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 for sudden cardiac death.

Methods: A national inventory of clinical JLNS cases was performed. Genotype and area of origin were ascertained in index families. Retrospective clinical data was collected from medical records and a personal interview.

Results

The inventory identified 19 JLNS cases in 13 Swedish families. A JLNS prevalence of >1:200 000 in Sweden was revealed. (five living cases below 10 years of age, population < 10 years ~1 million)

Mutation spectrum:

8 *KCNQ1* mutations, whereof p.R518X in 12/24 alleles (**Table 1**).

Table 1. Inventory of *KCNQ1* mutations identified in 12 Swedish JLNS probands

Nucleotide change	Amino acid change	Region	Mutation type	Alleles, n*
c.1522C>T	p.R518X	C-terminal	Nonsense	12 (3)
c.572_576del	p.R192Cfs91X	S2-S3	Frame-shift	4 (2)
c.332A>G	p.Y111C†	N-terminal	Missense	2 (1)
c.1588C>T	p.Q530X	C-terminal	Nonsense	2
c.477+1G>A	p.M159	S2	Splice error	1
c.568C>T	p.R190W†	S2-S3	Missense	1
c.828_830del	p.S277del†	S5	Frame-shift	1
c.1046C>G	p.S349W†	S6	Missense	1

* Number of homozygous probands is given in parenthesis
†Mutation not previously reported in association with JLNS, to our knowledge

