PRKAG2 non-sarcomeric proteins Familial Hypertrophic Cardiomyopathy Syndrome – An Update

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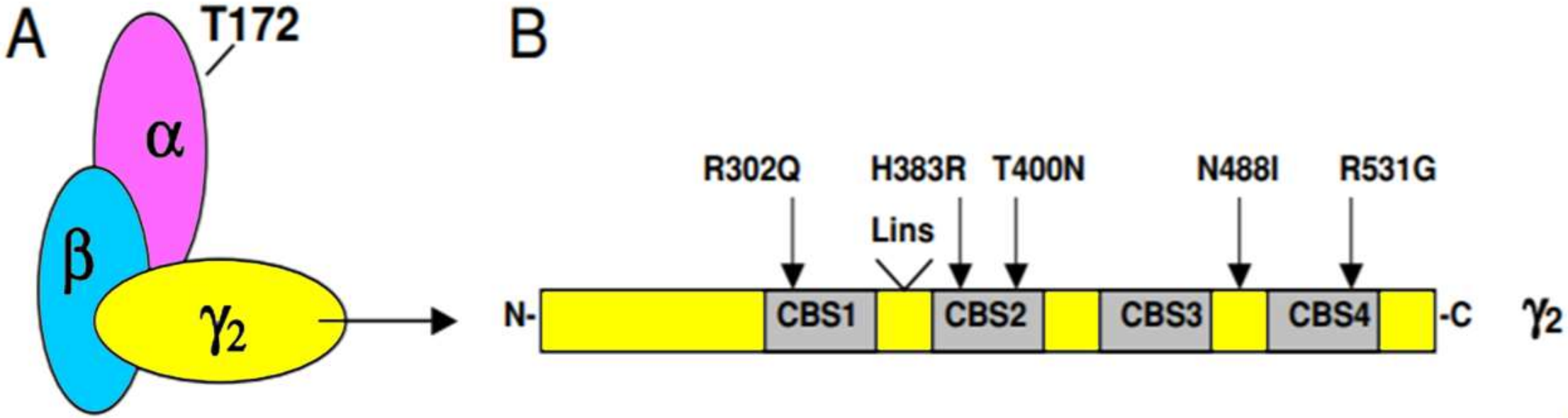
Introduction

PRKAG2 Cardiac (PC) syndrome or PRKAG2 syndrome is a rare autosomal dominant cardiac syndrome classified as a glycogen storage disease combining cardiac hypertrophy, Wolff–Parkinson–White syndrome, (WPWS) and progressive conduction system disease with conduction block It is frequently accompanied by chronotropic incompetence and advanced heart blocks, leading to premature pacemaker implantation after the second decade (**van der Steld 2017**). Additionally, ventricular dilatation and even congestive heart failure (**Siu 1999**). The association of these clinical features had previously been recognized by several studies since the second half of the twentieth century (**Lev1966; Gulotta1977; Khair 1985**). PC is consequences of mutations in the γ2 subunit of AMP activated protein kinase (AMPK) (**Gollob 2001**). Skeletal muscle involvement with myalgias or muscle weakness may also occur in a minority of patients (**Murphy 2005**). AMPK is a cellular energy sensor, that is activated by exercise in muscle and increase in AMP: ATP ratio, stimulating fatty acid oxidation, glycolysis and glucose oxidation. This enzyme form a heterotrimeric complex comprising a catalytic subunit (α) and two regulatory subunits (β and γ). Three isoforms of the γ subunits are known (γ1, γ2 and γ3) with different tissue expression (**Cheung 2000**), and each contain four repeats of a structural module known as a cystathionine β-synthase (CBS) domains. The function of γsubunits is uncertain although they could play an important role in the binding of adenosine moieties of AMP and ATP. Pathological examinations of hearts revealed vacuoles containing polysaccharide in patients with PRKAγ2 mutations (**Arad 2002**), and an abundant glycogen accumulation is also observed in the myocardium of transgenic mice overexpressing mutant PRKAγ2, with a disruption of the AV connections providing a possible explanation for the electrophysiological abnormalities. Unexpectedly, histopathological aspect of skeletal muscle reported in two patients who complained of myalgia exhibited mitochondrial proliferation with only minimal glycogen excess (**Murphy 2005**). Nagata et al reported the observation of a patient with a new mutation in PRKAγ2 gene presenting a skeletal muscle involvement leading to the demonstration of a glycogen accumulation in muscle, cardiomyopathy with an important basal diastolic septal thickness of 18 mm, a left ventricular(LV) diastolic diameter of 42 mm, and a normal LV ejection fraction(LVEF) (60%). At clinical examination, the limbs muscle bulk and strength were normal. Upper and lower limbs muscle CT scan was normal. A forearm exercise test was performed twice with an isometric exercise at 70% of the maximal voluntary contraction during 30 s in non-ischemic conditions. The grip strength was within the normal ranges considering the patient age, gender, weight and forearm circumference. Despite a sufficient amount of physical work (80% of predicted mechanical values), a moderate increase of lactate levels was observed after exercise after exercise for the first and second test, respectively with a relative steadiness of ammonia concentration (**Nagata 2010**). PS is ocasioned to a unique defect of the cardiac cell metabolism and has a distinctive histopathology with excess intracellular glycogen, and prognosis different from sarcomeric hypertrophic cardiomyopathy (HCM). In 1995 PS was mapped to the locus 7q 36 (**MacRae1991**), and in 2001 Gollob et al. (**Gollow 2001a**) identified the responsible gene encoding for the 5' Adenosine Monophosphate-Activated Protein Kinase (AMPK), specifically for its γ_2 regulatory subunit (PRKAδ2). AMPK is an enzyme deeply involved in cellular ATP metabolic regulation (**Zaha 2012**).

Adenosine Monophosphate-Activated Protein Kinase (AMPK) structure

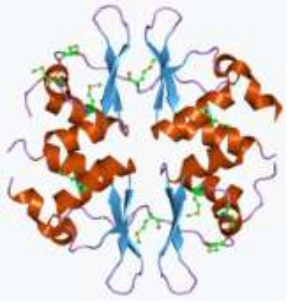


A: AMPK is a heterotrimeric enzyme consisting of α catalytic α-subunit that can be activated by upstream kinases such as LKB1 via phosphorylation of the T172 residue. The β- and γ 2-subunits are regulatory and modulate enzyme activity via glycogen (β) and AMP (γ). **AMPK kinase and *PRKAG2* subunit** AMPK is a highly conserved serine/threonine protein kinase responsible for cellular energetic homeostasis control. Stimulated by high adenosine monophosphate (AMP) concentration and AMPK-kinase activity, the enzyme counterbalances ATP depletion (**Gollob 2001; Zaha 2012; Hardie 1997**). It is comprised of a catalytic subunit (α) and two regulatory subunits (β and γ). γ -2 regulatory subunit of Adenosine Monophosphate–Activated Protein Kinase (PRKAG2) binds AMP, enhancing the α subunit activation (**Zaha 2012**). AMPK is highly expressed in cardiac tissue, skeletal muscle, brain, placenta, liver, kidneys, and pancreas (**Cheung 2002**). In cardiomyocytes the enzyme regulates the glucose (**Wojtaszewski 2002**) and fatty acids (**Habets2007**) 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 (**Arad 2003; Ahmad2005**).

B: Relative positions of some of the human PRKAG2 mutations found in the γ 2-subunit. CBS = Cystathionine β Synthase repeat sequences that form the AMP binding region.

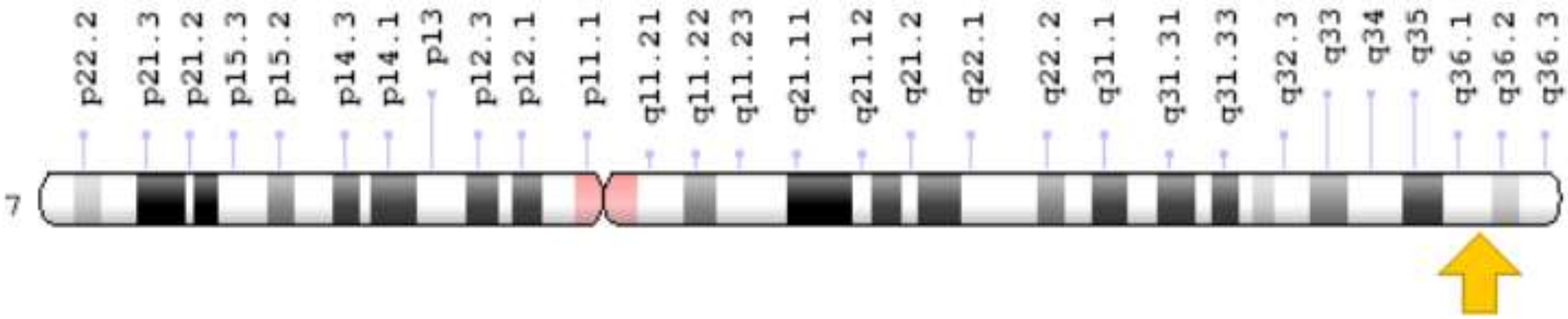
Adenosine Monophosphate-Activated Protein Kinase (AMPK) is a heterotrimeric protein composed of:
A catalytic α-subunit; 2) A noncatalytic β-subunit, and 3) A noncatalytic regulatory γ-subunit. Various forms of each of these subunits exist, encoded by different genes. AMPK is an important energy-sensing enzyme that monitors cellular energy status and functions by inactivating key enzymes involved in regulating de novo biosynthesis of fatty acid and cholesterol. This gene is a member of the AMPK γ-subunit family and encodes a protein with four cystathionine beta synthase, (**CBS**) **domains**. Mutations in this gene have been associated with ventricular pre-excitation (WPW syndrome), progressive conduction system disease and cardiac hypertrophy. Alternate transcriptional splice variants, encoding different isoforms, have been characterized.

CBS domains



Chromosomal locations

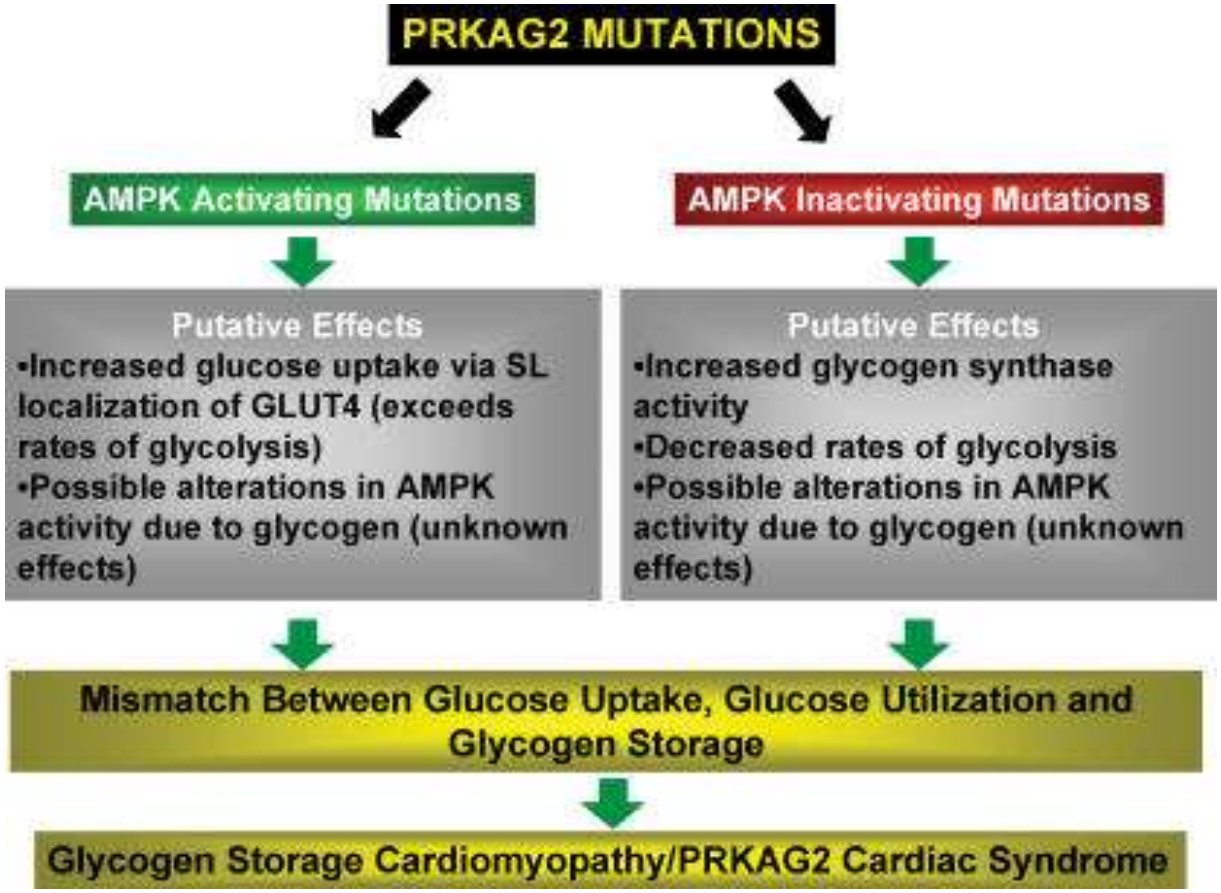
Cytogenetic Location: 7q36.1, which is the long (q) arm of chromosome 7 at position 36.1 (**MacRae 1995**).
Molecular Location: base pairs 151,556,114 to 151,877,231 on chromosome 7 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Others name of *PRKAG2* gene (**Daniel 2002**) AAKG, AAKG2, AAKG2_HUMAN, AMP-activated protein kinase γ2 subunit, AMPK γ2, CMH6, H91620p, protein kinase, AMP-activated, γ 2 non-catalytic subunit and WPWS

