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# *MYH9*-Related Disease

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## Summary

### Clinical characteristics

*MYH9*-related disease (*MYH9*-RD) is characterized in all affected individuals by hematologic features present from birth consisting of platelet macrocytosis (i.e., >40% of platelets larger than 3.9 µm in diameter), thrombocytopenia (platelet count <150 x $10^9$/L), and aggregates of the MYH9 protein in the cytoplasm of neutrophil granulocytes. Most affected individuals develop one or more additional extrahematologic manifestations of the disease over their lifetime, including sensorineural hearing loss, renal disease (manifesting initially as glomerular nephropathy), presenile cataracts, and/or elevation of liver enzymes.

### Diagnosis/testing

The diagnosis of *MYH9*-related disease **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *MYH9* identified by molecular genetic testing.

### Management

*Treatment of manifestations:* For most active hemorrhages, consider local measures as the first-line treatment; transfusion of platelet concentrates should be used for active hemorrhages that cannot be otherwise managed, life- or organ-threatening hemorrhages, and/or bleeding at critical sites. Whenever necessary, eltrombopag or platelet transfusion should be used to prepare affected individuals for elective surgery. Antifibrinolytic agents and desmopressin are also used for covering hemostatic challenges or treating hemorrhages. Hearing loss, renal complications, and cataracts are managed in a standard fashion; individuals with severe/profound deafness benefit from cochlear implantation.

*Surveillance:* For individuals with moderate or severe thrombocytopenia: at least annual (and in case of bleeding and/or changes in bleeding diathesis) microscopic assessment of platelet count and blood count to screen for anemia. Screening for individuals not currently under treatment for the following: annually (or every 6 months

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in individuals with high-risk *MYH9* genotypes) for nephropathy, and every three years for hearing loss, cataracts, and abnormal liver enzymes.

*Agents/circumstances to avoid:* Drugs that inhibit platelet function or reduce platelet count, and drugs that are ototoxic, nephrotoxic, or hepatotoxic should be used only after assessment of risk-to-benefit ratio. Hazardous noise and activities with high risk of injury should be avoided.

*Evaluation of relatives at risk*: Clarify the status of all first-degree relatives of an affected individual in order to establish appropriate management (including treatment and surveillance) and awareness of agents and circumstances to avoid.

*Pregnancy management*: Deliveries should be managed as they are in women with other forms of thrombocytopenia; in general, a platelet count of ≥50 x $10^9$/L is recommended for delivery.

## Genetic counseling

*MYH9*-RD is inherited in an autosomal dominant manner. Approximately 35% of probands represent simplex cases, most of whom have a documented *de novo* pathogenic variant. Each child of an individual with *MYH9*-RD has a 50% chance of inheriting the *MYH9* pathogenic variant. Once the *MYH9* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

# *GeneReview* Scope

In the past, the phenotypes included in *MYH9*-related disease (*MYH9*-RD) were known as Epstein syndrome, Fechtner syndrome, May-Hegglin anomaly, Sebastian syndrome (Sebastian platelet syndrome), and autosomal dominant deafness 17 (DFNA17). The first four phenotypes, all characterized by thrombocytopenia and platelet macrocytosis, were classified on the basis of the presence of Döhle-like bodies and different combinations of the other manifestations of *MYH9*-RD. DFNA17 was initially described as nonsyndromic deafness, but subsequent investigations showed that this condition is associated with the other manifestations of *MYH9*-RD. Because the phenotype of a person with an *MYH9* pathogenic variant often evolves over time and because the five named phenotypes do not define all the possible manifestations resulting from a heterozygous *MYH9* pathogenic variant, *MYH9*-RD was proposed as a new nosologic entity. The term *MYH9*-RD encompasses all individuals with a *MYH9* pathogenic variant who present typical congenital hematologic features (i.e., macrothrombocytopenia and aggregates of the MYH9 protein in neutrophils) and may develop one or more extrahematologic manifestations of the disease over the course of life.

# Diagnosis

No consensus clinical diagnostic criteria for *MYH9*-related disease (*MYH9*-RD) have been published.

## Suggestive Findings

*MYH9*-RD **should be suspected** in individuals with the following clinical and laboratory findings and family history.

**Clinical findings**

- Manifestations of thrombocytopenia
  - Easy bruising
  - Spontaneous mucocutaneous bleeding
  - Excessive bleeding after hemostatic challenges (major or minor surgery, deliveries, treatment with antiplatelet drugs)

- Sensorineural hearing loss ranging from a slight defect occurring in the elderly to profound deafness that may manifest at a young age
- Glomerular nephropathy manifest as proteinuria, with possible evidence of chronic kidney disease
- Presenile cataract (occurring in early or middle life)

**Laboratory findings**

- **Platelet abnormalities**
  - Thrombocytopenia. Platelet count <150 x $10^9$/L (normal: 150-400 x $10^9$/L)
  - Platelet macrocytosis. Extreme platelet macrocytosis present from birth, a hallmark of *MYH9*-RD, is a crucial suggestive finding. Mean platelet diameter was 4.5 µm (95% confidence interval, 4.2-4.8) in 125 persons with *MYH9*-RD compared to 2.6 µm (95% confidence interval, 2.4-2.7) in 55 healthy controls [Noris et al 2014a].

    Giant platelets (i.e., platelets larger than red blood cells) are invariably present on examination of blood smears of persons with *MYH9*-RD.

    Moreover, a mean platelet diameter >3.7 µm and/or the finding that >40% of platelets are larger than 3.9 µm (i.e., about half the diameter of a red blood cell) has very good sensitivity and specificity in distinguishing *MYH9*-RD from the other forms of inherited or acquired thrombocytopenia (see Differential Diagnosis) [Noris et al 2014a].

    Note: Electronic cell counters do not recognize the largest platelets of individuals with *MYH9*-RD, and therefore underestimate both platelet count and size.
- **Neutrophil abnormalities**
  - Döhle-like bodies. Faint, slightly basophilic inclusion bodies in the cytoplasm of neutrophils (similar to the Döhle bodies that may be found in persons with an infection) are observed on microscopic assessment of a peripheral blood smear after conventional staining (e.g., May-Grünwald-Giemsa).

