Prevalence, mutation spectrum, and cardiac phenotype of the Jervell and Lange-Nielsen syndrome in Sweden

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Aims
To explore the national prevalence, mutation spectrum, cardiac phenotype, and outcome of the uncommon Jervell and Lange-Nielsen syndrome (JLNS), associated with a high risk of sudden cardiac death.

Methods and results
A national inventory of clinical JLNS cases was performed. Genotype and area of origin were ascertained in index families. Retrospective clinical data were collected from medical records and interviews. We identified 19 cases in 13 Swedish families. A JLNS prevalence of 1:200,000 was revealed (five living cases, 10 years of age). The mutation spectrum consisted of eight KCNQ1 mutations, whereof p.R518X in 12/24 alleles. Geographic clustering of four mutations (20/24 alleles) and similarities to Norway’s mutation spectrum were seen. A high prevalence of heterozygotes was suggested. Three paediatric cases on β-blockers since birth were as yet asymptomatic. Seven symptomatic cases had suffered an aborted cardiac arrest and four had died suddenly. QTc prolongation was significantly longer in symptomatic cases (mean 605 ± 62 vs. 518 ± 50 ms, P = 0.016). β-Blockers reduced, but did not abolish, cardiac events in any previously symptomatic case. β-Blocker type, dosage, and compliance probably affect outcome significantly. Implantable cardioverter-defibrillator therapy (ICD, n = 6) was associated with certain complications; however, no case of sudden death.

Conclusion
Founder effects could explain 83% of the Swedish JLNS mutation spectrum and probably contribute to the high JLNS prevalence found in preadolescent Swedish children. Due to the severe cardiac phenotype in JLNS, the importance of stringent β-blocker therapy and compliance, and consideration of ICD implantation in the case of therapy failure is stressed.

Keywords
Jervell and Lange-Nielsen syndrome • Founder effects • KCNQ1 gene • Cardiac phenotype • Therapy efficacy

Introduction
The Jervell and Lange-Nielsen syndrome (JLNS), first reported in Norway 1957, is characterized by congenital hearing loss, marked prolongation of the QT interval, a propensity for life-threatening ventricular arrhythmias, and a high risk of sudden cardiac death.1,2 Jervell and Lange-Nielsen syndrome prevalence remains largely unknown due to the high mortality in infancy and lack of comprehensive neonatal screening methods. Norway is, to date, the country where this uncommon hereditary disorder is reported most often, with a JLNS prevalence estimated to at least 1:200,000.3 Jervell and Lange-Nielsen syndrome is caused by homozygous or compound heterozygous mutations that affect the KCNQ1 and/or KCNE1 genes, encoding subunits that co-assemble into a voltage-gated potassium ion (K+)-channel.4–7 The function of the K+ channel is essential for the endolymph production of the inner-ear and the slow rectifier current of the myocyte action potential. The loss of function caused by the
JLNS mutations corresponds to the associated surdocardiac phenotype.\textsuperscript{2,8,9} Heterozygous carrier-ship of JLNS mutations is associated with the long QT syndrome (LQTS), where QT prolongation, but not hearing loss, is inherited via an autosomal-dominant pattern with incomplete penetrance.\textsuperscript{10}

In Sweden, where strong founder effects have caused a high regional prevalence of KCNQ1 mutations, a high probability for JLNS occurrence would intuitively be inferred.\textsuperscript{11} The aim of this study was to explore the prevalence, mutation spectrum, cardiac phenotype, and outcome of JLNS in Sweden.

Methods

In Sweden, no diagnostic code for JLNS has been available, and the prevalence of JLNS is previously unknown. A national inventory of clinical JLNS cases was performed between 2007 and 2010, and all Swedish clinics or departments of paediatric cardiology, cardiology, medicine, clinical genetics, otorhinolaryngology, audiology, and cochlear implantation were approached and asked for knowledge of cases (number, gender, and birth year). All Swedish schools teaching deaf children were similarly approached, and information regarding the inventory was spread at national meetings in paediatric cardiology, cardiology, and molecular genetics.

All identified cases and families were first approached by the tending clinicians and asked for approval of first contact. A letter was provided to each case or family with information regarding the study and an invitation to participate. A signed informed consent to participate in the study was obtained from all living cases or their legal guardian and the study was approved by the Regional Ethical Review Board, Umeå University.

