voiding difficulty. These symptoms started manifesting in her early adulthood. As a child, the proband could not run fast. In her late 30s, she complained of weakness in her legs but remained ambulatory. She underwent transverse carpal tunnel release surgery at the age of 36. She has one younger sister and two brothers: None of them have complaints regarding gait disturbance [Figure 1a]. A neurologic examination taken at the age of 43 revealed weakness in the bilateral legs. The weakness in the hip and knee joint movement was grade four based on the Medical Research Council grade. Other parts of limbs appeared normal. The knee jerk increased to 4+ and pathologic reflexes including Babinski sign and ankle clonus were positive, revealing an upper motor neuron disorder. However, the proband showed no nystagmus or any cognitive impairment.

Brain magnetic resonance imaging performed at the age of 41 showed high intensities on the internal capsule posterior limb and optic radiations on fluid-attenuated inversion recovery image [Figure 1b]. Nerve conduction studies (NCS) demonstrated slow sensory (28.1–38.8 m/s at the distal part of median and ulnar nerves) and motor (36.6–49.5 m/s in the upper extremities) conduction velocities, with markedly prolonged terminal latency of the bilateral median nerve (>6.0 ms). Somatosensory evoked potential tests showed a central conduction defect in the left median and bilateral tibial nerve stimulations.

She has been clinically diagnosed to have spastic paraplegia and has remained genetically undiagnosed so far. At the age of 46, we performed commercially available WES. Briefly, the DNA samples extracted from white blood cells were captured by an Agilent SureSelect Human All Exon V6 (Santa Clara, California, USA) and the captured libraries were sequenced through an Illumina NovaSeq 6000 (San Diego, California, USA). This analysis identified the novel heterozygous variant c. 520dupG (p.Val174Glyfs*30, NM_000533.5, chrX: 103,042,793 on GRCh 37, Supplementary materials 1 and 2) of PLP1 in this patient: This variant is not listed on the Genome Aggregation Database (gnomAD) or Leiden Open Variation Database (https://databases.lovd.nl/shared/genes/PLP1). This variant is classified as “pathogenic,” according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines, satisfying one very strong and one strong evidence, a null variant (nonsense) in a gene whose loss of function is a known mechanism of disease and de novo (both maternity and paternity confirmed) in a patient with the disease and no family history, respectively.

Sanger sequencing showed the wild type in asymptomatic family members; thus, de novo mutation in the patient was confirmed [Figure 1c].

We were able to establish SPG2 as the diagnosis through WES. Moreover, the variant, c. 520dupG in PLP1, has not been
reported yet. The patient did not present CNS involvement or nystagmus except spasticity; therefore, this variant can be associated with the SPG phenotype rather than PMD.

The clinical spectrum of PLP1-related disorders includes severe connatal PMD, intermediate classical PMD, and mild phenotype of SPG. Although a genotype–phenotype correlation is complicated, missense mutations affecting highly conserved amino acids are generally associated with severe PMD, which is implicated by the pathomechanism of protein misfolding, endoplasmic reticulum retention, trafficking errors, and ultimately oligodendrocytic death. PLP1 duplications correlate to classic PMD. Several animal experiments of PLP1 duplications suggested evidence for dysfunction, including myelin swellings, oligodendrocyte maturation arrest, and fewer oligodendrocyte differentiation processes. Interestingly, the disease severity in these mice models is proportional to the proteolipid protein (PLP) expression level. Reduced PLP expression results in mild phenotypes, SPG or PLP1-null phenotypes, which are caused by deletions, nonsense mutations, or mutations affecting splicing.

Regarding PLP1 heterozygous females, symptomatic carriers have been reported since 1910. The risk of symptomatic female carriers is significant for the null expression of PLP by insertions, deletions, or nonsense mutations. Furthermore, other types of mutations have also been reported in symptomatic female carriers, including duplications or missense mutations. Similar to clinical severity in females with homozygous PLP-null mutations, in female carriers with diminished PLP expression it is mild. This can be explained based on PLP-mutant oligodendrocytes or the domination of wild-type cells.

SPG2 patients may exhibit peripheral polyneuropathy. Most such cases are axonal neuropathies caused by the disruption of the PLP-mediated axonal-glial interaction. However, some SPG2 patients show mixed axonal and demyelinating peripheral polyneuropathies. Interestingly, although peripheral polyneuropathy often occurs in patients with diminished PLP expressions, it rarely occurs in patients with PLP1 duplications. Some PMD patients carrying null mutations also exhibit demyelinating peripheral polyneuropathies with mild clinical severity. Our patient showed findings of demyelination during NCS. This observation echoes the results of a previous report. The exact pathomechanism of demyelination in peripheral nerves is not yet fully understood.

We reported a novel PLP1 mutation associated with SPG2. The patient presented with relatively mild clinical features but a definite symptom of SPG, which has a heterozygous variant,
resulting in premature truncation. Genetic analysis of more female SPG2 cases will help expand the genotype spectrum.

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Conflicts of interest
There are no conflicts of interest.

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The insertion of guanine is identified at the chrX: 103,042,794 on GRCh 37.

