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# GLUCOSE-6 PHOSPHATE DEHYDROGENASE DEFICIENCY

# Physiology of G6PD- Deficiency





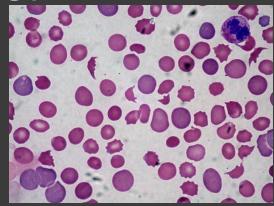


fig 2.



fig 3

- Most common enzyme-deficiency disorder in the world, with rates reaching around 25%
- Indication of symptoms only upon a reaction, or a "trigger"
- Symptoms usually manifest as either neonatal jaundice (infant) or acute hemolytic anemia
- Jaundice is the yellowing of skin and whites of eyes (bilirubin levels exceed normal)
- Hemolytic anemia is anemia stemming from excess hemolysis, which is the rupturing of erythrocytes
- Ohronic Nonspherocytic Hemolytic Anemia can arise, a condition where anemic symptoms can develop even without a "trigger:
- Patients, if correct substances are avoided, are capable of living perfectly normal lives.
- Favism is a specific condition, where fava beans will cause a serious reaction

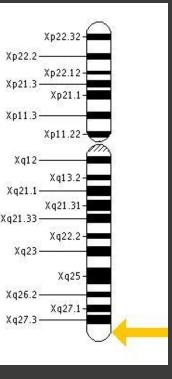


fig 4.

### Molecular Cause

- The G6PD gene is located on the long arm, at position 28
- There are over 400 known variants of the mutation, usually in the form of substitutions or deletions of single nucleotides.
- The most common variant is the G6PD B-, or the G6PD
   Mediterranean variant (also displays most severe symptoms)
- G6PD is the first enzyme in the hexose monophosphate shunt
- This is critical for generating nicotinamide adenine dinucleotide phosphate, which is used to regenerate reduced glutathione
- Reduced glutathione is used to detoxify oxidants created from the interaction of hemoglobin/oxygen, as well as drugs, infection, and metabolic acidosis
- Without the presence of reduced oxidants, oxidative stress is generated, which aggregates Heinz bodies (denatured hemoglobin)

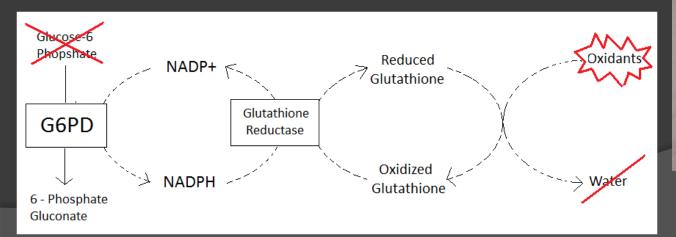


fig 5.

### Current Therapies

- The most common and efficient 'solution' to G6PD-Deficiency is a modified diet
- Hemolytic reactions are not often serious enough to provoke physical manifestation of symptoms
- Symptoms are treated individually; patients with jaundice respond positively to phototherapy and hydration. If symptoms worsen to the point of hemolytic anemia, blood transfusions/resuscitation will be required.
- For babies display neonatal jaundice, frequent feedings are encouraged to facilitate removal of bilirubin through the stool
- Immediate treatment of any open wounds and cuts are also mandatory
- Being aware of <u>all</u> potential triggers is very difficult. Patients with different variants suffer various degrees of G6PD deficiency, hence forth varying degrees of reactions
- Fava beans (the main culprit trigger) is a staple in a number of nations with peaking rates
- Blood transfusions can be very difficult to deliver, as well as a number of complications.

### Proposed Cure & Limitations

- Scientists have managed to utilize retroviral vectors pseudotyped with vesicular stomatitis virus G glycoprotein that harbors complimentary DNA for the G6PD gene.
- Upon transduction in human stem cells, and introducing it to mice for testing, a majority of G6PD-Deficient mice demonstrated a correctedphenotype, with sufficient levels of G6PD created
- Using extracted stem cells from a patient (stem cell aspiration), the cells are to be transduced with the MPSV-G6PD A vector. They are then to be delivered via stem cell transplant.
- A minority of mice (1 of 26 mice did not show signs of G6PD, and 9 out of the other 25 lost expressions within weeks). Applied globally, efficiency and effectiveness of the proposal may be severely flawed.
- In the successful experiments, G6PD expression was only 5-10% of the normal expression rate, but it was enough to relieve the phenotype.
- The successful test results were in respect to a mouse's physiology;
   whether or not sufficient G6PD within a human environment is under question
- Delivery of cells is also dangerous; stem cell transplant has the potential of leading a multitude of complications, including death.

