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Jervell and Lange-Nielsen Syndrome

Synonym: JLNS

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Summary

Clinical characteristics

Jervell and Lange-Nielsen syndrome (JLNS) is characterized by congenital profound bilateral sensorineural hearing loss and long QTc, usually >500 msec. Prolongation of the QTc interval is associated with tachyarrhythmias, including ventricular tachycardia, episodes of *torsade de pointes* ventricular tachycardia, and ventricular fibrillation, which may culminate in syncope or sudden death. Iron-deficient anemia and elevated levels of gastrin are also frequent features of JLNS. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright. Fifty percent of individuals with JLNS had cardiac events before age three years. More than half of untreated children with JLNS die before age 15 years.

Diagnosis/testing

The diagnosis of JLNS is established in a child with congenital sensorineural deafness, long QT interval, and presence of biallelic pathogenic variants in either *KCNQ1* or *KCNE1*.

Management

Treatment of manifestations: Cochlear implantation to treat hearing loss; beta-adrenergic blockers for long QT interval (Note: Beta-blocker treatment is only partially effective.); implantable cardioverter defibrillators (ICDs) for those with a history of cardiac arrest and/or failure to respond to other treatments; ensure availability of automated external defibrillators where appropriate; standard treatment for those with iron-deficiency anemia.

Prevention of secondary complications: Special precautions during anesthesia are necessary because of the increased risk for cardiac arrhythmia.

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Surveillance: Beta-blocker dose should be regularly assessed for efficacy and adverse effects, with evaluation every three to six months during rapid growth phases; periodic evaluations of ICDs for inappropriate shocks and pocket or lead complications.

Agents/circumstances to avoid: Drugs that cause further prolongation of the QT interval; activities known to precipitate syncopal events in persons with long QT syndrome.

Evaluation of relatives at risk: Hearing evaluation by standard newborn hearing screening programs and electrocardiograms for at-risk sibs; molecular genetic testing to confirm the diagnosis if the pathogenic variants in an affected family member are known.

Pregnancy management: Consideration should be given as to whether a mother who has a fetus affected with JLNS herself has long QT syndrome.

Other: Training for family members in cardiopulmonary resuscitation; use of an ID bracelet explaining the diagnosis; notifying local emergency medical services of high-risk persons with JLNS.

Genetic counseling

JLNS is inherited in an autosomal recessive manner. Parents of a child with JLNS are usually heterozygotes; rarely, only one parent is heterozygous (i.e., the proband has one inherited and one *de novo* pathogenic variant). Parents may or may not have the long QT syndrome (LQTS) phenotype. At conception, each sib of an affected individual usually has a 25% chance of being affected with JLNS, a 50% chance of being a carrier of a JLNS-causing pathogenic variant and potentially at risk for LQTS, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Jervell and Lange-Nielsen syndrome (JLNS) **should be suspected** in a proband with the following features:

- Profound congenital sensorineural deafness
- Long QTc interval (>500 msec), often manifest as syncope, most often elicited by emotion or exercise.
  Note: Normal QTc interval in males is <440 msec and in post-pubertal females is <460 msec.

Establishing the Diagnosis

The diagnosis of JLNS **is established** in a proband with the above suggestive findings. Identification of biallelic pathogenic (or likely pathogenic) variants in either *KCNQ1* or *KCNE1* confirms the diagnosis, particularly if clinical features are inconclusive.

Note: (1) It is not currently known how many children with molecularly confirmed JLNS have a borderline QTc interval (440-500 msec) or a normal QTc interval. (2) Hearing loss commonly occurs in individuals with long QT syndrome (LQTS). The hearing loss may be entirely unrelated to the etiology of the LQTS, particularly if the hearing loss is moderate. (3) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (4) Identification of biallelic *KCNQ1* or *KCNE1* variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Serial single-gene testing.** Sequence analysis of *KCNQ1* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found. If only one or no *KCNQ1* pathogenic variant is identified, sequence analysis of *KCNE1* should be performed next.

  In countries with *KCNQ1* founder variants (e.g., Norway) *KCNQ1* sequencing should be carried out with knowledge of these variants to ensure they will be detected (see Molecular Genetics) [Tranebjærg et al 1999, Tranebjærg 2004, Berge et al 2008, Siem et al 2008].

- **A multigene panel** that includes *KCNE1, KCNQ1* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **More comprehensive genomic testing** (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Jervell and Lange-Nielsen Syndrome

Gene [1, 2]	Proportion of JLNS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
KCNE1	<10% [6]	~100% [7]	See footnote 8.

Table 1. continued from previous page.

Gene [1, 2]	Proportion of JLNS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
KCNQ1	~90% [6]	>95%	1 family [9, 10]

1. Genes are listed alphabetically.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. In a study of ten families, nine had pathogenic variants in *KCNQ1* [Tyson et al 2000]. Of 63 families, six (9.5%) had pathogenic variants in *KCNE1* [Schwartz et al 2006]. None of the individuals of Norwegian ancestry with JLNS have been shown to have *KCNE1* pathogenic variants [Tranebjærg et al 1999, Berge et al 2008, Siem et al 2008]. Pathogenic variants have been found in either *KCNQ1* or *KCNE1* in 94% of individuals with clinical JLNS undergoing molecular testing [Schwartz et al 2006].
7. Three variants in *KCNE1*, all detectable by Sanger sequencing, have been associated with JLNS [Schulze-Bahr et al 1997, Tyson et al 1997].
8. No deletions or duplications of *KCNE1* have been reported to cause JLNS.
9. Sung et al [2014]
10. Both deletion and duplication of one or more exons of *KCNQ1* are known to cause long QT syndrome [Zehelein et al 2006, Eddy et al 2008, Sung et al 2014]; their frequency is unknown.

