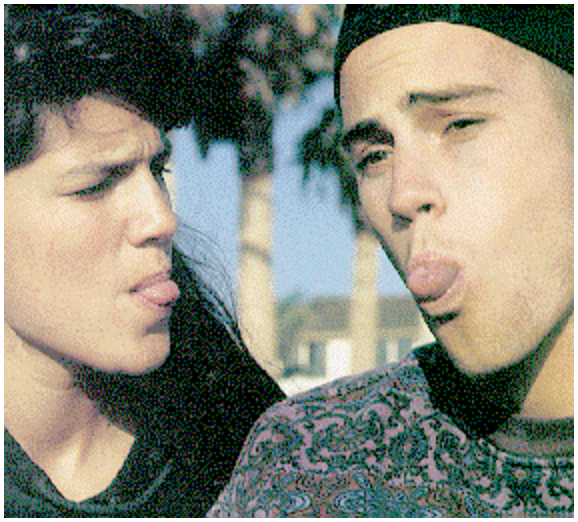
Psych 3102
Lecture 4

Mendelian genetics in humans



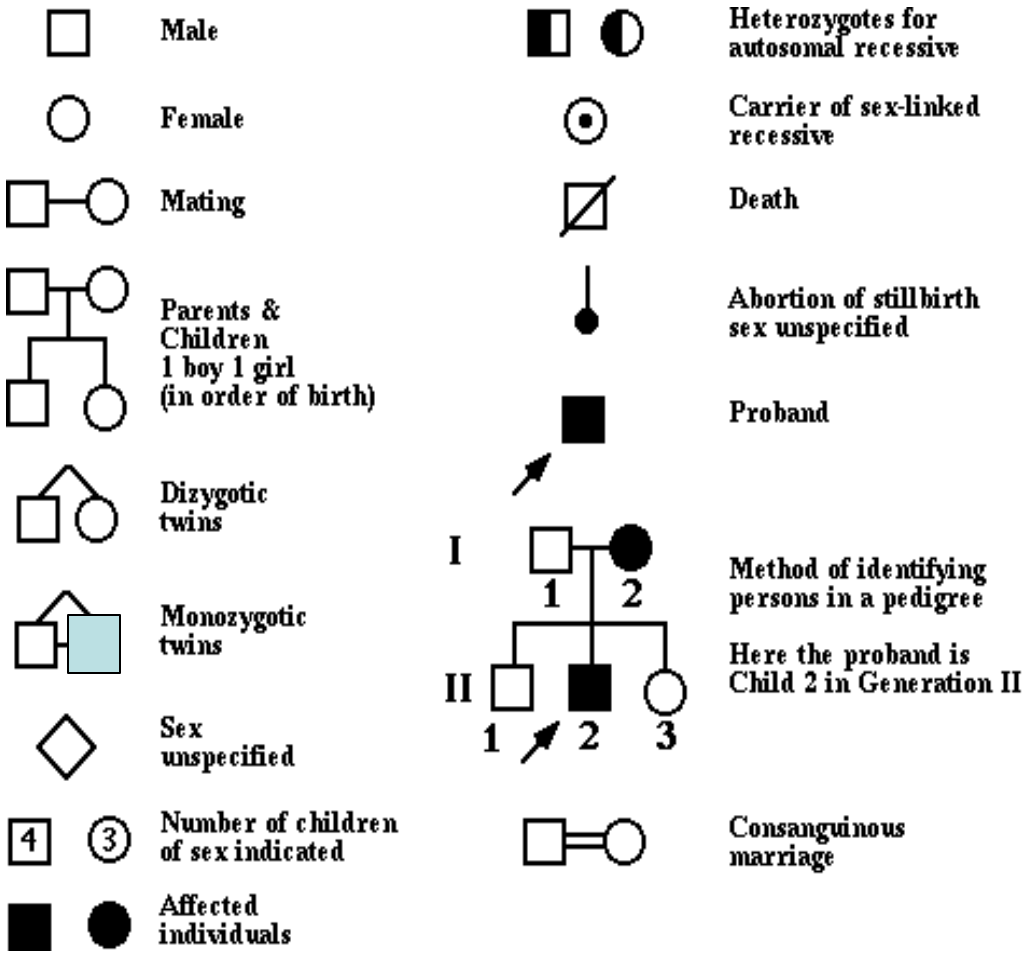
Problems

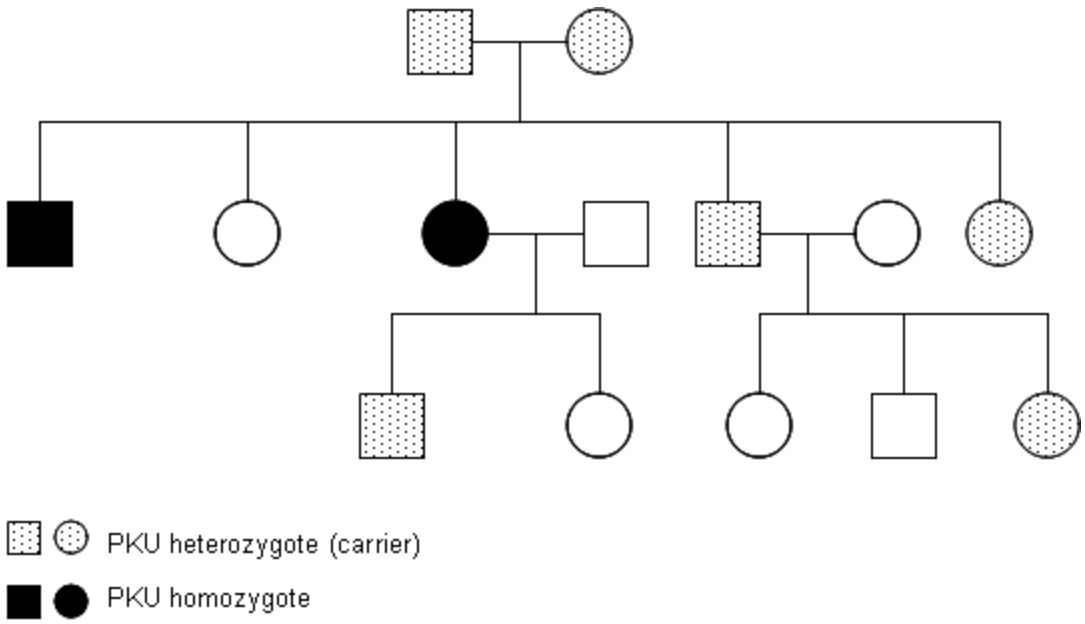
- no controlled mating
- unknown genetic background
- long generation time
- small family size
- no environmental control

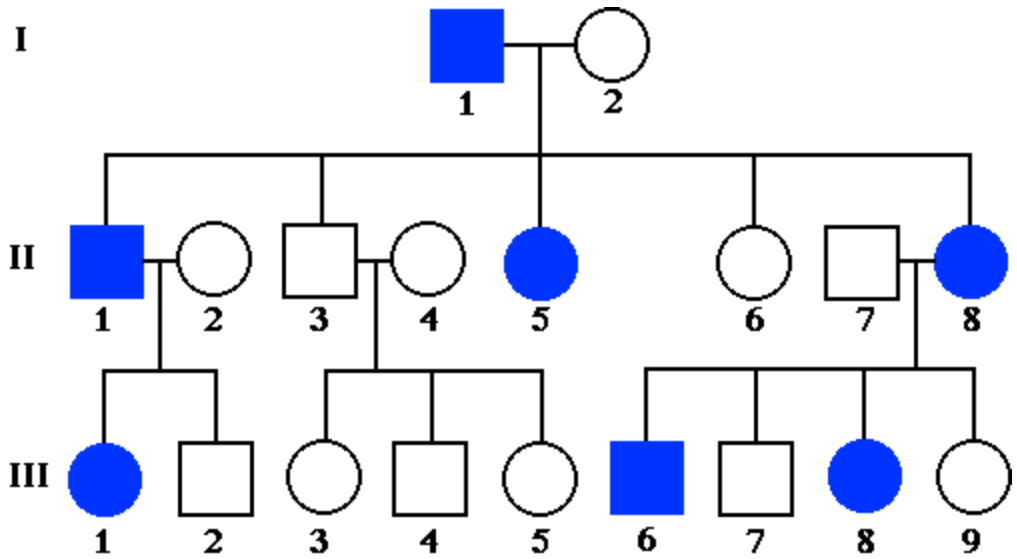
To look for Mendelian inheritance patterns, employ the use of

large pedigrees – large family trees showing relationships and phenotypes

pedigree analysis – try to infer genotypes and hence inheritance patterns


Male
Female
Mating
Parents & Children
1 boy 1 girl
(in order of birth)
Dizygotic twins
Monozygotic twins
Sex unspecified
4
3
Number of children of sex indicated
Affected individuals
Heterozygotes for autosomal recessive
Carrier of sex-linked recessive
Death
Abortion of stillbirth sex unspecified
Proband
I
1
2
II
1
2
3
Method of identifying persons in a pedigree
Here the proband is Child 2 in Generation II
Consanguinous marriage


PKU heterozygote (carrier)
PKU homozygote



Pedigree 1. An idealized pedigree of a family with hypercholesterolemia, an autosomal dominant disease where the heterozygote has a reduced number of functional low density lipoprotein receptors.

