Genotype Variation, Mutations and Recombination

Genotype and variation

The **genotype** is the part (DNA sequence) of the genetic makeup of a cell, and therefore of an organism or individual, which determines a specific characteristic (phenotype) of that cell/organism/individual. Genotype is one of three factors that determine phenotype, the other two being inherited epigenetic factors, and non-inherited environmental factors. DNA mutations which are acquired rather than inherited, such as cancer mutations, are not part of the individual's genotype; hence, scientists and physicians sometimes talk for example about the (geno)type of a particular cancer, that is the genotype of the disease as distinct from the diseased.

An example of how genotype determines a characteristic is petal color in a pea plant. The genotype of an organism is the inherited map it carries within its genetic code. The genetic constitution of an organism is referred to as its genotype, such as the letters Bb. (B - dominant genotype and b - recessive genotype). Zygosity is the degree of similarity of the alleles for a trait in an organism.

Most eukaryotes have two matching sets of chromosomes; that is, they are diploid. Diploid organisms have the same loci on each of their two sets of homologous chromosomes, except that the sequences at these loci may differ between the two chromosomes in a matching pair and that a few chromosomes may be mismatched as part of a chromosomal sex-determination system. If both alleles of a diploid organism are the same, the organism is homozygous at that locus. If they are different, the organism is heterozygous at that locus. If one allele is missing, it is hemizygous, and, if both alleles are missing, it is nullizygous.

The DNA sequence of a gene often varies from one individual to another. Those variations are called alleles. While some genes have only one allele because there is low variation, others have only one allele because deviation from that allele can be harmful or fatal. But most genes have two or more alleles. The frequency of different alleles varies throughout the population. Some genes may have two alleles with equal distribution. For other genes, one allele may be common, and another allele may be rare. Sometimes, one allele is a disease-causing variation while the other allele is healthy. Sometimes, the different variations in the alleles make no difference at all in the function of the organism. In diploid organisms, one allele is inherited from the male parent and one from the female parent. **Zygosity** is a description of whether those two alleles have identical or different DNA sequences. In some cases the term "zygosity" is used in the context of a single chromosome.

Mutations

A **mutation** is the permanent alteration of the nucleotide sequence of the genome of an organism, virus, or extrachromosomal DNA or other genetic elements. Mutations result from errors during DNA replication or other types of damage to DNA, which then may undergo error-prone repair (especially microhomology-mediated end joining), or cause an error during other forms of repair, or else may cause an error during replication (translesion synthesis). Mutations may also result from insertion or deletion of segments of DNA due to mobile genetic elements.

Mutations may or may not produce discernible changes in the observable characteristics (phenotype) of an organism. Mutations play a part in both normal and abnormal biological processes including: evolution, cancer, and the development of the immune system, including junctional diversity.

Diploid organisms (e.g., humans) contain two copies of each gene—a paternal and a maternal allele. Based on the occurrence of mutation on each chromosome, we may classify mutations into three types.

- A **heterozygous mutation** is a mutation of only one allele.
- A **homozygous mutation** is an identical mutation of both the paternal and maternal alleles.
- **Compound heterozygous mutations** or a genetic compound consists of two different mutations in the paternal and maternal alleles.

A **wild type** or homozygous non-mutated organism is one in which neither allele is mutated.

Mutations by impact on protein sequence

- A **frameshift mutation** is a mutation caused by insertion or deletion of a number of nucleotides that is not evenly divisible by three from a DNA sequence. Due to the triplet nature of gene expression by codons, the insertion or deletion can disrupt the reading frame, or the grouping of the codons, resulting in a completely different translation from the original. The earlier in the sequence the deletion or insertion occurs, the more altered the protein produced is. In contrast, any insertion or deletion that is evenly divisible by three is termed an in-frame mutation
- A **nonsense mutation** is a point mutation in a sequence of DNA that results in a premature stop codon, or a nonsense codon in the transcribed mRNA, and possibly a truncated, and often nonfunctional protein product. (See Stop codon.)
- **Missense mutations** or nonsynonymous mutations are types of point mutations where a single nucleotide is changed to cause substitution of a different amino acid. This in turn can render the resulting protein nonfunctional. Such mutations are responsible for diseases such as Epidermolysis bullosa, sickle-cell disease,

and SOD1-mediated ALS.

- **A neutral mutation** is a mutation that occurs in an amino acid codon that results in the use of a different, but chemically similar, amino acid. The similarity between the two is enough that little or no change is often rendered in the protein. For example, a change from AAA to AGA will encode arginine, a chemically similar molecule to the intended lysine.
- **Silent mutations** are mutations that do not result in a change to the amino acid sequence of a protein, unless the changed amino acid is sufficiently similar to the original. They may occur in a region that does not code for a protein, or they may occur within a codon in a manner that does not alter the final amino acid sequence. The phrase silent mutation is often used interchangeably with the phrase synonymous mutation; however, synonymous mutations are a subcategory of the former, occurring only within exons (and necessarily exactly preserving the amino acid sequence of the protein). Synonymous mutations occur due to the degenerate nature of the genetic code.

Recombination

Genetic recombination is the production of offspring with combinations of traits that differ from those found in either parent. In eukaryotes, genetic recombination during meiosis can lead to a novel set of genetic information that can be passed on from the parents to the offspring. Most recombination is naturally occurring.

During meiosis in eukaryotes, genetic recombination involves the pairing of homologous chromosomes. This may be followed by information transfer between the chromosomes. The information transfer may occur without physical exchange (a section of genetic material is copied from one chromosome to another, without the donating chromosome being changed); or by the breaking and rejoining of DNA strands, which forms new molecules of DNA.

Recombination may also occur during mitosis in eukaryotes where it ordinarily involves the two sister chromosomes formed after chromosomal replication. In this case, new combinations of alleles are not produced since the sister chromosomes are usually identical. In meiosis and mitosis, recombination occurs between similar molecules of DNA (homologs). In meiosis, non-sister homologous chromosomes pair with each other so that recombination characteristically occurs between non-sister homologues. In both meiotic and mitotic cells, recombination between homologous chromosomes is a common mechanism used in DNA repair.

Genetic recombination and recombinational DNA repair also occurs in bacteria and archaea, which use asexual reproduction. Recombination can be artificially induced in laboratory (in vitro) settings, producing recombinant DNA for purposes including vaccine development.

V(D)J recombination in organisms with an adaptive immune system is a type of site-specific genetic recombination that helps immune cells rapidly diversify to recognize and adapt to new pathogens.