Acta Biomed 2019; Vol. 90, Supplement 10: 20-29 DOI: 10.23750/abm.v90i10-S.8751

Review

Cardiac conduction defects

Giulia Guerri[1], Geraldo Krasi[2]*, Vincenza Precone[3], Stefano Paolacci[1], Pietro Chiurazzi[4,5], Luca Arrigoni[6], Bernardo Cortese[7], Astrit Dautaj[2], Matteo Bertelli[3]*

[1] MAGI's Lab, Rovereto (TN), Italy; [2] MAGI Balkans, Tirana, Albania; [3] MAGI Euregio, Bolzano, Italy; [4] Istituto di Medicina Genomica, Università Cattolica del Sacro Cuore, Rome, Italy; [5] UOC Genetica Medica, Fondazione Policlinico Universitario "A. Gemelli", Rome, Italy; [6] Section of Cardiovascular Diseases, Department of Clinical and Surgical Specialities, Radiological Sciences and Public Health, University and Spedali Civili Hospital of Brescia, Italy; [7] Cardiac Department, San Carlo Clinic, Milan, Italy

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)

Key words: 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).

* Authors have equally contributed to this work

Table 1. Genes associated with various forms of Brugada syndrome (BrS).

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
SCN5A	600163	BrS1	601144	AD, DR	Mediates voltage-dependent Na^+ permeability of excitable membranes
GPD1L	611778	BrS2	611777	AD	Decreases cardiac Na^+ current
CACNA1C	114205	BrS3	611875	AD	Pore-forming, alpha-1C subunit of voltage-gated Ca^{2+} channel
CACNB2	600003	BrS4	611876	AD	Increases cardiac peak Ca2+ current, regulates voltage-dependent activation, controls alpha-1 subunit recruitment
SCN1B	600235	BrS5	612838	AD	Regulates assembly, expression and function of Na^+ channel complex
KCNE3	604433	BrS6	613119	AD	Modulates gating kinetics, stabilizes channel complex
SCN3B	608214	BrS7	613120	AD	Modulates channel gating kinetics
HCN4	605206	BrS8	613123	AD	Contributes to native pacemaker currents in the heart that regulate heartbeat rhythm
KCND3	605411	BrS9	616399	AD	Pore-forming subunit of voltage-gated rapidly-inactivating A-type K^+ channels
ABCC9	601439	BrS	/	AD	Subunit of ATP-sensitive K_+ channels
SCN10A	604427	BrS	/	AD	Mediates voltage-dependent Na^+ permeability of excitable membranes
SLMAP	602701	BrS	/	AD	Excitation-contraction coupling
SCN2B	601327	BrS	/	AD	Assembly, expression and modulation of Na^+ channel complex
CACNA2D1	114204	BrS	/	AD	Regulates Ca^{2+} current density and activation/inactivation of Ca^{2+} channel
KCNJ8	600935	BrS	/	AD	Inward-rectifier K^+ channel
PKP2	602861	BrS	/	AD	Maintains transcription of genes that control intracellular calcium cycling
TRPM4	606936	BrS	/	AR, DR	Ca^{2+}-activated non selective cation channel that depolarizes membranes

AD=autosomal dominant; AR=autosomal recessive; DR= digenic recessive.

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	Ca^{2+} channel triggers cardiac muscle contraction
CASQ2	114251	CPVT2	611938	AR	Regulates release of luminal Ca^{2+} via RYR2
TECRL	617242	CPVT3	614021	AR	Ca^{2+} transport into myocytes
CALM1	114180	CPVT4	614916	AD	Regulates release of Ca^{2+} via RYR2
TRDN	603283	CPVT5 with/without muscle weakness	615441	AR	Regulates release of luminal Ca^{2+} 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 *KCNQ1*, *KCNH2* and *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
KCNQ1	607542	LQT1	192500	AD	Repolarizes cardiac action potential
		JLNS1	220400	AR	
KCNH2	152427	LQT2	613688	AD	Pore-forming subunit of voltage-gated inwardly rectifying K^+ channel
SCN5A	600163	LQT3	603830	AD	Mediates voltage-dependent Na^+ permeability of excitable membranes
ANK2	106410	LQT4	600919	AD	Coordinates assembly of Na/Ca exchanger, Na/K ATPase and InsP3 receptor in sarcoplasmic reticulum of cardiomyocytes
KCNE1	176261	LQT5	613695	AD	Modulates gating kinetics and enhances stability of voltage-gated K^+ channel complex
		JLNS2	612347	AR	
KCNE2	603796	LQT6	613693	AD	Modulates gating kinetics and enhances stability of voltage-gated K^+ channel complex
KCNJ2	600681	LQT7	170390	AD	Establishes neuron and muscle action potentials and excitability
CACNA1C	114205	LQT8	601005	AD	Pore-forming, alpha-1C subunit of voltage-gated Ca^{2+} channel
CAV3	601253	LQT9	611818	AD	Regulates voltage-gated K^+ channels
SCN4B	608256	LQT10	611819	AD	Interacts with voltage-gated alpha subunits to change Na^+ channel kinetics
AKAP9	604001	LQT11	611820	AD	Effector in regulating K^+ channel
SNTA1	601017	LQT12	612955	AD	Interacts with pore-forming alpha subunit of cardiac Na^+ channel
KCNJ5	600734	LQT13	613485	AD	Allows K^+ flow into cells
CALM1	114180	LQT14	616247	AD	Mediates ion channel control
CALM2	114182	LQT15	616249	AD	Mediates ion channel control
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, hypercalcemia, 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-

Table 4. Genes associated with various forms of short QT syndrome

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

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/dupli-

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
KCNA5	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^+, Ca^{2+} 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
KCND3	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
NKX2-5	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)

Table 5 ***(continued)*****.** Genes associated with various forms of atrial fibrillation, familial (ATFB)

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
RYR2	180902	ATFB	/	AD	Ca^{2+} channel that triggers cardiac muscle contraction
GATA4	600576	ATFB	/	AD	Regulates genes involved in myocardial differentiation and function
GATA5	611496	ATFB	/	AD	Required for cardiovascular development
GATA6	601656	ATFB	/	AD	Required for cardiovascular development
PITX2	601542	ATFB	/	AD	May play a role in proper localization of asymmetric organs such as heart
TBX5	601620	ATFB	/	AD	Regulates transcription of several genes involved in heart development
ZFHX3	104155	ATFB	/	AD	Regulates myogenic differentiation
SHOX2	602504	ATFB	/	AD	Transcriptional regulator involved in pattern formation in vertebrates
PRRX1	167420	ATFB	/	AD	Role in establishment of diverse mesodermal muscle types
KCNN3	602983	ATFB	/	AD	Forms a voltage-independent K^+ channel activated by intracellular Ca^{2+}

AD=autosomal dominant; AR=autosomal recessive

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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Received: 5 August 2019
Accepted: 5 September 2019
Correspondence:
Stefano Paolacci
Via delle Maioliche 57/D
38068 Rovereto (TN), Italy
E-mail:stefano.paolacci@assomagi.org