Hereditary nephritis with macrothrombocytopenia: no longer an Alport syndrome variant

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The nephrologist’s story

In 1972, two families were described with thrombocytopenia, giant platelets (macrothrombocytopenia), nephritis (N) and high frequency sensorineural hearing defect (D), inherited in an autosomal-dominant mode (Epstein syndrome) [1]. Later, cataracts and leukocyte inclusions were found to be associated with the preceding abnormalities, and the term ‘Fechtner syndrome’ was coined [2]. Additional families were subsequently reported, leading to a total of approximately 30 families (including four unpublished personal kindreds).

The haematologist’s story

However, haematologists were aware of two other autosomal dominant disorders with macrothrombocytopenia and leukocyte inclusions, the May-Hegglin (MH) anomaly and the Sebastian platelet syndrome, distinguished by subtle ultrastructural features of the inclusion bodies found in neutrophils. In the latter two syndromes, N and D were absent.

Reunification under the same gene

Molecular genetics has considerably clarified the field by demonstrating that a similar molecular defect was involved in these four syndromes. It was first shown that these syndromes were linked to the same locus on chromosome 22q [3–6]. Then the gene involved—the gene encoding non-muscle myosin heavy chain 9 (MYH9)—was identified and mutations were found in three of the four syndromes, May-Hegglin (13 families), Sebastian (one family) and Fechtner (one family), whereas MYH9 mutations are highly probable in Epstein syndrome [7,8].

Non-muscle myosins

Non-muscle subclass II myosins are hexameric enzymes composed of three pairs of heavy chains, light chains, and regulatory light chains. They belong to the cytoskeleton. Heavy chain dimerization yields a polar structure with two distinct regions. The N-terminal domain forms the actin and ATP-binding globular head required for motor activity whereas the α-helical, C-terminal coiled-coil region is involved in homodimerization [9]. Non-muscle cells contain two distinct isoforms: myosin-IIA (MYH9) mapped to 22q11.2, and myosin IIB (MYH10), assigned to 17q13. Platelets express MYH9 only. MYH9 is also present in monocytes and granulocytes where it is upregulated during differentiation, as well as in different tissues, including the kidney and the auditory system (see below). However, its precise distribution within the kidney is unknown.

Medical dictionaries are full of eponyms. They delight the cultured specialists whereas they frustrate others. These eponyms have been useful for identification and classification of diseases or syndromes, but they have maintained an apparent complexity in some fields, due to the lack of an alternative solution. Molecular medicine has promoted a new order based on the mechanism of disease. The four ‘syndromes’ described here belong in fact to the same entity characterized by defective MYH9, and it will be necessary in the future to find an adequate denomination reconciling the phenotypic diversity and the genotypic defect.

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What to conclude and what remains to be elucidated?

No longer an Alport variant

First, the entity with MH, N and D (‘MYH9 disease’) should be clearly differentiated from Alport syndrome (type IV collagen disease). This conclusion has been suggested by the fact that microscopic haematuria is much less constant than in AS and by immunocytochemistry studies showing that distribution of α3, α4 and α5 chains of type IV collagen was normal in kidneys of patients with N + MH + D [10]. In addition, autosomal dominant inheritance is very rare, albeit possible in Alport syndrome, where it is secondary to COL4α3 (coding for the α3 chain of type IV collagen) defect [11].

How does MYH9 defect lead to renal disease?

Second, it is unknown how MYH9 defect leads to renal disease. Glomerular ultrastructural changes similar to those found in Alport syndrome have been described in rare patients with nephritis and giant platelets [1,2,12], but this finding remains to be confirmed. What is the relationship between MYH9 defect and GBM changes? If the GBM is not altered, how does the MYH9 cytoskeleton defect lead to renal disease?

Intrafamilial phenotypic variability

Third, it has been noted in some families [13,14] that carrier subjects (including males) may suffer only macrothrombocytopenia and deafness whereas nephritis develops in the offspring. This feature is completely different from what is found in X-linked Alport syndrome where all affected males progress to renal failure. What could explain this clinical heterogeneity within a given family? Which modifying gene(s) may influence the tissue specific expression/function of MYH9?

One more MYH9-related disease

Fourth, an MYH9 mutation has been detected in a family with a non-syndromic hereditary autosomal dominant hearing impairment, called DFNA17 (in the absence of extraauditory abnormalities). MYH9 was immunolocalized in the organ of Corti, the subcentral region of the spiral ligament, and the Reissner membrane [15]. A defect in other myosins, myosins VIIA and XV, has been involved in other types of inherited deafness [16].

Towards genotype–phenotype correlations?

It remains mysterious why mutations in MYH9 are responsible either for MH or D only, or for the whole spectrum MH + N + D. MYH9 mutations may also be detected in the future in some autosomal dominant forms of giant platelet syndrome, in the absence of leukocyte inclusions. Only a few mutations in MYH9 have so far been identified. Two recurrent mutations have been found in MH, one of them being identified in six different families [7,8]. MYH9 mutations identified in MH, SBS and Fechtner are heterozygous and have expected consequences on the structure and function of this myosin subunit. A truncated mutation deletes the C-terminal tailpiece necessary for homodimerization. Missense mutations in the globular head domain are predicted to impose electrostatic and conformational changes and could impair the conformational changes that occur in the myosin head during force generation coupled to ATP hydrolysis. Other missense mutations affect highly conserved coiled-coil domain positions like the D1424H substitution identified in a Fechtner syndrome family [7]. Phenotype–genotype correlations and in vitro experiments will have to be performed to perhaps better understand phenotypic diversity. The spectrum of MYH9 disease may be broader than currently thought. The phenotype may be restricted to blood cell changes or to deafness. Are there families with MYH9 mutations and only renal diseases, without extrarenal abnormalities?

References