# References

### References Frank, J. (n.d.). Diagnosis and Management of G6PD Deficiency - October 1, 2005 - American

Family Physician. Home Page -- AAFP. Retrieved March 21, 2013, from http://www.aafp.org/afp/2005/1001/p1277.html G6PD Gene - GeneCards | G6PD Protein | G6PD Antibody. (n.d.). GeneCards V3 - Human

Genes | Gene Database | Gene Search. Retrieved March 21, 2013, from

http://www.genecards.org/cgi-bin/carddisp.pl?gene=G6PD Glucose-6-phosphate dehydrogenase deficiency - Genetics Home Reference. (n.d.). Genetics Home Reference - Your guide to understanding genetic conditions. Retrieved March 21, 2013, from http://ghr.nlm.nih.gov/condition/glucose-6-phosphate-dehydrogenase-

Glutathione metabolism and its implications for health. [J Nutr. 2004] - PubMed - NCBI. (n.d.).

National Center for Biotechnology Information. Retrieved March 21, 2013, from http://www.ncbi.nlm.nih.gov/pubmed/14988435

Hemolytic anemia - PubMed Health. (n.d.). National Center for Biotechnology Information.

Retrieved March 21, 2013, from

deficiency

http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001597/

Martin, A. (n.d.). www.bioinf.org.uk: Dr. Andrew C.R. Martin's Group at UCL.

www.bioinf.org.uk : Dr. Andrew C.R. Martin's Group at UCL. Retrieved March 21, 2013, from http://www.bioinf.org.uk/g6pd/db/

Nussbaum, R. L., McInnes, R. R., Willard, H. F., & Thompson, M. W. (2004). Thompson & Thompson genetics in medicine Robert L. Nussbaum, Roderick R. McInnes, Huntington F. Willard; with clinical case studies prepared by Cornelius F. Boerkoel, III. (6th ed.). Philadelphia: Saunders. Ethnasios, R. (n.d.). THE G6PD DEFICIENCY HOMEPAGE. Rialto - Home. Retrieved March 11, 2013, from http://rialto.com/g6pd/index.htm Reference - Your guide to understanding genetic conditions. Retrieved March 11, 2013, from http://ghr.nlm.nih.gov/gene/G6PD

G6PD - glucose-6-phosphate dehydrogenase - Genetics Home Reference. (n.d.). Genetics Home

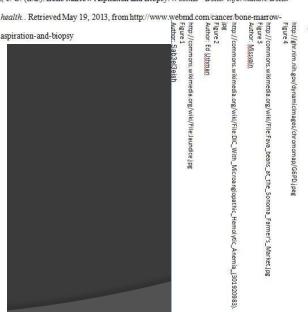
G6PD Deficiency and Favism Information. (n.d.). G6PD Deficiency and Favism Information. Retrieved March 11, 2013, from http://g6pddeficiency.org/

Receiving Your New Cells. (n.d.). Be The Match: Hope for patients with leukemia, lymphoma, blood cancer and sickle cell disease. Retrieved May 7, 2013, from http://marrow.org/Patient/Transplant Process/Transplant Day/Receiving Your New C

ells.aspx

Rovira, A., Angioletti, M., Camacho-Vanegas, O., Liu, D., Rosti, V., Gallardo, H., et al. (n.d.). Stable in vivo expression of glucose-6-phosphate dehydrogenase (G6PD) and rescue of G6PD deficiency in stem cells by gene transfer. Blood. Retrieved May 7, 2013, from bloodjournal.hematologylibrary.org/content/96/13/4111.full.pdf

Biopsies, e. U. (n.d.). Bone Marrow Aspiration and Biopsy. WebMD - Better information. Better



Newborn jaundice: MedlinePlus Medical Encyclopedia. (n.d.). MedLine Plus. Retrieved May 19

2013, from http://www.nlm.nih.gov/medlineplus/ency/article/001559.htm Trials, Viral Vectors and Patient Information. Retrieved May 19, 2013, from

Stem cell transplant: What you can expect - MayoClinic.com (n.d.). Mayo Clinic. Retrieved

http://www.nlm.nih.gov/medlineplus/ency/article/000528.htm