Brugada syndrome variant caused by TRPM4 mutation

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In this manuscript presented by Janin et al, the authors present a case of a 64-year-old hypertensive man, chronic kidney, and coronary artery disease in which a rare mutation was observed in the autosomal recessive TRPM4 gene associated only with the Brugada 1 pattern (they denominated Brugada like) The authors used the molecular strategy based on the panel sequencing of 19 genes associated with Brugada syndrome. The proband was a carrier of 2 TRPM4 null alleles [IVS9 + 1G> A and p. Trp525X] resulting in the absence of hTRPM4 functionality

Janin A1, Bessière F2, Georgescu T3, Chanavat V1, Chevalier P

2, Millat G4.TRPM4 mutations to cause autosomal recessive and not autosomal dominant Brugada type 1 syndrome.Eur J Med Genet. 2018 Aug 21. pii: S1769-7212(18)30217-9. doi: 10.1016/j.ejmg.2018.08.008. [Epub ahead of print]

To follow I show you what is known about the Brugada and this rare TRPM4 mutacion

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Gene: TRPM4 (transient receptor potential melastatin channel subfamily M member 4).TRPM4 is a calcium-activated, phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P_2) -modulated, non-selective cation channel that belongs to the family of melastatin-related transient receptor potential (TRPM) channels;

Cytogenetic location:19q13.33;HGNCID:17993 (Liu et al., 2013);

Other phenotypes associated: progressive familial heart block type 1B or progressive cardiac conduction disease (PCCD) is one of the most common cardiac conduction disturbances. It has been causally related to rare mutations in several genes including SCN5A, SCN1B, TRPM4, LMNA and GJA5 (Daumy et al., 2016; Duan et al., 2018; Kruse et al., 2009). TRPM4 could account for a small percentage of LQTS patients.

TRPM4 contribution to the QT interval might be multifactorial by modulating whole cell current but also, as shown inTRPM4-/-mice, by modulating cardiomyocyte proliferation. TRPM4 enlarges the subgroup of LQT genes (KCNJ2 in Andersen Tawil syndrome type 1 and CACNA1C in Timothy syndrome) known to increase the QT interval through a more complex pleiotropic effect than merely AP alteration (Hof et al., 2017).

Liu et al. Screened TRPM4 for anomalies in BrS cases. The DNA of 248 BrS cases with no SCN5A mutations were screened for TRPM4 mutations. Among this cohort, 20 patients had 11 TRPM4 mutations. Two mutations were previously associated with cardiac conduction blocks and 9 were new mutations (5 absent from ~14'000 control alleles and 4 statistically more prevalent in this BrS cohort than in control alleles). In addition to Brugada, three patients had a bifascicular block and 2 had a RBBB. Functional and biochemical studies of 4 selected mutants revealed that these mutations resulted in either a decreased expression (p.Pro779Arg and p.Lys914X) or an increased expression

(p.Thr873Ile and p.Leu1075Pro) of TRPM4 channel. TRPM4 mutations account for about 6% of BrS. Reduction or increase of TRPM4 channel function may both reduce the availability of Na^+ channel and thus lead to BrS (Liu et al., 2013).

Exploring 66 cardiac genes using a new custom next-generation sequencing panel, Gualandi et al. identified a double heterozygosity for pathogenic mutations in SCN5A and TRPM4 in a BrS patient. The parents were heterozygous for each variation. This novel finding highlights the role of mutation load in BrS and strongly suggests the adoption of a gene panel to obtain an accurate genetic diagnosis, which is mandatory for risk stratification, prevention, and therapy (Gualandi et al., 2017).