GENEReviews

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Romano-Ward Syndrome

[*Long QT Syndrome, Autosomal Dominant; Romano-Ward Long QT Syndrome. Includes: LQT1, LQT2, LQT3, LQT5, LQT6*]

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Summary

Disease characteristics. Romano-Ward syndrome (RWS) is purely a cardiac electrophysiologic disorder, characterized by QT prolongation and T-wave abnormalities on the ECG and the ventricular tachycardia *torsade de pointes* (TdP). TdP is usually self-terminating, thus causing a syncopal event, the most common symptom in individuals with RWS. Syncope typically occurs during exercise and high emotions, less frequently at rest or during sleep, and usually without warning. In some instances, TdP degenerates to ventricular fibrillation and causes aborted cardiac arrest (if the individual is defibrillated) or sudden death. Approximately 50% of individuals with a disease-causing mutation in one of the genes associated with RWS have symptoms, usually one to a few syncopal spells. While cardiac events may occur from infancy through middle age, they are most common from the pre-teen years through the 20s.

Diagnosis/testing. Diagnosis of RWS is established by prolongation of the QTc interval in the absence of specific conditions known to lengthen it (for example, QT-prolonging drugs) and/or molecular genetic testing of the following genes known to be associated with RWS: *KCNQ1* (locus name LQT1), *KCNH2* (locus name LQT2), *SCN5A* (locus name LQT3), *KCNE1* (locus name LQT5), and *KCNE2* (locus name LQT6). In the past, approximately 30% of families meeting clinical diagnostic criteria for RWS did not have detectable mutations in any one of the five previously associated genes using current test methods; at this time, it is not known what proportion of these mutation-negative families may have a mutation in the recently identified *SCN4B* gene (proposed locus name LQT10).

Management. *Treatment of manifestations:* beta-blocker medication for symptomatic persons with the LQT1 and LQT2 phenotypes; possible use of a pacemaker in those individuals with LQT1 and LQT2 phenotypes with symptomatic bradycardia associated with beta-blocker therapy; implantable cardioverter-defibrillator (ICD) for symptomatic individuals with the LQT3 phenotype. *Prevention of primary manifestations:* prophylactic use of beta blockers in asymptomatic children and adults under age 40 years who have the LQT1 or LQT2 phenotype to prevent syncope, cardiac arrest, and sudden death; possible ICD for those with beta-blocker-resistant symptoms, inability to take beta blockers, and/or history of cardiac arrest. *Surveillance:* regular assessment of beta-blocker dose for efficacy and adverse effects in all individuals and, in particular, every three to six months in children during rapid growth; regular 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 or

provoke *torsade de pointes;* competitive sports/activities associated with intense physical activity and/or emotional stress. *Testing of relatives at risk:* presymptomatic diagnosis and treatment to prevent syncope and sudden death. *Other:* for some individuals, availability of automatic external defibrillators at home, at school, and in play areas.

Genetic counseling. RWS is inherited in an autosomal dominant manner. Most individuals diagnosed with RWS have an affected parent. The proportion of cases caused by *de novo* mutations is small. Each child of an individual with RWS has a 50% risk of inheriting the disease-causing mutation. Prenatal testing for pregnancies at increased risk in families in which the disease-causing mutation is known may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

The diagnosis of Romano-Ward syndrome (RWS) is made on the basis of **one** of the following:

- A prolonged QT interval on the ECG
- Typical T-wave abnormalities and typical LQTS-type syncope with a parent having diagnostic QT prolongation or positive molecular genetic testing
- Two or more offspring with diagnostic QT prolongation or positive molecular genetic testing
- Identification of a mutation in *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, or *KCNE2* in the absence of profound congenital sensorineural deafness (the presence of which strongly suggests Jervell and Lange-Nielsen syndrome; see Genetically Related Disorders).

