Sex-biased reduction in reproductive success drives selective constraint on human genes

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Summary

Genome-wide sequencing of human populations has revealed substantial variation among genes in the intensity of purifying selection acting on damaging genetic variants. While genes under the strongest selective constraint are highly enriched for Mendelian disorders, most of these genes are not associated with disease and therefore the nature of the selection acting on them is not known. Here we show that genetic variants that damage these genes reduce reproductive success substantially in males but much less so in females. We present evidence that this reduction is mediated by cognitive and behavioural traits, which renders male carriers of such variants less likely to find mating partners. Our findings represent strong genetic evidence that Darwin's theory of sexual selection is shaping the gene pool of contemporary human populations. Furthermore, our results suggest that sexual selection can account for about a quarter of all purifying selection acting on human genes.

Main text

The most damaging genetic variants, gene deletions and protein-truncating variants (PTVs), are removed from the population by selection with strength that varies substantially from gene to gene[1,2]. The strength of selection against heterozygous PTVs has been estimated by the selection coefficient, s_{het}, which exhibits a continuous spectrum across human genes[3,4], although most attention has been focused on a subset of ~3,000 genes with the highest 'probability of Loss-of-function Intolerance' (pLI)[1].

The selection pressures acting on these most selectively constrained genes have not been fully characterised, but, *a priori*, could include natural selection increasing pre-reproductive mortality or decreasing fertility, and sexual selection acting on mate choice or intra-sexual competition[5,6]. Gene deletions and PTVs in these genes have been shown to be associated with lower educational attainment[5,7] and general intelligence[8], as well as increased risk of intellectual disability, and some psychiatric disorders[9]. Moreover, these constrained genes are strongly enriched for dominant early-onset Mendelian diseases (including many

neurodevelopmental disorders), many of which are associated with increased pre-reproductive mortality, indicating that natural selection likely makes a substantive contribution to this selective constraint. However, the majority (65%) of constrained genes (pLI>0.9) have not yet been associated with a Mendelian disease. This raises the fundamental question of whether natural selection represents the sole mechanism imposing this form of selective constraint on human genes, or whether other forms of selection are at work.

To explore the nature of selection acting on these genes we identified PTVs and genic deletions in the UK Biobank[10] comprising largely post-reproductive individuals (median age at recruitment: 58 years, range: 39-73 years), and investigated the association with reproductive success. We called large copy number variants (deletions and duplications) from SNP genotyping array data on 340,925 unrelated participants of European ancestry (Supplementary Figure 1), and identified PTVs from exome sequencing among a subset of 34,812 participants (Supplementary Figure 2)[11]. For each participant, we then calculated the cumulative burden of private (only observed in one individual) genic deletions and PTVs by combining s_{het} selection coefficients of each autosomal gene impacted by these variants (under the assumption that fitness is multiplicative, see Methods), which we term their s_{het} burden. The distribution of s_{het} burden was statistically indistinguishable between males and females: for participants with only genic deletion data available, 0.56% and 0.54% respectively had an s_{het} burden ≥ 0.15 (Fisher's p=0.66; Figure 1B), and for participants with both genic deletion and PTV data available the analogous proportions were 6.99% and 7.06% (Fisher's p=0.80; Figure 1C).

We assessed the relationship between s_{het} burden and number of children, using a linear regression correcting for age and population structure (Methods; Supplementary Figure 3). We observed that an s_{het} burden of 1 is associated with a decrease in the overall total number of overall children for both males (0.54 fewer children [95% CI 0.36-0.71], $p=1.5x10^{-9}$) and females (0.18 fewer children [95% CI 0.02-0.34], p=0.03) when combining results from deletion and PTV-based analyses.

To determine if our observed effect of s_{het} burden was due to an actual reduction in overall number of children or a result of selection against having children at all, we performed two analyses. Firstly, we evaluated childlessness using logistic regression. We again observed a striking sex difference in participants' probability of having any children given their s_{het} burden, for both PTVs and genic deletions (Figure 1, Supplementary Table 1). Combining the analyses of genic deletions and PTVs, we found that an s_{het} burden of 1 decreases the probability of males having any children (OR=0.28 [95 %CI 0.20-0.39], $p=4.0x10^{-14}$) much more than females (OR=0.69 [95% CI 0.48-0.95], p=0.03). Secondly, if we remove childless individuals from the analysis, s_{het} burden ceases to have a significant effect on the number of offspring, confirming that the observed decrease in reproductive success is determined largely by increased childlessness (Supplementary Figure 4). As UK Biobank participants included in our model are biased towards females (54%), our observed sex bias is not due to having greater statistical power to detect an effect on reproductive success in males. We also observed that private duplications and likely damaging private missense variants exhibit similar but weaker effects on childlessness (Supplementary Figure 8).

We observed consistent sex-bias in the association of s_{het} with childlessness when performing this analysis in different ways, including: (i) limiting our analyses to carriers of private genic deletions or PTVs in the genes under most selective constraint (following thresholds set by their authors: pLI ≥ 0.9 or s_{het} ≥ 0.15; Supplementary Figure 5), (ii) extending our analysis to more frequent, but still rare genic deletions and PTVs (Supplementary Figure 6), (iii) excluding genes known to cause Mendelian disorders (male OR=0.31 [95% CI 0.21-0.47], p=1.4x10^{-8}), (iv) restricting our analysis to individuals in specific age ranges (Supplementary Figure 7).

