

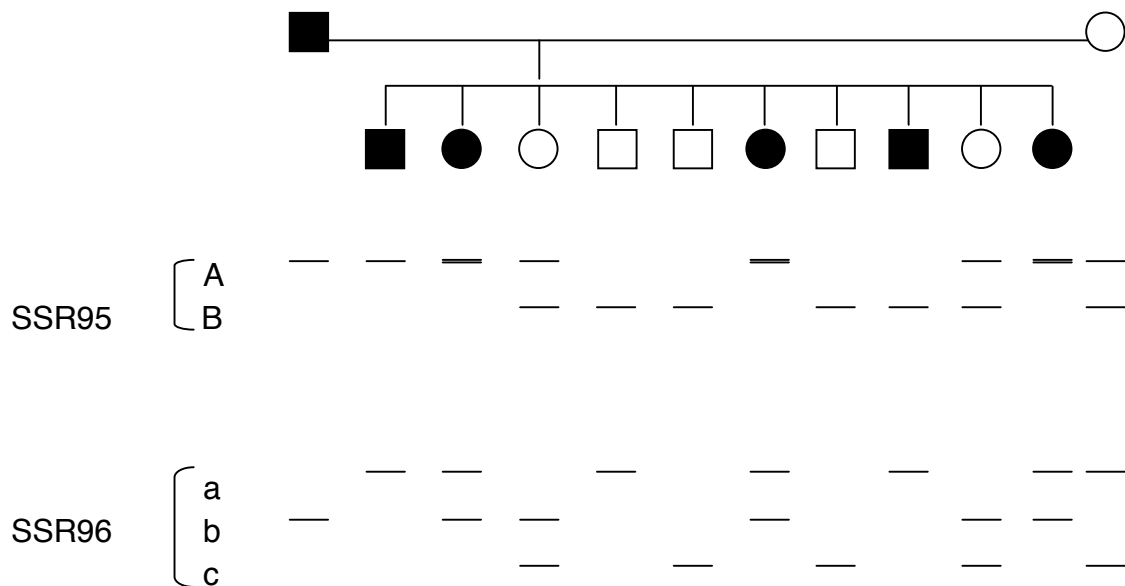
**Problem set questions from Final Exam – Human Genetics, Nondisjunction, and Cancer**

**Mapping in humans using SSRs and LOD scores**

**1.** You set out to genetically map the locus for color blindness with respect to SSR markers. Color blindness shows X-linked recessive inheritance and therefore is usually found in males. However, the mutant allele frequency is sufficiently high that colorblind females do occur.

Alleles:            + (normal)                      cb (associated with color blindness)

Here is a family in which some individuals are affected:



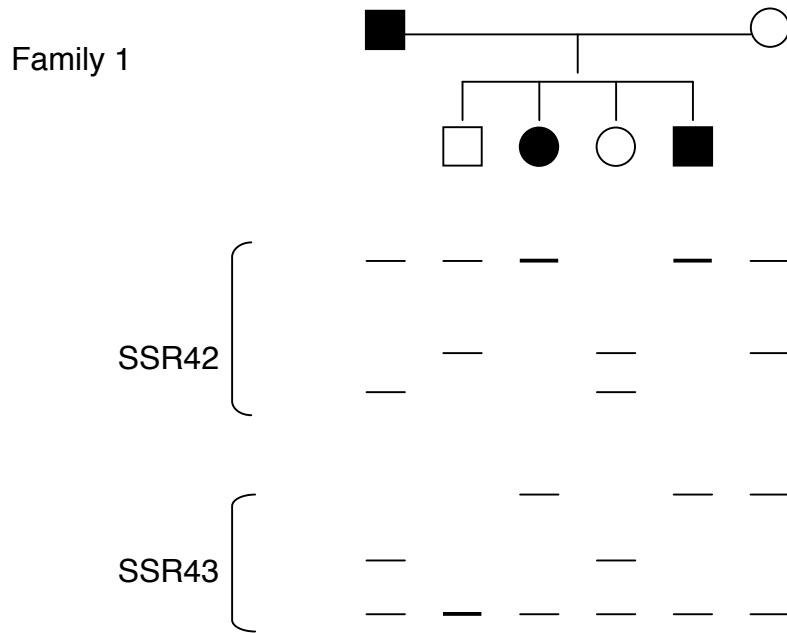
**(a)** Diagram the two possible phase relationships between the SSR95 and SSR96 alleles in the mother.

