All India Institute of Medical Sciences Rishikesh (AIIMSR)
Department of Paediatrics

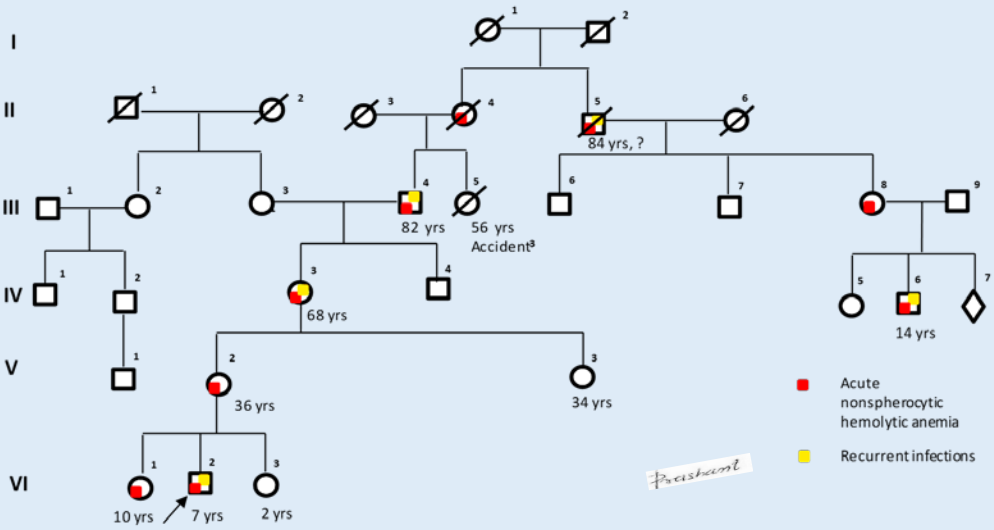
Rishi Vansh

Volume 2, Issue 19, December 2021

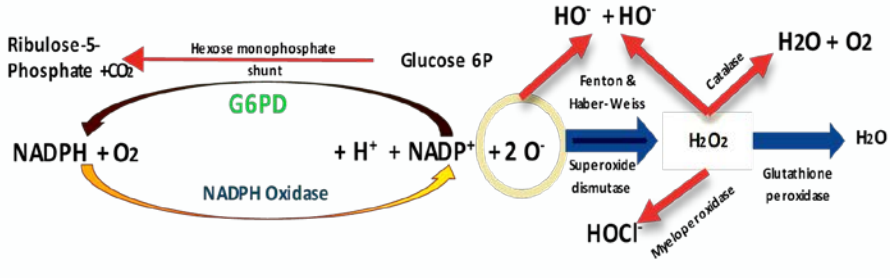
From the desk of Editor

The Department of Paediatrics is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and a deliberate attempt to enhance awareness for genetic disorders with recent updates.

Hereditary disorders of RBCs -**VII: G6PD** (Glucose-6-phosphate dehydrogenase) deficiency



Respiratory burst pathways in the phagocyte system



Insight:

1. How would you diagnose a case of G6PD?
2. What could be the effect of G6PD deficiency on Leukocyte function?
3. What is the Fenton and Haber-Weiss reaction?
4. What is the WHO classification of G6PD variants?
5. What could be the consequences of G6PD deficient blood transfusion to the newborn?
6. What are common genomic variants predominantly reported in India?

Plausible tenets:

G6PD (Xq28) 16,183 bases pairs, 13 exons

Protein: 515 amino acids, 39 domains & features, homotetramer; dimer of dimers, Catalyzes the rate-limiting step of the oxidative pentose-phosphate pathway, which helps in fatty acid & nucleic acid synthesis besides keeping NADPH in reduced state

- **X-linked dominant inheritance; the most common enzyme deficiency in humans; 400** million people worldwide affected; > **400** different biochemical variants reported; majority do not have any **symptoms without triggering factors**
- **Symptomatic Clinical presentation: Hemolytic anemia** in **all ages** & **hyperbilirubinemia** in neonatal age **(20 %** kernicterus **)**
- Selected Type I cases reported with a ***CGD-like** clinical picture due to **impaired respiratory burst in WBCs [<20% (particularly <5%) Reducd G6PD activity shows abnormal bactericidal action]**
- **Diagnosis: Quantitative tests:** Spectrophotometric assay, Flow cytometric analysis (Gold standard); **Qualitative tests** include Fluorescent spot test (FST), G6PD rapid diagnostic test (RDT), Methemoglobin reduction test (MRT) & calorimetric test
- **Treatment- supportive care & removal & stop further exposure for all triggers such as food or drug; blood transfusion if needed & symptomatic management for acute kidney injury, prevent kernicterus in neonates**
- G6PD-deficient RBCs could be hemolysed if transfused accidentlly, especially in preterm new-borns; so need to do G6PD testing before doing exchange transfusion

