De Novo Occurrence of Novel SPG3A/Atlastin Mutation Presenting as Cerebral Palsy

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Background: Mutations in the SPG3A gene (atlastin protein) cause approximately 10% of autosomal-dominant hereditary spastic paraplegia. For many subjects with an SPG3A mutation, spastic gait begins in early childhood and does not significantly worsen even over many years. Such subjects resemble those with spastic diplegic cerebral palsy. To date, only 9 SPG3A mutations have been reported.

Objective: To analyze the SPG3A coding sequence in an individual with childhood-onset spastic gait, who, prior to the birth of her similarly affected child, had no previous family history of hereditary spastic paraplegia.

Methods: The SPG3A coding sequence was analyzed in DNA samples from the proband, her affected child, her unaffected parents, and control subjects by polymerase-chain-reaction amplification of each exon followed by direct DNA sequencing. Seventeen microsatellite polymorphisms were amplified and analyzed to confirm reported paternity.

Results: We identified a novel SPG3A mutation (L157W) in the proband and her affected child. This mutation was absent in the proband’s unaffected parents. Results of microsatellite polymorphism analysis were consistent with paternity as reported. These results indicate that this novel SPG3A mutation arose de novo in the proband.

Conclusions: We report the de novo occurrence of a novel SPG3A mutation in a subject with childhood-onset, nonprogressive, spastic diplegia who had no previous family history of hereditary spastic paraplegia until the birth of her similarly affected son. Although rare, the occurrence of a de novo hereditary spastic paraplegia gene mutation must be considered in subjects with spastic diplegic cerebral palsy for whom no other cause is identified. This is extremely important for correct genetic counseling because recurrence risk may be as high as 50% when a mutation is detected.

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SPG3A gene (atlastin protein) mutations cause approximately 10% of autosomal-dominant hereditary spastic paraplegia (HSP). To date, only 9 SPG3A mutations have been reported. We report about a 34-year-old woman in whom childhood-onset, nonprogressive, spastic gait was considered to represent spastic diplegic cerebral palsy. The diagnosis was changed to autosomal-dominant HSP when her child developed similar symptoms at 10 months of age. Each subject was heterozygous for a novel SPG3A mutation (SPG3A cDNA nucleotide 638 T→C) that resulted in the substitution of tryptophan for leucine at amino acid 157 (L157W). Genetic analysis of the proband’s parents (unaffected) indicated that the mutation arose de novo in the proband. Although rare, the occurrence of de novo HSP gene mutation must be considered in subjects with spastic diplegic cerebral palsy for whom no other cause is identified.

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Methods:

A 34-year-old woman (subject II:3, Figure 1A) with nonprogressive spastic paraplegia dating to infancy and her 8-year-old son (subject III:1, Figure 1A), for whom spastic paraplegia was observed before age 1 year, presented for evaluation and genetic counseling. Each individual was the product of full-term, uncomplicated gestation, labor, and delivery. There was no parental consanguinity. Neurologic examination of the woman and her son revealed brisk lower limb tendon reflexes, clonus, and waddling gait with normal bulbar and upper limb function, normal bowel and urinary control, and normal intelligence. Diagnostic evaluation results, including those of a computed tomographic scan of the brain and routine laboratory studies, were normal for both the mother and child. A diagnosis of autosomal-dominant, uncomplicated, early-onset HSP was made on the basis of neurologic findings and family history.

Control subjects were older than age 60 years and had been interviewed and examined by neurology and psychiatry house officers. All subjects were found to be free of personal or family history of neurologic disease.

