Cardiac conduction defects

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Summary. Defects in cardiac electric impulse formation or conduction can lead to an irregular beat (arrhythmia) that can cause sudden death without any apparent cause or after stress. In the following sections, we describe the genetic disorders associated with primary cardiac conduction defects, primarily caused by mutations in ion channel genes. Primary indicates that these disorders are not caused by drugs and are not secondary to other disorders like cardiomyopathies (described in the next section). (www.actabiomedica.it)

Keywords: Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, long QT syndrome, short QT syndrome, Wolff-Parkinson-White syndrome, familial atrial fibrillation

Brugada syndrome

Brugada syndrome (BrS) is a genetic heart disorder with an ion channel dysfunction associated with progressive age-related conduction abnormalities. It is more prevalent among males. It is estimated to be responsible for up to 20% of all sudden deaths in individuals with apparently normal hearts (1). BrS has a prevalence of 5:10000 (2).

Diagnosis is based on clinical and family history and electrocardiographic examination. Penetrance and expressivity are highly variable (3). Symptoms are often absent in the first year of life, and in adults usually manifest as syncope or sudden death at rest, during sleep or with fever. Sometimes they manifest on administration of drugs such as sodium channel blockers.

BrS is usually inherited in an autosomal dominant manner, however digenic or autosomal recessive inheritance in patients with mutations in SCN5A and TRPM4 has been reported (4,5). The genes associated with BrS encode subunits of cardiac sodium, potassium and calcium channels and proteins involved in the trafficking or regulation of these channels (Table 1). Only ~35% of BrS patients have been found to have a well-defined genetic cause, one third of whom carry a pathogenic mutation in SCN5A (6). All other genes together are responsible for about 5% of BrS cases. Pathogenic variants are usually point mutations or small insertions/deletions, however partial SCN5A gene deletion has been reported (7). Most of the reported patients inherit the mutation from one of their parents, while de novo variants account for <1% (8).

We use a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes, and multiplex ligation-dependent probe amplification (MLPA) assay to detect duplications and deletions in SCN5A. Worldwide, 81 accredited medical genetic laboratories in the EU and 57 in the US, listed in Orphanet (9) and GTR (10) databases, respectively, offer genetic tests for Brugada syndrome. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (11) and GeneReviews (12).

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Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited heart disorder characterized by electrical instability in a structurally normal heart during acute activation of the adrenergic nervous system, as in physical activity or emotional stress. Release of catecholamines causes a calcium-ion channel dysfunction in myocytes, leading to ventricular arrhythmia. Episodes of ventricular tachycardia can cause dizziness and syncope. Spontaneous recovery from the arrhythmia is possible, but unless recognized and treated, ventricular tachycardia may cause cardiac...
arrest and sudden death. These symptoms typically begin in childhood. The exact prevalence of CPVT in the population is not known, but is estimated at about 1:10000 (13).

Clinical diagnosis may be difficult because echocardiograms and electrocardiograms are normal in resting state. Testing must therefore be performed under stress. Differential diagnosis should consider long-QT syndrome, arrhythmogenic right ventricular cardiomyopathy, short coupled ventricular tachycardia and Andersen-Tawil syndrome.

Preventive drugs (beta-blockers and flecainide) and other treatments (implantable cardioverter defibrillator and left cardiac sympathetic denervation) are available for susceptible individuals.

The disorder may have autosomal dominant or recessive inheritance and the associated genes are involved in calcium homeostasis in myocytes (Table 2). Most pathogenic variants are point mutations or small insertions/deletions. However, large deletions/duplications and complex genomic rearrangements have been reported in RYR2 (1). Pathogenic variants in these genes account for 55-65% of CPVT cases with a penetrance of 83% for RYR2-mutations carrier(13).

We use a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the genes in Table 2. Worldwide, 25 accredited medical genetic laboratories in the EU and 19 in the US, listed in Orphanet (9) and GTR (10) databases, respectively, offer genetic tests for catecholaminergic polymorphic ventricular tachycardia. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (11), GeneReviews (13) and EuroGentest (14).

