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ETHNICITY AND PHENOTYPE IN THE SCN5A E1784K MUTATION

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Background: Long QT (LQTS) and Brugada syndromes (BrS) are inherited arrhythmia syndromes characterised by risk of sudden cardiac death (SCD) and highly variable penetrance. Mutations in SCN5A, which encodes the Nav1.5 cardiac ion channel responsible for the inward cardiac sodium current, are responsible for 5-10% of LQTS and associated with 20% of BrS. The E1784K mutation in SCN5A is the most commonly identified SCN5A mutation in both LQTS and BrS, and causes the Long QT type 3 (LQT3)/BrS overlap disease with variable phenotypic expression. Carriers within the same pedigree may exhibit LQT3 phenotype, BrS phenotype or both.

The aim of this international project was to determine if there are any associations between phenotype and ethnicity within a unique cohort of E1784K mutation carriers.

Methods: 93 E1784K mutation carriers belonging to 33 families from 6 different countries including Japan were included. Data was collected on age, gender, symptoms, family history and the ECG. Non-digital and digital ECG data were analysed using proprietary software. Automatic readings and measurements from 2 observers were taken. A 3rd observer reviewed the ECGs where there was inter-observer discrepancy between the measurements. Statistical significance was determined using either the 2-tailed t-test or Chi-squared test as appropriate.

Results: QTc intervals were significantly longer amongst Japanese E1784K mutation carriers, who were more symptomatic albeit with a lower incidence of SCD. Results are summarised in Table 1. The spontaneous type 1 BrS ECG pattern also appeared to be more prevalent in the Japanese compared to Caucasian mutation carriers although the numbers were small. Mean QRS duration was longer amongst Caucasian mutation carriers. Drug-induced BrS phenotype was unmasked in 63% of Caucasians (34/54) who underwent a test. A family history of SCD was present in 50% of Caucasian families compared to only 13.6% of Japanese families ($p = 0.015$).

Conclusions: There is variation in expression of E1784K between ethnicities with ethnic differences in severity and risk of sudden death. These results support a strong role for genetic modifiers of phenotype and risk which deserves further study.

Table 1 Clinical characteristics

	Total (n = 93)	Caucasian (n = 64)	Japanese (n = 29)	p-value
Age (years, mean, range)	28, 1-67	30, 1-67	23, 6-62	0.0826
Sex-male (n,%)	47, 51	32, 50	15, 52	0.8776
Spontaneous BrS (n,%)	4, 4	1, 2	3, 10	0.0531
QTc (ms, mean, range)	480, 404-579	472, 404-533	499, 430-579	0.0001
PR (ms, mean, range)	167, 116-302	167, 116-302	166, 149-180	0.8952
QRS (ms, mean, range)	96, 60-139	99, 68-139	90, 60-120	0.0145
Pre-syncope/syncope (n,%)	17, 18	8, 13	9, 31	0.0741
Aborted SCD (n,%)	6, 6	6, 9	0, 0	0.0882