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REVIEW ARTICLE

MYH9-related inherited thrombocytopenia: the genetic spectrum, underlying mechanisms, clinical phenotypes, diagnosis, and management approaches

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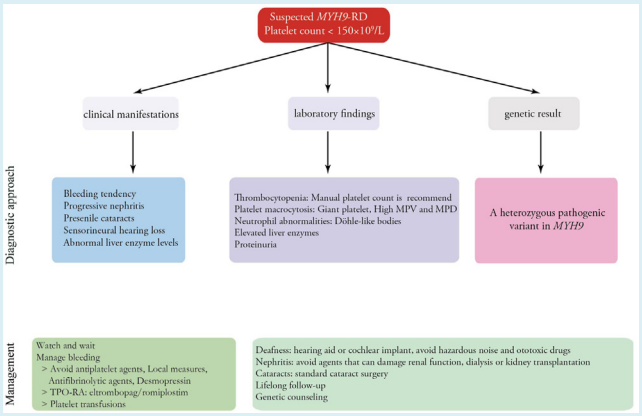
Abstract

Inherited thrombocytopenias have been considered exceedingly rare for a long time, but recent advances have facilitated diagnosis and greatly enabled the discovery of new causative genes. *MYH9*-related disease (*MYH9*-RD) represents one of the most frequent forms of inherited thrombocytopenia, usually presenting with nonspecific clinical manifestations, which renders it difficult to establish an accurate diagnosis. *MYH9*-RD is an autosomal dominant-inherited thrombocytopenia caused by deleterious variants in the *MYH9* gene encoding the heavy chain of nonmuscle myosin IIA. Patients with *MYH9*-RD usually present with thrombocytopenia and platelet macrocytosis at birth or in infancy, and most of them may develop one or more extrahematologic manifestations of progressive nephritis, sensorial hearing loss, presenile cataracts, and elevated liver enzymatic levels during childhood and adult life. Here, we have reviewed recent advances in the study of *MYH9*-RD, which aims to provide an updated and comprehensive summary of the current knowledge and improve our understanding of the genetic spectrum, underlying mechanisms, clinical phenotypes, diagnosis, and management approaches of this rare disease. Importantly, our goal is to enable physicians to better understand this rare disease and highlight the critical role of genetic etiologic analysis in ensuring accurate diagnosis, clinical management, and genetic counseling while avoiding ineffective and potentially harmful therapies for *MYH9*-RD patients.



KEYWORDS
genetic diseases, inherited thrombocytopenia, *MYH9*-RD, nonmuscle myosin IIA, platelets

Essentials

- *MYH9*-RD is often misdiagnosed, causing underdiagnosis.
- *MYH9*-RD presents with macrothrombocytopenia and 1 or more extrahematologic manifestations.
- Diagnosis relies on clinical features, laboratory results, and genetic testing.
- Management involves addressing bleeding, extrahematologic issues, and genetic counseling.

1 | INTRODUCTION

Although thrombocytopenia is one of the most frequent hematologic disorders, making a timely and definite identification of the cause of thrombocytopenia is still tricky, and differentiating inherited thrombocytopenia from acquired thrombocytopenia remains quite challenging [1,2]. Acquired thrombocytopenia is generally secondary to a wide variety of immune or nonimmune factors such as autoimmune conditions, certain drugs or heparin exposures, infections, pregnancy, solid tumors, or hematologic malignancies, and so on [3–6]; among them, immune thrombocytopenic purpura (ITP) is the most prevalent form [7]. In contrast, inherited thrombocytopenia comprises a heterogeneous group of hereditary disorders that mainly manifests as an abnormally low level of platelets at an early age, usually defined as a circulating platelet count $< 150 \times 10^9$/L (reference: $150 \sim 450 \times 10^9$/L) and many of them may also have abnormal platelet function and variable platelet size, and subsequently develop impaired hemostasis [8]. Due to the overlapping clinical manifestations and laboratory findings, there exists a significant likelihood of misdiagnosis between inherited and acquired thrombocytopenia. Recently, Miltiadous et al. [9] estimated that an incidence of 15% of individuals with inherited thrombocytopenia were misdiagnosed with refractory ITP and subsequently received inappropriate or ineffective treatments. Misdiagnosis of genetic diseases as acquired disorders may lead to unfavorable therapeutic interventions, potentially deleterious clinical management, and absence of genetic counseling; it is of vital importance to establish a definitive genetic diagnosis for underlying inherited thrombocytopenia patients.

In the past 20 years, thanks to the remarkable advances in clinical and laboratory research, inherited thrombocytopenia has been extensively studied. Especially with the advent of high-throughput sequencing technology and its increasing application in clinical practice, our understanding of inherited thrombocytopenia in molecular etiology and genetic landscapes has been substantially improved, and growing novel disease-associated mutations in an expanding list of causative genes have been elucidated [10–12]. To date, genetic defects responsible for inherited thrombocytopenia involve an expanding list of >40 causative genes, which affect every step of the complex megakaryopoiesis/thrombopoiesis processes [11,12] (Figure 1).

The inherited thrombocytopenias, with an increasing number of well-defined forms, constitute a highly heterogeneous group of bleeding diseases of variable degrees of thrombocytopenia, platelet size, pattern of inheritance, and clinical course. Figure 2 illustrates the relative frequency of major forms of inherited thrombocytopenias, which was generated from 5 independent studies encompassing a total of 544 patients worldwide (Supplementary File S1). Consistent with prior reports, *MYH9*-related disease (*MYH9*-RD) represents the most common form and accounts for approximately one-third of all affected individuals [13]. In this review, we will focus on *MYH9*-RD, one of the most frequent forms of inherited thrombocytopenia, the genetic spectrum, underlying mechanisms, clinical phenotypes, diagnosis, and management approaches of this rare disease.

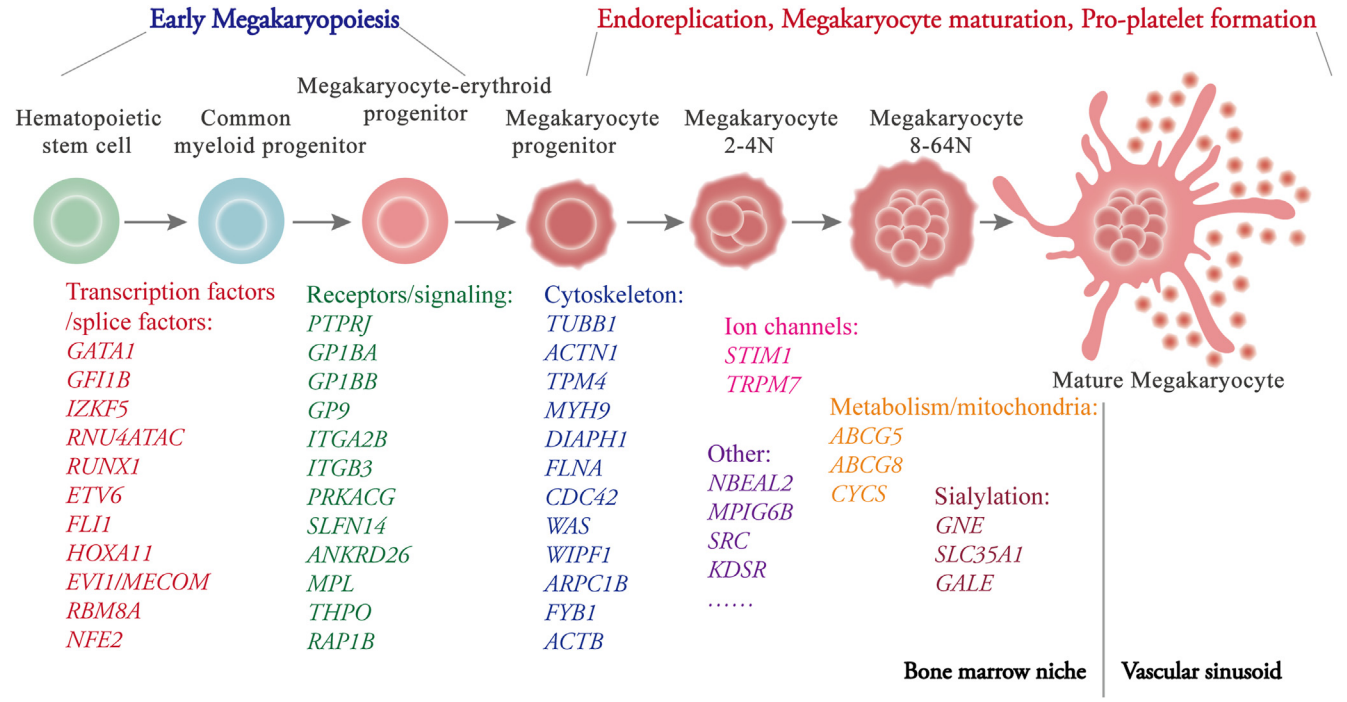


FIGURE 1 Schematic representation of the major steps of megakaryopoiesis and thrombopoiesis and an expanding list of >40 genes involved in every step of these complex processes that can cause inherited thrombocytopenias.

