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Genetic Factors Contributing to Anemia in Pregnancy: A Review

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Abstract

Anemia in pregnancy is a prevalent global health issue, significantly impacting maternal and fetal outcomes. While nutritional deficiencies and infections are well-established causes, genetic factors also contribute to the development and severity of anemia during pregnancy. This review comprehensively examines genetic determinants such as hemoglobinopathies, enzyme deficiencies, and polymorphisms affecting nutrient metabolism, all of which influence anemia risk in pregnant women. Hemoglobinopathies, including sickle cell disease and thalassemias, are major genetic contributors to anemia, leading to chronic hemolysis and impaired erythropoiesis. Additionally, enzyme deficiencies like glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase (PK) deficiencies compromise red blood cell survival, exacerbating anemia under physiological stress. Furthermore, genetic polymorphisms in folate metabolism (MTHFR), iron regulation (TMPRSS6), and vitamin B12 transport (TCN2) impair micronutrient absorption and utilization, increasing the risk of anemia during pregnancy.

Keywords: Genetic predisposition, Hemoglobinopathies, Iron, Erythropoiesis, Pregnancy, anemia

Introduction

Anemia in pregnancy is a widespread public health concern that poses serious risks to both maternal and fetal health. Defined by the World Health Organization (WHO) as a hemoglobin concentration below 11 g/dL, anemia affects an estimated 40% of pregnant women globally, with higher prevalence in low- and middle-income countries. It contributes significantly to maternal morbidity and mortality, as well as to adverse perinatal outcomes such as preterm birth, low birth

weight, and increased neonatal mortality.[1] The primary causes of anemia in pregnancy are multifactorial, with iron deficiency being the most common. Other nutritional deficiencies, infections (such as malaria and HIV), and chronic diseases also play crucial roles. However, the influence of genetic factors on anemia has gained increasing attention due to their significant contribution to the disease's complexity and severity. Genetic factors influencing anemia in pregnancy primarily include inherited blood disorders like hemoglobinopathies, enzymatic defects, and genetic polymorphisms that affect micronutrient metabolism. Hemoglobinopathies, such as sickle cell disease and thalassemias, are prevalent in certain regions and significantly impact red blood cell function and survival. These inherited disorders often lead to chronic anemia and heightened vulnerability to complications during pregnancy.[2-3] Enzyme deficiencies, particularly glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase (PK) deficiency, further contribute to anemia in pregnancy. These enzymatic defects impair red blood cell metabolism, making cells more susceptible to oxidative stress and hemolysis. Pregnant women with these deficiencies are at increased risk for anemia, especially when exposed to certain medications, infections, or dietary triggers.[4] In addition to structural and enzymatic abnormalities, genetic polymorphisms affecting micronutrient metabolism play a critical role in anemia susceptibility. Mutations in genes like methylenetetrahydrofolate reductase (MTHFR) impair folate metabolism, while variants in TMPRSS6 influence iron regulation. Similarly, mutations in the transcobalamin 2 (TCN2) gene impact vitamin B12 absorption, all contributing to increased anemia risk during pregnancy.[5] The interaction between genetic predispositions and environmental factors further complicates anemia in pregnancy. For example, women with hemoglobinopathies or enzyme deficiencies may experience more severe anemia when exposed to infections, poor nutrition, or high physiological demands of pregnancy. This gene-environment interplay underscores the need for holistic approaches to anemia management.[6]

Hemoglobinopathies

Hemoglobinopathies are inherited disorders caused by genetic mutations in the globin genes responsible for hemoglobin production. These conditions result in abnormal hemoglobin structure or reduced production, leading to impaired oxygen transport and chronic anemia. The two most common types of hemoglobinopathies are sickle cell disease and thalassemias, both of which pose significant health risks during pregnancy.[7] Sickle Cell Disease (SCD) is caused by a mutation in the β-globin gene (HBB), resulting in the production of hemoglobin S (HbS). Under low-oxygen conditions, HbS polymerizes, causing red blood cells to assume a sickle shape. These misshapen cells are prone to hemolysis and can obstruct blood vessels, leading to vaso-occlusive crises, chronic hemolytic anemia, and increased risk of pregnancy complications such as preeclampsia, intrauterine growth restriction, and preterm labor.[8] Thalassemias are a group of inherited blood disorders characterized by reduced or absent synthesis of one or more globin chains. Alpha-thalassemia results from mutations in the HBA1 and HBA2 genes, while beta-thalassemia arises from mutations in the HBB gene. These mutations disrupt hemoglobin synthesis, leading to ineffective erythropoiesis, chronic anemia, and splenomegaly. Pregnant women with thalassemia, particularly beta-thalassemia major, often require regular blood transfusions and iron chelation therapy to manage anemia and prevent complications.[9]

