

Red Cell Enzymopathies

Shiro Miwa

Red cell enzymopathies (erythroenzymopathies) are defined as a group of red cell disorders, including hemolytic anemia, methemoglobinemia and erythrocytosis, caused by inherited abnormality of one of red cell enzymes. In this article, red cell enzymopathies associated with hereditary hemolytic anemia will be discussed, followed by hereditary methemoglobinemia due to cytochrome *b5* reductase deficiency and erythrocytosis caused by diphosphoglycerate mutase deficiency.

I. Erythroenzymopathies Associated with Hereditary Hemolytic Anemia

Since the discovery of glucose 6-phosphate dehydrogenase (G6PD) deficiency in 1956 and pyruvate kinase (PK) deficiency in 1961, erythroenzymopathies associated with hereditary hemolytic anemia have been extensively investigated.^(1,2) G6PD deficiency is the most common known enzymopathy. It is estimated to affect 400 million people worldwide. Major clinical manifestations are drug-induced acute hemolysis and/or neonatal jaundice and a very small proportion of G6PD-deficient individuals have a chronic hemolytic anemia (CHA) (class I G6PD deficiency). PK deficiency is the most common enzymopathy of anaerobic glycolysis resulting in CHA. Several hundred patients with PK deficiency have been reported. In approximately equal numbers, PK and class I G6PD deficiencies comprise the two most common erythroenzymopathies associated with CHA. Although other enzyme deficiencies (such as hexokinase, glucosephosphate isomerase, phosphofructokinase, triosephosphate isomerase, phosphoglycerate kinase, γ -glutamylcysteine synthetase, glutathione synthetase, glutathione peroxidase, glutathione reductase, adenylate kinase and pyrimidine 5'-nucleotidase) as well as overproduction of adenosine deaminase have been known to cause CHA, they account for less than 20 percent of all the erythroenzymopathies associated with CHA.

A. Clinical and Laboratory Features

Erythroenzymopathies associated with CHA show common findings of CHA, but the degree of hemolysis greatly varies from case to case even in one enzyme deficiency. Anemia of variable degree, jaundice due to increased indirect-reacting bilirubin, reticulocytosis, and splenomegaly are usually seen. Peripheral blood smears usually show anisocytosis and polychromasia of erythrocytes, but it is noteworthy that other morphological abnormalities such as spherocytosis and elliptocytosis cannot be seen. Because of these characteristics, these erythroenzymopathies belong to the so-called hereditary nonspherocytic hemolytic anemias. The only exception is pyrimidine 5'-nucleotidase deficiency, which is characterized by marked basophilic stippling of red cells as in acute lead poisoning. As a matter of fact, acute lead poisoning can cause hemolytic anemia because lead strongly inhibits pyrimidine 5'-nucleotidase activity. To look for the presence of echinocytes is often helpful when erythroenzymopathies

associated with CHA in glycolytic pathway, such as PK deficiency, are suspected, particularly in postsplenectomy cases.

In most cases of G6PD deficiency, acute hemolysis is caused by oxidant drugs such as primaquine or infection. In some cases, after eating fava beans, anemia and/or neonatal jaundice are the common features. Although glutathione reductase deficiency would cause the same symptoms, it is rare.

B. Diagnosis

G6PD deficiency can be diagnosed by a simple screening test.⁽³⁾ When we encounter a case with long-standing chronic nonspherocytic hemolytic anemia, either red cell enzymopathies or unstable hemoglobin hemolytic anemia should be suspected. The isopropanol test is a simple and reliable screening test to detect unstable hemoglobin.⁽⁴⁾ Direct red cell enzyme activity assay is necessary to diagnose erythroenzymopathies associated with CHA.⁽³⁾ It is important to remove leukocytes before making the red cell hemolysate, particularly in diagnosing PK deficiency, because leukocytes possess 300 times more PK activity than red cells. In addition, leukocytes have a different isozyme, which has normal activity in PK deficient cases.

The mode of inheritance is as follows: G6PD and phosphoglycerate kinase deficiencies are X-linked, adenosine deaminase overproduction is autosomal dominant, while other erythroenzymopathies associated with CHA are autosomal recessive.

C. Treatment and Prevention

Nonspecific supportive measures such as red cell transfusions provide the only currently accepted approach. Splenectomy is not curative but is frequently of value, especially in infants and young children with severe disease. Hemoglobin concentrations often increase 1 to 3 g/dl, reducing or even eliminating transfusion requirements. Phototherapy is recommended in case of neonatal hyperbilirubinemia, but exchange transfusion may become necessary in severe cases.