Normal function and genetic mutation

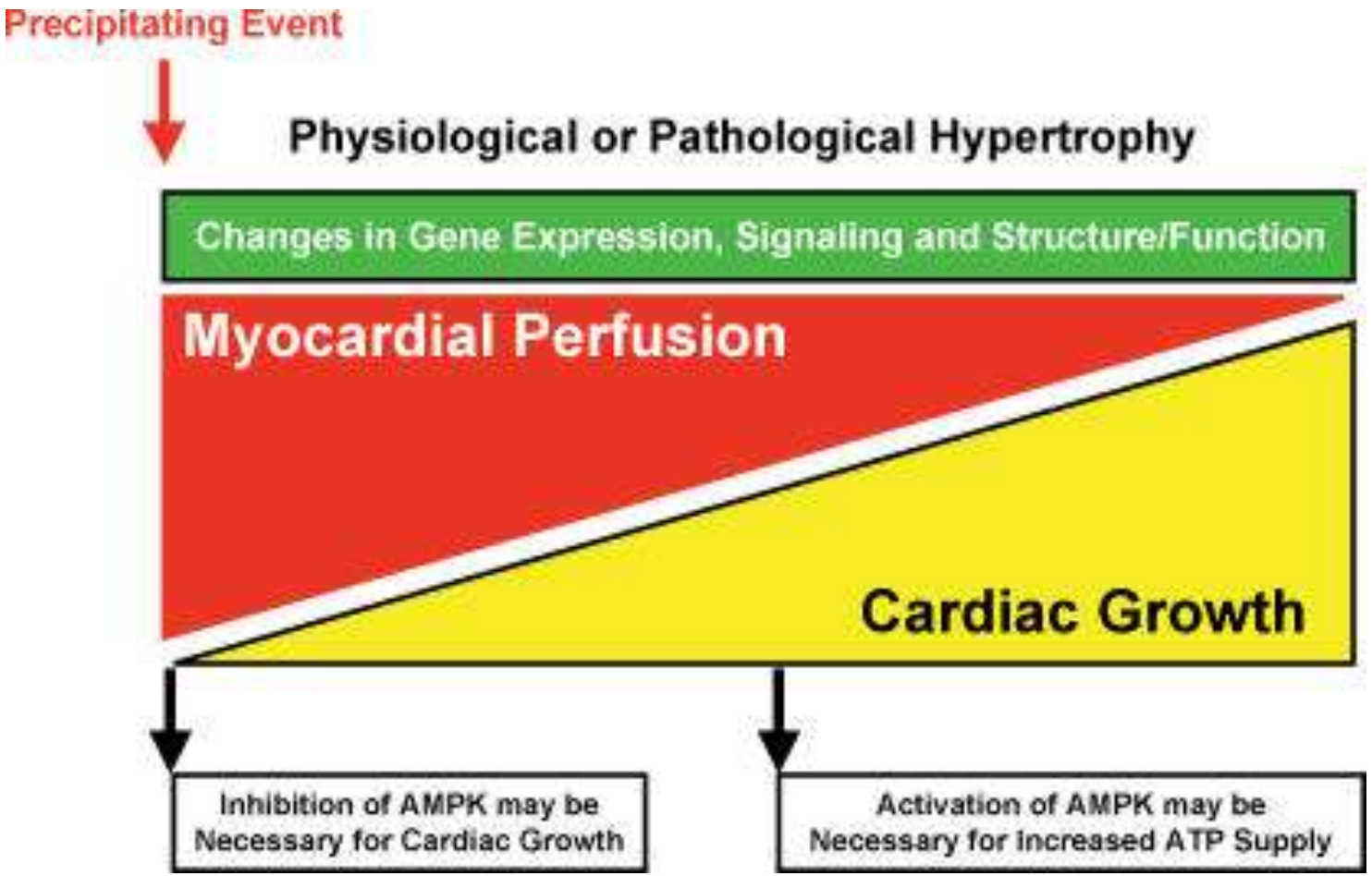
The *PRKAG2* gene provides instructions for making one part (the γ-2 subunit) of a larger enzyme called AMP-activated protein kinase (AMPK). This enzyme helps sense and respond to energy demands within cells. It is active in many different tissues, including cardiac muscle and muscles and skeletal muscles. AMP-activated protein kinase is likely involved in the development of the heart before birth, although its role in this process is unknown. AMP-activated protein kinase regulates chemical pathways involving the cell's main energy source, a adenosine triphosphate (ATP). The breakdown of ATP releases energy to drive many types of chemical reactions. AMP-activated protein kinase is activated during times of cellular stress (such as low oxygen levels or muscle exercise), when ATP is broken down rapidly to produce energy. If ATP levels become too low, the enzyme restores the balance of energy by limiting chemical reactions that require ATP and stimulating pathways that generate ATP. Studies suggest that AMP-activated protein kinase may play a role in controlling the activity of other genes, although many of these genes have not been identified. The enzyme may also regulate the activity of certain ion channels in the heart. These channels, which transport positively charged atoms (ions) into and out of heart muscle cells, play critical roles in maintaining the heart's normal rhythm. *PRKAG2* genetic mutations are rare and have been recognized mainly in the context of patients with non-sarcomeric familial HCM associated with WPWS (**Murphy2005**). At least seven mutations that cause WPWS have been identified in the *PRKAG2* gene. Some people with these mutations also have features of HCM. Researchers are uncertain how *PRKAG2* mutations lead to the development of these heart conditions. They suggests that these mutations alter the activity of AMP-activated protein kinase in the heart, disrupting the enzyme's ability to respond to changes in cellular energy demands. It is unclear, however, whether the genetic changes overactivate the enzyme or reduce its activity. Studies indicate that changes in AMP-activated protein kinase activity allow a complex sugar called glycogen to build up abnormally within cardiac muscle cells. The accumulation of this substance enlarges these cells, which may lead to HCM. Researchers continue to investigate whether an abnormal buildup of glycogen in the heart is also responsible for the problems with electrical signaling that are characteristic of WPWS. Altered AMP-activated protein kinase activity is related to changes in the regulation of certain ion channels in the heart. These changes may help explain the increased risk of arrhythmias in people with WPWS. 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 (**Murphy2005; Blair 2001; Gollow 2001b**). Mutation data are available Human Gene Mutation Database (www.hgmd.org). PRKAG2 mutations inheritance pattern is autosomal dominant. Almost all studies report missense mutations (**Gollow 2001a; Murphy2005; Zhang 2011**). Blair et al. (**Blair 2001**) documented an insertion mutation (Exon 5:InsLeu) (The most commonly reported mutation were C.905G>A (Arg302Gln) and c.1463A>T (Asn488Ile), with 110 and 40 cases (respectively 57% and 21%).



The PC syndrome. Mutations in the γ_2 subunit of AMPK (the *PRKAG2* gene) appear to cause both activating and inhibiting forms of cardiac AMPK. Various changes in the control of glucose utilization and storage ensue that result in a glycogen storage cardiomyopathy that is associated with the development of Wolff–Parkinson–White Syndrome and cardiac hypertrophy.

Epidemiology The prevalence of PS is currently unknown. One study identified PS in 1 of 100 subjects affected by HCM with premature sinoatrial or atrioventricular (AV) conduction disease (1%).

Arad et al. found genetically confirmed PS in 7 of 24 patients (29%) among a subgroup with both LVH and WPWS (**Arad 2005**). 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.



The involvement of AMPK in the development of cardiac hypertrophy Following the precipitating event, a number of mechanisms (including reduced myocardial perfusion) can promote cardiac myocyte growth. Hypertrophic growth can be adaptive (physiological hypertrophy) but can also become maladaptive (pathological hypertrophy). AMPK appears to have a dual role in the hypertrophic process, where in the early stages inhibition of AMPK may be necessary for cardiac growth (or if not directly involved in the pathway, pharmacological activation of AMPK in the early phase of cardiac hypertrophy may be able to prevent hypertrophic growth), while in the later stages AMPK activation may become essential for maintaining adequate ATP supply.

Decreased activity during he advanced phase (**Sidhu 2005**); a study demonstrated an impaired myocardial glycogen uptake in adult patients with PS **(Ha 2009).** In humans, AMPK dysfunction alters the myocyte glucidic uptake and metabolism causing the deposition of glycogen and amylopectin, as seen in glycogen storage cardiomyopathies **(Gollob 2003**). During cardiogenesis, the disruption of the annulus fibrosus by glycogen-filled myocytes interferes with the normal AV septation, and can lead the way to ventricular preexcitation and reciprocating arrhythmias (**Patel 2003; Sternick 2011**). A study on mice confirmed the correlation of glycogen deposits with ventricular preexcitation is PS; the study also demonstrated that cardiac hypertrophy, independently of glycogen storage, is caused by an enhanced insulin sensitivity and protein kinase B activation (**Kim 2014**). Another study on mice implicated that mutated AMPK could unbalance the phosphorylation state of cardiac troponin and myocardial contractility (**Oliveira 2012**), leading the way towards HF. AMPK dysfunction was found to be related with cellular autophagy and apoptosis in animal models (**Nagata 2010**).

A representation of postulated intracellular effects of *PRKAG2* related enzyme dysfunction. However, the precise biological mechanisms and their correlations with the clinical phenotypes of PS, especially in humans, are still unclear (**Gollob 2001;Blair 2001; Sidhu 2005**).

Cardiac hypertrophy mainly involves the LV and it is often progressive and associated with both diastolic and systolic HF. 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. Restrictive mitral inflow Doppler pattern, hemodynamically significant LVOT obstruction, and dilated progression were leading causes to cardiac transplant or SCD. In all studies ultrasound imaging was routinely used to assess cardiac hypertrophy; only a minority of patients underwent cardiovascular magnetic resonance (CMR) for tissue characterization) (**Fabris 2013**). To date, no CMR specific pattern was found to be associated with PS.

