GK Gene Analysis in Glycerol Kinase Deficiency

CLINICAL FEATURES

Glycerol kinase deficiency (GKD) is a disorder characterized by elevated plasma or urine glycerol. It may occur as an isolated form caused by pathogenic variants of the *GK* gene alone or as part of a contiguous gene syndrome involving the *DAX1* and *DMD* genes on chromosome Xp21.3. Individuals with isolated GKD may be asymptomatic or symptomatic with episodes of vomiting, acidosis and lethargy that may progress to coma or central nervous system crisis. Phenotypic variability occurs even within families.[1] Symptomatic individuals usually present with signs of hypoglycemia, ketoacidosis, and/or seizures. Symptoms may be brought on by catabolic stress, particularly in children.[2] Asymptomatic patients are often identified through hyperlipidemia testing when they are mistaken as having hypertriglyceridemia, as elevated plasma glycerol concentrations can result in overestimation of plasma triglycerides. Isolated GKD has also been found in children with dysmorphic features and intellectual disability; however, at this time, it is not clear whether or not these features are related to GKD alone.[2,3] Individuals with GKD as part of the Xp21.3 contiguous gene syndrome also have features of congenital adrenal hypoplasia and/or Duchenne muscular dystrophy.

GENETICS

Isolated GKD is caused by pathogenic variants in the *GK* gene. The *GK* gene encodes the glycerol kinase enzyme that catalyzes the phosphorylation of dietary glycerol to glycerol-3-phosphate, which is used in the synthesis of lipids. Deficient glycerol kinase activity results in elevated urine and plasma glycerol. Elevated plasma glycerol concentrations can mistakenly result in an overestimation of plasma triglycerides, known as pseudohypertriglyceridemia. The *GK* gene is located on chromosome Xp21.3 and has 21 exons. Individuals with GKD as part of the Xp21.3 contiguous gene syndrome may also have biochemical findings related to congenital adrenal hypoplasia and/or Duchenne muscular dystrophy such as hypoglycemia, hyponatraemia, hyperkalaemia and elevated creatine kinase.

INHERITANCE PATTERN

Isolated GKD has an X-linked recessive inheritance pattern.

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *GK* gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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VARIANT SPECTRUM

GK variants consist of missense, nonsense, splice-site, small deletions/insertions, and large deletions.[6] The N288D missense variant in the *GK* gene has been identified in individuals from the Saguenay Lac-St.-Jean region of Quebec with severe hyperglycerolemia but otherwise no frequent variants have been reported.[5] Genotype-phenotype correlations have not been established.[2,4,7]

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