

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 CIDEA 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](#)

