Biology 321 Spring 2013 ***Assignment Set #8***
9th edition users should consult the 10th edition for this assignment set

Required Reading Assignments:
Reread article assigned earlier in the quarter: GENOMES UNZIPPED:
The complicated relationship between genotype & phenotype
http://fire.biol.wwu.edu/trent/trent/genepheneunzipped.pdf

Google.doc assignment: Why Skinny Moms Sometimes Produce Heavy Kids
http://fire.biol.wwu.edu/trent/trent/skinnymoms.pdf

Optional Reading Assignment:
Trauma and Stress: from child to adult
http://fire.biol.wwu.edu/trent/trent/traumastress.pdf

Reading and Problem Assignments Text
Linkage & Molecular Markers: **Chapter 4**

- pgs 121-132 (linkage basics up to but not including three-point testcross)
- **Figure 4-13** on pg 136
- Section 4.3 pgs 137-141 (Mapping with molecular markers; be sure to look carefully at Figures 4-15 & 4-16)
- Section 4.7 pgs. 148-150 (Using recombination-based maps in conjunction with physical maps)
- For your personal enrichment: Section 4.8 (The molecular mechanism of crossing-over)

Work solved-problem 1 & problems 12, 13, 17, 18, 20, 27, 29, 32, 34 (review), 63

Positional cloning**: Chapter 10**

- Section 10.5 pg 364-367

Haplotypes & Molecular Markers: Chapter 18

- pg 637-643

Inheritance of Complex Traits**: Chapter 19**

- pg 683-685; pg 717-723
- think about problem 18

Epigenetics **Chapter 12**

- pgs 426 – 432 Section 12.3: Dynamic Chromatin
- *Optional:* Section 12.6 (pgs 441-444) Gender-specific silencing…….

Additional Linkage Problems

Problem -1 Draw a clearly labeled picture to illustrate the following genotype in a 2n=4 cell: ***A/A; BC/bc***

- The cell should be in metaphase I of meiosis and should not show any crossing over events.
- Label ***a pair of sister chromatids***; ***a pair of homologs.***
- ***Indicate ALL copies of ALL alleles -- do not use any shorthand notation***

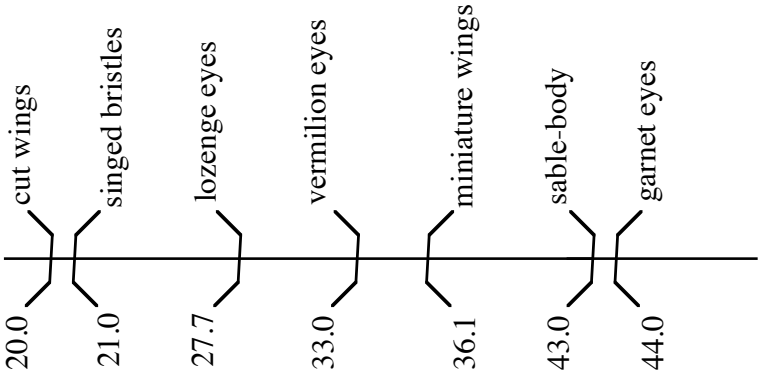
Problem 0 Genes A and B are linked. On the average, there is one cross-over between these genes (involving two non-sister homologous chromatids) for every 25 meiotic divisions. What is the map distance between these genes?
NOTE: The answer is *not* 4 map units

Problem 1
An organism of genotype AaBbCc is test-crossed. The genotypes of the progeny were as follows:

Genotype	# of progeny
AaBbCc	90
AaBbcc	10
aabbcc	90
aabbCc	10

a. If these three genes were all assorting independently of each other, how many genotypic classes would you expect in the progeny of the testcross?
b. If these three genes were so tightly linked that crossing-over never occurred between them, how many genotypic classes would you expect in the progeny of the testcross?
c. What can you conclude from this data?

