Types of mutations (gene variants)

A mutation is a permanent change in a gene's DNA sequence. DNA is read three bases at a time (codons). Types as MedlinePlus Genetics (US National Library of Medicine) defines them.

Type	What changes	Effect on the protein
Substitution	one nucleotide replaced by another	missense: swaps one amino acid, may alter function; nonsense: makes a stop signal, the protein is cut short; silent: same amino acid, no change
Insertion	one or more nucleotides added	frameshift if not a multiple of three; otherwise extra amino acids
Deletion	at least one nucleotide removed (large ones can remove whole genes)	frameshift if not a multiple of three; otherwise missing amino acids
Indel	a deletion and an insertion at the same spot	by the net change
Duplication	a stretch copied and repeated next to the original	extra sequence; frameshift if not a multiple of three
Inversion	a stretch replaced by the same sequence reversed	the codons inside are scrambled
Frameshift	an insertion, deletion or duplication that shifts the reading frame	every amino acid downstream changes; usually a non-working protein
Repeat expansion	more copies of a short repeat (three or four nucleotides)	a longer protein or a disrupted gene

Frameshift in words: THE CAT ATE THE RAT, delete the first T: HEC ATA TET HER AT. Everything after the change is wrong.

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Harmful, beneficial, neutral; germline and somatic

Effect	Example	The facts (MedlinePlus)
Harmful	sickle cell disease	one HBB gene variant makes hemoglobin S; autosomal recessive; about 100,000 Americans, 1 in 500 African Americans, 1 in 1,000 to 1,400 Hispanic Americans; millions worldwide
Beneficial	lactase persistence	a change in the regulatory element inside MCM6 that controls LCT keeps lactase switched on after infancy; autosomal dominant; about 65% of people are lactase nonpersistent (70 to 100% East Asian descent, about 5% Northern European)
Neutral	silent substitutions; changes between genes	the same amino acid, or no protein affected: most of the differences between two people's genomes

	Germline	Somatic
Where	an egg or sperm	a body cell after conception
Cells affected	every cell of the child	that cell's descendants only
Inherited?	yes	no
Example	sickle cell disease; lactase persistence	most cancers; a sunburnt skin cell

Causes: copying errors during replication, radiation (UV, X-rays), chemicals that react with DNA, some viruses; spontaneous when there is no outside cause. A mutagen raises the rate.

Practice

[ ] 1. GCA (alanine) becomes GCG (alanine). Type and effect?
[ ] 2. CAG (glutamine) becomes TAG (stop). Type?
[ ] 3. Two bases are inserted into a coding sequence. Effect on the frame?
[ ] 4. Three bases are deleted. Effect?
[ ] 5. A variant arises in a sperm cell. Germline or somatic?
[ ] 6. Give one harmful, one beneficial and one neutral example.
[ ] 7. Is the sickle cell variant 'in hemoglobin'? Correct the sentence.
[ ] 8. Why are most variants neutral?

Answers

1) silent substitution; none. 2) nonsense. 3) frameshift. 4) one amino acid missing, frame kept. 5) germline. 6) HBB/sickle cell; MCM6 regulatory/lactase persistence; a silent substitution. 7) it is in the HBB gene, which makes beta-globin, part of hemoglobin. 8) most DNA is between genes, and many changes do not alter an essential protein.

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