

Genetics & Genomics: The Real Base of Evidence-Based Nursing Practice

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TNA Convention

October 2010

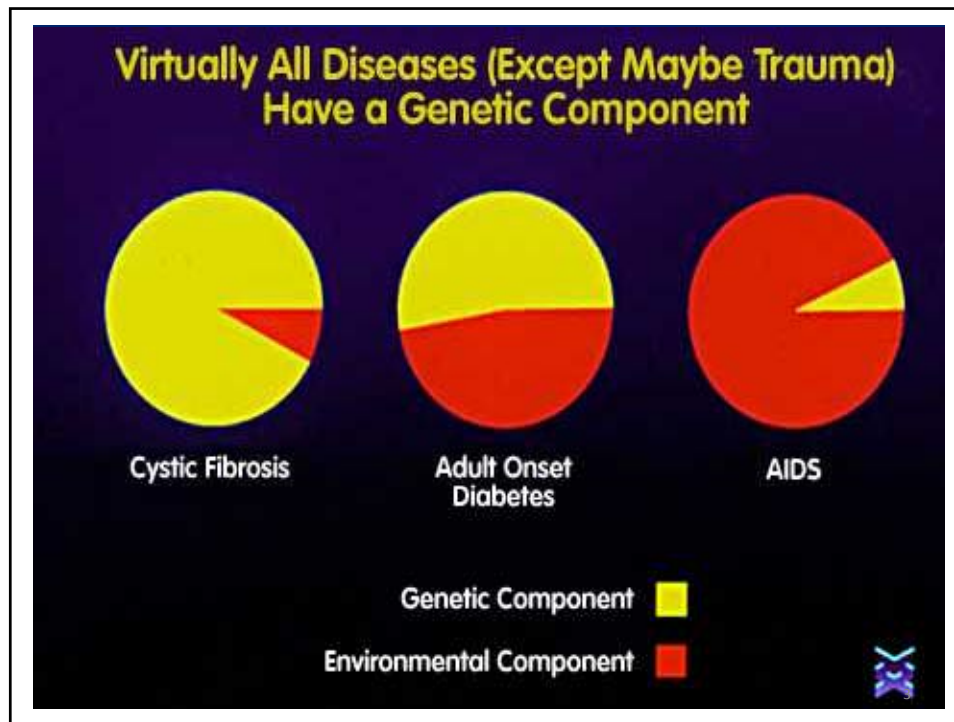


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I'm not a genetics nurse, so why should I know about genetics?

- “Genomics will be to the 21st century what infectious disease was to the 20th century for public health” (Gerard, Hayes, & Rothstein, 2002)
- Patients with childhood genetic diseases are living longer and will have the usual health problems of adults
- Drug metabolism is affected by genetic differences in liver enzyme networks: Plavix!

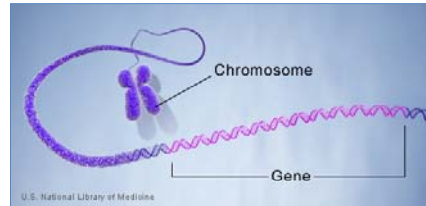
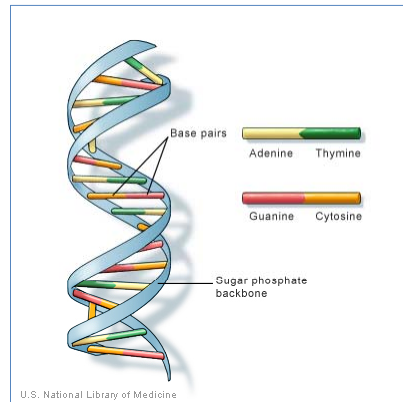
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Speaking the Language: Terminology

- Genes are the structures that carry the instructions for all our inherited traits, and a gene is a segment of DNA
- Genetics is the scientific study of heredity, which is the passing of traits of all kinds from biological parents to their children
- Genome is the entire set of genetic instructions found in a cell
- Genomics is the study of the organization, function, and evolution of the genome
- DNA (deoxyribonucleic acid) is a double helix macromolecule that is the primary carrier of genetic information: recipes for our proteins
- Chromosomes are made up of tightly-wound DNA