PRKAG2 syndrome clinical manifestations

Supraventricular tachyarrhythmias (SVT) were mainly represented by atrial fibrillation (AF) and flutter. SVT have been frequently the first clinical sign in PS patients; their complications were represented by stroke and by the development of rapid ventricular arrhythmias, in some cases leading to SCD (**Brembilla-Perrot 2006; Krikler 1980**). SVT were reported in 38% of PS patients, and a considerable proportion of them was associated with accessory pathways (APs) on electrophysiological studies (EPS). Pre-excitation was thus found to be associated with both common APs and decremental AV connections or fasciculoventricular pathways (**Gollob 2002; Charron2007**). Many authors reported different types of APs in Arg302Gln mutated patients, 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 due to 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. Overall, conduction system dysfunction had a prevalence of 44%, and PM implantation was performed in

Most cases of WPWS occur in people with no apparent family history of the condition. These cases are described as sporadic and are not inherited. Familial WPWS accounts for only a small percentage of all cases of this condition. The familial form of the disorder typically has an autosomal dominant pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the condition. In most cases, a person with familial WPWS has inherited the condition from an affected parent. Family studies, as well as molecular genetic investigations, indicate that WPWS, along with associated preexcitation disorders, may have a genetic component. It may be inherited as a familial trait, with or without associated congenital heart defects (CHDs) (**Ehtisham 2005**); 3.4% of those with WPWS have first-degree relatives with preexcitation. The familial form is usually inherited as a mendelian autosomal dominant trait. Although rare, mitochondrial inheritance has also been described. The WPWS may also be inherited with other cardiac and noncardiac disorders, such as familial atrial septal defects, familial hypokalemic periodic paralysis, and tuberous sclerosis. Clinicians have long recognized the association of WPWS with autosomal dominant familial HCM. However, only comparatively recently was a genetic substrate linking HCM to WPWS and skeletal myopathy described (**Gollob 2001**). Patients with mutations in the γ 2 subunit of adenosine monophosphate (AMP)-activated protein kinase (PRKAG2) develop cardiomyopathy characterized by ventricular hypertrophy, WPWS, AV block, and progressive degenerative conduction system disease. The mutation is believed to produce disruption of the annulus fibrosus by accumulation of glycogen within myocytes, which causes preexcitation. This is thought to be the case in Pompe disease, Danon disease, and other glycogen-storage diseases. Infantile Pompe disease or glycogen-storage disease type II is a fatal genetic muscle disorder that is caused by deficiency of acid α-glucosidase (GAA). These patients have a shortened PR interval, large left ventricular (LV) voltages, and an increased QT dispersion (QTd). Investigators appeared to have identified a novel locus in a family with WPW, MYH6 p.E1885K. All of the family members with WPW but none of the unaffected relatives demonstrated this variant. MYH6 variants have been associated with atrial septal defects, cardiomyopathies, and sick sinus syndrome (**Bowles 2015**).

Mutations in the lysosome-associated membrane protein 2 (LAMP2), which cause accumulation of cardiac glycogen, are thought to be the etiology of a significant number of HCMs in children, especially when skeletal myopathy, WPWS, or both are present.

Danon disease is an X-linked lysosomal cardioskeletal myopathy; males are more often and more severely affected than females. It is caused by mutations in the LAMP2 that produce proximal muscle weakness and mild atrophy, LVH, WPW syndrome, and mental retardation.

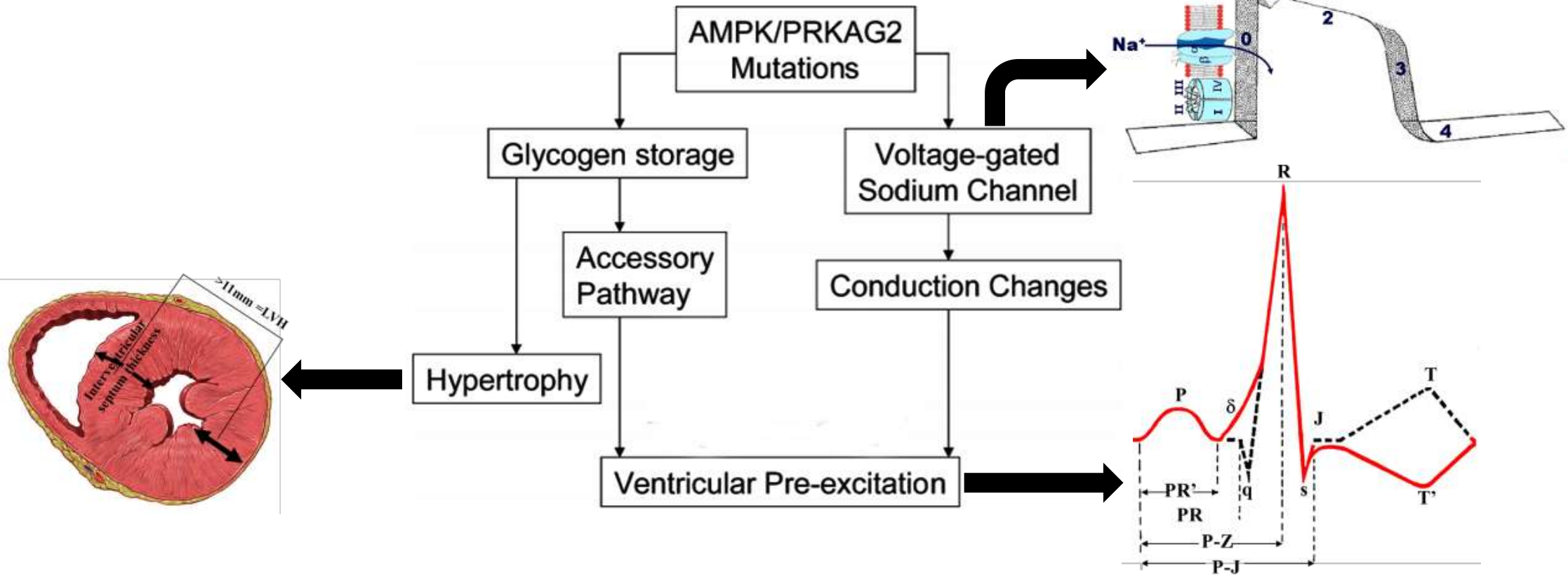
Patients with the Ebstein anomaly may develop WPWS. They frequently have multiple APs, mostly on the right, in the posterior part of the septum or the posterolateral wall of the right ventricle. The orthodromic reciprocating tachycardia in such patients often exhibits RBBB and a long ventriculoatrial (VA) interval.

Preexcitation can be surgically created, as in certain types of Bjork modifications of the Fontan procedure, if atrial tissue is flapped onto and sutured to ventricular tissue. Certain tumors of the AV ring, such as rhabdomyomas, may also cause preexcitation.

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.

Heart failure 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% to 63%).

Possible mechanisms for the pro-arrhythmogenic phenotype in patients with PRKAG2 mutations.

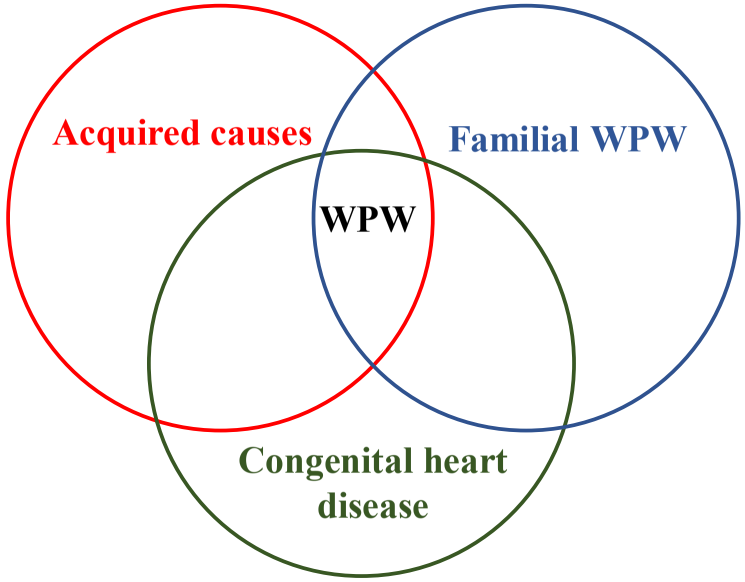


Altered regulation of AMPK activity may lead to excessive glycogen storage and thinning of the atrio-ventricular border region known as the annulus fibrosis, resulting in accelerated AV conduction and a shortened or absent PR interval. AMPK mediated changes in the properties of voltage-gated sodium channels may similarly cause pre-excitation by alterations in conduction velocity (see text for details).

Preexcitation syndrome possible etiologies

Adquired causes

- Myocardial infarction
- Surgically created Bjork modifications of the Fontan procedure, if atrial tissue is flapped onto and sutured to ventricular tissue.
- Certain tumors of the AV ring, such as rhabdomyomas.
- Thyreotoxicosis
- Cushing syndrome
- Metabolic dysregukation



Congenital heart disease

- Ebstein anomaly isolated or associated with atrial septal defect(**Hasan 2017**)
- Complex congenital heart surgery hypoplastic left heart syndrome (HLHS), with AV canal defect (pseudo-preexcitation) (**Carlson 2015**)

Familial preexcitation syndrome Genetic origin

- Familial atrial septal defects(**Gutiérrez Rojas 1999**)
- Familial hypokalemic periodic paralysis (**Robinson 2000**).
- Tuberous sclerosis is a neurocutaneous syndrome with autosomal dominant inheritance (**Jiménez Casso 2014**)
- PC syndrome (**Yang 2017; Vaughan 2003**)
- Pompe disease or glycogen-storage disease type II (**van der Beek 2008**)
- Danon disease (**Cheng 2012**)
- Alagille syndrome: Microdeletions of the short arm of chromosome 20 20p12.320p12.3 chromosomal rearrangements, non-immune hydrops fetalis due to prenatal heart failure and congnitve disfunction (**Mills 2013**)
- MYH6 p.E1885K (**Bowles 2015**)

WPW syndrome could be due to genetic origin, but there are contributions from metabolic alterations and endocrine disorders that could lead to glycogen accumulation and cardiac dysfunction as seen with WPWS. Wolff-Parkinson-White (WPW) syndrome. *MayoClinic.com*. March 19, 2014; http://www.mayoclinic.org/diseases-conditions/wolff-parkinson-white/basics/definition/con-20043508?METHOD=print.

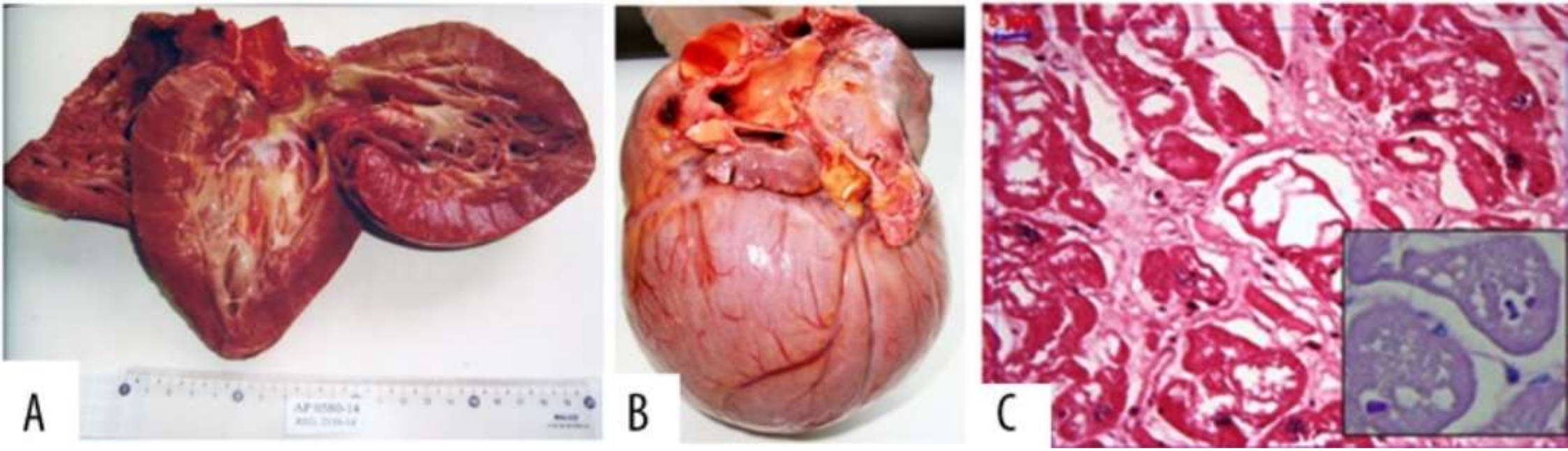
Non-sarcomeric genes involved in HCM

Non-sarcomeric genes are also involved in HCM, and nonsarcomeric genes have been postulated as modifiers of the phenotypic heterogeneity for this rason some researchers have proposed that the disease should be reclassified into sarcomeric and non-sarcomeric because pathophysiology and prognosis differ significantly between these groupings (**Olivotto 2011; McNally 2015**). Olivotto et al demonstrated the increased prevalence of systolic dysfunction in patients with HCM with sarcomere myofilament gene mutations when compared with non-sarcomeric and postulated an association between genetic status and coronary microvascular dysfunction. Patients with HCM with sarcomere myofilament mutations are characterized by more severe impairment of microvascular function and increased prevalence of myocardial fibrosis, compared with genotype-negative individuals. These findings suggest a direct link between sarcomere gene mutations and adverse remodeling of the microcirculation in HCM, accounting for the increased long-term prevalence of ventricular dysfunction and heart failure in genotype-positive patients (**Olivotto 2011)**. The variable penetrance and expressivity in HCM means that the same mutation may cause severe disease in one person, but a completely normal phenotype in another. Aditionally, HCM is known to be manifested by mutations in 12 sarcomeric genes and dilated cardiomyopathy (DCM) is known to manifest due to cytoskeletal mutations. Studies have revealed that sarcomeric mutations can also lead to DCM. (**Tanjore 2010**). Genotypically positive but phenotypically negative patients have perplexed researchers, and suggest a role of modifier genes in clinical outcomes (**García-Honrubia 2016**).

