REQUIRED READING


LECTURE OBJECTIVES

1. Identify several ways that gene(s) can contribute to common diseases/conditions.
2. Describe multifactorial inheritance.
3. Describe the genetic, especially molecular, aspects of several common diseases.
4. Using intellectual or cognitive disability (formerly termed mental retardation) as an example, describe how you would determine if a child’s condition was due to a major gene, a susceptibility gene or multifactorial inheritance.

STUDENT OBJECTIVES

1. Describe multifactorial inheritance.
2. Describe what aspects of a clinical presentation are associated with a greater genetic influence.
3. Describe at least one Mendelian condition associated with each of the common conditions presented.
4. Appreciate that understanding of genetic differences (variants) will increasingly influence screening practices, the evaluation of clinical trial results, the care of patients and outcomes.
5. Appreciate the role of genetics in the patient's or family’s understanding of his or her condition.

*Everyone who is born holds dual citizenship, in the kingdom of the well and the kingdom of the sick.* Susan Sontag, *Illness as Metaphor*

1. **Meeting a Patient**

   A. What can I do to help you today?
   B. Why does this particular patient have this particular presentation at this time?
   C. How can I best understand the family-genetic context?
D. Common diseases/conditions are most common, but young age, multiple-unusual-persistent findings make high load of genetic contribution more likely. Think genetically!
E. Genetic differences (variants) will increasingly influence screening practices, the evaluation of clinical trial results, the care of patients, and outcomes.

II. **What is a Common Disease/Condition?**

A. Readily identified, countable, and prevalent
B. Significant public health burden
C. Culturally accepted as non-healthy or atypical

III. **Current Concepts**

A. Diseases/health conditions/illnesses are due to interactions of genetic and environmental factors (including lifestyle).
B. There is a continuum of genetic contributions, from genetic syndromes (OGOD-one gene one disease) to smaller effects.
C. ~5-10% of many common conditions are strongly genetic.
D. A condition is more likely to have a significant genetic basis when there is younger age of onset, multiple affected sites, and more affected persons in the pedigree.
E. Individual susceptibilities will vary across a broad range of severity.
F. Genetic testing for susceptibility, severity and prognosis is complex and evolving.

**Figure 1.** Determinants of Disease (from McGinnis JM, Williams-Russo P, & Knickman JR, 2001)
IV. We All Have (or Carry) Something.

A. Multifactorial inheritance

1. Conditions are due to the additive effects of genes (ranging from some to many) and environmental factors (plus nurture).
2. Quantitative traits (like height or blood pressure) have a bell-shaped distribution.
3. Qualitative traits or conditions are present or absent (e.g., neural tube defects, cleft lip) and are characterized by a liability distribution where threshold must be exceeded. The traits show discontinuous variation.

4. Conditions with multifactorial/complex inheritance often show familial aggregation because relatives of an affected person are more likely to share susceptibility genes (alleles) than are unrelated individuals.

B. What are the most prevalent conditions?

1. Children
   a. Birth defects ~3-4%
   b. Asthma ~5-15%
   c. Injuries ~2-4%
   d. Obesity ~5-25%
   e. Intellectual or cognitive disabilities ~1-3%

2. Adults
   a. Obesity (>120% ideal body weight) ~ 50 million
   b. Hypertension ~ 25-30 million
   c. Alcoholism ~ 10 million
   d. Type 2 diabetes ~ 5-10 million
   e. Cancer (all types) ~ 6 million
   f. Coronary heart disease ~5 million
   g. Alzheimer disease ~ 4 million
   h. Schizophrenia ~ 2 million
   i. Epilepsy ~ 2 million
   j. Bipolar affective disorder ~ 1 million
   k. Type 1 diabetes ~ 1 million

C. How do you decide if a condition is more attributable to a “single” or major gene or multifactorial inheritance?

1. Take a family history.

   CAVEATS that influence its utility include adoption, small families, “skeletons in closet”, incompleteness and reliability.

