Mendelian Genetics

With Selected Human Diseases

Mini-Glossary

- *Genetic locus*: chromosomal location of the two copies of a gene.
- *Allele*: a gene at an allele which may be present in two or more different forms.
- *Pleitropism*: 1 gene that provides for 2 or more phenotypes.
- *Dominant*: refers to the phenotype, NOT to the genotype; tells us that the mutation in this type of gene presents clinically with only a single dose, i.e., heterozygous; this is at the gene level.
- *Recessive*: refers to phenotype, NOT to the genotype; tells us that the mutation in this kind of gene presents clinically with a double dose, i.e., homozygous; this is at the gene level.
- <u>It is, therefore, inappropriate to refer to GENES as dominant or recessive: genes are either expressed or NOT expressed.</u>

- Sickle cell anemia: recessive trait: homozygous. BUT, sickle cell gene is expressed with one dose, too, which produces carriers with hemoglobin S (HbS; $\alpha_2\beta_2^s$) and HbA ($\alpha_2\beta_2$) that may cause sickling when exposed to low pO_2: heterozygous; this is expressed at the BIOCHEMICAL LEVEL.
- A recessive trait may, therefore, be termed codominant at the biochemical level of gene product (HbS and HbA) or dominant under changed environmental conditions (heterozygous sickling).
- If a patient has a disease that is demonstrable to follow Mendelian rules, in all probability, the disease -- regardless how involved the disease is -- comes from 1 gene.

Introduction

- There are many aspects to genetics. The aspect with which we have an interest is how or why we are the way we are. There are many complicated ways in which to examine genetics, but the simplest manner is still that which Gregor Mendel developed in 1865. Mendel began his work by observing that some pea plants had different characteristics from other pea plants. The same has been observed for a number of other plants, most notably the petunia.

Mendel’s Laws

- During Mendel's work with plants, he developed three laws:
- 1. Law of Unit Inheritance: genetic factors keep their own identity and do not blend/merge/fuse in a hybrid, i.e., each gene has its own individual identity.
- 2. Law of Segregation: 2 alleles of one particular pair of genes are never found in the same reproductive cell, but always segregate between multiple gametes (1/2 to one cell and 1/2 to another).
- 3. Law of Independent Assortment: That different chromosomes conglomerate to reproductive cells in a manner that requires no dependence on other chromosomes (1/2 of chromosomes go to 1 cell and 1/2 to another BUT don't follow other chromosome halves in a dependent manner).

- To understand Mendel's work, we must accept that there is one genetic characteristic that is expressed, or is dominant, and one genetic characteristic that that is not expressed, or is recessive.
- Also remember that genes, as a general rule (and particularly as applied to humans) come in pairs. The idea here is that if a gene that is expressed (gives a dominant phenotype) is mixed with another gene that is expressed, then the phenotype is expressed.
- If a gene that is not expressed is mixed with another like gene, then the phenotype is expressed.
- If, however, a gene that is expressed is mixed with a gene that is not expressed, then the characteristic that is expressed is mostly the dominant characteristic (with some "leaking" of the recessive trait).
- The only manner in which recessive traits may be observed is having both recessive traits combined.

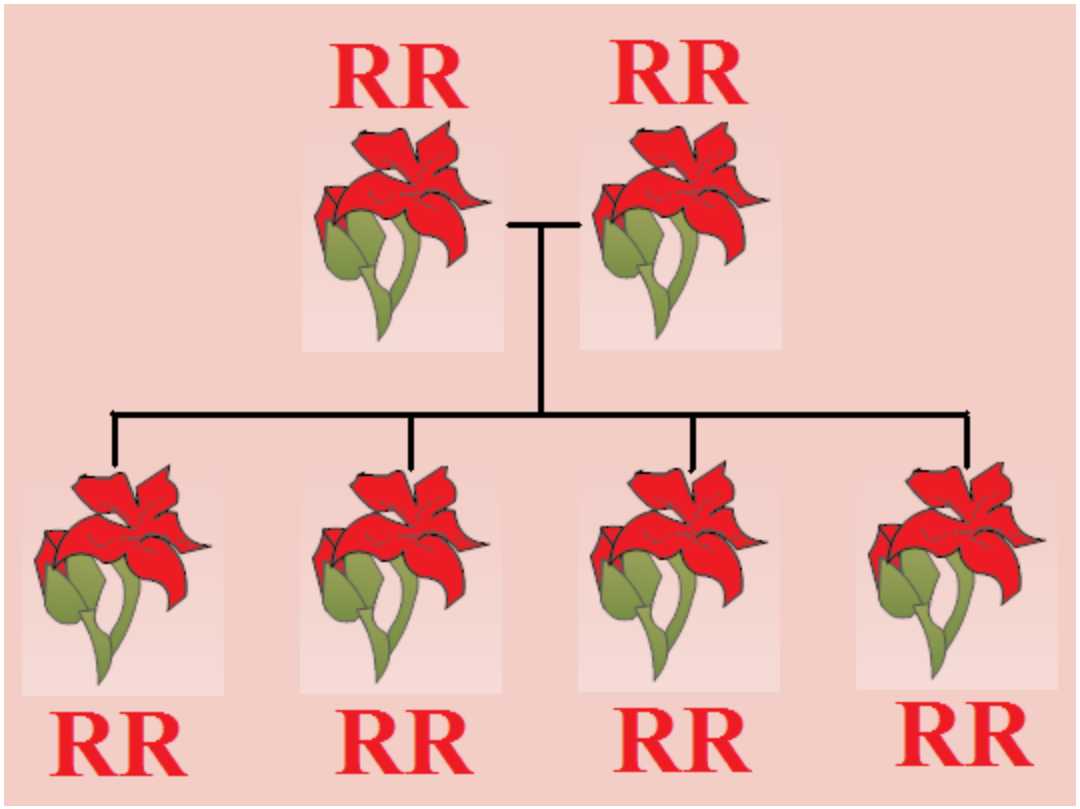
- When gametes undergo meiosis, they reduce their numbers of chromosomes by half so that when chromosomes rearrange, they, i.e., the zygote, have the right number, i.e., a pair, of chromosomes.
- Geneticist R.C. Punnett many years after Mendel's death developed the Punnett Square as he noticed this phenomenon. His method greatly assisted in understanding Mendel's results and methods.

- To understand how the Punnett square works, let us examine two families of petunias: one that is all red and one that is all white.
- Let us assign the following characteristics to the red petunias: RR (the upper case letter says this gene is “dominant”), where the R is the "code" for the red color.
- Let us assign the following characteristics to the white petunias: ww (the lower case letter says this gene is “recessive”), where the w is the "code" for the white color.
- It is easy to see if the red petunias reproduce only with themselves, that the genetics will stay the same, i.e., all flowers will be RR.
- The same will happen with the ww. Let's look at Punnett's square to determine how this works:

Gametes	R	R		Gametes	w	w
R	RR	RR	F_1	w	ww	ww
R	RR	RR		w	ww	ww
Color	red	red		Color	white	white

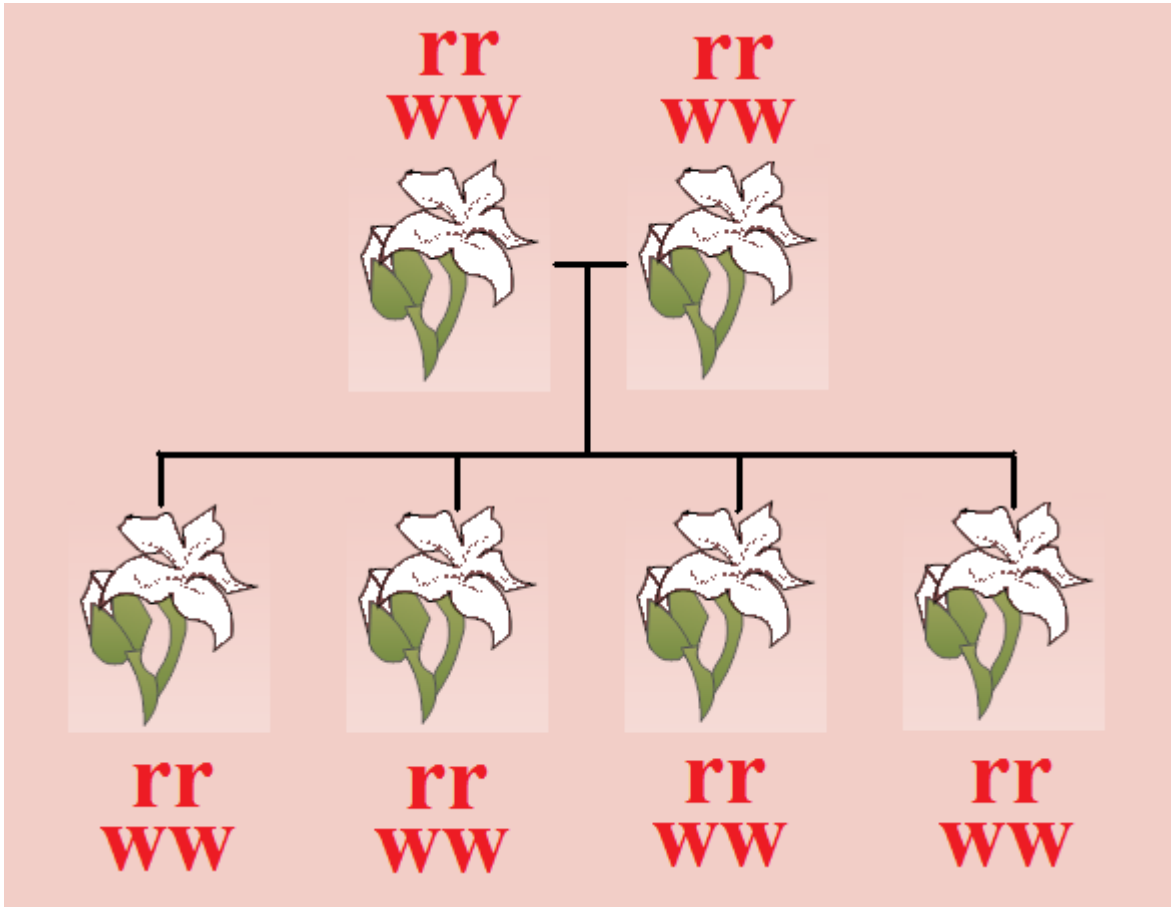
- Each gene pair separated in half, then rearranged following reproduction. All RR plants are red; all ww plants are white.
- In both cases, the offspring receive one chromosome from each parent, which aligns appropriately to give the expected characteristic.
- The genetic characteristics in the two Punnett squares, above, are for the parent (P) generation.
- The genetic characteristics that are expressed after parental conjugation are expressed in the family (F), first generation (1), F_1.

Q&D: Mendelian Genetics – Pure Red Flowers



Q&D: Mendelian Genetics – Pure White Flowers

(NOTE: "rr" = "ww" to match text)



What would happen if we were to cross the F_1 RR generation with the F_1 ww generation?

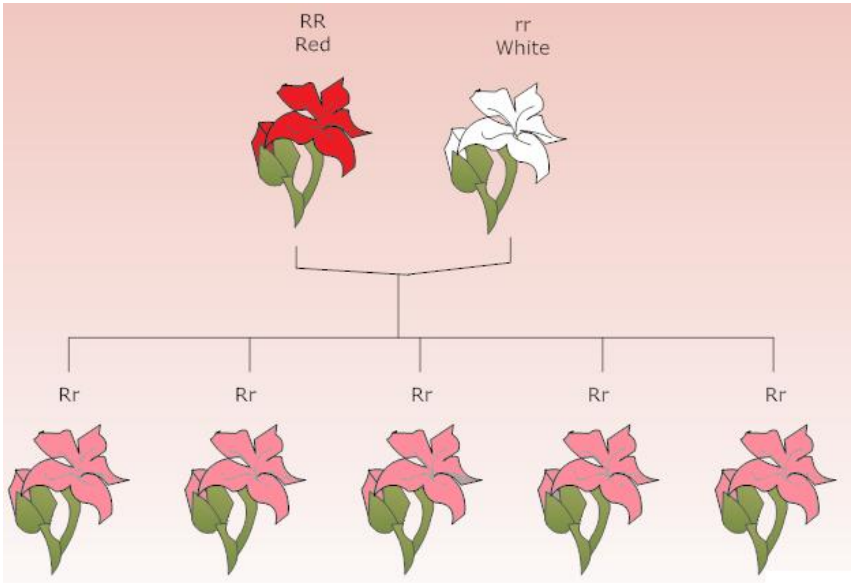
Gametes	R	R		Gametes	R	R
w	Rw	Rw	F_2	w	wR	wR
w	Rw	Rw		w	wR	wR
Color	pink	pink		Color	pink	pink

The F_2 generation so conceived consists of the expressed gene (R) and the unexpressed gene (w).
According to what has been previously discussed, this generation ought to be red (R is expressed).
In reality, though, they are pink.
The genetic makeup of F_2 is Rw; this is called its GENOTYPE.
The color that is expressed is pink and is called the PHENOTYPE.

Q&D: Mendellian Genetics et Punnett Square – Pink Flowers

(NOTE: "r" = "w" from previous slide)

	R	R
r	Rr	Rr
r	Rr	Rr



What would happen if we were to cross the F_2 Rw with the F_2 wR generation?

Gametes	R	w		Gametes	w	R
w	Rw	ww	F_3	R	wR	RR
R	RR	Rw		w	ww	wR
Color	pink	pink		Color	pink	pink

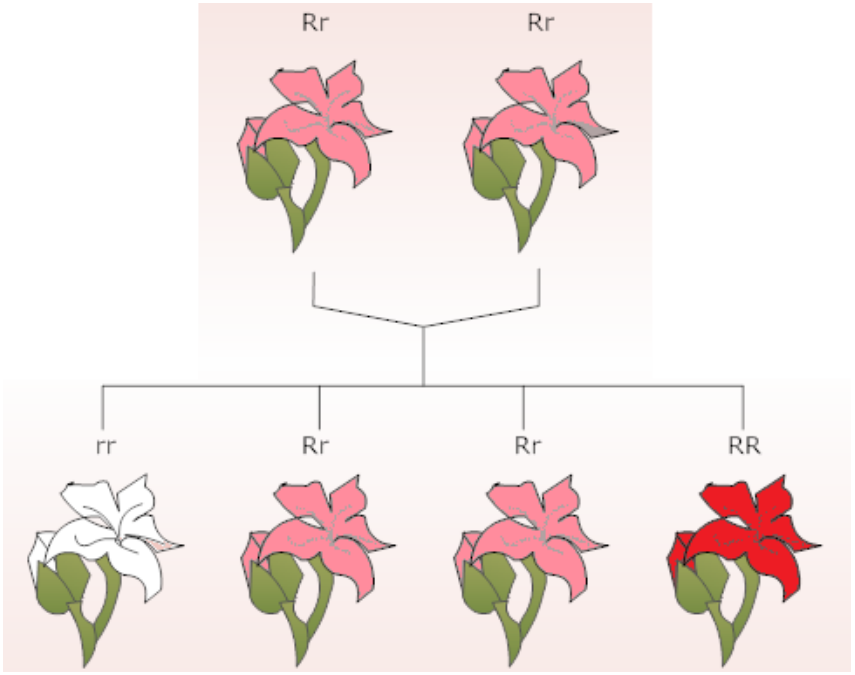
- Now, we know that of the F_3 generations, 1 (or 25%) will be red, 2 (or 50%) will be pink and 1 (or 25%) will be white.
- Another point, however, is that 75% of the F_3 generation has the gene that is expressed (R).
- It appears, then, that when blending the two F_2 generations, one would have a 3:1 ratio of dominant to recessive traits.

