Cardiovascular Innovations and Applications

Vol. 1 No. 2 (2016) 187–197
ISSN 2009-8618
DOI 10.15212/CVIA.2016.0002

REVIEW

Inherited Wolff–Parkinson–White Syndrome

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Abstract

Wolff–Parkinson–White (WPW) syndrome is a congenital disorder of cardiac conduction system characterized by electrocardiographic preexcitation and episodes of paroxysmal supraventricular tachycardia. It is caused by a cardiac developmental defect in the electrical insulation between the atria and the ventricles due to the presence of an accessory pathway. WPW syndrome is a common cause of supraventricular tachycardia with benign prognosis. However, this clinical entity also predisposes patients to an increased risk of sudden cardiac death, especially in the setting of preexcited atrial fibrillation. WPW syndrome is usually sporadic and of unknown etiology in most cases. During the past 10 years, a significant heritable factor is increasingly recognized. Identification of the genetic basis among patients with WPW syndrome has important implications for understanding the molecular mechanism of ventricular preexcitation and the development of therapeutic strategies for risk stratification and management. The goal of this review is to examine the previous studies on hereditary variants, as well as to outline potential future avenues toward defining the heritability of WPW syndrome.

Keywords: Wolff–Parkinson–White syndrome; ventricular preexcitation; genetics

Introduction

Wolff–Parkinson–White (WPW) syndrome is a clinical entity characterized by electrocardiographic preexcitation during sinus rhythm and documented episodes of tachyarrhythmias or symptoms consistent with tachyarrhythmias [1]. Electrocardiographic findings of ventricular preexcitation include short PR intervals and wide QRS complexes with slurred upstrokes. WPW syndrome was first fully described in 1930, but isolated case reports of the same entity were previously reported many times [2]. It is now well known that WPW syndrome arises from a cardiac developmental defect in the atrioventricular electrical insulation due to the presence of an accessory pathway. Atrioventricular conduction through the abnormal connection, bypassing the atrioventricular node, causes early eccentric activation of the ventricles and the electrocardiographic pattern of ventricular preexcitation. The degree of preexcitation is not invariable, depending on the relative contribution from ventricular excitation by the atrioventricular node and His–Purkinje system versus the accessory pathway. Electrocardiographic preexcitation affects about 0.15% of the general population [3]. Patients with WPW syndrome are prone to paroxysmal supraventricular tachycardia that is maintained by the

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accessory pathway, but not all patients with ventricular preexcitation develop paroxysmal supraventricular tachycardia. WPW syndrome also predisposes patients to an increased risk of sudden cardiac death, especially in the setting of preexcited atrial fibrillation. The reported incidence of sudden cardiac death in patients with WPW syndrome ranged from 0.15% to 0.39% over a 3- to 10-year follow-up [4]. In the minority of patients, the first and only symptomatic manifestation of the disease is sudden cardiac death. WPW syndrome is usually sporadic and of unknown cause in most cases.

During the past 10 years, a preponderance of evidence suggests a large genetic contribution to this condition. The earliest report of familial WPW syndrome was described 70 years ago [5]. Since then, it has become apparent that WPW syndrome can be transmitted genetically in isolation or in association with other cardiac diseases or multisystem syndromes [6–11]. Epidemiological investigation has found that individuals who have a family member with electrocardiographic preexcitation carry an increased risk. Vidaillet et al. [12] determined the prevalence of preexcitation in the first-degree relatives of 383 consecutive patients with electrophysiologically proven accessory pathways. For 13 of the 383 probands (3.4%), accessory pathways were documented in one or more first-degree relatives. Preexcitation was present in at least 13 of the 2343 relatives (0.55%), which was a significantly higher rate than that in the general population (0.15%) [3, 12]. With the emerging reports of a genetic contribution, identification of the genetic basis among patients with WPW syndrome has significant implications for understanding the molecular mechanism of ventricular preexcitation and the development of therapeutic strategies for risk stratification and management. The purpose of this review is to examine the previous studies on hereditary variants, to address the genetic factors, inheritance patterns, and clinical characteristics, and to describe future avenues toward defining the heritability of WPW syndrome.