QTc values on resting ECG. The QTc on resting ECG is neither completely sensitive nor specific for the diagnosis of RWS. Table 1 shows the diagnostic criteria for the resting ECG QTc value in the absence of the following, all of which can lengthen the QTc interval and cause a form of acquired LQTS [Vincent et al 1992,Vincent 2000]:

- QT-prolonging drugs
- Hypokalemia
- Certain neurologic conditions including subarachnoid bleed
- Structural heart disease

Table 1. Utility of the Resting QTc or Exercise ECG Maximum QTc Interval in Diagnosis of Romano-Ward Syndrome (RWS)

Certainty of Romano-Ward Syndrome Diagnosis	% of Affected Individuals	QTc	
		Males	Females
Positive	68%	>470 msec	>480 msec
Uncertain	20%	450-460 msec [1]	460-470 msec [1]
	11%	400-450 msec	400-450 msec
Negative	<<1%	<390 msec [2]	<400 msec [2]

1. In a member of a family with documented RWS, the diagnosis of RWS is suspected in males with a QTc >450 msec and in females with a QTc >460 msec. These criteria are not applicable to the general population, which includes many more normal than abnormal individuals with these values.
2. QT measurement varies by observer; therefore, some differences in reports exist. However, only a few instances of an individual with a disease-causing mutation and QTc <400 msec have been reported.

QTc on exercise and ambulatory ECG and during pharmacologic provocation testing. These tests are particularly helpful for further evaluation of individuals with "uncertain" QTc values on resting ECG:

- **Exercise ECG** commonly shows failure of the QTc to shorten normally [Jervell & Lange-Nielsen 1957, Vincent et al 1991, Swan et al 1998] and prolongation of the QTc to values in Table 1. Many individuals develop characteristic T-wave abnormalities [Zhang et al 2000].
- **Ambulatory ECG** may demonstrate similar findings [Viitasalo et al 2002] but less frequently than the exercise ECG. QTc as high as 500 msec may be seen on ambulatory ECG in normal individuals, and thus a higher value is required for suspicion of RWS.
- **Intravenous pharmacologic provocation testing**, such as with epinephrine, may be helpful by demonstrating inappropriate prolongation of the QTc interval [Ackerman et al 2002]. The sensitivity and specificity have not been evaluated in a large sample of individuals with LQTS and normals. With the small risk of induction of arrhythmia, such provocative testing is best performed in laboratories experienced in arrhythmia induction and control.

Other ECG changes. T-wave patterns characteristic of each phenotype may assist in diagnosis [Zhang et al 2000]. The heart rate may be lower than normal. The presence of the ventricular arrhythmia *torsade de pointes* is characteristic of QT prolongation syndromes but not specific for RWS.

History. A family history or personal history of syncope, aborted cardiac arrest, or sudden death in a child or young adult may lead to suspicion of RWS. The syncope is typically precipitous and without warning, thus differing from the common vasovagal and orthostatic forms of syncope in which presyncope and other warning symptoms occur. Absence of aura, incontinence, and postictal findings help differentiate RWS from seizures.

Family history. A family history consistent with autosomal dominant inheritance supports the diagnosis.

Testing

No other routine clinical tests are helpful in the diagnosis of RWS.

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.

Molecular Genetic Testing—Genes. Five genes *(KCNQ1, KCNE1, KCNH2, KCNE2,* and *SCN5A*) [Splawski et al 2000, Mohler et al 2003] are known to be associated with RWS.

Other genes

- ***SCN4B***. A mutation in *SCN4B* was identified in a 21-month-old female with intermittent 2:1 AV block and QTc of 712 ms [Medeiros-Domingo et al 2007]. The mutation caused a significant increase in late sodium current, similar to that seen in the LQT3 phenotype. It has been suggested that *SCN4B* be designated LQT10; with additional verification, it may be added as the sixth gene to be associated with RWS.

- ***ANK2*** and ***KCNJ2*** have been proposed as LQT4 and LQT7, respectively. Whether the LQTS designation is appropriate is uncertain [Zhang et al 2005]; further study is underway.
- ***CAV3***. Mutations in *CAV3*, the gene encoding caveolin 3, which has been proposed as LQT9, have been associated with sudden infant death syndrome (SIDS). These mutations cause an increase in late sodium current similar to that seen in the LQT3 phenotype. *CAV3* mutations are also associated with a range of muscular disease (see Caveolinopathies). The caveolin 3 disorder may become one of the "atypical" or "complex" long QT syndromes [Vatta et al 2006, Amestad et al 2007, Cronk et al 2007].
- Approximately 30% of families with clinically diagnosed RWS do not have a detectable mutation in one of the five genes *(KCNQ1, KCNE1, KCNH2, KCNE2,* and *SCN5A*) known to be associated with RWS, suggesting that mutations in other genes can also cause RWS and/or that current test methods do not detect mutations (e.g., exonic or whole-gene deletions or other rearrangements) in these genes.