2 | *MYH9*-RD

MYH9-RD was previously thought to encompass 4 distinct entities with overlapping features, ie, the May–Hegglin anomaly, Epstein syndrome, Fechtner syndrome, and Sebastian syndrome [14]. They all present with early-onset macrothrombocytopenia and may develop 1 or more extrahematologic manifestations of the disease later in life, including sensorineural hearing loss, renal failure, and presenile

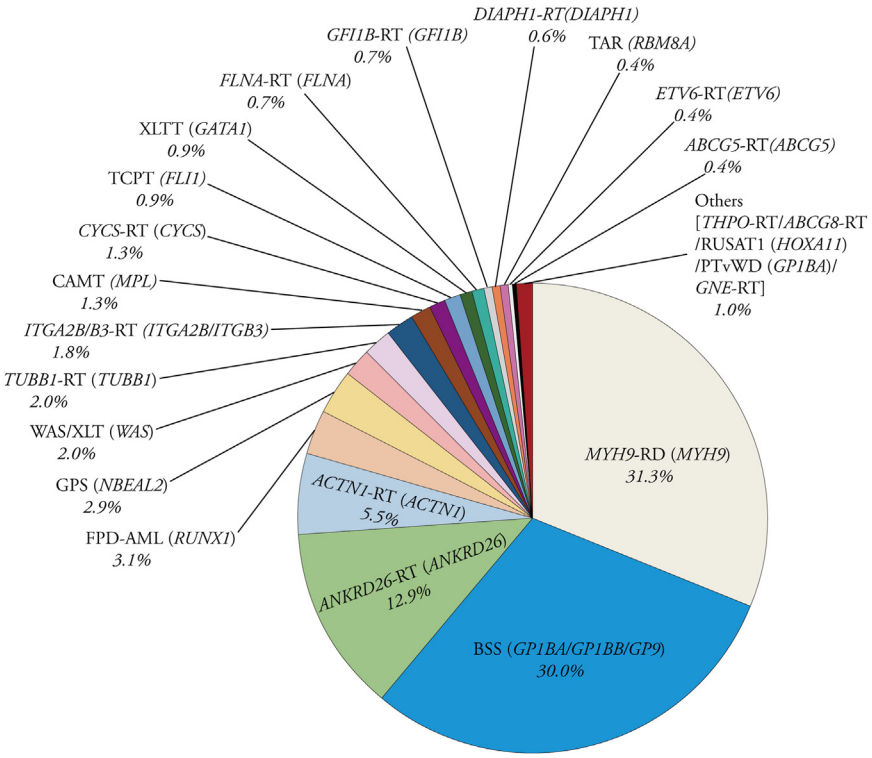


FIGURE 2 Relative frequencies of various forms of inherited thrombocytopenias in a total of 544 patients worldwide from 5 independent studies. BSS, Bernard–Soulier syndrome; CAMT, congenital amegakaryocytic thrombocytopenia; FPD-AML, familial platelet disorder and predisposition to acute myeloid leukemia; GPS, Gray platelet syndrome; *MYH9*-RD, *MYH9*-related disease; PTvWD, platelet-type von Willebrand disease; RT, related thrombocytopenia; RUSAT1, radioulnar synostosis with amegakaryocytic thrombocytopenia-1; TAR, thrombocytopenia-absent radius syndrome; TCPT, Paris–Trousseau thrombocytopenia; WAS/XLT, Wiskott–Aldrich syndrome/X-linked thrombocytopenia; XLTT, X-linked thrombocytopenia with β-thalassemia.

cataracts. The history of *MYH9*-RD began in 1909 and 1945 when Richard May and Robert Hegglin independently described a congenital bleeding disorder characterized by thrombocytopenia, extremely large platelets, and leucocyte inclusion bodies, which was recognized as Mendelian disease and later termed the May–Hegglin anomaly [15]. In the following 5 decades, other 3 disease entities, namely the Epstein syndrome (in 1972) [16], Fechtner syndrome (in 1985) [17], and Sebastian syndrome (in 1990) [18], were gradually found. For a long time, although sharing common features of autosomal dominant macrothrombocytopenia while distinguished by other different combinations of clinical and laboratory characteristics, they were classified into 4 distinct types of disease. However, it was only in the year 2003 that the above 4 disease entities were gradually considered to be a single disorder because of the common genetic background [14].

The *MYH9* gene encodes myosin heavy chain 9 (MYH9), a protein of 1960 amino acids, also known as nonmuscle myosin heavy chain IIA (NMIIA-HC), which participates in many crucial physiological processes such as chemotaxis, cell migration, adhesion, cytokinesis, and maintenance of cell shape [19–21]. Heterozygous *MYH9* germline variants are responsible for autosomal-dominant Mendelian susceptibility to *MYH9*-RD (OMIM: #155100). In general, *MYH9*-RD refers to a spectrum of complex phenotypes characterized by a variable degree of inherited macrothrombocytopenia at birth and possible late-onset extrahematologic manifestations of progressive nephritis, sensorial hearing loss, presenile cataracts, and elevated liver enzymatic levels [13,22]. Of note, mutations in the *MYH9* gene can also lead to autosomal dominant nonsyndromic sensorineural deafness-17 (OMIM: #603622), which is recognized as a separate disease entity without hematological manifestations and excluded from *MYH9*-RD in this review [23]. *MYH9*-RD is considered a rare disease with an estimated prevalence of 3.75:1,000,000 in Italy; however, due to a substantial fraction of patients remaining undiagnosed or misdiagnosed with other disorders, the actual prevalence is likely higher [24].

Here, to gain a deeper understanding of this disease, Figure 3 presents a potential case of familial *MYH9*-RD diagnosed in our hospital; full descriptions and details are provided in Supplementary File S2.

3 | GENETIC SPECTRUM

The *MYH9* gene is a large gene localized on chromosome 22q12.3 with 41 exons, ie, 1 5′-untranslated exon and 40 coding exons spanning almost 107 kb [21]. Currently, direct Sanger sequencing for variant screening remains time-consuming and laborious. High-throughput sequencing technology appears to be a powerful tool for detecting the causative variants [25]. Previous studies have already depicted a spectrum of pathogenic variants identified in patients with *MYH9*-RD [13,22,25–27]; however, we want to make an update and extend the genetic spectrum. We generated a disease-causing variants database for *MYH9*-RD by using a joint ClinVar/Human Gene Mutation Database (HGMD) strategy, excluding individuals with uncertain diagnoses or without clinical signs of macrothrombocytopenia as of April 2024. At last, 107 previously reported variants, including 74 missense and nonsense variants, 30 insertion and/or deletions < 50 bp (indels) variants, and 3 splicing variants, were derived from (1) ClinVar: 53 "pathogenic" and/or "likely pathogenic" variants with interpretation condition of *MYH9*-RD and 2 or more stars; (2) HGMD public version: 93 "disease-causing" variants with a phenotype of *MYH9*-RD. The number of reported disease-causing variants from ClinVar and/or HGMD is illustrated in Figure 4A. Moreover, the number of reported cases for each variant was also counted by using the data derived from ClinVar/HGMD/LitVar 2.0 (https://www.ncbi.nlm.nih.gov/research/litvar2/), and a total of 778 *MYH9*-RD cases corresponding to the 107 variants were identified. Details are provided in Supplementary File S3.

