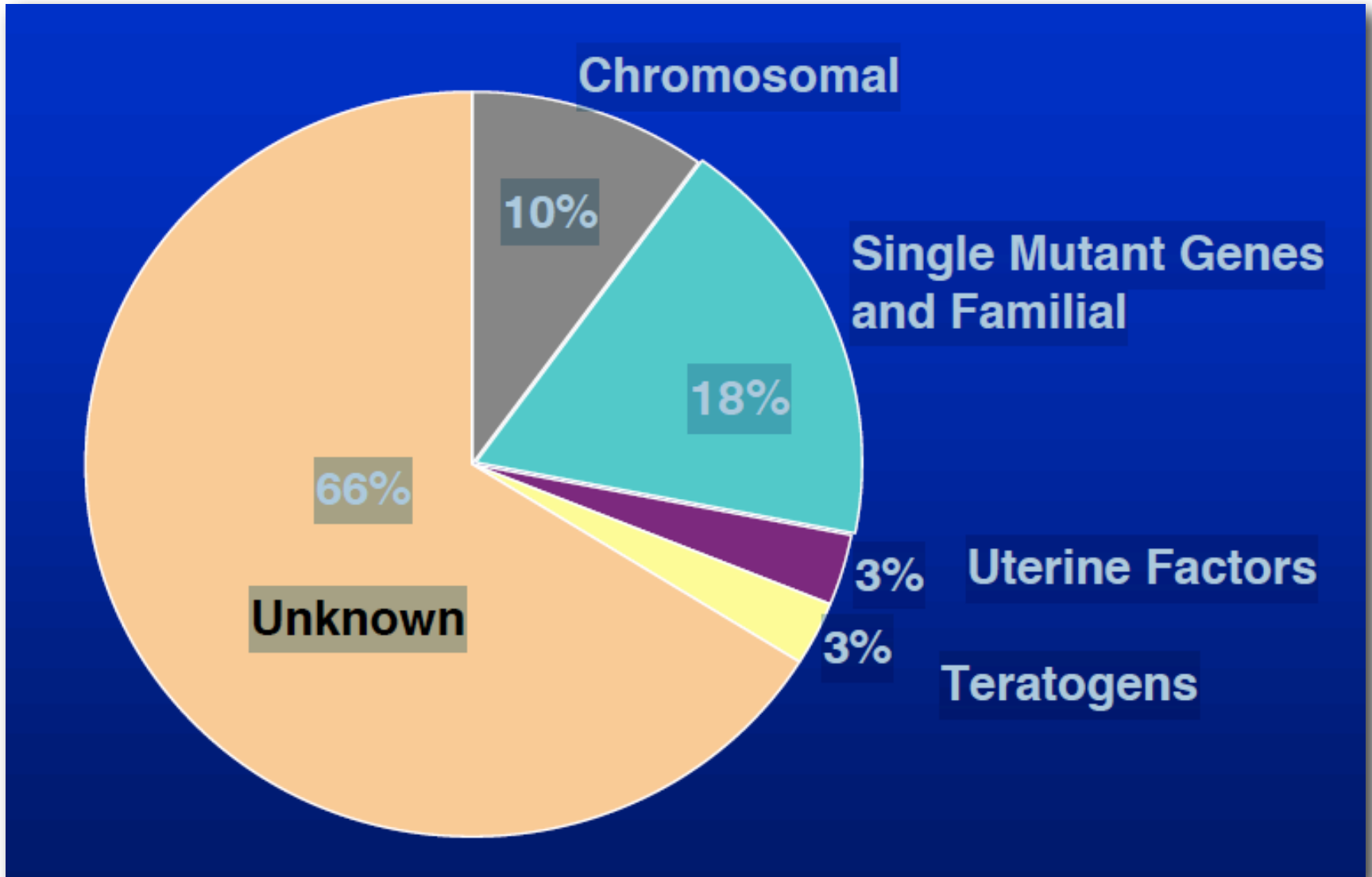


Causes of Birth Defects



Some medical / genetic terms:

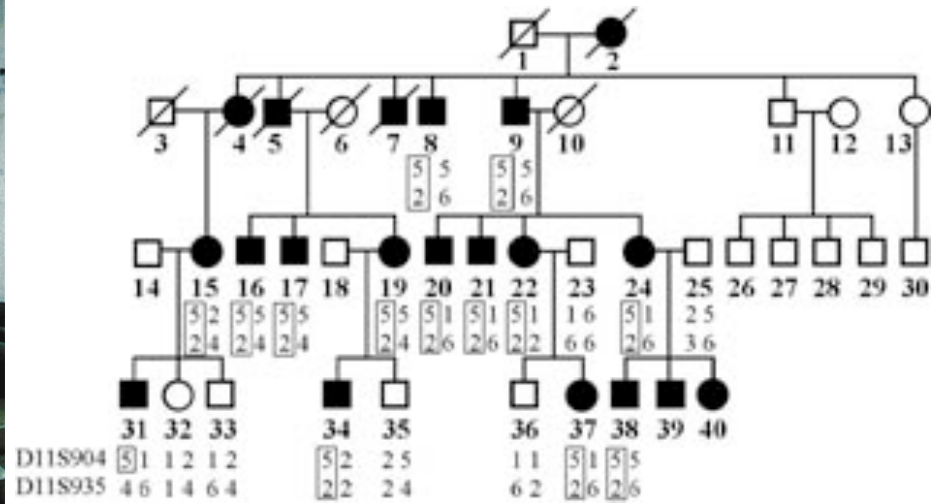
congenital defects: visible defects present at birth (due to *any* cause (genetic, developmental error...)).

syndrome: the symptoms that characterize *any* abnormal condition (due to genetics, development, chronic injury, etc.).

