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HST.161 Molecular Biology and Genetics in Modern Medicine
Fall 2007

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Problem set # 1 HST 161 Fall 2007 Due September 18,2007

1. Ron and Lucinda Smith have a family of ten children. Ron's mother Mabel had hypertrophic cardiomyopathy diagnosed by echocardiography. Ron's father, Michael, did not exhibit any symptoms of hypertrophic cardiomyopathy. Ron has hypertrophic cardiomyopathy diagnosed by echocardiography while Lucinda is not affected. Five of their adult children, Ann, Bobby, Charles, Diane and Edward have hypertrophic cardiomyopathy diagnosed by echocardiography, while the remaining five adult children Frank, Grace, Herb, Iris and Jane have no symptoms of hypertrophic cardiomyopathy when tested by echocardiography. Calculate a LOD score for linkage between the marker gene and the hypertrophic cardiomyopathy gene in each of the cases given below assuming a model in which hypertrophic cardiomyopathy is transmitted in an autosomal dominant pattern in this family and 100% penetrance is observed by adulthood for gene carriers when echocardiography is used for diagnosis.

A.

Family member	Genotype at D3S2375
Mabel	1,1
Ron	1,2
Lucinda	2,3
Ann	1,2
Bobby	1,2
Charles	1,3
Diane	1,2
Edward	1,3
Frank	2,3
Grace	2,2
Herb	2,3
Iris	2,2
Jane	2,2

What is the lod score at $\theta=0$ for linkage between the hypertrophic cardiomyopathy locus segregating in this family and D3S2375?

What is the lod score at $\theta=0.1$ for linkage between the hypertrophic cardiomyopathy locus segregating in this family and D3S2375?

B.

Family member	Genotype at the marker locus D3S6781
Mabel	2,2
Ron	2,4
Lucinda	3,4
Ann	2,4
Bobby	2,4
Charles	2,3
Diane	2,4
Edward	3,4
Frank	2,4
Grace	4,4
Herb	2,4
Iris	4,4
Jane	4,4

What is the lod score at $\theta=0$ for linkage between the hypertrophic cardiomyopathy locus segregating in this family and D3S6781?

What is the lod score at $\theta=0.1$ for linkage between the hypertrophic cardiomyopathy locus segregating in this family and D3S6781?

2. For the families in this question, you should assume that familial hypertrophic cardiomyopathy (FHC) is inherited in an autosomal dominant manner. Diagnosis is carried out by echocardiography or by pathology at autopsy. FHC shows age dependent penetrance, reaching a value of 100% by age 20.

A series of families are referred to cardiac genetics clinic. Each of the following genes has been identified to be responsible for FHC in a number of families: beta cardiac myosin, cardiac troponin T, alpha tropomyosin, myosin binding protein C, ventricular/slow myosin essential light chain, cardiac/slow myosin regulatory chain, and cardiac troponin.

Microsatellite loci have been identified which are less than 50 kbp from the start of transcription for each of these genes and are listed below:

MS1 near beta cardiac myosin gene on chromosome 14

MS2 near cardiac troponin T gene

MS3 near alpha tropomyosin gene on chromosome 15

MS4 near myosin binding protein C gene on chromosome 11

MS5 near ventricular/slow myosin essential light chain gene on chromosome 1

MS6 near cardiac/slow myosin regulatory chain gene on chromosome 12

MS7 near cardiac troponin gene on chromosome 19

For each family given below indicate which gene or genes should be sequenced in the hope of identifying a mutation responsible for the cardiac disease in that family.

Explain how you have reached your conclusion for each family.

(Note that in some cases the data for a marker in a family does not allow you to reach a conclusion as to whether sequencing the gene near that marker in a family would be useful. In these cases, explain why the genotype of a specific individual prevents you from reaching a conclusion.)

a. Lisa Smith, age 32, has hypertrophic cardiomyopathy. Her brothers, Sal 29, and Mark, 27 are examined and are unaffected. Her uncles on her mother's side, Jim, 49, and Steve, 51 both are examined by echocardiography and are also shown to have hypertrophic cardiomyopathy. Lisa has two aunts on her mother's side, Ann, 54 and Mary, 57, who are examined and are unaffected. Lisa's mother, Francine was killed in an automobile accident ten years ago. Her father, George is examined and shown to be unaffected. DNA samples are obtained from all family members, and genotyped for all seven microsatellite markers.