**(b)** Calculate the LOD score for linkage at  $\theta = 0.2$  between SSR95 and SSR96 in this family.

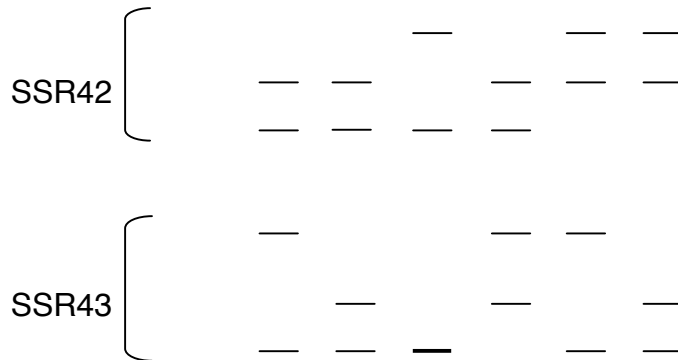
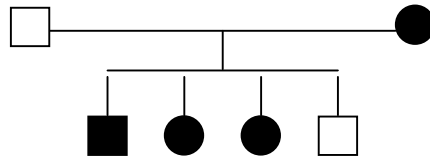
(c) Diagram the two possible phase relationships between the SSR95 alleles and the alleles at the color blindness locus in the mother.

(d) Calculate a LOD score for linkage at  $\theta = 0.2$  between SSR95 and the color blindness locus in this family.

2. You are conducting genetic linkage studies to search for a locus (whose chromosomal location has not been firmly established) associated with an autosomal recessive disease. You are focused on two SSR markers that may be linked to each other and to the disease. Here are two families in which some individuals are affected:



Family 2



Calculate LOD scores for linkage at  $\theta = 0.02$  between:

- (a) The disease and SSR42 in Family 1.
- (b) The disease and SSR43 in Family 1.
- (c) The disease and SSR42 in Family 2.
- (d) The disease and SSR43 in Family 2.
- (e) SSR42 and SSR43 in Family 1.
- (f) SSR42 and SSR43 in Family 2.

Is it appropriate to add together the LOD scores calculated in:

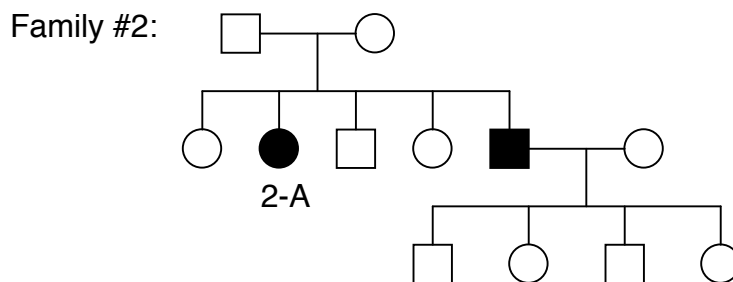
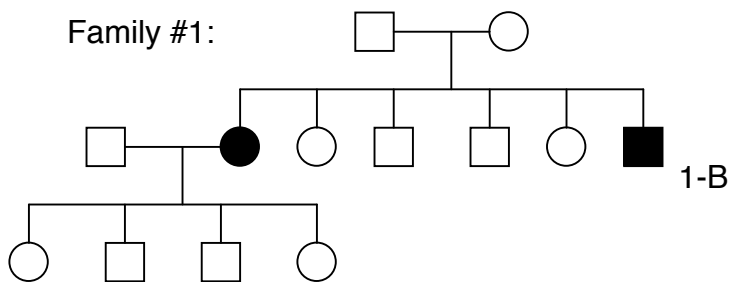
(g) Parts (a) and (b) of this question? Why or why not?

(h) Parts (b) and (d) of this question? Why or why not?

(i) Parts (e) and (f) of this question? Why or why not?

