






# Novel polygenetic variants evidenced in a patient with Jervell and Lange-Nielsen syndrome

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Jervell and Lange-Nielsen syndrome (JLNS) is an ion channel-caused cardioauditory syndrome characterized by a congenital neurosensorial bilateral deafness and a long QT interval. JLNS is inherited in an autosomal recessive manner and is caused by mutations in the *KCNQ1* gene (potassium voltage-gated channel subfamily Q member 1) [1].

The proband was an 8-year-old male who presented with a family history of sudden death and congenital sensorineural deafness. Initial clinical evaluation of the proband showed a mild cranial trauma and minor occipital subgaleal hematoma. No significant cardiovascular findings were noted, but electrocardiography (ECG) analysis (ECG Edan SE-1200, USA) revealed a prolonged QT/QTc in the lead II (420/460 ms) (Fig. 1A, left). Despite the use of beta-blocker (2 mg/kg/day) therapy at home, the patient experienced a syncopal event related to emotional stress.

Viskin test [2] was performed, and the results did not support an long QT syndrome (LQTS)-related orthostatic event (baseline QTc 465 ms in resting phase, QTc MHR of 492 ms, and QTc recovery of 444 ms). An adrenaline test [3] was performed at doses of 0.025 µg/kg/min, enabling a QTc of 550 ms without an arrhythmic event

(Fig. 1A, right), and met LQTS electrocardiographic criteria. QTc 686 ms was observed under stress after placement of the implantable cardioverter-defibrillator (ICD) and beta-blockers. At follow up, the patient was ventricular arrhythmia-free or shock therapy during the 4 years after ICD implantation. After clinical and cardiac electrophysiology, the patient was diagnosed with JLNS.

Molecular genetic analysis was performed by next generation sequencing in the proband, and 4 family members were clinically affected (Fig. 1B). Electrocardiographic assessment of the mother and maternal grandparents revealed borderline QTc values. The electrocardiographies were measured by the Bazett formula. Only the index case was genotyped and the family members declined to do genetic testing until there was more evidence that genetic testing had to be recommended by a genetic counselor.

High throughput DNA sequencing was performed using an Ion Torrent Personal Genome Machine to target and sequence 87 candidate genes linked with inherited cardiac arrhythmia syndromes. These candidate genes were selected based on their relative expression in the human heart and their ability to modulate ion channel

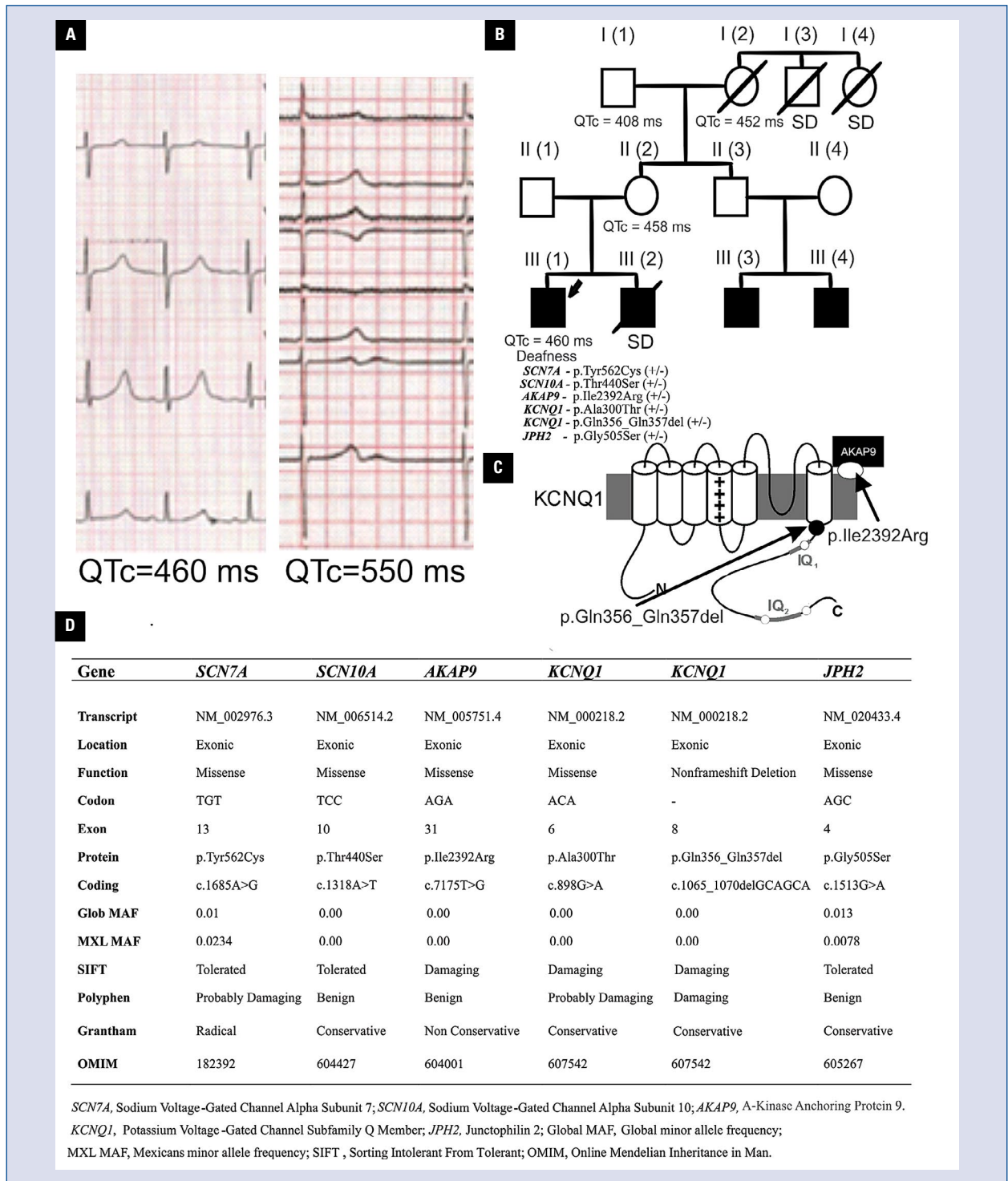
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Received: 2.12.2020