2. Know the literature - twin and epidemiologic (e.g. migration, longitudinal) studies, laboratory evidence, genetic epidemiologic studies.

   CAVEATS that influence the literature include unique families, locus heterogeneity, complex genotypes, tendency to describe or identify “worst” or most obvious cases first, challenges of excellent clinical descriptions/categorization
3. Examine the patient carefully. Are findings of a syndrome present?

4. Review environmental, other medical history

5. Consider the total patient in family context with availability, risk/benefit of current genetic testing.

6. For many common conditions, it is not yet clear whether the genetic architecture will conform to the "common variant - common disease" model in which some common polymorphisms have modest but widespread effects on risk or the "multiple rare variants - common disease" model where multiple different rare alleles underlie genetic susceptibility.

D. We see what we know.

1. Theories change.
2. Evidence changes.
3. Examples – smoking and association with cancer, ulcers and associations with stress vs. bacterial infection, macular degeneration and complement Factor H
4. Keep an open mind.
5. Survival likely to be influenced by a range of responses to differing environments and challenges (e.g. viruses, diets, etc.).
6. Trust your instincts; train them!
7. Remember informed consent and genetic counseling.
8. Science works to get to the roots; use "umbrella" analogy with families

E. How do you talk with patients about genetic causes? (LISTEN non-judgmentally)

1. Try to understand what the patient understands; nature and nurture, not nature vs. nurture.
2. When accurate, try to give a name, e.g. syndrome or category, to the condition.
3. Describe as familial, inherited, higher risk, genetic.
4. Consider giving relative risk compared to someone without family history or genotype.
5. Give natural frequencies of occurrence or risk, unless patient uses percentages him or herself.
6. Draw picture(s), diagrams, and pedigrees to enhance patient understanding.
7. Accept and be prepared to say, “I don’t know, but I will try to find out.”

V. Scene 1

Your 54-year-old maternal uncle has become increasingly forgetful. Last week he had to call the police because he could not remember where he parked his car. The police found
him in the waiting room at the nursing home where your maternal grandmother has been for the last 3 years. What’s the diagnosis?

A. Alzheimer disease (AD)

Refer to Thompson and Thompson Clinical Case Study #3 in text.

1. Progressive impairment in multiple cognitive areas (e.g. memory, calculation, judgment, personality) exceeding impairment expected with age.
2. Age 60 years typically used to differentiate early and late onset.
3. 4th leading cause of death in elderly, after heart disease, cancer, and stroke.

B. Genetics

1. Amyloid cascade hypothesis - mutations cause more aggregation of insoluble amyloid fibrils that make up senile plaques.

2. AD early onset forms caused by missense mutations in 3 genes - ch 21 amyloid precursor protein gene, ch 14 presenilin gene, and ch 1 presenilin gene.

3. apoE e4 allele linked with late onset disease, accelerated amyloid deposition.
   a. Neither necessary or sufficient to cause Alzheimer disease
   b. A susceptibility test, not a predictive test
c. Population attributable fraction ~ 20%, greater than all of the known rare high-risk alleles combined.

d. A person with one apoE e4 allele has up to 50% chance of Alzheimer disease by 80 years

e. Boxers in 12 or more bouts who have apoE e4 have greater risk of dementia pugilistica

C. Should susceptibility testing for Alzheimer disease be offered?

1. How specific (minimizing false positives) and sensitive (minimizing false negatives) should the test be before it is offered?
2. At what age should testing be performed?
3. Who should decide?
4. Who should pay for it?
5. Can you think when/if you would want it?

VI. Scene 2

Your fiancé’s father died of a heart attack 3 years ago at 49 years of age. He smoked for 30 years and was an air traffic controller. He avoided doctors except for physicals required for work. Your future mother-in-law says, “You’re going to be the doctor. Make sure this doesn’t happen to my son.” What do you do?