Inclusion criteria were congenital bilateral hearing loss (incomplete or complete) and a clinical JLNS diagnosis (a personal history of syncope or electrocardiographic findings of a prolonged QT interval, often in combination with a family history of LQTS).

The causative mutations in participating JLNS families and cases were identified either through medical records or sequencing of the KCNQ1 and KCNE1 genes, using DNA extracted from whole-blood by standard methods, previously described in detail by the authors.\textsuperscript{11} The geographic origin of cases and recent ancestors was noted on a regional map.

Clinical data were collected from full medical records and a personal interview. The semi-structured interview was conducted with cases and/or family members, lasted on average between 2–4 h, and focused on symptoms and experiences throughout life living with JLNS. During the interview, an amnestic information regarding any deceased relative with JLNS diagnosis, and knowledge of cardiac symptoms occurrence in first-degree relatives without hearing-loss (parents, siblings, and children), were asked for specifically. Standard 12-lead electrocardiograms (ECGs), preferably recorded at the time of JLNS diagnosis, were acquired from medical records and manually measured by one observer. The measurement method has been previously described in detail.\textsuperscript{12}

Statistical analysis was performed using the Mann–Whitney U test for comparison between numerical and nominal variables and the \(\chi^2\) test for comparison between nominal variables. A two-tailed value for \(P < 0.05\) was considered statistically significant.

A rough estimation of the prevalence of heterozygous mutation-carriers in the Swedish population, derived from the number of genotype-ascertained JLNS probands, was calculated using the Hardy–Weinberg equilibrium, with the reservation that the principle is based on assumptions that are not fulfilled outside a laboratory setting.\textsuperscript{13}

Regarding the aim of estimating JLNS prevalence, we took the high mortality before adulthood in JLNS into consideration, and deemed a preadolescent paediatric population most appropriate for prevalence estimation. During the last decade, routine ECG screening has been implemented in the national cochlear implant clinic and the Swedish schools teaching deaf children, rendering the risk of non-detection of JLNS in children <10 years of age low. Population demographics are available through Statistics Sweden (www.scb.se) and the annual birth count is \(\approx 100,000\), rendering the number of Swedish children <10 years of age approximately one million.

Results

Thirteen JLNS index families of Swedish descent were identified in the national inventory, including a total of 19 JLNS cases (11 females, Table 1). Seven families (12 cases) were previously known from clinical practice and/or the authors’ LQTS research in the northern Swedish region, including five deceased cases. Among the deceased JLNS cases, four cases (two females) had died from suspected JLNS-related death (drowning or sudden cardiac death) and one adult male had died due to malignancy.

The prevalent JLNS cases (\(n = 14\), whereof 9 females), from 12 genotyped families, were invited to a personal interview. Mean age was 31 ± 24 years (median 31 years, range 5–88 years), and median age was the same (31 years) in both males and females.

Five now living cases <10 years of age (mean age 6 years, range 5–8 years) were identified, corresponding to a rough estimate of at least one JLNS case being born every other year, and an absolute minimum JLNS prevalence of 1 : 200 000 in Swedish children <10 years of age.

Genotype and mutation spectrum for Jervell and Lange-Nielsen Syndrome in Sweden

Genotype was investigated and ascertained in all but one of the 13 families, 6 of homozygous genotype and 6 of compound heterozygous genotype (Table 1). All identified mutations (\(n = 8\)) were located in the KCNQ1 gene, and were previously reported, either as associated with JLNS or LQTS.\textsuperscript{3,4,6,14–19} The identified KCNQ1 mutations included three missense mutations (4/24 alleles), two frame-shift mutations (5/24 alleles), one splice site mutation (1/24 alleles), and two nonsense mutations (14/24 alleles), whereof one specific nonsense mutation (p.R518X) in 12/24 alleles (Table 2). The p.Y111C missense mutation, a Swedish founder mutation with dominant negative properties, never before reported as a causative of JLNS, was identified in homozygous form in one proband.\textsuperscript{11,12} Three additional KCNQ1 mutations identified in the Swedish probands, p.R190W, p.S349W, and p.S277del, have not to our knowledge been reported previously in association with JLNS (Table 2). No KCNE1 mutations were identified.