    Note: Döhle-like bodies, present in 42%-84% of individuals with *MYH9*-RD, may escape detection because they can be very faint and/or small [Kunishima et al 2003, Seri et al 2003, Pecci et al 2018].
  - Typical aggregates of the MYH9 protein in the cytoplasm of neutrophils observed on immunofluorescence staining of a peripheral blood smear:
    - Are present at birth and throughout the life span;
    - Can be detected in all individuals with *MYH9*-RD. For this reason, assay of immunofluorescence staining of MYH9 protein distribution in neutrophils has been validated as a diagnostic test for *MYH9*-RD with close to 100% specificity and sensitivity [Kunishima et al 2003, Savoia et al 2010, Kitamura et al 2013, Greinacher et al 2017].

      Note: in neutrophils of unaffected individuals, MYH9 protein is uniformly distributed.
- **Elevated liver enzymes** (serum alanine aminotransferase and/or aspartate aminotransferase and occasionally serum gamma-glutamyltransferase)

**Family history** may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations) or the affected individual may represent a simplex case (i.e., a single occurrence in a family). Therefore, absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of *MYH9*-related disease **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *MYH9* identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *MYH9* variant of uncertain significance does not establish or rule out the diagnosis of this disorder. In these cases, the search for typical aggregates of the MYH9 protein in neutrophils on immunofluorescence staining of blood smears may be a useful tool to assess the pathogenicity of the variant [Greinacher et al 2017].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing and genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *MYH9*-related disease has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

**Single-gene testing.** Sequence analysis of *MYH9* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

**A multigene panel** that includes *MYH9* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

### Option 2

**Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

**Table 1.** Molecular Genetic Testing Used in *MYH9*-Related Disease

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method |
|---|---|---|
| *MYH9* | Sequence analysis [3] | 98% [4] |
| | Gene-targeted deletion/duplication analysis [5] | Unknown [6] |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on allelic variants detected in this gene.
*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*4.* Savoia et al [2010]
*5.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
*6.* The only *MYH9* gross deletions/duplications identified to date are deletions/duplications of 21 or 42 bp within exons 21, 24, and 25, which can be detected by sequence analysis. However, because a deletion of 1220 nucleotides with the breakpoints in intron 25 and intron 26 leads to an in-frame removal of exon 26 [Kunishima et al 2008], gene-targeted deletion/duplication analysis may be appropriate in families with a strong clinical history and no identifiable *MYH9* pathogenic variant on sequence analysis.

# Clinical Characteristics

## Clinical Description

*MYH9*-related disease (*MYH9*-RD) is characterized in all affected individuals by hematologic features present from birth consisting of platelet macrocytosis (i.e., >40% of platelets >3.9 µm in diameter), thrombocytopenia (platelet count <150 x $10^9$/L), and aggregates of the MYH9 protein in the cytoplasm of neutrophil granulocytes. Most affected individuals develop one or more additional extrahematologic manifestations of the disease over their lifetime, including sensorineural hearing loss, renal disease (manifesting initially as glomerular nephropathy), presenile cataracts, and/or elevation of liver enzymes [Pecci et al 2014a, Pecci et al 2018].

**Table 2.** *MYH9*-Related Disease: Frequency of Select Features

| Feature | % of Persons w/Feature | Comment |
|---|---|---|
| **Platelet macrocytosis** | 100% | Present from birth |
| **Thrombocytopenia** | 98% | Present from birth. Very few persons have platelet counts at lower limit of normal range. |
| **Bleeding tendency** | 80%-90% | ~30% have spontaneous bleeding. [1] Most persons only have ↑ risk of bleeding secondary to thrombocytopenia after hemostatic challenges. |
| **Sensorineural hearing loss** | 80%-85% | Present in ~50% of persons at mean age of 33 yrs [1] & occurs in most persons over time |
| **Abnormal liver enzymes** | 50% | Develop later in life [2] |
| **Nephropathy** | 25% | Mean age at onset: 27 yrs [1] |
| **Cataracts** | 20% | Mean age at onset: 37 yrs [1]; however, congenital cataracts have been reported. |

*1.* Pecci et al [2014a]
*2.* Pecci et al [2012]

**Platelet macrocytosis** is present from birth in all individuals with *MYH9*-RD (see Diagnosis, Suggestive Findings).

**Thrombocytopenia** ranges from mild to severe. The degree of thrombocytopenia usually remains stable in each individual throughout life. Because platelet counts at the lower limit of the normal range have been reported in

very few individuals with *MYH9*-RD, platelet macrocytosis and aggregates of the MYH9 protein in neutrophils are the only findings shared among all affected individuals.

Presence and severity of a spontaneous **bleeding tendency** correlate with the degree of thrombocytopenia. Most affected individuals have no spontaneous bleeding or only easy bruising, and are at risk of significant hemorrhages only after hemostatic challenges. About 30% of persons with *MYH9*-RD have spontaneous mucocutaneous bleeding – mainly menorrhagia, epistaxis, and gum bleeding [Pecci et al 2014a]. Life-threatening bleeding is rare.

**Sensorineural hearing loss** is present in about 50% of individuals evaluated at a mean age of 33 years and is expected to occur in most individuals over time [Pecci et al 2014a]. The mean age at onset is 31 years. Onset of hearing loss is distributed evenly from the first to sixth decade. Of those who develop hearing loss, 36% do so before age 20 years, 33% between ages 20 and 40 years, and 31% after age 40 years.

Hearing loss is usually bilateral. Once diagnosed, hearing loss frequently progresses over time, although it can remain stable in a minority of affected individuals. Earlier-onset hearing loss often progresses more rapidly and may result in severe-to-profound deafness [Verver et al 2016].

Hearing loss interferes with activities of daily living in 90% of individuals who have an abnormal audiometric examination [Pecci et al 2014a].

**Glomerular nephropathy** presents with proteinuria and microhematuria. However, in *MYH9*-RD, hematuria may result from thrombocytopenia rather than glomerular disease; therefore, proteinuria is the more reliable indicator of glomerular involvement.