- Genotypes like RR and ww are homozygous; Rw or wR (identical, by the way) are called heterozygous.

Q&D: Ibid – Multihybridized Flowers

(NOTE: "r" = "w" from previous slide)

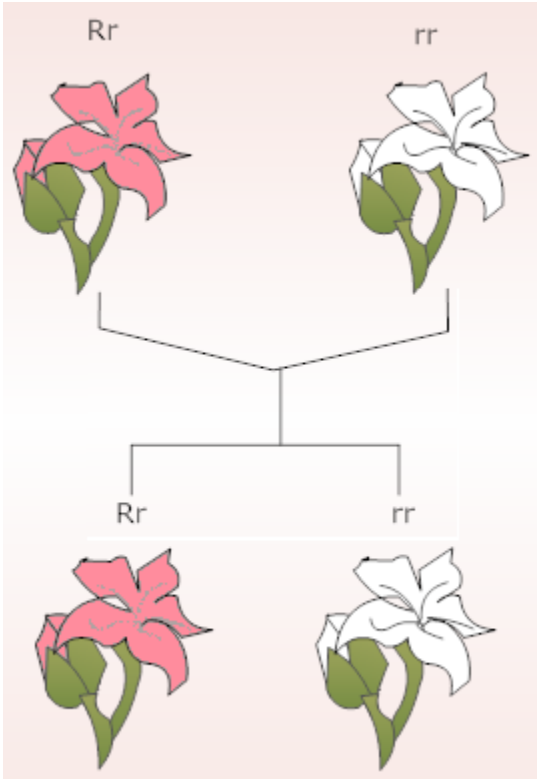
	R	r
R	**RR**	**Rr**
r	**Rr**	**rr**



Q&D: Ibid

(NOTE: “r” = “w” from previous slide)

	R	r
r	Rr	rr
r	Rr	rr



•We can apply the same kinds of concepts to humans.
•Let us take a tall family, coded TT, and a short family, coded ss, and apply Mendel's ideas through Punnett's square:

Gametes	T	T		Gametes	s	s
T	TT	TT	F_1	s	ss	ss
T	TT	TT		s	ss	ss
trait	tall	tall		trait	short	short

The tall family will all have tall members in F_1 (TT) and the short family will have all short members in F_1.

What, though, would happen if a TT mated with an ss?

Gametes	T	T
s	sT	sT
s	sT	sT
trait	tall	tall

- All members if this mating (F_2) will be tall (sT and Ts): the tall gene is expressed.
- The short gene is partially expressed, as well.
- These people will be taller than their short parent, but be shorter than their tall parent.

What if two F_2 people mate?

Gametes	T	s
T	TT	sT
s	sT	ss
trait	tall	tall and short

- Notice that the F_3 follows the same pattern that the petunias followed: 3:1 dominant traits to recessive traits, hence, 25% will be tall, 50% will be shorter (but, relatively speaking, tall) and 25% will be short.
- Overall, 75% will be tall and 25% short.

• What about applying this concept to various genetic diseases? This is very easy.
•Let's use phenylketonuria (PKU; an inborn error in metabolism that blocks appropriate metabolism of phenylalanine -- an amino acid -- but increases the levels of toxic metabolites which causes retardation) as our example.
•PKU is an autosomal recessive mutation. This means it is NOT sex-linked and both recessive traits must be present to have the metabolic error (a double dose of the genes that are not normally expressed).
•Let's assign "P" as the expressed, normal, gene and "p" as the unexpressed, abnormal, gene and go back through the Punnett squares as we have done with the previous examples:

Gametes	P	P		Gametes	p	p
P	PP	PP	F_1	p	pp	pp
P	PP	PP		p	pp	pp
trait	Normal	Normal		trait	PKU	PKU

•In the first case, we looked at the combination of homozygous genes that are expressed.
•The phenotype is normal phenylalanine metabolism.
•In the second case, above, we looked at the combination of homozygous genes that are not normally expressed as a single dose.
•The phenotype is abnormal phenylalanine metabolism, i.e., PKU.

Let's combine PP with pp to make the second-generation offspring:

Gametes	P	P
p	Pp	Pp
p	Pp	Pp
trait	Normal Phe metabolism	

- All F_2 are heterozygous Pp.
- The phenotype is normal phe metabolism, BUT each offspring is a CARRIER for PKU.

Let's combine two Pp offspring:

Gametes	P	p
P	PP	Pp
p	Pp	pp

•In this combination, the genotypes are 25% PP, 50% Pp and 25% pp.
•The phenotype is 75% normal phenylalanine metabolism and 25% PKU.

Listed below in the table are selected hereditary traits in humans along with the letter that is used to code for the genotype.

Trait	Letter	Trait	Letter
Curly hair	C	Near/far sighted	G
Dark brown hair	H	Normal hearing	E
Brown eyes	B	Large eyes	S
Male pattern baldness	M	Migraines	A

Note that all the letters are upper case: these are dominant traits.

Listed below are selected hereditary traits in humans along with the letter that is used to code for the genotype. Note that the letters are lower case to represent recessive traits.

Trait	Letter	Trait	Letter
Straight hair	c	Normal vision	g
All other hair colors	h	Deafness	e
Blue or gray eyes	b	Small eyes	s
Have hair	m	No migraines	a

It is important to also remember that the expression of various genotypes is based upon probability. For our purposes, probability (P) is defined as the following:

$$P = \frac{Frequency that\ X\ happened}{Frequency that\ X + Y + Z + n\ happened}$$

If X is guaranteed to happen every time, then the probability is 1. If X is guaranteed to happen 1 out of 2 times, then the probability is (1)/(2) = 0.5. If X is guaranteed to happen one out of eight times, then the probability is (1)/(8) = 0.125.

This is a nice simple introduction into probability. Is it always this simple? No. The reason it is not always this simple is because we have not taken into account the probability of X happening progressively. To determine if X will happen progressively, one must multiply the probability of X happening at all times itself the number of times you wish X to occur. Let's use sex of offspring as our example and the Punnett square (a means of getting to the frequency of "X" happening:

Gametes	X	Y
X	XX	XY
X	XX	XY

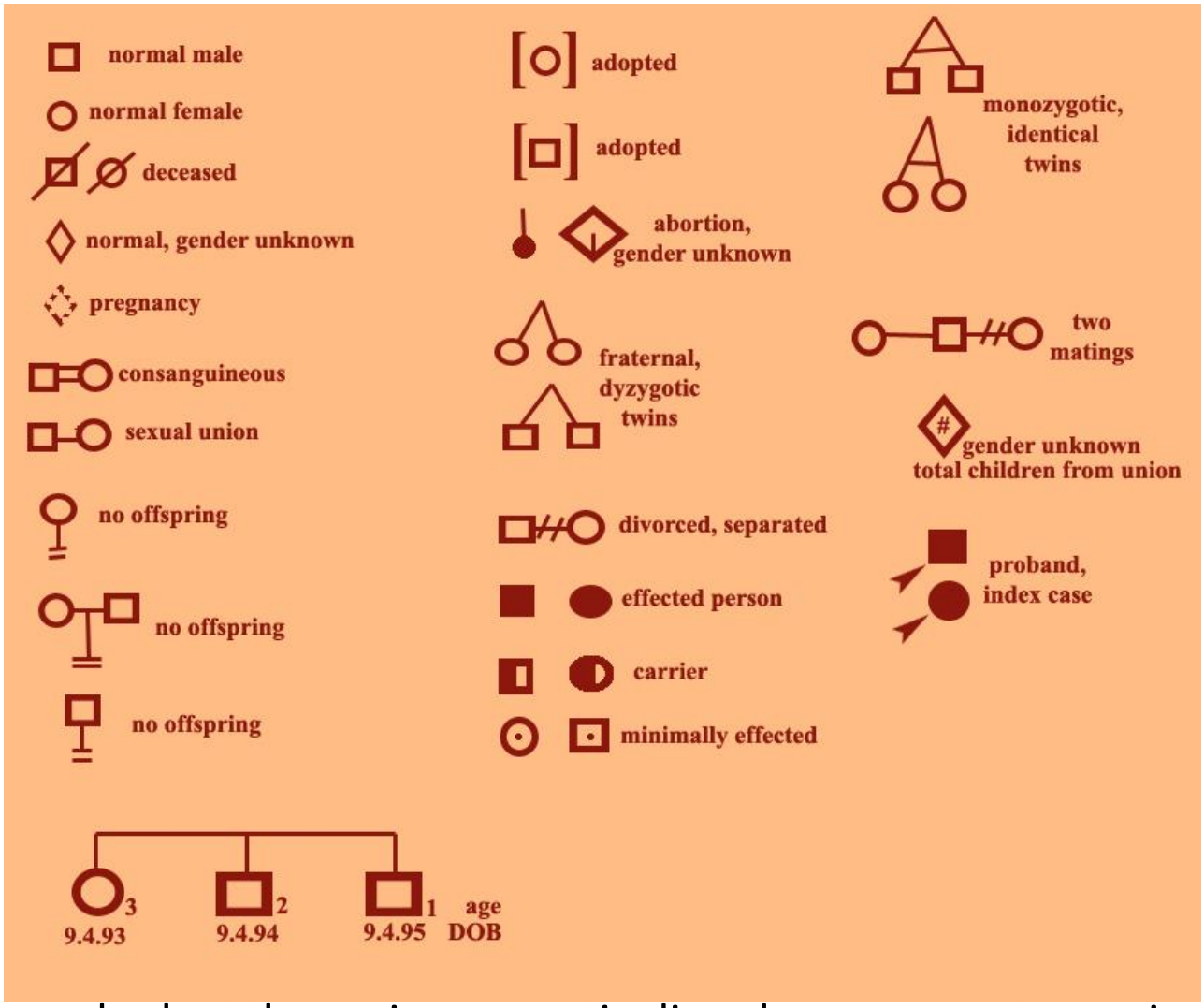
By phenotype, when a man and a woman mix their chromosomes, 50% of the offspring will be female (XX) and 50% will be male (XY).
BUT, what if you wanted to determine the probability of a family having 5 boys in a row?

$$P = \frac{1*1*1*1*1}{2*2*2*2*2} = \frac{1}{32}$$

The probability of having a boy is 1/2. For the probability of five of them to be born in a row, one must multiply 1/2 times itself 5 times. Hence, the probability is not real good that two parents will have an all-male basketball team in the family, i.e., 1 out of 32 times this will happen.

Genetic Disorders

- There are three categories of Genetic disorders we are interested in:
  - **chromosomal,**
  - **simply inherited disorders (Mendelian) and**
  - **multifactorial disorders**.
- **Chromosomal disorders** are defined as a loss, addition or abnormal arrangement of chromosomes (monosomy, trisomy).
- **Simply inherited disorders** are subdivided into autosomal and X-linked disorders.
- These two classes of disorders may be further sub-divided into dominant and recessive.
- In each case, the disorder comes from a SINGLE mutant gene.
- The last case, the **multifactorial disorders**, involve polygenic interactions with multiple exogenous/environmental factors.
- The inheritance risk with these disorders is less than with Mendelian disorders.

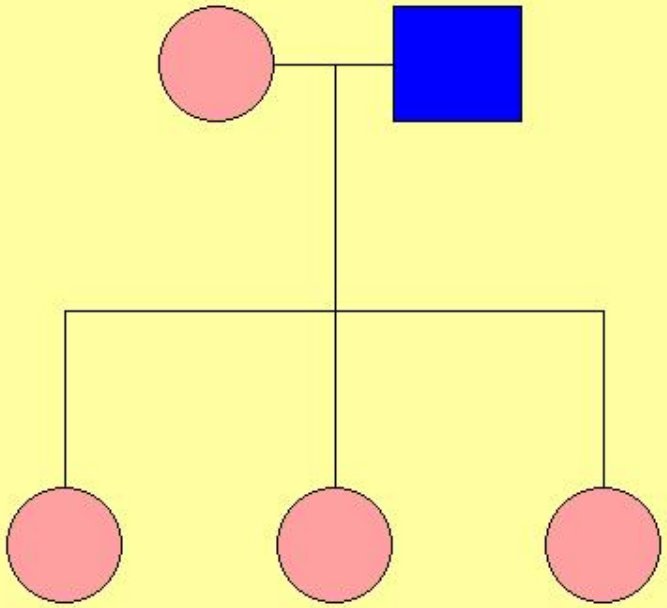


- Before we look at the various genetic disorders, we must examine how to identify which steps are necessary to learn more about the "possible genetic disorder". This requires a detailed family history. It also requires developing a family tree. The code for following a family tree is presented, above.

Proband or Index Case

- When taking the family history, it is necessary to identify as many family members as possible.
- It starts with the "proband" or the "index case".
- This is the person with the disorder.
- This individual is marked on the family tree with an arrow.

