02nd – 04th May 2024

# 9th International ERCİYES MEDICAL GENETICS Congress

## Speech Texts

**SPEECH TEXTS**

## Who, When and Which Tests Should be Performed in Rare Childhood Hematological/Oncological Diseases?

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**Abstract**

In pediatrics, the majority of hematological and oncological disorders are rare. In most cases, manifestations usually accompany a rare genetic syndrome. When we classify these disorders in two main groups such as “hematological” and "oncological", hematological disorders include:

- Erythrocytic series diseases,
- Leukocyte diseases: non-erythrocyte myeloid series disorders and lymphoid series disorders,
- Platelet-related diseases,
- Primary immune-deficiencies,
- Coagulation pathway disorders.

Single gene analyses are preferred in phenotypes thought to be due to a single gene defect, while next generation sequencing panels are preferred in diseases with genetic heterogeneity, and methods such as whole exome sequencing and whole genome sequencing are preferred in cases with complex and syndromic phenotypes. Although all childhood cancers are rare, some are ultra-rare. The ultra-rare hematological malignancies in childhood are:

- Myelodysplastic neoplasms,
- Germline predisposition syndrome related hematological neoplasms: e.g. Noonan syndrome and juvenile myelomonocytic leukemia,
- Rare AML types: e.g. with *MECOM* rearrangement, *KAT6-CREBBP* fusion, *FLT3-ALM* fusion,
- Rare Lymphoid neoplasma: e.g. T-cell large granular lymphocytic leukemia.
- Ultra-rare solid tumors are classified as tumors with an incidence of <2/1,000,000 and include 14 malignancies: Nasopharyngeal carcinoma, adrenocortical tumors, pleuro-pulmonary blastoma, etc. Such rare tumors are usually predisposed by germline mutations of various genes: e.g. *DICER1* gene mutation and pleuro-pulmonary blastoma.

In addition to germline genetic tests, it is important to test somatic gene alterations and/or fusion genes and proteins, as well as SNVs, CNVs, rearrangements, methylations in tumor-associated genes. Appropriate tests are selected according to the tumor type.

**Keywords:** Rare pediatric cancers, rare pediatric hematological disorders, ultra-rare pediatric cancers, pediatric onco-genetics, pediatric hemato-genetics

## Interpreting Genetic Results Accurately by Clinicians in Rare Childhood Hematologic and Oncologic Diseases

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**Abstract**

In rare childhood hematologic and oncologic diseases, disease panels containing numerous genes are utilized for accurate diagnosis, risk assessment, prognosis prediction, and treatment strategy due to the diversity of genetic causes and unexpected genotype-phenotype relationships. The classification of variants identified in genetic tests is an ongoing process of data collection, and can change based on accumulated genetic data. Moreover, the compatibility of clinical findings with variants is influenced by numerous factors. Variants are interpreted using clinical findings, zygosity, minor allele frequency (<1%), population and patient data, segregation data, *de novo* data, functional data, and computational and prediction-based data. The most significant challenge in variant interpretation is the presence of “variants of uncertain significance” (VUS). When there is insufficient relevant data to determine whether a variant disrupts gene function, it is referred to as a VUS. VUS should not be used in clinical management or reproductive decision-making. Clinical decisions should be based on personal and family history. As genomic information advances and information for variant classification accumulates, a variant may be reclassified from one category to another. Only 10% of VUS can be reclassified to pathogenic/likely pathogenic upon accumulation of additional evidence. Segregation analysis often sheds light on VUS due to its familial specificity. *De novo* occurrence of the variant and consistent segregation in affected and unaffected siblings provide information about the variant’s pathogenicity. Advancements in genomic technologies and a more comprehensive understanding of the human genome will assist clinicians in accurately interpreting genetic results.

