Probability and pedigree analysis pdf

5.1: Prelude to Pedigrees and PopulationsTo study the inheritance patterns of genes in humans and other species for which controlled matings are not possible, geneticists use the analysis of family trees and populations.5.2: Family tree AnalysisPedigree graphs are diagrams that show the phenotypes and/or genotypes for a particular organism and its ancestors. Although they are often used in human families to track genetic diseases, they can be used for any species and any hereditary trait.5.3: Deducing the method of inheritance indicates a family tree of an uncharacterized disease or trait, one of the first tasks is to determine which modes of inheritance are possible and then which method of inheritance is most likely. This information is essential in calculating the likelihood that the property will be inherited in future offspring. We will usually take into account five main types of inheritance: autosomal dominant (AD), autosomal recessive (AR), X-linked dominant (XD), X-linked recessive (XR) and Y-linked (Y).5.4: Sporadic and non-hereditary diseasesMany diseases that have a hereditary component, have more complex inheritance patterns due to (1) the involvement of multiple genes and/or (2) environmental factors.5.5: Calculating probabilityProbilities in family trees are calculated using knowledge of Mendeian inheritance and the same basic methods as are used in other areas. The first formula is the product rule: the joint probability of two independent events is the product of their individual proprobability; this is the probability of an event and another event occurring.5.6: Population Genetics population is a large group of individuals of the same species, who are capable of mating with each other. It is useful to know the frequency of certain alleles within a population, as this information can be used to calculate disease risks. Population genetics is also important in ecology and evolution, as changes in allele frequencies can be associated with migration or natural selection.5.E: Pedigrees and populations (Exercises)These are homework exercises to guide Nickle and Barrette-Ng's Online Open Genetics TextMap.5.S: Pedigrees and Populations (Summary) When you see this post, it means we have problems loading external sources on our website. If you're behind a web filter, make sure that the domains *.kastatic.org and *.kasandbox.org unblocked. Calculating probability and risks in family tree analysis: Elementary principles The family tree shows the occurrence of an autosomal recessive property, where black squares have genotype aa. We want to probability calculate that IV-1 (shown as ?) will either be affected (aa), or a wearer heterozygous (Aa). (1) In order to be a degraded recessive homozygous, he/she must inherit an allele from the father and mother. Given that II-1 should be aa, both great-grandparents (I-1 (I-1 I-2) must be Aa. II-2 shows the dominant phenotype and therefore has at least one A allele: the probability of the other being one is 1/2. II-3 is from outside the affected family tree and can be assumed to be a. Like his father, III-1 shows the dominant phenotype, and therefore has at least one A. Then the probability is that III-1 Aa is the probability that II-2 is heterozygous and it passed an allele to III-1: (1/2) x (1/2) = 1/4. The same reasoning leads to the conclusion that III-2 is heterozygous with a probability of 1/4. So, for IV-1 to be aa, both parents must be Aa, and they must both pass the allele to their offspring: 1/4 x 1/4 x 1/4 = (2) Alternatively, for IV-1 to be a heterozygous, carrier, either s/he most inherit an an allele from the father, or from the mother. The probability that either parent is a heterozygous is 1/4, as calculated above. Then, the chances of both parents being heterozygotes, and the probability that two heterozygotes will have a heterozygous 1/4 x 1/4 x 1/2 = (3) Finally, the probability that IV-1 is a dominant homozygous is 1 - 1/64 - 1/32 = (64 - 1 - 2)/64 = 61/64. This can also be calculated more annoyingly by listing the alternative probableties on each of the above steps. The calculations in this example concerned a distinction between a priori and a posteriori probability, which are often misrepresented in elementary genetics manuals. To take a simple case: the a priori probability of getting heads on a single piece of a penny is 1/2, because there are two equal possibilities, H or T. Then, given two cents randomly 120 000, HH, HT, TH, and TT are all equally likely. The a priori chance of getting at least one head is 3/4. The a priori probability that a combination with at least one head will have two tails (HT or TH vs HH) is 2/3. However, consider an experiment in which I have 1ssed two cents. I'll show you that one is an H, and ask, What are the chances that the other is H? The a posteriori probability