Intrafamilial Relationships



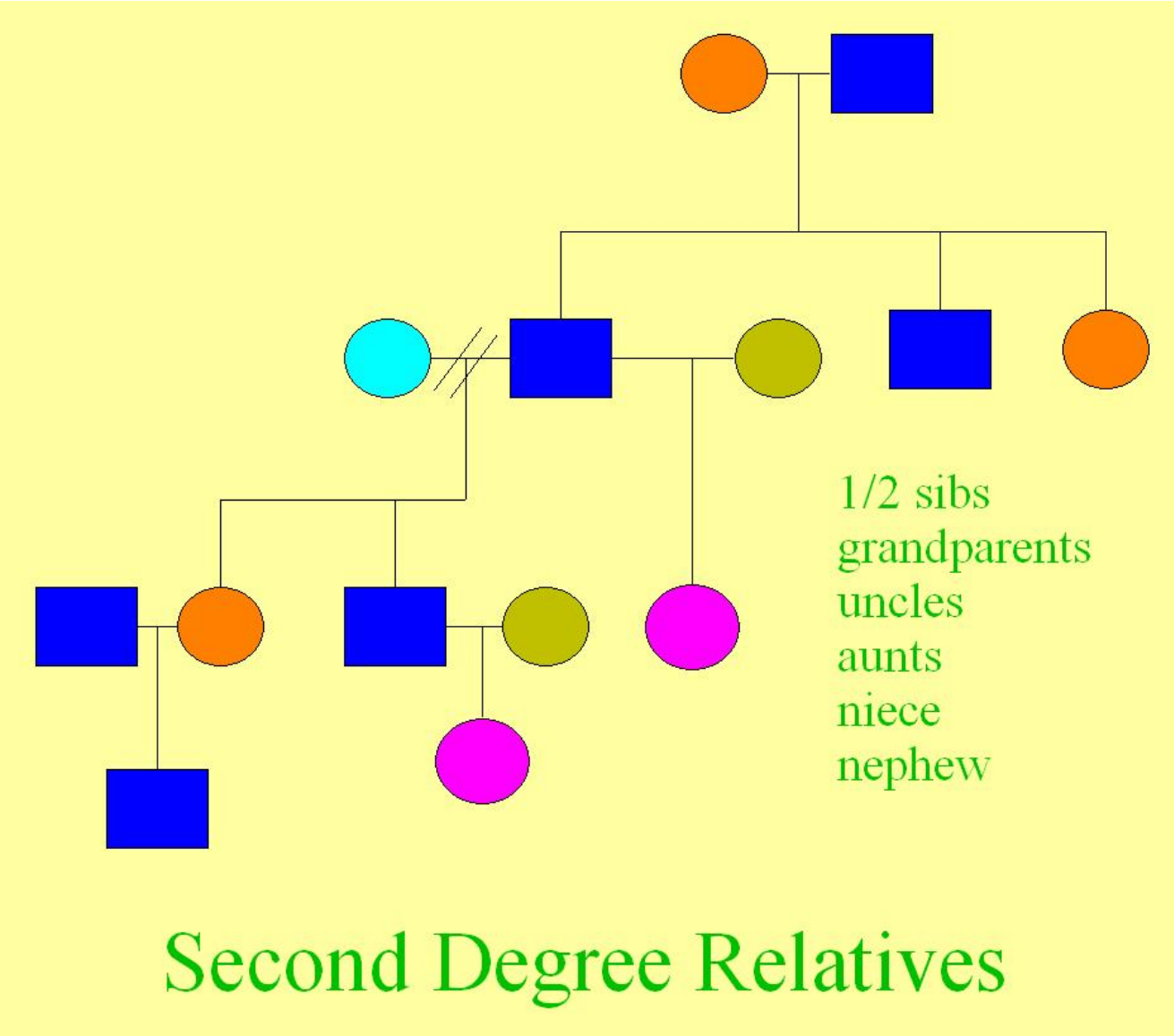
Parents

Siblings

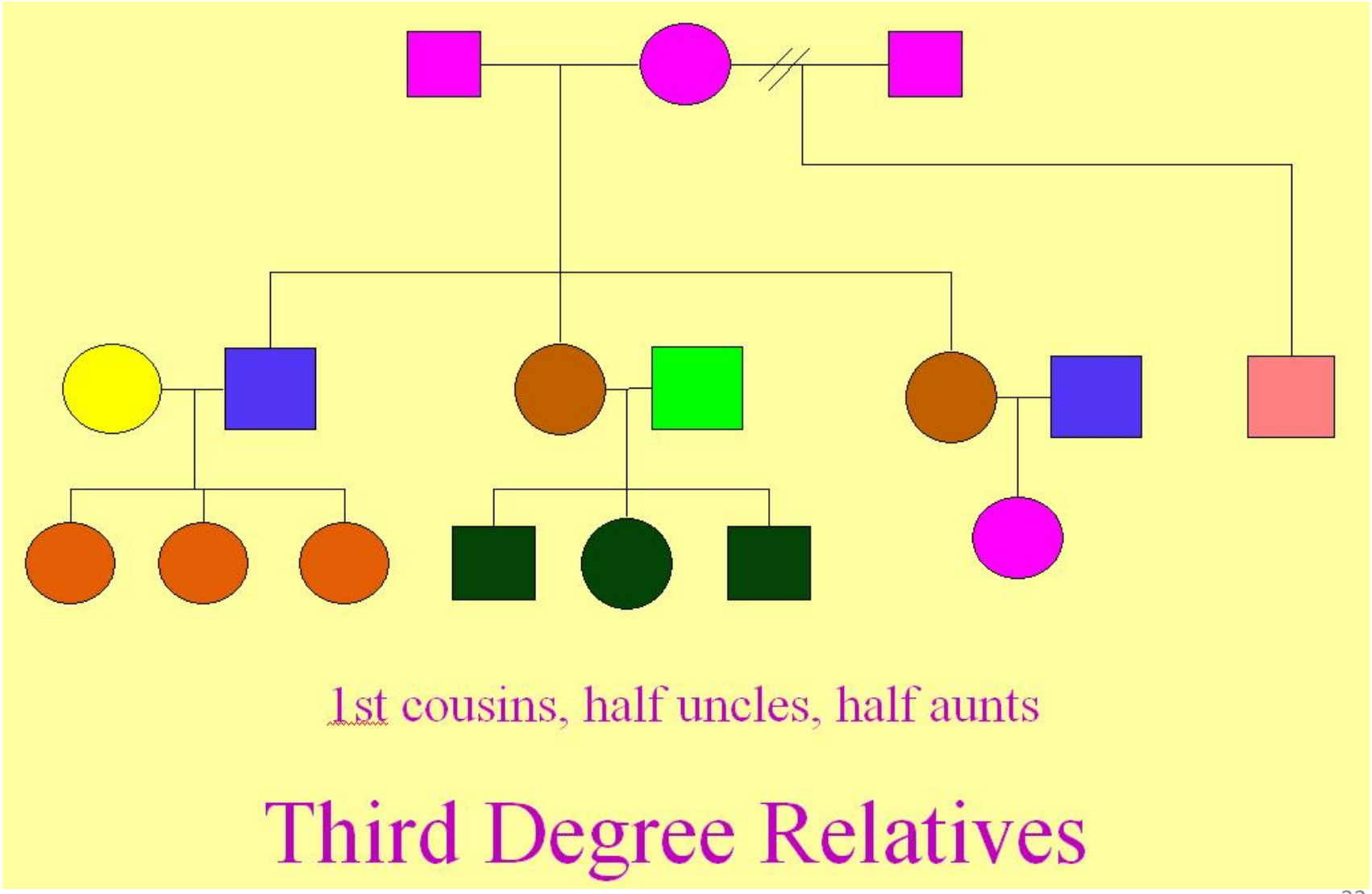
Proband Offspring

First Degree Relatives

Intrafamilial Relationships



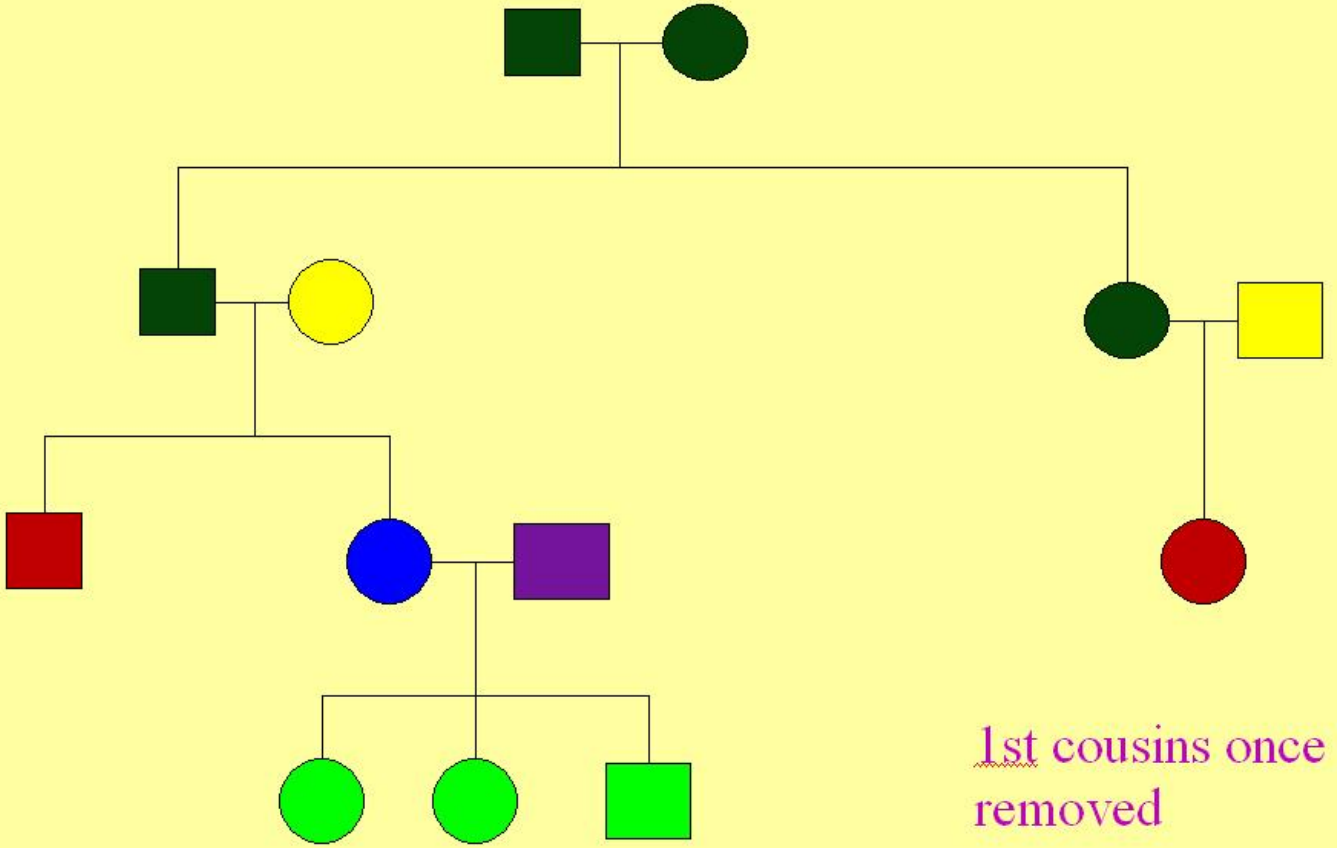
Intrafamilial Relationships



1st cousins, half uncles, half aunts

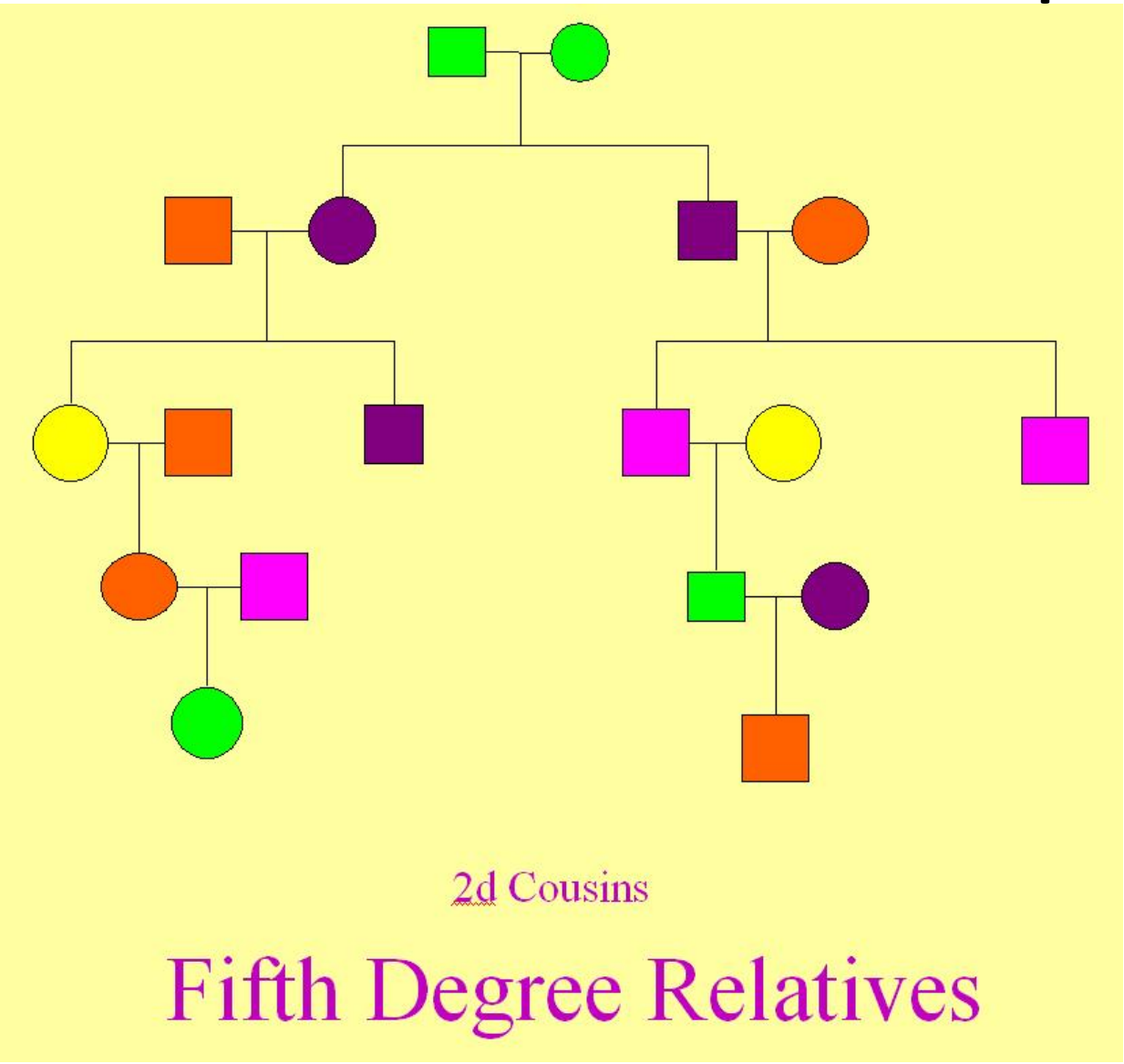
Third Degree Relatives

Intrafamilial Relationships



Fourth Degree Relatives

Intrafamilial Relationships



Intrafamilial Relationships

Primary (1°) relatives	Secondary (2°) relatives	Tertiary (3°) relatives	Quaternary (4°) relatives	Pentanary (5°) relatives
First degree	Second degree	Third degree	Fourth degree	Fifth degree
Parents, siblings, offspring of the proband	Half-sibs, grandparents, uncle, aunt, niece, nephew	1st cousins, half uncles, half aunts	1st cousins once removed	2d cousins
Share half of genes	Share a quarter of genes	Share an eighth of genes	Share a sixteenth of genes	Share a thirty-second of genes

Some of the information to obtain from these individuals is as follows:

1. All names used by each person. Their date of birth (DOB) with current age. How old were people when they died. What caused their death. Name or describe the disease/defect/deficiency. What sex were they.