Glycogen Storage Diseases

PRKAG2 Cardiac Syndrome

The syndrome was initially described in 1986 by Cherry and Green, who observed an autosomal dominant mode of inheritance with a high degree of penetrance and variable clinical expressivity in a five-generation French-Canadian family [13]. Affected family members presented with ventricular preexcitation, supraventricular arrhythmias, progressive conduction system disease, and cardiac hypertrophy. The disease-causing gene responsible for both familial WPW syndrome and hypertrophic cardiomyopathy was subsequently mapped to chromosome 7 by use of genetic linkage analysis. In 2001 Gollob et al. [14] and Blair et al. [15] identified the gene to be *PRKAG2*, which is located at 7q36 and encodes the AMP-activated protein kinase (AMPK) γ_2 regulatory subunit [16, 17]. AMPK is a highly conserved heterotrimeric protein composed of a catalytic α subunit and regulatory β and γ subunits. It is an important energy-sensing enzyme that monitors cellular energy status, maintains energy balance, and functions by phosphorylation of key enzymes in lipid metabolism and by increasing expression and translocation of glucose transporters [18]. The function attributed to the γ_2 subunit is regulation of AMPK activity by binding two molecules of either AMP or ATP [19]. AMPK is activated by AMP and inhibited by ATP, but the homeostasis can be disrupted by disease mutations in *PRKAG2*. Defects in *PRKAG2* are typically associated with a cardiac syndrome triad consisting of familial ventricular preexcitation, conduction system disease, and cardiac hypertrophy mimicking hypertrophic cardiomyopathy. However, patients with *PRKAG2* cardiac syndrome could also present with electrophysiological abnormalities and absence of cardiac hypertrophy [20].

Since this original description, 15 *PRKAG2* mutations, including a 3-bp insertion and 14 missense mutations, have been identified [21]. Each mutation has been shown to cosegregate with the disease phenotypes with complete penetrance. Histological studies of myocardial tissue from affected individuals [21–24] and transgenic mice expressing mutant forms (N488I [25], R302Q [26, 27], R531G [28], and T400N [29–31], respectively) of the *PRKAG2* gene confirmed glycogen storage as the pathological basis for this cardiac syndrome. The mechanisms that lead to ventricular preexcitation in *PRKAG2* cardiac syndrome might include developmental failure to eradicate remnants of atrioventricular connections during cardiogenesis due to AMPK malfunction, or

promotion of electrical cell coupling and acceleration of conduction velocity caused by glycogen accumulation [32]. Although the relationship between *PRKAG2* mutations and familial forms of WPW syndrome associated with or not associated with other structural heart disease has been well established, such mutations are not identified in patients with sporadic isolated WPW syndrome [33].

Danon Disease

Danon disease is an X-linked dominant multisystem disorder affecting predominantly cardiac and skeletal muscles and caused by mutation in the lysosome-associated membrane protein 2 gene (*LAMP2*) [34]. In 2000 Nishino et al. [35] first identified *LAMP2* defects in ten unrelated patients with Danon disease. All of the ten different mutations resulted in premature termination of lysosome-associated membrane protein 2. Western blot analysis of skeletal muscle biopsy specimens from the patients showed marked deficiency or complete absence of lysosome-associated membrane protein 2. From these results and the finding that a similar cardioskeletal myopathy is present in *LAMP2*-deficient mice as in humans [36], Nishino et al. concluded that primary *LAMP2* deficiency is the cause of Danon disease. The pathological hallmark of the disease is intracytoplasmic vacuoles containing autophagic material and glycogen in skeletal and cardiac muscle cells [35, 37–41]. As opposed to glycogen storage throughout the myocytes in *PRKAG2* cardiac syndrome, *LAMP2* mutations accumulate glycogen in lysosomes [42].

Major clinical features include skeletal and cardiac myopathy, cardiac conduction abnormalities, mild intellectual disability, and retinal disease. Hepatic and pulmonary disease may also be present but are less prevalent symptoms [36, 42–44]. Males are typically affected earlier and more severely than females because of haploinsufficiency of the X-linked *LAMP2* gene. Danon cardiomyopathy typically manifests itself as a hypertrophic phenotype (88%) in men but with an equal prevalence of dilated cardiomyopathy (27.7%) and hypertrophic cardiomyopathy (33.3%) in women [9]. Conduction abnormalities are also common, presenting in more than three quarters of patients [9, 44]. Preexcitation is the most usual electrocardiographic finding, present in 68.2% of men and 27% of women [9]. The mechanism for ventricular preexcitation is incompletely understood in Danon disease. It is likely that there is a common mechanism in Danon disease and *PRKAG2* cardiac syndrome for both *LAMP2* and *PRKAG2* mutations causing glycogen-storage cardiomyopathies. Because of similar echocardiographic features, glycogen-storage cardiomyopathy produced by *LAMP2* or *PRKAG2* mutations could be misdiagnosed as hypertrophic cardiomyopathy. Recognition of electrophysiological abnormalities, particularly ventricular preexcitation, may help to distinguish these disorders, and genetic analysis can definitively establish the cause of unexplained left ventricular hypertrophy [41].

