Andersen–Tawil Syndrome With Novel Mutation in KCNJ2: Case Report

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Andersen–Tawil syndrome (ATS) is a rare autosomal dominant disorder characterized by a classic symptom triad: periodic paralysis, ventricular arrhythmias associated with prolonged QT interval, and dysmorphic skeletal and facial features. Pathogenic variants of the inwardly rectifying potassium channel subfamily J member 2 (KCNJ2) gene have been linked to the ATS. Herein, we report a novel KCNJ2 causative variant in a proband and her father showing different ATS-associated symptoms. A 15-year-old girl was referred because of episodic weakness and periodic paralysis in both legs for 2–3 months. The symptoms occurred either when she was tired or after strenuous exercise. These attacks made walking or climbing stairs difficult and lasted from one to several days. She had a short stature (142 cm, <3rd percentile) and weighed 40 kg. The proband also showed orbital hypertelorism, dental crowding, mandibular hypoplasia, fifth-digit clinodactyly, and small hands. Scoliosis in the thoracolumbar region was detected by chest X-ray. Since she was 7 years old, she had been treated for arrhythmia-associated long QT interval and underwent periodic echocardiography. Brain MRI revealed cerebrovascular abnormalities indicating absence or hypoplasia of bilateral internal carotid arteries, and compensation of other collateral vessels was observed. There were no specific findings related to intellectual development. The proband’s father also had a history of periodic paralysis similar to the proband. He did not show any cardiac symptoms. Interestingly, he was diagnosed with hyperthyroidism during an evaluation for paralytic symptoms. Clinical exome sequencing revealed a novel heterozygous missense variant: Chr17(GRCh37):g.68171593A>T, NM_000891.2:c.413A>T, p.(Glu138Val) in KCNJ2 in the proband and the proband’s father.

Keywords: KCNJ2 gene, KIR2.1, periodic paralysis, long QT syndrome, potassium channel, genetic disorder, dysmorphic feature, Andersen–Tawil syndrome

INTRODUCTION

Andersen–Tawil syndrome (ATS; MIM 170390) is a rare autosomal dominant disorder characterized by a classic triad of recurrent flaccid muscle weakness (periodic paralysis), cardiac arrhythmias, and distinctive skeletal and facial features (1). Since the first ATS case presenting with muscle weakness, extrasystoles, and multiple developmental anomalies was reported (2), ATS prevalence is estimated at 0.8–1 in 1,000,000 (3, 4). However, the actual prevalence is expected to be
higher than previously reported because the reported prevalence is from a specific population and subgroup of ATS patients (5) and ATS is a rare disease with a broad phenotypic heterogeneity that is difficult to diagnose. Affected individuals present with episodes of periodic paralysis or cardiac symptoms in their first or second decade (6); however, highly variable phenotypes and incomplete penetrance make diagnosis challenging. Cardiac arrhythmias include ventricular arrhythmias associated with prolonged QT interval and prominent U waves. Skeletal and facial features include low-set ears, broad forehead, ocular hypertelorism, small mandible, dental abnormalities, fifth digit clinodactyly, syndactyly, short stature, and scoliosis (7). The KCNJ2 and KCNJ5 are causative genes of ATS. KCNJ2 on chromosome 17q24.3 encodes an inward rectifier potassium channel protein (Kir2.1), which plays an important role in setting and stabilizing the resting membrane potential primarily in the skeletal muscles, heart, and brain (8). KCNJ5 (11q24.3) encodes a G-protein-activated inward rectifier potassium channel 4 protein (Kir3.4) that induces an inhibitory effect on the inward rectifier potassium current (9). Therefore, the diagnosis of ATS is established in individuals with two or more symptoms of the classic triad or individuals with one of the classic triad and at least one family member with ATS and/or identification of pathogenic variants in KCNJ2 and KCNJ5. Here, we report a family with ATS with a novel causative missense variant in KCNJ2 c.413A>T, p.(Glu138Val) and compare their phenotypes along with a literature review.