DNA, Genes and Chromosomes



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- **Locus**: place on a chromosome where specific genes are arranged in a linear fashion to encode for a particular protein (their address on the chromosome)
 - Example: the locus for eye color
- **Allele**: alternative forms of a gene
 - Example: at the locus (“address”) for eye color, I have one allele for blue and one allele for brown

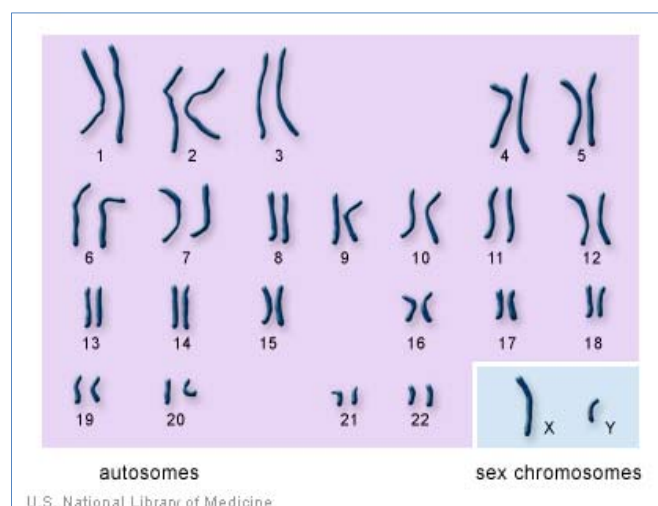
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Chromosomes

- 22 pair of autosomes: non-sex chromosomes common to both sexes
- 1 pair of sex chromosomes: XX or XY
- Normal human chromosome number in most somatic (body) cells is 46 (23 pair): one of each pair from the mother and one of each pair from the father
- Gametes (ova and sperm) contain 23 chromosomes (22 autosomes + 1 sex chromosome): ready for fertilization

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Normal Human Male Karyotype: 46,XY



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- Genotype: an individual's genetic makeup
 - E.g., XX = genetic female
- Phenotype: physical traits produced by the genotype
 - E.g., smaller features, breast development, less musculature are characteristics of the female phenotype and the genotype XX
- Some genetic shorthand
 - 46,XX: normal female with a total of 46 chromosomes, two of which are X chromosomes
 - 46,XY: normal male with a total of 46 chromosomes, one of which is an X chromosome and the other of which is a Y chromosome

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Mutation

- Definition: A change (usually permanent) in DNA
- Occurs during the process of cell division: mitosis or meiosis
- Can occur spontaneously or after a cell is exposed to radiation (even UV light), certain chemicals (like alcohol), or viruses (think about the human papillomavirus [HPV] being a risk for cervical cancer)
- Mutation is carried forward in the mutated cell's offspring

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INHERITANCE PATTERNS

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Single-Gene Disorders

- Often called Mendelian traits from work by Austrian monk Gregor Mendel in his studies of garden peas in 1860s
- What happens? An error occurs at a single gene site on the DNA strand and then the error becomes part of the pattern from which copies are made
- Single-gene disorders are inherited in clearly identifiable patterns

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Patterns in Single-Gene Disorders

- There are 4 basic, clearly-identifiable patterns of single-gene inheritance
- Most hereditary disorders are caused by mutations in the autosomes

	Dominant	Recessive
Autosomal	Autosomal Dominant	Autosomal Recessive
X-linked	X-linked Dominant	X-linked Recessive

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Punnett Square: Used to Depict Single Gene Disorders

	B	b
b	Bb	bb
b	Bb	bb

B = brown eyes (dominant), b = blue eyes (recessive)

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ROLE OF FAMILY HISTORY & PEDIGREE CONSTRUCTION

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Why is it Important?

- To identify conditions in families that may be inherited and require further follow-up
- To assist in risk assessment for particular conditions that have a genetic basis
- When the condition is in a child, the parents need information about future childbearing
- Immensely useful in general practice as well as specialty practice
- Newborn screening is revealing information that parents need to know about: CF (a single gene disorder) is included in Tennessee's newborn screen, for example

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What Should It Include?