The mean age at onset is 27 years. Of those who develop renal disease, 72% are diagnosed before age 35 years. In most individuals with nephropathy, kidney damage is progressive and evolves to end-stage renal disease (ESRD). Among those with nephropathy, the overall annual rate for progression to ESRD is 6.79 per 100 affected persons. After a median follow up of 36 months, 64% of 61 individuals with nephropathy developed chronic kidney disease and 43% developed ESRD [Pecci et al 2014a]. In some cases, kidney damage may appear later in life and/or show a slower progression.

**Cataracts.** The mean age of onset of cataracts is 37 years, but congenital cataracts have been reported. In most individuals, cataracts are bilateral and progress over time.

**Elevated liver enzyme levels.** Elevated aspartate aminotransferase and/or alanine aminotransferase (possibly associated with increased gamma-glutamyltransferase) usually remains stable over time. In some affected individuals, normalization of enzyme levels has been observed. Progression to impairment of liver function has not been reported in any affected individual [Pecci et al 2012, Favier et al 2013].

## Genotype-Phenotype Correlations

Observed genotype-phenotype correlations are discussed in this section. (See Molecular Genetics, Table 8 for more details.)

Individuals with pathogenic variants involving the head domain of the MYH9 protein have more severe thrombocytopenia compared to those with pathogenic variants affecting the tail domain.

The risk of developing kidney damage, hearing loss, and cataract also depends on the specific *MYH9* pathogenic variant [Pecci et al 2014a].

- Pathogenic variants in the codon for arginine residue 702 (located in the short functional SH1 helix of the head domain) are associated with the most severe phenotype. Individuals with Arg702 substitutions present with severe thrombocytopenia (platelet count usually <50 x $10^9$/L), and all are expected to develop

nephropathy and severe hearing loss before age 40 years. Moreover, nephropathy usually progresses rapidly to ESRD in these individuals.

- The p.Asp1424His substitution is associated with an intermediate-to-high risk of developing extrahematologic manifestations over time. All individuals with this variant are expected to develop hearing loss by age 60 years; most affected individuals develop kidney disease before age 60 years; the risk for cataracts is higher than in those with other genotypes.
- Pathogenic variants encoding the residues at the interface between the SH3-like motif and the upper 50-kd subdomain of the head domain or those resulting in substitutions of the arginine residue 1165 are associated with a high risk for hearing loss (all are expected to develop hearing loss before age 60 years) and a low risk for nephropathy and cataract.
- The p.Asp1424Asn and p.Glu1841Lys substitutions, as well as the nonsense or frameshift pathogenic variants resulting in alterations of the carboxy-terminal nonhelical tailpiece of the MYH9 protein, are associated with low risk of developing the manifestations that develop over time; thus, macrothrombocytopenia usually remains the only clinically relevant disease feature throughout life [Pecci et al 2014a].

To date, no significant genotype-phenotype correlations have been identified for the occurrence of elevated liver enzyme levels [Pecci et al 2012].

## Penetrance

Penetrance is complete for the following congenital findings:

- Platelet macrocytosis with giant platelets
- Aggregates of the MYH9 proteins in neutrophils

Except for a very few individuals in whom platelet count was just above the conventional cut-off value for thrombocytopenia (150 x $10^9$/L), thrombocytopenia is a congenital manifestation of the disease.

Expressivity varies for onset and severity of sensorineural deafness, glomerular nephropathy, presenile cataract, and alterations of liver enzymes.

## Nomenclature

In the past, the conditions now collectively referred to as *MYH9*-RD were known as Epstein syndrome, Fechtner syndrome, May-Hegglin anomaly, Sebastian syndrome (Sebastian platelet syndrome), and autosomal dominant deafness 17 (DFNA17). The first four phenotypes, all characterized by macrothrombocytopenia with giant platelets, were classified on the basis of the presence of Döhle-like bodies on conventional staining of blood smears and different combinations of the other manifestations of *MYH9*-RD (see Table 3). DFNA17 was initially described as a nonsyndromic sensorineural hearing loss deriving from the single NM_002473.5:c.2114G>A (p.Arg705His) pathogenic variant [Lalwani et al 2000] (see also Hereditary Hearing Loss and Deafness Overview). However, subsequent investigations showed that individuals who are heterozygous for the p.Arg705His substitution present other manifestations typical of *MYH9*-RD along with hearing loss [Saposnik et al 2014, Verver et al 2015].

**Table 3.** *MYH9*-Related Disease: Formerly Used Terminology

| Formerly Used Disorder Name | Clinical Findings | | | | |
|---|---|---|---|---|---|
| | Macro-thrombo-cytopenia | Döhle-like bodies | SNHL | Cataract | Nephropathy |
| DFNA17 | – | – | + | – | – |
| Epstein syndrome | + | – | + | – | + |

*Table 3. continued from previous page.*

| Formerly Used Disorder Name | Clinical Findings | | | | |
|---|---|---|---|---|---|
| | Macro-thrombo-cytopenia | Döhle-like bodies | SNHL | Cataract | Nephropathy |
| Fechtner syndrome | + | + | + | + | + |
| May-Hegglin anomaly | + | + | – | – | – |
| Sebastian syndrome | + | + | – | – | – |

Modified from Table 1 in Seri et al [2003]
DFNA17 = autosomal-dominant deafness 17; SNHL = sensorineural hearing loss

## Prevalence

*MYH9*-RD is considered a rare disease. The Italian Registry for *MYH9*-RD includes 225 Italian affected individuals, indicating that the prevalence of the disorder in Italy is at least 3.75:1,000,000. Because mild forms are often discovered incidentally and severe forms are often misdiagnosed as other disorders, the actual prevalence is expected to be higher. Of note, other estimates – based on the frequency of *MYH9* loss-of-function pathogenic variants in the EXAC database– suggest a much higher prevalence (~1:20,000-25,000) [Fernandez-Prado et al 2019].

*MYH9*-RD has been diagnosed worldwide, and there is no evidence of variation in prevalence across different populations.

# Genetically Related (Allelic) Disorders

In addition to *MYH9*-related disease, germline heterozygous pathogenic variants in *MYH9* are known to be associated with MALTA (*MYH9*-associated elastin aggregation) syndrome. MALTA syndrome is characterized by cutaneous lesions (including non-malignant sweat duct proliferation, atrophodermia vermiculata, multiple syringomata, and milia) that are associated with the irregular distribution of elastin fibers in the dermis. *MYH9* in-frame deletions and missense and frameshift pathogenic variants have been described in five unrelated families [Fewings et al 2019].