(j) What conclusion (with respect to genetic linkage) can you publish based on these findings?

**3.** Childhood deafness is often hereditary. Consider two pedigrees in which some individuals were deaf from birth due to a rare form of hereditary deafness. Assume complete penetrance and no new mutations.

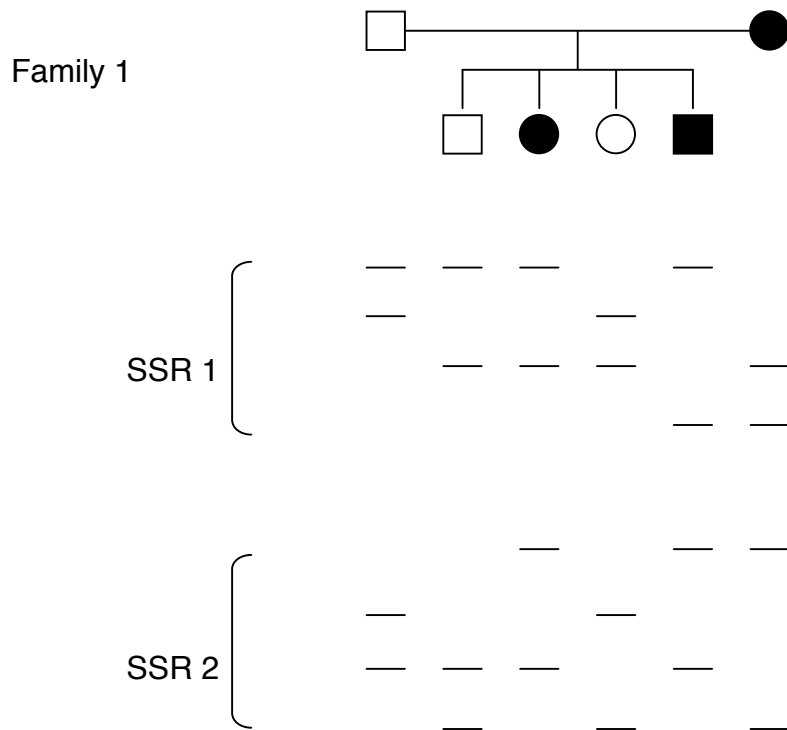


(a) What is the likely mode of inheritance of this deafness from birth?

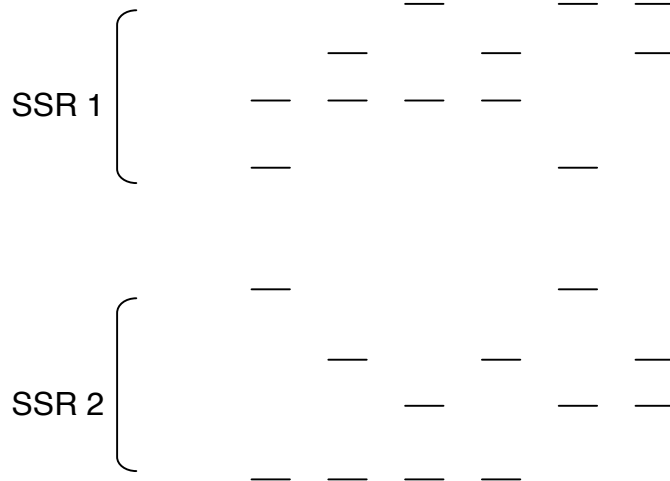
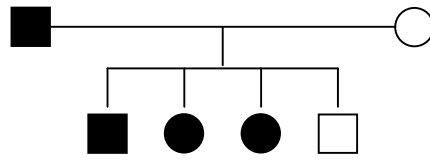
(b) The affected male from Family #1 (individual 1-B) and the affected female from Family #2 (individual 2-A) attend the same school for deaf children, and they ultimately marry and have two children. Both children have normal hearing. Provide a likely genetic explanation for their children having normal hearing.

(c) You find an SSR that shows linkage to the locus for hereditary deafness in Family One, and calculate the corresponding LOD score. Is it reasonable to use the same SSR to calculate a LOD score for Family Two, and then add together the LOD scores calculated from two families? Why or why not?

