Clinical Spectrum of PRKAG2 Syndrome

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PRKAG2 syndrome (PS) is a rare, early-onset autosomal dominant inherited disease, characterized by ventricular pre-excitation, supraventricular arrhythmias, and cardiac hypertrophy. It is frequently accompanied by chronotropic incompetence and advanced heart blocks, leading to premature pacemaker implantation.

The association of these clinical features had previously been recognized by several studies since the second half of the 20th century.1–3 In 1991, PRKAG2 syndrome was mapped to the locus 7q 36,4 and in 2001, Gollob et al5 identified the responsible gene.

The syndrome is caused by mutations in the gene encoding for the 5' AMP-activated protein kinase (AMPK), specifically for its γ regulatory subunit (PRKAG2).

AMPK is an enzyme deeply involved in cellular ATP metabolic regulation.6 PRKAG2 genetic mutations are rare and have been recognized mainly in the context of patients with nonsarcomeric familial hypertrophic cardiomyopathy associated with Wolff–Parkinson–White syndrome.7

PS can show different expressivity both of ventricular hypertrophy and arrhythmic features, ranging from an asymptomatic condition to sudden cardiac death (SCD). PS can occasionally lead to heart failure (HF) or demonstrate systemic involvement.7–9

This review aims to describe the various features and clinical implications of PS, providing clinicians and researchers with a summary of the published literature to improve the diagnosis and to better manage the clinical course of the disease.

Materials and Methods

A search of the English literature was performed using PubMed up to September 2014 on the clinical features, genetics, and pathophysiology of PS syndrome. The term PRKAG2 combined with either cardiomyopathy, Wolff–Parkinson–White syndrome, atrial fibrillation, familial, left ventricular hypertrophy, atrioventricular (AV) block, pacemaker, SCD, HF, clinical characteristics, genotype, phenotype, or mutations was used.

Observational studies, case reports, and reviews were included in our search. References were carefully evaluated for missing publications. Mutation data were obtained from the publically available Human Gene Mutation Database (www.hgmd.org).

Information on genetic mutations, molecular pathophysiology, clinical characteristics, and treatment strategies were extracted from the literature. The main end-point data are represented by ages of symptoms onset, pacemaker implantation, heart transplant, SCD, implantable cardioverter defibrillator (ICD) implantation, and number of discharges.

Statistical analysis was performed using SPSS statistical software (version 10.0, SPSS Inc, Chicago, IL). All data are expressed as mean values±SD (range) or frequency (%).

The Pearson χ² test or Fischer exact test was used for comparisons between dichotomous variables. Missing data were accounted for by decreasing the denominator of the total number of patients.

Results

Fifty-five studies were found; 24 of them were observational. After excluding 1 publication with data from the same patients of another study, we selected 23 observational studies with genetically tested patients to build a table comprehensive of the main clinical features of PS and the relative mutations. Some studies reported data from proband relatives not tested for PS; we excluded such data from the statistical analysis but we narratively discuss about these patients in our review.

A total of 193 genetically confirmed patients and 13 different mutations of PRKAG2 gene were found.

Epidemiology

The prevalence of PS is currently unknown. One study identified PS in 1 of 100 subjects affected by hypertrophic cardiomyopathy (HCM) with premature sinoatrial or AV conduction disease (1%).7 Arad et al8 found genetically confirmed PS in 7 of 24 patients (29%) among a subgroup with both left ventricular hypertrophy (LVH) and pre-excitation on ECG.

The observed prevalence may be rising because of a larger availability of genetic testing for HCM. Case reports of the syndrome have been described worldwide, suggesting that PS can affect patients of any ethnic group.

PRKAG2 Mutations

PRKAG2 mutation inheritance pattern is autosomal dominant. Almost all studies report missense mutations.5–21 Only Blair et al9 documented an insertion mutation (Exon 5:InsLeu). The most commonly reported mutation were C.905G>A

Received April 24, 2015; accepted July 24, 2015.

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The Data Supplement is available at http://circep.ahajournals.org to lookup/supp/doi:10.1161/CIRCEP.115.003121/-/DC1.

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(Circ Arrhythm Electrophysiol. 2016;9:e003121. DOI: 10.1161/CIRCEP.115.003121.)

