GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Jervell and Lange-Nielsen Syndrome

[*Cardioauditory Syndrome of Jervell and Lange-Nielsen, JLNS, Surdo Cardiac Syndrome*]

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Initial Posting: July 29, 2002.
Last Update: March 19, 2007.

Summary

Disease characteristics. Jervell and Lange-Nielsen syndrome (JLNS) is characterized by congenital profound bilateral sensorineural hearing loss and long QTc, usually greater than 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. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright. Fifty percent of individuals had cardiac events before age three years. More than half of untreated children with JLNS die prior to age 15 years.

Diagnosis/testing. The diagnosis of JLNS is established in a child with congenital sensorineural deafness, long QT interval, and presence of two disease-causing mutations in either *KCNQ1* or *KCNE1*, the only two genes known to be associated with JLNS. Such molecular genetic testing is clinically available.

Management. *Treatment of manifestations:* cochlear implantation to treat hearing loss; beta-adrenergic blockers; implantable cardioverter defibrillators for those with a history of cardiac arrest and/or failure to respond to other treatments. *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. *Testing 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 disease-causing mutations in an affected family member are known. *Other:* Train family members in cardiopulmonary resuscitation; wear an ID bracelet explaining the diagnosis; notify 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 a carrier and the other mutation is *de novo*. 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 disease-causing mutation and at risk for LQTS, and a 25% chance of being unaffected and not a carrier. Prenatal testing may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

The diagnosis of Jervell and Lange-Nielsen syndrome (JLNS) is definitively established in individuals with all of the following:

- Congenital sensorineural deafness
- Long QT interval, often manifest as syncope, most often elicited by emotion or exercise
- Presence of two disease-causing mutations in either *KCNQ1* or *KCNE1* [Priori et al 1999]

Hearing loss. All individuals with molecularly confirmed JLNS have profound congenital sensorineural deafness (see Deafness and Hereditary Hearing Loss Overview.)

Long QTc. Based on existing diagnostic criteria, all individuals with JLNS have a QTc interval greater than 500 msec (average 550 msec), indicating increased time for ventricular depolarization and repolarization [Tyson et al 2000]. Generally, the upper limit of normal for the QTc is 440 msec for males and 460 msec for post-pubertal females [Priori et al 1999, Allan et al 2001].

Note: (1) In the "pre-molecular" era, diagnosis of JLNS relied upon clinical criteria alone, and thus it is not currently known how many children with molecularly confirmed JLNS have a borderline QTc interval prolongation of 440 msec to 500 msec or how many children with molecularly confirmed JLNS have a QTc that falls within the "normal" range. This issue will be resolved as data on more affected individuals are gathered. A recent review [Schwartz et al 2006] gives a comprehensive summary of the natural history, molecular basis, and clinical characteristics of 186 affected individuals from 135 families, in whom mutations were identified in 63 (47%). (2) Hearing loss commonly occurs in the setting of familial long QT syndrome (LQTS) (see Romano-Ward Syndrome). In this situation, the hearing loss may be entirely unrelated to the etiology of the LQTS, particularly if the hearing loss is moderate.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. JLNS is caused by mutations in one of two genes: *KCNQ1* and *KCNE1* [Neyroud et al 1997, Splawski et al 1997, Duggal et al 1998, Chen et al 1999].

- ***KCNQ1***(sometimes called *JLN1*) mutations account for more than 90% of individuals with JLNS. In a study of ten families, nine had mutations in *KCNQ1* [Tyson et al 2000]. Of 63 families, 57 (90.5%) had mutations in *KCNQ1* [Schwartz et al 2006].
- ***KCNE1***(sometimes called *JLN2*) mutations account for fewer than 10% of individuals with JLNS. Of 63 families, six (9.5%) had mutations in *KCNE1* [Schwartz et al 2006].

Clinical uses

- Diagnostic testing
- Carrier testing

Clinical testing

- **Sequence analysis/mutation scanning.** Mutations have been found in either *KCNQ1* and *KCNE1* in 94% of individuals with clinical JLNS undergoing molecular testing [Schwartz et al 2006]. The mutations may be located in all coding exons, and current experience indicates that 33% are compound heterozygotes [Schwartz et al 2006].

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Proportion of JLNS Attributed to Mutations in This Gene	Mutation Detection Frequency [1]	Test Availability
Sequence analysis / mutation scanning	*KCNQ1* sequence alterations	90%	94% [2]	Clinical Testing
	KCNE1 sequence alterations	10%		Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by test method
2. Schwartz et al 2006

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

1. Test *KCNQ1*, as mutations in this gene account for the majority of JLNS. In countries with founder mutations, like Norway, particular mutations should be tested first [Tranebjærg et al 1999, Tranebjærg 2004].
2. If no *KCNQ1* mutation is identified, test *KCNE1*.

