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Health and population effects of rare gene knockouts in adult humans with related parents

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Examining complete gene knockouts within a viable organism can inform on gene function. We sequenced the exomes of 3222 British Pakistani-heritage adults with high parental relatedness, discovering 1111 rare-variant homozygous genotypes with predicted loss of gene function (knockouts) in 781 genes. We observed 13.7% fewer than expected homozygous knockout genotypes, implying an average load of 1.6 recessive-lethal-equivalent LOF variants per adult. Linking genetic data to lifelong health records, knockouts were not associated with clinical consultation or prescription rate. In this dataset we identified a healthy *PRDM9* knockout mother, and performed phased genome sequencing on her, her child and controls, which showed meiotic recombination sites localized away from *PRDM9*-dependent hotspots. Thus, natural LOF variants inform upon essential genetic loci, and demonstrate *PRDM9* redundancy in humans.

Complete gene knockouts, typically caused by homozygous loss of function (LOF) genotypes, have helped identify the function of many genes, predominantly through studies in model organisms and of severe Mendelian-inherited diseases in humans. However, information on the consequences of knocking out most genes in humans is still missing. Naturally occurring complete gene knockouts offer the opportunity to study the effects of lifelong germline gene inactivation in a living human. A survey of LOF variants in adult humans demonstrated ~100 predicted LOF genotypes per individual, describing around ~20 genes carrying homozygous predicted LOF alleles and hence likely completely inactivated (*1*). Almost all these homozygous genotypes were at common variants with allele frequency >1%, in genes likely to have weak or neutral effects on

fitness and health (*1*). In contrast, rare predicted LOF genotypes were usually heterozygous and thus of uncertain overall impact on gene function. A large exome sequencing aggregation study (ExAC), of predominantly outbred individuals, identified 1775 genes with homozygous predicted LOF genotypes in 60,706 individuals (*2*). Furthermore, 1171 genes with complete predicted LOF were identified in 104,220 Icelandic individuals (*3*), and modest enrichment for homozygous predicted LOF genotypes shown in Finnish individuals (*4*). However, even in these large samples, homozygous predicted LOF genotypes tend to be for variants at moderate (around 1%) allele frequency, and hence these approaches will not readily assess knockouts in most genes, which are lacking such variants.

Here, we identify knockouts created by rare homozygous

predicted loss of function (rhLOF) variants by exome sequencing 3222 Pakistani-heritage adults living in the UK who were ascertained as healthy, type 2 diabetic, or pregnant (5). These individuals have a high rate of parental relatedness (often with parents who are first cousins) and thus a substantial fraction of their autosomal genome occurs in long homozygous regions inferred to be identical by descent from a recent common ancestor (autozygous). We link the genotype to healthcare and epidemiological records, with the aims of (i) describing the properties of, and assessing the health effects of, naturally occurring knockouts in an adult population, (ii) understanding the architecture of gene essentiality in the human genome, through the characterization of the population genetics of LOF variants, and (iii) studying in detail a knockout of the *PRDM9* gene which plays a role in human meiotic recombination (6).

On average, 5.6% of the coding genome was autozygous, much higher than that in outbred European heritage populations (Fig. 1A and fig. S4). We identified, per subject, on average 140.3 non-reference predicted LOF genotypes comprising 16.1 rare (minor allele frequency <1%) heterozygotes, 0.34 rare homozygotes, 83.2 common heterozygotes and 40.6 common homozygotes. Nearly all rhLOF genotypes were found within autozygous segments (94.9%) (5), and the mean number of rhLOF per individual was proportional to autozygosity (Fig. 1B). Overall we identified 1111 rhLOF genotypes at 847 variants (575 annotated as LOF in all GENCODE-basic transcripts) in 781 different protein-coding genes (Fig. 1C) (5) in 821 individuals. Autozygous segments were observed across all exomic sites with a density distribution not significantly different from random (5) (Shapiro-Wilks $P = 0.112$). From these values we estimate that 41.5% of individuals with 6.25% autozygosity (expected mean for individual with first-cousin related but otherwise outbred parents) will have one or more rhLOF genotypes (Fig. 1B).