- Symbols used in human pedigree analysis
- autosomal recessive traits
- autosomal dominant traits

you need to be familiar with symbols and typical pedigrees

- deleterious = harmful

If the allele producing a deleterious trait is dominant, the individual is almost always heterozygous. Why?

- allele will be rare, chances of being a homozygote are therefore low
- both parents would have to be affected
- the homozygous condition is often lethal in utero

Deleterious dominants can survive in the population by exhibiting:

- late onset

- variable expressivity people with the same genotype show varying phenotypic expressions

- low (incomplete) penetrance some people with a particular genotype do not show any aspect of the expected phenotype

If: 60% with Aa show expected phenotype (ie A allele is penetrant in these people)

40% with Aa do not show expected phenotype (ie. A allele is not penetrant in these people)

Penetrance of this A allele = 60% , ie it shows low or incomplete penetrance in the population

How do deleterious recessive alleles survive in a population?

effects of the allele are not present in heterozygotes

- allele is not selected against in heterozygotes

heterozygous advantage

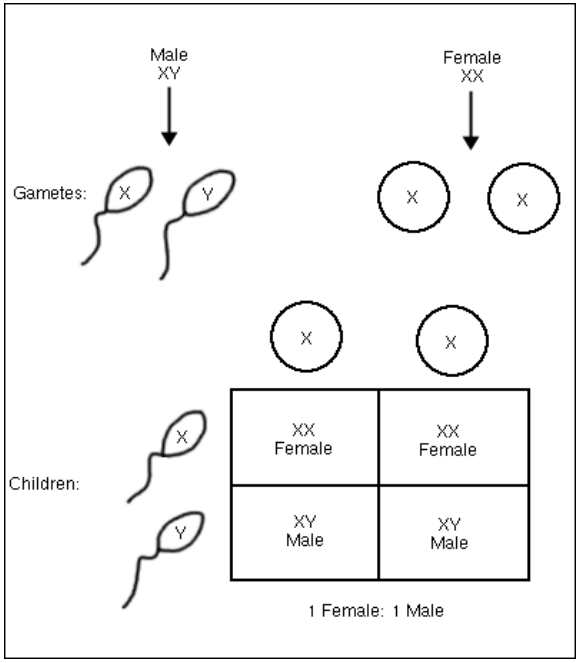
a way in which incompletely dominant/recessive deleterious alleles may become more common than expected

- heterozygote does not show full effects of the deleterious allele
- heterozygote actually has a phenotypic advantage under certain environmental conditions

Beyond Mendel
- Extensions of Mendelian genetics

Sex Linkage

- genes for the trait are on the X or Y chromosome



- genes on male parent X never inherited by his sons
- genes inherited from mother's X will always be expressed in a son

Example – Duchenne muscular dystrophy (DMD)

Inheritance: X-linked recessive

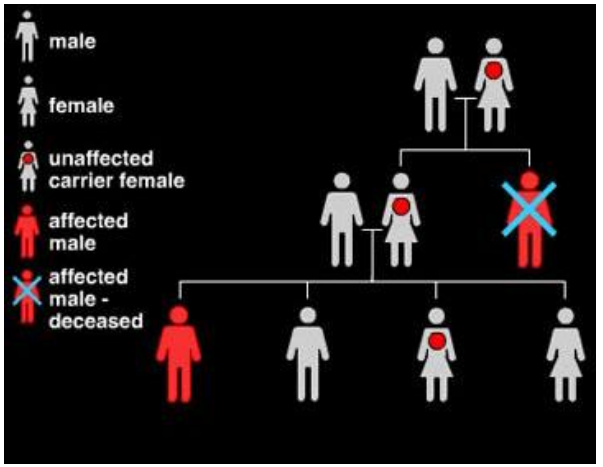
Prevalence: 1 in 3500 males

Phenotype: neuromuscular disorder

progressive wasting of muscles

death by age 20

neurons in brain also affected



Inheritance pattern for X-linked recessive alleles

- Example

X^D = normal allele on X chromosome

X^d = Duchenne dystrophy allele

P normal mother x affected father (hypothetical, for illustration)