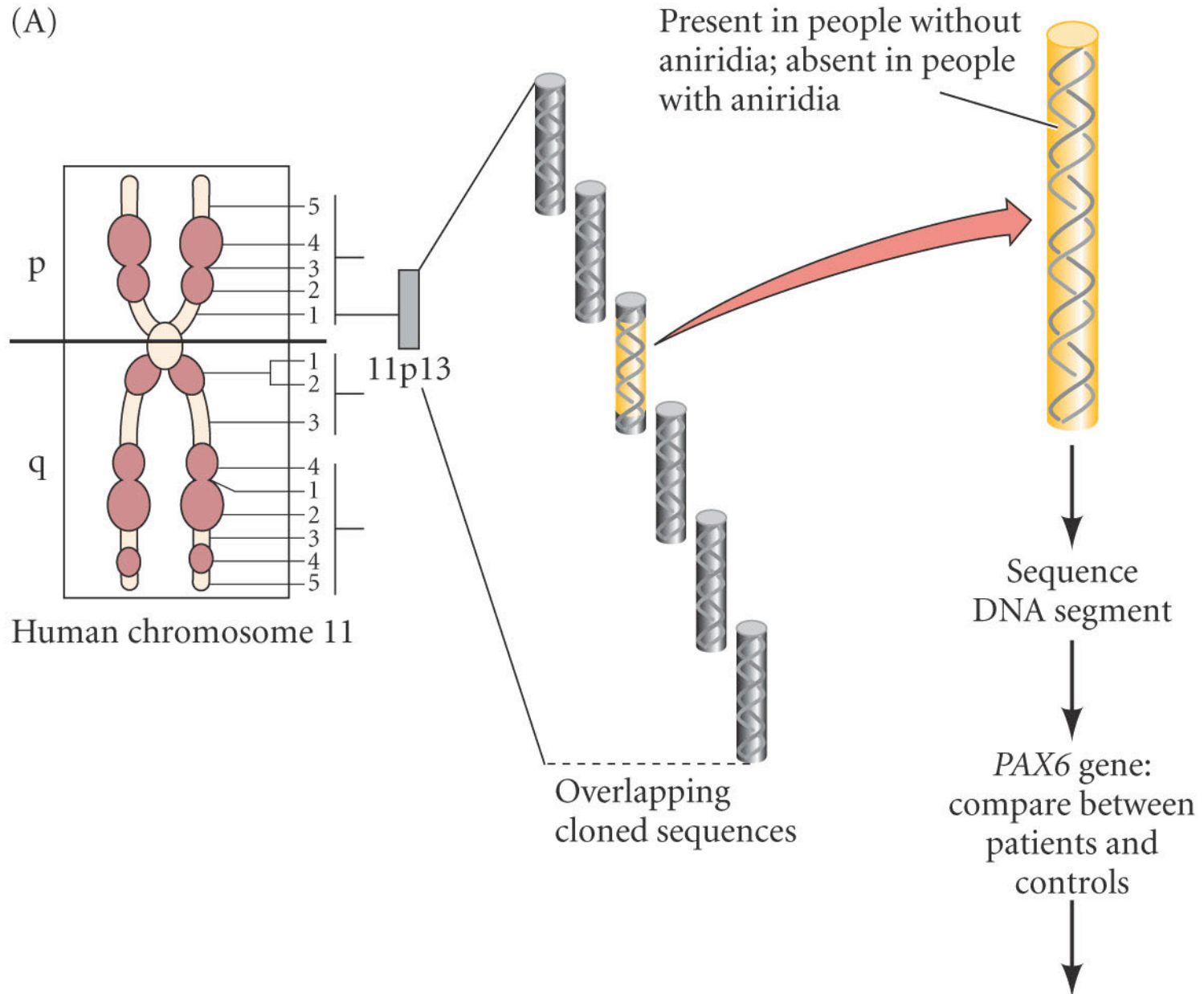
pleiotropy: refers to the multiple structures effected by one gene *or* one mutant gene.

Haploinsufficiency occurs when a diploid organism only has a single functional copy of a gene (with the other copy inactivated by mutation) and the single functional copy of the gene does not produce enough of a gene product (typically a protein) to bring about a wild-type condition, leading to an abnormal or diseased state. It is responsible for some but not all autosomal dominant disorders.

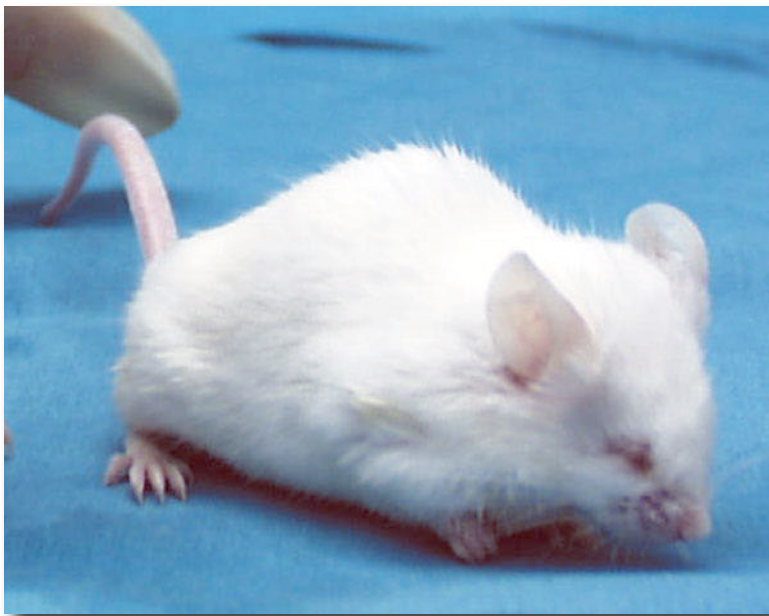
Pedigree analysis



(A)



Pax6 heterozygous mice



Pax6 overexpression causes extra eyes in flies

Pax3 +/-

Pax6 +/-



Other birth defect genes can be identified *with prior knowledge* as in similar defects seen in animal models

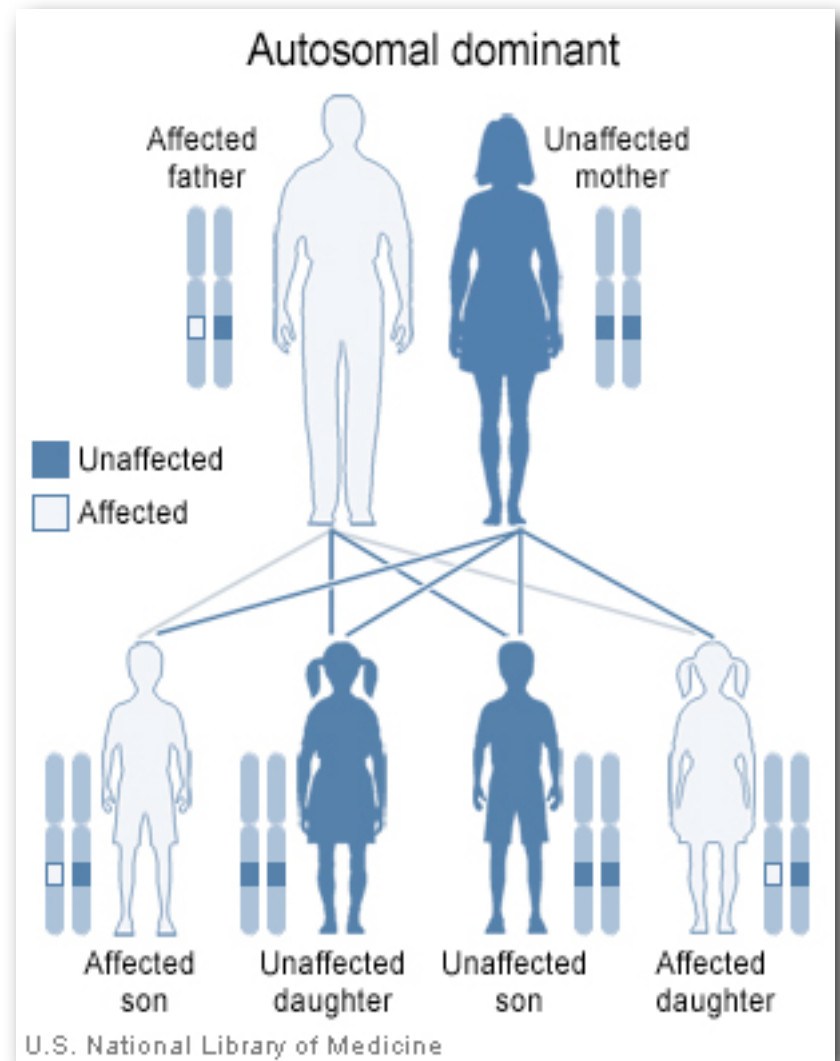
→ candidate gene mapping

→ Animal model systems of diseases



Waardenburg Syndrome

- Very pale or brilliantly blue eyes, eyes of two different colors (complete heterochromia), or eyes with one iris having two different colours (sectoral heterochromia);
- A forelock of white hair (poliosis), or premature graying of the hair;
- Wide-set eyes (hypertelorism) due to a prominent, broad nasal root (dystopia canthorum—particularly associated with type I);
- Moderate to profound hearing impairment (higher frequency associated with type II); and
- A low hairline and eyebrows that touch in the middle.
- Patches of white pigmentation on the skin have been observed in some people. Sometimes, abnormalities of the arms, associated with type III, have been observed.