**Keywords:** Genetic, segregation, variant, VUS

**SPEECH TEXTS**

# Gene Editing Therapies in Hemoglobinopathies

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**Abstract**

Hemoglobinopathies, such as transfusion-dependent β-thalassemia (TDT) and sickle cell disease (SCD), are prevalent monogenic disorders with significant global health impacts. Traditional treatments like transfusions, chelation therapy, and bone marrow transplantation have limitations and risks. Recent advancements in gene editing technologies, particularly CRISPR-Cas9, offer promising curative approaches. CRISPR-Cas9 technology uses a single guide RNA and the Cas9 protein to create precise genetic modifications, revolutionizing gene therapy. This abstract highlights cutting-edge developments in gene editing therapies for hemoglobinopathies, focusing on the mechanisms and clinical applications of treatments like Casgevy and Lyfgenia. Casgevy, the first CRISPR-based therapy to receive approval, targets the *BCL11A* gene, a transcription factor that represses γ-globin production postnatally. By disrupting *BCL11A*, Casgevy reactivates γ-globin expression, compensating for defective β-globin in TDT and SCD patients. Clinical trials show that a single dose of Casgevy significantly reduces severe vaso-occlusive crises and achieves transfusion independence in most patients. Lyfgenia, using a lentiviral vector, modifies hematopoietic stem cells to produce anti-sickling hemoglobin (HBs). It introduces a variant Hbs with an amino acid substitution that prevents sickle HBs polymerization. This anti-sickling variant, HbAT87Q, inhibits red blood cell sickling, reducing vaso-occlusive crises and hemolysis in SCD patients. Clinical trials demonstrate that Lyfgenia decreases painful crises frequency and improves overall HBs levels. These therapies represent a significant advancement in treating hemoglobinopathies, offering potential cures and improved quality of life. As gene editing technologies evolve, they promise to transform the therapeutic landscape for various genetic disorders.

**Keywords:** Hemoglobinopathies, transfusion-dependent β-thalassemia, sickle cell disease, CRISPR-Cas9

# Current Treatment Approaches in Erythrocyte Membrane and Enzyme Defects

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**Abstract**

Pyruvate kinase (PK) deficiency is the most common glycolytic pathway (Embden-Meyerhof pathway) enzyme defect that causes non-spherocytic hemolytic anemia. PK provides adenosine triphosphate (ATP) synthesis by catalyzing the conversion of phosphoenolpyruvate to pyruvate in the Embden-Meyerhof pathway. More than 600 families have been reported in the literature, and more than 300 mutations in the gene that causes PKLR have been identified. The clinic findings vary widely, such as mild, moderate, or severe anemia. Mitapivat or etavopivat treatment is among the current treatments for severe and transfusion-dependent PK deficiency. Mitapivate (AG-348) is a novel oral small molecule allosteric activator of the enzyme PK. Mitapivat regulates erythrocyte PK, increasing ATP production, decreasing 2,3-diphosphoglycerate levels, and increasing PK activity. It was found that anemia improved, and hemolytic anemia symptoms decreased in patients with PK deficiency. According to current literature, it was determined that the hemoglobin increase was higher in patients with homozygous missense mutations, and the PK protein level was higher in patients with missense mutations. Mitapivat or etopivat treatment is recommended, especially in patients with homozygous or heterozygous missense mutations. It was determined that PK deficiency patients without a missense mutation did not benefit from these treatments. In the open-label, single-arm ACTIVATE-T Phase 3 study conducted in 20 centers in Europe, North America, and Asia, patients over the age of 18 with no regular erythrocyte suspension (ES) transfusion and patients over the age of 18 with regular ES transfusion at least 6 times a year with PK deficiency were included in the ACTIVATE-T Phase 3 study. It was used for a period of 24 weeks by increasing the dose to 2x5 mg per day, 2x25 mg per day, and 2x50 mg per day. At the end of the study, A≥33% decrease in the number of ES transfusions and an improvement in hemolysis findings were detected. Side effects related to medication, such as increased liver dysfunction, headache, nausea, and vomiting, have been observed. Non-drug-related side effects such as joint swelling, hypertriglyceridemia, ovarian cysts, and renal colic have been reported. Etavopivate (FT-4202), another PK allosteric activator, was determined as the most effective dose of 400 mg once a day as a result of Phase 1 studies.