- 3 generations: grandparents, siblings, half-siblings, parents, offspring, aunts, uncles, and cousins
- Racial, ethnic, and country-of-origin information
- Age and cause of death of deceased individuals
- Presence of birth defects, intellectual and developmental disabilities, familial traits, and similarly affected family members

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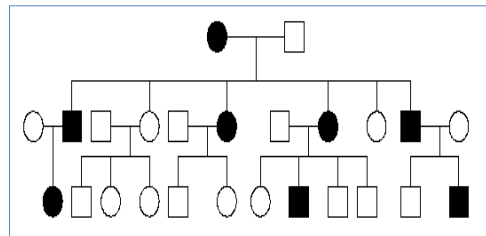
Pedigree

- A pictorial representation or diagram of the family history
- Allows visualization of relationships of affected individuals
- Can make clear the pattern of inheritance in a specific family
- Unfortunately, there is no formal standard for symbols ☹️

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What to Look For in the Pedigree?

- Consanguinity (matings between blood relatives; usually only those closer than first cousin are genetically important)
- Male-to-male transmission
- Female-to-male transmission
- Whether males and females are affected in equal numbers
- Look for the trait to appear in subsequent generations



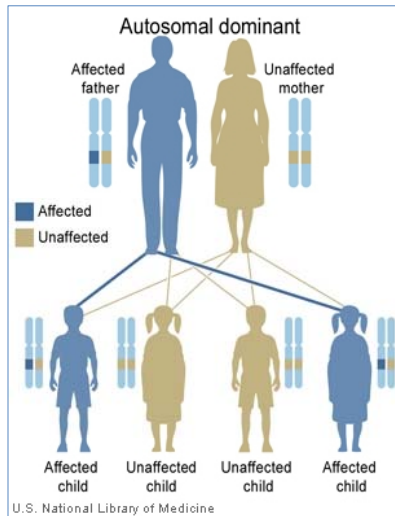
Autosomal Dominant Pedigree

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Characteristics of Autosomal Dominant Disorders

- Males and females have equal risk to inherit the disorder since the affected gene is on an autosome
- Since the trait for the disorder is dominant, the condition occurs in heterozygotes (Bb) as well as homozygotes (BB)
- There's a 50% risk for each child to inherit the mutated gene from the affected parent
- Autosomal dominant disorders account for >50% of mendelian disorders

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With autosomal dominant disorders, each pregnancy has a 50% likelihood of producing a child with the disorder and a 50% likelihood of producing an unaffected child. There is no carrier state in autosomal dominant disorders.

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Example of an Autosomal Dominant Condition



Achondroplasia: Most common form of dwarfism

- Since most achondroplastic dwarves are born to normal-height parents, it is thought to most often be the result of a spontaneous gene mutation: “*de novo*” or “*sporadic*” mutation
- “Little People Big World” on TLC: both parents are dwarves, and of their 4 children, 3 are normal height and 1 is a dwarf (his fraternal twin is normal height)

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If Both Parents are Heterozygous for Dwarfism (AD)