Pompe Disease

Pompe disease is an autosomal recessive disorder caused by the absence or deficiency of acid α-glucosidase (encoded by *GAA*), a lysosomal enzyme responsible for the cleavage of the α-1,4- and α-1,6-glycosidic bonds of glycogen to form glucose [45]. The deficiency resulting in the accumulation of glycogen in the lysosomes disrupts the cytoarchitecture and function of affected cells, leading to multisystem disease and often to early death. The severity of clinical presentations, the tissue involvement, and the age of symptom onset strongly correlate with the nature of the *GAA* mutations and the level of residual enzyme activity [46]. The classic infantile form, described by Pompe in 1932, is caused by complete or near complete loss of *GAA* activity, and is the severest subtype, in which cardiomyopathy and muscular hypotonia are the cardinal features and symptoms begin within the first months of life [47, 48]. Most infants do not survive beyond the first year of life and die of cardiorespiratory complications [47, 48]. Similar clinical presentations in infants with milder myopathy, absence of left ventricular outflow obstruction, and somewhat longer survival with assisted ventilation and supplemental intubation have been classified as a nonclassic infantile form [49]. In the juvenile and adult forms, involvement of skeletal muscles dominates the clinical picture. Laforêt et al. [50] reported the clinical features of 21 unrelated patients with juvenile- or adult-onset *GAA* deficiency. The mean age at onset of obvious muscle complaints was 36 years, and most patients had predominant pelvic girdle muscle dysfunction without significant distal leg involvement .

Herzog et al. [46] reported a long-term observation of clinical manifestations in 37 nonclassic patients. They found that lower limbs and paraspinal muscles are frequently affected first, followed by respiratory muscles. As the disease progresses, many patients become wheelchair dependent and require assisted ventilation. Respiratory failure is the main cause of increased morbidity and mortality.

WPW syndrome and a shortened PR interval are commonly seen in patients with both infantile- and late-onset Pompe disease [10, 51–57]. These are thought to be due to disruption of the annulus fibrosis by glycogen-filled myocytes allowing ventricular preexcitation [25, 55].

Fabry Disease

Fabry disease is an X-linked disorder caused by a deficiency in the lysosomal enzyme α-galactosidase A due to mutations in the *GLA* gene [58]. This enzymatic deficiency leads to systemic accumulation of globotriaosylceramide and related glycosphingolipids within lysosomes of various tissues and organs, including heart, kidney, and the nerve system. Fabry disease was previously considered to be an X-linked recessive disorder, but Wang et al. [59] found that heterozygous females have significant multisystemic diseases requiring medical intervention . The disorder is a systemic disease, which manifests itself as progressive renal failure, cardiac disease, cerebrovascular disease, small-fiber peripheral neuropathy, and skin lesions, among other abnormalities [60]. Patients with some residual *GLA* activity have atypical clinical presentations of Fabry disease with predominantly cardiac abnormalities, while having little or no kidney dysfunction and no painful acroparesthesia [61, 62].

Cardiac involvement is common in Fabry disease patients, most frequently concentric left ventricular hypertrophy, and is one of the most important reasons for reduced life expectancy and disease-related death [63, 64]. In 1973 Roudebush et al. [65] reported the first cases of abbreviated PR interval in Fabry disease. Subsequently, recurrent SVT associated with ventricular preexcitation was also described in two brothers with Fabry disease [11]. A study of cardiac manifestations in 20 hemizygous male patients by Senechal and Germain [66] demonstrated an incidence of 40% short PR interval on electrocardiogram. An association between Fabry disease and fasciculoventricular accessory pathways has been well established by electrophysiological study [67]. Evidence suggests that the electrocardiographic finding may be due to glycolipid deposition in the conducting system around the atrioventricular node.

Mitochondrial Diseases

Leber Hereditary Optic Neuropathy

Diseases due to mutations in the nuclear genome often follow Mendelian inheritance rules, such as autosomal dominant, autosomal recessive, or X-linked inheritance. In contrast, those with primary mutations in the mitochondrial genome (mitochondrial DNA, mtDNA) have unique patterns of inheritance and penetrance governed by the principles of maternal inheritance, heteroplasmy, replicative segregation, and the tissue-specific threshold effect [68].