Clinical Characteristics

Clinical Description

The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright.

Hearing loss. All individuals with molecularly confirmed JLNS have profound bilateral congenital sensorineural deafness (see Genetic Hearing Loss Overview).

Long QTc. Individuals with JLNS have a QTc interval greater than 500 msec (average 550 msec), indicating increased time for ventricular depolarization and repolarization [Winbo et al 2012, Winbo et al 2014]. Abnormal cardiac depolarization and repolarization may result in tachyarrhythmias (including ventricular tachycardia, episodes of *torsade de pointes* ventricular tachycardia, and ventricular fibrillation), which may culminate in syncope or sudden death.

QTc prolongation in JLNS, particularly when severe, appears to be associated with increased risk for death in infancy (SIDS). In the Schwartz et al [2006] study of 135 families with JLNS, the QTc was markedly prolonged (557±65 msec); 50% of individuals had cardiac events before age three years, with emotion and exercise being the primary triggers. Although more than half of untreated children with JLNS die before age 15 years, some individuals are reported to have survived several syncopal episodes during adulthood. Note, however, that selection bias for severely affected individuals cannot be excluded: individuals with putative JLNS but no clinical manifestations other than deafness until adulthood (and to age 50 years in one individual) have been described.

Anemia. Individuals with *KCNQ1*-related JLNS have an increased incidence of iron deficiency anemia and hypergastrinemia [Winbo et al 2013]. This may be due to loss of the KCNQ1 potassium channels and reduced gastric acid secretion.

Other. The sex ratio among individuals with JLNS is even, but females are at lower risk for cardiac arrest/sudden death [Schwartz et al 2006]. Vestibular dysfunction was found in 14/14 deaf individuals with JLNS, irrespective of previous cochlear implantation. The proposed mechanism was disruption of the endolymph homeostasis [Winbo & Rydberg 2015]

Physical examination is unremarkable except for deafness.

Heterozygotes. Individuals who are heterozygous for pathogenic variants associated with JLNS usually have normal hearing. In some heterozygotes, QTc prolongation, fainting, and sudden death never occur. In contrast, some individuals heterozygous for pathogenic variants associated with JLNS may have QTc prolongation associated with fainting and death heritable in an autosomal dominant manner. This form of LQTS is called Romano-Ward syndrome (RWS).

Histopathology of temporal bone. Histologic examination of a few temporal bones was performed prior to the availability of molecular genetic testing, but not since. In one Norwegian individual with JLNS resulting from homozygosity for the c.572_576del pathogenic variant in *KCNQ1*, histopathologic examination of the temporal bones showed severe atrophy of the stria vascularis and the organ of Corti with absence of cochlear nerve fibers [Tranebjærg L & Merchant SM, unpublished data (2012)].

Phenotype Correlations by Gene

Among six asymptomatic individuals reported by Schwartz et al [2006], two had biallelic *KCNQ1* pathogenic variants and four had biallelic *KCNE1* pathogenic variants, further confirming the milder presentation of JLNS associated with *KCNE1* pathogenic variants compared to JLNS associated with *KCNQ1* pathogenic variants.

***KCNQ1*.** Individuals with *KCNQ1*-related JLNS have an increased incidence of iron deficiency anemia and hypergastrinemia [Winbo et al 2013].

Genotype-Phenotype Correlations

Among 63 individuals who were genotyped, 33% were compound heterozygotes [Schwartz et al 2006]. No clinical difference was evident between persons with at least one inactivating variant (e.g., insertion/deletion, splice variant, truncation) and those with missense variants.

Nomenclature

Lange-Nielsen syndrome has also been called cardioauditory syndrome of Jervell and Lange-Nielsen and surdo-cardiac syndrome.

JLNS is now appreciated to be a true syndrome, in which the cardiac and cochlear pathologies are attributable to a common molecular etiology. Although there are several case reports in the older literature of individuals with long QT syndrome and non-profound hearing loss, in many of these reports it is likely that the hearing loss and prolonged QT interval have different etiologies (see Differential Diagnosis).

Prevalence

Prevalence varies depending on the population studied:

- Norway has an unusually high prevalence of at least one in 200,000 [Tranebjærg et al 1999]. This prevalence stems from four Norwegian founder variants [Berge et al 2008, Siem et al 2008, Winbo et al 2012].
- Sweden also has a prevalence of one in 200,000 based on a study of preadolescent children, identifying 19 affected individuals from 13 families. Eight *KCNQ1* pathogenic variants were identified, of which

p.Arg518Ter constituted 12/24 alleles [Winbo et al 2012]. Founder variants accounted for 83% of pathogenic variants [Winbo et al 2014].
- In a study of 350 children with congenital deafness in Turkey, one in 175 had JLNS [Ocal et al 1997].
- A particular missense *KCNQ1* variant has been identified in the heterozygous state in autosomal dominant LQTS and in the homozygous state in JLNS in a few individuals from Finland; however, prevalence of JLNS was not increased in Finland [Piippo et al 2001].
- An overview of worldwide occurrence was published by Tranebjærg [2004]

These data are the best available; however, diagnostic criteria using a QTc >440 msec in children are likely to include some false positives, perhaps as many as 15%-20% [Allan et al 2001]. The design of the review by Schwartz et al [2006] did not allow refinement of prevalence estimates.

Genetically Related (Allelic) Disorders

Heterozygosity for pathogenic variants in *KCNQ1* and *KCNE1* has been observed in children without hearing loss who have long QT syndrome (LQTS) inherited in an autosomal dominant manner [Towbin et al 2001] (also called Romano-Ward syndrome) (see Differential Diagnosis).

