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Pure hereditary spastic paraplegia due to a de-novo mutation in the *NIPA1* gene

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Hereditary spastic paraplegia (HSP) is a group of diseases with heterogeneous mode of inheritance and is characterized primarily by progressive spasticity of the lower limbs due to degeneration of long pyramidal tract. HSP type 6 (SPG6) is caused by mutations in the *NIPA1* gene [1] (OMIM #600363) and accounts for less than 1% of autosomal dominant cases among Caucasians patients [2]. Traditionally, SPG6 was considered a pure (uncomplicated) form of HSP. Recent observations, however, expanded the phenotypic spectrum and linked *NIPA1* mutations to some cases of more complex forms of HSP [3, 4]. We report here a family with a pure form of HSP due to a *de novo* transition mutation in the *NIPA1* gene.

The three affected members of the family were a 46 year-old parent and two children, aged 21 and 15 years of age. They all developed slowly progressive spastic gait that started during the first half of their second decade of life. Medical history was absent except for mild delayed speech development and attention deficit in the younger child and a single questionable generalized seizure in the older child that was not documented on electroencephalogram. This episode included a sudden loss of consciousness, lasted only few seconds and was associated with tongue biting and twitching of the left fingers but

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without clear postictal period. The proband, 36 years after symptom onset, had difficulty ambulating and was assisted by a walker. Both children had spastic gait but walked without assistance. Neurological examination of the affected family members was significant for marked spasticity, mild weakness of hip extensors, bilateral ankle clonus, globally hyperactive deep tendon reflexes that were more prominent in the lower extremities and extensor plantar responses. Cognition, ocular movements and cerebellar functions were all normal.

Sequencing of the *NIPA1* gene (Athena Diagnostics, Inc) revealed in all the affected family members a point mutation causing transition from adenine to guanine (G→A) at position 316. This mutation led to an amino acid change, from glycine to arginine, in codon 106. This specific mutation has been previously reported as pathogenic [3, 5] of a pure form of HSP, although cases of complicated HSP with epilepsy have been also documented [3]. Other ancillary tests included brain MRI studies, genetic testing for other autosomal dominant HSPs (SPG3A, SPG4 and SPG31) and extensive metabolic work-up were all normal. An MRI study of the proband's thoracic spine showed spinal cord atrophy.

Lack of symptoms or clinical signs in the parents of the proband led us to test them for a mutation in the *NIPA1* gene (after they signed an informed consent for a research protocol approved by Columbia University IRB). The mutation was not present in the non-manifesting parents of the proband. True parenthood was confirmed using a panel of six highly informative unlinked microsatellite markers. To ensure specificity of this method, genetic polymorphism was also tested by three CEPH (1331-1, 1332-12, 1347-1) and showed perfect concordance.

This finding supports the hypothesis that this was a *de novo* mutation. According to our knowledge, *de novo* mutations were never documented to cause SPG6 although such mutations were sparsely documented in other HSPs [6]. This finding strengths the assumption that this is a pathogenic mutation and emphasizes the need to consider autosomal dominant HSP even in the absence of family history.

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