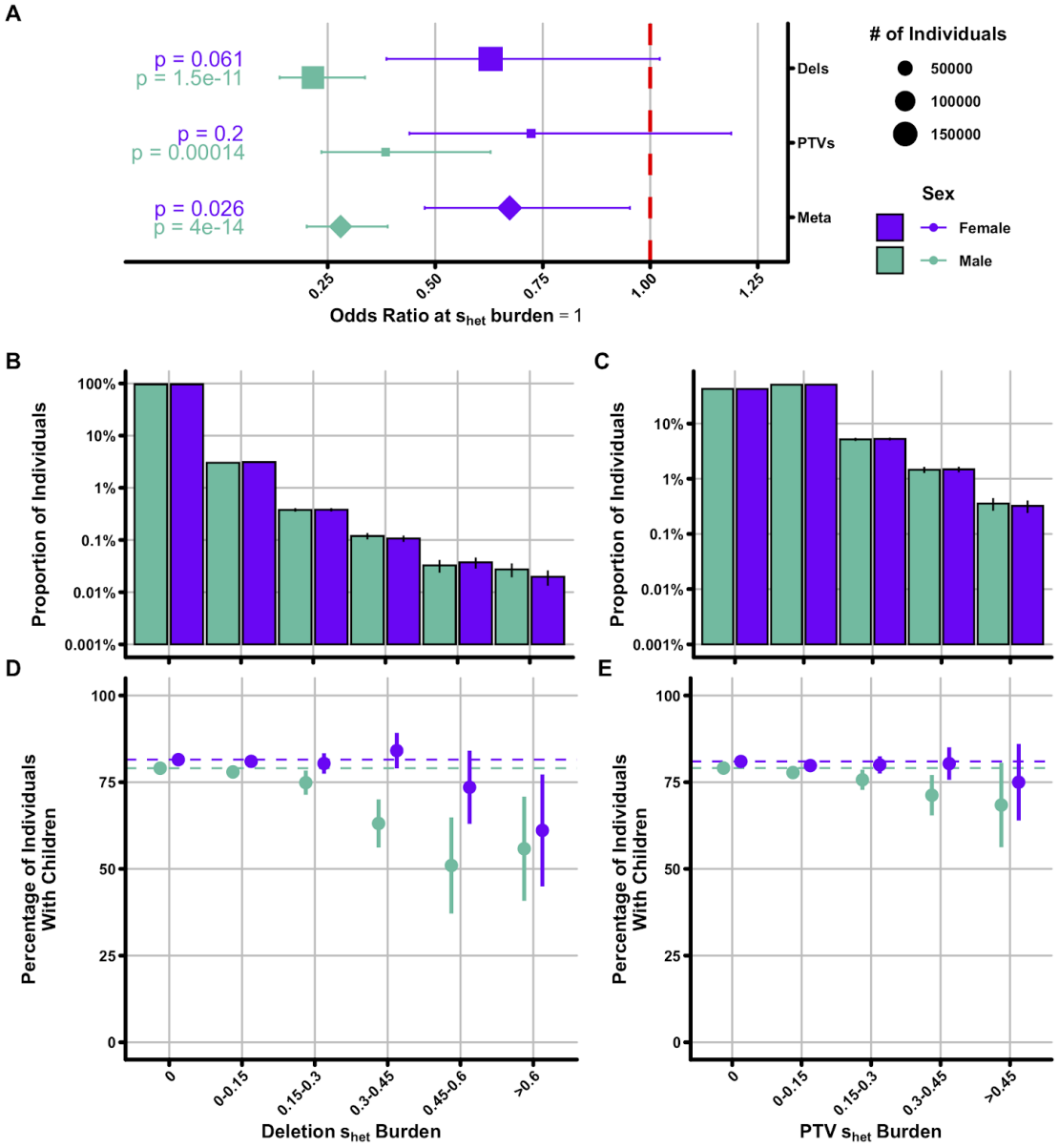

Figure 1. Differences in male and female reproductive success as a function of cumulative rare deleterious genetic variation. *(A) Odds ratio estimates for the effect of cumulative deleterious variation for deletions, PTVs, and a combined meta-analysis on childlessness separated for males (jade) and females (violet). Number of individuals included in each analysis is indicated by the size of the point. (B; C) Proportion of individuals in 0.15 s_{het} bins for deletions (B) and PTVs (C). (D; E) Percentage of individuals with children in bins based on s_{het} burden for deletions (D) and PTVs (E). All error bars are 95% confidence intervals calculated on the population proportion.*

We considered two hypotheses that could account for increased childlessness: (i) impaired fertility (e.g. inability to produce viable gametes), and (ii) cognitive and behavioural factors (which could decrease ability to find a mate, or increase voluntary childlessness). Two lines of evidence suggest impaired fertility is not the predominant cause of this observation. First, removing all 150 autosomal genes for which at least limited evidence exists of an association to male infertility[12] had minimal impact on the association with male reproductive success (OR=0.28 [95% CI 0.20-0.39], $p=4.7x10^{-14}$). Second, genes under the highest selective constraint ($s_{het} \geq 0.15$) are not associated with higher expression levels in testis, unlike the genes currently known to be associated with male infertility (Supplementary Figure 9).

By contrast, there is substantial existing evidence that behavioural and cognitive traits influence reproductive success in a sex-biased manner. First, the reduced reproductive success associated with a range of psychiatric disorders is much more pronounced in males than in females[13]. Second, personality traits associated with increased reproductive success differ between males and females, with increased extraversion in males but greater neuroticism in females being linked to increased reproductive success[14]. Third, although the most highly ranked mate characteristics are highly concordant between the sexes[15], some mate preferences differ between the sexes, with males placing greater value on physical attractiveness and females valuing cues relating to earning potential[14,16–18]. Finally, low socioeconomic status and low educational attainment have been more strongly linked to increased childlessness in males than females across populations[19–22]. This has typically been ascribed to males of lower socioeconomic status finding it harder to attract a partner[23,24].

Some of these observations about sex-biased reproductive success have been related to parental investment theory[25]. This hypothesis posits that sexual selection by mate choice is driven, in large part, by different levels of investment by males and females in their offspring. This drives the sex that invests more in offspring (typically female) to be more discriminating in their choice of mates, especially with regard to their potential to invest in offspring. However, a sex-biased reduction in reproductive success need not be caused by sex differences in mate preferences; it could also be caused by a sex bias in trait severity coupled to mate choice preferences that are not sex-biased. These mechanisms are not mutually exclusive; both could be contributing to an overall sex-biased reduction in reproductive success, albeit on different traits.

