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Current Understanding of the Molecular Mechanisms Underlying Glucose-6-Phosphate Dehydrogenase Deficiency and Its Impact on Human Health

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Abstract: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common blood disorder, presenting multiple symptoms, including hemolytic anemia. It affects 400 million people worldwide, with more than 160 single mutations reported in G6PD. The most severe mutations (about 70) are classified as class I, leading to more than 90% loss of activity of the wild-type G6PD. The crystal structure of G6PD reveals these mutations are located away from the active site, concentrating around the noncatalytic NADP+-binding site and the dimer interface. However, the molecular mechanisms of class I mutant dysfunction have remained elusive, hindering the development of efficient therapies.

Keywords: *Molecular Mechanisms, Impact on Human Health*

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Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is red blood cells' most common enzymatic disorder, affecting approximately 400 million people worldwide (Israel, et al., 2023). It is caused by mutations in the G6PD gene, resulting in reduced enzyme activity and a range of clinical manifestations, including hemolytic anemia, neonatal jaundice, kernicterus, and increased susceptibility to infections. There are over 70 known G6PD mutant genes that cause severe symptoms. This section provides a comprehensive overview of the molecular mechanisms underlying G6PD deficiency and its impact on human health (Israel, et al., 2023).

G6PD serves as a crucial rate-limiting enzyme within the pentose phosphate pathway (PPP), which plays a vital role in the synthesis of nucleotides as well as the biosynthesis of fatty acids, cholesterol, steroid hormones, and catecholamines through the utilization of NADPH. This enzyme facilitates the transfer of protons and electrons from glucose-6-phosphate (G6P) to NADP+, resulting in the production of NADPH, which is essential for mitigating reactive oxygen species (ROS) and generating a reduced form of glutathione (Horikoshi et al., 2021). Consequently, the activity of G6PD is fundamental for the reduction of ROS. Notably, G6PD is the primary enzyme responsible for NADPH production in red blood cells (RBCs), which do not possess mitochondria or alternative sources of NADPH. As a result, a deficiency in G6PD activity within RBCs can lead to acute hemolysis when exposed to oxidative stress, which may be triggered by infections, certain medications, or dietary components such as fava beans (Horikoshi et al 2021).

Over 160 distinct missense mutations have been identified within the coding region of the G6PD gene. The World Health Organization (WHO) has categorized these mutations into five classes based on the degree of enzyme activity and the associated symptoms experienced by carriers. Class I mutations are considered the most severe, as the enzymes produced exhibit less than 10% of the activity seen in the wild type, leading to congenital nonspherocytic hemolytic anemia (Horikoshi et al 2021).

Human G6PD consists of 515 amino acids and features two binding sites for NADP+ as well as one binding site for G6P. Among the two NADP+-binding sites, the one adjacent to the G6P-binding site is referred to as the catalytic site, while the other, located further away from G6P, is designated as the structural (noncatalytic) site. G6PD functions as a homodimer and/or a homotetramer, with the monomeric form being inactive (Horikoshi et al 2021).

Molecular Mechanisms of G6PD Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency arises from inherited mutations in the X-linked G6PD gene, leading to impaired enzyme function and oxidative vulnerability in red blood cells (RBCs) (Luzzatto et al., 2020). This enzyme plays a crucial role in the pentose phosphate pathway, which is essential for maintaining the balance of reactive oxygen species (ROS) within cells, particularly red blood cells (RBCs). The condition primarily results from missense mutations causing amino acid substitutions, which disrupt enzyme activity through three key mechanisms; G6PD catalyzes the conversion of glucose-6-phosphate to 6-phosphoglucono-δ-lactone, generating NADPH in the process. That is vital for maintaining glutathione in its reduced form, which scavenges ROS, protecting RBCs from oxidative damage (Luzzatto et al., 2020). Mutations in the G6PD gene leading to structural changes in the enzyme, impairing its ability to bind NADP+ or altering its active site. These changes result in reduced enzyme activity, making RBCs more susceptible to oxidative stress from exogenous triggers such as drugs (e.g., primaquine), certain chemicals, or fava beans (favism. Endogenous stress. Infections, inflammation, or metabolic imbalances. This oxidative stress triggers hemolysis, which manifests as anemia, jaundice, or hemoglobinuria (Alakbaree et al., 2023). Over 160 mutations have been identified, with majority being single-nucleotide substitutions that cause amino acid changes (Sarker et al., 2016).