Recently, DNA diagnosis has become available in many erythroenzymopathies. However, it is still not simple because there are several or many mutations even in one enzyme deficiency. If the mutation(s) in a particular family is (are) already known, DNA diagnosis is relatively easy, and prenatal diagnosis is possible.

G6PD-deficient patients should be advised to avoid potentially hemolytic drugs or, in case of necessary drugs, to ensure they are used in subhemolytic doses.

D. Molecular Basis

Normal genomic DNA or cDNA for most of the enzymes causing hereditary hemolytic anemia has been isolated, rapidly advancing understanding of the molecular basis of erythroenzymopathies associated with hereditary hemolytic anemia.^(5,6) Molecular abnormalities determined so far (including unpublished mutations) are listed in Table 1.

Table 1. Molecular Abnormalities of Erythroenzymopathies Associated with Hereditary Hemolytic Anemia

Enzymes	Molecular defects					Total
	Missense	Nonsense	Deletion	Insertion	Splicing	

Hexokinase	1	0	1	0	0	2
Glucosephosphate isomerase	18	0	1	0	0	19
Phosphofructokinase	8	0	1 (fs-pt;1)	0	4	13
Aldolase	1	0	0	0	0	1
Triosephosphate isomerase	7	1	0	0	0	8
Phosphoglycerate kinase	5	0	0	0	1	6
Pyruvate kinase	43	5	5 (term;1: fs-pt,2)	4 (fs-pt;2)	5	62
Glucose 6-phosphate dehydrogenase	89	1	5	0	1	96
Adenylate kinase	1	0	0	0	0	1
Total	173	7	13	4	11	208

fs-pt, frameshift/Epremature termination: term, termination. Unpublished data are included.

1. Pyruvate kinase deficiency. PK, a key enzyme in the glycolytic pathway, has four isozymes: M1, M2, L, and R. R-type PK is exclusively expressed in red cells. L- and R-types differ from M1- and M2-types, and these two kinds of isozymes are under the control of different genes (L-gene on chromosome 1 and M-gene on chromosome 15). Different tissue-specific promoters are employed to generate R and L mRNAs. Like leukocytes and platelets, erythroid progenitor cells possess M2-type PK, and the isozyme switches from M2- to R-type during erythroid differentiation.⁽⁷⁾ Recent results showed that the switching is achieved by activation of the R-PK promoter activity and the involvement of erythroid specific transcription factor(s).⁽⁸⁾ R-type PK cDNA encodes 574 amino acids, 31 amino acids longer than L-type at amino terminal. L-PK gene has 12 exons.

In 1979, recommended procedures for the biochemical characterization of PK variants were issued by a subcommittee of the International Committee for Standardization in Haematology.⁽⁹⁾

To date, 62 gene mutations have been identified.⁽⁶⁾ Most PK-deficient patients are compound heterozygotes of mutant PK genes, while some true homozygotes have also been reported. Among the 12 homozygous PK-deficient families (Japanese, American Amish⁽¹⁰⁾ and Chinese) we have analyzed, six distinct missense mutations, a one-base deletion, and a splicing mutation have been identified. According to the information on the three-dimensional structure of PK deduced from the crystallographic study of cat muscle,⁽¹¹⁾ these mutations mostly locate near the substrate binding site, or in exon 10, which is important for both the intersubunit contact and allostericity.⁽¹²⁾ These variant enzymes may change the conformation of the active site or the tetramer formation of PK subunits, resulting in a drastic loss of activity.

PK Beppu, a severe PK variant, shows that the M2-type PK persists in the mature red cell. This variant was found to be homozygous with a one-base deletion, resulting in the frame-shift and premature termination of translation. The truncated R-PK subunit lacks about two-thirds of the C-terminal portion and expectedly has no catalytic activity. The affected red cells may survive by a compensatory M2-PK expression.⁽¹³⁾ A point mutation in 5'-donor site of intron 7 of PK-L gene was identified in PK Kowloon. In this severe transfusion-dependent homozygous case, premature termination would occur in the region encoded by intron 7 sequence, causing severe anemia with the persistence of M2-type PK.⁽¹⁴⁾

In a compound heterozygous case, PK “Osaka,” one allele had a missense mutation near the active site, while R-PK mRNA was decreased to 60 percent of normal, suggesting that another mutation probably inherited from the patient’s mother might be involved in the region which regulated transcriptional activity in erythroid cells.⁽¹²⁾

Recently, murine PK deficiency with severe hemolytic anemia accompanied by the persistence of M2-type PK in the erythrocytes due to a missense mutation was found.^(15,16) This mutant CBA strain mouse is a useful animal model for understanding the pathophysiology of PK deficiency and for developing new therapeutic methods for severe PK deficiency

2. G6PD deficiency. G6PD catalyzes the first step in the hexose monophosphate pathway, and it produces NADPH, which is required for the maintenance of reduced glutathione (GSH). GSH is essential for protecting red cells from oxidative damage. G6PD is distributed in all cells. The active enzyme form is made up of either two or four identical subunits. Human G6PD monomer consists of 515 amino acids, and the cDNA consists of 13 exons. The DNA region upstream from the transcription initiation site has features similar to those found in other housekeeping gene promoters.