2. Give the survey to the rest of the family:

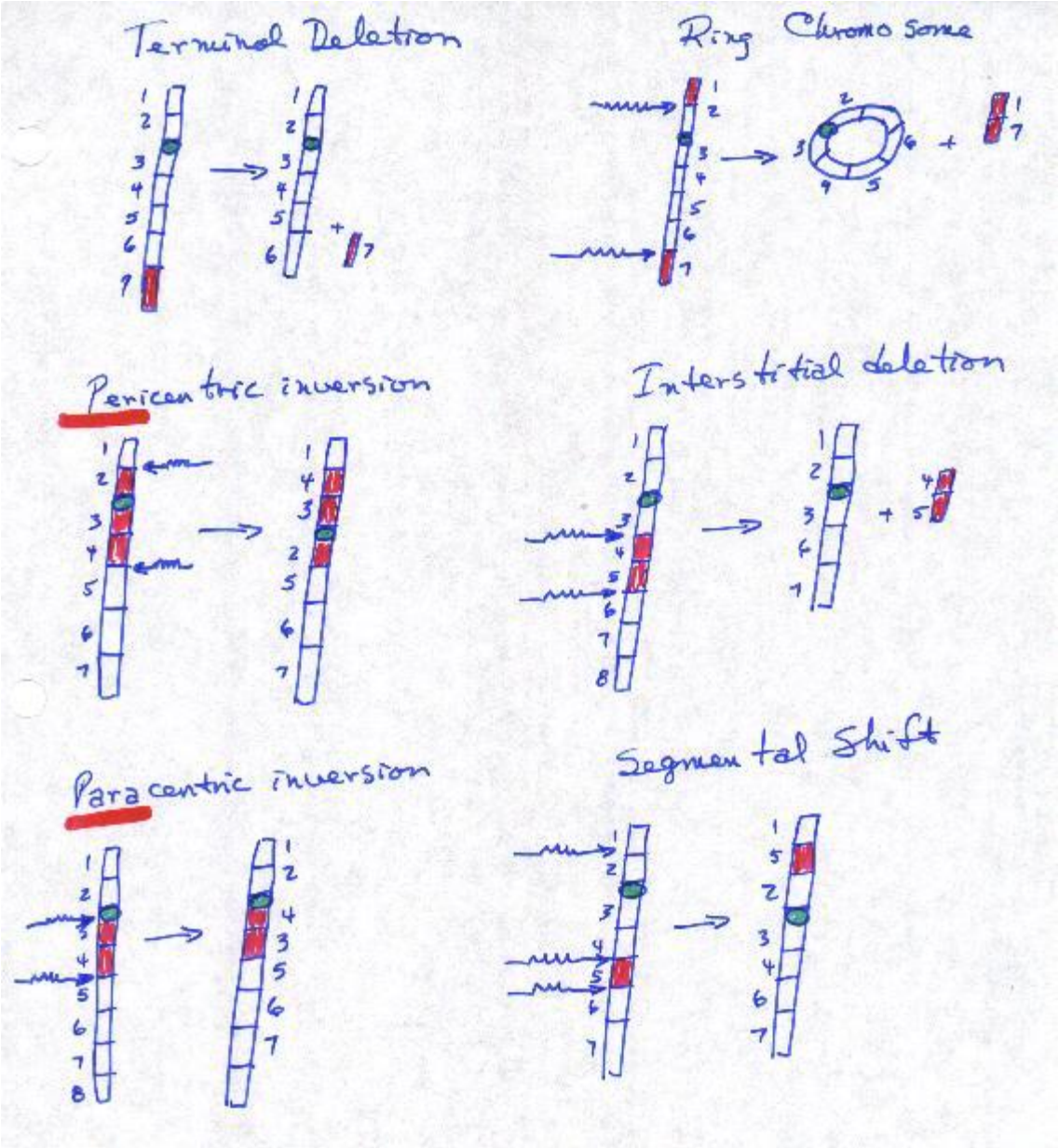
a. Anyone else got it?
b. Anyone else have a trait that proband does not, but is known to be part of the same defect?
c. Anyone else in the family have another trait that is genetic (to confirm hereditary disease even though may not be involved with proband's defect)?
d. Anyone else with rare disease -- or died from it? -- may help to identify defects in family members that may be related to the index case.
e. Any consanguinity in the marriage? This rules out (R/O) homozygous recessive traits).
f. Any common last names in families of mating pairs -- consanguinity may be unknown to proband.
g. What is the ethnic origin? Some ethnic groups have increased chances of genetic disease. Examples are listed in the table, below:

Ethnic group	Disease
African American	Sickle cell anemia
Ashkenazi Jews	Tay-Sachs
Chinese	Glucose-6-phosphate dehydrogenase deficiency
Mediterranean	β-thalassemia
Northern Europe	Cystic fibrosis
Scandinavians	α1-antitrypsin deficiency

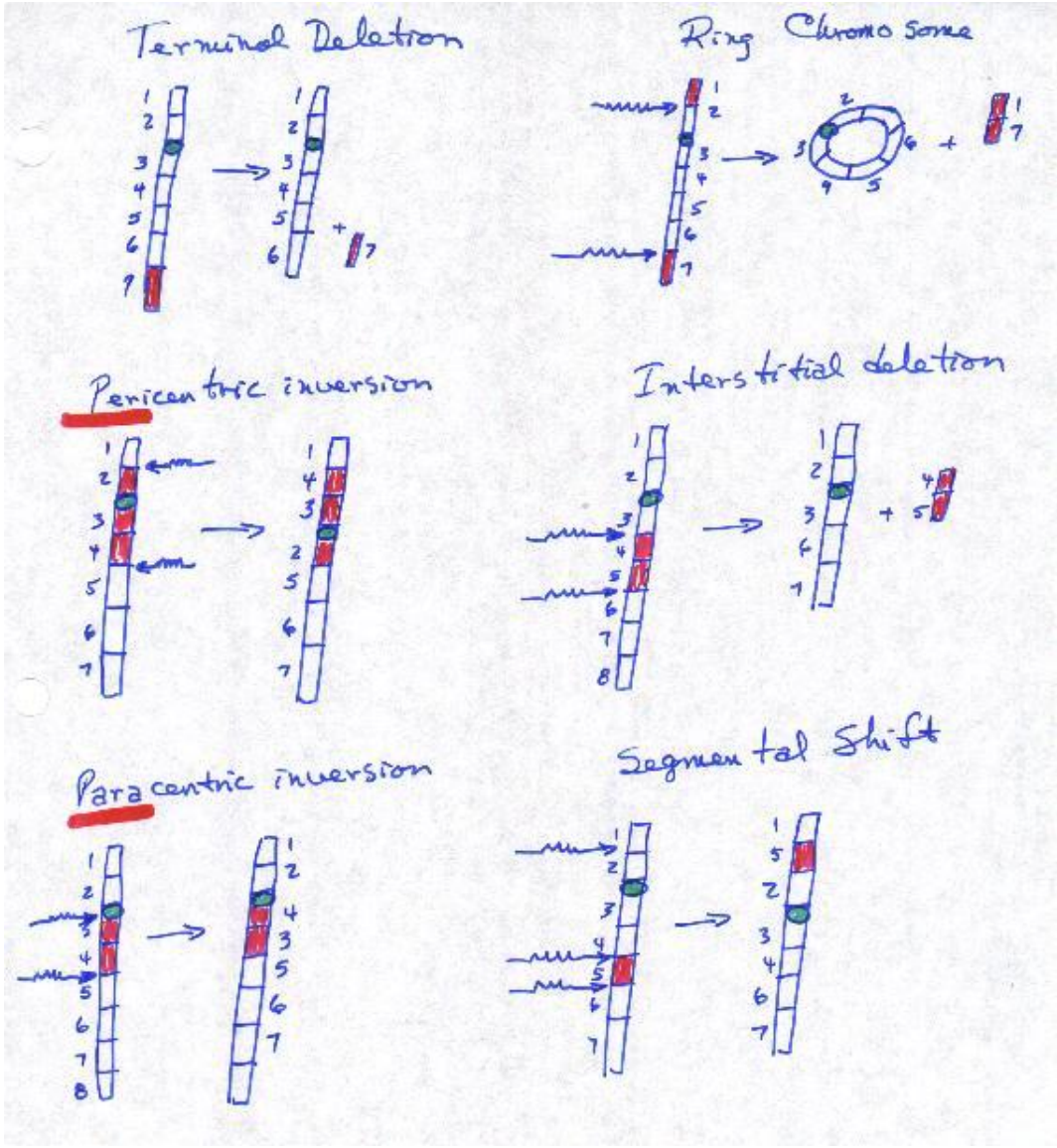
The two simplest classes of genetic disorders will be examined first.
In a nutshell, each of us has 46 chromosomes: 23 pairs. 22 of these pairs are called autosomes and the last pair is called the sex chromosomes.
The abnormalities that fall into the chromosomal category include variations in the number of chromosomes, e.g.:

Chromosome type	Genetic description	Name of Disorder
Autosome	Trisomy 21	Down Syndrome
Sex	47, XXY	Klinefelter's Syndrome
Sex	45, X	Turner's Syndrome

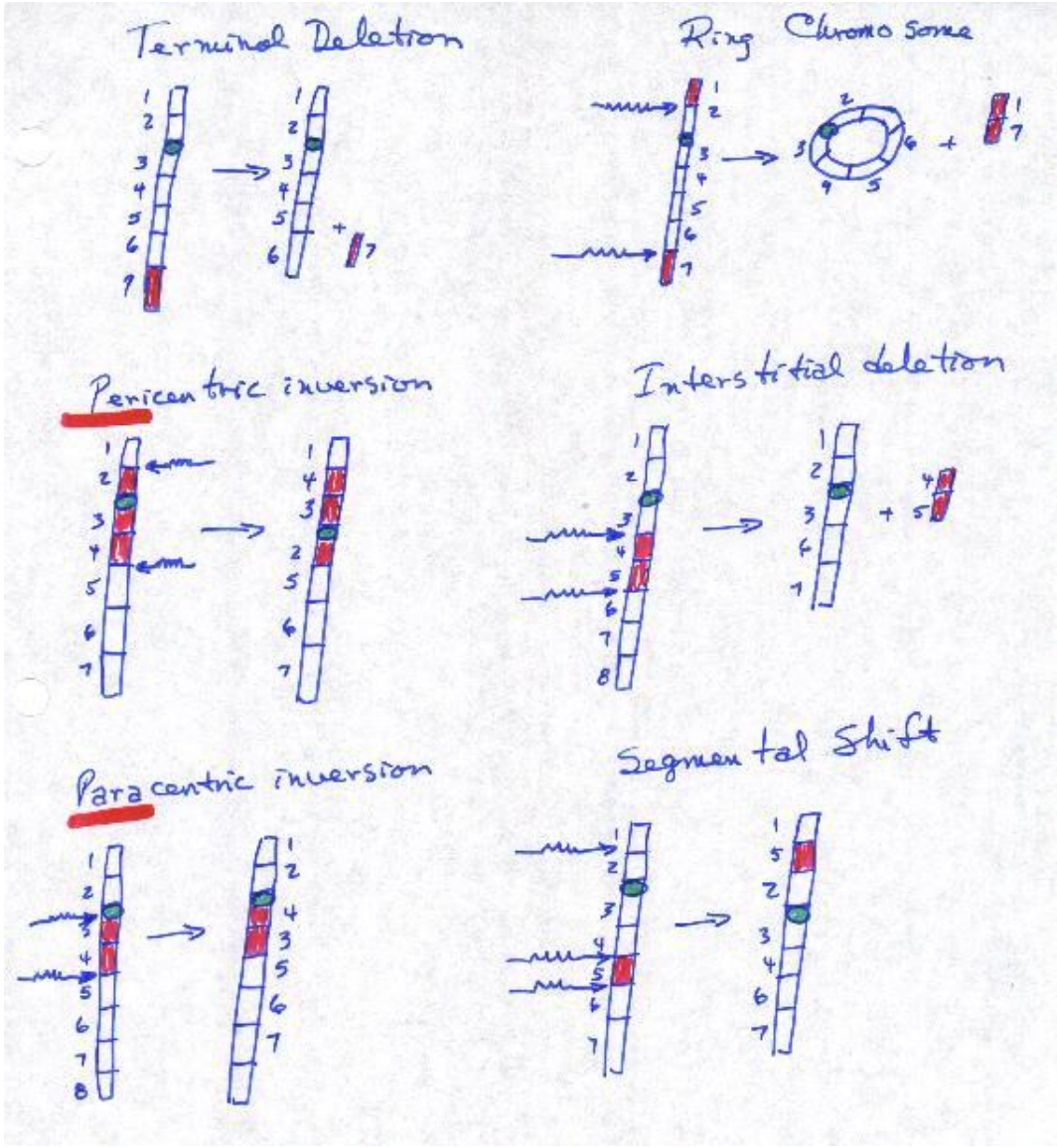
Chromosomal rearrangements are in this category, as well



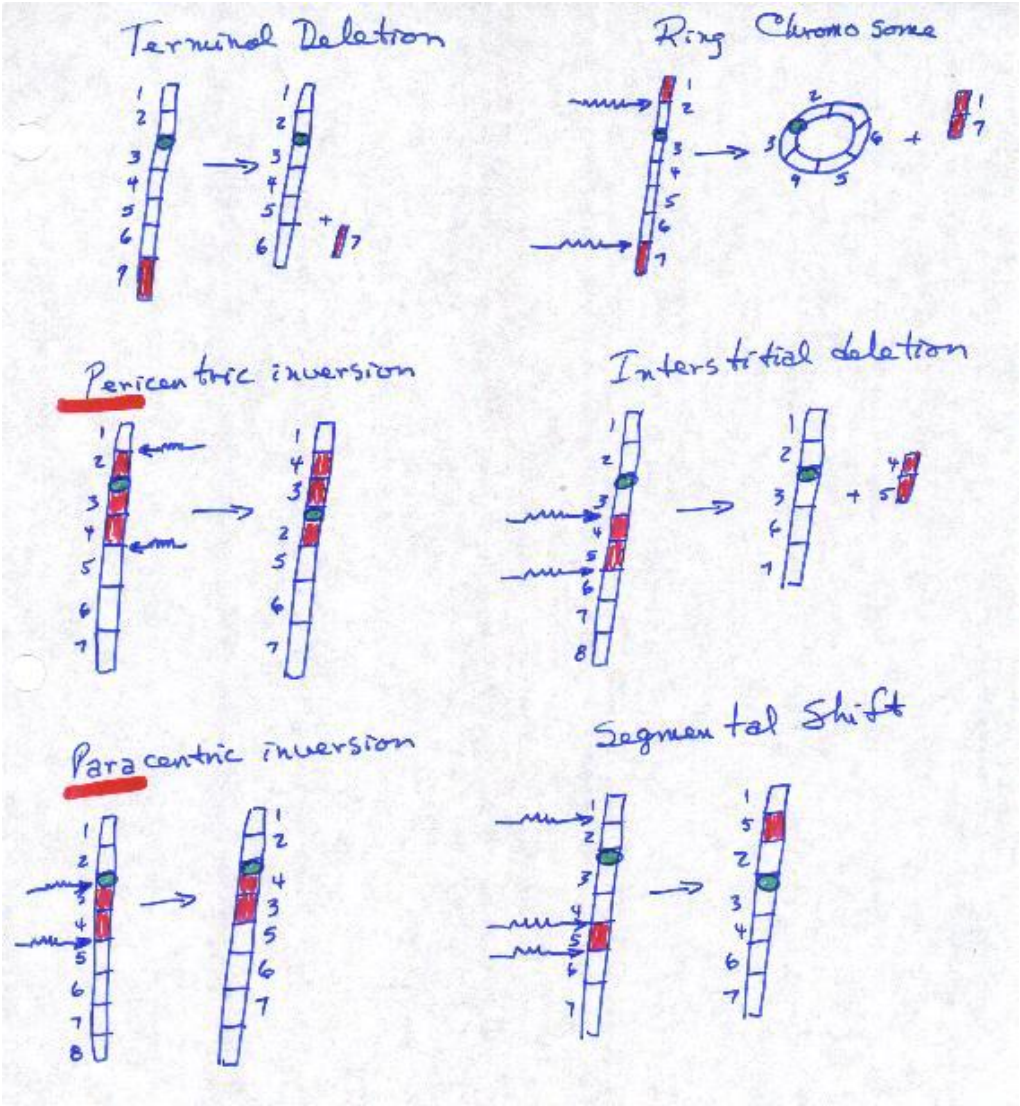
- Robertsonian translocation is in this classification, although it is not included graphically.
- Six other rearrangements are, however, illustrated, right:
  - Terminal deletion,
  - Ring chromosome,
  - PERIcentric inversion,
  - Interstitial deletion,
  - PARAcentric inversion and
  - Segmental shift.



