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Autosomal Recessive Spinocerebellar Ataxia Caused by a Novel Homozygous *ANO10* Mutation in a Consanguineous Chinese Family

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Dear Editor,

Autosomal recessive spinocerebellar ataxia (SCAR) is a clinically and genetically heterogeneous group of neurodegenerative disorders. SCAR10 caused by *ANO10* mutations was first described in 2010 in a Dutch family.[1] We report the first Chinese SCAR10 patient and a novel *ANO10* mutation. The research was approved by the local ethics committee, and informed consent was obtained from the patient.

A 41-year-old previously healthy Chinese woman born to consanguineous parents (Fig. 1A) presented with progressive gait instability and slurred speech that had first appeared 4 years previously. She experienced obvious unsteadiness when walking down stairs and turning around. No cognitive decline, psychiatric symptom, seizure, bowel or bladder dysfunction, or limb weakness was reported. A physical examination revealed dysarthria, trunk and limb ataxia, horizontal gaze-evoked nystagmus, down-beating nystagmus, hypometric saccades, brisk deep tendon reflexes, Hoffman's sign, the Babinski sign, and ankle clonus (Supplementary Video 1 in the online-only Data Supplement). Parkinsonism, muscle wasting, fasciculation, pes cavus, and tortuosity of the conjunctival vessels were absent. Her Montreal Cognitive Assessment score was 27/30. Nerve conduction studies and electromyography produced unremarkable findings, and her electroencephalogram was normal. MRI indicated the presence of striking cerebellar atrophy (Fig. 1B and C).

Genetic testing was performed in the patient using a gene panel containing 521 genes known to be related to movement disorders (Supplementary Material in the online-only Data Supplement). The patient was found to have a novel homozygous mutation of *ANO10*, a nonsense mutation of c.1244C>G (p.Ser415*) (NM_018075). Sanger sequencing confirmed this condition and indicated that her healthy parents (III-4 and III-5) and 39-year-old brother (IV-2) were heterozygous for this mutation (Fig. 1D).

SCAR10 is caused by a homozygous or compound heterozygous mutation in *ANO10*, and presents mainly with gait and limb ataxia, dysarthria, and nystagmus associated with cerebellar atrophy, with onset typically occurring in late adolescence or young adulthood.[1] SCAR10 has been mainly reported in Europe, and this is only the second case reported in Asia (the first was a Japanese case).[2]

ANO10 encodes a transmembrane protein composed of 660 amino acids, with 8 transmembrane domains predicted by TMHMM Server (version 2.0, http://www.cbs.dtu.dk/services/TMHMM/) (Supplementary Fig. 1 in the online-only Data Supplement). Although deletion of *ANO10* resulted in cellular defects through deregulated calcium signaling in animal experiments, the exact pathogenesis remains unclear.[3] Our patient had a homozygous nonsense mutation that led to early protein truncation of approximately 40% of the amino acid chain (Fig. 1E). MutationTaster (www.mutationtaster.org/) testing indicated the dis-