Problem 2.1
The following diagram is a map of the **X chromosome** of *Drosophila*:

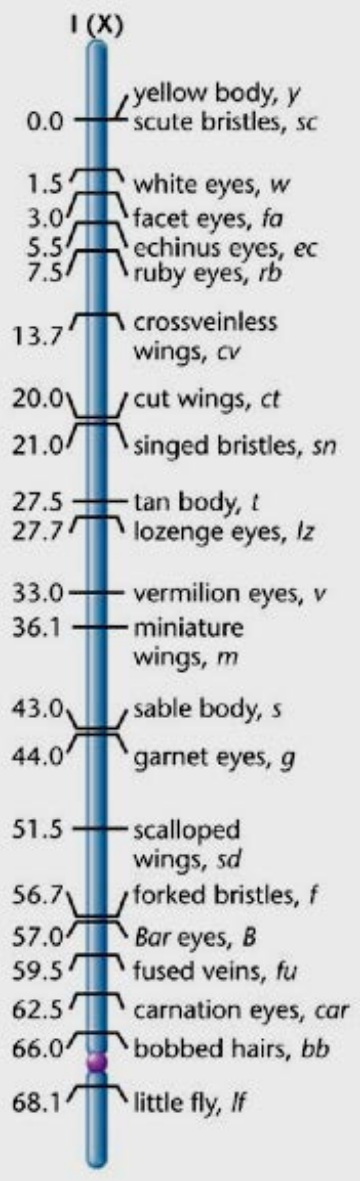


Values are map units measured from the gene closest to the end of the chromosome.

A true-breeding wild-type female is crossed with a vermilion-eyed, sable-bodied male. The F1 females are wildtype. If the F1 males and F1 females are crossed to each other, what proportion of their male progeny will be:

a. wild-type **b.** vermilion-eyed and sable-bodied
c. vermilion-eyed **d.** sable-bodied

Problem 2.2 Examine the map of the Drosophila ***X chromosome***
Check your work carefully before selecting your answer. Partial credit possible.



(i) A female of genotype $m^+ g / m g^+$ is crossed with a phenotypically wild-type male. All female progeny are wild-type. ***The percentage of male progeny that will have miniature wings and garnet eyes is:*** *a. 4% b. 8 % c. 46% d. 92% e. 50% f. 100% g. not enough info to determine h. none of the above*

(ii) A female heterozygous for both the sable body and garnet eye genes is crossed with a phenotypically wild-type male. All female progeny are wild-type. ***The percentage of male progeny that will have both sable bodies and garnet eyes is:*** *a. 0.5% b. 1 % c. 49.5% d. 99% e. 50% f. 100% g. not enough info to determine h. none of the above*

(iii) A female of genotype $sc^+ lf^+ / sc\ lf$ is crossed with a phenotypically wild-type male. All female progeny are wild-type. ***The percentage of progeny males that will be wild type for both traits is:*** *a. 0% b. 16 % c. 25% d. 34% e. 50% f. 68% g. not enough info to determine h. none of the above*

Problem 3

Your lab partner has a strain of Drosophila which has bent wings *(w)* , a recessive mutation on the X chromosome. He also has a different strain which has stubbly bristles *(b),* a recessive mutation also on X and about 1 map unit away from the bent wing gene. He does the following experiment to generate a doubly mutant male:

Cross: bent wing ♀ X stubby bristle ♂

Cross: F1 ♀ X wild-type ♂

He scores 100 male progeny for bent wings and stubby bristles and finds no doubly mutant flies. He gives up in disgust and goes to see *The Fly*, hoping for an inspiration.

Your lab partner thinks that his failure to bind a bent-winged, stubbly-bristled male means that the doubly mutant phenotype is lethal. But you look at the outline of his experiment and suggest that he redo it with one modification. What do you suggest and why? Be explicit about what you think he needs to do and why.