A. Coronary artery disease (CAD)

1. Accounts for ~25% of adult deaths
2. Risk factors - obesity, smoking, hypertension, elevated cholesterol, positive family history
3. In general, one 1st degree relative increases relative risk 2-7X
4. Myocardial infarction - 25-60% heritability

B. Mendelian conditions

1. Autosomal dominant familial hypercholesterolemia - ~1 in 500 are carriers; use diet and drugs that interfere with cholesterol reabsorption and synthesis (Refer to Clinical Case Study #14 in text).
2. Autosomal dominant cardiomyopathy due to mutations with abnormal protein contractile function
3. Autosomal dominant prolonged QT syndromes - pacemakers to prevent sudden death (Refer to Clinical Case Study #25 in text).

C. Is atherosclerosis an inflammatory disease?

1. Early endothelial dysfunction or injury
2. Increases procoagulant and inflammatory response with modification of lipoproteins
3. Observation - high homocysteine may be associated with increased risk of symptomatic CAD, and children-young adults with homocystinuria can have myocardial infarction

VI. **Scene 3**

A 3-year-old girl has fainted twice at preschool and tells her parents her head hurts. The doctor’s office encourages over the counter pain medications and not allowing her to use excuses to avoid preschool.

A. **Hypertension**
   1. Norms available by age; in adults systolic blood pressure (SBP) >140-150 mmHg and diastolic blood pressure (DBP) >90-95 mmHg
   2. About twice as common in African-Americans than Caucasians
   3. Complex homeostatic process
   4. Take blood pressures!

B. **Genetics**
   1. Twin correlations SBP MZ ~0.5; DZ ~0.25
   2. Genetic conditions that can include hypertension-neurofibromatosis, Wilms tumor (childhood kidney tumor), polycystic kidney disease, Alport (X-linked hearing loss and kidney failure) syndrome, pheochromocytoma, Cushing syndrome, coarctation of the aorta, and others.

C. **Can we modify environments sufficiently to treat most genetic conditions?**
   1. Diet, lifestyle
   2. Avoid certain medications, exposures
   3. Conduct early screening
   4. Use certain medications, tailor therapy with pharmacogenomic information
   5. Have transplants available
   6. Consider prenatal diagnosis or preconceptional planning
   7. Other options

VII. **Scene 4**

You were adopted. Your birth mother died of cancer at age 25. You will be 25 next year and are trying to decide whether to get more information about her.
A. Cancer

1. Common condition
2. Today majority of individuals survives, but hype such as WAR ON CANCER, “eaten by cancer” support fears

B. Colon cancer

1. Signs - asymptomatic, blood in stool, anemia, weight loss, constipation or change in form of stool, diarrhea, abdominal pain

C. Familial adenomatous polyposis (FAP)

Refer to Thompson and Thompson Clinical Case Study # 13 in text.

1. 100's-1000's of precancerous polyps develop at mean age of 16 years.
2. Other findings can include other cancers, jaw cysts, soft tissue tumors.
3. Autosomal dominant condition, APC gene at 5q21-22
4. Testing by sequencing, mutation scanning, linkage analysis or protein truncation.

D. Hereditary nonpolyposis colon cancer (HNPCC)

Refer to Thompson and Thompson Clinical Case Study # 19 in text.

1. Autosomal dominant, 2-4% of colon cancers
2. Proximal colon tumors with increased uterine, ovarian, gastric, small bowel, and urinary tract tumors
3. Mutations in DNA repair enzymes including hMSH2, hMLH1, hPMS2
4. Sporadic mutations in DNA repair may cause up to 15% of colon cancer
5. May screen the tumor itself with immunostaining or microsatellite instability testing

E. Why test?

1. In FAP, average age of inevitable colon cancer is 36 years; 7% of untreated patients will develop by 21 years.
2. Sigmoidoscopy is recommended every 1-2 years beginning at age 10-12
3. Annual colonoscopy if colectomy delayed >1 year after polyps emerge
4. Treatment includes colectomy with attention for other growths and consideration of clinical trials (clinicaltrials.gov)
VIII. Scene 5

The parents of a 2 year old girl who had formerly been a poor eater are delighted because the child now wants to eat everything. Although her height is at the 50th percentile, weight is now 50 lbs., 50th percentile for a five year old, so it is difficult to find clothes to fit.

