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CASE REPORT

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A case of *MYH7* and *MYH9* genes variants with cardiomyopathy and macrothrombocytopenia

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Key Clinical Message.

A 15-year-old girl developed inherited cardiomyopathy and macrothrombocytopenia revealing pathogenic variants of both *MYH7* and *MYH9* genes. This underlies the importance of repeated genetic testing in diagnosing and managing inherited disorders.

Abstract

The *MYH7* and *MYH9* genes encode for distinct myosin heavy chain proteins. Our case features a 15-year-old girl, presenting with inherited cardiomyopathy and macrothrombocytopenia, revealing distinct pathogenic variants of both *MYH7* and *MYH9* genes. This underlines the relevance of genetic testing and personalized medicine in diagnosing and managing inherited disorders.

KEYWORDS

cardiomyopathy, macrothrombocytopenia, MYH7, MYH9

1 | INTRODUCTION

MYH7 and *MYH9* encode myosin heavy chain proteins. However, they are distinct genes with different functions and locations within the body. The *MYH7* gene, located on chromosome 14q11.2, encodes the cardiac myosin heavy chain beta protein, a major component of heart muscle fibers.[1] Heterozygous mutations in the *MYH7* gene have been associated with various inherited heart diseases, including familial hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and restrictive cardiomyopathy. Pioneering studies by Christine and Jonathan Seidman have led to partial elucidation of the molecular genetic basis of HCM.[2] The discovery of the p.Arg403Glu mutation in the *MYH7* gene, encoding sarcomere protein beta myosin heavy chain (MYH7) in the

French-Canadian family described by Pare et al, paved the way for important subsequent discoveries.[3] The identification of multiple separate mutations in the principal causal genes, all encoding sarcomere proteins, established HCM as a genetically heterogenous disease. Among the known causal genes, MYH7 and myosin binding protein C (MYBPC3) are the two most common, together being responsible for approximately half of the patients with familial HCM.[4,5] The *MYH9* gene, located on chromosome 22q12.3, encodes the nonmuscle myosin heavy chain IIA protein, which plays a role in cell motility, adhesion, and cytokinesis.[6] Heterozygous mutations in the *MYH9* gene have been reported to be linked to several disorders, including May-Hegglin anomaly, Fechtner syndrome, Epstein syndrome, and Sebastian syndrome, all of which are characterized by macrothrombocytopenia, Döhle-like bodies in leukocytes, hearing loss, cataracts, and nephropathy.[7] This report presents a rare case of double *MYH7* and *MYH9* variants that resulted in cardiomyopathy and macrothrombocytopenia.

2 | CASE REPORT

A 15-year-old girl was referred to our hospital for a cardiac workup due to an abnormal electrocardiogram. She had a strong family history of cardiomyopathy and chronic thrombocytopenia (Figure 1). Her mother had DCM, glaucoma, and chronic thrombocytopenia ($60\times10^3/\mu L$), while her maternal grandmother had chronic thrombocytopenia ($80\times10^3/\mu L$). Her elder sister succumbed to the surgical complication of a ventricular septal defect at age three. None of the family members developed congenital hearing loss, cataracts, or nephropathy.

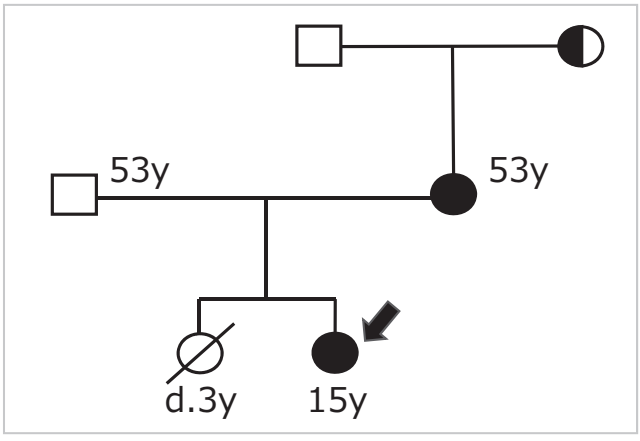

FIGURE 1 Family pedigree chart. The arrow indicates the patient. The right side of the black line corresponds to cardiomyopathy. The black line on the left represents chronic thrombocytopenia.

Echocardiography and electrocardiography demonstrated HCM (Figure 2A), and her blood smear showed macrothrombocytopenia ($66\times10^3/\mu L$) and Döhle-like bodies in neutrophils (Figure 2B). Given the family history of chronic thrombocytopenia and blood smear findings suggestive of MYH9-related disorders, genetic testing for congenital thrombocytopenia was performed. Subsequently, the pathogenic *MYH9* (c.3493C>T,p.Arg1165Cys) gene mutation was identified in both the patient and her mother.[6] Since MYH9-related disorders have not been reported to cause cardiomyopathy, further genetic testing for inherited cardiomyopathy was conducted. A previously reported pathogenic *MYH7* (c.2596T>C,p.Ser866Pro) mutation was detected in both the patient and her mother.[8,9]

3 | DISCUSSION

With the widespread availability of genetic testing for specific conditions, a broad spectrum of clinical features involving multiorgan systems that fall into overlapping phenotypes can be unified under a single monogenic disease, such as GATA2 deficiency, which encompasses MonoMAC syndrome, dendritic cell, monocyte B, and NK lymphoid (DCML) deficiency, Emberger syndrome, and familial predisposition to myelodysplastic syndrome and acute myeloid leukemia.[10] Pediatric patients, in particular, may present with various symptoms associated with a single disease. Consequently, pediatricians often attribute all symptoms to a single condition. However, when symptoms cannot be explained by a single monogenic disease, such as in the case of MYH9-related disorders and cardiomyopathy, reconsideration of alternative causes is warranted.

