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HST.161 Molecular Biology and Genetics in Modern Medicine
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Lecture 10

Williams Syndrome

Williams Syndrome

Lecturer: B. Pober

- uncommon (1/10,000)
- microdeletion (1.5 Mb, loss of ~23 genes) on chromosome 7q11.23
- model disorder for genotype-phenotype correlations
- unique developmental disorder; characteristic physical and cognitive abnormalities and traits

- 1961, 1962 Dr. Williams and Dr. Beuren independently noted 4 and 12 cases (respectively) of the syndrome

Cardiovascular pathology

- Problem causing greatest morbidity is cardiovascular pathology (e.g. supravalvar aortic stenosis (SVAS) and other stenoses)
- overgrowth of smooth muscle cells lining the blood vessel; creates extremely narrow passage for the blood

Cognitive Profile

- mean full-scale IQ is 55-65 (mild to moderate mental retardation)
- have a pattern of strengths and weaknesses:
 - o strengths: language skills, fund of knowledge, long-term memory, face processing; musicality
 - o weaknesses: visual-spatial processing (handwriting, folding laundry, etc); fine motor skills; problem solving; abstract reasoning; arithmetic
- “verbal high, spatial low”
- Profile suggests a selective sparing of neural pathways

Behavioral features:

- charming
- empathic, sensitive
- musical
- outgoing, disinhibited – hypersocial
- attention problems, hyperactive
- phobias
- anxiety, depression, social isolation

Cause:

- abnormal vitamin D or calcium metabolism in mother
- teratogenic exposure

- chromosomes look normal in WS
- Low copy number repeats predispose the region to the chromosomal deletion
- linkage analysis revealed the location of the mutation

- they looked for elastin mutations, due to the CV pathologies, and didn't find it because WS patients have normal elastin from one chromosome, and no elastin from the abnormal chromosome (since it's a deletion)
- official diagnosis is by FISH – chromosome 7 centromere-specific tag with an elastin probe; By FISH, see two 7 centromeres but only one elastin, because other one is deleted = WS
- looks like autosomal dominant; most WS patients don't reproduce (they're not infertile; it's usually a choice)

Genotype-Phenotype Correlation:

- Some patients have an “atypical” deletion, a smaller deletion.
- Elastin knockout mice models have been made
- There are some hypotheses about the loss of which genes causes what phenotypes, but not much is known, other than the loss of elastin causes the SVAS
- Patients can have duplication of the WS genotype, and yet they don't exhibit the same phenotype; in fact, some phenotypical traits can be almost the opposite (e.g. instead of being verbally expressive, they have speech *impediments*)
- “sum may be greater than the total of the parts” with respect to the genotype-phenotype correlation

End of Guest Lecture

Chromosomes Part II by Anne

FISH: fluorescence in situ hybridization. Denature chromosomes, use fluorescently labeled probe that hybridizes to the chromosomal DNA.

- Quick, since you can do this on uncultured cells; you can do this test overnight
- Gives much better resolution than looking by eye; FISH lights up sequences that are a couple of kb long; by eye you can only see a few Mb.

Whole Chromosome Paint: chromosome-specific “paint” that will color all DNA from a particular chromosome (so you can look for rearrangements, and find pieces of one chromosome on a different chromosome). This is very similar, molecularly, to FISH, except that the probes comprise the whole chromosome instead of being only centromere-specific and gene-specific.

Multicolor FISH (M-FISH) or Spectral Karyotyping (Sky): like whole-chromosome paint, for all chromosomes, with all chromosomes fluorescing in different colors. This makes karyograms easy to organize.

Rainbow FISH (Rx): paints chromosomes in a rainbow of colors that shows different bands in the chromosomes, so instead of matching by single colors to match chromosomes, you match the rainbow pattern on chromosomes; it's not much easier than matching chrom's regularly.

Deletions:

- aka contiguous gene syndromes, segmental aneusomy syndromes
- phenotype is dependent on the number of genes deleted and on the functions of the genes

Most deletion syndromes actually have a lot of the same characteristics (facial characteristics, mental retardation, etc.), and these characteristics are somewhat variable.

Chromosome rearrangements are mediated by “low copy repeats” (just a few copies of sequences located relatively close to each other, as opposed to “high copy repeats,” of which there are thousands spread throughout the genome).

Ring chromosomes: formed by breakage of arms and subsequent linkage at the break points, with loss of genes on distal ends of chromosomes

Fragile sites: look like an unstained region (constriction) on the chromosome. Everyone has fragile sites; these by themselves don't cause a phenotype.

- Only 3 fragile sites associated with pathology; >100 fragile sites exist normally.
- May be implicated in cancer.

X and Y chromosomes:

- Females have 2 copies of X, males have XY. The Y chromosome is solely responsible for creating a male.
- Females should have only one active X chromosome, otherwise they'd have twice the amount of chromosomes as males and that would be abnormal; so, the X chromosomes have an inactivation site. Inactivation is random and occurs in each cell, so typically about half the mother's and half the father's X chromosomes will be inactivated.
 - o Sometimes X chromosomes can escape inactivation; causes abnormal phenotype.

Frequencies of sex chrom aneuploidies:

- 1/400 – 1/500 liveborns
- Most common: 47,XXX, 47,XXY, 47,XYY (each are about 1/1000 of their respective sex)
- Turner syndrome: 45,X (1/5000 females)

Klinefelter syndrome: 47,XXY or 47,XXXY: phenotype gets more abnormal with more X's. Treatment with testosterone from an early age can help immensely.