Pax3 or Mitf heterozygotes

human *Greigs'* cephalopolysyndactyly



A

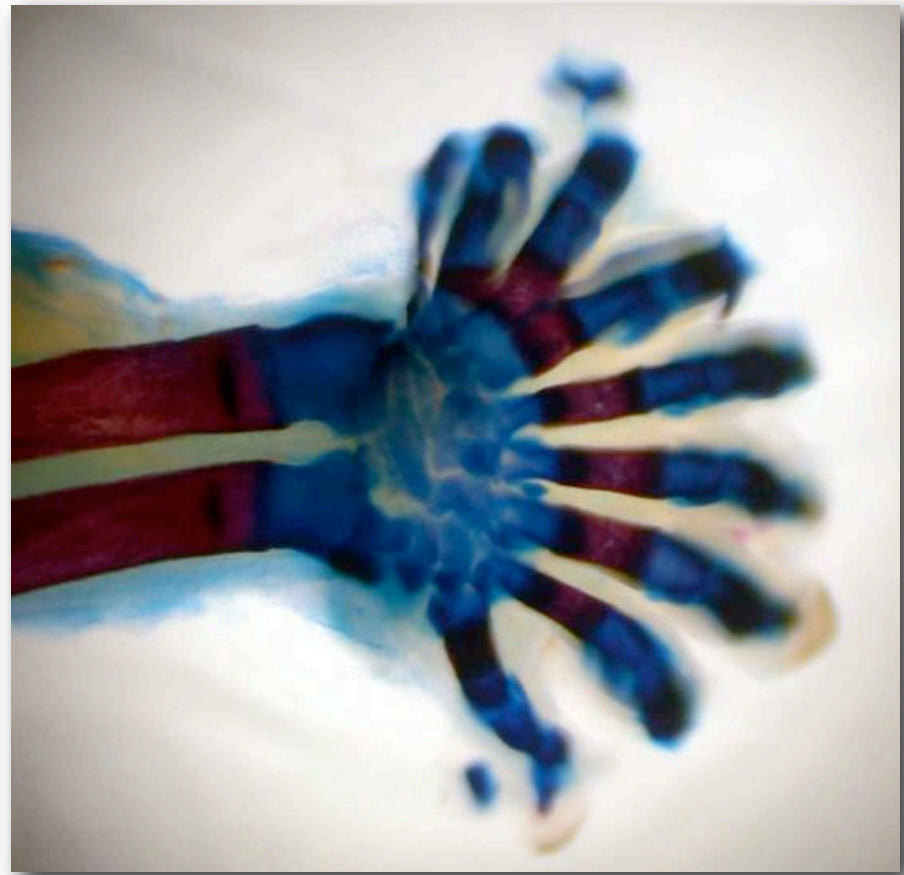


B

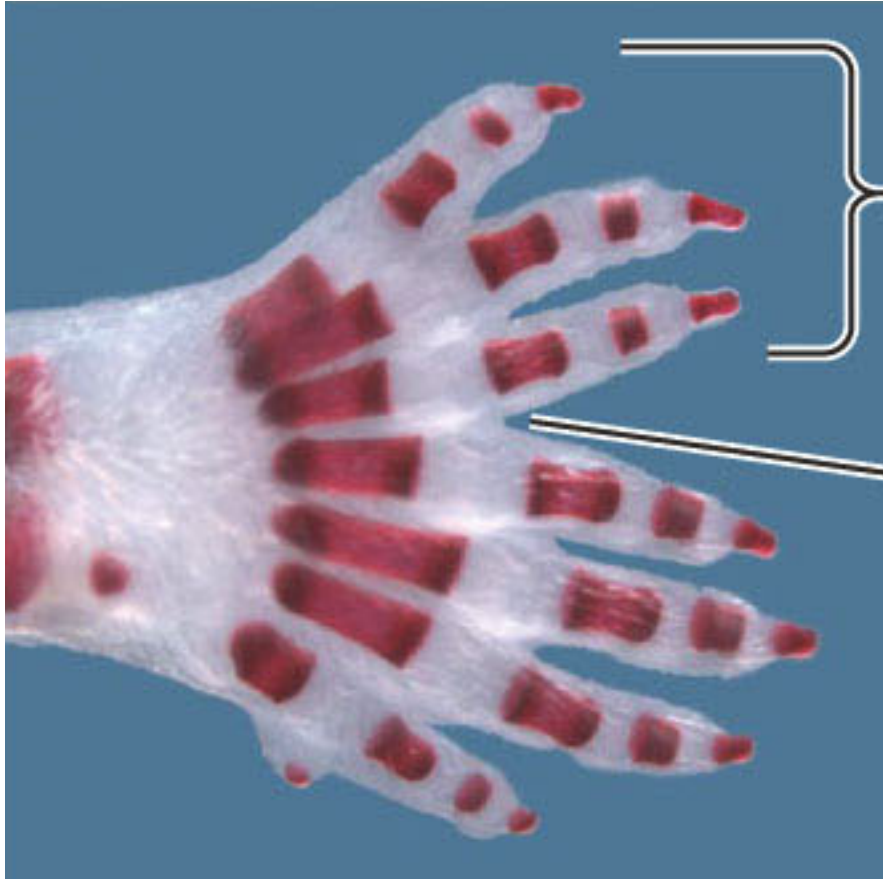


C

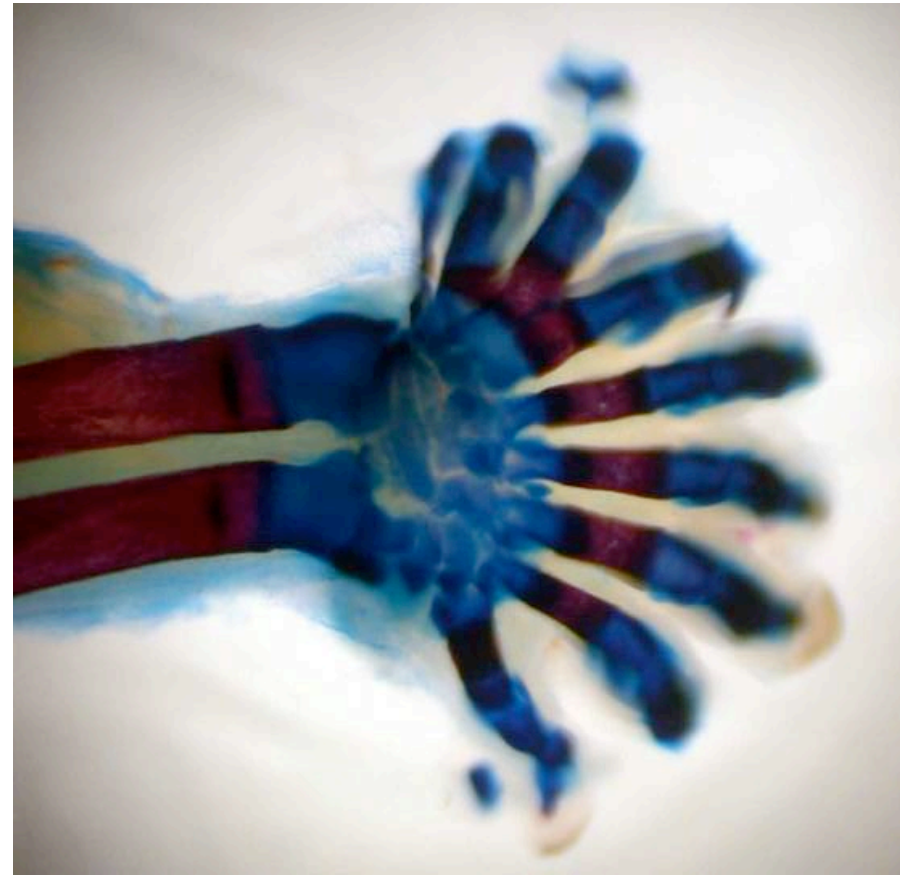
human *Greigs' cephalopolysyndactyly*
Gli-3 mutation, identified by candidate gene mapping