**CASE REPORT**

The proband is a 15-year-old girl who presented with recurrent episodes of leg weakness and paralysis lasting several days beginning 2–3 months prior. These episodes recently became more severe and frequent, occurring at least twice a week. The severity of the weakness during the episodes varied from mild (weakness and difficulty climbing stairs) to severe (inability to walk). Triggers were intensive exercise or feeling tired. Clinical evaluation included medical and family history and previous medical record review where applicable. She had been taking flecainide for an arrhythmia associated with a long QT interval since she was 7 years old and had been receiving regular echocardiogram (ECG) follow-up. Her serum potassium levels tested during hospitalization were normal. Thyroid function test results were also within the reference interval. Electromyography (EMG) showed no specific findings. Brain magnetic resonance imaging (MRI) revealed suspicious congenital absence or hypoplasia of both internal carotid arteries (ICA) with supply to the anterior circulation via carotid-vertebrobasilar anastomoses and hypertrophy of the posterior communicating artery (PCOM). No intellectual disability was observed during development. Chest X-rays showed mild scoliosis in the thoracolumbar region. During physical examination, she was 142 cm tall (<3rd percentile) and weighed 40 kg (3rd percentile). Additional physical examination during genetic counseling revealed that the proband had dysmorphic features, including orbital hypertelorism, mandibular hypoplasia, dental crowding, clinodactyly of the fifth finger, and small hands.

Family history revealed that her 37-year-old father had similar episodes that began during adolescence. He was hospitalized for three quadriplegic attacks, and he took potassium supplement 600 mg once or twice a year when he experienced generalized weakness attacks. His potassium levels were low (lowest: 2.2 mmol/L) during his acute episodes. His medical history included transient hyperthyroidism but no cardiac symptoms. Since age 25, he had not experienced a paralysis severe enough to be hospitalized but continued to have periodic paralysis once every few years. His paralysis events were mild and improved without going to the hospital by taking a potassium supplement, applying hot compresses, and receiving massages. However, from March to May 2020, at the age of 35, he was hospitalized almost every 2 weeks with severe general paralysis during which he could not even move his fingers. His blood thyroid function test indicated hyperthyroidism. After taking thyroid medication for 2–3 months, he underwent three thyroid function tests, all of which were within the normal range. He remained well without any uncomfortable symptoms after that. However, detailed records (i.e., thyroid hormone levels) were not obtained as data by the hospital at that time. His height and weight were 163.5 cm (~3rd percentile) and 51.25 kg, respectively. Hypertelorism, small mandible, tooth crowding, and small hands were also observed. Table 1 provides a summary of the clinical characteristics of our patients.

**GENETIC TESTING**

Genomic DNA was extracted from peripheral blood samples using the QIAsymphony DSP DNA mini kit (Qiagen, Hilden, Germany). Sequencing was performed using a TruSight One Expanded sequencing panel (Illumina Inc., San Diego, CA, USA) consisting of 6,700 genes associated with known Mendelian genetic disorders on a NextSeq 550 (Illumina, CA, USA). The obtained sequence reads were aligned to the human reference genome sequence 19 (hg19) from University of California, Santa Cruz (UCSC) [original GRCh37 from National Center for Biotechnology Information (NCBI), February 2009] using Burrows–Wheeler Aligner (BWA version 0.7.7-isis-1.0.0). The BAM files were then processed by base quality recalibration, duplicate removal, and local realignment following the Genome Analysis Toolkit (GATK version 1.6-23-gf0210b3) for variant calling. Annotation and filtering were performed with Illumina Annotation Service (IAS version 3). Clinical exome sequencing revealed a novel causative heterozygous missense Chr17(GRCh37):g.68171593A>T, NM_000891.2:c.413A>T, p.(Glu138Val) variant in KCNJ2, which was thought to be causal of ATS syndrome. This domain (H5, intramembrane pore loop) is highly preserved, and the mutation is predicted to be damaging by the protein function prediction software SIFT and PolyPhen-2. It was not present in the general population databases such as the Genome Aggregation Database (gnomAD; https://gnomad.broadinstitute.org/), the Single Nucleotide Polymorphism Database (dbSNP; https://www.
TABLE 1 | Clinical details of ATS patients with pathogenic/likely pathogenic variants in Kir2.1 at position 138.