A. Fat - so what?

1. Is health being in harmony with nature and culture?
2. Adult illnesses and premature death - diabetes, heart disease, impaired mobility, pulmonary insufficiency, liver disease, breast cancer
3. Youth - (>20% with obesity) diabetes, isolation, sleep apnea, aseptic necrosis of hip

B. Obesity - who has it?
1. After infancy, more females than males
2. Less common in African-Americans than Caucasians in childhood, reverses in teens
3. Severe obesity occurs independently of socio-economic status
4. Pima in Mexico still thin with low incidence of diabetes

C. Obesity - what is it?

1. Anthropometry (wt/ht vs. expected)
2. >110% overweight; >120% obese
3. Skinfold or midarm circ >95%
4. Body mass index (BMI), wt/(htxht) >95%
5. Body composition - nl. range of fat/wt ~12-30%
6. Eye of beholder, social attitudes

D. Genetics

1. If both parents obese, 2/3 of children will be
2. If one parent obese and other not, 1/2
3. If neither parent obese, 1/11 will be obese
4. In MZ twins, little discordance even when raised apart
5. Major factors - energy requirements, nutrient partitioning, dietary intake, and physical activity - are influenced by genotypes and interact
6. 40-80% heritable
7. Major gene(s) include Prader-Willi syndrome, Bardet-Biedl syndrome, small no. of patients with leptin and related receptor mutations
8. Physical activity helps prevent obesity whatever the genetic predisposition

E. Molecular genetics - so what?

1. Complex web of chemicals with redundancy
2. Various combinations probably offer survival advantage in different environments
3. May influence treatments someday (serotonin agonists recalled by FDA)

F. Complex problem

1. Prevention is key - obese 6 yo -25% chance, obese 12 yo - 75% chance of being obese adult
2. No simple short fixes
3. Community concern
4. Passive strategies - school food items, bus stops, Head Start physical activity, sports clubs, drinking water, role models, walk up stairs
5. Major area of genetic and drug research
The Human Genome Project
The human genome is the total genetic information of a human being. It is stored in 23 pairs of chromosomes. These 46 chromosomes, which are found in most cells, house DNA, a chemical compound containing the instructions needed to direct the body’s biological activities. DNA looks like a ladder twisted into a coil—the famous double helix. By analyzing strands of DNA, scientists have identified the sections—the genes—with the coded messages that contribute to life processes. Each human being has an estimated 21,500 genes. The Human Genome Project, conducted for the National Institutes of Health under the direction of Francis Collins, M.D., mapped 99 percent of them, although scientists are still learning what all the genes do.

Major Landmarks
1953: James Watson and Francis Crick figure out the three-dimensional structure—the double helix—of DNA.

1990: Human Genome Project begins.

1993-95: Genes discovered for breast cancer, Alzheimer disease, and colon cancer.

2003: Human Genome Project completed.

2004: National Human Genome Research Institute awards grants for the development of $100,000 tests for individual genome sequencing.

2005: Gene discovered for macular degeneration.


Cancer Genome Project launched.

2007: Project launched to find genetic and environmental causes of common disease.

More type 2 diabetes genes and breast cancer genes found.

James Watson becomes the first person to receive his own genome map.

2008: Grants awarded to develop $1,000 tests for individual genome sequencing.
Your 18 month old nephew, or friend’s son, for whom you sometimes baby sit, is not talking yet. The bus you take downtown has a sign on it that reads – “Act early. Know the signs. 1 in 160 children has autism.” 50-70% of individuals with autism have a cognitive or intellectual disability. You decide you need to learn more about autism and intellectual (cognitive) disabilities, formerly and sometimes still called mental retardation.

