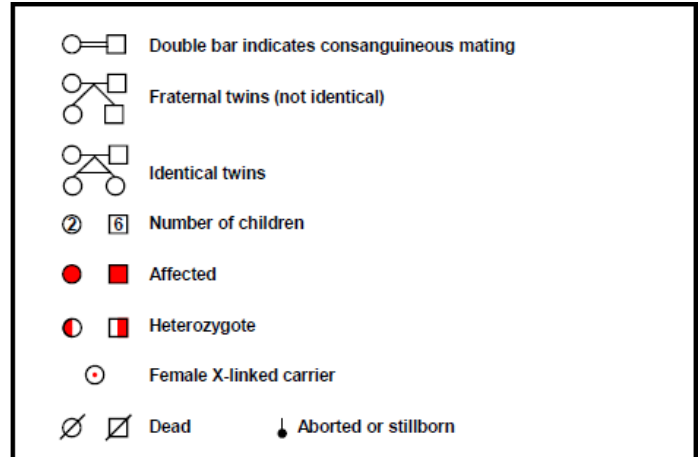
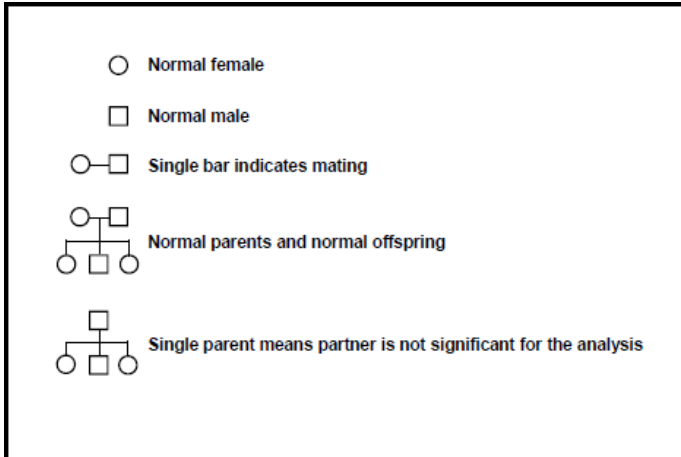


LECTURE 1 – INTRO TO GENETICS

- 20% genetic disease – classic Medical genetics, single gene, early onset (pediatric)
- 80% genetic susceptibility – common gene variation and environment, delayed onset (adult)

Pedigree



- Children, siblings, parents
- Nuclear family – age/date birth, health status, age/date death, cause of death
- Proband – individual who brings pedigree to your attention, does not necessarily have to be affected

General Info

- DNA → RNA → Protein → Function
- Changes in environment:
 - Both have common DNA variants
 - Change in gene transcription profile
 - Change in protein profile
- SNP – single nucleotide polymorphism (single nucleotide difference)
- Human genome – 3,000 Mbp
 - 25,000 – 30,000 genes
 - Exons contain <1.5% of DNA
 - Gene distribution is uneven
 - Knowing the sequence of the genome makes it easy to locate genes and variants quickly
- NCBI Human Genome Sequence Components
 - Human DNA sequence
 - Human mRNA (transcriptome)
 - Variations
 - Usable database
- The ENCODE project – encyclopedia of DNA elements project – to discover all functional elements in human genome and release the information to the public
 - Genes can give many different proteins via splicing (post ENCODE?)

Advancements in Technology

- 1990 – radioactive methods – 3Kbp per day
- 1998 – ABI Prism – 300Kbp per day
- 2009 – Helicos Genetic Analysis – 21-28Gbp per run
- While costs and speed have gone down dramatically for sequencing, the costs for analysis are still very high

Variation and Disease

- Everyone has 5-50 significant genetic flaws → all diseases have some genetic component (susceptibility)
 - Down/up regulate expression
 - Directly affect protein function (structure)
 - Alter mRNA splicing/processing/stability
 - Genetic disequilibrium with an unknown functional SNP
- Homocysteine (intermediate product in protein catabolism) – removed via:
 - Remethylation to methionine
 - Transulfuration to cysteine
 - Rs1801133
 - C → T substitution at nt 677
 - Alanine → valine substitution at codon 222
 - Altered protein (T allele) is thermolabile → reduced activity → increased plasma homocysteine
 - Increased coronary heart disease, cleft palate, thrombosis
 - Increased risk with increased affected relatives
 - Increased risk with genetics
 - Increased risk with living in SE USA
 - Increased risk with decreased folic acid intake
 - Pre/perinatal folic acid therapy reduces frequency of NTDs (SB and anencephaly)
- Big Variations – pathogenic variation (causes big change in gene function), single gene abnormalities (dominant/recessive), chromosomal disorders (trisomy, deletions), not common (less than 1/1000)
- Small variations – polymorphic variation (small/moderate changes), diseases and conditions with genetic susceptibility, common (1/2 – 1/100)