Orenes-Piñero et al have shown for the first time that the CYP11B2 polymorphism is an independent predictor for AF development in HCM patients. This highlights the importance of non-sarcomeric genes in the phenotypic heterogeneity of HCM. The association with higher aldosterone serum levels could relate to greater fibrosis and cardiac remodelling.(**Orenes-Piñero 2014**)

Necropsy study with **electron microscopy image**

(Courtesy from Dr. Lenises de Paula van der Steld, Escola Baiana de Medicina e Saúde Pública - Salvador, BA - Brazil)



(A) Macroscopic image of a heart of a 22-year-old male patient who died suddenly. He suffered from WPW and VH. He was 160 cm tall and weighed 60 Kg.

(B) The heart weighed 786 g, with obvious predominance of biventricular hypertrophy and severe symmetrical cardiomegaly, in both ventricles. There was non-specific endocardial thickening.

(C) An electron microscopy image of glycogen storage in the myocardial fibers of a mutation carrier patient (c.869A>T, p.K290I). The LV myocardium shows severe vacuolization of the myocardial fiber cytoplasm in an interstitial fibrosis area (HE; 400×). The remains of PAS-positive deposits inside cytoplasmic vesicles are shown in the bottom right quadrant. The scale bar is 5 μm.

Electrocardiographic features in PRKAG2 Cardiac syndrome

1. **Bradycardia,**
2. **Short PR interval,** which is largely attributed to excessive glycogen accumulation in myocytes(**Porto 2016; Gollob 2003**). During cardiogenesis, collagen-containing fibrous rings separate the atria and ventricle, and can be disrupted by glycogen-filled myocytes, resulting in ventricular pre-excitation (VPE) and reciprocating arrhythmias(**Arad 2003**.)
3. **Very high QRS voltages**: **Cardiac ventricular hypertrophy:** More than 50% of PS patients present with LVH, yet excessive glycogen deposition may not totally account for the cardiac hypertrophy. A recent study showed that the contribution of glycogen to increased heart mass was <5% in TG^{T400N} mice which recapitulates symptoms of patients with PRKAG2T400N mutation (**Banerjee 2010**). Proliferation and hypertrophy pathways are found to be involved in the development of PRKAG2 cardiomyopathy. In the TG^{T400N} mouse model, Banerjee et al. (**Banerjee 2010**). demonstrated that early activation of the NF-κB and Akt signaling pathway, which are triggered by inappropriate AMPK activation, mediated cardiac hypertrophy. Kim et al suggested that the FoxO and mTOR signaling cascades were involved in activation of the proliferation and hypertrophy pathway related to AMPK-γ2 mutation(**Kim 2014**).
4. **A widened QRS complex:** consequence of ventricular preexcitation, or bundle branch block,
5. **ST segment–T wave,** directed opposite the major δ wave and QRS complex, reflecting altered depolarization and/or LVH
6. **Progressive AV block**
7. **Paroxysmal supraventricular tachycardia**
8. **Delta wave:** A slurring and slow rise of the initial upstroke of the QRS complex (δ wave)
9. Atriofascicular Mahaim (AFM) pathway(see next slide) AV bypass tract, which was observed in the proband in the current PS family, is the most described AP in PS cases. **(van der Steld LP 2017)**
10. Nodoventricular and fasciculoventricular pathways are also observed in patients with PS, suggesting an important role for PRKAG2 in development of the cardiac conduction system(**Govindan 2010; Sternick 2011; Tan 2008**)
11. **Orthodromic atrioventricular re-entry tachycardia (AVRT)**
12. **Antidromic atrioventricular re-entry tachycardia (AVRT)**
13. **Mahaim-Type Pre-excitation** Reentry tachycardia with typical LBBB morphology
14. **Preexited AF & Atrial Flutter in WPW:** The shortest preexcited R-R interval during AF frequently 190 milliseconds, and the mean R-R interval of 200 milliseconds. Frequente hemodynamic collapse, losing consciousness. With indication of direct-current cardioversion (**Zhang 2011**)
15. **Ventricular tachycardias**

Atriofascicular Mahaim (AFM) pathway

AFM has been reported to account for approximately 3% of all the APs. Differential diagnosis between AFM and WPWS is very important because both of them cause AVRT.

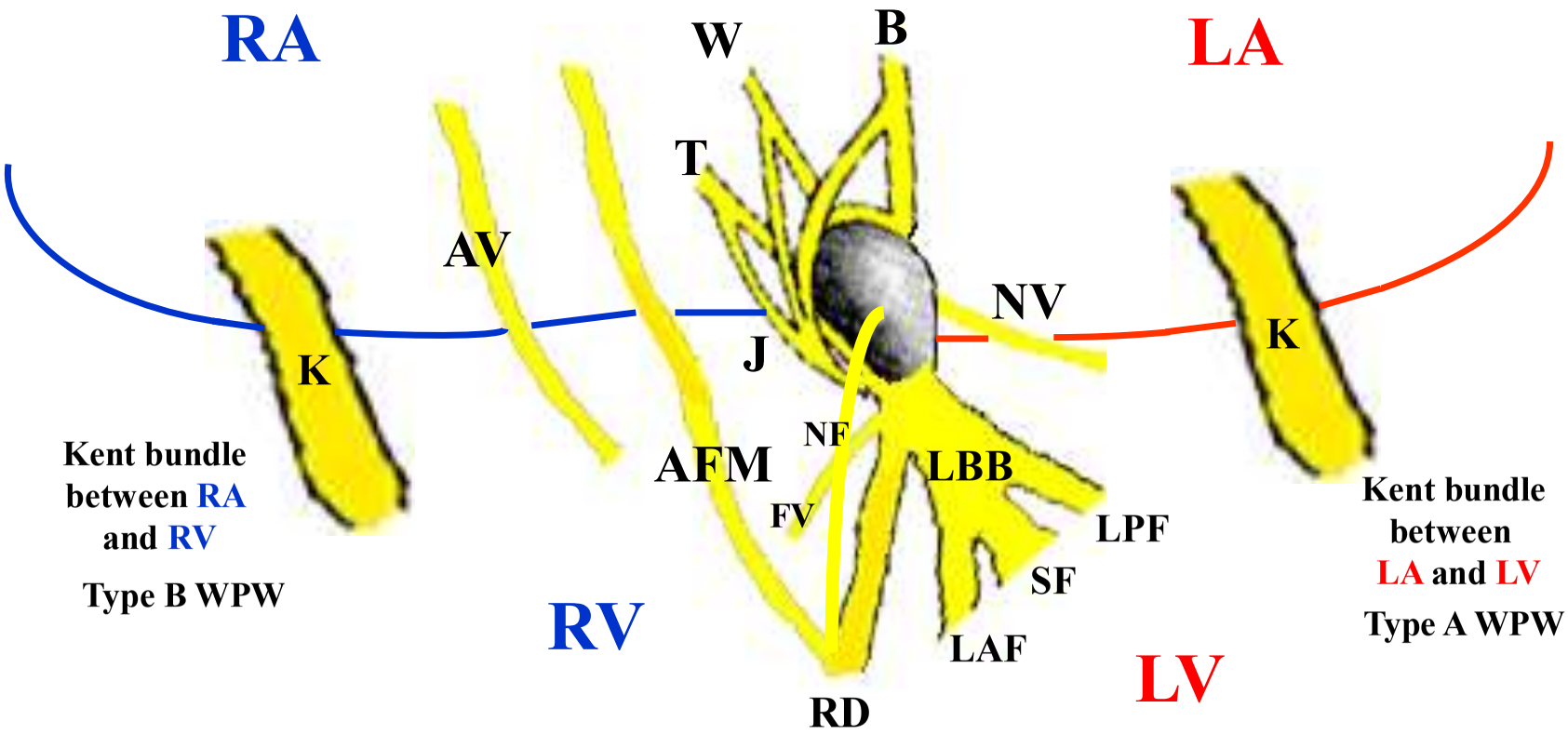
One of the points to consider differentiating AFM from WPW syndrome is the change of PR interval. In WPW syndrome, PR interval during sinus rhythm is stable because APs do not exhibit decremental conduction property. Meanwhile in AFM, both PR interval and QRS waveform often change due to decremental conduction property in the Mahaim fiber. Sometimes, the Holter monitoring demonstrated a change in the PR interval and narrowing of the QRS complex, which supported the diagnosis of AFM rather than WPWS.

Sternik et al reported that 61% of AFM patients showed rS pattern QRS waveforms in lead III in contrast with only 6% of normal heart patients with palpitations (**Sternick 2004**).

It has been reported that left bundle branch block causes remarkable left ventricular dysynchrony, which could lead to future development of congestive heart failure and similarly, AFM could development of congestive heart failure.

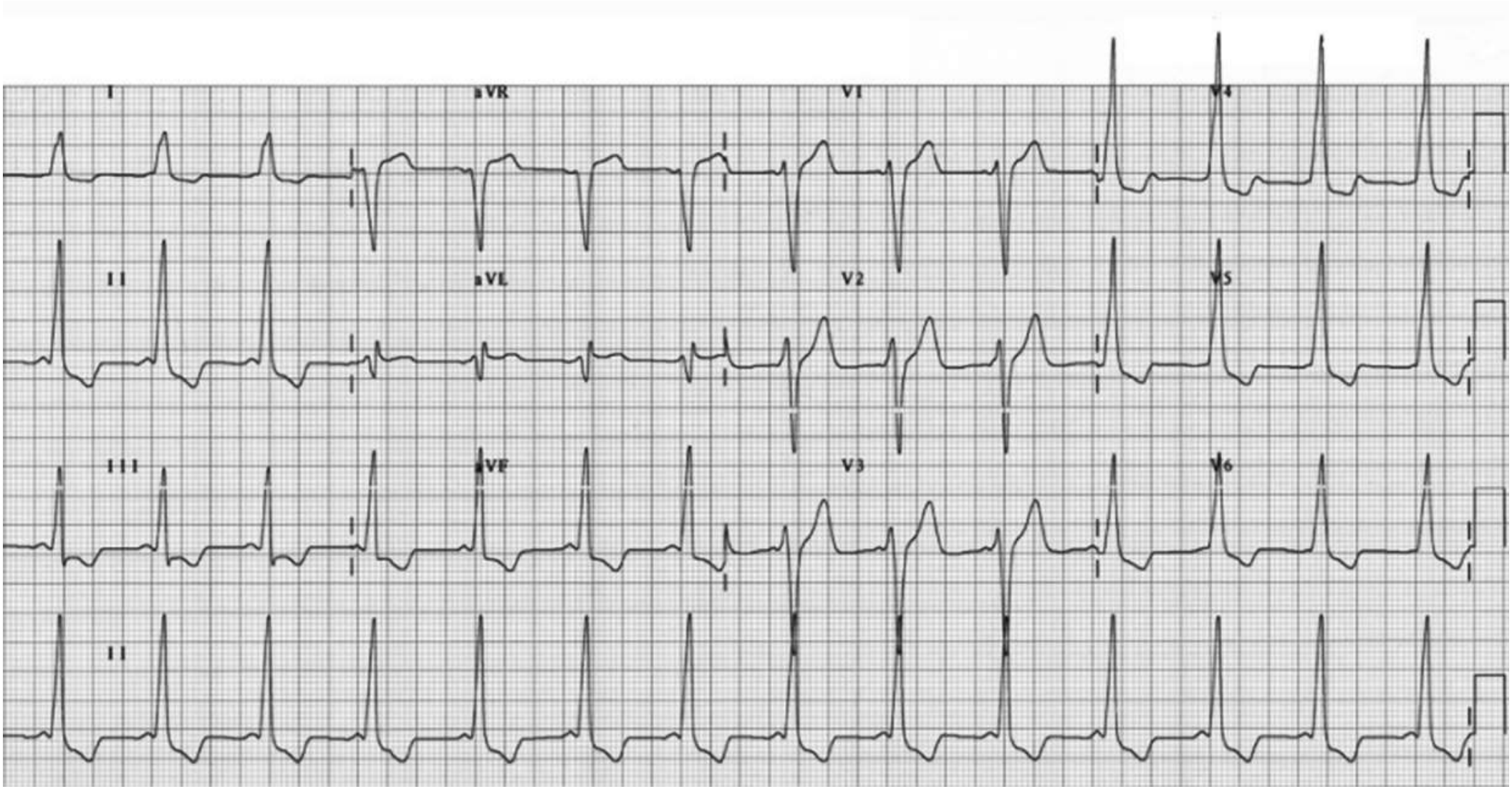
It has been reported that the most common site on the atrium edge of AFM fibers was 8:00–10:00 on the tricuspid valve ring (87%). Of those, 67% demonstrated Mahaim potential on tricuspid valve ring, which was considered the preferred ablation site (**Bohora 2008.**). Generally, due to slow conduction velocity in the atriofascicular Mahaim pathway , dual anterograde AV conduction causes fusion beats. See The anatomical substrate of ventricular preexcitation in the next slide.