| Patients             | Causative variant KCNJ2 in amino acid 138 | Sex/age at diagnosis (years) | Age with first symptoms (years) | Typical triad of Andersen–Tawil syndrome                  | Other additional features                                                                 |
|----------------------|-------------------------------------------|-----------------------------|--------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------|
| Proband              | E138V                                     | F/15                        | 7                              | Yes                                                      | Yes (long QT interval)                                                                      |
|                      |                                           |                             |                                 | Short stature (<3 percentile), hypokalemia, micrognathia, dental crowding, clinodactyly of the fifth finger, small hands | Cerebrovascular abnormality (congenital hypoplasia of both internal carotid arteries)         |
| Proband’s father     | E138V                                     | M/37                        | 19                             | Yes                                                      | No                                                                                       |
|                      |                                           |                             |                                 | Short stature (163.5 cm), hypertelorism, micrognathia, dental crowding, small hands | Transient hyperthyroidism and ictal exacerbation of periodic paralysis                      |
| Kostera-Pruszczyk et al. (10), same position variant case as our patients | E138K                         | M/5                         | In utero                       | Yes                                                     | Yes (long QT interval)                                                                      |
|                      |                                           |                             |                                 | Short stature (<3 percentile), hypertelorism, micrognathia, clinodactyly of the fifth finger, small hands | Not described                                                                             |

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DISCUSSION

In this case report, we identified two ATS patients in a family with the novel KCNJ2 c.413A>T variant. Our proband had all triad symptoms, while her father had only two symptoms and no cardiac symptoms. It is very challenging to diagnose ATS early due to the rarity and high degree of phenotypic variability. Fifty-eight to seventy-eight percent of ATS patients present with all three symptoms (12). Moreover, patients can present with only one of the triad symptoms (5). Dysmorphic features are usually subtle in ATS patients (13), as shown in our patients (we recognized retrospectively), and are easy to overlook unless suspected of ATS. Therefore, ATS should always be considered even in patients with only periodic paralysis or cardiac arrhythmias.

Approximately 60% of ATS cases have causal variants in KCNJ2 (6, 14). Most KCNJ2 pathogenic variants in ATS are missense variants (1, 6) that result in loss of function of the Kir2.1 channel and is expressed in skeletal muscle, heart, and bone. This channel plays a role in prolonged depolarization of the action potential, and thereby cause periodic paralysis and cardiac arrhythmia (14). Additionally, KCNJ2 variants can affect skeletal dysmorphic features because KCNJ2 is expressed during the early stages of craniofacial development in Xenopus and mice (15). However, as reports by variable penetrance of ATS cases suggest, a subset of individuals with pathogenic variants do not exhibit any associated symptoms (16–18). A subset of KCNJ2 pathogenic variants that cause ATS is identified at the phosphatidylinositol-4,5-biphosphate (PIP2) binding site, a known regulator of the Kir2.1 channel. Another subset of KCNJ2 pathogenic variants is found in the pore-forming loop of Kir2.1. In addition, pathogenic variants in regions such as a slide helix have also been reported (5, 19–21), suggesting various mechanisms. The p.(Glu138Val) variant in our patients was located in the pore region of the Kir2.1 channel. Further study showed the same position but other missense change (c.412G>A, p.E138K) as our case variant (c.413A>T, p.E138V) (10). Although not able to perform physiological studies to identify the nature of the alteration in channel function, other studies showed that this subunit pathogenic variant was unable to form functional
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In summary, we identified a novel causative variant in KCNJ2 in ATS patients and provided detailed clinical findings to expand the genotype–phenotype correlation. The heterogeneous phenotype of ATS should alert physicians to perform genetic analysis for ATS even in patients with only one or two among the typical triad symptoms.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Seoul St. Mary’s Hospital Institutional Review Board. Written informed consent for participation was not provided by the participants’ legal guardians/next of kin: Because the patient did not return to our hospital, written consent could not be obtained. However, it has been approved by the Ethics Committee of our hospital, and the patient’s identification information is not included in this case.

AUTHOR CONTRIBUTIONS

JY and MyK wrote the manuscript. JY, KK, MiK, and GL conducted genetic analyses. All authors contributed to the manuscript.
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