**Long QT syndrome**

Long QT syndrome (LQT) is a genetic heart disease characterized by prolongation of the QT interval in the absence of other conditions known to lengthen it (such as QT-prolonging drugs). This may lead to arrhythmia that can cause palpitations, syncope or sudden death. Typically LQTS manifests in patients under 40 years of age, sometimes in early infancy. The mean age of onset of symptoms is 12 years and earlier onset is usually associated with severer forms (15,16).

LQT follows two distinct patterns of inheritance: autosomal dominant with an estimated prevalence of 1:2000-5000 (17,18,19) and autosomal recessive (Jervell and Lange-Nielsen syndrome) with an estimated prevalence of 1:1000000-4000000 (20).

Clinical diagnosis is based on clinical findings, ECG, medical and family history. The genetic test is useful for diagnosis confirmation, differential diagnosis, recurrence risk evaluation and prenatal diagnosis.

### Table 2. Genes associated with various forms of catecholaminergic polymorphic ventricular tachycardia

| Gene   | OMIM gene | Disease          | OMIM disease | Inheritance | Function                                                                 |
|--------|-----------|------------------|--------------|-------------|--------------------------------------------------------------------------|
| RYR2   | 180902    | CPVT1            | 604772       | AD          | Ca²⁺ channel triggers cardiac muscle contraction                         |
| CASQ2  | 114251    | CPVT2            | 611938       | AR          | Regulates release of luminal Ca²⁺ via RYR2                               |
| TECRL  | 617242    | CPVT3            | 614021       | AR          | Ca²⁺ transport into myocytes                                             |
| CALM1  | 114180    | CPVT4            | 614916       | AD          | Regulates release of Ca²⁺ via RYR2                                       |
| TRDN   | 603283    | CPVT5 with/without muscle weakness | 615441 | AR          | Regulates release of luminal Ca²⁺ release via RYR1 and RYR2              |
| KCNJ2  | 600681    | CPVT             | /            | AD          | Establishes action potential and excitability of neurons and muscles     |

AD=Autosomal dominant; AR=Autosomal recessive
Differential diagnosis should consider QT-prolonging drugs, hypokalemia, structural heart disease, sudden infant death syndrome, vasovagal syncope, seizures, familial ventricular fibrillation, hypertrophic cardiomyopathy, dilative cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (21).

Syndromic LQT may have autosomal dominant (Timothy syndrome, Andersen-Twail syndrome and Ankyrin B syndrome) (22,23,24) or autosomal recessive inheritance (Jervell and Lange-Nielsen syndromes) (20). Up to 80% of cases of LQT are due to pathogenic variants in the \textit{KCNQ1}, \textit{KCNH2} and \textit{SCN5A} genes. Other associated genes account for less than 5% of all cases (21) (Table 3).