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| DNA change | Protein       | DNA change (hg19) | Condition | Reference          |
|-----------|---------------|------------------|-----------|--------------------|
| c. 1A > G | p.Met1Val     | g. 103031924A > G| PMD       | Plecko 2003        |
| c. 2T > C | p.Met1Thr     | g. 103031925T > C| SPG2      |                    |
| c. 92T > G| p.Leu31Arg    | g. 103040598T > G| PMD       | Martínez-Montero 2013|
| c. 98G > A| p.Cys33Tyr    | g. 103040604G > A| PMD       | Martínez-Montero 2013|
| c. 103T > C| p.Cys35Arg    | g. 103040609T > C| PMD       | Hübner 2005        |
| c. 115G > A| p.Ala39Thr    | g. 103040621G > A| PMD       | Hübner 2005        |
| c. 128C > T| p.Thr43Ile    | g. 103040634C > T| PMD       | Martínez-Montero 2013|
| c. 137T > C| p.Leu46Pro    | g. 103040643T > C| PMD       | Hübner 2005        |
| c. 140T > C| p.Ile47Thr    | g. 103040646T > C| SPG2      |                    |
| c. 149A > G| p.Tyr50Cys    | g. 103040655A > G| PMD       | Hübner 2005        |
| c. 157A > G| p.Lys53Glu    | g. 103040663A > G| PMD       |                    |
| c. 166C > T| p.Gln56*      | g. 103040672C > T| PMD       |                    |
| c. 169G > T| p.Asp57Tyr    | g. 103040675G > T| PMD       | Arena 1992         |
| c. 226G > C| p.Ala76Pro    | g. 103041428G > C| PMD       | Hübner 2005        |
| c. 238_240del| p.Phe80del   | g. 103041440_103041442del| SPG2 | Martínez-Montero 2013|
| c. 247G > A| p.Gly83Arg    | g. 103041449G > A| PMD       | Shimojima 2010     |
| c. 254T > C| p.Leu85Pro    | g. 103041456T > C| PMD       | Shimojima 2010     |
| c. 331C > A| p.Lys111Gln   | g. 103041453A > C| PMD       |                    |
| c. 365A > G| p.Lys122Arg   | g. 103041457A > G| SPG2      |                    |
| c. 370_374del| p.Arg124Phefs*78| g. 103041457_103041459del| PMD null syndrome | Martínez-Montero 2013|
| c. 385C > T| p.Cys139Serfs*15 | g. 103041458C > T| PMD       | Hübner 2005        |
| c. 409C > G| p.Arg137Gly   | g. 103041611C > G| PMD       |                    |
| c. 415_418delinsAGT| p.Gln129* | g. 103041587C > T| PMD       | Hübner 2005        |
| c. 418C > T| p.His140Tyr   | g. 103041620C > T| SPG2      | Bonneau 1993       |
| c. 422C > T| p.His148Tyr   | g. 103041644C > T| PMD       | Hübner 2005        |
| c. 481_482dup| p.Val162Leufs*37 | g. 103042754_103042755dup| PMD | Hübner 2005        |
| c. 485C > T| p.Val162Glu   | g. 103042758T > A| PMD       | Hübner 2005        |
| c. 489G > A| p.Trp163*     | g. 103042762G > A| SPG2      |                    |
| c. 508T > C| p.Ser170Pro   | g. 103042781T > C| PMD       | Hübner 2005        |
| c. 509C > T| p.Ser170Phe   | g. 103042782C > T| PMD       | Hodes 1998         |
| c. 517C > T| p.Pro173Ser   | g. 103042790C > T| PMD       | Hübner 2005        |
| c. 544A > C| p.Thr182Pro   | g. 103042817A > C| Strautnieks 1992|
| c. 560T > C| p.Ile187Thr   | g. 103042833T > C| SPG2      | Edgar 2004         |
| c. 613A > G| p.Arg205Gly   | g. 103042886A > G| -         |                    |
| c. 619T > C| p.Tyr207His   | g. 103042892T > C| SPG2      | Martinez-Montero 2013|
| c. 632del| p.Pro211Hisfs*25 | g. 103043375del| PMD       | Hübner 2005        |
| c. 670C > T| p.Leu224Phe   | g. 103043413C > T| PMD       | Martinez-Montero 2013|
| c. 671T > C| p.Leu224Pro   | g. 103043414T > C| -         |                    |
| c. 674T > C| p.Leu225Pro   | g. 103043417T > C| PMD       | Hübner 2005        |
| c. 709T > G| p.Phe237Val   | g. 103044274T > G| PMD       |                    |
| c. 710C > G| p.Phe237Ser   | g. 103044275T > C| SPG2      | Donnelly 1996      |
| c. 712_713insTGCAGTTCCAATG| p.His238Leufs*26 | g. 103044277_103044278insTGCAGTTCCAATG| PMD | Hübner 2005        |
| c. 716T > C| p.Leu239Pro   | g. 103044281T > C| PMD       | Hübner 2005        |
| c. 737G > C| p.Gly246Ala   | g. 103044302G > C| SPG2      | Hübner 2005        |
| c. 791A > T| p.Asn264Ile   | g. 103045483A > T| PMD       | Martínez-Montero 2013|
| c. 81T > C| p.Arg273*     | g. 103045509C > T| SPG2      |                    |

Exonally pathogenic variants filtered from the Leiden Open Variation Database (https://databases.lovd.nl/shared/genes/PLP1) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). PMD; Pelizaeus-Merzbacher disease, SPG2; spastic paraplegia 2

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