**Keywords:** Pyruvate kinase deficiency, mitapivate, etavopivate

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**SPEECH TEXTS**

## Genetic Origins of Fanconi Anemia

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**Abstract**

Fanconi anemia (FA) is the most common inherited cause of aplastic anemia and represents a clinical spectrum characterized by susceptibility to hematologic malignancies and solid tumors. The majority of FA patients feature growth retardation, pigmentary abnormalities, and variable multisystem malformations including limb defects, genitourinary and gastrointestinal anomalies. FA is genetically heterogeneous, with mutations in 22 genes related to the interstrand cross-link repair pathway. Dysfunction in these genes results in cellular hypersensitivity to cross-linking agents, spontaneous chromosome breakage, genomic instability, and cell-cycle disturbance which underlie the clinical hallmark features of FA such as impaired growth, defective hematopoietic stem cell (HSC) proliferation, and predisposition to cancer. Currently, allogeneic HSC transplantation is the only curative treatment for FA-associated bone marrow failure. Recent successes in gene therapy studies, wherein autologous HSCs are genetically modified *ex vivo* to express wild-type FA genes prior to reinfusion into patients, offer promising alternatives for the future. In this talk, I will review the FA pathway genes according to functional roles in ICL repair, explore the clinical and cellular phenotypes associated with FA, and discuss genotype-phenotype correlations. In particular, I will spotlight a preclinical study examining whether caloric restriction might hold potential as a therapeutic strategy in FA (this study is ongoing as part of the TC-NER consortium brought together by the European Joint Programme, Rare Diseases 2020 Joint Transnational Call, and is funded by TUBITAK with project number 121N277).

**Keywords:** Fanconi anemia, therapy, gene therapy, caloric restriction

## Fanconi Aplastic Anemia from the Perspective of a Pediatric Hematologist

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**Abstract**

Fanconi anemia (FA) is a rare multisystem genetic disease, characterized by the triad of progresive bone marrow failure, physical abnormalities (including shortstature, microcephaly, developmental delay, café-au-lait skin lesions, hand, arm and other skeletal anomalies, kidney problems) and tendency to develop malignancy, primarily myeloid leukaemia and epithelial cancers. FA is caused by mutations in any of the 23 genes that are involved in the FA/BRCA pathway, named *FANC* genes. Bi-allelic mutations in FANCA are the most common mutations and are seen in 60-70% of patients. Demonstration of increased chromosome breakage, either spontaneously or with DEB or MMC, G2 phase arrest in flow cytometry, germline genetic tests are used to make a diagnosis. The current standard and curative treatment for Fanconi Aplastic Anemia patients is hematopoietic stem cell transplantation. Hematopoietic stem cell transplantation is a treatment associated to exposure to chemotherapy, immunological complications, plus opportunistic infections from prolonged immune incompetence or increased risk of morbidity. New gene therapy models include gene addition therapy, genome editing using CRISPR-Cas9 nuclease, and hematopoietic stem cell generation from induced pluripotent stem cells. Although gene therapy seems promising, it is not still in the routine use. Even if bone marrow failure disappears after hematopoietic stem cell transplantation, patients should be closely monitored throughout their lives for congenital anomalies and possible malignancies.