A key prediction of the hypothesis that mate choice underpins the observation of a male-biased association of s_{het} burden with increased childlessness is that males with a high s_{het} burden should find it harder to find mates than females. We observed that UK Biobank participants with high s_{het} burden were also significantly less likely to be currently living with a partner, and that, like reproductive success, this effect was significantly stronger in males than in females (Figure 2A). Given the very strong association for UK Biobank males between currently living with a partner and having children (OR=5.79 [95% CI 5.63-5.95] , $p < 1x10^{-100}$; Supplementary Figure 10), we estimated that the lower likelihood of currently living with a partner explains a substantial fraction (~30%) of the association between s_{het}

burden and increased male childlessness. We note that the status of currently living with a partner is an imperfect proxy for partner status during peak reproductive years, but the latter information is not currently available in UK Biobank. Therefore, it is likely that the lack of a partner during peak reproductive years likely explains a greater fraction of increased male childlessness than estimated here. We observed no significant impact of s_{het} burden on the likelihood of having engaged in same sex sexual behaviour (OR=1.25 [95% CI 0.59-2.68], p=0.56; Supplementary Figure 11), which is also strongly associated with increased childlessness in UK Biobank (male OR=0.14 [95% CI 0.13-0.15], $p<1x10^{-100}$; female OR=0.27 [95% CI 0.25-0.29] $p<1x10^{-100}$; Supplementary Figure 10).

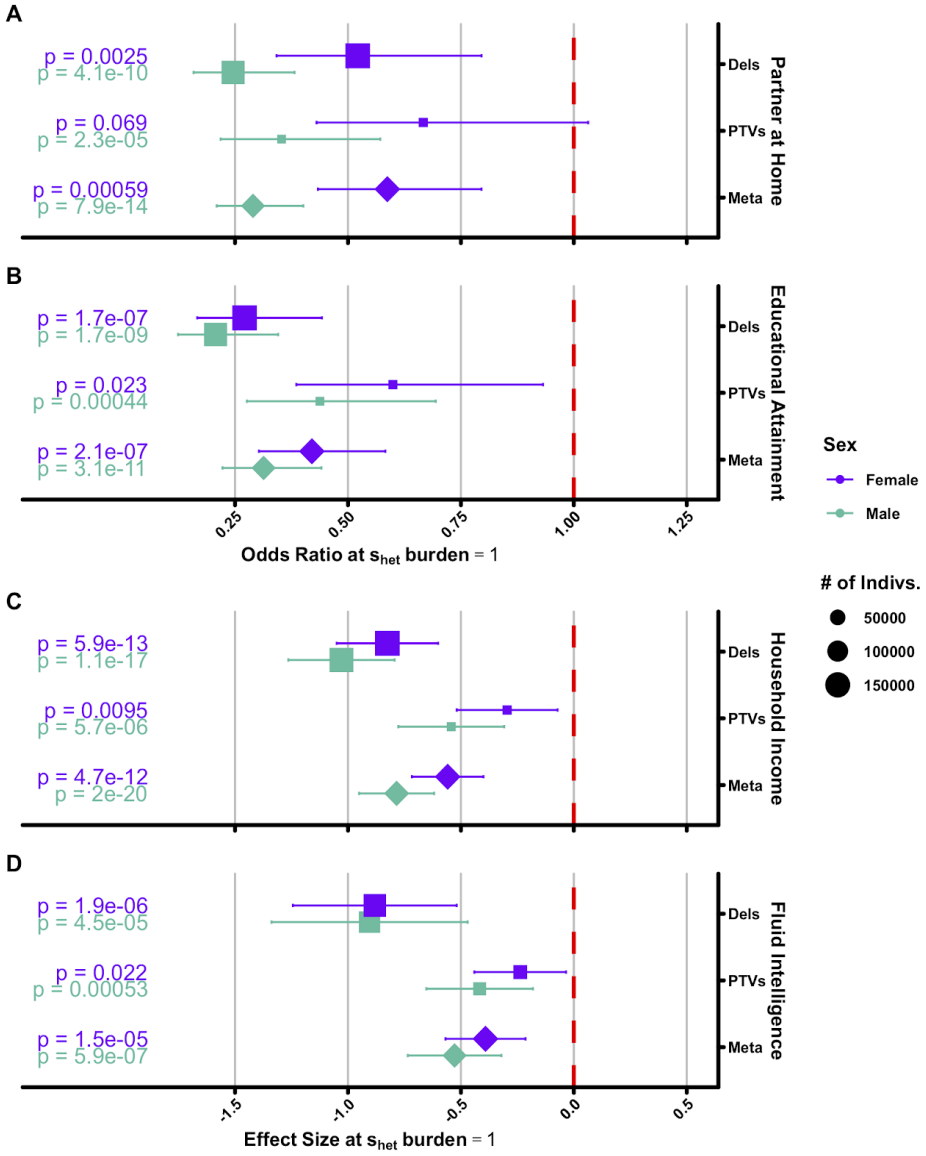

Figure 2. Effect of s_{het} burden on traits known to be associated with reproductive success. *Shown are similar plots to Figure 1a, except for four phenotypes which have been previously associated with reproductive success: (A) having a partner at home, (B) educational attainment as measured by college completion, (C) household income (as measured by income bracket and corrected for having a partner at home; see methods), and (D) fluid intelligence (in standard deviations). For each trait, we tested using a logistic (A,B) or linear (C,D) model the effect of s_{het} burden on each phenotype shown above, corrected for age, age^2, and the first ten ancestry principal components.*

We explored in UK Biobank whether the impact of s_{het} burden on reproductive success might plausibly be mediated through some of the specific factors highlighted by the previous psychiatric, demographic and psychosocial research summarised above. Firstly we investigated its impact on cognition as measured by fluid intelligence in 110,190 (51,378 males, 58,812 females) UK Biobank participants. We found that s_{het} burden was associated with significantly reduced fluid intelligence scores of males and females with similar effect sizes (Figure 2D). Increasing s_{het} burden is also associated with lower household income and educational attainment (Figure 2B,C), again with similar effect sizes in males and females. To evaluate the potential impact of this reduced cognition on male reproductive success, we extended previously published work relating the results of IQ tests taken by 95% of Swedish males (during military conscription) to their completed family size[26]. We estimated that the decrement in cognition observed in UK Biobank males accounts for 6.3% [95% CI 5.3%-8.6%] of the reduced male reproductive success associated with high s_{het} burden (Supplementary Figure 12, Methods). We also note that the decrease of reproductive success with decreasing IQ was most pronounced in males with IQ<70 (Supplementary Figure 13)[26], who are likely depleted in UK Biobank relative to the general population.