4. Your colleague, a human geneticist, is conducting genetic linkage studies on the locus associated with an autosomal dominant disease. Your colleague is presently focused on two SSR markers that may be linked to each other and to the disease. Here are two families in which some individuals are affected:



Family 2



Calculate LOD scores for linkage at  $\theta = 0$  between:

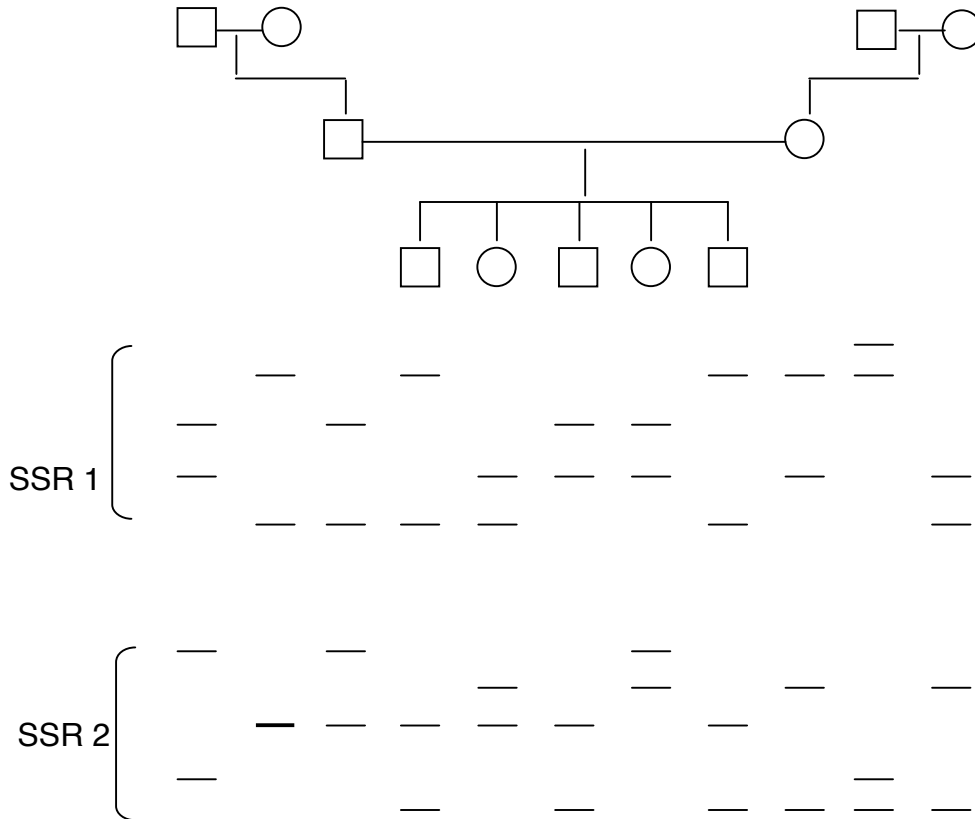
(a) The disease and SSR1 in Family 1.

(b) SSR1 and SSR2 in Family 1.

(c) The disease and SSR1 in Family 2.

(d) SSR1 and SSR2 in Family 2.

**5.** As we have discussed in class, SSR-based genetic linkage studies in human families can be used to chromosomally localize the loci associated with heritable traits, including diseases. Such studies can also be used to build genetic maps among the SSRs themselves, and indeed this is how detailed genetic maps of the human genome were constructed in the 1990's. Shown here are results of genotyping the members of a family for two SSRs on chromosome 12.



**(a)** Calculate a LOD score for linkage at  $\theta = 0.1$  between SSR1 and SSR2 in this family.

**(b)** Identify a value of  $\theta$  at which this family will yield a higher LOD score for linkage between SSR1 and SSR2 than was calculated in part **(a)**. Calculate the LOD score for linkage between SSR1 and SSR2 at that new  $\theta$  value.

**(c)** Estimate (roughly) the genetic distance between SSR1 and SSR2 in cM. (Assume that additional family studies confirm that SSR1 and SSR2 are located on the same chromosome and are genetically linked.)