  Note: Among those individuals with clinically suspected LQTS who do not have a mutation identified in one the five known RWS-related genes, the majority have T-wave patterns consistent with the phenotype associated with one of the known genes, suggesting that undetected mutations of the known genes may be the primary cause of the negative genetic test results (see Research testing).

Clinical testing

- **Mutation scanning and sequence analysis.** Mutation scanning and sequence analysis of *KCNQ1, KCNH2, SCN5A, KCNE1,* and *KCNE2* are available on a clinical basis.

Research testing. Zhang et al [2004] reported that mutations in intronic sequences other than invariant splice sites can cause RWS. As these mutations are not identifiable using sequence analysis of coding regions, they may account for some or all of the approximately 30% of individuals with RWS in whom a mutation has not yet been identified.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Romano-Ward Syndrome (RWS)

Gene Symbol	Proportion of RWS Attributed to Mutations in This Gene	Test Method	Mutation Detection Frequency by Gene and Test Method	Test Availability
KCNQ1	58%	Sequence analysis/ mutation scanning	70%[1]	Clinical Testing
KCNH2	35%		70%[1]	Clinical Testing
SCN5A	5%		70%[1]	Clinical Testing
KCNE1	1%		Unknown	Clinical Testing
KCNE2	1%		Unknown	Clinical Testing

1. Not all laboratories do (or have done in the past) locus mapping before sequence analysis; thus, the mutation detection frequency for each gene is not known [Author, personal observation].

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

Testing Strategy

To confirm the diagnosis in a proband

- Identification of prolonged QTc on exercise or ambulatory ECG, or during pharmacologic provocation testing
- Identification of a disease-causing mutation in one of the five genes known to be associated with RWS: *KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2*

  Note: The clinical phenotype has been shown to predict the genotype with a high degree of accuracy [Zhang et al 2004]. Consequently, molecular genetic testing is more efficient if the gene(s) associated with the individual's clinical phenotype (e.g., LQT1, LQT2 or LQT3) are tested first.

Predictive testing for at-risk asymptomatic family members can be performed by **one** of the following:

- QTc analysis on resting and exercise ECGs

Note: The diagnostic accuracy by QTc analysis is considerably improved by evaluation of the exercise ECG QTc intervals, in addition to the resting ECG, using the QTc values listed in Table 1.

- Specific mutation testing when the disease-causing mutation in the family is known

Genetically Related (Allelic) Disorders

Jervell and Lange-Nielsen syndrome(JLNS) is characterized by congenital profound bilateral sensorineural hearing loss and long QTc interval 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. More than half of untreated individuals with JLNS die before age 15 years. JLNS, inherited in an autosomal recessive manner, is caused by homozygous disease-causing mutations in either *KCNQ1* (locus name LQT1) or *KCNE1* (locus name LQT5).

Brugada syndrome. Mutations in *SCN5A* (locus name LQT3) are associated with rapid polymorphic ventricular tachycardia/ventricular fibrillation and sudden death.

Acquired, drug-induced long QT syndrome. Some individuals with drug-induced LQTS have a genetic predisposition to LQTS caused by a mutation of one of the five genes associated with RWS [Napolitano et al 2000].

Clinical Description

Natural History

Romano-Ward syndrome (RWS) is characterized by QT prolongation and T-wave abnormalities on ECG, which are associated with tachyarrhythmias, typically the ventricular tachycardia *torsade de pointes* (TdP). TdP is usually self-terminating, thus causing syncope,

the most common symptom in individuals with RWS. Syncope is typically precipitous and without warning. In some instances, TdP degenerates to ventricular fibrillation and aborted cardiac arrest (if the individual is defibrillated) or sudden death.

Three clinical phenotypes are recognized in individuals with RWS (see Table 3):

- LQT1, caused by mutations in *KCNQ1* or *KCNE1* and leading to abnormal IKs potassium channel function
- LQT2, caused by mutations in *KCNH2* or *KCNE2* and leading to IKr potassium channel dysfunction
- LQT3, caused by mutations in *SCN5A*, the cardiac sodium channel gene, and leading to abnormal INa channel function

The LQT1 phenotype accounts for approximately 60% of cases, LQT2 approximately 35%, and LQT3 fewer than 5%.