Problem 4 Drosophila melanogaster has one pair of sex chromosomes (XX or XY) and three pairs of autosomes, referred to as chromosomes 2, 3, and 4. A male fly with short legs was discovered in a wild-type stock of flies by an observant genetics student. Using this male, the student was able to establish a pure breeding stock. Next the student constructed a homozygous strain carrying the short mutation (sh), the mutation black body (b gene located on chromosome 2) and the mutation cardinal eyes (cd gene located on chromosome 3). A female from the short, black, cardinal eye stock was mated to a wild-type male. All the progeny were wild type. The F1 females from this cross were then testcrossed. The F2 progeny were as follows:

	wild-type	cardinal eye	short, black	cardinal eye, short, black
females	63	58	57	62
males	59	62	55	60

Which chromosome is the short gene located on? You must show your work and briefly explain your answer in order to get full credit.

NOTE: first thing you should do is "translate" F2 phenotypes to the genotype of the gamete received from the female parent. Then, assess linkage by looking at the genes two at a time.

Problem 5 Many theories have been proposed to explain the universality of sexual reproduction. Common to most is the idea that since sex is so popular there must be some long-term evolutionary advantages for a population that reproduces this way. Most of the arguments fall into two general categories: ***sex combines good mutations together*** *or* ***sex gets rid of bad mutations*****.**

The first argument suggests that in the face of changing environmental conditions, the more genetically variable the offspring, the more likely that a winning genetic combination will be present. Sexual reproduction brings advantageous combinations of genetic material together that can spread through a population by natural selection.

The second line of argument says that sexual reproduction results in the purging of harmful mutations, that would continue to collect in asexual populations. Underlying this argument are two genetic facts of life. Fact one: mutations occur. Fact 2: Many mutations are harmful. Evolutionary geneticists have estimated that a mutation rate of one harmful mutation per individual per generation will give sexually reproducing organisms the competitive edge over asexually reproducing organisms.

Consider an organism (2n=4) of genotype A/a; Bc/bC. The uppercase alleles of each gene are wild-type. The lowercase alleles are incompletely dominant loss-of-function mutations that are deleterious to the organism.

Part A. This eukaryotic organism undergoes asexual reproduction. In asexual reproduction, can the offspring have fewer mutations than the parent cells?

- ***Briefly explain your answer with a diagram.*** (Label: type of cell division and stages)
- Be sure that all alleles of each of the 3 genes are shown on your diagram.
- Note: in answering this question ignore the rare possibility of reverse mutation.

Part B. Two organisms, both of genotype **A/a; Bc/bC**, mate with each other. Draw a diagram (with the appropriate labels) to show how an offspring from this mating can have fewer mutations than its parents.

- The offspring should be of genotype **A/A; BC/BC.**
- Be sure that your drawing is detailed enough so that it clearly illustrates the difference in sexual vs. asexual reproduction. Label type of cell division and stages.
- Be sure that all alleles of each of the 3 genes are shown on your diagram.

Problem 6 In the life cycle of wasps and bees, unfertilized eggs develop as haploid males while fertilized eggs develop as diploid females.

Wild-type wasps have "dark purple" eyes. Mutants with scarlet eyes have been isolated. Wild-type wasps have ungnarled bristles. Mutant wasps have gnarled bristles. *Female wasps heterozygous for recessive mutations in these two genes are generated and allowed to lay eggs without mating. 1000 haploid ♂ progeny are scored for eye and bristle phenotypes*

Eye Color	*Bristle*	*Genotype*	*# ♂ progeny*
wild-type	wild-type		459
wild-type	gnarled		42
scarlet	wild-type		38
scarlet	gnarled		461

S wild-type s scarlet eye
G makes wild-type (ungnarled) bristles, g results in gnarled bristles

(i). Choose the correct statement.
The gnarled-bristled and scarlet genes are
a. ~4 map units apart b. 8 map units apart
c. 46 map units apart d. 92 map units apart
e. tightly linked and no crossing-over is observed
f. assorting independently g. cannot be determined from this data, since parents not given and testcross not done