In individuals with G6PD deficiency, oxidative stress can lead to the accumulation of ROS, causing damage to hemoglobin and RBC membranes. This damage results in hemolysis, which is often triggered by specific substances like fava beans, certain medications, or infections (Alakbaree et al., 2023). The G6PD gene is located on the X chromosome (Xq28), making G6PD deficiency an X-linked recessive disorder. Males are more frequently affected, while females can be carriers or symptomatic if they are homozygous or have skewed X-chromosome inactivation (Tripathi, et al., 2019).

Clinical Consequences

Clinical consequences of G6PD include episodes of acute hemolysis which can occur in response to oxidative stressors, leading to acute hemolytic anemia. In severe cases, chronic hemolysis may occur, resulting in non-spherocytic hemolytic anemia. Furthermore, G6PD-deficient neonates are at risk of neonatal hyperbilirubinemia (Jaundice) due to an imbalance in bilirubin production and conjugation (Gronich et al., 2024).

Variants and Severity

Different G6PD variants, such as G6PD A- and G6PD Mediterranean, vary in severity and are classified by the World Health Organization based on enzyme activity levels and clinical manifestations. The severity of the deficiency determines the risk and frequency of hemolytic episodes (Pfeffer, et al., 2022).

Table 1: Key Variants and Their Pathophysiology

Variant	Mutation Effect	Outcome
Mediterranean	Catalytically defective	Rapid enzyme degradation due to structural instability.
Seattle-like	Functionally active	Enhanced proteasomal breakdown despite normal synthesis.
Other mutations	Variable impacts	Range from mild instability to complete loss of activity.

(Alakbaree, et al., 2022)

Genetic and Clinical Implications

The X-linked recessive inheritance pattern causes males (hemizygous) to be more severely affected than females (heterozygous). Female carriers may exhibit symptoms due to unbalanced X-chromosome inactivation, leading to a majority of deficient RBCs in some cases. Over 400 million people globally are affected, with regional prevalence linked to malaria-endemic areas. G6PD deficiency stems from mutations that disrupt enzyme stability/function, impairing antioxidant defense and predisposing RBCs to oxidative damage (Basta and Pandya, 2023).

Structure and Function of G6PD

G6PD is the first enzyme in the pentose phosphate pathway, responsible for converting glucose-6-phosphate into 6-phosphoglucono-1,5-lactone while generating nicotinamide adenine dinucleotide phosphate (NADPH) (Mason and Vulliamy, 2006; Stanton et al., 2012). NADPH is crucial for maintaining cellular redox balance by reducing glutathione, which protects cells from oxidative damage. In erythrocytes, which lack mitochondria, G6PD is the sole source of NADPH, making these cells particularly vulnerable to oxidative stress in G6PD deficiency. Because NADPH is required for various biosynthetic functions as well as the detoxification of free radicals and peroxidase within cells, G6PD deficiency is associated with chronic drug- or food-induced hemolytic anemia and neonatal jaundice (Stanton, 2012; Xiao et al., 2018).

Role of Mutations in G6PD Deficiency

G6PD deficiency is caused by mutations in the G6PD gene, which is located on the X chromosome at position Xq28. These mutations lead to amino acid substitutions that impair enzyme stability, activity, or both. Over 160 mutations have been identified, with some variants causing severe enzyme deficiency (Class I) and others resulting in milder forms (Classes II and III) (Zhao et al., 2010; Luzzatto et al., 2020).

Class I Mutations: These mutations are associated with the most severe enzyme deficiency, often leading to chronic hemolytic anemia. They are typically located near the dimer interface or the noncatalytic NADP+ binding site, disrupting enzyme dimerization and stability (Cunningham and Mochly-Rosen, 2017; Horikoshi et al., 2021).

Class II and III Mutants: These variants result in less severe enzyme deficiency but can still cause hemolytic episodes

triggered by oxidative stress, such as infections, certain drugs, or fava bean consumption (Efferth et al., 2006; Koralkova et al 2014).

Structural Defects in G6PD Variants

Molecular dynamics simulations and structural studies have revealed that mutations in G6PD disrupt critical regions of the enzyme, including the dimer interface and the NADP+ binding site. For example, mutations such as G6PDZacatecas (R257L) and G6PDDurham (K238R) compromise the structural stability of the dimer interface by disrupting salt bridges and hydrogen bonds, leading to reduced enzyme activity (Chandran et al., 2024). Similarly, mutations in the non-catalytic NADP+ binding site can impair enzyme tetramerization, which is essential for G6PD activity (Cunningham and Mochly-Rosen, 2017; Chandran et al., 2024). These mutations primarily affect the enzyme's stability and function without necessarily altering the active site. Key features of these defects include: Mutations like P396L, R393H, and F381L disrupt interactions between non-catalytic NADP+ binding sites, β-sheets, and α-helices, leading to disordered structural elements and impaired enzymatic function termed Long-range structural disruptions (Horikoshi et al., 2021). Variants such as G6PD A (-) exhibit reduced stability due to loss of β-sheet and α-helix interactions, although the secondary structure remains largely intact. This leads to decreased intracellular stability (Ramírez-Nava et al., 2017).

