Human Knockout Genes

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Why in news?

A recent study from Pakistan has identified naturally occurring 'human knockout genes' on an unprecedented scale.

- **Knockout gene** – A gene whose function is effectively switched off because loss-of-function (LoF) mutations disrupt its activity.
- **Human knockout genes** – When both copies (maternal and paternal) of a gene carry disruptive variants, the person may have little or no functional protein from that gene.
    - Consanguinity increases the likelihood of inheriting the same rare recessive variant from both parents.

Consanguinity is a blood relationship between two people who share a common ancestor.

- **Medical importance –** It helps identify
    - Whether a gene causes disease when lost.
    - Whether gene loss has beneficial effects.
    - Whether a gene is a good or bad drug target.
- Lacking functional copies of APOC3 had substantially lower fasting triglyceride concentrations and a smaller rise in triglycerides after consuming a fat-rich meal.
    - ***olezarsen***, a medicine designed to reduce APOC3 production.
- loss of the gene PLA2G7 substantially reduced Lp-PLA2 levels (high levels of which are associated with an increased risk of coronary artery disease).
    - ***darapladib***, designed to inhibit the same enzyme, had already failed to improve outcomes in large cardiovascular trials.
- **Recent study** – Analysis of 1,73,303 people identified human knockouts involving 6,476 genes, demonstrating the value of population-scale genomics.
    - The study also demonstrated the value of 'recall by genotype'.
- **Lessons for medicine**
    - The clinical implications go beyond rare genetic diseases.
    - Loss of the gene CIDEB was associated with lower liver enzyme concentrations and a lower risk of fatty liver disease, making the pathway potentially interesting for drug development.

    - The gene LRRK2 is an important therapeutic target in Parkinson's disease.

- **India relevance** – India has similar reasons for investing in population-specific genomics.
- GenomeIndia has already sequenced 10,000 genomes from 83 population groups, providing an important reference map of Indian genetic variation.
- **Key limitation** – A person may naturally live their whole life without a working gene, but a drug may only block that gene partly and only after adulthood.
- **Significance** – Researchers naturally can observe what happens when a particular gene is absent.

Reference

The Hindu| Human Knockout Genes