Approximately 50% or fewer individuals with a disease-causing mutation in one of the genes associated with RWS have symptoms and 50% or more never show symptoms [Vincent et al 1992, Zareba et al 1998]. The number of syncopal events in symptomatic individuals ranges from one to hundreds, averaging just a few.

The primary triggers for cardiac events in RWS [Schwartz et al 2001a]:

- LQT1. Exercise and sudden emotion
- LQT2. Exercise/emotion/sleep
- LQT3. Sleep

Cardiac events may occur from infancy through middle age but are most common from the pre-teen years through the 20s, with the risk generally diminishing throughout that time period. The usual age range of events differs somewhat for each genotype. Cardiac events are uncommon after age 30-40 years; when present, they are often triggered by administration of a QT-prolonging drug or hypokalemia or are associated with the LQT3 phenotype.

Of individuals who die of complications of RWS, death is the first sign of the disorder in an estimated 10%-15%. The risk for sudden death from birth to age 40 years has been reported at approximately 4% in each of the phenotypes [Zareba et al 1998]. Although syncopal events are most common in LQT1 (63%), followed by LQT2 (46%) and LQT3 (18%), the incidence of death is similar in all three.

Table 3. Romano-Ward Phenotypes

Percent of Individuals with RWS	Phenotype [1]	Gene Symbol	Average QTc	ST-T-Wave Morphology	Incidence of Cardiac Events	Cardiac Event Trigger	Sudden Death Risk
>60%	LQT1	*KCNQ1*; *KCNE1*	480 msec	Broad-base T-wave	63%	Exercise, emotion	4%
~35%	LQT2	*KCNH2 (HERG)*; *KCNE2*		Bifid T-waves	46%	Exercise, sleep startle	4% [2]
<5%	LQT3	*SCN5A*	~490 msec	Long ST, small T	18%	Sleep	4%

1. Phenotype: LQT1 caused by mutations in *KCNQ1* or *KCNE1*; LQT2 caused by mutations in *KCNH2* or *KCNE2*; LQT3 caused by mutations in *SCN5A*

2. Sudden death risk may be higher in individuals with specific *KCNH2* mutations.

QTc range is similar across phenotypes (~400-600+ msec). The average QTc values are similar for the LQT1 and LQT2 phenotypes and somewhat longer for the LQT3 phenotype. T-wave patterns characteristic for the LQT1, 2, and 3 phenotypes have been reported and can assist in directing molecular genetic testing strategies to identify the gene involved [Zhang et al 2000]. The predominant triggering stimuli for cardiac events vary by phenotype. In general, the phenotype does not vary much by mutation type; however, a recent study indicated that individuals with the LQT2 phenotype and mutations in the pore region of *KCNH2* had a higher risk of sudden death than those individuals with mutations in other regions of the *KCNH2* gene. In those individuals with *KCNQ1* mutations, the risk is the same in pore versus other region mutations.

Genotype-Phenotype Correlations

The known genotype-phenotype correlations are described in Table 3.

Penetrance

RWS exhibits reduced penetrance of the ECG changes and symptoms. Overall, approximately 31% of individuals with a disease-causing mutation have a QTc between 400 and 460 msec (Table 1), values that overlap with those of normals; 12% with the LQT1 phenotype, 17% with the LQT2 phenotype, and 5% with the LQT3 phenotype (Table 3) actually have a normal QTc (defined as <440 msec) on baseline ECG.

Approximately 80% of individuals with a disease-causing mutation have a T-wave pattern characteristic for their genotype.

As noted in Table 3, penetrance for symptoms is also reduced. At least 37% of individuals with the LQT1 phenotype, 54% with the LQT2 phenotype, and 82% with the LQT3 phenotype remain asymptomatic.

Anticipation

Genetic anticipation has not been identified in individuals with RWS.