Ten out of 13 identified JLNS families had ancestral roots in upper northern Sweden (Table 1). Among the four mutations present in at least two alleles there were evidences of geographical clustering of probands and recent ancestors (Figure 1). Eleven of the p.R518X alleles and all p.Y111C alleles (\(n = 2\)) originated
from two northern regions, and 1 p.Q530X allele and all

c.572_576del alleles (n = 4) originated from two mid-western

regions on the Norwegian border (Figure 1). Similarities between

the JLNS mutation spectra in Sweden and Norway regarding

three mutations (p.R518X, c.572_576del and p.Q530X) were

seen and a high frequency of heterozygous mutation-carriers was

suggested by the relatively high prevalence of JLNS probands

(Table 3).

**Cardiac phenotype**

An overview of the cardiac phenotype seen over time in 19 JLNS
cases (11 females), whereof 5 deceased cases (2 females), is
depicted in Figure 2. Experience of a first cardiac event was

present in 16/19 cases. The three cases without experience of a

first cardiac event (all females) were between 4 and 6 years at

the time of the study, and had received prophylactic β-blocker

therapy since birth. Age at first cardiac event was available in 11/

16 symptomatic cases; mean age 2.4 ± 1.2 years, median 2.5

years, and range 0.5–4.5 years (Table 4). In five cases (all siblings),
symptoms debut according to anamnesis occurred in ‘early child-

hood’, the parents of the siblings were deceased, and there were

no medical records available (Figure 2).

Cardiac symptoms in the JLNS cases were often interpreted as

seizures by witnesses or medical personnel and six cases (four

females) had undergone electroencephalography. In three cases

two females there were reports of ‘fever spells’ and ‘seizures’

Table I  Genotype and geographic region of origin in 13 Swedish Jervell and Lange-Nielsen syndrome families

<table>
<thead>
<tr>
<th>Family</th>
<th>KCNQ1 mutations (amino acid change)</th>
<th>Region of origin (bold allele)</th>
<th>Gender (F/M)</th>
<th>Case (no.)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWE1</td>
<td>M159/R518X</td>
<td>North</td>
<td>2 F</td>
<td>1, 3b</td>
</tr>
<tr>
<td>SWE2</td>
<td>R518X/R190W</td>
<td>North</td>
<td>F</td>
<td>2</td>
</tr>
<tr>
<td>SWE3</td>
<td>Q530X/R518X</td>
<td>Mid-West</td>
<td>M</td>
<td>4</td>
</tr>
<tr>
<td>SWE4</td>
<td>R518X/R518X</td>
<td>North</td>
<td>F</td>
<td>5</td>
</tr>
<tr>
<td>SWE5</td>
<td>S349W/R518X</td>
<td>North</td>
<td>M</td>
<td>6</td>
</tr>
<tr>
<td>SWE6</td>
<td>R518X/R518X</td>
<td>North</td>
<td>F/M</td>
<td>7, 8b</td>
</tr>
<tr>
<td>SWE7</td>
<td>R192Cfs91X/R192Cfs91X</td>
<td>Mid-West</td>
<td>F</td>
<td>9</td>
</tr>
<tr>
<td>SWE8</td>
<td>R518X/Q530X</td>
<td>North</td>
<td>F</td>
<td>10</td>
</tr>
<tr>
<td>SWE9</td>
<td>S277del/R518X</td>
<td>North</td>
<td>M</td>
<td>11</td>
</tr>
<tr>
<td>SWE10</td>
<td>Y111C/Y111C</td>
<td>North</td>
<td>F</td>
<td>12</td>
</tr>
<tr>
<td>SWE11</td>
<td>R192Cfs91X/R192Cfs91X</td>
<td>Mid-West</td>
<td>F</td>
<td>13</td>
</tr>
<tr>
<td>SWE12</td>
<td>R518X/R518X</td>
<td>North</td>
<td>F</td>
<td>14, 16−19c</td>
</tr>
<tr>
<td>SWE13</td>
<td>DNA not available</td>
<td>North</td>
<td>M</td>
<td>15c</td>
</tr>
</tbody>
</table>

Mutations present in ≥ 2 alleles are depicted in bold.

F, female; M, male.

aCase number (no.) in accordance with Figure 2 (living cases 1−14 according to age at study, deceased cases 15−19 according to birth year).

bThe cases in families SWE1, SWE6 and SWE12 are siblings. SWE12 has been previously described.29 We present data derived from direct contact with the proband in 2009.

cJervell and Lange-Nielsen syndrome cases in family SWE12 and SWE13 are, as of 2011, all deceased.