**6.** You are studying a mutation that causes an autosomal recessive phenotype of blindness in humans. Through genetic linkage analysis, you map the mutation to a 0.6-Mb region of chromosome 12.

**(a)** Using electronic tools, you identify three predicted genes within this region, which are 2 kb, 15 kb, and 100 kb in length. You know that one mRNA produced from this region is ~1900 bp long. Based only on the information that you have been given, can you tell which of the three predicted genes is likely (or unlikely) to be the source of the ~1900-bp mRNA? Briefly explain your answer.

**(b)** You obtain DNA samples from 10 patients who are blind because of the mutation mapping to this region. You also obtain DNA samples from 10 individuals with normal vision. How would you determine which one of the three predicted genes is responsible for the blindness that maps to this region?

## Calculating Phenotypic concordance using twin studies

**1.** Congenital pyloric stenosis (an obstruction to the stomach's outlet to the small intestine) has a population incidence of 0.5% in newborn boys and of 0.1% in newborn girls. When a disease is more common in newborn boys than in newborn girls, two possibilities come to mind: 1) X-linked recessive inheritance, 2) autosomally inherited disease susceptibility modified by sex hormones (e.g. increased by high levels of testosterone).

**(a)** Which of these 2 possibilities are consistent with the observed population incidence in newborn males and that in females? Explain your answer.

**(b)** Can you be confident, based on this data alone, that there is a genetic component to the risk of congenital pyloric stenosis? Explain your answer.

**(c)** The concordance rate in MZ twins is 22% while that in DZ twins is 1.5%. Are you now confident that this is a genetic component, and, if so, how many genes are involved? Is there an environmental component? (Assume the disease phenotype is recessive.)

**(d)** 5.5% of the sons and 2.4% of the daughters of males with congenital pyloric stenosis are affected. By contrast, 19.4% of the sons and 7.3% of the daughters of females with congenital pyloric stenosis are affected. Why might the offspring of affected females be at higher risk than the offspring of affected males?

**2.** What phenotypic concordance rates (approximate answers will suffice) might you expect in MZ twins, DZ twins, and first cousins for each of the following diseases? Briefly justify each of your responses.

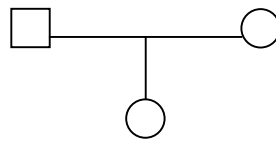
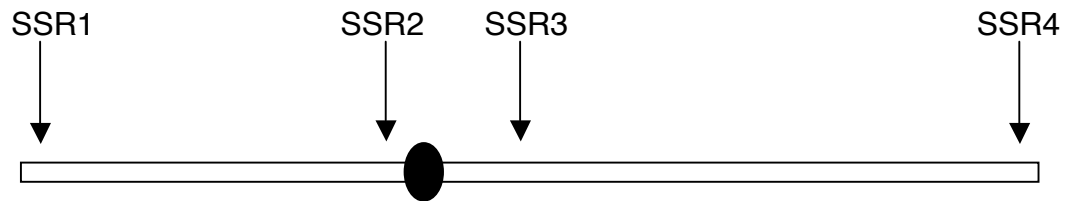
**(a)** Chicken pox, a very common and contagious viral disorder.

**(b)** Tay-Sachs disease, a rare autosomal recessive disorder in which environmental effects are negligible.

**(c)** An autosomal dominant trait in which both environment and a single gene are important determinants of risk.

**Meiosis and chromosome loss/gain by non-disjunction**

**1.** While working as a medical geneticist, you encounter an unusual patient: a 47,XXY girl. You prepare DNA samples from the girl and from her parents. You confirm that the stated father is in fact the biological father by testing the family for a large number of autosomal SSRs. You also test the family for a series of SSRs distributed along the X chromosome. A diagram of the X chromosome is shown below, with the centromere indicated by an oval.



