GENE KNOCKOUTS IN HUMANS

In the mouse, knocking out a gene has long been the standard way to find out what it actually does. In humans, deliberate gene knockouts are obviously off-limits, but nature sometimes does the experiment for us. In populations where consanguineous marriages are common, long runs of homozygosity enrich the pool of rare variants carried in biallelic state, producing living, phenotyped adults in whom both copies of a gene are inactivated. Pakistan and Bangladesh (~60% first-cousin marriages) are among the most informative settings, and the large diaspora from these regions in the UK has made British South Asians a particularly attractive cohort for this kind of genetics.
Saleheen et al. (1) first laid out this rationale in PROMIS (Pakistan Risk of Myocardial Infarction Study), a Pakistani case-control cohort, uncovering homozygous loss-of-function (LoF) mutations in >1,300 genes and sketching the roadmap for a "human knockout project."
Heng et al. (2) then showed in the British Pakistani and Bangladeshi Genes & Health cohort (G&H project) that this same autozygosity unmasks 185 recessive loci for common diseases; signals routinely missed by additive genome-wide association studies (GWAS).
The new Nature Genetics paper (March 2026) from the G&H team delivers the full exome resource: whole-exome sequencing of 44,028 participants linked to longitudinal electronic health records from the UK National Health Service (NHS), now publicly available.
Key findings:
a) 2,991 genes with biallelic predicted loss-of-function or predicted damaging genotypes, 546 of them novel human knockouts.
b) >100 novel gene–phenotype associations from exome-wide association on 645 traits derived from electronic health records (EHR) and meta-analyses with UK Biobank.
c) Drugs targeting genes with adult human knockouts are ~2.2× more likely to progress beyond phase 1 clinical trials, a compelling argument for naturally occurring human LoF variants in drug target validation.
From PROMIS to G&H: proof of concept → recessive signals beyond GWAS → an open exome resource already delivering novel biology and drug-target insight. For rare-variant and translational genetics in non-European ancestries, G&H is becoming hard to ignore.

1. https://www.nature.com/articles/nature22034
2. https://www.cell.com/ajhg/fulltext/S0002-9297(25)00141-7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0002929725001417%3Fshowall%3Dtrue
3. https://www.nature.com/articles/s41588-026-02553-7