Leber hereditary optic neuropathy (LHON) is one of the most common inherited optic neuropathies causing bilateral central vision loss [69]. In more than 90% of cases worldwide, the disorder results from one of three point mutations in mtDNA which encode complex I of the respiratory chain, including 3460G>A in *MTND1*, 11778G>A in *MTND4*, and 14484T>C in *MTND6* [70]. Cardiac conduction defects have been noted in some LHON families. Among Finnish patients, Nikoskelainen et al. [71] found WPW syndrome in 14 of 163 patients (9%) with mtDNA mutations. In studies of 35 Japanese LHON families, Mashima et al. [72] indicated that, as in Finnish families, WPW syndrome was relatively common and seen in five of 63 individuals (8%) with mtDNA mutations. WPW syndrome in association with structural heart abnormalities has also been described in patients with LHON [73].

Leigh Syndrome

Leigh syndrome, also known as *subacute necrotizing encephalomyelopathy,* is the most common pediatric presentation of mitochondrial disease. This neurodegenerative disorder is genetically heterogeneous, and to date more than 75 disease genes have been identified, encoded by mitochondrial and nuclear genomes, most of which encode structural

components of the oxidative phosphorylation pathway, or proteins required for their assembly, stability, and activity [74]. Generally, onset of clinical presentations occurs by the age of 2 years [75]. Patients develop neurological symptoms, including abnormal motor findings (hypotonia, abnormal tendon reflexes, and dystonia), abnormal ocular findings (nystagmus, strabismus, visual impairment, optic atrophy, ptosis, and ophthalmoplegia), mental retardation, epileptic seizures, and respiratory dysfunction [75]. The presentation can also be multisystemic; cardiac, hepatic, gastrointestinal, and renal dysfunction have been observed. Abnormal findings on neuroimaging include bilateral symmetrical lesions in the basal ganglia and/or thalamus and/or brainstem. Cardiac involvement is present in one fifth of patients with Leigh syndrome, with more than half having hypertrophic cardiomyopathy [75]. WPW syndrome is also noted in Leigh syndrome patients. A mitochondrial 13513G>A mutation in *MTND5* is frequently identified in these patients [76–79]. Despite the great variability in clinical presentation, WPW syndrome seems to be a quite specific and frequent feature in patients with the mitochondrial 13513G>A transition.

Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like Episodes

Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome is a genetically heterogeneous mitochondrial disorder with multiorgan involvements. The mitochondrial 3243A>G mutation in the *MT-TL1* gene encoding transfer RNA$^{Leu(UUR)}$ is found in 80% of MELAS syndrome cases [80]. Clinical manifestations include stroke-like episodes, dementia, epilepsy, lactic acidemia, myopathy, recurrent headaches, hearing impairment, diabetes, and short stature [81]. Childhood is the typical period of onset, with 65–76% of affected individuals presenting at or before the age of 20 years. Cardiomyopathy occurs in 18–30% of affected individuals [82, 83]. Both dilated and hypertrophic cardiomyopathies have been observed in MELAS syndrome; however, more typical is a nonobstructive concentric hypertrophy [84]. Cardiac conduction abnormalities, including WPW syndrome, have been reported in 13–27% of individuals with MELAS syndrome [83, 85–87].

Muscular Dystrophies

Duchenne and Becker Muscular Dystrophy

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X-linked inherited neuromuscular disorders responsible for more than 80% of all muscular dystrophies and both are caused by mutations in the dystrophin gene [88]. Approximately 65% of the mutations in both forms are deletions of one or more exons in the dystrophin gene. Mutations leading to dystrophin deficiency cause DMD, whereas mutations leading to partially functional protein cause BMD [89]. DMD is characterized by progressive muscle weakness and wasting due to the absence of dystrophin, which causes degeneration of skeletal and cardiac muscle. The first signs or symptoms occur at a mean age of 2.5 years, but the mean age at definitive diagnosis of DMD is 4.9 years. BMD is the milder form of dystrophinopathy [90]. BMD typically presents later, usually between 5 and 15 years [91]. Myocardial involvement appears in DMD patients at about 6 years of age in a high percentage of cases and increases progressively until the last years of life, when cardiac damage occurs in 95% of cases. The percentage of myocardial involvement in BMD patients is very low before 13 years of age, but increases progressively until 20 years, when cardiac damage occurs in 80% of cases; severe cardiomyopathy does not occur before the age of 21 years [92]. Cardiac involvement may sometimes be the only manifestation of the dystrophin mutation in carriers. Mirabella et al. [93] reported two carriers with dilated cardiomyopathy and no symptoms of muscle weakness in whose heart biopsy specimens dystrophin was absent in many fibers. WPW syndrome has been described recently in both DMD and BMD patients [94–96]. The mdx^{5cv} mouse model of DMD recapitulates also electrophysiological abnormalities seen in DMD patients [97].