### Table 3. Genes associated with various forms of long QT syndrome

| Gene   | OMIM gene | Disease | OMIM disease | Inheritance | Function                                                                 |
|--------|------------|---------|--------------|-------------|--------------------------------------------------------------------------|
| \textit{KCNQ1} | 607542 | LQT1    | 192500       | AD          | Repolarizes cardiac action potential                                     |
|         |           | JLNS1   | 220400       | AR          |                                                                           |
| \textit{KCNH2} | 152427 | LQT2    | 613688       | AD          | Pore-forming subunit of voltage-gated inwardly rectifying K\(^+\) channel |
| \textit{SCN5A} | 600163 | LQT3    | 603830       | AD          | Mediates voltage-dependent Na\(^+\) permeability of excitable membranes  |
| \textit{ANK2}  | 106410    | LQT4    | 600919       | AD          | Coordinates assembly of Na/Ca exchanger, Na/K ATPase and InsP3 receptor in sarcoplasmic reticulum of cardiomyocytes |
| \textit{KCNE1} | 176261 | LQT5    | 613695       | AD          | Modulates gating kinetics and enhances stability of voltage-gated K\(^+\) channel complex |
|         |           | JLNS2   | 612347       | AR          |                                                                           |
| \textit{KCNE2} | 603796 | LQT6    | 613693       | AD          | Modulates gating kinetics and enhances stability of voltage-gated K\(^+\) channel complex |
| \textit{KCNJ2} | 600681 | LQT7    | 170390       | AD          | Establishes neuron and muscle action potentials and excitability          |
| \textit{CACNA1C} | 114205 | LQT8    | 601005       | AD          | Pore-forming, alpha-1C subunit of voltage-gated Ca\(^{2+}\) channel       |
| \textit{CAV3}  | 601253    | LQT9    | 611818       | AD          | Regulates voltage-gated K\(^+\) channels                                 |
| \textit{SCN4B} | 608256    | LQT10   | 611819       | AD          | Interacts with voltage-gated alpha subunits to change Na\(^+\) channel kinetics |
| \textit{AKAP9} | 604001    | LQT11   | 611820       | AD          | Effector in regulating K\(^+\) channel                                   |
| \textit{SNTA1} | 601017    | LQT12   | 612955       | AD          | Interacts with pore-forming alpha subunit of cardiac Na\(^+\) channel     |
| \textit{KCNJ5} | 600734    | LQT13   | 613485       | AD          | Allows K\(^+\) flow into cells                                           |
| \textit{CALM1} | 114180    | LQT14   | 616247       | AD          | Mediates ion channel control                                            |
| \textit{CALM2} | 114182    | LQT15   | 616249       | AD          | Mediates ion channel control                                            |
| \textit{CALM3} | 114183    | LQT     | /            | AD          | Mediates ion channel control                                            |

AD=autosomal dominant; AR=autosomal recessive; JLNS=Jervell and Lange-Nielsen syndrome
Pathogenic variants may be sequence variations (missense, nonsense, splicing, small insertions and deletions, small indels). Large deletions/duplications have been reported in KCNH2, KCNQ1 and KCNJ2 (21,23). We use a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes, and MLPA assay to detect duplications and deletions in KCNH2, KCNQ1 and KCNJ2.

Worldwide, 52 accredited medical genetic laboratories in the EU and 4 in the US, listed in the Orphanet (9) and GTR (10) databases, respectively, offer genetic tests for long QT syndrome. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (11), GeneReviews (20,21,22,23,24) and EuroGentest (14).

Short QT syndrome

Short QT syndrome (SQT) is a rare genetic heart disease characterized by an abnormally short QT interval and increased risk of arrhythmia and sudden death. Clinical presentation is heterogeneous. Some patients may be totally asymptomatic and others may have episodes of syncope or fall victim to sudden cardiac death. SQT may occur at any time of life from early infancy to old age. The estimated prevalence is 1-5:1000 (26,27,28,29).

According to the 2013 consensus statement of major world heart associations, the recommended criteria for diagnosis of SQT are QTc <330 msec or <360 msec with one or more of the following: a pathogenic mutation, family history of SQT, family history of sudden death under 40 years of age, or survival of a ventricular tachycardia/ventricular fibrillation event without underlying heart disease (30).

Differential diagnosis should consider the secondary causes of SQT interval (hyperkalaemia, hypercalcaemia, hyperthermia, acidosis, effects of catecholamines or drugs such as digitalis) (31) and other arrhythmic disorders, such as Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, cardiac arrest and sick sinus syndrome (Table 4).

Pathogenic variants may be sequence variations (missense, nonsense, splicing, small indels). Large deletions/duplications associated with SQT have not yet been reported in the above genes.

MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes. 26 accredited medical genetic laboratories in the EU and 32 in the US, listed in the Orphanet and GTR databases, respectively, offer genetic tests for short QT syndrome. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (11).