Websites for Info

- NCBI – national center for biotechnology information
 - Public databases, research in computational biology, software tools for analyzing genome data, disseminates biomedical info for the better understanding of molecular processes affecting human health and disease
- Pubmed – online catalogue of published papers
- OMIM (online mendelian inheritance in man) – information on genetic diseases
 - Systematic arrangement/classification of diseases
- SNP – common variants
- Gene – information on genes, map viewer
- Gene Cards – database on human genes, products, and involvement in disease
 - Concise info about functions of all human genes that have an approved symbol and other selected genes.

LECTURE 2: CYTOGENETICS 1

Intro to Cytogenetics:

- Involves the study of chromosomes, both the number and the structure are analyzed by conventional techniques (G-banding)
- Molecular Cytogenetics (FISH and microarrays) have extended capabilities of identifying abnormalities
- Constitutional studies: chromosome abnormalities present at birth
 - o Prenatal Diagnosis: CVS, Amniocentesis, Products of conception (villi)
 - o Postnatal Diagnosis: peripheral blood (skin biopsy)

Tissues appropriate for conventional cytogenetic study:

- That can undergo cell division (during mitosis is best)
- Chorionic villi, amniotic fluid, peripheral blood (lymphocytes), skin (fibroblasts), bone marrow
 - After culturing in vitro, a proportion of cells are arrested in mitosis, and are then 'harvested' for chromosome analysis
 - o MOST COMMON tissue used to search for a constitutional abnormality is peripheral blood
 - After harvesting, the cell preparations are dropped onto glass slides and stained. For most chromosome analysis, a G-banding technique is utilized for staining
 - Each chromosome has a unique G-banding pattern that is constant from individual to individual

ISCN (International System for Cytogenetic Nomenclature):

- P=short arm
- Q=long arm
- Centromeres= p10 and q10
- Telomeres = 6 bp sequence repeat at ends of chromosomes: pter, qter
- Band numbers increase as move from the centromere to the telomere

A single G-band typically contains more than 3 MB of DNA

- Therefore, most constitutional chromosome abnormalities are associated with multiple congenital anomalies
- Therefore, deletion of a single gene cannot be detected by G-banding

Clinical findings in Down Syndrome:

- Recurrent respiratory infections, GI tract anomalies, increased risk for leukemia, mental retardation, Alzheimer's disease
 - o Phenotype Mapping for Down Syndrome:
 - APP = amyloid beta precursor
 - RUNX1 = leukemia
 - Dyrk = neurogenesis

Pregnant women in 19 weeks gestation showing abnormal findings: FISH is done because it is faster

Fluorescence-in-situ hybridization (FISH): get results in 24 hrs (G-banding takes a week for culture of amniotic fluid)

- Probe DNA, label with fluorescent dye, and denature and hybridize

Down Syndrome can also result from structural chromosomal abnormalities:

- Trisome 21:
 - o 95% due to meiotic nondisjunction
 - o 4% due to Robertsonian translocation
 - o 1% due to mosaicism

In general, TRANSLOCATIONS may be classified as BALANCED or UNBALANCED:

- **Balanced:** no net gain/loss of essential genetic info

- **Unbalanced:** net loss or gain of essential genetic material
- Carriers of balanced translocations are typically phenotypically normal, but are at risk for generating gametes with unbalanced translocations

LECTURE 3: CYTOGENETICS 2

Gain of an extra sex chromosome:

- XXY and XYY (1:1000 males)
- XXX (1:1000 females)
- Most do not cause clinical suspicion in the newborn period

47, XXY

- 6 yr old presenting with behavior issues, 15 hr old presenting with gynecomastia (large mammary glands in men), 30 yr old male presenting with history of infertility
- Taurodontism: enlarged pulp chamber at expense of roots in the molar teeth

“Micro” deletion Syndromes:

- Involve the loss of a very small amount of material from the chromosome
- Typically associated with a specific clinical syndrome
- Can be very difficult to detect by G-banding therefore, typically characterized by FISH or microarray

Di George Syndrome and Velocardiofacial Syndrome

- 85% have a deletion of gene 22q11.2
- **VCFS:** cleft palate, cardiac anomalies, characteristic faces
- **Di George:** developmental defects of the 3rd and 4th pharyngeal pouches, resulting in thymic and parathyroid hypoplasia and cardiac defects

Congenital anomalies in 22q deletion syndrome:

- Cardiac: 74%
- Hearing impairments: 39%
- Hypocalcemia: 49%
- T-cell immune deficiency

The most recent advance in cytogenetic technology: Array based-comparative Genomic Hybridization (a-CGH):

- You take a patient genomic DNA and a control genomic DNA: restrict and quantify them and label each with different fluorochromes and combine in a 1:1 ratio.
- Then hybridize to “chip” onto which DNA probes have been “spotted”
- Ratio equals 0: no copy number gains or losses
 - o Less than -0.3 = deletion
 - o More than 0.3 = gain (duplication)

Two data bases that are most informative:

- UCSC Genome Browser
- TCAG: Toronto Center for Applied Genomics: Database for Genomic Variants

Acquired Chromosomal Abnormalities:

Most cancer cells have associated chromosomal abnormalities:

- The abnormalities are acquired
- The abnormalities are clonal (2 or more cells have the same abnormality)
- The abnormalities are limited to the tissues involved in the malignancy

Identification of these abnormalities is important for:

- Differential diagnosis
- Determining therapy
- Providing info about prognosis

Identification of acquired clonal chromosomal abnormalities has also led to:

- Elucidation of the genetic events involved in leukemogenesis
- Development of specific gene-product targeted therapies

42 yr old woman suffers from fatigue, RBC low and WBC 180,000 (super high) and a bone marrow biopsy is performed to rule out leukemia:

- Karyotype reveals: t(9;22)(q34;q11.2)
- Derivative chromosome 22 is commonly known as the Philadelphia chromosome
- Translocation results of the breakpoint cluster region (BCR) in band 22q11.2 to the Abelson murine leukemia virus oncogene (ABL) from band 9q34
- The novel BCR/ABL gene leads to generation of a protein with altered tyrosine kinase activity
 - o Gleevec: drug that targets abnormal tyrosine kinase

Natural history of CML:

- **Chronic Phase:** t(9;22) is typically the sole abnormality
- **Accelerated phase:** 75% of cases gain additional abnormalities
- **Blast crisis:** additional abnormalities typically present as in accelerated phase

LECTURE 4: MUTATIONS IN FAMILIES (Inheritance of genetic conditions)

Mutations: change in DNA sequence that leads to a change in protein expression

Allele: refers to different forms of the same gene

- Wildtype (normal), Mutant (different DNA sequence), and Null (mutation that doesn't lead to a protein or deleted)

Phenotype: the physical appearance of a trait

Genotype: the allele associated with a trait

Classes of Mutations:

- Missense: nucleotide change leads to amino acid change (most common C to T)
- Nonsense: change leads to STOP codon
- Insertions: addition of nucleotide that lead to frameshift
- Deletions: deletion of nucleotides
- Splice site: changes RNA splicing
- Expansion of repeating units

ins or del

- o 3 bp - ins or del one AA (most common mutation in CF delF508)
- o 2 bp ins or del - frame shift
- o 1 bp ins or del - frame shift
- **1 bp substitution**
 - o Silent - "wobble"
 - o Nonsense - AA to "stop"
 - o Missense
 - Conservative - changes AA to same or similar AA
 - Non-conservative - changes AA by function or charge
 - May not change a basepair but may change the RNA splice recognition site

Changes in more than 3 BP:

- Whole gene deletions or duplications
 - o Often due to repeated sequences and mispairing in replications
- Portion of gene deleted or fragment inserted

- Often due to aberrant splicing

Normal THE BIG RED DOG RAN OUT.

Missense THE BIG RAD DOG RAN OUT.

Nonsense THE BIG RED.

Frameshift (1 bp deletion) THE BGR EDD OGR ANO....

Frameshift (1 bp insertion) THE BIG RED DOO GRA NOU

Frameshift (3bp deletion) THE BIG DOG RAN OUT.

Triplet repeat expansion THE BIG BIG BIG BIG BIG RED DOG RAN OUT.

