Lecture 4

From the last lecture, we followed gene segregation in a cross between a true breeding strain with a shibire mutation and flies from a wild-type strain.

shibire mutant x wild-type

↓

F_1: all not paralyzed

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F_2: 3 not paralyzed : 1 paralyzed

This is the segregation pattern expected for a single gene. But in an actual experiment how do we know that the phenotypic ratio is really 3 : 1 ?

There is no logical way to prove that we have exactly a 3 : 1 ratio. Nevertheless, we can think of an alternative hypothesis then show that the alternative hypothesis does not fit the data. Usually, we then adopt the simplest hypothesis that still fits the data.

A possible alternative hypothesis is that recessive alleles in two different genes can result in a paralyzed fly, but that a paralyzed fly could result with from homozygous recessive alleles at either gene.

In this case a true breeding paralyzed fly would have genotype: **a/a** , **b/b**

Whereas wild-type would have genotype: **A/A** , **B/B**

F_1: **A/a B/b** not paralyzed

F_2: p(**a/a** and **b/b**) = $(1/4)^2$ = 1/16

p(**a/a** and **B/–**) = 1/4 x 3/4 = 3/16

p(**A/–** and **b/b**) = 3/16

p(**A/–** and **B/–**) = the rest = 9/16

This is the classic ratio for two gene segregation 9 : 3 : 3 : 1
paralyzed

For our hypothesis we should see a paralyzed fly with genotype **a/a** or **b/b**.
In this case the phenotypic ratio would be 9 not paralyzed : 7 paralyzed.

Therefore, to distinguish one-gene segregation from two-gene segregation we need a statistical test to distinguish 3 : 1 from 9 : 7. Intuitively, we know that in order to get statistical significance, we need to look at a sufficient number of individuals.

For a **chi-square test** you start with a specific hypothesis that gives a precise expectation. The test is then applied to the actual experimental results and will give the probability of obtaining the results under the hypothesis. The test is useful for ruling out hypotheses that would be very unlikely to give the actual results.

Say we look at 16 flies in the F_2 and observe exactly the ratio expected for one gene: 12 not paralyzed and 4 paralyzed flies.

Under the hypothesis of two genes we expect 9 not paralyzed flies and 7 paralyzed fly.

We calculate the value χ^2 using the formula below. Where O is the number of individuals observed in each class and E is the number of individuals expected for each class.

$$\chi^2 = \sum_{\text{(all classes)}} \frac{(O - E)^2}{E} = \frac{9}{9} + \frac{9}{7} = 1 + 1.29 = 2.29$$

degrees of freedom (df) = number of classes – 1

χ^2 (df = 1)	.016	.46	2.7	3.8	5.0	6.6	7.9
p value:	0.9	0.5	0.1	0.05	0.025	0.01	0.005

From the table $\chi^2 = 2.29$ using 1 df, $p > 0.05$

We use the convention that $p \leq 0.05$ constitutes a deviation from expectation that is significant enough to reject the hypothesis. Therefore, on the basis of this sample of 16 flies we can't rule out the hypothesis that two genes are required.

Now say we look at 32 F_2 flies and find that 8 are paralyzed. For the hypothesis of two genes the expectation is that 14 would be paralyzed. The χ^2 for this data is the sum:

$$\chi^2 = \frac{6^2}{18} + \frac{6^2}{14} = 2 + 2.57 = 4.6$$

From the table $p < 0.05$ so we reject the two-gene hypothesis.

Clearly the new data still fits the one gene hypothesis. Thus, on the basis of this experiment we haven't proven the hypothesis that the paralyzed fly is the result of single gene segregation, but we have eliminated a major alternative hypothesis.

So far, the hypothesis that one gene is responsible for the paralyzed trait is the simplest explanation that fits the data.

The way to distinguish most easily between a heterozygote and a homozygote expressing a dominant trait is to cross to a homozygous recessive test strain.

Test cross: cross to homozygote recessive

A/A x **a/a** gives all **A/a** i.e. all offspring will express the dominant trait.

A/a x **a/a** gives 1/2 **A/a** and 1/2 **a/a** i.e. one half of the offspring will express the dominant trait.

Mendelian inheritance in humans

For humans we can't do test crosses, of course, but by following inheritance of a trait for several generations the modes of inheritance can usually be identified by applying basic principles of Mendel. The following are guidelines for identifying different modes of inheritance in pedigrees.

Autosomal dominant

i) Affected individuals must have at least one affected parent

Exceptions to this rule will occur if a new mutation arises in one of the parents (in real life a more likely explanation is extramarital paternity). Another possibility is incomplete penetrance, where other genetic or environmental factors prevent the trait from being expressed in one of the parents.

ii) For rare dominant traits, if one parent is affected most likely half of the children will be affected.

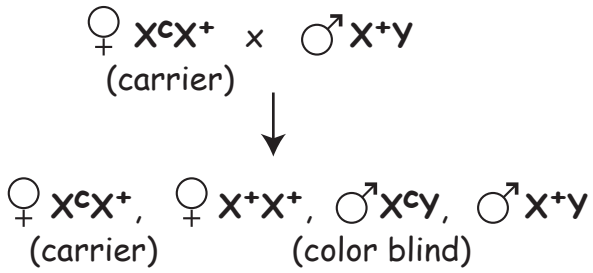
Autosomal recessive

i) When both parents are carriers, on average 1/4 of the children will be affected.

ii) When both parents are affected, then all of the children will be affected.

iii) If the trait is very rare then consanguinity is likely. That is, it is likely that parents of affected children are themselves related (e.g. cousins).

X-linked inheritance



i) When parents are a carrier ♀ and an unaffected ♂, then on average, 1/2 of the daughters will be carriers and 1/2 of the sons will be affected.

If the trait is rare then the vast majority of affected individuals will be male which is the hallmark of X-linked traits.

ii) Affected sons inherit the allele from mother

- Maternal uncles often affected
- Since inherited only from mother, inbreeding doesn't increase the probability of an affected ♂ .