4. Genome-Editing Strategy- Science & Technology

A study in Nature recently revealed that researchers have developed a method to address many nonsense mutation diseases using a single genome-editing strategy

Overview of the PERT Approach

1. Prime-Editing-mediated Readthrough of Premature Termination Codons (PERT) is an advanced genome engineering strategy designed to address diseases caused by nonsense mutations.
2. Instead of directly correcting each individual mutation, PERT reprogrammes one of the cell's endogenous genes into a molecular tool that overrides premature stop signals.
3. The approach enables the cell's protein synthesis machinery to ignore faulty stop codons and continue translation, thereby restoring production of full-length, functional proteins.
4. This represents a proof-of-concept for a gene-agnostic therapy, meaning it can potentially be applied across multiple diseases caused by similar types of mutations rather than targeting a single gene disorder.
5. The strategy could reduce the need for designing disease-specific therapies for every individual nonsense mutation.

Genetic Disorders and Nonsense Mutations

Nature of Genetic Disorders

1. Genetic disorders arise from errors in the DNA sequence that alter gene expression or protein function.
2. Even a single nucleotide change can produce severe physiological consequences if it disrupts protein synthesis.
3. Many rare and inherited disorders stem from such small but functionally significant mutations.

What is a Nonsense Mutation?

A nonsense mutation occurs when a single incorrect DNA base introduces a premature termination codon (PTC) in the coding sequence of a gene. During translation, the ribosome encounters this premature stop signal and halts protein synthesis earlier than intended. The resulting truncated protein is often non-functional or unstable.

This leads to absence or deficiency of essential proteins such as-

1. Enzymes
2. Structural proteins
3. Transporters
4. Signalling molecules

Disease Burden of Nonsense Mutations

Nonsense mutations account for approximately 25% of known disease-causing genetic alterations.

Disorders associated with nonsense mutations include-

1. Cystic fibrosis
2. Duchenne muscular dystrophy
3. Batten disease
4. Certain forms of cancer
5. Various metabolic and neurological disorders

Each mutation typically disrupts a different gene and halts protein synthesis at a distinct location. Consequently, conventional therapy development requires mutation-specific design, testing, and regulatory approval. This process is time-consuming, costly, and inefficient for rare diseases with small patient populations.

Therapeutic Limitations of Current Approaches

1. Most gene therapies are tailored to specific genes and specific mutations.
2. Designing separate treatments for each nonsense mutation increases regulatory burden and development costs.
3. Rare diseases face limited commercial incentives, further slowing therapeutic innovation.
4. There is a need for mutation-type-based therapies rather than gene-specific solutions.

Understanding the Genome

The genome refers to the complete set of DNA instructions within a cell.

In humans, the genome consists of-

1. 23 pairs of chromosomes located in the nucleus
2. A small mitochondrial chromosome

The genome contains all the information required for-

1. Development
2. Growth
3. Cellular function
4. Reproduction

Genes are segments of DNA that encode proteins, which carry out most biological functions. Mutations alter the nucleotide sequence of genes, potentially affecting protein synthesis and function.

Genome Editing Technologies

Concept

Genome editing technologies enable targeted modification of DNA sequences. These tools function like molecular scissors that cut DNA at specific locations.

After cutting, scientists can-

1. Remove defective DNA
2. Insert corrected sequences
3. Replace mutated segments

Evolution of Genome Editing

Early genome editing tools were developed in the late 20th century. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), developed in 2009, revolutionised genome editing by making it-

1. Simpler
2. Faster
3. More affordable
4. More precise

CRISPR-Cas systems allow programmable targeting of DNA sequences. Prime editing is a more refined evolution of CRISPR technology, enabling precise base modifications without creating double-stranded DNA breaks.

Gene Therapy

Definition

Gene therapy involves using genetic material to treat, prevent, or cure diseases.

It can function by-

1. Replacing faulty genes
2. Deactivating harmful genes
3. Introducing new genes to restore normal function

Types of Gene Therapy

Germline Therapy

1. Targets reproductive cells such as sperm or eggs.
2. Genetic changes are heritable and passed to future generations.
3. Raises significant ethical and regulatory concerns.
4. Currently prohibited or tightly regulated in most countries.

Somatic Therapy

1. Targets non-reproductive cells such as muscle, liver, or blood cells.
2. Changes affect only the treated individual.
3. Considered ethically more acceptable and widely pursued in clinical research.
4. Most current gene therapies fall under this category.

Significance of PERT as a Gene-Agnostic Strategy

1. PERT shifts the paradigm from correcting each gene individually to targeting a common mutation mechanism.
2. By enabling readthrough of premature stop codons, it could potentially treat multiple diseases caused by nonsense mutations.
3. This reduces duplication in therapy design.
4. It accelerates translational research for rare diseases.
5. It enhances cost-efficiency in therapeutic development.
6. It represents an example of next-generation precision medicine.

Ethical and Regulatory Considerations

Genome editing technologies raise concerns regarding-

1. Off-target effects
2. Long-term safety
3. Germline modifications
4. Equity of access
5. Potential misuse

Regulatory oversight must ensure-

1. Rigorous clinical trials
2. Transparent reporting
3. Long-term follow-up studies

Ethical governance frameworks are essential to balance innovation and safety.

Broader Implications

Advances in gene editing may extend beyond human health to-

1. Agricultural biotechnology

2. Conservation biology
3. Synthetic biology
4. Industrial biotechnology

However, applications must be guided by-

1. Scientific rigor
2. Ecological sensitivity
3. Social acceptance
4. International regulatory coordination

Conclusion

Prime-Editing-mediated Readthrough of Premature Termination Codons (PERT) represents a promising innovation in genetic medicine. By targeting the mechanism of nonsense mutations rather than individual genes, it offers a scalable and potentially cost-effective therapeutic approach for a wide range of rare diseases.

However, the translation of such technologies into clinical practice requires strong ethical safeguards, robust regulatory oversight, and interdisciplinary collaboration. A balanced approach that integrates scientific advancement with responsible governance is essential to ensure safe and equitable use of emerging genetic technologies.

Source- https-//www.thehindu.com/sci-tech/science/single-genome-editing-strategy-pert-promises-treat-multiple-disorders/article70638055.ece