Genetically Related (Allelic) Disorders

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

Clinical Description

Natural History

Homozygotes. Deafness is congenital, bilateral, profound, and sensorineural in all individuals with molecularly confirmed Jervell and Lange-Nielsen syndrome (JLNS) (see Deafness and Hereditary Hearing Loss Overview).

Abnormal cardiac depolarization and repolarization may result in prolongation of the QT interval and tachyarrhythmias (including ventricular tachycardia, episodes of *torsade de pointes* ventricular tachycardia, and ventricular fibrillation), which may culminate in syncope or sudden death. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright.

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 emotions and exercise being the primary triggers. Note, however, that selection bias for severely affected individuals cannot be excluded: individuals have been described with putative JLNS without any clinical manifestations other than deafness until adulthood, and to age 50 years in one case.

QTc prolongation in JLNS, particularly when severe, appears to be associated with increased risk of death in infancy (SIDS). Although over half of untreated children with JLNS die prior to age 15 years, some individuals are reported to have survived several syncopal episodes during adulthood.

The sex ratio among individuals with JLNS is even, but females are at lower risk for cardiac arrest/sudden death [Schwartz et al 2006].

Physical examination is unremarkable except for deafness.

Heterozygotes. Heterozygotes usually have normal hearing. In some individuals who are heterozygous for mutations associated with JLNS, QTc prolongation, fainting, and sudden death never occur. In contrast, some individuals heterozygous for mutations associated with JLNS may have QTc prolongation associated with fainting and death heritable in a dominant manner. This form of LQTS is called Romano-Ward syndrome (RWS). RWS can also be caused by mutations in several genes that do not cause deafness/JLNS in a homozygous form (see Differential Diagnosis.) These mutations may be associated with highly variable QTc intervals, from normal to markedly abnormal.

Histopathology of temporal bone. Histologic examination of a few temporal bones was performed prior to the availability of molecular genetic testing, but none since. In a mouse model, with knock-out for the *Kcnq1* gene, which can be considered an animal model for JLNS in humans, there is marked atrophy of the stria vascularis and collapse of the endolymphatic compartments and surrounding membranes. Complete degeneration of the Organ of Corti and associated degeneration of the spiral ganglion were found [Rivas & Francis 2005].

Genotype-Phenotype Correlations

Data to establish better predictors for a correlation between genotype and phenotype were provided from a large number of individuals with molecularly confirmed JLNS. 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 complex mutation (insertion/deletion, splice mutation, truncation) and those with missense mutations.

Among six asymptomatic individuals in the study of Schwartz et al (2006), two had *KCNQ1* mutations and four had *KCNE1* mutations, further confirming the milder presentation of JLNS associated with *KCNE1* mutations compared to JLNS associated with *KCNQ1* mutations.

Prevalence

Prevalence varies depending on the population studied.

- Norway has an unusually high prevalence of at least 1:200,000 [Tranebjærg et al 1999].
- The syndrome is more common in cultures in which consanguineous marriage is common.
- In a study of 350 children with congenital deafness in Turkey, one in 175 had JLNS [Ocal et al 1997].
- A particular missense *KCNQ1* mutation 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, no clustering of JLNS was observed in Finland, in contrast to that observed in several other rare autosomal recessive disorders [Piippo et al 2001].
- A recent overview of worldwide occurrence was published by Tranebjærg (2004).

These data are the best available; however, diagnostic criteria using a QTc greater than 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 recent review by Schwartz et al (2006) did not allow refinement of prevalence estimates.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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. RWS was commonly diagnosed in persons with LQTS and normal hearing.
- Some children with JLNS may be misdiagnosed with epilepsy and incorrectly treated with antiepileptic drugs before the correct diagnosis of JLNS is established [Tranebjærg et al 1999].

Romano-Ward syndrome (RWS, long QT syndrome). The diagnosis of Romano-Ward syndrome (RWS) is made on the basis of a prolonged QT interval on the ECG or identification of a mutation in *KCNQ1* (locus name LQT1), *KCNH2* (locus name LQT2), *SCN5A* (locus name LQT3), *KCNE1* (locus name LQT5), or *KCNE2* (locus name LQT6) in the absence of profound congenital sensorineural deafness (the presence of which is highly suggestive of Jervell and Lange-Nielsen syndrome). Two other genes, *ANK2* and *KCNJ2*, have been proposed as LQT4 and LQT7, respectively, but uncertainty exists as to whether the long QT syndrome (LQTS) designation is appropriate for these conditions and further study is underway. Diagnostic

criteria have been established for the resting ECG QTc value in the absence of specific conditions known to lengthen the QTc interval. Table 2 summarizes the genes known to be associated with RWS. Only *KCNQ1* and *KCNE1* have been implicated in both RWS and JLNS.