The majority of identified genes with rhLOF genotypes (422) had not been previously reported, although 167 had been reported as containing homozygous or compound heterozygous LOF genotypes in Iceland, and 299 in ExAC. In total, 107 rhLOF genes were common to all three datasets (5) suggesting a subset of genes either tolerant of LOF and/or with higher rates of mutation. 89 rhLOF genotypes were homozygotes without observed heterozygotes, and we observed three subjects each with 5 rhLOF genotypes. On the basis of these observations we predict that in 100,000 subjects with first-cousin related parents of the same genetic ancestry we would expect at least one knockout in ~9000 of the ~20,000 human protein-coding genes (fig. S3) (5).

We observed a lower density of annotated rare LOF variants within autozygous tracts, where they are homozygous, compared to outside autozygous tracts, where they are typically heterozygous, indicative of direct negative selection on

a fraction of homozygotes (Fig. 2A). We matched each of the 16,708 rare annotated LOF (heterozygous and homozygous) variants to a randomly selected synonymous variant of the same allele frequency, and observed 842 rare LOF variants with ≥ 1 homozygous genotype versus an average of 975.5 rare synonymous variants with ≥ 1 homozygote, indicating a deficit of 13.7% (95% confidence interval 8-20%) of variants with rhLOF genotypes (Fig. 2B) (5). We attribute this deficit to some rhLOF genotypes resulting in early lethality or severe disease and thus being incompatible with our selection criteria as healthier adults, although our data does not inform whether these are due to fewer high-penetrance, or more low-penetrance variants. This deficit is higher than in the Icelandic population (6.4%) (3), consistent with that analysis being biased toward more common variants already subject to selection.

We then combined the calculated deficit rate with the observed number of heterozygous annotated LOF variants, integrating across allele frequencies, to obtain a direct estimate of the recessive lethal load per person. This suggests that a typical individual from the population we sampled carries 1.6 recessive annotated LOF lethal-equivalent variants in the heterozygous state (5). This is similar to previous estimates of the lethal load calculated by correlating the number of miscarriages, stillbirths and infant mortalities with the level of autozygosity (Fig. 2C) (7, 8), and also similar to measurements in other species (9). Using epidemiological data from 13,586 mothers from the same Born In Bradford birth cohort studied in our genetic analysis, we estimated 0.5 lethal equivalents resulting in miscarriage, stillbirth or infant mortality per individual in our population (5). The difference between our two estimates can be accounted for by the fact that the first includes embryonic lethals, whereas the second only involves deaths after a registered pregnancy, suggesting that there are twice as many recessive mutations that are embryonically lethal as those that result in fetal or infant death. Controlling for other effects by comparing to synonymous mutations, we see a significant but moderate decrease ($R_{A/B}$ jackknife test $P = 0.04$) in the rhLOF mutational load in our Pakistani heritage population dataset compared to outbred populations from the 1000 Genomes Project, although this is less than that caused by the historic bottleneck in the Finnish population (FIN in Fig. 2D) (5).

We examined 215 genes with rhLOF in our dataset that have an exact 1:1 mouse:human gene ortholog. From mouse gene knockout data there were 52 genes where a lethal mouse phenotype had been reported on at least one genetic background (10). Whether or not the mouse ortholog knockout is lethal is not associated with alteration of protein function, duplication or changes in gene expression (5). Genes containing rhLOF showed 50% fewer molecular in-

teractions compared to all genes in the STRING interactome dataset (Kruskal-Wallis $P = 3.4 \times 10^{-9}$), predominantly driven by the Binding Interaction class (Kruskal-Wallis $P = 9.3 \times 10^{-11}$). We saw a similar reduction in the Icelandic data (table S4), in contrast to both known pathogenic LOF variants and pathogenic gain-of-function (GOF) variants reported in Orphanet, which showed increased overall molecular interactions ($P = 1.1 \times 10^{-6}$, 2×10^{-12} respectively) (5). Furthermore rhLOF genes that are drug targets have 11.4% phase I to approval rate versus 6.7% for all target-indication pairs (chi-squared $P = 0.046$), although we observed no difference in the proportion of genes known or predicted to be druggable targets (11) for rhLOF genes (15%) compared to all genes (13%, $P = 0.098$) (5).