The underlying mechanisms leading to the coexistence of mutations in both *MYH7* and *MYH9* in the patient and her mother remain elusive. Notably, while the *MYH7* gene is located on chromosome 14q11.2, the *MYH9* gene is located on chromosome 22q12.3. One theory positing a plausible explanation for the simultaneous inheritance of these double variants hinges on the occurrence of a Robertson translocation, a chromosomal event known to amalgamate certain chromosome pairs. We performed an in-depth analysis of peripheral blood cell karyotypes to investigate this possibility further and obtain a definitive answer. However, the findings revealed 46,XX female karyotype effectively ruling out Robertsonian translocation involvement.

Digenic inheritance, a genetic phenomenon wherein mutations in two distinct genes collectively contribute to the manifestation of a disease, has been observed in various disorders, such as Bardet–Biedl syndrome and

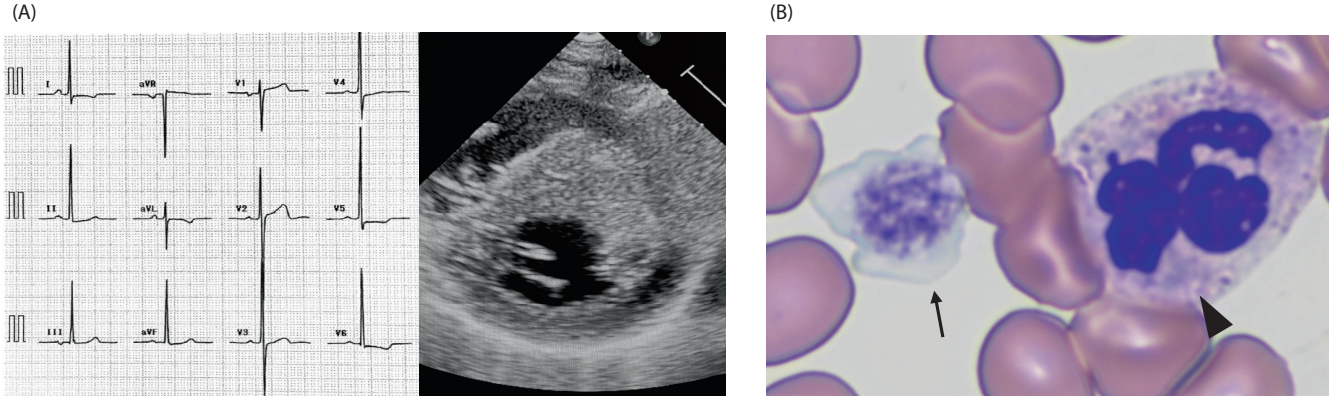

FIGURE 2 Cardiac function test and a blood smear of the patient. (A) Electrocardiography and echocardiography of the patient. Electrocardiography shows a strain pattern in V5 and V6 leads. Echocardiography demonstrates left ventricular hypertrophy. (B) A blood smear of the patient. Giant platelets (arrow) and Döhle-like bodies (arrowhead) are shown.

Axenfeld–Rieger syndrome.[11] Although no specific instances of digenic inheritance involving the *MYH7* and *MYH9* genes have been reported to date, the possibility remains that mutations in both genes encoded for myosin heavy chain protein could interact in unique ways, potentially influencing the development or severity of specific myopathies or related disorders. Further research is needed to explore the role of MYH7-MYH9 digenic inheritance in disease manifestation and its potential implications in diagnostics, prognosis, and targeted therapies.

In conclusion, this rare case emphasizes the importance of genetic testing and personalized medicine in diagnosing and managing inherited disorders. Our findings in this case can guide future research to elucidate the relationship between *MYH7* and *MYH9*.

AUTHOR CONTRIBUTIONS

Yasuhiro Ikawa: Conceptualization; investigation; methodology; project administration; writing – original draft. **Taichi Nakamura:** Conceptualization; writing – review and editing. **Noboru Fujino:** Formal analysis; software; writing – review and editing. **Toru Uchiyama:** Data curation; software; writing – review and editing. **Akira Ishiguro:** Data curation; funding acquisition; software; writing – review and editing. **MIka Takenaka:** Investigation; writing – review and editing. **Yuta Sakai:** Data curation; writing – review and editing. **Kazuhiro Noguchi:** Investigation; writing – review and editing. **Toshihiro Fujiki:** Investigation; writing – review and editing. **Taizo Wada:** Supervision; writing – review and editing.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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