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Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org DOI: 10.1161/CIRCEP.115.003121
(Arg302Gln) and c.1463A>T (Asn488Ile), with 110 and 40 cases (57% and 21%, respectively).

**AMPK Kinase and PRKAG2 Subunit**

AMPK is a highly conserved serine/threonine protein kinase responsible for cellular energetic homeostasis control. Stimulated by high AMP concentration and AMPK-kinase activity, the enzyme counterbalances ATP depletion.\(^5,6,22\) It is composed of a catalytic subunit (\(\alpha\)) and 2 regulatory subunits (\(\beta\) and \(\gamma\)). \(\gamma2\) regulatory subunit of AMPK (PRKAG2) binds AMP, enhancing the \(\alpha\)-subunit activation.\(^6\) AMPK is highly expressed in cardiac tissue, skeletal muscle, brain, placenta, liver, kidneys, and pancreas.\(^23\) In cardiomyocytes, the enzyme regulates the glucose\(^24\) and fatty acids\(^25\) uptake, storage, and utilization.

PRKAG2 mutations are suspected to modify the tridimensional structure of AMPK, altering its affinity for AMP and modifying the enzyme activity. Studies on transgenic mice have showed an enhanced enzymatic activity during the early stage of PS\(^26,27\) and a decreased activity during the advanced phase;\(^28\) a recent study demonstrated an impaired myocardial glycogen uptake in adult patients with PS.\(^29\)

In humans, AMPK dysfunction alters the myocyte glucidic uptake and metabolism causing the deposition of glycogen and amylopectin, as seen in glycogen storage cardiomyopathies.\(^30\) During cardiogenesis, the disruption of the annulus fibrosus by glycogen-filled myocytes interferes with the normal AV separation and can lead to ventricular pre-excitation and reciprocating arrhythmias.\(^5,7,9,26,31,32\) A recent study on mice confirmed the correlation of glycogen deposits with ventricular pre-excitation and reciprocating arrhythmias.\(^5,7,9,26,31,32\) A recent study on mice confirmed the correlation of glycogen deposits with ventricular pre-excitation and reciprocating arrhythmias.\(^5,7,9,26,31,32\)

Another study on mice implicated that mutated AMPK could unbalance the phosphorylation state of cardiac tropinin and myocardial contractility,\(^34\) leading the way toward HF. AMPK dysfunction was found to be related with cellular autophagy and apoptosis in animal models.\(^35\)

A representation of postulated intracellular effects of PRKAG2-related enzyme dysfunction is depicted in Figure 1. However, the precise biological mechanisms and their correlations with the clinical phenotypes of PS, especially in humans, are still unclear.\(^5,8,28\)

**PRKAG2 Phenotype**

The main clinical features of PS are represented in Table I in the Data Supplement and summarized in Table 1.

**Characteristic Electrocardiographic Features**

The most common electrocardiographic feature of PS is a short PR interval present in 68% of patients.\(^5,7,19\) A bundle branch block, mainly affecting the right branch, was also widely reported along with a short PR.\(^19\) In addition to complete bundle branch blocks, slurred QRS depolarization phases and eccentric patterns of intraventricular conduction delays >120 ms are reported.\(^7,19\) Advanced and clinically significant AV or sinoatrial blocks were also common.\(^4,17\)

High-voltage QRS complexes with secondary repolarization abnormalities frequently developed even without echocardiographic evidence of LVH, sometimes accompanied by left axis deviation.\(^7\) Figure 2A shows a typical ECG from a young patient with PS.

**Cardiac Hypertrophy**

Cardiac hypertrophy mainly involves the left ventricle and it is often progressive and associated with both diastolic and systolic HF.\(^5,7,8,11,12,17\) Maximal ventricular wall thickness varied widely among the studies, ranging from normal values to a mean of 24 mm (confidence interval, 13–45 mm) among Asn488Ile patients and 32.8±7.9 mm in Glu506Lys patients.\(^12\) Restrictive mitral inflow Doppler pattern,\(^3\) hemodynamically significant left ventricular outflow tract obstruction,\(^12\) and dilated progression were leading causes to cardiac transplant or SCD.\(^4\) In all studies, ultrasound imaging was routinely used to assess cardiac hypertrophy; only a minority of patients underwent cardiovascular magnetic resonance for tissue characterization (Figure 2B and 2C).\(^36\) To date, no cardiovascular magnetic resonance–specific pattern was found to be associated with PS.

