In cardiac myocytes, the Kv7.1 (α subunit, encoded by KCNQ1) assembles with the minK (β-subunit, encoded by KCNE1) and forms the I_{Ks} channel (slowly activating delayed rectifier potassium channel/current). \[I_{Ks}\] is responsible for the later phase of the repolarization process in the cardiac action potential and is highly sensitive to adrenergic stimuli, enabling action potential shortening during increased heart rate. The same \[I_{Ks}\] channel in the inner ear maintains the homeostasis of the K⁺ in the endolymph and thereby keeps the hearing function intact.\[I_{Ks}\]

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Jervell and Lange-Nielsen syndrome (JLNS, Online Mendelian Inheritance in Man [OMIM] no. 220400 and 612347) is a cardiac rhythm defect and hearing impairment syndrome, caused by the total absence of \[I_{Ks}\]. This total absence of \[I_{Ks}\] is either caused by homozygous or compound heterozygous mutations in 1 of the 2 genes, \[KCNQ1\] or \[KCNE1\]. On the contrary, heterozygous, dominant, or loss of function mutations in the \[KCNQ1\] or \[KCNE1\] genes could cause the disease restricted to cardiac rhythm defect without any hearing impairment (Romano Ward Syndrome, Online Mendelian Inheritance in Man no. 192500). The cardiac restricted phenotype attributable to heterozygous mutations in the \[KCNQ1\] or \[KCNE1\] genes are known as Long QT syndrome, type 1 (LQT1) or type 5 (LQT5), respectively. Both patients with JLNS and LQT1 (or LQT5) usually have QTc prolongation on their ECGs; they could suffer from cardiac arrhythmias, repeated syncope, and also from sudden cardiac deaths; symptoms usually are provoked by adrenergic stimulation. But, the dogma of single mutation synonymous with \[I_{Ks}\] was challenged when a case of LQT1 with double \[I_{Ks}\] channel (homozygous) mutation in the \[KCNQ1\] gene was reported.\[I_{Ks}\]

Subsequently, multiple reports of autosomal recessive (AR) LQT1 without any auditory phenotype have appeared.\[I_{Ks}\]

In 2007, we have reported several children with AR LQT1 in the southern part of Saudi Arabia. On molecular analysis, we found a homozygous mutation c.387-5T>A in the intron 1 (ie, upstream of exon-2) of the \[KCNQ1\] gene, which caused skipping of exon-2, leading to aberrant \[KCNQ1\] mRNA and eventually affecting the \[I_{Ks}\] property. None of our patients with the homozygous mutation had any hearing defect, but, on the contrary, patients with exon-2 skipping mutation from Germany had JLNS, that is, patients had both the cardiac and auditory phenotype. Molecular analysis led us to decipher the pathophysiology into the discordance of phenotypes. In the patients from Saudi Arabia, despite exon-2 skipping, 10% of the \[KCNQ1\] allele transcribed normally, and eventually, patients still had >10% of normal \[I_{Ks}\], which was the only difference between the patients reported by Zehelein et al (2006) and Bhuiyan et al (2007). These findings could be considered a direct proof about the \[I_{Ks}\] dose requirement in maintaining the hearing and lead to the conclusion that the ear clearly needs less \[I_{Ks}\] than the heart to function properly.

So, it is now well-established fact that homozygous/compound heterozygous mutations in the \[KCNQ1\] gene could cause a cardiac only phenotype (ie, AR LQT1), but, the question remains whether this cardiac only phenotype is comparable to the patients who harbor only a single mutation. In case, if there exists any discordance in cardiac phenotype severity, to what extent the severity implies? This, perhaps, intrigued Giudicessi and Ackerman\[I_{Ks}\] to conduct the study that they published in the present issue of this journal. Clinical and ECG data from the patients discussed above showed that all patients with homozygous mutations (with or without hearing defect) had baseline (without provocation) QTc >500 ms and also had comparatively severe cardiac events. But, a (genotyped) cohort study on this matter was not available. Giudicessi and Ackerman\[I_{Ks}\] conducted a retrospective analysis among the homozygous (compound heterozygous) mutation carriers in the \[KCNQ1\] gene. The authors also looked at the mutation types and their location, which might influence the cardiac or hearing phenotype.\[I_{Ks}\]

Of 15 patients with biallelic (homozygous/compound heterozygous), \[KCNQ1\] mutations from the Mayo Clinic’s LQT syndrome clinic, only 4 patients had JLNS, and the remaining 11 patients were classified as AR LQT1. To increase the numbers, they included published clinical and genotype data. Nontruncating mutations (missense or in-frame small deletions) were differentiated from truncating (nonsense, frame-shift, or splice site) mutations; patients with JLNS had significantly more truncating mutations compared with AR LQT1 cases, which probably is not unexpected.

**I_{Ks} in Heart and Hearing, the Ear Can Do with Less than the Heart**

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because functional analysis results were more in favor for such finding.9,14,15 Mutation location did not make any difference that could make a differentiation between the patients between JLNS and recessive LQT1.16 Patients with AR LQT1 had more frequently a family history of LQT-related serious events compared with patients with JLNS, and they tended to be more seriously affected (Table 2 in ref 16); perhaps, this requires further study in a larger cohort.

We attempted to summarize the present (ref 16) and earlier published data in NCBI into a general scheme (Figure). Homozygosity (or biallelic compound heterozygosity) of truncating nonsense mutations (including insertions/deletions) will give rise to JLNS. Homozygosity of an exon skipping mutation will also lead to JLNS, when there is no residual protein production. In case of incomplete exon skipping, with residual protein levels as low as 10%, will result in AR LQT1.14 Heterozygosity of any of these mutations will usually lead to a mild phenotype. Homozygosity (or biallelic compound heterozygosity) of missense mutations that lead to a protein product that does not traffick to the cell membrane (or is subject to nonsense mediated decay) will lead to JLNS. In contrast, homozygosity (or biallelic compound heterozygosity) of missense mutations that impact on channel function and do express into the membrane lead to AR LQT1. Ala300Thr mutation in the KCNQ1 gene may serve, in this context, as an example in not causing a total loss of I(Ks).9 Apparently, in homozygous Ala300Thr mutation carriers, residual I(Ks) through aberrant channels is enough to maintain the K+ homeostasis in the inner ear endolymph to keep auditory function intact.9 Heterozygosity of a missense mutation will usually lead to a severe phenotype, when their product trafficks properly and stably expresses in the cell membrane, and will lead to a milder phenotype, when their product does not make it to the cell membrane (completely or significantly lesser extent or less stable if transported) for whatever reason (Figure). Complicating factors are of course the modifying genes (eg, NOS1AP), and the explored and yet unexplored various genetic and interacting factors influencing expression of KCNQ1 protein.17,18

On the basis of this reasoning, one could potentially draw conclusions on the functional characteristics of the several variants identified in the Mayo cohort. Hence, the missense mutations identified in their JLNS cases that associate with a nonsense mutation most likely do not make it to the membrane (ie, C122Y and D202N), the caveat being that there is differential expression in the heart and the ear. To the contrary, missense mutations in AR LQT1 cases that associate with a nonsense mutation (or are homozygous) should traffick to the membrane (G179S, G568R, V524G, K362R, V215M). It is likely that the clinical phenotype of the heterozygous carriers of the former group (C122Y and D202N) will be less severe and comparable to nonsense mutations, than the phenotype of the latter group (mutations that do traffick to the membrane).

**Disclosures**

Dr Wilde is a member of the Advisory Board of Sorin.

**References**


**Key Words:** Editorials, genetics, genotype, long QT syndrome, potassium channels
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