is 1/2 : given the knowledge that one coin is H, the other is H or T with equal probability. In anticipation of the experiment, the a priori probability of HT given H- is 2/3. When analyzing the results of a particular experiment, the added information changes a posteriori's probability. In the example above, we know that I-1 and I-2 are heterozygotes and II-2 shows the dominant phenotype. We therefore know a posteriori that he has inherited a dominant alleles from one parent, and the probability that he will inherit a recessive alleles from the other parent and heterozygous is 1/2. It is incorrect to reason that, since 2/3 of all unaffected children (i.e., all non-aa) heterozygotes are a priori, risk is also 2/3. Stated another way, by knowing the nature of an allele, we have lost a statistical degree of [In the simplest case: the probability that the next child of I-1 and I-2 will be a boy is a priori 1/2: once the child is born, the probability is a posterior or 0 or 1]. Two further extensions of this idea. For this scenario, assume that a genetic test is available to distinguish AA from Aa, but II-5 has died and III-2 will not take the test. (4) Set III-2 has a heterozygous sibling. How does this change the risk of the IV-I calculation? This would mean that II-5 should be a heterozygous with a probability of 1, not 1/2 as before. Then the probability that III-2 is a heterozygous 1/2, the probability that the father (III-1) is a heterozygous remains 1/4, and the probability that IV-1 aa is 1/2 x 1/4 x 1/4 = 1/16. (5) Set III-2 has one or more siblings who test as untouched homozygotes (AA). How does this change the calculation of the risk of IV-1? Note that while the birth of a heterozygous sibling proves that the mother (II-5) is a heterozygous, the birth of untouched homozygous offspring cannot prove that she is a homozygous. However, multiple births of unaffected siblings reduce the likelihood of her being a heterozygous, as follows. The probability that a heterozygous does not pass on an allele to a offspring is 1/2. Then the chances are that she won't pass it on to either of the two offspring (1/2)(1/2) = 0.52 = 1/4. The probability that they will pass it on to none of the three offspring is 0.53 = 1/8, neither of the four is 1/16, and so on. Less than 0.1% of all families with ten children would have known with an alleles, if II-5 were a heterozygous. In other words, this is strongly a posteriori proof that II-5 is a homozygous, which if true means that IV-1 cannot be affected. Of course, the birth of an eleventh child proves that Aa is immediately that II-5 is heterozygous, and gives the risk calculation of IV-1 back to 1/16, as in (4) above.. In humans, controlled crosses cannot be made, so geneticists should resort to examining family data in the hope that informative matings have been created that can be used to deduce dominance and distinguish autosomal from X-linked inheritance. The researcher traces the history of a variant phenotype back through the history of the family and establishes a family tree, or family tree, using the standard symbols in Figure 4-17. The clues in the family tree should be interpreted differently depending on whether one of the contrasting phenotypes is a rare condition or whether both phenotypes are from a few common morphs of polymorphism. Human genetic disorders can be dominant or recessive phenotypes and may be autosomal or X-linked. four categories are discussed in the following sections. The unusual phenotype of a recessive disorder is determined by homozygosity for a recessive allele, and the unaffected phenotype is determined by the corresponding dominant dominant In chapter 3 we saw that phenylketonuria (PKU) is a recessive phenotype. PKU is determined by an allele that we can call p, and the normal condition by P. Therefore, patients of this disease are genotype p/p, and unaffected people are either P/P or P/p. What patterns in a family tree would reveal such an inheritance? Two important points are that generally the disease appears in the offspring of unaffected parents and that the affected offspring include both men and women equally. When we know that both male and female phenotypic proportions are similar, we can assume that we are dealing with autosomal inheritance, not X-linked inheritance. The following typical family tree illustrates the main point that affected children are born to unaffected parents:From this pattern we can immediately deduce autosomal inheritance, with the recessive allele responsible for the exceptional phenotype (indicated by shadow). In addition, we can infer that parents should have both heterozygoten, P/p. (Both must have a p allele, because each one contributed to each affected child, and both must have a P allele, because people are phenotypically normal.) We can identify the children's genotypes (in the order