History of discovery in classical genetics

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This chapter chronicles the fascinating history of discovery in classical genetics, which is the study of how genetic traits are transmitted in organisms.

Key Concepts covered:

- Mendel’s laws of heredity was rediscovered and gain wide acceptance in 1900.
- The chromosomal theory of heredity states that genes reside on chromosomes and that chromosomal dynamics underlie the patterns of Mendelian inheritance.
- A fundamental observation in classical genetics was the ‘ one gene makes one protein’ relationship. It is now known that the relationship between genes and proteins is much more complex.
- Genetic Science has to be reconciled to other fields of biology.

The Rediscovery of Mendel’s Work (1900)

Darwin knew his theory of evolution is not complete without a compatible theory of heredity. In 1868, he announced that he had found a solution to heredity, but had never published it. After his death, scientists were running through his works to find clues to the theory of heredity that had gone missing. Among them was a Dutch botanist called Hugo de Vries (1848-1935).

To support his theory of pangenes, de Vries conducted a series of experiments with plant hybrids in the 1890s. Unaware of Mendel’s work, de Vries had independently discovered Mendel’s Laws of Heredity.

He was about to publish his work when a friend sent him a copy of Mendel's original paper. Later, de Vries claimed he had discovered the sames principles on his own before learned of Mendel's experiments. But he gave Mendel credit in his paper which he published in 1900.

Two other scientists also independently rediscovered Mendel's work: Carl Correns (1864-1933) and Erich Tschermak von Seysenegg (1871-1962). Correns was a German raised in Switzerland, and a student of Karl von Nageli – the professor who had discouraged Mendel. Tschermak was an Austrian whose grandfather had been one of Mendel's teachers at the University of Vienna.

Mendel received wide recognition in the scientific community after William Bateson (1861-1926), an English biologist, became a passionate advocate for the new science. While riding on a train to London, Bateson read de Vries' paper with its reference to Mendel; he immediately realized the significance of Mendel's work.

In 1905, Bateson called the new science ' genetics'. A few years later, Wilhelm Johannsen (1857-1927), a Danish botanist, used the word ' genes' to refer to the units of heredity. Johannsen also invented the terms ' genotype' and ' phenotype'. ' Genotype' is the totality of all the organism's genes. ' Phenotype' is the organism's physical characteristics, which are products of both the underlying genes and the effects of the environment.

Chromosomal Theory of Heredity and Gene Maps

As Mendel's ideas was gaining acceptance in the scientific world, cell biologists wanted to figure out the physical nature of genes. What are genes

made of? In the 1890s, Theodor Boveri (1862-1915), a German embryologist, pursued the question in a series of experiments with sea urchins. The eggs of sea urchins are large, transparent, and easy to study under the microscope. Because both sperm and eggs carried genes, and sperm were little more than a nucleus with a tail attached, Boveri concluded that genes must reside in the threadlike filaments called chromosomes in the nucleus of cells.

Boveri's hypothesis was corroboated by the discovery of two other scientists – Walter Sutton (1877-1916) and Nettie Stevens (1861-1912). Sutton, a graduate student at Columbia University in New York, discovered chromosomes when he studied the chromosomes of grasshoppers in 1902.

Stevens, a former student of Boveri, discovered X and Y sex chromosomes in 1905, and proposed that all genes reside on chromosomes.

The Birth of the Modern laboratory

Thomas Hunt Morgan (1866-1945) was a professor of zoology at Columbia University in New York. He began breeding flies around 1905 and established the famous " fly room" in Columbia University. Between 1905 and 1925, the Fly Room at Columbia was the epicenter of genetics, a catalytic chamber for the new science.

The Chromosomal Theory of Heredity

Mendel showed that, in principle, genes were inherited independently. The color of a pea had no influence on whether it was wrinkled or round. But as Morgan experimented with increasing number of fly mutants, he discovered exceptions. In 1910, mating fly mutants with white eyes to ordinary red-eyed

flies, Morgan found out surprisingly that all white-eyed descendants were male. The eye-color gene must be linked to the sex gene, he thought. In 1911, he confirmed his suspicion: the eye-color gene and the sex gene are linked because they lived on the same chromosome – the X chromosome.

After examining thousands upon thousands of flies, Morgan discovered an important modification to Mendel's laws, now known as the chromosomal theory of heredity: *Genes on different chromosomes are inherited independently, but genes on the same chromosome are usually inherited together* . The emphasis is on " usually." In rare cases, genes on the same chromosome were not inherited together. Morgan called this phenomenon ' crossing over'; today known as recombination.

Gene Maps

Morgan's study on " crossing over" resulted in a new discovery: *Genes that were closer to each other on the chromosome would never be unlinked; Genes were more prone to unlink if they were farther apart on the chromosome; Genes that had no linkage must lived on separate chromosomes.*

In 1911, Alfred Sturtevant (1891-1970), a twenty-year-old student of Morgan's lab, collected Morgan's data on the linkage of fruit fly genes and took it home. In a single night, Sturtevant plotted the first map of genes in fruit flies by using the gene linkage to set up the relative positions of genes on chromosomes. The map showed the order of genes on the chromosome and their relative distances from one another. In that evening, Sturtevant

had laid the groundwork for the future cloning of genes. He had also poured the foundation for the Human Genome Project.