F_1

	X^d	Y
X^D	X^DX^d	X^DY
X^D	X^DX^d	X^DY

all children are unaffected

all females are carriers

no sex differences

P carrier mother x normal father

F_1

	X^D	Y
X^D	X^DX^D	X^DY
X^d	X^DX^d	X^dY

50% sons affected

50% daughters carriers, all unaffected

1 in 4 but all male

sex differences

Gene Therapy (2008) 15, 1077–1078

www.nature.com/gt

Treatments for muscular dystrophy

Increased treatment options for Duchenne and related muscular dystropies

DJ Wells

Gene Therapy (2008) 15, 1077–1078; doi:10.1038/gt.2008.97;
published online 5 June 2008

The last few years have been an exciting time for all those committed to developing treatments for muscular dystrophies with the emergence of a number of clinically applicable treatments. The recent paper by Millay *et al.*[1] makes an important contribution as it opens up a new area of disease modification by reducing mitochondrial-dependent necrosis to alleviate the effects of muscular dystrophy in mice. Potentially, this could also be helpful for other conditions involving mitochondrial-dependent necrosis.

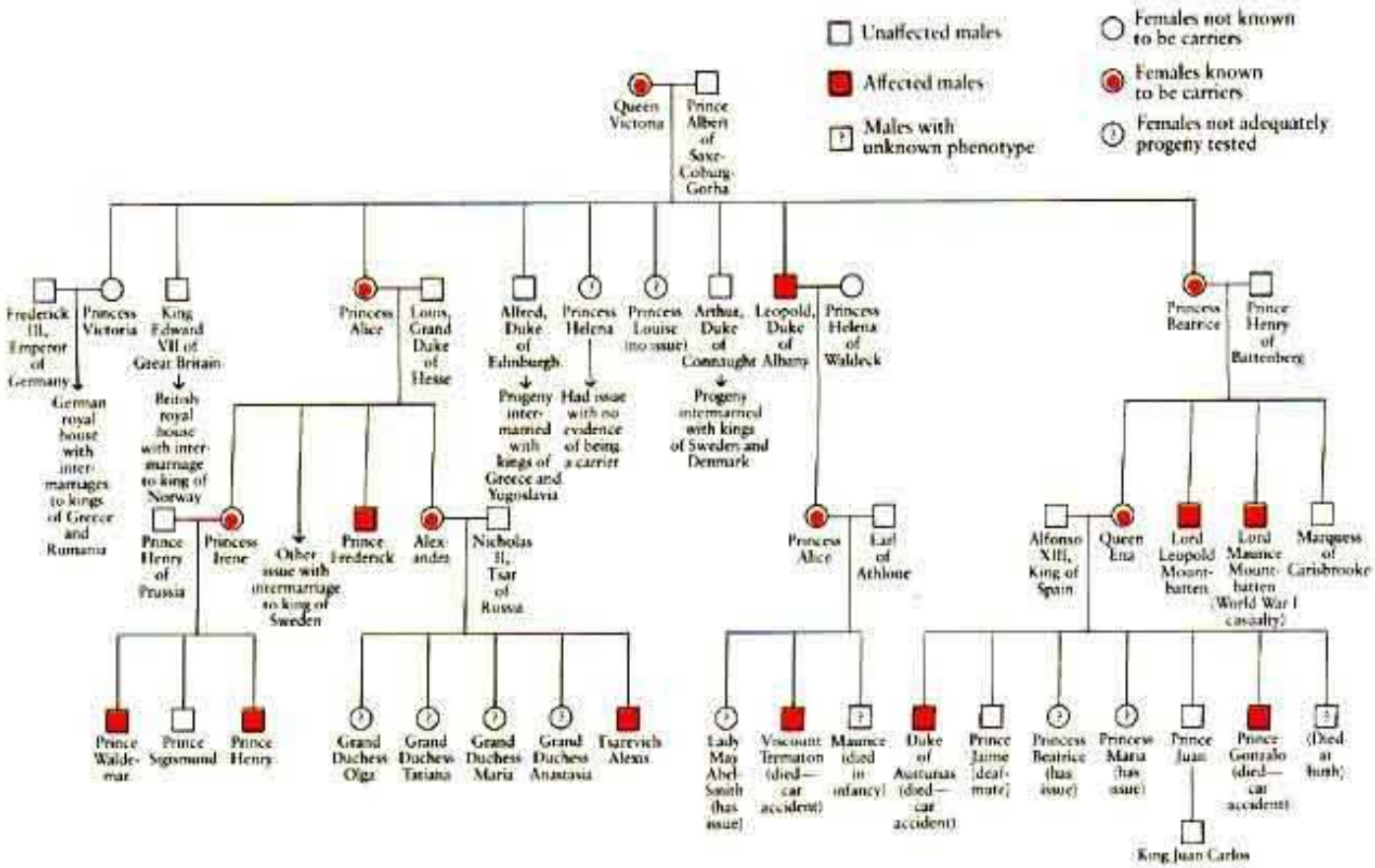
Muscular dystrophies are a group of inherited disorders characterized by progressive muscle wasting often presenting in early childhood. The most common is Duchenne muscular dystrophy (DMD), which affects 1 in 3500 male births. DMD is caused by defects in the largest gene in the human genome, which spans 2.5 Mb. This gene encodes a large cytoskeletal protein called dystrophin that links the cytoskeleton, and hence contractile apparatus, of the muscle cell with the extracellular matrix. Dystrophin is attached to the cytoskeleton by its amino terminus and through a region close to the carboxy terminus to β-dystroglycan embedded in the cell membrane. This in turn links to α-dystroglycan and hence to proteins in the extracellular matrix including laminin α2. A complex of membrane associated proteins (sarcoglycans) is linked to the stabilised β-dystroglycan. A deficiency in any one of the associated or linking proteins causes muscular dystrophy (reviewed in[2]).