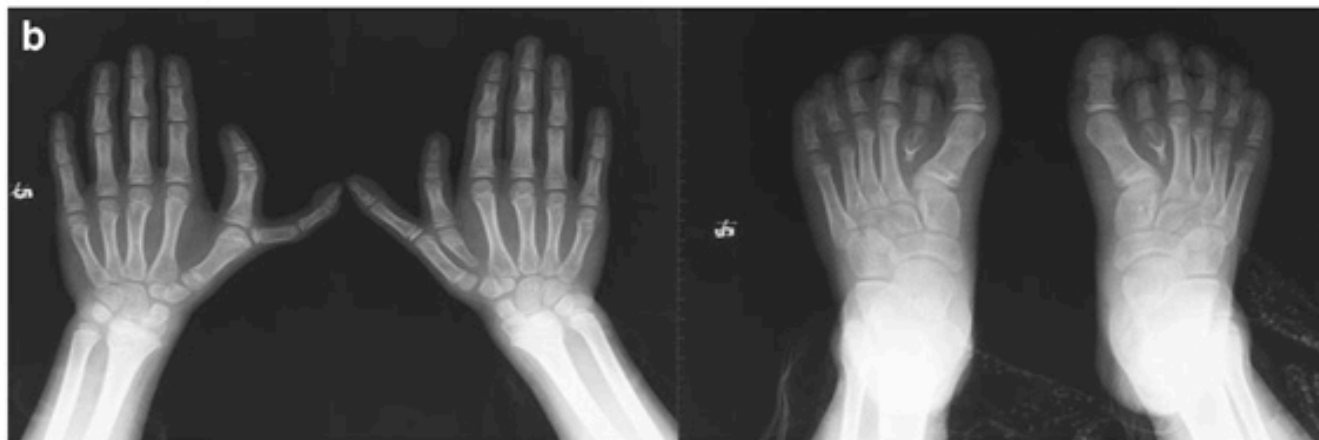


mouse *hemimelic extra-toes* =
dominant mutation of *Shh*



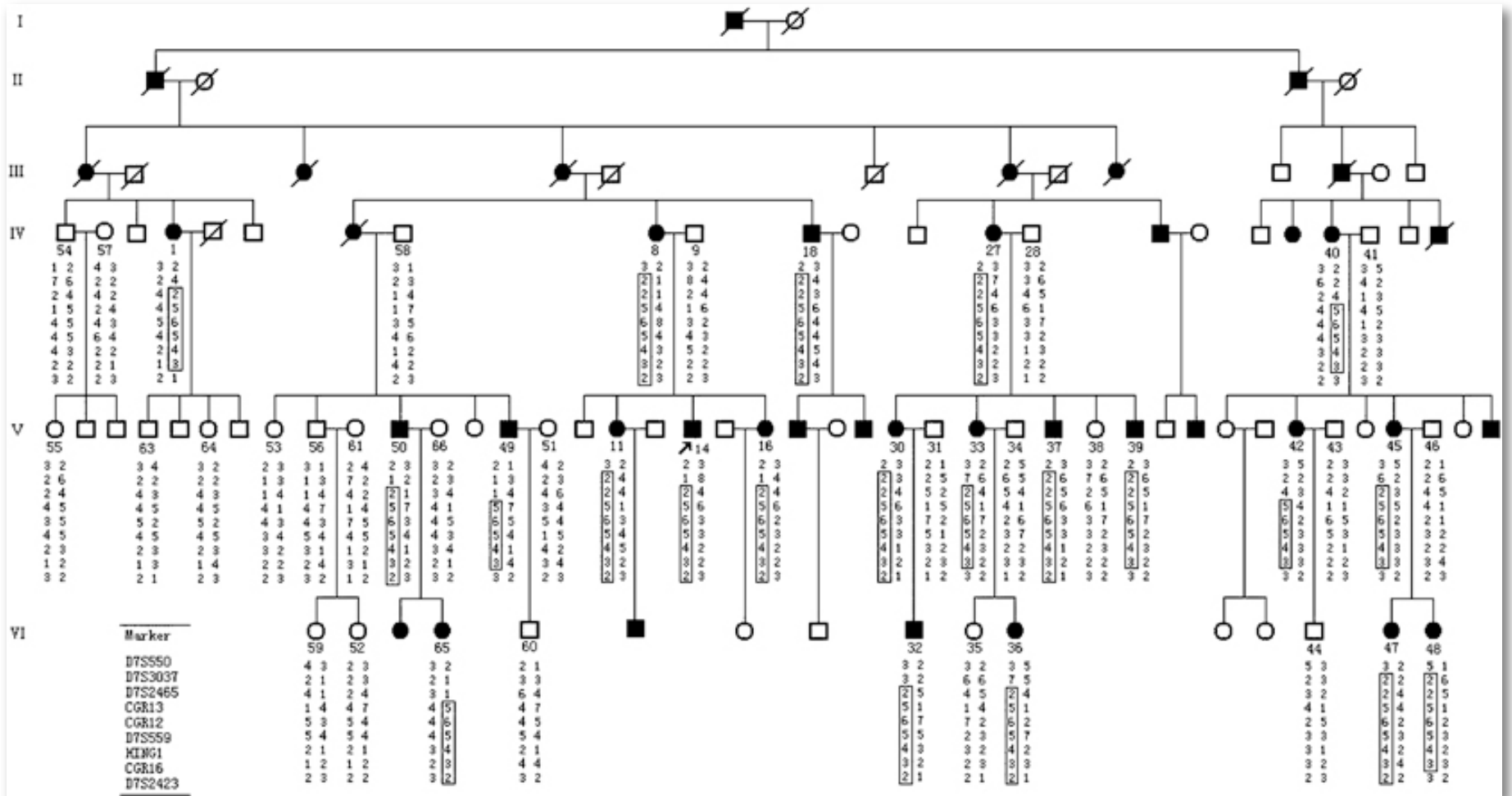
mouse *extra toes* = mutation of
Gli-3, a target of *Shh* signaling