Non-coding mutations that affect gene function

- Promoter/enhancer element Trinucleotide repeats in 5 and 3'UTRs
- Splice sites

Effects of mutation on gene product

- Null allele (loss of function) - no gene product
- Hypomorph - decreased amt/activity
- Gain of function - increased amt/activity
- Dominant negative - antagonizes normal product
- Neomorph - novel activity of product

Predicting that a gene product won't do the job

- Deletion, nonsense, frameshift of sequence are deleterious
- Mutation in a splice site usually bad
- Missense mutations
 - Depends on location in protein
 - Is it non-conservative in terms of AA type?
- Is the AA conserved in evolution?

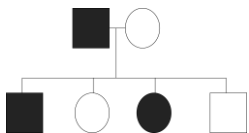
Which ones will cause disease?

- All but silent or conservative missense sequence changes are likely to significantly alter product function
- Among frameshifts, location of mutation alters likelihood of severity
- Mutations in coding sequence are identified most frequently...but this may change

Polymorphism:

- A change in DNA sequence that is not disease causing
- Occurs usually in greater than 1% of population
- Usually does not change an amino acid sequence or produces a significant change (ie: valine for isoleucine)

Autosomal Dominant:



Autosomal Dominant Inheritance:

- males and females equally affected
- 1 in 2 chance of affected offspring from an affected parent
- male to male transmission
- structural genes, transcription factors

- only one abnormal copy of the gene (allele) to have the phenotype

Autosomal Dominant probabilities:

		Mother		
		D	d	
Father	d	Dd	dd	Daughters 50% normal 50% affected
	d	Dd	dd	Sons 50% normal 50% affected

Neurofibromatosis

- Café au lait spots In Neurofibromatosis
- A large plexiform neurofibroma
- Caused by a mutation in the NF1 gene on chromosome 17.
- This is one of the largest genes in the genome.
- This is the most common autosomal dominant condition.
- This condition is fully penetrant; every one who had a mutation in this gene will have the condition.
- Expression can be variable; individuals with the same mutation can have different disease severity.
- more than 6 café-au lait spots
- > 5mm (prepubertal) or
- > 15mm (postpubertal)
- 2 or more neurofibromas
- 2 or more Lisch nodules of the iris
- inguinal or axillary freckling
- optic pathway tumor
- osseous lesion: sphenoid wing dysplasia or thinning of long bone cortex
- 1st degree relative with NF
- diagnosis by 2 or more of the above findings.

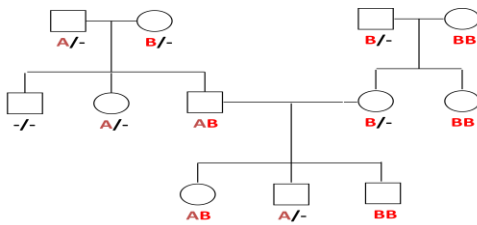
Variations: Co-dominant expression:

Definition: alleles that are both expressed when they occur in the heterozygous state.

Example: ABO blood group antigens

- **ABO Blood Groups**
 - Defined by the presence or absence of two antigens on the surface of the red cell
 - A and B
 - if you have A, you have anti-B antibodies
 - if you have B you have anti-A antibodies
 - if you have neither (O) you have both anti- A and -B
 - Absence of A or B = O
 - Three allele states: I^a I^b I^{null}

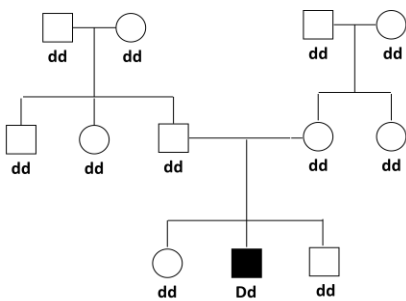
ABO blood typing: co-dominant alleles



Variations: New Mutations

- Occur at a rate of 10^{-4} to 10^{-7} per locus per cell division
- More easily seen in a very large gene
- Paternal age effects

Autosomal dominant: new mutation



Achondroplasia:

- Autosomal dominant
- 100% penetrance
- 1/26000: most common genetic dwarfism
- 80% new mutations
- Features
 - rhizomelic dwarfism (upper arms and thighs are short)
 - lumbar lordosis (lower spine curves out)
 - large head
 - small foramen magnum
 - intact intellect
 - Mutation in FGFR3: activating mutation