**Table 2  Inventory of KCNQ1 mutations identified in 12 Swedish JLNS probands**

<table>
<thead>
<tr>
<th>Nucleotide change</th>
<th>Amino acid change</th>
<th>Region</th>
<th>Mutation type</th>
<th>Alleles identified (n)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1522C &gt; T16,19</td>
<td>p.R518X</td>
<td>C-terminal</td>
<td>Nonsense</td>
<td>12 (3)</td>
</tr>
<tr>
<td>c.572_576del6</td>
<td>p.R192Cfs91X</td>
<td>S2−S3</td>
<td>Frame-shift</td>
<td>4 (2)</td>
</tr>
<tr>
<td>c.332A &gt; G18</td>
<td>p.Y111C</td>
<td>N-terminal</td>
<td>Missense</td>
<td>2 (1)</td>
</tr>
<tr>
<td>c.1588C &gt; T3</td>
<td>p.Q530X</td>
<td>C-terminal</td>
<td>Nonsense</td>
<td>2</td>
</tr>
<tr>
<td>c.477 + 1G &gt; A4,14</td>
<td>p.M159</td>
<td>S2</td>
<td>Splice error</td>
<td>1</td>
</tr>
<tr>
<td>c.568C &gt; T17</td>
<td>p.R190W</td>
<td>S2−S3</td>
<td>Missense</td>
<td>1</td>
</tr>
<tr>
<td>c.828_830del19,27</td>
<td>p.S277del</td>
<td>S5</td>
<td>Frame-shift</td>
<td>1</td>
</tr>
<tr>
<td>c.1046C &gt; G18</td>
<td>p.S349W</td>
<td>S6</td>
<td>Missense</td>
<td>1</td>
</tr>
</tbody>
</table>

aNumber of homozygous probands is given in parentheses.

bMutation not previously reported in association with JLNS, to our knowledge.
in infancy, possibly representing manifestations of cardiac events, indicating that symptoms debut could have occurred earlier than reported.

All symptomatic cases experienced recurrent syncopal episodes, ranging between a minimum of two reported cardiac events (Case 5) and over 30 cardiac events (Case 9). Ten out of 12 symptomatic cases (83%) with available data had experienced 10 or more cardiac events.

Cardiac events typically occurred more frequently in childhood in all cases (≏2–12 years of age, Figure 2). Adult females commonly continued to experience cardiac events in adulthood, including later periods of more frequent cardiac events, while in males the frequency of attacks abated in adulthood (Figure 2).

Experience of life-threatening cardiac events was common among the JLNS cases (10/19). Seven cases (three females) suffered an aborted cardiac arrest that required resuscitation (mean age 22 ± 27 years, median 6 years) and four cases (two females) suffered a probable fatal cardiac event (at age 5, 20, 27, and 37 years, respectively). Three of the sudden deaths occurred in relation to entering into, or swimming, in cold water.

If regarding verified fast ventricular tachycardia (260–500 beats per minute in Case 4) or ventricular fibrillation (Case 10) as a proxy for life-threatening cardiac events, 12/19 Swedish JLNS cases had experienced a life-threatening cardiac event (Table 4).

Triggers for cardiac events were typically physical exercise or emotional excitement (such as stress, fear, or anger), and in ≏10% of described events two or more concurrent triggers were present. A cold temperature, both regarding water when swimming and air-temperature during physical exercise, appeared to be a common trigger potentiator. Out of all described cardiac events (≏100), the attributable fraction of each reported trigger was 47% for physical exercise, 35% for emotional excitement, 14% for swimming/cold water, 9% for fever/infections, 8% for unspecified, and 2% for a forgotten b-blocker dose.

Electrocardiography

Electrocardiograms from 14/19 cases (nine females) were available, whereof three asymptomatic cases (Table 3). Mean QTc was markedly prolonged in the JLNS cases at 587 ± 69 ms, median 563 ms, and range 461–735 ms, with no significant difference between the sexes. One case presented with a QTc < 500 ms and 11/14 cases had a QTc > 550 ms. QTc prolongation was significantly longer in symptomatic cases (mean 605 ± 62 ms, median 584 ms) vs. asymptomatic cases (mean 518 ± 50 ms, median 540 ms, P = 0.016).

