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The role of hypomorphic mutations in POLR3A in progressive sporadic and recessive spastic ataxia

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About half of patients with rare movement disorders such as hereditary spastic paraplegias and cerebellar ataxias remain genetically unexplained, implicating novel genes and unrecognized mutations in known genes. Non-coding DNA variants are suspected to account for a substantial part of undiscovered causes of rare diseases. Whole-exome sequencing findings in a recessive spastic ataxia family turned our attention to intronic variants in POLR3A, a gene previously associated with hypomyelinating leukodystrophy type 7. We screened a cohort of hereditary spastic paraplegia and cerebellar ataxia cases (n=618) for mutations in POLR3A and identified compound heterozygous POLR3A mutations in 3.1% of index cases. Interestingly, >80% of POLR3A mutation carriers presented the same deep-intronic mutation (c.1909+22G>A), which activates a cryptic splice site in a tissue and stage of development-specific manner and leads to a novel distinct phenotype. The phenotype is characterized by adolescent-onset progressive spastic ataxia with frequent occurrence of tremor, involvement of the central sensory tracts and dental problems (hypodontia, early onset of severe and aggressive periodontal disease). Instead of the typical hypomyelination magnetic resonance imaging pattern associated with classical POLR3A mutations, cases carrying c.1909+22G>A demonstrated hyperintensities along the superior cerebellar peduncles. These hyperintensities may represent the structural correlate to the cerebellar symptoms observed in these patients. We demonstrate that autosomal-recessive mutations in POLR3A are a frequent cause of hereditary spastic ataxias, accounting for about 3% of hitherto genetically unclassified autosomal recessive and sporadic cases; hypomyelination is frequently absent in POLR3A-related syndromes, especially when intronic mutations are present, and thus can no longer be considered as the unifying feature of POLR3A disease. Our results demonstrate that substantial progress in revealing the causes of Mendelian diseases can be made by exploring the non-coding sequences of the human genome..

Recent Publications

1. Azmanov D N, Siira S J, Chamova T, Kaprelyan A, Guergueltcheva V, Shearwood AJ, et al (2016) Transcriptome-wide effects of a POLR3A gene mutation in patients with an unusual phenotype of striatal involvement. Hum Mol Genet. 25:4302–14.
2. Schule R, Wiethoff S, Martus P, Karle KN, Otto S, Klebe S, et al (2016) Hereditary spastic paraplegia -clinico-genetic lessons from 608 patients. Ann Neurol 79:646–58.
3. Cayami F K, La Piana R, Van Spaendonk R M, Nickel M, Bley A,Guerrero K, et al (2015) POLR3A and POLR3B mutations in unclassified hypomyelination. Neuropediatrics 46:221–8.
4. Pyle A, Smertenko T, Bargiela D, Griffin H, Duff J, Appleton M, et al (2015) Exome sequencing in undiagnosed inherited and sporadic ataxias. Brain 138(2):276–83.
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Biography

Muhammad Mahajnah is an Assistant Professor of Pediatrics and Pediatric Neurology at the Technion Faculty of Medicine, Israel. He completed his Medical degree at Bruce and Ruth Rappaport Faculty of Medicine, Technion, Israel in 1992 and his PhD degree in 1998. He trained in Pediatrics at Carmel Medical Center and completed fellowship in Pediatric Neurology at Schneider Children Medical Center, Tel Aviv. He has worked with children neurological disorder for about 20 years and has special interest in neurodevelopmental disorders and neuro genetic disorders and devotes his time to both clinical work and research.

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