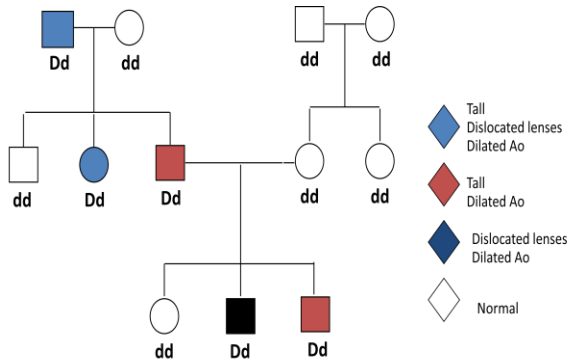
Achondroplasia and FGFR

- Mutations in FGFR3 cause achondroplasia
- Despite frequent new mutations almost all are caused by the same mutation (G → A at nt 1138, causes gly 380 arg)
- An individual can inherit a mutation in FGFR3 from an affected parent and have achondroplasia.
- The majority of individuals have parents who are not affected.
- How does this occur? New mutation (de novo event).

Marfan Syndrome: pleiotropy and variable expression:

- Skeletal findings- disproportionate long bone growth
- Tall Stature
- Eyes- dislocated lenses
- Heart-dilation of aortic arch

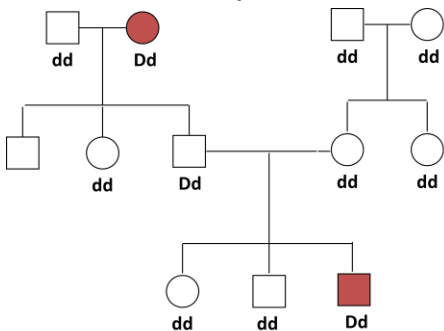
AD traits are often variable in expression:



Variations: reduced penetrance:

- An individual may carry an altered allele and never manifest phenotypic evidence of this.
- Penetrance: an “all or nothing” phenomenon in expression of a trait in a population
 - phenotype, NOT genotype

Variation: reduced penetrance:



Familial Retinoblastoma: a recessive state in the cell inherited as AD trait:

Case history: 6 month old child found to have leucocoria (white pupil) On exam there is a large mass in the eye. The other eye has a small lesion. Father gives the history that his mother had only one eye because the other was removed when she was a baby. He and his 2 sibs were healthy and have both eyes

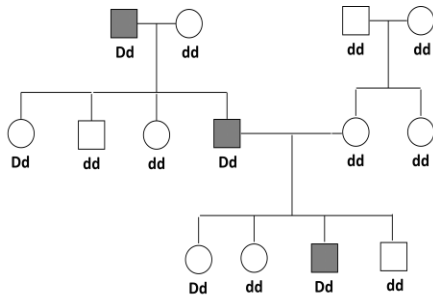
Explanation:

REDUCED PENETRANCE of this trait

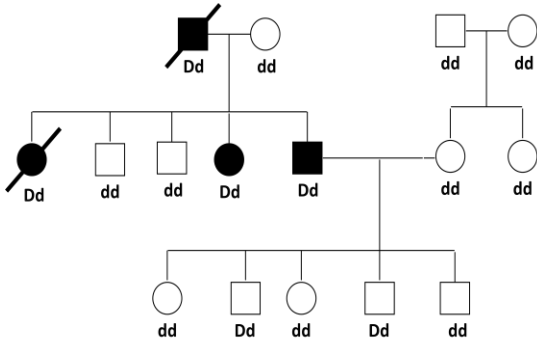
A sex-limited AD trait:

- Familial male precocious puberty
- Pubertal onset in males by age 4.
- Due to gain of function mutation that keeps the leutinizing hormone (LH) receptor in an “on” state

Autosomal Dominant: sex limited trait:



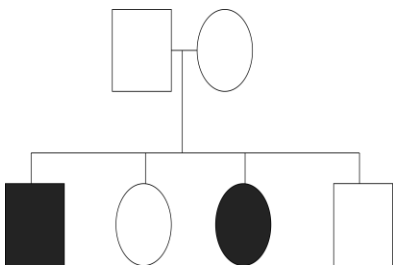
Autosomal Dominant: variation in age of onset:



Variation: Altered age of onset

- Huntington's Chorea
 - Progressive dementia
 - Choreiform movements
- Autosomal Dominant pattern
- Triplet repeat expansion in the Huntington gene that can expand
- Age of onset usually after 30 but varies based on size of the expansion and parent of origin

Autosomal Recessive Inheritance



Autosomal Recessive : pattern of inheritance

- Males and females equally affected
- Condition seen in sibs but not usually in other relatives
- Risk of recurrence in sibs 25%
- 2/3 of unaffected sibs are carriers
- Consanguinity increases risk

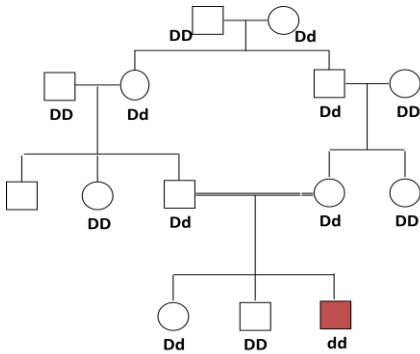
Autosomal Recessive Probabilities:

25% affected

2/3 of unaffected are carriers

		Mother	
		A	a
Father	A	AA	Aa
	a	Aa	aa

Effect of consanguinity: Consanguinity increases the risk of sharing a common ancestral mutation



Loss of function alleles:

- Likely when point mutations give the same phenotype as deletion of an allele
- Inherited as recessive traits when 50% of expression is sufficient for normal phenotype
- Loss of function and gain of function changes in the same gene will cause different diseases

Generalizations about genes inherited as AR traits:

- Transcription from one allele is sufficient
- Severity dependent on nature and location of mutation
- What we describe in inheritance pattern as homozygosity is USUALLY compound heterozygosity at molecular level. Allelic heterogeneity is COMMON

Concept: Phenotypes can vary based on the nature of a mutation

- Oculocutaneous Albinism
 - autosomal recessive condition
 - Absent or reduced pigment in melanosomes
 - poor protection against sun damage/skin cancer
 - Reduced visual acuity
 - many patients will not be able to drive
 - optic nerve misrouting
 - foveal hypoplasia
 - nystagmus
 - strabismus

Albinism: similar phenotype multiple loci

- Other genes in the pathway of pigment production can give albinism
- Four autosomal genes involved in separate albinism conditions
- TYR (tyrosinase), P locus, TRP1 (tyrosinase related protein 1) and MATP: all encode enzymes needed for pigment formation

X linked inheritance

Consequences of “Lyonization”

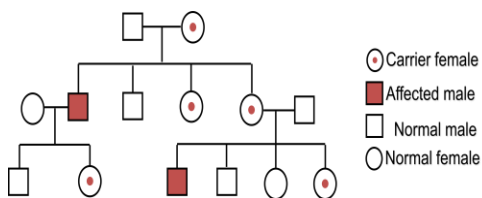
- Females are mosaic for their X-linked gene manifestations
 - should be roughly equal
- All are functionally hemizygous
 - dosage compensation: have the same number of copies as males
- Inactive X may be evident in cells
 - The Barr body
- Shifting from random distribution may result in manifestation of disease in females
 - skewed lyonization

X-linked recessive “rules”

- Affects mainly males
 - Affected males are usually born to unaffected parents
 - Females can be affected if born to an affected father and carrier mother
 - Females can be affected if they have very skewed lyonization
- No male to male transmission
- Males born to carrier mother have 50% risk of inheriting altered gene

X-linked recessive

What does the pattern look like?



X-linked recessive recurrence risks:

		Mother		
		X_1	X_2	
Father	X_1	X_1X_1	X_1X_2	Daughters 50% normal 50% carriers
	Y	X_1Y	X_2Y	

Duchenne/Becker Muscular Dystrophy

- Mutations in dystrophin gene
- Duchenne
 - Typically del/dup but frameshift
 - Severe
 - No protein product
- Becker
 - Also del/dup in frame so milder
 - Shortened protein

Clinical manifestations of Duchenne MD

Onset before age 5

Calf pseudohypertrophy

1/3500 males

Elevated creatine kinase

Severe muscle wasting

Affects resp and cardiac mm

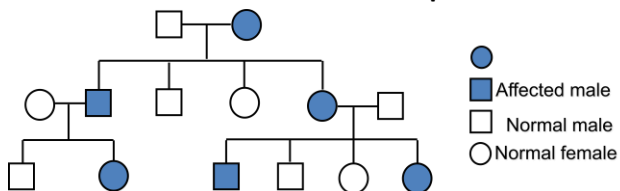
Females 8-10% some weakness

CK > 95%tile in 2/3 of carriers

X-linked dominant “rules”