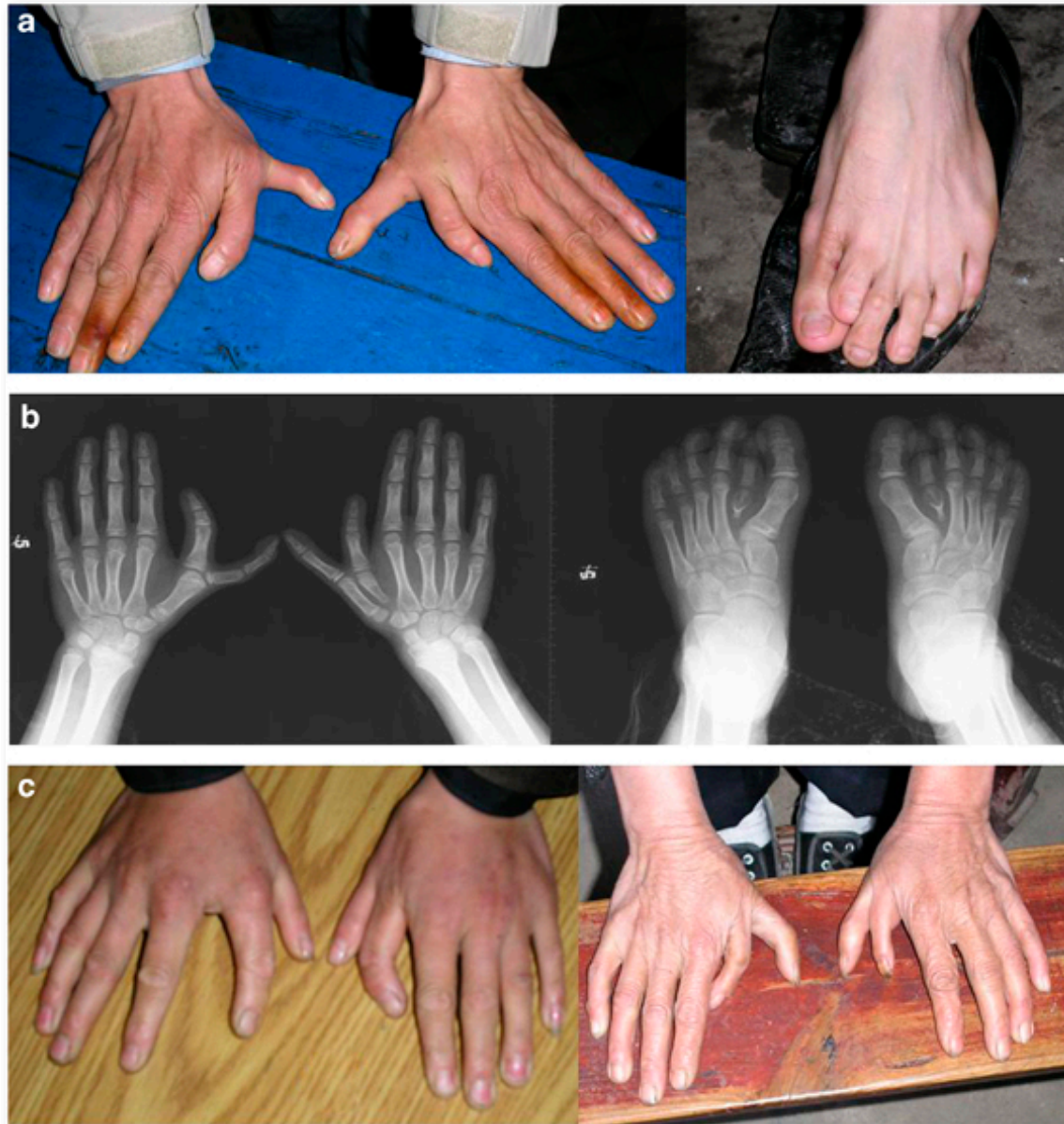


A large pedigree.....

What is the pattern of inheritance?

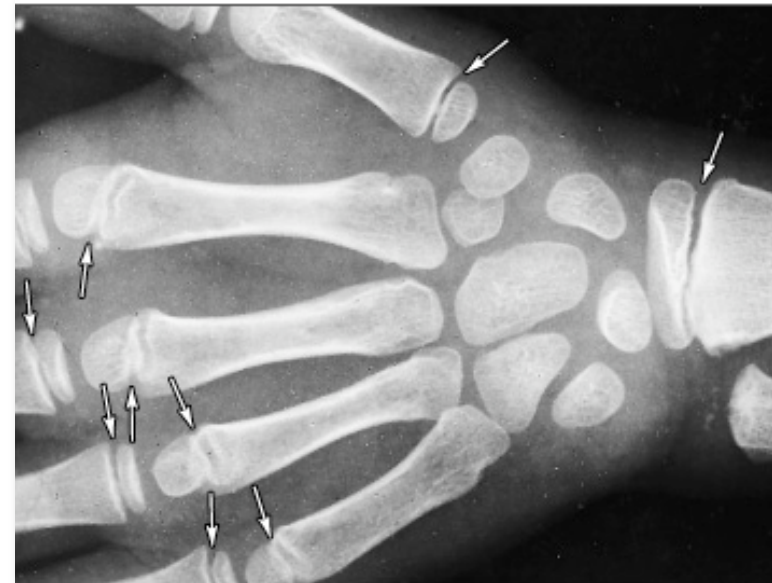


Mutation in *Shh* enhancer, causing extra expression in the developing limbs





Achondroplasia (dominant dwarfism). Caused by activated form of FGF3 receptor premature ossification of growth plates



The mutations for many birth defects are described as 'dominant'--but that is generally a simplification.

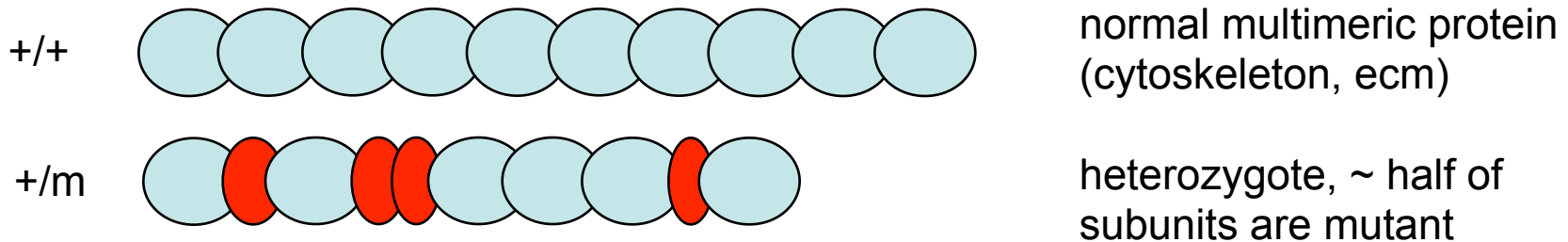
Several kinds of dominant mutations:

(A) Haploinsufficient: mutation is really loss-of-function, but one mutant copy gives a phenotype (A^+/a). Examples: Waardenburg Syndrome, Greig cephalopolysyndactyly.

-- most haploinsufficients are also recessive lethal (!)

(B) Dominant gain-of-function: mutations are genes expressed in ectopic locations / gene products that are over-active. Example: *hemimelic extra-toes*, dominant dwarfism (achondroplasia) caused by activated form of FGF3 receptor.

(C) Dominant negative mutations are loss of function alleles that effect wildtype gene products.



ex.: Marfan syndrome: effects fibrin protein in elastic connective tissue.