Three families with autosomal recessive Romano-Ward syndrome without hearing loss have been well studied [Larsen et al 1999]

.Table 2. Genes Associated with Autosomal Dominant Long QT Syndrome (Romano-Ward Syndrome)

Locus Name	Gene	Protein Function	Proportion of Individuals with RWS
LQT1	*KCNQ1*	I_{Ks} K+ channel α subunit	55%-60%
LQT2	*HERG*	I_{Ks} K+ channel α subunit	35%-40%
LQT3	*SCN5A*	I_{Na} Na+ channel α subunit	3%-5%
LQT4 [1]	Unknown	Unknown	
LQT5	*KCNE1*	I_{Ks} K+ β subunit	
LQT6	*MiRP1*/ *KCNE2*	I_{Kr} K+ channel β subunit	
LQT7 [1]	Unknown	Unknown	

From Keating & Sanguinetti 2001
LQT = Long QT
I_{Kr} = rapidly activating delayed rectifier potassium current
I_{Ks} = slowly activating delayed rectifier potassium channel
1. From Romano-Ward *GeneReview*. Two other genes, *ANK2* and *KCNJ2*, have been proposed as LQT4 and LQT7 respectively, but uncertainty exists as to whether the long QT syndrome (LQTS) designation is appropriate for these conditions; further study is underway.

Other genetic disorders considered to be cardiac channelopathies associated with LQTS include the following [Ackerman 2005]:

- Timothy syndrome
- Andersen-Tawil syndrome
- Brugada syndrome

Causes of 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 Deafness and Hereditary 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 upon identification of deafness-causing mutations in the *GJB2* gene and/or the *GJB6* gene that alter the gap junction beta-2 protein (connexin 26) and the gap junction beta-6 protein (connexin 30), respectively. Molecular genetic testing detects more than 99% of mutations in these genes. JLNS should be suspected in any infant who has profound bilateral sensorineural hearing loss, no identifiable *GJB2* or *GJB6* mutations, and a normal physical examination.

Acquired causes of LQTS

- 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.qtdrugs.org [Woosley 2001]

- Primary myocardial problems: cardiomyopathy, myocarditis, ischemia
- Central nervous or autonomic system injury; subarachnoid hemorrhage; stellate ganglion blockade

Sudden infant death syndrome (SIDS). Recent data from multicenter studies indicate that 9.5% of sudden infant death syndrome (SIDS) cases may be heterozygous for functionally significant mutations in one of the seven known LQTS genes *(KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CAV3*) [Arnestad et al 2007, Berul & Perry 2007, Wang et al 2007]. Sudden arrhythmic death may thus be an important contributor to SIDS, and it is unknown which proportion of such cases have or would develop profound hearing impairment. Recent implementation of universal neonatal hearing screening, supplemented with early electrocardiography, may have the potential to identify high-risk children.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Jervell and Lange-Nielsen syndrome (JLNS), the following evaluations are recommended:

- Formal audiologic evaluation for extent of hearing loss
- Cardiac examination including calculation of QTc
- A three-generation thorough family history on cardiac disease, syncope, and hearing

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 Deafness and Hereditary Hearing Loss Overview).

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, since 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 of 32 (56%) 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. In contrast to RWS, 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 with individuals with RWS. 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 (such as asthma, diabetes, and depression) should also be considered.
- Cardiac pacemakers may be a prudent first step in management of children with JLNS [Carboni & Garson 1998, Schwartz et al 2000].
- Implantable cardioverter defibrillators (ICDs) may 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:

- QTc interval >550 msec
- Syncope before age five years
- Male gender, age <20 years with *KCNQ1* mutation

Sudden cardiac death appears to be low in individuals younger than age five years, but medical therapy should be administered early on in these high-risk individuals and ICD placement should be 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 used with effect for some patients.

Prevention of Primary Manifestations

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

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.qtdrugs.org [Woosley 2001] for a complete and updated list.
- 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
  - Scary movies
  - Jumping into cold water

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

Testing of Relatives at Risk

Standard newborn screening programs are sufficient to identify hearing loss in children with JLNS.

Because of the relationship between JLNS and Romano-Ward syndrome, electrocardiograms should be considered for relatives at risk for JLNS even if they have normal hearing.