- Males and females both affected, but typically males are worse than females.
- If male lethal, only affected females observed.
- Affected males will only have affected daughters and unaffected sons.
- No male → male transmission seen

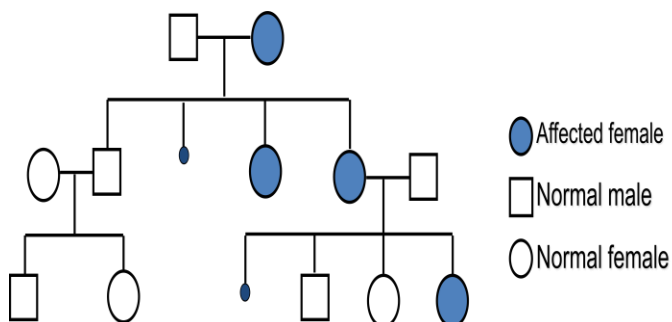
X-linked dominant: What does the pattern look like?



Example with male survival

X-linked dominant, male lethal

What does the pattern look like?



X-linked dominant recurrence risks:

		Mother	
		X_1	X_2
Father	X_1	X_1X_1	X_1X_2
	Y	X_1Y	X_2Y

Daughters
50% normal
50% affected

Sons
50% normal
50% affected

Incontinentia pigmenti X-linked dominant (male lethal condition):

- Linear blisters in newborn girls
- “Crops” followed by scarring
- Small teeth
- Eye abnormalities
- Patchy hair loss
- Only girls are affected
- Males are typically not affected

Potentially confusing in X-linked pedigree analysis:

- Male lethal X-linked conditions
- New mutations may be hard to recognize as X-linked
- Sex-limited conditions may look X-linked
- With carrier mother and affected father can see “male to male” inheritance

LECTURE 5: INHERITED ORAL DISEASE

NAME:
MODE OF TRANSMISSION:
GENE:
CLINICAL PRESENTATION:

Papillion-LeFevre Syndrome

Autosomal Recessive

Cathepsin Gene

Severe hyperkeratosis, dramatic periodontitis, floating teeth

Cherubism

Autosomal Dominant

NO gene

Expansion of posterior mandible, eyes upturned, radiograph shows multilocular radiolucency with massive expansion on Mn, cherub-like face

Cleidocranial Dysplasia

Autosomal Dominant and sporadic pattern (spontaneous mutation)

Cbfa1/Runx2 gene

Bone defects in clavicle or skull, clavicle may be absent, short stature w/ large head, skull sutures remain open, high-arched palate, many unerupted teeth

Crouzon Syndrome (Craniofacial Dysostosis)

Autosomal Dominant

FGFR2 gene

Ocular proptosis (eyes sticking out), headaches, normal intelligence, underdeveloped maxilla, crowding of Mx teeth, bifid uvula, "beaten metal" skull

Aperts Syndrome (Acrocephalosyndactyly)

Autosomal Dominant

FGFR2 gene

Similar to Crouzon but more severe, Syndactyly of the 2nd, 3rd, and 4th digits, mental retardation, pseudo cleft palate due to swellings of the lateral hard palate and crowding of Mx teeth, bifid uvula

Treacher-Collins Syndrome (mandibulofacial Dysostosis)

Autosomal Dominant, 60% spontaneous mutation

TCOF1 gene

Characteristic face: narrow face with depressed cheeks and downward slanting palpebral fissures, coloboma (notch) at the outer portion of lower eyelid, ear anomalies, underdeveloped mandible, lateral facial clefting and cleft palate

Multiple Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome)

Autosomal Dominant

Patched mutation, chr. 9

Multiple basal cell carcinomas even in areas not exposed to the sun, odontogenic keratocysts, epidermal cysts, palmar/plantar pits, calcified falx cerebri, bifid ribs, hypertelorism, big head, develop tumors in spinal cord