Current treatments for DMD are symptomatic and significantly improve longevity and quality of life but do little to prevent loss of muscle function. Experimental therapies currently under investigation fall into three categories. The first restores expression of dystrophin to halt progression of the disease and a number of approaches modify processing of the gene or introduce a recombinant version of dystrophin. These include antisense-mediated exon-skipping, read-through of premature stop mutations and viral gene transfer, which are all currently at clinical trial stage.[3,4] The second involves overexpression of compensating genes either through gene transfer or by upregulating expression using small molecules. Genetic candidates include utrophin, the autosomal homologue of dystrophin, α7 integrin and IGF-1.[2] The final category involves modifying the disease process downstream of the dystrophin deficiency and a number of disease-modifying agents such as angiotensin II type 1 receptor blockade (Losartan), a blockade of TNF-α and coenzyme Q10 have been tested and shown to be effective in the mouse model of DMD.[5,6] The results presented by Millay *et al.*[1] are an important addition to this latter category and present a novel treatment target.

In many muscular dystrophies the missing protein leads to a destabilization of the sarcolemma with an associated increase in the influx of calcium ions into the muscle fibre. In an effort to remove the excess calcium the mitochondria become overloaded, which triggers an increase in mitochondrial permeability. If left unchecked, this leads to necrotic and/or apoptotic cell death. An important regulator of this process is Cyclophilin D and mice lacking the gene for this protein (*Ppif*) are resistant to calcium-induced swelling and ischemia/reperfusion-induced cell death.[7] Millay *et al.* demonstrate that crossing these $Ppif^{-/-}$ mice with mice lacking δ sarcoglycan ($Scgd^{-/-}$, a mouse model of limb girdle muscular dystrophy 2F) or laminin α2 ($Lama2^{-/-}$, a mouse model of congenital muscular dystrophy 1A), markedly attenuated the disease process, although it did not prevent it entirely.[1] They also showed that two times daily treatment for 6 weeks with Debio-025, a cyclophilin inhibitor, substantially reduced the disease in *mdx* and $Scgd^{-/-}$ mice.

Debio-025 is a synthetic cyclosporine analogue with no immunosuppressive capacity but a high inhibitory potency against cyclophilin A-associated *cis–trans* prolyl isomerase activity. It is under development by the Debiopharm Group as a treatment for hepatitis C and has recently completed a Phase IIa clinical trial (http://www.debiopharm.com/products/pipeline/debio-025.html). The results of the Millay paper suggest that the use of Debio-025 offers new treatment strategies for muscular dystrophies including DMD; however, it is important to be cautious in extrapolating directly from mouse to man. A key concern would be the determination of a safe and effective dose of Debio-025 in man. Most pre-clinical studies essentially dose for effect whereas human doses are necessarily driven by safety issues rather than maximum effectiveness. Furthermore, any successful treatment for muscular dystrophies is likely to require continuous or repeated cycles of treatment and little is known about the long-term toxicity in man of many of the therapies that have been acutely tested in mouse models. Finally, mice may not be the best model of the disease. In the case of DMD, it would be very interesting to see the results of using Debio-025 in the canine model, the golden retriever muscular dystrophy. GRMD dogs have a more severe disease than *mdx* mice with a marked reduction in mobility and premature death. This happens during the first year of the dog's life and will therefore allow clinical assessment of the benefit of a therapeutic approach.

