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Titel des Beitrags: Analysis for Genetic Modifiers of Disease Severity in Patients With Long-QT Syndrome Type 2.

Abstract: Considerable interest exists in the identification of genetic modifiers of disease severity in the long-QT syndrome (LQTS) as their identification may contribute to refinement of risk stratification. We searched for single-nucleotide polymorphisms (SNPs) that modulate the corrected QT (QTc)-interval and the occurrence of cardiac events in 639 patients harboring different mutations in KCNH2. We analyzed 1201 SNPs in and around 18 candidate genes, and in another approach investigated 22 independent SNPs previously identified as modulators of QTc-interval in genome-wide association studies in the general population. In an analysis for quantitative effects on the QTc-interval, 3 independent SNPs at NOS1AP (rs10494366, P=9.5×10^{-8}; rs12143842, P=4.8×10^{-7}; and rs2880058, P=8.6×10^{-7}) were strongly associated with the QTc-interval with marked effects (>12 ms/allele). Analysis of patients versus general population controls uncovered enrichment of QTc-prolonging alleles in patients for 2 SNPs, located respectively at NOS1AP (rs12029454;
odds ratio, 1.85; 95% confidence interval, 1.32-2.59; P=3×10(-4)) and KCNQ1 (rs12576239; odds ratio, 1.84; 95% confidence interval, 1.31-2.60; P=5×10(-4)). An analysis of the cumulative effect of the 6 NOS1AP SNPs by means of a multilocus genetic risk score (GRS(NOS1AP)) uncovered a strong linear relationship between GRS(NOS1AP) and the QTc-interval (P=4.2×10(-7)). Furthermore, patients with a GRS(NOS1AP) in the lowest quartile had a lower relative risk of cardiac events compared with patients in the other quartiles combined (P=0.039). We uncovered unexpectedly large effects of NOS1AP SNPs on the QTc-interval and a trend for effects on risk of cardiac events. For the first time, we linked common genetic variation at KCNQ1 with risk of long-QT syndrome.