The genetic inheritance patterns of hemoglobinopathies play a critical role in disease expression and severity. Both SCD and thalassemias follow an autosomal recessive inheritance pattern, meaning that offspring are at risk if both parents are carriers. Genetic counseling and prenatal screening are essential in high-prevalence regions to identify at-risk couples and provide reproductive guidance.[10] Management of hemoglobinopathies in pregnancy requires a multidisciplinary approach, including routine monitoring, blood transfusions, and preventive care to minimize maternal and fetal risks. Advances in gene therapy and targeted treatments offer promising avenues for future interventions,

potentially reducing the disease burden and improving outcomes for affected pregnant women.[11] Enzyme deficiencies, particularly glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase (PK) deficiency, further contribute to anemia in pregnancy. These enzymatic defects impair red blood cell metabolism, making cells more susceptible to oxidative stress and hemolysis. Pregnant women with these deficiencies are at increased risk for anemia, especially when exposed to certain medications, infections, or dietary triggers.[12] In addition to structural and enzymatic abnormalities, genetic polymorphisms affecting micronutrient metabolism play a critical role in anemia susceptibility. Mutations in genes like methylenetetrahydrofolate reductase (MTHFR) impair folate metabolism, while variants in TMPRSS6 influence iron regulation. Similarly, mutations in the transcobalamin 2 (TCN2) gene impact vitamin B12 absorption, all contributing to increased anemia risk during pregnancy.[13] Despite growing awareness, routine screening for genetic causes of anemia in pregnancy remains limited in many healthcare settings. Integrating genetic testing and counseling into prenatal care can enhance early detection, allow for personalized treatment strategies, and improve maternal and fetal health outcomes. Emphasizing genetic research and public health interventions can contribute to more effective anemia prevention and management globally.[14]

Polymorphisms Affecting Iron Metabolism

Iron metabolism is a highly regulated process that ensures a balance between iron absorption, storage, and utilization to meet the body's needs. Dysregulation of this balance can lead to various iron-related disorders, including iron deficiency anemia and iron overload conditions like hemochromatosis. Genetic polymorphisms—variations in DNA sequence that occur in at least 1% of the population—can significantly affect iron metabolism. This review explores the role of these polymorphisms in regulating iron homeostasis and their impact on health.[15]

2. Genes Involved in Iron Metabolism

Several key genes regulate iron homeostasis, and polymorphisms in these genes can alter iron metabolism. These genes include those involved in iron absorption, transport, and storage.

- **HFE Gene and Hemochromatosis**: The HFE gene, which encodes a protein that interacts with the transferrin receptor to regulate iron absorption in the gut, is associated with hereditary hemochromatosis. Two common polymorphisms, C282Y and H63D, in the HFE gene lead to impaired regulation of iron absorption, resulting in excessive iron accumulation in tissues and organs. The C282Y homozygous mutation is the most common cause of primary hemochromatosis.[16]

- **TFRC Gene (Transferrin Receptor)**: The TFRC gene encodes the transferrin receptor, a protein responsible for the uptake of iron bound to transferrin into cells. Polymorphisms in TFRC can affect the receptor's affinity for transferrin and influence iron uptake, potentially contributing to iron deficiency or overload.

- **Ferroportin (SLC40A1)**: Ferroportin, encoded by the SLC40A1 gene, is the only known iron exporter, facilitating the transfer of iron from cells into the bloodstream. Polymorphisms in SLC40A1 can cause either iron deficiency or iron overload, depending on the type of mutation. A common mutation, FPN1, is associated with ferroportin disease, a condition characterized by impaired iron export leading to iron overload in the macrophages and liver.[17]

- **Hepcidin (HAMP Gene)**: Hepcidin is a key regulator of iron homeostasis, produced mainly by the liver. It acts by binding to ferroportin, thereby preventing iron from being exported into the bloodstream. Polymorphisms in the HAMP gene can affect hepcidin production, altering iron

regulation. Mutations in HAMP can lead to hereditary iron overload disorders such as juvenile hemochromatosis, while lower levels of hepcidin are also associated with iron deficiency anemia.

