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Monogenic causes in pediatric patients with nephrolithiasis or nephrocalcinosis

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Nephrolithiasis, a condition in which stones are present in the urinary system, affects 5~10% of individuals in their lifetime worldwide and leads to significant medical costs and morbidity. To date, mutations in more than 30 genes have been described in nephrolithiasis. Previously, we revealed that a monogenic cause could be detected in 11.4% of individuals with adult-onset nephrolithiasis or nephrocalcinosis and in 16.7-20.8% of individuals with onset before 18 years of life using gene panel sequencing of 30 known genes. More than 80% cases are still molecularly unexplained, suggesting that additional nephrolithiasis-associated genes remain to be identified. To identify additional genes linked to nephrolithiasis when defective, we performed targeted next-generation sequencing in 350 unrelated individuals with kidney stones. We thereby detected biallelic mutations in SLC26A1 (solute linked carried family 26 member 1) in two individuals from two unrelated families. We show by immunofluorescence, immunoblotting and glycosylation analysis that variant protein mimicking p.Thr185Met has defects in protein folding or trafficking. In addition, by measuring anion transporting exchange activity of SLC26A1, we demonstrate that all the identified mutations in SLC26A1 lead to decreased transporter activity. Our data identify SLC26A1 mutations as causing a recessive Mendelian form of nephrolithiasis.