**Keywords:** Fanconi anamia, bone marrow failure, hematopoietic stem cell transplantation

**SPEECH TEXTS**

# Genetics of Thalassemia in the Turkish Population

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**Abstract**

Hemoglobinopathies are the most common monogenic diseases in the world. Thalassemia is a hereditary disease caused by a production defect in the chains that form the protein (globulin) part of hemoglobin. There are 2 alpha and 2 beta chains in the protein structure of hemoglobin A. Damages in the production of these chains cause thalassemia. Defects in the alpha chain are called α-thalassemia, and defects in the beta chain are called β-thalassemia. It is estimated that more than 5% of the world's population is an α-thalassemia carrier and approximately 1.5% is a β-thalassemia carrier. In Turkish society, the frequency of α-thalassemia carriage varies from region to region and is generally around 0.25%, while the frequency of β-thalassemia carriage varies between 1.4-13% from region to region and is generally around 2.1%. Consanguineous marriages play a major role in the high frequency of thalassemia in these parts of the world. In genetic analysis, many variants with regional differences are observed. The 639 patients with a preliminary diagnosis of thalassemia who applied to the department of Medical Genetics at Erciyes University between 2012 and 2014 were examined. Sanger sequencing analysis was performed for *HBB* gene examination. A total of 2595 variants were detected. Fifty-seven percent of the detected variants were clinically relevant pathogenic/possibly pathogenic. The most common variant (44%) was the IVSI-110(G->A) variant, which is consistent with the literature. Multicenter genetic-based studies on thalassemias (especially α-thalassemia) need to be planned to obtain clearer information about the population genetics of hemoglobin A in Türkiye.

**Keywords:** Thalassemia, α-thalassemia, β-thalassemia, Turkish society, Türkiye

# Erythrocyte Membrane and Enzyme Defects: A Pediatric Hematologist's Perspective

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Hemolytic anemias result from a shortened lifespan of erythrocytes due to either intrinsic erythrocyte abnormalities or external factors. These can include erythrocyte membrane disorders (membranopathies), erythrocyte enzyme disorders (enzymopathies), and erythrocyte hemoglobin (Hb) disorders (hemoglobin opathies).

**I. Erythrocyte Membrane Disorders (MEMBRANOPATHIES)**

The erythrocyte membrane consist of lipids, carbohydrates, and proteins. A loss of membrane proteins, whether hereditary or acquired, leads to lipid layer deterioration and a reduction in surface area. This disruption in the surface-volume ratio results in impaired membrane function.

**Types of Erythrocyte Membrane Disorders:**

**A. Due to Loss or Dysfunction of Erythrocyte Membrane Proteins:**

- Hereditary spherocytosis (HS),

- Hereditary elliptocytosis,

- Hereditary pyropoikilocytosis.

**B. Due to Altered Cation Permeability of the Erythrocyte Membrane (Stomatocytosis Group Diseases):**

- Hereditary stomatocytosis,

- Hereditary xerocytosis.

**C. Due to Quantitative or Structural Disturbances of Erythrocyte Membrane Lipids:**

- Erythrocyte membrane disorders characterized by acanthocytosis,

- Erythrocyte membrane disorders characterized by target cells.

**Hereditary Spherocytosis (HS):**

HS is the most common non-immune hemolytic anemia,

It is caused by vertical structural defects due to mutations in spectrin, ankyrin, and protein band 3, which are essential membrane proteins,

These defects cause the erythrocyte shape to change from a biconcave disc to a spherical form. As a result, erythrocytes are more readily trapped and destroyed in the spleen due to their reduced ability to deform and navigate capillaries.

**Clinical Features:**

- The diverse nature of membrane pathology results in a wide range of phenotypes and clinical presentations. Symptoms can appear at any time, reflecting the variability in membrane defects,

- Anemia, jaundice (jaundice in the first 24 hours of ND, prolonged jaundice) and splenomegaly are the most common findings.

**Laboratory Findings:**

- Anemia,

- Spherocytic erythrocytes in peripheral blood smear,

- Normal or increased mean corpuscular volume, which may be due to folate deficiency or reticulocytosis,

- Typically, increased mean corpuscular Hb concentration (>35 g/dL) and increased red cell distribution width,

- Increased osmotic fragility and decreased resistance,

- Protein abnormalities in membrane electrophoresis,

- Indirect hyperbilirubinemia and increased lactate dehydrogenase LDH.