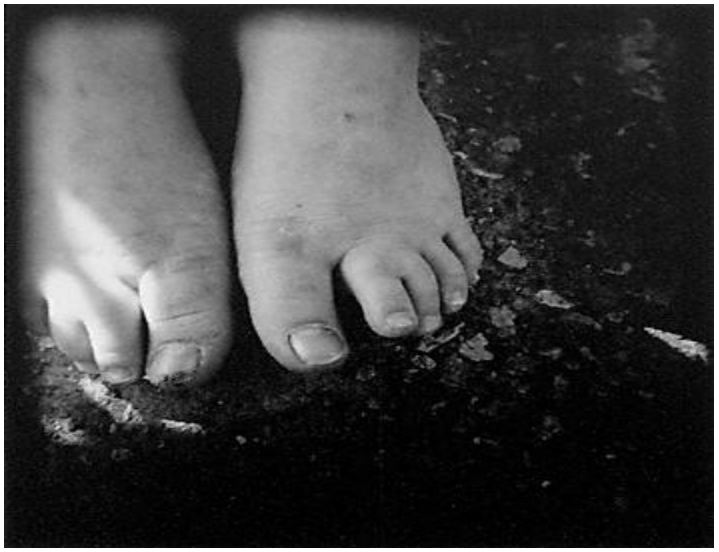
Despite these reservations, the reduction of mitochondrial-dependent necrosis is an important addition to the range of potential treatments for DMD and related muscular dystrophies. It is likely that no single treatment will be sufficient to completely halt or reverse the progression of these diseases but a combination of treatments may one


Unaffected males
Affected males
Males with unknown phenotype
Females not known to be carriers
Females known to be carriers
Females not adequately progeny tested
Queen Victoria
Prince Albert of Saxe-Coburg-Gotha
Frederick III, Emperor of Germany
Princess Victoria
King Edward VII of Great Britain
German royal house with intermarriages to kings of Greece and Rumania
British royal house with intermarriage to king of Norway
Princess Alice
Louis, Grand Duke of Hesse
Alfred, Duke of Edinburgh
Princess Helena
Princess Louise (no issue)
Arthur, Duke of Connaught
Leopold, Duke of Albany
Princess Helena of Waldeck
Princess Beatrice
Prince Henry of Battenberg
Progeny intermarried with kings of Greece and Yugoslavia
Had issue with no evidence of being a carrier
Progeny intermarried with kings of Sweden and Denmark
Prince Henry of Prussia
Princess Irene
Other issue with intermarriage to king of Sweden
Prince Frederick
Alexandra
Nicholas II, Tsar of Russia
Princess Alice
Earl of Athlone
Alfonso XIII, King of Spain
Queen Ena
Lord Leopold Mountbatten
Lord Maurice Mountbatten (World War I casualty)
Marquess of Carisbrooke
Prince Waldemar
Prince Sigismund
Prince Henry
Grand Duchess Olga
Grand Duchess Tatiana
Grand Duchess Maria
Grand Duchess Anastasia
Tsarevich Alexis
Lady May Abel-Smith (has issue)
Viscount Termaton (died—car accident)
Maurice (died in infancy)
Duke of Asturias (died—car accident)
Prince Jaime (deaf-mute)
Princess Beatrice (has issue)
Princess Maria (has issue)
Prince Juan
Prince Gonzalo (died—car accident)
(Died at birth)
King Juan Carlos

Inheritance pattern for X-linked dominant allele

1. affected male will have no normal daughters but no affected sons
2. heterozygous female transmits to 50% progeny of either sex
3. affected females are more common than affected males

examples: webbing of toes



Rett syndrome (RTT)

- 1 in 10,000 girls (lethal in boys)
- severe mental and physical disability within first year of life, phenotypic heterogeneity with some unaffected female 'carriers'
- spontaneous mutation

leads to loss of MECP2 across neurons in brain after birth (MECP2 is a protein that controls methylation of DNA and hence expression of other genes)