Wolff-Parkinson-White syndrome

Wolff-Parkinson-White syndrome (WPWS), also known as “pre-excitation syndrome”, is a genetic heart disorder characterized by arrhythmia due to an abnormal electrical pathway in the heart, a so-called accessory pathway that allows electrical signals to by-

| Gene   | OMIM gene | Disease | OMIM disease | Inheritance | Function                                      |
|--------|-----------|---------|--------------|-------------|-----------------------------------------------|
| KCNH2  | 152427    | SQT1    | 609620       | AD          | Pore-forming subunit of voltage-gated inwardly rectifying K+ channel |
| KCNQ1  | 607542    | SQT2    | 609621       | AD          | Repolarizes cardiac action potential           |
| KCNJ2  | 600681    | SQT3    | 609622       | AD          | Establishes action potential and excitability of neurons and muscles |

AD=autosomal dominant; AR=autosomal recessive
Cardiac conduction defects

Cardiac conduction defects pass the atrioventricular node and move faster than normal from the atria to the ventricles. It may also transmit reverse electrical impulses, resulting in arrhythmias (32).

Wolff-Parkinson-White syndrome may present clinically with palpitations, dyspnea, dizziness or even syncope. In rare cases it can lead to cardiac arrest and sudden death (33). Although age of onset ranges from 11 to 50 years, complications can occur at any age. Some patients, however, are totally asymptomatic or never experience any complication associated with this condition.

In most patients, WPWS is sporadic, though in a minority of cases it can be familial (34) or complicated underlying diseases, such as Ebstein’s anomaly (35), mitochondrial disease (36), hypertrophic cardiomyopathy (37) or a lethal congenital form of glycogen storage disease (38). The estimated prevalence of WPWS is 1.5-3.1:1000 in western countries (33).

Clinical diagnosis is based on clinical history, physical examination, resting 12-lead ECG and Holter monitoring. Genetic testing is useful for confirming diagnosis and for differential diagnosis, recurrence risk calculation and prenatal diagnosis in families with a known mutation. Differential diagnosis should consider other primary channelopathies and secondary causes of arrhythmia, such as electrolyte abnormalities, hyperthyroidism and/or side effects of substances such as digoxin and alcohol (39).

Familial WPWS only accounts for a small percentage of cases, most of which occur in persons with no apparent family history of the condition. The familial form has autosomal dominant inheritance and is associated with variations in the PRKAG2 gene (OMIM gene 602743; OMIM disease 194200). Pathogenic variants may be missense, nonsense, splicing or small insertions/deletions.

No genetic tests are listed in the Orphanet database but 10 accredited medical genetic laboratories in the US, listed in the GTR database, offer genetic testing for WPWS. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (11). MAGI uses an NGS approach to detect nucleotide variations in coding exons and flanking introns of the above gene.

Familial atrial fibrillation

Familial atrial fibrillation (FAF) is a heterogeneous genetic heart disorder characterized by chaotic electrical activity in the atria and an irregular ventricular response. This is also known as “irregularly irregular rhythm”. If untreated, it can lead to reduction in cardiac output and atrial thrombus formation, which may be responsible for episodes of stroke or sudden death. Atrial fibrillation may manifest clinically with palpitations, dyspnea, chest pain, dizziness or even syncope (40). The risk of developing atrial fibrillation increases with age and complications can occur at any age. However, some patients are totally asymptomatic or never experience any complication associated with this condition. The estimated prevalence of FAF ranges from 0.4% to 1% in the general population (40) and increases with age (41).

Clinical diagnosis is based on clinical history, physical examination, ECG and Holter monitoring. Echocardiography is performed to evaluate left chamber dimensions and systolic/diastolic performance. Genetic testing is useful for confirming diagnosis, and for differential diagnosis, recurrence risk calculation and prenatal diagnosis in families with a known mutation. Differential diagnosis should consider: reversible causes of atrial fibrillation (AF), such as alcohol intake, surgery, myocardial infarction, myocarditis and pericarditis; metabolic disorders associated with AF, such as obesity and hyperthyroidism; other heart diseases associated with AF, such as valve disease, heart failure, hypertension, hypertrophic cardiomyopathy and dilated cardiomyopathy (40, 42).

Eligibility criteria for genetic testing (43) are:

1- ECG characteristics: absence of P waves; irregular R-R intervals;
2- clinical presentation: AF as major clinical manifestation (phenotype) with early onset (before age 60 years);
3- family history: at least one affected first or second-degree family member.

Familial atrial fibrillation is highly heterogeneous and can have autosomal dominant or recessive inheritance (Table 5).

