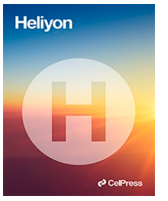
Heliyon 10 (2024) e36203

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

Unraveling MYH9-related disease: A case study on misdiagnosis with idiopathic thrombocytopenic purpura, confirmed through genetic

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ARTICLE INFO

Keywords:
MYH9-RD
Thrombocytopenia
Giant platelets
Dohle-like bodies
Genetic mutation
Misdiagnosis

ABSTRACT

This paper presents a detailed analysis of a case initially misdiagnosed as Idiopathic Thrombocytopenic Purpura (ITP), which was later correctly identified as MYH9-related disease (MYH9-RD), a rare genetic disorder characterized by thrombocytopenia, large platelets, and Döhle-like inclusion bodies in neutrophils. Using advanced slide reading technology, our team identified hallmark features of MYH9-RD in the patient's blood samples, leading to genetic testing that confirmed a spontaneous mutation in the MYH9 gene. This report highlights the diagnostic journey, emphasizing the crucial role of recognizing specific hematologic signs to accurately diagnose MYH9-RD. By comparing our findings with existing literature, we highlight the genetic underpinnings and clinical manifestations of MYH9-RD, emphasizing the necessity for heightened awareness and diagnostic precision in clinical practice to prevent similar cases of misdiagnosis. This case demonstrates the importance of integrating genetic testing into routine diagnostic protocols for unexplained thrombocytopenia, paving the way for improved patient care and treatment outcomes.

1. Introduction

With the rapid advancement in genetics and molecular biology, our understanding of hereditary blood disorders has significantly deepened [1]. Immune Thrombocytopenia (ITP), a common hematological condition, has seen relatively developed diagnostic and therapeutic approaches [2–4]. However, recent studies have identified that some cases long diagnosed as ITP are caused by specific genetic mutations leading to rare blood diseases, with MYH9-Related Disease (MYH9-RD) being a prime example [5–7]. This rare case was chosen for reporting due to its significance in improving clinical diagnostic awareness. The misdiagnosis of MYH9-RD as ITP highlights the necessity for incorporating genetic testing in routine diagnostic protocols for unexplained thrombocytopenia. By

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https://doi.org/10.1016/j.heliyon.2024.e36203
Received 1 April 2024; Received in revised form 12 August 2024; Accepted 12 August 2024
Available online 13 August 2024

presenting this case, we emphasize the importance of recognizing specific hematologic signs and utilizing advanced diagnostic methods to prevent similar misdiagnoses. Current research on the MYH9 gene has provided new insights into the genetic mechanisms underlying this disorder, offering potential pathways for more accurate diagnosis and targeted therapies.

MYH9-RD, an autosomal dominant genetic disorder triggered by mutations in the MYH9 gene, has an incidence rate of 1/20,000 to 1/25,000, with over 30 % of cases being new mutations [8]. It is primarily characterized by thrombocytopenia, macrothrombocytopenia, and Döhle-like bodies within neutrophils [9,10]. Conditions previously considered as separate entities—May-Hegglin Anomaly (MHA), Fechtner Syndrome (FTNS), Epstein Syndrome (EPS), and Sebastian Syndrome (SBS)—are now recognized as different manifestations of MYH9-RD, all sharing the clinical triad of thrombocytopenia, macrothrombocytopenia, and neutrophil Döhle-like bodies [5,11,12]. Due to their similarity to ITP, MYH9-RD cases are frequently misdiagnosed, leading to unnecessary treatments such as corticosteroids, immunosuppression, or even splenectomy [13], thus missing optimal treatment opportunities [14].