Differential Diagnosis

Deafness and prolonged QTc with or without long QT syndrome (LQTS) both have multiple etiologies, including genetic and environmental causes. In many individuals with both deafness and prolonged QTc (or LQTS), the deafness and prolonged QTc (or LQTS) have separate etiologies. All of these possibilities must be considered in each affected individual, particularly in the absence of parental consanguinity or an affected sib. The following considerations are relevant in an individual who has both deafness and prolonged QTc:

- Prior to the availability of molecular genetic testing, the diagnosis of Jervell and Lange-Nielsen syndrome (JLNS) was based on clinical criteria alone. (Romano-Ward syndrome was commonly diagnosed in persons with LQTS and normal hearing.)
- Some children with JLNS may be misdiagnosed with epilepsy and incorrectly treated with anti-seizure medication before the correct diagnosis of JLNS is established [Tranebjærg et al 1999].

Long QT syndrome. Long QT multigene panels may include testing for a number of the genes related to disorders discussed in this section. Note: The genes involved and methods used vary by laboratory.

Romano-Ward syndrome. The term "Romano-Ward syndrome" (RWS) refers to forms of long QT syndrome with a purely cardiac electrophysiologic disorder, inherited in an autosomal dominant manner (LQTS types 1-3, type 5, type 6, and types 9-15). RWS is characterized by QT prolongation and T-wave abnormalities on EKG and the ventricular tachycardia *torsade de pointes* (TdP). The diagnosis of RWS is made on the basis of a prolonged QT interval on EKG, clinical presentation, and family history; or identification of a pathogenic variant in one or more of the 15 genes known to be associated with LQTS (of which *KCNQ1*, *KCNH2*, and *SCN5A* are the most common) in the absence of profound congenital sensorineural deafness (the presence of which is highly suggestive of Jervell and Lange-Nielsen syndrome). Individuals with pathogenic variants in *KCNE1* may also have atrial fibrillation [Olesen et al 2012]. Diagnostic criteria have been established for the resting EKG QTc value in the absence of specific conditions known to lengthen the QTc interval. For a summary of the genes known to be associated with RWS, see Long QT Syndrome. Only *KCNQ1* and *KCNE1* have been implicated in both RWS and JLNS.

Timothy syndrome is a multisystem disorder characterized by cardiac, hand/foot, facial, and neurodevelopmental features. Typical cardiac findings include a rate-corrected QT interval >480 msec,

functional 2:1 AV block with bradycardia, tachyarrhythmias, and congenital heart defects (patent ductus arteriosus, patent foramen ovale, ventricular septal defect, tetralogy of Fallot, hypertrophic cardiomyopathy).

Andersen-Tawil syndrome is characterized by a triad of episodic flaccid muscle weakness (i.e., periodic paralysis), ventricular arrhythmias and prolonged QT interval, and anomalies including low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis.

Acquired causes of QTc interval prolongation include the following:

- Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia
- Malnutrition or liquid protein diet
- Drugs: vasodilators, tricyclic antidepressants, organophosphates, antihistamines, phenothiazines, procainamide, disopyramide, quinidine, and many others. For a complete, updated list see www.crediblemeds.org (registration required).
- Primary myocardial problems: cardiomyopathy, myocarditis, ischemia
- Central nervous or autonomic system injury; subarachnoid hemorrhage; stellate ganglion blockade

Hearing loss. The differential diagnosis for hearing loss includes consideration of other forms of syndromic and nonsyndromic disorders, as well as acquired disorders. For more information on hereditary hearing loss, see Genetic Hearing Loss Overview.

One disorder that should be noted specifically is DFNB1, the most common autosomal recessive form of nonsyndromic hearing loss. DFNB1 is characterized by congenital, non-progressive, mild-to-profound sensorineural hearing impairment. No other associated medical findings are present. Diagnosis of DFNB1 depends on molecular genetic testing to identify biallelic pathogenic variants in *GJB2* (sequence variants as well as variants in upstream *cis*-regulatory elements that alter expression of the gap junction beta-2 protein [connexin 26]). JLNS should be suspected in any infant who has profound bilateral sensorineural hearing loss, no identifiable *GJB2* pathogenic variants, and a normal physical examination.

Brugada syndrome is characterized by cardiac conduction abnormalities (ST-segment abnormalities in leads V1-V3 on EKG and a high risk for ventricular arrhythmias) that can result in sudden death.

Sudden infant death syndrome (SIDS) (OMIM 272120). Data from multicenter studies indicate that 9.5% of infants with SIDS may be heterozygous for functionally significant variants in one of the known LQTS-related genes. Sudden arrhythmic death may thus be an important contributor to SIDS; it is unknown what proportion of infants with SIDS have or would develop profound hearing impairment. Implementation of universal neonatal hearing screening, supplemented with early electrocardiography, may have the potential to identify high-risk children. However, a recent large population study did not find a higher incidence of JLNS in newborns identified with hearing loss by universal screening [Chang et al 2014].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Jervell and Lange-Nielsen syndrome (JLNS), the following evaluations are recommended if they have not already been completed:

- Formal audiology evaluation for extent of hearing loss
- Cardiac examination including calculation of QTc
- A three-generation family history that focuses on cardiac disease, syncope, and hearing ability
- Complete blood count to screen for anemia. If anemia is present, screening for iron deficiency is recommended.
- Consultation with a clinical geneticist

Treatment of Manifestations

Hearing loss in JLNS may be treated successfully with cochlear implantation, an intervention that does not interfere with bipolar pacemakers [Green et al 2000, Chorbachi et al 2002] (see Genetic Hearing Loss Overview). To date, the cumulative published experience includes approximately 20 individuals with JLNS who have received cochlear implantation. Of note, the diagnosis of JLNS was only verified with molecular genetic testing in four Norwegian individuals, all of whom had pathogenic variants in *KCNQ1*. An increase in sound-related syncopal episodes was noted after cochlear implantation in one child [Al-Aama et al 2015].