- **DMT1 (Divalent Metal Transporter 1)**: DMT1, encoded by the SLC11A2 gene, is responsible for the absorption of dietary iron in the small intestine. Polymorphisms in the DMT1 gene can influence the efficiency of iron absorption, potentially leading to altered iron status and susceptibility to iron-related disorders.[18]

3. Polymorphisms and Iron Deficiency

Iron deficiency is the most common nutritional disorder worldwide, often caused by insufficient dietary intake, blood loss, or increased demand (e.g., during pregnancy). Genetic polymorphisms can also contribute to the development of iron deficiency
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- **Polymorphisms in the HFE and TFRC Genes**: Variations in these genes may influence an individual's susceptibility to iron deficiency by affecting the regulation of iron absorption and storage. For example, individuals with polymorphisms in the HFE gene may absorb more iron than necessary, exacerbating deficiencies under conditions of increased demand or poor dietary intake.

- **DMT1 Polymorphisms**: Some genetic variants of DMT1 can alter the transporter's efficiency in absorbing iron from the gut, which may result in an increased risk of iron deficiency, particularly in populations with low dietary iron availability.[19]

4. Polymorphisms and Iron Overload

Iron overload is typically caused by excessive iron absorption or defective iron regulation, leading to toxic accumulation of iron in tissues. Several genetic polymorphisms are associated with this condition:

- **HFE Gene Mutations**: Homozygosity for the C282Y mutation in the HFE gene is the most common genetic cause of hereditary hemochromatosis, a disorder characterized by excessive iron absorption and deposition in organs such as the liver, heart, and pancreas. This can lead to organ damage, diabetes, liver cirrhosis, and cardiovascular disease.

- **Ferroportin Mutations**: Polymorphisms in the SLC40A1 gene that affect the function of ferroportin can lead to conditions like ferroportin disease, characterized by iron accumulation in macrophages and the liver. These mutations impair the ability of ferroportin to export iron, resulting in increased iron levels in cells and tissue damage.

- **HAMP Gene Mutations**: Mutations in the HAMP gene, leading to decreased hepcidin production, result in uncontrolled iron absorption and deposition, contributing to iron overload conditions like juvenile hemochromatosis.[20]

5. Interaction Between Genetic and Environmental Factors

The expression of iron-related genetic polymorphisms can be influenced by environmental factors, including diet, infections, and inflammation. For instance, infections can increase hepcidin levels, which suppress iron absorption, while inflammation can exacerbate conditions like iron deficiency anemia or anemia of chronic disease. Dietary intake of iron and other micronutrients also plays a role in modulating the effects of genetic polymorphisms on iron metabolism.

Genetic Mutations in Erythropoiesis

Erythropoiesis is the process by which red blood cells are produced from hematopoietic stem cells in the bone marrow. This process is tightly regulated by various transcription factors, signaling pathways,

and cellular interactions. Genetic mutations affecting key genes involved in erythropoiesis can disrupt normal RBC production and lead to diseases with varying degrees of severity. The consequences of these mutations may include ineffective erythropoiesis, abnormal RBC morphology, hemolysis, or failure of the bone marrow to produce enough RBCs. This review focuses on the genetic mutations involved in erythropoiesis and their associated disorders, with an emphasis on the molecular mechanisms and clinical manifestations.[21]

2. Genes Involved in Erythropoiesis

The development of red blood cells involves the coordinated expression of several key genes that regulate cellular proliferation, differentiation, and maturation. Mutations in these genes can lead to various hematological conditions. Some of the critical genes include:

- **GATA1**: GATA1 is a transcription factor essential for the differentiation of erythroid progenitors. Mutations in the GATA1 gene can result in abnormal RBC development, leading to X-linked thrombocytopenia and anemia. In severe cases, GATA1 mutations can result in megakaryocyte and erythroid lineage defects, leading to reduced RBC production.