Interestingly, the mutational landscape of *MYH9*-RD is peculiar (Figure 4B, C). Disease-causing variants are most frequently missense/nonsense, which accounts for 91.5% (712/778). The disease-causing variants are widely scattered throughout the *MYH9* gene, which may affect all the protein domains of the motor/head, neck, coiled-coil/rod, and nonhelical tailpiece (NHT). In addition, nonsense and frameshift variants have been mainly detected in the last exon 41, while small in-frame deletion/duplication frameshift variants are prevalently found in exon 25, probably due to the presence of repetitive DNA sequences [28]. In line with prior studies [13,22,26,29], we find that approximately 68.9% of all the disease-associated variants are concentrated in 6 specific mutational hotspot residues: R702 (12.1%, exon 17) and S96 (5.4%, exon 2) located in the motor/head domain, D1424 (19.0%, exon 31), R1165 (8.9%, exon 27) and E1841 (10.9%, exon 39) in the coiled-coil/rod, and R1933 (12.6%, exon 41) in the NHT (Figure 4B). Besides, although *MYH9*-RD has been demonstrated as a dominantly inherited disease, nearly 30% of patients are sporadic cases with no family history, which may be due to *de novo* variants, somatic or germline mosaicism, or incomplete penetrance of the *MYH9* variants [13,22,30].

Previous works have already provided evidence that genotype-phenotype correlations in *MYH9*-RD exist where patients bearing distinct mutations may present with a combination of diverse phenotypes [26,29,31]. In general, mutations affecting the motor/head domain of NMIIA-HC may result in more severe phenotypes, ie, more serious macrothrombocytopenia and a higher risk of developing glomerulonephritis and deafness than those located in the coiled-coil/rod or NHT domain, which usually lead to mild macrothrombocytopenia and an intermediate- or low-risk of serious extrahematologic complications. For instance, patients harboring R702 mutations associated with the most severe phenotypes may present with severe thrombocytopenia at birth, and all are expected to develop aggressive nephropathy and progressive hearing loss before the age of 45 or 40 years [26,29,32]. In contrast, nonsense and frameshift mutations in the NHT domain are frequently associated with moderate macrothrombocytopenia and a very low risk of developing extrahematologic manifestations; thus, for many affected individuals, macrothrombocytopenia usually remains the only obvious clinical feature throughout their lifespans. For example, patients with R1933 nonsense mutation usually exhibit a relatively low propensity to develop kidney impairment, presenile cataracts, and nonsyndromic

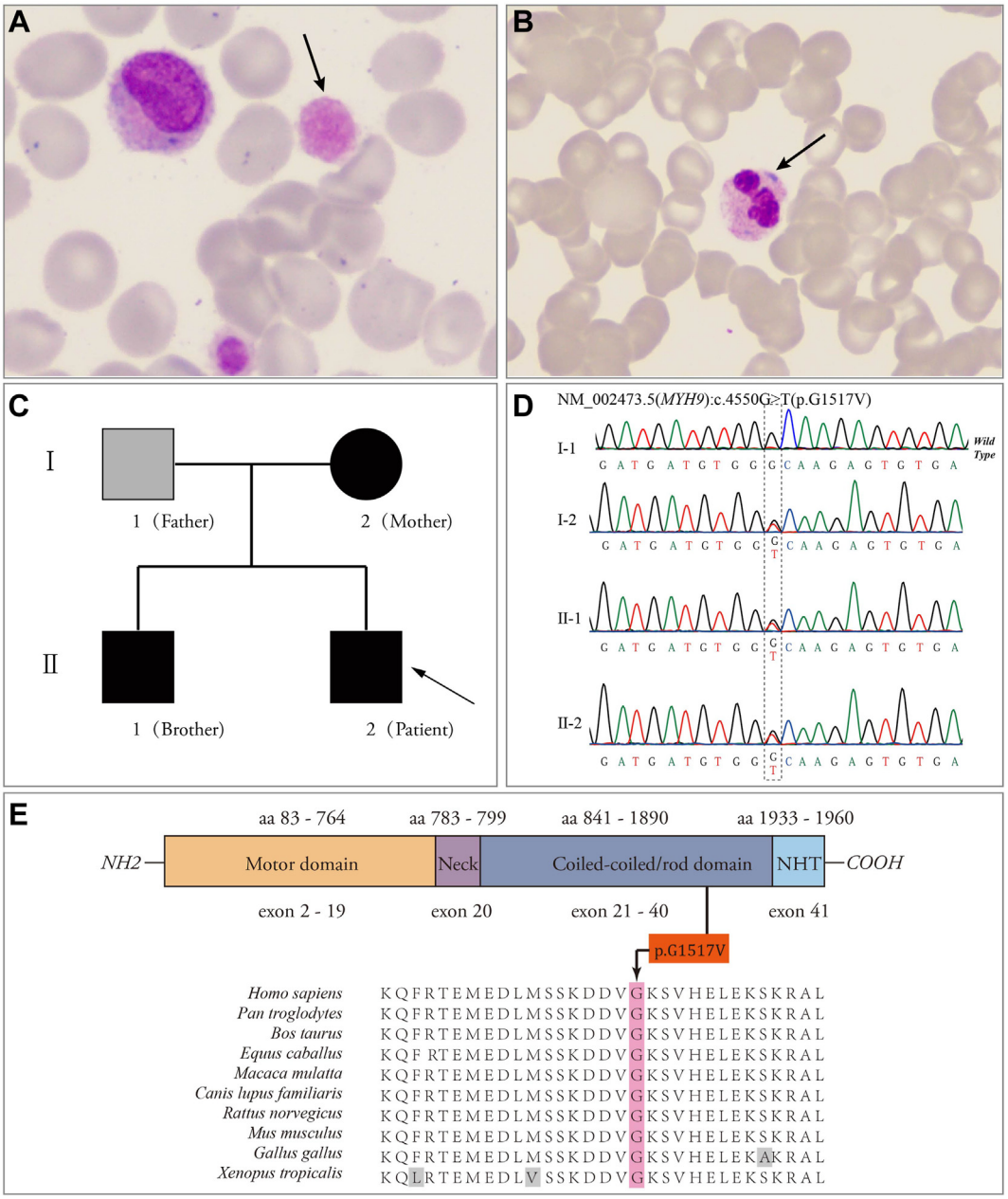


FIGURE 3 An example of a potential case of familial *MYH9*-related disease caused by a heterozygous *MYH9* p.G1517V mutation diagnosed in our hospital. (A–B) The patient's peripheral blood smear reveals giant platelets and Döhle-like inclusions in neutrophils (magnification ×100, Wright–Giemsa stain). (C–D) The family pedigree shows segregation of *MYH9* p.G1517V mutation in the inherited thrombocytopenia family. The square signifies male and the circle female, filled black symbols represent the affected subjects, and the arrow marks the proband. Sanger sequencing chromatograms were performed on the buccal swab samples. (E) Schematic illustration of the MYH9 protein showing its domains and localization of p.G1517V mutation. NHT, nonhelical tailpiece.

sensorineural deafness [26,29,33]. Mutations affecting the coiled-coil/rod domain are generally linked with moderate macrothrombocytopenia and an intermediate risk of extrahematologic manifestations [26,29].