**Question 1. How is autism currently defined?**

We see what we know. You need to develop your skills at diagnosis and have standardized methods/tools for screening and identifying conditions. You understand that we often do screening tests as a first step in assessing a potential medical condition (e.g. one blood pressure measurement does not diagnose hypertension).

**Question 2. Find the current American Academy of Pediatrics recommended algorithm for screening for autism** (sometimes called autism spectrum disorder (ASD) to include children who may not quite meet the narrow definition but who have many of the features).

You learn that having a sibling with autism, and a parent/caregiver/or pediatricians’ concern about the child’s development merit using a specific autism screening tool and potentially referral for further evaluation and diagnosis.

**Question 3. How would you contact the Developmental Disorders Assessment Clinic (also known as the ASD clinic) at VCUHS?**

The diagnosis of ASD is confirmed at this clinic with the ADOS (Autism Diagnostic Observation Schedule) instrument. You understand that autism may be seen in some single gene disorders, untreated metabolic conditions (e.g. PKU), some teratogenic conditions, some chromosome conditions, as well as be a complex condition with multiple genes contributing.

**Question 4. How would you begin to develop a differential diagnosis list of the Mendelian disorders and genes that may be associated with ASD?**

Databases can be very helpful (so long as you know or check what is included) in generating differential lists.

**Question 5. Can you find a recent Genome Wide Association Study (GWAS) that described possible loci that contribute to the autism phenotype?**

A Genome Wide Association Study is a study that compares the complete DNA of people with a disease or condition to the DNA of people without the disease or condition. These studies help find the genes involved in a disease, and may help prevent, diagnose, or treat the disease. A
GWAS typically compares SNPs (single nucleotide polymorphisms) between a large number of well-defined “cases” of the condition and a large number of controls. The strength of the evidence for a true association between a SNP (and nearby nucleotides) and the condition/phenotype depends on the likely number of true associations and the study’s power (sample size and effect sizes) to detect them.

**Question 6. This boy is found to have a head circumference above the 97th percentile (macrocephaly), a few birth marks, and a mother with breast cancer at 35 years of age. What is a potential diagnosis and what test(s) would you consider doing?**

The ultimate goal is to use genetic techniques for prevention and treatment.

**Question 7. How would you find out more about research studies on new treatments?**

Train your instincts. Be a lifelong learner. Know your resources. Use your power for good.

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**SUMMARY**

1. 5-10% of most common conditions have strongly heritable susceptibility; virtually all other diseases are due to genetic and environmental interactions
2. Young age, multiple affected sites, multiple affected relatives often more highly genetic
3. Genes are not destiny but are part of continuum of causation
4. Train your instincts, THINK GENETICALLY

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**FOR FURTHER STUDY**

Incorporating new information in a well-grounded framework of medical knowledge is the lifelong task of being a good physician. The federal Maternal and Child Health Bureau sponsored an initiative to develop curriculum materials for Genetics in Primary Care. If you are interested in building your basic understanding of genetics as it relates to the foundations of clinical medicine, go to the genes-r-us.uthscsa.edu website and the button for the Genetics in Primary Care (GPC) training manual. There are case studies on: breast and ovarian cancer, cardiovascular disease, colorectal cancer, congenital hearing loss, dementia, development delay, and ethical, legal, and social issues (ELSI), along with links that are updated.

**REFERENCES**

Alcohol Alert, Newsletter from National Institute on Alcohol Abuse and Alcoholism (call 1-800-729-6686 for information)

Faroogi IS and O’Rahilly S (2007) Genetic Factors in Human Obesity, Obesity Reviews 8 (Sup. 1): 37-40


“NEW” WORDS

1. Cardiomyopathy - heart muscle disease
2. Cirrhosis - replacement of normal liver with connective tissue
3. Colectomy - removal of the colon
4. Macroorchidism - large testes
5. Pheochromocytoma – adrenal tumor
6. Phlebotomy - opening a vein for giving blood
7. Population attributable fraction - fraction of the disease that could be eliminated if the risk factor were removed
8. Rhabdomyomas - muscle tumors