- **EPO and EPOR**: Erythropoietin (EPO) is a hormone produced by the kidneys that stimulates erythropoiesis in response to low oxygen levels. Erythropoietin binds to its receptor (EPOR) on erythroid progenitors to initiate differentiation. Mutations in the EPO or EPOR gene can result in erythropoietic defects, leading to congenital erythropoietin-responsive anemia.[22]

- **HBB (Hemoglobin beta gene)**: Mutations in the HBB gene, which encodes the beta-globin chain of hemoglobin, are the cause of sickle cell disease and beta-thalassemia. These mutations lead to either the production of abnormal hemoglobin (in sickle cell disease) or reduced hemoglobin production (in beta-thalassemia), both of which disrupt RBC function.

- **ALAS2 (Aminolevulinic acid synthase 2)**: ALAS2 is involved in the heme biosynthesis pathway, and mutations in this gene can cause X-linked sideroblastic anemia. This condition leads to defective heme production and impaired RBC maturation, resulting in microcytic anemia.[23]

- **TP53 (Tumor protein p53)**: TP53 is a tumor suppressor gene that regulates cell cycle progression and apoptosis. Mutations in TP53 can lead to defects in erythropoiesis, as it is crucial for maintaining the integrity of erythroid progenitors. TP53 mutations are associated with various hematologic malignancies, including acute myeloid leukemia (AML) and certain forms of myelodysplastic syndromes (MDS)

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3. Genetic Mutations and Their Impact on Erythropoiesis

- **Thalassemia**: Thalassemia is a group of inherited blood disorders characterized by defective hemoglobin production. Mutations in the alpha-globin (HBA) or beta-globin (HBB) genes impair hemoglobin synthesis, leading to ineffective erythropoiesis and anemia. Alpha-thalassemia results from mutations in the HBA1 and HBA2 genes, while beta-thalassemia is due to mutations in the HBB gene. These mutations lead to the production of abnormal hemoglobin molecules and cause RBCs to become fragile and prone to premature destruction.[24]

- **Sickle Cell Disease (SCD)**: Sickle cell disease is caused by a point mutation in the HBB gene, where glutamic acid is replaced by valine at position 6 of the beta-globin chain. This mutation leads to the formation of hemoglobin S (HbS), which polymerizes under low oxygen conditions, causing RBCs to assume a sickle shape. These sickled cells are less flexible, leading to blockages in blood vessels, hemolysis, and decreased RBC lifespan.

- **Hereditary Spherocytosis**: This condition is caused by mutations in genes encoding membrane proteins such as ankyrin, spectrin, and band 3. These mutations lead to the production of

abnormally shaped RBCs (spherocytes) that are less deformable and more prone to premature destruction in the spleen. Hereditary spherocytosis results in hemolytic anemia and splenomegaly.[25]

- **Congenital Erythropoietic Porphyria**: Mutations in the UROS gene, which encodes uroporphyrinogen III synthase, lead to a defect in porphyrin metabolism, causing the accumulation of porphyrin precursors in RBCs. This condition affects erythropoiesis and results in symptoms such as photosensitivity, hemolysis, and splenomegaly.

- **Diamond-Blackfan Anemia (DBA)**: DBA is a rare congenital form of pure red cell aplasia characterized by defective erythropoiesis in the bone marrow. It is caused by mutations in ribosomal protein genes (e.g., RPS19, RPL5). These mutations impair ribosomal function, leading to the failure of erythroid progenitors to differentiate into mature RBCs, resulting in severe anemia.[26]

- **Hereditary Hemochromatosis**: This condition is characterized by excessive iron absorption and deposition in tissues, leading to iron overload. Genetic mutations in the HFE gene (C282Y, H63D) impair the regulation of iron homeostasis and cause excessive iron to accumulate in erythroid progenitors, leading to anemia and other systemic complications.

