LQTS 3 variant and Brugada syndrome. Are they similar or the same?

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The Cardiac Sodium Channel

The gene encoding the α subunit of the cardiac sodium channel (*SCN5A*) was cloned by Gellens *et* . in 1992 (1) and mapped to chromosome 3p21 by George *et al.* in 1995 (2). This channel is a transmembrane protein composed of four homologous domains (DI-DIV) each containing six transmembrane segments (S1-S6). The alpha subunit alone is per se able to conduct a current closely resembling the I_{Na} current recorded in cardiac myocytes, the major determinant of the phase 0 (upstroke) of the cardiac action potential. However, two closely associated proteins have been also isolated, the so-called beta1 and beta2 subunits. The function of such auxiliary subunits remain to be fully elucidated although some studies have suggested they may play a role in modulating the ionic flux through the channel (3,4).

Upon depolarization and repolarization of myocardial cells, *SCN5A* is finely regulated (activation and inactivation) mainly by the changes of the transmembrane voltage, thus constituting a so-called voltage gated channel. During depolarization, the channel promptly opens in 1-2 ms and readily inactivates after approximately 10 ms (fast inactivation). Another inactivation process, “slow inactivation” occurs with a much slower time course in the range of seconds. The voltage sensor responsible for the opening of the channel resides in the S4 of each domain, a lysine rich domain. The region of the channel involved in the fast inactivation is the cytoplasmic loop connecting the domain III and the domain IV, while the C terminus tail of the channel is responsible for the slow inactivation (5).

Beside role in cardiac depolarization, the cardiac sodium channel is also a key player in the control the impulse conduction through the cardiac tissue. Thus, it has a crucial physiological role in the control of the cardiac electrical activity.

Long QT syndrome type 3

Genetic bases and Clinical features

When linkage to chromosome 3 was established to the region 3p21-p23 (6), *SCN5A* was immediately considered as a most likely candidate for Long QT Syndrome (LQTS). The first mutations, identified by Wang *et al.* (7), were clustered in regions functionally relevant to the channel inactivation (delKPQ, R1623Q, N1325S). Other mutations have been reported thereafter (7),(3,8-11) spanning almost the entire structure of the protein with the exception of the N-terminous and the first transmembrane domain where no LQTS-related defect have been so far reported (see also: http://pc4.fsm.it:81/cardmoc). The relative prevalence of LQT3 among LQTS patient is estimated to be 10-15% (11).

Pathophysiology

Initially the most striking functional consequence of the first mutation identified in LQT3 patients was that of a gain of function of the channel with an increased late inward sodium current (I_{Na+}) (12). Subsequently more subtle changes as for example a slower inactivation rate were identified (13-16). Overall, it may be observed that Na^+ channel mutations originate the LQTS phenotype by inducing a gain of function of the protein with enhanced inward current that prolongs action potential duration.

Brugada Syndrome

Genetic bases and Clinical features

Brugada Syndrome (BrS) is a disease characterized by distinguishing ECG features consisting in complete or incomplete right bundle branch block and ST segment elevation in the right precordial leads (V1.V3) and by syncope and cardiac arrest typically occurring in the third and fourth decade of life, and usually at rest or during

sleep. In the earlier reports a remarkably high rate of events was shown (17). However, more recent reports have pointed to the fact that there are subgroups of BrS patients that may be at low risk of cardiac events (18-21).

The prevalence of BrS is not known. Overall, consistently with the vast majority of genetic diseases, it appears to be a relatively uncommon condition, and a prevalence of 1-10/10.000 appears a realistic estimate. *SCN5A* mutations have been reported for the first time in BrS patients by Chen *et al.* (22), and several additional genetic defects have been reported thereafter (http://pc4.fsm.it:81/cardmoc). However, only 20-25% of clinically affected individuals harbor a mutation in this gene and, despite a novel BrS locus was mapped on chromosome 3 (23) no additional genes have been identified.

