

# Hematologically Important Mutations: Molecular Abnormalities of Phosphoglycerate Kinase

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Phosphoglycerate kinase (ATP: 3-phosphoglycerate 1-phosphotransferase; EC 2.7, 2.3; abbreviation PGK) plays an important role for ATP generation in the glycolytic pathway. There are two functional PGK genes in humans. The autosomal gene, located at chromosome 19, encodes the enzyme which is specifically expressed in the testis (1). The X-linked gene located at Xq13, consists of 11 exons and encodes the enzyme which is ubiquitously distributed in various tissues including red blood cells (2-4). The mature PGK, encoded by this gene, consists of 416 amino acid residues with acetyl-serine at the NH<sub>2</sub>-terminal, and isoleucine at the COOH-terminal, and the monomeric enzyme (MW about 48,000 dalton) is catalytically active (5).

An inherited deficiency of the X-linked PGK is associated with clinical problems. Depending upon the degree of red cell and tissue enzyme deficiency, clinical severity of affected males

ranges widely. In the most severe case (PGK-New York in Table 1) originally found in a large Chinese kindred in the New York area, all affected males had suffered from chronic hemolytic anemia and mental retardation, and have died at a pre-adult age spanning three generations (6,7). Other sporadic PGK variants are associated with mild to severe hemolytic anemia (chronic or occasional), rhabdomyolysis, and mental retardation. PGK-München, associated with relatively mild deficiency (about 20% of normal) (8), and three common electrophoretic variants (PGK-II, -III and -IV) with normal activity are not associated with any clinical problem (9).

Thus far, the molecular abnormalities of twelve PGK variants, listed in Table 1, have been identified. In addition, several cases of PGK deficiency associated with clinical problems have been reported, but the molecular abnormalities of these cases have yet to be determined.

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**Table 1.**

Variant Name	cDNA Substitution	Amino Acid Substitution	Exon w/mutation	Ref
Uppsala	617 G → C	205 Arg → Pro	6	10
Matsue	263 T → C	88 Leu → Pro	3	11
Shizooka	473 G → T	157 Gly → Val	5	12
Amien-New York	491 A → T	163 Asp → Val	5	7, 13
Alabama	573–575 delAAG	del 190 Lys	7	14
Antwerp	755 A → C	251 Glu → Ala	5	15
Tokyo	795 C → G	265 Val → Met	8	16
München	802 G → A	267 Asp → Asn	8	17
Crêteil	943 T → C	314 Asp → Asn	9	13
Michigan	946 T → G	315 Cys → Arg	9	18
PGK II	1055 C → A	351 Thr → Asn	9	19
North Carolina	g → t at 5' end of intron 4, insertion of 10 amino acids between 138 Lys and 139 Val			20

Note: Nucleotide numbers are counted from adenine of the chain initiation codon, and amino acids are counted from the NH<sub>2</sub>-terminal acetyl-serine of the enzyme.

Clinical and hematological characteristics, degree of enzyme deficiency in red cells and other tissues, kinetic abnormality, molecular stability, and level of variant mRNA of some of these PGK variants are also reported in the references.

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