Accepted: 8.06.2021

Early publication date: 16.06.2021

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**Figure 1. A.** Clinical electrocardiography analysis; **Left.** Electrocardiography during the first syncopal event with QTc of 460 ms by Bazett formula; **Right.** Electrocardiography during the adrenaline test with QTc 550 ms by Bazett formula at the second syncopal event; **B.** Patient’s pedigree; I (1). Maternal grandfather; I (2). Maternal grandmother; I (3). Maternal granduncle; I (4). Maternal grandaunt; II (1). Patient’s father; II (2). Patient’s mother; II (3). Maternal uncle; III (1). Patient; III (2). Patient’s brother; III (3). Patient’s cousin; III (4). Patient’s cousin; SD — sudden death; **C.** Schematic molecular genetics and localization of *KCNQ1* mutation and *AKAP9* novel genetic variant. Long QT syndrome, like severe Jervell and Lange-Nielsen syndrome, is associated with sudden cardiac death syndromes. *KCNQ1* mutation and *AKAP9* variant and proteins location and possible interaction in the C-Terminus in the plasma membrane that maybe expressed in the brain, muscle and heart tissues; **D.** Molecular genetics of novel genetic variants (*AKAP9*; *JPH2*; *SCN10A*; *SCN7A*) and *KCNQ1* mutations using bioinformatics.

expression and function: *ABCC8*, *ABCC9*, *ACTC1*, *ACTN2*, *AGTR1*, *AKAP9*, *ANK2*, *CACNA1C*, *CACNA2D1*, *CACNA2D2*, *CACNB1*, *CACNB2*, *CACNB3*, *CACNB4*, *CACNG4*, *CACNG5*, *CACNG6*, *CALM1*, *CALM2*, *CASQ2*, *CAV1*, *CAV2*, *CAV3*, *DSG2*, *DSP*, *DPP6*, *DPP7*, *DPP8*, *DPP9*, *DPP10*, *FGF12*, *FGF13*, *GATAD1*, *GJA5*, *GLA*, *GPD1L*, *HCN2*, *HCN4*, *HEY2*, *IRX3*, *IRX4*, *IRX5*, *JPH2*, *KCNA4*, *KCNA5*, *KCNN1*, *KCNN2*, *KCNN3*, *KCNK1*, *KCNK2*, *KCNK3*, *KCND3*, *KCNE1*, *KCNE2*, *KCNE3*, *KCNE4*, *KCNE5*, *KCNH2*, *KCNIP2*, *KCNJ2*, *KCNJ8*, *KCNJ9*, *KCNJ10*, *KCNQ1*, *KCNQ2*, *PKP2*, *PRKAG2*, *PXDNL*, *RYR2*, *SCN1A*, *SCN2A*, *SCN3A*, *SCN4A*, *SCN5A*, *SCN7A*, *SCN10A*, *SCN1B*, *SCN2B*, *SCN3B*, *SCN4B*, *SEMA3C*, *SNTA1*, *SUR1A*, *SUR2A*, *TBX5*, *TRPM4*, *TTN*. All genetic variants uncovered were confirmed using the gold standard Sanger sequencing. Polymerase chain reaction (PCR) products were purified with a commercial enzyme (ExoSAP-IT, USB, Cleveland, OH) and directly sequenced from both directions using BigDye Terminator v3.1 chemistry on an Applied Biosystems 3730DNA Analyzer (Life Technologies, Carlsbad, CA).

