GENETIC DISORDERS
DISEASES

- GENETIC
- ENVIRONMENTAL
- BOTH
MUTATIONS

• PERMANENT change in DNA

• **GENE** MUTATION: (may, and often, result in a single base error)

• **CHROMOSOME** MUTATION: (visible chromosome change)

• **GENOME** MUTATION: (whole chromosome)

Base pair → triplet → gene → chromosome segment → whole chromosome → genome
GENE MUTATION

• DELETION OF A SINGLE BASE
• SUBSTITUTION OF A SINGLE BASE
POINT MUTATION
GENE MUTATION

- **POINT MUTATION** within a coding sequence: VAL-GLU
- **MUTATIONS** in NON-coding sequences ➔ defective transcription, regulation, apop.
- **DELETIONS/INSERTIONS** ➔ “frameshift” mutation, involvement is NOT a multiple of 3
- Tri-nucleotide **REPEATS**, e.g., CGG repeats many times in fragile X syndrome, CAG in others
GENE MUTATIONS

- **INTERFERE** with protein synthesis
- **SUPPRESS** transcription, DNA → RNA
- **PRODUCE** abnormal mRNA
- **DEFECTS** carried over into **TRANSLATION**
- **ABNORMAL** proteins **WITHOUT** impairing syntheses
GENETIC DISORDERS

• **SINGLE** gene mutations, following classical MENDELIAN inheritance patterns the most

• **MULTIFACTORIAL** inheritance

• **CHROMOSOMAL** disorders

• **NON-MENDELIAN** disorders
MENDELIAN inheritance patterns

• AUTOSOMAL DOMINANT
• AUTOSOMAL RECESSIVE
• SEX-LINKED (recessive), involving “X” chromosome
AUTOSOMAL DOMINANT

- Disease is in HETEROZYGOTES
- NEITHER parent may have the disease (NEW mut.)
- REDUCED PENETRANCE (environment?, other genes?)
- VARIABLE EXPRESSIVITY (environment?, other genes?)
- May have a DELAYED ONSET
- Usually result in a REDUCED PRODUCTION or INACTIVE protein
AUTOSOMAL DOMINANT

- HUNTINGTON DISEASE
- NEUROFIBROMATOSIS
- MYOTONIC DYSTROPHY
- TUBEROUS SCLEROSIS
- POLYCYSTIC KIDNEY
- HEREDITARY SPHEROCYTOSIS
- VON WILLEBRAND DISEASE
- MARFAN SYNDROME
- EHLERS-DANLOS SYNDROMES (some)
- OSTEOGENESIS IMPERFECTA
- ACHONDROPLASIA
- FAMILIAL HYPERCHOLESTEROLEMIA
- ACUTE INTERMITTENT PORPHYRIA
AUTOSOMAL DOMINANT PEDIGREE

1) BOTH SEXES INVOLVED

2) GENERATIONS NOT SKIPPED
AUTOSOMAL RECESSIVE

• Disease is in HOMOZYGOTES

• More **UNIFORM** expression than AD

• Often **COMPLETE PENETRANCE**

• Onset usually **EARLY in life**

• NEW mutations rarely detected clinically

• Proteins show **LOSS of FUNCTION**

• Include ALL inborn errors of metabolism

• MUCH more common than autosomal dominant
AUTOSOMAL RECESSIVE

- CF
- PKU
- GALACTOSEMIA
- HOMOCYSTINURIA
- LYSOSOMAL STORAGE
- A-1 ANTITRYPSIN
- WILSON DISEASE
- HEMOCHROMATOSIS
- GLYCOGEN STORAGE DISEASES
- Hgb S
- THALASSEMIAS
- CONG. ADRENAL HYPERPLASIA
- EHLERS-DANLOS (some)
- ALKAPTONURIA
- NEUROGENIC MUSC. ATROPHIES
- FRIEDREICH ATAXIA
- SPINAL MUSCULAR ATROPHY
AUTOSOMAL RECESSIVE PEDIGREE

1) BOTH SEXES INVOLVED
2) GENERATIONS SKIPPED
SEX ("X") LINKED

• MALES ONLY

• HIS SONS are OK, right?