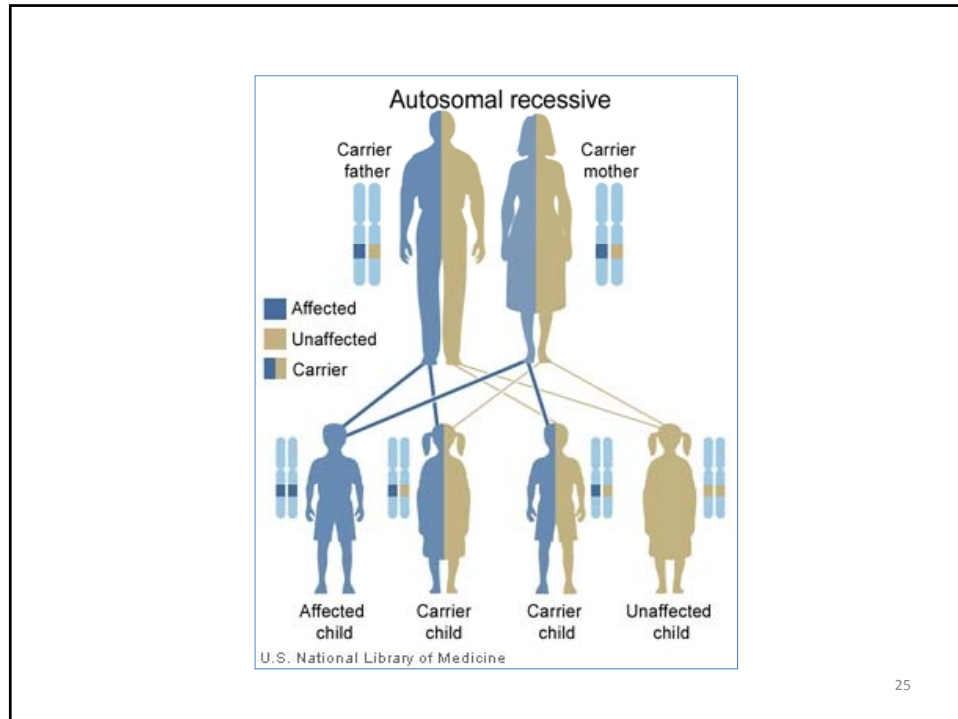
	A	D
A	AA	AD
D	AD	DD

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Characteristics of Autosomal Recessive Disorders

- The parents are not affected (normal phenotype), but both must be carriers (heterozygous for the trait; abnormal genotype) for a child to possibly be affected
- Each offspring has a 25% risk of being affected when both parents are carriers of the trait
- Males and females are equally affected since the disorder affects autosomes, not the sex chromosomes
- Autosomal recessive disorders may occur even when there is no family history of the disease: both parents must contribute the defective gene

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Example of an Autosomal Recessive Disorder

- Cystic fibrosis: CF
- Mutations affect chloride transport in epithelial cells
 - CF causes very thick secretions in lungs, causing affected individuals to have lots of lung infections and pneumonia
 - CF also causes very thick secretions in the pancreas, which makes it hard for affected individuals to digest their food well and their nutritional status may be poor
- The incidence of CF really varies with where the patient's ancestors came from:

• Caucasians (especially from northern Europe)	1/3,300
• Hispanics	1/8,000
• African Americans	1/15,000
• Asian Americans	1/32,000

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Punnett Square for Cystic Fibrosis with Unaffected Parents, Both of Whom are Carriers (Aa)

	A	a
A	AA Unaffected	Aa Unaffected but a carrier
a	Aa Unaffected but a carrier	aa Affected

- With each pregnancy this couple has, there is a:
 - 25% chance of having two normal genes and no chance of passing the trait on
 - 50% chance of being a carrier who can pass along the abnormal gene
 - 25% chance of being affected
- Since the trait is recessive, it takes an abnormal gene from each parent to have the disorder be manifested in the child

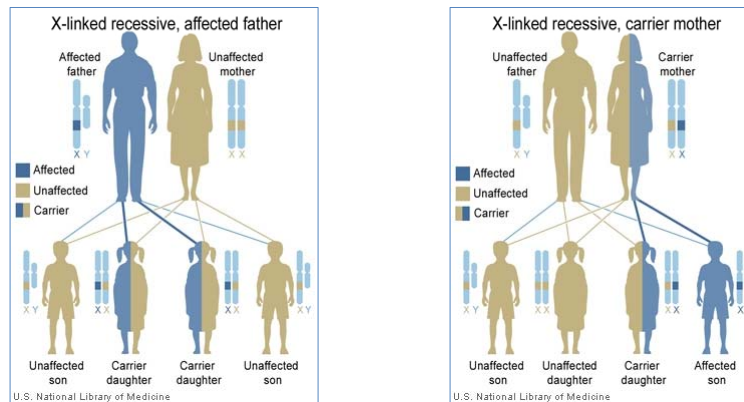
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Characteristics of X-Linked Recessive Inheritance

- Definition: Genetic disorder caused by genes located on the sex chromosomes
- Most sex-linked disorders are inherited through the X chromosome and are recessive traits
- The incidence is much higher in males than females since females have two X chromosomes
- Heterozygous females (carriers of the trait) are usually unaffected, but there may be variable severity
- Most people who express X-linked recessive traits are males who have unaffected parents

