

Genetic background of long QT syndrome in infants, children, and adolescents

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Introduction: Little data are available for the prevalence of genotypes of long QT syndrome (LQTS) in pediatric patients. A school-based ECG screening program to screen cardiovascular diseases uncovered many children and adolescents with LQTS in Japan. The aim was to determine the genetic characteristics of childhood LQTS in Japan.

Methods: The study population included 102 unrelated probands (0–17 years, median: 9.8 years; M:F = 57:45) who were referred to our centers from 1993–2011. Total family members were 197. Genomic DNA was isolated from blood and direct sequencing for LQT1–LQT12 (LQT4 & LQT11 excluded) was performed. When multiple mutations were present, each was counted in each genotype. Of 102 probands, 57 were screened by the program, 35 visited hospitals because of symptoms (Symptomatic) and 13 subjects were diagnosed by family study or by chance.

Results: Genotypes were identified in 63 of 102 probands and in 100 of 197 family members. *KCNQ1* was found in 31 probands (48 family members), *KCNH2* in 19 (26), *SCN5A* in 11 (22), and others in 7 (14). The prevalence of *SCN5A* in probands (11/57) and in family members (22/91) among three main mutations was significantly higher ($p = 0.006$ and $p = 0.0004$, respectively) than for the adult population (11/192 in probands and 82/812 in family members in the literature). Of 102 probands, the screened subjects showed a higher rate of genotypic determination (40/55) than symptomatic subjects (15/34, $p = 0.01$). Conversely, the symptomatic group showed a higher rate of multiple mutations than the Screened group (4/15 vs 2/40, $p=0.04$).

Conclusions: Clinical and genetic analysis in fetus, neonate, and infants revealed that LQT3 patients diagnosed during these periods presented critically ill and needed intensive care. A high prevalence of the *SCN5A* genotype in the pediatric population suggests progress in the medical management of these patients during infancy and childhood. School-based ECG screening and genetic testing may help prevent LQTS-related symptoms and improve order-based medicine in Japan. Numerous undetected mutations exist in symptomatic patients.