REVISITING HUMAN KNOCKOUTS IN A NEW LIGHT

Consanguinity is a major force shaping the human genome in certain populations. In Pakistan, an estimated 60% of marriages occur between first cousins, leading to widespread homozygosity. This creates unique opportunities to discover recessive genetic effects, not only for rare Mendelian diseases, but also for common complex conditions.

The 2017 Nature study by Saleheen et al.[1] pioneered this approach, analyzing over 10,000 individuals from a Pakistani cohort. They identified more than 1,300 genes "knocked out" in humans, some with clear biological effects, like dramatically reduced triglyceride responses in APOC3 knockouts.

In 2025, Heng et al.[2] followed through. Using the Genes & Health cohort of 44,000 British Pakistanis and Bangladeshis, similarly characterized by high consanguinity, they tested for recessive associations across 898 diseases. The study identified 185 genetic regions strongly linked to disease, many of which would have gone unnoticed using the usual methods that only look for effects from a single mutated copy of a gene.

Highlights include:

- A protective missense variant in SGLT4 against hypertension.
- A recessive risk variant in PNPLA3 for fatty liver disease.
- Several new hits for thalassemia and bilirubin metabolism.

The two studies—eight years apart—tell a coherent story. What was first a bold idea has now become a proven method for mapping human gene function through autozygosity.

1. https://www.nature.com/articles/nature22034
2. https://www.cell.com/ajhg/fulltext/S0002-9297(25)00141-7