# Differential Diagnosis

The differential diagnosis of *MYH9*-related disease (*MYH9*-RD) should take into consideration acquired and inherited forms of thrombocytopenia as well as collagen IV-related nephropathies.

## Acquired Thrombocytopenia

**Idiopathic (autoimmune) thrombocytopenic purpura (ITP).** Differentiating between *MYH9*-RD and ITP (the most frequent form of acquired thrombocytopenia) is challenging and individuals with *MYH9*-RD are frequently misdiagnosed with ITP. Misdiagnosis with ITP often leads to treatments (immunosuppressive drugs and splenectomy) that are not only ineffective in individuals with *MYH9*-RD but also potentially harmful. For instance, among individuals enrolled in the Italian Registry for *MYH9*-RD, about 60% of index cases had received a previous diagnosis of ITP and 30% received inappropriate treatments, including splenectomy [Pecci et al 2018].

If the genetic origin of thrombocytopenia is not obvious because a family history is absent or unclear, the following findings on microscopic evaluation of peripheral blood slides are a simple and effective way to distinguish individuals with *MYH9*-RD from those with ITP [Noris et al 2014a]:

- Platelets are significantly larger in persons with *MYH9*-RD than in those with ITP: a mean platelet diameter >3.7 µm distinguishes *MYH9*-RD from ITP with 86% sensitivity and 87% specificity.
- More than 40% of platelets >3.9 µm (i.e., about half the diameter of a red blood cell) distinguishes *MYH9*-RD from ITP with 85% sensitivity and 87% specificity.

Assay of immunofluorescence staining of MYH9 protein distribution in neutrophils can also be used to differentiate *MYH9*-RD from ITP (see Diagnosis, Suggestive Findings). Molecular genetic testing provides confirmation of the diagnosis of *MYH9*-RD.

## Inherited Thrombocytopenia

Table 4 summarizes the main forms of inherited thrombocytopenia with platelet macrocytosis (inherited macrothrombocytopenias) that should, therefore, be considered in the differential diagnosis of *MYH9*-RD.

Note: All congenital macrothrombocytopenias are very rare disorders.

**Table 4.** Inherited Macrothrombocytopenias in the Differential Diagnosis of *MYH9*-Related Disease

| Gene / Genetic Mechanism | Diff Dx Disorder | MOI | Associated Clinical Characteristics (in addition to macrothrombocytopenia) |
|---|---|---|---|
| 11q23 deletions | Jacobsen syndrome (OMIM 147791)<br>Paris-Trousseau thrombocytopenia (OMIM 188025) | AD | Physical growth delay, ID, craniofacial dysmorphism, cryptorchidism, malformations of multiple organs |
| *ACTN1* | *ACTN1*-RT (OMIM 615193) | AD | NA (nonsyndromic) |
| *CDC42* | Takenouchi-Kosaki syndrome w/ macrothrombocytopenia (OMIM 616737) | AD | Defective growth & psychomotor development; ID; facial abnormalities; brain, cardiac, genitourinary, &/or skeletal malformations |
| *DIAPH1* | *DIAPH1*-related disorder (OMIM 124900) | AD | Progressive sensorineural deafness develops during infancy or childhood. |
| *FLI1* | *FLI1*-RT (OMIM 617443) | AD<br>AR | NA (nonsyndromic) |
| *FLNA* | *FLNA*-RT [1] | XL | Periventricular nodular heterotopia & chronic idiopathic intestinal pseudo-obstruction are assoc in the vast majority of affected persons. |
| *GFI1B* | *GFI1B*-RT (OMIM 187900) | AD | Red-cell anisocytosis or anisopoikilocytosis present in most affected persons |
| *GNE* | *GNE*-RT [2] | AR | Skeletal muscle damage reported in some affected persons |
| *GP1BA*<br>*GP1BB*<br>*GP9* | Biallelic Bernard-Soulier syndrome (OMIM 231200) | AR | NA (nonsyndromic); platelets can be as large as in *MYH9*-RD. |
| *GP1BA*<br>*GP1BB* | Monoallelic Bernard-Soulier syndrome [3] (OMIM 153670) | AD | NA (nonsyndromic) |
| *ITGA2B*<br>*ITGB3* | *ITGA2B* / *ITGB3*-RT (OMIM 187800) | AD | NA (nonsyndromic) |
| *NBEAL2* | Gray platelet syndrome (OMIM 139090) | AR | NA (nonsyndromic); hallmark finding is "pale" (gray) platelets on peripheral blood films due to lack of alpha granules. |
| *SLFN14* | *SLFN14*-RT (OMIM 616913) | AD | NA (nonsyndromic) |
| *SRC* | *SRC*-RT (THC6) (OMIM 616937) | AD | Facial dysmorphism, edentulism, severe osteoporosis, &/or myelofibrosis |

*Table 4. continued from previous page.*

| Gene / Genetic Mechanism | Diff Dx Disorder | MOI | Associated Clinical Characteristics (in addition to macrothrombocytopenia) |
|---|---|---|---|
| *TUBB1* | *TUBB1*-RT (OMIM 613112) | AD | NA (nonsyndromic) |

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; NA = not applicable; RT = related thrombocytopenia; THC6 = thrombocytopenia 6; XL = X-linked

*1.* Vassallo et al [2020]
*2.* Futterer et al [2018]
*3.* Sivapalaratnam et al [2017]

## Hereditary Nephritis

**Alport syndrome.** The spectrum of renal involvement in Alport syndrome ranges from isolated non-progressive hematuria to progressive nephropathy characterized by hematuria, proteinuria, and chronic kidney disease and end-stage renal disease. Affected individuals often have sensorineural hearing loss and characteristic ocular abnormalities. Rare individuals have associated aortic disease or diffuse leiomyomatosis. Alport syndrome is caused by pathogenic variants in *COL4A3*, *COL4A4*, or *COL4A5* and can be transmitted in an X-linked, autosomal dominant, or autosomal recessive manner.

Platelet defects have not been described in Alport syndrome. Therefore, whenever nephropathies are associated with macrothrombocytopenia, *MYH9*-RD should be strongly considered.