Part 2 An investigator isolated three more strains with recessive mutations resulting in a scarlet-eyed phenotype (called mutants 2-4). He crosses true-breeding females of each mutant strain with males of each mutant strain and observes the diploid female cross progeny. The results are as follows
(+) = wild-type (purple) eyes (-) = scarlet eyes

Mutant	#1	#2	#3	#4
#1	—	—	+	—
#2		—	+	—
#3			—	+
#4				—

(ii). Choose the best restatement of these data
a. This is a complementation test which shows that mutants 1, 2 & 4 are linked. Mutant 3 is unlinked.
b. This is a complementation test which shows that 1, 2 & 4 are mutations in different genes.
c. This is a complementation test which shows that mutations 1, 2 & 4 are alleles of the same gene. Mutation 3 is in a different gene. There is no information about linkage between the two genes defined by these mutations.
d. None of the conclusions are valid.

Problem 7 The human X-linked gene for *red/green colorblindness* is **3 map units** away from the *hemophilia A* gene. A doubly heterozygous woman is married to a normal man. The woman's father was normal for both traits. The mutant alleles are recessive to the wild-type alleles for both traits.

a. Write out the genotypes of the woman and her husband ***using the nomenclature for linked genes.*** Use these allele symbols:

h+ wildtype h= hemophilia c+ = wildtype c= colorblind

WOMAN:

HUSBAND:

b. What is the probabilty that the first son ***has hemophilia, but is <u>not</u> colorblind? Show your analysis and circle your answer.***

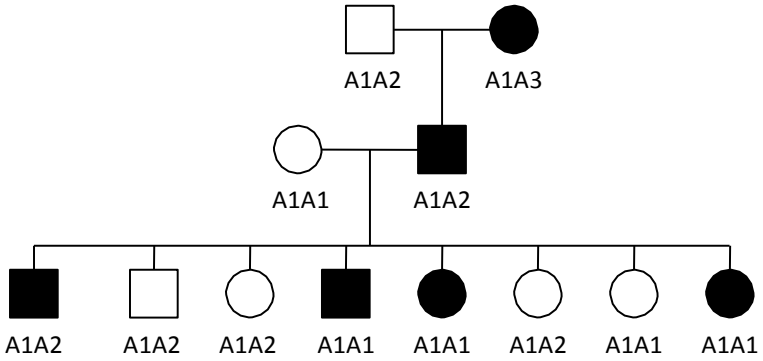
Problem 8 <u>(SEE ALSO SIMILAR PROBLEM IN lecture notes on positional cloning)</u>

Below is a pedigree for a family showing the genotype of a certain genetic marker for all individuals. Individuals with large noses are marked with filled in shapes. The schnozz phenotype is controlled by a single locus with two alleles: N, which is dominant and leads to the large nose phenotype; and n, which produces a normal nose.

A1 and A2 are SNPs

a. What is the haplotype configuration of the father in generation 2?

b. How many children in generation 3 inherited a recombinant chromosome from their father?



Problem 9 Examine the pedigree below which shows inheritance of an adult-onset dominant disease state. The second generation couple want to know the likelihood that the son received the mutant allele from his father. Since the disease gene is not cloned, a direct assay for the mutant allele is not possible; instead, a molecular test for a linked polymorphism is performed.
Alleles of linked polymorphism: pA pB pC [**20 map units** from disease gene.]
Examine the pedigree. The probability that the son is $D\ d^+$ is
Choose all correct answers.
You must show your work (on one of the pedigrees below) to get full credit for this answer.