Note: Although cochlear implantation appears to be safe, special precautions are necessary during anesthesia because of the increased risk for cardiac arrhythmia [Daneshi et al 2008, Siem et al 2008, Yanmei et al 2008]. One affected individual died during a perioperative cardiac arrest [Broomfield et al 2010].

Cardiac issues. The main goal in management of JLNS is prevention of syncope, cardiac arrest, and sudden death. Note that efficacy of beta-blocker treatment is only partial: 51% of treated individuals had cardiac events and 27% had cardiac arrest or sudden death. Even with additional therapies (e.g., pacemaker, implantable cardioverter/defibrillator, left sympathetic denervation), 18 (56%) of 32 individuals experienced additional symptoms, including sudden death in seven [Schwartz et al 2006].

- Administration of beta-adrenergic blockers has been the traditional first-line medical therapy for cardiac events, but more aggressive, immediate treatment may be appropriate. Cardiac events in JLNS frequently occur despite beta blockade [Schwartz et al 2006]. Goldenberg et al [2006] demonstrated markedly increased mortality in individuals with JLNS treated exclusively with beta-blockers in comparison to individuals with Romano-Ward syndrome. A mortality rate of 35% over five years was observed for individuals receiving beta-blockers exclusively; 86% of individuals treated exclusively with beta-blockers experienced a cardiac event. The interactions of beta-blockers with other medical conditions (e.g., asthma, diabetes mellitus, depression) should also be considered. Propranolol and nadolol have been shown to be more effective than metoprolol in suppressing cardiac events [Chockalingam et al 2012, Winbo et al 2014]. A recent consensus statement advocates use of nadolol as the preferred beta-blocker for drug therapy of individuals with long QT syndrome [Ackerman et al 2017].
- Implantable cardioverter defibrillators (ICDs) should be considered in individuals with a history of cardiac arrest or failure to respond to other treatments [Goel et al 2004]. More recent recommendations have strongly urged ICD placement for high-risk individuals, defined by the following criteria [Schwartz et al 2006]:
  - QTc interval >550 msec
  - Syncope before age five years
  - Male sex, age >20 years with *KCNQ1* pathogenic variant
- The risk for sudden cardiac death appears to be low in individuals younger than age five years, but medical therapy should be administered early in these high-risk individuals and ICD placement considered after age five years [Richter & Brugada 2006].
- In certain cases, the availability of automated external defibrillators in the home, workplace, or school may be applicable, as is appropriate CPR training of family members and those who have regular contact with individuals with JLNS.
- Left cardiac sympathetic denervation has been effective for some individuals.

Iron deficiency anemia. The treatment of iron deficiency anemia should follow standard guidelines.

Prevention of Primary Manifestations

See Treatment of Manifestations regarding prevention of syncope, cardiac arrest, and sudden death.

Prevention of Secondary Complications

Special precautions during anesthesia are necessary because of the increased risk for cardiac arrhythmia [Daneshi et al 2008, Siem et al 2008, Yanmei et al 2008].

Surveillance

Beta-blocker dose should be regularly assessed for efficacy and adverse effects, and doses altered as needed. Because dose adjustment is especially important in growing children, evaluation is appropriate every three to six months during rapid growth phases.

Regular, periodic evaluation of implantable cardioverter defibrillators (ICDs) for inappropriate shocks and pocket or lead complications is indicated.

Agents/Circumstances to Avoid

The following should be avoided:

- Drugs that cause further prolongation of the QT interval or provoke *torsade de pointes*; see www.crediblemeds.org for a complete and updated list (registration required).
- Triggers for intense or sudden emotion; activities that are known to precipitate syncopal events in individuals with long QT syndrome, including:
  - Competitive sports
  - Amusement park rides
  - Frightening movies
  - Jumping into cold water

A cardiologist should make recommendations for activity restrictions based on the effectiveness of medical intervention.

Evaluation of Relatives at Risk

It is appropriate to evaluate sibs and parents of a proband in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk family members.
- If the pathogenic variants in the family are not known, EKG testing should be undertaken to evaluate for QT prolongation.
- Standard newborn screening programs are sufficient to identify hearing loss in children with JLNS.

Because of the relationship between JLNS and long QT syndrome, EKG should be considered for relatives at risk for JLNS even if they have normal hearing.

If the JLNS-causing pathogenic variants in an affected family member are known, molecular genetic testing of a relative with congenital profound sensorineural hearing loss is recommended to confirm the diagnosis of JLNS.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Consideration should be given as to whether a mother who has a fetus affected with JLNS herself has long QT syndrome [Seth et al 2007].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Family members of individuals with JLNS should be trained in cardiopulmonary resuscitation (CPR) as up to 95% of individuals with JLNS have a cardiac event before adulthood [Schwartz et al 2006].

Affected individuals should wear an ID bracelet explaining their diagnosis.

