PKD1 and PKD2 genes: Deletion/Duplication Analysis for Autosomal Dominant Polycystic Kidney Disease

Clinical Features:

Autosomal dominant polycystic kidney disease is a multisystem disorder characterized by the development of multiple cysts in the kidney and other extrarenal features. The prevalence of autosomal dominant polycystic kidney disease (ADPKD) is 1:400 to 1:1000 [1, 2]. ADPKD results in renal symptoms including hypertension and renal insufficiency, and end state renal disease. These symptoms are related to the development of renal cysts. Clinical variability in terms of onset, ranging from the antenatal period to late adulthood, and degree of severity of disease, even within the same family, has been described [2]. However, penetrance is believed to be very high, with most affected adults eventually developing bilateral renal cysts.

Extrarenal features include formation of cysts in other organs including the liver, pancreas and arachnoid membranes, and seminal vesicles in males [2]. Hepatic cysts are the most common manifestation, and similar to renal cysts has an age dependent manner of development. Vascular abnormalities including intracranial aneurysms, subarachnoid hemorrhage, dilation of the aortic root and abnormalities of the cardiac calves is also observed [1, 2].

A subset of individuals present with severe polycystic kidney disease as well as phenotypic features of tuberous sclerosis complex due to a contiguous gene deletion involving PKD1 and the adjacent TSC2 gene [3].

Genetics:

Disease-causing variants in the PKD1 and PKD2 genes are mostly inherited in an autosomal dominant manner. Approximately 10% of cases are due to *de novo* variants, and 90% are familial [4]. Germline and somatic mosaicism for variants in PKD1 and PKD2 has been reported [5]. Rarely, pathogenic biallelic variants in PKD1 have been reported in individuals with early onset severe cystic renal disease. In these cases, affected individuals have inherited a PKD1 pathogenic variant from each of their unaffected parents [6, 7].

PKD1 encodes polycystin-1, which forms a complex with polycystin-2, encoded by PKD2; this complex regulates multiple pathways involved in maintaining renal tubular structure and function [8]. Abnormalities in polycystins during development leads to dilation of renal tubules and the formation of fluid filled cysts, characteristic of this condition [8]. Pathogenic variants in the PKD1 and PKD2 cause overlapping phenotypes, although PKD1 variants tend to be associated with more severe disease, and an earlier age of onset and progression to end-stage renal failure [9].

Test Sensitivity:

This test is designed to identify copy number changes in the PKD1 and PKD2 genes, as well as large multigene deletions involving PKD1 and TSC2. Heterozygous pathogenic variants in PKD1 and PKD2 account for approximately 90% of cases with autosomal dominant polycystic kidney disease. Most pathogenic variants (85%) occur in PKD1, while PKD2 variants account for the remainder (15%) [10, 11]. Sequencing analysis of the PKD1 or PKD2 genes is expected to reveal the majority of disease-causing variants. Large copy number changes, including intragenic or whole gene deletions/duplications or rearrangements account for approximately 4% of

pathogenic variants in PKD1 and <1% of variants in PKD2 [3]. Additionally, large deletions encompassing the PKD1 gene and the adjacent TSC2 gene result in a contiguous gene deletion syndrome characterized by earlier onset of PKD and features of Tuberous Sclerosis Complex; such multigene deletions will also be detected by this test [3].

Test Methods:

Genomic DNA from the submitted specimen is obtained and Multiplex Ligation-dependent Probe Amplification (MLPA) is performed to determine the copy number of the relevant genes in this specimen compared to control specimen(s); for methodology see Schouten et al., (2002)[12]. The test is designed to identify most intragenic deletions or duplications involving one (PKD2) or two or more (PKD1) exons, as well as to evaluate for the presence of a contiguous gene deletion involving the TSC2 gene (not applicable for deletion/duplication testing of PKD2 alone). Reportable copy number variant(s) are confirmed by an alternate method when possible, and reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines.

References:

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