Cardiology in the Young

cambridge.org/cty

Brief Report

Cite this article: Umapathi KK, Schmidt SB, and Kohli U (2025) A rare genetic variant in *PRDM16* is associated with Wolff–Parkinson–White syndrome with complex accessory pathway characteristics and left ventricular non-compaction cardiomyopathy. *Cardiology in the Young* **35**: 620–627. doi: 10.1017/S1047951124036631

Received: 28 July 2024
Revised: 7 December 2024
Accepted: 10 December 2024
First published online: 3 February 2025

Keywords:
PRDM16; Wolff–Parkinson–White; left ventricular non-compaction

Corresponding author:
Utkarsh Kohli; Email: uk10004@hsc.wvu.edu

A rare genetic variant in *PRDM16* is associated with Wolff–Parkinson–White syndrome with complex accessory pathway characteristics and left ventricular non-compaction cardiomyopathy

Krishna Kishore Umapathi[1], Stanley B. Schmidt[2] and Utkarsh Kohli[3]

[1]Division of Pediatric Cardiology, Department of Pediatrics, Charleston Area Medical Center, Charleston, WV, USA; [2]Department of Cardiology, Division of Electrophysiology, West Virginia University School of Medicine and Heart and Vascular Institute, Morgantown, WV, USA and [3]Division of Pediatric Cardiology, Department of Pediatrics, West Virginia University School of Medicine and West Virginia University Children's Heart Center, Morgantown, WV, USA

Abstract

Not only has Wolff–Parkinson–White syndrome been associated with congenital cardiac abnormalities and cardiomyopathies, but familial clustering of Wolff–Parkinson–White syndrome has also been reported. Despite these well-known associations, direct genetic aetiology is rarely implicated in patients with Wolff–Parkinson–White syndrome. We report a 17-year-old girl with Wolff–Parkinson–White syndrome and left ventricular non-compaction cardiomyopathy due to a rare genetic variant in PR-domain containing protein 16. The report is supplemented by a comprehensive review of literature on association between *PRDM16*, left ventricular non-compaction and Wolff–Parkinson–White syndrome.

Background

Wolff–Parkinson–White syndrome has been associated with congenital cardiac abnormalities such as corrected transposition of great arteries [1] and Ebstein's anomaly of tricuspid valve[2] and cardiomyopathies including left ventricular non-compaction and hypertrophic cardiomyopathy.[3,4] Familial clustering of Wolff–Parkinson–White syndrome has also been reported.[5] Despite these well-known associations, direct genetic aetiology is rarely implicated in patients with Wolff–Parkinson–White syndrome.[6] We report a 17-year-old girl with Wolff–Parkinson–White syndrome and left ventricular non-compaction cardiomyopathy due to a rare genetic variant in PR-domain containing protein 16 (PRDM16). The report is supplemented by a comprehensive review of literature.

Case report

A 17-year-old girl presented with palpitations and Wolff–Parkinson–White pattern on electrocardiogram (Figure 1). Her echocardiogram was suggestive of left ventricular non-compaction with preserved ejection fraction (Figure 2A, Video 1). This was confirmed on cardiac magnetic resonance imaging per criteria proposed by Petersen et al (Figure 2B, Video 2).[7] She underwent an exercise stress test during which pre-excitation persisted at a peak heart rate of 171 beats per minute suggesting a possible high-risk pathway. She subsequently underwent an electrophysiology study during which orthodromic reentrant tachycardia was induced (cycle length of 460 msec) with programmed atrial stimulation. On decremental atrial pacing, the accessory pathway block cycle length was < 200 milliseconds and the shortest preexcited RR interval during atrial fibrillation measured 174 msec (Figure 3), findings which confirmed the pathway to be high risk. The episode of atrial fibrillation resulted in haemodynamic instability and required immediate cardioversion. Mapping was therefore only performed during pre-excited sinus rhythm. Earliest ventricular activation during sinus rhythm was noted over a broad area in mid coronary sinus and superolateral mitral annulus. However, application of radiofrequency energy at these sites was not successful in eliminating pre-excitation (Figure 4). She was started on sotalol until she underwent another EP study a month later. This time, the earliest ventricular activation during sinus rhythm was recorded over a broad area located from 2 to 4 o'clock along the mitral valve annulus. Empiric radiofrequency ablation was performed at the site. Orthodromic reentrant tachycardia was induced following initial ablations (Figure 5A), but no tachycardia could be induced following consolidation of the site. No ventriculoatrial conduction was noted following consolidation. Anterograde accessory pathway conduction, however, persisted, but antegrade pathway block occurred at an atrial