Medical therapy and interventions

All now living and one of the deceased cases received prophylactic b-blocker therapy. Mean age at therapy start was 6.8 ± 13 years, median 2 years (Table 3). Type of b-blocker prescribed at therapy start was typically propranolol (80%) and to a lesser extent pindolol (13%) or alprenolol (7%). β-Blocker dosage was noted to increase over time, with lower doses being prescribed during the 70s and early 80s (i.e. propranolol <1 mg/kg per day). One case (Case 15) received the lower, then recommended, dose up until his fatal cardiac event at 5 years of age (0.6 mg/kg per day). Among the 11 cases on a propranolol dose ≥1 mg/kg per day
Table 4  Clinical data, stratified by gender, regarding 19 Swedish Jervell and Lange-Nielsen syndrome cases

<table>
<thead>
<tr>
<th></th>
<th>All cases</th>
<th>Females</th>
<th>Males</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases, n (%)</td>
<td>19 (100)</td>
<td>11 (58)</td>
<td>8 (42)</td>
<td>–</td>
</tr>
<tr>
<td>Experience of a first CE, n (%)</td>
<td>16 (84)</td>
<td>8 (73)</td>
<td>8 (100)</td>
<td>0.23</td>
</tr>
<tr>
<td>Age at first CE, years (median)</td>
<td>2.4 ± 1.2 (2.5)</td>
<td>2.7 ± 1.2 (3)</td>
<td>2.1 ± 1.4 (2)</td>
<td>0.08</td>
</tr>
<tr>
<td>ACA/SCD, n (%)</td>
<td>12 (63)</td>
<td>6 (55)</td>
<td>6 (75)</td>
<td>0.63</td>
</tr>
<tr>
<td>ECG, n (%)</td>
<td>14 (74)</td>
<td>9 (82)</td>
<td>5 (63)</td>
<td>–</td>
</tr>
<tr>
<td>QTc, ms, (median)</td>
<td>587 ± 69 (563)</td>
<td>587 ± 84 (559)</td>
<td>586 ± 36 (565)</td>
<td>0.98</td>
</tr>
<tr>
<td>≥550 ms, n (%)</td>
<td>11 (79)</td>
<td>6 (67)</td>
<td>5 (100)</td>
<td>0.26</td>
</tr>
<tr>
<td>β-Blocker therapy, n (%)</td>
<td>15 (79)</td>
<td>9 (82)</td>
<td>6 (75)</td>
<td>–</td>
</tr>
<tr>
<td>Age at therapy start, years (median)</td>
<td>6.8 ± 13 (2)</td>
<td>3.4 ± 4 (2)</td>
<td>12 ± 20 (3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Total follow-up, years (median)</td>
<td>30 ± 22 (30)</td>
<td>27 ± 18 (30)</td>
<td>34 ± 28 (25)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

CE, cardiac event; ACA, aborted cardiac arrest or verified ventricular fibrillation/fast ventricular tachycardia; SCD, sudden cardiac death.

Figure 2  Figure depicting the timing of cardiac events and interventions during the lifetime of 19 Swedish JLNS cases. Cases are numbered on the vertical axis (in accordance with Table 1) according to age at study (youngest—oldest, cases 1—14). Deceased cases are numbered according to birth year (youngest—oldest, cases 15—19). F, female; M, male. After 45 years the time-scale on the x-axis is disrupted and the age at study/death of cases >45 years of age given in the right hand margin. Case 17 died from malignancy at 59 years of age (†).
3 were as yet asymptomatic (27%) and 8 (73%) had experienced at least one cardiac event while on therapy. A total of six cases (55%) had suffered a maximum of one cardiac event on propranolol therapy at the time of the study (mean time on therapy 15 ± 14 years, median 7 years, sum 91 years). In adulthood four cases (Cases 7, 9, 10, and 13) were switched to metoprolol and all experienced recurrence of frequent cardiac events, including two aborted cardiac arrests (mean time on therapy 17 ± 6 years, median 17 years, sum 67 years).

Three cases (Cases 6, 9, and 10) were treated with left cardiac sympathetic denervation (LCSD) due to recurrent syncopal episodes in spite of β-blocker treatment. Mean time to symptom recurrence after the procedure (all cases) was ~1 year, median 1 year. Recurrences occurred while on β-blocker therapy (propranolol ≥1 mg/kg per day) in two cases and after a gradual planned discontinuation of β-blocker therapy in one case (Case 10).

