

“The linear arrangement of six sex-linked factors in drosophila, as shown by their mode of association” (1913), by Alfred Henry Sturtevant

In 1913, Alfred Henry Sturtevant published the results of experiments in which he showed how genes are arranged along a chromosome. Sturtevant performed those experiments as an undergraduate at Columbia University, in New York, New York, under the guidance of Nobel laureate Thomas Hunt Morgan. Sturtevant studied heredity using *Drosophila*, the common fruit fly. In his experiments, Sturtevant determined the relative positions of six genetic factors on a fly's chromosome by creating a process called gene mapping. Sturtevant's work on gene mapping inspired later mapping techniques in the twentieth and twenty-first centuries, techniques that helped scientists identify regions of the chromosome that when mutated cause organisms to develop abnormally and to create treatments to cure those kinds of disorders.

Throughout the early 1900s, many scientists studied the physical materials and processes that control heredity. In 1902, researchers Theodor Boveri working in Germany and Walter Sutton working in the US each proposed that chromosomes, the threadlike structures found in the nucleus of cells, carry the physical materials that underlie heredity. Although Boveri and Suttons' hypotheses were later supported, many scientists initially rejected or were skeptical of their theory. Morgan was among those skeptics. In 1910, Morgan published an article outlining his disagreements. However, later that year, he published research results that provided experimental evidence that physical heritable factors, or genes, are found on chromosomes.

After that experiment, Morgan and the researchers in his laboratory at Columbia University continued to learn more about the processes that control heredity. Morgan began studying a process called crossing over, or recombination, which occurs between two of the paired chromosomes in the gamete cells of organisms. During crossing over, one of the paired chromosomes, inherited from that father, comes together and exchanges genetic information with its chromosome pair, which was inherited from the mother. That exchange of information forms two new chromosomes that contain a mix of paternal and maternal genetic information. A mixed chromosome is called a recombinant. As Morgan, Sturtevant, and the rest of Morgan's research team showed, bits of the chromosomes, which they called factors and later called genes, were organized along chromosomes in some way.

As a result of that organization, in 1911, Morgan hypothesized that the likelihood of any two factors crossing over together depended on how far apart they were on the chromosome. From what Morgan and other scientists had observed, the location of genetic factors that crossed over seemed random. Given that randomness, Morgan hypothesized that the farther apart any two factors were on a chromosome, the more likely they were to be separated by recombination. In other words, factors near each other on a chromosome were more likely to remain together when crossing over than were factors that were farther apart. Morgan further proposed that the frequency of recombination between any two factors was proportional to the distance they were separated on the chromosome.

Later that same year, in 1911, Morgan gave recombination data to Sturtevant, an undergraduate researcher in Morgan's lab. Morgan had studied *Drosophila* and had observed the frequency of recombination between various factors controlling eye color, body color, and wing shape. According to Sturtevant, he realized that those frequencies could be used to create a genetic map of where factors were located on chromosomes. Sturtevant reported that he went home that night and, to the neglect of his homework, determined the order in which the factors were arranged along the

chromosome. Over the next several years, Sturtevant performed further experiments to validate his hypothesized arrangement. In 1913, he published his results in the *Journal of Experimental Zoology*. Sturtevant's article was titled "The linear arrangement of six sex-linked factors in *Drosophila*, as shown by their mode of association."

In his experiments, Sturtevant obtained flies with six different types of genetic factors, some of which Morgan had discovered among the flies he had bred in his lab. Sturtevant named the different factors B, C, O, P, R, and M. In developing flies, those factors affected the flies' eye color, body color, and wing shape. Previously, scientists had observed that C and O never appeared to recombine, meaning that they always appeared together in the same fly. Sturtevant treated those factors as if they shared the same location on a chromosome, and called them CO throughout his research report.

Sturtevant theorized that if genetic factors were arranged linearly across the chromosome, he could deduce the order of those factors by determining all of the distances between pairs of factors. Sturtevant described the logic in his article. He stated that if there were three hypothetical genetic factors arranged in order, A, B, and C, the distance between A-C would be the sum of the distances between A-B and B-C.

With that logic, Sturtevant developed a method to determine the relative distances between the six individual genetic factors. According to Morgan's hypothesis, the distance between two factors was related to the frequency with which those factors recombined. In other words, the more likely two factors appeared together in a fly, the more likely they were located close to each other on the chromosome. Therefore, Sturtevant sought to determine how often each of the factor pairs recombined, a measure called the recombination frequency, in order to find the respective distances between those pairs. He mated two flies that had chromosomes with differences in two of their genetic factors and observed the number of recombinants that were found in later generations of the offspring. Sturtevant used that method for all pairs of factors. For instance, he observed how many times there was recombination between B and CO, B and P, B and M, B and O, CO and P, etc. He then calculated the recombination frequency between each of those pairs of factors by dividing the respective number of recombinant offspring by the total number of offspring.

After calculating the recombination frequencies, Sturtevant used the data to determine the arrangement of the factors on the chromosome. By assuming that factors with the largest recombination frequencies were located the farthest apart, Sturtevant determined which factors were on opposite ends of the chromosome. He further analyzed the recombination data to determine the positioning of the factors between the two outermost factors. The data supported Sturtevant's theory that the factors were arranged linearly on the chromosome. Furthermore, Sturtevant found that the specific order of the factors was B, CO, P, R, and M.

Sturtevant recognized that the distances between the factors may not be entirely accurate due to a process he called double recombination. Double recombination occurs when paired chromosomes recombine two times, which can cause the resulting offspring to appear as if recombination never occurred. Sturtevant and other members of Morgan's lab later studied double recombination to determine how to make more accurate genetic maps. Despite not accounting for double recombination, Sturtevant's arrangement was validated by later research.

Throughout the twentieth century, other researchers modified Sturtevant's method to develop more accurate forms of gene mapping that were eventually used to map human genomes. In 1984, an international collaboration of researchers called the Human Genome Project began mapping the human genome. Over the following decades, researchers working on the Human Genome Project identified portions of the genome. In 2001, they published a complete first draft of the entire human genome.

The development of gene mapping techniques also enabled scientists to create a method, called gene therapy, of treating and preventing diseases. Gene therapy often relied on identifying genes that cause or promote disease, finding their location, removing them, and then replacing them with different genes. In 1990, scientists at the National Institute of Health headquartered in Bethesda, Maryland, conducted the first human application of gene therapy to cure disease. They successfully treated a four-year-old girl that had adenosine deaminase deficiency, a disease that causes infants

to be born with severe immunodeficiency. Scientist's later developed treatments for other genetic diseases, including cancer, cystic fibrosis, acquired immune deficiency syndrome, and Alzheimer's disease.

Sturtevant's 1913 experiments provided scientists with an early method of gene mapping that was later used to treat diseases.

Sources

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