PK Deficiency
PYRUVATE KINASE DEFICIENCY

Illuminating the Cause of a Chronic, Hereditary Hemolytic Anemia
PK Deficiency Overview

PK deficiency is caused by reduced pyruvate kinase (PK) activity, resulting in chronic, hereditary hemolytic anemia.¹

Patient presentation is highly variable, with symptoms consistent with conditions characterized by persistent hemolysis.²

The disease may be underrecognized and misdiagnosed, particularly in adults and patients on the milder end of the disease spectrum.¹-⁴

Prevalence

As with many rare diseases, the prevalence of PK deficiency is not well understood. ¹

Estimated prevalence ranges from ~1:20,000 to ~1:485,000. ¹⁻⁴

PK deficiency is the most common disorder of glycolysis responsible for hereditary non-spherocytic hemolytic anemia. ⁵

Red Blood Cells Are Dependent on Glycolysis for ATP Generation

- Glycolysis is the metabolic pathway by which red cells obtain energy
- In glycolysis, glucose is broken down, ultimately producing adenosine triphosphate (ATP)
- PK mutations (mPK) lead to diminished PK enzyme activity and ATP levels

Low ATP Levels Result In Decreased Red Cell Life Span, Hemolysis and Anemia

- ATP is critical for maintaining cell structure and function
- PK deficiency typically results in low ATP levels in RBCs, shortened RBC lifespan, hemolysis and anemia

Genetics

• PK deficiency is transmitted as an autosomal recessive trait

• Affected individuals are homozygotes or compound heterozygotes (i.e., they possess two different mutations of the same gene)¹

• Approximately 250 different causative mutations have been identified²

A link between specific genetic mutations and disease severity is unclear.³⁴

Clinical Manifestations\(^1-4\)

PK DEFICIENCY PRESENTATION IS HIGHLY VARIABLE\(^1,5\)

- Anemia
- Dyspnea
- Iron overload
- Scleral icterus
- Splenomegaly
- Fatigue and weakness
- Exercise intolerance
- Jaundice
- Abdominal pain
- Gallstones

Hemolysis can be influenced by illness, acute infections, stress and pregnancy.\(^2,6\)

PK deficiency is not consistently associated with any specific hematologic features; thus, diagnosis focuses on two diagnostic tests.¹

1. PYRUVATE KINASE (PK) ENZYME ACTIVITY
2. GENETIC TESTING

Diagnosis can be challenging, especially without a known family history of the disease.²

Many laboratories offer these tests. Visit knowPKdeficiency.com for more information.

Diagnosis

PYRUVATE KINASE (PK) ENZYME ACTIVITY

- Analysis of PK enzymatic activity is the standard for diagnostic testing, and often suffices to diagnose PK deficiency\(^1,2\)
- PK activity should be interpreted relative to other RBC enzyme activities\(^3\) and may incorrectly appear normal post-transfusion\(^1\)
- PK activities at the low end of normal in the context of normal/elevated levels of other glycolytic pathway enzymes is suggestive of PKD

Diagnosis

GENETIC TESTING

Genetic testing, such as molecular PKLR analysis, can help confirm diagnosis in equivocal cases, and should be considered if the patient:

1. Has normal or decreased PK activity in the presence of elevated activity of other age dependent red cell enzymes
2. Is chronically transfused
3. Has low PK activity but no family history

Diagnosis

WHEN TO TEST FOR PK DEFICIENCY

Hemolytic Anemia? YES

Findings suggestive of an acquired autoimmune process, red cell membrane defect, or hemoglobinopathy?

NO

Test for PK Deficiency

Potential Differential Diagnoses

**ACQUIRED HEMOLYTIC ANEMIA**
- Autoimmune hemolytic anemias
- Paroxysmal nocturnal hemoglobinuria

**OTHER HEREDITARY HEMOLYTIC ANEMIA**

Inherited disorders of RBC cell membranes, such as
- Hereditary spherocytosis
- Hereditary elliptocytosis

Inherited disorders in RBC enzymes, such as
- Glucose-6-phosphate dehydrogenase deficiency

Hemoglobinopathies, such as
- Thalassemias
- Sickle cell disease

Diagnostic Challenges

PK deficiency may be underrecognized and misdiagnosed.¹

- Patients on the milder end of the spectrum may go years without a diagnosis²
- Infants with PK deficiency may sometimes undergo unnecessary investigations and experience a delay in diagnosis of up to 1.5 years³

Proper patient identification and diagnosis are important to further understand the disease and identify opportunities for future investigational studies.¹
Disease Management

Current Treatment Strategies are Supportive

- Transfusion therapy
- Cholecystectomy
- Splenectomy
- Iron chelation

No disease specific therapy is currently available.

Burden of Disease Management

COMMON TREATMENT STRATEGIES AND THEIR POTENTIAL EFFECTS

- **RBC Transfusions**
  - Increases hemoglobin levels\(^1\)
  - Increases risk of iron overload\(^2\)

- **Splenectomy**
  - Increases hemoglobin levels\(^3\)
  - Increases risk of sepsis, iron overload\(^3\)

Disease management approaches may directly or indirectly impact health-related **quality of life.**\(^{1,4,5}\)

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Future Directions

Although our understanding of PK deficiency has advanced greatly over the past 5 decades, **treatment of patients is still focused on supportive care** and has changed little over this time.¹

Agios is committed to better understanding the burden of PK deficiency, and to **supporting ongoing research that addresses the unmet need.**

Learn more about our clinical development programs at **agios.com.**
Learn more about PK deficiency at **knowpkdeficiency.com.**

Preclinical and Clinical Research in PK Deficiency

Natural History Study (ongoing, non-interventional) – Boston Children’s Hospital, in cooperation with Agios

Preclinical studies involving gene therapy for PK deficiency

Clinical trials of novel small molecule activator of pyruvate kinase-R (PKR)
**Key Takeaways**

- An underdiagnosed cause of chronic, hereditary hemolytic anemia¹,²
- Results from insufficient activity of the enzyme pyruvate kinase (PK)
- Patient presentation is highly variable³,⁴
- Treatment is supportive and unchanged for decades
- Disease complications and treatment may adversely impact quality of life³-⁵

Agios is currently planning Phase 3 trials.

To learn more about eligibility criteria or becoming a trial site, please contact Agios Medical Information at medinfo@agios.com.
Appendix
Burden of Disease Management

IRON OVERLOAD IS COMMON IN PK DEFICIENCY\(^1\)

1. R. Grace, poster presented at EHA Annual Meeting 2015, Vienna.