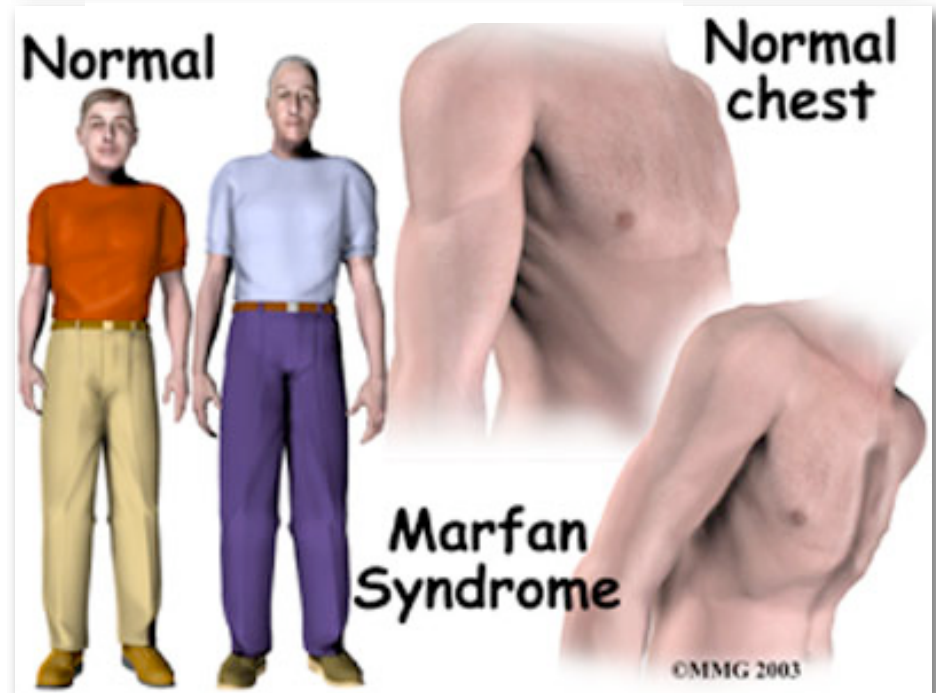
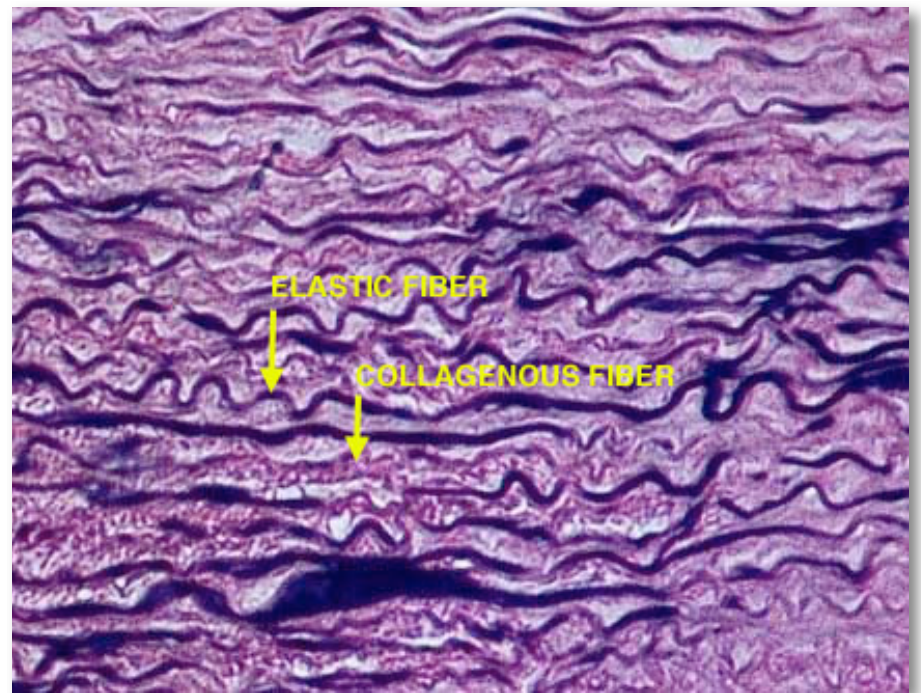
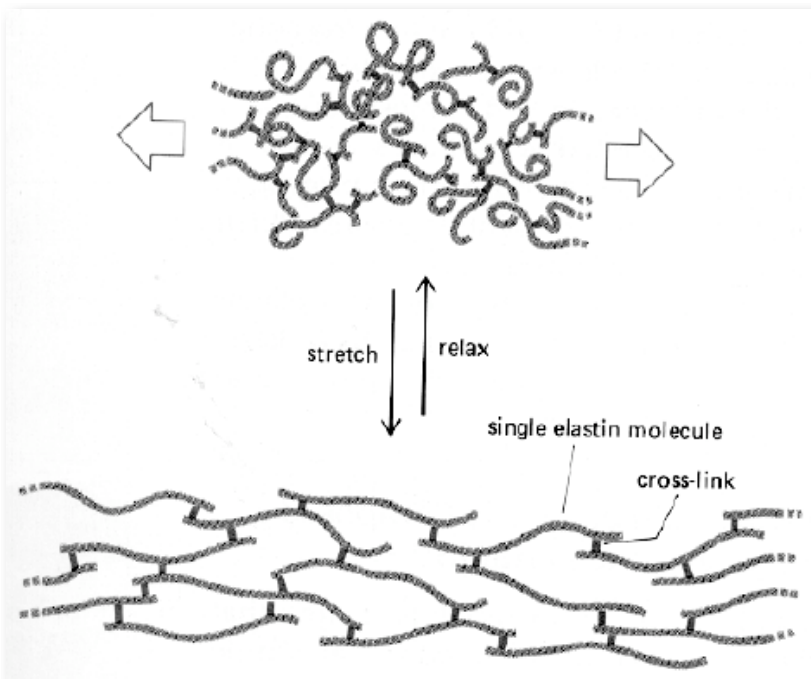
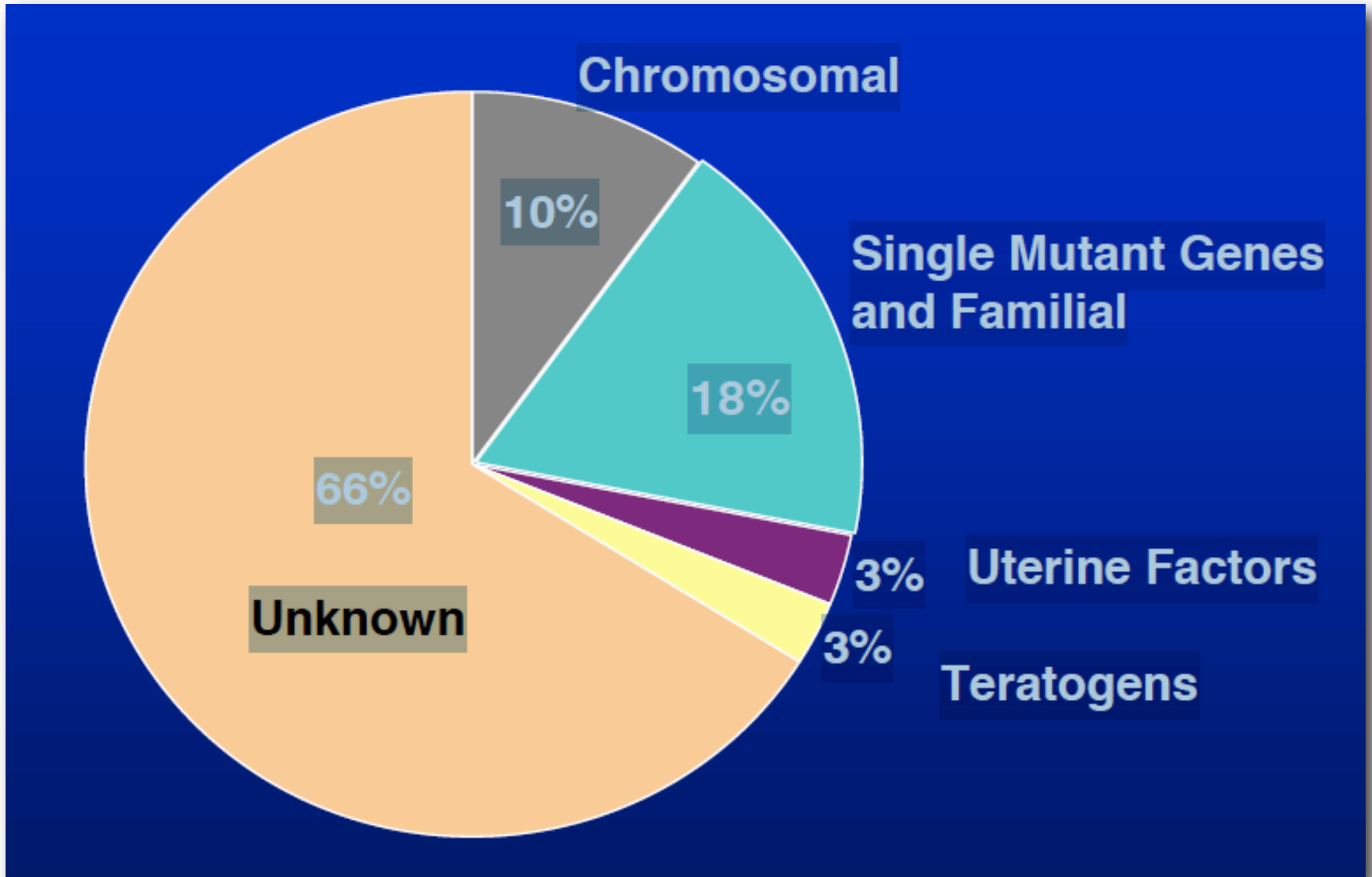