After signal processing and basecalling, the Ion Torrent Suite software was used to map the sequencing reads to the DNA reference sequence (hg19) and identify variants through the Variant Caller plugin as well as the Ion Reporter analysis tool. Ion Reporter compares all variations identified against NCBI's dbSNP to rule out common SNPs, as well as the 1000 Genomes Project and Exome Sequencing Project to get published frequencies. All variations uncovered were probed in 200–400 healthy ethnically matched controls. Genetic variant under 0.05% minor allele frequency were considered mutations and above 0.05–2.5% rare variants, following American College of Medical Genetics (ACMG) recommendations [4]. All variants were analyzed using several pathogenicity *in silico* prediction tools such as PolyPhen-2, SIFT and Grantham.

Three novel heterozygous exonic were identified, likely benign variants to be associated in this index patient diagnosed with JLNS, *AKAP9*(p.Ile2392Arg); *JPH2*(p.Gly52Ser); *SCN10A*(p.Thr440Ser), and one moderate pathogenic rare variant *SCN7A*(p.Tyr562Cys) [4]. Two mutations in *KCNQ1* were already discovered in the patient (p.Gln356\_Gln357del and p.Ala300Thr) [5, 6]. According to available research, this is the first evidence of polygenic variants in a confirmed case of clinically severe JLNS. In this case, polygenic variants may be explained by consanguineous relations among the patient's relatives,

consistent with local traditions still prevalent in small populations. Surprisingly, the ECG abnormalities manifested only in the index patient who carried the mutations and genetic variants in five different genes with a very interesting double deletion in *KCNQ1* with a close physical protein–protein interaction with the *AKAP9* gene (Fig. 1C). Based on the clinical and ECGs phenotype associated with LQTS one of the main culprit genes could be the double mutations in the *KCNQ1* gene and genetic variant in *AKAP9* to induce QT prolongation. It has been described that multiple genes identified could play together a role in the development of the LQTS phenotype at the same time or to be associated with any cardiac arrhythmia syndrome [6].

Genetic variants found in the case reported have been rarely associated with disease in previous reports. The observed variant *JPH2* (p.Gly505Ser) has been related to hypertrophic cardiomyopathy [7], whereas the relationship of the observed variants in *SCN10A* and *SCN7A* genes have not been previously characterized for a JLNS-related phenotype. In another context, almost 30 pathogenic genetic variants of *KCNQ1* gene have been associated with JLNS [8], meanwhile, both deletion and duplication of one or more exons of *KCNQ1* are known to cause LQTS [9]. In the present study the two mutations in *KCNQ1* have been related with LQTS and sudden unexpected death syndromes [5, 6]. *KCNQ1* also has been found to co-interact with *AKAP9* by reducing the IKs channels, and it has been associated with prolongation of the QT interval as a potential marker for long QT type 1-modified effects [10].

Localization of the *KCNQ1* mutations and *AKAP9* genetic variant in the proband are shown in Figure 1D. The hypothesis herein, is based on the possible loss-of-function in the potassium in comparison to WT channels when predicted by *in silico* prediction [11]; however, *in vitro* functional studies may need it to clarify the ionic mechanisms. These potential pathophysiological deficiencies may alter the phenotypic manifestation of LQTS as well as the responsiveness to pharmacological therapies.

In summary, four novel genetic variants were found [*AKAP9*(p.Ile2392Arg); *JPH2*(p.Gly52Ser); *SCN10A*(p.Thr440Ser) and *SCN7A*(p.Tyr562Cys)] and two known mutations in *KCNQ1* in a patient with ventricular arrhythmias with similarities to long QT type 1-modified effects. Moreover, none of these variants has been linked to either LQTS or other sudden cardiac death syndromes.

**Conflict of interest:** None declared

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