Editorial

Molecular Genetics: Is it Making an Impact in the Management of Inherited Arrhythmogenic Syndromes?

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In the early nineties, the progressive interaction between molecular biology and clinical cardiology contributed to the identification of the genetic bases of several inherited diseases causing sudden cardiac death (SCD) in young individuals with a structurally intact heart. The awareness that an "electrical imbalance", caused by mutations on the genes that encode for cardiac ionic channels, may provoke ventricular arrhythmias and SCD has allowed us to understand that many cases of idiopathic ventricular fibrillation are caused by diseases such as the long QT syndrome (LQTS), the Brugada syndrome (BS), catecholaminergic polymorphic ventricular tachycardia (CPVT) or the recently described short QT syndrome (SQTS).

At present, many genes have been associated with such syndromes and it is now possible to evaluate the impact that genetics has had, not only on the understanding of the pathophysiology of SCD, but also in shaping a "locus specific" clinical management of patients. This article will focus on the existing relationships between clinical manifestations and genetic defects in the field of inherited arrhythmias and on the future challenges for basic research if the challenge to develop molecular curative strategies has to be faced.

The complexity of inherited arrhythmia syndromes

Inherited arrhythmogenic syndromes are monogenic disorders; therefore, the disease is caused by a specific mutation in one gene. Based on this simple assumption, it was initially hoped that each disease was caused by mutations in one gene. However, it has rapidly become clear that this is not the real situation. All genetic arrhythmia syndromes identified until now are "genetically heterogeneous": i.e. there are several genes that account for one phenotype (Table 1). As a consequence, the assumption "one disease = one gene" is not true. The level of complexity is even broader than this and if we compare patients with the same disease who carry mutations in the same gene, we have to face an unexpected variability in the clinical phenotype. Even members of the same family, carriers of the same mutation, may have very different clinical manifestations. This level of complexity was unexpected and today represents one of the mysteries that still surround genetic arrhythmic syndromes.

LQTS and the unknown modifiers of the phenotype

LQTS is in this respect an emblematic disease. One observation that had puzzled in-

Table 1. Genes associated with inherited arrhythmogenic diseases.

Locus Name	Chromosomal locus	Inheritance	Gene symbol	Protein	Phenotype
LQT1	11p15.5	AD	*KCNQ1*	I_{Ks} potassium channel alpha subunit (KvLQT1)	Long QT
LQT2	7q35-q36	AD	*KCNH2*	I_{Kr} potassium channel alpha subunit (HERG)	Long QT
LQT3	3p21	AD	*SCN5A*	Cardiac sodium channel alpha subunits (Nav 1.5)	Long QT
LQT4	4q25-q27	AD	*ANK2*	Ankyrin B, anchoring protein	Long QT, atrial fibrillation
LQT5	21q22.1-q22.2	AD	*KCNE1*	I_{Ks} potassium channel beta subunit (MinK)	Long QT
LQT6	21q22.1-q22.2	AD	*KCNE2*	I_{Kr} potassium channel beta subunit (MiRP)	Long QT
LQT7	17q23.1-q24.2	AD	*KCNJ2*	I_{K1} potassium channel (Kir2.1)	Long QT, Potassium sensitive periodic paralysis, dysmorphic features
LQT8	12p13.3	AD	*CACNA1C*	ICa L-type	Long QT, syndactyly, hypoglycemia, hypothermia, mental retardation, cardiac malformation
JLNS1	11p15.5	AR	*KCNQ1*	I_{Ks} potassium channel alpha subunit (KvLQT1)	Long QT, Deafness
JLNS2	21q22.1-q22.2	AR	*KCNE1*	I_{Ks} potassium channel beta subunit (MinK)	Long QT, Deafness
BrS1	3p21	AD	*SCN5A*	Cardiac sodium channel (Nav 1.5)	ST segment elevation, RBBB
SQTS1	7q35-q36	AD	*KCNH2*	I_{Kr} potassium channel alpha subunit (HERG)	Short QT interval
SQTS2	11p15.5	AD	*KCNQ1*	I_{Ks} potassium channel alpha subunit (KvLQT1)	Short QT interval
ATFB1	11p15.5	AR	*KCNQ1*	I_{Ks} potassium channel alpha subunit (KvLQT1)	Atrial fibrillation
ATFB2	21q22.1-q22.2	AD	*KCNE2*	I_{Kr} potassium channel beta subunit (MiRP)	Atrial fibrillation
CPVT1	1q42.1-q43	AD	*RyR2*	Cardiac Ryanondine receptor	Exercise-induced arrhythmias, normal resting ECG, bradycardia
CPVT2	1p13.3-p11	AR	*CASQ2*	Cardiac Calsequestrin	Exercise-induced arrhythmias, normal resting ECG, bradycardia

