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A Familial Case of Childhood Ataxia with Leukodystrophy Due to Novel *POLR1C* Mutations

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Dear Editor,

Of the 17 subunits of RNA polymerase III (POLR3), POLR3A and POLR3B are the largest and second largest, respectively, which together form the catalytic core of the polymerase. Most cases of POLR3-related leukodystrophy are caused by mutations in *POLR3A* or *POLR3B*, with *POLR1C* mutations causing about 5% of cases.[1] Distinctively, POLR1C is a shared subunit of both RNA polymerase I (POLR1) and POLR3, and molecular defects selectively modify the availabilities of these enzymes, leading to two distinct clinical conditions: Treacher Collins syndrome with autosomal recessive inheritance, and POLR3-related leukodystrophy.[1] Only 20 *POLR1C* mutations presenting with the spectrum of POLR3-related leukodystrophy have been reported worldwide. Here we report two Korean siblings with ataxia and leukodystrophy caused by novel *POLR1C* mutations.

A 5-year-old girl visited our clinic with an ataxic gait. She showed tremor and clumsiness affecting her hands, and mild dysarthria. An ocular examination revealed myopia with mild optic nerve atrophy. Neurocognitive profiles revealed mild mental retardation with an intelligence quotient of 65. Brain MRI showed diffuse hypomyelination, except for T2-weighted hypointensities in the ventrolateral thalamus and optic radiation, without cerebellar atrophy (Fig. 1A, B, and C). She underwent menarche at 13 years of age, without evidence of hypogonadotropic hypogonadism. No dental or skeletal abnormalities were found. Her ataxia, tremor, and dysarthria were worsening at her current age of 15 years. She scored 28/40 on the Scale for the Assessment and Rating of Ataxia (SARA).

The younger brother of the proband also showed slow progressive ataxia, tremor, and dysarthria from 5 years of age with similar MRI findings (Fig. 1D, E, and F). He had difficulty walking, with ataxia and myoclonus (Supplementary Video 1 in the online-only Data Supplement). Myopia with mild optic nerve atrophy was also noted. No dental or endocrine abnormalities have been found at his current age of 12 years. He had a SARA score of 13/40. Neither sibling exhibited spasticity, dystonia, or seizures.

Because of the extreme genetic heterogeneity of leukodystrophy and ataxia, we performed whole-exome sequencing and analyzed the candidate genes causing hypomyelination and ataxia, including *POLR3A*, *POLR3B*, *PLP1*, *GJC2*, and *TUBB4A*, which did not reveal any pathogenic variants in them. We identified compound heterozygous *POLR1C* mutations: a frameshift mutation (c.698_699insAA: p.Tyr233fs) and a missense mutation (c.713A>G: p.Asp238Gly) validated with Sanger sequencing (Fig. 1G). The identified variants were classified as pathogenic based on the 2015 guidelines of the American College of Medical Genetics and Genomics, with evidence levels of PVS1, PM2, and PM3 for p.Tyr233fs, and PS3, PM1, PM2, PM3, and PP4 for p.Asp238Gly.[2]

POLR3 synthetizes small noncoding RNAs that play essential roles in cells, including transcription, and RNA processing and translation.[3] Therefore, members of the POLR3 family are considered housekeeping genes that require strict regulation. *POLR1C* mutations, which

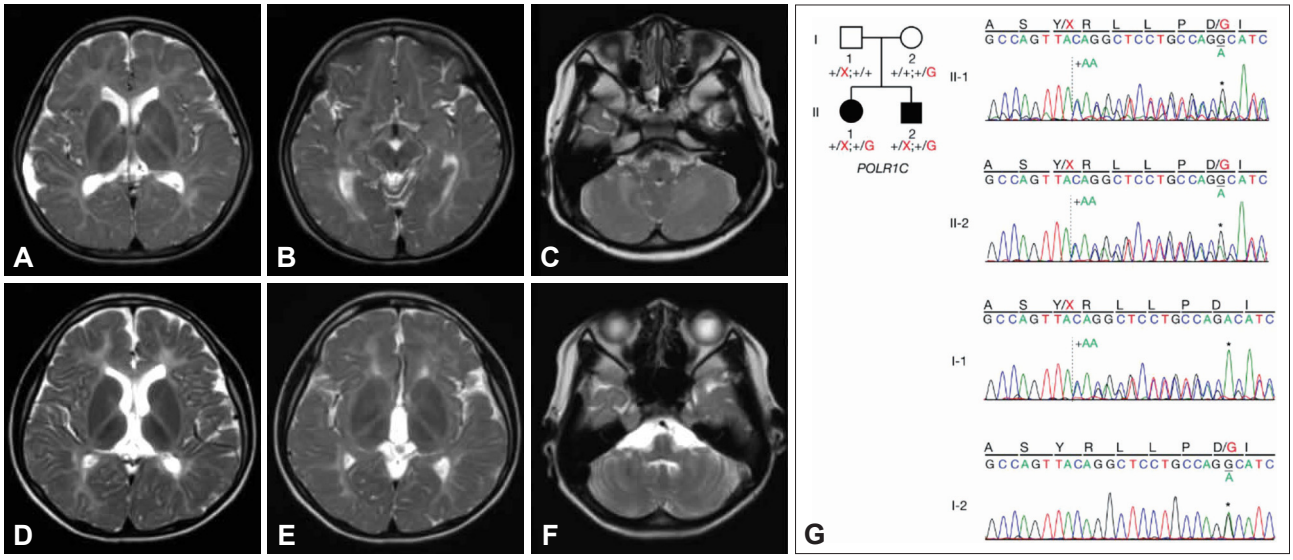

Fig. 1. Neuroimaging (A–F) and Sanger sequencing (G) findings. Besides diffuse hypomyelination, relative T2-weighted MRI hypointensities in the ventrolateral thalamus and optic radiation are evident in the proband (A and B) and her affected brother (D and E). Hypomyelination of the cerebellar white matter is visible, without cerebellar atrophy (C and F). (G) Compound heterozygous variants in *POLR1C* are shown in the pedigree: a frameshift mutation (c.698_699insAA: p.Tyr233fs) and a missense mutation (c.713A>G: p.Asp238Gly). Solid symbols indicate clinically affected and genetically confirmed patients: the proband (II-1) and the affected brother (II-2). One variant was inherited from their mother, the other from their father.

impair the assembly and nuclear import of POLR3 and result in decreased binding to its target genes, are thought to reduce the transcription of tRNAs or other small noncoding RNAs that are central to the synthesis of proteins essential for central nervous system myelin development; however, the underlying pathophysiology is not yet fully understood. Although previously described as five distinct entities, these are now recognized as various clinical spectra of POLR3-related leukodystrophy.[4] Other than diffuse hypomyelination, additional relatively characteristic findings are known to occur with or without cerebellar atrophy, such as T2-weighted MRI hypointensities in the ventrolateral thalamus, dentate nuclei, the posterior limb of the internal capsule, and the optic radiation. These findings suggest the presence of myelinating structures early in development and better preserved myelination of the pyramidal tract.[5,6]

Here we have expanded the clinical and genetic spectrum of POLR3-related leukodystrophy caused by *POLR1C* mutations.[1,7] Integrating clinical features such as myopia, characteristic MRI patterns, and next-generation sequencing will facilitate the making of definitive diagnoses in unresolved atypical cases with hypomyelination and ataxia.

Our patients' parents gave written informed consent for the video publication.

Supplementary Video Legend

This video of the affected brother at 11 years of age shows his difficulty in walking with ataxia and myoclonus.

Supplementary Material

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.2.338.

Author Contributions

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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