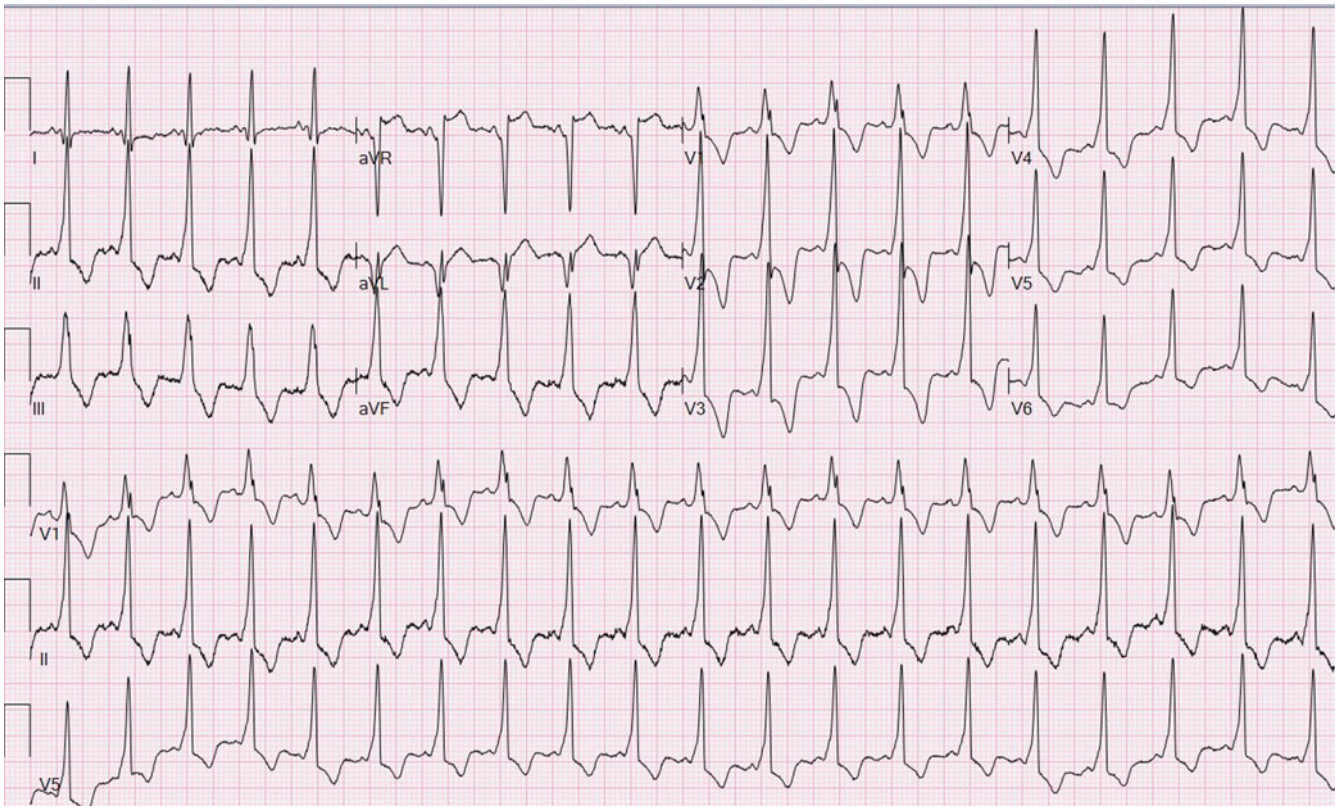

Figure 1. 12-lead electrocardiogram shows ventricular pre-excitation with left anterior pathway location.

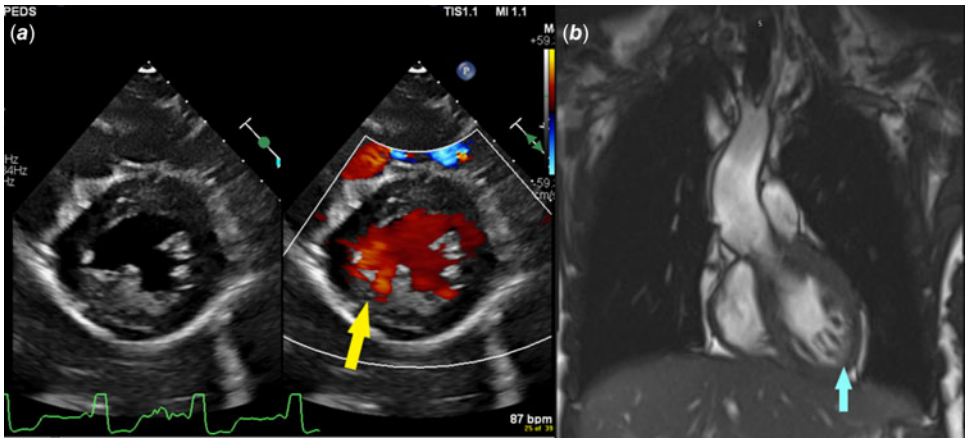

Figure 2. Panel A: parasternal short axis 2D echocardiographic still frame image with colour compare shows left ventricular non-compaction. With colour, flow is noted within crypts. Panel B: the diagnosis is confirmed on a cardiac MRI which shows a ratio of non-compacted mass to total mass of 34 % (> 25% diagnostic of non-compaction).

pacing cycle length of 450 msec suggesting that the pathway had been modified. Eighteen months following the second ablation, the patient presented to the emergency department in supraventricular tachycardia, which was terminated with adenosine (Figure 5B). She is currently treated with flecainide 75 mg twice daily and is doing well.

The family history was negative for arrhythmias or cardiomyopathies. Genetic testing (Invitae arrhythmia and cardiomyopathy panel, San Francisco, CA) revealed a variant of uncertain significance in the *PRDM16* (c.2666C > T, p.Pro889Leu). This sequence change replaces proline with leucine at codon 889 of the PRDM16 protein. This missense mutational change has been observed in individuals with Wolff–Parkinson–White syndrome.[8] There is also preliminary evidence supporting a correlation with autosomal dominant left ventricular non-compaction (MedGen UID: 349005) and dilated cardiomyopathy (OMIM: 615373). This variant is present in population databases (rs201814961, gnomAD 0.03%). ClinVar also contains an entry for this variant (Variation ID: 487607).