**PRKAG2 Syndrome Clinical Manifestations**

**Supraventricular Tachyarrhythmias**

Supraventricular tachyarrhythmias (SVT) were mainly represented by atrial fibrillation and flutter. SVT have been frequently the first clinical sign in patients with PS; their complications were represented by stroke and by the development of rapid ventricular arrhythmias, in some cases leading to SCD.\(^5,7,11,21,37,38\) SVT were reported in 38% of PS patients, and a considerable proportion of them was associated with accessory pathways on electrophysiological studies (EPS).\(^5,8,17,21\) Pre-excitation was thus found to be associated with both common accessory pathways and decremental AV connections or fasciculoventricular pathways.\(^5,7,39,40\) Many authors reported different types of accessory pathways in Arg302Gln-mutated patients,\(^5,8,17,21\) some of which were capable of maintaining an AV reciprocating tachycardia.

**Conduction System Dysfunction, Chronotropic Incompetence, and Pacemaker Implantation**

Characteristically, PS leads to chronotropic incompetence mostly because of advanced AV blocks, marked sinus bradycardia, or sinus blocks. This stage of the disease almost invariably occurs within the third or fourth decade of age.\(^5,11,19\) Overall, conduction system dysfunction had a prevalence of 44%, and pacemaker implantation was performed in 43% of patients.

Clinically, chronotropic incompetence was characterized by recurrent syncope, Adam Stokes syndrome, and often by a rapid and critical onset with severe hemodynamic instability.\(^5,7\)

**HF and Systolic/Diastolic Dysfunction**

HF was reported in about 12% of PS patients; when present, it was often severe and characterized by progressive ventricular dysfunction. In Glu506Lys, exon5:InsLeu, and His142Arg carriers, HF symptoms were frequently reported (33%–63%).\(^8,12\)

**Sudden Cardiac Death**

SCD occurred in 8.7% of a total of 171 patients with available data (mean age of death, 33.4 years). From the data available,
SCD in PS can occur both in the presence and the absence of severe cardiac hypertrophy; some studies reported cases of SCD during sleep.

Current data are not sufficient to clearly define the prevailing pathophysiologic process leading to SCD, which could be because of both an abrupt advanced heart block and ventricular fibrillation, the latter deriving from SVT degeneration (fast conduction through accessory pathways) or from massive LVH. In those patients in whom EPS were performed, ventricular fibrillation was induced only by high atrial pacing and not by ventricular extrastimuli.

**Outcomes**

The age of symptoms onset was seldom available. In general, the clinical onset ranged from intrauterine period, general childhood, adolescence to the fourth or fifth decade of age. The mean age at diagnosis among the studies with available records is 30.1 years.

Overall, 82 subjects (43%) were implanted with permanent pacemaker because of advanced heart blocks or sinus node disease, often within the third or fourth decade of age. Few studies reported data on heart transplant: where such data were available, transplant was performed at 19, 8 and 42 years of age.

SCD occurred in 8.7% of patients, and the mean age of death was 33.4 years; 171 of 189 patients had available data about SCD.

In the largest report available from Murpy et al, ICDs were implanted for primary prevention in 2 patients (age: 20 and 22 years) with massive LVH, 1 of whom had ventricular

### Table 1. Summary Data of the Main Clinical Features of PRKAG2 Syndrome

<table>
<thead>
<tr>
<th>PRKAG2 Syndrome</th>
<th>Mean Age at Diagnosis, y</th>
<th>Penetrance</th>
<th>Short PR, % (No. of Patients)</th>
<th>SVT, % (No. of Patients)</th>
<th>SND, AVB, ECI, % (No. of Patients)</th>
<th>PM, % (No. of Patients)</th>
<th>Syncope, % (No. of Patients)</th>
<th>SCD, % (No. of Patients)</th>
<th>LVH, % (No. of Patients)</th>
<th>HF, % (No. of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features</td>
<td>30.1*</td>
<td>99%</td>
<td>68 (129)</td>
<td>38 (55)</td>
<td>44 (56)</td>
<td>43 (82)</td>
<td>22 (31)</td>
<td>8.7 (15) [33.4]</td>
<td>53 (98)</td>
<td>12.5 (18)</td>
</tr>
<tr>
<td>Patients with available data</td>
<td>143</td>
<td>183</td>
<td>189</td>
<td>144</td>
<td>127</td>
<td>190</td>
<td>140</td>
<td>171</td>
<td>185</td>
<td>144</td>
</tr>
</tbody>
</table>

