

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PDD)



G6PD Deficiency

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Ned's Med Human Genetics Period 6

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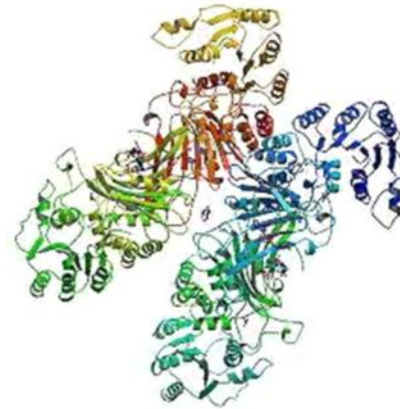
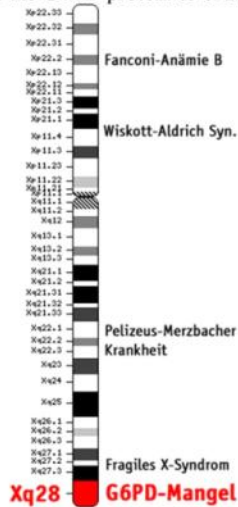
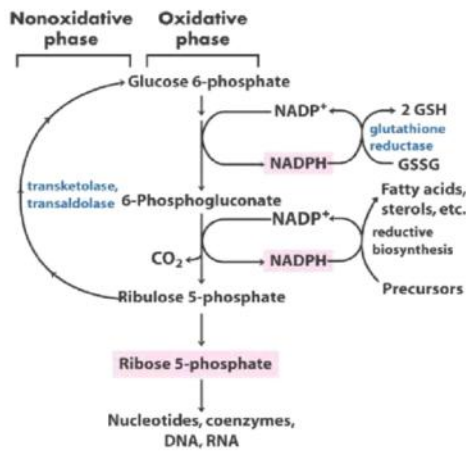
Physiology



- The most common enzyme deficiency in the world, affecting about 500 million people worldwide (approximately 10% of the world population)
- Most people are asymptomatic
- Onset is neonatal
- Any signs of G6PDD are not displayed until RBCs are exposed to certain chemicals in food or medicine. This is a trigger. Three types of triggers:
 - Food induced (aka Favism)- fava beans, other food triggers, depending on your specific mutation
 - Drug Induced- reaction to many types of drugs, but varies. Most commonly, drugs containing NSAIDS (non-steroid anti-inflammatory drug), found in common drugs like Ibuprofen, aspirin, and Tylenol.
 - Infection induced- make sure all cuts and wounds are treated immediately
- There are quite a few symptoms. The more serious cases include Acute Hemolytic Anemia- the self destruction of erythrocytes (fancy way of saying “RBCs start popping”). This first leads to abdominal pain, which a few days later becomes darkened urine and jaundice (the whites of the eyes turn yellow).
- Other symptoms include, but are not limited to: an enlarged spleen, fatigue, paleness, rapid heart rate, shortness of breath.
- Fun Fact: Known to have higher prevalence in places where malaria is an endemic, which is cool because it offers partial protection from malaria.