**Osmotic Fragility (OF) Test:**

- The OF test assesses the "resistance of erythrocytes to hypotonic solutions." Normal erythrocytes swell but do not hemolyze in 0.9%, 0.8%, 0.7%, 0.6%, and 0.5% NaCl solutions. Hemolysis typically begins at concentrations below 0.5% NaCl. In HS, hemolysis can occur at higher NaCl concentrations where normal erythrocytes remain intact. Thus, osmotic fragility is increased and resistance is decreased. In 30% of patients, the test may be normal. Sensitivity can be enhanced by incubating erythrocytes at 37°C for 2 hours before performing the test.

**Diagnosis:**

- Clinical findings,

- Presence of spherocytes in peripheral blood smear,

- Family history of hemolytic anemia,

- Increased osmotic fragility test results,

- neonates, anemia, reticulocytosis, and spherocytosis may be absent, and the reliability of the osmotic fragility test is reduced. An MCHC greater than 36 g/dL is indicative, with high specificity and sensitivity.

**Complications of Hereditary Spherocytosis:**

- Aplastic crisis (often due to parvovirus infection),

- Folate deficiency leading to megaloblastic crisis,

- Gallstones,

- Leg ulcers,

- Extramedullary hematopoiesis,

- Transfusion-related iron overload.

**II. Erythrocyte Enzyme Disorders (Enzymopathies)**

**To maintain a normal erythrocyte lifespan:**

1. The erythrocyte must be energetically efficient.

2. Hb and intracellular proteins must be protected from oxidative damage.

Erythrocytes lack mitochondria and other organelles, and they do not have the ability to proliferate, synthesize proteins, or perform oxidative phosphorylation. They rely on two primary pathways for energy production:

1. Anaerobic Glycolysis (Embden-Meyerhof Pathway): Provides approximately 90% of the energy. The key enzyme in this pathway is pyruvate kinase.

2. Pentose Phosphate Pathway: Contributes about 10% of the energy through the production of NADPH. The main enzyme here is glucose-6-phosphate dehydrogenase (G6PD).

Erythrocyte enzymes are crucial for glucose metabolism and nucleotide metabolism in the cytoplasm. These processes are essential for erythrocyte survival, functionality, and the removal of accumulated toxic metabolites (Figure 1).

The most common enzyme deficiencies are shown in Figure 2. The most common of these are deficiencies of G6PD, pyruvate kinase and pyrimidine 5' nucleotidase (P5N) enzymes.

**Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency**

Discovered in 1932, G6PD is known as the "enzyme that protects erythrocytes from oxidative damage." The deficiency was first described in the 1950s when American soldiers taking antimalarial drugs experienced acute hemolysis. While G6PD is present in all cells, erythrocytes are the most affected by this deficiency. In Turkey, the prevalence of G6PD deficiency is approximately 0.5%, with higher rates of 8.2% reported in the Çukurova region. The frequency of hyperbilirubinemia in newborns varies between 10.5% and 22.1%.

G6PD deficiency is most common in regions such as Africa, the Mediterranean, the Middle East, Southeast Asia, and India. It is more prevalent in individuals of African descent compared to those of European descent. The deficiency provides protection against Plasmodium falciparum malaria, particularly during childhood. The World Health Organization G6PD enzyme deficiency classification is shown in table 1. Certain G6PD variants are more prevalent in specific regions. The G6PD-A variant is commonly found in Africa; the Mediterranean variant is prevalent in southern Italy, Sardinia, and other Mediterranean areas; and the G6PD-Canton variant is frequently observed in southern China.

**Pathophysiology of G6PD Enzyme Deficiency**

G6PD is essential for glutathione metabolism. In the absence of G6PD, NADPH production is impaired, which in turn disrupts glutathione metabolism. Without NADPH, oxidized glutathione cannot be reduced back to its active form. As NADPH levels decrease, free oxygen radicals accumulate, and the antioxidant defense mechanism is compromised. The detoxification of hydrogen peroxide ($H_2O_2$) within erythrocytes is hindered. When exposed to oxidant substances, Hb becomes oxidized, forming Heinz bodies that precipitate and adhere to the cell membrane, compromising membrane stability. This disruption leads to hemolysis (Figure 3).

