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In search of the genetic variants of human sex ratio at birth: was Fisher wrong about sex ratio evolution?

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The human sex ratio (fraction of males) at birth is close to 0.5 at the population level, an observation commonly explained by Fisher's principle. However, past human studies yielded conflicting results regarding the existence of sex ratio-influencing mutations—a prerequisite to Fisher's principle, raising the question of whether the nearly even population sex ratio is instead dictated by the random X/Y chromosome segregation in male meiosis. Here we show that, because a person's offspring sex ratio (OSR) has an enormous measurement error, a gigantic sample is required to detect OSR-influencing genetic variants. Conducting a UK Biobank-based genome-wide association study that is more powerful than previous studies, we detect an OSR-associated genetic variant, which awaits verification in independent samples. Given the abysmal precision in measuring OSR, it is unsurprising that the estimated heritability of OSR is effectively zero. We further show that OSR's estimated heritability would remain virtually zero even if OSR is as genetically variable as the highly heritable human standing height. These analyses, along with simulations of human sex ratio evolution under selection, demonstrate the compatibility of the observed genetic architecture of human OSR with Fisher's principle and render it plausible that multiple OSR-influencing genetic variants segregate among humans.

1. Introduction

In most dioecious species, especially mammals, the population-level sex ratio (fraction of males) at birth, or PSR, is approximately 0.5 [1–4], meaning that roughly equal numbers of males and females are born in a population. This parity is commonly explained by Fisher's principle, an idea that can be traced back to Charles Darwin [3], Carl Düsing [5] and Ronald Fisher [6]. Briefly, because the total number of offspring is the same for all males of a population combined and for all females of the population combined, when the population has more males than females (PSR > 0.5), on average a female has more offspring and therefore higher fitness than a male. If the mean parental investment in a male offspring equals that in a female offspring, the lower the offspring sex ratio (OSR) of a genotype, the higher its fitness. Hence, genotypes with lower OSRs are selected for until the PSR reaches 0.5, at which point genotype fitness becomes independent of its OSR. Conversely, when PSR < 0.5, genotypes with higher OSRs are favoured until the PSR reaches 0.5. This elegant adaptive model, acclaimed as 'the most celebrated argument in evolutionary biology' [7], is the prevailing explanation of sex ratio evolution [8–15].

The operation of Fisher's principle has been documented in some species under laboratory [16–19] or natural [20–23] environments. However, most of these species use non-chromosomal sex determination (e.g. temperature-influenced sex determination in Atlantic silverside, paternal genome elimination

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in sciarid flies, haplodiploidy in ants). In species using chromosomal sex determination (e.g. the XY system in mammals and ZW system in birds), evidence for Fisher's principle is scarce [24].

Humans exhibit a PSR of 0.52 to 0.54 depending on the population surveyed [25]. Under the assumption that this approximately even PSR is an outcome of Fisher's principle, OSR should be subject to mutation and genetic variation, because Fisher's principle stops working if OSR is not genetically variable. Surprisingly, despite decades of research, unequivocal evidence for the genetic variation of human OSR is lacking [26–33]. For example, some authors reported that female carriers of BRCA1 and BRCA2 mutations tend to have a reduced OSR [34,35], but others attributed this observation to an ascertainment bias [36]. Boraska *et al.* conducted a large-scale genome-wide association meta-analysis to identify autosomal and X-linked single-nucleotide polymorphisms (SNPs) associated with a participant's sex [33]. The meta-analysis was conducted across 51 studies with a total of 114 863 individuals of European ancestry, with a focus on common variants (i.e. minor allele frequency or MAF > 5%). However, no significantly associated SNPs were detected. Using records of the Swedish population registry, Zietsch *et al.* estimated the heritability of human sex ratio by measuring the concordance in OSR between full siblings [37]. Specifically, a logistic regression with cluster-robust standard errors was applied to the sex of 14 015 421 Swedish cousin pairs (an individual could be included in multiple cousin pairs). The tetrachoric correlation coefficient of the sex of cousins was calculated to estimate the heritability of OSR, which turned out to be not significantly different from zero, with a 95% confidence interval of [−0.00076, 0.00196]. Given that almost every human quantitative trait examined has a significant heritability [38], Zietsch *et al.* argued that their finding means that human OSR is not subject to mutation and thereby Fisher's principle is inapplicable to humans [37]. They proposed that a genetically invariant OSR that slightly exceeds 0.5 results from the random segregation between X and Y chromosomes in male meiosis coupled with a general between-sex difference in embryonic mortality [37]. Furthermore, under this hypothesis in which OSR is not subject to mutation, sex chromosome segregation distorters are presumably absent; hence, selection is not needed to maintain an approximately even PSR.

Several authors objected to Zietsch *et al.*'s rejection of Fisher's principle by arguing that a zero heritability of OSR at present does not preclude past selections on OSR [39,40]. By simulating sex ratio evolution under Fisher's principle, Zietsch *et al.* countered that Fisher's principle does not predict a loss of OSR's heritability if it was once present [41,42]. Despite these disputes, all agreed that human OSR is not heritable at present [37,39–42].

