

# Genes in Jeopardy!

USMLE Step 1 Genetics Review Quiz  
By James Winters

Anemia  
Anthem

Guess that  
Cancer!

Inborn Errors  
of Metabolism

Try a  
trinucleotide!

Single Gene  
Jumble

10

10

10

10

10

20

20

20

20

20

30

30

30

30

30

40

40

40

40

40

50

50

50

50

50


Category 1 questions follow



Deficiency in clotting factor VIII (8 for you non-roman numeral barbarians) causes this Hemophilia.

Hemophilia A, because eight is greAt!

Without nine, you won't B fine! (factor 9 is deficient in hemophilia B)



If all your RBC's look like Death's favorite agricultural implement, you have a 2 defective copies of this gene:

Beta globulin, because B comes before C  
(sickle Cell)



In Red Blood Cells  
Oxidative Stress isn't sweet  
If this gene product ain't replete.

Glucose-6-phosphatase makes NADPH, which  
is used to regenerate glutathione. It's energy  
cost is like paying your taxes to pay for cops to  
protect you.



The spleen is the villain of the poor, portly erythrocyte in this structural problem.

Hereditary Spherocytosis. Most are caused by spectrin or ankyrin defects.  
Spectrin forms a *ghostly* outline (structural)  
Ankyrin *anchors*




This one is called an anemia, but the anemia is the least of your problems. Hint: CANCER

Fanconi anemia: This can be caused by a defect in any of 15 genes that are a fan of DNA repair, so watch out for a bad FAN at the CON.

Category 1




Category 2 questions follow




This is a shag carpet that you don't get in your 70's, and it's not from the 70s either. Treatment isn't pleasant; it might leave you with the 2<sup>nd</sup> punctuation mark in this sentence.

Familial Adenomatous Polyposis (FAP) You would need an APC to fit the army of polyps.



A patient presents with tumors: one in the pituitary, one hiding behind his thyroid, and a biggy hiding in the head by his stomach.


MEN1: besides the three P's (pituitary, parathyroid, and pancreas), the locations form a "diamond" and you want 1 man (MEN1) to give you a diamond



Pheochromocytomas occur in these two MEN2 syndromes: this differentiates them. And a second working copy of this gene would *rectify* either condition.

In MEN2A, you get A pair a' pairs (adrenals and parathyroids come in pairs

In MEN2B, you B marfanoid, and cancer can B in your mouth and medullary thyroid



When you have cancer everywhere you see,  
you should be thinkin' about this fast food  
joint and gene.

RB gene in retinoblastoma



Brain Tumor Blitz!

One likes twos:

ears, cataracts, gene names and chromosomes

This one marks your skin like you spilled café coffee


It sounds like a German demolition company

Neurfibromatosis Type 2: NF2 on chromosome 2

Neurfibromatosis Type 1: Café-au-lait spots/ tumors

Von Recklinghausen


Category 3 questions follow



After falling through a time portal into Appalachia, you encounter untanned individuals whose urine smells “musky.” Identify the disorder, and please explain why you are smelling someone’s urine while dueling banjos play eerily.

Phenylketonuria: Because if you smelled musky urine, your initial reaction would be “Pee-Kay-Uuuu” (PKU) Lighter skin color because tyrosine (produced from phenylalanine) is required for melanin

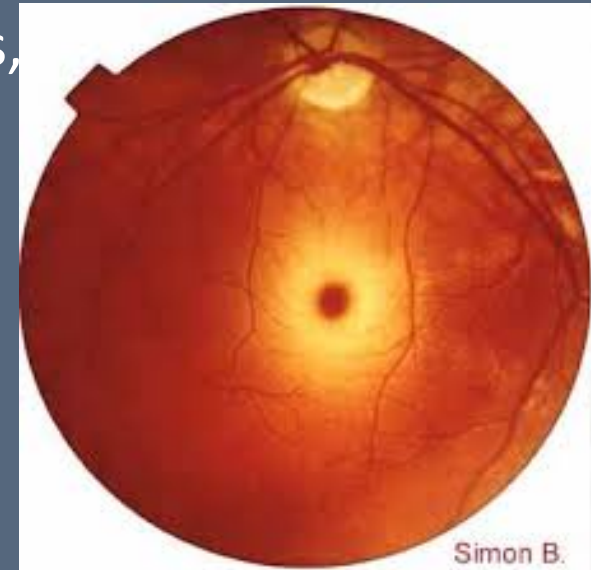




While examining a child whose physical and mental delay is notable, your whiff of their urine sample transports you to the northeast, and fills your mind with images of red forests in fall, and delicious pancakes. What enzyme in the patient caused your urine-induced trip down memory lane?