Notably, although many genotype-phenotype correlation studies have been published, it remains evident that using simple genotypes to specify phenotype or guide therapies in individual patients may probably deviate from reality. It should be kept in mind that this genotype-phenotype relationship may not always accurately guide clinical practice. There are certainly exceptions to this rule. Patients with coiled-coil/rod or NHT variants may also experience severe thrombocytopenia or have a high risk of extrahematologic manifestations. For instance, patients with the D1424H mutation also have a high risk of developing all the extrahematologic manifestations over time, and patients with R1165 mutations are expected to display a high risk of hearing loss [26]. Additional pathogenetic mechanisms are

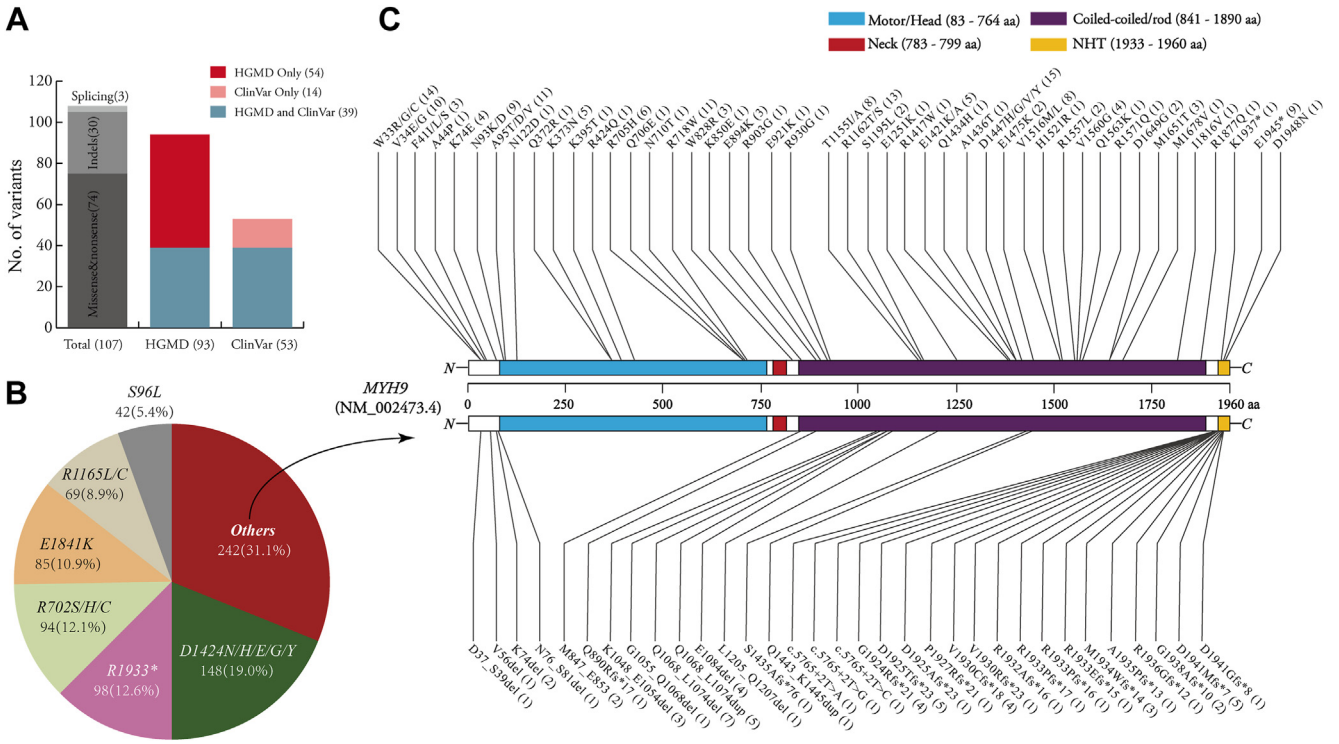


FIGURE 4 Molecular spectrum of *MYH9* variants in *MYH9*-related disease (*MYH9*-RD). (A) A total of 107 disease-causing variants, including 74 missense and nonsense variants, 30 insertion and/or deletions < 50 bp (indels) variants, and 3 splicing variants, were derived from ClinVar (53) and/or Human Gene Mutation Database (HGMD) (93). (B) A total of 778 *MYH9*-RD cases corresponding to the 107 variants were identified, and 68.9% (536) of all the *MYH9*-RD cases harbored the variants clustered in 6 hotspot residues. (C) Spectrum of nonhotspot variants identified in the 242 (31.1%) remaining *MYH9*-RD cases. The number of cases that each variant correlated with is shown in parentheses. NHT, nonhelical tailpiece.

involved in the alteration of nonmuscle myosin IIA (NMIIA) function; further studies are still needed.

4 | UNDERLYING MECHANISMS

The myosin superfamily is composed of >18 classes (encoded by approximately 40 genes) of evolutionarily conserved motor proteins that can interact with actin filaments (F-actin) and utilize energy derived from adenosine triphosphate hydrolysis to generate mechanical force and movement [34,35]. Myosins play a fundamental role in several cellular processes and pathways, including contractile ring constriction, vesicle trafficking, organelle morphology and translocation, membrane deformation, and cell motility (such as cell division, cell migration, and adhesion) [36]. Most myosins belong to the class II (myosin II) subfamily, which includes muscle (skeletal, cardiac, and smooth muscle) myosin II, as well as nonmuscle myosin II (NMII). Based on the 3 different heavy chains of NMII, ie, the NMIIA-HC (encoded by *MYH9*), NMIIB-HC (*MYH10*), and NMIIC-HC (*MYH14*), isoforms of NMII are usually referred to as NMIIA, NMIIB, and NMIIC, respectively [19]. All 3 NMII isoforms are ubiquitously present in mammalian cells, and most cell types express more than 1 isoform. However, NMIIA is the only isoform type of myosin protein expressed in megakaryocytes (MKs) and platelets, which may address why NMIIA is quite indispensable for organelle distribution and F-actin organization in MKs and platelets [37,38].

Similar to all myosins of class II, the NMIIA molecule is a hexamer that consists of 3 pairs of peptides: 2 230 kDa heavy chains (NMIIA-HCs, gene *MYH9*) that form parallel homodimers and serve as backbones, 2 20 kDa regulatory light chains (gene *MYL12A/B*) that regulate NMIIA activity by phosphorylation of regulatory light chain residue serine 19, and 2 17 kDa essential light chains (gene *MYL6*) that stabilize the heavy chain structure (Figure 5A) [19]. NMIIA-HC protein comprises 4 functional domains, as follows: an N-terminal globular motor/head domain (exons 2-19), containing the actin-binding regions and the adenosine triphosphate hydrolysis domain; a neck domain (exon 20), acting as a lever arm to amplify head rotation and transforming the chemical energy of adenosine triphosphate into mechanical movement; a long α-helical coiled-coil/rod domain (exons 21-40), mediating NMIIA dimerization to form the hexamer; a C-terminal NHT domain with the last 34 amino acid residues encoded by exon 41, regulating filament formation [21,22]. NMIIA molecules assemble into functional bipolar filaments that bind to F-actin to generate mechanical forces, driving cellular reshaping and movement (Figure 5B).

To date, the molecular mechanisms contributing to disease in patients with *MYH9*-RD remain incompletely defined. Because of the intrinsic complexity of biological systems, making a satisfactory explanation for every clinical manifestation is almost impossible. Here,