The anatomical substrate of ventricular preexcitation

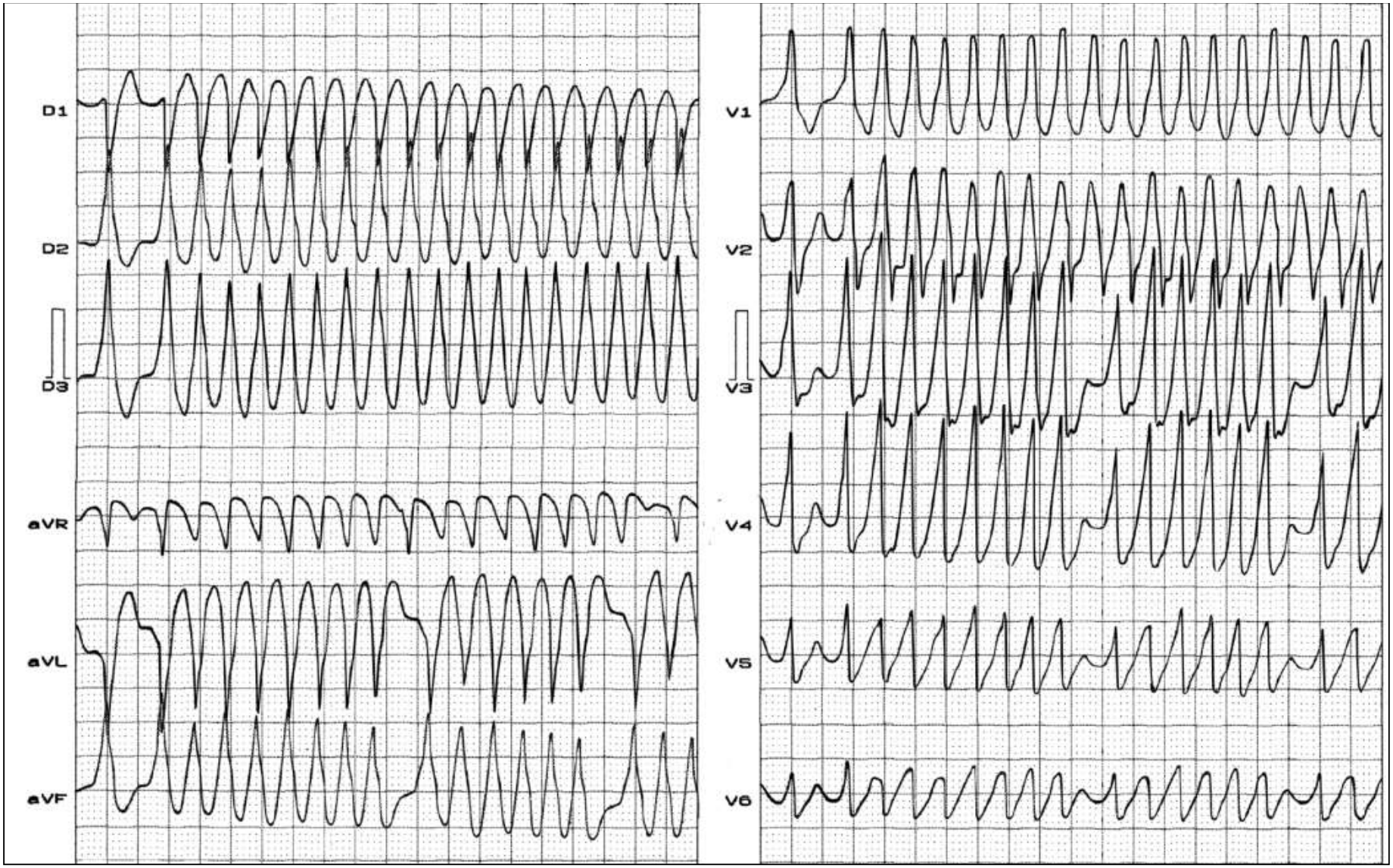


B, W and T: Bachman, Wenckebach, and Thorel internodal tracts.
J: Bypass bundle of James.
K and K': Kent bundles. These are AV connections.
AFM and NF: Atriofascicular Mahaim pathway and Nodo-fascicular tracts.

AV, NV and FV: Atrioventricular, Nodoventricular and Fascicular-ventricular connections.
a: Preferential nodal pathway.
RA and LA: Right and left atria.
LAF, SF, and LPF: left anterior, septal and left posterior fascicles of the left bundle branch (LBB) of the His bundle.

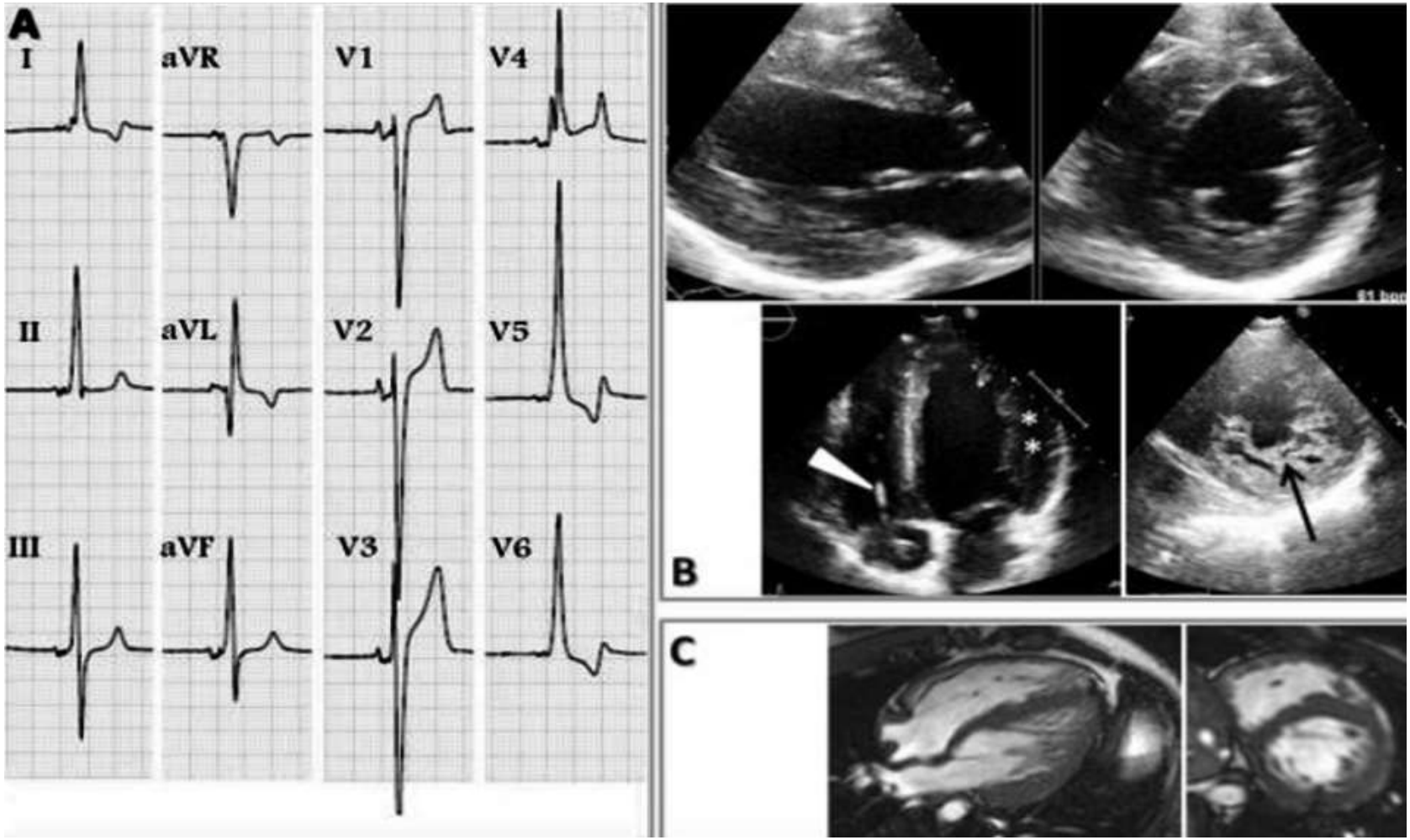


Sinus rhythm, short PR interval, broad QRS complexes with a slurred upstroke (δ) to the QRS complexes, type B" WPW (right-sided AP dominant S wave in V1), tall R waves and inverted T waves in the inferior leads and V4-6 the appearance of underlying LVH and/or secondary to anomalous ventricular depolarization.

