Complementation refers to a relationship between two different strains of an organism which both have homozygous recessive mutations that produce the same phenotype (for example, a change in wing structure in flies) but which do not reside on the same (homologous) gene.

These strains are true breeding for their mutation. If, when these strains are crossed with each other, some offspring show recovery of the wild-type phenotype, they are said to show “genetic complementation”. When this occurs, each strain’s haploid supplies a wild-type allele to “complement” the mutated allele of the other strain’s haploid, causing the offspring to have heterozygous mutations in all related genes. Since the mutations are recessive, the offspring will display the wild-type phenotype.

A complementation test (sometimes called a “cis-trans” test) refers to this experiment, developed by American geneticist Edward B. Lewis. It answers the question: "Does a wild-type copy of gene X rescue the function of the mutant allele that is believed to define gene X?". If there is an allele with an observable phenotype whose function can be provided by a wild type genotype (i.e., the allele is recessive), one can ask whether the function that was lost because of the recessive allele can be provided by another mutant genotype. If not, the two alleles must be defective in the same gene. The beauty of this test is that the trait can serve as a read-out of gene function even without knowledge of what the gene is doing at a molecular level.
Figure: Complementation Test: Example of a complementation test. Two strains of flies are white eyed because of two different autosomal recessive mutations which interrupt different steps in a single pigment-producing metabolic pathway. Flies from Strain 1 have complementary mutations to flies from Strain 2 because when they are crossed the offspring are able to complete the full metabolic pathway and thus have red eyes.

Complementation arises because loss of function in genes responsible for different steps in the same metabolic pathway can give rise to the same phenotype. When strains are bred together, offspring inherit wildtype versions of each gene from either parent. Because the mutations are recessive, there is a recovery of function in that pathway, so offspring recover the wild-type phenotype. Thus, the test is used to decide if two independently derived recessive mutant phenotypes are caused by mutations in the same gene or in two different genes. If both parent strains have mutations in the same gene, no normal versions of the gene are inherited by the offspring; they express the same mutant phenotype and complementation has failed to occur.

In other words, if the combination of two haploid genomes containing different recessive mutations yields a mutant phenotype, then there are three possibilities: Mutations occur in the same gene; One mutation affects the expression of the other; One mutation may result in an inhibitory product. If the combination of two haploid genomes containing different recessive mutations yields the wild type phenotype, then the mutations must be in different genes.

Key Points

- A complementation test answers the question: "Does a wild-type copy of gene X rescue the function of the mutant allele that is believed to define gene X? ".
- Complementation arises because loss of function in genes responsible for different steps in the same metabolic pathway can give rise to the same phenotype.
- When strains are bred together, offspring inherit wildtype versions of each gene from either parent.
Key Terms

- **Complementation**: In genetics, complementation refers to a relationship between two different strains of an organism which both have homozygous recessive mutations that produce the same phenotype (for example, a change in wing structure in flies) but which do not reside on the same (homologous) gene.

- **Mutation**: Any heritable change of the base-pair sequence of genetic material.

- **Homozygous**: of an organism in which both copies of a given gene have the same allele.