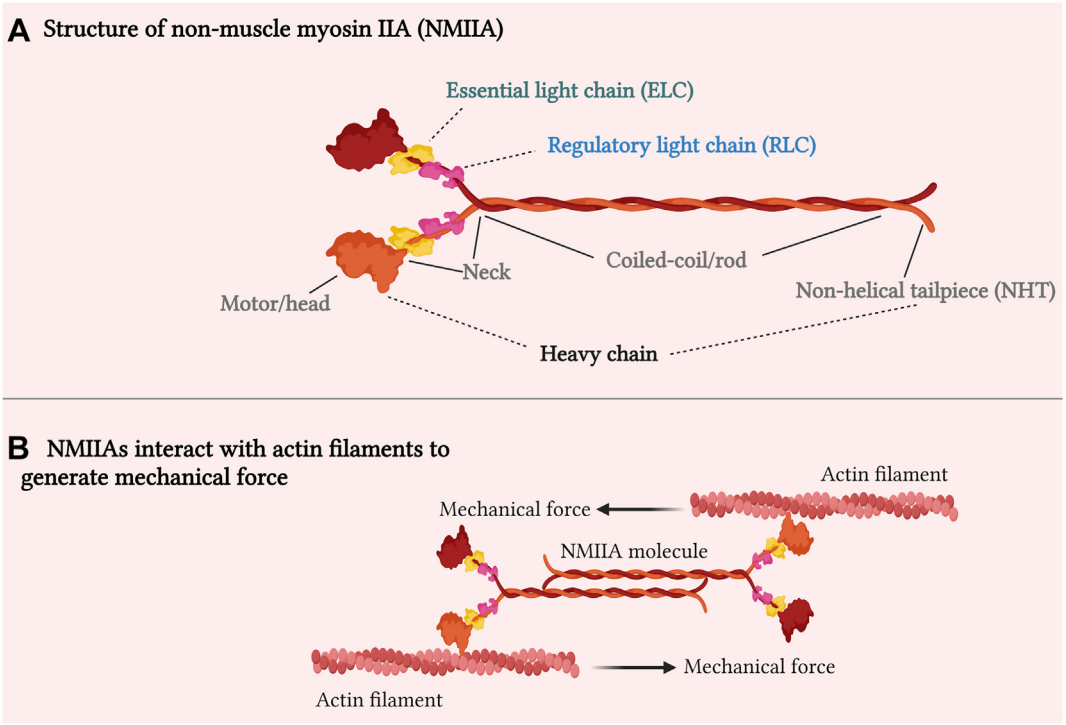


FIGURE 5 Subunit structure of nonmuscle myosin IIA (NMIIA) and bipolar NMIIA filaments. (A) NMIIA is a hexamer consisting of 3 pairs of subunits: 2 heavy chains, 2 regulatory light chains (RLCs), and 2 essential light chains (ELCs). NMIIA heavy chain comprises 4 functional domains: an N-terminal globular motor/head domain, a neck domain, a long α-helical coiled-coil/rod domain, and a C-terminal nonhelical tailpiece (NHT) domain. (B) NMIIA molecules assemble into bipolar filaments, interacting with actin filaments to generate mechanical force.

several potential explanations are proposed: (1) NMIIA plays a crucial role in the final stages of platelet biogenesis, including MK polyploidization, proplatelet formation, and release, and additionally regulates MK chemotaxis and migration [38–40]. Thus, dysfunctional NMIIAs impair the migration of MKs from the bone marrow niche toward the vascular sinusoid, where platelets are formed and released. The combination of the decreased presence of MKs in the sinusoid and impaired excising force generated by NMIIA-driven constriction leads to a decreased number but a giant volume of proplatelet production (Figure 6). (2) The reason why *MYH9*-RD tends to develop nephropathy is thought to mainly derive from defects in the function of the podocytes, which are highly specialized renal glomerular epithelial cells that are indispensable for the integrity of the glomerular filtration barrier [41]. NMIIA is expressed in the podocyte and mesangial cells, as well as in the arteriolar and peritubular capillaries. An *MYH9* pathogenetic mutation may lead to a dysfunctional NMIIA molecule that substantially alters podocyte cytoskeletal structure and impairs its filtration barrier function, therefore causing proteinuria and progressive kidney disease [42,43]. (3) The underlying mechanisms of hearing loss in *MYH9*-RD remain poorly characterized; however, it may be partly because of impaired functions of the inner ear sensory hair cells resulting from dysfunctional NMIIA molecules [44,45]. (4) We currently do not know the reason for the cataracts and elevated liver enzymatic levels in *MYH9*-RD, and further studies are needed to understand the pathogenesis.

5 | CLINICAL PHENOTYPE

The clinical features of *MYH9*-RD are summarized in Figure 7. Hematologic features, including platelet macrocytosis, thrombocytopenia, and Döhle-like bodies in neutrophils, are the most obvious clinical manifestations and are present in nearly all affected individuals from birth [46]. Extrahematologic complications involving the eye lens, inner ear, and kidney usually present at a relatively low frequency and occur at a later time. The possible explanation for this difference is that, although NMIIA is widely distributed in tissues, blood cells such as MKs and platelets express exclusively NMIIA and lack functional compensation [19,21,38]. In contrast, extrahematologic tissues may express other NMII isoforms (ie, NMIIB and NMIIC), and the dysfunctional NMIIA can be partially compensated [47].

5.1 | Hematologic features

Early-onset thrombocytopenia with platelet macrocytosis is a hallmark of *MYH9*-RD as well as a crucial suggestive clue for accurate disease identification. As already reported, mean platelet diameter (MPD) and mean platelet volume (MPV) were both useful parameters for differentiating *MYH9*-RD from immune thrombocytopenia [48–50]. The mean MPD was 4.5 μm in 125 *MYH9*-RD patients compared with 2.6 μm in 55 healthy controls [51]. An MPD > 3.3 μm differentiated *MYH9*-RD

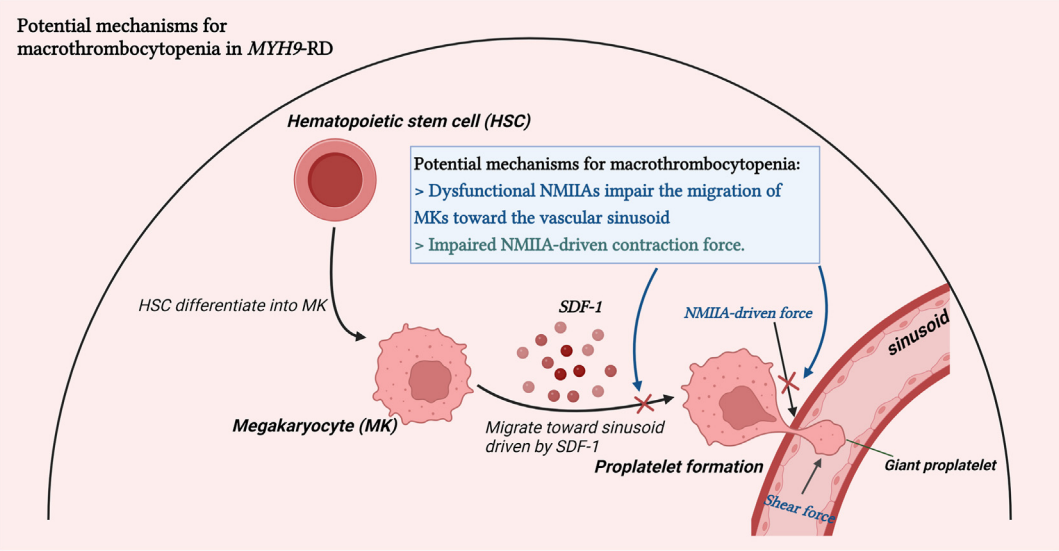


FIGURE 6 Potential mechanisms of macrothrombocytopenia in *MYH9*-related disease (*MYH9*-RD). NMIIA, nonmuscle myosin IIA; SDF-1, stromal cell-derived factor 1.

and Bernard–Soulier syndrome from ITP with 89% sensitivity and 88% specificity, and an MPV > 12.4 fL had 83% sensitivity and 89% specificity [48]. The platelet count varies greatly among *MYH9*-RD patients, from slight reduction to severe decrease of $<10 \times 10^9$/L, and usually remains stable throughout life [13,21]. Of note, routine automated blood cell counters using impedance or optical light scatter technology have limitations in platelet counting, as these methods cannot distinguish giant platelets from similar-sized erythrocytes [52,53]. Therefore, because of platelet macrocytosis, not only the platelet counts but also the MPV and MPD parameters acquired using the automated cell counting method may be significantly underestimated compared with the manual platelet counting obtained by optical microscopy. In a case series of 167 patients with *MYH9*-RD, the median platelet count measured by automated instruments was 26×10^9/L compared with 70×10^9/L by microscopic platelet count [26].