AVB indicates atrioventricular block (advanced degree); ECI, exercise chronotropic incompetence; HF, heart failure; LVH, left ventricular hypertrophy; PM, pacemaker (implantation); SCD, sudden cardiac death; SND, sinus node dysfunction; and SVT, supraventricular tachyarrhythmia.

*Median cannot be calculated because of missing data.
fibrillation during rapid right atrial pacing at EPS. After a mean follow-up of 31 months, there were no ICD discharges. Two patients were implanted in other studies, 1 for primary prevention and 1 after cardiac arrest. To date, no data have been published about their long-term ICD follow-up.

Genotype–Phenotype Association of the 2 Most Frequent Mutations

A trend toward certain phenotypic features being associated with specific mutations was noted. C.905G>A (Arg302Gln) and c.1463A>T (Asn488Ile) were the most common mutations with 110 and 40 cases (57% and 21%, respectively). Considering those patients with available data for each selected clinical feature, we estimated a genotype–phenotype association between these 2 mutations. (Table 2; Figure 3).

C.905G>A patients seem to have a trend toward a greater prevalence of pre-excitation (79% versus 58%, P = 0.008) compared with c.1463A>T mutation. Moreover, among C.905G>A carriers, there was a higher frequency of syncope (35% versus 12%, P = 0.010) and rate of pacemaker implantation when compared with c.1463A>T patients (55% versus 30%, P = 0.006). Conversely, LVH seems to have a higher frequency in c.1463A>T group than in C.905G>A subjects (70% versus 42%, P = 0.004).

There was not a statistically significant difference of SCD frequency between the 2 groups (9.7% C.905G>A versus 2.5% c.1463A>T, P = nonsignificant).

Interesting Outliers Mutations and Extracardiac Involvement

To date, the most severe mutation, c.1592G>A (Arg531Gln), was reported by Burwinkel et al. It is characterized by an extreme early onset and a severe clinical course leading to death for cardiogenic shock within the first 3 months of life.

Although PRKAG2 mutations mainly affect the heart, some studies reported features of systemic involvement. In the subset of c.1463A>T (Asn488Ile) mutated subjects, a 15% frequency of skeletal myopathy was observed. Skeletal myopathy with elevated creatine phosphokinase was also seen.

Table 2. Clinical Features Comparison Between Recurrent Arg302Gln and Asn488Ile Mutations

<table>
<thead>
<tr>
<th>PRKAG2 Mutations</th>
<th>Mean Age at Diagnosis, y</th>
<th>Short PR, % (No. of Patients)</th>
<th>SVT, % (No. of Patients)</th>
<th>SND, AVB, % (No. of Patients)</th>
<th>PM, % (No. of Patients)</th>
<th>Syncope, % (No. of Patients)</th>
<th>SCD, % (No. of Patients)</th>
<th>LVH, % (No. of Patients)</th>
<th>HF, % (No. of Patients)</th>
<th>Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg302Gln</td>
<td>36*</td>
<td>79 (87)</td>
<td>44 (30)†</td>
<td>47 (23)‡</td>
<td>55 (61)</td>
<td>35 (22)§</td>
<td>9.7 (10)‖</td>
<td>42 (44)#</td>
<td>3.6 (4)#</td>
<td>110</td>
</tr>
<tr>
<td>Asn488Ile</td>
<td>19</td>
<td>58 (23)</td>
<td>30 (12)</td>
<td>35 (16)</td>
<td>30 (12)</td>
<td>12 (5)</td>
<td>2.5 (1)</td>
<td>70 (28)</td>
<td>NA</td>
<td>40</td>
</tr>
<tr>
<td>P</td>
<td>NA</td>
<td>0.008</td>
<td>NS</td>
<td>NS</td>
<td>0.006</td>
<td>0.010</td>
<td>NS</td>
<td>0.001</td>
<td>NA</td>
<td>‖</td>
</tr>
</tbody>
</table>