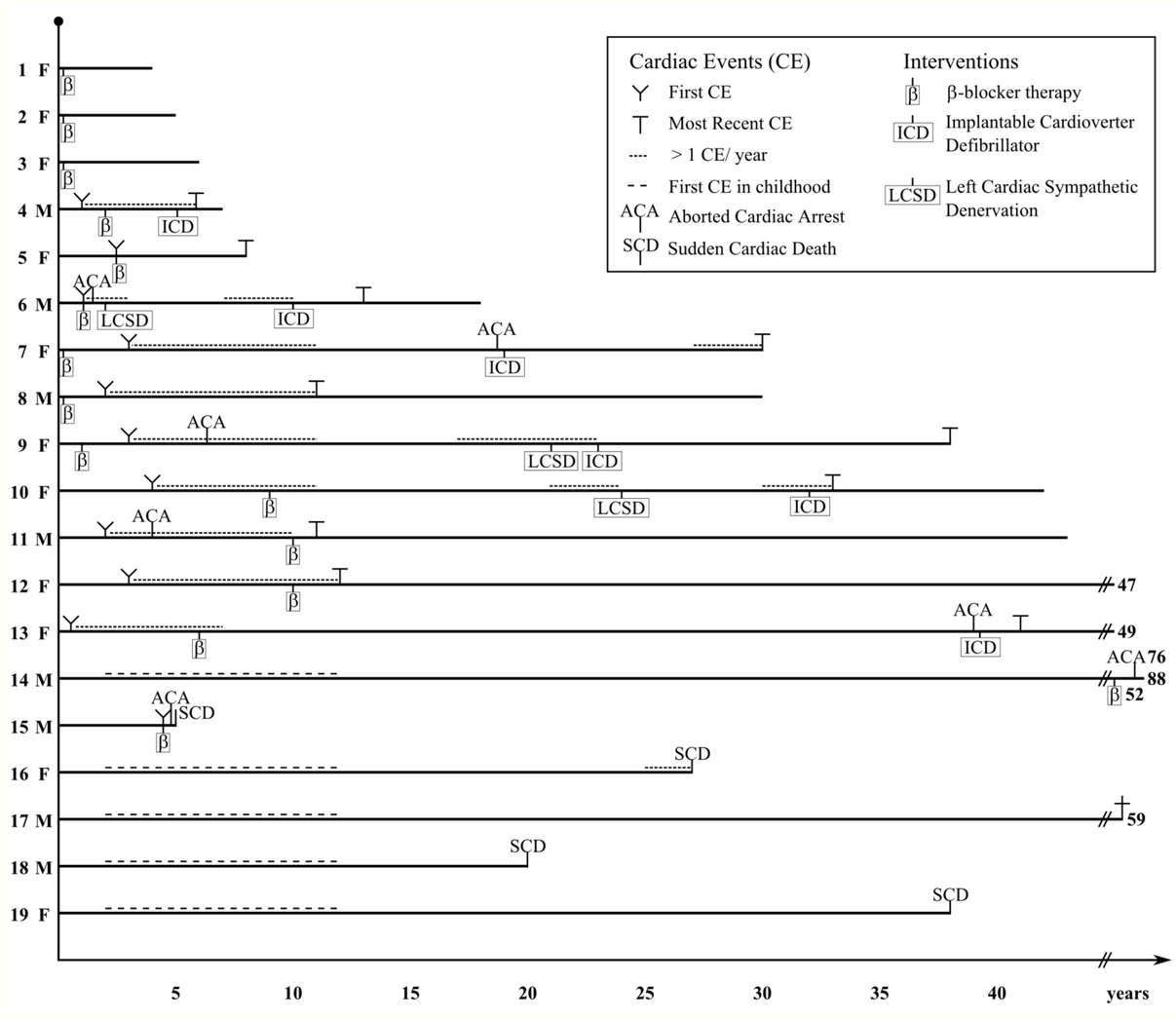

Figure 2. Timing of cardiac events and interventions over time for 19 JLNS cases. F= female, M= male
Cases are numbered on the vertical axis according to age at study (youngest-oldest, case 1-14)
Deceased cases are numbered according to birth year (youngest-oldest, case 15-19)
The x-axis is disrupted after 45 years, and the age at study/death of cases given in the right hand margin

Geographic clustering of four *KCNQ1* mutations, (20/24 alleles) was evident (**Figure 1**) as well as similarities to the mutation spectrum in Norway, suggestive of Scandinavian founder effects (**Table 2**).

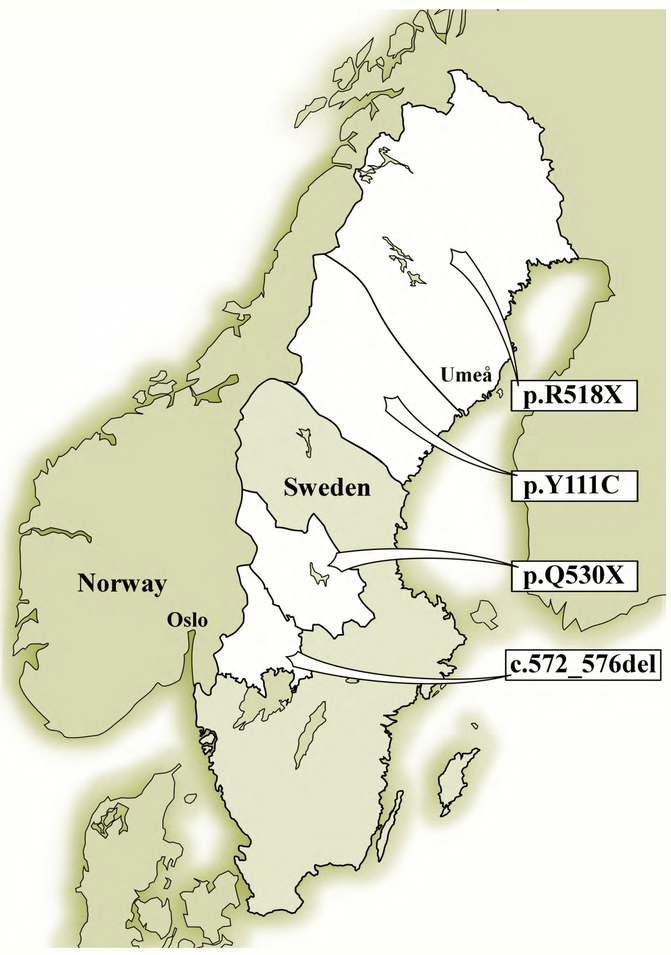

Figure 1. Map of Sweden. All but one of the p.R518X alleles (n=11) originated from the upper northern region, all p.Y111C alleles (n=2) from the mid-northern region and all c.572_576del alleles (n=4) originated from a mid-western region. Two p.Q530X alleles originated from the upper northern region and a mid-western region on the Norwegian border, respectively.

Table 2. Comparison between the JLNS mutation spectra, including associated prevalence estimates regarding heterozygotes, in Sweden and Norway

Mutation (*KCNQ1*)	12 Swedish probands (alleles=24)	12 Norwegian probands* (alleles=24)
p.R518X, n (%)	12 (50)	5 (21)
c.572_576del, n (%)	4 (17)	12 (50)
p.Q530X, n (%)	2 (8)	6 (25)
Sum, n (%)	18 (75)	23 (96)
Estimation of heterozygotes**	1:300-600 (95% CI)	1:317*

*Berge et al. Scandinavian Journal of Clinical and Laboratory Investigation. 2008;68(5):362-8.)
**Calculated using the Hardy-Weinberg equilibrium of allele frequencies

The cardiac phenotype was generally severe (**Figure 2**):

- QTc 587±69 ms
- 16/19 (84%) had experienced a first cardiac event
- age at onset was 2.4±1.2 years
- seven cases (37%) had suffered an aborted cardiac arrest
- four cases (21%) had died suddenly

Three pediatric cases on β-blockers since birth were as yet asymptomatic. 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.

Conclusions

Scandinavian 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 case of therapy failure is stressed.

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