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Example of X-Linked Recessive Disorder: Hemophilia A



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X-Linked Dominant Disorders

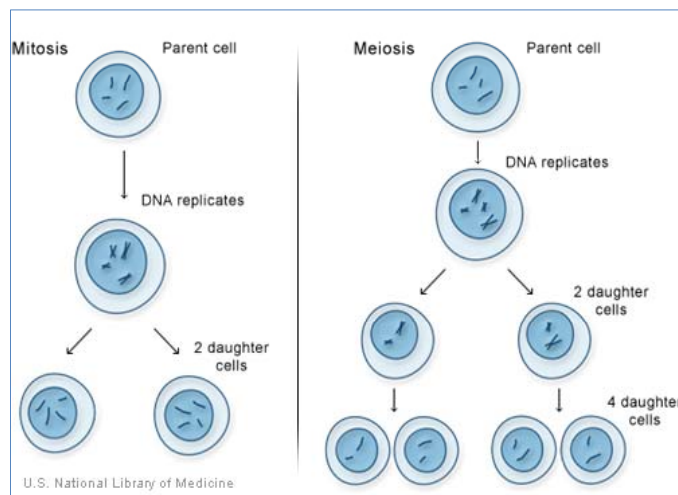
- Disorders are quite rare
- Mostly seen in females since the affected male fetuses rarely live to term
- Affected females have a normal X chromosome to counterbalance the affected X chromosome a bit
- Examples: Rett Syndrome (classified as one of the autism spectrum disorders) and Aicardi Syndrome (characterized by profound mental retardation)

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CHROMOSOME DEFECTS

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Cell Division in Autosomes (Mitosis) and Germ Cells (Meiosis)



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Errors in the Number of Chromosomes

- Chromosomes normally separate during both meiosis and mitosis
- If the chromosomes do not separate normally, the two resulting cells get unequal numbers of chromosomes: nondisjunction
- Gain or loss of chromosomes is usually caused by nondisjunction of autosomes or sex chromosomes during meiosis: particularly an issue with increased maternal age (older moms)
 - Monosomy: one copy of a chromosome
 - Trisomy: 3 copies present (only trisomy 13, 18 and 21 are compatible with life; no sex chromosome trisomies are compatible with life)

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Maternal Age	Trisomy 21: Down Syndrome	Trisomy 18: Edwards Syndrome	Trisomy 13: Patau Syndrome
15 – 19	1:1600	1:17,000	1:33,000
20 – 24	1:1400	1:14,000	1:25,000
40 – 44	1:70	1:700	1:1600
45 – 49	1:20	1:650	1:1500

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Trisomy 21: Down Syndrome

- Genotype: 47,XX or XY+21
- Phenotype:
 - Hypotonia
 - Growth retardation (short stature)
 - Higher social functioning than intellectual functioning
 - Birth defects: cardiac (40%), GI (12%), vertebral (26%)
 - It's an imbalance of multiple genes (an entire chromosome), so multiple systems are affected



"Friends don't count chromosomes!" 😊

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Trisomy 18: Edwards Syndrome

- Genotype: 47,XX or XY+18
- Phenotype: Mental retardation, failure to thrive, often severe cardiac malformations
 - Ears are low-set and malformed
 - Fists clench with 2nd and 5th digits overlapping 3rd and 4th
 - "Rocker bottom" feet
- ~95% spontaneously abort
- Postnatal survival is poor



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Trisomy 13: Patau Syndrome

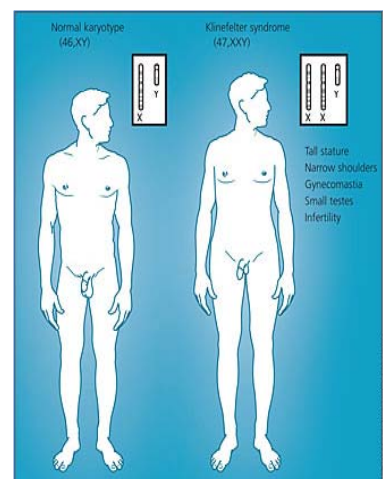
- Genotype: 47, XX or XY, +13
- Phenotype: microcephaly, cleft lip and/or palate, polydactyly, cardiac defects
- Has many commonalities with trisomy 18



