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A SPLICING MUTATION IN THE *OPHN1* GENE CAUSES MENTAL RETARDATION AND CEREBELLAR HYPOPLASIA IN A THREE GENERATION ITALIAN FAMILY

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A three-generation family was referred to our clinic with two maternal cousins and an uncle affected by moderate mental retardation without facial dysmorphism. All patients had strabism and ataxic gait. A CT scan was available for the first cousin, who presented during infancy with triventricular hydrocephalus and cerebellar hypoplasia, while several brain NMR scans were performed on the other cousin, who also displayed marked hypoplasia of the cerebellar vermis and asymmetric hypoplastic cerebellar lobes. The X-linked pedigree and the presence of the cerebellar malformation suggested a mutation in the *OPHN1* gene, located in Xq12. Blood samples were obtained from patients, obligate and potential carriers as well as from three unaffected maternal uncles. Linkage analysis confirmed the location of the mutant gene between recombinant markers DXS991 (Xp11.21) and DXS990 (Xq21.32). We then performed a mutation screening on the entire ORF of the *OPHN1* gene by DHPLC and sequencing, detecting a 2-bp deletion at the start of intron 7 (IVS7+2_3delTA) that abolishes the donor splicing site. Subsequent sequencing of cDNA prepared from a new blood sample, confirmed the inclusion of 48-bp tract of intron 7, leading to production of a mutant *OPHN1* protein with 818 instead of 802 aminoacids. Expression of the mutant transcript was confirmed by real-time RT-PCR at increased levels. Western blot analysis suggests the presence of the mutant protein, whose function may be impaired by the 16-aminoacid insertion, that also undergoes partial degradation. To our knowledge this is the first case of a *OPHN1* mutation that does not result in the production of a truncated protein or in its complete loss.

Acknowledgements: We thank Dr. Pierre Billuart of the Department of Genetic and Development, Institut Cochin, Paris for the anti-*OPHN1* antibody.