Statistical analysis was obtained using Fisher exact test for the sudden cardiac death variable; for the other variables, χ² test was used. AVB indicates atrioventricular block (advanced degree); ECI, exercise chronotropic incompetence; HF, heart failure; LVH, left ventricular hypertrophy; NA, data not available; NS, not statistically significant; PM, pacemaker (implantation); SCD, sudden cardiac death; SND, sinus node dysfunction; and SVT, supraventricular tachyarrhythmia.

Statistic based on *70, †67, ‡49, §62, ‖103, and #105 patients with available data for the selected feature.
present in Ser548Pro patients. C.1591C>G (p. Arg531Gly) and c. 1453A>G (Lys485Glu) mutations were related to the development of arterial hypertension in adolescence (50% of patients). Some studies suggest that systemic hypertension observed in these patients could represent extracardiac involvement as well.

Of note, no extracardiac involvement was reported among patients with the most frequent mutation (Arg302Gln).

**Discussion**

**Differential Diagnosis**

PS should be suspected in the setting of autosomal dominant HCM coexisting with Wolff–Parkinson–White syndrome, with negative test for sarcomeric mutation. In this scenario, the lacking evolution to conduction system dysfunctions can help to exclude the diagnosis of PS. However, conduction system disease is not always present in PS, and moreover it could occur later in the clinical course.17,21

Although the clinical manifestations and the inheritance pattern may help with the diagnostic process, the diagnosis of PS can be confirmed only with genetic testing by an identification of a PRKAG2 mutation.

Genetic syndromes that could mimic PS are listed in Table 3; the more significant among them are Danon’s disease and Anderson-Fabry disease (AFD). The first is characterized by massive LVH, HF, ventricular pre-excitation, and an arrhythmic burden unmanageable even with defibrillator therapy, with a mean survival rate <25 years of age. AFD is characterized by concentric LVH, a short PR interval, and conduction system dysfunctions. Recognition of AFD is relevant as enzyme replacement therapy is related to a better outcome regarding stability and regression of symptoms.

Both Danon’s disease and AFD are inherited in an X-linked pattern and they have wide extracardiac features (respectively intellectual disability and skeletal myopathy in Danon’s disease, and acroparesthesias, renal failure, cryptogenic stroke, angiokeratomas, corneal and lenticular opacities, and gastrointestinal symptoms in AFD).

**PRKAG2 Management**

To date, there are no specific guidelines for PS. Clinicians should therefore refer to the recent 2014 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of HCM, keeping in mind the nonsarcomeric nature of PS. We propose a red flags–based approach for diagnosis (Table 4) and management (Table 5) according to PS clinical manifestations.

PS onset of symptoms frequently occurs within the first 3 decades of age, and it is often characterized by tachyarrhythmias and bradyarrhythmias. Much less frequently, HF symptoms or SCD can be the first manifestations of the disease. Prolonged dynamic ECG monitoring and exercise stress testing could be useful tools in those patients with syncope, palpitations, or with a familial history of SCD. Ultrasound imaging
and cardiovascular magnetic resonance are the gold-standard diagnostic techniques for the identification and characterization of cardiac hypertrophy. Standard antiarrhythmic therapy should be initiated in those patients with supraventricular or ventricular tachyarrhythmias. If clinically appropriate, EPS can be useful for diagnosis and treatment of accessory pathways.

Given the numerous life threatening consequences of PRKAG2 syndrome, a prompt management of its complications is mandatory. Pacemaker implantation is recommended in patients with cardiac syncpe or signs of chronotropic incompetence. Heart transplant is indicated for end-stage HF patients.

