

Mutations in *TCF2* and Renal Cysts – an Overview

Introduction

Polycystic kidney disease is the most common cause of chronic renal failure (1). Several genes have been implicated in the development of renal cysts, including *PKD1* and *PKD2* (autosomal dominant polycystic kidney disease, ADPKD), *PKHD1* (autosomal recessive polycystic kidney disease, ARPKD), *TCS1*, *TCS2* (Tuberous Sclerosis Complex, TSC), *VHL* (von Hippel-Lindau Disease, VHL), and *TCF2* (Renal Cysts and Diabetes, RCAD) (2-6). ADPKD, TSC, VHL, and RCAD all show autosomal dominant mode of inheritance (2).

RCAD was identified in 36% of children and 18% of adults with renal cysts that were not associated with other known hereditary causes (5,6). In addition to renal cysts, RCAD is also associated with maturity onset diabetes of the young (MODY5), a dominantly inherited, progressive form of non-ketotic diabetes mellitus (7). Genetic testing for mutations in *TCF2* can identify RCAD as the cause of renal cysts and alert physicians and patients to the risk of MODY5, facilitating timely treatment of hyperglycemia. In addition, genetic testing can allow early diagnosis of RCAD in affected family members.

Molecular Pathophysiology

TCF2 codes for a homeodomain-containing transcription factor, HNF1beta, that is known

to play a role in the embryonic development of the kidneys, liver, and pancreas. HNF1beta may also be involved in the transcriptional regulation of other genes associated with renal cyst development, such as *PKHD1* or *PKD2* (8). Deletions of the entire *TCF2* sequence account for 33 to 64% of loss-of-function mutations associated with structural renal anomalies and MODY5 (6,9).

Clinical Presentation

Congenital structural renal anomalies associated with mutations in *TCF2* include renal cysts, renal dysplasia, hypoplastic glomerulocystic kidney disease, single kidney, and horseshoe kidney (5,6,10). About half of patients are also affected by progressive diabetes mellitus (MODY5), which typically first becomes apparent in adolescence or young adulthood. Pancreatic atrophy and internal genital malformations have also been reported.

Diagnosis

Clinical diagnosis of RCAD is based on symptoms and family history. Since published studies have established a causal relationship between certain variants of *TCF2* and RCAD, diagnosis of RCAD may be confirmed or established through genetic testing.

References

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