Movement Disorders
CLINICAL PRACTICE
LETTER: GENOTYPE AND PHENOTYPE

Childhood-Onset Cerebellar Ataxia from Homozygous *XRCC1* c.1293G>C Variant

Giovana Ribeiro, MD,[1] Monica Ferrer-Socorro, MD,[2] Amy Tam, BSc,[2] Joshua Rong, BSc,[2] Enrique Gonzalez Saez-Diez, MD,[2] Darius Ebrahimi-Fakhari, MD, PhD,[2] and Kathryn Yang, MBChB, FRCPC[2,*]

Defects in single-strand DNA break repair (SSBR) are increasingly recognized as a cause of hereditary cerebellar ataxia, linking genome maintenance to cerebellar integrity.[1,2] Among these, biallelic *XRCC1* variants have been described in only a few patients with variable combinations of ataxia, oculomotor apraxia, and axonal neuropathy.[3,4] We report a child with early-onset ataxia associated with a homozygous *XRCC1* missense variant, further delineating the phenotypic spectrum and reinforcing *XRCC1* as a bona fide recessive ataxia gene.

The proband, a 4-year-old male of Indian ancestry, was born to non-consanguineous parents after an uncomplicated pregnancy and delivery. Early motor development was delayed (sitting at 8 months, walking at 17 months) with early axial instability and frequent falls. Cognitive and language milestones were age-appropriate. Family history was negative for neurologic disease.

Neurologic examination revealed striking axial and appendicular cerebellar ataxia (Video 1, part 1). Gait was broad-based with truncal sway (Video 1, part 2); dysmetria and dysdiadochokinesis were present, but there was no oculomotor apraxia or nystagmus. Deep tendon reflexes were present yet diffusely reduced. The Scale for the Assessment and Rating of Ataxia (SARA) score was 17.5. Brain MRI at age 3 years showed no cerebellar atrophy.

Trio exome sequencing identified a homozygous likely pathogenic variant in *XRCC1*: NM_006297.3:c.1293G>C p.(Lys431Asn). Both parents were heterozygous carriers. *XRCC1* encodes X-ray repair cross-complementing protein 1, a scaffold protein coordinating base excision and single-strand break repair through interaction with DNA ligase III, PARP1, and polynucleotide kinase phosphatase.[3,5] Notably, c.1293G>C is a missense variant that simultaneously affects splicing. Multiple splice prediction algorithms indicate loss of the exon 11 donor site, and functional studies by Hoch et al demonstrated aberrant transcript retention and reduced XRCC1 mRNA and protein levels in patient-derived fibroblasts carrying this allele in trans with a truncating variant.[3,6] A limitation of our report is the lack of patient-derived RNA analysis, which would have allowed direct confirmation of the splicing defect and assessment of residual transcript levels in the homozygous state of the variant.

This variant has been previously reported in three individuals of South Asian ancestry: An adult of East Indian descent with oculomotor apraxia, progressive ataxia, sensorimotor axonal neuropathy, and cerebellar atrophy and two unrelated patients of Pakistani origin with onset at age three, slowly progressive gait ataxia, and sensorimotor neuropathy but only mild ocular abnormalities. One of the reported patients had a dual diagnosis involving CLCN1. Homozygosity mapping revealed a shared haplotype on chromosome 19, supporting a founder effect in South Asian populations.[3,4] Our patient demonstrates an even earlier onset (<1 year) and absent oculomotor findings, extending the phenotypic range to infantile-onset "pure" cerebellar ataxia with likely evolving neuropathic features. The variant is extremely rare in population databases (gnomAD v4.1.0, AC: 22, AF: 0.00001363), observed exclusively in South Asian populations (MAF: 0.0002416) with one reported homozygote of unknown phenotype.

Across these cases, p.Lys431Asn appears as a recurrent, South Asian-founder variant.[3,4] Its phenotypic variability—from early childhood to adulthood and with or without oculomotor signs—suggests partial functional disruption of XRCC1-ligase III interactions rather than complete loss of SSBR function. In contrast, null alleles might be embryonically lethal, consistent with *XRCC1*-knockout mouse data showing early lethality and widespread apoptosis.[3,7] Future functional studies will be essential to elucidate how *XRCC1* variants disrupt single-strand break repair and contribute to cerebellar and peripheral nerve vulnerability, as well as to determine whether heterozygous or homozygous carriers may have an increased susceptibility to malignancy.[8,9]

Clinically, *XRCC1*-associated ataxia should be distinguished from other SSBR-related disorders such as those associated with *APTX* (AOA1) and *PNKP* (AOA4), which share overlapping

[1]*Department of Neurology, Child Neurology Unit, University of Campinas (UNICAMP), São Paulo, Brazil;* [2]*Movement Disorders Program, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA*

***Correspondence to:** Kathryn Yang, Movement Disorders Program, Department of Neurology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA; E-mail: kathryn.yang@childrens.harvard.edu
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Video 1. Part 1. Cerebellar ataxia is evident at rest, characterized by marked axial instability. Part 2. During gait assessment, the patient demonstrates marked instability, with a broad-based gait and truncal sway.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70551

features but more consistently exhibit oculomotor apraxia and cerebellar atrophy.[2,5] Early recognition of the *XRCC1* phenotype—particularly when MRI and ocular findings are not yet present—supports timely genomic testing, anticipatory management, and genetic counseling.

In summary, the biallelic variants in *XRCC1* cause early childhood-onset cerebellar ataxia. Recognition of this genotype–phenotype correlation facilitates accurate diagnosis within the expanding group of DNA repair-associated ataxias.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of first draft, B. Review and critique

G.R.: 1B, 1C, 3A.
M.F.: 1B, 1C, 3B.
A.T.: 1B, 1C, 3B.
J.R.: 1B, 1C, 3B.
E.G.: 2C, 3C.
D.E.F.: 1A, 2C, 3B.
K.Y.: 1A, 1B, 1C, 3B.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Data S1. Disclosure.