The limited literature available on PRKAG2 syndrome suggests that sudden death occurs in about 10% of patients and can be because of an abrupt advanced heart block or ventricular fibrillation (mainly deriving from SVT degeneration).\textsuperscript{7,19,32,37,41} However, the various PRKAG2 pathological processes (glycolgen accumulation, massive hypertrophy, or cellular apoptosis) potentially leading to ventricular arrhythmias do not exclude the primitive genesis of ventricular fibrillation. Because of the small number of events and the lacking of follow-up data published, risk stratification for ventricular arrhythmias remains challenging. The identification of those patients who could benefit from ICD therapy for primary prevention is still not clear. Individual risk factors should be evaluated: familial history of SCD, syncope of suspected arrhythmic origin, magnitude of hypertrophy, nonsustained ventricular tachycardia, or particular cardiovascular magnetic resonance patterns.\textsuperscript{41} EPS can also have a potential role of risk stratification, considering selected patterns of pre-excitation with SVT and AV conduction defects. According to these features, an individual and tailored strategy should be applied case by case.

Finally, a focused familial screening and, where appropriate, genetic testing, represent a useful tool for diagnosis and it can often have implication in genetic counseling as well.

### Limitations

The main limits of this review are the small number of patients involved and the case report–fashion of the studies considered. Some papers were missing of clearly codified data about PS clinical features or outcomes: for this reason certain characteristics or outcomes could not be described (for instance sex ratio). Other features were delineated, but missing data were accounted for by decreasing the denominator at descriptive statistics.

Moreover, because of the lack of long follow-up periods, important outcomes, such as SCD, medium and long-term death, and even the rate of pacemaker implantation, could be more frequent.

### Conclusions

PRKAG2 syndrome is a rare, early-onset autosomal dominant disease characterized by ventricular pre-excitation, SVT,

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**Table 4. Red Flags for PRKAG2 Syndrome**

<table>
<thead>
<tr>
<th>Clinical Examinations</th>
<th>Red Flags</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Positive familial history for cardiac hypertrophy and sudden death (autosomal dominant inheritance)</td>
</tr>
<tr>
<td>Age</td>
<td>Young (I–IV decade)</td>
</tr>
<tr>
<td>ECG</td>
<td>Bradycardia, short PR interval,,* delta wave,,* bundle branch block, and very high voltages</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Concentric left ventricular hypertrophy</td>
</tr>
<tr>
<td>Dynamic ECG monitoring</td>
<td>Supraventricular arrhythmias and signs of chronotropic incompetence*</td>
</tr>
<tr>
<td>Electrophysiological study</td>
<td>Evidence of accessory pathways</td>
</tr>
<tr>
<td>Other</td>
<td>Myalgia, epilepsy, and early-onset hypertension</td>
</tr>
</tbody>
</table>

*The more specific features.

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**Table 5. Suggested Treatment Guidelines for PRKAG2 Syndrome**

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Diagnosis</th>
<th>Proposed Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG at least every 1 y</td>
<td></td>
<td>Standard heart failure treatment and specifically:</td>
</tr>
<tr>
<td>Echocardiography at baseline and every 1–2 y (depending on morphological changes or clinical progression)</td>
<td></td>
<td>Appropriate fluid management avoiding dehydration especially when hypertrophy is more severe</td>
</tr>
<tr>
<td>Exercise stress testing with O\textsubscript{2} consumption for effort inducible arrhythmias and for prognostic assessment</td>
<td></td>
<td>Prompt consideration for cardiac transplantation in those patients with clinical progression or end-stage heart failure</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Serum BNP at baseline and for clinical progression</td>
<td>Standard antiarrhythmic treatment</td>
</tr>
<tr>
<td>Holter ECG monitoring/event monitor to stratify the risk for sudden cardiac death or if symptomatic patients</td>
<td></td>
<td>Early consideration for PM implantation</td>
</tr>
<tr>
<td>Consider individual risk factors for SCD and specific EPS patterns</td>
<td></td>
<td>ICD implantation</td>
</tr>
<tr>
<td>Electrophysiological assessment</td>
<td></td>
<td>AV accessory pathway ablation</td>
</tr>
<tr>
<td>Dynamic arterial pressure monitoring for patients with hypertension</td>
<td></td>
<td>Hypertension treatment avoiding dehydrating drugs if systolic and diastolic functions preserved</td>
</tr>
<tr>
<td>Skeletal myopathy</td>
<td>Specialist neuromuscular evaluation</td>
<td>Physical therapy and rehabilitation</td>
</tr>
<tr>
<td>Muscle biopsy may be performed for diagnostic workup</td>
<td></td>
<td>Genetic and reproductive risk counseling</td>
</tr>
<tr>
<td>Genetic</td>
<td>Accurate familial history and PRKAG2 genetic testing for probands and for at-risk relatives</td>
<td></td>
</tr>
</tbody>
</table>