SSR1	[	A	—	—	—
		B	—	—	—
		C		—	—
SSR2	[	A		—	—
		B		—	—
		C	—		
SSR3	[	A		—	—
		B		—	—
		C	—		
SSR4	[	A	—		
		B			
		C		—	—

**(a)** During the development of which parent's gametes did nondisjunction occur?

**(b)** In which division of meiosis did nondisjunction occur?

**(c)** Draw the following steps in the meiosis that created the gamete that led to the production of the XXY child shown in the pedigree. Please label each SSR allele and the centromere on each homolog of the X chromosome. Assume that SSR alleles 1A, 2B, 3B, and 4C are on a single chromosome in the mother's somatic cells. Draw these steps only:

i) the cell in metaphase I with its chromosomes lined up showing any crossover events occurring

ii) the two cells in metaphase II with their chromosomes lined up

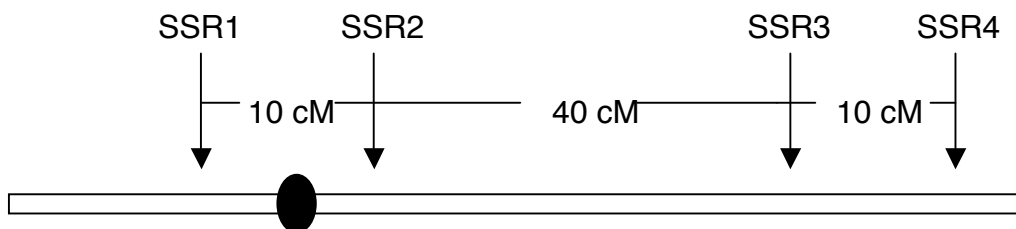
iii) the four final products of the meiosis (Please indicate the gamete that led to the creation of the XXY child with a star.)

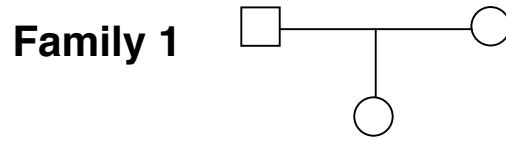
**(d)** What might account for this girl having developed as a female despite the presence of a Y chromosome? Explain how you would test your hypothesis.

**(e)** How would you account for the presence in the XXY girl of a paternal allele for SSR1?

**(f)** Later you have the opportunity to study a boy with one X chromosome and two Y chromosomes. You realize that you do not even need to use SSRs or other genetic markers to figure out the meiotic division in which nondisjunction occurred. In which parent and at which meiotic division did nondisjunction occur?

**2.** Trisomy X (that is, XXX) is one of the most common trisomies observed in human populations. XXX women are usually fertile and phenotypically indistinguishable from XX females. You prepare DNA samples from two unrelated girls, both with trisomy X, and from their parents. You then genotype the girls and their parents for four SSRs distributed along the X chromosome. Below is shown a diagram of the X chromosome, with an oval denoting the centromere.





(a) During the development of which parent's gametes did nondisjunction occur?

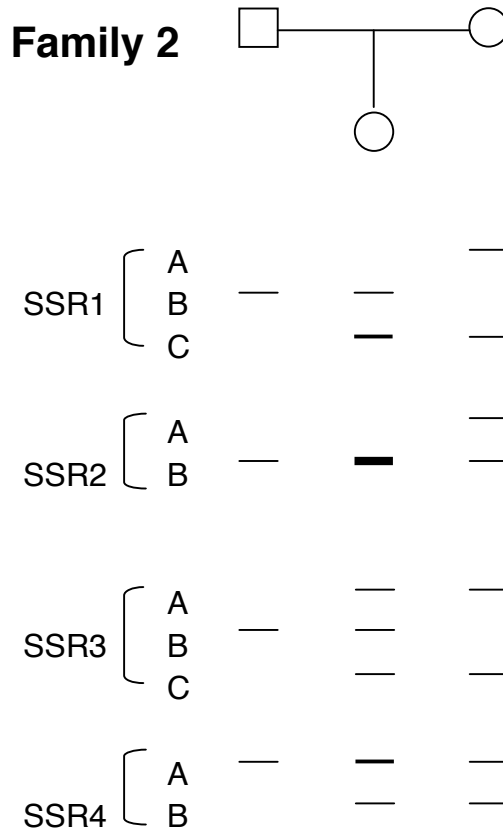
(b) In which division of meiosis did nondisjunction occur?

