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Genetic and Molecular Basis of Arrhythmias

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The enormous amount of information brought from the basic research laboratories to the clinicians thanks to the new knowledge achieved by applying the molecular biology techniques to the study of the cardiac inherited arrhythmogenic disorders, has radically changed the clinical management of patients in the last few years. Indeed, significant advancements have been accomplished in the understanding of the pathophysiologic bases of the most relevant inherited cardiac disease. From this standpoint the Long QT Syndrome (LQTS) is one of the first cardiac disorders for which the molecular analysis was successful in identifying the genetic defects responsible for the clinical manifestations of the disease and therefore many genotype-phenotype have been so far completed.

LQTS: molecular basis and clinical features

The LQTS is an inherited form of cardiac arrhythmias caused by genetically determined defects in transmembrane ion channel forming proteins [1]. LQTS typically presents with a QT prolongation and a high incidence of life threatening cardiac arrhythmias, often developing during physical or acute emotional stress, and potentially leading to sudden cardiac death [2, 3].

Six genes, when mutated, have the potential to induce the LQTS phenotype *KVLQT1*, *HERG*, *SCN5A*, *KCNE1*, *KCNE2* [1, 4], and different mutations have been reported throughout the coding region of these genes in several families, thus indicating a considerable genetic heterogeneity.

It is common experience for the physicians that the clinical manifestations of LQTS may be highly variable, going from patients presenting with markedly prolonged QT interval, repeated episodes of loss of consciousness and cardiac arrest requiring aggressive therapy, to patients who remain asymptomatic despite the QT interval prolongation. Among the same line, QT interval duration in LQTS patients may be extremely increased (e. g. > 600 ms) but only borderline increased in other cases.

LQTS: Has the "molecular" knowledge changed the way of managing the disease and of treating the patients?

Despite the fact that the LQTS related gene are known only from few years a number of clinical studies have already been performed in the attempt of correlating the clinical manifestation of the disease and the risk of cardiac event with the genetic defect found in patients. Population based studies have been able to exploit relevant information allowing to delineate the overall clinical picture of LQTS according to specific genotypes. The availability of detailed clinical information of a large population of LQTS patients collected over the last 20 years from the International Registry of the LQTS [5] constituted the bulk of an epidemiological study showing that the incidence of car-

diac events (syncope or cardiac arrest) is significantly higher in LQT1 patients while an higher lethality of such events is present within LQT3 patients carrying a mutation on the cardiac sodium channel gene [6]. Among the same line, the analysis of a large group of genotyped LQTS patients have led to observation that LQT1 patients tend to develop most of their cardiac events during physical activity while their appear to be at lower risk at rest or during sleep [7] and "typical" electrocardiographic patterns can be identified for each specific LQTS genetic subtype [8].

Overall these clinical experiences outlined some general features of the disease by genotype. However, when we try to extrapolate practical guidelines for the quantification of the individual risk in the daily clinical activity we unavoidably have to face the sometimes unpredictable clinical manifestations of the disease. This problem mainly concerns the possible variable expressivity of the LQTS mutations.

Indeed it has been shown that the clinical manifestation of the disease may be very different also in patients carrying the same molecular defect and within the same family [9, 10].

Incomplete penetrance of LQTS mutations

In 1985 Schwartz [2] proposed that some patients with Long QT Syndrome could present a normal QT interval duration. After the discovery of LQTS genes, the first identified mutations were associated with a high degree of correlation between the genetic defect and the clinical diagnosis with a penetrance (i. e. the percentage of gene carriers showing the clinical phenotype) close to 100 %. Subsequently, however, Vincent et al. demonstrated variable expressivity in a large KVLQT1-linked kindred [11] and we recently [12] reported the unsuspected presence of families with a very low penetrance. In this study we demonstrated that apparently "sporadic" cases can be actually hereditary, as a consequence of low penetrance, other non-penetrant family members who are genetically affected [12].

An extreme manifestation of incomplete penetrance is the demonstration of a recessive pattern of inheritance in Romano-Ward patients [13]. Indeed, overcoming the classical Mendelian concept that a recessive disease is caused by the inheritance of two diseased alleles from consanguineous heterozygous parents, the evidence of a non-deaf proband with a homozygous mutation may be viewed as the consequence of the very low penetrance of the specific mutation. Accordingly unless a "double" dose of the defect is present the defect remains silent. The fact that both parents of the homozygous individual had a normal QT interval and presented no clinical history of syncope or of ventricular arrhythmias points to the existence of abnormalities in cardiac ion channels that may be so subtle to create only a predisposition to ventricular arrhythmias.