Mutation and Transformation

For evolution to occur, an organism must be able to generate genetic variations. This section covers two kinds of genetic alterations at the cellular level – mutation and transformation.

Mutation

Mutations are – by definition – alterations of the genetic material. Mutations result from errors during DNA replication or other types of damage to DNA, which then may undergo error-prone repair.

Mutation was first discovered by Hugo de Vries (1848-1935) in 1900, who had also independently rediscovered Mendel's laws. At that time, scientists had to wait for mutations to happen in nature; they could not cause them.

But that was change in 1926 when Hermann Muller (1890-1967), a former student of Thomas Morgan, discovered X-ray Mutagenesis. He discovered that radiation can greatly increase the frequency of mutation – a discovery for which he received a Nobel Prize in 1946.

Discovery of Transformation Principle (1928)

Throughout the biological world, genes generally travel vertically – ie, from parents to children, or from parent cells to daughter cells. Rarely, though, genetic materials can cross from one organism to another – not between parent and child, but between two unrelated strangers. This horizontal exchange of genes is called transformation.

Transformation was discovered by an English bacteriologist named Frederick Griffith (1879-1941). In 1928, Griffith performed a series of experiments using two live strains of pneumococcus bacteria: The rough coat strain was non-lethal, while the smooth coat strain was lethal. Griffith killed the lethal smooth coat strain by applying heat. He then inoculated the mice with a mixture of the dead bacteria and the live rough coat strain which was harmless. He expected the mice to live, but the mice died quickly. The experiment had proved that the genetic make-up of the non-lethal bacteria was altered by debris of the dead bacteria, causing the non-lethal bacteria to become lethal. Griffith autopsied the mice and found that the rough bacteria had changed: they had acquired the smooth coat – the pathogenic-determining factor – merely by contact with the debris from the dead bacteria. The harmless bacteria had somehow “ transformed” into the lethal one.

The One Gene-One Enzyme Hypothesis (1941)

In the 1930s, scientists working in classical genetics were trying to figure out how genes affect the physical characteristics such as eye color in an organism. Two scientists, George Beadle (1903-89) and Edward Tatum (1909-75), had developed evidence that eye color, which is heritable, is affected by a series of genetically produced chemicals. But the complexity of flies makes it difficult to show a link between specific genes and their chemical products.

In 1941, they turned to experiment on a bread mold. The fungus has a short life cycle with a simple chromosomal structure. In the experiment, Beadle and Tatum first irradiated numerous bread molds, producing molds with

mutant genes. They then crossed these mutants with ordinary bread molds to create more mutants. Genetic crosses revealed that every mutant was defective in only one gene.

For a bread mold to grow, all its metabolic functions have to be intact. If a mutation inactivates even one function, the mold could not grow. Beadle and Tatum used this technique to track the missing metabolic function in every mutant. They noted that every mutant was missing a single metabolic function, corresponding to the activity of a single protein enzyme. In other words, the mutation in one gene was associated with the missing of one enzyme.

In this experiment, Beadle and Tatum had discovered the " one gene-one enzyme hypothesis." The hypothesis says one gene directly produces one enzyme, which consequently affects an individual step in a metabolic pathway.

Reconciliation of genetics with Other Fields of Biology

This chapter tries to reconcile the concepts in genetics to the various fields of biology. These reconciliations attempt to explain nature's past, present and future through the lens of the gene. Evolution describes nature's past. Variation describes its present. And embryogenesis attempts to capture the future.

1. Genes had to explain the phenomenon of variation

The question is: How could discrete units of heredity explain that human heights, for instance, do not have six discrete sizes but seemingly 6 billion continuous variants?

The answer was provided by an English mathematician Ronald Fisher (1890-1962) in his paper " The Correlation between Relatives on the Supposition of Mendelian Inheritance," published in 1918. Fisher suggested that real-world traits such as height resulted from genes with multiple states, not a single gene with two states. Using mathematical modeling, he showed that one could generate nearly perfect continuity in phenotype on large populations.

2. Genes had to explain evolution

The question is: What causes species to change?

Answer: Mutation creates variations. A mutation is a change in the gene material. Mutations result from errors during DNA replication or other types of damage to DNA. The changes in the gene created changes in forms that could be selected by natural forces.

3. Genes had to explain development

The question is: How could individual units of instruction prescribe the code to create a mature organism out of an embryo? See section 3. 5: From Genes to Genesis.

4. Reconciliation between Genotypes and Phenotypes

We are all unique. Even monozygotic twins, who are genetically identical, always have variation in the way they look and act. The observable physical characteristics of an individual organism are determined by the genetic make-up, environmental influences, change, and other factors:

Genotype + environment + triggers + chance = phenotype