She lives with her adoptive parents and has 5 half-siblings from the same biological mother but different fathers. These siblings have undergone testing and have had negative genetic testing, electrocardiograms, and echocardiograms. She also has a full biological sibling who lives with her biological father. She is, however, not in contact with her biological family, and it is therefore not known whether her full biological sibling and her biological parents have been tested.

https://doi.org/10.1017/S1047951124036631 Published online by Cambridge University Press

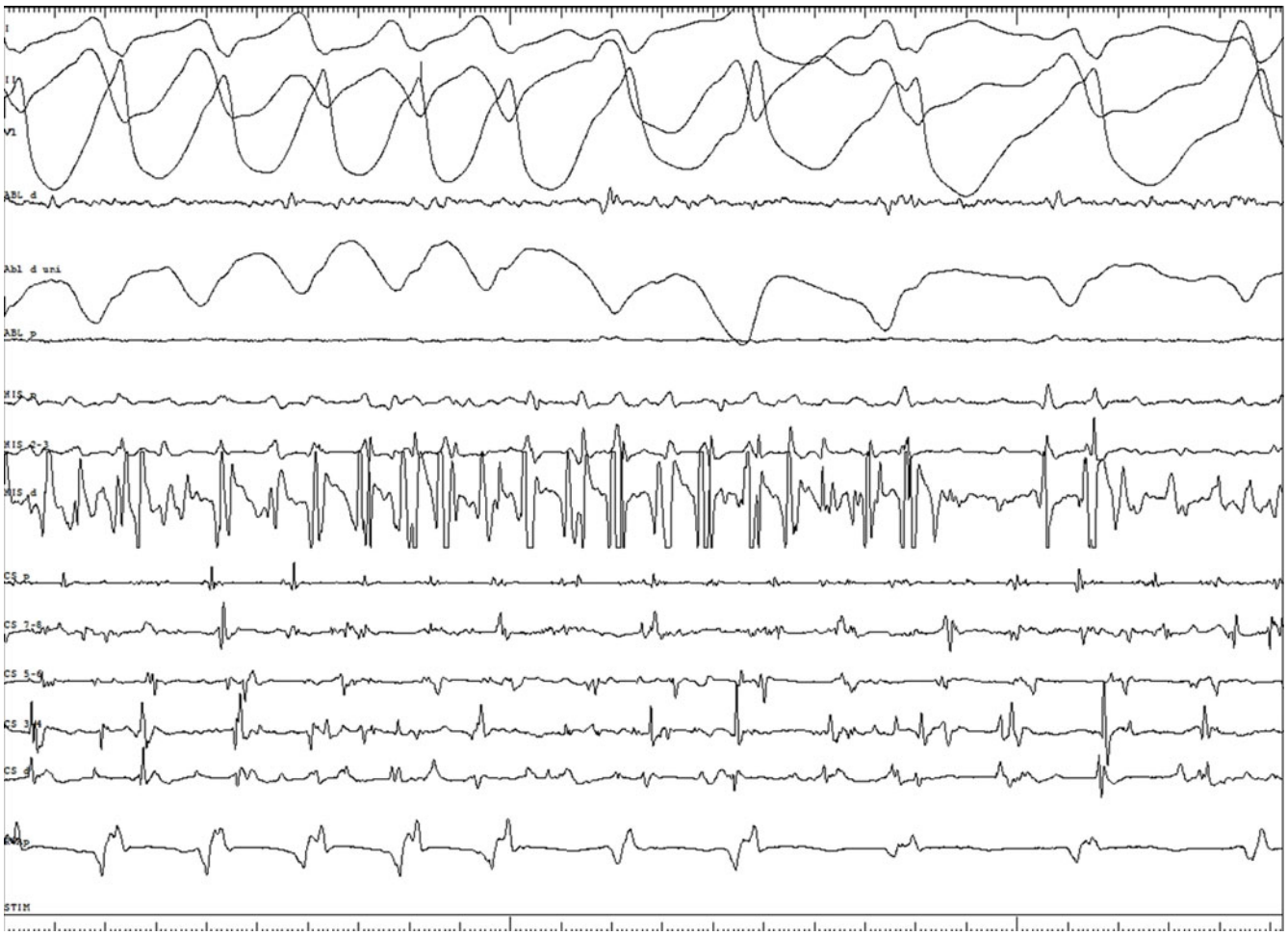

Figure 3. Shortest preexcited RR interval during atrial fibrillation measures 174 msec suggesting a high-risk pathway.

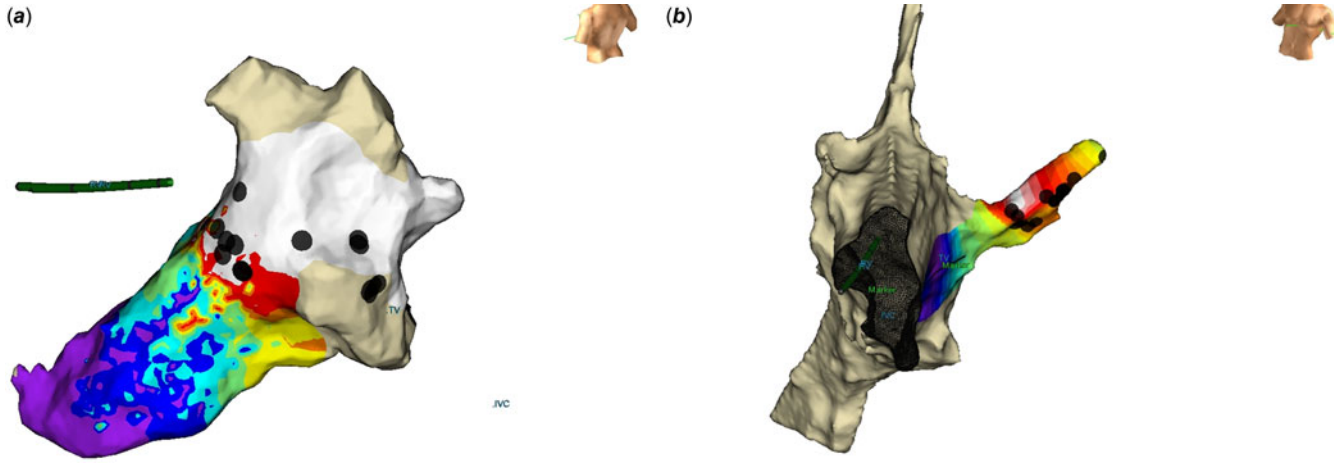

Figure 4. Broad area of RF ablation along the lateral mitral annulus (Panel A) and coronary sinus (Panel B) failed to eliminate pre-excitation.

