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section 21 Disorders of the kidney and urinary tract 4918 21.8.2 Thin membrane nephropathy Peter Topham and John Feehally ESSENTIALS Thin membrane nephropathy is a common autosomal dominant glomerular disorder that results in persistent nonvisible haema- turia and is pathologically characterized by the presence of dif- fuse and uniform thinning of the glomerular basement membrane. Recent genetic studies have identified mutations in the COL4A3 and COL4A4 genes in 40% of affected families. There is no specific treat- ment. Prognosis is excellent for most people, but a few cases with progressive renal impairment have been described. Introduction and definition Thin membrane nephropathy (TMN) is an autosomal dominant condition diagnosed by examination of a renal biopsy by electron microscopy, which shows glomerular basement membranes (GBMs) that are thin but otherwise morphologically normal. Historically, the term ‘benign familial haematuria’ was used in the era before the GBM abnormality had been identified. About 30 to 50% of cases of TMN have an identifiable family history of haematuria. Aetiology, genetics, and pathogenesis The similarity between the basement membrane changes seen in early Alport’s syndrome and those seen in TMN suggested the presence of a similar underlying genetic defect. It has been demonstrated that 50% of families with TMN have haematuria that segregates with the COL4A3/COL4A4 locus, and identical mutations have been described in both TMN and autosomal recessive Alport’s syndrome. TMN pa- tients with these mutations can therefore be considered as carriers of autosomal recessive Alport’s syndrome. A significant number of dif- ferent

COL4A3 and COL4A4 mutations have been identified in fam- ilies with TMN, most being single nucleotide substitutions that are different in each family. In some families, linkage with the COL4A3 andCOL4A4 genes has not been found; some of these cases may be ex- plained by de novo mutations or incomplete penetrance, but it is prob- able that the remainder are due to the presence of other TMN loci. Pathology The pathological findings in TMN are limited to diffuse thinning of the GBM which is otherwise morphologically normal (Fig. 21.8.2.1). This contrasts with Alport's syndrome in which the GBM is thick- ened and lamellated and the normal lamina densa of the GBM is dis- rupted. The normal range for GBM thickness must be determined in each laboratory because of the influence of techniques used for fixing the biopsy, but normal GBM thickness is typically 350 to 450 nm and a reduction to less than 250 nm involving over 50% of the GBM is diagnostic of TMN. Clinical features TMN is common and accounts for 20 to 25% of patients presenting to a nephrologist with isolated nonvisible haematuria. Autopsy and kidney transplant donor studies suggest it may be present in 5 to 9% of the population. It is an autosomal dominant condition but may (a) GBM U GBM EP EP U GBM (b) Fig. 21.8.2.1 Thin membrane nephropathy. Electron micrographs contrasting (a) glomerular basement membrane (GBM) of normal thickness (350–450 nm) with (b) uniform membrane thinning (150–200 nm) in thin membrane nephropathy. Space between the heads of the short arrows defines GBM width. Ep, visceral epithelial cells; U, urinary space. Magnification ×20 000.

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