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Proarrhythmias as a manifestation of "forme fruste" of LQTS

Having demonstrated incomplete penetrance of LQTS mutations it becomes possible to speculate that individuals who carry silent mutations may not present the phenotype of LQTS yet they may be particularly susceptible to ventricular arrhythmias under specific circumstances. We recently reported [14] a patient who survived a cardiac arrest and after resuscitation presented a markedly prolonged QT interval. At that moment the patient was treated with cispripide that was promptly withdrawn and in the following few days QT interval shortened to normal values. Genetic analysis revealed the presence of a point mutation in the KVLQT1 gene allowing to define the patient as a "forme fruste" of Long QT Syndrome. A HERG mutation has been reported by Schulze-Bhar in another patient with drug-induced TdP [15]. Recently an amino acid substitution in the KCNE2 encoded protein (the HERG channel beta subunit) has been reported to slightly impair IKr current and to be more frequently present in a group with drug-induced TdP [16], thus, confirming the pathogenic link between low penetrant ion channel genetic defects and the predisposition to abnormal cardiac iatrogenic reactions. These "mild mutations" indeed are not able to induce a clinical overt LQTS but create a substrate that may lead to onset of malignant arrhythmias when an appropriate trigger is concomitantly present (e. g. drugs or electrolytes disturbances).

Low penetrance mutations as modifier factors in LQTS

In a recent preliminary study, contrary to common practice, we completed the screening of all the known LQTS genes even when a mutation on one of them had already been identified. So far, screening of the entire coding region of LQTS genes has allowed to identify three cases of two independent mutations [17]. Therefore apparently normal individuals may actually have a sub-threshold reduction of repolarizing currents, likely to decrease cardiac electrical stability while not manifesting a prolongation of the QT interval.

SCN5A: a gene for two diseases

The cardiac sodium channel is the gene altered in LQT3 and in Brugada Syndrome. It was quite unexpected that an inward current defect would lead to prolongation of QT interval and therefore *SCN5A* was not one of the first candidates for the disease. It turned out that at variance with mutations on *HERG* and *KVLQT1* that reduce or abolish channel function, *SCN5A* mutations in LQTS produce a gain of function [18, 19]. Only few mutations [20, 21] have been identified in the LQT3 gene (*SCN5A*). When expressed in heterologous systems they result in a small, sustained inward current which is likely to disrupt the normal balance between inward and outward currents during the plateau phase, and hence prolong cardiac action potentials.

Recently it has been demonstrated that mutations are the genetic cause of another arrhythmogenic disease, namely Brugada Syndrome [22]. In other words the sodium channel related variant of Long QT Syndrome (LQT3) and Brugada Syndrome are allelic diseases. Mutations identified in Brugada syndrome include one single aminoacidic substitution in regions not involved in the sodium current inactivation. The functional consequences of the Brugada syndrome mutations is in general represented by a loss of function of the INa current. It is likely that in analogy with LQTS and other inherited cardiac diseases the sodium channel is only one of several genes implicated in Brugada syndrome. Ac-

cordingly, only approximately 15 % of Brugada syndrome patients have mutations in the *SCN5A* gene.

Conclusions

The genetically determined defects in ion channel proteins may present with a wide range of clinical phenotypes. In the clinically overt LQTS, the affected individuals may present with very severe form of the disease (extreme QT interval prolongation and repeated episodes of life threatening arrhythmias). However, borderline QT interval prolongation and no symptoms may also characterize the clinical presentation of this disease. Low penetrance and variable expressivity seem to be rather common features in several LQTS families. Going one step further, even in the normal QT range, we can still find individuals carrying ion channel gene mutations. Some genetic studies show that these individuals are likely to be at higher risk of developing drug induced Torsades de Pointes. Finally, the demonstration of a "second" genetic defect in LQTS probands points to the fact that ion channel defects are likely to be much more prevalent in the general population than previously thought and that the presence of a "second" mutation may be the first identified modifier in LQTS. Overall, the data emerging from the genetic epidemiology and from the functional characterization of the molecular defects of ion channel proteins unveil previously unsuspected results. In particular, it is becoming evident that beside their role in determining well clinically characterized phenotypes, these defects may also play a role as predisposing (risk) factors for cardiac arrhythmias. Only the availability of more extensive information of the functional consequences and of the prevalence of genetic ion channel defects, will allow to clarify the picture of their role in the pathogenesis of cardiac arrhythmias in patient groups other than the individuals presenting with the "classical" Mendelian inherited phenotypes.