Analysis of psychiatric disorders in UK Biobank is complicated by both recruitment bias away from more severe psychiatric disorders[10,27,28] and incomplete data on participants. Mental health data for most UK Biobank participants are only available from ICD10 codes derived from secondary care data (hospital-based; Supplementary Table 1), which likely underestimates the true prevalence of mental health disorders. More complete data is available on a subset of UK Biobank individuals from a mental health questionnaire for which participants were invited by email[28]. We observed that a high s_{het} burden was very strongly associated with not having an email address (male OR=0.30 [95% CI 0.22-0.42], $p=2.6x10^{-13}$; female OR=0.48 [95% CI 0.35-0.65], $p=3.5x10^{-6}$; Supplementary Figure 14), which likely explains why individuals with a high s_{het} burden are under-represented among individuals completing the questionnaire (male OR=0.44 [95% CI 0.32-0.61], $p=1.2x10^{-6}$; female OR=0.40 [95% CI 0.30-0.55], $p=6.6x10^{-9}$; Supplementary Figure 14).

Despite the limitations of mental health data in UK Biobank, they corroborated that a high s_{het} burden increases the risk of psychiatric disorders previously associated with reduced reproductive success (schizophrenia, autism, attention deficit hyperactive disorder, and bipolar disorder), and that these psychiatric disorders are associated with increased childlessness in both male (OR=0.30 [95% CI 0.26-0.35], $p=1.5x10^{-55}$) and female (OR=0.65 [95% CI 0.56-0.77], $p=3.2x10^{-7}$) UK Biobank participants, albeit with substantial sex-bias (Supplementary Figure 10). This finding accords with a previous study showing that copy number variants associated with increased risk of schizophrenia are also associated with disproportionately reduced reproductive success in males[29]. Carriers of well-characterized neurodevelopmental disorder-associated copy number variants, which include those with a strong association to schizophrenia (Methods), only account for 3.7% (n = 12,593) of individuals in UK Biobank. Removal of these individuals from our dataset does not significantly alter the association of s_{het} burden with reduced male reproductive success (OR=0.28 [95% CI 0.20-0.40], $p=8.8x10^{-13}$).

We subsequently limited the analysis of the impact of s_{het} burden on childlessness to individuals without any evidence of a mental health disorder associated with reduced reproductive success (from either ICD10 codes or the mental health questionnaire). We observed very similar effect sizes to when analysing all individuals (male OR=0.29 [95% CI 0.20-0.40], $p=1.5x10^{-13}$; female OR=0.69 [95% CI 0.49-0.99], p=0.04), suggesting that the effect on childlessness is not predominantly driven by this subset of mental health disorders. We explored this further, using data external to UK Biobank that are less affected by the limitations described above. Using previous estimates of the increased risk of mental health disorders caused by PTVs in highly constrained genes[9], and the reduced reproductive success associated with those disorders[13], we estimated that these mental health disorders likely account for 14% [7-31%] of the reduced male reproductive success associated with high s_{het} burden (Methods).

Thus, in UK Biobank, both reduced fluid intelligence and increased risk of psychiatric disorders account for only modest proportions of increased male childlessness due to s_{het} burden. A much larger proportion of the predicted reduction in overall fitness is explained by not currently having a partner (32% [31-32%]; Methods; Supplementary Figure 12).

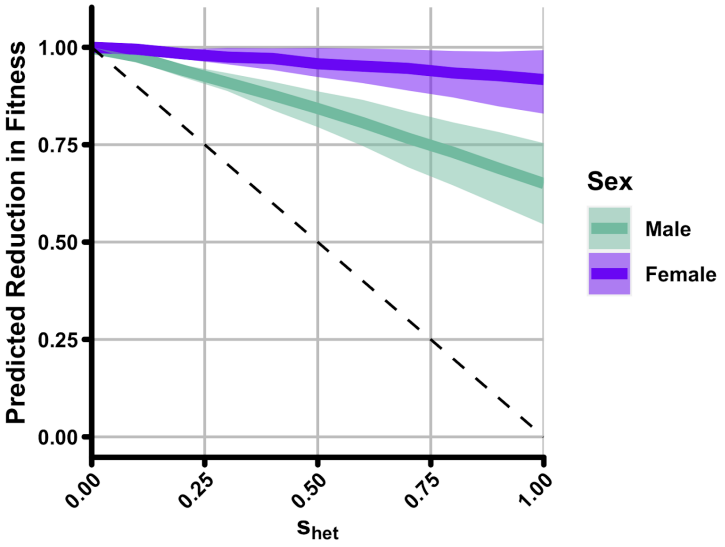

Figure 3. Predicted reduction in overall fitness as a factor of individual s_{het} burden. *Displayed is the expected reduction in fitness as a factor of increasing s_{het} burden, independently for each sex. Error is shown as the lighter shaded area surrounding the trend line, and was determined based on the simulation of 100,000 individuals at varying s_{het} burdens based on the confidence intervals on the odds ratio as determined by our logistic regression model (Methods). The dashed line represents the theoretical reduction in fertility as predicted by s_{het}.*

Overall, we find that reduced reproductive success due to s_{het} burden explains 22% [13-31%] (Figure 3; Supplementary Figure 12) of the total reduction in fitness expected due to purifying selection against PTVs (Methods), with this reduction in fitness being much stronger in males. This suggests that such selection may not be borne equally by males and females. We note that current estimates of s_{het} are based on data from aggregated research cohorts. Participation in research has been shown to be biased with respect to gender, socioeconomic status and genetic variation[30]. As a consequence, individuals with high s_{het}

burden may well be under-represented within research cohorts and PTVs within genes under strong selective constraint may well be segregating at higher frequencies in the general population than in research cohorts. This bias could result in the true value of s_{het} being lower than currently estimated, and, consequently, the contribution of reduced reproductive success to the overall reduction in fitness due to purifying selection being greater than estimated here.

These estimates of reproductive success and selection coefficients are inevitably reflective of a population at a particular point in time. The proportionate contribution of reduced reproductive success to the overall reduction in fitness associated with genic purifying selection is likely to change over time. Medical advances over recent decades have altered the landscape of infertility and pre-reproductive mortality substantially. Moreover, overall childlessness is highly dynamic over time. Demographic data demonstrate that population-wide childlessness can double in just two decades, a nationwide trend that is readily apparent in UK Biobank (Supplementary Figure 15).