Over 200 G6PD variants are associated with enzyme deficiency, with each variant potentially leading to different clinical outcomes due to variations in enzyme stability and activity (Costa, et al., 2024). These structural defects compromise the enzyme's ability to function correctly, resulting in G6PD deficiency.

Table 2: Common G6PD Mutations and Their Regional Distribution

Mutation	Regional Prevalence	Citation
G6PD Mediterranean	Mediterranean and African	(Moiz et al., 2011) (Mohanty et al., 2004)
G6PD Orissa	India (tribal populations)	(Mohanty et al., 2004)
G6PD Kerala-Kalyan	India (southern regions)	(Mohanty et al., 2004)
Ala44Gly	Bangladesh	(Sarker et al., 2016)
Gly163Ser	Bangladesh and Pakistan	(Sarker et al., 2016) (Moiz et al., 2011)
G6PD Chatham	Pakistan	(Moiz et al., 2011)
G6PD Karachi	Pakistan	(Moiz et al., 2011)

This table highlights the regional distribution of common G6PD mutations, emphasizing the genetic diversity of the disorder.

Impact of G6PD Deficiency on Human Health

G6PD deficiency is a genetic disorder primarily impacting red blood cells' ability to withstand oxidative stress, and impacts human health mainly by increasing the risk of hemolytic anemia. This condition arises from a deficiency or malfunction of the G6PD enzyme, which normally protects red blood cells from oxidative damage[1][2]. The condition has several implications for human health, ranging from acute hemolytic episodes to potential long-term effects on cardiovascular health. This can be triggered by certain infections ((Karunarathna et al., 2024).

Impact on Red Blood Cells and Health

G6PD deficiency primarily impacts human health through the increased vulnerability of red blood cells to oxidative damage, leading to hemolytic anemia under certain triggers. This condition manifests clinically with symptoms related to anemia and jaundice, especially in newborns (Kwok et al., 2016).

Hemolysis and Hemolytic Anemia

Without sufficient G6PD enzyme activity, red blood cells cannot effectively protect themselves from oxidative stress caused by certain triggers such as infections, some medications (e.g., primaquine, sulfonamides), certain foods like fava beans, and chemicals like naphthalene. This leads to the breakdown of red blood cells, a process called hemolysis, resulting in hemolytic anemia. Symptoms of this anemia include tiredness, dizziness, paleness, jaundice (yellowing of skin and eyes), dark urine, fatigue, and shortness of breath, and in severe cases, a hemolytic crisis requiring immediate medical attention (Orman et al., 2023).

Neonatal Jaundice

In newborns, G6PD deficiency can present as jaundice within the first few days of life, which, if severe and untreated, may lead to brain damage (kernicterus). Neonatal jaundice frequently occurs in infants especially in areas where G6PD deficiency is widespread. This condition arises from the impaired production of NADPH, which hinders the conjugation of bilirubin, causing its buildup in the brain. If not addressed, this accumulation can lead to serious neurological issues (Lee, et al., 2022). Hence, screening newborns suspected of having the deficiency is important.

Broader Health Implications

Beyond acute hemolysis, G6PD deficiency may transiently affect physical development, such as slightly delayed pubic hair growth and lower body mass index (BMI) gain during adolescence, although overall physical and mental health indicators tend to be

similar to those without the deficiency (Kwok et al., 2016). There is evidence suggesting both protective and adverse effects of G6PD deficiency on cardiovascular health. Some studies indicate a reduced risk of coronary heart disease, while others suggest increased susceptibility to heart failure and hypertension (Hecker, et al., 2013).

