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Adolescent with Unexplained Cardiac Hypertrophy, Ventricular Pre-Excitation, Conduction System Disease: *PRKAG2* Cardiac Syndrome as a Rare Mimicker of Hypertrophic Cardiomyopathy

E-PAGE ORIGINAL IMAGE

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A 19-year-old male presented to the hospital with chest pain and recurrent syncope. Electrocardiogram and Holter monitoring demonstrated right bundle branch block, left anterior fascicular block, intermittent ventricular pre-excitation, and left ventricular hypertrophy (Figure 1A and B). Echocardiography revealed uniform hypertrophy of the interventricular septum and left ventricle. No significant left ventricular outflow tract obstruction or systolic anterior motion of the mitral valve was observed at rest (Figure 1C and D; Videos 1 and 2). Cardiac magnetic resonance imaging demonstrated biventricular hypertrophy, with evidence of myocardial edema, injury, and fibrosis in hypertrophied regions (Figure 1E-H; Video 3). Based on these initial findings, a preliminary diagnosis of hypertrophic cardiomyopathy was made. Clinical whole-exome sequencing (WES) identified a heterozygous missense rare variant in the *PRKAG2* gene (chr7:151576412; c.905G>A; p.Arg302Gln) (Figure 2A and B). The patient was definitively diagnosed with *PRKAG2* cardiac syndrome.

PRKAG2 cardiac syndrome is a rare autosomal dominant genetic disorder caused by variants in the *PRKAG2* gene, which encodes the γ2 regulatory subunit of 5'-adenosine monophosphate-activated protein kinase.[1] Hallmark features include ventricular preexcitation, supraventricular arrhythmias, conduction system disease, and cardiac hypertrophy.[2] *PRKAG2* cardiac syndrome is frequently misdiagnosed as hypertrophic cardiomyopathy; thus, genetic testing is warranted in patients clinically diagnosed with hypertrophic cardiomyopathy. This case emphasizes that clinicians should consider *PRKAG2* cardiac syndrome in adolescents presenting with myocardial hypertrophy, ventricular pre-excitation, and conduction system disease.

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and accompanying videos.

Declaration of Interests: The authors have no conflicts of interest to declare.

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Video 1: Echocardiography revealed uniform hypertrophy of the interventricular septum and left ventricle.

Video 2: No significant left ventricular outflow tract obstruction or systolic anterior motion of the mitral valve was observed at rest.

Video 3: The short-axis cine images of the entire heart demonstrate uniform hypertrophy of the interventricular septum and left ventricular myocardium. The hypertrophied segments exhibit reduced wall motion amplitude and decreased systolic wall thickening rate.