In summary, we find that reduced reproductive success, especially in males, makes a substantial contribution to purifying selection acting on human genes, and that this is likely mediated by mate choice on cognitive and behavioural traits. Mate preferences are multi-dimensional, and vary across cultures and time[18]. It is likely that male-biased reduced reproductive success associated with increasing s_{het} burden involves multiple cognitive and behavioural traits. The negative impact of s_{het} burden on fluid intelligence, household income and educational attainment, together with the previously documented female-biased preference for mates with good financial prospects[15,17] suggest that sex-biased mate preferences contribute in part to the sex-bias in reproductive success with increasing s_{het} burden. However, as we are not able to assess the effect of s_{het} burden on all characteristics that are valued in a mate, especially those that are ranked most highly by both sexes (e.g. emotional stability and maturity)[15], we cannot exclude that sex biases in the impact of s_{het} burden on these traits also contribute to the sex bias in reproductive success.

Our findings may help to explain, at least in part, why only a minority of genes under the highest selective constraint have been associated with single gene disorders that increase pre-reproductive mortality or cause infertility. While there are clearly many more single gene disorders to be discovered among these genes[31], we anticipate that these highly constrained genes will not be neatly divided into those that cause single gene disorders and those that impact on reproductive success without causing a clinical condition. Rather, we predict that damaging variants in many of these genes will perturb neurodevelopment resulting in a broad spectrum of cognitive and behavioural outcomes, which will increase an individual's risk of childlessness, but only in some cases result in a clinically-ascertainable condition.

When investigating sex-biased patterns of genetic associations for cognitive and behavioural traits, the potential contribution of reproductive success and mate choice ought to be considered. For example, it has been posited that the preferential transmission from mothers of inherited alleles increasing risk of neurodevelopmental disorders potentially relates to the greater 'resilience' of females to such alleles[32]. However, our findings that the impact on cognition of the damaging genetic variation studied here is similar between the sexes

suggests that mate choice may be a more plausible explanation for such observations, as seen for the 22q11.2 deletion[32,33].

Our analyses have several limitations. First, we do not have longitudinal relationship data for UK Biobank participants that might shed more light on the impact of s_{het} burden on the ability to attract a partner during peak reproductive years. Second, we have not been able to explore the impact of s_{het} burden on the full range of cognitive and behavioural traits that relate to mate preferences and influence reproductive success. We anticipate that teasing out the relative contributions of correlated cognitive and behavioural traits will be challenging. Third, UK Biobank participants are biased towards higher health, educational attainment and socioeconomic status, and as such our estimates of the negative effect of s_{het} burden on reproductive fitness possibly underestimate the true effects in the general population.

Our study focused on individuals of European ancestry and analogous studies across different populations and cultures are needed. Males have considerably greater variance in reproductive success than females across cultures[34], including higher levels of childlessness than females[21], highlighting the potential for sexual selection acting on male reproductive success to act across populations. We also note that many of the fundamental trends relating to mate preferences and male childlessness have been shown to be cross-cultural in nature[15,20,34]. We look forward to future studies that integrate genome-wide sequencing data on large population samples from a range of ancestries to more fully characterise the impact of sexual selection on our species.

Our study represents an important validation of the relevance of Darwin's theory of sexual selection[6] to contemporary human populations. Much recent evolutionary genetic research into selection on human cognitive traits has tended to focus on the fixation of alleles that increase brain size and complexity and thus evolutionary fitness[20,35]. Our work suggests a substantial role for purifying selection truncating the phenotypic distribution in the evolution of cognitive traits in humans. We contend that a full understanding of the evolution of human cognition will need to integrate patterns of both positive and negative selection.

Methods

Sample Selection and Phenotype Collation

To collate phenotypes for all individuals in UK Biobank, we downloaded bulk phenotype files from the UK Biobank data showcase (https://www.ukbiobank.ac.uk/data-showcase/; data acquired 22 Jan 2020). Due to ascertainment biases with post-recruitment data (Supplementary Figure 14), we only retained data which were ascertained at time of recruitment (i.e. instance 0 in the UK Biobank data showcase). Please see Supplementary Table 1 for detailed descriptions of all phenotypes assessed in this manuscript, including how they were processed, if applicable. Individuals with missing data for a relevant phenotype were excluded from analysis when testing that phenotype.

Following phenotype collation, we next selected for final analysis individuals of broadly European ancestry as determined by[36], which left a total of 409,617 individuals. To identify and remove related individuals, we first downloaded the relatedness file from the UK Biobank data showcase using the ukbbgene tool, which contains 107,124 relatedness pairs among UK Biobank participants[36]. Next, we sorted individuals by the total number of related pairs within this file, and removed the individual with the most related pairs and recalculated the total number of relationships for all other individuals. We repeated this process until no related pairs remained, which left a total of 342,717 individuals for downstream analysis.

Calling, Quality Control, and Annotation of Copy Number Variants from SNP Microarrays

To ascertain copy number variants from 488,377 UK Biobank participants with available genetic data[36], we utilized the PennCNV CNV-ascertainment pipeline[37]. Raw CEL files were downloaded in 107 independent batches, of which 95 batches were genotyped with the standard UK Biobank array platform and 12 batches were genotyped with the UKBiLEVE array platform. Each batch was then processed independently through the following calling pipeline: first, raw CEL files were genotyped with Affymetrix power tools (http://media.affymetrix.com/support/developer/powertools/changelog/index.html) 'genotype' with default settings. Next, using the 'generate_affy-geno_cluster.pl' and 'normalize_affy_geno_cluster.pl' scripts provided as part of PennCNV, genotyped samples within each batch were clustered and normalized, respectively. Normalized clustering output was then split into one file per individual and provided as input to 'detect_cnv.pl' to generate an initial call set of CNVs. Finally, initial CNVs were then passed to the 'clean_cnv.pl' script with "-fraction" set to 0.25 in order to merge nearby CNV calls in each individual. Following CNV calling, we dropped all individuals with ≥ 20 CNVs and absolute waviness factor > 0.3, and all variants on either the X or Y chromosome, which left 485,593 individuals and 3,070,510 raw redundant CNVs.