Discussion

The prevalence of Wolff–Parkinson–White varies from 3 to 11% in patients with left ventricular non-compaction,[3,9,10,11] which is much higher than the estimated 0.1–0.3% prevalence reported in the general population.[12] It is hypothesised that primitive AV connections can persist in patients with left ventricular non-compaction due to an arrest in cardiac development, resulting in direct continuity between the atrial and ventricular myocardium across the fibrous annulus.[13] More importantly, in a large cohort of patients with left ventricular non-compaction, 84% of patients with Wolff–Parkinson–White pattern were reported to have cardiac dysfunction compared to 52% of those without Wolff–Parkinson–

https://doi.org/10.1017/S1047951124036631 Published online by Cambridge University Press

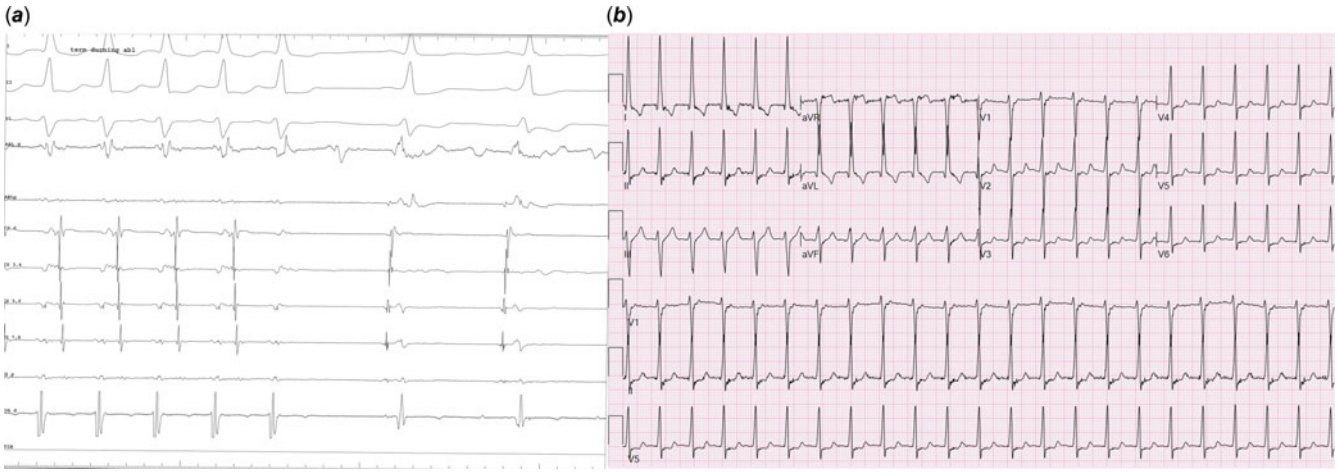

Figure 5. Panel a shows loss of retrograde pathway conduction with RF ablation during the second EP study. Panel B shows narrow QRS SVT (orthodromic reentrant tachycardia) 18 months after second ablation which required adenosine for termination.

White pattern suggesting that ventricular pre-excitation could be associated with a risk of cardiac decompensation in patients with left ventricular non-compaction.[3]

The familial form constitutes approximately 20–40% of all patients with left ventricular non-compaction.[14] The first genetic mutation reported in children with left ventricular non-compaction involved the TAFAZZIN gene in patients with Barth syndrome.[15] However, accumulating genetic data indicates that left ventricular non-compaction is genetically heterogeneous[16] with mutations in *MYH7*, *TTN,* and *MYBPC3* being the most common.[17] Wolff–Parkinson–White syndrome is mostly sporadic with rare reports of genetic associations.[6,8] The gain-of-function mutation in *PRKAG2*, which encodes the gamma-2 regulatory subunit of adenosine monophosphate activated protein kinase, is most commonly implicated in familial Wolff–Parkinson–White syndrome. Hypertrophic cardiomyopathy is often an associated finding in these patients.[18] In addition, variants in genes associated with hypertrophic cardiomyopathy such as *MYH6* (c.5653G > A; pGlu1885Lys) and *MYH7* have also been associated with Wolff–Parkinson–White syndrome.[19,20]

PRDM16 (positive regulatory domain 16) functions as a compact myocardium-enriched transcription factor and is involved in the activation of genes required for compact myocardium growth and in the repression of genes associated with trabeculae formation. In *PRDM16* knockout mice, the development of left ventricular non-compaction likely results from a shift in the transcriptional profile of compact cardiomyocytes.[21] Consistent with data from *PRDM16* knockout mice, *PRDM16* mutations have been associated with non-syndromic forms of left ventricular non-compaction in humans.[22] In particular, truncating variants in *PRDM16* have been associated with severe left ventricular non-compaction.[23] The frequency of *PRDM16* variants in patients with left ventricular non-compaction has been estimated at 0.5 to 4%.[24,25]

