Variant type	Definition/ notes	Example
Silent variants (synonymous)	-Do not change the amino acid (p.Ala123Ala). -Mostly benign but may impact splicing(exon-intron boundaries) or RNA secondary structure.	CFTR gene, responsible for cystic fibrosis, **Ile507-ATC (normal) ⟶ Ile507-ATT(cystic fibrosis)**. This synonymous variant is known to be a disease causing (cystic fibrosis) although substitution in the codon from ATC to ATT will still encode for Isoleucine in position 507 and it's not an issue of exon-intron boundaries, **its location influence the half-life stability of mRNA thus causing the disease.**
Missense variants (Non-synonymous)	-Change in the amino acid (substitution) -2 types > conservative: new amino acid has similar properties as the the original. > non-conservative: new amino acid has different properties than the original. - may be benign or pathogenic.	**HBB c. 17A>T (p. Glu6Val)** Glutamate [acidic, -ve charged] change to Valine [hydrophobic] at position 6 of HBB gene encoding beta-globin leads to beta-globin protein aggregates ⟶causes **Sickle cell anemia.**
Non-sense variants	-Cause errors in translation. -Change a codon to a termination codon (UAA, UAG, UGA). -Not always pathogenic. - May result in nonsense mediated decay (NMD), truncated protein, or splicing impact. # What determines which one of these two fates will take place is how early the premature stop codon is in that exon, so if no. of nucleotides between the premature termination signal and 3' end of exon is 55 nucleotides or less mRNA will not go through NMD rather the mRNA upstream of the stop signal will be translated and the mRNA downstream	**HBB c. 118C>T (p. Gln39*)** In HBB gene encoding beta-globin, codon CAG encodes for the amino acid at position 39 which is Glutamine, if we substitute C by T ⟶ TAG, on the RNA level ⟶ UAG which is a stop signal ⟶ premature termination codon.

	won't be translated which yields a truncated protein in the cell (incomplete protein) which could be unfunctional or even a harmful protein. And if the no. of nucleotides between the premature termination signal and 3' end of exon is more than 55 nucleotides the cell will recognize the mRNA carrying the premature termination and degrades it (Nonsense mediated decy NMD).	
Frameshift variants	-Cause errors in translation. -Alter the mRNA reading frame. -Often lead to a premature termination codon downstream. -Not always pathogenic	**GJB2 c. 35delG (p. Gly12fs)** GJB2 is a gene responsible for bilateral prelingual sensorineural hearing loss, a mutation at which is mostly inherited in an autosomal recessive fashion. ↳ The most common mutation of GJB2 is deletion of G-nucleotide on the position of c.35 this leads to (p.Gly12fs) which means that a frameshift started at the amino acid no.12 (Glycine) and anything after the glycine also changes. If you compare normal sequence with 35 del G, you will see that glycine no.12 changed to valine and a frameshift due to this variant leads to truncation signal or premature stop codon.
In-frame deletions and insertions	-Deletions or insertions of bases in multiples of 3 (3,6,9,…). -Lead to deletions or insertions of amino acids without altering the reading frame. -May be benign or pathogenic.	**CFTR c.(p. Phe508del - ΔF508)** CFTR phenylalanine deletion (amino acid no.508) c. (p.Phe508del / ΔF508) which is caused by a deletion of the whole codon (TTT) or (UUU) on the mRNA level, and that causes a block in protein processing leading to cystic fibrosis.

Splice site variants	-A genetic alteration in the DNA sequence that occurs at the boundary of an exon and an intron (splice site). This change can disrupt RNA splicing resulting in the loss of exons or the inclusion of introns and an altered protein-coding sequence. # variants that likely impact splicing: -splice donor & acceptor positions (+/- 1,2) destruction of 5'/3' splice consensus sequence, typically leads to exon skipping # variants that may impact splicing: - other positions in splice consensus sequence (+/- 15) - variants affecting 1st and 3rd bases of an exon # other point mutations also have potential to impact splicing	**No examples were mentioned!!**
Regulatory variants	-May be in promoter, enhancer or UTRs -Result in altered protein expression	**HBB c. -101>T** a variant in the promoter of HBB gene encoding for beta-globin leads to decreased expression of β-globin. (c.-101C>T) means that there is a nucleotide substitution C to T 101 nucleotides upstream the first exon.

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