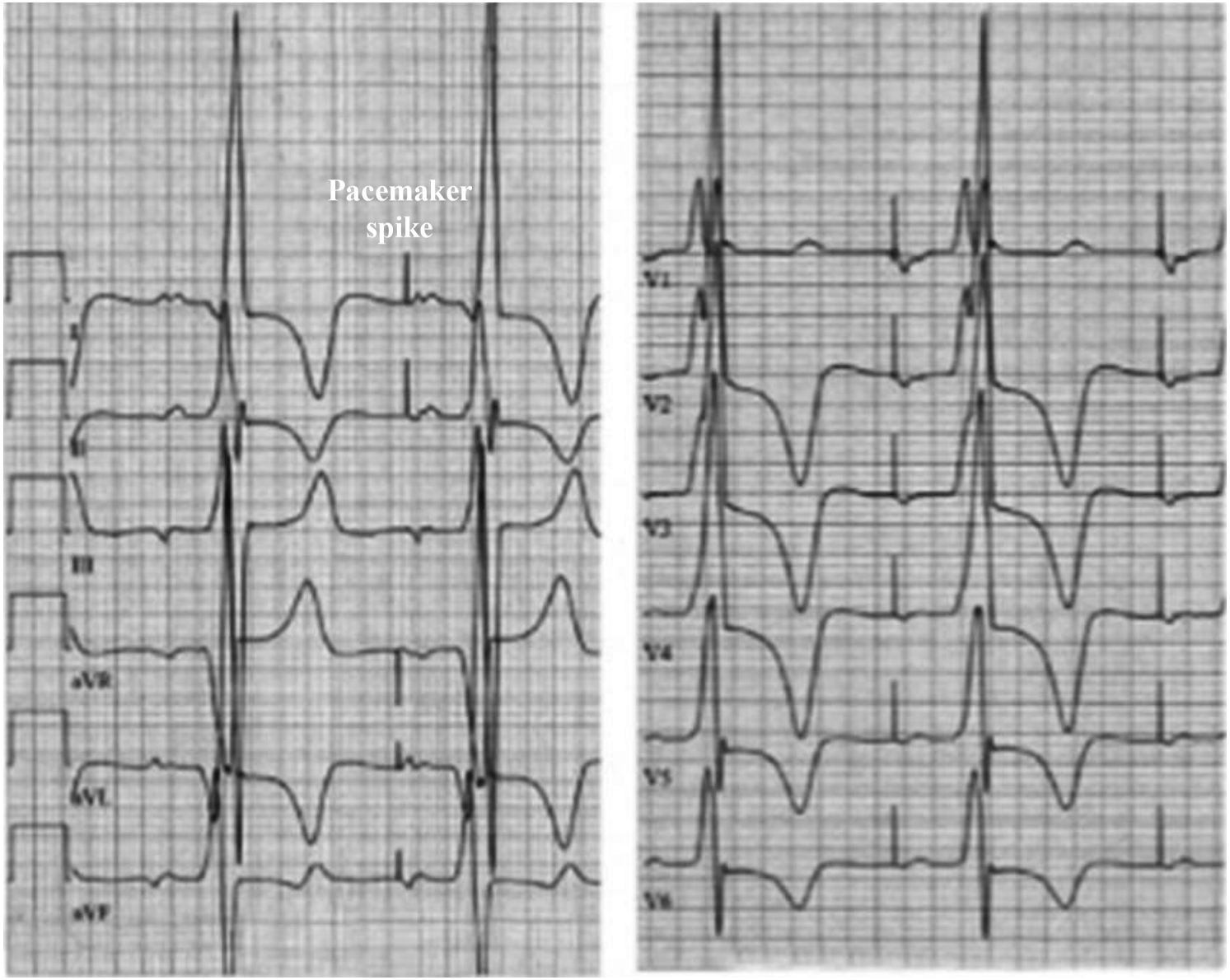


ECG showing a wide and irregular QRS complex tachycardia with a variable R-R interval and very high HR (near 300 bpm).
Conclusion: preexcited AF in a patient with WPWS.

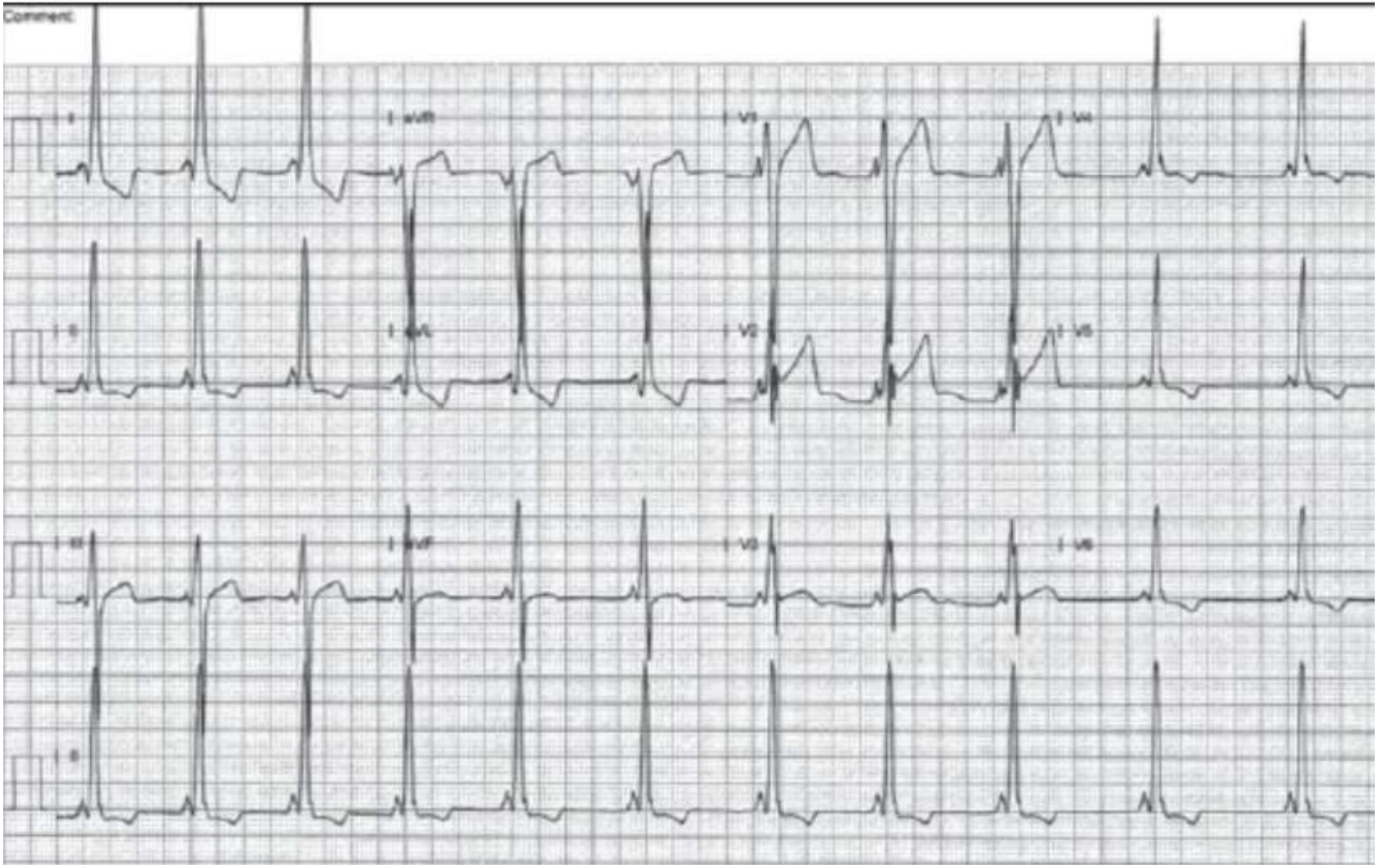
Panel A. ECG of a patient with PC syndrome, showing a short PR with a delta wave (negative in aVL, positive in I and inferior leads), very high voltages in the QRS complexes, which appear fragmented in V4. **Panel B.** Transthoracic echo of the same patient, showing only mildly increased wall thickness of the lateral wall (14mm, asterisks). A pacemaker lead (triangle) is visible in the right side of the heart. Short axis image of the left ventricular apex demonstrates evident trabecules (arrow). **Panel C.** RNM of the same patient (cine images) confirming the echocardiogram findings. T2 weighted images and T1 weighted images post contrast were unremarkable.



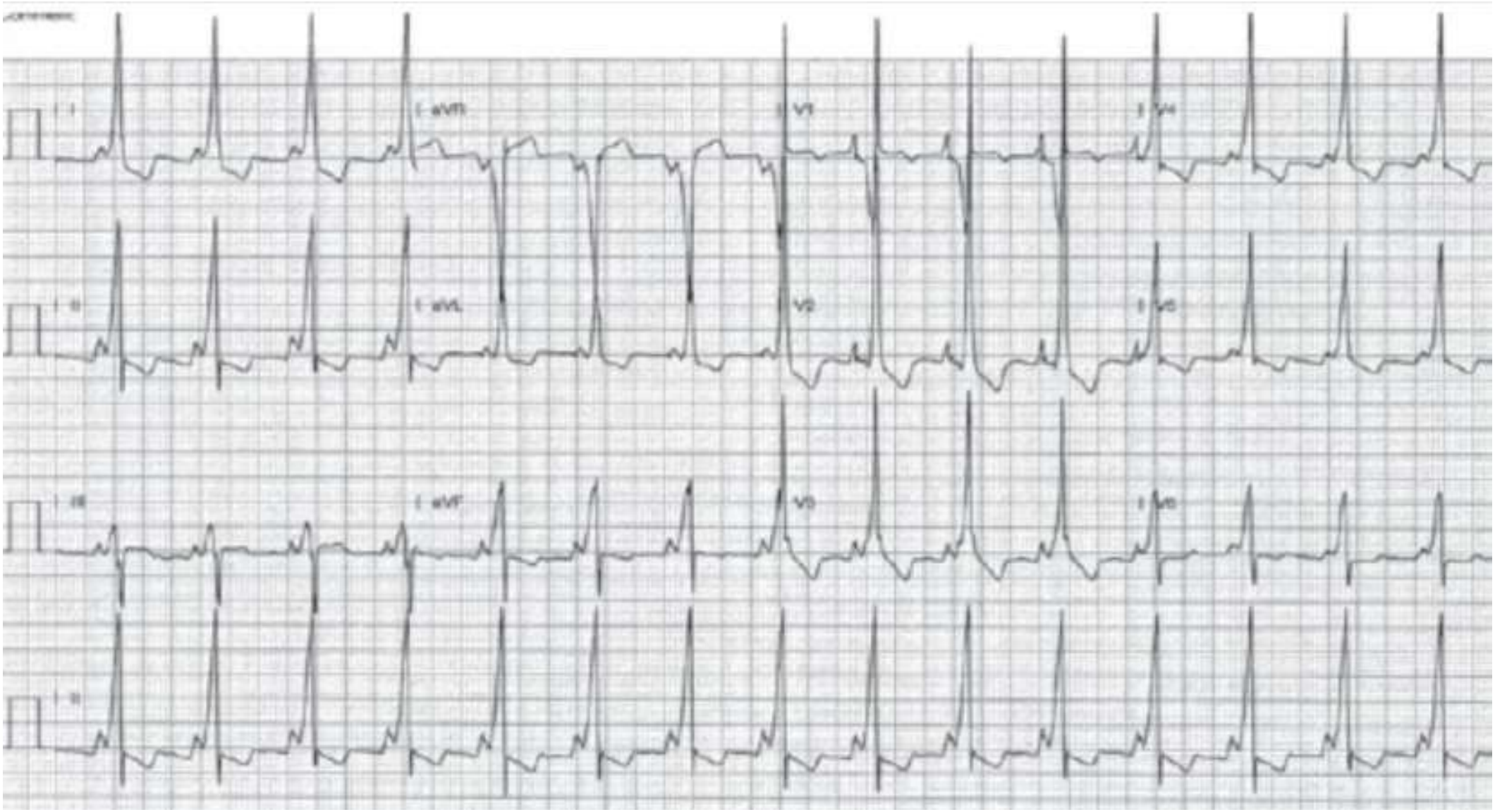
The most common ECG feature of PS is a short PR interval, present in 68% of patients. A bundle branch block, mainly affecting the right branch, was also widely reported along with a short PR. In addition to complete bundle branch blocks, slurred QRS depolarization phases and eccentric patterns of intraventricular conduction delays > 120 msec are reported. Advanced and clinically significant atrio-ventricular or sino-atrial blocks were also common. High-voltage QRS complexes with secondary repolarization abnormalities frequently developed even without echo evidence of LVH, sometimes accompanied by left axis deviation. (Panel A) shows a typical ECG from a young patient with PS.



