Chapter 12

The Chromosomal Theory of Inheritance Continued
By the beginning of the 20th century, cytologists had observed that chromosome number is constant in all cells of a species, but varies widely between species.

Sutton and Boveri (1902) independently realized the parallel between Mendelian inheritance and chromosome transmission, and proposed the chromosome theory of inheritance, which states that Mendelian factors (genes) are located on chromosomes.
Sex Chromosomes

The behavior of sex chromosomes offers support for the chromosomal theory.

McClung, Stevens, and Wilson independently indicated that chromosomes are different in male and female insects.
Sex Linkage

• Morgan (1910) found a mutant white-eyed male fly, and used it in a series of experiments that showed a gene for eye color located on the X chromosome.
a) P generation

Parental phenotype
Red eyes (wild type) | White eyes
---|---
Diploid parental genotype
\( w^+w \) | \( w^+ \)
Haploid gametes
\( XX \) | \( XY \)

F<sub>1</sub> generation

\( w^+w \) (or \(+/w\)) | \( w^+ \)
---|---
\( w^+w \) | \( w^+ \)
F<sub>1</sub> genotypes: \( 1/2 w^+/w \) (or \(+/w\)), \( 1/2 w^+/Y \) (or \(+/\))

F<sub>1</sub> phenotypes: \( 1/2 \) female, \( 1/2 \) male
All red-eyed (wild type)

b) F<sub>1</sub> generation

\( \varphi \) | \( \sigma \)
---|---
Diploid F<sub>1</sub> genotypes
\( w^+w \) | \( w^+w \)
Haploid F<sub>1</sub> gametes
\( XX \) | \( XY \)

F<sub>2</sub> generation

\( w^+w \), \( w^+w^+ \), \( w^+/Y \), \( w/Y \)
F<sub>2</sub> genotypes: \( 1 w^+/w \), \( 1 w^+/w^+ \), \( 1 w^+/Y \), \( 1 w/Y \)

F<sub>2</sub> phenotypes: \( 3/4 \) red eyes (2\( \varphi \), 1\( \sigma \)) \( 1/4 \) white eyes (1\( \sigma \))
Morgan’s hypothesis was that this eye color gene is located on the X chromosome. If that was to be truth, then

1. Males are **hemizygous**, because there is no homologous gene on the Y. The original mutant male’s genotype was $X^wY$ (hemizygous with the recessive allele).

2. Females may be **homozygous or heterozygous**. The wild-type female in the original cross was $w^+w^+$ (homozygous for red eyes).

3. The F1 flies were $w^+w$ (females) and $w^+Y$ (males). The females all heterozygous, the males **hemizygous dominant**.

4. The F2 data complete a **crisscross inheritance pattern**, with transmission from the mutant fly through his daughter (who is heterozygous) to his grandson. The F2 were:
   
   $X^{w^+}X^{w^+}$; $X^{w^+}X^w$; $X^wY$ and $X^wY$.
• Morgan’s hypothesis was confirmed by an experiment **reciprocal** to the original cross.

• In this case, a white-eyed female (\(w/w\)) was crossed with a wild-type male (\(w^+/Y\)).

• **Results of the reciprocal cross:**
  All F1 females had red eyes (\(Xw^+/Xw\)).
  All F1 males had white eyes (\(XwY\)).
• Morgan’s discovery of X-linked inheritance showed that when results of reciprocal crosses are different, and ratios differ between progeny of different sexes, the gene involved is likely to be X-linked (sex-linked).
• This was strong evidence that genes are located on chromosomes. Morgan received the 1933 Nobel Prize for Physiology or Medicine for this work.
The strange case of no sex chromosomes or the case of too many.....
Nondisjunction of X Chromosomes

• Morgan’s work showed that crossing a white-eyed female (ww) with a red-eyed male (w+Y) produces an F1 of white-eyed males (w/Y) and red-eyed females (w+w). His student, Bridges, found that about 1 in 2,000 of the offspring was an exception, either a white-eyed female or red-eyed male.

