Clinical/Scientific Notes

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ATAXIA PLUS MYOCLONUS IN A 23-YEAR-OLD PATIENT DUE TO *STUB1* MUTATIONS

More than 1,000 mutations mapping to 60 different loci have been recognized as the cause of hereditary ataxias. However, almost 50% of the cases are still genetically uncharacterized, with etiology remaining to be identified.[1] Diagnosis and research in rare diseases such as ataxia has been significantly improved with the recent availability of next-generation sequencing technologies.[2] In order to expand the phenotype recently described in ataxia due to *STUB1* mutations and to illustrate the utility of clinical genomics in the diagnosis of ataxias, we present a 23-year-old patient who had ataxia plus myoclonus in whom exome sequencing revealed novel compound heterozygous mutations in the *STUB1* gene.

Case report. A 23-year-old man presented to consultation because of progressive development of gait impairment, dysarthria, dysphagia, and cognitive decline. He was born full term after an uneventful pregnancy from a nonconsanguineous family without history of neurologic diseases. His development, school performance, and social interaction were normal. Gait disturbance and deterioration of balance, dysarthria, and hand tremors insidiously and progressively developed when he was 15. Cognitive deficiencies started to be manifested 3 years later. Upon neurologic examination, the patient showed severe dysarthria, fractionated pursuit eye movements, hypometric saccades, and nystagmus without ophthalmoparesis. Assessment of other cranial nerves function was unremarkable. Axial and appendicular ataxia were overtly manifested, scoring 17 points on the Scale for the Assessment and Rating of Ataxia. The presence of increased tendon reflexes and pathologic signs in the 4 limbs suggested pyramidal tract dysfunction. Furthermore, the action and postural tremor in upper limbs and action and postural myoclonus in both hands and facial muscles was remarkable. Mnesic, attention failures, executive dysfunction, and low speed in information processing were formally revealed in the battery of neuropsychological tests administered. The clinical examination of other systems was unremarkable, without any sign of poor development of secondary sexual characteristics. MRI brain scans revealed cerebellar atrophy. Metabolic and endocrinologic studies did not show any abnormalities. Other genetic causes including spinocerebellar ataxia types 1, 2, 4, and 6, Friedreich ataxia, and secondary causes of ataxia were also discarded.

Whole-exome sequencing revealed no significant variants in a set of 136 genes, a priori selected as recognized or probable causes of ataxia (table e-1 on the *Neurology*® Web site at Neurology.org). However, using ANNOVAR's variant reduction script[3] (table e-2), we obtained a list of candidate genes harboring rare variants according to a recessive model where 2 heterozygous variants (c.612+1G>C and c.823C>G; p.Leu275Val) in *STUB1* gene were highlighted. We initially reported these mutations as potential causes of the patient's phenotype to the family but with diagnostic uncertainty.

Discussion. Two sisters with a syndrome of ataxia and hypogonadism, who were homozygotes for a pathogenic mutation in *STUB1*, were recently reported.[4] Our patient presented a progressive ataxia with accompanying myoclonus with a similar age at onset but without any evidence of hypogonadism. A spectrum of symptoms caused by *STUB1* mutations could thus be inferred, which does not always include hypogonadism.

STUB1 encodes the protein CHIP, which is a molecular co-chaperone and an E3-ligase involved in protein quality control processes via the ubiquitin-proteasome system. CHIP behaves as a molecular triage, managing the outcome of misfolded proteins.[5] CHIP dysfunction has been related to protein misfolding and aggregation in different genetic mouse models of neurodegenerative disorders, such as Alzheimer disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis.[6] Moreover, CHIP directly interacts and co-localizes with *ATXN1* and *ATXN3*, highlighting its putative role in ataxia's dysfunctional pathways.