To perform quality control of ascertained CNVs, we developed a novel approach which uses individuals for which CNVs have been ascertained with both array and exome-based approaches. In short, we started with the basic logistic regression concept outlined in Mace et al.[38] but instead used the intersect of array- and WES-ascertained CNVs as the dependent variable in a random forest model[39], with various per-individual and per-CNV metrics as predictors. To train this model, we utilized an additional set of 46,856 individuals collected as part of the INTERVAL study[40] genotyped on the same array as participants in UK Biobank, of which 4,465 also had matched WES data. For INTERVAL individuals, we performed array-based CNV calling identically to the method as described above and ascertained exome-based CNVs using three different algorithms with default settings: XHMM[41,42], CANOES[43], and CLAMMS[44]. For each INTERVAL participant for which we had both array and exome-based CNVs, we then determined a "WES overlap score" as a product of the overlap of each array-based CNV with the three WES-based callers, corrected for whether or not any overlap was possible due to probe/exon bias. Scoring results in a roughly continuous metric for each array-ascertained CNV of between zero and three, where zero represents a lack of overlap with any WES CNV call and three represents a perfect overlap with all three algorithms. For predictor covariates, we used several metrics already shown to be of high quality for CNV quality control[38,45], per-CNV metrics based on these (e.g. mean log R ratio for each probe within a CNV rather than for all probes across an entire individual), and a novel metric which uses specific probes on the array known to be biased for CNV calls on bad arrays (Supplementary Table 2; see code availability). To determine estimated sensitivity/specificity of our model we performed 10-fold cross-validation, where all array CNVs which overlapped at least two exons were split into equal test and training sets and provided, separately for deletions and duplications, as input into the randomForest implementation in R as a linear predictor with nTrees set to 500. To generate a call set of final quality controlled CNVs for downstream analyses, we then trained a final random forest using all INTERVAL individuals with matched array and WES data and generated predicted WES overlap scores for all 3,070,510 raw UK Biobank CNVs identified with PennCNV as described above. CNVs were then filtered based on a predicted sensitivity of 95% based on cross-validation, leaving a remaining 1,597,419 CNVs (1,036,930 deletions, 560,489 duplications).

CNVs passing quality control were then provided as input to a custom java pipeline which merged all CNVs, regardless of whether they were deletions or duplications, based on 75% reciprocal overlap to generate a set of 171,118 nonredundant loci. Following filtering to 342,717 unrelated individuals of broadly European ancestry for which CNV data was available, each locus was quantified for allele frequency. Loci were then assessed for overlap with a set of known pathogenic CNVs identically to Crawford, et al.[45] and annotated using Variant Effect Predictor (VEP) v97[46]. Only loci with an annotation of 'transcript_ablation' or 'feature_trunctation' and ‘coding_sequence_variant’ for deletions, and 'transcript_amplification' or 'feature_elongation' and ‘coding_sequence_variant’ for duplications were considered to be affecting a target gene. A total of 1,109,051 redundant CNVs remained for downstream analysis following all filtering and annotation (717,420 deletions, 391,631 duplications; Supplementary Figure 1).

Processing SNV/InDel Data from WES

To collate protein truncating, missense, and synonymous variants for all 49,960 individuals whole exome sequenced by UK Biobank, we downloaded the GRCh38-aligned population-level variant files from the UK Biobank (UK Biobank field 23160) and converted them to variant call format. All autosomal variants were then annotated with VEP v97[46], CADDv1.5[47], allele frequency from gnomAD[48], PEXT[49] and, where relevant, MPC[50] and LOFTEE[48]. PEXT and MPC scores were converted from build37 to build38 using the CrossMap tool[51]. Variants were assigned to a gene based on the primary ENSEMBL transcript with the most severe consequence. Variants were considered to be PTVs if they were annotated by VEP as having a splice acceptor/donor, stop gained, or frameshift consequence. We then retained only variants with a gnomAD or UK Biobank-specific allele frequency ≤ $1x10^{-3}$ and with a PEXT mean cerebellum score > 0.1. Missense variants were only retained if they had MPC > 2 and CADD > 25. PTVs were only retained if they were annotated by LOFTEE as high confidence, had CADD > 25, and were not located in the last exon or intron of the canonical transcript as annotated by ENSEMBL[52]. This filtering approach left a total of 2,658,431 redundant autosomal SNVs and InDels across all 34,812 unrelated individuals of broadly European ancestry included in this study (Supplementary Figure 2).

It has recently been reported that the UK Biobank exome sequencing data is missing variant calls in regions where all reads were assigned MAPQ=0 (for more details, see Jia et al.[53]). While this issue affects 702 genes with an s_{het} value assessed in this study, genes with the highest constraint scores (i.e. $s_{het} \geq 0.15$) are less likely to be affected by this problem (3.3% of genes with $s_{het} \geq 0.15$, 4.5% of genes with $s_{het} < 0.15$; Fisher's p=0.02). Secondly, this issue is consistent across all individuals with WES within the UK Biobank and thus results in a simple loss of power equivalent to having insufficient coverage to call variants across ~4% of the exome. Finally, as CNV calling was performed using genotyping arrays, and thus unaffected by issues with sequence alignment, our findings are independently robust. Information on exome capture baits and genes affected by alignment issues for producing this statement were acquired from the UK Biobank data showcase (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1911).

Calculating s_{het} Burden for UK Biobank Participants

To calculate an individual's s_{het} burden, and assuming that fitness is multiplicative and that there is no epistasis between genes which are lost, we utilized the following formula:

$$s_{het[i,v]} = 1 - \prod_{g}(1 - s_{het[i,v,g]})$$

where $s_{het[i,v]}$ indicates individual i's s_{het} burden for variant class v and $s_{het[i,v,g]}$ indicates the s_{het} score for gene g with a qualifying annotation for variant type v in individual i. Possible values for v are PTV, missense, synonymous, deletion, or duplication. As indicated by the formula above, s_{het} values were calculated independently for each variant type. Per-gene s_{het} values were obtained from Weghorn et al.[3], under their demographic model which includes

drift and scores for 16,189 protein coding genes which we were able to definitively map to an ENSEMBL gene ID.

To explore if genes known to be associated with male infertility were responsible for our observed effect on male reproductive success, we also generated individual s_{het} scores for each variant class excluding a set of 150 autosomal genes known to be associated with male infertility (Supplementary Table 4 from Oud et al.[12]). Genes with an annotation of limited, moderate, strong, or definitive evidence were excluded from calculated s_{het} scores.