It is appropriate to notify local emergency medical services (EMS) of high-risk persons, including those with JLNS [Hazinski et al 2004].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Jervell and Lange-Nielsen syndrome (JLNS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- Parents of a child with JLNS are usually obligate heterozygotes (i.e., carriers of one *KCNQ1* or *KCNE1* pathogenic variant). In rare cases, only one parent is heterozygous and the other pathogenic variant in the proband is *de novo* [Schwartz et al 2000].
- Parents may or may not have the long QT syndrome (LQTS) phenotype. Studies have documented autosomal dominant inheritance of moderately prolonged QTc intervals in some, but not all, families in which one or more sibs have JLNS [Splawski et al 1997].
- Recommendations for evaluation of the parents of a child with JLNS include:
  - Molecular genetic testing if the pathogenic variants have been identified;
  - Comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Sibs of a proband

- If both parents of the proband are heterozygous for a JLNS-related pathogenic variant (i.e., both of the variants identified in the proband are inherited), the typical risks at conception to each sib are:
  - A 25% chance of inheriting two pathogenic variants and being affected with JLNS;
  - A 50% chance of inheriting one pathogenic variant. A sib who inherits one pathogenic variant would not be expected to have JLNS but is at risk for LQTS if the inherited pathogenic variant is associated with the LQTS phenotype (approximately 67% of JLNS-associated pathogenic variants are also known to also be associated with autosomal dominant LQTS) [Al-Aama et al 2015];

    - A 25% chance of inheriting neither of the pathogenic variants identified in the proband. A sib who inherits neither of the JLNS-related pathogenic variants is not at increased risk for JLNS or, potentially, LQTS.
- If only one parent of the proband is heterozygous for a JLNS-related pathogenic variant (i.e., the proband has one inherited and one *de novo* pathogenic variant), sibs are not at increased risk for JLNS but 50% are potentially at risk for LQTS if the inherited pathogenic variant is associated with the LQTS phenotype.
- Recommendations for evaluation of sibs of a proband with JLNS include:
    - Audiology evaluation;
    - Electrophysiologic evaluation for evidence of LQTS;
    - Molecular genetic testing if the pathogenic variants in the proband are known;
    - Comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Offspring of a proband

- The offspring of an individual with JLNS inherit one pathogenic variant; thus, 100% of the proband's offspring are potentially at risk for LQTS.
- In the event that the reproductive partner of the proband is also heterozygous for a pathogenic variant in the same gene in which two pathogenic variants have been identified in the proband, the risk to offspring of having JLNS is 50%.
- Recommendations for evaluation of the offspring of an individual with JLNS include comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Other family members. Sibs of a proband's parents may also be at 50% risk of having a pathogenic variant in *KCNQ1* or *KCNE1* and at potential risk for LQTS.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *KCNQ1* or *KCNE1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Because prolonged QTc interval in families with JLNS may follow an autosomal dominant inheritance pattern, it is important that family members at risk undergo electrocardiographic testing for evidence of LQTS early in life. Individuals with LQTS are at increased risk for sudden death and thus require cardiologic intervention. The actual risk for LQTS in family members of individuals with JLNS is not known.

Individuals who are heterozygous for a JLNS-related pathogenic variant have a single pathogenic variant in a gene associated with LQTS that may cause QTc prolongation or LQTS in either a clinically significant or clinically insignificant form. Whether the variant is clinically significant or insignificant, it may be transmitted in a clinically significant fashion to future generations as either autosomal dominant LQTS (i.e., Romano-Ward syndrome) or JLNS, a confusing phenomenon during pedigree evaluation.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygous, or are at risk of being heterozygous.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *KCNQ1* or *KCNE1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Jervell and Lange-Nielsen syndrome
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  Phone: 801-948-0654
  www.sads.org
- **International Long QT Syndrome Registry**
  Heart Research Follow-Up Program
  Phone: 585-276-0016
  Fax: 585-273-5283
  Email: heartajm@heart.rochester.edu

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Jervell and Lange-Nielsen Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KCNE1	21q22.12	Potassium voltage-gated channel subfamily E member 1	CCHMC - Human Genetics Mutation Database (KCNE1) KCNE1 @ ZAC-GGM	KCNE1	KCNE1

Table A. continued from previous page.

KCNQ1	11p15.5-p15.4	Potassium voltage-gated channel subfamily KQT member 1	KCNQ1 @ LOVD KCNQ1 @ ZAC-GGM	KCNQ1	KCNQ1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Jervell and Lange-Nielsen Syndrome (View All in OMIM)

176261	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 1; KCNE1
220400	JERVELL AND LANGE-NIELSEN SYNDROME 1; JLNS1
607542	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 1; KCNQ1
612347	JERVELL AND LANGE-NIELSEN SYNDROME 2; JLNS2

Molecular Pathogenesis

Jervell and Lange-Nielsen syndrome (JLNS) is caused by an aberration in a potassium channel found in the stria vascularis of the cochlea (inner ear) and the heart. Note that a minority of pathogenic variants in *KCNQ1* and *KCNE1* cause JLNS; the majority cause LQTS (see Differential Diagnosis).

- *KCNQ1* and *KCNE1* encode the alpha and beta subunit proteins (K_VLQT1/minK) for the slow potassium current, I_{Ks} of the cochlea and the heart.
- When stimulated by sound, potassium from the scala media of the cochlea passes through the apex of the hair cells, depolarizing the hair cells and causing a calcium-channel-induced release of neurotransmitter onto the auditory nerve. Depolarizations of the auditory nerve are sent centrally where they are perceived as sound. The maintenance of high potassium concentration in the endolymphatic fluid of the inner ear is required for normal hearing. The potassium-rich fluid of the scala media is created by the I_{Ks} potassium channels (exclusively K_VLQT1/minK) in the stria vascularis.
- Malfunction in these channels in the cochlea causes deafness.
- Malfunction in these channels in the heart results in abnormal ventricular electrical activity and LQTS.

KCNQ1

Gene structure. *KCNQ1* consists of 16 exons spanning approximately 400 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Nearly 30 of the more than 500 reported pathogenic variants in *KCNQ1* are associated with JLNS; ten result in frameshift and premature truncation [Tyson et al 2000, Wang et al 2002, Ning et al 2003, Zehelein et al 2006, Bhuiyan et al 2008, Ohno et al 2008, Zhang et al 2008, Baek et al 2010, Wang et al 2011, Gao et al 2012]. Both deletion and duplication of one or more exons of *KCNQ1* are known to cause long QT syndrome [Zehelein et al 2006, Eddy et al 2008, Sung et al 2014].