Pathogenic variants may be missense, nonsense, splicing or small small indels. Large deletions/duplic-
Table 5. Genes associated with various forms of atrial fibrillation, familial (ATFB)

| Gene     | OMIM gene | Disease | OMIM disease | Inheritance | Function                                                                                                                                 |
|----------|-----------|---------|--------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------|
| KCNQ1    | 607542    | ATFB3   | 607554       | AD          | Repolarizes cardiac action potential                                                                                                    |
| KCNE2    | 603796    | ATFB4   | 611493       | AD          | Modulates gating kinetics and enhances stability of voltage-gated K+ channel complex                                                      |
| NPPA     | 108780    | ATFB6   | 612201       | AD          | Key role in regulation of natriuresis, diuresis, vasodilation                                                                           |
| KCN45    | 176267    | ATFB7   | 612240       | AD          | Mediates transmembrane potassium transport in excitable membranes                                                                       |
| KCNJ2    | 600681    | ATFB9   | 613980       | AD          | Establishes action potential and excitability of neurons and muscles                                                                      |
| SCN5A    | 600163    | ATFB10  | 614022       | AD          | Mediates voltage-dependent Na+ permeability of excitable membranes                                                                    |
| GJA5     | 121013    | ATFB11  | 614049       | AD          | Allows passive diffusion of small molecules, including glucose, K+, Ca2+ and cAMP                                                        |
| ABCC9    | 601439    | ATFB12  | 614050       | AD          | Subunit of ATP-sensitive K+ channels                                                                                                   |
| SCN1B    | 600235    | ATFB13  | 615377       | AD          | Regulates assembly, expression, function of Na+ channel complex                                                                        |
| SCN2B    | 601327    | ATFB14  | 615378       | AD          | Assembly, expression, modulation Na+ channel complex                                                                                     |
| SCN3B    | 608214    | ATFB16  | 613120       | AD          | Modulates channel-gating kinetics                                                                                                       |
| SCN4B    | 608256    | ATFB17  | 611819       | AD          | Interacts with voltage-gated alpha subunits to change Na+ channel kinetics                                                              |
| MYL4     | 160770    | ATFB18  | 617280       | AD          | Encodes a myosin alkali light chain expressed in embryonic muscle and adult atria                                                         |
| NUP155   | 606694    | ATFB15  | 615770       | AR          | Plays a role in fusion of nuclear envelope vesicles and may also be involved in heart physiology                                           |
| KCN4D    | 605411    | ATFB    | /            | AD          | Pore-forming subunit of voltage-gated rapidly-inactivating A-type K+ channels                                                          |
| KCNE1    | 176261    | ATFB    | /            | AD          | Modulates gating kinetics and enhances stability of voltage-gated K+ channel complex                                                    |
| KCNH2    | 152427    | ATFB    | /            | AD          | Pore-forming subunit of voltage-gated inwardly rectifying K+ channels                                                                   |
| LMNA     | 150330    | ATFB    | /            | AD          | Component of nuclear lamina and required for cardiac homeostasis                                                                       |
| NKKX2-5  | 600584    | ATFB    | /            | AD          | Transcription factor involved in heart formation and development                                                                       |
| PRKAG2   | 602743    | ATFB    | /            | AD          | Energy-sensing enzyme that monitors cell energy status and functions; inhibits de novo biosynthesis of fatty acids and cholesterol         |

(continued on next page)
cations have also been reported in KCNQ1, KCNA5, KCNJ2, SCN5A, GATA4, PTX2, TBX5 and GJA5. MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes and MLPA assay to detect duplications and deletions in KCNQ1, KCNA5, KCNJ2, SCN5A, GATA4, PTX2, TBX5 and GJA5.

19 accredited medical genetic laboratories in the EU and 23 in the US, listed in the Orphanet and GTR databases, respectively, offer genetic tests for familial atrial fibrillation. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (11).

Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with genetic cardiac disorders. When a suspect of cardiac conduction defect is present we perform the analysis of all the genes present in this short article.

In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of ≥99% (coverage depth ≥10x).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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