Besides association with left ventricular non-compaction, patients with *PRDM16* mutation have been noted to have Wolff–Parkinson–White pattern and supraventricular tachycardia.[8] The first reported patient was Caucasian who carried a *de novo* missense mutation [c.2666C > T, *p.* (Pro889Leu)], which is identical to the mutation carried by our patient. The second reported patient was Hispanic and had an inherited missense mutation [c.2855C > T, p. (Thr952Met)]. He also had atrial septal defect, ventricular septal defect, and hypothyroidism. They both, however, did not have any evidence of cardiomyopathy. There are two other submissions in ClinVar of *PRDM16* mutations in patients with Wolff–Parkinson–White syndrome including [c.1642C > A (p.Pro548Thr)] and [c.706G > A (p.Asp236Asn)]. The second patient also had left ventricular non-compaction. Thus, there is accumulating evidence that genetic mutations in *PRDM16* can be associated with both Wolff–Parkinson–White syndrome and left ventricular non-compaction. This, however, is the first detailed report where a genetic mutation in *PRDM16* resulted in a combined phenotype of both Wolff–Parkinson–White syndrome and left ventricular non-compaction.

Less than 100 patients with Wolff–Parkinson–White and left ventricular non-compaction have been reported till date. Characteristics of these patients with both Wolff–Parkinson–White syndrome and left ventricular non-compaction are summarised in Table 1. It is noteworthy that despite left ventricular non-compaction being left-sided disease, the accessory pathways in patients with left ventricular non-compaction can either be left or right sided. Brescia et al and Paszkowska et al each described a patient each with Wolff–Parkinson–White pattern within their left ventricular non-compaction cohorts, but no accessory pathway was identified on the electrophysiology study suggesting that the patients had pseudo pre-excitation.[10,46] Howard et al reported that 12 out of their cohort of 38 patients with Wolff–Parkinson–White syndrome and left ventricular non-compaction underwent an ablation procedure with a reported acute success rate of 83%. Four patients with cardiac dysfunction were successfully ablated, with 3 showing improvement in cardiac function.[3] The authors concluded that the presence of an accessory pathway in left ventricular non-compaction contributed to left ventricular dyssynchrony and eventually systolic dysfunction, which could increase the risk of arrhythmias and sudden cardiac death. They emphasised that ablation could improve left ventricular ejection fraction in these patients, implicating Wolff–Parkinson–White pattern as a bad prognostic indicator in patients with left ventricular non-compaction.[3]

Electrophysiologic characteristics of PRDM16-associated accessory pathways have not been well characterised. Our patient had a broad and likely epicardial pathway that could not be completely ablated despite two attempted ablations by experienced operators suggesting that accessory pathway ablation in patients

https://doi.org/10.1017/S1047951124036631 Published online by Cambridge University Press

Table 1. Characteristics of patients with WPW and LVNC

Study author	Age (years)	Gender	Race	Arrhythmias	EF	Pathway location/EP study and ablation	Cardiac anomalies	Other anomalies
Ichida et al[26]	4	M	A	None	55%	Not reported	None	
Ichida et al[26]	2.9	M	A	None	↓	Not reported	None	Cataract
Ichida et al[26]	0.2	F	A	SVT	66%	Not reported	None	
Ichida et al[26]	0.2	F	A	SVT	↓ 41%	Not reported	PHTN	Facial dysmorphism
Hussein et al[27]	5.5	F	Not known	VE	N	Not performed	Mitral regurgitation, septal dyssynchrony	
Yasukawa et al[28]	0.75	F	A	VE, VF	↓	Not reported	None	Sudden death due to VF
Ozkutlu et al[29]	5	M	A	SVT	56%		Congestive heart failure	
Nihei et al[30]	0.75	F	A		↓↓	Right AS	None	Sudden death
Nihei et al[30]	0.5	F	A	None	81%	Right AS	Cardiomegaly on CXR	
Nihei et al[30]	9	F	A	None	N	Right AS	None	
Jost et al[31] (n = 5)			Not known	Not reported		Not reported	Ebstein's anomaly	
Celiker et al[32]	7	M	A	VE, SVT	↓	Not reported	None	
El-Menyar et al[33]			A			EP study and catheter ablation		
Fichet et al[34]	18	F	Not reported	Aborted VF arrest, NSVTx2, SVT	N	Left free wall AP (APERP: 290 ms), successful RF ablation, inducible polymorphic VT, ICD	None	Melnick Fraser Syndrome (Facial dysmorphism, deafness, VUR)
Munehisa et al[35]	24	F (pregnant)	A	None	↓ 45%	Not reported	Restrictive dysfunction during pregnancy	Genetic testing negative
Salerno et al[36]	0.5	M	Not reported	Bradycardia	N	Moderate risk pathway on transoesophageal EP study, no inducible arrhythmia	LVH	Died after an episode of respiratory distress
Ho et al[37]	14	M	AA	None	N	Right posterior pathway successfully ablated using RF, no inducible arrhythmia during EP study	None	ICD also implanted
Yoshinga et al[38]	0.12	M	A	SVT	↓ 50%	EP study and ablation, pathway location not reported	None	Rapid decline in EF requiring heart failure therapy to stabilize
Garcia-Diaz et al[39]	0.1	M	C	None	↓ 52%	Not reported	HCM with biventricular hypertrophy	Mitochondrial disorder

Table 1. (*Continued*)