In subjects from the Born In Bradford study, where full health record data was available, we observed 54 rhLOF genotypes in 52 individuals in Online Mendelian Inheritance in Man (OMIM) confirmed recessive disease genes. Our expectation was that these would be enriched for false positive observations (1). After a quality control analysis of the sequence-based genotype calls (5), we inspected the annotation of these variants (1). We considered 16 of 54 rhLOF genotypes to be possible genome annotation errors (i.e., incorrectly described as LOF) (5) (table S2). Only six of the remaining 38 rhLOF subjects had definite lifetime primary health record diagnoses recorded consistent with the OMIM phenotype, with a further three genotypes suggestively compatible (table S3). We suggest that the remaining 29 are due to a combination of incomplete penetrance (12–16), late onset of disease (i.e., not yet having occurred), individuals with mild symptoms not seeking medical attention, unrecognized technical issues with sequencing or annotation (e.g., tissue specific alternative splicing), or dubious evidence to support the gene-phenotype assignment (in table S3 we assess the available evidence for these possibilities).

We next assessed electronic health records in the Born In Bradford adults, focusing on the time since study recruitment (5). Drug prescription rate and clinical staff consultation rate have previously been shown to correlate strongly with health status (17). We compared individuals with one or more rhLOF ($n = 638$) to individuals without rhLOF ($n = 1524$), and found no association with prescription rate (logistic regression, OR 1.001, 95% CI 0.988 - 1.0144) or consultation rate (OR 1.017, 95% CI 0.996 - 1.038), nor any associations in rhLOF subgroups (5).

One of our subjects was a healthy adult mother with a predicted rare homozygous LOF mutation in *PRDM9*, which we confirmed experimentally (5) (fig. S7, A and B). *PRDM9* is the major known determinant of the genomic locations of meiotic recombination events in humans and mice through its DNA binding site zinc finger domain (6, 18, 19). We excluded that this rhLOF was from a somatic loss of heterozy-

gosity event on the basis that this subject is heterozygous, not homozygous, on both sides of the 25 Mb autozygous region (fig. S7C). Her lifetime primary and secondary care health records were unremarkable. Her genotype predicts protein truncation in the SET methyltransferase domain (thus lacking the DNA-binding zinc-finger domain) which we confirmed in an in vitro expression system (fig. S8A). We observed absence of increase in H3K4Me3 global methylation on transfection (20) of the truncation allele (fig. S8A), and that R345Ter specifically disrupted *PRDM9*-dependent H3K4Me3 methylation at hotspots (fig. S8B).

We determined the locations of meiotic recombination in the maternal gamete transmitted from the mother to her child by 10X Genomics long-range molecularly-phased whole-genome sequencing and identified 39 candidate crossovers (5). Using double strand break (DSB) maps and a maximum likelihood model to account for variability in region size and hotspot density (18), we estimated that only 5.9% (2 log unit confidence interval: 0 - 24%) of the observed *PRDM9* knockout duo maternal gamete crossovers matched DSB sites from wild type *PRDM9-A* allele homozygotes (5). In comparison, in a control mother-child CEPH pedigree duo homozygous for *PRDM9-A* we estimated that 52.1% (confidence interval: 36 - 69%) of the crossovers occurred in known DSB sites. Using similar methods we saw that 18.5% of crossovers observed in the *PRDM9* knockout duo (confidence interval: 1% - 42%) occurred in linkage disequilibrium based hotspots versus 75.7% in the control duo [confidence interval 57%-89% consistent with a previously published estimate of an average of 60% of crossovers occurring at hotspots (18)] (5).

