Single Genome-Editing Strategy for Multiple Genetic Disorders

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Why in News?

Recently, a study published in Nature reported a new genome-editing strategy (PERT) that can potentially treat multiple genetic disorders caused by nonsense mutations.

- **Genes –** They are made of DNA (deoxyribonucleic acid).
  - It contains instructions for cell functioning and the characteristics that make a person unique.

Genetic disorders occur when a mutation (a harmful change to a gene, also known as a pathogenic variant) affects an individual's genes. It disrupts the cell's ability to build a complete, functional protein.

- **Genome editing –** Technologies that *give scientists the ability to change an organism's DNA.*
- It allows genetic material to be added, removed, or altered at particular locations in the genome.
- It is also called gene editing. And the best example is CRISPR-Cas9.
- **Background –** A nonsense mutation is a type of genetic mutation where a wrong DNA letter changes a normal codon into a "stop" codon.
  - A codon is a group of 3 DNA/RNA letters that tells the cell which amino acid to add to a protein.
- ***Nonsense mutations account for about one-fourth of all known disease-causing genetic changes.***
  - As it stops protein synthesis early.
- **Mutation-Specific Therapy –** Currently, each mutation requires a separate therapy, making treatment slow and costly.

Genome editing does not involve the introduction of foreign genetic material while genetic engineering does.

- **New Technique –** ***PERT (Prime-Editing-mediated Readthrough of premature***

Termination codons).

- This technique uses a normal tRNA (transfer RNA) to create a suppressor tRNA permanently.
    - The suppressor tRNA bypasses early stop signals so a full protein is made.
- Hence, the PERT technique becomes applicable to many rare genetic diseases.

Protein synthesis happens when information passes from DNA to mRNA to tRNA and then to the ribosome.

- **Mechanism –** Human cells contain 418 tRNA genes. Leucine, arginine, tyrosine, and serine tRNAs are identified as promising candidates among them.
- **Prime Editing –** tRNA genes are hard to edit, so scientists used a special gene-editing method called prime editing with many guide RNAs to find the right spot.
- They also *developed a new editing enzyme called PE6c*, which made the process more accurate and effective.
- **Key Results – Editing efficiency – *60–80% that is higher than the standard repair method at 10–20%.***
- Restored enzyme activity in Batten disease, Tay-Sachs disease, etc. (17–70% of normal).
- No major off-target effects or toxicity observed.
- **Challenges –** Issues in delivery to different tissues, long-term safety, and durability.
- Clinical translation still requires further validation.
- **Significance –** Offers a single universal therapeutic platform for precision gene therapy with broad clinical applications in rare genetic disorders.

Quick Fact

CRISPR-Cas9
• **CRISPR –** It stands for Clustered Regularly Interspaced Short Palindromic Repeats. • **CRISPR-Cas9 –** Most prominent technology that enables editing parts of the genome by removing, adding or altering sections of the DNA sequence. • **Components –** Consists of two key molecules that introduce a change mutation into the DNA. - **Cas9 –** An enzyme that acts as a pair of 'molecular scissors' that can cut the two strands of DNA at a specific location in the genome. - **Guide RNA (gRNA) –** The gRNA is designed to find and bind to a specific sequence in the DNA. • **Mechanism –** • The Cas9 follows the guide RNA to the same location in the DNA sequence and makes a cut across both strands of the DNA. • At this stage, the cell recognises that the DNA is damaged and tries to repair it. • Can be used to introduce changes to one or more genes in the genome of a cell of interest. • The technology replicates a natural defence mechanism in some bacteria that uses a similar method to protect itself from virus attacks.

Reference

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