Malagoli et al[40]	14	M	AA	None		Left posteroseptal AP	Ebstein's anomaly, BAV	
Alper et al[41]	28	F	A	Inducible ORT during EP study	65%	ParaHisian pathway successfully ablated using RF (APERP: 270 msec)	Grade 1 diastolic dysfunction	Fabry disease
Finsterer et al[42]	66	M	C	VE, NSVT	N	Left lateral AP but ablation not performed during EP study due to bizarre conduction system	Enlarged atria, LVH, diastolic dysfunction, hypertension	LHON (m.3460G>A), ICD proposed but refused by the patient
Finsterer et al[42,43]	48	M	C					LHON (m.3460G>A), sudden death
Moceri et al[44]	58	M	Not reported	AF, VF	↓	EP study performed but pathway location not reported	Enlarged LV	
Sengul et al[11] (n = 2)			A		>45%	EP study and catheter ablation (n = 1)		
Chin et al[45]	4	F	Not reported	SVT, VT, VF	↓	Not reported		
Paszkowska et al[10]			Not reported	SVT	N	No AP noted on EP study (pseudo pre-excitation)		
Brescia et al[46] (n = 20)				SVT (n = 6), WPW, inducible VT (n = 4), spontaneous monomorphic VT (n = 2)		EP study with successful SVT ablation (n = 5), monomorphic VT ablation (n = 2), ventricular stimulation study (n = 11), pseudo pre-excitation (n = 1)		ICD implantation (n = 11), transplant (n = 2), sudden death (n = 1)
Howard et al[3] (n = 38)	0.3 - 12.6	55% M	34% C 37% AA 29% H	45% SVT, 47% Dyssynchrony	↓ 84%		Enlarged LV 45%, HCM 13%, Mixed 13%	Sudden death (n = 1) Cardiac death or transplantation (n = 8, 21%)

WPW = Wolff–Parkinson–White; LVNC = Left ventricular non-compaction; *M* = Male; *F* = Female; *A* = Asian, AA = African; *C* = Caucasian; *H* = Hispanic; SVT = Supraventricular tachycardia; VE = Ventricular ectopy; NSVT = Non-sustained ventricular tachycardia; VF = Ventricular fibrillation; AF = Atrial fibrillation; EF = Ejection fraction; *N* = Normal; PHTN = Pulmonary hypertension; CXR = Chest X-ray; VUR = Vesicoureteral reflux; AS = Anteroseptal; APERP = Accessory pathway effective refractory period; ORT = Orthodromic reentrant tachycardia; RF = Radiofrequency; LVH = Left ventricular hypertrophy; HCM = Hypertrophic cardiomyopathy; BAV = Bicuspid aortic valve; LV = Left ventricle; ICD = Implantable cardioverter defibrillator; LHON = Leber's hereditary optic neuropathy.

with *PRDM16* mutation associated with Wolff–Parkinson–White syndrome, and left ventricular non-compaction may be challenging due to complex pathway characteristics. These findings inform the need for systematic evaluation of association between *PRDM16* mutation, left ventricular non-compaction, and Wolff–Parkinson–White pattern.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951124036631.

Data availability statement. The majority of data associated with this study are provided in text and figures. Additional data will be made available upon request.

Financial support. This study was supported by an internal grant from the Department of Pediatrics at West Virginia University.