vestigators since its first description was the evidence that some affected patients presented, at variance with their family members, mildly prolonged QT intervals.[1,2] After the genetic bases of LQTS had been disclosed we learnt that approximately 30% of genetically affected individuals have a perfectly normal QT interval (Priori and Napolitano, unpublished data). Even if their ECG is unremarkable, these silent mutation carriers have a 15-20% risk of becoming symptomatic for syncope or cardiac arrest before age 40.[3] Moreover they are at increased risk of torsades des pointes if exposed to predisposing environmental factors such as hypokalemia or if they take drugs that block the potassium current I_{Kr}.[4] It is intriguing to speculate that these individuals can cope better than their relatives with the mutation that they have inherited. In other words, they possess a "protective" factor that is able to mitigate the consequence of the primary defect. We still do not know what these protective factors are. Active investigations are ongoing because if we knew what makes these individuals "resistant" to genetic defects, we could attempt to provide the same type of protective factor to the other affected individuals.

The value of genetic analysis for diagnosis of inherited arrhythmogenic diseases

Even if several aspects of genetic diseases are still unclear, the availability of genetic investigation is of major clinical value (Table 2). Genetic investigations are fundamental for establishing the correct diagnosis. This is true for borderline cases: the patient with an ST segment elevation of 2 mm during flecainide challenge,[5] the patient with cardiac arrest during exercise who is resuscitated and shows bidirectional couplets during exercise stress testing, can greatly benefit from a molecular screening that shows that they carry mutations to confirm diagnosis of BS and CPVT,[6] respectively.

Equally if not even more important is the value of molecular diagnosis for those family members who would be considered as not affected because they lack the clinical phenotype of the disease, where only genetic analysis may correctly identify them as silent carriers of the genetic defect. By knowing their status as carriers these patients can protect themselves by avoiding precipitating factors for arrhythmias or taking prophylactic treatments. They may also be aware of the probability of having affected children. Finally, prenatal diagnosis is emerging as an option for families affected by highly lethal forms of inherited arrhythmogenic diseases.

Genotype-phenotype correlation may help risk stratification and treatment

One of the most important contributions of genetic analysis to the clinical management of patients is provided by the opportunity of using genetic information to provide better risk stratification. In fact, it is possible to identify specific features that distinguish individuals with each genetic form of a disease. For example, data on large numbers of genotyped patients have demonstrated that the situations that precipitate cardiac arrhythmias in LQTS are different in the various forms of the disease.[7] LQT1 individuals, who carry loss of function mutations on the gene for the I_{Ks} potassium current, experience most of their events during exercise and, even more precisely, during swimming. LQT2, affected by loss of function mutations on the gene *KCNH2* that encodes the channel conducting the I_{Kr} potassium current, have symptoms under emotional stress, and even more specifically during acoustic stimuli. In contrast, LQT3 subjects, who have gain of

Table 2. Role of genetic analysis in clinical practice.

	Diagnosis of borderline cases	Identification of silent carriers	Prenatal diagnosis	Risk stratification	Therapy selections
LQTS	X	X	X	X	X
Brugada	X	X	X	–	–
SQTS	X	X	X	–	–
CPVT	X	X	X	–	–
A Fib	X	X	–	–	–

LQTS-Long QT syndrome; Brugada-Brugada syndrome; SQTS-Short QT Syndrome; CPVT-Catecholaminergic polymorphic ventricular tachycardia; A Fib-Atrial fibrillation.

function mutations on the gene for the sodium current, present most of their arrhythmic events at rest.[7]

This information has an important clinical impact, as it suggests how to deal with patients, for example avoiding swimming in a LQT1 child or eliminating any source of loud and abrupt noise, such as telephone and alarm clock in the bedroom of LQT2 individuals.

Recent studies on the largest group of genotyped patients ever reported have demonstrated that genotype is a strong factor that influences clinical outcome.[3] We have provided data on 647 genotyped patients that showed how LQT1 patients have a lower risk of becoming symptomatic compared to LQT2 and LQT3 subjects.[3] Therefore, for the clinical cardiologist, knowing that a newly diagnosed patient belongs to a specific genetic variant of LQTS provides a very important clue for predicting the natural history of the disease in that individual.