To our knowledge, this is the second reported case of ataxia due to mutations in *STUB1* and the first showing ataxia plus myoclonus, expanding the phenotype of this new type of ataxia. Exome sequencing for rare disease diagnosis showed uncertain results in 70% of the cases.[7] However, it is a common occurrence that good candidate genes emerge from the analysis of the thousands of variants identified. A

Supplemental data at Neurology.org

typical clinical setting precludes the use of animal model or functional validation studies to allow the confirmation of pathogenicity. Nevertheless, both variants predict to be pathogenic (appendix e-1) and compromise the same protein domain that was disrupted in the first patient described with ataxia caused by *STUB1* mutations.[3] A frequent approach is to wait until another case is published in the literature; when similar genetic findings are observed, the uncertainty is reduced. Our case illustrates this common situation in clinical genomics and points to a possible explanation for the apparent low diagnostic yield of exome sequencing.

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1. Hersheson J, Haworth A, Houlden H. The inherited ataxias: genetic heterogeneity, mutation databases, and future directions in research and clinical diagnostics. Hum Mutat 2012;33:1324–1332.
2. Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. Nat Rev Genet 2013;14:681–691.
3. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res 2010;38:e164.
4. Shi CH, Schisler JC, Rubel CE, et al. Ataxia and hypogonadism caused by the loss of ubiquitin ligase activity of the U box protein CHIP. Hum Mol Genet 2013;23:1013–1024.
5. McDonough H, Patterson C. CHIP: a link between the chaperone and proteasome systems. Cell Stress Chaperones 2003;8:303–308.
6. Kumar P, Pradhan K, Karunya R, Ambasta RK, Querfurth HW. Cross-functional E3 ligases Parkin and C-terminus Hsp70-interacting protein in neurodegenerative disorders. J Neurochem 2012;120:350–370.
7. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med 2013;369:1502–1511.

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PRRT2 AND HEMIPLEGIC MIGRAINE: A COMPLEX ASSOCIATION

Hemiplegic migraine (HM) is a rare migraine subtype characterized by hemiparesis during the attack and is associated with at least 3 genes: *CACNA1A*, *ATP1A2,* and *SCN1A*.[1] Recent reports suggested that the proline-rich transmembrane protein *PRRT2* gene might be the fourth gene for HM.[2] In the vast majority of cases, *PRRT2* is associated with paroxysmal kinesigenic dyskinesia, benign familial infantile seizures (BFIS), or infantile convulsion choreoathetosis syndrome. In families with such a "typical *PRRT2* phenotype," HM was reported in a few *PRRT2* mutation carriers. Most of these cases also had a "typical *PRRT2* phenotype."[2] Vice versa, *PRRT2* mutations were found in 5 out of over 200 index cases with HM; 2 of these 5 *PRRT2* mutation carriers also had features of "typical *PRRT2* phenotypes."[3,4]

The discovery of *PRRT2* as a BFIS gene prompted us to reinvestigate a family with an *ATP1A2* mutation and partially cosegregating HM and BFIS (figure).[5] Although we originally attributed both disorders to the *ATP1A2* mutation, we now conclude that the *ATP1A2* mutation is only responsible for the HM and that the BFIS phenotype is caused by a *PRRT2* mutation. Because of this experience, we systematically and critically re-evaluated reports from literature suggesting that *PRRT2* mutations cause HM. Furthermore, we screened 14 index cases with familial HM, but no mutation in *CACNA1A*, *ATP1A2*, or *SCN1A*, for *PRRT2* mutations. We conclude that (1) contrary to our earlier report, a *PRRT2* mutation rather than the *ATP1A2* mutation is responsible for BFIS in our family; and (2) at present, there is insufficient evidence to support the claim that *PRRT2* is the fourth gene for (familial) HM.

Methods. The clinical and genetic information (on *ATP1A2*) of the family with HM and BFIS has been published before.[5] For the present study, we updated the clinical information on the 2 youngest generations and sequenced all 4 exons and flanking intronic sequences of *PRRT2* in all available DNA samples of this family and in 14 index cases of HM families that were negative for mutations in the *CACNA1A*, *ATP1A2*, and *SCN1A* genes, and which had not reported BFIS. The study was approved by the Medical Ethics Committee of Leiden University Medical Center and all participants provided informed consent.