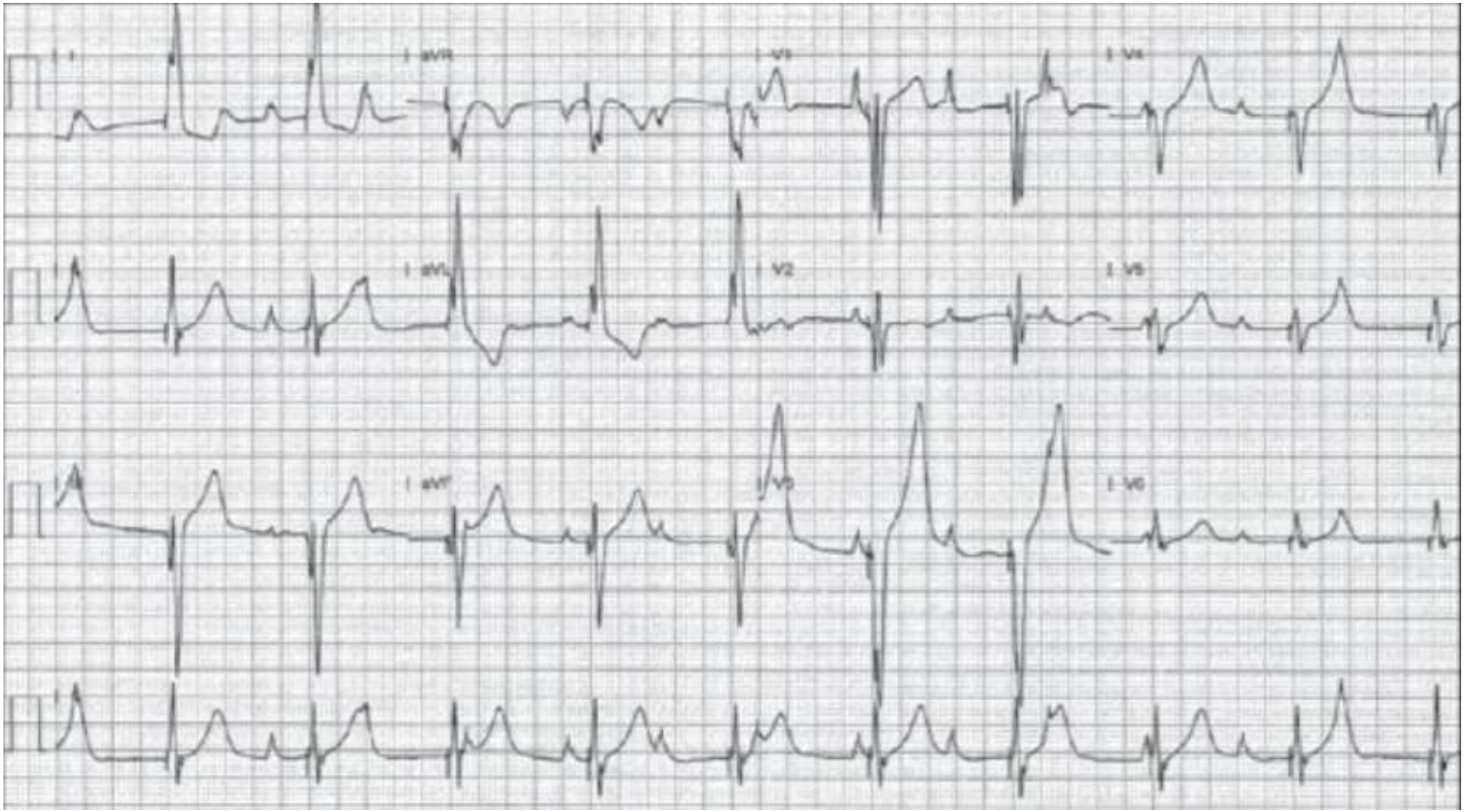
The electrocardiogram of a patient with the R302Q mutation. Atrial pacing with large QRS deflections and pathologic T waves



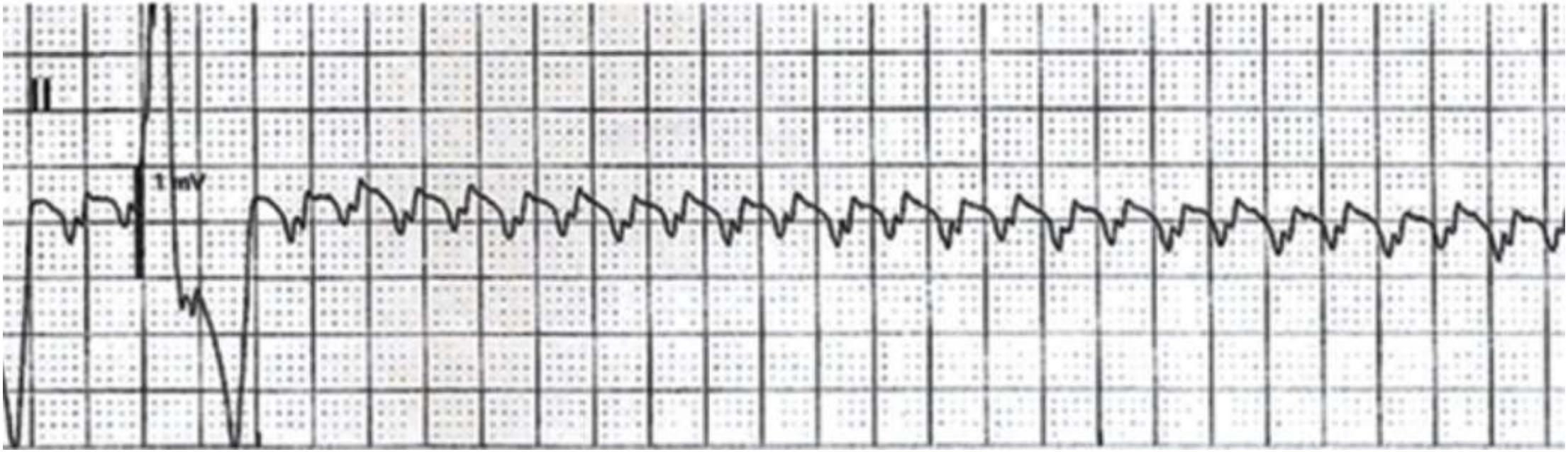
ECG performed at presentation to hospital showing pre-excitation characteristic of antegrade conduction through AV node and the AP. Note the short PR interval, slurred upstroke of QRS complex, and characteristic tall R waves (**Aggarwal 2015**)



ECG post RFCA day 1 showed persistent pre-excitation, though a different pattern as compared to her baseline, (**Aggarwal 2015**)



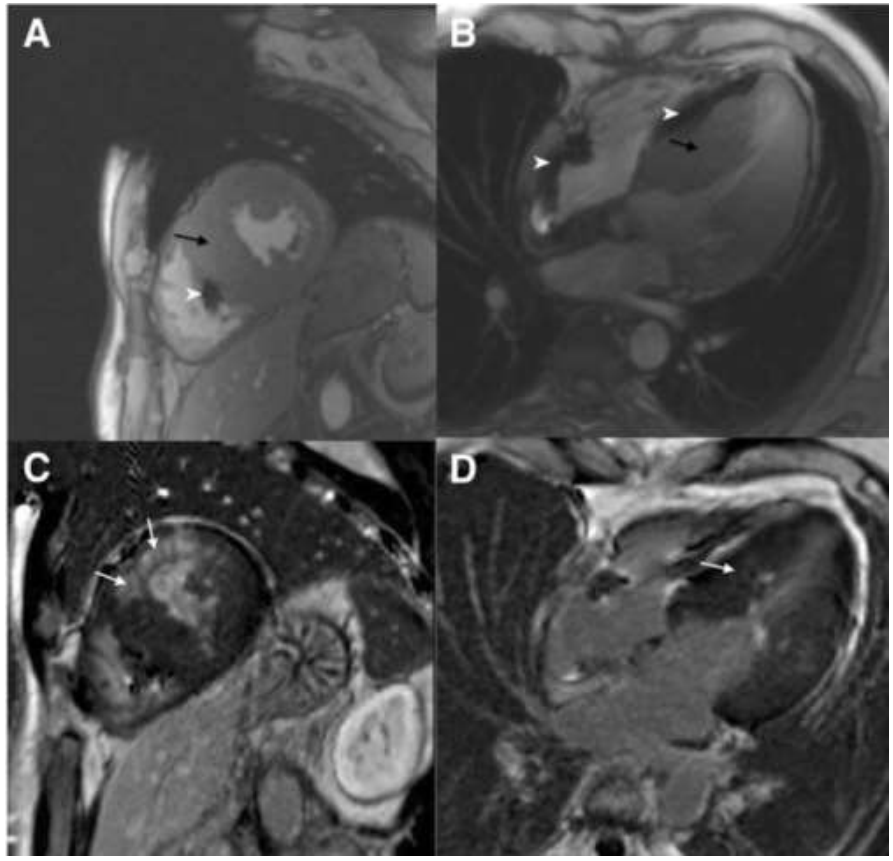
ECG after ICD) implantation (post ablation day 6) showing complete AV block and ventricular paced rhythm, (**Aggarwal 2015**)



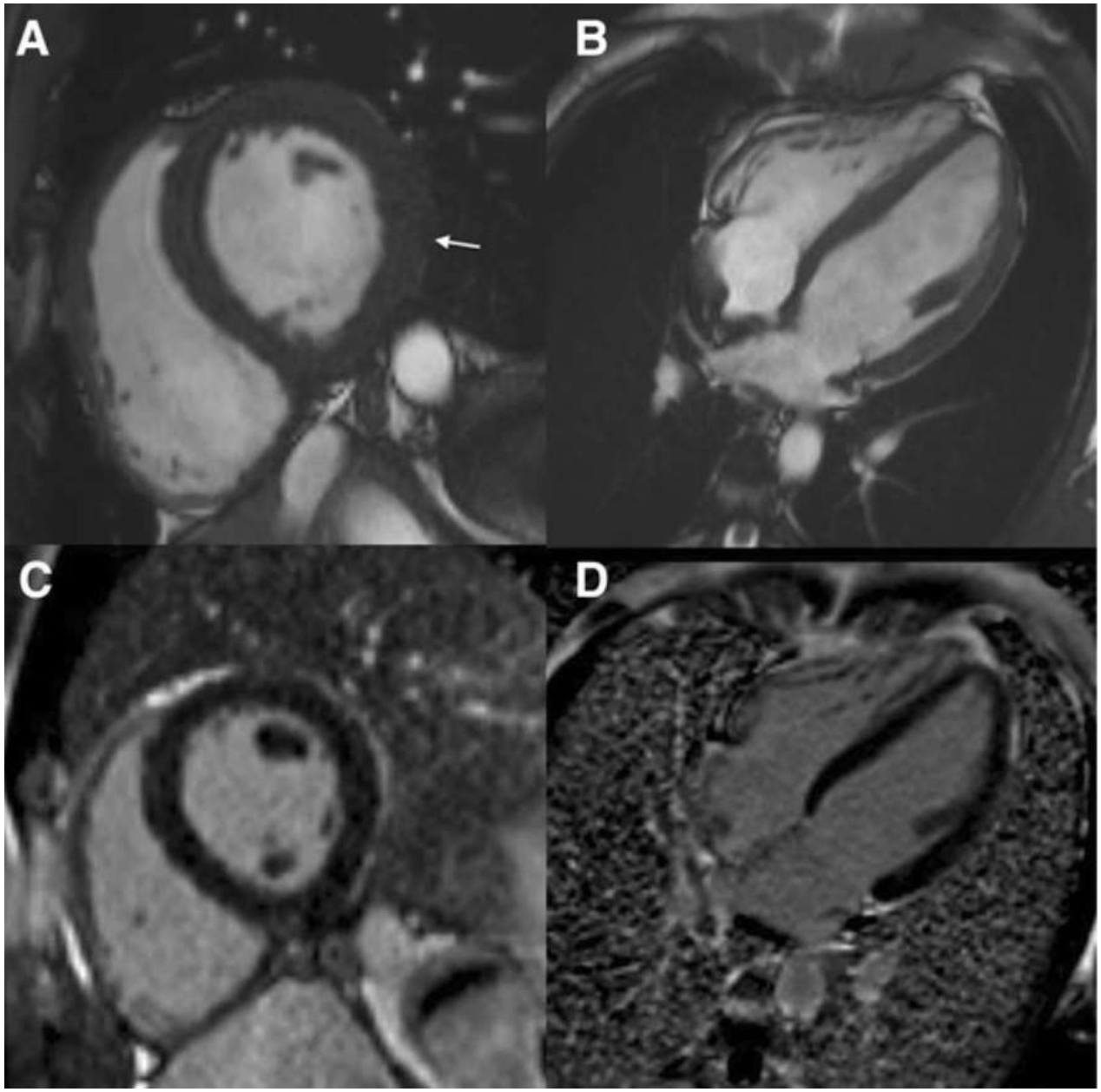
Mechanism of a documented cardiac arrest in a 20-year-old male patient. Atrial flutter with total AV block (**van der Steld LP 2017**).