# Management

No clinical practice guidelines for *MYH9*-related disease (*MYH9*-RD) have been published.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *MYH9*-RD, the evaluations summarized in Table 5 are recommended at the time of diagnosis.

**Table 5.** Recommended Evaluations Following Initial Diagnosis in Individuals with *MYH9*-Related Disease

| System/Concern | | Evaluation | Comment |
|---|---|---|---|
| **Thrombocytopenia** | | Microscopic assessment of platelet count | Phase contrast microscopy by counting chamber is most reliable method to assess platelet count in persons w/*MYH9*-RD (see Diagnosis). |
| **Bleeding episodes** | | • Assessment of bleeding history incl spontaneous & provoked bleeding episodes<br>• Complete blood count to evaluate for anemia | • Use of standardized questionnaires (e.g., ISTH Bleeding Assessment Tool [1]) recommended to obtain bleeding history<br>• In persons w/anemia, serum concentration of iron & ferritin to evaluate for iron deficiency |
| **SNHL** | **Screening** | Audiogram (See Hereditary Hearing Loss and Deafness Overview.) | In persons w/severe-to-profound deafness, speech recognition tests |
| | **Known** | Consultation w/audiologist/ otolaryngologist | |
| **Nephro-pathy** | **Screening** | Urinalysis, 24-hour protein, or protein (or albumin) to creatinine ratio on a spot urine sample; serum concentration of creatinine | |
| | **Known** | Consultation w/nephrologist | |
| **Cataract** | | Ophthalmologic eval incl slit lamp exam | |

*Table 5. continued from previous page.*

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Abnormal liver enzymes** | Measurement of serum concentration of AST, ALT, & GGT | |
| **Genetic counseling** | By genetics professionals [2] | To inform affected persons & their families re nature, MOI, & implications of *MYH9*-RD to facilitate medical & personal decision making |
| **Family support/ resources** | Assess:<br>• Use of community or online resources such as Parent to Parent;<br>• Need for social work involvement for parental support;<br>• Need for home nursing referral. | |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; ISTH = International Society on Thrombosis and Haemostasis; MOI = mode of inheritance; SNHL = sensorineural hearing loss
*1.* Gresele et al [2020]
*2.* Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

## Treatment of Manifestations

Multidisciplinary management by different specialists including hematologists or internists with expertise in hemostasis, nephrologists, otolaryngologists, and ophthalmologists is recommended.

**Table 6.** Treatment of Manifestations in Individuals with *MYH9*-Related Disease

| Manifestation/ Concern | Treatment | Considerations/Other |
|---|---|---|
| **Thrombo-cytopenia & bleeding tendency** | • Treatments incl local measures, transfusion of platelet concentrates, eltrombopag, antifibrinolytics drugs, desmopressin.<br>• See Thrombocytopenia and/or Bleeding Tendency.<br>• Treatments should be administered by hematologist or internist w/expertise in hemostasis. | • Thrombocytopenia cannot be prevented.<br>• Education re drugs that affect platelet function to prevent bleeding (See Agents/Circumstances to Avoid.)<br>• Oral contraceptives to prevent or control menorrhagia<br>• Regular dental care to prevent gum bleeding |
| **SNHL** | • Treatments incl hearing aids, cochlear implantation.<br>• See Hereditary Hearing Loss and Deafness Overview.<br>• See Sensorineural Hearing Loss.<br>• Treatments should be administered by audiologist/otolaryngologist. | Education re potentially damaging drugs to prevent occurrence &/or worsening of hearing loss (See Agents/ Circumstances to Avoid.) |
| **Nephropathy** | • Treatments incl angiotensin converting enzyme inhibitors &/or angiotensin receptor blockers, dialysis, kidney transplantation.<br>• See Nephropathy.<br>• Treatments should be administered by nephrologist. | Education re potentially damaging drugs to prevent occurrence &/or worsening of nephropathy (See Agents/ Circumstances to Avoid.) |
| **Cataract** | Cataract surgery, per treating ophthalmologist | Education re drugs predisposing to cataract (See Agents/ Circumstances to Avoid.) |

*Table 6. continued from previous page.*

| Manifestation/ Concern | Treatment | Considerations/Other |
|---|---|---|
| **Abnormal liver enzymes** | No specific treatment | Education re potentially hepatotoxic drugs (See Agents/ Circumstances to Avoid.) |

SNHL = sensorineural hearing loss

## Thrombocytopenia and/or Bleeding Tendency

**Local measures,** the first-line treatment for most mucocutaneous hemorrhages, are often sufficient to control mild or moderate bleeding. Local measures include nasal packing or endoscopic cauterization of the bleeding site for treatment of epistaxis; suturing for hemorrhages from accidental or surgical wounds; and compression and application of gauzes soaked in tranexamic acid for bleeding from superficial wounds. Mouthwash with tranexamic acid may be useful for gingival bleeding.

**Transfusions of platelet concentrates** are currently used to transiently increase platelet count, and are effective in stopping bleeding episodes; however, they expose treated individuals to the risk of acute reactions, transmission of infectious diseases, and alloimmunization with consequent refractoriness to subsequent platelet transfusions. Thus, platelet transfusions should be limited to treatment for active hemorrhages that cannot be otherwise managed, life- or organ-threatening hemorrhages, and/or bleeding at critical sites. Transfusion of platelet concentrates can also be used as prophylaxis to prepare for hemostatic challenges such as surgery and childbirth. Whenever available, platelets from HLA-matched donors should be used to prevent and/or overcome alloimmunization.

**Eltrombopag** is an oral drug mimicking the activity of thrombopoietin, the natural hormone that stimulates platelet production. Two prospective Phase II clinical trials showed that a three- to six-week course of eltrombopag is effective in increasing platelet count and reducing/abolishing bleeding tendency in most individuals with *MYH9*-RD. The first trial tested 12 individuals, of whom 11 showed a response to the drug [Pecci et al 2010]; a more recent trial enrolled nine individuals with *MYH9*-RD, all of whom responded [Zaninetti et al 2020]. Treatment was well tolerated in both studies.