Nomenclature

Articles in the medical literature may use the terminology LQT1, LQT2 (etc) to refer to any of the following:

- The locus name of genes involved in long QT syndrome (See Molecular Genetics)
- Individuals with mutations in the specific genes at those loci
- Phenotypes associated with mutations in specific genes (see Table 3)

For clarity and to enable appropriate diagnosis and management, it is suggested that forms of inherited long QT syndrome other than RWS be called “atypical” or “complex” LQTS because they include:

- High-frequency, bidirectional ventricular tachycardia (Andersen-Tawil syndrome [LQT7] rather than TdP)
- Non-cardiac features (Andersen-Tawil syndrome [LQT7], Timothy syndrome [LQT8], and caveolinopathy [proposed as LQT9])
- QT prolongation in only a minority of individuals with a mutation (*ANK2* disorder [LQT4] and Andersen-Tawil syndrome [LQT7])

Prevalence

RWS is the most common form of inherited long QT syndrome.

The prevalence of RWS has been estimated at 1:3000-1:7000, with the ~1:3000 figure progressively appearing the more likely.

The disorder has been identified in all races. Prevalence studies by race have not been performed.

A founder effect has been reported in the state of Utah (US) and in Finland with a prevalence of around 1:5000 [Piippo et al 2001]. Preliminary evidence suggests a lower prevalence in Africans.

Differential Diagnosis

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

LQTS with syndactyly (Timothy syndromeor syndactyly-related LQTS). Timothy syndrome is characterized by: cardiac (LQTS and/or congenital heart defects), hand (variable unilateral or bilateral cutaneous syndactyly of fingers or toes), facial and neurodevelopmental features. LQTS typically manifests with a rate-corrected QT interval between 480 ms and 700 ms. Facial anomalies include: flat nasal bridge, low-set ears, thin upper lip, and round face. Neurologic symptoms include: autism, seizures, mental retardation, and hypotonia. Ventricular tachyarrhythmia is the leading cause of death; average age of death is 2.5 years. Timothy syndrome is diagnosed by clinical features and by the presence of the *de novo* Gly406Arg mutation in the $Ca_V1.2$ calcium channel gene, *CACNA1C*, the only gene known to be associated with Timothy syndrome [Splawski et al 2004].

This disorder is designated LQT8 and best fits as one of the "atypical" or "complex" forms of LQTS (see Nomenclature).

Jervell and Lange-Nielsen syndrome, Brugada syndrome. See Genetically Related Disorders.

Andersen-Tawil syndrome. Andersen-Tawil syndrome (ATS) 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, ocular hypertelorism, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis. *KCNJ2* is the only gene known to be associated with ATS [Plaster et al 2001, Ai et al 2002, Tristani-Firouzi et al 2002, Zhang et al 2005]. Approximately 70% of individuals with ATS have a detectable mutation in *KCNJ2*.

ATS1 type Anderson syndrome has been proposed as LQT7, but this proposal is controversial at present. Current evidence suggests that the average QTc values in ATS1 are within the normal range. The large U waves in this condition may complicate accurate measurement of the QT interval and QTc calculation. Thus, further investigation is required to clarify whether Andersen-Tawil syndrome should be designated as an LQTS subtype. If so, it would be classified under the "atypical" or "complex" LQTS forms (see Nomenclature).

LQT4 is caused by mutation of *ANK2*, a member of the complex family of versatile membrane adapter genes, leading to dysfunction of a variety of cellular processes. LQT4 appears to be rare. Because of very small numbers of families/individuals with LQT4 reported to date, the rate of death and symptoms are not certain in this genotype. Similar to LQT7, current evidence

suggests that the average QTc values in the proposed LQT4 phenotype are within the normal range. The large U waves in these conditions may complicate accurate measurement of the QT interval and QTc calculation. The phenotype of LQT4 is distinctive in that atrial abnormalities are common, particularly significant sinus bradycardia and atrial fibrillation.

Other causes of syncope or sudden death to be considered in children and young adults:

- Sudden infant death syndrome (SIDS) is commonly defined as unexpected sudden death within the first year of life. Death during the first year of life in families with RWS appears to be rare, yet a percent of infants dying of SIDS have been shown to have mutations of one of the LQTS-related genes [Ackerman et al 2001, Schwartz et al 2001b, Arnestad et al 2007]. While it seems probable that these mutations were the cause of the SIDS, the association is uncertain; and the frequency of pathogenic mutations in SIDS cases has been questioned [Wedekind et al 2006].
- Vasovagal (neurally mediated) syncope, orthostatic hypotension
- Seizures
- Familial ventricular fibrillation, now known to be Brugada syndrome in many cases
- Subtle hypertrophic cardiomyopathy
- Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)
- Catecholaminergic polymorphic ventricular tachycardia
- Anomalous coronary artery
- Drug-induced long QT syndrome (see drugs at www.qtdrugs.org)

