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Abstract: MYH9-related disease (MYH9RD) is a rare autosomal dominant disorder caused by mutations in the gene MYH9 coding for the non-muscle myosin heavy chain IIa (myosin-9). The common hematologic phenotype of the disease is a congenital macrothrombocytopenia and abnormal subcellular localization of myosin-9 in neutrophils, often seen as Döhle body-like inclusion bodies. Some of the patients develop non-hematologic manifestations like glomerulonephritis, sensorineural hearing loss or presenile cataracts. Recent studies demonstrated a correlation between the position of MYH9 mutations and the severity of MYH9RD. Most individuals with mutations affecting the motor domain of the myosin-9 protein have severe thrombocytopenia and a high risk of developing glomerulonephritis and deafness. Instead, individuals with mutations affecting the coiled-coil rod have a milder thrombocytopenia and a lower risk for other manifestations. We report on the molecular data and clinical aspects of 11 German MYH9RD patients from 5 families. In all patients we detected mutations affecting the coiled-coil rod domain or the extreme C-terminus of myosin-9, including one novel mutation in exon 40 (p.Met1934fsX14). Accordingly, nearly all patients showed a mild phenotype with no signs of nephritis, cataract or hearing impairment.

1 Letter to the Editor

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3 **MYH9-related disease - Report on 5 German families and description of a novel**
4 **mutation**

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Dear Editor,

1 MYH9-related disease (MYH9RD) is a rare autosomal dominant disorder caused by
2 mutations in the gene MYH9 coding for the non-muscle myosin heavy chain IIa (myosin-9)
3 [1-3]. The common hematologic phenotype of the disease is a congenital
4 macrothrombocytopenia and abnormal subcellular localization of myosin-9 in neutrophils.
5 Some of the patients develop non-hematologic manifestations like glomerulonephritis,
6 sensorineural hearing loss or presenile cataracts. Recent studies demonstrated a genotype-
7 phenotype correlation in MYH9RD: Most individuals with mutations affecting the motor
8 domain of the myosin-9 protein have severe thrombocytopenia and a high risk of developing
9 glomerulonephritis and deafness. Instead, individuals with mutations affecting the coiled-coil
10 rod have a milder thrombocytopenia and a lower risk for other manifestations [4]. We
11 analyzed the *MYH9* gene in 5 German families with suspected MYH9RD because of the
12 presence of myosin-9 aggregates in neutrophils. Macrothrombocytopenia was asymptomatic
13 in most of the cases and had been detected by chance in the index patients. Clinical data
14 and molecular findings are summarized in Tab. 1. Direct sequencing analysis of the *MYH9*
15 gene allowed us to identify mutations in all five families, all affecting the tail domain of
16 myosin-9 (s. Table 1). A novel single nucleotide deletion (c.5800delA) was detected in
17 affected members of family 5. This mutation leads to a frameshift which deletes the last part
18 of the region coding for the C-terminal 26 amino acids and replaces them with a new 13
19 amino acid segment (p.Met1934TrpfsX14). All nonsense or frameshift mutations reported so
20 far for patients with MYH9RD are located in this region and result in a deletion of the last C-
21 terminal residues of myosin-9. They are predicted to have a good prognosis concerning the
22 risk of non-hematologic manifestations. In family 5 a macrothrombocytopenia was detected
23 in the 3 years old index patient (F5-III-1) as well as in his father (F5-II-2) and grandfather (F5-
24 I-1). The father (F5-II-2) suffered from bilateral juvenile glaucoma which led to the removal of
25 the right eye at age 4 after retinal detachment. As an adult he developed cataract in the
26 remaining eye. The study of Pecci et al. [4] revealed that the occurrence of cataracts in
27 MYH9RD represents an exception to the observation of better prognosis of mutations
28 affecting the tail domain of myosin-9 – the prevalence was similar for mutations affecting the
29 motor head domain or the tail domain, respectively. However, we cannot rule out factors
30 independent from the *MYH9* mutation as the cause of juvenile glaucoma and cataract in
31 patient F5-II-2. Although most of the patients with MYH9RD reported here had a benign
32 phenotype with asymptomatic macrothrombocytopenia, a correct diagnosis is important to
33 avoid inappropriate and detrimental treatment and to carefully screen for non-hematologic
34 manifestations which often occur later in life. Notably, two of the patients in this study have
35 been treated with corticoids (F1-I-1, F4-II-1) and splenectomy has been recommended in one
36 case (F1-I-1). Since a definitive prediction of the clinical course is not possible from our
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present state of knowledge it is necessary to regularly follow up MYH9RD patients for the development of nephritis, hearing impairment and cataract formation.

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Fam	Mutation (Exon)	Protein	Pat.	Age at last exam. [years]	platelet count / bleeding tendency	Hearing impairment	Renal impairment	ophthalmo-logic findings	other findings
F1	c.4270G>A (E30)	p.Asp1424Asn	I-1	26	15-25 G/l / epistaxis	no ¹	no	no	megakaryocytic hyperplasia
			II-1	6	24-70 G/l / -	no ¹	no	no	ASD, VSD
F2	c.5797C>T (E40)	p.Arg1933X	I-2		51 G/l / -	n.a.	n.a.	n.a.	died from pancreatic carcinoma
			II-1	38	42 G/l / -	no	no	no	
			III-1	7	55-70 G/l / -	no	no	no	
F3	c.5797C>T (E40)	p.Arg1933X	II-1	22	23 G/l / easy bruising / menorrhagia	no	no	no	heterozygous for thrombotic risk factors factor V Leiden, MTHFR C677T and A1298C
F4	c.5797C>T (E40)	p.Arg1933X	I-2		30 G/l / -	no ¹	n.a.	no	autoantibodies against gpIIb/IIa, initially diagnosed as ITP
			II-1		25-100 G/l / -	no ¹	n.a.	no	
F5	c.5800delA (E40)	p.Met1934TrpfsX14	I-1	76	31 G/l / -	no ¹	no	no	colorectal carcinoma at age 73
			II-2	37	15 G/l / -	mild hearing impairment	no	bilateral glaucoma congenitum , juvenile cataract	
			III-1	2	47 G/l / -	no	no	no	perimembranous VSD and tricuspid insufficiency (both spontaneously resolved)

Table 1: Molecular and clinical findings in the analyzed families

Abbreviations: ASD: atrial septal defect; VSD: ventricular septal defect, ITP: idiopathic thrombocytopenic purpura; n.a.: data not available

¹ according to self-assessment, no audiometric data;

***Conflict of interest**

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