The non-muscle myosin heavy chain IIA (NMMHC-IIA), encoded by the MYH9 gene, plays a crucial role in various cell types, including platelets and leukocytes [15–17]. Mutations in the MYH9 gene directly affect platelet formation and function and the structure of neutrophils, leading to a spectrum of clinical manifestations [18–20]. Current research on MYH9-RD primarily focuses on its genetic mutation mechanisms, clinical presentations, and therapeutic approaches [11,21]. However, due to the rarity of cases and diagnostic limitations, the actual prevalence of this disease might be underestimated [22,23]. Past studies have shown that hematological examinations and genetic analysis can effectively identify MYH9-RD. Yet, in clinical practice, a lack of awareness about the disease often leads to misdiagnosis as ITP or other common hematological disorders [14,20], adversely affecting treatment outcomes and increasing the psychological and financial burden on patients. Thus, enhancing physicians' awareness of MYH9-RD and mastering accurate diagnostic methods are crucial for improving patient prognosis.

In light of this, our study aims to explore the diagnostic challenges and clinical implications of MYH9-RD through an in-depth analysis of a case long misdiagnosed as ITP. This rare case was chosen for reporting due to its significance in improving clinical diagnostic awareness and emphasizing the necessity of integrating genetic testing into routine diagnostic protocols for unexplained thrombocytopenia. By presenting this case, we aim to highlight our study's innovations and unique contributions compared to existing research, such as combining comprehensive clinical data, laboratory tests, and gene sequencing results. Additionally, the rarity and diagnostic challenges associated with MYH9-RD underscore the value of this case analysis in enhancing diagnostic accuracy and providing more appropriate treatment options for patients. Our report also delves into the current state of research on the MYH9 gene, offering new insights into the genetic mechanisms underlying this disorder, which can pave the way for more accurate diagnosis and targeted therapies. By emphasizing these aspects, our study aims to reduce the rates of misdiagnosis and missed diagnosis, ultimately