How confident are we that human OSR is not currently heritable? Given the number of offspring (n) of a person, the standard error of its OSR estimate as a fraction of its OSR is $\mathrm{CV}=\sqrt{\mathrm{OSR}(1-\mathrm{OSR})/n}/\mathrm{OSR} \approx 1/\sqrt{n}$ when OSR ≈ 0.5. That is, the estimation error of OSR equals 100, 71 and 58% of its true value when n = 1, 2 and 3, respectively. Although some authors estimated an individual's OSR from all of his/her offspring [28], this practice causes unequal OSR estimation errors among individuals, complicating downstream statistical analysis. As a result, many past studies estimated one OSR from each child of the individual. That is, if a person has three children, three separate estimates of OSR for the person are obtained, one per child [37]. Regardless of how OSR is estimated, due to the small number of offspring per human individual, especially in modern societies, OSR estimates are associated with enormous measurement errors. Such errors are expected to hinder the detection of OSR-influencing genetic variants and cause a substantial underestimation of OSR's heritability.

In this study, we first demonstrate that previous large-scale genetic studies of human OSR are underpowered. We then conduct a more powerful genome-wide association study (GWAS) in the UK Biobank (UKB) [43] that leads to the detection of a rare, large-effect SNP that is associated with OSR. Additionally, a gene-based burden test identifies two OSR-associated genes. We show that OSR's imprecise measurement would cause its observed heritability to be virtually zero even if its genetic architecture equals that of human standing height, which has one of the highest heritabilities of all human polygenic traits [44]. Finally, using simulations of sex ratio evolution respectively under stabilizing and directional selection, we show that the observed genetic architecture of human OSR is compatible with Fisher's principle, suggesting the plausibility of segregating OSR-influencing genetic variants in humans.

2. Results

(a) Statistical power of prior large-scale genetic analyses of human OSR

As mentioned, two previous studies of large samples found no genetic variants [33] and no significant heritability [37] of human OSR. We first assessed the power of Zietsch *et al.*'s study [37] by simulating an OSR-influencing SNP in a hypothetical sample where the sample size matched that in the original study. Note that while the original study considered 14 015 421 redundant cousin pairs, we simulated the same number of independent cousin pairs, potentially overestimating the power of the original study (see §4). By specifying the MAF and effect size on OSR (β) of the SNP, we generated artificial sex configurations of the sample. Applying the statistical method used in the original study, we explored whether the simulated data exhibit a significant OSR heritability. The simulation was repeated 1000 times and the probability of detecting a significant OSR heritability was estimated (figure 1*a*). Let us classify a SNP by MAF into three bins: extremely rare (<1%), rare (≥1% but <5%), and common (≥5%). We similarly classify a SNP by β (in unit of OSR) into three categories: small-effect (<0.01), intermediate-effect (≥0.01 but <0.05) and large-effect (≥0.05). We found the power of Zietsch *et al.*'s study to be generally low; it could not detect a significant OSR heritability even in the presence of a common, large-effect SNP. For example, the chance of detecting a significant heritability is smaller than 0.1% even when the SNP has MAF = 10% and β = 0.1 (i.e. having one mutant allele changes OSR from 0.52 to 0.62 or 0.42). Given the simulation scheme mentioned, the actual power of Zietsch *et al.*'s study is probably even lower due to double counting the same participants in different cousin pairs.

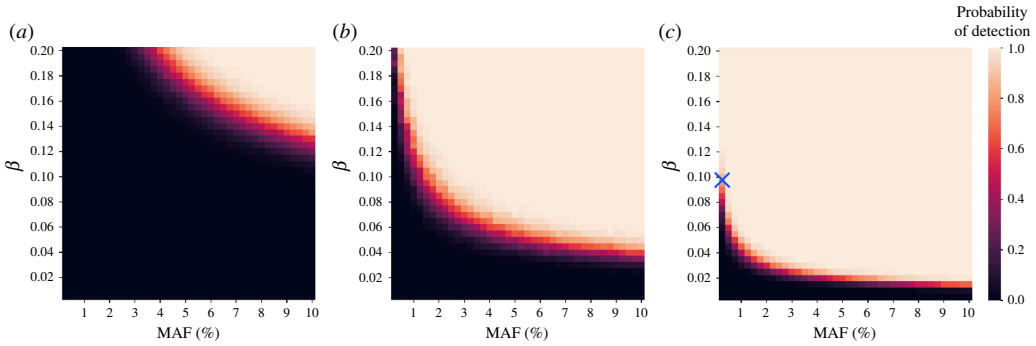

Figure 1. Statistical power analysis. (*a*) Probability of detecting a significant heritability of offspring sex ratio (OSR) by Zietsch *et al.*'s study. (*b*) Probability of detecting a significant OSR-associated SNP by Boraska *et al.*'s GWAS. (*c*) Probability of detecting a significant OSR-associated SNP by the present UKB-based GWAS. The blue cross represents the MAF (0.25%) and |β| (0.097) of rs144724107. MAF, minor allele frequency; β, effect size on OSR. Colours show the probability of detection based on 1000 simulation replications.