**Clinical Presentation**

- Jaundice, dark yellow-orange urine, pallor, and fatigue may be observed in the skin and mucous membranes,

- G6PD deficiency can manifest in four clinical forms: acute hemolytic anemia, neonatal jaundice, chronic hemolysis, and favism.

**Acute Hemolytic Anemia**

Hemolysis can be triggered by drugs, infections, and chemicals. During periods between hemolytic episodes, patients typically exhibit no clinical symptoms and may have normal Hb levels. Table 2 outlines the various triggers of hemolysis in G6PD deficiency. Patients diagnosed with G6PD deficiency should be provided with a comprehensive list of medications and foods to avoid to prevent hemolytic episodes.

**Neonatal Jaundice**

Hyperbilirubinemia is significantly more pronounced in neonates with G6PD deficiency, and approximately 20% of kernicterus cases are associated with this

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condition. Jaundice typically appears on the 2nd or 3rd day of life and may become severe enough to require blood exchange. While anemia may not always be evident, oxidant exposure can exacerbate hemolysis.

**Chronic Nonspherocytic Hemolytic Anemia**

Reticulocytosis is commonly observed. Unlike in spherocytic anemia, spherocytes are absent from the peripheral smear, leading to the classification of this condition as chronic nonspherocytic hemolytic anemia. Hb levels usually range from 8 to 10 g/dL, and hemolysis in this case is primarily extravascular.

**Favism**

Favism involves the consumption of broad beans, which contain oxidants like divisin that increase reactive oxygen species. This condition is most prevalent in boys aged 1 to 5 years. Ingesting broad beans can lead to intravascular hemolysis and severe anemia within 5 to 24 hours (up to 48 hours) after consumption. Symptoms may include nausea, vomiting, abdominal pain, fever, and altered consciousness. Urine may appear dark due to Hburia.

**Laboratory Findings:**

**- Anemia:** Normocytic with a negative Direct Coombs test,

**- Peripheral Blood Smear:** Anisocytosis, poikilocytosis, bitten cells, and Heinz bodies may be present. Supravital staining with methylene blue or crystal violet reveals Heinz bodies precipitated in erythrocytes. The characteristic "bite cells" appear due to the removal of Heinz bodies by the spleen,

**- Additional Tests:** Increased LDH, reticulocytes, and indirect bilirubin; decreased haptoglobin levels,

**- Urine Analysis:** Hburia and red to black-colored dark urine,

**- G6PD Levels:** Decreased or normal.

**Diagnosis of G6PD Deficiency:**

- The diagnosis is established by demonstrating the absence of G6PD enzyme activity. Enzyme deficiency can be assessed qualitatively, using a fluorescence spot test to detect NADPH formation from NADP, or quantitatively, using spectrophotometric measurement. Results are expressed in units of enzyme activity per gram of Hb. It is important to repeat the test after 2-3 months, as results may be falsely negative during acute hemolysis periods. DNA analysis is crucial for a definitive diagnosis. PCR testing identifies specific mutations and is useful for family screening and prenatal diagnosis.

**Pyruvate Kinase Deficiency:**

- Pyruvate kinase deficiency is the most common congenital enzyme deficiency in the glycolytic pathway. It leads to the accumulation of 2,3-DPG, which inhibits Hb's oxygen binding. The clinical spectrum ranges from asymptomatic cases to severe, life-threatening anemia. In neonates, it can present as severe hyperbilirubinemia, anemia, and hydrops requiring blood exchange, whereas in adults, it may be first detected as compensated hemolysis.

