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NOS1AP variants affecting QTc in the long QT syndrome- mainly a male affair?

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Introduction: Single nucleotide polymorphisms (SNPs) in the NOS1AP gene have repeatedly been reported to influence QTc, albeit with moderate effect sizes. In the long QT syndrome (LQTS) this may contribute to the substantial variance seen in QTc among carriers of identical pathogenic sequence variants. Here we assess three previously reported NOS1AP SNPs for association with QTc in two large Swedish LQT1 founder populations.
Methods: This study included 312 individuals (180 females) from two LQT1 founder populations, whereof 227 genotype positive (133 females) segregating either Y111C (n=148, 84 females) or R518* (n=79, 49 females) pathogenic sequence variants in the KCNQ1 gene, and 85 genotype negative (47 females). All were genotyped for NOS1AP SNPs rs12143842, rs16847548 and rs4657139, and tested for association with QTc length (effect size presented as mean difference between derived and wildtype, in ms). Mean QTc was obtained by repeated manual measurement (preferably in lead II) by one observer using coded 50 mm/s standard 12-lead ECGs.
Results: A substantial variance in mean QTc was seen; all genotype positive 475±33 ms (Y111C 482±30 ms; R518* 462±34 ms) and genotype negative 433±24 ms. Female sex was significantly associated with QTc prolongation in all groups ($p<0.01$) with effect sizes ranging from 14 ms (genotype negatives) to 16 ms (Y111C), 20 ms (genotype positives) and 30 ms (R518*). Two derived NOS1AP SNPs (rs12143842 and rs16847548) were significantly associated with QTc prolongation in genotype positives (10 ms, $p=0.02$), in genotype negatives similar results were seen (9 ms, $p=0.07$). Notably, among genotype positives, when stratified by sex neither of these two SNPs were significantly associated with QTc in females (all 6 ms, $p=0.2$; Y111C 9 ms, $p=0.1$; R518* 1 ms, $p=0.9$) while in males, a prolongation of 16 ms, $p=0.03$ was seen (Y111C 15 ms, $p=0.07$; R518* 27 ms, $p=0.007$). In genotype negatives, while non-significant, the same SNPs were associated with a 5 ms (females) and 10 ms (males) QTc prolongation.
Conclusions: Our findings suggest specific genotype and most importantly sex affects the effect size of NOS1AP SNPs on QTc. This may be of clinical significance when applying NOS1AP genotype to clinical risk stratification.