shown) as P/–, p/p, p/p and P/–. Hence the family tree can be rewrittenA another interesting feature of family tree analysis: although Mendelian rules are at work, Mendelian ratios are rarely observed in single families because sample sizes are too small. In the example above, we see a 1:1 phenotypic ratio in the progeny of what is clearly a monohybrid cross, in which we can expect a 3:1 ratio. If the couple were to have, say, 20 children, the relationship would undoubtedly be something like 15 unaffected children and 5 with PKU (the expected monohybrid 3:1 ratio), but in a sample of four each relationship is possible and all relationships are often found. In the case of a rare recessive allele, in the population most of these alleles will be found in heterozygotes, not in homozygotes. The reason is a matter of probability: to think of a recessive homozygous, both parents must have had the p allele, but to think of a heterozygous, one parent with the allele is needed. The formation of an affected individual usually depends on the chance union of unrelated heterozygotes, and for this reason the family trees of autosomal look rather bare, generally with only siblings of a cross affected. Inbreeding (mating between family members) increases the likelihood that mating between two heterozygotes will be. An example of a cousin marriage is shown in Figure 4-18. Individuals III-5 and III-6 are cousins and two children. You can see from the figure that an ancestor who is a heterozygous can produce many offspring that are also heterozygoten. Pairings between family members are therefore at a higher risk of producing abnormal homozygous recessions than non-family members. It is for this reason that first cousin marriages are responsible for much of the recessive diseases in the human population. Albinism (Figure 4-19) is another rare condition inherited in a Mendelian way as an autosomal recessive phenotype in many animals, including humans. The striking white phenotype is caused by a defect in an enzyme that synthesizes melanin, the pigment responsible for most of the black and brown dyes of animals. In humans, such staining is most evident in hair, skin, and retina, and its absence in albinos (which is homozygous recessive genotype a/a) leads to white hair, white skin, and eye pupils that are pink because of the unmasking of the red hemoglobin pigment in blood vessels in the retina. The inheritance and molecular genetics of albinism are integrated into Figure 4-20. In family trees, an autosomal recessive disorder is revealed by the appearance of the phenotype in the male and female offspring of unaffected individuals. In autosomal dominant disorders, the normal allele is recessive and the abnormal allele is dominant. It may seem paradoxical that a rare condition can be dominant, but remember that dominance and recessiveness are simply reflections of how acting alone and are not defined in terms of dominance in the population. An example of a rare autosomal dominant phenotype is achondroplasia, a type of dwarfism (see Figure 4-21). In this case, people with a normal stature are genotypical d/d, and the dwarf pheenotype could in principle be D/d or D/D. However, it is believed that in D/D individuals, the two doses of the D allele produce such a severe effect that this genotype is fatal. If it's true, all achondroplastics are heterozygotes. In family tree analysis, the main evidence for identifying an autosomal dominant disorder is that the phenotype tends to appear in every generation of the family tree and that affected fathers and mothers pass the phenotype to both sons and daughters. Again, the representation of both sexes among the affected offspring argues against X-linked inheritance. The phenotype appears in each generation, because generally the abnormal allele worn by an individual must come from a parent in the previous generation. (Abnormal alleles can arise de novo by mutation. This is relatively rare, but should be kept in mind as a possibility.) A typical family tree for a dominant condition is shown in Figure 4-22. Again, note that Mendelian ratios are not necessarily observed in families. As with recessive disorders, individuals with a copy of the rare allele /a) are much more common than those with two copies (A/A), so most affected people are heterozygotes, and virtually all matings involving dominant disorders are A/a × a/a. Thus, when the offspring of such matings is in total, a 1:1 ratio is expected of unaffected (a/a) (a/a) (A/a). Huntington's disease is an example of an autosomal dominant condition. The phenotype is one of neural degeneration, which leads to convulsions and premature death. However, it is a late illness, the symptoms generally do not appear until after the person has started to have children. Each child of a carrier of the abnormal allele has a 50 percent chance of inheriting the