Branched chain  $\alpha$ -ketoacid dehydrogenase, without which valine, leucine, and isoleucine produce ketoacids that produce the enchanting smell of Maple Syrup Urine Disease

After being healthy for six months, a child of jewish descent begins losing developmental milestones. Fundoscopic exam reveals what you see here.




Tay-sachs disease: when the Red Dot Tie and Sock gang have the nerve to be premature.

Haiku-ish:  
red dots in eye,  
nerves prematurely die,  
gangliosides



A child who had been previously happy has experienced nausea, vomiting, and lethargy after the mother attempted to introduce baby food into her child's diet. The child had previously taken the infant cereals without problem. State the child's problem, and what accumulates in the child's cells.


Hereditary Fructose Intolerance  
Fructose-6-phosphate accumulates due to  
aldolase B deficiency



A child has a history of nervous system impairment (delayed sitting up, never learned to walk or crawl). He has already suffered from a kidney stone. The patient is now 3 years old, and his parents are concerned because he has started harming himself. State his disease, and the biochemical cause.

Lesch-Nyhan syndrome, caused by a defective purine metabolism (hypoxanthine-guanine phosphoribosyltransferase or HGPRT)  
Kidney stone results from uric acid


Category 4 questions follow



This condition is associated with a fragile version of something half the population doesn't have a backup for.


Fragile X syndrome.

At least Kaplan loves to use this condition to ask how you would confirm. Answer: test for trinucleotide repeat. It is associated with macroorchidism, hand-flapping, and a fragile-looking X chromosome on cytogenetic analysis, but just look for the cause.



A patient comes to you worried about his chances of having Huntington's disease. Given a family history of Huntington's disease, state what you should anticipate about the age of presentation. Bonus if you can name the part of the brain most affected, and what pathway "gives out"


Genetic anticipation is a classic feature of Huntington's disease, and the expected age of onset is lower in each subsequent generation. Protein is Huntingtin, and the gene is found on chromosome 4 ("Hunt" has four letters.) Remember Buzzword in neural imaging: "Boxcar caudate" signifies an atrophic, flattened caudate. Indirect pathway is affected



This trinucleotide repeat disorder is the New Mexico favorite, with a classic presentation in the patient's fifties, with an initial presentation of ptosis, dysphagia, and dysphonia.


Oculopharyngeal Muscular Dystrophy (OPMD)  
caused by expansion of a polyalanine tail  
Fun fact: Phase 2/3 clinic trials are actually starting for a drug to treat this condition.





An 11 year old patient presents with “sloppy writing and walking problems”, and had previously been diagnosed with a hypertrophic cardiomyopathy. State the name of the disease, and what defective protein is no longer able to iron out the problem.

Friedreich’s Ataxia is caused by a defect in frataxin (just take the name and mash it into a protein name and you’re good. Frataxin removes iron from the cytoplasm around mitochondria. Remember: “I don’t have the heart to stand with an iron in my hand.”



You question why you didn't choose to be a clinical geneticist as yet another patient comes to you. He is balding early, complaining of excessive daytime sleepiness that is interfering with his ability to work. He has cataracts, and was recently diagnosed with a complete heart block. His complaints include difficulty chewing and swallowing. Name the disease that is driving you to consider a genetics residency.

Myotonic Muscular dystrophy: caused by a defect in the gene DMPK. "I want to sleep because I feel DuMPpy, K?"


Category 5 questions follow



You are accosted by this mighty knight, whose short stature, prominent forehead, flattened nasal bridge, and shortened proximal limbs. Can you diagnose his condition before he cuts you down with his razor-sharp wit?