4. Molecular Mechanisms of Erythropoiesis Dysregulation

Mutations in genes that regulate erythropoiesis can disrupt various stages of RBC development, from hematopoietic stem cell differentiation to mature RBC function. Some key molecular mechanisms include:

- **Impaired Hemoglobin Synthesis**: Mutations in the globin genes (HBB, HBA) lead to defective hemoglobin production, disrupting the oxygen-carrying capacity of RBCs. In thalassemia, reduced globin chain production leads to an imbalance in hemoglobin composition, while in sickle cell disease, abnormal hemoglobin polymerization causes RBC deformation.[27]

- **Altered Erythroid Progenitor Differentiation**: Mutations in transcription factors such as GATA1 and in signaling molecules like EPO and EPOR can impair the differentiation of erythroid progenitors, leading to reduced RBC production or ineffective erythropoiesis.

- **Defective Heme Biosynthesis**: Mutations in genes such as ALAS2 lead to defective heme production, impairing RBC maturation and resulting in microcytic anemia.

- **Impaired Erythrocyte Membrane Integrity**: Mutations in genes encoding RBC membrane proteins (e.g., ankyrin, spectrin) result in the production of abnormally shaped RBCs, which are more prone to hemolysis and reduced lifespan.[28]

- **Folate and Vitamin B12 Metabolism**

Folate (vitamin B9) and vitamin B12 are crucial micronutrients involved in the one-carbon metabolism pathway, which is essential for the synthesis of nucleotides and amino acids. Both vitamins are interdependent, and a deficiency in either can lead to similar pathophysiological conditions. Folate is primarily involved in the synthesis of purines and thymidylate, while vitamin B12 is required for the conversion of homocysteine to methionine and for the synthesis of methylmalonyl-CoA. Several genetic variants have been identified in the enzymes that metabolize these vitamins, and these variants can influence individual susceptibility to folate and vitamin B12 deficiency and associated health issues.[29]

2. Folate and Vitamin B12 Metabolism Pathways

- **Folate Metabolism**: Folate is converted to its active form, tetrahydrofolate (THF), through a series of enzymatic reactions. The key enzymes involved in folate metabolism include methylenetetrahydrofolate reductase (MTHFR), serine hydroxymethyltransferase (SHMT), and dihydrofolate reductase (DHFR). Folate is involved in the transfer of one-carbon units required for DNA synthesis and methylation reactions.

- **Vitamin B12 Metabolism**: Vitamin B12, also known as cobalamin, is required for two essential enzymatic processes: the conversion of homocysteine to methionine (catalyzed by methionine synthase) and the conversion of methylmalonyl-CoA to succinyl-CoA (catalyzed by methylmalonyl-CoA mutase). Vitamin B12 is absorbed in the ileum and binds to intrinsic factor (IF) for transport and cellular uptake.[30]

3. Genetic Variants in Folate Metabolism

Several genetic variants have been identified in enzymes involved in folate metabolism. These variants can affect the availability of folate derivatives and influence individual susceptibility to folate deficiency and related disorders.

- **Methylenetetrahydrofolate Reductase (MTHFR) Gene Variants**: MTHFR is one of the most studied enzymes in folate metabolism. MTHFR catalyzes the reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the active form of folate used in methylation reactions. Two common genetic polymorphisms, C677T and A1298C, are associated with reduced MTHFR activity.[31]

  - **C677T Mutation**: The C677T mutation results in a substitution of cytosine for thymine at position 677 in the MTHFR gene. This mutation leads to a thermolabile enzyme with reduced activity. Individuals with homozygous TT genotypes (C677T) have lower levels of 5-methyl tetrahydrofolate, leading to an increased risk of elevated homocysteine levels, which is a known risk factor for cardiovascular diseases, pregnancy complications, and neural tube defects.

  - **A1298C Mutation**: The A1298C mutation results in an amino acid change in the MTHFR enzyme, leading to impaired enzyme function. This variant is also associated with elevated homocysteine levels, though the impact is less severe than the C677T mutation. Individuals with both C677T and A1298C mutations may have more significant impairments in folate metabolism.[32]

- **Other Folate-Related Gene Variants**:

  - **Serine Hydroxymethyltransferase (SHMT)**: SHMT plays a key role in the interconversion of serine and glycine and is involved in the transfer of one-carbon units in folate metabolism. Genetic variants in SHMT1 and SHMT2 can affect folate metabolism and increase the risk of folate deficiency.[3]

  - **MTHFD1**: The MTHFD1 gene encodes an enzyme that catalyzes reactions in the folate cycle. Variants in MTHFD1 can lead to altered folate metabolism and increased risk of neural tube defects in fetuses.