A recent retrospective case series from a single center reported 11 consecutive surgical procedures in individuals with *MYH9*-RD, severe thrombocytopenia, and high bleeding risk prepared with eltrombopag administration: in ten, the drug allowed surgery to proceed without bleeding or other complications and without the need for platelet transfusion [Zaninetti et al 2019]. Based on these results, a short-term course of eltrombopag can be used in individuals with *MYH9*-RD to transiently increase platelet count in preparation for elective surgery or other invasive procedures. Note: At the present time, eltrombopag is approved in the US and Europe only for individuals with some forms of acquired thrombocytopenia or aplastic anemia.

**Antifibrinolytic agents.** Several authors recommend the systemic administration of antifibrinolytic agents, such as tranexamic or epsilon-aminocaproic acid, to treat mild or moderate mucocutaneous bleeding [Althaus & Greinacher 2009]. Antifibrinolytic drugs are also used empirically as prophylaxis to cover surgery or other hemostatic challenges, especially low-risk procedures, in persons with *MYH9*-RD [Orsini et al 2017].

**Desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP)** shortened bleeding time in some individuals with *MYH9*-RD [Balduini et al 1999]. Successful surgery after prophylaxis with DDAVP has also been reported [Pecci et al 2014b]. However, clinical studies on the efficacy of DDAVP in *MYH9*-RD are still lacking.

The need for prophylactic intervention in preparation for surgery or other invasive procedures (including platelet transfusion, short-term eltrombopag, and/or empiric use of antifibrinolytics drugs or desmopressin) should be established based on the type of procedure, the individual's previous history of bleeding, and platelet count before the procedure.

**Oral contraceptives** are often effective in preventing and/or controlling menorrhagia. The risk of thrombosis associated with the administration of oral contraceptives containing estrogens should be taken into account in women with *MYH9*-RD.

Regular dental care and good oral hygiene are essential to prevent gingival bleeding.

### Sensorineural Hearing Loss

**Hearing aids** are used for individuals with clinically significant hearing loss.

**Cochlear implantation.** A retrospective analysis of ten individuals and a few case reports indicated that cochlear implantation is effective in restoring hearing function in most persons with *MYH9*-RD who have severe-to-profound deafness [Pecci et al 2014b, Pecci et al 2018].

### Nephropathy

**Angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs).** Some retrospective observations indicated that the administration of ACE inhibitors and/or ARBs early during the course of kidney disease may induce the reduction or remission of proteinuria [Pecci et al 2008, Sekine et al 2010], which, in turn, may delay the progression of kidney damage.

**Renal replacement therapy (dialysis and kidney transplantation)** is the only possible treatment for individuals who develop end-stage renal disease.

### Cataracts

**Cataract surgery** should be carried out when indicated.

## Surveillance

**Table 7.** Recommended Surveillance for Individuals with *MYH9*-Related Disease

| System/Concern | | Evaluation | Frequency |
|---|---|---|---|
| **Thrombocytopenia** | | • Microscopic assessment of platelet count<br>• Note: Electronic cell counters do not recognize the largest platelets of persons w/*MYH9*-RD & thus underestimate platelet count & size. | At least annually AND in case of bleeding &/or reported changes in bleeding diathesis AND prior to hemostatic challenges (surgery, delivery, other invasive procedures) |
| **Bleeding episodes** | | • Assessment of person's bleeding history through standardized questionnaires (e.g., ISTH Bleeding Assessment Tool) [1]<br>• Blood count to screen for anemia | Annually AND in case of bleeding &/or reported changes in bleeding diathesis AND prior to hemostatic challenges |
| **SNHL** | **Screening** | Audiogram | Every 3 yrs AND in case of reported worsening of hearing function |
| | **Known** | Per treating audiologist/ otolaryngologist | Per treating audiologist/ otolaryngologist |
| **Nephropathy** | **Screening** | Urinalysis, 24-hour protein, or protein (or albumin)-to-creatinine ratio on a spot urine sample; serum concentration of creatinine | Annually, or every 6 mos in genotypes w/high risk of kidney damage (See Genotype/Phenotype Correlations.) |
| | **Known** | Per treating nephrologist | Per treating nephrologist |
| **Cataract** | **Screening** | Ophthalmologic exam incl slit lamp | Every 3 yrs AND in case of reported symptoms suggestive for cataract |
| | **Known** | Per treating ophthalmologist | Per treating ophthalmologist |

*Table 7. continued from previous page.*

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Abnormal liver enzymes** | Measurement of serum AST, ALT, & GGT | Every 3 yrs |
| | If other causes of liver damage are excluded when liver enzymes are altered | Frequency of liver enzyme measurements depends on severity of alteration. |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; ISTH = International Society on Thrombosis and Haemostasis; SNHL = sensorineural hearing loss
*1.* Gresele et al [2020]

# Agents/Circumstances to Avoid

## Bleeding Tendency

**Agents.** Drugs that can inhibit platelet function or reduce platelet count should be administered only after a careful assessment of the risks versus the benefits. Patients and treating physicians should be informed about such drugs.

- Drugs that inhibit platelet function include:
  - Nonsteroidal anti-inflammatory drugs, especially aspirin, which are strong inhibitors of platelet aggregation;
  - Other drugs that interfere with platelet function, including some antidepressants, antibiotics, and anesthetics.
- Drugs that may reduce platelet count include oncologic treatments and some antibiotics.

Antithrombotic drugs (such as heparin or oral anticoagulants) should be prescribed with caution and after a careful assessment of the risk-to-benefit ratio, as in patients affected with other forms of thrombocytopenia. *MYH9* pathogenic variants are usually not associated with defects of platelet function, and therefore platelet function is usually normal in patients with *MYH9*-RD.

**Circumstances.** In individuals with severe thrombocytopenia and significant bleeding tendency, activities at high risk of trauma (e.g., contact sports) should be avoided.

## Hearing Loss

**Agents.** Ototoxic drugs (e.g., aminoglycoside antibiotics, salicylates in large quantities, loop diuretics, some oncologic drugs) should be used only after a careful assessment of the risks versus the benefits, especially in patients with established hearing involvement or with *MYH9* pathogenic variants associated with high risk of hearing loss (see Genotype-Phenotype Correlations).

