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Case Report Open Access

Spg3a Mutation Co-Segregates with Hereditary Spastic Paraplegia Phenotype Whereas SPG31 Duplication Does Not

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Abstract

Hereditary Spastic Paraplegia (HSP) is a heterogeneous group of inherited neurodegenerative disorders with weakness and spasticity of the lower limbs as its main clinical feature. This case presents the coexistence of two different mutations, a missense mutation in the SPG3A-gene, encoding atlastin 1, and a duplication of exon 2-7 in the SPG31-gene in a 4-year-old girl with muscle weakness and spasticity of the lower limbs, her symptomatic mother and maternal grandfather, while the asymptomatic brother only carries the SPG31 duplication. Duplications of exons 2-7 of SPG31, encoding the protein REEP, has previously been described to possibly cause autosomal dominant hereditary spastic paraplegia. In the family presented here, we conclude that the SPG3A-gene mutation co-segregated with HSP disease phenotype, whereas the SPG31 mutation did not.

Keywords: Hereditary spastic paraplegia; Paresis

Introduction

Hereditary spastic paraplegia (HSP), also called hereditary spastic paraparesis, familial spastic paralysis and Strümpell-Lorrain syndrome was first reported in 1876 by Seeligmüller, followed by reports by Strumpell and Lorraine. HSP is a heterogeneous group of neurodegenerative disorders with progressive lower limb spasticity and weakness leading to abnormal gait as the principal clinical feature [1]. HSP is generally classified as pure when lower limb spasticity and weakness, hyperreflexia, extensor-plantar responses, decreased vibration sense at the ankles, bladder dysfunction, pes cavus and scoliosis are the only signs; if there are additional neurologic or extraneurologic signs, it is classified as complicated HSP [2].

The primary neuropathology of pure HSPs is axonal degeneration of the long sensory and motor axons, affecting primarily the distal ends of the corticospinal tracts at the thoracic level, and the dorsal column fibers (especially fasciculus gracilis) at the cervico-medullary level [3]. Diagnosis is based on the following diagnostic criteria: 1) The presence of HSP symptoms (as listed above); 2) neurologic signs; 3) family history; and 4) exclusion of other disorders. However, to confirm HSPs, the only existing method is gene analysis and laboratory analysis, neuroimaging and neurophysiologic studies are performed to exclude other possible disorders. Differential diagnoses to have in mind are: cerebral palsy, structural disorders of the brain and spinal cord, disturbance of CNS white matter, infectious diseases, neurodegenerative disorders and environmental toxins [3,4].

The inheritance pattern of HSP can be autosomal dominant (AD), autosomal recessive and X linked. The most frequent cause of AD-HSP is mutation in the SPAST-gene (SPG4) and represents approximately 40% of the cases. The second most common mutation is found in the SPG3A gene (encodes atlastin1), accounting for approximately 10% of the cases, and mutations in the more recently identified SPG31-gene encoding for Receptor Expression-Enhancing Protein 1 (REEP1) are the third most common, representing between 2.3% and 6.5% of the cases [3,5-7]. The present report describes an unusual case of a 4-year-old girl with abnormal gait who carries two different mutations (on SPG3A and SPG31) described to possibly cause AD-HSP.

Case Report

The index case is a girl with muscle weakness and spasticity of the lower limbs. Birth and neonatal periods were normal. She sat independently at the age of 6 months and started walking at 14 months of age. At 18 months she started falling repeatedly and she was found to have waddling gait with internal rotation of the legs. Radiology of the hips was normal why expectation was recommended. The girl continued falling and her gait progressively worsened why she was sent to a neurologist at the age of three. The neurologic examination showed abnormal gait with internal rotation of the feet, she had no contractures and the patellar reflexes were brisk. She also had tendency to increased muscle tone in the lower limbs. Babinski sign was negative. Video gait analysis was performed, which showed internal rotation of the hips and feet while walking and running. When walking barefooted she dragged the upper side of her toes, this was more pronounced when running. With shoes, the plantar flexion was less evident and with ankle-foot-orthoses she stepped down plantigrade and could even step with the heels first. There was no big difference in the internal rotation of the legs between walking with orthoses or only shoes.

The first hypothesis was cerebral paresis with periventicular leukomalacia, although later rejected when neuroradiology was found normal. The family history of the girl was at the beginning unclear. The maternal grandfather was confined to a wheelchair since childhood, supposedly after being hit on the head, and the mother had abnormal gait since childhood although she had never been diagnosed. HSP was suspected and arrangements were made for further investigation. MRI of the brain was mainly normal though slight hypotrophy of the white substance along the posterior horns of the lateral ventricles was found; the pathological importance of this finding was doubtful. MRI of the spinal cord was performed with and without intravenous contrast, although no pathologic anomalies were found.