  - **Riboflavin (Vitamin B2) Metabolism**: Riboflavin, through its active form, FAD, acts as a cofactor for the MTHFR enzyme. Riboflavin deficiency has been linked to impaired MTHFR function, and variants in the riboflavin metabolism pathway can exacerbate folate metabolism disruptions

4. Genetic Variants in Vitamin B12 Metabolism

Vitamin B12 is metabolized through complex pathways that involve multiple enzymes and cofactors. Genetic variations affecting these enzymes can lead to impaired vitamin B12 absorption, transport, or conversion, resulting in cobalamin deficiency.

- **Methionine Synthase (MTR) Gene Variants**: The MTR gene encodes methionine synthase, an enzyme required for the conversion of homocysteine to methionine, which also involves vitamin B12 as a cofactor. Variants in the MTR gene, such as the A2756G mutation, can lead to reduced enzyme activity and increased homocysteine levels, contributing to the risk of cardiovascular diseases, anemia, and neurological disorders.

- **Methionine Synthase Reductase (MTRR) Gene Variants**: MTRR encodes methionine synthase reductase, an enzyme that reactivates methionine synthase by regenerating its methyl-B12 cofactor. Mutations in the MTRR gene, such as the I22M and A66G variants, can impair this process and lead to functional vitamin B12 deficiency, even in individuals with normal B12 levels.[3]

- **Cobalamin Transport and Absorption Variants**: Genetic mutations in the **cobalamin transporters**, including the **TCN2** (transcobalamin II) and **MMACHC** (cobalamin cblC type) genes, affect the absorption and transport of vitamin B12. Mutations in these genes can lead to congenital cobalamin deficiency, causing disorders such as methylmalonic acidemia and homocystinuria.

- **Intrinsic Factor (IF) Gene Variants**: Intrinsic factor is a glycoprotein produced in the stomach that binds to vitamin B12 and facilitates its absorption in the ileum. Mutations in the IF gene can lead to congenital vitamin B12 deficiency due to impaired absorption, a condition known as **pernicious anemia**.

Gene-Environment Interactions in Anemia

Anemia is a condition characterized by a decrease in the number of red blood cells or the amount of hemoglobin in the blood, leading to reduced oxygen delivery to tissues. It is a multifactorial disorder, with both genetic and environmental components contributing to its development. Gene-environment interactions in anemia are particularly relevant in conditions such as iron-deficiency anemia, sickle cell anemia, thalassemia, and anemia associated with chronic diseases. Environmental factors such as dietary intake, infections, and exposure to toxins can exacerbate or mitigate the effects of genetic mutations that predispose individuals to anemia.

2. Genetic Factors in Anemia

Several genetic mutations are associated with inherited forms of anemia, including hemoglobinopathies and thalassemias. These genetic disorders result in abnormal red blood cell production or structure, leading to anemia.

- **Hemoglobinopathies**: Hemoglobinopathies, such as sickle cell disease and various forms of thalassemia, are caused by mutations in the globin genes. The most common genetic mutation in sickle cell disease is the substitution of valine for glutamic acid at position 6 of the β-globin chain (HBB gene). This mutation leads to the formation of abnormal hemoglobin (HbS), which causes red blood cells to become rigid and sickle-shaped, leading to vaso-occlusion, anemia, and organ damage.

- **Thalassemia**: Thalassemia results from mutations that affect the synthesis of α- or β-globin chains. Individuals with β-thalassemia have reduced or absent β-globin chain production, resulting in ineffective erythropoiesis, hypochromic microcytic anemia, and excessive iron accumulation. α-Thalassemia is caused by deletions in the α-globin gene, leading to imbalanced globin chain production and abnormal hemoglobin formation.

- **Hereditary Spherocytosis**: This genetic disorder is caused by mutations in genes encoding red blood cell membrane proteins (e.g., ankyrin, spectrin). These mutations lead to the production of spherocytes, which are prone to premature destruction, resulting in hemolytic anemia.[35]
- **G6PD Deficiency**: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a genetic condition that impairs the antioxidant defense of red blood cells. Individuals with G6PD deficiency may develop hemolytic anemia in response to oxidative stress caused by infections, certain drugs, or foods (e.g., fava beans).