If the JLNS disease-causing mutations 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.

Therapies Under Investigation

Search ClinicalTrials.gov 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) since 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 such as those with JLNS [Hazinski et al 2004].

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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. In rare cases, only one parent is a carrier and the other mutation is *de novo* [Schwartz et al 2000].
- Parents may or may not have the 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 comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Sibs of a proband

- At conception, each sib of an individual with JLNS usually has a 25% chance of being affected with JLNS, a 50% chance of being heterozygous for a JLNS-associated mutation and at risk for LQTS, and a 25% chance of being unaffected and not a carrier. Thus, at conception, each sib of a proband with JLNS has a 3/4 chance of having either JLNS or LQTS.
- Sibs with normal hearing have a 2/3 risk of being carriers of a mutation causing JLNS and being at risk for LQTS.
- Sibs of a proband who has a *de novo* mutation are not at increased risk of having JLNS but are at 50% risk for LQTS.
- Recommendations for evaluation of sibs of a proband with JLNS include: audiologic evaluation, electrophysiologic evaluation for evidence of LQTS, molecular genetic testing if the disease-causing mutations in the proband are known, and 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 abnormal allele; thus, 100% of the proband's offspring are at risk for LQTS.
- In the event that the reproductive partner of the proband is also a carrier for a mutation in the same gene in which two mutations have been identified in the proband, the risk to offspring for 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 mutation in *KCNE1* or *KCNQ1* and at risk for LQTS.

Carrier Detection

Carrier testing is available on a clinical basis for family members once the mutations have been identified in the proband.

Related Genetic Counseling Issues

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 of sudden death and should obtain cardiologic intervention. The actual risk of LQTS is not known.

Carriers for JLNS have a single mutation in a gene for LQTS that may cause QTc prolongation or LQTS in either a clinically significant or clinically insignificant form. Whether the mutation is clinically significant or insignificant, it may be transmitted in a clinically significant fashion to future generations as either LQTS or JLNS, a confusing phenomenon during pedigree evaluation.

Family planning. The optimal time for determination of genetic risk and clarification of carrier status is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our

understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of Jervell and Lange-Nielsen syndrome are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as LQTS that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in the family. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Jervell and Lange-Nielsen Syndrome

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
LQT1	*KCNQ1*	11p15.5	Potassium voltage-gated channel subfamily KQT member 1
LQT5	*KCNE1*	21q22.1-q22.2	Potassium voltage-gated channel subfamily E member 1

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Jervell and Lange-Nielsen Syndrome

176261	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 1; KCNE1
192500	LONG QT SYNDROME 1; LQT1
220400	JERVELL AND LANGE-NIELSEN SYNDROME; JLNS1
607542	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 1; KCNQ1

Table C. Genomic Databases for Jervell and Lange-Nielsen Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
KCNQ1	KCNQ1	3784 (MIM No. 607542)	KCNQ1
KCNE1	KCNE1	3753 (MIM No. 176261)	KCNE1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic 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.

- *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*—Normal allelic variants:** The gene consists of 16 exons spanning approximately 400 kb. No benign polymorphisms have been identified in the coding region of the gene.

Pathologic allelic variants: At least 12 JLNS-causing mutations in *KCNQ1* are known, nine resulting in frameshift and premature truncation [Tyson et al 2000, Wang et al 2002, Ning et al 2003].

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 regiofns. It co-assembles with the protein encoded by *KCNE1* to form the functional channel I_{Ks}.

Abnormal gene product: Mutations in the gene result in premature truncation and inability to co-assemble with the protein encoded by *KCNE1* to form the functional channel I_{Ks}. In vitro, recessive mutations may exhibit a dominant negative effect that is not clinically observed in affected individuals, suggesting post-translational processing effects in vivo.

***KCNE1*—Normal allelic variants:** The gene consists of three exons spanning approximately 40 kb. No benign polymorphisms have been identified in the coding region of the gene.

Pathologic allelic variants: Four JLNS-causing mutations have been identified in *KCNE1*, all of which are missense.

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 co-assembles with the protein encoded by *KCNQ1* to form the functional channel I_{Ks}.

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

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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Jervell and Lange-Nielsen syndrome

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Chapter Notes

Revision History

- 19 March 2007 (me) Comprehensive update posted to live Web site
- 29 July 2004 (me) Comprehensive update posted to live Web site
- 13 January 2003 (gg) Revision: Molecular Genetic Testing

- 29 July 2002 (me) Review posted to live Web site
- 8 October 2001 (gg) Original submission