
Alport syndrome (ATS) is a progressive hereditary nephropathy characterized by hematuria and proteinuria. It can be associated with extrarenal manifestations. In contrast, thin basement membrane nephropathy (TBMN) is characterized by microscopic hematuria, is largely asymptomatic, and is rarely associated with proteinuria and end-stage renal disease. Mutations have been identified in the COL4A5 gene in ATS and in the COL4A3 and COL4A4 genes in ATS and TBMN. To date, more than 1000 different mutations in COL4A5, COL4A3, and COL4A4 are known. In this study mutational analysis by exon sequencing and multiplex ligation-dependent probe amplification was performed in a large European cohort of families with ATS and TBMN. Molecular diagnostic testing of 216 individuals led to the detection of 47 novel mutations, thereby expanding the spectrum of known mutations causing ATS and TBMN by up to 10 and 6%, respectively, depending on the database. Remarkably, a high number of ATS patients with only single mutations in COL4A3 and COL4A4 were identified. Additionally, three ATS patients presented with synonymous sequence variants that possible affect correct mRNA splicing, as suggested by in
silico analysis. The results of this study clearly broaden the genotypic spectrum of known mutations for ATS and TBMN, which will in turn now facilitate future studies into genotype-phenotype correlations. Further studies should also examine the significance of single heterozygous mutations in COL4A3 and COL4A4 and of synonymous sequence variants associated with ATS.