*The neutrophil NADPH oxidase function requires six protein subunits (p91, p22, p47, p67, p40, and RAC2); any of the five subunit mutations can lead to CGD (**chronic granulomatous disease**)

WHO G6PD variants classification (based on enzyme deficiency & severity of hemolysis) G6PD Phenotypes

Class I: chronic hemolytic anemia with severe deficiency
Class II: severe deficiency with intermittent hemolysis
Class III: intermittent hemolysis with moderate deficiency
Class IV: no hemolysis or deficiency

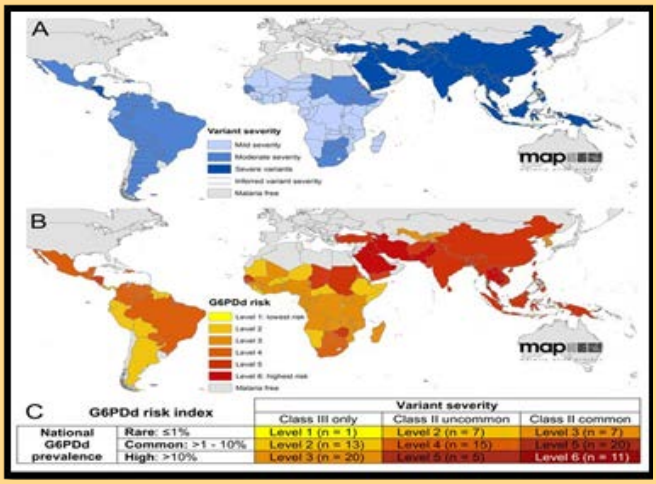
In India, **high prevalence (up to 24.7%) & 11 types are predominantly reported**: Mediterranean(C563T), Orissa(C131G), Gond(G477C), Coimbra Shunde(C592T), Nilgiri (G593A), Ludhiana(G929A), Kalyan-Kerala [G949A], Jamnagar [G949A], Rohini: [G949A], Insuli (G989A) and Guadalajara (C1159T).

Web resources for family with G6PD deficiency: https://www.ihtc.org/G6PD, https://www.g6pd.org/, https://kidsnewtocanada.ca/conditions/g6pd

The most common G6PD variants

Variant	Distribution	The World Health Organization (WHO) Class and specificity
G6PDA+	20% of African-Americans	IV (faster electrophoretic mobility)
***G6PDA−**	10–15% of African-Americans	The most common variant for III, *ONLY old RBCs affected*
G6PD^{B}	Almost all Caucasians & African	IV, wild-type enzyme
***G6PD^{Mediterranean}**	Mediterranean area	The most common variant for II (regional)#
G6PD^{Canton}	Asians	II

* **The most prevalent G6PD variant,** # G6PD^{Mediterranean} has a very short RBCs half-life



Genetic counselling
Inherited X-linked dominant
- Heterozygote's female has cells populations: G6PD (-) >> G6PD (+)
- Homozygous G6PD (-) also quite common in endemic areas

- **Molecular testing needed only for research purposes**

In 1950, First noticed as primaquine induced self-limited hemolysis

In 1956, Carson and colleagues discovered (G6PD) enzyme

Thought Riveting:

- ***Why the white (Europeans) with severe G6PD deficiency suffer from leucocyte dysfunction in comparison to blacks?***
- ***How does mutation of the G6PD gene frequently lead to skewed X-inactivation and symptomatic females?***
- ***What are the additional genetic factors or genetic modifiers for Favism besides G6PD deficiency?***
- ***What is the molecular interaction between G6PD and malaria infection?***
- ***Why not should G6PD testing be mandatory for every blood donation?***
- ***What is the role of G6PD in platelets & endothelial functions? Which pathways would be likely to get affected?***

Author: Dr. Prashant Kumar Verma, Dr. Swathi Chacham, Dr. Manisha Naithani
Reviewer: Dr. Raksha Ranjan, Dr Vinod Kumar