Prdm9 knockout mice demonstrate abnormal location of recombination hotspots with enrichment at gene promoters and enhancers, and also fail to properly repair double-stranded breaks and are infertile (both sexes sterile) (21, 22). Dogs, which lack *Prdm9*, retain recombination hotspots which unlike humans or knockout mice occur in high GC content regions (23). It has been speculated that dog recombination is controlled by an ancestral mammalian mechanism, and that *PRDM9* competes and usurps these sites when active in non-canids (23, 24). However we did not see an increased overlap in our *PRDM9*-knockout duo crossover intervals with promoters and their flanking regions or enrichment in GC content, compared to the control duo (5). Thus the healthy and fertile *PRDM9*-deficient adult human suggests differences from both mice and dogs, and supports the possibility of alternative mechanisms of localizing human meiotic crossovers (25, 26).

Together these data suggest that apparent rhLOF genotypes identified by exome or genome sequencing from adult populations require cautious interpretation. Although this class of variants has the greatest predicted effect on protein

function, loss of most proteins is relatively harmless to the individual, and even in previously annotated disease genes predicted rare LOF homozygotes may not always be as clinically relevant as often considered. This becomes of increasing importance now that exome and genome sequencing is rapidly expanding into healthier adults. We anticipate that further efforts to identify naturally occurring human knockouts, whether in bottlenecked populations, or more efficiently as here in subjects with related parents, will yield both new data relevant to clinical interpretation, and new biological insights, as exemplified by our investigation here of a *PRDM9* deficient healthy and fertile woman.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

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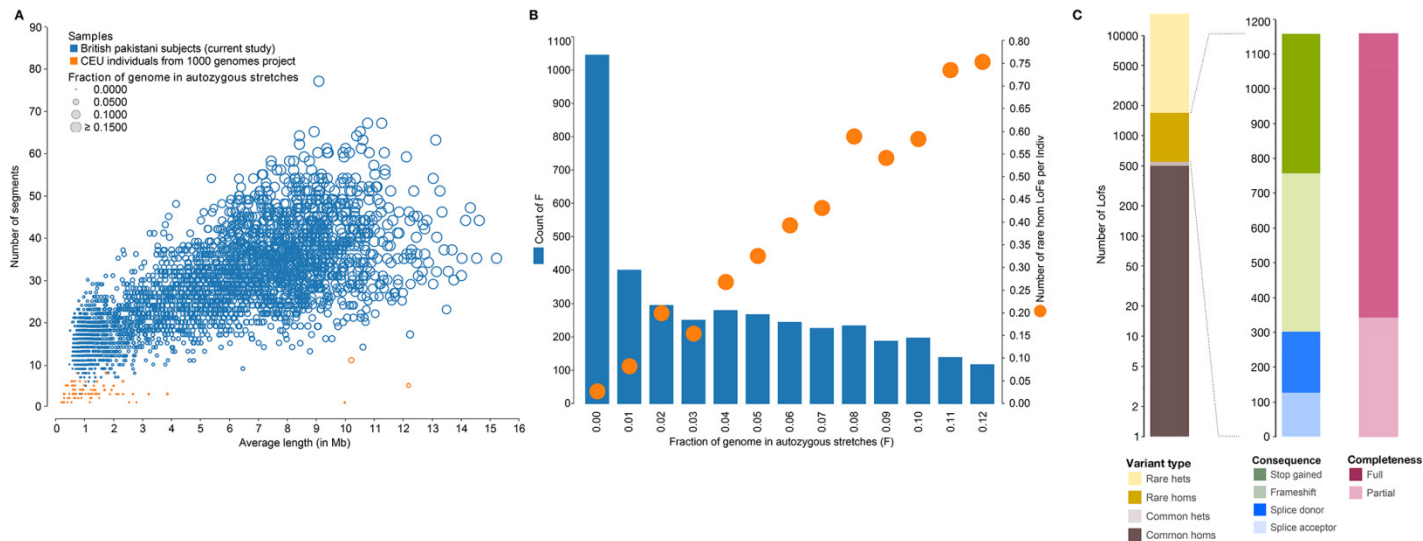


Fig. 1. Discovery and annotation of rhLOF variants. (A) Autozygous segment numbers and length for Pakistani heritage subjects in the UK, and 1000 Genomes project European (CEPH Utah residents with ancestry from northern and western Europe; CEU) individuals. (B) Autozygosity and rhLOF in 3222 individuals. Count of number of individuals (left Y axis, blue columns) binned by fraction of autozygous genome (X axis, showing values from 0.00 to 0.12), with mean number of rhLOF genotypes per individual (right Y axis, orange circles). (C) Distribution of LOF variants by allele frequency, heterozygous or homozygous genotype, predicted protein consequence, and whether predicted for a full or partial set of GENCODE Basic transcripts for the gene.