In individuals of Norwegian descent, it is important to confirm that molecular genetic testing includes detection of the most common *KCNQ1* pathogenic variants reported in this population: c.573_577delGCGCT, p.Arg518Ter, and p.Gln530Ter [Tranebjærg et al 1999].

Table 2. *KCNQ1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.1552C>T	p.Arg518Ter [2]	NM_000218.2 NP_000209.2
c.1588C>T	p.Gln530Ter	
c.573_577delGCGCT (572del5 or 575del5)	p.Arg192CysfsTer91	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. See Prevalence.

Normal gene product. The gene product is potassium voltage-gated channel subfamily KQT member 1 (also known as voltage-gated potassium channel protein KvLQT1); this alpha subunit has six transmembrane regions and forms a heteromultimer with the protein encoded by *KCNE1* to form the functional channel I_{Ks}.

Abnormal gene product. Pathogenic variants in the gene result in premature truncation and inability to form multimers with the protein encoded by *KCNE1* to form the functional channel I_{Ks}. In a mouse model, recessive variants may exhibit a dominant-negative effect that is not clinically observed in affected individuals, suggesting post-translational processing effects in vivo [Thomas et al 2007, Hothi et al 2009].

KCNE1

Gene structure. *KCNE1* consists of three exons spanning approximately 40 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Four pathogenic variants associated with JLNS have been identified in *KCNE1*, all of which are missense. The majority of pathogenic variants in *KCNE1* are associated with LQTS.

Normal gene product. Potassium voltage-gated channel subfamily E member 1 (also known as minK potassium channel protein beta subunit) is a protein of 130 amino acids with one transmembrane region. It forms multimers with the protein encoded by *KCNQ1* to form the functional channel I_{Ks}.

Abnormal gene product. The specific effect of each pathogenic variant differs in the manner in which it impairs potassium channel function.

Chapter Notes

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References

Published Guidelines / Consensus Statements

American College of Medical Genetics. Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. Genetic evaluation of congenital hearing loss expert panel. Available online. 2002. Accessed 8-17-23.

American College of Medical Genetics. Statement on universal newborn hearing screening. Available online. 2000. Accessed 8-17-23.

Literature Cited

Ackerman MJ, Priori SG, Anne Dubin A, Kowey P, Linker NJ, Slotwiner D, Triedman J, Van Hare GF, Gold MR. Beta blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: are all beta blockers equivalent? Heart Rhythm. 2017;14:e41-e44. PubMed PMID: 27659101.

Al-Aama JY, Al-Ghamdi S, Bdier AY, AlQarawi A, Jiman OA, Al-Aama N, Al-Aata J, Wilde AA, Bhuiyan ZA. Genotype-phenotype analysis of Jervell and Lange-Nielsen syndrome in six families from Saudi Arabia. Clin Genet. 2015;87:74-9. PubMed PMID: 24372464.

Allan WC, Timothy K, Vincent GM, Palomaki GE, Neveux LM, Haddow JE. Long QT syndrome in children: the value of the rate corrected QT interval in children who present with fainting. J Med Screen 2001;8:178-82 PubMed PMID: 11743033.

Baek JS, Bae EJ, Lee SY, Park SS, Kim SY, Jung KN, Noh CI (2010) Jervell and Lange-Nielsen syndrome: novel compound heterozygous mutations in the KCNQ1 in a Korean family. J Korean Med Sci. 25:1522-5. PubMed PMID: 20890437.

Berge KE, Haugaa KH, Früh A, Anfinsen O-G, Gjjesdaj K, Siem G, Øyen N, Greve G, Carlsson A, Rognum TO, Hallerud M, Kongsgård E, Amlie JP, Leren TP. Molecular genetic analysis of long QT syndrome in Norway indicating a high prevalence of heterozygous mutation carriers. Scand J Clin Lab Invest 2008; 68:362-8 PubMed PMID: 18752142.

Bhuiyan ZA, Momenah TS, Amin AS, Al-Khadra AS, Alders M, Wilde AA, Mannens MM (2008) An intronic mutation leading to incomplete skipping of exon-2 in KCNQ1 rescues hearing in Jervell and Lange-Nielsen syndrome. Prog Biophys Mol Biol. 98:319-27. PubMed PMID: 19027783.

Broomfield SJ, Bruce IA, Henderson L, Green KMJ, Ramsden RT. Cochlear impantation in Jervell & Lange-Nielsen syndrome: a cautionary report. Cochlear Implants Int. 2010;11:163-5 PubMed PMID: 21756604.

Chang RK, Lan YT, Silka MJ, Morrow H, Kwong A, Smith-Lang J, Wallerstein R, Lin HJ. Genetic variants for long QT syndrome among infants and children from a statewide newborn hearing screening program cohort. J Pediatr. 2014;164:590-5.e1-3.

Chockalingam P, Crotti L, Girardengo G, Johnson JN, Harris KM, van der Heijden JF, Hauer RNW, Beckmann BM, Spazzolini C, Rordorf R, Rydberg A, Clur SB, Fischer M, van den Heuvel F, Kaab S, Blom NA,

Ackerman MJ, Schwartz PJ, Wilde AAM. Not All beta-blockers are equal in the management of long QT syndrome types 1 and 2. J Am Coll Cardiol 2012;60:2092-9. PubMed PMID: 23083782.