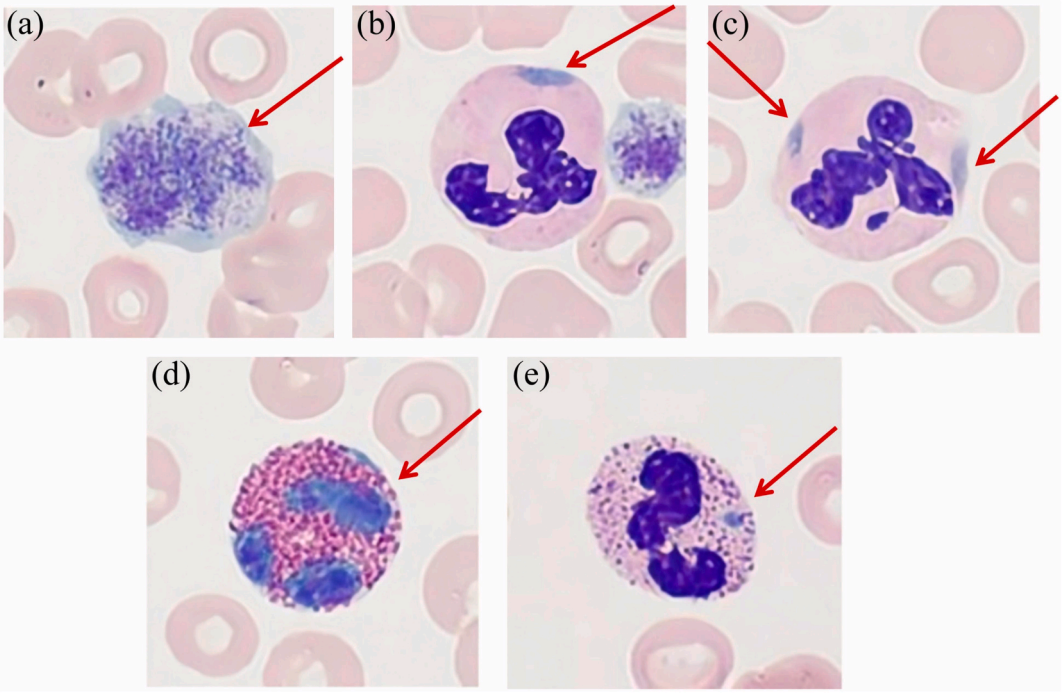

Fig. 1. Microscopic Images of Blood Cells in a Patient with MYH9-RD (Wright-Giemsa Stain × 1000).
Note: (a) Giant Platelets: Platelets significantly larger than normal, unusually enlarged; (b) "Dohle-like bodies" in Neutrophils: Distinctive inclusions visible in the cytoplasm of most neutrophils; (c) Two "Dohle-like bodies" in Neutrophils: Observations of two "Dohle-like bodies" coexisting in some neutrophils; (d) "Dohle-like bodies" in Eosinophils: Uncommonly, "Dohle-like bodies" also found in eosinophils; (e) Döhle Bodies in Neutrophils: Displaying different morphological features compared to "Dohle-like bodies".

improving patient outcomes.

Not only did we uncover a spontaneous mutation in the patient's MYH9 gene, but we also delved into the clinical features, genetic mechanisms, and therapeutic options for MYH9-RD through literature review and data analysis. By emphasizing the rarity and diagnostic challenges of MYH9-RD, this case analysis underscores the necessity for heightened clinical awareness and diagnostic precision, ultimately aiming to reduce the rates of misdiagnosis and missed diagnosis and to provide patients with more appropriate treatment options. This study seeks to enhance the diagnostic accuracy of MYH9-RD, reduce the rates of misdiagnosis and missed diagnosis, and provide patients with more appropriate treatment options.

2. Clinical case report

2.1. Patient history and initial presentation

This case involves an 18-year-old female who has been suffering from thrombocytopenia since childhood. She underwent a bone marrow biopsy at the age of 1 year and 8 months due to a significant reduction in platelet count. Over the years, she was diagnosed with ITP and underwent treatment, including long-term administration of corticosteroids, which did not yield substantial improvements. Additionally, since the age of 10, she has been diagnosed and treated for Tourette Syndrome, including ongoing therapy with tetrabenazine and a regimen of levetiracetam and Vitamin B12 oral solution. The patient has no history of bleeding, and her vision and hearing remain normal. Regarding family history, the patient's father is healthy, while her mother suffers from uremia. The patient is an only child with no history of consanguineous marriage in the family.

2.2. Laboratory findings

Routine blood tests revealed a markedly reduced platelet count of 46×10^9/L in the patient. A detailed analysis of the patient's blood sample was conducted using a slide reader to further investigate. The analysis identified a significant presence of giant platelets, an uncommon finding in standard blood tests (Fig. 1a). After correcting the platelet count using optical methods, the count was adjusted to 101×10^9/L (Table 1). We utilized an advanced optical method for accurate platelet counting to ensure precision and reproducibility. The procedures are: (1) Preparation of Blood Samples: Whole blood samples were collected in EDTA-anticoagulated tubes. (2) Sample Dilution: The blood samples were diluted with a phosphate-buffered saline (PBS) solution to achieve an optimal concentration for counting. (3) Slide Preparation: A small drop of the diluted blood sample was placed on a microscope slide and covered with a coverslip. (4) Microscopic Examination: The slides were examined under a high-resolution optical microscope (Olympus BX43) at 1000× magnification. (5) Image Analysis: Images of the blood smear were captured using a digital camera attached to the microscope. The images were then analyzed using ImageJ software to count the number of platelets. (6) Correction and Validation: The platelet count was corrected based on the dilution factor, and the results were validated by comparing with counts obtained using an automated hematology analyzer. This optical method allowed for accurate detection and quantification of platelets, including identifying giant platelets, ensuring reliable results for further analysis.

Additionally, most neutrophils contained distinctive "Dohle-like bodies" (Fig. 1b), with a few displaying two such bodies (Fig. 1c). Surprisingly, these "Dohle-like bodies" were observed not only in neutrophils but also in eosinophils (Fig. 1d), marking a clear distinction from the typical Döhle bodies observed (Fig. 1e).