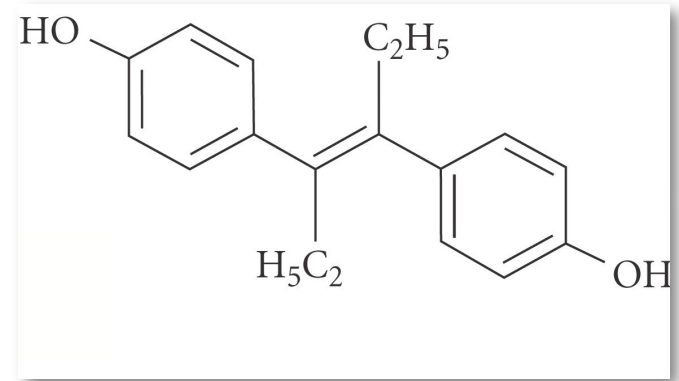
TABLE 21.1 Some genes encoding human transcription factors and phenotypes resulting from their mutation

Gene	Mutation phenotype
Androgen receptor	Androgen insensitivity syndrome
<i>AZF1</i>	Azoospermia
<i>CBFA1</i>	Cleidocranial dysplasia
<i>CSX</i>	Heart defects
<i>EMX2</i>	Schizencephaly
Estrogen receptor	Growth regulation problems, sterility
<i>Forkhead-like 15</i>	Thyroid agenesis, cleft palate
<i>GLI3</i>	Grieg syndrome
<i>HOXA13</i>	Hand-foot-genital syndrome
<i>HOXD13</i>	Polysyndactyly
<i>LMX1B</i>	Nail-patella syndrome
<i>MITF</i>	Waardenburg syndrome type 2
<i>PAX2</i>	Renal-coloboma syndrome
<i>PAX3</i>	Waardenburg syndrome type 1
<i>PAX6</i>	Aniridia
<i>PTX2</i>	Reiger syndrome
<i>PITX3</i>	Congenital cataracts
<i>POU3F4</i>	Deafness and dystonia
<i>SOX9</i>	Campomelic dysplasia, male sex reversal
<i>SRY</i>	Male sex reversal
<i>TBX3</i>	Schinzel syndrome (ulna-mammary syndrome)
<i>TBX5</i>	Holt-Oram syndrome
<i>TCOF</i>	Treacher-Collins syndrome
<i>TWIST</i>	Seathre-Chatzen syndrome
<i>WT1</i>	Urogenital anomalies

Causes of Birth Defects



Endocrine disruptors

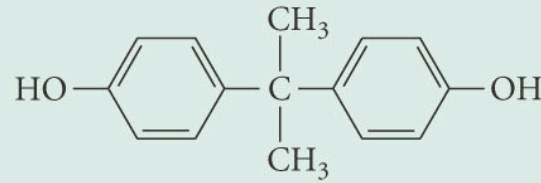


- A large number of drugs, environmental chemicals either mimic *or* interfere with hormones.
- ex.: Diethylstilbestrol (DES)
 - 1950's-60's, prescribed to pregnant women to prevent premature labor and miscarriage
 - Found to damage female reproductive system, cause abnormal development of male reproductive system.
 - Now banned, major example of an environmental estrogen
- Environmental estrogens are a major class of chemicals that mimic estrogen-- Now a HUGE area of research and friction with plastics and pesticides industry

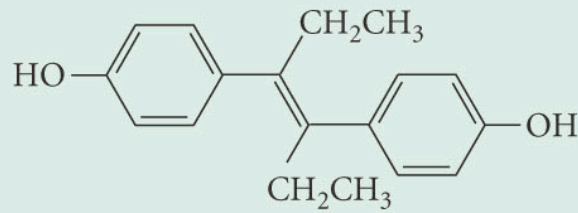
Some environmental estrogens

(A)