Chorbachi R, Graham JM, Ford J, Raine CH. Cochlear implantation in Jervell and Lange-Nielsen syndrome. Int J Pediatr Otorhinolaryngol 2002;66:213-21 PubMed PMID: 12443809.

Daneshi A, Ghassemi MM, Talee M, Hassanzadeh S. Cochlear implantation in children with Jervell and Lange-Nielsen syndrpome J Laryngol Otol 2008;122:314-7 PubMed PMID: 17498328.

Eddy CA, MacCormick JM, Chung SK, Crawford JR, Love DR, Rees MI, Skinner JR, Shelling AN. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. Heart Rhythm 2008; 5:1275-81 PubMed PMID: 18774102.

Gao Y, Li C, Liu W, Wu R, Qiu X, Liang R, Li L, Zhang L, Hu D (2012) Genotype-phenotype analysis of three Chinese families with Jervell and Lange-Nielsen syndrome. J Cardiovasc Dis Res. 3:67-75. PubMed PMID: 22629021.

Goel AK, Berger S, Pelech A, Dhala A (2004) Implantable cardioverter defibrillator therapy in children with long QT syndrome. Pediatr Cardiol. 25:370-8. PubMed PMID: 14994181.

Goldenberg I, Moss AJ, Zareba W, McNitt S, Robinson JL, Qi M, Towbin JA, Ackerman MJ, Murphy L. Clinical course and risk stratification of patients affected with the Jervell and Lange-Nielsen syndrome. J Cardiovasc Electrophysiol 2006;17:1161-8 PubMed PMID: 16911578.

Green JD, Schuh MJ, Maddern BR, Haymond J, Helffrich RA. Cochlear implantation in Jervell and Lange-Nielsen syndrome. Ann Otol Rhinol Laryngol Suppl 2000;185:27-8 PubMed PMID: 11140992.

Hazinski MF, Markenson D, Neish S, Gerardi M, Hootman J, Nichol G, Taras H, Hickey R, OConnor R, Potts J, van der Jagt E, Berger S, Schexnayder S, Garson A Jr, Doherty A, Smith S, et al (2004) Response to cardiac arrest and selected life-threatening medical emergencies: the medical emergency response plan for schools: A statement for healthcare providers, policymakers, school administrators, and community leaders. Circulation. 109:278-91. PubMed PMID: 14707021.

Hothi SS, Thomas G, Killeen MJ, Grace AA, Huang CL (2009) Empirical correlation of triggered activity and spatial and temporal re-entrant substrates with arrhythmogenicity in a murine model for Jervell and Lange-Nielsen syndrome. Pflugers Arch. 458:819-35. PubMed PMID: 19430811.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Ning L, Moss AJ, Zareba W, Robinson J, Rosero S, Ryan D, Qi M. Novel compound heterozygous mutations in the KCNQ1 gene associated with autosomal recessive long QT syndrome (Jervell and Lange-Nielsen syndrome). Ann Noninvasive Electrocardiol 2003;8:246-50 PubMed PMID: 14510661.

Ocal B, Imamoglu A, Atalay S, Ercan Tutar H (1997) Prevalence of idiopathic long QT syndrome in children with congenital deafness. Pediatr Cardiol. 18:401-5. PubMed PMID: 9326683.

Ohno S, Kubota T, Yoshida H, Tsuji K, Makiyama T, Yamada S, Kuga K, Yamaguchi I, Kita T, Horie M (2008) A novel mutation associated with Jervell and Lange-Nielsen syndrome in a Japanese family. Circ J. 72:687-93. PubMed PMID: 18441444.

Olesen MS, Bentzen BH, Nielsen JB, Steffensen AB, David JP, Jabbari J, Jensen HK, Haunsø S, Svendsen JH, Schmitt N (2012) Mutations in the potassium channel subunit KCNE1 are associated with early-onset familial atrial fibrillation. BMC Med Genet. 13:24. PubMed PMID: 22471742.

Piippo K, Swan H, Pasternack M, Chapman H, Paavonen K, Viitasalo M, Toivonen L, Kontula K. A founder mutation of the potassium channel KCNQ1 in long QT syndrome: implications for estimation of disease prevalence and molecular diagnostics. J Am Coll Cardiol 2001;37:562-8 PubMed PMID: 11216980.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint

consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Richter S, Brugada P. Risk-stratifying Jervell and Lange-Nielsen syndrome from clinical data. J Cardiovasc Electrophysiol 2006;17:1169-71 PubMed PMID: 16987380.

Schulze-Bahr E, Wang Q, Wedekind H, Haverkamp W, Chen Q, Sun Y, Rubie C, Hördt M, Towbin JA, Borggrefe M, Assmann G, Qu X, Somberg JC, Breithardt G, Oberti C, Funke H. KCNE1 mutations cause jervell and Lange-Nielsen syndrome. Nat Genet. 1997;17:267-8. PubMed PMID: 9354783.

Schwartz PJ, Priori SG, Dumaine R, Napolitano C, Antzelevitch C, Stramba-Badiale M, Richard TA, Berti MR, Bloise R. A molecular link between the sudden infant death syndrome and the long-QT syndrome. N Engl J Med 2000;343:262-7 PubMed PMID: 10911008.

Schwartz PJ, Spazzolini C, Crotti L, Bathen J, Amlie JP, Timothy K, Shkolnikova M, Berul CI, Bitner-Glindzicz M, Toivonen L, Horie M, Schulze-Bahr E, Denjoy I. The Jervell and Lange-Nielsen syndrome: natural history, molecular basis, and clinical outcome. Circulation 2006;113:783-90 PubMed PMID: 16461811.

