**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. In 1991, PRKAG2 syndrome was mapped to the locus 7q36, and in 2001, Gollob et al identified the responsible gene.

The syndrome is caused by mutations in the gene encoding for the γ regulatory subunit (PRKAG2).

AMPK is an enzyme deeply involved in cellular ATP metabolic regulation. 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.

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.

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%). Arad et al found genetically confirmed PS in 7 of 24 patients (29%) among a subgroup with both left ventricular hypertrophy (LHV) 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. Only Blair et al documented an insertion mutation (Exon 5:Ins4Leu). The most commonly reported mutation were C.905G>A
(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 (α) and 2 regulatory subunits (β and γ). γ2 regulatory subunit of AMPK (PRKAG2) binds AMP, enhancing the α-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 uptake, fatty acid 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 PS26,27 and a decreased activity during the advanced stage of PS26.27 A recent study demonstrated an impaired myocardial glycogen uptake in adult patients with PS.29

In humans, AMPK dysfunction alters the myocyte glidic 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 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 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 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 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 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 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 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 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 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 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 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.
SCD in PS can occur both in the presence and 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, early 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, 7 ICDs were implanted for primary prevention in 2 patients (age: 20 and 22 years) with massive LVH, 1 of whom had ventricular fibrillation.
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 prevention19 and 1 after cardiac arrest.32 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, \( P = \text{nonsignificant} \)).5,7,11,17,19,21

Interesting Outliers Mutations and Extracardiac Involvement

To date, the most severe mutation, c.1592G>A (Arg531Gln), was reported by Burwinkel et al.13 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.7 Skeletal myopathy with elevated creatine phosphokinase was also

<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 (NS)</td>
<td>NS</td>
<td>0.006</td>
<td>0.010</td>
<td>NS</td>
<td>0.001</td>
<td>NA</td>
<td>40</td>
<td>...</td>
</tr>
</tbody>
</table>

Statistical analysis was obtained using Fisher exact test for the sudden cardiac death variable; for the other variables, \( \chi^2 \) 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, †167, §49, ¶62, ||103, and #105 patients with available data for the selected feature.
present in Ser548Pro patients. C1591C>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,43 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

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**Figure 3.** Bar chart comparing the main clinical features between the recurrent Arg302Gln and Asn488Ile mutations. Square brackets: patients with clinical feature/total number of patients with available data. Statistical analysis was obtained using Fisher exact test for the sudden cardiac death (SCD) variable; for the other variables, $\chi^2$ test was used. LVH indicates left ventricular hypertrophy; ns, not statistically significant; and PM, pacemaker (implantation).

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**Table 3.** Cardiomyopathies Associated With Wolff–Parkinson–White Syndrome or Short PR

<table>
<thead>
<tr>
<th>Syndrome/Disease</th>
<th>Type of CMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRKAG2 syndrome</td>
<td>HCM</td>
</tr>
<tr>
<td>Danon disease</td>
<td>HCM, DCM</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>HCM</td>
</tr>
<tr>
<td>Pompe disease</td>
<td>HCM</td>
</tr>
<tr>
<td>Duchenne/Becker muscular dystrophy</td>
<td>DCM</td>
</tr>
<tr>
<td>MELAS syndrome</td>
<td>HCM, DCM</td>
</tr>
<tr>
<td>Kears-Sayre syndrome</td>
<td>DCM</td>
</tr>
<tr>
<td>Leigh syndrome</td>
<td>HCM, DCM</td>
</tr>
<tr>
<td>MERRF syndrome</td>
<td>HCM, DCM</td>
</tr>
<tr>
<td>Oncocytic CMP</td>
<td>HCM</td>
</tr>
</tbody>
</table>

CMP indicates cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; and MERRF, myoclonic epilepsy with ragged red fibers.
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 appropriated, 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 syncope 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).7,19,32,37,41 However, the various PRKAG2 pathological processes (glycogen 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.43 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,
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

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Disclosures

None.

References


Key Words: atrioventricular block ■ cardiomyopathy, hypertrophic ■ death, sudden, cardiac ■ defibrillators, implantable ■ Wolff-Parkinson-White syndrome.
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**SUPPLEMENTAL MATERIAL**

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

<table>
<thead>
<tr>
<th>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;</th>
</tr>
</thead>
</table>

* 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>Penetration %</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Short P-R % (n/tot.)</td>
<td>SVT % (n/tot.)</td>
<td>SND, AVB, ECI % (n/tot.)</td>
</tr>
<tr>
<td>c.905G&gt;A</td>
<td>p.Arg302Gln</td>
<td>39</td>
<td>100</td>
<td>65 (28/43)</td>
</tr>
<tr>
<td>c.905G&gt;A</td>
<td>p.Arg302Gln</td>
<td>31</td>
<td>100</td>
<td>50 (10/20)</td>
</tr>
<tr>
<td>c.905G&gt;A</td>
<td>p.Arg302Gln</td>
<td>25</td>
<td>100</td>
<td>60 (3/5)</td>
</tr>
<tr>
<td>c.905G&gt;A</td>
<td>p.Arg302Gln</td>
<td>44</td>
<td>100</td>
<td>25 (1/4)</td>
</tr>
<tr>
<td>c.905G&gt;A</td>
<td>p.Arg302Gln</td>
<td>NA</td>
<td>100</td>
<td>60 (3/5)</td>
</tr>
<tr>
<td>c.905G&gt;A</td>
<td>p.Arg302Gln</td>
<td>17</td>
<td>100</td>
<td>25 (1/4)</td>
</tr>
<tr>
<td>c.1463A&gt;T</td>
<td>p.Asn488Ile</td>
<td>19</td>
<td>100</td>
<td>58 (23/40)</td>
</tr>
<tr>
<td>c.1516G&gt;A</td>
<td>p.Glu506lys</td>
<td>31</td>
<td>100</td>
<td>0 (0/8)</td>
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<tr>
<td>c.1050_1051</td>
<td>p.Arg350_Glu +</td>
<td>351insLeu</td>
<td>56</td>
<td>100</td>
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<tr>
<td>c.1591C&gt;G</td>
<td>p.Arg531Gly</td>
<td>31</td>
<td>100</td>
<td>75 (3/4)</td>
</tr>
<tr>
<td>c.1148A&gt;G</td>
<td>p.His383Arg</td>
<td>14</td>
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<td>66 (2/3)</td>
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<tr>
<td>c.1592G&gt;A</td>
<td>p.Arg531Gln</td>
<td>1</td>
<td>100</td>
<td>100 (3/3)</td>
</tr>
<tr>
<td>c.1459T&gt;C</td>
<td>p.Tyr487His</td>
<td>NA</td>
<td>100</td>
<td>33 (1/3) ‡</td>
</tr>
<tr>
<td>c.1589A&gt;G</td>
<td>p.His530Arg</td>
<td>1 dec.</td>
<td>100</td>
<td>33 (1/3) ‡</td>
</tr>
<tr>
<td>c.1199C&gt;A</td>
<td>p.Thr400Asn</td>
<td>42</td>
<td>100</td>
<td>33 (1/3) ‡</td>
</tr>
<tr>
<td>c.1732T&gt;C</td>
<td>p.Ser548Pro</td>
<td>38</td>
<td>100</td>
<td>33 (1/3) ‡</td>
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<tr>
<td>c.1453A&gt;G</td>
<td>p.Lys485Glu</td>
<td>19</td>
<td>100</td>
<td>33 (1/3) ‡</td>
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