To test if our observed relationship was robust when excluding genes with a known disease annotation, we also generated individual s_{het} scores where we removed 4,414 disease-associated genes. We considered a gene to be disease-associated based on being a confirmed or probable developmental disorder gene in the Developmental Disorders Genotype-Phenotype Database (DDG2P; https://decipher.sanger.ac.uk/info/ddg2p), in the Online Mendelian Inheritance in Man (OMIM; https://omim.org/) Morbid Map after excluding 'non disease' and 'susceptibility to multifactorial disorder' entries, or in ClinVar[54] with a pathogenic/likely pathogenic variant linked to a phenotype.

Logistic and Linear Modelling of Phenotypes

To test the association of each s_{het} burden (i.e. $s_{het[i,v]}$) per variant class with a given phenotype (e.g. those in Supplementary Table 1), we used a general linear model via the 'glm' function in R of the form:

$$phenotype \sim s_{het[i,v]} + age + age^2 + PC1..PC10$$

All models were run separately for males and females. For binary phenotypes, 'family' was set to 'binomial' and for continuous phenotypes 'family' was set to 'gaussian'. To combine the effect sizes or log odds ratios for CNVs and PTVs (e.g. for Figure 1A), we used the 'metagen' function from the 'meta' package[55] in R to perform a fixed-effects meta analysis. For logistic regression, we set parameters 'method.tau' to 'SJ' and 'sm' to 'OR'. For linear regression, we set the parameter 'sm' to "SMD". To avoid including an individual twice in our meta analysis, for samples with both CNV and PTV data available, we prioritized PTV-derived s_{het} scores.

When using raw variant counts as in Supplementary Figure 5, the s_{het} term in the above formula was changed to the total number of qualifying genes affected per individual, where qualifying genes were either those with pLI ≥ 0.9[48] or those with s_{het} ≥ 0.15[3]. Individuals with > 3 genes lost for deletions (pLI ≥ 0.9 n = 42; s_{het} ≥ 0.15 n = 16) and PTVs (pLI ≥ 0.9 n = 2; s_{het} ≥ 0.15 n = 1) were removed prior to regression analyses.

To test the effect of individual phenotypes on likelihood of having children (Supplementary Figure 10), we used a general linear model in R with 'family' set to 'binomial' of the form:

$$has.children \sim phenotype + age + age^2 + PC1..PC10$$

As with estimating the contribution of s_{het} burden to phenotypes, all analyses were run separately for both males and females. For all models involving household income, we additionally included partner at home status as a covariate, as household income was recorded per household, not per recruited individual.

All odds ratios, effect sizes, standard errors, p values, and total individuals per association test reported in this manuscript can be found in Supplementary Table 3.

Evaluation of Gene Expression in Testis

To determine the expression in testis of all genes assessed in this study, we downloaded processed median transcripts per megabase values for all genes provided by v7 of the GTEx study (https://storage.googleapis.com/gtex_analysis_v8/rna_seq_data/GTEx_Analysis_2017-06-05_v8_RNASeQCv1.1.9_gene_median_tpm.gct.gz). Only genes for which an s_{het} score was available[3] were retained from this file. We then determined if each gene was affected by either a private deletion or PTV in a UK Biobank individual. We then plotted $\log_e$(testis expression) as a factor of being a male infertility gene or not or having or not having a qualifying variant (Supplementary Figure 9). To determine significance we used a one-sided Wilcoxon test, with the alternate hypothesis that expression in testis of male infertility genes or genes with private variants is greater than the alternative set.

Modelling the Contribution of Phenotypes to Observed Reduction in Fitness

Variant s_{het} Burden

To estimate the contribution of s_{het} to overall fitness (Figure 3), we extracted log odds ratio estimates for the effect of s_{het} on having children from our logistic model and estimated the proportion of childless individuals at various s_{het} scores (0 to 1 at 0.1 intervals; Supplementary Figure 12). We then simulated 100,000 individuals at each s_{het} score for both males and females, with individuals randomly assigned as childless using the ‘rbinom’ function in R. Childlessness at s_{het}=0 was based on the overall mean childlessness for UK Biobank (males = 21.1%; females = 18.5%). As we have shown that s_{het} burden does not affect the number of children amongst individuals with children (Supplementary Figure 4), individuals simulated to have children were then assigned the mean number of children for individuals with children in the UK Biobank (2.23 children for males, 2.21 for females). We then averaged the number of children across all simulated individuals, regardless of simulated childlessness, to obtain an estimated overall fertility for each s_{het} score. Estimated mean fertility was then divided by the mean fertility for individuals in UK Biobank (1.76 children for males, 1.80 for females) to determine an estimated reduction in fitness (Figure 3). To calculate the error in our estimates, we used the 95% confidence intervals for the s_{het} burden log odds ratio from our original logistic regression. Since expected fitness at s_{het} = 1

is 0, the estimated percentage of reduced fitness at $s_{het} = 1$ due to individual s_{het} burden is simply 1 - reduced fitness as calculated above.

General Cognition

When possible, we used independent estimates from population level or external data to alleviate biases in UK Biobank phenotype ascertainment (Supplementary Figure 14). As such, data on cognitive ability and fertility are collected from Swedish population level government administrative registers that have been linked to Swedish conscription registers[56]. To assess assignment into different branches of a universal conscription for Swedish men, the Swedish government included an extensive cognitive ability test which all men in Sweden had to take part in. Information on childbearing is based on birth records, and linkage to both men and women is nearly universal, partly due to universal government identity numbers, combined with serious paternity investigations in case of missing information of the biological father. This information was used to calculate reproductive fertility histories in 2012 for all men included in this study. We include data on all Swedish born men who participated in the military conscription test at age 18-20 who were born 1965-1967. The conscription registers are described in more detail elsewhere[26,57].