Most patients experience no spontaneous bleeding or only mild bleeding, such as easy bruising. However, some may be prone to an increased risk of excessive bleeding following hemostatic challenges,

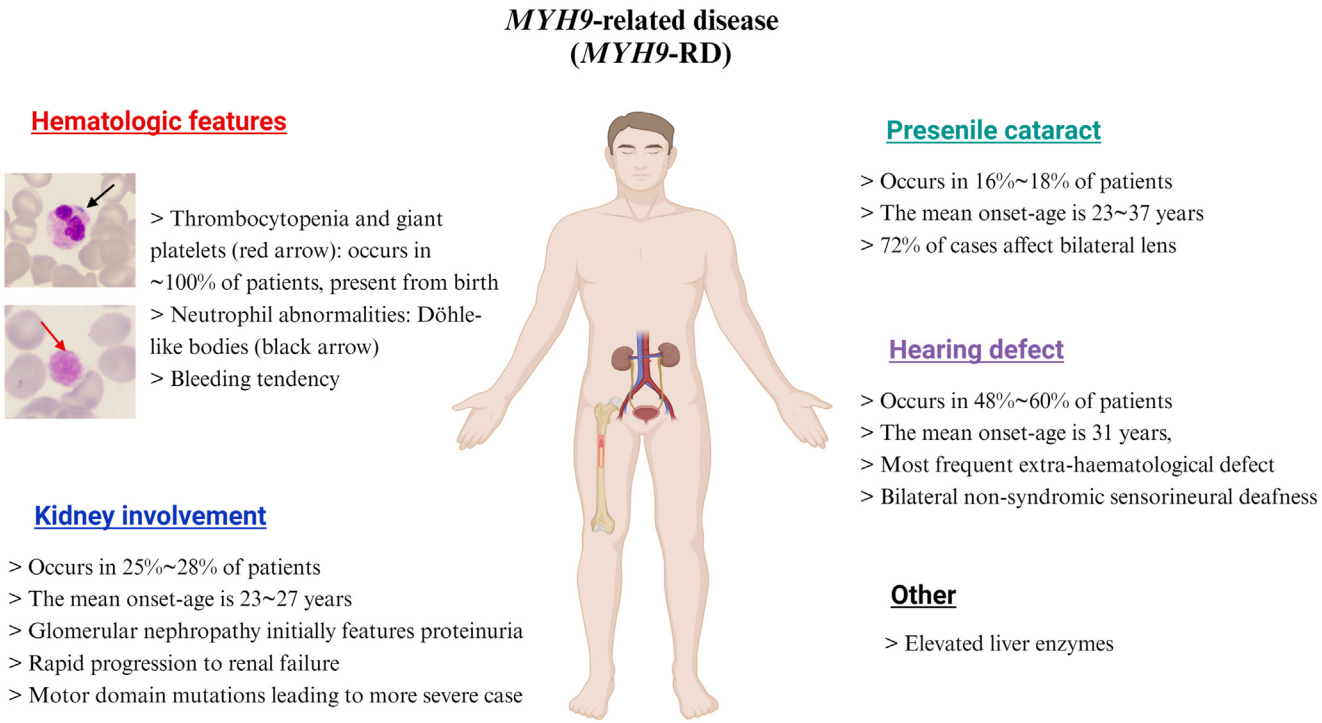


FIGURE 7 The summary of clinical phenotypes in *MYH9*-related disease (*MYH9*-RD).

including trauma, surgery, delivery, and treatment with antiplatelet drugs [26,54–56]. Approximately 28% of patients experience spontaneous mucosal bleeding, such as menorrhagia, epistaxis, and gingival bleeding. Life-threatening hemorrhage events have been rarely reported. Recent suggestions indicate that hemorrhagic complications arise not only from thrombocytopenia but also from qualitative structural and functional defects in platelets. *MYH9* mutant platelets present with reduced contractile force generation and impaired clot retraction, thus leading to decreased thrombus formation and stability as well as increased bleeding tendency [57–59].

Another prominent characteristic of *MYH9*-RD is the presence of Döhle-like bodies in neutrophil cytoplasm on peripheral blood smear analysis. These bodies appear as faint, light blue, basophilic inclusion bodies resembling Döhle-like bodies. They consist of a ribonucleoprotein complex containing aggregates of abnormally accumulated NMIIA protein, *MYH9* mRNA, and clusters of ribosomes [46,60,61]. These inclusion bodies can be classified into types I, II, and III according to their abnormal localization pattern of NMIIA aggregates, such as number, size, and shape [62,63]. Type I comprises 1 or 2 large and intensely stained cytoplasmic foci. Type II comprises up to 20 small cytoplasmic spots with circular to oval shape. Type III appears as a "speckled" pattern characterized by >20 small circular aggregates (<0.5 μm). Types II and III are often not visible on Wright–Giemsa-stained blood smears. However, all 3 types are detectable by immunofluorescence assay of neutrophils with a detection specificity and sensitivity of approximately 95% and 100%, respectively [46]. However, by the Giemsa staining method, these aggregates are only detectable in a relatively small percentage of around 50% [64,65]. Moreover, types I and II are mainly associated with *MYH9* mutations in the C-terminal coiled-coil/rod or NHT domain, while type III is more strongly related to mutations in the N-terminal motor/head or neck domain.

5.2 | Kidney involvement

Two previous large-scale studies reported that kidney involvement usually manifests as progressive nephritis, occurring in approximately 25% to 28% of *MYH9*-RD cases [26,29]. Nephritis initially features proteinuria with or without microhematuria, and some of them may rapidly evolve into chronic renal failure (CRF) or end-stage renal disease (ESRD) requiring dialysis or kidney transplant within a few years. Hematuria may result from thrombocytopenia rather than nephritis; therefore, proteinuria serves as a more reliable and valid indicator of kidney involvement [66]. Patients with motor/head domain mutations often show a greatly increased risk of developing the most severe cases of glomerular nephropathy. All patients with R702 substitutions are expected to develop kidney damage before the age of 45 years.

In 2008, Pecci et al. [29] reported that 26 of 93 evaluable *MYH9*-RD patients (28%) developed nephritis at a mean onset age of 23 years, and 77% of cases were diagnosed before the age of 30 years; 19 of 26 cases with nephritis (73%) had evolved into CRF at the time of evaluation with a mean onset age of 26 years. Five years later, as the number of patients rose from 108 to 255 and the observation time increased, they reported again that 61 of 247 evaluable patients (25%) developed proteinuric nephropathy with a mean onset age of 27 years, and 72% of patients were diagnosed before the age of 35 years. After a median follow-up of 36 months, 40 of the 61 patients with nephropathy (66%) developed CRF, and the mean age at onset of CRF was 31 years; 26 patients (43%) also developed ESRD at a mean age of 30 years [26].

5.3 | Presenile cataracts

Presenile cataracts are the rarest extrahematologic manifestations of *MYH9*-RD patients, with an approximate incidence of 16% to 18%, and 72% of cases affected bilateral lens [26,29]. The mean age at onset was 23 or 37 years, and the p.D1424H mutation had the highest incidence risk of cataracts. Due to its low prevalence, the clinical characteristics of this complication remain to be fully elucidated.

5.4 | Hearing defect

Hearing loss represents the most common late-onset complication of *MYH9*-RD patients, affecting approximately 48% to 60% of cases over their lifetime. Pecci et al. [26,29] reported that the mean age at onset of sensorineural deafness was 31 years, and the ages at onset were homogeneously distributed over the decades from first to sixth. Similar to nephropathy, patients with motor/head domain variants tend to show a relatively higher susceptibility to hearing defects [67,68].

5.5 | Other manifestations

Some *MYH9*-RD patients may experience benign alterations in liver enzyme levels later in life. Pecci et al. [69] reported that 38 of 75 evaluable cases (50.7%) displayed elevated alanine transaminase and/or aspartate transaminase levels, and 17 of 63 (27.0%) showed increased gamma-glutamyl transferase levels, ranging from 1.9- to 2.7-fold the upper limit of normal.