• Bridges’s hypothesis was that chromatids failed to separate normally during anaphase of meiosis I or II, resulting in nondisjunction.
Nondisjunction can involve either autosomes or sex chromosomes. For the eye-color trait, X chromosome nondisjunction was the relevant event. Nondisjunction in an individual with a normal set of chromosomes is called primary nondisjunction.
• Nondisjunction explains Bridges’s findings:
  • a. Nondisjunction, a rare event, in a \(ww\) female would result in eggs with two X chromosomes (XX), and those with none (O).

  • b. If these are fertilized with normal sperm from a wild-type male (\(w^+Y\)), the results are:
    - YO, which die due to lack of an X chromosome.
    - XXX, which die, presumably due to the extra dose of X genes.
    - Red-eyed X\(w^+O\) sterile males who received X\(w^+\) from the father and no sex chromosome from the mother.
    - White-eyed X\(wXwY\) females that received two X\(w\) chromosomes from the mother and Y from the father.
P generation

<table>
<thead>
<tr>
<th>Parent 1 ♀</th>
<th>Parent 2 ♂</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenotypes</strong></td>
<td></td>
</tr>
<tr>
<td>White eyes</td>
<td>Red eyes (wild type)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diploid genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>wXX</td>
</tr>
<tr>
<td>wXY</td>
</tr>
</tbody>
</table>

Nondisjunction gametes in ♀; normal gametes in ♂

<table>
<thead>
<tr>
<th>Expected progeny</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent 1 ♀ gametes (exceptional eggs)</td>
</tr>
<tr>
<td>Parent 2 ♂ gametes</td>
</tr>
</tbody>
</table>

F<sub>1</sub> genotypes:

\[ \frac{1}{4} w^+w, \frac{1}{4} YO, \frac{1}{4} w/w, \frac{1}{4} Y/w \]

F<sub>1</sub> phenotypes:

\[ \frac{1}{2} \text{ usually die in early development} \]
\[ \frac{1}{4} \text{ white-eyed females} \]
\[ \frac{1}{4} \text{ red-eyed males (sterile)} \]
• The odd inheritance pattern matches specific aneuploid types (XO and XXY), clearly associating a specific phenotype with a specific chromosome complement.

• Thus, gene segregation mirrors chromosome behavior in meiosis (Figure 12.23). Mendel’s principles of segregation and independent assortment of genes correlate with the movement of chromosomes during meiosis.
Sex Determination

1. Some mechanisms of sex determination include:
   a. Genotypic sex determination, in which sex is governed by genotype (sex chromosomes)
   b. Genic sex determination, in which sex chromosomes are not involved.
Genotypic Sex Determination

*Sex Determination in Mammals*

1. **Mammals** use the Y-chromosome mechanism of sex-determination, in which the Y chromosome determines sex by conferring maleness.

2. **Why?** Sex of mammals is determined by a **gene** on the Y chromosome, testis-determining factor. In the absence of this gene, gonads develop into ovaries.
Evidence for the Y Chromosome Mechanism of Sex Determination

• A. XO individuals, who are sterile females exhibiting Turner syndrome (Figure 12.24). Most XO fetuses die before birth. Surviving Turner syndrome individuals become noticeable at puberty, when secondary sexual characteristics fail to develop. Other traits include: Below-average height, weblike necks, poorly developed breasts, immature internal sexual organs and reduced ability to interpret spatial relationships.
• B. XXY individuals, who are male and have Klinefelter syndrome. Other traits include: Above-average height, breast development in about 50% of XXY individuals and subnormal intelligence in some cases.

• C. XYY individuals are male, and tend to be taller than average. Fertility is sometimes affected.

• D. XXX individuals are usually normal women, although they may be slightly less fertile and a few have below-average intelligence.

• E. Higher numbers of X and/or Y chromosomes are sometimes found, including XXXY, XXXXY, and XXYY. The effects are similar to Klinefelter syndrome.
Dosage Compensation Mechanism for X-Linked Genes in Mammals

- Gene dosage varies between the sexes in mammals, because females have two copies of X while males have one. Early in development, gene expression from the X chromosome must be equalized to avoid death. Different dosage compensation systems have evolved in different organisms.