Six cases (all previously symptomatic) have received an implantable cardioverter-defibrillator (ICD). Indication for ICD implantation was in the three previously mentioned cases with LCSD continuous recurrent syncopal episodes in spite of surgical intervention and β-blocker therapy, and in the other three cases either recurrent cardiac events in spite of β-blocker therapy (Case 4) or aborted cardiac arrests (Cases 7 and 13). Mean age at implantation was 22 ± 13 years, median 21 years, and range 6–39 years. Two cases suffered peri-operative or post-operative complications (pericarditis and heart tamponade). All cases with ICDs have received appropriate shocks after implantation, according to medical records (cardiologists’ appraisal and/or after device interrogation). Two cases (Cases 4 and 7) received >25 shocks each during the first years after implantation. In Case 4, cardiac events were often noted to occur in the afternoon before administration of the evening dose, and frequency of shocks and syncopal events were significantly reduced after changing from a three per day to four doses per day β-blocker administration and an overall tightened compliance.

**Phenotype in hearing first-degree relatives**

Cardiac phenotype in first-degree relatives with normal hearing was largely asymptomatic, according to the interview data. Syncope was reported in 5/36 (14%) of heterozygous first-degree relatives (4/26 parents and 1/10 hearing siblings/children with ascertained genotype), and in none of the first-degree relatives with normal or uncertain genotype (n = 6). The symptomatic heterozygous cases were of p.M159sp (1/1), p.S349W (1/2), p.R518X (1/18), and c.572_576del (2/6) genotype (where the denominator is the total number of heterozygous first-degree relatives with available anamnestic information in the JLNS index families, for the specific allele).

Mean QTc in confirmed heterozygous first-degree relatives with available ECGs (n = 12, all of heterozygous p.R518X genotype) was 463 ± 19 ms, range 429–486 ms (P < 0.001 as compared with JLNS cases). A prolonged QT interval and other electrocardiographic aberrations were additionally reported in three cases (whereof two symptomatic) where an ECG was not available.

**Discussion**

We have performed a national inventory and identified 13 JLNS families, including a total of 19 cases. Among children <10 years of age, five now living cases were identified, corresponding to a rough JLNS prevalence of at least 1:200 000 infants (annual birth rate ~100 000), comparable with that reported in Norway. Importantly, as the study was not designed to identify deceased cases, JLNS prevalence might be underestimated.

**Mutation spectrum and founder effects**

The JLNS mutation spectrum in Sweden consisted solely of KCNQ1 mutations (n = 8). The majority (20/24) of the identified alleles were frame-shift, splice, or nonsense mutations, in accordance with the concept that JLNS is more commonly caused by mutations in the heterozygous form cause haploinsufficiency.

The mutation spectrum was dominated by the p.R518X nonsense mutation, a C to T transition (c.1552C > T) leading to an amino acid exchange of the residue Arginine-518 (R) for a premature stop codon (X), resulting in a C-terminal truncation and a non-functioning protein. Worldwide, p.R518X is a commonly occurring hot spot mutation, associated with both LQTS and JLNS. In Sweden and Norway, defined by geographical proximity and the historical union between the two kingdoms in 1814–1905, the geographic clustering of JLNS probands according to genotype (p.R518X, c.572_576del and p.Q530X) and the here revealed similarities between the mutation spectra is suggestive of a Scandinavian founder effect.

While the presence of strong founder effects and the mild cardiac phenotype seen specifically in first-degree p.R518X relatives probably have contributed to the relatively high prevalence of JLNS in Sweden, it surprised us that the Y111C founder mutation, identified in over 170 heterozygous mutation-carriers and with a documented high regional prevalence, was found in only one homozygous proband and in none of the compound heterozygotes. It has been reported that a mere 10% residual KCNQ1 function rescues hearing in homozygous mutation-carriers, and it could be seen as a limitation that the national inventory was not designed to detect such cases. Furthermore, a Swedish family in which compound heterozygosity for p.R518X and p.A525T resulted in a severe cardiac phenotype without hearing loss has been described, suggesting that the national prevalence of cases with a genotype predisposing for a severe cardiac phenotype might be well over the presented JLNS prevalence estimate.