**Clinical Features:**

- Common findings include extravascular hemolysis and iron accumulation. Symptoms may include fatigue, weakness, tachycardia, splenomegaly (80-85%), jaundice (40-70%), gallstones (30-45%), and cholecystitis. Less commonly, patients may experience aplastic crisis, bone deformities, extramedullary erythropoiesis, delayed puberty, hyperpigmentation, leg ulcers, and pulmonary hypertension.

**Laboratory Findings:**

- Anemia is typically macrocytic and normochromic, with Hb values usually ranging from 8-12 g/dL in older children. Reticulocytosis is often observed. Increased MCHC due to dehydration from ATP deficiency may occur, and spicule cells or spur cells can be seen in the peripheral smear.

**Diagnosis:**

- Diagnosis involves measuring increased 2,3-DPG levels (which can sometimes be normal), decreased pyruvate kinase activity (using spectrophotometric methods), and detecting mutations in the PKLR gene associated with primary deficiency. Mild hemolysis may occur in heterozygous carriers. Secondary deficiencies, such as those seen in HS or acute leukemia, can complicate diagnosis. Potential pitfalls include:

- Retrieval of pyruvate kinase levels post-transfusion,

- Elevated enzyme levels in reticulocytes due to reticulocytosis,

- Incomplete separation of leukocytes from erythrocytes (as pyruvate kinase activity in leukocytes is normal),

In suspicious cases, genetic examination is recommended.

**Other Enzyme Deficiencies**

**Erythrocyte Nucleotide Metabolism Defects:**

• Enzymes involved in nucleotide (purine and pyrimidine) metabolism are essential for removing toxic nucleotide precursors from erythrocytes. Key enzymes include P5N for pyrimidine metabolism, and adenylate kinase and adenosine deaminase for purine metabolism. Deficiencies in these enzymes can lead to hereditary nonspherocytic hemolytic anemia.

**Pyrimidine 5'-Nucleotidase Deficiency (Pyr 5'-N):**

- This is the most common nucleotide metabolism disorder and has two isoforms in erythrocytes: type 1 and type 2. Hemolytic anemia is primarily caused by type 1.

**Pyrimidine 5'-Nucleotidase Deficiency:**

- Deficiency leads to impaired RNA degradation and accumulation of basophilic punctuations. Patients may develop mild to moderate chronic anemia or may become transfusion-dependent. Gallstones, jaundice, and splenomegaly may also be present. Diagnosis is confirmed by decreased nucleotidase activity and increased pyrimidine nucleotides.

- Some of these enzymes are also found in muscle and brain tissues. Neurological deficits, mental retardation, and myopathy may occur. When these neurological symptoms are accompanied by hemolytic anemia, further evaluation for metabolic diseases is warranted.

**Conclusion**

Erythrocyte membrane and enzyme defects are types of hemolytic anemia resulting from intrinsic erythrocyte pathologies. Despite differing underlying mechanisms, these defects often present with similar clinical and laboratory features. Collaboration with genetics is essential for accurate diagnosis. Multidisciplinary meetings involving hematologists and geneticists can significantly reduce unnecessary tests and improve diagnostic accuracy.

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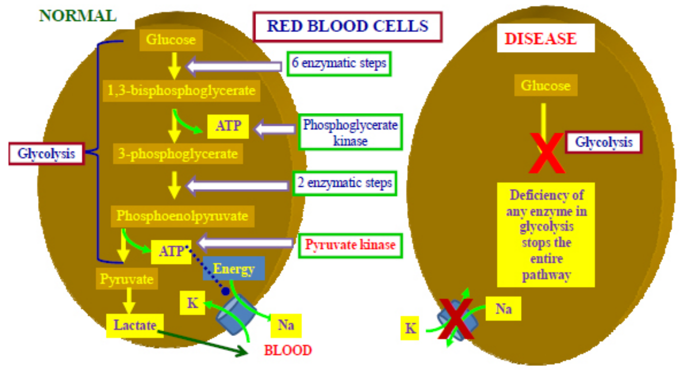