6 | DIAGNOSIS

An accurate and timely diagnosis of *MYH9*-RD, as for many rare inherited diseases, is essential for making optimal treatment decisions, avoiding inappropriate interventions, providing proper counseling, and preventing complications. To achieve this, we propose a diagnostic algorithm for patients with suspected *MYH9*-RD based on comprehensive evidence, including information on clinical manifestation, laboratory findings, and molecular genetic results (Figure 8) [13,21,26,29]. *MYH9*-RD should be suspected in a patient whenever

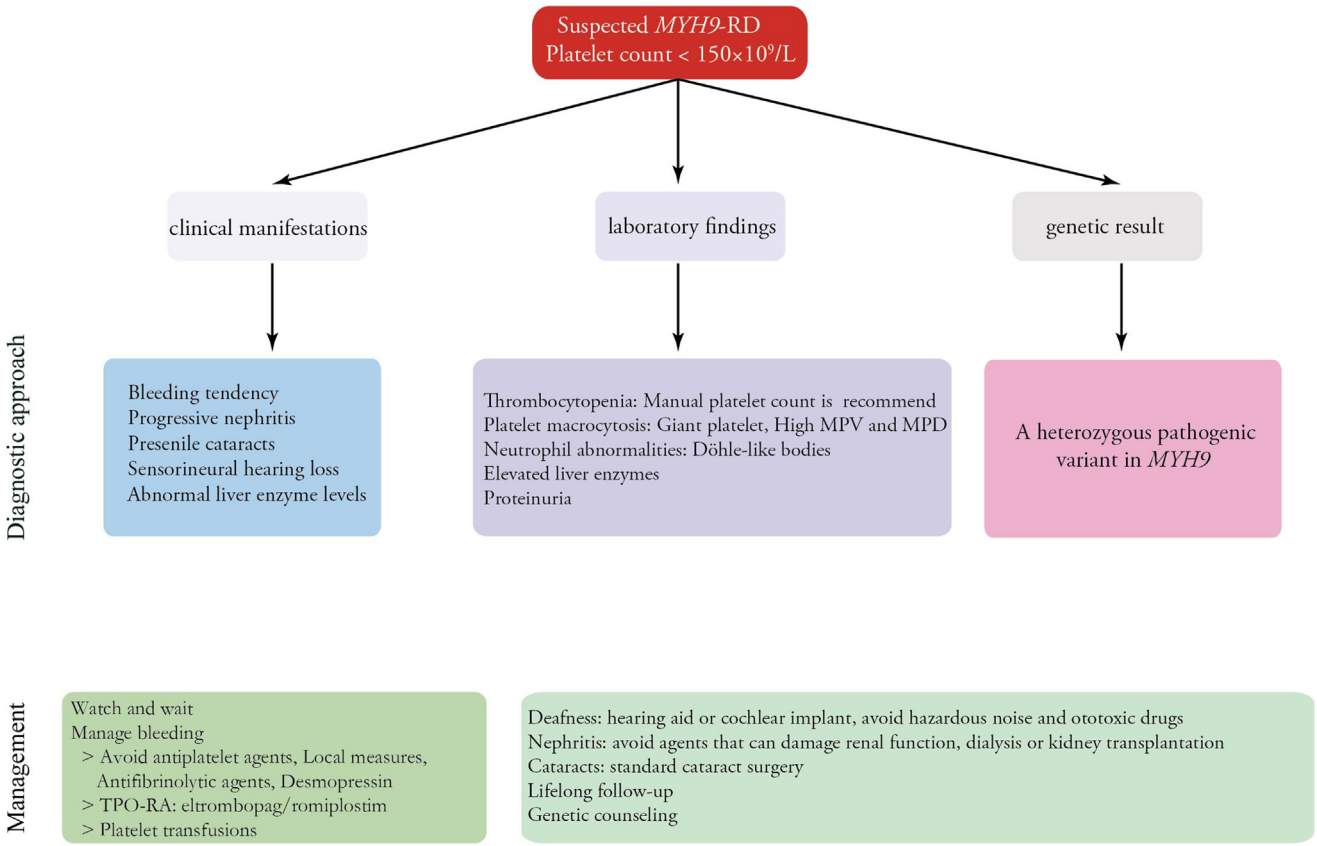


FIGURE 8 The comprehensive diagnosis and management approach of *MYH9*-related disease (*MYH9*-RD). MPD, mean platelet diameter; MPV, mean platelet volume; TPO-RA, thrombopoietin-receptor agonist.

inherited macrothrombocytopenia occurs during childhood or adolescence. Diagnostic suspicion tends to be stronger when macrothrombocytopenia is accompanied by Döhle-like bodies in neutrophil granulocytes at examination of a peripheral blood smear, and the presence of 1 or more of the extrahematologic manifestations of progressive nephritis, sensorineural deafness, presenile cataracts, and elevated liver enzymatic levels.

There are several pitfalls potentially affecting the accurate diagnosis of atypical patients: (1) the true platelet count and platelet size (MPV and MPD). Owing to platelet macrocytosis, some automated cell counting methods may underestimate the platelet count, as well as MPV and MPD parameters. Therefore, platelet count and platelet diameters should be manually verified again using optical microscopy for suspected *MYH9*-RD patients [52,53,70]. (2) As a useful indicator, basophilic Döhle-like inclusion bodies in the cytoplasm of neutrophils may not be correctly identified in the peripheral blood smear by the conventional Giemsa staining method. However, immunofluorescence staining with anti-*MYH9* antibody has been demonstrated to be a much more sensitive and specific method [46]. (3) Genetic testing is critical for an accurate diagnosis [25,26,29]. High-throughput sequencing, including targeted next-generation sequencing, whole exome sequencing (WES), and whole genome sequencing (WGS), has recently emerged as a promising new approach for the diagnosis of inherited thrombocytopenia [71–73]. Sanger sequencing, a gold standard tool for DNA sequencing but with low sensitivity and efficiency, is routinely used for confirming WES or WGS variants [74]. Since the *MYH9* gene comprises 41 exons and spans almost 107 kb, direct Sanger sequencing is not recommended due to its significant limitations in terms of low throughput production and relatively high cost. As a result, targeted panel next-generation sequencing, WES, or WGS should be used up front for molecular diagnosis.

7 | MANAGEMENT APPROACHES

A comprehensive approach to managing *MYH9*-RD involves not only treatments to prevent or manage hemorrhagic tendencies but also addressing accompanying extrahematologic disorders. For patients without spontaneous bleeding tendencies, a watch-and-wait approach is typically recommended, with regular follow-up assessments, including complete blood counts and physical examinations [1,2,75]. Interventions are occasionally considered only when hemostatic challenges arise.

7.1 | Management of hemorrhages

Similar to other forms of inherited thrombocytopenias, an important aspect of the clinical management of *MYH9*-RD is to prevent or stop active bleeding [8,76,77]. Patients should avoid drugs that may impair platelet function, reduce platelet count, or facilitate bleeding.

Nonsteroidal anti-inflammatory drugs, especially aspirin, are the most available platelet aggregation inhibitors [78]. Other antiplatelet agents mainly include some antibiotics, cardiovascular, psychotropic, oncological drugs, etc. [79,80]. Patients should consult their physicians and assess the benefit-risk ratio of each treatment. Treatment and/or prophylactic interventions are usually required when patients have active bleeding or delayed-onset bleeding problems.

The management of bleeding in females is probably a topic of concern for doctors and patients. It may be relevant to mention that females (girls and women), rather than males with *MYH9*-RD, not different from some other inherited thrombocytopenias, may experience an increased risk of having bleeding disorders during the menstrual phase, in pregnancy, or at delivery [81]. Noris et al. [82] reported that delivery-related bleeding risk was higher in inherited thrombocytopenias than in the general population for both mothers and affected newborns. They also found that the platelet counts at delivery $<50 \times 10^9$/L and a history of severe bleeding tendency were potentially predictive of the risk of delivery-related bleeding. Girls/women-specific bleeding, referring to reproduction and menstrual cycle, may require a patient-centered multidisciplinary management approach [83,84]. Administration of combined hormonal contraceptives is usually effective in preventing menorrhagia, but physicians should take care of the increased risk of thrombosis [85]. During the first 8 months of pregnancy, treatment should be initiated when the platelet count is $<20 \times 10^9$/L or if the patient experiences bleeding; A platelet count $> 50 \times 10^9$/L or $>70 \times 10^9$/L to facilitate epidural anesthesia is generally recommended for vaginal delivery or cesarean section [84].