Seth R, Moss AJ, McNitt S, Zareba W, Andrews ML, Qi M, Robinson JL, Goldenberg I, Ackerman MJ, Benhorin J, Kaufman ES, Locati EH, Napolitano C, Priori SG, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Long QT syndrome and pregnancy. J Am Coll Cardiol. 2007;49:1092-8. PubMed PMID: 17349890.

Siem G, Früh A, Leren TP, Heimdal K, Teig E, Harris S. Jervell and Lange-Nielsen syndrome in Norwegian children: Aspects around cochlear implantation, hearing, and balance. Ear Hear 2008;29:261-9 PubMed PMID: 18595190.

Splawski I, Timothy KW, Vincent GM, Atkinson DL, Keating MT. Molecular basis of the long-QT syndrome associated with deafness. N Engl J Med 1997;336:1562-7 PubMed PMID: 9164812.

Sung JY, Bae EJ, Park S, Kim SY, Hyun YJ, Park SS, Seong MW. Large deletion in KCNQ1 identified in a family with Jervell and Lange-Nielsen syndrome. Ann Lab Med. 2014;34:395-8. PubMed PMID: 25187895.

Thomas G, Killeen MJ, Gurung IS, Hakim P, Balasubramaniam R, Goddard CA, Grace AA, Huang CL (2007) Mechanisms of ventricular arrhythmogenesis in mice following targeted disruption of KCNE1 modelling long QT syndrome 5. J Physiol. 578:99-114. PubMed PMID: 17095567.

Towbin JA, Wang Z, Li H. Genotype and severity of long QT syndrome. Drug Metab Dispos. 2001;29:574–9 PubMed PMID: 11259355.

Tranebjærg L. Jervell and Lange-Nielsen syndrome. In: Willems PJ, ed. *Genetic Hearing Loss*. New York, NY: Marcel Dekker Publications; 2004:117-34.

Tranebjærg L, Bathen J, Tyson J, Bitner-Glindzicz M. Jervell and Lange-Nielsen syndrome: a Norwegian perspective. Am J Med Genet 1999;89:137-46 PubMed PMID: 10704188.

Tyson J, Tranebjaerg L, Bellman S, Wren C, Taylor JF, Bathen J, Aslaksen B, Sørland SJ, Lund O, Malcolm S, Pembrey M, Bhattacharya S, Bitner-Glindzicz M. IsK and KvLQT1: mutation in either of the two subunits of the slow component of the delayed rectifier potassium channel can cause Jervell and Lange-Nielsen syndrome. Hum Mol Genet. 1997;6:2179-85. PubMed PMID: 9328483.

Tyson J, Tranebjærg L, McEntagart M, Larsen LA, Christiansen M, Whiteford ML, Bathen J, Aslaksen B, Sorland SJ, Lund O, Pembrey ME, Malcolm S, Bitner-Glindzicz M. Mutational spectrum in the cardioauditory syndrome of Jervell and Lange-Nielsen. Hum Genet 2000;107:499-503 PubMed PMID: 11140949.

Wang RR, Li N, Zhang YH, Wang LL, Teng SY, Pu JL (2011) Novel compound heterozygous mutations T2C and 1149insT in the KCNQ1 gene cause Jervell and Lange-Nielsen syndrome. Int J Mol Med. 28:41-6. PubMed PMID: 21380488.

Wang Z, Li H, Moss AJ, Robinson J, Zareba W, Knilans T, Bowles NE, Towbin JA. Compound heterozygous mutations in KvLQT1 cause Jervell and Lange-Nielsen syndrome. Mol Genet Metab 2002;75:308-16 PubMed PMID: 12051962.

Winbo A, Stattin EL, Diamant UB, Persson J, Jensen SM, Rydberg A Prevalence, mutation spectrum, and cardiac phenotype of the Jervell and Lange-Nielsen syndrome in Sweden. Europace. 2012;14:1799-806. PubMed PMID: 22539601.

Winbo A, Sandström O, Palmqvist R, Rydberg A Iron-deficiency anaemia, gastric hyperplasia, and elevated gastrin levels due to potassium channel dysfunction in the Jervell and Lange-Nielsen Syndrome. Cardiol Young. 2013;23:325-34. PubMed PMID: 22805636.

Winbo A, Stattin E-L, Nordin C, Diamant UB, Persson J, Jensen SM, Rydberg A. Phenotype, origin and estimated prevalence of a common long QT syndrome mutation: a clinical, genealogical and molecular genetics study including Swedish R518X/KCNQ1 families. BMC Cardiovasc Disord. 2014;14:22 PubMed PMID: 24552659.

Winbo A, Rydberg A (2015) Vestibular dysfunction is a clinical feature of Jervell and Lange-Nielsen Syndrome. Scand Cardiovasc J 2015; 49:7-13 PubMed PMID: 25471708.

Yanmei F, Yagin W, Haibo S, Huiqun Z, Zhengnong C, Dongzhen Y, Shankai Y. Cochlear implantation in patients with Jervell and Lange_Nielsen syndrome, and a review of the literature. Int J Pediatr Otorhinolaryngol. 2008;72:1723-9 PubMed PMID: 18805595.

Zehelein J, Kathoefer S, Khalil M, Alter M, Thomas D, Brockmeier K, Ulmer HE, Katus HA, Koenen M. Skipping of exon 1 in the KCNQ1 gene causes Jervell and Lange-Nielsen Syndrome. J Biol Chem 2006; 281:35397-403 PubMed PMID: 16987820.

Zhang S, Yin K, Ren X, Wang P, Zhang S, Cheng L, Yang J, Liu JY, Liu M, Wang QK (2008) Identification of a novel KCNQ1 mutation associated with both Jervell and Lange-Nielsen and Romano-Ward forms of long QT syndrome in a Chinese family. BMC Med Genet. 9:24. PubMed PMID: 18400097.

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