• ALL his DAUGHTERS are CARRIERS

• The “Y” chromosome is NOT homologous to the “X”, i.e., the classic concept of dominant/recessive has no meaning here

• HETEROZYGOUS FEMALES have no phenotypic expression (carriers)....usually, this means autosomal “recessive”, right?
SEX ("X") LINKED

- DUCHENNE MUSCULAR DYSTROPHY
- HEMOPHILIA, A and B
- G6PD DEFICIENCY
- AGAMMAGLOBULINEMIA
- WISKOTT-ALDRICH SYNDROME
- DIABETES INSIPIDUS
- LESCH-NYHAN SYNDROME
- FRAGILE-X SYNDROME
SEX LINKED PEDIGREE

1) MALES ONLY, sons of affected males are OK
2) GENERATION SKIPPING DOESN’T MATTER
SINGLE GENE DISORDERS

• **ENZYME DEFECT** (Most of them, e.g., PKU)
  – Accumulation of substrate
  – Lack of product
  – Failure to inactivate a protein which causes damage

• **RECEPTOR/TRANSPORT PROTEIN DEFECT** (Familial Hypercholesterolemia)

• **STRUCTURAL PROTEIN DEFECT** (Marfan, EhI-Dan)
  – Structure
  – Function
  – Quantity

• **ENZYME DEFECT WHICH INCREASES DRUG SUSCEPTIBILITY**: G6PD ⇔ Primaquine
STRUCTURAL PROTEIN DEFECTS

• Marfan Syndrome
  – Fibrillin-1 defect (not -2 or -3)
  – Tall, dislocated lens, aortic arch aneurysms, etc.
  – Abraham Lincoln?, Osama bin-Laden?

• Ehlers-Danlos Syndromes (AD, AR)
  – Multiple (6?) different types
  – Classical, Hypermob., Vasc., KyphoSc., ArthChal., Derm
  – Various collagen defects
  – Hyperelastic skin, hyperextensible joints
RECEPTOR PROTEIN DEFECTS

• FAMILIAL HYPERCHOLESTEROLEMIA
  – LDL RECEPTOR defect
  – Cholesterol TRANSPORT across liver cell impaired
  – ergo, → CHOLESTEROL BUILDUP IN BLOOD

• “Scavenger System” for CHOL kicks in, i.e., MACROPHAGES

• YOU NOW KNOW THE REST OF THE STORY

• YOU NOW KNOW WHY MACROPHAGES are “FOAMY”
ENZYME DEFICIENCIES

• BY FAR, THE LARGEST KNOWN CATEGORY
  — SUBSTRATE BUILDUP
  — PRODUCT LACK
  — SUBSTRATE could be HARMFUL

• LYSOSOMAL STORAGE DISEASES comprise MOST of them
LYSOSOMAL STORAGE DISEASES

• GLYCOGEN STORAGE DISEASES
• SPHINGOLIPIDOSSES (Gangliosides)
• SULFATIDOSSES
• MUCOPOLYSACCHARIDOSSES
• MUCOLIPIDOSES
• OTHER
  – Fucosidosis, Mannosidosis, Aspartylglycosaminuria
  – WOLMAN, Acid phosphate deficiency
GLYCOGEN STORAGE DISEASES

- MANY TYPES (at least 13)
- Type 2 Pompe (acid-α-glucosidase), von Gierke (Glu-6P-ase), McArdle (phosphorylase), most studied and discussed, and referred to
- Storage sites: Liver, Striated Muscle (Skel + Ht)
SPHINGOLIPIDOSSES

• MANY types, Tay-Sachs most often referred to
  – GANGLIOSIDES are ACCUMULATED
  – Ashkenazi Jews (1/30 are carriers)
  – CNS neurons a site of accumulation
  – CHERRY RED spot in Macula
  – Usually fatal by age 4
SULFATIDOSES