**Circumstances.** Avoid exposure to hazardous noise. If noise exposure cannot be avoided, use ear devices (e.g., earplugs, headphones) to attenuate intense sound.

## Nephropathy

**Agents.** The balance between the risks and the benefits of agents that can damage renal function, including radiographic contrast agents, antibiotics, NSAIDs, diuretics, and oncologic drugs, should be carefully considered, especially in individuals with established kidney involvement or with *MYH9* pathogenic variants associated with high risk of kidney damage (see Genotype-Phenotype Correlations).

## Cataract

**Agents.** Glucocorticoids, which predispose to development of cataracts, should be used only after a careful assessment of the risk-to-benefit ratio.

### Elevation of Liver Enzymes

**Agents.** In individuals with *MYH9*-RD who have liver enzyme elevation, potentially hepatotoxic drugs should be used with caution.

## Evaluation of Relatives at Risk

It is appropriate to clarify the status of all first-degree relatives of an affected individual in order to establish: (1) appropriate management (including follow-up evaluations, treatment, and surveillance) and (2) awareness of agents and circumstances that should be avoided.

Evaluations to clarify the status of at-risk family members include:

- Examination of peripheral blood smear to search for platelet macrocytosis, assessment of platelet count, and immunofluorescence search for aggregates of the MYH9 protein;
- Molecular genetic testing if the *MYH9* pathogenic variant has been identified in an affected family member.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

Deliveries should be managed as they are in women with other forms of thrombocytopenia. (Note that *MYH9*-RD is not usually associated with defects of platelet function.) As expected, severe thrombocytopenia and previous history of severe bleeding are associated with a higher incidence of delivery-related bleeding. In general, a platelet count of $\geq 50 \times 10^9$/L is recommended for delivery. Infants born vaginally to women with severe thrombocytopenia are considered at increased risk for neonatal intracranial bleeding [Noris et al 2014b].

## Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

*MYH9*-related disease (*MYH9*-RD) is inherited in an autosomal dominant manner.

## Risk to Family Members

**Parents of a proband**

- Approximately 65% of probands diagnosed with *MYH9*-RD have an affected parent.

- An individual with *MYH9*-RD may have the disorder as the result of a *de novo MYH9* pathogenic variant. About 35% of probands represent simplex cases (i.e., a single occurrence in a family) [Savoia et al 2010]; most of these individuals have the disorder as the result of a *de novo* pathogenic variant [Pecci et al 2108].
- If neither parent of the proband is known to have *MYH9*-RD, the following evaluations are recommended for the parents in order to confirm their status and to allow reliable recurrence risk counseling:
  - Molecular genetic testing for the *MYH9* pathogenic variant identified in the proband;
  - If the causative pathogenic variant has not been identified in the proband or a mild phenotype resulting from potential somatic mosaicism is suspected in a parent, appropriate hematologic testing (e.g., evaluation of platelet number and size and distribution of the MYH9 protein in neutrophils; see Diagnosis) should be considered.
- If the pathogenic variant found in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Both germline mosaicism and somatic mosaicism including the germline have been reported [Kunishima et al 2005, Kunishima et al 2009, Kunishima et al 2014]. Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present only in the germ cells.

    Note: A parent with somatic mosaicism for an *MYH9* pathogenic variant may be mildly/minimally affected. In two families, apparently healthy parents of probands with typical *MYH9*-RD had *de novo* somatic/germline pathogenic variants with 14% or 24% of neutrophils with MYH9 aggregates but not thrombocytopenia [Kunishima et al 2005, Kunishima et al 2014]. In another family, the father of a proband with a severe syndromic phenotype had only mild macrothrombocytopenia associated with somatic mosaicism [Gresele at al 2013].
- The family history of some individuals diagnosed with *MYH9*-RD may appear to be negative because of failure to recognize the disorder in family members and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband and/or appropriate hematologic testing has been performed.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. A sib who inherits an *MYH9* pathogenic variant may have a different phenotype (within the spectrum of *MYH9*-RD) than the proband.
- If the proband has a known *MYH9* pathogenic variant that cannot be detected in the leukocyte DNA of either parent and/or both parents have normal results on hematologic testing, the risk to sibs is low but greater than that of the general population because of the possibility of parental germline mosaicism [Kunishima et al 2005, Kunishima et al 2009, Kunishima et al 2014].

**Offspring of a proband.** Each child of an individual with *MYH9*-RD has a 50% chance of inheriting the *MYH9* pathogenic variant.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the *MYH9* pathogenic variant and/or is known to be affected, his or her family members may be at risk.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

**DNA banking** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *MYH9* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **American Society for Deaf Children**
  **Phone:** 800-942-2732 (ASDC)
  **Email:** info@deafchildren.org
  deafchildren.org
- **MedlinePlus**
  Thrombocytopenia
- **National Association of the Deaf**
  **Phone:** 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  **Fax:** 301-587-1791
  **Email:** nad.info@nad.org
  nad.org
- **National Eye Institute**
  31 Center Drive
  MSC 2510
  Bethesda MD 20892-2510
  Cataracts

- **National Kidney Foundation**
  **Phone:** 855-NKF-CARES; 855-653-2273
  **Email:** nkfcares@kidney.org
  kidney.org
- **Platelet Disorder Support Association**
  **Phone:** 877-528-3538
  **Email:** pdsa@pdsa.org
  www.pdsa.org
- **Italian Registry of MYH9-Related Disease**
  Clinica Medica III IRCCS Policlinico
  San Matteo Foundation
  Piazzale Golgi, 2
  Pavia 27100
  Italy
  **Phone:** +39 0382.526284; +39 0382 501358
  **Fax:** +39 0382 526223
  **Email:** alessandro.pecci@unipv.it
  www.registromyh9.org

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** MYH9-Related Disease: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *MYH9* | 22q12.3 | Myosin-9 | Hereditary Hearing Loss Homepage (MYH9)<br>MYH9 database | MYH9 | MYH9 |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for MYH9-Related Disease (View All in OMIM)

| | |
|---|---|
| 155100 | MACROTHROMBOCYTOPENIA AND GRANULOCYTE INCLUSIONS WITH OR WITHOUT NEPHRITIS OR SENSORINEURAL HEARING LOSS; MATINS |
| 160775 | MYOSIN, HEAVY CHAIN 9, NONMUSCLE; MYH9 |

## Molecular Pathogenesis

*MYH9* encodes myosin-9, a protein of 1960 amino acids also known as the heavy chain of the non-muscle myosin IIA. Myosin-9 dimerizes and assembles with two essential and two regulatory light chains to constitute a hexameric molecule, the non-muscle myosin IIA (NMMIIA). NMMIIA assembles into functional bipolar filaments, which – interacting with actin – generate the mechanical force necessary for a variety of cellular processes, including motility and migration, cytokinesis, shape maintenance and change, and polarization.