Genetic data will have to be used by clinicians in the near future just like any other parameter that contributes to defining the clinical profile of patients. The results provided by the diagnostic laboratory are not dissimilar to the outcome of programmed electrical stimulation or the result of an ultrasound examination: they contribute, together with the other clinical indicators, to predicting the prognosis of the individual patient.

In support of this view, we have shown that in LQTS multivariate analysis identifies genotype together with QT interval duration and gender as independent predictors of cardiac events at follow up.[3]

The awareness that the genotype plays such an important role in the clinical presentation of patients has suggested that it might be profitable to investigate whether the response to medical therapy could be different among genotypes. Beta-blockers are the mainstay treatment for LQTS, but it is known that they do not confer complete protection in all individuals. Our group recently provided data about the different responsiveness to beta-blockers found among LQT1, LQT2 and LQT3 patients.[8]

Besides having a QT interval >500 ms and having experienced a first cardiac event very early on in life (before age 7) the presence of LQT2 or LQT3 genotype represented a significant risk indicator of failure of beta-blockers to prevent cardiac arrest.[8] Based on these data, when seeing a symptomatic patient with a very prolonged QT interval and affected by LQT2 or LQT3 the physician should consider adding an ICD to the conventional anti-adrenergic therapy.

In the case of LQTS the information provided by the molecular diagnostic laboratory is pivotal in helping clinicians to decide the most appropriate therapy for their patients.

In LQTS it has been possible to make this impressive advance and to move genetic analysis from the bench to the bedside, because of a few important factors. On the one hand, basic science has moved rapidly and has identified many of the key genes that cause the disease. On the other, large numbers of patients have been referred for genetic screening and all the data have been collected in our large Italian database. It is anticipated that if more genes are identified for BS or atrial fibrillation, and if large numbers of genotyped patients thus become available, it will also be possible to demonstrate the fundamental role of genetic data in these other arrhythmogenic diseases.

Future directions

The identification of several genes associated with inherited arrhythmogenic diseases has allowed using molecular features to shape new strategies of clinical management and therapeutic approach to patients. However, these discoveries have also highlighted the fact that the molecular bases of inherited arrhythmias are much more complex than previously thought. As a matter of fact, it has become evident that functional consequences of different mutations may cause different phenotypes. Mutations on the same gene may cause different and even opposite diseases, as is the case for the long QT syndrome and the short QT syndrome.[1,9,10]

This complexity has to be carefully evaluated and placed into perspective so that we do not get lost but rather use the evidence to reshape our knowledge. Molecular genetics is already a major diagnostic tool, but in some diseases it is more than that: it is information that clinicians should use when deciding on therapy for their patients.

What is in the future of this field? First of all, the advances that have been achieved so far only in LQTS will have to become available for the other arrhythmogenic diseases. This will require a strong international collaboration to reduce the time required to gather a critical mass of genotyped patients that allows the discovery of genotype-phenotype correlation data in large groups of patients.

The real focus of investigators in the field is to strive for a molecular cure for patients. This is not an easy goal and the fundamental strategies still have to

be shaped but, needless to say, this objective is the fuel that is propelling molecular cardiology laboratories today to go further in the hope of defeating these diseases that still cost too many young lives.

References

1. Schwartz PJ, Priori SG, Napolitano C: The Long QT Syndrome, in Zipes DP, Jalife J (eds.): Cardiac Electrophysiology. From Cell to Bedside. WB Saunders Co, Philadelphia, 2000; pp 597-615.
2. Priori SG, Napolitano C, Schwartz PJ: Low penetrance in the long-QT syndrome: clinical impact. Circulation 1999; 99: 529-533.
3. Priori SG, Schwartz PJ, Napolitano C, et al: Risk stratification in the long-QT syndrome. N Engl J Med 2003; 348: 1866-1874.
4. Napolitano C, Schwartz PJ, Brown AM, et al: Evidence for a cardiac ion channel mutation underlying drug-induced QT prolongation and life-threatening arrhythmias. J Cardiovasc Electrophysiol 2000; 11: 691-696.
5. Wilde AA, Antzelevitch C, Borggrefe M, et al: Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002; 106: 2514-2519.
6. Priori SG, Napolitano C, Memmi M, et al: Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 2002; 106: 69-74.
7. Schwartz PJ, Priori SG, Spazzolini C, et al: Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001; 103: 89-95.
8. Priori SG, Napolitano C, Schwartz PJ, et al: Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA 2004; 292: 1341-1344.
9. Bellocq C, van Ginneken AC, Bezzina CR, et al: Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation 2004; 109: 2394-2397.
10. Brugada R, Hong K, Dumaine R, et al: Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation 2004; 109: 30-35.