Jervell and Lange-Nielsen syndrome (JLNS) - 2010

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The Jervell and Lange-Nielsen syndrome (JLNS) is an autosomal recessive form of LQTS with associated congenital deafness. It is caused specifically by mutation of the KCNE1 and KCNQ1 genes. In untreated individuals with JLNS, about 50 percent die by the age of 15 years due to ventricular arrhythmias.

This condition is an autosomal recessive disorder that affects an estimated 1.6 to 6 in 1 million children, and is responsible for less than 10 percent of all cases of long QT syndrome.

Mutations in the KCNE1 and KCNQ1 genes cause Jervell and Lange-Nielsen syndrome. The proteins produced by these two genes work together to form a potassium channel that transports positively charged potassium ions out of cells. The movement of potassium ions through these channels is critical for maintaining the normal functions of the inner ear and cardiac muscle.

About 90 percent of cases of Jervell and Lange-Nielsen syndrome are caused by mutations in the KCNQ1 gene. KCNE1 mutations are responsible for the remaining 10 percent of cases. Mutations in these genes alter the usual structure and function of potassium channels or prevent the assembly of normal channels. These changes disrupt the flow of potassium ions in the inner ear and in cardiac muscle, leading to the hearing loss and irregular heart rhythm characteristic of Jervell and Lange-Nielsen syndrome.

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 with JLNS 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 testingis clinically available.

Management. *Treatment of manifestations*: cochlear implantation to treat hearing loss; beta-adrenergic blockers for long QT interval; 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 testingto 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. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the disease-causing mutations In the family are known.

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 [Allan et al 2001, Priori et al 1999].

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

Genes. JLNS is caused by [mutations](#) in one of two genes: KCNQ1 and KCNE1[[Chen et al 1999](#),[Duggal et al 1998](#),[Neyroud et al 1997](#),[Spla wski et al 1997](#)].

·**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](#)]. In a second study of 63 families, 57 (90.5%) had [mutations](#) in KCNQ1 [[Schwartz et al 2006](#)]. In a Norwegian study 12 out of 13 unrelated JLNS patients had four different Norwegian founder [mutations](#) [[Berge et al 2008](#)].

·**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](#)]. None of the Norwegian patients with JLNS have been shown to have KCNE1 mutations[[Berge et al 2008](#), [Siem et al 2008](#),[Tranebjaerg et al 1999](#)].

Clinical testing

·*Sequence analysis/mutation scanning*. [Mutations](#) have been found in either KCNQ 1 or KCNE1 in 94% of individuals with clinical JLNS undergoing molecular testing [[Schwartz et al 2006](#)]. The [mutations](#) may be located in all coding exons. Current experience indicates that 33% are [compound heterozygotes](#) [Schwartz et al 2006].

·**Deletion/duplication analysis**. Both [deletion](#) and [duplication](#) of exon(s) of KCNQ1are known to cause long QT syndrome [[Eddy et al 2008](#)].

Table 1. Summary of [Molecular Genetic Testing](#) Used in Jervell and Lange-Nielsen Syndrome

Gene Symbol/Locus	Proportion of JLNS Attributed to [Mutations](#) in This Gene	Test Method	[Mutations](#) Detected	[Mutation Detection Frequency by Gene](#) and Test Method[1]	Test Availability by
KCNQ1	90%	Deletion/duplicationanalysis[2]	Partial- or complete-[genedeletion](#)	Unknown	Clinical
		Sequence analysis/mutation scanning	Sequence variants	94%[3]	
KCNE1	10%	Sequence analysis/mutation scanning	Sequence variants		Clinical
		Deletion/duplicationanalysis[2]	Partial- or complete-[genedeletion](#)	Unknown	

Test Availability refers to availability in the [GeneTests Laboratory Directory](#). Gene Reviews 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 wit h the laboratories to verify information.

1. The ability of the test method used to detect a mutation that is present in the indicated gene

2. Testing that identifiesdeletions/duplications not detectable by sequence analysis of genomic DNA; a variety of methods including quantitative PCR, real-time PCR, multiplex ligation-dependent probe amplification (MLPA), and array GH may be used.