- In **terminal deletion**, a terminal portion of a chromosome is lost.
- In the formation of a **ring chromosome**, a segment may be lost and the remainder of the chromosome "closes itself up".
- **Interstitial deletions** involve the loss of a portion of the chromosome.
- A **segmental shift** occurs when one segment of the chromosome is removed from its normal site and place in a new site.



- PERIcentric and PARAcentric inversions have been saved for last as their names are very similar.
- In **PERIcentric inversion**, a segment that includes the centromere is inverted and re-inserted in the chromosome between the same segments.
- In **PARAcentric inversion**, a region of the chromosome adjacent to the centromere, but EXCLUDING the centromere, is inverted and re-inserted in the same site.

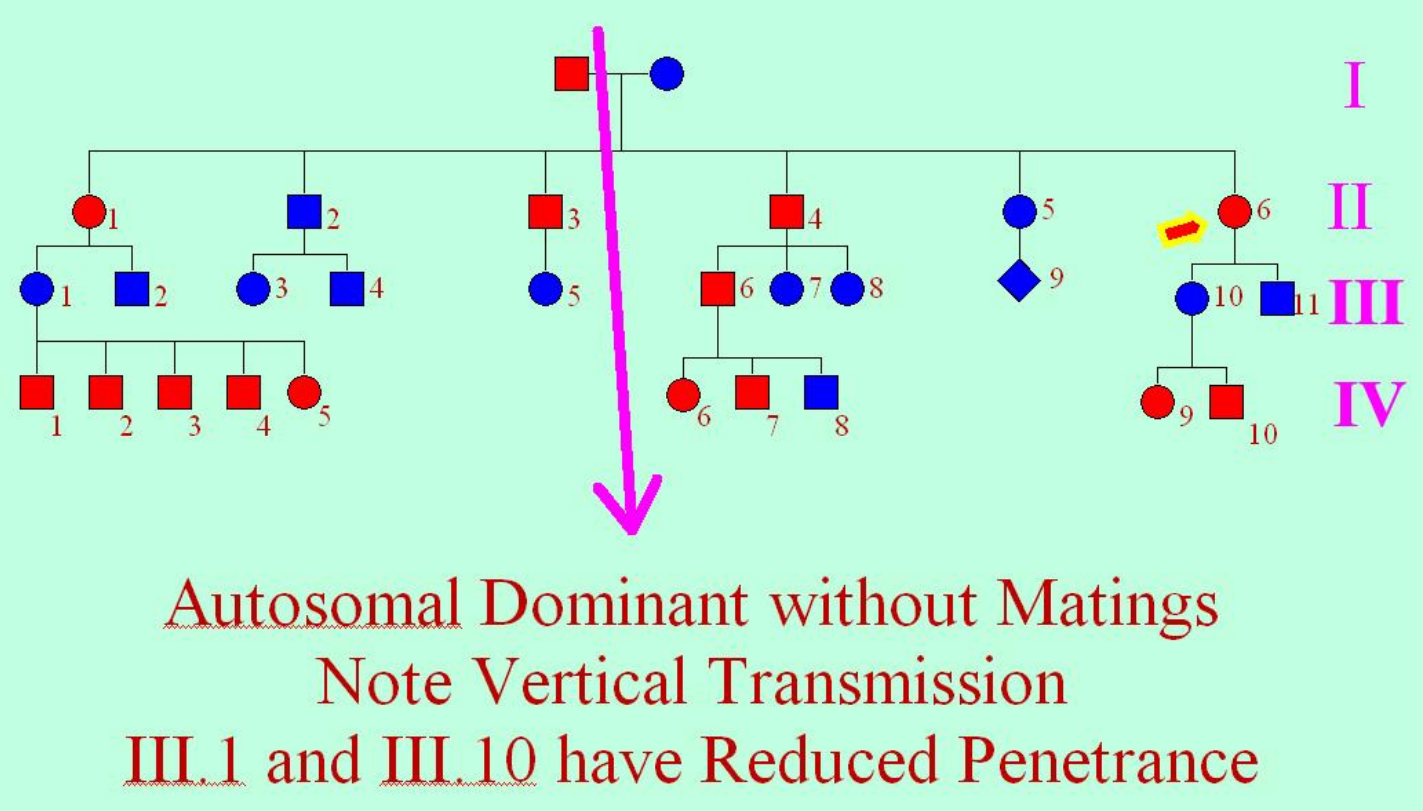


- Genetic disorders that fit into the multi-factorial classification may best be described by the following.
- They are not inherited in standard Mendelian manner.
- The inheritance risks are less than those with Mendelian inheritance risks to siblings (sibs) and children.
- The risks of recurrence increases with increased members of the family being effected.
- The risks of recurrence decrease with increasing distance between family members, approaching zero for third degree family members.
- Consanguinity (mixing the same blood; in-breeding) increases the risk of recurrence.
- Pedigrees (family trees) may superficially resemble Mendelian characteristics in SMALL families.
- The gene may express greater in one sex than the other, e.g., male pattern baldness.

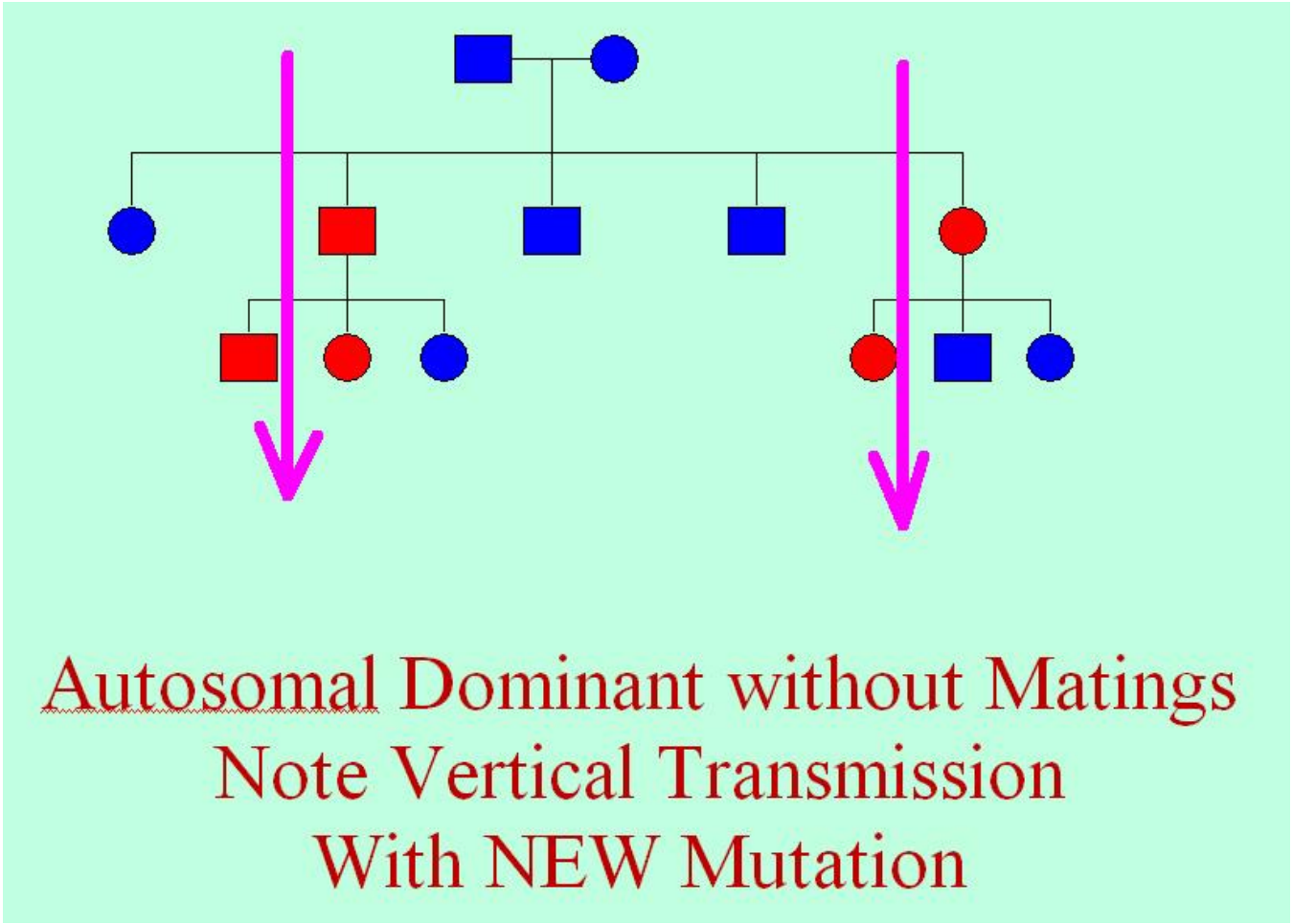
The last classification of genetic disorders, the simply inherited disorders (Mendelian-type) is more detailed and will be subdivided into autosomal disorders and X-linked disorders.
In autosomal disorders, the genes are situated on all BUT the X or Y-chromosomes. When two alleles -- B and b, for example -- occupy each locus of a chromosome pair, there are three possible combinations:

BB	Bb	bb
Homozygous	Heterozygous	Homozygous
Trait is dominant	Trait is dominant	Trait is recessive
Double dose of "B"	Single dose of "B"	"No" dose for "B"; double dose for "b"

Autosomal Dominant Disorders

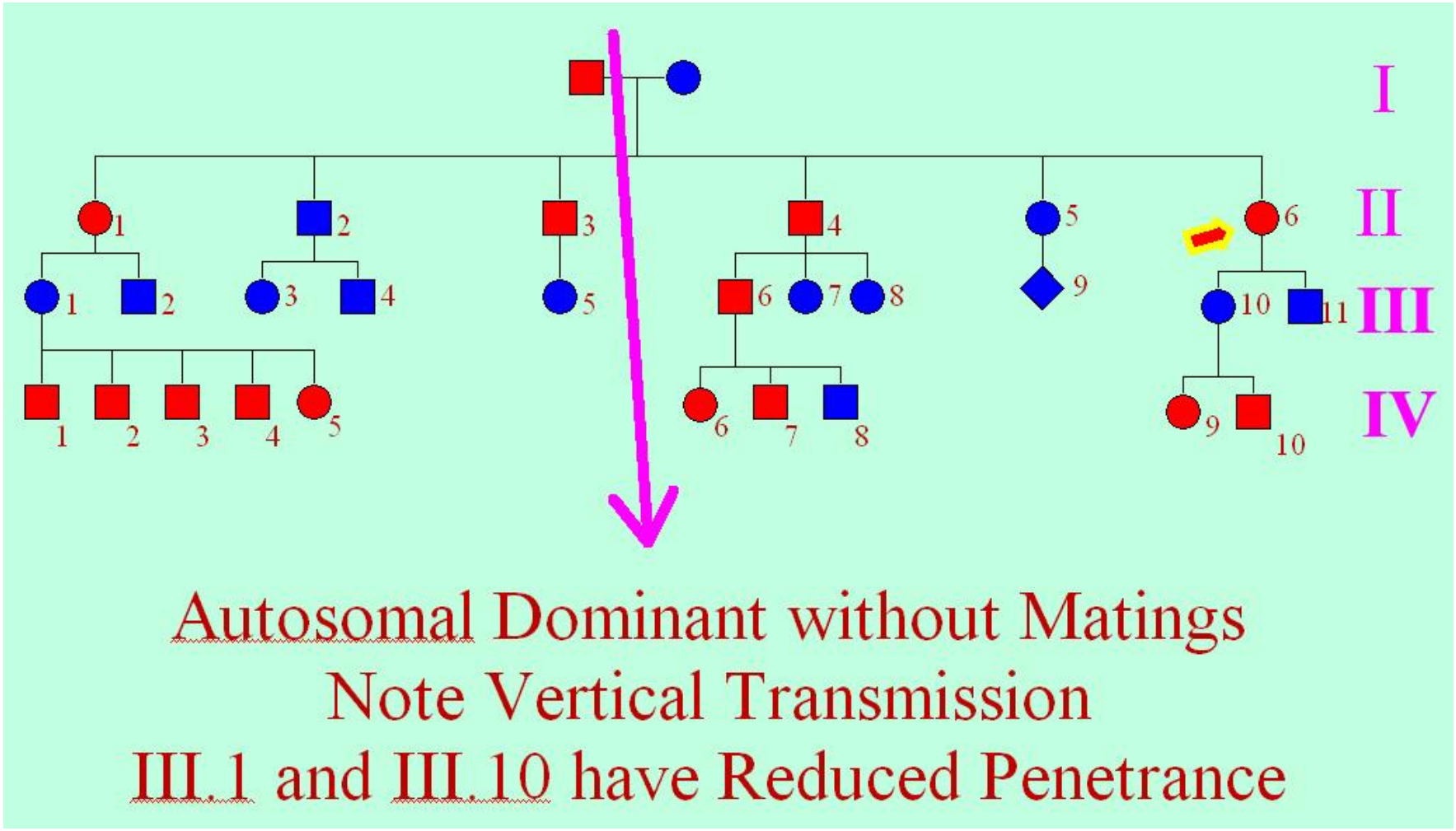


- These disorders are transmitted from 1 generation to the next by both sexes. Both sexes are at equal risk of being effected. It is vertically transmitted.
- Three or more male-to-male transmittances prove autosomal dominant transmission. The chance to pass along the gene is 50% per conception.
- It may present as "reduced penetrance", i.e., it may appear to "skip" a generation. It is identified after the effected offspring is born from an "uneffected" parent OR by molecular biology techniques.



- The risk of the child to have the clinical disease is equal to the product of 0.5 (for 50% chance to inherit the gene) and the percent of carriers with the disease (penetrance). Age of onset varies making it difficult to determine age of risk or if the patient is beyond the age of risk. A unique case MAY be due to a new mutation.