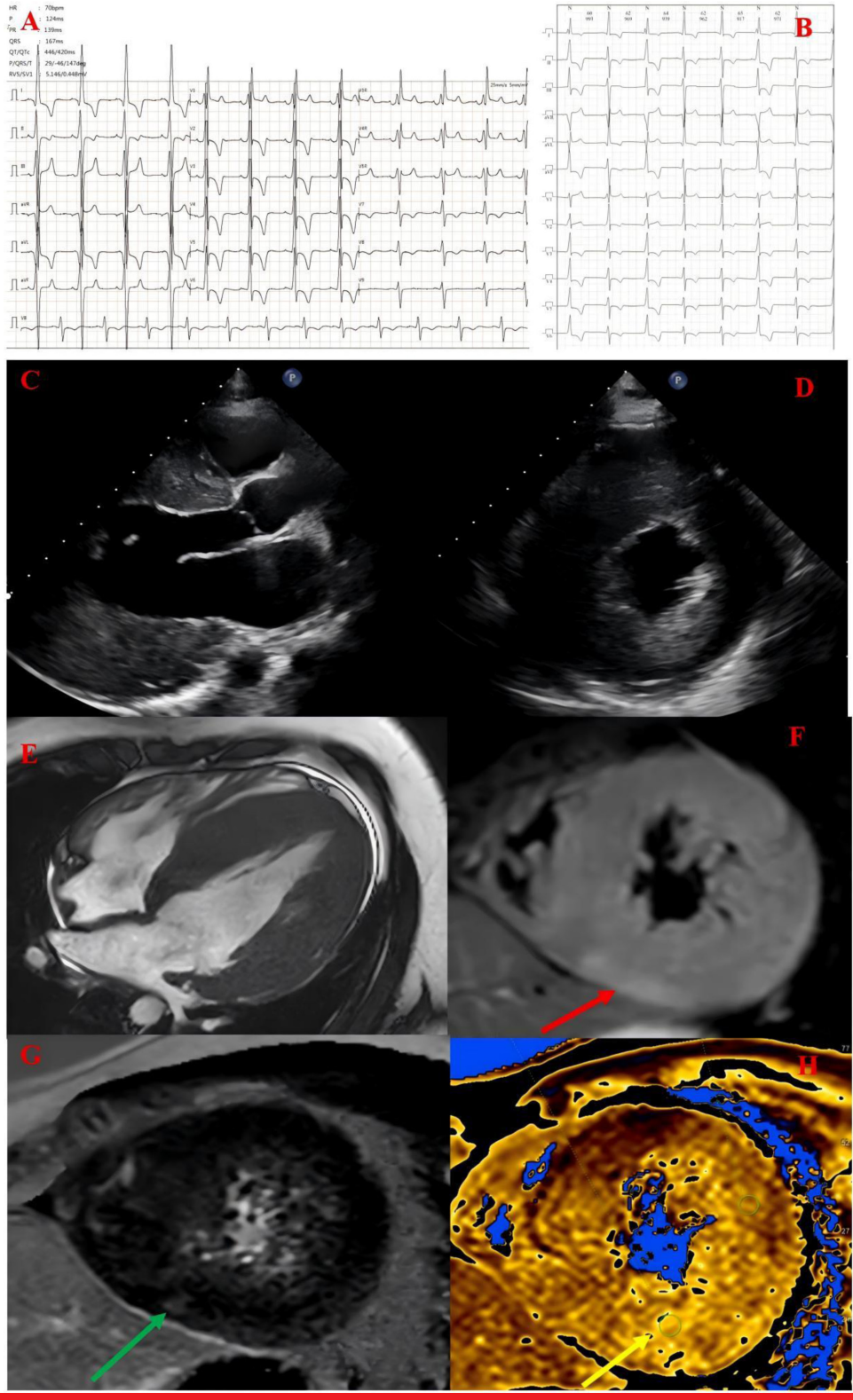

Figure 1. (A) Electrocardiography demonstrated right bundle branch block, left anterior fascicular block, left ventricular hypertrophy, abnormal Q waves in the high lateral leads, and nonspecific ST-T changes; (B) 24-hour Holter Monitoring: Revealed intermittent ventricular pre-excitation, characterized by the occasional presence of delta waves and a short PR interval, suggestive of an accessory pathway; (C-D) Echocardiography revealed uniform hypertrophy of the interventricular septum and left ventricle; (E-F) Cardiac magnetic resonance imaging demonstrates uniform left ventricular hypertrophy with myocardial edema (red arrow); (G) Quantitative T2 mapping revealed myocardial edema with prolonged relaxation times (66.3 ms, green arrow); (H) Cardiac magnetic resonance imaging demonstrates myocardial fibrosis (yellow arrow).

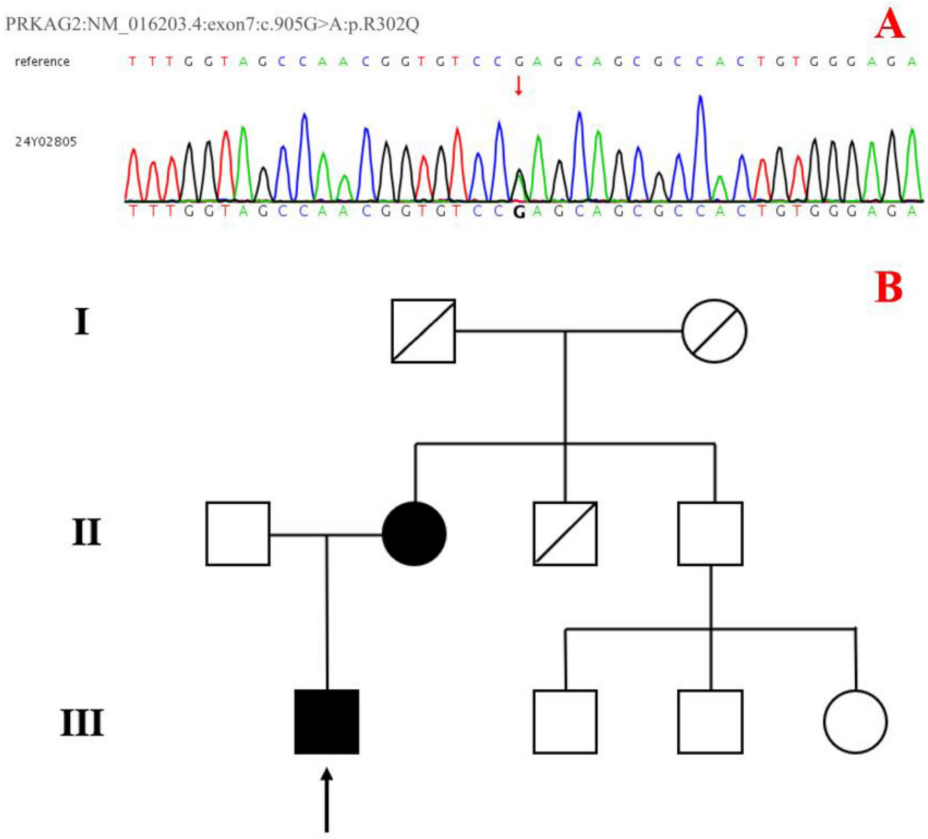

Figure 2. (A) Whole-exome sequencing (WES) identified a heterozygous missense rare variant in the *PRKAG2* gene (chr7:151576412; c.905G>A; p.Arg302Gln), resulting in substitution of arginine by glutamine at codon 302; (B) Pedigree of the family. Whole-exome sequencing revealed that the patient's mother carries the same rare variant, while the father, one of the maternal uncles, and the maternal uncle's three children do not carry the rare variant. The maternal grandparents and another maternal uncle are deceased, and their status is unknown. (The proband is indicated by a black arrow; filled symbols represent carriers of the rare variant, unfilled symbols represent non-carriers; circles represent female family members, squares represent male family members; a slash through the symbol indicates deceased family members).

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