For the current study, we did not rely on the official cognitive ability scores assigned for each man following their cognitive ability test as in Kolk and Barclay[58], but instead made manual calculations to create a more finely grained measure from raw test scores based on a battery of cognitive ability tests that are available for 3 years in our conscription registers. The Swedish military created an official IQ-measure based on a 9-score stanine scale that has been used in a large number of scientific studies[58,59]. In the current study we developed a more detailed score using information on the actual test scores of men participating in the test. The conscription test consisted of 4 large subtests measuring different dimensions of IQ with logical, spatial, verbal, and technical subtest[57,60,61]. To get a more finely tuned IQ measure than the official stanine measure we used the raw test scores of each of these four tests and summed the total number of correct questions for these 4-sub tests. Within each stanine IQ score, we then examined the distribution of test scores and after standardizing the test scores using only variation within each stanine score, calculated a new detailed IQ score. This procedure is done to anchor our new IQ measure in the official stanine IQ score. As our test scores have some missing values for men with very high and very low stanine scores, this procedure results in a slightly underdispersed distribution and our new calibrated IQ score has $\mu = 100$ & $\sigma = 12$, as compared to the official stanine measure with $\mu = 100$ & $\sigma = 15$.

This score allows us to calculate cognitive ability by single digit IQ scores (Supplementary Table 4); however, as we had to rely on only observations with complete test scores for all test batteries, our data has a higher share of excluded men than the official cognitive ability scores (used by Kolk and Barclay[26] and others). In addition to the ~5% of men that did not take the test (e.g. they were ineligible for military service due to handicap such as visual impairments, that they were abroad, or were conscripted at an atypical age), we additionally excluded a number of men for which scores of all test batteries were not available. Our manually computed fine-grained measure was later standardized against the official

cognitive ability test score to maintain comparability and to assure our slightly smaller population is still representative of the complete cohort. Compared to most other measures of cognitive ability in the scientific literature, we argue that our population is unusually representative as little (indirect) pre-selection due to cognitive ability took place.

We first estimated the effect of overall s_{het} burden on fluid intelligence (Figure 2D) and, because fluid intelligence is normalized and IQ is normally distributed, converted this effect to a predicted change of IQ using the following formula:

$$\Delta_{IQ} = \beta_{fluid.intel} * \sigma_{IQ}$$

Based on this formula, a male with an s_{het} burden of 1 would have a predicted mean change of -6.11 IQ points (Supplementary Figure 12). To then estimate childlessness and fertility for low IQ values not actually observed in the general population, we fit actual observations to a sigmoidal model using the function 'nls' in R (Supplementary Figure 13; Supplementary Table 4). We then simulated 100,000 individuals, with individual IQ values selected from our original Swedish IQ distribution (μ = 100, σ = 12) with the mean shifted by the expected reduction in IQ as explained by our s_{het} model. We then matched simulated individuals IQ values to both fitted childlessness and fertility scores and calculated predicted fitness and childlessness as above for per-variant s_{het} burden (Supplementary Figure 12). Proportion of reduced reproductive success explained by IQ (and by extrapolation, other traits) is given by the formula:

$$\frac{1 - reduced.fitness_{IQ}}{1 - reduced.fitness_{s_{het}}}$$

Mental Health Traits

As with general cognition, we used estimates from external studies to alleviate biases in UK Biobank phenotype ascertainment (Supplementary Figure 14). In this case, as we were unable to accurately estimate the increased risk of developing a mental health trait as a factor of individual s_{het} burden, we instead utilized odds ratios from Ganna et al.[9]. Only odds ratios for schizophrenia, autism spectrum disorder, and bipolar disorder were retained. As Ganna et al.[9] estimated the risk based on total count of high pLI (≥0.9)[48] genes with PTVs per individual, we assumed that an individual carrying one such variant had an s_{het} burden of 0.162, or the mean of s_{het} value of all high pLI genes. We then converted this into a proportion of individuals with a given mental health trait, *t* at s_{het} *x* by scaling the odds ratio with the following formula:

$$log(OR_{s_{het}[x,t]}) = \frac{log(OR_{ganna}) * s_{het}[x]}{0.162}$$

To establish a baseline expectation for the incidence of each mental health trait at s_{het} 0 we utilized population-level data from Power et al.[13] and extrapolated the incidences for each trait at increasing s_{het} values (Supplementary Figure 12P, S-U). With our expected incidences, we then simulated 100,000 male and female individuals for each s_{het} value (0 to 1, at 0.1 intervals), with individuals randomly assigned as having schizophrenia, autism, or bipolar disorder based on our calculated expected incidences. To generate an expected mean number of children for simulated individuals with mental health traits, we used fertility statistics generated by Power et al.[13]. As Power et al.[13] did not provide childlessness data, we were unable to generate expected childlessness as we did for other traits. Overall

615 predicted reduced fitness attributable to mental health and all values used for performing the
616 above analyses are provided in Supplementary Table 5.

617 Partner at Home, Educational Attainment, and Household Income

618 To determine estimated reduced fitness explained by having a partner at home or
619 educational attainment (Figure 2), we used the log odds ratio from our logistic regression on
620 the effect of individual s_{het} burden for each phenotype (e.g. phenotype ~ s_{het}) to estimate the
621 mean expected value for each phenotype at various s_{het} burdens. We then used the logistic
622 model for the effect of each phenotype on having children (e.g. having children ~ phenotype)
623 to predict mean childlessness and overall reduced fitness through simulations as above
624 (Supplementary Figure 12).
625
626 Due to the UK Biobank recording income in uneven bins and for the entire household rather
627 than each participant, as well as the lack of studies exploring the relationship of rare variant
628 burden with income (e.g. with mental health traits), we were unable to independently model
629 the effect of income on overall fitness as we did for other traits.

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637 Author Contributions

638 E.J.G, M.D.C.N, and K.E.S. assessed the contribution of rare genetic variation to the
639 phenotypes and vital statistics presented in this manuscript. E.J.G and G.K. performed CNV
640 calling. E.J.G. and M.E.K.N. annotated and assessed SNV and InDel variants from provided
641 WES data. K.B., M.K. E.J.G, and M.E.H. curated and analysed Swedish IQ data. E.J.G.,
642 K.E.S., H.C.M. and M.E.H. designed experiments, oversaw the study and wrote the
643 manuscript.

644 Data Availability

645 CNVs, SNVs and InDels included in this study will be returned to the UK Biobank following
646 study publication, as per UK Biobank guidelines.

Code Availability

Code used as part of this project to perform phenotype testing, CNV calling, variant quality control, and generate all main text figures, supplementary figures and supplementary tables is available on github: https://github.com/eugenegardner/UKBBFertility.

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