Molecular Cause

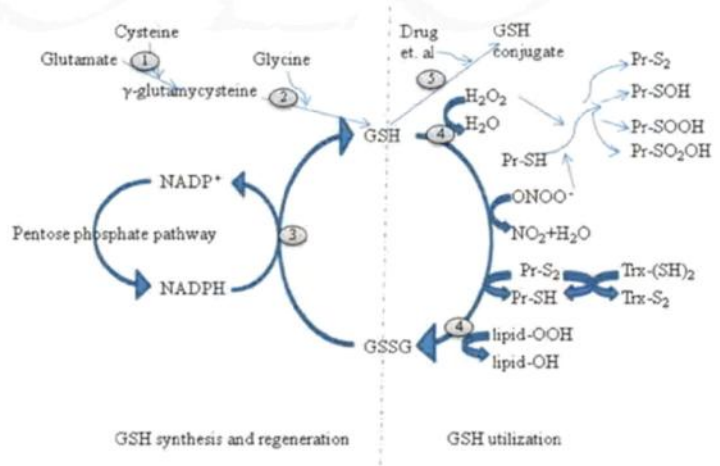
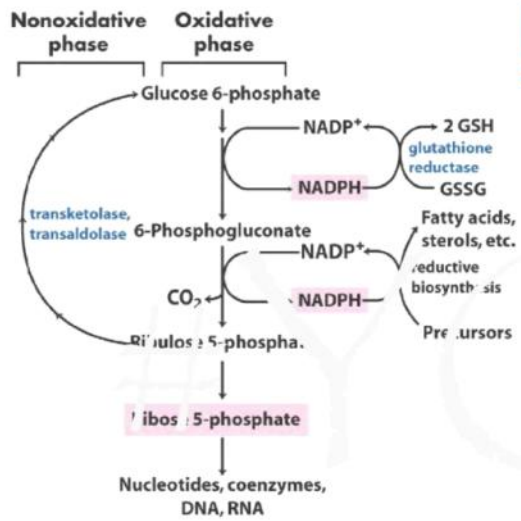
- G6PD gene is on the Xq28 genetic marker of the long distal arm of the X chromosome; it is X-Linked Recessive
- G6PD is the main part of the Pentose Phosphate Pathway, where its job is to oxidize NADP⁺ into NADPH; The disruption of this step prevents the formation of GSH, or the oxidized state of glutathione from GSH, the reduced state
- Glutathione's job as an antioxidant is to give up its electron to free radicals (foreign materials that has an affinity for electrons) to prevent them from disturbing the state of balance in erythrocytes
- For the Mediterranean variant of G6PDD, which is the focus of my project, it is the result of a C-T point mutation at nucleotide 563, which cause amino acid 188 of the G6PD protein to change from a serine to a phenylalanine, there is also a silent C-T mutation at nucleotide 1311





Current Cure or Treatment

- There is currently no cure as of now (Who knows what'll happen in the future?)
- There are a handful of treatments out there, but none of them are all that good
- Avoidance
 - Doctors will tell you to stay away from the triggers which were mentioned previously, like not ingesting any of the triggers, or and taking vaccines against hepatitis A and B that may induce an infection induced attacks
- Limitations of Avoidance
 - Sometimes, people may unknowingly ingest a trigger, and it is nearly impossible to know every single trigger, and this makes the avoidance treatment a little harder to abide by
- Medicinal
 - There are some drugs that have been made, but most of them don't work. The one which remotely works is NAC (N-acetyl-cysteine), derived from the amino acid L-cysteine. My proposal is actually a pursuit of this. (more details given in proposal)
- Limitation of Medicinal
 - NAC only works for a short time, which means that one must take the pills very often.
 - Side effects of NAC include pulmonary arterial hypertension, nausea, vomiting, diarrhea, heartburn, rectal bleeding, and epigastric pain
- Sometimes, blood transfusions may be necessary, and may be an effective treatment. Blood transfusions however run the risk of rejection which presents a death situation for the patient.





Proposed Cure

- Instead of trying to fix the source, I tried to fix the problem.
- The problem isn't not having the G6PD protein, it's that Glutathione is not being produced, which is vital in managing oxidative stress.
- Even though the PPP is the only way of making NADPH (which is used to make Glutathione), there is one other way of making Glutathione: Cysteine.
- This other pathway is rarely used, since Cysteine is a rate limiting factor- not much of it is made in the body. Furthermore, Cysteine is so fragile that it doesn't get past our digestive system.
- However, a recently patented dietary supplement called Immunicol has been made, and it contains cystine, which is basically two cysteines connected with a disulfide bond. This makes it much more stable and it is now able to pass through the body easily.
- Immunicol has whey proteins extracted from raw milk, the source of the Cysteine.
- By raising Cysteine levels in the body, Immunicol also helps increase Glutathione levels, and thus solving the problem of G6PDD.
- Although Immunicol is in the market and doctors can prescribe it to whomever, it has not yet been chosen as an actual treatment for G6PDD.
- Why does this work better than other treatments? It's completely natural, and has close to no side effects, unless you are allergic to milk, or are taking an immunosuppressive in wait for an organ transplant. Also, the use of this supplement is flexible, and can be prescribed based on the severity of an individual's G6PDD.
- Problems of Immunicol may include stomach cramps or bloating, while other rare side effects are rashes, either signifying a detoxification reaction or allergies, both of which will stop with intake.
- One of the better qualities about this treatment, as compared to the cure, is that since you are not affecting the actual disease, if the person had protection against malaria because of the G6PDD then they would still be resistant to it.