(c) Draw the following steps in the meiosis that created the gamete that led to the production of the XXX child shown in family 1. Please label each SSR allele and the centromere on each homolog of the X chromosome. Assume that SSR alleles 1A, 2A, 3B, and 4B are on a single chromosome in the mother's somatic cells. Draw these steps only:

i) the cell in metaphase I with its chromosomes lined up showing any crossover events occurring

ii) the two cells in metaphase II with their chromosomes lined up

iii) the four final products of the meiosis (Please indicate the gamete that led to the creation of the XXX child with a star.)



(d) During the development of which parent's gametes did nondisjunction occur?

(e) In which division of meiosis did nondisjunction occur?

(f) Draw the following steps in the meiosis that created the gamete that led to the production of the XXX child shown in family 2. Please label each SSR allele and the centromere on each homolog of the X chromosome. Assume that SSR alleles 1A, 2A, 3C, and 4A are on a single chromosome in the mother's somatic cells. Draw these steps only:

i) the cell in metaphase I with its chromosomes lined up showing any crossover events occurring

ii) the two cells in metaphase II with their chromosomes lined up

iii) the four final products of the meiosis (Please indicate the gamete that led to the creation of the XXX child with a star.)

**3.** A married couple who already had a child with cystic fibrosis approach you because they wish to have another child, but only if they can be assured that the child will not have cystic fibrosis. You genotype the woman and discover that she is a heterozygote for Del508, the most common mutation causing cystic fibrosis. You suggest that the couple consider first polar body testing, in which several unfertilized oocytes (each with its first polar body) are retrieved from the woman, the first polar bodies are removed, and PCR tests are conducted on DNA from each of the first polar bodies. The couple agrees, and you obtain the following results:

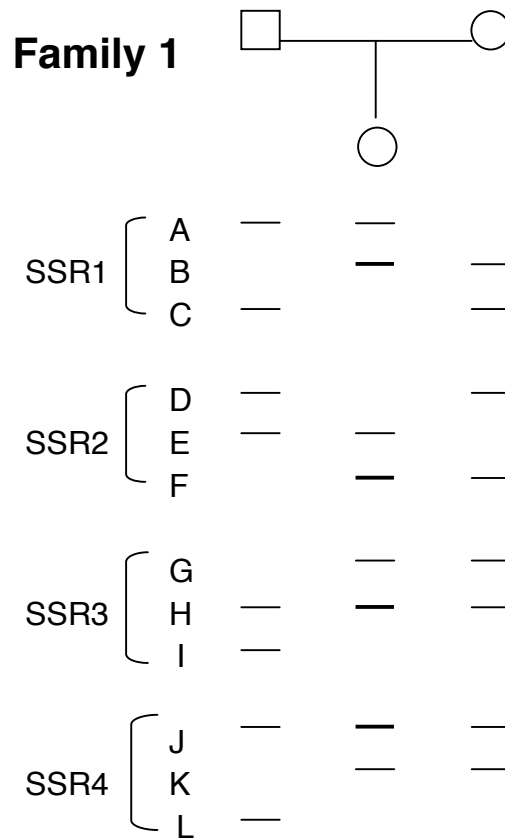
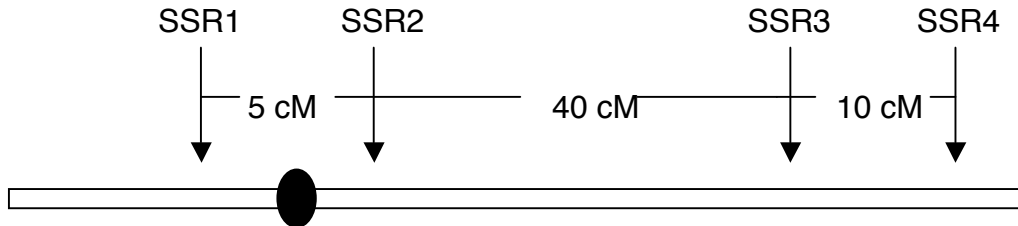
Oocyte	PCR test of first polar body DNA for presence of	
	Del508	wild-type sequence
#1	+	+
#2	+	-
#3	+	-
#4	-	+
#5	+	+
#6	-	+

(a) Propose an explanation for the observation that the polar bodies for oocytes #1 and #5 test positive for both Del508 and the wild-type sequence, while the polar bodies for the other oocytes have either one or the other. (Do not appeal to nondisjunction.) Illustrate your explanation with a sketch of the various stages of meiosis through which oocyte #1 has proceeded.