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Klinefelter Syndrome: 47,XXY

- Occurs in 1/500 males
- Usually becomes apparent at puberty when the secondary sex characteristics develop
- Can be caused by maternal or paternal nondisjunction
- Phenotype:
 - Tall, somewhat female physique
 - Testicles fail to mature
 - Infertility
 - Gynecomastia



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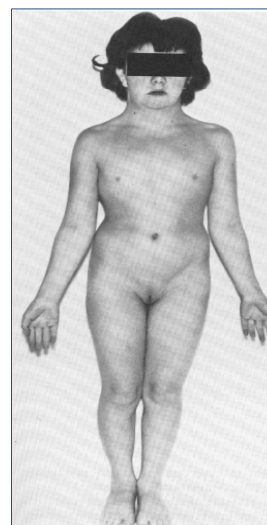
Klinefelter Syndrome: 47,XXY



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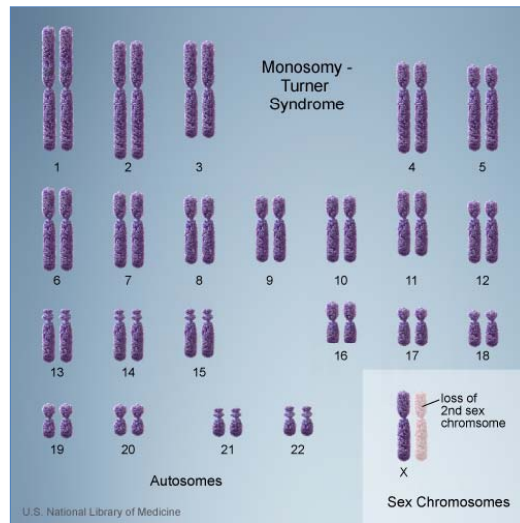
Turner Syndrome: 45,X

- One of the X chromosomes is lost from either ovum or sperm through nondisjunction
- Phenotype features:
 - Infertility due to streak ovaries (98%)
 - Short stature
 - Webbed neck, low posterior hairline; "shield chest" with laterally displaced nipples; increased carrying angle of lower arms
 - 40% have cardiac malformations; 30% have renal malformations



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Turner Syndrome: 45,X



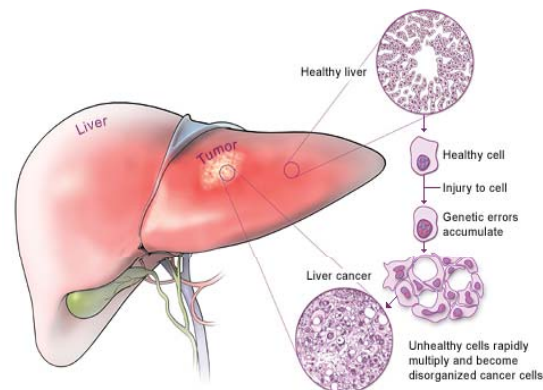
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THE GENETICS OF SELECTED CANCERS

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Cancer: When Good Cells Go Bad

Genetic mutation and cancer development



U.S. National Library of Medicine

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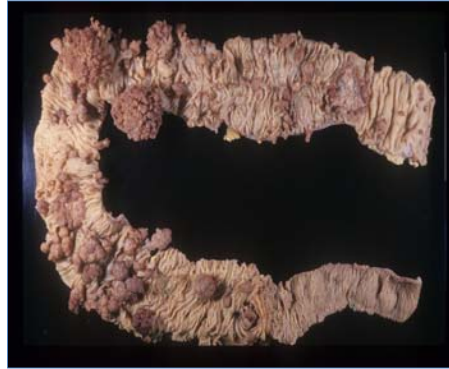
BRCA1 and BRCA2