Previous research evidence suggest that G6PD deficiency might confer a protective effect against malaria, which may explain its high prevalence in certain regions. However, the broader implications of this trade-off on human fitness and health remain under investigation (Kwok et al., 2016). G6PD deficiency may be associated with an increased risk of diabetes and renal failure, though more research is needed to confirm these associations (Hecker, et al., 2013). On a cellular level, G6PD plays a key role in producing NADPH via the pentose phosphate pathway, which is crucial for cellular antioxidant defenses and cholesterol synthesis. Deficiency limits NADPH production, potentially impacting other metabolic pathways (Kwok et al., 2016). The evolutionary Perspective, G6PD deficiency is thought to have evolved as a protective mechanism against malaria, which is prevalent in regions where the deficiency is common. This protective effect may contribute to its high prevalence in certain populations (Luzzatto et al., 2020).

Although most individuals remain asymptomatic unless exposed to triggers, the deficiency necessitates awareness and avoidance of known oxidative stress factors to prevent hemolytic crises. Its genetic basis and epidemiological distribution relate to evolutionary pressures such as malaria resistance. This multifaceted impact underscores the importance of diagnosis, trigger avoidance, and prompt treatment of symptoms to manage the condition effectively (Kwok et al., 2016).

Immunodeficiency and Infections

Severe G6PD deficiency has been linked to immunodeficiency, as activity of NADPH oxidase in phagocytes (such as neutrophils and macrophages) is reduced. NADPH oxidase is crucial for the respiratory burst that produces reactive oxygen species (ROS), which are essential for killing pathogens. This reduction leads to compromised bactericidal activity of phagocytes, resulting in a form of immunodeficiency that predisposes patients to recurrent infections. Such patients can present symptoms similar to chronic granulomatous disease (CGD), a known immunodeficiency disorder (Siler et al., 2017; Sun et al., 2022). The deficiency impairs ROS-mediated activation of immune pathways such as the NF-κB pathway, and decreases expression of inflammatory cytokines necessary to mount an effective immune response. This impaired immune activation compromises intracellular bacterial killing and the overall innate immune defense (Sun et al., 2022; Shah et al., 2024).

Increased Risk of Infections and Autoimmune Diseases

Individuals with G6PD deficiency have been observed to have increased rates of various infections. For example, there is a higher risk of infections like hepatitis A and B, likely related to impaired interferon responses and deficient ROS production in immune cells (Shah et al., 2024). Epidemiological data also reveal higher rates of autoimmune disorders among G6PD-deficient populations, including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and others. This suggests that immune dysregulation due to altered NADPH availability may play a role not only in susceptibility to infections but also in autoimmune pathogenesis (Israel, et al., 2023).

Role of G6PD in Immune Cell Function

G6PD plays a pivotal role in the pentose phosphate pathway (PPP), which generates NADPH. NADPH fuels the production of ROS in immune cells, which are critical for: Activation of inflammasomes, particularly the NLRP3 inflammasome, which mediates production of pro-inflammatory cytokines such as IL-1β, and pathogen killing by phagocytes Shah et al., 2024). G6PD is also involved in the regulation of systemic inflammatory responses, including cytokine production like TNF-α and IL-6. Furthermore, it links innate and adaptive immunity through upregulating molecules such as immunoresponsive gene 1 (IRG1) and major histocompatibility complex I (MHC I) expression in macrophages. Consequently, G6PD deficiency can blunt these immune functions, leading to diminished immune responses to pathogens and altered inflammatory signalling (Shah et al., 2024).

Cardiovascular Disease

The relationship between G6PD deficiency and cardiovascular disease (CVD) is complex and somewhat contradictory, with evidence suggesting both protective and harmful roles: G6PD deficiency may reduce coronary artery disease risk in some populations but is linked to hypertension, cardiac dysfunction, and inflammation-driven vascular damage. The outcome likely depending on genetic background, environmental oxidative stressors, and concurrent health conditions

Protective Effects Against Atherosclerosis

Population studies indicate G6PD deficiency may lower CVD risk. A Sardinian study found G6PD-deficient men had fewer cases of coronary artery disease (11.8% in cases vs. 18.6% in controls) and lower cardiovascular-associated mortality during follow-up (Hecker et al., 2013)[4]. Limited NADPH production in deficient individuals might reduce oxidative stress-mediated atherogenesis by lowering lipid peroxidation or inflammatory responses in certain contexts (Hecker et al., 2013; Dore et al., 2021).