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Neurophysiologic studies were made to assess peripheral nerve and muscle involvement. Electroneuronography (ENeG) and quantitative electromyography were, however, normal. Genetic studies started with analysis of SPG4 since this is the most common cause of AD-HSP. The analysis of SPG4 was negative and supplementary request analysis was made for mutations in SPG2, SPG3A and SPG7. These genes were analyzed by PCR and sequencing of both DNA strands of the entire coding region and of the highly conserved exon-intron splice junctions. In addition, MLPA analysis was performed to test for large deletions in the SPG7 gene. These analyses revealed a nucleotide substitution, c.650G>A in the SPG3A gene [8], which leads to an amino acid change R217Q, previously reported in another patient with SPG3A [9]. In addition, four further nucleotide substitutions were detected that were classified as clinically irrelevant polymorphisms. MLPA analysis further revealed a duplication of exon 2-7 of the SPG31 gene. A similar mutation, duplication involving exon 2-7 of SPG31 (REEP), has been reported in an Irish family with HSP [10]. It was there suggested to be of pathogenetic significance, although not proven to be so. Due to the unknown significance of the SPG31 duplication, further testing of symptomatic and asymptomatic family members was performed.

Both parents, the grandfather and the two year older brother were tested, as well as a maternal uncle. The father, brother, and uncle were both asymptomatic while the grandfather was wheelchair-bound and the mother had abnormal gait. The results, summed up in Table 1, showed that the grandfather and the mother both carried the mutations on SPG3A and SPG31, while the brother only carried the duplication on SPG31 (Figure 1). The father and maternal uncle carried no mutation.

Discussion

Since the first reports of the disorder at the end of the 1800s, great advances have been made in understanding the molecular genetics of HSP, although there is still more to accomplish. At least 39 loci have been localized [2,4], 17 genes have been identified and numerous mutations associated with HSP have been found in the different genes. Most of the mutations are private, making it difficult to perform correlations between genotype and phenotype. Today it is possible to molecularly diagnose over 50% of the AD-HSP cases when tests are performed for SPG4 and SPG3A, which are the most recurrent mutations [11]. In addition, SPG6 (NIPA1), SPG8 (KIAA0196), SPG10 (KIF5A), SPG13 (HSPD1), SPG17 (BSCL2), SPG31 (REEP1) and SPG33 (ZFYVE27) can be analyzed. Despite the possibility to confirm the diagnosis with gene analysis it is important to have in mind that a gene analysis negative for mutations does not necessarily exclude HSP.

The identification of many different mutations in different genes, associated with HSP, and the proteins they encode suggest that there must be diverse pathways leading to axonal degeneration and specifically to degeneration of the long axons of the spinal cord. A number of different cellular pathogenic mechanisms have been proposed including abnormal intracellular trafficking and transport, altered cell recognition and signaling, abnormalities of myelination and mitochondrial abnormalities [12]. The mutations are thought to act through loss-of-function, however it is still being discussed if they act via haploinsufficiency or dominant negative effect.

Atlastin1, encoded by SPG3A has been reported to be localized to cis-golgi membranes and might be a functional golgi component [13]. In addition, atlastin1 has been reported to be implicated in neurite outgrowth, and ER and Golgi morphogenesis [4]. Beetz et al. [14] reported a case with four HSP affected family members, two of them carrying a deletion in SPG4 and SPG3A and the two other only carrying a deletion on SPG4. The finding suggested the SPG3A deletion to be

	Index case	Mother	Father	Brother	Maternal grandfather	Maternal uncle
Symptomatic:	+	+	-	-	+	-
SPG3A exon 1	wt					
SPG3A exon 2	SNP					
SPG3A exon 3	SNP					
SPG3A exon 4	SNP					
SPG3A exon 5	wt					
SPG3A exon 6	SNP					
SPG3A exon 7	**c.650G>A**	**c.650G>A**	**wt**	**wt**	**c.650G>A**	**wt**
SPG3A exon 8	wt					
SPG3A exon 9	wt					
SPG3A exon 10	wt					
SPG3A exon 11	wt					
SPG3A exon 12	wt					
SPG3A exon 13	wt					
SPG3A exon 14	wt					
SPG31 exon 1	wt					
SPG31 exon 2-7	Dup	Dup	wt	Dup	Dup	wt

Mutation analysis (Centogene, Rostock, Germany) of SPG3A (Atlastin) and SPG31 (REEP1). wt = wildtype, SNP = single nucleotide polymorphism, Dup = duplication of exons. Only mutations suspected to be of clinical significance were analyzed in relatives to index case.