allele and its associated disease. This tragic pattern has led to a drive to find ways to identify people who carry the abnormal allele before they experience the onset of the disease. The discovery of the molecular nature of the mutant allele, and of neutral DNA mutations that act as markers close to the affected allele on the chromosome, has revolutionized this type of diagnosis. Family trees of autosomal dominant disorders show affected men and women in each generation and also show affected men and women transmitting the condition to equal proportions of their sons and daughters. In human populations, there are many examples of polymorphisms (generally dimorphisms) where the alternative phenotypes of the character are determined by alleles of a single gene, for example, the dimorphisms for kin dimple versus no, attached earlopes versus unattached, widow peak versus none, and so on. The interpretation of family trees for dimorphisms is somewhat different from that for rare diseases, because by definition the morphs in a dimorphism are common. Let's look at a family tree for an interesting human morphism. Most human populations are dimorphic for the ability to taste the chemical phenylthiocarbamide (PTC): people can detect it as a foul, bitter taste or - much to the surprise and disbelief of tasters - can't taste it at all. The family tree in Figure 4-23 shows that two tasters sometimes produce nontaster children. This makes it clear that the allele for the ability to taste is dominant and that the allele for non-endearing is recessive. Note, however, that almost all people who marry in this family carry the recessive allele, either in heterozygous or in homozygous state. Such a family tree is therefore different from that of rare recessive disorders, for which it is conventional to assume that everyone who marries in a family homozygous is normal. As both PTC alleles are common, it is not surprising that all but one of the family members in this family tree married individuals with at least one copy of the recessive allele. In polymorphism, the contrasting morphs are often determined by alleles of a single autosomal gene. Family trees of rare X-linked dominant phenotypes exhibit the following characteristics:1.Affected males indicate condition to all their daughters, but to none of their sons (Figure 4-27).2.Females married to unaffected males pass on the condition to half of their sons and daughters. There are few examples of X-linked dominant phenotypes in One is hypophosphatmy, a type of vitamin D-resistant rickets. The mechanisms of X-linked dominance and recessiveness in humans are somewhat complicated by the phenomenon of X chromosome inactivation found in mammals. This topic will be covered in chapter 16.When a disease allele is known to be present in a family, knowledge of simple gene transmission patterns can be used to calculate potential parents' likelihood of having a child with the condition. For example, a couple discovered that each had an uncle with Tay-Sachs disease (a severe autosomal recessive disease). The family tree is as follows: The probability that their child with Tay-Sachs can be calculated the following way. The question is whether the man and woman are heterozygoten (it is clear that they do not have the disease), because if they are both heterozygoten then they have a chance of having an affected kind.1.De grandparents of the man must have both been heterozygotes T/t because they caused a t/t child (the uncle). That's why they actually formed a monohybrid cross. The father of the man could be T/T or T/t, but we know that the relative probability of these genotypes must be 1/4 and 1/2 respectively (the expected offspring ratio in a monohybrid cross is 1/4 T/T, 1/2 T/t and 1/4 t). Therefore, there is a 2/3 chance that the father is a heterozygous [calculated as 1/2 divided by (+ 1/4+1/2)].2.The mother of the man should be believed to be T/T, because she married in the family and the disease alleles are generally rare. So if the father is T/t, then the mating to the mother was a cross T/t × T/T and the expected offspring are 1/2 T/T and 1/2 T/t.3.The overall probability that the man is a heterozygote should be calculated using a statistical rule called the product rule, which states that the probability of two independent events both takes place, the product is of their individual probability. Hence the likelihood that the man is a heterozygous, the chance that his father is a heterozygous, times the chance that the father has a heterozygous, that is 2/3 × 1/2 = 1/3.4.Similarly, the chance that the wife of the man becomes heterozygous also 1/3.5.If they are both heterozygous (T/t), then the probability that their child will have a t/t child is 1/4, overall the chance of the couple having an affected child is 1/3 × 1/3 × 1/4 = 1/36; in other words, a 1 in 36 chance. Chance.