2.3. Genetic testing and family analysis

Given the patient's persistent thrombocytopenia without improvement and her blood test results, our team recommended genetic testing for MYH9-RD. After thorough discussions with the doctors, the patient and her parents consented to undergo high-throughput sequencing. The results revealed a heterozygous mutation in the MYH9 gene of the patient: nucleotide 5521 changed from guanine (G) to adenine (A) (c.5521G > A), leading to the amino acid at position 1841 being substituted from glutamic acid to lysine (p. Glu1841Lys). Further family verification showed that neither parent had any mutation at this site. Although the mother suffers from uremia, her MYH9 gene did not show the mutation, confirming the patient's mutation as spontaneous (Fig. 2a–c).

2.4. Treatment and follow-up

After being diagnosed with MYH9-RD, we provided patients with detailed treatment plans and follow-up care measures. In terms of supportive care measures, we strengthened the patient's dietary, psychological, and skin care; we regularly monitored the patient's platelet levels and administered platelet transfusions during episodes of severe thrombocytopenia; and, based on this, we also conducted regular monitoring for potential complications such as kidney disease and hearing loss.

Table 1
Complete blood count data at different time points.

Time Point	WBC (10^9/L)	Hb (g/dL)	Platelet (10^9/L)	MPV (fL)	PCT (%)	PDW (fL)
Initial (Date)	4.6	13.2	101	12.1	0.28	17.2
Follow-up (Date)	5.1	12.5	150	11.8	0.34	16.7

