# *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. Patients who are symptomatic in childhood may become symptom free. Asymptomatic patients are often identified through hyperlipidemia testing when they are mistaken as having hypertriglyceridemia, as elevated plasma glycerol concentrations can erroneously 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:**
Variant analysis of the *GK* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the coding exons and corresponding intron/exon boundaries. In addition, if no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available for females to evaluate for a deletion or duplication of one or more exons of this gene. Variants found in the first person of a family to

be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

**Test Sensitivity:**
In a series of small studies of males with confirmed isolated GKD, a *GK* variant was identified in all individuals.[2-7] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

**Variant Spectrum:**
*GK* variants consist of missense, nonsense, splice-site, small deletions/insertions, and large deletions.[8] 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.[2,4,9]

**References:**

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