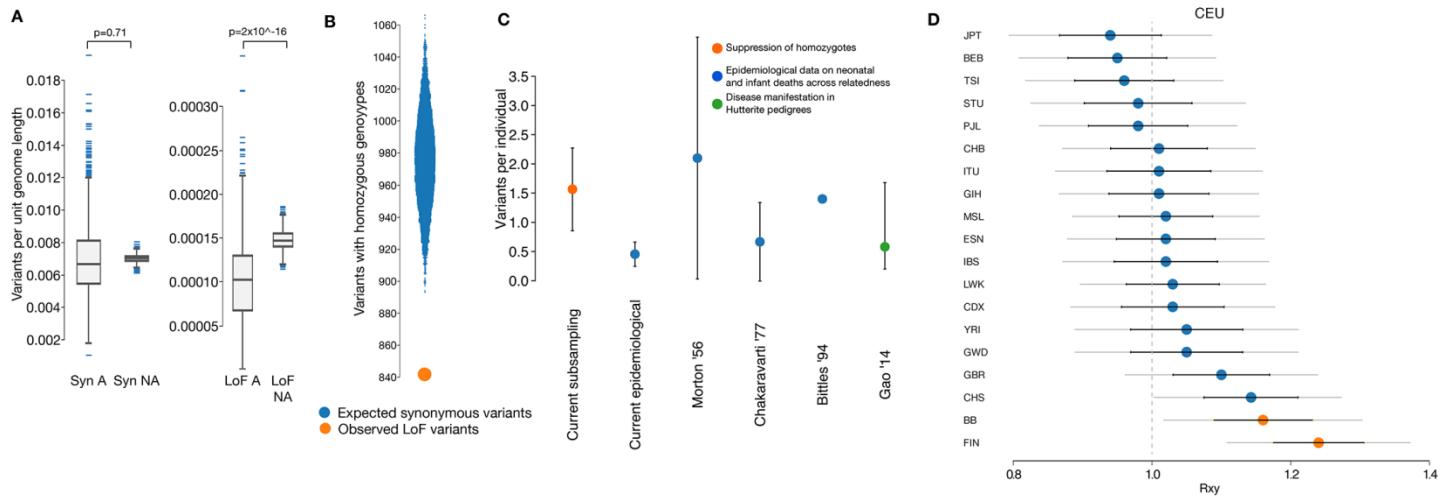


Fig. 2. Population genetic analysis of rhLOF variants. (A) Comparison of number of LOF variants per unit length in autozygous regions (LOF A) with expected rate from non-autozygous sections (LOF NA) showing suppression of rhLOFs (t-test). A similar analysis of synonymous (Syn) variants shows no significant differences. (B) Observed number of variants with homozygote genotypes in 16,708 rare LOF variants (orange circle) versus a frequency matched subsampling of synonymous variants (blue violin plot). (C) Quantification of the recessive lethal load carried on average by a single individual. Direct subsampling estimate for rhLOF variants from current study (orange circle); epidemiological estimates from correlating infant mortality rates to estimated autozygosity in current and published data (blue circles); direct estimate from large Hutterite pedigree (green circle). 95% confidence intervals as black bars. (D) Relative number of derived LOF alleles that are frequent in one population and not another (under neutrality the expectation is 1.0), calculated for 1000 Genomes Project populations and the current Birmingham/Bradford Pakistani heritage population (BB), compared to the CEU population. Error bars represent ± 1 (black) or 2 (gray) standard errors, and significant differences ($R_{A/B}$ jackknife test) versus CEU population are highlighted in orange circles.

Health and population effects of rare gene knockouts in adult humans with related parents

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