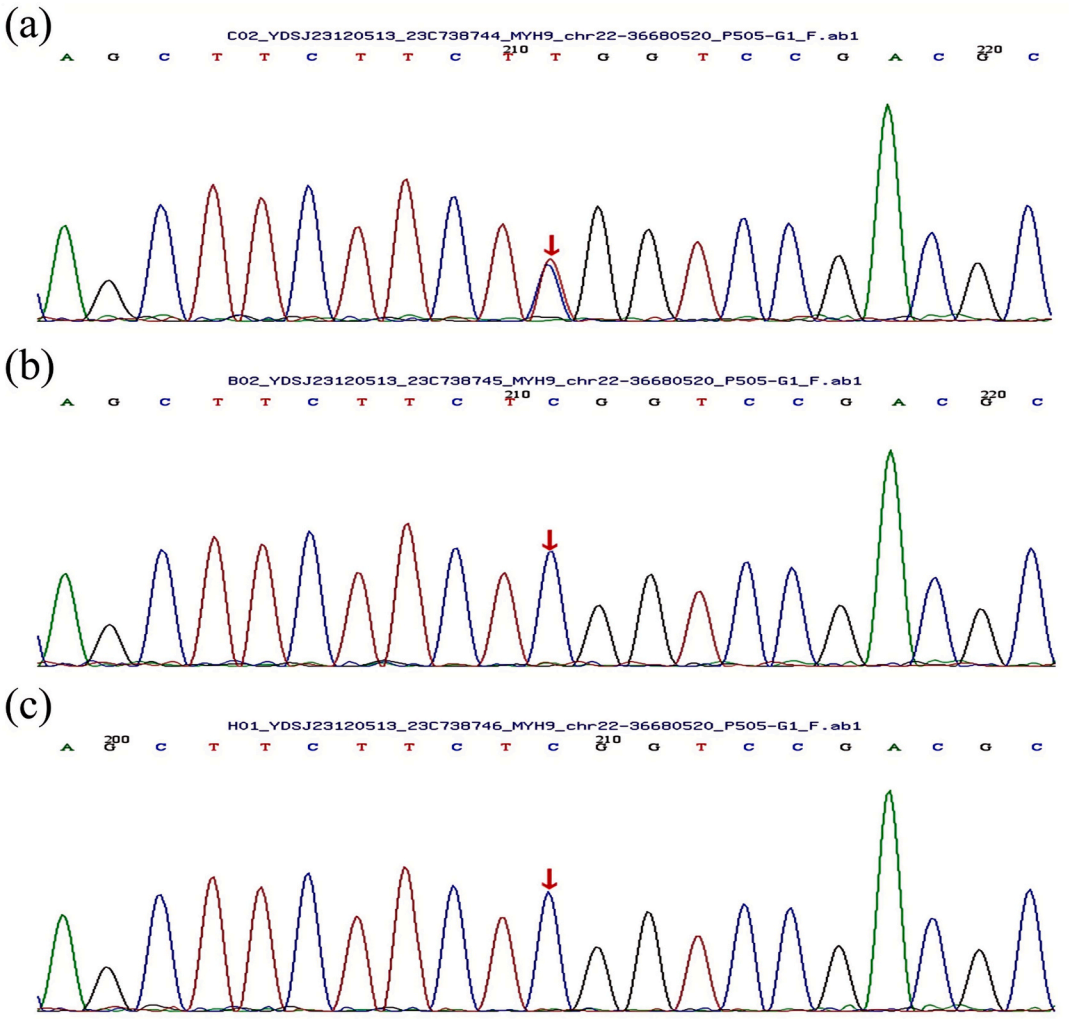

Fig. 2. Genetic Test Results of the MYH9-RD Patient and Her Parents: Confirmation of a Spontaneous Mutation.
Note: (a) The patient's genetic test results show a heterozygous mutation at nucleotide 5521 in the MYH9 gene; (b) Genetic testing of the father indicates no mutation at the same site; (c) Genetic testing of the mother shows that, despite her uremia, no mutation was found at the same site, further confirming the patient's mutation as spontaneous.

3. Discussion and conclusion

3.1. MYH9 gene: structure and function

The MYH9 gene on chromosome 22q12.3–13.1 comprises 41 exons and encodes the NMMHC-IIA [24]. NMMHC-IIA, a hexamer consisting of two heavy chains and four light chains with a molecular weight of 453,000, primarily forms the cytoskeleton in non-muscle cells. It is ubiquitously expressed in various tissues, including leukocytes, the lens, the kidneys, and the cochlea, playing a crucial role in cell division, migration, and morphological maintenance. NMMHC-IIA is the only NMMHC isoform expressed in

Fig. 3. Schematic of Non-Muscle Myosin Heavy Chain IIA (NMMHC-IIA) and Key Mutation Sites.
Note: Green: HD, Yellow: ND, Blue: TD, Purple: NHTD, Red marked positions: Key mutation sites, often associated with more severe clinical symptoms.

platelets, essential for their contractile and secretory functions [25]. The NMMHC-IIA protein features four distinct structural domains: the N-terminal globular head domain (HD) (encoded by MYH9 exons 2–19), the neck domain (ND) (encoded by MYH9 exon 20) which binds to the light chains, the C-terminal α-helical coiled-coil tail domain (TD) (encoded by MYH9 exons 21–40), and the non-helical tail domain (NHTD) (encoded by MYH9 exon 41) [26] (Fig. 3). The HD contains actin-binding sites and ATPase activity, the ND transmits the force generated by the HD and binds myosin light chains, the TD is crucial for heavy chain dimerization and myosin filament assembly, and the NHTD functions as a phosphorylation and regulatory domain [27].