- In mammals, female somatic cell nuclei contain a Barr body (highly condensed chromatin) while male nuclei do not (Figure 12.26). The Lyon (Mary Lyon) hypothesis explains the phenomenon:
• A Barr body is a condensed and (mostly) inactivated X chromosome. Lyonization of one chromosome leaves only one transcriptionally active X, equalizing gene dose between the sexes. An X is randomly chosen in each cell for inactivation early in development (in humans, day 16 postfertilization).

• Lyonization allows extra sex chromosomes to be tolerated well. No such mechanism exists for autosomes, and so an extra autosome is usually lethal.

• The number of Barr bodies is the number of X chromosomes minus one.
An interesting application

- In cats some of the genes involved in fur color (for phaeomelanin) are located in the X chromosome. The *Orange* gene, $O$, which in its dominant form, $X^O$, produces orange fur, and in its recessive form, $X^o$, produces black fur.

- A male cat will be $X^OY = \text{Orange}$
- A male cat will be $X^oY = \text{Black}$
- A female $X^OX^O = \text{Orange}$
- A female $X^oX^o = \text{Black}$
- A female $X^OX^o = \text{Orange-Black}$
• And now…The white spot gene! White spots in cats is an incomplete dominant gene. SS is very large spots, Ss is small spots and ss is not spots. The white spot gene is located in an autosome. Now, let’s combine.

• A male cat will be X^OY = Orange and SS, Ss or ss?
• A male cat will be X^oY = Black and SS, Ss, ss?
• A female X^OX^O = Orange and SS, Ss, ss?
• A female X^oX^o= Black and SS, Ss, ss?
• A female X^OX^o= Orange-Black and SS, Ss, ss?
Sex Chromosomes in Other Organisms

• 1. Sex chromosome composition in birds, butterflies, moths, and some fish is opposite that of mammals, with the male the homogametic sex (ZZ) and the female heterogametic (ZW). Z-linked genes behave like X-linked genes in mammals, but the sexes are reversed. The genes on the Z and W chromosomes are very different from those on X and Y, indicating that these sex chromosomes evolved independently, from different pairs of autosomes.

• 2. In plants, the arrangement of sex organs varies: Dioecious species (e.g., ginkgo) have plants of separate sexes, one with male parts, the other with female. Some dioecious plants have sex chromosomes and use an X chromosome–autosome balance system, but many other sex determination systems also occur in dioecious plants.
Genic Sex Determination

1. Other eukaryotes use a genic system instead of entire sex chromosomes. A single allele determines the mating type (e.g., $MAT_a$ and $MAT_a$ in *Saccharomyces cerevisiae*).

2. Yeast mating types have identical morphologies, but are able to fertilize gametes only from the opposite mating type.
X-Linked Recessive Inheritance in Humans

1. Human traits involving recessive alleles on the X chromosome are **X-linked recessive** traits. A famous example is hemophilia A among Queen Victoria’s descendants. Other X-linked recessive traits are Duchenne muscular dystrophy and two forms of color blindness.

2. X-linked recessive traits are expressed much more frequently among males, who are hemizygous. A female would express a recessive X-linked trait only if she were homozygous recessive at that locus.
Some characteristics of X-linked recessive inheritance:

- Affected fathers transmit the recessive allele to all daughters (who are therefore carriers), and to none of their sons.

Father-to-son transmission of X-linked alleles generally does not occur.

Many more males than females exhibit the trait.

All sons of affected (homozygous recessive) mothers are expected to show the trait.

With a carrier mother, about 1/2 of her sons will show the trait and 1/2 will be free of the allele.

f. A carrier female crossed with a normal male will have 1/2 carrier and 1/2 normal daughters.
X-Linked Dominant Inheritance

Only a few X-linked dominants are known. Examples include:

Hereditary enamel hypoplasia (faulty and discolored tooth enamel).

Webbing to the tips of the toes.
Constitutional thrombopathy (severe bleeding due to lack of blood platelets).

Patterns of inheritance are the same as X-linked recessives, except that heterozygous females show the trait (although often in a milder form).
Y-Linked Inheritance

1. Y-linked (holandric) traits, except for maleness itself (resulting from SRY on the Y chromosome), have not been confirmed, but many genes on the Y chromosome have been identified.

2. The hairy ears trait may be Y linked, but it is a complex phenotype, and might also be the result of autosomal gene(s) and/or effects of testosterone.