In 1967, a committee of the World Health Organization proposed standard biochemical procedures to characterize variants such as enzyme activity, Km for glucose 6-phosphate, heat stability and so forth.⁽¹⁷⁾ According to these procedures, nearly 400 apparently different variants have been described by 1983. It has become increasingly difficult to decide whether a new variant actually differs from all those that had been described before.⁽¹⁸⁾

Based on gene analysis, 96 (84 published) variants have been determined. It is noteworthy that many variants that were regarded as distinct based on their biochemical characteristics have been found to be the same. On the other hand, occasional variants that were regarded as identical have turned out to be different.⁽¹⁸⁾

Some of these have polymorphic frequencies in different populations, such as G6PD A- and G6PD Mediterranean, because female carriers have a selective advantage against malaria infection.⁽¹⁹⁾ In contrast to these polymorphic variants which belong to so-called class II, 17 class I variants, characterized by CHA that is further exacerbated by oxidant stress are sporadic variants and have been described in many parts of the world, regardless of whether the common types of G6PD deficiency are endemic in the region. For instance, many cases have been reported from Japan.^(2,6)

Most of the variant enzymes are produced by one or two missense mutations. G6PD Vancouver is caused by three nucleotide substitutions. Although nucleotide deletions or nonsense mutations are not uncommon molecular abnormalities that may cause a variety of genetic disorders, they are rare in G6PD deficiency, except for G6PD Georgia,⁽²⁰⁾ which is a heterozygote of nonsense mutation. In-frame nucleotide deletions have been found only in five variants: G6PD Sunderland, Urayasu, Tsukui, Stonybrook and Nara, each of which causes a deletion of not more than eight amino acid residues. A splicing mutation at the 3' end of intron 10 has been found.⁽²⁰⁾ The low frequency of amino acid deletion as a cause of G6PD deficiency implies that the severe tissue dysfunction usually associated with such a drastic structural aberration is presumably lethal unless the involved region is functionally insignificant, because G6PD is necessary in all tissues. Recently, a model of the three dimensional structure has been constructed

based on the solved structure of G6PD from *Leuconostoc mesenteroides*, which will supply useful information to explain its molecular pathology.⁽²¹⁾

3. Other enzymopathies. Fifteen unrelated families with hexokinase (Hx) deficiency have been reported. Most show CHA, but some manifested associated disorders such as multiple malformation, latent diabetes mellitus, and psychomotor retardation. Recently, the molecular defect has been determined in a compound heterozygous case.^(1,6)

Glucosephosphate isomerase (GPI) deficiency is the fourth most common hereditary enzyme defect causing CHA. More than 40 unrelated families have been reported. Although GPI is expressed in virtually all tissues, clinical manifestations are limited to CHA, with a few exceptions. A human cDNA for neuroleukin has proved to be identical with GPI. Seven homozygotes with different missense mutations, five compound heterozygotes with different missense mutations and one compound heterozygote with missense and deletion mutations have been determined. These mutations seem to induce enzyme instability.^(1,6)

Phosphofructokinase (PFK) deficiency is associated with a heterogeneous group of clinical symptoms characterized by myopathy (Tarui disease) and/or mild CHA. More than 34 unrelated families with PFK deficiency have been described. In two Japanese patients and an Ashkenazi Jewish family with Tarui disease, 5'-splice junction mutations, resulting in splicing to a cryptic site within an exon, or exon skipping, were identified. Other splicing mutations as well as missense mutations have been identified.⁽⁶⁾

Only two families with aldolase deficiency have been reported. A missense mutation that produces thermolabile variant enzyme has been identified in one homozygous case.⁽²²⁾

Triosephosphate isomerase (TPI) deficiency shows severe clinical manifestations, including CHA, neurological dysfunction, sudden cardiac death, and increased susceptibility to infection. More than 25 unrelated families have been described. Homozygous missense mutations, compound heterozygosity for missense/nonsense mutations or missense mutation/reduced mRNA have been reported.^(1,6)