a. 50% if no recombination occurred between the two sites

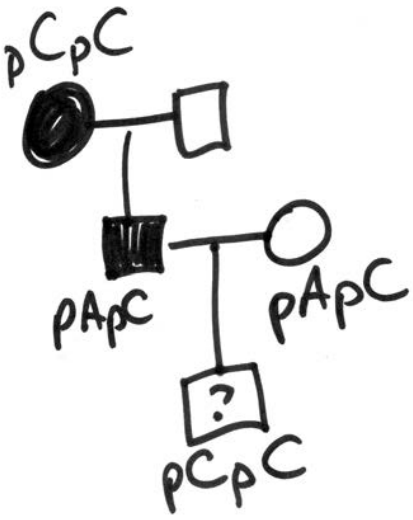
b. 10% c. 20%

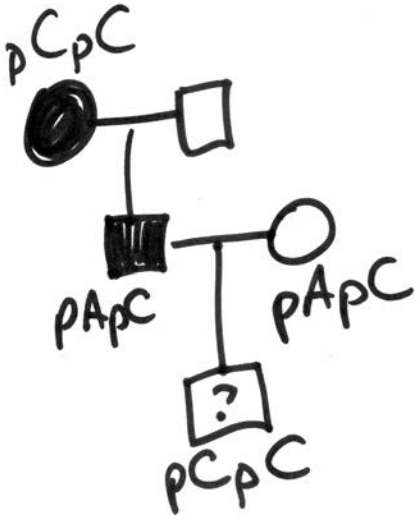
d. 40% e. 80%

f. 0% if the son was produced from a recombinant paternal gamete

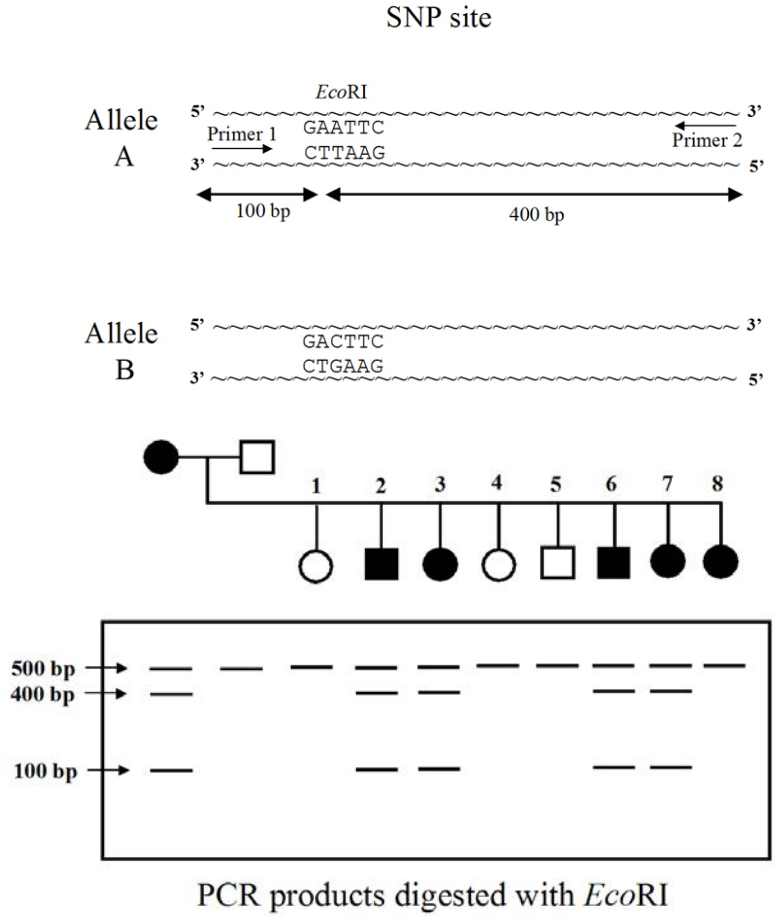
g. 100% if the son was produced from a recombinant paternal gamete

h. There is not enough info to answer this question.





Problem 10 The pedigree shown below illustrates the inheritance pattern of a rare autosomal disease state. Each person in the pedigree has been typed to determine his/her genotype for a specific SNP (single-nucleotide polymorphism). This SNP is 10 map unit from the disease gene. Assume expression of the disease phenotype shows NO complications.



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10 a. Individual #7 is married to an unaffected man of genotype BB and is expecting her first child. She has a prenatal test which shows that the child's SNP genotype is AB. Given this information, what is the probabilty that the child is heterozygous for the disease allele?
You must show your work and provide a brief explanation to get credit for your answer.