Achondroplasia, caused by a mutation in Fibroblast growth factor receptor 3 (FGFR3) To remember try: Fumbling Growth, Flattened Ridge (FGFR) 3 is for trident hand






You encounter a patient with marked hypopigmentation, astigmatism, and irregular rapid eye movements, but without any signs of developmental deficits. Name the disorder, and explain which molecule they can't produce, and why it make them as white as winter.

Albinism! Can't make melanin from tyrosine, so you can see hypopigmentation in PKU, and in Angelman and Prader-Willi syndromes (One causative gene for albinism is located in the affected region of both)




A young man presents at an infertility clinic because of difficulty conceiving with his wife. He has had multiple bouts of sinus infections, bronchitis, and ear infections. You go to listen to his mitral valve heart sounds, and hear clear lung sounds (you are listening in the correct location). Name that syndrome, and the affected cellular structure.

Primary Ciliary Dyskinesia (PCD), or Kartagener's syndrome. Bonus: what are the chances of someone with this syndrome having situs inversus



A child is brought into the emergency room with his fifth broken bone in the past 2 years. The presence of what finding on the HEENT exam would steer you away from Abuse?

Blue sclera. It is a sign seen with MOST types of Osteogenesis Imperfecta due to the thinning of the sclera, revealing the network of veins underneath. To remember: “You would be blue if your bones broke too.”



A patient comes to you with a complaint of headaches and vomiting. She also reports a mild hematuria the past couple months. At birth she was diagnosed with a rhabdomyoma in her heart. She had multiple light areas on her skin that were shaped like ash leaves, and that's why her parents named her Ashley. She reports that when she was a teenager, the rhabdomyoma resolved. MRI reveals dilated ventricles, caused by a giant cell astrocytoma, along with multiple angiomyolipomas in her kidneys. Name her condition, and the two proteins associated with it.

Tuberous sclerosis, and the affected proteins are hamartin and tuberin, both tumor suppressors.



## Outline:

- Glucose-6-phosphate dehydrogenase Deficiency
  - In red blood cells, the glucose-6-phosphate dehydrogenase is necessary for producing NADPH, which is used to reduce glutathione. Reduced glutathione is used by the enzyme glutathione peroxidase to detoxify hydrogen peroxide.
  - Normally, things work well enough for cells to get by. Until you whack the system with an oxidative stress, then the cell can't keep up with the oxidative damage
  - Massive oxidative damage builds up, hemoglobin precipitates out into Heinz bodies, that then gets shredded by the spleen.
  - End Result: Boom! Hemolytic anemia from oxidative stress
- Retinoblastoma
  - RB is an important regulator of the cell cycle. It is regulated by Cyclin D, which is expressed when a cell is cycling from S to G1. RB holds onto the transcription factor E2F, preventing it from initiating transcription of S phase genes. The importance of RB in controlling the cell cycle by preventing inappropriate initial of entry into the cell cycle makes it a gatekeeper gene.
  - Bilateral retinoblastomas indicate an inherited germ line mutation, as opposed to a spontaneous mutation
- Fanconi Anemia
  - It's called an anemia, but it is named because it was identified as an inherited syndrome in which bone marrow production is disrupted by a leukemia or a myelodysplastic syndrome. It is mostly recessive, and thus precipitated by homozygous or doubly heterozygous mutations in any of 15 genes (including BRCA2). It can also cause a variety of birth defects ranging from short stature to skeletal, craniofacial, cutaneous, and genitourinary.
  - 75% of patients with this condition have at least one birth defect.
- Phenylketonuria
  - Most common inborn error of metabolism
  - Caused by a mutation in phenylalanine hydroxylase
  - Associated physical findings in untreated patients
    - Fair hair and skin (impaired melanin synthesis)
      - Phenylalanine → Tyrosine → melanin
    - Intellectual disability
    - "Musty" or "mousy" odor, especially in urine
- MSUD
  - Caused by defective branched-chain  $\alpha$ -ketoacid dehydrogenase, which is required for the breakdown of valine, leucine, and isoleucine. The buildup of these amino acids, along with their  $\alpha$ -ketoacid breakdown products, causes the patient's urine to smell like Maple Syrup.
  - Results in mental and physical retardation.
- Hereditary Fructose Intolerance
  - Caused by defective Aldolase B enzyme function, which results in a buildup of Fructose-1-P inside the cells, causing damage.