The DNA samples were prepared from peripheral blood samples from the proband (affected), her affected child, and each of her parents (unaffected subjects I:1 and I:2, Figure 1A). The SPG3A exon was polymerase-chain-reaction amplified and sequenced as previously described. Microsatellite polymorphisms (D1S199, D1S207, D1S238, D1S2697, D1S2868, D1S413, D1S425, D1S230, D1S199, D1S207, D1S238, D1S2697, D1S2868, D1S413, D1S425,...
D19S865, D19S1034, D19S216, D19S894, D19S120, D19S247, D19S922, D19S406, and D14S976) were amplified and analyzed as previously described.2

RESULTS

Sequence analysis revealed that the proband (affected) and her affected child were each heterozygous for a missense mutation at SPG3A complementary DNA (cDNA) position 638 (Figure 1B). This occurs in SPG3A exon 4 and substitutes tryptophan for leucine at amino acid 157 (L157W). The remainder of the SPG3A coding sequence, including intron-exon boundaries, was analyzed and found to be normal. Sequencing SPG3A exon 4 in samples from each of the proband’s parents and 100 control subjects did not reveal any mutation. Analysis of genotypes from 17 microsatellite polymorphisms (data not shown) were completely consistent with paternity as reported.

COMMENT

SP3A mutations cause approximately 10% of dominantly inherited, uncomplicated HSP. Among dominantly inherited HSP kindreds with early childhood onset, however, approximately 25% had SPG3A mutations.3 Ten SPG3A mutations have been reported (including the novel mutation described herein) (Figure 2). Analysis of emerging genotype-phenotype correlations may improve the ability to provide counseling to patients with SPG3A mutations. The very early onset of apparently nonprogressive spastic paraplegia in the present kindred is very similar to that observed in affected subjects with 247His→Pro,4 239Cys→Arg,1 and 258His→Arg,1 somewhat younger than in subjects with either 259Ser→Tyr (onset usually less than 5 years) (written communication, T. Heiman Patterson, November 2001) or 217Arg→Gln (average, 8.3 years),5 and significantly younger than in subjects with the frameshift mutation (1688insA) that causes premature translation termination at residue 522.5 Subjects with a 1688insA mutation reported symptoms beginning on average at age 18 years (range, 5-39 years).6 It is possible that relatively delayed onset of symptoms in subjects with a 1688insA mutation is due to some degree of residual atlastin function (which is terminated at residue 522 instead of 559). Both childhood-onset HSP and late-onset HSP (after age 40 years) occurred with the recently reported 161Ala→Pro mutation.4 This wide range of ages at symptom onset for unrelated subjects with the same SPG3A mutation indicates the influence of other modifying factors (presumably modifying genes) in determining the phenotype. Clinical information was not reported for the other known SPG3A mutations (151Phe→Ser and 315Ile→Ser).7

Figure 1. A, Hereditary spastic paraplegia (HSP) kindred with novel SPG3A mutation (L157W). Arrow indicates proband. B, SPG3A sequence results. cDNA indicates complementary DNA; nt, nucleotide.

Figure 2. SPG3A mutations in hereditary spastic paraplegia. The SPG3A coding sequence is divided into 14 exons (black boxes). The location of hereditary spastic paraplegia–specific SPG3A mutations is shown.
The presence of the mutation in the proband but not her unaffected parents raised the possibility of either nonpaternity or de novo mutation. Analysis of genotypes from 17 informative microsatellite polymorphisms (data not shown) were completely consistent with paternity as reported. This supports the occurrence of the proband’s novel SPG3A mutation as a de novo or spontaneous event.

The function of SPG3A’s encoded protein atlastin is unknown. As noted previously, atlastin contains conserved GTPase motifs and shows homology to human guanyl binding protein 1 (hGBP1). The novel SPG3A mutation we identified (T638C) disrupts a putative phosphorylation site, indicating the functional importance of this motif. The emerging “morbid map” (Figure 2) of SPG3A mutations may provide insight into important functional domains, which in turn gives clues to atlastin’s function and the molecular mechanisms that underlie HSP.

The early-onset and relatively nonprogressive nature of lower extremity spasticity in this family resembled that of spastic diplegic cerebral palsy. The proportion of subjects diagnosed with spastic diplegic cerebral palsy whose disorder is due to de novo SPG3A mutation subjects is unknown. Although rare, the occurrence of de novo HSP gene mutation must be considered in subjects with spastic diplegic cerebral palsy for whom no other cause is identified. This is extremely important for correct genetic counseling because recurrence risk may be as high as 30% when a mutation is detected, and families may be interested in using this information for prenatal genetic testing.

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