Management

Evaluations to Establish the Diagnosis

To establish the diagnosis in an individual suspected of having Romano-Ward syndrome (RWS), determine whether symptoms are attributable to LQTS or to some other disorder. For example, dizziness, pre-syncope, palpitations, vasovagal syncope, and orthostatic syncope are common in the general population and rarely caused by LQTS. Treatment decisions should be based on LQTS-related events, not on unrelated disorders.

Treatment of Manifestations

All symptomatic persons should be treated. Complete cessation of symptoms is the goal. Management is focused on the prevention of syncope, cardiac arrest, and sudden death through use of the following:

- **Beta blockers.** Beta blockers are the mainstay of therapy for the LQT1 phenotype (see Table 3) and the LQT2 phenotype; however, their use in the management of the LQT3 phenotype is controversial. Some individuals have symptoms despite the use of beta blockers [Moss et al 2000]:
  - In some individuals, recurrence of events while on medication is the result of inadequate dosing; thus, the dose must be adjusted regularly in growing children, and the efficacy must be evaluated by assessment of the exercise ECG or ambulatory ECG.
  - Many events “on beta blockers” appear to be caused by non-compliance (failure to take the medication). It is important to emphasize that beta blockers *must* be taken daily and to have strategies in place in case of missed doses.

- Many events "on beta blockers" appear to be caused by the administration of QT-prolonging drugs (see Agents/Circumstances to Avoid). QT-prolonging drugs should **not** be administered to persons with LQTS without careful consideration of risk versus benefit by patient(s) and physician(s).
  - **Pacemakers.** Pacemakers may be necessary for those individuals with symptomatic bradycardia associated with beta-blocker therapy [Viskin 2000].
  - **External defibrillators.** Having automatic external defibrillators readily available at home, at school, and in play areas may be appropriate in some cases.
  - **Implantable cardioverter-defibrillators (ICDs).** ICDs may be necessary for those individuals with beta-blocker-resistant symptoms, inability to take beta blockers (significant asthma, severe fatigue), history of cardiac arrest, and LQTS associated with syndactyly (Timothy syndrome). ICD therapy may be best for symptomatic individuals with the LQT3 phenotype [Wilde 2002].

    Note: Implantable cardioverter-defibrillators have largely replaced left thoracic sympathectomy as the preferred treatment in individuals for whom beta blockers are ineffective.

Prevention of Primary Manifestations

Although the percent of affected individuals who experience cardiac arrest or sudden death is small, all affected but asymptomatic persons younger than age 40 years should be treated prophylactically (usually with beta blockers) because it is not possible to identify those individuals who are at greatest risk for these events.

Because symptoms occur primarily in the pre-teen years to early 20s, prophylactic treatment may not be necessary for those affected individuals who (1) are older than age 40 years at diagnosis and (2) either are life-long asymptomatic or have a very remote history of LQTS-type syncope.

As emphasized in Treatment of Manifestations, QT-prolonging drugs should **not** be used unless the benefit of taking the QT-prolonging drug clearly outweighs the risk of *torsade de pointes*.

Prevention of Secondary Complications

Examine the past medical history for asthma, orthostatic hypotension, depression, and diabetes mellitus because these disorders may be exacerbated by treatment with beta blockers.

Although the incidence of arrhythmias during elective interventions such as surgery, endoscopies, childbirth, or dental work is low, it is prudent to monitor the ECG during such interventions and to alert the appropriate medical personnel in case intervention is needed.

Surveillance

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

Affected individuals should have regular, 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 or provoke *torsade de pointes* should be avoided. See www.qtdrugs.org [Woosley 2001] for a complete and updated list.

Epinephrine given as part of local anesthetics can trigger arrhythmias and is best avoided.

Individuals with the LQT1 or LQT2 phenotype should be advised to avoid competitive sports and activities likely to be associated with intense physical activity and/or emotional stress (e.g., amusement park rides, scary movies, jumping into cold water).

