



A Novel *APT*X Variant and Ataxia with Oculomotor Apraxia Type 1

Humera Manzoor^a
Ihtisham Bukhari^{b*}
Muhammad Wajid^c
Yuanwei Zhang^b
Huan Zhang^b
Norbert Brüggemann^d
Christine Klein^e
Qinghua Shi^b
Sadaf Naz^a

^aSchool of Biological Sciences, University of the Punjab, Quaid-i-Azam Campus, Lahore, Pakistan

^bUSTC-Shenyang Jinghua Hospital Joint Center of Human Reproduction and Genetics, School of Life Sciences, University of Science and Technology of China, Anhui, China

^cUniversity of Okara, Okara, Pakistan

^dDepartment of Neurology, University of Lübeck, Lübeck, Germany

^eInstitute of Neurogenetics, University of Lübeck, Lübeck, Germany

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Correspondence

Qinghua Shi, PhD
USTC-Shenyang Jinghua Hospital Joint Center of Human Reproduction and Genetics, School of Life Sciences, University of Science and Technology of China, Hefei, Anhui 230027, China
Tel +86-551-63600344
Fax +86-551-63600344
E-mail qshi@ustc.edu.cn

Sadaf Naz, PhD
School of Biological Sciences, University of the Punjab, Quaid-i-Azam Campus, Lahore 54590, Pakistan
Tel +92-42-99231819
Fax +92-42-99230980
E-mail naz.sbs@pu.edu.pk

*Present Address: Department of Biochemistry, King Saud University, Riyadh, Kingdom of Saudi Arabia

Dear Editor,

Ataxia with oculomotor apraxia type 1 (AOA1, MIM 208920) is an autosomal recessive disorder characterized by early-onset cerebellar ataxia, polyneuropathy, oculomotor apraxia, hypoalbuminemia, and hypercholesterolemia.¹ It is caused by pathogenic variants of *APT*X, which encodes the aprataxin protein that is involved in DNA strand-break repair.¹

We recruited a consanguineous family (coded as RDHM-02) with individuals affected by an undiagnosed movement disorder (Fig. 1A). The proband (VI:11, aged 40 years) was identified by personal contact. He had dysarthria and weakness of lower limb muscles. The disease onset reportedly occurred at ages of 2–6 years. The family history was obtained, and the affected individuals underwent standardized videotaping. The videos were evaluated by movement-disorders experts (C.K. and N.B.) after exome sequencing results were obtained. The proband and the other affected individuals in family RDHM-02 had cerebellar ataxia with severe gait impairment. Individual VI:11 exhibited severe polyneuropathy and a complete loss of ambulation by the age of 7 years, while individuals VI:13, VII:1, and VII:6 had ocular apraxia. Mild upper limb and moderate lower limb dystonia were observed in all affected family members except individual VI:11. Individual VII:6 exhibited a distinct high-frequency dystonic hand tremor and mild distal chorea of the upper limbs. The serum cholesterol level (234 mg/dL) was elevated in the oldest affected individual (who was aged 40 years), while the albumin levels were normal (Supplementary Table 1 in the online-only Data Supplement).

Genomic DNA was extracted from blood samples.² Whole-exome sequencing was performed for two individuals (VI:11 and VI:12), and the variants were prioritized.³ Sanger sequencing confirmed the segregation of a novel homozygous nonsense mutation [c.388C>T (p.Gln130Ter)] in *APT*X (NM_175073.2) associated with the phenotype (Fig. 1A and B). The variant was absent from public databases and the DNA of 100 controls (200 chromosomes were analyzed).

*APT*X (Fig. 1C) encodes aprataxin, which is composed of three main domains: FHA (an N-terminal forkhead-associated domain), HIT (a histidine triad domain), and Znf (a C-terminal Cys₂His₂ zinc finger domain) (Fig. 1D). Relatively few variants of *APT*X result in complete deletion of the HIT and Znf domains.¹ The mutation c.388C>T (p.Gln130Ter) in affected members of family RDHM-02 introduced a stop codon into the *APT*X open reading frame (Fig. 1D). This is probably a null allele due to invoking either nonsense-mediated decay of the mRNA⁴ or degradation of the truncated protein. Western-blot analysis of lymphoblastoid cell lines derived from AOA1 patients homozygous for different nonsense mutations (Fig. 1C) has revealed undetectable levels of aprataxin,¹ which supports the present hypothesis.

Frame-shift, splice-site, and nonsense mutations of *APT*X are believed to cause early onset and more-severe phenotypes compared to those caused by the missense mutations.⁵ This is supported by the patients in family RDHM-02 having severe features of AOA1 with an early