Pathophysiology

Initially the expression of BrS mutations, showed quite consistently a loss of sodium current (reduced current density), at variance with the excess of current associated with LQT3 defects. However, more recent data show that they may also be associated with a more heterogeneous cellular phenotype. Some mutations cause a reduction of window current with hyperpolarizing shift of both activation and inactivation curves, resulting in a reduced inward current during later phases of action potential (24,25,25,26). Other mutations result in a faster inactivation (26). Furthermore, not only transmembrane current abnormalities but also intracellular trafficking defects of the mutant channels were reported in BrS patients (27). In summary it is true that the BrS associated mutations cause a impairment of the cardiac sodium current but multiple mechanisms have been identified other than the simple reduction in current density

Lev-Lenegre Syndrome

Genetic bases and Clinical features

The third SCN5A associated clinical phenotype is the progressive cardiac conduction defect (PCCD), also called Lev-Lenegre disease (28,29). Using the candidate gene approach Schott *et al.* (30) reported the first

mutation in the *SCN5A* gene in a French family who had been diagnosed with Lenegre-Lev disease. Currently, at least 8 mutations are known to be associated with a "pure" form of conduction block in the absence of signs of the typical electrocardiographic manifestations of LQT3 or BrS. Two of them, G514C and S1710L (31), exhibit a faster decay of the current, The former, though, shows a shift in the depolarizing direction of the gating parameters, while in the latter, the availability curve and the voltage dependence of the activation are shifted in the opposite direction. Moreover, there is an enhancement in the development of the slow inactivation and a pronounced close-state inactivation. Interestingly, while these changes are consistent also with a Brugada mutation phenotype, cellular phenotype of the G514C (a faster recovery from the inactivated state and a reduced close-state inactivation) resembles a LQT3 phenotype. Thus, taken together these data point to the fact that the pathways leading from the genetic defect a progressive slowing of impulse conduction are far from being fully understood.

Overlapping Phenotypes

Clinical findings and Pathophysiology

Among the clinical features of BrS, the occurrence of cardiac events during rest or sleep(21) and the inhibiting effect of beta adrenergic stimulation on the electrocardiographic abnormalities (32), were reported as being very distinctive of this disorder. However, also LQT3 is typically associated with cardiac events at rest (33) and with QT interval shortening or normalization during tachycardia (34). The common clinical features shared by LQT3 and BrS suggested the possibility that phenotypic overlapping could exist between the two diseases. Among this line, we demonstrated that the two phenotypes may coexist with mutations affecting the same codon (13), while Bezzina *et al.* (10) provided the evidence of this concept by identifying a single SCN5A mutation (1760insD) associated with LQTS and BrS phenotypes in the same family. Clancy & Rudy, by means of computer simulation showed that 1795insD induces a loss of action potential dome in epicardial cells consistent with the current pathophysiological interpretation of BrS (35), but also a prolongation of the action potential at slow heart rates, which is consistent with LQTS. Although computer simulation models may not perfectly resemble reality,

this paper provides clues on how a single genetic defect may manifest with phenotypes that, at clinical level, were classified as two distinct entities.

Finally in a recent paper we showed that a single *SCN5A* mutation, a Lysine deletion a position 1500 may cause, in the same family three different phenotypes: LQT3, BrS, and PCCD (36). In this family some individuals also presented sinus blocks with pauses exceeding several seconds. The relationship between sinus block and sodium channel mutations remains undefined at present time.

CONCLUSION

The realization of the blurred border between the three *SCN5A*-related phenotypes is not only scientifically appealing but it has tangible implication as it brings in the decision of how to treat these “transitional” patients. Indeed, it challenges the concept of a differential therapeutic approach for LQTS, usually treated with beta blockers, BrS in whom the only proven effective treatment is ICD implant in higher risk subjects (37), and PCCD where a pacemaker is advised for symptomatic individuals.

Functional consequences of *SCN5A* mutations found in families with overlapping phenotypes have been characterized in expression studies showing several functional abnormalities, including a faster current decay, opposing shifts of the activation and the availability curves, an accentuated slow inactivation and a pronounced close state inactivation ((16). A deletion in position 1500 (36) also lead to the development of the sustained current due to the enhancement of the bursting mode of the channel. A mutation found in a French family produce a channel that do not exhibit current when expressed in a mammalian system, even though the protein is correctly processed to the cell membrane (38).

The evidence of patients harboring a *SCN5A* mutation and overlapping clinical presentation bears the compelling need for a revision of the traditional classification of the above mentioned diseases. It is now probably more appropriate to consider the “sodium channel syndrome” as a unique clinical entity that may manifest itself with a spectrum of possible phenotypes.

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