Testing of Relatives at Risk

Presymptomatic diagnosis of at-risk relatives by ECG and/or molecular genetic testing (if the disease-causing mutation in the family is known) followed by treatment is necessary to prevent syncope and sudden death in those individuals who are affected. At-risk family members should be alerted to their risk and the need to be evaluated.

Note: Relatives at high potential risk who require further testing include members of a family:

- That has documented LQTS
- In which evaluation for LQTS has not been performed

Relatives at low potential risk who do not require further testing include members of a family in which the symptomatic ancestor:

- Had a low probability of LQTS based on QTc interval (see Table 1) and no relative who experienced LQTS-type events
- Had a negative molecular genetic test result and normal QTc interval

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

Most affected individuals live normal lifestyles. Education of adult individuals and the parents of affected children is an important aspect of management.

No other medications have been proven to be effective in preventing the arrhythmias and symptoms.

Individuals with LQTS do not need antibiotics for SBE prophylaxis.

Genetics clinics are a source of 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 (below) may include disease-specific and/or umbrella support organizations.

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

Romano-Ward syndrome (RWS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with RWS have an affected parent.
- A proband with RWS may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is small.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include exercise ECG evaluation and (when possible) molecular genetic testing.

Note: Although most individuals diagnosed with RWS have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or reduced penetrance.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low:
  - If the disease-causing mutation identified in the proband cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband.
  - Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of the proband has a 50% chance of inheriting the disease-causing mutation.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents. If a parent is affected, his or her family members are at risk.

Specific risk issues. With the reduced penetrance of symptoms in individuals with RWS, careful ECG evaluation, including exercise ECG, is often necessary to identify affected family members accurately. The absence of a family history of sudden death is common and does not negate the diagnosis or preclude the possibility of sudden death in relatives.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic adults and children. Testing of at-risk asymptomatic adults for RWS is available using the same techniques described in Molecular Genetic Testing. Such testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. To facilitate the use of morbidity-/mortality-reducing interventions, presymptomatic testing of all at-risk family members, including individuals younger than age 18 years, should be considered (see Management, Testing of Relatives at Risk). When testing at-risk individuals for RWS, an affected family member should be tested first to identify the disease-causing mutation in the family.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made 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 or at risk of having inherited a disease-causing mutation.

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 when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis for RWS are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as RWS that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within 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 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 Romano-Ward Syndrome

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
LQT1	*KCNQ1*	11p15.5	Potassium voltage-gated channel subfamily KQT member 1
LQT2	*KCNH2*	7q35-q36	Potassium voltage-gated channel subfamily H member 2
LQT3	*SCN5A*	3p21	Sodium channel protein type 5 subunit alpha
LQT5	*KCNE1*	21q22.1-q22.2	Potassium voltage-gated channel subfamily E member 1
LQT6	*KCNE2*	21q22.1	Potassium voltage-gated channel subfamily E member 2

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 Romano-Ward Syndrome

152427	POTASSIUM CHANNEL, VOLTAGE-GATED, SUBFAMILY H, MEMBER 2; KCNH2
176261	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 1; KCNE1
192500	LONG QT SYNDROME 1; LQT1
600163	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT; SCN5A
603796	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 2; KCNE2
603830	LONG QT SYNDROME 3; LQT3
607542	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 1; KCNQ1

Table C. Genomic Databases for Romano-Ward Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
KCNQ1	KCNQ1	3784 (MIM No. 607542)	KCNQ1
KCNH2	KCNH2	84920 (MIM No. 152427)	KCNH2
SCN5A	SCN5A	6331 (MIM No. 600163)	SCN5A
KCNE1	KCNE1	3753 (MIM No. 176261)	KCNE1
KCNE2	KCNE2	9992 (MIM No. 603796)	KCNE2

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

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The genes causing RWS encode for potassium or sodium cardiac ion channels [Splawski et al 2000]. Mutations cause abnormal ion channel function: a loss of function in the potassium channels and a gain of function in the sodium channel. This abnormal ion function results in prolongation of the cardiac action potential and susceptibility of the cardiac myocytes to early after depolarizations (EADs), which initiate the ventricular arrhythmia, *torsade de pointes* (TdP).

***KCNQ1*—Normal allelic variants:** *KCNQ1* was initially reported to contain 16 exons spanning 400 kb [Splawski et al 1998]; subsequent reports corrected it to 19 exons spanning approximately 400 kb [Neyroud et al 1999]. At least 49 potentially benign polymorphisms have been identified.