(b) Given the couple's desire to have a child without cystic fibrosis, which oocytes would you employ in vitro fertilization? Briefly explain or illustrate your answer.

(c) Which additional oocytes would you consider fertilizing if you could then 1) retrieve the second polar body for PCR testing and 2) selectively return "unaffected" embryos to the woman's uterus? Briefly explain or illustrate your answer.

**4.** Trisomy 18 is one of the most common trisomies observed in human populations. You prepare DNA samples from two unrelated infants, both with trisomy 18, and from their parents. You then type the infants and their parents for four SSRs distributed along chromosome 18. Below is shown a diagram of chromosome 18; the oval indicates the centromere.



**(a)** During the development of which parent's gametes did nondisjunction occur in Family 1?

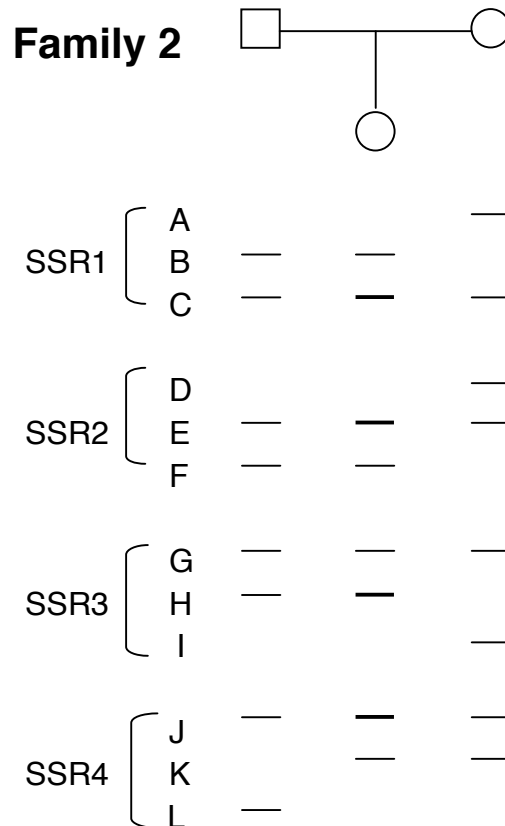
**(b)** In which division of meiosis did nondisjunction occur in Family 1?

(c) Draw the following steps in the meiosis that created the gamete that led to the production of the child with trisomy 18 shown in the pedigree of Family 1. Please label each SSR allele and the centromere on each homolog of chromosome 18. Assume that SSR alleles A, D, H, and J are on a single chromosome in the father's somatic cells. Assume that SSR alleles B, F, H, and J are on a single chromosome in the mother's somatic cells. Draw these steps only:

i) the cell in metaphase I with its chromosomes lined up showing any crossover events occurring

ii) the two cells in metaphase II with their chromosomes lined up

iii) the four final products of the meiosis (Please indicate the gamete that led to the creation of the child with trisomy 18 with a star.)



**(d)** During the development of which parent's gametes did nondisjunction occur in Family 2?

**(e)** In which division of meiosis did nondisjunction occur in Family 2?

**(f)** Draw the following steps in the meiosis that created the gamete that led to the production of the child with trisomy 18 shown in the pedigree of Family 2. Please label each SSR allele and the centromere on each homolog of chromosome 18. Assume that SSR alleles B, E, H, and J are on a single chromosome in the father's somatic cells. Assume that SSR alleles C, D, G, and J are on a single chromosome in the mother's somatic cells. Draw these steps only:

i) the cell in metaphase I with its chromosomes lined up showing any crossover events occurring

ii) the two cells in metaphase II with their chromosomes lined up

iii) the four final products of the meiosis (Please indicate the gamete that led to the creation of the child with trisomy 18 with a star.)