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an autosomal dominant, predominantly neurocutaneous, multisystem disorder characterized by widespread hamartomas in several organs, including the brain, skin, heart, kidneys, and lung. Mutations in the *TSC1* gene or *TSC2* gene lead to disruption of the TSC1-TSC2

Table 1 Genetic Basis Associated with Wolff–Parkinson–White Syndrome.

Disease	Clinical features	Gene			OMIM entry
		Symbol or location	Inheritance	Protein	
PRKAG2 cardiac syndrome	Ventricular preexcitation, conduction system disease, cardiac hypertrophy	*PRKAG2*	Autosomal dominant	AMPK γ_2 subunit	194200
Danon disease	Cardiomyopathy, cardiac conduction abnormalities, skeletal myopathy, mental retardation, retinal disease, hepatic disease, pulmonary disease	*LAMP2*	X-linked dominant	Lysosome-associated membrane protein 2	300257
Pompe disease	Infantile-form cardiomyopathy, muscular hypotonia; juvenile and adult forms of progressive myopathy	*GAA*	Autosomal recessive	Acid α-glucosidase	232300
Fabry disease	Progressive renal failure, cardiac disease, cerebrovascular disease, peripheral neuropathy, skin lesions	*GLA*	X-linked dominant	α-Galactosidase A	301500
LHON	Bilateral central vision loss	mtDNA	Maternal		535000
Leigh syndrome	Neurodegenerative symptoms	Mitochondrial and nuclear genomes	Maternal and autosomal		256000
MELAS syndrome	Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes	mtDNA	Maternal		540000
DMD	Progressive muscle weakness	*DMD*	X-linked dominant	Dystrophin	310200
BMD	Progressive muscle weakness	*DMD*	X-linked dominant	Dystrophin	300376
TSC	Widespread hamartomas	*TSC1*, *TSC2*	Autosomal dominant	Hamartin (*TSC1*), tuberin (*TSC2*)	191100, 613254

AMPK, AMP-activated protein kinase; BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; mtDNA, mitochondrial DNA; TSC, tuberous sclerosis complex.

intracellular protein complex, causing overactivation of the mammalian target of rapamycin protein complex [98]. The *TSC2* gene accounts for as many as 90% of the clinical cases [99]. The most common cardiac manifestation of this disease is cardiac rhabdomyomas, which occur most frequently in children younger than 2 years, usually regress spontaneously with increasing age, and rarely necessitate therapeutic interventions [100]. A review of tuberous sclerosis and cardiac rhabdomyomas suggests that 9–13% of patients with rhabdomyomas have WPW syndrome [101]. Some of the cells in the cardiac rhabdomyomas found in patients with tuberous sclerosis are structurally identical to normal Purkinje cells, and their tumorlike accumulation in the atrioventricular annulus may contribute to the occurrence of accessory pathways [102]. However, cases of tuberous sclerosis and WPW syndrome without cardiac rhabdomyomas have also been reported [103]. A synopsis of these genes associated with WPW syndromes is presented in the Table 1.

Other Genes

WPW syndrome can be associated with microdeletions or duplication of chromosome region 20p12.3 [104, 105]. It is possible that more than one gene within the 20p12.3 region is responsible for the WPW phenotype. Members of the T-box gene family of transcription factors are important early regulators in development and function of the cardiac conduction system and have been implicated in human genetic syndromes with congenital cardiac malformations. Two recent studies from T-box gene family–deficient mice demonstrate that myocardium-specific inactivation of *Tbx2* or *Tbx3* leads to the formation of fast conducting accessory pathways, malformation of the annulus fibrosus, and ventricular preexcitation [106, 107]. More recently, the myosin heavy chain 6 gene (*MYH6*) has also been identified as a novel candidate locus responsible for WPW syndrome [108]. Defects in this gene were previously identified in patients with atrial septal defects, cardiomyopathies, and sick sinus syndrome.

Conclusions and Take-Home Messages

1. Recent studies have identified several rare genetic variants associated with WPW syndrome.
2. Present data account for only a limited percentage of the heritability of WPW syndrome.
3. Patients with heritable WPW syndrome have a phenotype that is clearly different from that of those with sporadic WPW syndrome, who typically have structurally normal hearts.
4. No gene defect associated with typical WPW syndrome has yet been identified.
5. In most well-recognized cases, ventricular preexcitation is accompanied by various cardiac or noncardiac clinical manifestations.
6. Integration of next-generation sequencing technologies, improved identification of disease-causing genetic variants, and a more complete understanding of causative mechanisms behind WPW syndrome risk loci will be required.

Acknowledgment

The study was supported by grants from the National Natural Science Foundation of China (NSFC-81400259) and the Natural Science Foundation of Guangdong Province (2014A030310470) to Yang Liu.

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