

All questions below are multiple choice questions with one true and three false alternatives. Partial or complete solutions may be handed in, but will be considered only if the final score is slightly below 60% of the maximum score attainable. Do not forget to put your full name on each page of the exam paper and also on each page of any solutions handed in. Good luck!

1. Siblings share 0, 1, or 2 alleles IBD at a marker locus with probabilities  $p_0 = 0.25$ ,  $p_1 = 0.5$ , and  $p_2 = 0.25$ , respectively under the null hypothesis of no linkage, but what is the corresponding IBD-distribution for father and son? (1p)
  - $p_0 = 0, p_1 = 1$ , and  $p_2 = 0$ ;
  - $p_0 = 0, p_1 = 0.5$ , and  $p_2 = 0.5$ ;
  - $p_0 = 0.25, p_1 = 0.5$ , and  $p_2 = 0.25$ ;
  - $p_0 = 0.5, p_1 = 0.5$ , and  $p_2 = 0$ ;
  
2. The generally accepted definition of significant linkage in a parametric linkage analysis is (1p)
  - $Z(\theta) \geq 1.0$ ;
  - $Z(\theta) \geq 2.0$ ;
  - $Z(\theta) \geq 3.0$ ;
  - $Z(\theta) \geq 4.0$ ;
  
3. If the parental genotypes are both (1 2) at a marker locus  $x$ , what is the probability that a child will receive the (1 2)-genotype? (1p)
  - $P(\text{genotype (1 2)}) = 0$ ;
  - $P(\text{genotype (1 2)}) = 0.125$ ;
  - $P(\text{genotype (1 2)}) = 0.25$ ;
  - $P(\text{genotype (1 2)}) = 0.5$ ;

4. Three small nuclear families have been genotyped at a marker locus  $x$ , and the observed genotypes are:

Family 1: Father (1 2) Mother (3 4) Child 1 (1 3) Child 2 (1 2)

Family 2: Father (1 2) Mother (1 2) Child 1 (1 2) Child 2 (1 2)

Family 3: Father (1 1) Mother (2 2) Child 1 (1 2) Child 2 (1 1)

How many of the three genotype sets above are possible under the Mendelian laws of segregation? (1p)

- 0;
- 1;
- 2;
- 3;

5. Assume that all the seven members of a nuclear family (mother, father, and five children) have been genotyped at a marker locus  $x$ . The mother and three of the children are affected with a rare autosomal dominant disorder, whereas the other family members are unaffected. Let us assume that the penetrance is complete and that no phenocopies exist. Since the disease allele is rare, we can also confidently assume that the affected individuals are heterozygous at the disease locus. Which are the lowest and highest possible lod scores at  $\theta = 0$ ? (1p)

- $Z_{min}(0) = -\infty$ , and  $Z_{max}(0) = 1.2$ ;
- $Z_{min}(0) = -\infty$ , and  $Z_{max}(0) = 1.5$ ;
- $Z_{min}(0) = 0$ , and  $Z_{max}(0) = 1.2$ ;
- $Z_{min}(0) = 0$ , and  $Z_{max}(0) = 1.5$ ;

6. A Single Nucleotide Polymorphism (SNP) has (1p)

- 1 allele;
- 2 alleles;
- 3 alleles;
- 4 alleles;

7. A genetic model is characterized by disease allele frequency  $p = 0.01$ , and penetrances  $f = (f_0 \ f_1 \ f_2) = (0.001 \ 0.001 \ 0.99)$ . Under the assumption of Hardy-Weinberg Equilibrium, what is the probability that a randomly chosen affected individual in the population is homozygous for the normal allele  $a$  at the disease locus? (1p)
- $P(aa|Affected) = 0.0011$ ;
  - $P(aa|Affected) = 0.011$ ;
  - $P(aa|Affected) = 0.11$ ;
  - $P(aa|Affected) = 0.89$ ;
8. The IBD-status for each of 10 affected sib-pairs has been determined at a marker locus  $x$ . Let  $n_0, n_1$ , and  $n_2$  denote the number of pairs sharing 0, 1, and 2 alleles IBD, respectively. Is it possible reach an NPL-score above 4.0? (1p)
- Yes, but only if  $n_2 = 10$ ;
  - Yes, if  $n_2 = 10$  or ( $n_2 = 9$  and  $n_1 = 1$ );
  - Yes, if  $n_2 \geq 9$ ;
  - No;
9. How many of the following three statements are true? (1p)
- 1: Lod scores are additive over independent families for a fixed  $\theta$ .
  - 2: A nuclear family is uninformative for linkage at a marker locus  $x$  if both parents are homozygous at that locus.
  - 3: Lod scores will always depend on population allele frequencies when the genotype of a founder is missing at a marker locus.
- 3;
  - 2;
  - 1;
  - 0;

10. All members of a the pedigree in Figure 1 have been genotyped at a marker locus x. Let us assume a recessive model with full penetrance and without phenocopies.

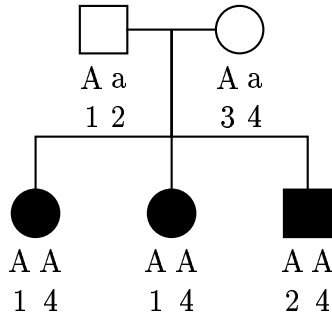


Figure 1: A nuclear family with three affected children.