10 b. Individual #8 is married to an unaffected man of genotype AB and is expecting her first child. She has a prenatal test which shows that the child's SNP genotype is AB. Given this information, what is the probabilty that the child is heterozygous for the disease allele?
You must show your work and provide a brief explanation to get credit for your answer.

Problem 11 Gorlin syndrome is a disorder that predisposes affected individuals to various cancers and developmental defects, which are obvious at birth. ***Examine the pedigrees shown on the next page.*** B1, B2 and B3 are alleles of a polymorphic site (called D9S29) that maps to chromosome 9. A genotype of **B1** means that the individual was homozygous for B1. (And likewise for **B2** and **B3**). Each pedigree represents a different kindred group. Assume the disease shows complete penetrance and that the D9S29 polymorphism is **4 map units** from the gene mutated in Gorlin syndrome.

a. What is the mode of inheritance of Gorlin syndrome? No explanation necesssary.

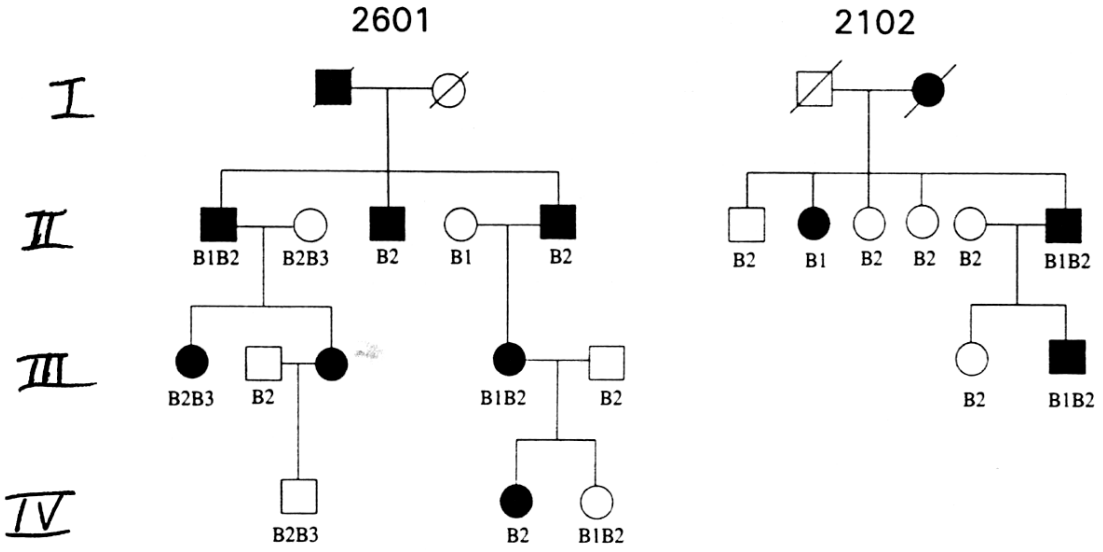
b. For kinship group 2601, which D9S29 allele is the disease allele is associated with? (No explanation necessary).

c. In kinship 2601, the B2B3 female from generation II contacts you for some advice. She is expecting her third child (father as indicated in the pedigree).
(i) What is the probability that the child will have Gorlin syndrome given no additional information. (no explanation required)

