Annals of Hematology (2019) 98:781–782
https://doi.org/10.1007/s00277-019-03597-y

LETTER TO THE EDITOR

Genotype–phenotype correlation of a novel MYH9 mutation (p.G736L) in a patient with macrothrombocytopenia and end-stage renal disease

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Received: 8 December 2018 / Accepted: 2 January 2019 / Published online: 7 January 2019

Dear Editor,

Myosin heavy chain 9–related disorders (MYH9-RD; MIM #160775) are rare autosomal dominant inherited disorders of the MYH9 gene. The MYH9 gene encodes the non-muscle myosin heavy chain IIA (NMMHC-IIA), a cytoskeletal contractile protein related to cytokinesis, phagocytosis, cell motility, and cell form maintenance. Megakaryocytes and platelets express this non-muscular myosin variation, which accounts for the presence of large platelets and thrombocytopenia associated with mutations in this gene [1]. The term MYH9-RD encompasses four syndromes that were previously described as distinct macrothrombocytopenic disorders, namely May–Hegglin anomaly (MIM #155100), Sebastian (MIM #605249), Fechtner (MIM #153640), and Epstein syndromes (MIM #153650) according to additional clinical features, which included Döhle-like body inclusions in leukocytes, glomerular nephropathy, presenile cataracts, and sensorineural hearing loss [2]. The severity of clinical manifestations observed in patients generally depends on MYH9 gene mutation sites [3–5]. We report a patient with MYH9-RD carrying a novel mutation (p.G736L), the first detected on exon 18, and describe the genotype–phenotype relationship of this mutation.

A 26-year-old female patient presented with thrombocytopenia and mild bleeding tendency. She had a history of hypertension starting at 15 years old, evolving to difficult-to-control arterial hypertension, proteinuria, and impaired renal function. Investigation for causes of secondary hypertension and autoimmune diseases showed negative results. Laboratory tests revealed normocytic and normochromic anemia (hemoglobin 9.1 g/dL), reticulocyte count 0.6%, white blood cell count 5540/μL, platelet count 21×10^3/μL with increased mean platelet volume 13.7 fL, urea 129 mg/dL, and creatinine 8.4 mg/dL. There were many giant platelets in her peripheral blood smear (Fig. 1), with no evidence of leukocyte inclusion bodies. Subsequently, she was referred for ophthalmological and otological evaluation and an early-stage cataract and a high-frequency hearing loss were detected. After a year, she progressed to end-stage renal disease. She is currently in hemodialysis and was referred for renal transplantation.

The MYH9 gene was analyzed using polymerase chain reaction (PCR) and sequencing of both DNA strands of the entire coding region and the highly conserved exon intron splice junctions. The patient had two variants in the MYH9 gene, c.2206G>T and c.2207G>T, which are located next to each other in exon 18. The first variant, c.2206G>T, is located in a highly conserved nucleotide and amino acid position, with large physicochemical differences between the exchanged amino acids. The second variant, c.2207G>T, is located in a highly conserved nucleotide and amino acid position with moderate physicochemical differences between the exchanged amino acids. As it is more likely to have one indel rather than two rare variants, the nomenclature of these two variants is probably c.2206_2207delinsTT (p.G736L), which is an in-frame indel that causes the loss of two highly conserved residues and the insertion of one leucine in the protein. To date, this variant has not been described in the Exome Aggregation Consortium, Exome Sequencing Project, or the 1000 Genomes Browser. Gene analysis was performed at Centogene AG, Rostock, Germany.

MYH9 is a large gene on chromosome 22q12.3-13.1 consisting of 41 exons. Almost 80 different MYH9 mutations

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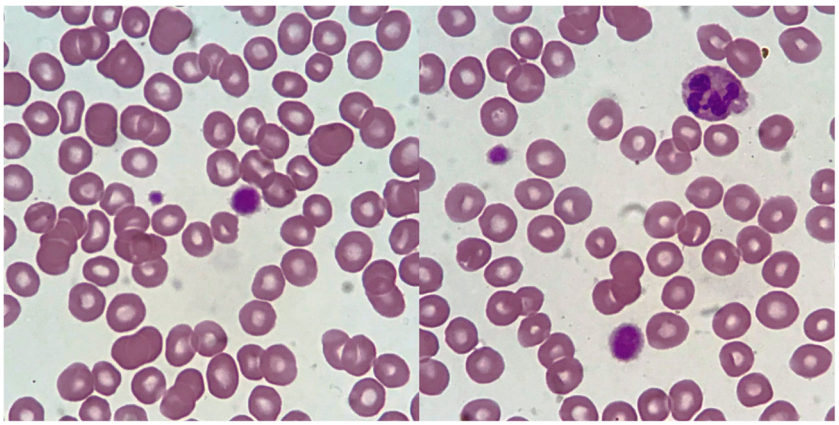

Fig. 1 Giant platelets as large as red blood cells in a peripheral blood smear (Wright–Giemsa stain × 1000)

have been identified, and all variants reported to date in patients with MYH9-RD were mainly amino acid substitutions that hit exons 2, 11, 17, 21, 22, 25, 26, 27, 28, 31, 32, 33, 35, 38, 39, 40, and 41. To date, no mutation in exon 18 has been described. In about 80% of the families, the mutations affected six residues: S96, R702, R1165, D1424, E1841, and R1933. Studies support an association of specific mutations with clinical features. Patients with mutations in the head domain (exons 2 to 19) have significantly lower platelet counts and higher incidence of extra-hematological features than affected individuals with mutations in the coiled-coil domain (21 to 41). Specifically, mutations affecting exon 17 (R702) correlate with severe phenotype, mutations in exon 2 (S96) are associated with intermediate phenotypes, and mutations in exon 31 (D1424) and 41 (R1933) correlate with mild phenotypes [6, 7].

We report the first patient with a G736 substitution in exon 18 of the MYH9 gene. This genetic mutation in the head domain leads to severe macrothrombocytopenia, glomerular nephropathy with early onset of end-stage renal disease, presenile cataracts, and sensorineural deafness. As in other head domain mutations, the leukocyte inclusion bodies are sometimes invisible in peripheral blood smears [8]. The clinical presentation is very similar to R702 mutations, the most severe phenotype deriving from MYH9 mutations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and informed consent All procedures followed were in accordance with the ethical standards of the institutional committee on human experimentation and with the Helsinki Declaration. Informed consent was obtained from the patient.

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