References:

1. Priori SG, Barhanin J, Hauer RNW, Haverkamp W, Jongsma HJ, Kleber AG, McKenna WJ, Roden DM, Rudy Y, Schwartz K, Schwartz PJ, Towbin JA, Wilde AM. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management. Part I and II. *Circulation* 1999; 99: 518–28.
2. Schwartz PJ. Idiopathic long QT syndrome: progress and questions. *Am Heart J* 1985; 109: 399–411.
3. Schwartz PJ, Priori SG, Napolitano C. Long QT syndrome. In: Zipes DP, Jalife J (eds). *Cardiac electrophysiology. From cell to bedside*. III edition. WB Saunders Co., Philadelphia, 2000; 597–615.
4. Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT, Goldstein SA. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 1999; 97: 175–87.
5. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: prospective longitudinal study of 328 families. *Circulation* 1991; 84: 1136–45.
6. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. *N Engl J Med* 1998; 339: 960–5.
7. Schwartz PJ, Moss AJ, Priori SG, et al. Gene-specific influence on the triggers for cardiac arrest in the long QT syndrome. *Circulation* 1997; 96 (Suppl): 212.
8. Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation* 1995; 92: 2929–34.
9. Priori SG, Napolitano C, Schwartz PJ, et al. Variable phenotype of long QT syndrome patients with the same genetic defect. *JACC* 1998; 30 (Suppl): 869–4.
10. Napolitano C, Priori SG, Schwartz PJ, Timothy K, Paganini V, Cantù F, Bloise R, De Fusco M, Spazzolini C, Casari G. Identification of a mutational hot spot in HERG-related long QT syndrome (LQT2): phenotypic implications. *Circulation* 1997; 96 (Suppl): 212.
11. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long QT syndrome. *New Engl J Med* 1992; 327: 846–52.
12. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long QT syndrome. Clinical impact. *Circulation* 1999; 99: 529–33.

13. Priori SG, Schwartz PJ, Napolitano C, Bianchi L, Dennis A, De Fusco M, Brown AM, Casari G. A recessive variant of the Romano-Ward long QT syndrome? *Circulation* 1998; 97: 2420–5.
14. Napolitano C, Priori SG, Schwartz PJ, Cantù F, Paganini V, De Fusco M, Pinnavaia A, Aquaro G, Casari G. Identification of a long QT syndrome molecular defect in drug-induced torsades de pointes. *J Cardiovasc Electrophysiol* 2000 (in press).
15. Schulze-Bahr E, Haverkamp W, Hördt M, et al. A genetic basis for quinidine-induced (acquired) long QT syndrome. *Eur Heart J* 1997; 18: 29.
16. Wei J, Abbott GW, Sesti F, et al. Prevalence of KCNE2 (Mirp1) mutations in acquired long QT syndrome. *Circulation* 1999; 100: I-495 (Abs).
17. Napolitano C, Memmi M, Ronchetti E, et al. Silent Mutation on Cardiac Ion Channel Genes and Sudden Death: A Lesson from the Long QT Syndrome. *Circulation* 1998; 99 (Suppl 1): I-8 (Abs).
18. Bennet PB, Yazawa K, Makita N, George AL Jr. Molecular mechanism for an inherited cardiac arrhythmia. *Nature* 1995; 376: 683–5.
19. Dumaine R, Wang Q, Keating MT, Hartmann HA, Schwartz PJ, Brown AM, Kirsch GE. Multiple mechanisms of sodium channel-linked long QT syndrome. *Circ Res* 1996; 78: 916–24.
20. Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, Moss AJ, Towbin JA, Keating MT. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995; 80: 805–11.
21. Wang Q, Shen J, Li Z, Timoty K, Vincent GM, Priori SG, Schwartz PJ, Keating MT. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. *Hum Mol Gen* 1995; 4: 1603–7.
22. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-Bahr E, Keating M, Towbin JA, Wang Q. Genetic Basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998; 392: 293–5.

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