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SCN5A mutants associated with familial cardiac sodium overlap syndrome characterized as sick sinus syndrome, atrial fibrillation, Brugada syndrome, and progressive conduction disease

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Objective: We identified familial arrhythmia in a Chinese family and investigated the genetic mechanisms.

Method: Genetic analysis was conducted in the coding and splicing regions of genes susceptible for cardiac arrhythmia diseases. A functional study of novel mutants was performed in human embryonic kidney 293 cells (HEK293).

Results: We identified a rare double mutant of SCN5A, R965C and R1309H. R965 and R1309 residues are highly conserved across all species. Furthermore, R965C is associated with Brugada syndrome. Compared to wild-type (WT) cells, Na⁺ current density was markedly reduced by 76% in cells carrying the R1309H mutant at membrane potentials ranging from -50 mV to -10 mV. The slope of R1309H-carrying cells was significantly less steep than that of WT cells ($P < 0.001$). Steady-state inactivation of R1309H cells was significantly left-shifted from that of WT cells at test potentials of -100 mV to -80 mV. The voltage of half-maximal inactivation for R1309H cells was significantly left-shifted by ~11.22 mV from that of WT cells ($P < 0.01$).

Conclusions: While the SCN5A R965C mutant appears solely related to Brugada syndrome, the R1309H mutant causes significant loss of function of the Nav1.5 sodium channel, which is potentially a key mechanism underlying familial CSCOS.

Biography

Yubi Lin has completed his PhD from Jinan University and Postdoctoral studies from Guangdong Cardiovascular Institute, Medical School of South China University of Technology. He is the Chief Expert of Guangdong Province Family Doctor Association Telemedicine and the expert committee member of CMIA Remote Heart Monitoring Professional Committee of China. He has published more than 27 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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