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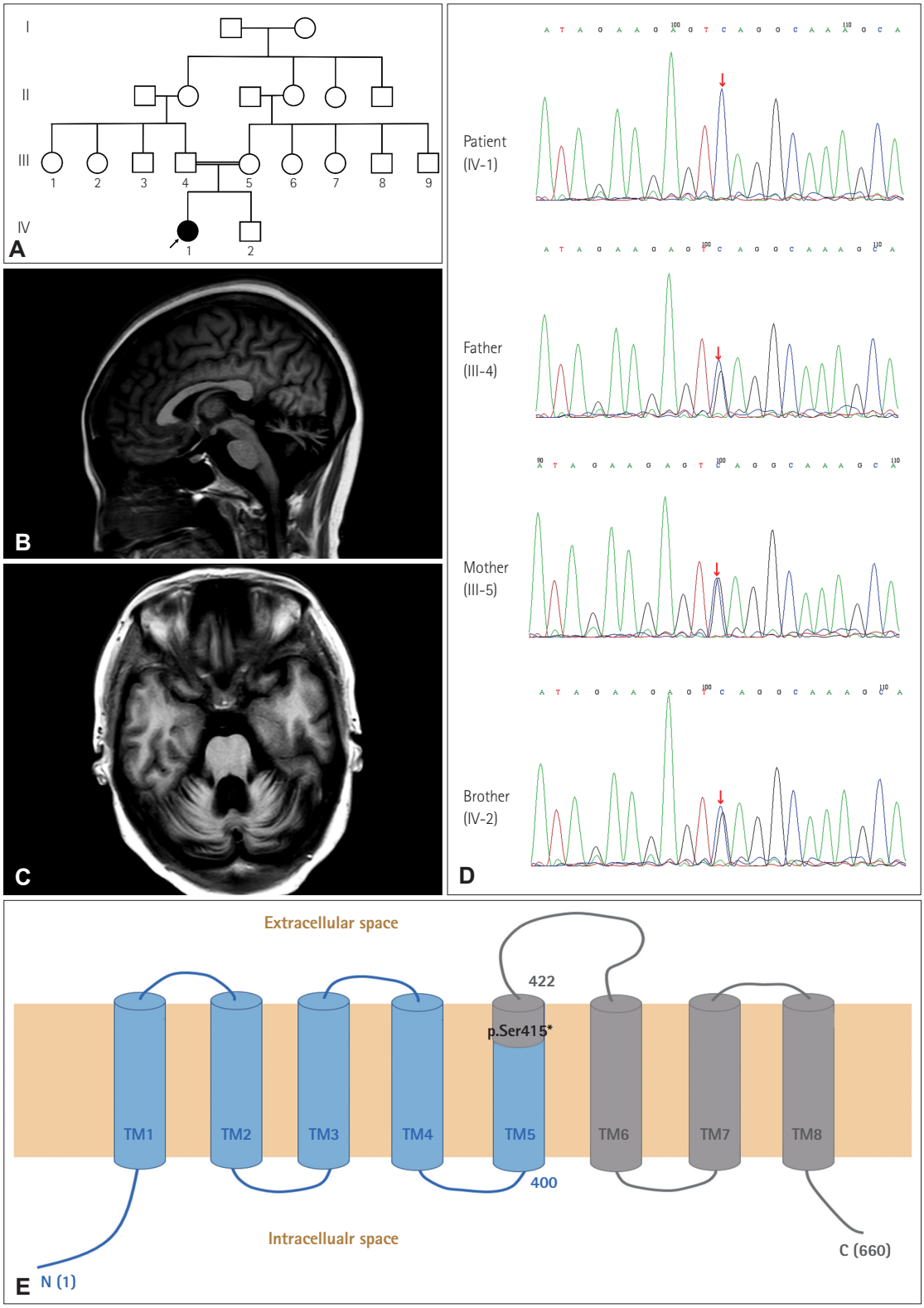

Fig. 1. Pedigree, brain MRI, Sanger sequencing, and schematic diagram of ANO10 protein and the mutation. A: The patient (IV-1, arrow) was born to consanguineous parents (III-4 and III-5). B and C: MRI showed striking cerebellar atrophy. D: Red arrows indicate the site of the mutation. Sanger sequencing confirmed the homozygous status for the c.1244C>G (p.Ser415*) mutation of *ANO10* in the patient (IV-1), and indicated that her parents (III-4 and III-5) and brother (IV-2) were all heterozygous for this mutation. E: ANO10 protein has eight transmembrane domains and cytosolic N- and C-termini. A nonsense mutation of p.Ser415* leads to early protein truncation with the loss of approximately 40% (shown in gray) of the amino acid chain. C: C-terminus, N: N-terminus, TM: transmembrane.

ease-causing potential of the mutation. The mutation is not present in the 1000G, ESP6500, ExAC, or genome AD database. According to American College of Medical Genetics and Genomics guidelines for variant classification, the mutation is considered to be pathogenic: one PVS1 (null variant), one PM2 (absent from population databases), and one PP3 (computational predictions).[4]

Missense mutations are the most-common types of mutations, although truncating mutations including nonsense and frameshift mutations have also been reported.[5,6] Homozygous truncating mutations of c.1150_1151del (p.Leu384fs) led to a significantly early onset of symptoms in 17 patients aged 6−30 years (median age 18 years).[1,7,8] However, the Japanese patient with a homozygous nonsense mutation of c.609C >G (p.Tyr203*) and the present Chinese patient had late onsets at 42 and 37 years old, respectively, which argue against the reported association between the genotype of two truncating mutations and an early age at onset.[6] We speculate that the function of the ANO10 protein is partially retained despite premature termination.

We have reported the first Chinese SCAR10 patient and a novel *ANO10* mutation that expands the genotype of SCAR10 and supports that the geographical distribution of this disease extends beyond Europe.

Supplementary Video Legend

Video 1. The patient showed trunk and limb ataxia, horizontal gaze-evoked nystagmus, down-beating nystagmus, hypometric saccades, Hoffman's sign, the Babinski sign, and ankle clonus.

Supplementary Material

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.2.333.

Author Contributions

Conceptualization: Shi-Lin Yang, Xiang Han. Data curation: Yu-Qiong Jiao. Formal analysis: Shi-Lin Yang, Zhi-Yuan Dong. Supervision: Qiang Dong, Xiang Han. Visualization: Shi-Lin Yang. Writing—original draft: Shi-Lin Yang, Shu-Fen Chen. Writing—review & editing: Xiang Han.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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