This table represents a simple guide and it is not to be considered complete or definitive. Suggested follow-up frequencies should be adapted on the basis of patient symptoms and clinical progression. AV indicates atrioventricular; BNP, brain natriuretic peptide; EPS, electrophysiological study; ICD, implantable cardioverter defibrillator; PM, pacemaker; PRKAG2, \( \gamma \) regulatory subunit of AMP-activated protein kinase; and SCD, sudden cardiac death.
and cardiac hypertrophy, frequently followed by paradoxical severe rhythm conduction disturbances, HF and SCD.

An accurate differential diagnosis behind a hypertrophic phenotype of cardiomyopathy is important because of the different timing of onset, clinical course and, sometimes, treatment strategies of sarcomeric and nonsarcomeric forms of the disease. A red flags approach could be useful to arise the suspicion of nonsarcomeric forms of HCM.

Familial screening and, where appropriate, genetic testing represent a useful tool for diagnosis and counseling. The main therapeutic goal is represented by careful risk stratification for SCD.

Acknowledgments

CRTrieste and Generali Assicurazioni Foundation to Dr Sinagra are gratefully acknowledged.

Sources of Funding

This study was supported by the National Institutes of Health grants 1R01HL116906, UL1 RR025780, and R01 HL69071 to Dr Mestroni; and by a Trans-Atlantic Network of Excellence CRTrieste and Generali Assicurazioni Foundations to Dr Sinagra.

Disclosures

None.

References


Key Words: arrivoventricular block ■ cardiomyopathy, hypertrophic ■ death, sudden, cardiac ■ defibrillators, implantable ■ Wolff-Parkinson-White syndrome
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_Circ Arrhythm Electrophysiol_. 2016;9:
doi: 10.1161/CIRCEP.115.003121

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/9/1/e003121

Data Supplement (unedited) at:
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**Supplemental Material**

**Supplementary Table 1.** Overview of PRKAG2 syndrome mutations and clinical features.

AP: accessory pathway/s; AVB: atrioventricular block (advanced degree); Abs.: feature absent; CPK: creatine phospho-kinase; Dec.: decade of life; ECI: exercise chronotropic incompetence; EPS: electrophysiological study; HF: heart failure; LAH: left anterior hemiblock; LBBB: left bundle branch block; LVH: left ventricular hypertrophy; MLVWT: maximal left ventricular wall thickness (mm); NA: data not available; PM: pacemaker (implantation); Pres.: feature present; RBBB: right bundle branch block; SCD: sudden cardiac death; SND: sinus node dysfunction; SVT: supraventricular tachyarrhythmia;

* The location of c.DNA mutations and aminoacid substitutions are referred to the isoform PRKAG2-a (NCBI Ref Seq: NM_016203.3; NP_057287).
† ECG data available only for 24 patients.
‡ Genetic test not performed. Patient excluded from statistical analysis.
§ Condition present/intervention performed, number of patients not reported.
|| condition absent but very young age of patients/early death.
<table>
<thead>
<tr>
<th>DNA change</th>
<th>Predicted effect</th>
<th>Mean age at diagnosis (years)</th>
<th>Penetrance %</th>
<th>Short P-R % (n/tot.)</th>
<th>SVT % (n/tot.)</th>
<th>SND, AVB, ECI % (n/tot.)</th>
<th>PM % (n/tot.)</th>
<th>Syncopenic % (n/tot.)</th>
<th>SCD % (n/tot.)</th>
<th>LVH % (n/tot.)</th>
<th>Mean MLVWT (mm)</th>
<th>HF % (n/tot.)</th>
<th>Other</th>
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<td>p.Arg302Gln</td>
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<td>65 (28/43)</td>
<td>35 (11/31)</td>
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<td>100</td>
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<td>50 (10/20)</td>
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<td>11 (1/9) +2 †</td>
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<td>32.8±7.9</td>
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