3.2. Pathogenesis of MYH9-RD

It is believed that the "Dohle-like bodies" in neutrophils of patients with MYH9-RD are related to NMMHC-II, including NMMHC-IIA, NMMHC-IIB, and NMMHC-IIC. NMMHC-IIA is expressed in the granulocyte, lymphocyte, and megakaryocyte lineages, with abnormal aggregation of NMMHC-IIA in neutrophils associated with "Dohle-like bodies" [28]. Mutations in the MYH9 gene lead to quantitative and functional anomalies in NMMHC-IIA, affecting the contractility of myosin, resulting in alterations and reorganization of the platelet cytoskeleton, pre-platelet defects, and release abnormalities, thereby causing macrothrombocytopenia and a reduction in platelet numbers [29,30]. The mechanisms underlying cataract formation and renal failure in MYH9-RD remain largely unknown. Renal failure is a major risk for many patients with MYH9-RD. Although certain mutations frequently lead to renal failure, others have minimal impact on renal function, with the reasons for these differences unclear. A few morphological and immunomorphological studies of renal biopsies from patients with MYH9-RD have shown defects in the distribution of NMMHC-IIA within podocytes, segmental disappearance of these cells, loss of slit diaphragms between podocytes, and rapid progression to focal segmental glomerulosclerosis, although the causes of these phenomena remain unknown [31]. There is also limited information on the mechanism of deafness in MYH9-RD. Studies indicate that NMMHC-IIA is expressed in the sensory hair cells of the inner ear cochlea. Mutations in MYH9 disrupt the integrity of the stereocilia structure, leading to hearing loss. It is similar to mutations in other myosin family members observed in deafness experimental models, such as myosin VI, VIIA, and XVA [32].

Additionally, MYH9 gene mutations may also affect red blood cells. While not causing anemia, they alter the red blood cell membrane skeleton, cell shape, and deformability, contributing to subclinical changes in MYH9-RD. However, due to limited research, whether this is a breakthrough remains to be further studied [33].

3.3. Clinical features of MYH9-RD

3.3.1. Thrombocytopenia and macrothrombocytosis

Research indicates that mutations in the HD of the MYH9 gene, particularly within exons 2, 11, and 17, are most common, resulting in an average platelet count of approximately 30×10^9/L. In contrast, TD mutations yield a higher average platelet count, around 80×10^9/L. It suggests that HD mutations are associated with more severe thrombocytopenia and a greater tendency towards macrothrombocytosis than TD mutations [10,34]. A global analysis by Bury et al. utilizing high-throughput sequencing across over one hundred centers, evaluated 3031 patients with thrombocytopenia, identifying 50 cases as MYH9-RD. Their findings corroborate that HD mutations correlate with more significant reductions in platelet count. Notably, while macrothrombocytosis is a universal finding in MYH9-RD patients, platelet counts can vary widely, ranging from 4 to 350×10^9/L, and may even fall within normal ranges [35,36].

3.3.2. Dohle-like bodies

Current research demonstrates the presence of Dohle-like bodies within the neutrophils of patients with MYH9-RD. These inclusions may not always be visible with Giemsa staining and may require immunofluorescence staining for detection [37,38].

3.3.3. Bleeding

Only about 30 % of MYH9-RD patients tend to spontaneous bleeding, primarily manifesting as menorrhagia, epistaxis, and spontaneous mucosal hemorrhages. Life-threatening bleeding episodes are rare [39].

3.3.4. Renal disease

Pecci and colleagues analyzed the genotype-phenotype correlations in 255 patients from 121 families with MYH9-RD, discovering that the probability of developing renal disease was 53 % for patients with TD mutations, compared to 17 % for those with HD mutations. Specifically, the R702C mutation within the HD was associated with an 89 % probability of renal impairment, while the D1424H mutation within the TD presented a 48 % risk [40]. Dong et al. also reported that mutations in the HD, particularly the R702C mutation, significantly increased the likelihood of nephritis. All seven patients with the R702C mutation in their study progressed to nephritis. Although HD mutations are linked to more severe renal diseases, kidney disease can also be observed with HD mutations, and even NHTD mutations might be associated with renal conditions [41].

3.3.5. Sensorineural hearing loss

Approximately 50 % of MYH9-RD patients experience sensorineural hearing loss, with a significantly higher incidence associated with HD mutations than TD mutations. The R702C mutation has the highest probability of causing hearing loss before age 40, followed by other mutations such as R1165C, D1424H, E1841K, and S96L [42,43].

3.3.6. Cataracts

Overall, the incidence of cataracts in MYH9-RD patients is relatively low, around 18 %. However, the D1424H mutation in the TD significantly increases the risk of developing cataracts [8].