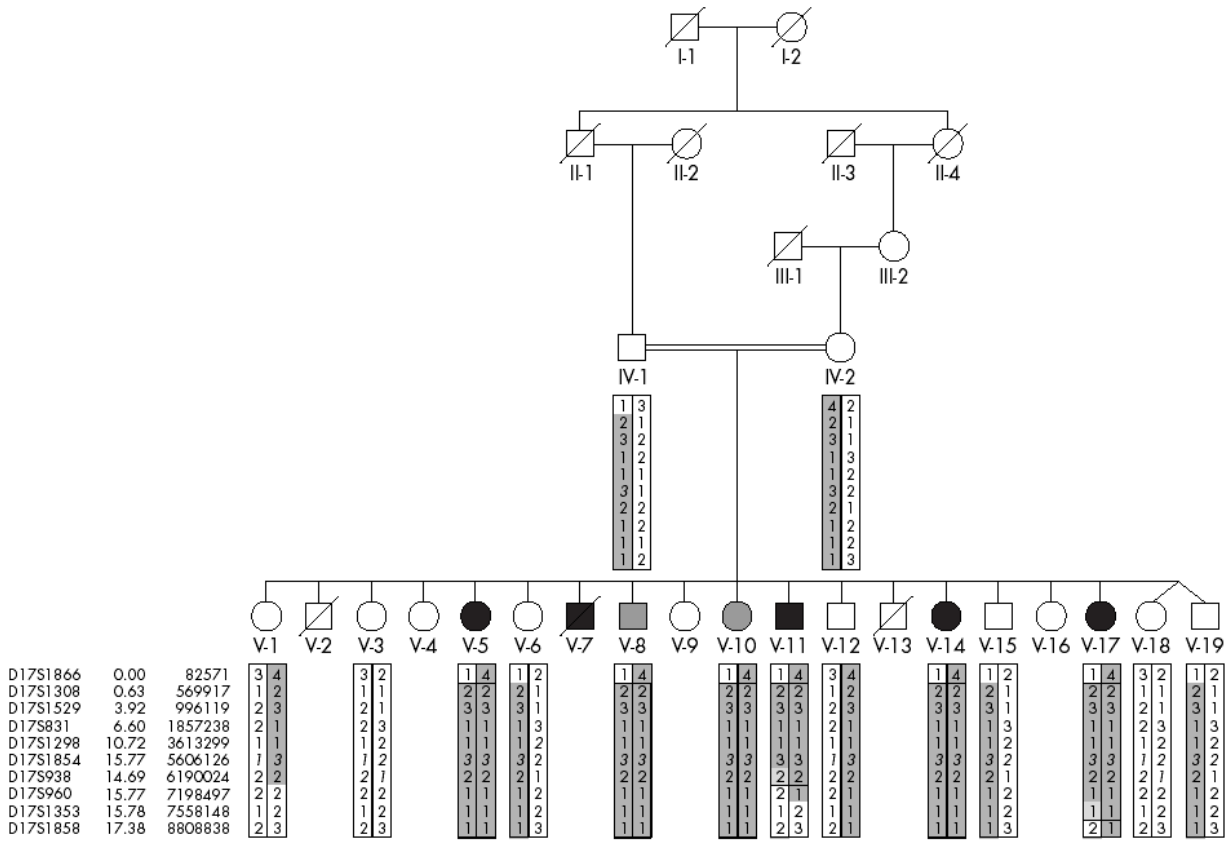
(ii) A prenatal test shows that the child is male and of genotype B2B3. Given this additional information, what is the probability that the child will have Gorlin syndrome?
FIRST: Start your answer by writing out the genotypes of the parents using the allele notation for linked genes

THEN: Show your calculation and circle your final answer.

d. In kinship 2601, the B2B3 daugher of the B2B3 generation II female is affected, but the B2B3 grandson is not. ***Briefly explain this apparent paradox. 2 sentences.***