Excessive perioperative bleeding remains a feared complication during and after surgery in patients with inherited thrombocytopenias. Based on a retrospective analysis of 829 surgical procedures carried out in 423 patients with inherited platelet disorders (including 75 *MYH9*-RD cases), Orsini et al. [86] evaluated the bleeding risk of surgery and its prevention and showed that bleeding history, type of disorder, type of surgery, and female sex were associated with higher bleeding frequency, and prophylactic treatments appeared to be associated with a lower bleeding incidence. Regarding *MYH9*-RD, they reported that the frequency of excessive bleeding was 15.5%, and platelet transfusion and antifibrinolytic agents were the most frequent prophylactic treatments.

As for controlling mild or moderate mucocutaneous hemorrhages, these measures are usually effective. Proper oral hygiene and scheduling regular dental visits are essential for preventing gum bleeding. Local interventions may involve nasal packing and/or endoscopic cauterization to halt epistaxis, suturing to control bleeding from accidental or surgical wounds, applying compression along with gauzes soaked in tranexamic acid for superficial wounds, and mouthwash containing tranexamic acid is recommended for gingival bleeding [8,13,76,77].

Platelet transfusions are the most effective therapeutic intervention to transiently increase platelet count and stop bleeding episodes; however, they also simultaneously expose patients to a greater risk of allergic transfusion reactions, infection, alloimmunization, and refractoriness to subsequent platelet transfusions [77]. Thus, platelet transfusions should be deliberately determined and limited to treatment for active hemorrhages when local measures fail, life-threatening hemorrhages, or preparing patients for elective surgery. The major predictive factors for the risk of severe bleeding are the presence and severity of previous medical history of bleeding, the overall clinical situation, and baseline platelet count [86]. Previous findings have recommended that the platelet count threshold for prophylactic transfusion can be as low as 10×10^9/L or less than 20×10^9/L if there are additional risk factors [87]. As for prophylactic platelet transfusion before surgery, a platelet count threshold of 50×10^9/L is recommended for most major surgeries and 100×10^9/L for critical site surgeries [88]. There is a competitive advantage of using human leukocyte antigens-matched donors to reduce the risk of future alloimmunization, but human leukocyte antigens-matched platelet transfusion is not always feasible or practical because it is costly and difficult to obtain. Alternatively, the strategies for preventing alloimmunization mainly involve leukoreduction of blood components, reducing donor exposure by using apheresis platelets from a single donor, and providing ABO-compatible or even crossmatch-compatible platelets [77,89]. If platelet transfusion refractoriness occurs, comprehensive approaches to diagnosis and management are available, as recommended by previous studies [89].

There are also some other hemostatic agents for the treatment of bleeding episodes or in preparation for hemostatic challenges. Antifibrinolytic agents such as tranexamic acid or epsilon aminocaproic acid are widely used to prevent or control bleeding and to reduce or avoid platelet transfusion in current medical practice [86]. The vasopressin analog desmopressin (1-deamino-8-D-arginine vasopressin), a selective vasopressin V2 receptor agonist, is known to raise circulating levels of von Willebrand factor and enhance the procoagulant activity of platelets [90]. As for *MYH9*-RD patients, a few case reports have also demonstrated that prophylactic administration of desmopressin is effective in preventing surgery-related bleeding and avoiding platelet transfusions [86,91].

Recently, the 2 thrombopoietin-receptor agonists, eltrombopag and romiplostim, have emerged as promising treatment options for inherited thrombocytopenias [92]. Previous studies indicated that eltrombopag or romiplostim could be successfully used to raise the platelet count of *MYH9*-RD patients with severe thrombocytopenia and recurrent episodes of spontaneous bleeding or in preparation for elective surgery and invasive procedures [93–95]. In the first prospective multicenter phase 2 trial (2010), 12 adult *MYH9*-RD patients with a platelet count of $<50 \times 10^9$/L received 3 or 6 weeks of eltrombopag treatment at a dose of 50 to 75 mg per day, 11 patients achieved a significant increase in platelet count, and only 1 patient did not respond [93]. In another phase 2 clinical trial (2020), 9 patients with *MYH9*-RD were enrolled to confirm the efficacy of eltrombopag (50-75 mg daily for 3-6 weeks), and 7 patients achieved a major response (platelet count $> 100 \times 10^9$/L), and 2 had a minor response (platelet count at least twice the baseline value) [96]. Currently, there are no published clinical trials on the use of romiplostim in patients

with *MYH9*-RD; sporadic case reports are the sole available sources. Rabbolini et al. [95] documented successful long-term romiplostim use in a *MYH9*-RD case. Treatment commenced with romiplostim at 1 μg/kg subcutaneously once weekly, escalating weekly by 1 μg/kg. Within 5 weeks, a 3-fold increase in platelet count (baseline 7×10^9/L) was achieved. Over 36 months of follow-up, a mean romiplostim dose of 6.3 μg/kg/wk maintained a mean platelet count of 33×10^9/L.

7.2 | Management of extrahematologic disorders

In patients with *MYH9*-RD, renal function should be regularly monitored, especially in subjects with high-risk *MYH9* mutations (eg, R702 mutation). As proteinuria is an excellent marker of kidney damage and can often be detected earlier, the occurrence of proteinuria is recommended to be investigated every 6 to 12 months. Of note, some drugs may cause kidney damage [97]. The balance between the benefits and risks of such agents should be carefully considered. As angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can reduce proteinuria and decrease the rate of progressive renal injury, patients with signs of initial kidney damage may benefit from the treatment [8,98]. Dialysis and kidney transplantation are available treatments for ESRD.

It is recommended to reduce exposure to hazardous noise and ototoxic drugs, which can exacerbate hearing loss, and perform a hearing screening test every 3 to 5 years. When hearing loss occurs, a hearing aid for mild to moderate hearing loss and a cochlear implant for severe to profound hearing loss are the 2 main hearing rehabilitation options [68]. Patients with *MYH9*-RD should be monitored regularly for the development of cataracts, with follow-up examinations recommended every 3 to 5 years. When cataracts are detected, standard surgical procedures should be performed as indicated.

7.3 | Genetic counseling

When the diagnosis is made, genetic counseling, baseline laboratory tests (blood cell count, blood smear examination), and physical examination are recommended for the family members [8]. Generally, each offspring of an affected individual harboring germline *MYH9* pathogenic variant has a 50% chance of inheriting the disease. Early recognition of at-risk relatives is paramount to allow timely diagnosis and direct personalized management. As for family planning, prenatal/preimplantation genetic testing makes it possible for young adult patients with fertility desire to determine potential risks to offspring and reproductive options [99].

8 | CONCLUSION AND FUTURE PROSPECTS

Although *MYH9*-RD is one of the most common forms of inherited thrombocytopenia, its true prevalence is likely underestimated due to frequent misdiagnosis and undertesting. Moreover, a significant portion of clinicians are still not aware of this rare disease in clinical practice. Early recognition of *MYH9*-RD is crucial to allow timely diagnosis and facilitate patient-tailored management. A stepwise diagnostic approach that integrates information on clinical manifestation, family history, laboratory findings, and molecular genetic results can help reach an accurate diagnosis. The optimal management of patients with *MYH9*-RD involves the prevention and treatment of hemorrhagic diathesis, a multidisciplinary approach aimed at the surveillance, prevention, and treatment of probable accompanied extrahematologic disorders, and professional genetic counseling of the patients and their family members.

Despite remarkable progress in *MYH9*-RD, challenges remain in several aspects, including but not limited to (i) reducing diagnostic delay to achieve early diagnosis and intervention, especially for those patients at high risk of disease progression; (ii) minimizing the gap between theory, research, and practice to guide better clinical management, genetic counseling, and decision making; and (iii) there is considerable phenotypic variability, although genotype-phenotype correlations can help identify, exceptions to the rule always exist. Further studies are needed to improve the disease evaluation, classification, and stratification.

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There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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