**Figure 1:** Glycolysis in normal erythrocytes and enzyme-deficient erythrocytes.
G6PD: Glucose-6-phosphate dehydrogenase

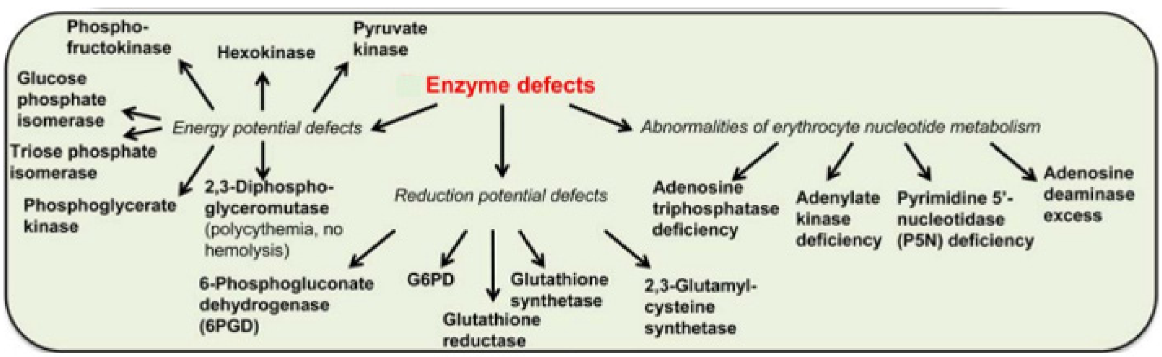


**Figure 2.** The most common enzyme deficiencies
G6PD: Glucose-6-phosphate dehydrogenase

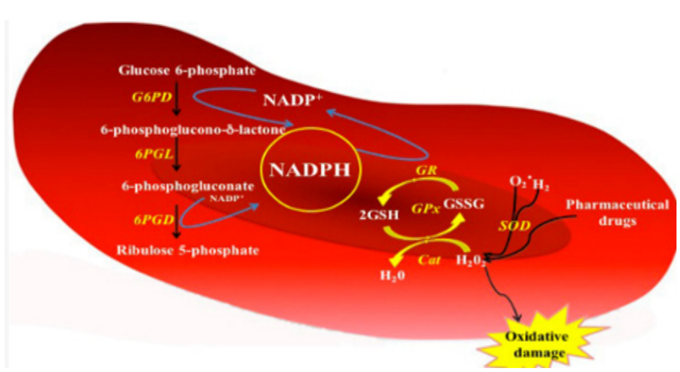


**Figure 3.** G6PD enzyme deficiency pathophysiology
G6PD: Glucose-6-phosphate dehydrogenase

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**Table 1. World Health Organization (WHO) classification of G6PD variant**

| | |
|---|---|
| **Class I variant** | **Chronic hemolysis due to severe G6PD deficiency, e.g., G6PD deficiency Harilaou.** |
| **Class II variant** | **Intermittent hemolysis in spite of severe G6PD deficiency, e.g., G6PD Mediterranean.** |
| **Class III variant** | **Intermittent hemolysis associated usually with drugs/infections and moderate G6PD deficiency, e.g., G6PDA variant.** |
| **Class IV variant** | **No hemolysis, no G6PD deficiency, e.g., normal G6PD (B variant)** |

G6PD: Glucose-6-phosphate dehydrogenase

**Table 2. Triggers of hemolysis in G6PD deficiency**

| | |
|---|---|
| Drugs | Dapson, primacine and primethamine, chlorocine, metilen blue, nitrofrantoine, nalidixic acid, PAS, ciprofloxacin, sulfamethoxazole, sulfasalazine, chloramphenicol, rasbirucase, doxorubicin |
| Chemicals | Naphtalene, broad bean, benzene |
| Infections | Viral, bacterial,.. |

G6PD: Glucose-6-phosphate dehydrogenase