In summary, the clinical manifestations of MYH9-RD patients show a significant correlation with the location of MYH9 gene mutations yet exhibit considerable heterogeneity. Not all patients' prognoses can be predicted based on mutation sites, as the same mutation may result in varying clinical outcomes, even within the same family [44]. The clinical presentation of MYH9-RD may be influenced by age, environmental factors, epigenetics, and other genetic factors, the specific reasons for which remain to be elucidated.

3.4. Diagnosis of MYH9-RD

The hallmark clinical features of MYH9-RD include thrombocytopenia, macrothrombocytosis, and the presence of Dohle-like bodies in neutrophils. The disease is highly prone to misdiagnosis. In a study by Rabbolini, which included 121 cases of thrombocytopenia, MYH9 gene mutations were identified in 17 cases; however, only one was correctly diagnosed as MYH9-RD, while six others were misdiagnosed as having Idiopathic ITP [13]. Misdiagnosis as ITP is common in other instances as well [35,39]. One distinguishing feature of MYH9-RD is the abnormal aggregation of Dohle-like bodies in neutrophils, a phenomenon directly related to the MYH9 genotype. Thus, early immunofluorescence testing is recommended for suspected MYH9-RD cases to improve the detection rate of Dohle-like bodies and aid diagnosis [45,46]. Genetic testing for MYH9 mutations offers precise identification of mutations, facilitating more reliable treatment and monitoring strategies. As such, genetic testing is advised for confirmation if feasible. In summary, MYH9 genetic testing is strongly recommended when the triad of peripheral blood abnormalities is present. In cases where Dohle-like bodies are absent in peripheral blood but unexplained thrombocytopenia persists, MYH9-RD should be considered, and immunofluorescence or genetic testing is recommended.

3.5. Treatment of MYH9-RD

MYH9-RD generally warrants supportive care. Patients without a bleeding tendency typically require no treatment, except in cases of severe thrombocytopenia or uncontrollable active bleeding, where emergency platelet transfusions are necessary. Medications that can impair platelet function, such as aspirin, should be avoided [47]. For MYH9-RD patients undergoing surgery, oral administration of eltrombopag and romiplostim has been shown to effectively increase platelet counts and reduce the risk of bleeding in a dose-dependent manner, with eltrombopag being widely used and highly successful without short-term adverse effects [48–50]. In cases of progressive nephritis, early use of ACEI/ARB medications can effectively reduce proteinuria, and kidney transplantation may be considered for irreversible end-stage renal disease [51]. For severe hearing loss and cataracts, cochlear implantation and artificial

