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Comprehensive Genetic Testing Can Save Lives in Hereditary Hearing Loss

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Hereditary deafness can be syndromic or nonsyndromic with extremely heterogeneous genetic etiology involving over 100 loci. The differential diagnosis is accomplished by family history, physical examination, and audiologic, otologic and ancillary tests such as temporal bone CT scanning and ECGs¹. Molecular genetic testing for the majority of identified hearing loss genes is either not available or not covered by insurance organizations.

Jervell and Lange-Nielsen syndrome (JLNS) is an autosomal recessive disorder with profound, bilateral, sensorineural hearing loss and long QT interval as detected by ECG. Its frequency ranges from 0.3% to 3.8% in the deaf population². Causative mutations in *KCNQ1* (MIM607542) or *KCNE1* (MIM176261) genes have been described in affected persons².

Prolongation of the QT interval is associated with tachyarrhythmias, including ventricular tachycardia, and ventricular fibrillation, which might result in syncope and sudden death. The syncopal episodes are more prominent during sympathetic activation such as stress, exercise, or fright. Half of the individuals with JLNS had cardiac events before age three years and more than half of the children die prior to age 15 years if untreated².

Here we present a Turkish family with two affected children with deafness. An 18-year-old female with congenital hearing loss was diagnosed with non-syndromic deafness after negative clinical and laboratory evaluations that included an ECG. Her 16-year-old brother was the only other deaf relative. Episodes of syncope or seizures were absent in the affected children as well as in their parents. In order to search for the causative mutations, the

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We declare that we don't have conflict of interest.

genomic DNA from the proband was collected after a written informed consent approved by the University of Miami IRB was obtained, and whole-exome sequencing was performed as previously described³. Analysis of data revealed that she was homozygous for a previously reported mutation causing long QT syndrome, c.1097G>A (p.R366Q), in *KCNQ1*⁴. Sanger sequencing showed that both affected children were homozygous and parents were heterozygous for the variant (Fig. 1A). Repeated ECGs showed marked sinus arrhythmia in both siblings (Fig. 1B). Sinus arrhythmia makes the determination of QT interval difficult as the heart rate differs in one cycle to another. The correction of the QT interval measurement (QTc) was made using Bazett's formula for the shortest RR interval, as suggested⁵. The QTc intervals of the proband and her brother were 458 ms (normal female < 460 ms) and 526 ms (normal male < 450 ms), respectively, confirming the diagnosis of JLNS. QTc intervals of the father (439 ms) and mother (431 ms) were normal. If QTc were calculated using the average RR, as also suggested⁶, it would be normal in the proband and slightly prolonged in the brother. Thus, the diagnosis of JLNS by an ECG screening alone is not straightforward and can be easily missed. This puts affected individuals at risk for deadly cardiac events.

Next-generation sequencing of the whole-exome or all known deafness genes is now available as a clinical diagnostic test. However, insurance companies rarely approve testing requests, claiming that the outcome would not alter clinical management. Our report strongly argues that genetic tests can make a big difference in the diagnosis and clinical management of deaf individuals.

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Figure 1.

(A) DNA sequencing by Sanger method shows that the proband and affected brother are homozygous and both parents are heterozygous for the c.1097G>A (p.R366Q) mutation in *KCNQ1*.

(B) 12 lead surface ECGs of the proband and her brother show the QTc intervals using shortest RR in lead II are 458 ms and 526 ms, respectively.