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Clinical exome sequencing leads to the diagnosis of mitochondrial complex I deficiency in a family with global developmental delays, ataxia, and cerebellar and pons hypoplasia

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Exome sequencing was performed on a 14-year-old female and her 3-year-old sister with nystagmus, ataxia, global developmental delays, hyperreflexia, clonus and MRI findings of cerebellar and pons hypoplasia. The family history was otherwise unremarkable and there was no consanguinity. Nearly a decade of molecular, cytogenetic, and biochemical testing was uninformative in the girls. Exome sequencing however revealed compound heterozygous alterations of the *NUBPL* gene (c.311T > C; p.L104P & c.815-27T > C). The c.311T > C missense alteration is located at a highly conserved amino acid. The c.815-27T > C alteration has been reported previously, is located at a highly conserved nucleotide and previous in vitro analyses demonstrated splicing defects. The parents carried one alteration. The *NUBPL* gene was first discovered in association with mitochondrial complex I deficiency syndrome (CI-deficiency) (MIM_252010) in 2010 and has only been reported in two other families, both of which displayed clinical overlap with the two siblings in this family.

Exome sequencing is an especially powerful tool to aid in the diagnosis of unknown disorders. Novel genes are thought to account for a large portion of patients without a molecular diagnosis. It is not surprising that CI-deficiency was not considered in this family given the extreme clinical and genetic heterogeneity of the disorder. After nearly a decade of unsuccessful analyses, diagnostic exome sequencing led to a diagnosis for the family and more effective treatment with potent mitochondrial agents.

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