- mouse model enabling better study

X^R = Rett allele on X chromosome

X^r = normal allele

P affected female X^RX^r x normal male $X^r Y$

F_1

	X^r	Y
X^R	X^RX^r	X^RY
X^r	X^rX^r	X^rY

50% of progeny have Rett

- no sex differences

Reciprocal cross (reverse phenotypes of sexes) shows sex differences

P normal female X^rX^r x Rett male $X^R Y$

F_1

	X^R	Y
X^r	X^RX^r	X^rY
X^r	X^RX^r	X^rY

all females affected

no males affected

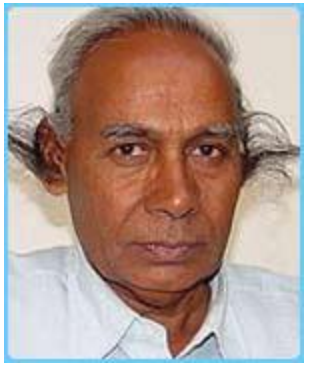
Y-linked inheritance

holandric traits

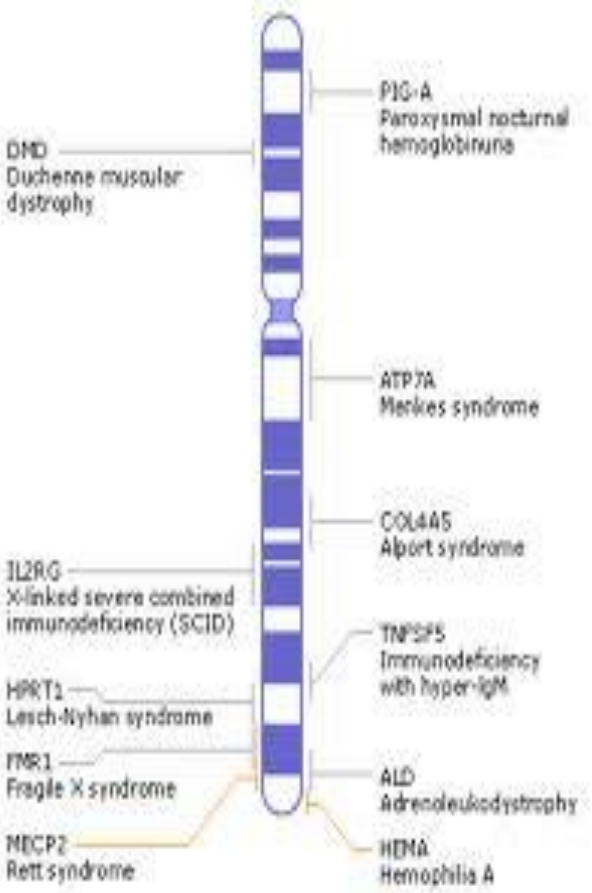
1. Never shown in females
2. every male with the allele will express it