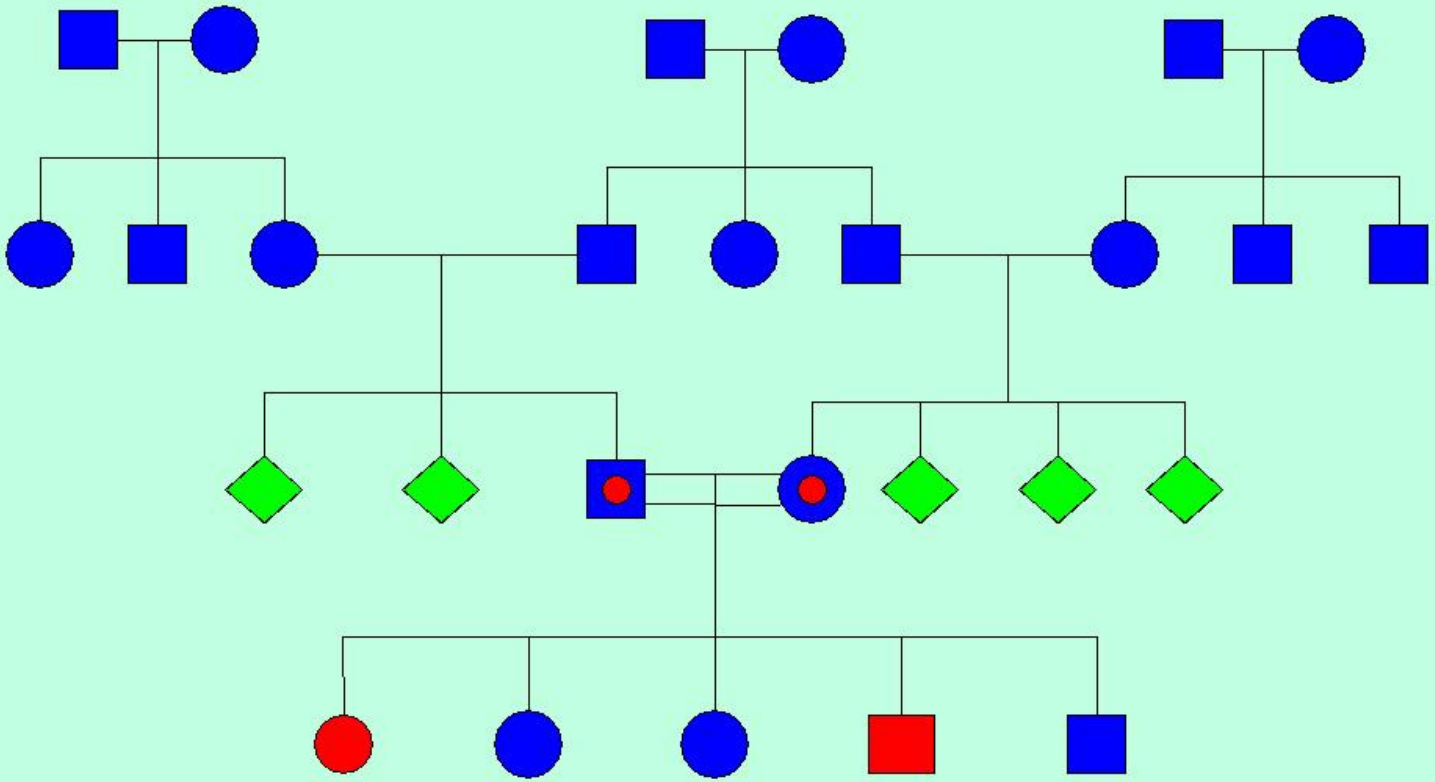
- Children of minimally effected parents may be severely effected. New mutations seem to happen more often in reproductive cells of fathers who are of older age (5-7 years older than the general population of paternally inherited mutations, approximately 30 vs. 37 years of age). With "new mutations", R/O reduced penetrance and "mistaken"/extramarital paternity.
- It may be possible that a defect is NOT autosomal dominant (may be a phenocopy: nongenetic conditions that mimic a specific genotype) or the defect may be similar to but genetically different with a different pattern of transmittance. Double-check this family's history very carefully!
- Autosomal dominant disorders are "generally" not due to enzyme defects (most biochemical defects are substrate-limited and NOT enzyme limited, hence, even with 50% of functioning enzymes, the reactions will continue to "run" as "ordered").



- Note in the Figure, that there are 4 generations of a family represented.
- Note also that III.1 (offspring 1 in the third generation) and
- III.10 show reduced penetrance -- one of their parents had the gene/effect, they don't express the effect, but their own offspring do.

Autosomal Recessive Disorders

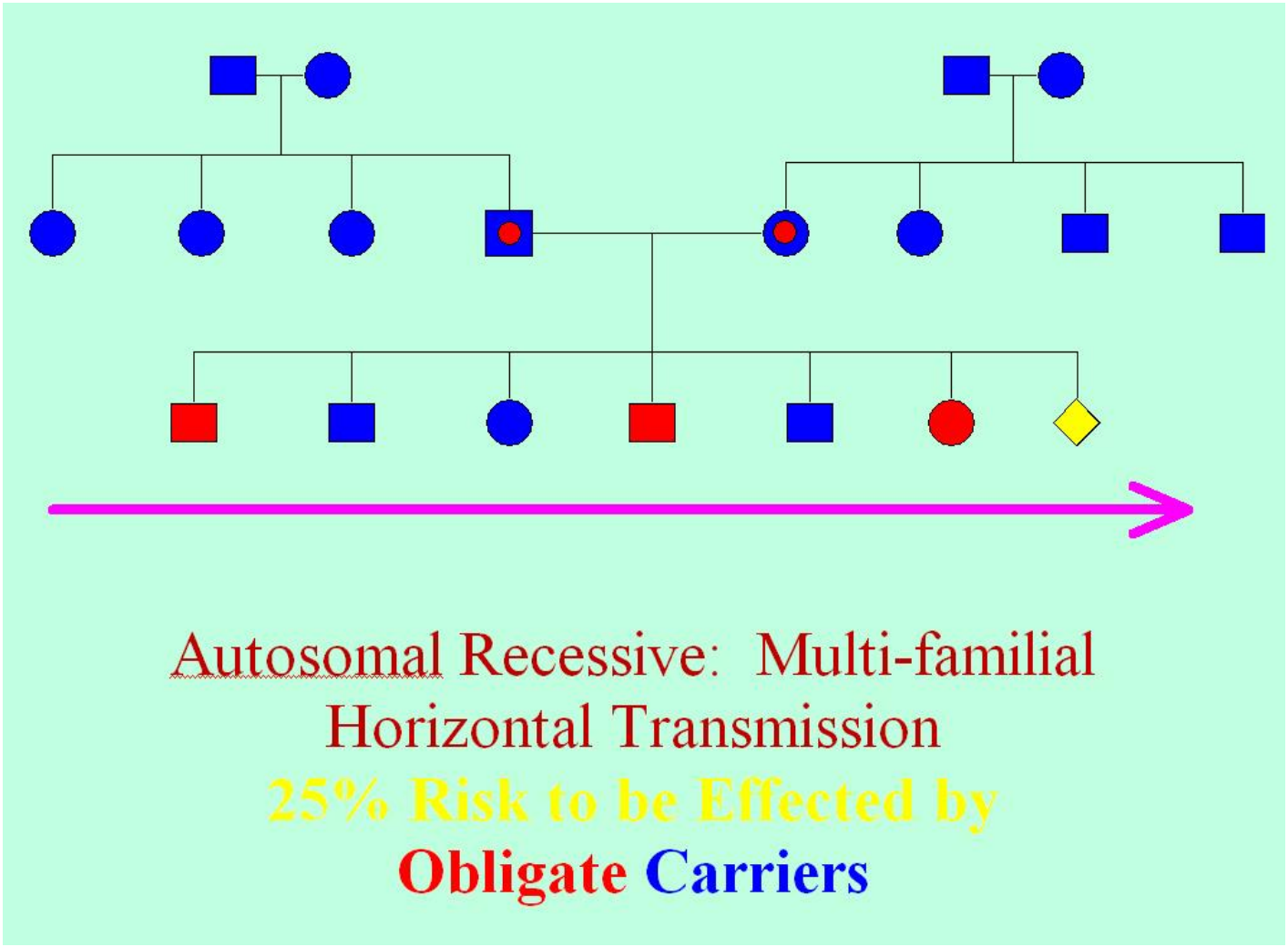
- Those not clinically effected/symptomatic are heterozygotic and usually identified AFTER a child with the disorder is born. These parents are called obligate carriers. Disorders are found only in sibs. Males and females are at equal risk. No other relatives are effected with the EXCEPTION of in-bred families.
- When both parents are carriers, the risk of having an effected child is 25% per conception; 50% for having a child who will be a carrier of the gene; 25% chance for having a child with homozygous "normal" inheritance. Sibs without the disorder born to people with the disorder have a 67% risk of being a carrier of the gene. Carrier testing MAY be available and, if so, identifies carriers.



Autosomal Recessive: Consanguineous (1st Cousins) -- Horizontal Transmission

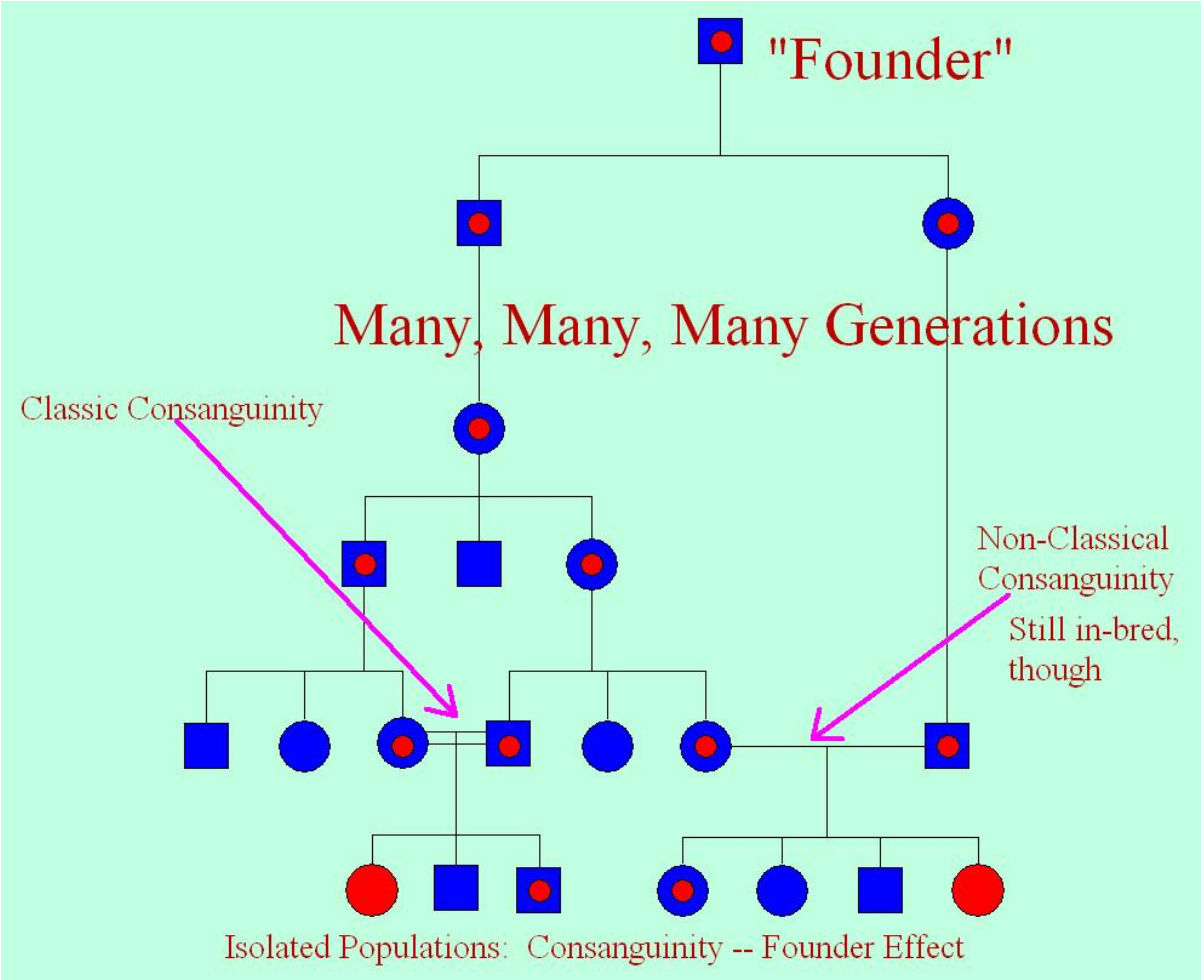
Obligate Carriers

- In general: the risk of children born to individuals with the disorder is NOT very high (EXCEPT in consanguinity) due to low population frequency of carriers. All offspring of people with the disorder, though, are carriers.
- When 2 parents with the same mutation on the same gene reproduce, all offspring will have the same disorder. Alternatively, when two parents with different mutations on different genes reproduce, no child will have the disorder. This is called assortative mating, e.g., albinism: two different genes with two different mutations cause this.
- The rarer the disorder, the more likely consanguinity exists somewhere. An increased frequency of consanguinity is not detected if the recessive disorder is common, e.g., sickle cell anemia and PKU. Spotty cases of autosomal recessive disorders are observed now because of people having small families.



- Vertical transmission does NOT occur, but HORIZONTAL transmission does:
- Many couples who are carriers may have children without the disorder. These carriers go undetected/unidentified. Autosomal recessive disorders are frequently associated with enzyme defects.

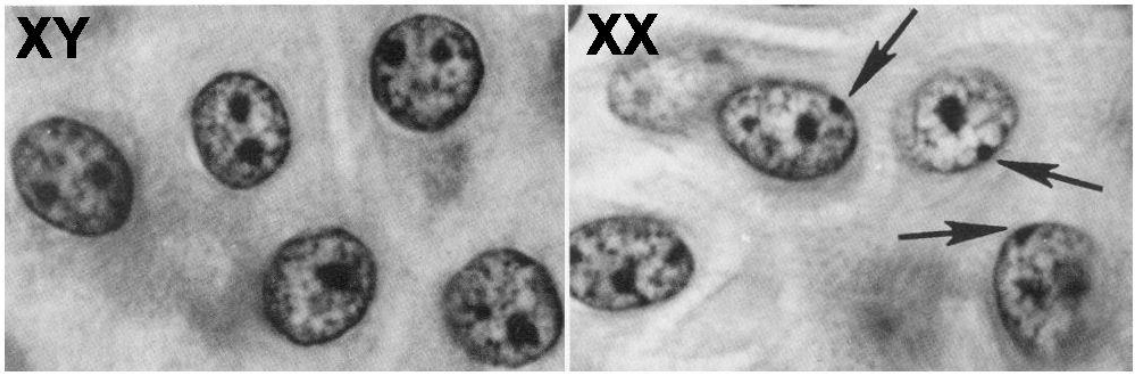
Isolated Populations -- Consanguinity



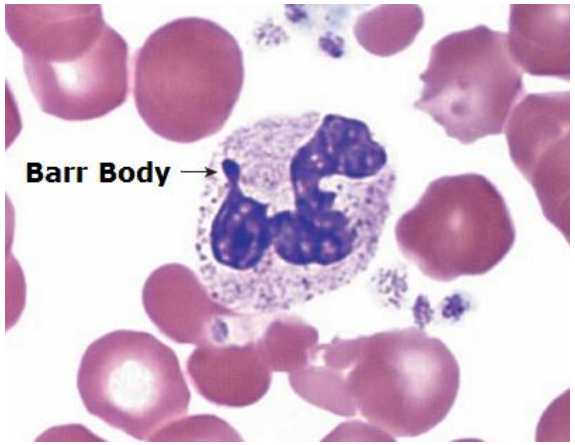
- Vertical transmission does NOT occur, but HORIZONTAL transmission does:
- Figure represents what happens in very small, isolated populations as you would expect to find in Switzerland, for example.