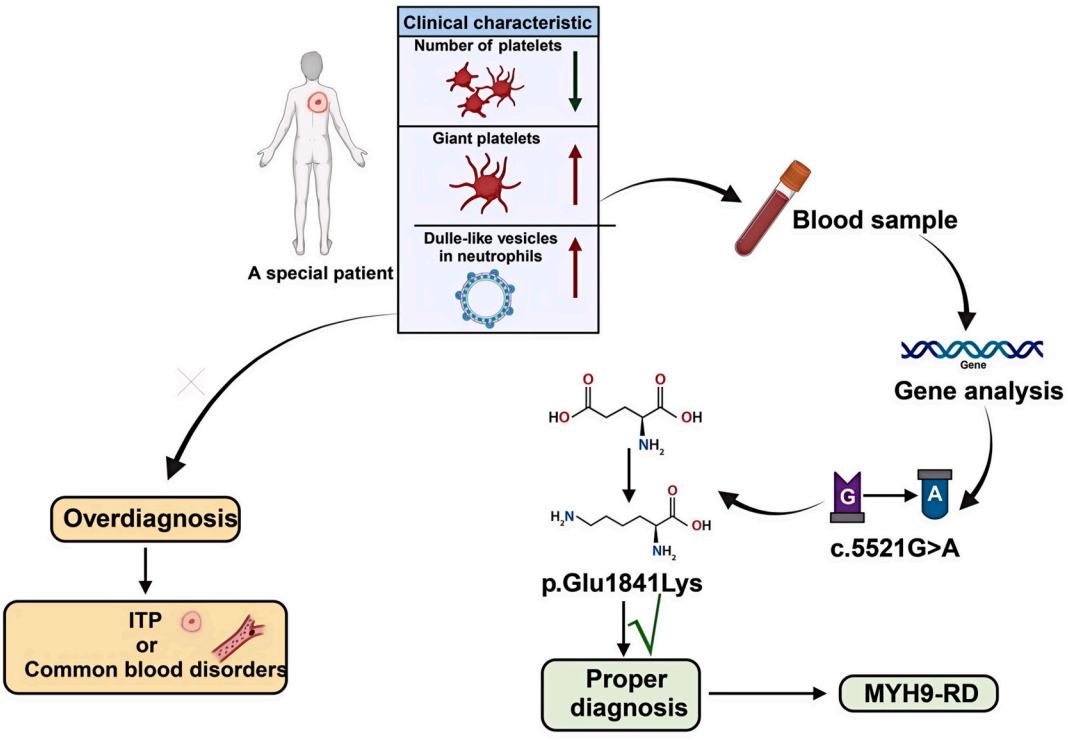

Fig. 4. This study reveals key discoveries from misdiagnosis to precise diagnosis of MYH9-RD and its clinical significance.

lens insertion may be beneficial [14]. Overall, regular follow-ups are crucial for MYH9-RD patients to monitor disease progression and adjust treatment as necessary, balancing the need to avoid overtreatment with the risk of delayed intervention that could result in irreversible damage.

4. Conclusion

Through in-depth analysis of a patient long misdiagnosed with ITP, this study successfully identified and confirmed MYH9-RD, highlighting the complexity and challenges in clinical diagnosis (Fig. 4). The diagnostic journey underscored the importance of laboratory testing in identifying platelet disorders, especially regarding platelet morphology and count variations. We found that combining hematological testing, microscopic morphological observations, and genetic sequencing can significantly improve diagnostic accuracy for MYH9-RD. The study also emphasizes the importance of early and accurate diagnosis to avoid unnecessary treatment and potential clinical risks. Furthermore, our findings are significant for understanding the pathogenesis and clinical manifestations of MYH9-RD. Our results support the direct link between MYH9 gene mutations and the formation of platelet abnormalities and Dohle-like bodies in neutrophils.

Additionally, genetic analysis of MYH9-RD patient families revealed cases of spontaneous mutation, underlining the importance of genetic testing even without a clear family history. Overall, this research provides new insights into the diagnosis and clinical management of MYH9-RD and supports the development of improved diagnostic strategies for rare platelet disorders. Future studies should continue to enhance disease awareness, optimize diagnostic procedures, and explore more effective treatments. Through these efforts, we can anticipate significant improvements in diagnosing and treating MYH9-RD and related diseases, thereby improving patient prognosis and quality of life.

Ethics approval and consent to participate

This study was approved by the Clinical Ethics Committee of The First People's Hospital of Shuangliu, Chengdu/West China (Airport) Hospital Sichuan University (No. 2023-5-13) and written informed consent was obtained from the patient for the publication of this case report.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Funding

This study was supported by 2023 Chengdu Medical Research Project (No. 2023423).

CRediT authorship contribution statement

Lixiu Cai: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Shuangyan Chen:** Writing – original draft, Project administration, Methodology, Investigation. **Yu Zhou:** Writing – original draft, Software, Resources, Project administration. **Hao Yu:** Writing – review & editing, Visualization, Validation, Supervision. **Ya Li:** Writing – review & editing, Visualization, Validation, Supervision. **Aiping Bao:** Writing – review & editing, Validation, Supervision, Software. **Jin Zhang:** Writing – review & editing, Resources, Methodology, Funding acquisition. **Qin Lv:** Writing – review & editing, Resources, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

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