Pathologic allelic variants: More than 145 mutations of *KCNQ1* have been reported (see Note).

Normal gene product: The potassium voltage-gated channel subfamily KQT member 1 is the alpha subunit forming the slowly activating potassium delayed rectifier IKs [Keating & Sanguinetti 2001].

Abnormal gene product: IKs channel with reduced function

***KCNE1*—Normal allelic variants:** The gene consists of three exons spanning approximately 40 kb. No benign polymorphisms have been described.

Pathologic allelic variants: At least 36 mutations have been described (see Note).

Normal gene product: The potassium voltage-gated channel subfamily E member 1 is the beta subunit forming the slowly activating potassium delayed rectifier IKs. The two subunits encoded by *KCNE1* and *KCNQ1* coassemble to form the IKs channel.

Abnormal gene product: IKs channel with reduced function

***KCNH2*—Normal allelic variants:** The gene consists of 16 exons, spanning approximately 19 kb. At least 37 potentially benign polymorphisms have been described.

Pathologic allelic variants: More than 145 mutations have been reported (see Note).

Normal gene product: The potassium voltage-gated channel subfamily H member 2 is the alpha subunit forming the rapidly activating potassium delayed rectifier Ikr.

Abnormal gene product: IKr channel with reduced function

***KCNE2*—Normal allelic variants:** The gene consists of three exons and spans approximately 40 kb. No benign polymorphisms have been reported.

Pathologic allelic variants: At least 12 mutations have been reported (see Note).

Normal gene product: The potassium voltage-gated channel subfamily E member 2 is the beta subunit forming the rapidly activating potassium delayed rectifier IKr. The two subunits encoded by *KCNH2* and *KCNE2* coassemble to form the IKr channel.

Abnormal gene product: IKr channel with reduced function

***SCN5A*—Normal allelic variants:** The gene consists of 28 exons and spans approximately 80 kb. A dinucleotide repeat polymorphism in intron 16 has been described. At least 34 potentially benign polymorphisms have been described.

Pathologic allelic variants: At least 34 mutations are known (see Note).

Normal gene product: The sodium channel protein type V alpha subunit is the alpha subunit forming the cardiac sodium channel.

Abnormal gene product: Cardiac sodium channel with increased persistent inward current

Note—More than 300 mutations of the five LQTS-related genes have been reported. A summary of mutations identified before 2000 was reported in Splawski et al [1998]. In that summary, 72% were missense mutations, 10% were frameshift mutations, and in-frame

deletions, nonsense mutations, and splice site mutations made up 5%-7% each. See Genomic databases table for subsequent details and descriptions.

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.

National Library of Medicine Genetics Home Reference
Romano-Ward syndrome

Canadian SADS Foundation
15-6400 Millcreek Drive Suite 314
Mississauga ON L5N 3E7
Canada
Phone: 877-525-5995; 905-826-6303
Fax: 905-826-9068
www.sads.ca

Cardiac Arrhythmias Research and Education Foundation (CARE)
427 Fulton Street
P.O. Box 69
Seymour WI 54165
Phone: 800-404-9500; 920-833-7000; 425-785-5836
Fax: 920-833-7005
Email: care@careforhearts.org
www.longqt.org

European Long QT Syndrome Information Center
Email: info@qtsyndrome.ch
www.QTsyndrome.ch

SADS Australia
Email: info@sads.org.au
www.sads.org.au

SADS UK
www.sadsuk.org

Sudden Arrhythmia Death Syndromes (SADS) Foundation
508 East South Temple Suite 20
Salt Lake City UT 84102
Phone: 800-786-7723; 801-531-0937
Fax: 801-531-0945
Email: sads@sads.org
www.sads.org

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

Published Statements and Policies Regarding Genetic Testing

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Chapter Notes

Revision History

- 21 May 2008 (me) Comprehensive update posted live
- 7 July 2005 (me) Comprehensive update posted to live Web site
- 28 February 2005 (gmv) Revision: sequence analysis clinically available; LQt4 moved to Differential Diagnosis
- 13 April 2004 (cd) Revision: *ANK2* testing clinically available
- 11 February 2004 (bp/gmv) Revisions
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