Phosphoglycerate kinase (PGK) deficiency is associated with CHA, neurological manifestations and often myopathy with recurrent myoglobinuria. Single amino acid substitutions have been clarified in several variants, first on the protein level in 1980-1981 by Fujii and Yoshida.⁽²³⁾ Recently, several PGK deficient patients have been analyzed using DNA. Structural changes have been related to functional abnormalities of PGK variants by inference from the three-dimensional structure for horse PGK.^(1,6,23)

An approximately hundredfold increase in red cell adenosine deaminase (ADA) is known to cause CHA with autosomal dominant inheritance. The hyperactivity is limited only to red cells, and the patients' red cell ADA was found to be normal. Recently, increased TAAA repeats located at the tail end of an Alu repeat about 1.1 kb upstream of the ADA gene have been identified in affected individuals.⁽²⁴⁾ These cis-acting mutations might cause the overexpression of ADA in red cells.^(1,6)

Although pyrimidine 5'-nucleotidase (P5N) deficiency appears to be the third most common cause of erythroenzymopathies associated with CHA, the precise molecular defect has not been clarified because the normal gene has not been isolated.^(1,6)

II. Enzymopenic Hereditary Methemoglobinemia

Hereditary methemoglobinemia can be divided into two forms. One is due to Hb M, which has autosomal dominant inheritance. The other is called enzymopenic hereditary methemoglobinemia due to an enzyme abnormality of NADH-dependent methemoglobin reductase system, cytochrome *b5* reductase deficiency,⁽²⁵⁾ which has autosomal recessive inheritance. Its main clinical feature is cyanosis, a bluish discoloration of the skin, lacking evidence of cardiac or pulmonary disease. Significant erythrocytosis is observed only occasionally. The two disorders can be diagnosed by the absorption spectrum of a clear, stroma-free hemolysate.

In most instances, enzymopenic methemoglobinemic patients are really more blue than sick, cyanosis being the only sign. Such cases are classified as type I. In these cases deficiency of cytochrome *b5* reductase is limited to the erythrocytes. A much more severe and lethal disorder occurs in 10 to 15 percent of patients with this disorder; it is referred to as type II. The symptoms include mental retardation, microcephaly, retarded growth, opisthotonos, and generalized hypertonia. Not only is the activity of cytochrome *b5* reductase markedly reduced in the type II patients' erythrocytes, but nearly total deficiency of microsomal cytochrome *b5* reductase is demonstrable in other tissues. In type I patients, therapy is ordinarily not necessary and is used mostly for cosmetic purposes.

Yubisui et al cloned cytochrome *b5* reductase cDNA.⁽²⁶⁾ At least five distinct missense mutations, one nonsense mutation and one mutation resulting in exon 5 skipping and premature termination have been described since then. Thus, allelic heterogeneity is sufficient to account for the phenotypic differences of the two types of the disorder. Mutations that reduce stability and leave catalytic function intact mainly cause problems in the erythrocyte, because the erythrocyte depends on enzyme synthesized up to the reticulocyte stage. Conversely, mutations that markedly reduce catalytic function cause a severe generalized type II phenotype.⁽²⁵⁾

III. Erythrocytosis Due to Erythroenzymopathy

Diphosphoglycerate mutase (DPGM) is a trifunctional enzyme whose main function is to synthesize 2,3-diphosphoglycerate (2,3-DPG), which profoundly influences the affinity of hemoglobin for oxygen. DPGM also displays two other activities, a phosphatase activity that degrades 2,3-DPG and a minor mutase activity identical to that of glycolytic phosphoglycerate mutase.⁽²⁷⁾ DPGM deficiency is very rare. The initial case of a complete deficiency of erythrocyte DPGM was documented in 1978 in a 42-year-old man who had ruddy cyanosis, hemoglobin concentration of 19g/dl, and no evidence of hemolysis.⁽²⁸⁾

Sequence studies of the propositus' DNA sample revealed that the total DPGM deficiency results from a genetic compound with one allele coding for an inactive enzyme and the other bearing a frameshift mutation.^(6,29)

In contrast to the case presented above, early in 1965, Schröter reported a neonate who had severe hemolytic anemia.⁽³⁰⁾ Although the red cells of the propositus were not examined because of frequent blood transfusions, the DPGM activity of the parents' red

cells (who are cousins) was subnormal, and it was hypothesized that the infant was a homozygote. The difference in clinical picture between these two cases suggests either that Schröter's patient had a defect other than or in addition to DPGM deficiency, or that there is marked variability in expression of total DPGM deficiency.

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