- (a) The pedigree likelihood is a polynomial in  $\theta$  of the same degree as the number of informative meioses. How many informative meioses do we have in this example? (1p)
- 2;
  - 3;
  - 4;
  - 6;
- (b) The maximum lod score is reached at  $\theta = 0.21$ . What is the maximum lod score? (1p)
- 0.125;
  - 0.50;
  - 0.75;
  - 1.00;
- (c) What is the lod score at  $\theta = 0.5$ ? (1p)
- $-\infty$ ;
  - 0;
  - 0.1;
  - 0.5;

11. What is the interpretation of the locus-specific, broad-sense heritability? (1p)
- the proportion of the total trait variance that is due to environmental influences;
  - the variance of the breeding values in the population;
  - the proportion of the total trait variance that is due to a given locus;
  - the proportion of the genetic variance that is due to additive allelic effects;
12. For a quantitative trait influenced by two biallelic QTL, how many different genotypic values are possible? (1p)
- 1;
  - 3;
  - 9;
  - infinitely many;
13. A quantitative trait is influenced by a single QTL. The additive genetic variance for the trait is  $V_A = 1.64$ . Only one of the following statements is true. Which one? (1p)
- The genetic covariance of two siblings sharing no alleles IBD at the QTL equals -1.64;
  - The genetic covariance of two relatives sharing no alleles IBD at the QTL equals 0;
  - The genetic covariance of two relatives sharing no alleles IBD at the QTL equals 0.82;
  - The genetic covariance of two siblings sharing no alleles IBD at the QTL equals 1.64;

14. A marker allele,  $M$ , with population relative frequency 0.05 is suspected to be associated with the occurrence of a certain disease. If 200 unrelated, affected individuals (cases) are sampled for a case-control design, what is the expected proportion of  $M$ -alleles among the cases if no association exists between the marker and disease? (You may assume the marker genotype distribution to be in Hardy-Weinberg equilibrium but it is really not necessary). (1p)

- 0%;
- 1%;
- 5%;
- 100%;

15. A quantitative trait is influenced by a single QTL with 2 different alleles,  $A_1$  and  $A_2$ . Assume that the trait value,  $Y$ , can be modelled according to  $Y = X + e$ , where the mean zero environmental deviation  $e$  is uncorrelated with the genotypic value  $X$ . Suppose that the average trait value in the population is 6 for  $A_1A_1$ -homozygous individuals. The genetic model is specified by a homozygous effect of 4 and a dominance coefficient equal to 0. Suppose further that the population relative frequency of the  $A_2$ -allele is 5%, that the population is in Hardy-Weinberg equilibrium, and that mating is random.

(a) Determine the genotypic values of  $A_1A_2$ -heterozygous individuals and  $A_2A_2$ -homozygous individuals, respectively. (1p)

- 10 and 14, respectively;
- 12 and 17, respectively;
- 6 and 14, respectively;
- both equal to 10;

(b) Calculate the additive allelic effects. (1p)

- $\alpha_1 = -3.80$  and  $\alpha_2 = 3.80$ ;
- $\alpha_1 = -3.00$  and  $\alpha_2 = 0.40$ ;
- $\alpha_1 = -0.20$  and  $\alpha_2 = 3.80$ ;
- $\alpha_1 = \alpha_2 = 0$ ;

- (c) What is the (total) genetic variance of the trait values? (1p)
- 1.76;
  - 16.12;
  - 3.32;
  - 1.52;
- (d) What is the (narrow-sense) heritability of the trait if the variance of the environmental deviation is assumed equal to 7? (1p)
- 0.1784;
  - 0.4529;
  - 0.3171;
  - 0.4952;

16. Assume a single-locus quantitative trait with additive variance equal to 1 and consider the trait values for a pair of half-sibs.

- (a) Calculate the kinship coefficient,  $\Theta$ , for the two half-sibs. (1p)
- 0;
  - 1/2;
  - 1/4;
  - 1/8;
- (b) Calculate the genetic covariance of the trait values for two half-sibs. (1p)
- 0;
  - 1/4;
  - 1/8;
  - 1/16;
- (c) Suppose that marker data in the region of the QTL suggests that the two half-sibs share one allele IBD with probability 0.91 and no alleles IBD with probability 0.09 at the location of the QTL. Calculate the genetic covariance of the trait values for two half-sibs in view of the observed marker data. (1p)

- 0.986;
- $-0.276$ ;
- 0.376;
- 0.455;

17. In a sample of 5 family trios (each consisting of both parents and one affected child), 6 parents were found to be heterozygous at a biallelic marker locus with alleles  $M_1$  and  $M_2$ . No parents were  $M_1M_1$ -homozygous while the remaining 4 parents were  $M_2M_2$ -homozygous. All 6 marker-heterozygous parents were found to have transmitted the  $M_2$ -allele to their affected offspring.

(a) How many  $M_2$ -alleles would you expect to observe among the 5 affected children if there was no association between marker and disease loci? (1p)

- 4;
- 7;
- 10;
- 11;

(b) What is the value of the TDT test statistic for these data? (1p)

- 3;
- 6;
- 36;
- 2.34;

(c) What is the probability of observing a value of the TDT-statistic at least as large as the value actually observed if there is no association between marker and disease? In other words, what is the p-value for the null hypothesis of no association? (1p)

- 0.0312;
- 0.0431;
- 0.05;
- 0.0654;