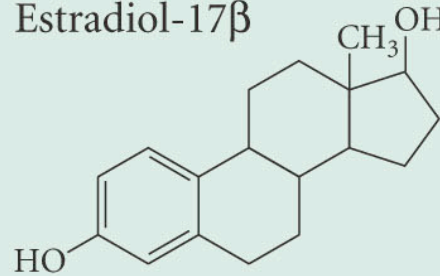
Bisphenol-A



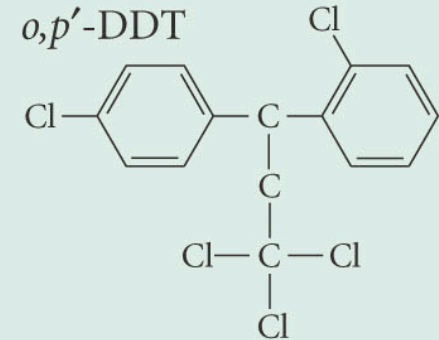
Diethylstilbestrol



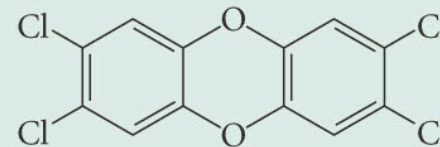
Estradiol-17 β



o,p'-DDT

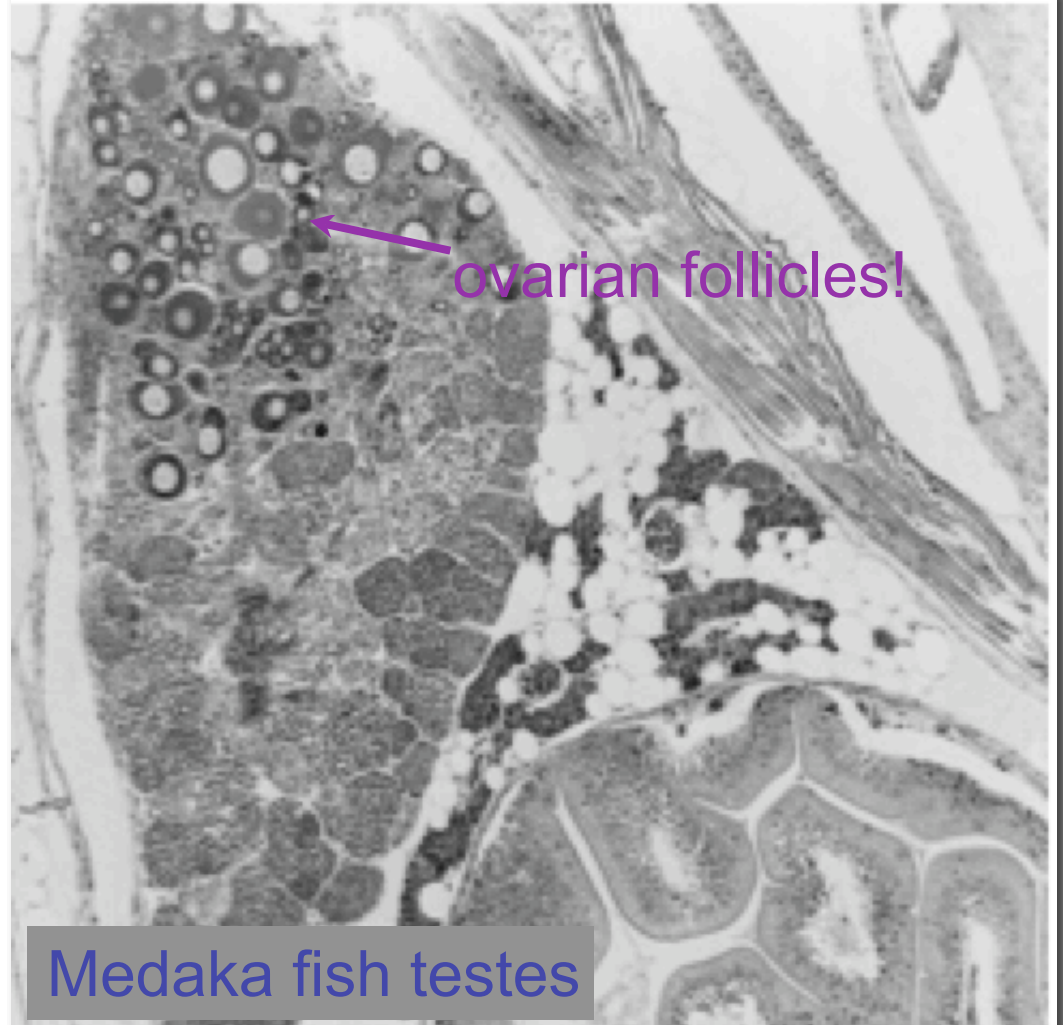
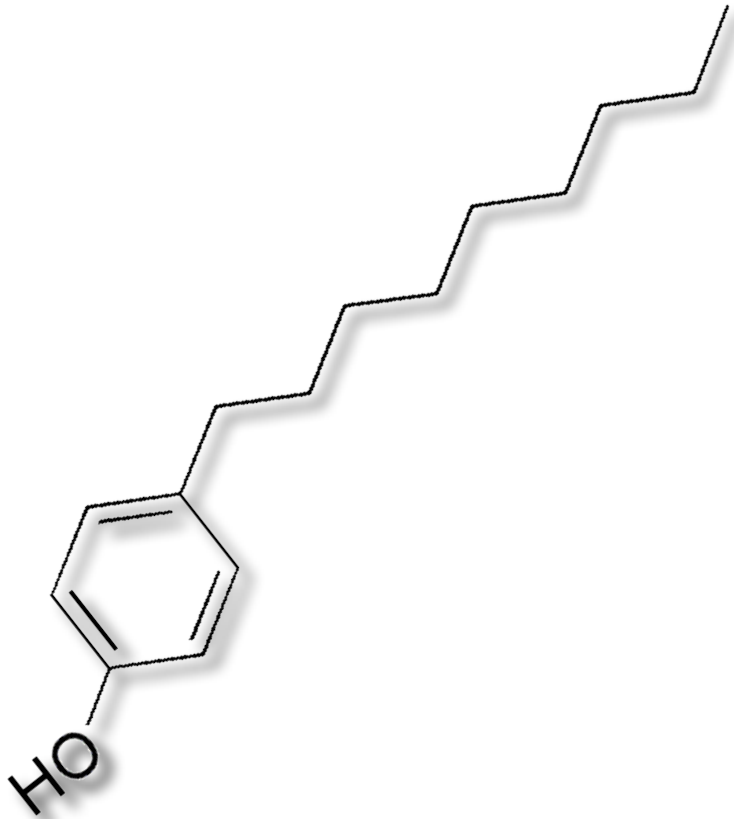


Dioxin



Nonylphenol:

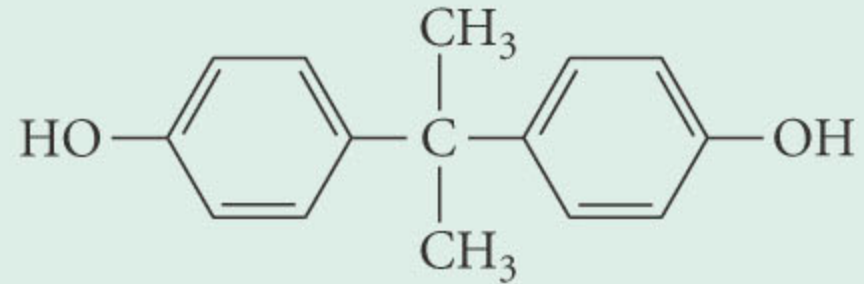
- Common stabilizer of plastics in food wrapping, PVC tubing, polystyrenes.
- Detectable in food after prolonged storage, microwave heating.
- Probable effects on feminizing aquatic vertebrates in industrialized areas.



Medaka fish testes

Bisphenol A (BPA):

Bisphenol-A



- First made as a synthetic estrogen.
- Later found to be useful component in plastics.
- Common in polycarbonate plastics (until recently: Nalgene) (soda containers, baby bottles, toys....)
- Many documented effects on gender development in lab animals.

Causes Chromosome non-disjunctions during meiosis (trisomies)

Effects of BPA (measured in studies of mice or rats)

Dose ($\mu\text{g}/\text{kg}/\text{day}$)

0.025	"Permanent changes to genital tract"
0.025	"Changes in breast tissue that predispose cells to hormones and carcinogens"
2	"increased prostate weight 30%"
2	"lower bodyweight, increase of anogenital distance in both genders, signs of early puberty and longer estrus."
2.4	"Decline in testicular testosterone"
2.5	"Breast cells predisposed to cancer"
10	"Prostate cells more sensitive to hormones and cancer"
10	"Decreased maternal behaviors"
30	"Reversed the normal sex differences in brain structure and behavior"
50	U.S. human exposure limit (not a result from an animal study, but a guideline set by EPA)

Indication for effects in human populations:

- cited increase in rates of breast cancer, prostate cancer
- *lowered* age of puberty in females
- *lowered* sperm counts in males.