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HST.161 Molecular Biology and Genetics in Modern Medicine
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Lecture 21

Complex Traits

How do you figure out genetics are involved if you don't see a Mendelian pattern?

- twin concordance *could* work but wouldn't always (i.e. childhood leukemia – twins who have leukemia in the first few years of life share a chromosome translocation that underlies childhood leukemia (possibly due to transference of hematopoietic stem cells during their time in the womb together), but perhaps only one of them, or both but at different times, obtain the second hit that causes them to actually develop leukemia)

Genome-wide scans for complex trait genes:

- how to do linkage analysis without Mendelian patterns? = Affected sib-pair method
- must use higher threshold than normal ($p = 0.001$, $LOD = 3$) when doing a genome-wide scan; otherwise, you'd get at least one "linkage" by chance

Hereditary Breast Ovarian Cancer

Guest lecture

Mutations: BRCA1 and BRCA2

- BRCA2's age-of-onset is shifted later but ends up similar for development of breast cancer; much less risk of ovarian cancer than with BRCA1 mutation
- Penetrance can be modified:
 - o Genotypic variation
 - o Modifier genes
 - o Lifestyle, exercise
 - o Reproductive factors: multiparity, age at 1st pregnancy (younger=better, older=increases risk), oral contraceptive use (reduces ovarian cancer risk)
 - o Oophorectomy, HRT, other hormonal modulation

Fanconi Anemia, type D1

- mutation found in BRCA2
- (most Fanconi Anemia subtypes have nothing to do with breast cancer)
- This particular pathway of disease development may help us gain insight into breast cancer in general

MRI better than mammograms at detecting breast cancer in young women, since the breast tissue is dense.

Hormone treatments after a hysterectomy actually increase risk (contraceptives reduce risk in younger women due to stopping the ovulation cycle; this does not apply after a hysterectomy)

Lactation – especially if at a younger age – is protective. Number of pregnancies is not terribly significant.