Genetic Architecture of Brugada Syndrome

Context:
Brugada syndrome is traditionally thought to be a primary electrical cardiac disease that is characterised by a specific electrocardiographic pattern and is associated with an increased risk of cardiac arrhythmias and sudden death. It associated with mutations in the SCN5A gene, which encodes the α-subunit of the voltage-gated Nav1. 5.

Summary:
Recent studies have shown that in Brugada syndrome has a complex genetic architecture. Individuals with SCN5A have longer QRS and PR intervals. An association between the degree of loss of function of SCN5A and clinical severity, including a longer resting PR interval and having more syncopal episodes, has been demonstrated.
Genome-wide association studies have found that common variants at SCN10A, SCN5A and HEY2 are associated with Brugada syndrome, and a polygenic risk score using this information have been shown to positively correlate with the probability of having drug-induced type 1 pattern and demonstrate ethnic transferability.
While Brugada syndrome behaves often like a monogenic disease, most rare variations are not strictly causative. Common and low frequency variations are important but may be ethnic specific. These should be taken into account during genetic counselling.

Message:
SCN5A variants suggest a higher risk of conduction disease and may be useful prognostically. Variant severity shows association with outcome/phenotype. Genome-wide association studies have identified common variations most strongly associated with the Brugada phenotype in patients who are SCN5A negative, have a spontaneous type 1 Brugada pattern, and have higher likelihood of positive ajmaline response. More research is required for the role of polygenic risk scores for diagnosis and outcome.

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