Osteopetrosis

Infant = AR

Adult = AD

No gene – just nonfunctioning Osteoclasts

Infantile form: have osteosclerosis, hematologic, and neurologic manifestations, most die before 20yrs old due to anemia (due to the replacement of the bone marrow compartment with bone) and infection, face: broad face, hypertelorism, snub face and frontal bossing, tooth eruption delayed, narrowing of cranial nerve foramen resulting in blindness, deafness, and facial paralysis, despite dense bones, pathologic fractures (very brittle), osteomyelitis of jaws (compaction of tooth extraction), radiographs: distinction between cortical and cancellous bone is lost

Adult form: more common, happens later in life, relatively mild, NO anemia, NO blindness, and NO hearing loss, fractures are uncommon but recover after an extraction are complicated

Neurofibromatosis (Von Recklinghausen disease of the skin)

Autosomal Dominant

NF1 most common gene, chr.17

Malignant transformations, benign neural tumors of the skin and oral cavity, 6 or more café au lait macules, axillary freckles, Lisch nodules (brown pigmentation spots of the iris), oral lesions, enlarged Mn foramen and Mn canal and fungiform papillae. (several criteria....refer in notes)

Multiple Endocrine Neoplasia, Type IIB

Autosomal Dominant, 50% new mutation

Mutation of ret proto-oncogene, chr.10

MEN IIB: MEN IIA and mucosal neuromas (tumors in the mouth), Marfanoid phenotype (long face and thick lips), narrow face, everted upper eyelid, oral lesions may be first sign!, common bilateral commissural neuromas, Pheochromactoma (secretion of catecholamines due to medulla tumor), sweating, diarrhea, headaches, flushing, heart palpitations, and hypertension, medullary carcinoma of the thyroid: calcitonin production, highly metastatic

Peutz-Jeghers Syndrome

Autosomal Dominant

No gene

Multiple perioral and oral ephelides or melanotic macules, intestinal polyposis, looks like freckles, on the palms and soles of feet.

Amelogenesis Imperfecta

Different modes of inheritance

Absence of systemic disorder, can be part of a syndrome, many different types, both dentition

Classification is impractical for clinicians, problems arise from the 3 stages of enamel formation:

1) Hypoplastic

- Inadequate deposition of organic matter, normal mineralization
- Generalized pitted: AD, pinpoint/head pits in rows and columns, in between the enamel is normal, across the surface, buccal surface more severely affected, DOES NOT correlate with pattern of environmental damage
- Diffuse Smooth: AD, thin/hard/glossy, like crown preparations, open bite, opaque white to brown

2) Hypomaturation

- Defect in the maturation of enamel crystals, normal shape, mottled appearance, white/yellow/brown, enamel is soft, radiodensity similar to dentin
- Diffuse Pigmented: mottled brown, chipping from dentin with an explorer, very uncommon anterior open bite, soft similar to hypocalcified, calculus
- Snow-capped teeth: AD, X-linked? Zone of white opaque enamel on incisal and occlusal surfaces, looks like fluorosis, both dentition

3) Hypocalcified

- AD or AR (more severe), no significant mineralization, normal shaped teeth at eruption, enamel very thin and easily lost, yellow or brown color, calculus, open bite

Treatment: restorations as soon as possible, dentures, veneers in mild cases, glass ionomers for better adhesion to dentin

Osteogenesis Imperfecta:

AD and AR

Mutation in type I collagen gene

Most common type of inherited bone disease, severity varies, weak bones, blue sclera, altered teeth, hearing loss, long bone and spine deformity, and joint hyperextension, shell teeth can be noted

Four major types of OI:

Type I: most common and mildest form

Type II: most severe, patients die before 4 weeks of age

Type III: most severe form beyond prenatal age

Type IV: mild to moderate form

Hypophosphatasia:

Autosomal Recessive

NO gene???

Decreased alkaline phosphatase, bone defects similar to rickets, increased blood and urinary phosphoethanolamine, premature loss of primary teeth without inflammatory response, NO CEMENTUM on teeth

Vitamin D – Resistant Rickets (hereditary Hypophosphatemic Rickets)

X-linked dominant trait

PHEX gene mutation

Males affected more severely than females, decreased capacity to reabsorb phosphate, teeth with large pulp chambers with pulp horns that extend to the DEJ leading to very small pulp exposures leading to multiple Periapical lesions and gingival sinus tracts.

LECTURE 6: GENETIC RISK FACTORS FOR PERIODONTITIS

(didn't do)

LECTURE 7: PROGRESSION FROM LEUKOPLAKIA TO ORAL CANCER

(Dr. Raj's lecture....on Tuesday)