Negative Cardiovascular Impacts

G6PD deficiency is linked to elevated blood pressure and premature arterial stiffening in humans and animal models (Hecker et al., 2013; Dore et al., 2021). Experimental data suggest impaired nitric oxide bioavailability and endothelial dysfunction due to oxidative stress (Dore et al., 2021). Severe deficiency increases susceptibility to oxidative cardiac injury, impairing calcium handling and contractility. Case reports associate G6PD deficiency with heart failure in patients with concurrent stressors like sarcoidosis (Drent et al., 2003; Hecker et al., 2013). G6PD deficiency exacerbates ROS-driven inflammation, promoting endothelial adhesion molecule expression (e.g., VCAM-1) and fibrogenesis, which may accelerate atherosclerosis in high oxidative stress environments (Dore et al., 2021).

Mechanistic Contradictions

While G6PD-derived NADPH fuels antioxidant systems (e.g., glutathione regeneration), it also supports NADPH oxidase-generated ROS in immune cells, creating a balance between protection and harm (Hecker et al., 2013; Dore et al., 2021). In low

oxidative stress, deficiency might limit pro-atherogenic ROS. Under high stress (e.g., hypertension, infection), deficient cells become overwhelmed, worsening endothelial damage (Dore et al., 2021). Recent studies have shown that G6PD deficiency is associated with an increased risk of cardiovascular disease (CVD). This is attributed to the activation of the TGF-β/NADPH oxidase/ROS signaling pathway, which promotes endothelial dysfunction and leukocyte adhesion to the vascular endothelium (Parsanathan and Jain, 2020).

Regional and Ethnic Variations in G6PD Deficiency

G6PD deficiency is highly polymorphic, with different mutations predominating in various populations. This variation is thought to have arisen due to the selective advantage G6PD-deficient individuals have against malaria, particularly Plasmodium falciparum (Luzzatto 2015).

G6PD deficiency exhibits significant regional and ethnic variations due to its association with malaria and historical population movements. Here's an overview of these variations. These variations are influenced by historical exposure to malaria, genetic drift, and population migration patterns. The distribution of G6PD deficiency variants also impacts the effectiveness of certain antimalarial drugs, such as primaquine (Howes, et al, 2013).

Regional Variations

1. **Africa**: In areas where *P. vivax* malaria is endemic, such as Ethiopia and Eritrea, the prevalence of G6PD deficiency is relatively low (≤1%). However, sub-Saharan Africa has higher prevalence rates, often linked to the distribution of *P. falciparum* malaria (Ali Albsheer et al., 2021).
2. **Middle East**: Saudi Arabia has one of the highest predicted prevalence rates, reaching up to 32.5%. The prevalence varies significantly across different populations within the region (Howes et al., 2012).
3. **Asia**: High prevalence rates are found in Southeast Asia, with notable hotspots in India (e.g., tribal groups in Orissa), the northern Lao/Thai border, and the Solomon Islands. The G6PD Mediterranean variant is common in Western Asia, including Turkey and parts of India (Howes et al., 2012).
4. **Americas**: Central and South America generally have low prevalence rates (≤1%), except for the Amazon region, where it ranges from 5 to 10% (Ali Albsheer et al., 2021).
5. **Mediterranean**: Countries bordering the Mediterranean, such as Turkey, have a higher prevalence compared to other parts of Europe. The Mediterranean region within Turkey shows the highest prevalence (Sayın et al., 2022).

Ethnic Variations

1. **Ethnic Groups in Asia**: In India, certain ethnic and tribal groups have higher prevalence rates due to consanguineous marriages and genetic isolation (Howes et al., 2012).
2. **Jewish Populations**: Some Jewish populations have a high prevalence of G6PD deficiency, with over 60% affected in certain groups (Sayın et al., 2022).
3. **African Populations**: In the United States, Black males are primarily affected, with a prevalence of about 10% (Ali Albsheer et al., 2021).
4. **Pacific Islands**: The Solomon Islands have a high prevalence of G6PD deficiency, while countries like Australia and New Zealand have very low rates (Sayın et al., 2022).

Common Mutations in Different Populations

- **Mediterranean and African Populations**: The G6PD Mediterranean mutation (563C>T) is the most common variant in these regions, leading to severe enzyme deficiency (Moiz et al., 2011).
- **Asian Populations**: In China, the most common mutations include c.1388G>A, c.1376G>T, and c.95A>G, while in India, G6PD Mediterranean, G6PD Orissa, and G6PD Kerala-Kalyan are prevalent (He et al., 2020).
- **Bangladeshi and Pakistani Populations**: The Ala44Gly and Gly163Ser mutations are the most common in Bangladesh, while in Pakistan, the G6PD Mediterranean variant (563C>T) predominates (Moiz et al., 2011; Sarker et al., 2016).