X-linked Disorders -- Dominant/Recessive Combined

- Disorders come from genes on the X-chromosomes. A female may be heterozygous or homozygous since she has 2 X-chromosomes. X-linked dominant and X-linked recessive refer ONLY to expression in females. A male has only 1 X chromosome, therefore, he is hemizygous for X-linked traits. Males express the trait regardless of whether the trait is dominant or recessive since they only have 1 X chromosome. Males transmit the X chromosome to ALL female offspring, therefore, females are called obligate carriers.
- Fathers do NOT transmit the trait to their sons. To make a male baby, the father provides the Y chromosome; the mother provides the X chromosome. **THE feature of X-linked transmittance/inheritance is total, complete lack of male-to-male gene passing.**
- Females have 2 X-chromosomes. One would think that this would translate to twice as much protein information in the female, BUT this is NOT the case: 1 X chromosome is inactivated **(called lyonization after Mary Lyon who discovered this phenomenon).**



Source: https://societyandgenetics.wordpress.com/spring-2013/testing-sex-for-competitive-sports/weapons/barr-body-testing/



Source: http://www.getmededu.com/barr-body.html

- After cellular differentiation, 1 of the 2 X chromosomes inactivates (Lyonizes) and condenses to form a Barr body.
- Barr bodies (arrows above) can be observed in cell nuclei that stain darker than the rest of the chromatin. If the Barr body is stained with a fluorescent stain, it will be the brightest spot in the nucleus.
- Inactivation of one of the X-chromosomes is a random activity: each cell may inactivate paternal- or maternal-derived X-chromosomes with equal probability.
- After inactivation, the SAME X remains inactivated throughout all following cell generations.
- Hence, a female at any one time in her cells has half of her father's X and half of her mother's X expressed.

X-linked Disorders -- Dominant/Recessive Combined – Cont'd

- Women may be carriers if they have at least:
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    - 1 son with the disorder OR
    - 1 brother with the disorder OR
    - 1 uncle on mom's side with disorder OR
    - 1 sister with a son who has the disorder

One Exception:

- The tip of the X chromosome is homologous to the Y chromosome.
- This allows XY recombination and pairing during meiosis.
- This region is NOT lyonized.

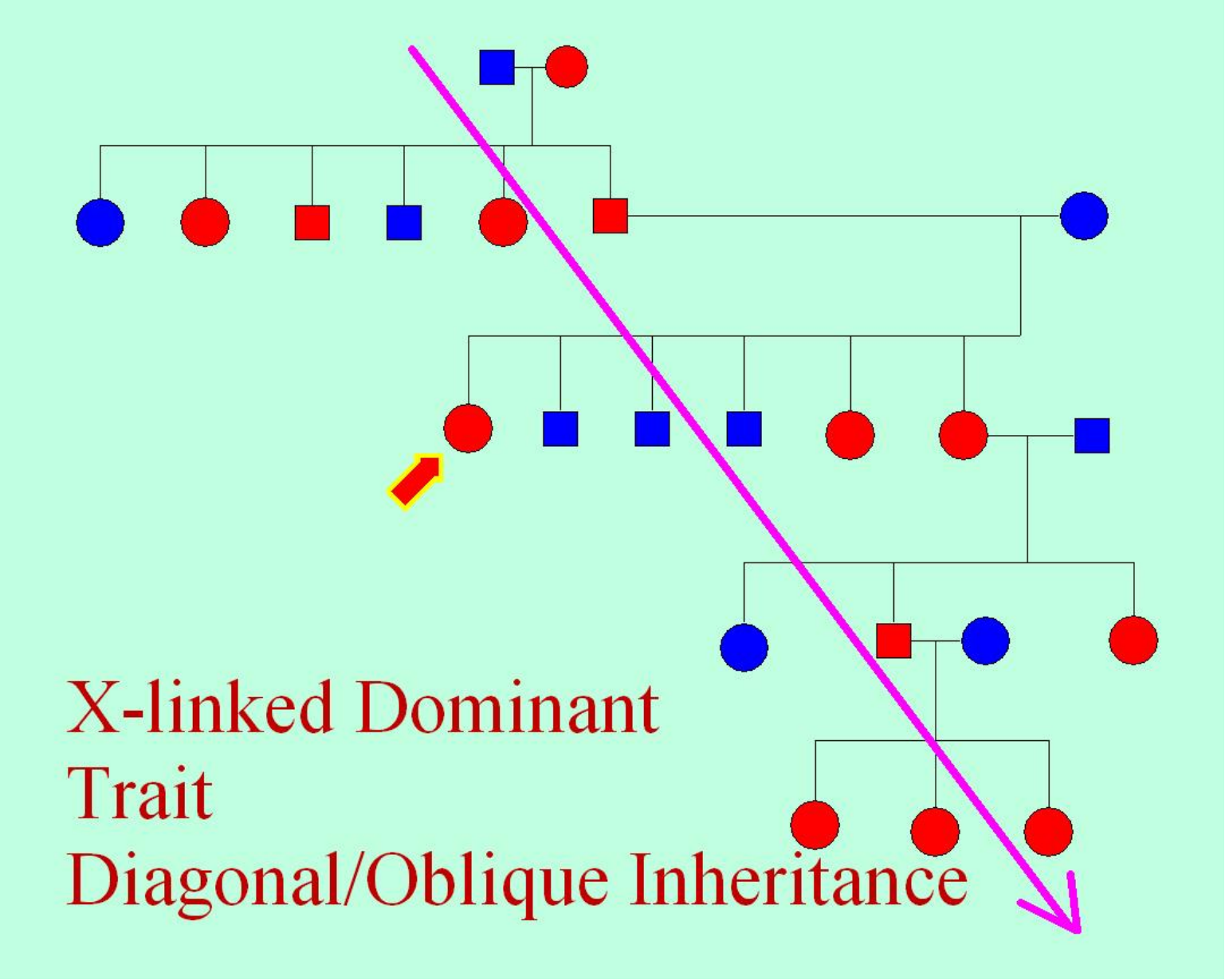
A “Twist” on Lyonization

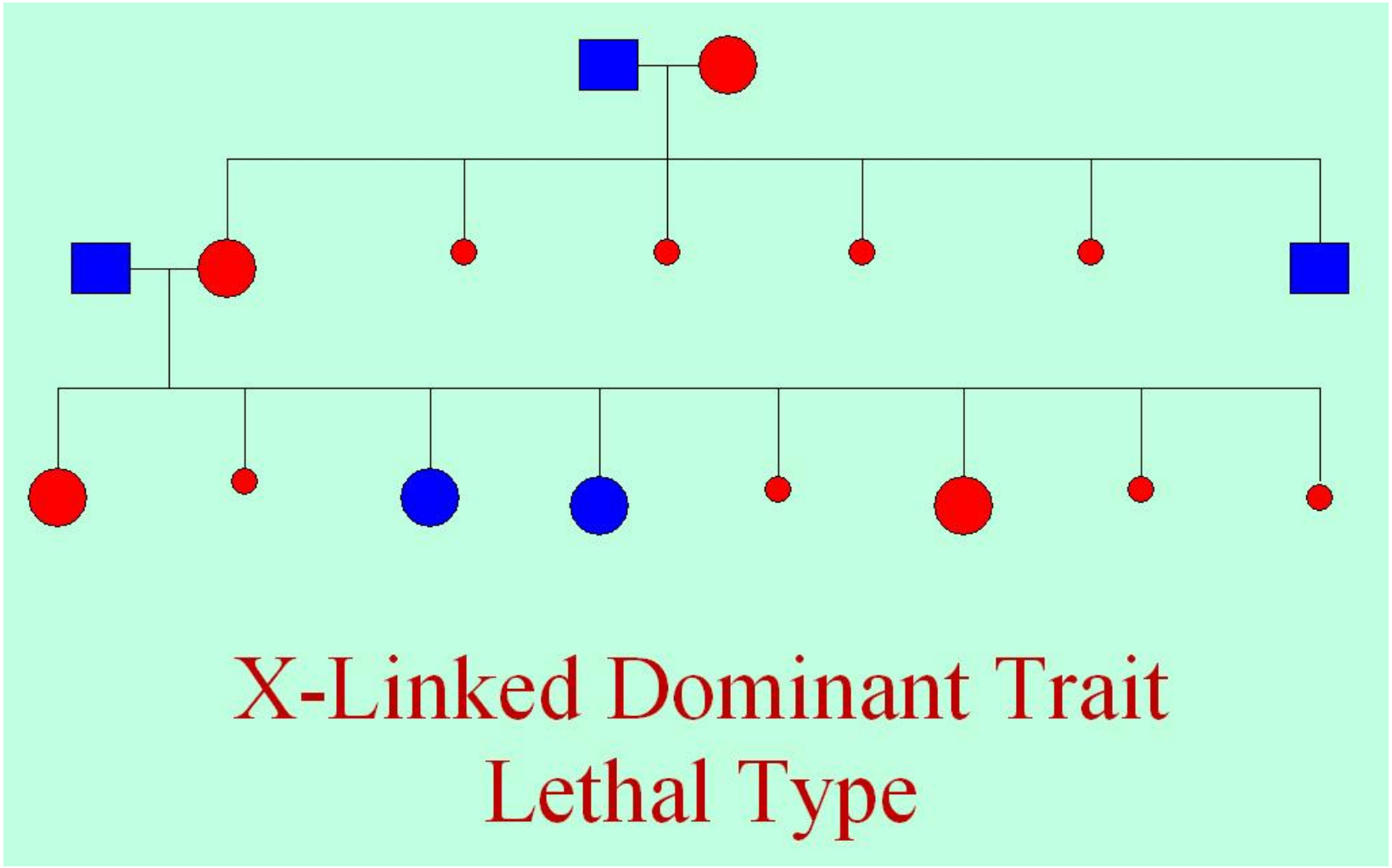
- Sven Bocklandt [1, 3, 4], Steve Horvath [1, 2], Eric Vilain[1] and Dean H. Hamer[3], Extreme skewing of X chromosome inactivation in mothers of homosexual men. **Human Genetics** 118:6 (691) 2006. [(1) Department of Human Genetics, University of California, Los Angeles, CA, USA; (2) Department of Biostatistics, University of California, Los Angeles, CA, USA; (3) Laboratory of Biochemistry, National Cancer Institute, Bethesda, MD, USA; (4) Gonda 5524, 695 Charles Young Drive South, Los Angeles, CA 90095-7088, USA]

- 97 mothers of homosexual men
- 103 age-matched control women without gay sons.
- The number of women with extreme skewing of X-inactivation was significantly higher in mothers of gay men (13/97=13%) compared to controls (4/103=4%) and increased in mothers with two or more gay sons (10/44=23%).
- Findings support a role for the X chromosome in regulating sexual orientation in a subgroup of gay men.
- Remember that the tip of the X is analagous to the Y – what does lyonization of this part of the X mean?

- Due to germline mosaicism, prenatal diagnosis needs to be offered to parents following the birth of a child with the disorder before another pregnancy is contemplated.
- Mosaicism occurs when two or more populations of cells that have slightly different genetics are present.
- Recurrence rates are very low.
- There is an increased risk to produce offspring with abnormal karyotype[s] if mosaicism occurs in reproductive cells.
- This increased risk is greater than the risk associated with Mendelian inherited disorders.
- Germ cell mosaicism apparently explains cases in which 2 offspring of normal parents are effected with a dominant condition.
  - One child may be diagnosed with a milder disorder later in life, while the other is diagnosed earlier in life with a more severe clinical presentation -- to the point of being lethal.

