Prioritization and burden analysis of rare variants in 208 candidate genes suggest they do not play a major role in CAKUT

Nayia Nicolaou1 , Sara L. Pulit1 , Isaac J. Nijman1 , Glen R. Monroe1 , Wout F.J. Feitz2 , Michiel F. Schreuder3 , Albertien M. van Eerde1 , Tom P.V.M. de Jong4 , Jacques C. Giltay1 , Bert van der Zwaag1 , Marlies R. Havenith1 , Susan Zwakenberg1 , Loes F.M. van der Zanden5 , Geert Poelmans6,7,8, Elisabeth A.M. Cornelissen3 , Marc R. Lilien9 , Barbara Franke7,8, Nel Roeleveld3,5, Iris A.L.M. van Rooij5 , Edwin Cuppen1 , Ernie M.H.F. Bongers7 , Rachel H. Giles10, Nine V.A.M. Knoers1 and Kirsten Y. Renkema1

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Abstract

The leading cause of end-stage renal disease in children is attributed to congenital anomalies of the kidney and urinary tract (CAKUT). Familial clustering and mouse models support the presence of monogenic causes. Genetic testing is insufficient as it mainly focuses on HNF1B and PAX2 mutations that are thought to explain CAKUT in 5–15% of patients. To identify novel, potentially pathogenic variants in additional genes, we designed a panel of genes identified from studies on familial forms of isolated or syndromic CAKUT and genes suggested by in vitro and in vivo CAKUT models. The coding exons of 208 genes were analyzed in 453 patients with CAKUT using next-generation sequencing. Rare truncating, splice-site variants, and non-synonymous variants, predicted to be deleterious and conserved, were prioritized as the most promising variants to have an effect on CAKUT. Previously reported disease-causing mutations were detected, but only five were fully penetrant causal mutations that improved diagnosis. We prioritized 148 candidate variants in 151 patients, found in 82 genes, for follow-up studies. Using a burden test, no significant excess of rare variants in any of the genes in our cohort compared with controls was found. Thus, in a study representing the largest set of genes analyzed in CAKUT patients to date, the contribution of previously implicated genes to CAKUT risk was significantly smaller than expected, and the disease may be more complex than previously assumed.

Short Summary

Monogenic defects implicated in CAKUT so far, involve mutation in around 23 genes and have been identified in only a small percentage ≤ 12% of pts investigated with insufficient data regarding their causative role. There is a need to expand the diagnostic toolbox for CAKUT. This study used targeted NGS to analyze 208 genes in a cohort of 453 CAKUT pts.

Variant identification and classification: Among the 11,885 variants identified, after a multistep quality control, 256 variants were studied and 180 were confirmed by Sanger sequencing. Then the validated variants were classified into 4 groups according to the probability to be a causative CAKUT mutation. 5 variants in 4 different genes detected in 6 pts met our criteria for being fully penetrant causal mutations autosomal dominant diseases. 3 pts with kidney dysplasia carried truncating PAX2 mutation. A novel frameshift variant SIX5 causes kidney dysplasia. A pts with MCKD had a novel truncating variant in HNF1B. Finally, in a family of kidney shrinkage, UMOD mutation in all affected members was found.

This study filters the data to identify the more penetrant variant that can be potentially linked to monogenic forms of CAKUT. The high locus and allelic heterogeneity, low penetrance mutations, and variable degree of severity suggest the role of complex genetic factors in CAKUT. This study highlights that investigating CAKUT is more challenging than previous study suggest and that more genetic approach such as whole-exome sequencing and copy-number variation analysis may increase to indentify more variants causing CAKUT.

In conclusion, this work propose a comprehensive list of candidate variants that have been classified on the basis of evidence supporting their pathogenicity and provide evidence that the contribution of previously implicated genes to CAKUT risks is much lower than reported and has been over-estimated.

Take home message: The detection of novel variants in any known genes should not by itself imply pathogenicity in clinical practice.