3. Schwartz et al [2006]

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

Testing Strategy To confirm/establish the diagnosis in a proband

·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 [Tranebjaerg et al 1999, Tranebjaerg 2004, Berge et al 2008, Siem et al 2008].

·2

If no KCNQ1 mutationis identified, test KCNE1.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

Heterozygosity formutations in KCNQ1and 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).

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 more than 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. Heterozygote ususually 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 mutationsmay 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 not since. In a mouse model with knock-out for the Kcnq1 gene (which can be considered an animal model for JLNS in humans), atrophy of the stria vascularis and collapse of the endolymphatic compartments and surrounding membranes are marked. 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.

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 with both the cardiac and the cochlear pathologies 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 Diagnoses).

Prevalence

Prevalence varies depending on the population studied:

·Norwayhas an unusually high prevalence of at least one in 200,000 [Tranebjaerg et al 1999]. This prevalence stems from four Norwegian founder mutations[Berge et al 2008, Siem et al 2008]

·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 inautosomal 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].

·An overview of worldwide occurrence was published by Tranebjaerg [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 Gene Tests 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 [Tranebjaerg 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 amutation 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	*KCNH2(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	*KCNE2*	I_{Kr}K+ channel β subunit	
LQT7[1]	Unknown	Unknown	

FromKeating & Sanguinetti [2001]

LQT = long QT

I_{Kr}= rapidly activating delayed rectifier potassium current

I_{Ks}= slowly activating delayed rectifier potassium channel

1. FromRomano-Ward. 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 non syndromic 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 on identification of deafness-causing mutations in the GJB2 gene and/or the GJB6 gene, which 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.azcert.org.

·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 (CI), an intervention that does not interfere with bipolar pacemakers [Green et al 2000, Chorbachi et al 2002 Deafness and Hereditary Hearing Loss Overview). To date, the cumulative published experience is about 15 individuals with JLNS.

Of note, the diagnosis of JLNS was only verified with molecular genetic testingin four Norwegian patients, all of whom had mutations in KCNQ1.

Note: Although cochlear implantation seems safe, special precautions are necessary during anesthesia because of the increased risk of cardiac arrhythmia [Daneshi et al 2008, Siem et al 2008 Yanmei et al 2008].

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 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 Romano-Ward syndrome (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 (e.g., asthma, diabetes mellitus, depression) should also be considered.

·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]:

o QTc interval >550 msec

o Syncope before age five years

o Male gender, older than 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.

Prevention of Secondary Complications

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

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.azcert.org 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:

　　　　o Competitive sports

　　　　o Amusement park rides

　　　　o Scary movies

　　　　o Jumping into cold water

A cardiologist should make recommendations for activity restrictions based on 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, electrocardiogram should be considered for relatives at risk for JLNS even if they have normal hearing.

If the JLNS disease-causing mutationsin anaffected 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 adult hood [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.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Genetic Counseling

Genetic counselingis 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 gene tics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Jervell and Lange-Nielsen syndrome (JLNS) is inherited in anautosomal recessivemanner.

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 acarrier and the other mutationis 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 for 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 mutationin 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 possible for family members once the mutations have been identified in the family.

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 for sudden death and thus require 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 (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 carrier status, and discussion of the availability of prenatal 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 carriers, or are at risk of being carriers.

DNA bankingis 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. See for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements

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, discussion of these issues is appropriate.

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

Molecular Genetics
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 regionof the gene.

Pathologic allelic variants. At least 13 JLNS-causing [mutations](#) in KCNQ1 are known, ten resulting in frameshift and premature truncation [[Tyson et al 2000](#),[Wang et al 2002](#), [Ning et al 2003](#), [Zehelein et al 2006](#)].

Normal gene product.The gene productis potassium voltage-gated channel subfamily KQT member 1 (also known as voltage-gated potassium channel protein KvLQT1); this alpha subunit has six transmembrane regions. 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 normal variants have been identified in thecoding regionof thegene.

Pathologic allelic variants. Four JLNS-causing [mutations](#) have been identified in KCNE1, all of which are missense (see[Table A](#)).

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}.

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