- Breast cancer 1, early onset and breast cancer 2, early onset
- Both are tumor suppressor genes: produce proteins that keep cell growth orderly and controlled by repairing damaged DNA, or destroying cells that cannot be repaired
- Gene mutations mean proteins are defective and cannot carry out their repair work: defective cells can grow and divide uncontrollably and form tumors
- Persons carrying the mutations may develop cancer at an earlier age, develop cancer in both breasts or ovaries, or have more than one type of cancer, such as breast and ovarian cancer in the same person
- Lifetime risk for a woman with either mutation to develop breast cancer is estimated at 50 – 85%
- Genes are inherited in an autosomal dominant manner, but just inheriting the gene does not ensure the person will develop cancer

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Colorectal Cancer

- Familial adenomatous polyposis (FAP): autosomal dominant inheritance
- Adenomatous polyp coli (APC) gene is tumor-suppressor that regulates colorectal epithelial cell
- Mutation leads to formation of thousands of polyps, which can progress to malignancy



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The Role of Ethnic Origins

- Groups that have traditionally been isolated have higher prevalence of mutations
- BRCA1 and BRCA2 mutations are particularly prevalent in Ashkenazi Jewish women
- A particular FAP mutation has been found in ~6% of Ashkenazi Jews tested

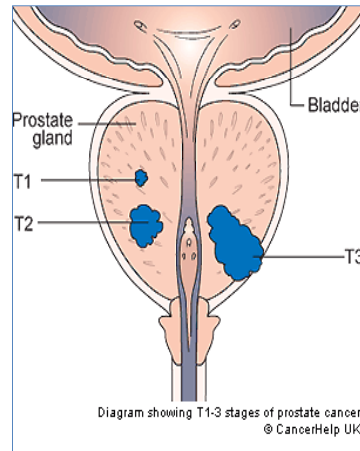


Ashkenazi Jews have origins in Central and Eastern Europe

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Prostate Cancer

- ~10-15% of cases are thought to result from mutated genes
- BRCA2 mutations put men at increased risk for early-onset cancer, BRCA1 mutations do so to a lesser degree
- For men with the mutation, those with a +FH, or African American men, consider instituting screening at an earlier age than general population



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Malignant Melanoma

- Familial malignant melanoma (FMM) accounts for ~10% of malignant melanoma
- Two susceptibility gene mutations have been identified: person with a mutation has 50% risk of developing FMM by age 50 but this is influenced by UV radiation exposure, having multiple or dysplastic nevi, and host characteristics (red hair, freckling, fair skin)



Dysplastic nevus

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THE CHARM & THE CHALLENGE OF THIS KNOWLEDGE

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Our Technology is Ahead of Our Policies!

- Genetic information is considered health information, so it is covered by HIPAA
- GINA: Genetic Information Nondiscrimination Act (2008) prohibits improper use of genetic information in health insurance and employment
 - But it does not cover life insurance, disability insurance, and long-term care insurance, or members of the military

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- 23andMe calls itself “a personal genetics company dedicated to helping individuals understand their own genetic information through DNA analysis technologies and web-based interactive tools.”



DNA Spit Party!

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- University of California, Berkley has encouraged all incoming freshmen in fall 2010 to send in a cheek swab in advance
 - Looking for 3 genes that metabolize alcohol, lactose and folate
 - Testing without counseling about results has raised eyebrows!
- Getting your personal genome sequenced for \$1K or less is on the horizon!



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Great Resources

- <https://familyhistory.hhs.gov/fhh-web/home.action>: My Family Health Portrait from the Surgeon General
- <http://ghr.nlm.nih.gov/>: Genetics Home Reference has great information on concepts and tools
- <http://www.nchpeg.org/>: National Coalition for Health Professional Education in Genetics has developed competencies for education and has lots of information on GINA

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Books

- Consensus Panel. (2009). *Essentials of genetic and genomic nursing: Competencies, curricula guidelines, and outcome indicators* (2nd ed.). Washington, DC: American Nurses Association. ISBN 978-1-55810-263-7
- Cummings, M.R. (2009). *Human heredity: Principles and issues* (8th ed.). Belmont, CA: Brooks/Cole Cengage Learning. ISBN 978-0-495-55445-5
- Lashley, F.R. (2007). *Essentials of clinical genetics in nursing practice*. New York, NY: Springer Publishing. ISBN 0-8261-0222-0

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