3. Environmental Factors Contributing to Anemia

Environmental factors, particularly nutrition, infections, and exposure to toxins, play significant roles in the development and exacerbation of anemia.

- **Iron Deficiency**: Iron deficiency is one of the leading environmental causes of anemia worldwide. Inadequate dietary intake of iron, poor absorption due to gastrointestinal disorders, or increased iron demand during periods of rapid growth or pregnancy can lead to iron-deficiency anemia. Iron deficiency also exacerbates the effects of inherited hemoglobinopathies, such as sickle cell disease and thalassemia, by increasing the severity of anemia.

- **Vitamin Deficiencies**: Deficiencies in vitamin B12 and folate can also lead to anemia by impairing DNA synthesis and red blood cell maturation. Poor dietary intake or malabsorption due to gastrointestinal disorders (e.g., celiac disease or pernicious anemia) can result in macrocytic anemia. Both folate and vitamin B12 deficiencies are commonly seen in populations with poor dietary habits or malnutrition.

- **Chronic Infections**: Chronic infections, particularly those caused by malaria, tuberculosis, and HIV, can lead to anemia through multiple mechanisms, including hemolysis, reduced erythropoiesis, and inflammatory cytokine-induced suppression of red blood cell production. Malaria-induced anemia is a result of both hemolysis of infected red blood cells and the immune-mediated destruction of uninfected red blood cells.[36]

- **Exposure to Toxins**: Environmental toxins such as lead and certain chemicals can impair erythropoiesis and contribute to anemia. Lead poisoning is associated with impaired heme synthesis and can lead to microcytic anemia. Similarly, toxins from industrial chemicals and pollutants can lead to oxidative stress, hemolysis, and bone marrow suppression.

4. Gene-Environment Interactions in Anemia

Gene-environment interactions occur when an individual's genetic susceptibility to anemia is influenced by environmental factors. These interactions can modulate the severity, progression, and response to treatment of anemia.

- **Iron Deficiency and Hemoglobinopathies**: Iron deficiency can exacerbate the severity of anemia in individuals with sickle cell disease and thalassemia. In sickle cell disease, iron deficiency can worsen anemia by decreasing the number of functional red blood cells. In thalassemia, iron deficiency may increase the risk of iron overload due to increased absorption of iron in an attempt to compensate for anemia. Therefore, managing iron deficiency in individuals with hemoglobinopathies is crucial to prevent worsening of anemia and complications related to iron overload

- **Nutrient-Gene Interactions in Folate and Vitamin B12 Metabolism**: Genetic variants in folate and vitamin B12 metabolism, such as mutations in the MTHFR gene, can influence an individual’s response to dietary folate and vitamin B12 intake. For example, individuals with the MTHFR 677T allele have reduced MTHFR enzyme activity, which affects folate metabolism and increases the requirement for dietary folate. In individuals with genetic predispositions to anemia, ensuring adequate intake of these vitamins can mitigate the risk of anemia associated with deficienc

- **G6PD Deficiency and Environmental Stressors**: Individuals with G6PD deficiency are more susceptible to hemolytic anemia triggered by environmental stressors, such as infections, certain medications (e.g., sulfa drugs), and exposure to fava beans. Genetic testing for G6PD deficiency can help identify

individuals at risk, enabling clinicians to avoid triggers and reduce the incidence of hemolytic episodes.

- **Chronic Inflammation and Anemia of Chronic Disease**: Chronic inflammatory conditions, such as rheumatoid arthritis and inflammatory bowel disease, can lead to anemia of chronic disease (ACD), where iron is sequestered in storage sites and is unavailable for erythropoiesis. Genetic variations in cytokine genes, such as interleukin-6 (IL-6), can influence the severity of anemia in individuals with chronic inflammation. In these cases, managing inflammation can help alleviate anemia.[36]

Conclusion

Gene-environment interactions are central to understanding the multifactorial nature of anemia, which is influenced by both inherited genetic mutations and environmental factors. These interactions can significantly impact the onset, severity, and progression of anemia, as well as the individual's response to treatment. Genetic factors, such as mutations in hemoglobinopathies, thalassemia, G6PD deficiency, and folate metabolism, interact with environmental factors like diet, infections, and exposure to toxins, shaping the clinical manifestations of anemia.

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