The following results are obtained:

	MS1	MS2	MS3	MS4	MS5	MS6	MS7
George	1,8	5,7	2,5	3,9	2,3	5,6	6,6
Lisa	3,8	6,7	1,2	5,9	3,3	5,8	2,6
Sal	1,3	4,5	4,5	4,9	2,6	2,6	3,6
Mark	6,8	4,7	2,4	3,5	3,6	5,8	2,6
Jim	4,6	6,9	3,6	1,8	3,8	2,2	4,5
Steve	2,3	4,6	1,6	5,6	4,7	2,8	4,5
Ann	3,4	3,4	1,8	1,6	3,7	4,8	2,3
Mary	2,6	3,9	3,8	5,8	4,7	4,8	2,5

b. Robert Jones, 41, is a member of a family in which hypertrophic cardiomyopathy has led to the death of three cousins. Robert is shown by echocardiography to be affected. His daughter Rachel, age 16, is also shown to be affected, but his son, Tyler, 11 is clinically unaffected. Robert's wife, Nancy is unaffected. His sister, Gwen 43, is affected. Her two daughters, Miranda, aged 18, and Heather, aged 16, are also affected. Gwen's husband, Jim is unaffected. DNA samples are obtained from all family members and genotyped for the seven microsatellite markers. The following results are obtained:

Marker	MS1	MS2	MS3	MS4	MS5	MS6	MS7
Robert	4,5	4,4	3,4	6,7	2,6	3,5	4,6
Nancy	2,6	3,7	1,6	2,7	2,3	2,9	2,2
Rachel	4,6	3,4	3,6	7,7	2,3	2,3	2,4
Tyler	2,5	3,7	3,6	2,6	2,6	5,9	2,4
Miranda	2,5	6,8	3,8	4,7	1,8	6,8	2,8
Heather	2,3	2,3	3,7	3,4	1,8	6,8	4,6
Gwen	3,5	3,6	3,9	4,4	2,8	3,8	6,8
Jim	2,2	2,8	7,8	3,7	1,1	6,7	2,4

c. Arthur Zhu, age 55, is adopted. He is diagnosed with hypertrophic cardiomyopathy. His three sons, Josh 32, Roger, 29 and Tim, 27, are also all shown to be affected. His daughter Samantha, 25 is also affected. His ex-wife, Mabel, is unwilling to be assessed clinically. DNA samples are obtained from Arthur and his four children and genotyped for the seven microsatellite markers. The following results are obtained:

Marker	MS1	MS2	MS3	MS4	MS5	MS6	MS7
Arthur	1,5	6,7	4,6	5,5	4,7	1,9	3,9
Josh	2,5	1,6	2,6	2,5	2,7	1,2	2,3
Roger	3,5	1,7	3,4	3,5	2,4	2,9	2,9
Tim	3,5	2,6	2,6	2,5	2,4	1,4	3,8
Samantha	2,5	2,7	2,4	3,5	2,7	4,9	8,9

3. This question refers to the paper by Lei Song et. al. (*Circulation* 2006;113:2186-2192).

a. In Table 2 on p. 2090 of this paper, the LOD score for linkage between FHC and D7S669 at $\theta=0.00$ is 4.105, while the LOD score for linkage between FHC and D7S3313 at $\theta=0.00$ is 2.291. Referring specifically to the genotyping data shown in Figure 1 of this paper, explain why a lower value for the LOD score is reached for D7S3313 compared to D7S669. (Hint—to answer this question you will want to identify which meioses are informative for each marker in this family)

b. The interval within which the disease gene may reside is identified as 27.2 megabases based on the data shown in Figure 3. Is any segment of this interval more likely to contain the disease gene than any other?

c. Could genotyping additional markers in this family permit the interval within which the disease gene must reside to be reduced in size? If so, explain the logic by which the interval might be reduced in size by further genotyping.