Competing interests. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

References

1. Keller N, Søorensen MR. Korrigeret transposition af de store arterier med venstresidig Ebstein-lignende anomali og WPW-syndrome. Et tilfaelde diagnosticeret ved ekkokardiografisk sektorscanning [Corrected transposition of the great arteries with a left-sided Ebstein-like anomaly and WPW-syndrome. A case diagnosed by two-dimensional echocardiography]. Ugeskr Laeger 1981; 143: 1971–1972, Danish. PMID: 7303220.
2. Delhaas T, Sarvaas GJ, Rijlaarsdam ME, et al. A multicenter, long-term study on arrhythmias in children with Ebstein anomaly. Pediatr Cardiol 2010; 31: 229–233. doi: 10.1007/s00246-009-9590-3. PMID: 19937010; PMCID: PMC2817085.
3. Howard TS, Valdes SO, Hope KD, et al. Association of wolff-parkinson-white with left ventricular noncompaction cardiomyopathy in children. J Card Fail 2019; 25: 1004–1008. doi: 10.1016/j.cardfail.2019.09.014. Epub 2019 Oct 15. PMID: 31626950.
4. Perosio AM, Suarez LD, Bunster AM, et al. Pre-excitation syndrome and hypertrophic cardiomyopathy. J Electrocardiol 1983; 16: 29–40. doi: 10.1016/s0022-0736(83)80156-3. PMID: 6682136.
5. Vidaillet HJ Jr, Pressley JC, Henke E, Harrell FE Jr, German LD. Familial occurrence of accessory atrioventricular pathways (preexcitation syndrome). N Engl J Med 1987; 317: 65–69. doi: 10.1056/NEJM198707093170201. PMID: 3587328.
6. Gollob MH, Green MS, Tang AS, Roberts R. PRKAG2 cardiac syndrome: familial ventricular preexcitation, conduction system disease, and cardiac hypertrophy. Curr Opin Cardiol 2002; 17: 229–234. doi: 10.1097/00001573-200205000-00004. PMID: 12015471.
7. Petersen SE, Selvanayagam JB, Wiesmann F, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2005; 46: 101–105. doi: 10.1016/j.jacc.2005.03.045. PMID: 15992642.
8. Coban-Akdemir ZH, Charng WL, Azamian M, et al. Wolff-parkinson-white syndrome: De novo variants and evidence for mutational burden in genes associated with atrial fibrillation. Am J Med Genet A 2020; 182: 1387–1399. doi: 10.1002/ajmg.a.61571. Epub 2020 Mar 31. PMID: 32233023; PMCID: PMC7275694.
9. Tian T, Yang Y, Zhou L, et al. Left ventricular non-compaction: a cardiomyopathy with acceptable prognosis in children. Heart Lung Circ 2018; 27: 28–32. doi: 10.1016/j.hlc.2017.01.013. Epub 2017 Mar 1. PMID: 28343948.
10. Paszkowska A, Mirecka-Rola A, Piekutowska-Abramczuk D, et al. Spectrum of clinical features and genetic profile of left ventricular noncompaction cardiomyopathy in children. Cardiogenetics 2021; 11: 191–203. doi: 10.3390/cardiogenetics11040020.
11. Sevinc SengulF, ErgulY, AyyildizP, et al. Effects of systolic dysfunction on clinical and diagnostic parameters in pediatric patients with isolated left ventricular non-compaction. Turk Kardiyol Dern Ars 2023; 51: 333–342.
12. CohenMI, TriedmanJK, CannonBC. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). Heart Rhythm 2012; 9: 1006–1024. doi: 10.1016/j.hrthm.2012.03.050. Epub 2012 May 10. PMID: 22579340.
13. Ichida F. Left ventricular noncompaction. Circulation Journal 2009; 73: 19–26. doi: 10.1253/circj.cj-08-0995. Epub 2008 Dec 4. PMID: 19057090.
14. Ichida F. Left ventricular noncompaction - risk stratification and genetic consideration. J Cardiol 2020; 75: 1–9. doi: 10.1016/j.jjcc.2019.09.011. Epub 2019 Oct 17. PMID: 31629663.
15. Bleyl SB, Mumford BR, Thompson V, et al. Neonatal, lethal noncompaction of the left ventricular myocardium is allelic with Barth syndrome. Am J Hum Genet 1997; 61: 868–872. doi: 10.1086/514879. PMID: 9382097; PMCID: PMC1715997.
16. Finsterer J, Stöllberger C. Left ventricular noncompaction syndrome: genetic insights and therapeutic perspectives. Curr Cardiol Rep 2020; 22: 84. doi: 10.1007/s11886-020-01339-5. PMID: 32648009.
17. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. Lancet 2015; 386: 813–825. doi: 10.1016/S0140-6736(14)61282-4. Epub 2015 Apr 9. PMID: 25865865.
18. Wolf CM, Arad M, Ahmad F, et al. Reversibility of PRKAG2 glycogen-storage cardiomyopathy and electrophysiological manifestations. Circulation 2008; 117: 144–154. doi: 10.1161/CIRCULATIONAHA.107.726752. Epub 2007 Dec 24. PMID: 18158359; PMCID: PMC2957811.
19. Bowles NE, Jou CJ, Arrington CB, et al. Baylor hopkins centers for mendelian genomics. Exome analysis of a family with wolff-parkinson-white syndrome identifies a novel disease locus. Am J Med Genet A 2015; 167A: 2975–2984. doi: 10.1002/ajmg.a.37297. Epub 2015 Aug 18. PMID: 26284702; PMCID: PMC4896306.
20. Bobkowski W, Sobieszczańska M, Turska-Kmieć A, et al. Mutation of the MYH7 gene in a child with hypertrophic cardiomyopathy and wolff-parkinson-white syndrome. J Appl Genet 2007; 48: 185–188. doi: 10.1007/BF03194677. PMID: 17495353.
21. Wu T, Liang Z, Zhang Z, et al. PRDM16 Is a compact myocardium-enriched transcription factor required to maintain compact myocardial cardiomyocyte identity in left ventricle. Circulation 2022; 145: 586–602. doi: 10.1161/CIRCULATIONAHA.121.056666. Epub 2021 Dec 17. PMID: 34915728; PMCID: PMC8860879.
22. Arndt AK, Schafer S, Drenckhahn JD, et al. Fine mapping of the 1p36 deletion syndrome identifies mutation of PRDM16 as a cause of cardiomyopathy. Am J Hum Genet 2013; 93: 67–77. doi: 10.1016/j.ajhg.2013.05.015. Epub 2013 Jun 13. PMID: 23768516; PMCID: PMC3710750.
23. Mazzarotto F, Hawley MH, Beltrami M, et al. Systematic large-scale assessment of the genetic architecture of left ventricular noncompaction reveals diverse etiologies. Genet Med 2021; 23: 856–864. doi: 10.1038/s41436-020-01049-x. Epub 2021 Jan 26. PMID: 33500567; PMCID: PMC8105165.
24. Dong X, Fan P, Tian T, et al. Recent advancements in the molecular genetics of left ventricular noncompaction cardiomyopathy. Clin Chim Acta 2017; 465: 40–44. doi: 10.1016/j.cca.2016.12.013. Epub 2016 Dec 15. PMID: 27989498.
25. Peña-Peña ML, Trujillo-Quintero JP, García-Medina D, Cantero-Pérez EM, De Uña-Iglesias D, Monserrat L. Identification by next-generation sequencing of 2 novel cases of noncompaction cardiomyopathy associated with 1p36 deletions. Rev Esp Cardiol (Engl Ed) 2020; 73: 780–782. doi10.1016/j.rec.2020.02.004. English, Spanish. Epub 2020 Mar 16. PMID: 32192878.
26. Ichida F, Hamamichi Y, Miyawaki T, et al. Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. J Am Coll Cardiol 1999; 34: 233–240. doi: 10.1016/s0735-1097(99)00170-9. PMID: 10400016.
27. Hussein A, Schmaltz AA, Trowitzsch E. Isolierte Fehlentwicklung ("Noncompaction") des Myokards bei drei Kindern [Isolated abnormality