Table 1: Summary of SPG3A and SPG31 mutations in the family of the index case.

a nonpathogenic polymorphism and therefore proposed it unlikely that haploinsufficiency would be a pathogenic mechanism in SPG3A-associated HSP. SPG31 encodes REEP1, for which in silico analysis has predicted two transmembrane domains, suggesting REEP1 is a mitochondrial membrane protein [6]. In a comprehensive screening of HSP and sporadic spastic paraplegia patients, 14 novel mutations were identified and the type of mutations were small insertion, deletions, splice site mutations, missense mutations and a large duplication. Many of these mutations led to pre-terminal stop codons, proposing haploinsufficiency to be a major molecular genetic mechanism in SPG31 [10].

Our patient, as well as her maternal grandfather and mother, carry two mutations described as possibly causative of AD-HSP (Figure 2 and 3).

In the family presented here, the SPG3A-gene mutation co-segregated with HSP disease phenotype, whereas the SPG31 mutation did not.

Interestingly, the mutations had co-segregated for three generations although the brother only carries the SPG31 duplication. Since the brother is still asymptomatic at 10 years of age, it is unlikely that the exon 2-7 duplication of the SPG31 gene is clinically relevant. It is more likely that it represents a duplication in a SPG31 pseudogene, alternatively represents a true SPG31-gene mutation leading to functional haploinsufficiency without clinical significance. It is also of interest to note that the affected girl carrying both mutations did not exhibit signs of peripheral nerve involvement in neurophysiological examination, which has been reported in SPG31-associated HSP [4]. All the symptomatic family members seem to have a SPG3A phenotype with childhood symptom-onset and pure HSP, supporting the hypothesis that they suffer from SPG3A-associated HSP and duplication of exon 2-7 represents an inactive pseudogene.

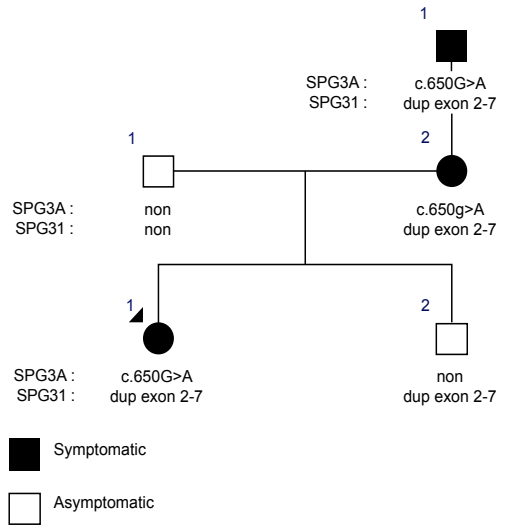

Figure 1: Pedigree illustrating mutations in SPG3A and SPG31 in affected and unaffected family members.

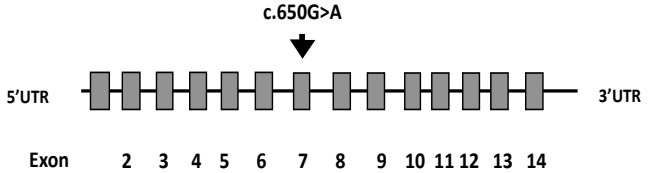

Figure 2: The index case carries a missense mutation, c.650G>A in the SPG3A gene. SPG3A is localized on chromosome 14q11-q21 and encodes atlastin1, a 558 amino acid protein with a molecular mass of 63.5 kD containing three conserved motifs (P-loop, DxxG and RD) characteristic of guanylate binding/GTPase activity.

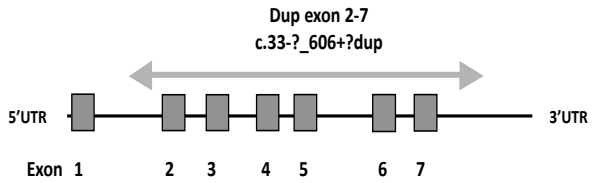

Figure 3: SPG31 is localized on chromosome 2p12 and encodes REEP1 which is localized to mitochondria. The duplication described here spans over exon 2-7.

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