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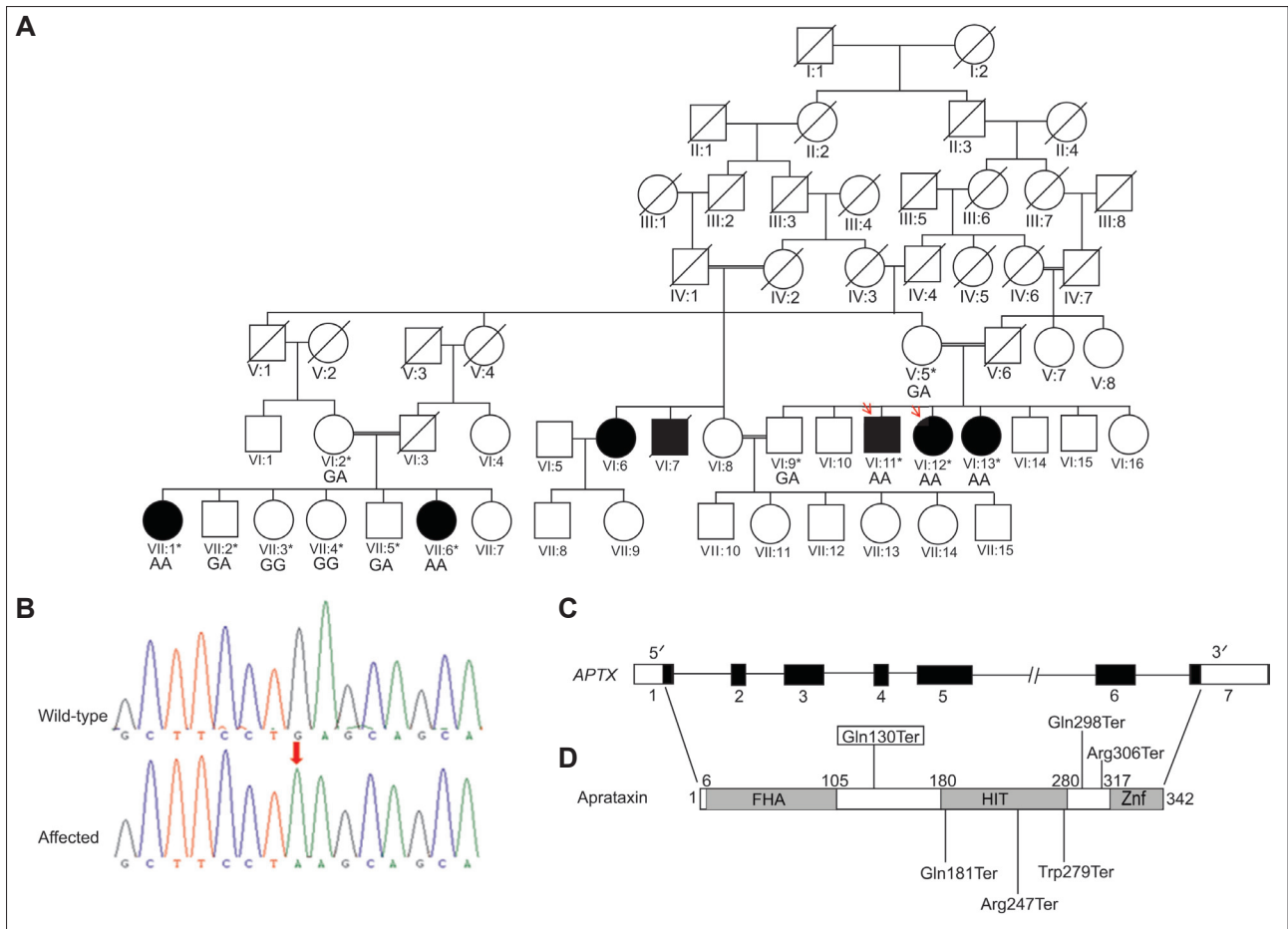


Fig. 1. The RDHM-02 family and nonsense *APTX* variant segregated based on the phenotype. A: RDHM-02 pedigree. *Individuals for whom DNA was available. The arrows denote individuals for whom whole-exome sequencing was performed. The genotypes of *APTX* (c.388C>T) are indicated below the corresponding symbols for individual subjects. B: Electropherogram of *APTX* sequence analyses. The site of the mutation is indicated by an arrow. C: Diagram of *APTX* (NM_175073.2), with black boxes denoting translated exons and plain boxes denoting 5' and 3' untranslated regions. Introns are depicted by horizontal lines. D: Aprataxin. The protein domains are shaded. All reported nonsense mutations are shown, and the p. Gln130Ter variant identified in family RDHM-02 is boxed. FHA: forkhead-associated domain at the N-terminal, HIT: histidine triad domain, Znf: zinc finger domain at the C-terminal.

disease onset. Oculomotor apraxia and chorea have been observed in 85% and 80% of cases, respectively,⁵ and the latter manifestations were present in some of the patients in family RDHM-02 (Supplementary Table 1 in the online-only Data Supplement). Polyneuropathy and a complete loss of ambulation have been reported in AOA1 patients at 7–10 years after the disease onset.⁵ However, these phenotypes were clinically observed only in individual VI:11 in the present study, with the limitation that none of the affected individuals were evaluated by electrophysiological testing since this was not available. Hypercholesterolemia (75%) and hypoalbuminemia (83%) are variable features in AOA1 and appear at 10–15 years after disease onset.⁵ The oldest present patient (individual VI:11) had elevated cholesterol but a normal albumin level (Supplementary Table 1 in the online-only Data Supplement). The phenotypic variability among the patients in family RDHM-

02 carrying an identical mutation underlines the difficulty of establishing genotype-phenotype correlations in autosomal recessive AOA1.

The current research has identified a new variant of *APTX* and highlights the utility of whole-exome sequencing in diagnosing a rare Mendelian disorder that could only have been diagnosed at a highly specialized movement-disorder center based on clinical findings. These findings have major implications for the family and their counseling, which can now be facilitated by utilizing whole-exome sequencing data.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2017.13.3.303>.

Conflicts of Interest

The authors have no financial conflicts of interest.

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