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Origin, genotype and clinical phenotype of the Long QT Syndrome R518X/KCNQ1 mutation in Sweden

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Introduction: In the Long QT Syndrome (LQTS), associated with syncope and sudden death at a young age, mutation-specific risk stratification could be of clinical importance. Here we investigate the clinical phenotype and origin of the worldwide common R518X/KCNQ1 mutation, in Sweden, causative of both recessive and dominant type LQTS.

Methods: Clinical data, including manually measured ECGs, were collected from medical records, a personal interview and a questionnaire. Genealogical investigations were performed, using parish records and genealogical databases. A haplotype analysis, including 14 microsatellite markers flanking the KCNQ1 gene, was performed in index families and healthy controls. Mutation age was estimated using ESTIAGE and DMLE computer software.

Results: We identified 97 mutation-carriers (59 females) in 19 Swedish R518X index families, whereof 11 cases (6 females) with double mutations (4 homozygotes) and concomitant hearing-loss, i.e. Jervell-Lange-Nielsen (JLNS) cases.

JLNS cases presented with a severe phenotype (QTc 576±61 ms; age at debut 2±1 years; syncope 73%; (aborted) cardiac arrest 55%).

In heterozygous carriers, during a mean follow-up before beta-blockers of 30±20 years, phenotypic variability was evident (QTc 464±31 ms, range 383-537 ms; age at debut 15±11 years, syncope 17%; (aborted) cardiac arrest 2%), with poor correlation between QTc prolongation and symptomatic phenotype (p=0.651). Four symptomatic cases presented with a normal QT interval. One previously asymptomatic case (QTc >500 ms) died suddenly during physical exertion in combination with a diet-induced hypokalaemia.

A common geographic origin in the upper northern region with focus in Pite River Valley was found for 17/19 families. A common haplotype (4-14 markers, median 8) was identified in 16/17 tested families. The age of the founder haplotype was estimated to 650 years (95% CI 425;1000) and 600 years (95% CI 400;950) by ESTIAGE and DMLE, respectively.

Conclusions: R518X is associated with a severe phenotype in JLNS cases and a highly variable, albeit mild, clinical phenotype in heterozygotes. Importantly, in R518X heterozygotes, QTc prolongation did not identify at-risk individuals.

The majority of Swedish R518X/KCNQ1 cases share an upper northern origin around the 14th century. Founder effects have resulted in a high frequency of R518X in Sweden, and a notably high JLNS prevalence.