Pathogenesis of the manifestations of *MYH9*-related disease is only partially understood. Macrothrombocytopenia results from defective production of platelets from megakaryocytes, their bone marrow

precursors. In particular, the platelet phenotypes result from defects of the latest events of platelet biogenesis – that is, the formation and release of platelets from mature megakaryocytes. At the end of their maturation process, megakaryocytes form platelets through the extension of long and thin cellular protrusions, called proplatelets, that protrude through the lumen of bone marrow vessels and release platelets directly into the bloodstream from their free ends (the so-called tips).

NMMIIA is dispensable for megakaryocyte production and maturation, but has a key role in the extension of proplatelets. In fact, megakaryocytes of individuals with *MYH9*-RD, as well as those of mouse models of the disease, present few proplatelets, with reduced branching and very large tips, resulting in defective platelet release as well as platelet macrocytosis [Pecci et al 2018]. Moreover, *MYH9* pathogenic variants may also impair migration of megakaryocytes within the bone marrow toward the marrow vessels, the site of platelet release; this mechanism can contribute to reduced platelet production [Pal et al 2020].

Kidney damage is thought to mainly result from defective function of the podocytes, highly specialized epithelial cells of the renal glomerular filtration barrier. Investigations of mouse models of *MYH9*-RD showed signs of podocyte damage, such as effacement of their foot processes with loss of the filtration slit between neighboring foot processes. These alterations resemble those observed in the few kidney biopsies of individuals with *MYH9*-RD analyzed to date. Moreover, in vitro studies demonstrated that *MYH9* pathogenic variants induce profound alteration in the structure and functions of the cytoskeleton of podocytes that are likely to cause alteration of the kidney filtration barrier, proteinuria, and, therefore, progressive kidney disease [Pecci et al 2018].

The mechanisms of hearing loss are poorly understood. However, the hearing defect is likely to derive from alteration of the functions of the hair cells of the cochlea of the inner ear – that is, the cells specialized in converting the sound stimulus into electric signals directed to the brain.

Pathogenesis of the other phenotypes of *MYH9*-RD is unknown [Pecci et al 2018].

**Mechanism of disease causation.** Because *MYH9*-RD is an autosomal dominant disorder and myosin consists of dimerization of two MYH9 protein molecules, the pathogenic mechanisms are likely to be associated with a dominant-negative effect of the pathogenic variants.

***MYH9*-specific laboratory technical considerations.** *MYH9* comprises 41 exons. The first exon does not code for amino acids; the first methionine of the open reading frame is in exon 2. Exon numbering may vary among different testing laboratories.

The spectrum of the *MYH9* pathogenic variants responsible for *MYH9*-related disease is mainly represented by missense variants or small in-frame deletions/insertions, most of which are identified in a few hot spots (exons 2, 17, 25, 26, 27, 31, and 39). The nonsense and frameshift pathogenic variants affect exclusively the last coding exon of *MYH9* (exon 41).

Moreover, almost 70% of affected individuals have pathogenic variants involving only six residues: Ser96 or Arg702 of the head domain; and Arg1165, Asp1424, Glu1841, or Arg1933 of the tail domain [Pecci et al 2018].

**Table 8.** Notable *MYH9* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | MYH9 Protein | | Comment [Reference] |
|---|---|---|---|---|---|
| | | | Domain | Region | |
| NM_002473.4 NP_002464.1 | c.279C>G | p.Asn93Lys | Head | SH3/MD i | |
| | c.287C>T | p.Ser96Leu | Head | SH3/MD i | |
| | c.2104C>T | p.Arg702Cys | Head | SH1 helix | Assoc w/most severe phenotype [1] |
| | c.2105G>A | p.Arg702His | Head | SH1 helix | |

*Table 8. continued from previous page.*

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | MYH9 Protein | | Comment [Reference] |
|---|---|---|---|---|---|
| | | | Domain | Region | |
| | c.3493C>T | p.Arg1165Cys | Tail | Coiled-coil | Assoc w/high risk for hearing loss & low risk for nephropathy & cataract [1] |
| | c.3494G>T | p.Arg1165Leu | Tail | Coiled-coil | |
| | c.4270G>C | p.Asp1424His | Tail | Coiled-coil | Assoc w/intermediate-to-high risk of developing disease manifestations over time [1] |
| | c.4270G>A | p.Asp1424Asn | Tail | Coiled-coil | Assoc w/thrombocytopenia, but low risk of developing other disease manifestations over time [1] |
| | c.4270G>T | p.Asp1424Tyr | Tail | Coiled-coil | |
| | c.4340A>T | p.Asp1447Val | Tail | Coiled-coil | |
| | c.5521G>A | p.Glu1841Lys | Tail | Coiled-coil | Assoc w/thrombocytopenia, but low risk of developing other disease manifestations over time [1] |
| | c.5797C>T | p.Arg1933Ter | Tail | NHT | Thrombocytopenia usually remains only disease manifestation throughout life [1] [Pecci et al 2014a]. |
| | c.5821delG | p.Asp1941MetfsTer7 | Tail | NHT | |

NHT = nonhelical tailpiece; SH3/MD i = interface between the SH3-like motif and the motor domain
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
*1.* See Genotype-Phenotype Correlations.

# Chapter Notes

## Author Notes

Alessandro Pecci works as a physician and researcher at the IRCCS Policlinico San Matteo Foundation and the University of Pavia, Pavia, Italy. His research interests focus on hemostasis and thrombosis, ranging from clinical to basic research. He is particularly interested in clinical aspects, management and pathogenetic mechanisms of inherited thrombocytopenias. Email: alessandro.pecci@unipv.it

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