Multifocal atrial and ventricular premature contractions with an increased risk of dilated cardiomyopathy caused by a Na_v1.5 gain-of-function mutation (G213D)

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Clinical presentation & Genetics

17 family members was found with a uniform distinct phenotype with frequent premature atrial (PACs) and ventricular contractions (PVCs). 5 patients was found with reduced LVEF function. Cascade screening identified 14 relatives heterozygote for Na_v1.5_G213D. Flecainide reduced PVC and PAC burden and reversed the reduced LVEF.

■ Arrhythmias ■ DCM

190 RDPWNWLDIFS 200 VIIMAYTTEF 210 VDLGNVSALR 220 TFRVLRAKLT 230 ISVISGLKTI VGAL
DI S3 DI S4

The G213D mutation alters a glycine residue located in the extracellular loop between S3 and S4 in domain I of the sodium channel.

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Electrophysiology

A-B) Peak sodium current ($p=0.2477$), C) Activation curves, the voltage of half-maximal ($V_{1/2}$) activation ($p<0.001$), D-E) fast and the slow phase of inactivation are slightly prolonged by G213D, which may contribute to a gain-of-function phenotype, F-G) The voltage of half maximal inactivation ($V_{1/2}$) ($p<0.0001$). larger fraction of Na_v1.5 would be released from inactivation.

A) demonstrating the size of the window currents, B-C) There was no significant difference between the relative persistent currents for WT and G213D at any time point.

Conclusion

The Na_v1.5_G213D mutation is associated with a gain-of-function phenotype, multifocal atrial and ventricular ectopy and dilated cardiomyopathy. Since patients with a MEPPC-like phenotype may specifically benefit from Class-1 antiarrhythmic drugs or amiodarone, clinical identification of this disease entity is important.