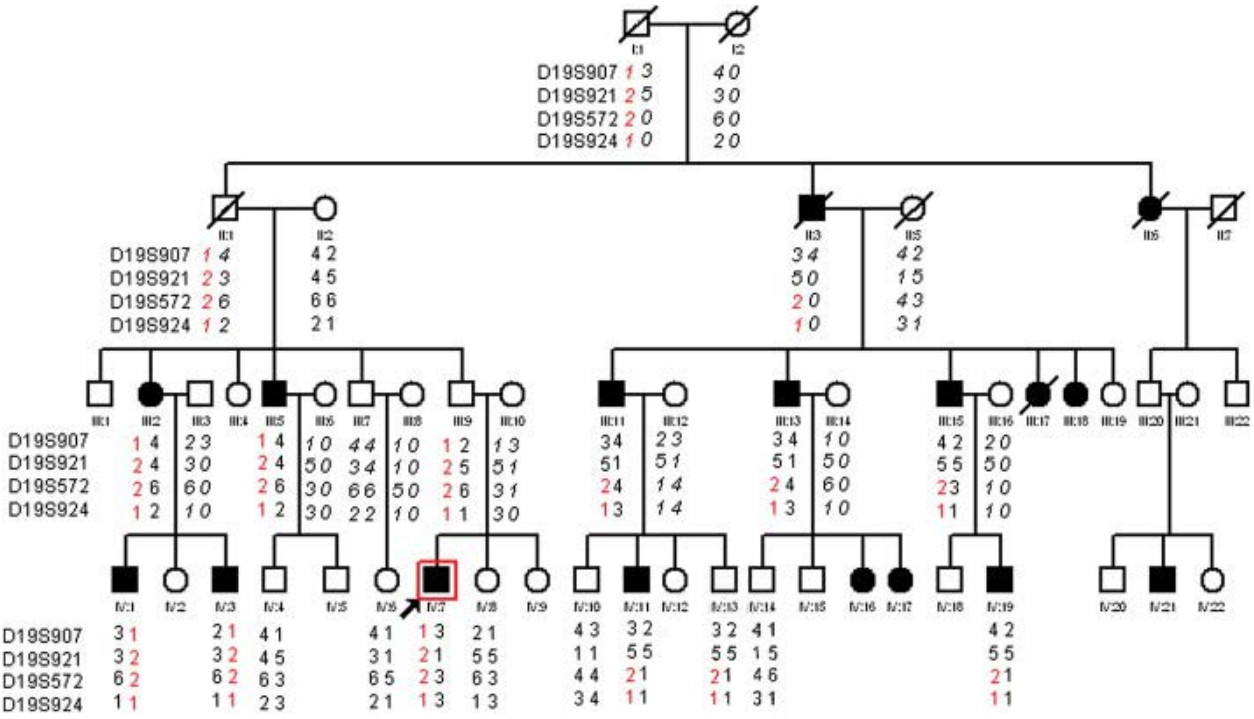


Problem 13 The pedigree below describes a family where individuals grow up walking on all fours, in addition to exhibiting mental retardation and reduced cerebellum function. Shaded symbols, regardless of the color of shading, indicate affected individuals. DNA was tested for the presence of a set of polymorphic alleles that together (as a haplotype) segregate with the disease phenotype. By this means, the authors of this study were able to pin down the probable location of the gene responsible for this trait to a particular region of chromosome 17. The polymorphic markers are in short tandem repeat sequences, and their formal designation is given on the extreme left hand side of the figure. The second column indicates a genetic map position, and the third column represents molecular coordinates (base pairs).



(a). Why do the markers that form the haplotype segregate together with the disease phenotype (ONE sentence)?
(b). What mode of inheritance is most likely for this trait? Provide TWO pieces of evidence.
(c). The haplotype analysis indicates that a gene responsible for this disorder when mutant is likely located between which two marker loci? The authors found no other regions in the genome that provided a co-segregating haplotype, strongly suggesting the culprit gene lies within this region.
(d) Once the gene has been tentatively identified, what further steps would you take to confirm the role of this gene in this disorder?

Problem 14_Examine the pedigree below which comes from a paper about a rare hereditary form of retinitis pigmentosa (a degenerative eye disease). Assume this is due to a monogenic trait.



a). Ignore the haplotypes for now. Is the mode of inheritance dominant or recessive? X-linked or autosomal?

b). How do the haplotypes confirm your conclusion in part a?

c). Is there evidence of incomplete penetrance? Where? (Don't consider dead people – no way to know whether they showed or not – information regarding penetrance not complete).

d). Where would you start looking for the disease allele?