TDF (SRY) testis-determining factor

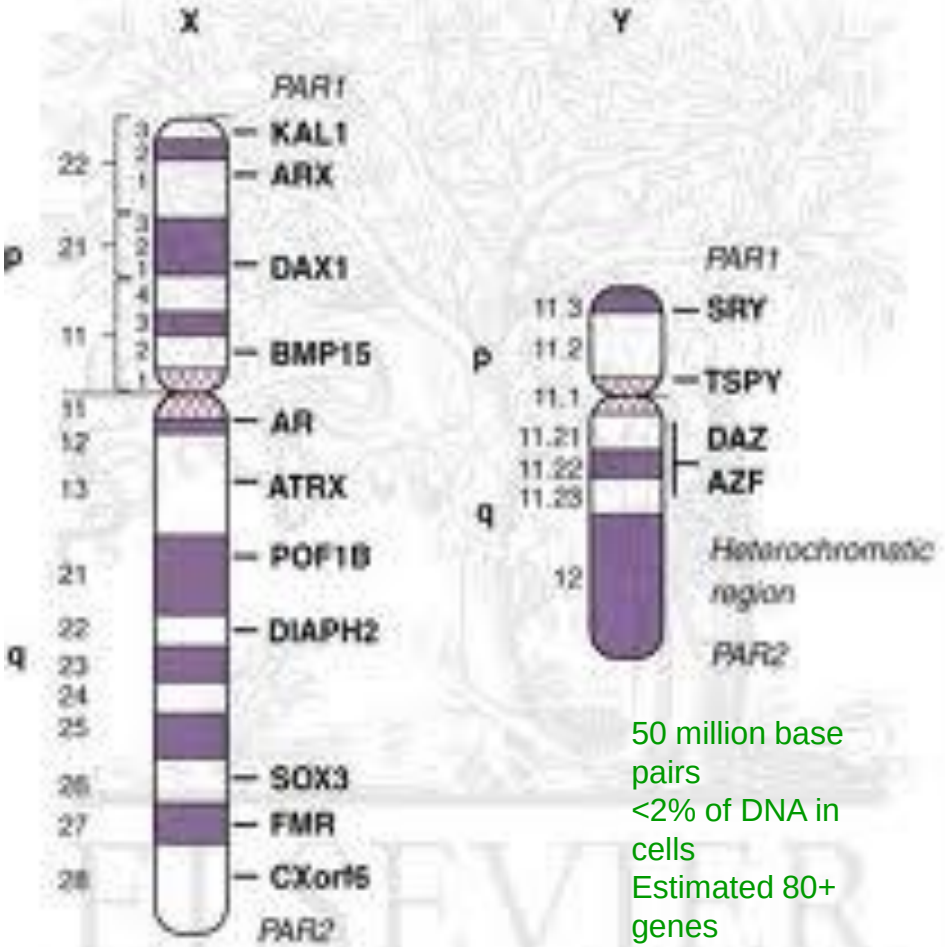
hairy ear syndrome – NOT Y linked



X



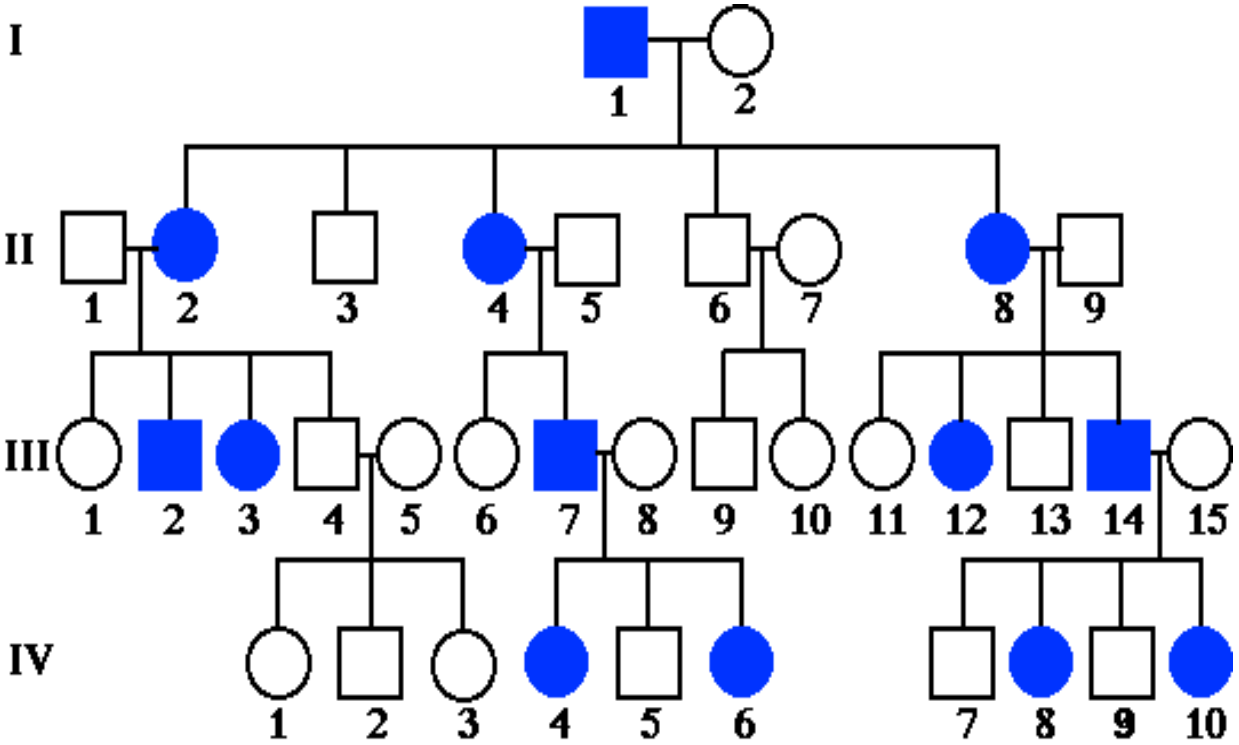
Relative sizes



153 million base pairs
5% of DNA in female cells
Estimated 1300+ genes

50 million base pairs
<2% of DNA in cells
Estimated 80+ genes

Likely mode of inheritance for this disorder?



Autosomal dominant

Recessive also works but would require allele to be common – not likely for a disorder