- Winds up sucking up a good portion of the phosphate in the affected cells.
- Tay-Sachs
  - Caused by defective HEXA gene, which results in a defect in ganglioside metabolism. Gangliosides accumulate in nerves, causing developmental delay, and accumulation in the eyes around the retinal fovea, resulting in a “cherry-red spots” on fundoscopic examination.
- OPMD
  - Trinucleotide repeat expansion causes a polyA tail on the nuclear poly(A) binding protein PABN1. This causes accumulations in muscle cells, which causes the cells to eventually die. On biopsy, muscle cells are replaced by fat.
  - Normally presents in 5<sup>th</sup> decade of life.
- Myotonic Muscular Dystrophy
  - Caused by a trinucleotide repeat in DMPK gene.
  - Causes difficulty in breathing, and is the muscular dystrophy with the most prominent sleep disorders, which includes excessive daytime sleepiness.
- Achondroplasia
  - Caused by a “gain of function” mutation in the FGFR3 gene, which is a negative inhibitor of bone growth.
  - Causes short stature, rhizomelic (“of the root” referring to proximal limb) shortening, macrocephaly, “trident hands” (Fingers widely opposed and of equal length), and a depressed nasal bridge.
- Albinism
  - Caused by an inability to produce melanin in the skin, but it mainly complaints regarding problems in the eyes.
  - Lack of melanin in development can cause almost all axons originating in the eye to cross over, as opposed to the normal 50/50 split.
  - Photophobia and decreased visual acuity result from light scattering in the eye that would normally be absorbed by melanin.
  - Relies on tyrosine as a precursor for melanin, so disorders (such as PKU) cause light skin and hair due to decreased availability of tyrosine for conversion to melanin.
  - Also more prone to sunburn.
  - One protein necessary for melanin production is located in the 15q11-13 chromosomal area associated with both Angelman and Prader-Willi syndromes. Hypopigmentation is associated with both.
- Osteogenesis Imperfecta
  - Genetic bone disorder associated with brittle bones and blue sclera.
  - History of multiple bone breaks in childhood more commonly caused by child abuse, not this rare disorder
  - Most common form is caused by decreased production of normal type 1 collagen.
  - Blue sclera is caused by the thinning of connective tissue revealing the choroid veins inside the eye.
- Tuberous Sclerosis
  - Associated with hamartomas (non-neoplastic tumor-like malformations)
  - Associated with Ash leaf spots and cardiac rhabdomyomas at birth

- Seizures, autism, and developmental delays associated with this disease present in infancy or childhood
- Facial angiofibromas (which can be mistaken for acne) originate in childhood or adolescence.
- Can cause subependymal giant cell astrocytomas (almost exclusive to tuberous sclerosis), which can cause an obstructive hydrocephalus
- Renal angiomyolipomas associated with this syndrome can present with hematuria.

Sources:

First Aid for Step 1 2014

Dr. Linda J. Butros's Retinoblastoma lecture from November 1, 2013

Dr. Rebecca Hartley's Cell Proliferation and cell cycle lecture from October 24, 2013

Medscape article on Fanconi Anemia at <http://emedicine.medscape.com/article/960401-overview#a0101>

Medscape article on Phenylketonuria at <http://emedicine.medscape.com/article/947781-overview>

Dr. Osgood's Amino Acid metabolism lecture from September 25, 2014

Dr. Heindenreich's lecture on Trinucleotide repeat disorders from the first week of genetics

Laberge L, Gagnon C, Dauvilliers Y. Daytime sleepiness and myotonic dystrophy. Accessed on pubmed at <http://www.ncbi.nlm.nih.gov/pubmed/23430686>

Achondroplasia Clinical presentation on Medscape at <http://emedicine.medscape.com/article/1258401-overview>

Achondroplasia Imaging on Medscape at <http://emedicine.medscape.com/article/415494-overview#a19>

Dr. Tom Cushing's Lecture Autosomal Inheritance and Disorders from the first week of Genetics

Albinism article from Medscape at <http://emedicine.medscape.com/article/1200472-overview>

Prader-Willi syndrome from Medscape at <http://emedicine.medscape.com/article/947954-overview>

Tuberous sclerosis article from Medscape at <http://emedicine.medscape.com/article/1177711-overview>