X-Linked Dominant Trait

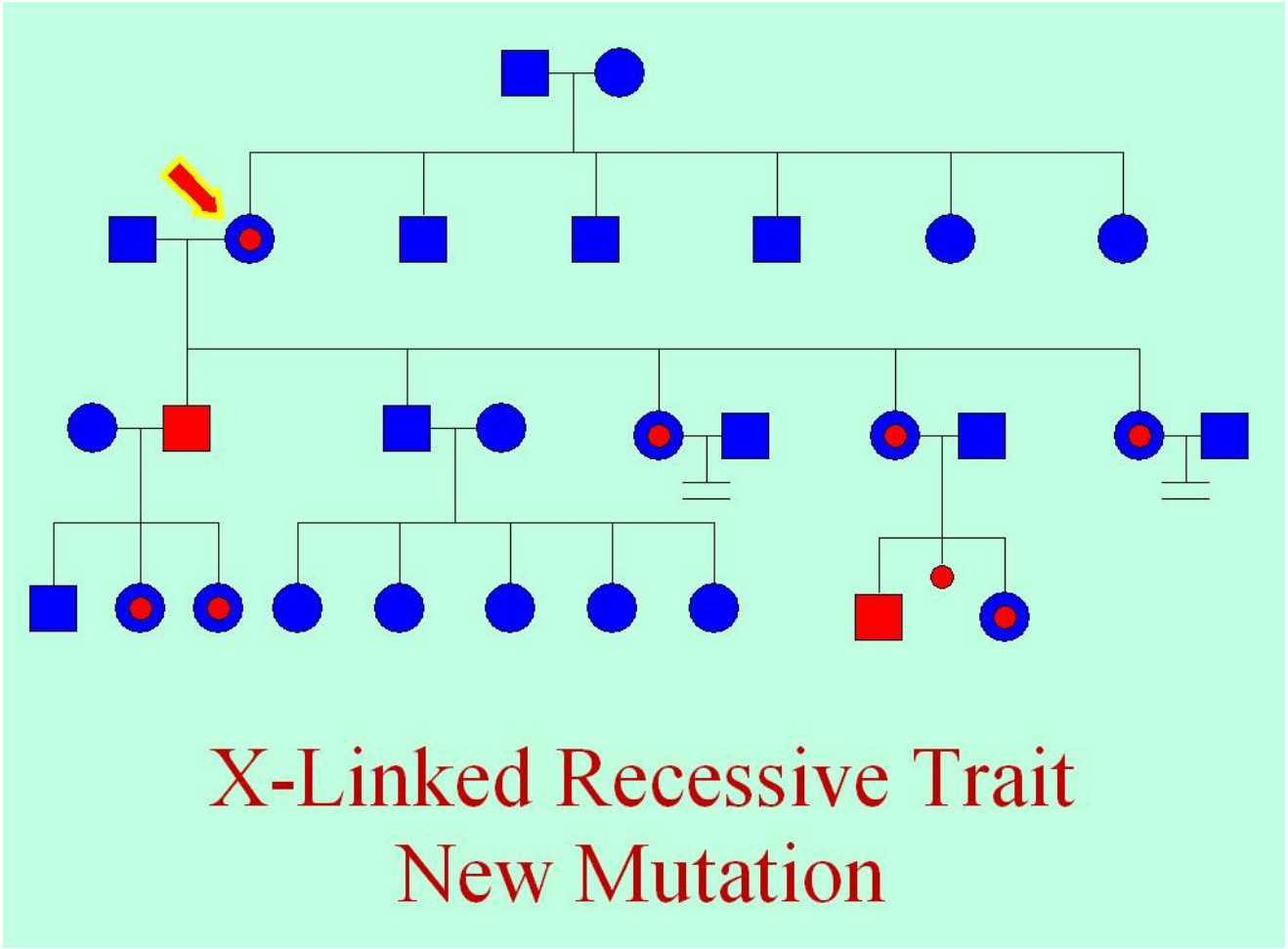




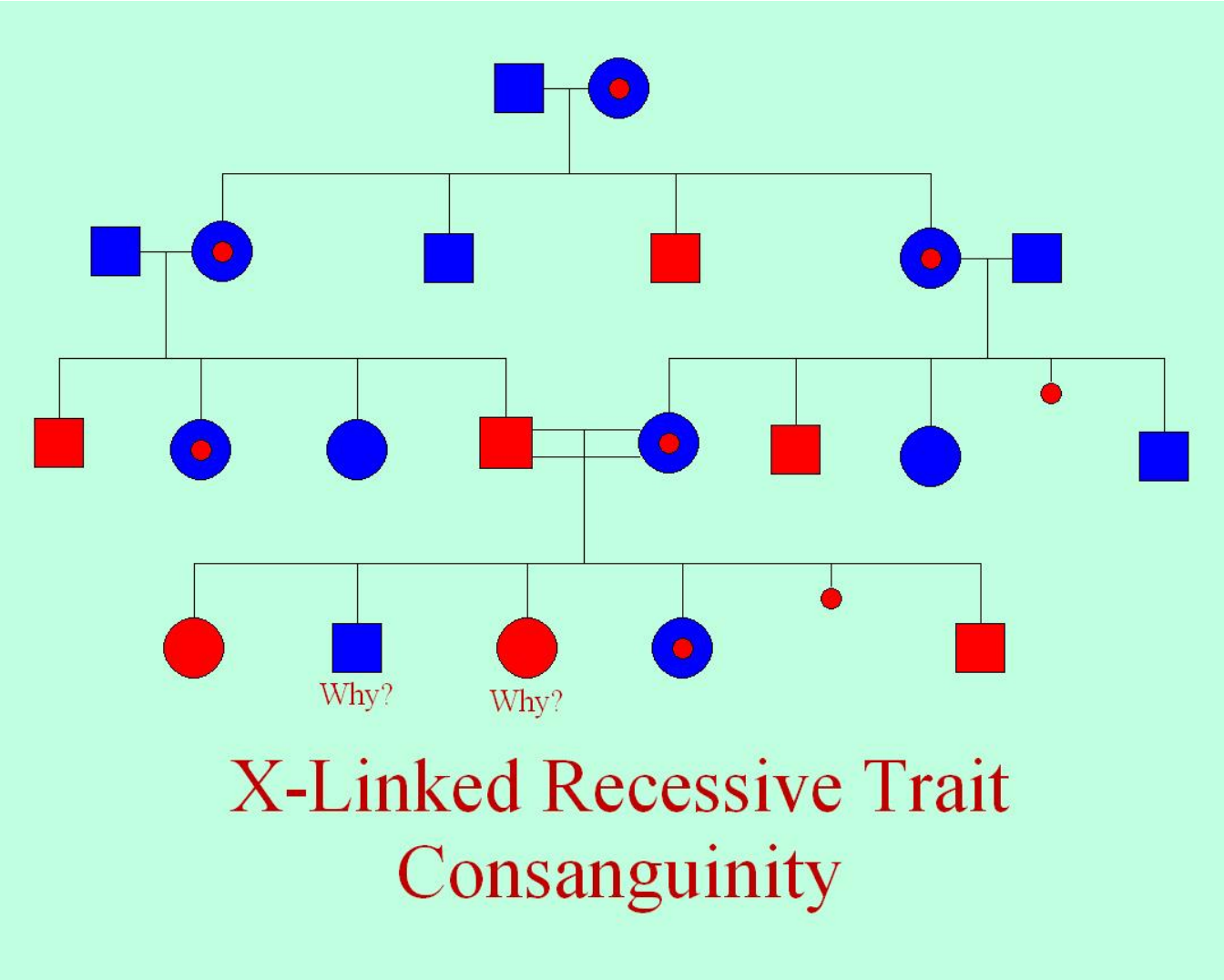
X-Linked Dominant Trait
Lethal Type

- X-linked dominant disorders are rare. If they occur in sons, they may be lethal. Effected women (with X-linked dominant disorder) have twice as many female offspring than males and have an increased frequency of abortion due to lethal transmittance to male zygote/embryos/fetuses.

X-Linked Recessive Trait



- A female carrier of an X-linked recessive trait has 50% chance of having female offspring as carriers and 50% chance of male offspring having the disorder.
- X-linked transmission -- whether dominant or recessive -- is diagonal or oblique



- and in consanguineous matings, as well.
- Note that IV.2 is uneffected and IV.3 is effected in the Figure in this instance. Can you think of why this is?

Selected Hereditary Diseases of Humans

Required Reading

Alkaptonuria

- Alkaptonuria is inherited as an autosomal recessive disorder. It has been mapped to chromosome 3 and is a disorder of homogentisate oxidase. Its classical diagnosis is based upon the fact that the urine turns brown/black on standing -- particularly if the urine is alkaline or has alkali added to it. It leads to a dark pigmentation of ligaments, cartilage, fat, skin and urine called "ochronosis". Ochronosis is a dark blue discoloration that is easiest observed in regions of skin that overly cartilage. This discoloration usually is present in/by the 3d and 4th decades of life. Alkaptonuria also causes degenerative joint disease (arthritis) of the spine and peripheral joints. Although the disease makes one miserable, there does not seem to be a reduced life expectancy.
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- Since this disease is, relatively speaking, benign, it is probably not necessary to reduce the amounts of phe and trp in the diet. Large doses of vitamin C seem to reduce oxidation/polymerization of homogentisate (in the test tube). Arthritis is treated with anti-inflammatory drugs.
- Recently (Feb. 2006), there have been some studies that have suggested that, while NSAID's work nicely to reduce inflammation, they may also be hindering prostaglandin-mediated osteoblastic repair of the bony surfaces – some are now advocating the use on non-NSAID's to mediate the pain of arthritis.
- 2009: some clinicians and researchers are suggesting that a combination (unstandardized as of yet) of acetaminophen and ibuprofen will provide narcotic levels of pain relief without addiction and other side effects of narcotics.

Alzheimer's Disease -- 1 Form

- Alzheimer's is inherited in a confusing manner: there seems to be at least 3 genes involved in this disease (21pter-q21; 14 (early onset) and 19 (late onset of this disease). Additionally, there is an incredible amount of reduced penetrance. It could be inherited autosomal dominant OR recessive. The involved protein is β-amyloid protein. This disease causes 50-70% of the cases of senile dementia. β-amyloid protein forms the core of plaque formation outside nerve cells and plays a role in the formation of neurofibrillary tangles in 2 regions of cells in the brain. Alzheimer's alters language skills, personality and causes seizures.
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- NOTE: there seems to be some sort of relationship with Down Syndrome: 1) patients with trisomy 21 who live to be 40 YOA show Alzheimer's pathology; 2) Alzheimer's patients report a higher incidence than expected of 1st degree relatives with trisomy 21 -- interesting the relationship with 14 and 21: perhaps Robertsonian translocation is involved, here, as well???????
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- Although determination of apolipoprotein E_4 levels is available for diagnostic testing, the results are unreliable. To date, the only way to ascertain Alzheimer's is at autopsy by examining brain tissue samples. Death by Alzheimer's is approximately 8-10 years after onset of the disease. The best therapy remains as managing depression and anxiety and other symptoms with symptomatic treatment.

α_1-antitrypsin (α_1-AT; aka A1PI) Deficiency

- This disorder is inherited autosomal recessive from 14q. The protein effected is α_1-AT.
- The lack of this protein increases the risks of premature COPD in smokers. (α_1-AT is produced in the liver and travels to the lungs where it inhibits elastase activity -- if elastase is not inhibited, this causes small airway destruction; with smokers, it causes COPD.)
- For those lacking α_1-AT secondary to the inherited disorder, there is commercially available protein available for replacement therapy.
- To determine whether one has this disease, fetal DNA testing may be performed, RFLP's may be used, fetal blood levels of α_1-AT may be taken by periumbilical blood sampling (PUBS) in the last half of gestation and arterial blood gases may be utilized, as well.
- The best therapy is to quit smoking, provide symptomatic treatment and treat infections to any part of the respiratory system aggressively.

Cystic fibrosis

- This disease is inherited autosomal recessive on 7q31-32.
- The protein involved is the cystic fibrosis transmembrane regulator (CFTR). This protein works with a chloride channel, but it is uncertain as to how.
- Although most of us are familiar with this disorder causing lung problems, it also causes GI disturbances (bulky, greasy stools), lots of gas and infertility in more than 95% of effected males (no vas deferens develops).
- Cor pulmonale develops in advanced cases; this is of poor prognosis.
- To some degree these symptoms may be treated with enzyme capsules to replace those not secreted by the pancreas. This patient may also need antacids.
- Diagnostic testing includes sweat chloride testing, probing for CFTR and a fecal test to test for presence of pancreatic enzymes. NOTE: 1 in 22 is a carrier of this disorder.

Hereditary Fructose Intolerance

- This disorder is inherited as an autosomal recessive disorder.
- There is a fructose-1-phosphate (F-1-P) aldolase deficiency.
- This disease causes hypoglycemia with increased accumulation of F-1-P in tissues.
- The patient fails to thrive and has nausea and vomiting (N/V), jaundice, an enlarged liver, which may develop into liver failure, proteins and amino acids in the urine and tyr in the urine, as well.
- Diagnostic testing is to "pre-load" the patient with fructose and observe for hypoglycemia and hypophosphatemia.
- Therapy is to discontinue cane sugar from the diet. Patients must double check over the counter (OTC) medications for sucrose additions as tablet binders.
- If the diet is discontinued, the patient has an increased risk of growth failure; on the diet, the patient will grow relatively normally.

Homocystinuria

- This disease is inherited autosomal recessive. There is a deficiency in cystathionine-β-synthetase. The life expectancy of a patient with this disorder is reduced in the untreated patient and in the pyridoxine (B_6)-unresponsive patient. It causes retardation, arachnodactyly (spider fingers -- long, slender, curved), osteoporosis, dislocated optic lenses, high risk to throw clots (idiopathic), may have seizures, MI, CVA and PE.
- Diagnostic testing is to detect homocystinuria and cyanocobalamin levels. Therapy is aimed at two groups:
  - Group 1 is vitamin responsive and their urinary homocystine excretion is reduced with doses at or greater than 200 mg of B_6 every day;
  - Group 2 is vitamin-unresponsive and must be treated by dietary modifications: reduce met in diet and increase cys in diet.

Maple Syrup Urine Disease (MSUD)

- This disease is inherited autosomal recessive; 5 forms are known.
- The most severe form involves the protein α-keto acid decarboxylase/acyl CoA dehydrogenase. The urine smells like maple syrup or burned sugar.
- Diagnostic testing examines the levels of branched chain amino acids (BCAA) and alloisoleucine in urine.
- Therapy includes dietary restrictions on BCAA.
- If caught within 10 days after birth, the child will undergo normal growth/development. BCAA's need to be monitored regularly.

Phenylketonuria (PKU)

- PKU is inherited as an autosomal recessive disorder. Classical PKU is on 1p; atypical PKU is on chromosome 4.
- Classic PKU is caused by a deficiency in phenylalanine hydroxylase.
- PKU causes mental retardation, hyperactivity, eczema; it is associated with blond, blue-eyed and fair-skinned individuals.
- The urine of patients with untreated PKU smells like a "mouse".
- Blood tests are now mandated within 2-3 days after a child is born.
- Urinary testing may also be undertaken.
- Therapy is to reduce phe in the diet. If the patient follows the diet, there will be normal development; if the patient does not follow the diet, mental retardation will set in.
- It is important to remember to titrate the phe levels carefully: phe is necessary to regulate the fever centers of the brain. Too little and the child has a fever constantly; too much and the child becomes irreversibly mentally retarded.

Tay-Sachs

- Tay-Sachs is inherited autosomal recessive.
- The protein effected is β-N-acetylhexosaminidase A.
- It is common in eastern European Jews.
- Onset of the disease occurs at about 3-6 months of age.
- The infant develops hypotonia, hyperacusia (abnormally sensitive hearing) and retardation.
- Death usually occurs by age 2-3 years.
- Diagnostic testing is available.
- Therapy seems to be symptomatic.

α-thalassemia

- This disease is inherited in a manner consistent with autosomal recessive characteristics.
- It seems to be on 16p. With inactivation of 3 of the 4 α-globin chains, a form of hemoglobin known as HbH forms.
- This causes hemolytic anemia.
- It is caused by the formation of a tetramer of beta subunits.
- The new tetramer has very high oxygen affinity and, hence, doesn't want to release oxygen to the cells.
- This disorder causes jaundice, hepatosplenomegaly. Diagnostic testing includes reticulocyte counts, MCV (mean corpuscular volume) and detection of lots of hypochromia on a peripheral blood smear.
- Prenatal screening includes electrophoresing parental Hb to identify the presence of the thalassemic Hb.
- Therapy does not include iron: it is needless and it may be toxic -- increase folate intake.
- NOTE: inactivation of all 4 of the α-globin chains = a stillborn baby. This is called hydrops fetalis.

β-thalassemia

- This disorder is likewise inherited as α-thalassemia, but on 11p. The gene effected is the β-globin gene. There are two variations of this disorder: major and minor.
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- **Major**: is the most common cause of transfusion-dependent anemia in childhood. The patients are normal at birth but develop anemia by their first year as fetal Hb (HbF) levels drop off. (HbF is a tetramer of $\alpha_2\gamma_2$; HbA_2 (to be discussed in a bit) is a tetramer of $\alpha_2\delta_2$.) Without treatment, patient develops a massively enlarged spleen and liver, develops enlarged medullary cavity with thinned cortex, prominent forehead and maxilla and pathologic fractures. May cause RBC sickling. Diagnostic testing includes looking for reduced MCV, elevated HbA_2 OR F -- normal Hb, HbA, is a tetramer of 2 alpha sub-units and two beta subunits ($\alpha_2\beta_2$) -- and electrophoresing Hb. Therapy consists of blood transfusions with iron chelation, bone marrow transplants. Hb must be maintained at or above 11 mg%. Splenectomy reduces transfusions. Pneuimmune vaccine before, after or without splenectomy and PCN after splenectomy reduce infection by *Streptococcus pneumoniae*.
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- **Minor**: usually asymptomatic. There seems to be no response to iron therapy.
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- Genetic counseling needs to be approached sensitively