O10-6

Single nucleotide polymorphisms in KCNQ1-3'UTR associated with allele-specific repression of transcription segregate with the phenotypically benign Swedish Long QT Syndrome type 1 founder mutations

Winbo A., Rydberg A.
Pediatrics, Clinical Sciences, Umeå, Sweden

Introduction: Strong allele-specific effects, worsening and/or possibly ameliorating Long QT Syndrome type 1 (LQT1) phenotypes depending on location, have been proposed for single nucleotide polymorphisms (SNPs) in KCNQ1-3'UTR. Here we assess three previously reported KCNQ1-3'UTR SNPs for allele-specific location and association with QTc in two large Swedish LQTS founder populations with a previously documented low incidence of sudden cardiac death.
Methods: This study included 312 individuals from two LQT1 founder populations, whereof 85 genotype negative family members and 227 genotype positive individuals segregating either the dominant-negative variant Y111C (n=148) or the haploinsufficiency-causing variant R518* (n=79) in the KCNQ1 gene. All were genotyped for KCNQ1-3'UTR SNPs rs2519184, rs8234 and rs10798. Allelic phase (cis/trans) was determined by trio analysis. Association between mean QTc, obtained by repeated manual measurement on coded 50 mm/s standard 12-lead ECGs, and allele-specific location of KCNQ1-3'UTR SNPs was tested within each founder population among carriers of identical mutations, testing between populations was not performed.
Results: Among all genotype positives, 92% had at least two KCNQ1-3'UTR SNPs in cis (rs8234 and rs10798 were in complete linkage disequilibrium) and 97% of R518* carriers had all three reported repressive SNPs in cis. Mean QTc was 482±30 ms and 462±34 ms among carriers of Y111C and R518*, respectively. No significant associations between QTc and allele-specific SNP location were found within the founder populations. Among the 16/148 Y111C carriers that lacked SNPs in cis, mean QTc was 490±36 ms as compared to 481±29 ms in carriers with SNPs in cis, and mean QTc was 4-10 ms longer in R518* carriers that in addition to 3 SNPs in cis also had 1-3 SNPs in trans (none of these findings were statistically significant).
Conclusions: Three KCNQ1-3'UTR SNPs, previously reported to repress transcription of the allele where they reside, were found to segregate with the Swedish LQT1 founder mutations (2/3 in cis with Y111C and 3/3 with R518X). This finding could relate to the surprisingly mild phenotypes previously described for both these populations, albeit no significant association between QTc and allele-specific location of SNPs could be seen in these relatively homogenous samples.