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HST.161 Molecular Biology and Genetics in Modern Medicine
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Lecture 6

Population Genetics, Hemophilia

Today's lecture returns to some of the material covered on Friday.

- Mutations that affect globin genes
- Population genetics calculations

Mutations:

- many mutations described in thalassemia
- alter function of either alpha or beta globin genes
- why are there so many? (strong selective pressure in areas afflicted with malaria, for one thing)

Normally, there are two β -globin genes (inherit one from each parent) and 4 α -globin genes (inherit two from each parent)

Nomenclature:

- β -thalassemia with both alleles affected: "thalassemia major"
- more minor phenotype, typically one allele affected: "thalassemia minor"
- α -thalassemia: when $\frac{3}{4}$ globin genes are missing/affected \rightarrow Hb H disease
- α -thalassemia: when $\frac{4}{4}$ globin genes are affected \rightarrow hydrops fetalis: mostly born dead, i.e., lethal
- one missing: silent carrier, two missing: "alpha thalassemia trait" (phenotype: microcytosis – abnormally small red blood cells)

Most common mutations:

- mutations that mess up splicing: changes what sequences are exons and what are introns. Can cause complete lack of β -globin creation.
- point mutations and deletions also happen
- mutations can happen in many places: promoter, 3' UTR, or poly-A site, for example. Also, the TATA box, upstream CCCC site, 5' cap, expression regulators.
- Deletion of β -globin gene can actually be better than a point mutation; gamma chain genes stay on, then

Population Genetics:

- balanced polymorphism
- Hardy-Weinberg equilibrium (large population, no mutation, no selection, random mating, no migration \rightarrow allele frequencies remain stable, predictable)
- Selection and assortative mating mess up H-W equilibrium
- Lethal events select against aa genotypes, especially over a lifetime
- Balanced selection: deviations from H-W happen in both directions (AA's and aa's), leaving the heterozygotes on top. These end up repopulating (to some extent) the homozygous classes.

- Reproductive fitness: proportion of individuals in that genotype class at the time of mating and their relative effectiveness at reproducing = proportion of offspring compared to “normal”

Malaria:

- Four types: *P. vivax*, *P. malariae* and *P. ovale* cause serious illness but not as much death as the fourth, *P. falciparum* (*P.* = Plasmodium)
- Does best in warm, wet areas
- Infection by *P. falciparum* causes RBCs to develop “knobs” which cause them to stick to endothelial walls and cause all kinds of devastating problems
 - o Immune response is not terribly effective; repeat infections possible.
- High frequency of α -thal and β -thal alleles in *different* areas with falciparum malaria (see maps in slides, pp. 45-46)

Why do different human pops have different allele frequencies for many genetic loci?

- genetic drift
- founder effects
- mutation
- selection

Genetic Drift:

- If you have a small population size, you can lose alleles relatively quickly; you can lose alleles by chance

Guest Lecturer: Ellis Neufeld

X-linked genes

Hemophilia is a defect in the blood clotting cascade.

Blood clotting cascade: Factors 1 - 11

Overview of Hemophilia:

- scope of the problem: Factor VIII deficiency seen in 1:5000 male births, Factor IX deficiency is a 10-fold less common
- Clinical picture in 21st century: Hapatitis C is major killer of adults (contracted HepC via blood clotting factor transfusions to treat hemophilia – this was before we could test for hepC in the blood supply). For children, the risk of inhibitors is the biggest problem.
- Standard treatment: joint bleeds, preventative bleeds and factor replacement
- Gene therapy?

Sex-linked inheritance wasn't that hard to figure out; see Queen Victoria's pedigree! (p. 7)

In some cases the mother is not actually a carrier; the mutation is NEW. About 1/6 of the time when only one child is affected, this is the case.

Joints/synovitis: proliferation of synovium, erosion of the cartilage, symptoms similar to osteoarthritis. The lining can get pinched, and bleed a lot in hemophiliacs.

Treatment: infusion of the missing factor (most commonly, Factor VIII)

- factor is very expensive
- different half-lives
- rare patients make inhibitors to exogenous factor