• MANY types, but the metachromatic leukodystrophies (CNS), Krabbe, Fabry, Gaucher, and Niemann-Pick (A and B) are most commonly referred to

• SULFATIDES, CEREBROSIDES, SPHINGOMYELIN are the accumulations
NIEMANN-PICK

- TYPES A, B, C
- **SPHINGOMYELIN** BUILDUP
- Sphingomyelinase (ASM), is the missing enzyme
- MASSIVE SPLENOMEGALY
- ALSO in ASHKANAZI JEWS
- OFTEN FATAL in EARLY LIFE, CNS, ORGANOMEGALY
GAUCHER DISEASE

- GLUCOCEREBROSIDE BUILDUP
- 99% are type I, NO CNS involvement
- ALL MACROPHAGES, liv, spl, nodes, marrow
MUCOPOLYSACCHARIDOSES

- HURLER/HUNTER, for I and II, respectively, 14 types
- DERMATAN sulfate, HEPARAN sulfate buildup, respectively
  - coarse facial features
  - clouding of the cornea
  - joint stiffness
  - mental retardation
  - URINARY EXCRETION of SULFATES COMMON
OTHER LYSOSOMAL STORAGE DIS.

• FUCOSIDOSIS
• MANNOSIDOSIS
• ASPARTYLGLYCOSAMINURIA
• WOLMAN (CHOL., TRIGLYCERIDES)
• ACID PHOSPHATE DEFICIENCY (PHOS. ESTERS)
ALCAPTONURIA

- NOT a LYSOSOMAL ENZYME DISEASE
- FIRST ONE TO BE DESCRIBED
- HOMOGENTISIC ACID
- HOMOGENTISIC ACID OXIDASE
  - BLACK URINE
  - BLACK NAILS (OCHRONOSIS), SKIN
  - BLACK JOINT CARTILAGE (SEVERE ARTHRITIS)
NEUROFIBROMATOSIS

• 1 and 2
  – 1-von Recklinghausen
  – 2- “acoustic” neurofibromatosis

• 1
  – Neurofibromas, café-au-lait, Lisch nodules
NEUROFIBROMATOSIS

• 1 and 2
• 1-von Recklinghausen
• 2- “acoustic” neurofibromatosis

• 2
  – Bilateral acoustic neuromas and multiple meningiomas
MULTIFACTORIAL INHERITANCE

• Multi-"FACTORIAL", not just multi-GENIC
• “SOIL” theory
• Common phenotypic expressions governed by “multifactorial” inheritance
  – Hair color
  – Eye color
  – Skin color
  – Height
  – Intelligence
  – Diabetes, type II
FEATURES of multifactorial inheritance

• Expression determined by NUMBER of genes
• Overall 5% chance of 1st degree relatives having it
• Identical twins >>>5%, but WAY less than 100%
• This 5% is increased if more children have it
• Expression of continuous traits (e.g., height) vs. discontinuous traits (e.g., diabetes)
“MULTIFACTORIAL” DISORDERS

• Cleft lip, palate
• Congenital heart disease
• Coronary heart disease
• Hypertension
• Gout
• Diabetes
• Pyloric stenosis
• MANY, MANY, MANY, MANY, MANY MORE.....
KARYOTYPING

- Defined as the study of CHROMOSOMES

- $46 = (22 \times 2) + X + Y$  

- Conventional notation is “46,XY” or “46,XX”  

- G(iemsa)-banding, 500 bands per haploid recognizable

- Short (“p”-etit) arm = p, other (long) arm = q
More KARYOTYPING info

- A, B, C, D, E, F, G depends on chromosome length
  - A longest
  - G shortest
- Groups within these letters depend on the p/q ratio
- **ARM** → **REGION** → **BAND** → **Sub-BAND**, numbering from the centromere progressing distad
F.I.S.H. (gene “probes”) greatly enhances G-banding

- **Fluorescent In-Situ Hybridization**
  - Uses fluorescent labelled DNA fragments, ~10,000 base pairs, to bind (or not bind) to its complement
FISH