WPWS is usually characterized by a shortened PQ interval, a widened QRS complex, and slowed δ wave. Prolongation of the QT interval is also a likely clinical correlate of AV block and premature ventricular beats (**Moroe 1988**) that are often observed in patients with WPW/PRKAG2 mutations (**Gollob 2001**). Alterations in the biophysical properties of cardiac voltage-gated sodium channels (such as prolonged inactivation) have previously been shown to prolong the QT interval and predispose the myocardium to arrhythmogenic phenotypes such as long QT syndrome and torsade de pointes (**Bennett 1997; Grant 2001**). Precisely how slowed inactivation of the cardiac voltage gated sodium channel may cause changes in conduction velocity and trigger ventricular pre-excitation (a hallmark of WPWS) in the absence or presence of hypertrophy is important and is therefore worthy of discussion. Data suggest that the predominant α-subunit sodium channel isoform NaV1.5 is mainly located in the intercalated disks at myocyte/myocyte gap junctions, and may therefore function to propagate the action potential from cell to cell (**Maier 2004; Kucera 2002**) in a manner roughly analogous to the nodes of Ranvier found in myelinated neurons. Computer modeling of gap junctional complexes indicate that the integral of the sodium current (total inward current) is a major determinant of conduction velocity, and increases in inward sodium current can speed up this process (**Kucera 2002; Rudy 2001**). Slowed inactivation of the sodium channel induced by CA-AMPK and a negative shift in the voltage-dependence of activation may manifest as pre-excitation of ventricular tissue due to accelerated action potential propagation through either existing or APs. For example, the bundle of His and Purkinje fiber network are particularly susceptible to alterations in sodium current due to the presence of prolonged action potentials. Furthermore, alterations in cell size/architecture also likely contribute to generalized changes in conduction velocity (**Kucera 2002**), a factor that is important when considering hypertrophy in the WPWS. Alterations in the biophysical properties of sodium channels can theoretically lead to ventricular pre-excitation.

RKAG2 cardiac syndrome may present with eccentric distribution of LVH, involving focal mid-infero-lateral pattern in the early disease stage, and more diffuse pattern but focusing on interventricular septum in advanced cases. In patients at earlier stages of disease, without LGE, T1 values may be reduced, while in the advanced disease stage T1 mapping may result in higher values caused by fibrosis. CMR is a valuable tool in detecting diffuse and focal myocardial abnormalities in PRKAG2 cardiomyopathy.



A 48-year-old male patient with PC syndrome and a pacemaker. In short-axis and four chamber cine images septum is severely hypertrophied (**A-B**) (black arrows). Maximal septal and lateral wall thickness was 31 mm and 25 mm, respectively. Papillary muscles were excluded in the measurements. Anteroseptal, hypertrophic areas exhibit patchy late gadolinium enhancement (**C-D**) (white arrows). White arrow heads indicate artefact from pacemaker lead.



A 16-year-old male patient with a *PRKAG2* mutation. In short-axis cine image (**A-B**) inferolateral left ventricular wall is mildly hypertrophied (10–11 mm, maximal z-score 2.3) (white arrow), no late gadolinium enhancement is present (**C-D**)

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 (**Murphy 2005; Blair 2001**) and the absence of severe cardiac hypertrophy (**Sternick 2006**); some studies reported cases of SCD during sleep (**Zhang. 2011**).

Current data are not sufficient to clearly define the prevailing pathophysiologic process leading to SCD, which could be due both to an abrupt advanced heart block (**Sternick2006**) and ventricular fibrillation, the latter deriving from SVT degeneration (fast conduction through APs) (**Maron 2003**; **Sternick 2006**; **Brembilla-Perrot 2006**) or from massive LVH (**Spirito 2000; Elliott 2014**). In those patients in which EPS were performed, ventricular fibrillation was induced only by high atrial pacing and not by ventricular extra-stimuli (**Murphy 2005; Sternick 2011**).

Outcomes

The age of symptoms onset was seldom available. In general, the clinical onset ranged from intrauterine period (**Burwinkel 2005**), early childhood (**Gollob 2001; Zhang 2011**), adolescence (**Sternick 2006; Gollob 2001; Fabris 2013**) to the fourth or fifth decade of age (**Arad 2005**). The mean age at diagnosis among the studies with available records is 30,1 years.

Overall, 82 subjects (43%) were implanted with permanent PM due to 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 was available, transplant was performed at 19, and 42 years of age (**Sternick 2006**).

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. (**Murphy 2005**) ICDs were implanted for primary prevention in two patients (age 20 and 22 years) with massive LVH, one of whom had VF 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, one for primary prevention (**Sternick 2006**) and one after cardiac arrest. To date, no data have been published about their long-term ICD follow-up.

Genotype-phenotype association of the two most frequent mutations

A trend towards certain phenotypical 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 (respectively 57% and 21%). Considering those patients with available data for each selected clinical feature, it was estimated a genotype-phenotype association between these two mutations.

Interesting outliers mutations and extra-cardiac 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 three months of life(2005). 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 (CPK) was also present in Ser548Pro patients (**Laforet 2006**). C.1591C>G (p. Arg531Gly) and c. 1453A>G (Lys485Glu) mutations were related to the development of arterial hypertension in adolescence (50% of patients) (**Liu 2013; Gollob 2001**). Some studies suggest (**Nagata 2010; Burwinkel 2005**) that systemic hypertension observed in these patients could represent extra-cardiac involvement as well.

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

Differential diagnosis

PS should be suspected in the setting of autosomal dominant HCM coexisting with WPWS, 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 (**Zhang 2011; Mehdirad 1999**).

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.

Main genetic syndromes that could mimic PS are listed in Table of next slide; the more significant among them are Danon's disease (DD) 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 below 25 years of age (**Boucek 2011**). 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 (**Weidemann 2011**). Both DD and AFD are inherited in an X-linked pattern, and they have wide extra-cardiac features (respectively intellectual disability and skeletal myopathy in DD, and acroparesthesias, renal failure, cryptogenic stroke, angiokeratomas, corneal and lenticular opacities, and gastrointestinal symptoms in AFD).

Cardiomyopathies associated with Wolff-Parkinson-White syndrome or short PR

Syndrome/Disease	Type of CMP	Characterzation
▪ **PC Syndrome** ▪ **Glycogen storage disease of the heart, lethal congenital.** Omin number 261740	HCM Heart failure (**Mizuta 1984**)	Progressive hypertrophy, Wolff–Parkinson–White syndrome, (WPWS) and progressive conduction system disease Only heart disease. Early death.
Danon disease Omin number 300257	HCM, DCM later and predominatly in females	X-linked dominant Mutation in *LAMP2* gene with skeletal(progressive proximal muscle weakness of the shoulders, neck, and legs), cardiac muscle disorder, mild intellectual difficulties, and retinal disease. Genetic defects in the lysosome-associated membrane protein 2 (*LAMP2*) gene. Males are affected earlier and more severely than females. (death occur 10–15 years later in females). WPWS,
Fabry disease	HCM	Genetic lysosomal storage disease, inherited in an X-linked manner. Excessive deposition of neutral glycosphingolipids in the vascular endothelium of several organs and in epithelial and smooth muscle cells. Anhidrosis or hypohidrosis, Reddish-purple skin rash in the bathing trunk area (angiokeratomas), Personal and/or family history of kidney failure, acroparesthesias, exercise, heat, or cold intolerance, unexplained cardiac hypertrophy
Pompe disease OMIM Number: 232300	HCM	Autosomal recessive, Mutation in *GAA* gene (reduced/absent acid maltase or acid-α-glucosidase) Two forms: Childhood, juvenile and adult-onset. With cardiomyopathy is referred to as classic Pompe disease and in the absence of cardiomyopathy as non-classic Pompe disease. Hypotonia, progressive weakness, macroglossia, hepatomegaly and HCM.

PS onset of symptoms frequently occurs within the first three decades of age, and it is often characterized by tachy 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 CMR are the gold-standard diagnostic techniques for the identification and characterization of cardiac hypertrophy. Standard anti-arrhythmic therapy should be initiated in those patients with supraventricular or ventricular tachyarrhythmias. If clinically appropriated, EPS can be useful for diagnosis and treatment of APs. Given the numerous life threatening consequences of PC syndrome, a prompt management of its complications is mandatory. PM 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 PC syndrome suggests that sudden death occurs in about 10% of patients, and can be due to an abrupt advanced heart block (**Sternick 2006**), or to VF (mainly deriving from SVT degeneration) (**Sternick 2006; Murphy 2005; Maron2003; Sternick 2011; Brembilla-Perrot 2006**). 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 VF. Due to the small number of events and to 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, non-sustained VT, or particular CMR patterns (**Elliott 2014**). EPS can also have a potential role for 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.

Conclusion and PRKAG2 management

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 non-sarcomeric forms of the disease. A red-flags approach could be useful to arise the suspicion of non-sarcomeric 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. At the present time, the mechanisms by which mutations in the PRKAG2 gene cause WPW syndrome are not clearly delineated. While there is a body of evidence suggesting that PRKAG2 induces a glycogen storage phenotype that precipitates WPWS and hypertrophy, other data suggests that some PRKAG2 mutations can cause WPWS in the absence of hypertrophy. Furthermore, a data suggests that sodium channel function is affected by altered AMPK activity. It is likely that the underlying cellular dysfunction occurring in familial WPWS may involve a combination of glycogen storage and excitability abnormalities depending on the PRKAG2 mutant in question and whether it is an activating or inactivating mutation. For example, the inactivating mutant R302Q and the activating mutant N488I both cause hypertrophy; yet the R531G activating mutant causes WPWS without hypertrophy. Therefore, it is important to perform further studies aimed at resolving some of these issues. The notion that sodium channel function is affected by AMPK may help explain some of the discrepancies apparent in the current body of knowledge in this area. Further research is warranted in order to provide additional data concerning the WPW/PRKAG2 mutations and the direct involvement of sodium channels and other ion channels in this familial disease. Even a patient with the classical phenotype may be missed because of lack of physician awareness. Diagnosis frequently is not considered for a long time with life-threatening arrhythmias. It is very important the early recognition of this entity because these patients have a progressive disease. Subjecting these patients to ablation procedures is fruitless as the aberrant conduction is due to swollen glycogen accumulated cardiac myocytes and not due to APs. Future possibility for gene therapy for this serious illness needs to be explored in detail. Until such disease reversing therapies are explored, these patients should be considered for early ICD placement as therapy for life-threatening arrhythmias and to prevent catastrophic events and SCD. 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 non-sarcomeric nature of PS. The authors propose a “red flags” based approach for diagnosis and management according to PS clinical manifestations. Xie et al. further combine adeno-associated virus-9 (AAV9) and the CRISPR/Cas9 gene-editing system to disrupt the mutant PRKAG2 allele encoding H530R while leaving the wild-type allele intact. A single systemic injection of AAV9-Cas9/sgRNA at postnatal day 4 or day 42 substantially restores the morphology and function of the heart in H530R PRKAG2 transgenic and knock-in mice. Together, this work suggests that in vivo CRISPR/Cas9 genome editing is an effective tool in the treatment of PC syndrome and other dominant inherited cardiac diseases by selectively disrupting disease-causing mutations (**Xie 2016**).

Red flags for PC syndrome; the more specific features are in bold

Clinical Examinations	Red Flags
History	Positive familial history for cardiac hypertrophy and sudden death (autosomal dominant inheritance)
Age	Young (I-IV decade)
ECG	Bradycardia, short PR interval, delta wave, bundle branch block, very high voltages
Echocardiogram	Concentric left ventricular hypertrophy
Dynamic ECG monitoring	Supraventricular arrhythmias, signs of chronotropic incompetence
EPS	Evidence of APs
Other	Myalgia, epilepsy, early onset hypertension

Suggested treatment guidelines for PC syndrome. 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

Clinical feature	Diagnosis	Proposed Treatment
Cardiomyopathy	ECG at least every 1 year	
	Echocardiography at baseline and every 1-2 years (depending on morphologic changes or clinical progression) Exercise stress testing with O2 consumption for effort inducible arrhythmias and for prognostic assessment Serum BNP at baseline and for clinical progression Holter ECG monitoring/event monitor to stratify the risk for sudden cardiac death or if symptomatic patients Consider individual risk factors for SCD and specific EPS patterns. EPS Dynamic arterial pressure monitoring for patients with hypertension	Standard heart failure treatment, and specifically: • appropriate fluid management avoiding dehydration especially when hypertrophy is more severe • prompt consideration for cardiac transplantation in those patients with clinical progression or end-stage heart failure Standard anti-arrhythmic treatment Early consideration for PM implantation ICD implantation AV AP ablation Hypertension treatment avoiding dehydrating drugs if systolic and diastolic functions preserved
Skeletal myopathy	Specialist neuromuscular evaluation	Physical therapy and rehabilitation
	Muscle biopsy may be performed for diagnostic workup	
Genetic	Accurate familial history and PRKAG2 genetic testing for probands and for at-risk relatives	Genetic screening

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