However, during our research we have not identified any additional homozygous or compound heterozygous Y111C mutation-carriers, irrespective of hearing loss. An alternative hypothesis that we are considering is that homozygous Y111C pregnancies are somehow selected against.

**Cardiac phenotype and therapy efficacy**

The severity of the JLNS phenotype is well documented; however, the differences in cardiac phenotype between the sexes seen over time need to be further elucidated.

Knowledge regarding clinical outcome with respect to different medical interventions is limited and methodological differences
over time (i.e. β-blocker type and dosage, techniques regarding LCSD procedures, etc.) complicate comparisons.

In this study, β-blocker therapy was associated with reduction of event frequency and in three cases asymptomatic phenotype, but was not successful in completely abolishing events in any previously symptomatic individual. However, inadequate dosage and possibly type of β-blocker used may at least partly explain the limited efficacy seen in this study. A more favorable outcome for propranolol as compared with metoprolol was suggested. Concerns regarding differences in efficacy between types of β-blockers in heterozygous LQTS patients have been reported.26,27

There is furthermore reason to suspect that therapy non-compliance played a more prominent role in triggering cardiac events than what was reported in this study, as has been shown for β-blocker treatment ‘failures’ in heterozygous LQT1 mutation-carriers.28 Not surprisingly, a positive effect on symptoms frequency via stringency regarding the timing of medication and avoidance of triggers was reported by many cases during the interviews.

Regarding LCSD, performed on only three of the Swedish cases, no convincing preventive effect was seen in this retrospective study, although this could be related to the surgical techniques used.

Among the cases treated with an ICD there was no case of sudden death, emphasizing the previously seen efficacy of the ICD in prevention of sudden cardiac death in JLNS.25 On the other hand, two out of six cases with an ICD suffered from frequent multiple discharges during the first years after implantation, two cases suffered from peri-/post-operative complications and, as is well known, device deployment in small children is associated with significant complications.

Based on our compiled data, we would, as initial therapy from birth and onwards, recommend β-blockers (propranolol 2–4 mg/kg per day, administrated 3–4 times per day) with utmost stress on patient compliance. Due to the rapid growth of children, these patients need close monitoring and dose adjustments. We recommend that the effect of the given therapy (and compliance) should be regularly evaluated by ambulatory 24 h electrocardiography, and dosage increased if appropriate, ensuring an adequate β-blockade over day and night. Furthermore, the level of β-blockade during physical exertion should be evaluated by exercise test when the child is old/tall enough to comply. In cases of true therapy failure, LCSD and/or ICD implantation must be considered. Further studies regarding efficacy of medical and surgical interventions in this high-risk group is needed.

In conclusion, a JLNS prevalence of at least 1 : 200 000 in Swedish children under 10 years of age was revealed. Scandinavian founder effects regarding four mutations (p.R518X, p.Q530X, c.572_575del, and p.Y111C) could explain as much as 83% of JLNS in Sweden and a high prevalence of heterozygous mutation-carriers was suggested.

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References

A 60-year-old man was presented with a Staphylococcus epidermidis bacteraemia of unknown origin, suspicious of cardiac device-related infection. Patient was pacemaker dependent for 30 years with multiple endovascular leads: four via the right and three via the left subclavian vein [attached to a biventricular internal cardioverter defibrillator (ICD)]. Intravenous antibiotic treatment was initiated and the ICD and five leads could be removed by using locking stylets and dilator sheaths (Cook Medical). Extraction of the remaining leads via the femoral vein was unsuccessful. Cultures of the ICD pocket and leads were negative, whereas a new blood culture was positive again for S. epidermidis. After an overnight fast, a fused 18F-labelled deoxyglucose (FDG) positron emission tomography/computed tomography scan showed pathological FDG-uptake at the venous part of one of the remaining pacemaker leads, suggestive of infection of the lead and/or local thrombus (blue arrows in the figure) and making other sites of infection unlikely. Therefore, a sternotomy was performed with opening of the superior caval vein and the right atrium and inspection of the right ventricle (RV) to remove the pacemaker leads and large amounts of fibrous tissue. A small part of the RV lead was left in place because of tight adherence to a papillary muscle. Cultures of the removed leads and fibrotic tissue were positive for S. epidermidis.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/PET-CT.pdf.