• SUBTLE MICRODELETIONS
• COMPLEX TRANSLOCATIONS
• AND TELOMERE ALTERATIONS
TRIPLE CHROMOSOME #20

A DELETION in CHROMOSOME #22
SPECTRAL KARYOTYPING
CYTOGENETIC DISORDERS

• DEFINITIONS:
  – EUPLOID (46XX or 46XY)
  – AN EUPLOID (NOT AN EXACT MULTIPLE OF 23)
    • MONOSOMY, AUTOSOME OR SEX
    • TRISOMY, AUTOSOME OR SEX
  – DELETION
  – BREAKAGE
MORE DEFINITIONS

TRANSLOCATIONS

Balanced reciprocal

Robertsonian

Lacked

ISOCHROMOSOMES

DELETIONS

Fragments

INVERSIONS

Paracentric

Pericentric

RING CHROMOSOMES

Fragments
COMMON CYTOGENETIC DISEASES

• AUTOSOMES
  – TRISOMY-21 (DOWN SYNDROME)
  – 8, 9, 13 (Patau), 18 (Edwards), 22
  – 22q.11.2 deletion

• SEX CHROMOSOMES
  – KLINEFELTER: XXY, XXXY, etc.
  – TURNER: XO
TRISOMY-21
TRISOMY-21

• Most trisomies (monosomies, aneuploidy) are from maternal non-disjunction
• (non-disjunction or anaphase lag are BOTH possible)
• #1 cause of mental retardation
• Maternal age related
• Congenital Heart Defects, risk for acute leukemias, Gl atresias
• Most LOVABLE of all God’s children
Chromosome 22q11.2 Deletion Syndrome

- Because of a DELETION, this cannot be detected by standard karyotyping and needs FISH.
- Cardiac defects, DiGeorge syndrome, velocardiofacial, CATCH*
Velocardiofacial Syndrome/
DiGeorge Syndrome

Daniel Avram

Keri Reigle
SEX CHROMOSOME DISORDERS

• Problems related to sexual development and fertility
• Discovered at time of puberty
• Retardation related to the number of X chromosomes
• If you have at least ONE “Y” chromosome, you are male
KLINEFELTER (XXY, XXXY, etc.)

• Hypogonadism found at puberty
• #1 cause of male infertility
• NO retardation unless more X’s
• 47, XXY  82% of the time
• L----O----N----G legs, atrophic testes, small penis
TURNER (XO)

- 45, X is the “proper” designation
- Mosaics common
- Often, the WHOLE chromosome is not missing, but just part
- **NECK “WEBBING”**
- EDEMA of HAND DORSUM
- CONGENITAL HEART DEFECTS most FEARED
- “STREAK” OVARIES
Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small finger nails
Brown spots (nevi)

Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation
HERMAPHRODITES

- GENETIC SEX is determined by the PRESENCE or ABSENCE of a "Y" chromosome, but there is also, GONADAL (phenotypic), and DUCTAL sex

- TRUE HERMAPHRODITE: OVARIES AND TESTES, often on opposite sides (VERY RARE)

- PSEUDO-HERMAPHRODITE:
  - MALE: TESTES with female characteristics (Y-)
  - FEMALE: OVARIES with male characteristics (XX)
SINGLE GENE, NON-Mendelian

- Triplet repeats
  - Fragile X (CGG)
  - Others: ataxias, myotonic dystrophy

- Mitochondrial Mutations: (maternal)
  - Leber Hereditary Optic Neuropathy

- Genomic “IMPRINTING”: (Inactivation of maternal or paternal allele, contradicts Mendel)

- Gonadal “MOSAICISM”: (only gametes have mutated cells)
MOLECULAR DX by DNA PROBES

- BIRTH DEFECTS, PRE- or POST- NATAL
- TUMOR CELLS
- CLASSIFICATIONS of TUMORS
- IDENTIFICATION of PATHOGENS
- DONOR COMPATIBILITY
- PATERNITY
- FORENSIC
H&E tissue structures

Immuno-Antigen Proteins

GENES that MAKE those PROTEINS