("noncompaction") of the myocardium in 3 children]. Klin Padiatr 1999; 211: 175–178. doi: 10.1055/s-2008-1043782. German. PMID: 10412129.
28. Yasukawa K, Terai M, Honda A, Kohno Y. Isolated noncompaction of ventricular myocardium associated with fatal ventricular fibrillation. Pediatr Cardiol 2001; 22: 512–514. doi: 10.1007/s002460010286. Epub 2001 Dec 4. PMID: 11894157.
29. Ozkutlu S, Ayabakan C, Celiker A, Elshershari H. Noncompaction of ventricular myocardium: a study of twelve patients. J Am Soc Echocardiogr 2002; 15: 1523–1528. doi: 10.1067/mje.2002.128212. PMID: 12464922.
30. Nihei K, Shinomiya N, Kabayama H, et al. Wolff-parkinson-white (WPW) syndrome in isolated noncompaction of the ventricular myocardium (INVM). Circ J 2004; 68: 82–84. doi: 10.1253/circj.68.82. PMID: 14695471.
31. Attenhofer Jost CH, Connolly HM, O.'Leary PW, Warnes CA, Tajik AJ, Seward JB. Left heart lesions in patients with Ebstein anomaly. Mayo Clin Proc 2005; 80: 361–368. doi: 10.4065/80.3.361. PMID: 15757018.
32. Celiker A, Ozkutlu S, Dilber E, Karagöz T. Rhythm abnormalities in children with isolated ventricular noncompaction. Pacing Clin Electrophysiol 2005; 28: 1198–1202. doi: 10.1111/j.1540-8159.2005.09498.x. PMID: 16359286.
33. El-Menyar AA, Gendi SM, Numan MT. Noncompaction cardiomyopathy in the state of Qatar. Saudi Med J 2007; 28: 429–434. Erratum in: Saudi Med J. 2008 May;29(5):787. PMID: 17334474.
34. Fichet J, Legras A, Bernard A, Babuty D. Aborted sudden cardiac death revealing isolated noncompaction of the left ventricle in a patient with wolff-parkinson-white syndrome. Pacing Clin Electrophysiol 2007; 30: 444–447. doi: 10.1111/j.1540-8159.2007.00690.x. PMID: 17367369.
35. Munehisa Y, Watanabe H, Kosaka T, Kimura A, Ito H. Successful outcome in a pregnant woman with isolated noncompaction of the left ventricular myocardium. Intern Med 2007; 46: 285–289. doi: 10.2169/internalmedicine.46.6186. Epub 2007 Mar 15. PMID: 17379995.
36. Salerno JC, Chun TU, Rutledge JC. Sinus bradycardia, wolff parkinson white, and left ventricular noncompaction: an embryologic connection? Pediatr Cardiol 2008; 29; 679–682. doi: 10.1007/s00246-007-9043-9. Epub 2007 Sep 1. PMID: 17786379.
37. Ho TQ, Lenihan DJ, Kantharia BK, Dougherty AH. Noncompacted ventricular myocardium: is syncope the only warning sign? Am J Med Sci 2010; 339: 497–500. doi: 10.1097/MAJ.0b013e3181d96ea8. PMID: 20386101.
38. Yoshinaga M, Ushinohama H, Sato S, et al. Electrocardiographic screening of 1-month-old infants for identifying prolonged QT intervals. Circ Arrhythm Electrophysiol 2013; 6: 932–938. doi: 10.1161/CIRCEP.113.000619. Epub 2013 Sep 13. PMID: 24036083.
39. García-Díaz L, Coserria F, Antiñolo G. Hypertrophic cardiomyopathy due to mitochondrial disease: prenatal diagnosis, management, and outcome. Case Rep Obstet Gynecol 2013; 2013: 472356. doi: 10.1155/2013/472356. Epub 2013 Jan 3. PMID: 23346437; PMCID: PMC3549387.
40. Malagoli A, Rossi L, Mastrojanni C, Villani GQ. A perfect storm: wolf parkinson white syndrome, Ebstein's anomaly, biventricular non-compaction, and bicuspid aortic valve. Eur Heart J Cardiovasc Imaging 2014; 15: 827. doi: 10.1093/ehjci/jet282. Epub 2014 Jan 26. PMID: 24469154.
41. Alper AT, Kaya A, Tekkesin Aİ., Öz A. Wolff-parkinson-white and left ventricular noncompaction in a fabry patient: a case report. Turk Kardiyol Dern Ars 2016; 44: 248–250. doi: 10.5543/tkda.2015.92800. PMID: 27138316.
42. Finsterer J, Stollberger C, Gatterer E. Wolff-Parkinson-White syndrome and noncompaction in Leber's hereditary optic neuropathy due to the variant m.3460G > A. J Int Med Res 2018; 46: 2054–2060. doi: 10.1177/0300060518765846. Epub 2018 Mar 22. PMID: 29562793; PMCID: PMC5991228.
43. Finsterer J, Stöllberger C, Kopsa W, Jaksch M. Wolff-parkinson-white syndrome and isolated left ventricular abnormal trabeculation as a manifestation of leber's hereditary optic neuropathy. Can J Cardiol 2001; 17: 464–466. PMID: 11329546.
44. Moceri P, Bertora D, Cerboni P, Gibelin P. Left ventricular non-compaction associated with wolff-parkinson-white syndrome: echo, contrast-echo and cardiovascular magnetic-resonance data. Arch Cardiovasc Dis 2008; 101: 503–505. doi: 10.1016/j.acvd.2008.06.001. Epub 2008 Jul 21. PMID: 18848694.
45. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium. A study of eight cases. Circulation 1990; 82: 507–513. doi: 10.1161/01.cir.82.2.507. PMID: 2372897.
46. Brescia ST, Rossano JW, Pignatelli R, et al. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. Circulation 2013; 127: 2202–2208. doi: 10.1161/CIRCULATIONAHA.113.002511. Epub 2013 Apr 30. PMID: 23633270.

https://doi.org/10.1017/S1047951124036631 Published online by Cambridge University Press