Genotype-Phenotype Correlation

The severity of G6PD deficiency correlates with the specific mutation and the resulting enzyme activity. For example, hemizygous males with Class I mutations typically have severe enzyme deficiency, while heterozygous females often exhibit milder symptoms due to lyonization (X-chromosome inactivation) (He et al., 2020)

Current Research and Therapeutic Advances

Recent advancements in understanding and managing G6PD deficiency focus on improving diagnostics, developing targeted therapies, and addressing comorbidities. Some of these key developments are:

Diagnostic Innovations

In December 2024, the WHO prequalified the **STANDARD G6PD System**, a semi-quantitative diagnostic tool enabling safer administration of anti-relapse treatments for *Plasmodium vivax* malaria (e.g., primaquine and tafenoquine). This test helps clinicians tailor treatments based on enzyme activity levels, reducing hemolysis risks (WHO. 2025).

Computational and Structural Studies

Advances in computational modeling and structural analysis have provided insights into the molecular mechanisms of G6PD deficiency. These studies have identified key regions, such as the dimer interface and the noncatalytic NADP+ binding site, as critical for enzyme stability and activity (Horikoshi et al., 2021; Chandran et al., 2024).

Mutation Databases and Diagnostic Tools

The creation of databases, such as G6PD-MutDB, has facilitated the identification and classification of G6PD mutations, enabling better genotype-phenotype correlations and improved diagnostic tools (Zhao et al., 2010).

Therapeutic Developments

Development of Small-Molecule Activators

Recent efforts have focused on identifying small-molecule activators to correct G6PD deficiency. For example, the compound AG1, identified via high-throughput screening, and shown to enhance activity and stability of multiple G6PD mutants (e.g., Canton, Mediterranean, A−, wild), offering a potential therapeutic strategy (Hwang et al., 2018). AG1, also reduces oxidative stress in human erythrocytes and zebrafish models, showing promise as a lead compound for pharmacological intervention. It improves cell viability and glutathione levels in fibroblasts with the Mediterranean variant, highlighting its potential to mitigate hemolysis and oxidative damage (Hwang et al., 2018).

Antimalarial Treatments

Research confirms G6PD deficiency protects against cerebral malaria but exacerbates severe malarial anemia. This dual effect informs malaria management strategies in endemic regions (Clarke et al., 2017). The WHO's synchronized prequalification of diagnostics and antimalarials (e.g., tafenoquine) aims to reduce *P. vivax* relapses while minimizing hemolytic risks (WHO, 2025).

Clinical Management Challenges

1. **Cancer Therapy**: G6PD-deficient patients face challenges with chemotherapy due to oxidative stress. A 2024 case report highlighted safe use of docetaxel, cisplatin, 5-fluorouracil, and cetuximab in a nasopharyngeal carcinoma patient, though data remain limited (Hesham et al., 2024).
2. **Comorbidities**:; Meta-analyses suggest G6PD deficiency may increase diabetes susceptibility due to impaired NADPH-dependent vasodilation. Conversely, reduced PPP activity may lower cancer risk by limiting NADPH availability for tumor growth (Ryan, et al., 2021).

Ongoing Research Directions

Over 25 trials are investigating drug safety, diagnostic validation, and pathophysiology in G6PD-deficient populations (Ryan, et al., 2021). These studies are providing evolutionary Insights and exploring how balancing selection (protection from cerebral malaria vs. severe anemia risk) maintains G6PD deficiency prevalence in malaria-endemic regions (Clarke et al., 2017).

Current Clinical Guidelines

While the challenges posed by G6PD deficiency are multifaceted, a comprehensive and integrated approach that encompasses education, dietary interventions, pharmacological therapies, and ongoing research holds great promise for mitigating the risks associated with this condition and enhancing the well-being of those impacted (Hamilton, and Stoimenov, 2024). Primary management remains avoiding oxidative stressors and other triggers (e.g., fava beans, certain drugs). Transfusions remain the only supportive care and are reserved for severe hemolytic anemia, with emphasis on neonatal screening to prevent kernicterus. These advances underscore progress in precision diagnostics and targeted therapies, though challenges persist in managing comorbidities and optimizing treatments for vulnerable populations (Karunarathna et al., 2024).

Conclusion

G6PD deficiency is a complex disorder with significant implications for human health. Understanding the molecular mechanisms underlying this condition, including the structural and functional defects caused by specific mutations, is essential for developing effective therapeutic strategies. Further research into the regional and ethnic variations of G6PD deficiency, as well as the development of small-molecule activators, holds promise for improving the management and treatment of this condition.

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