We similarly simulated datasets mimicking those in Boraska *et al.*'s study [33] to assess the probability of detecting an OSR-influencing SNP of a given MAF and β (figure 1*b*). We found that Boraska *et al.*'s study is more powerful than Zietsch *et al.*'s. For example, the hypothetical SNP in the preceding paragraph could be detected with a probability exceeding 99.9% in Boraska *et al.*'s study. However, its chance of detection becomes lower than 0.1% if MAF = 1% and $\beta = 0.1$ or if MAF = 10% and $\beta = 0.04$. Hence, Boraska *et al.*'s study is still not sufficiently powerful for detecting common, intermediate-effect SNPs or rare, large-effect SNPs.

(b) Statistical power of UKB-based GWAS of human OSR

Given the limited statistical power of the previous large-scale genetic studies of human OSR, we wondered whether a higher power might be achieved by using the UKB, which includes about 0.5 million British participants with genotype information. Specifically, we considered 452 557 UKB participants of European ancestry. However, because the UKB does not record the numbers of daughters and sons of each participant, we used the numbers of full sisters and full brothers of a participant to measure the OSR of the parents of the participant. The genetic relatedness between UKB participants and their parents permits a GWAS to identify SNPs associated with the above estimated OSR (see §4). To prevent double counting of siblings, we removed a further 20 822 participants whose full siblings had already been counted as participants, resulting in a final sample size of 431 735 participants with sex information for a total of 873 715 full siblings. As described in the preceding section, we used computer simulation to assess the power of this GWAS in identifying an OSR-influencing SNP.

Our simulation showed that, compared with the two previous studies, this UKB-based GWAS is more powerful and that it can detect extremely rare, large-effect SNPs and common, intermediate-effect SNPs (figure 1*c*). For example, the probability of detection is 87.0% when MAF = 0.25% and $\beta = 0.1$ and the probability of detection exceeds 99.3% when MAF = 10% and $\beta = 0.02$. However, this GWAS still lacks power in identifying small-effect SNPs (i.e., $\beta < 0.01$) and some rare, intermediate-effect SNPs (e.g. MAF < 5% and $\beta = 0.02$).

To assist future genetic studies of human OSR, we also used simulation to investigate the statistical power of GWAS conducted in samples that are respectively two, four, and eight times the size of the UKB. The ability to detect extremely rare or small/intermediate-effect OSR-associated SNPs is improved (electronic supplementary material, figure S1). For instance, when MAF = 0.25% and $\beta = 0.05$, the detection probability is 2.2, 21.2, 88.7% and >99.9% in samples that are one, two, four and eight times the size of the UKB, respectively. When MAF = 10% and $\beta = 0.01$, the detection probability is 7.7, 56.6, 99.6 and >99.9% in samples that are one, two, four and eight times the size of the UKB, respectively.

(c) UKB-based GWAS detects an OSR-associated SNP

Encouraged by the above power analysis, we performed a GWAS of OSR in the UKB, which yielded a single, genome-wide significant signal at rs144724107 in Chromosome 10 ($p = 3.36 \times 10^{-8}$) (figure 2*a*). The significant SNP exhibits a high imputation quality (INFO = 0.89, meaning that the effective data at the imputed SNP is approximately equivalent to a set of perfectly observed genotypes in 89% of samples) and is a G/A polymorphism where the derived A allele has a frequency of 0.25% among UKB participants. In the data analysed, GG individuals have a total of 451 365 brothers and 416 705 sisters, resulting in a sex ratio of 0.5200 (standard error s.e. = 0.0005); GA individuals have a total of 1517 brothers and 1700 sisters, resulting in a sex ratio of 0.472 (s.e. = 0.008); and AA individuals have a total of 0 brothers and 1 sister due to the rarity of the A allele. The MAF and effect size of the OSR-associated SNP detected fit the expectation of the power (82.7%) of our UKB-based GWAS (figure 1*c*).

A logistic regression found that the A allele at rs144724107 has an odds ratio of 0.823 per dose on sibling male/female ratio, meaning that having one A allele lowers the sibling male/female ratio to 0.823 times its normal level. To obtain the odds ratio on offspring male/female ratio from that on sibling male/female ratio, we performed simulations to find the relationship between the two odds ratios (see §4). From this relationship, we estimated that the A allele has an odds ratio of 0.677 per dose on offspring male/female ratio (electronic supplementary material, figure S2). That is, if GG individuals have an OSR of 0.520, GA and AA individuals are expected to have OSRs of 0.423 (or 19% reduction) and 0.332 (or 36% reduction), respectively.

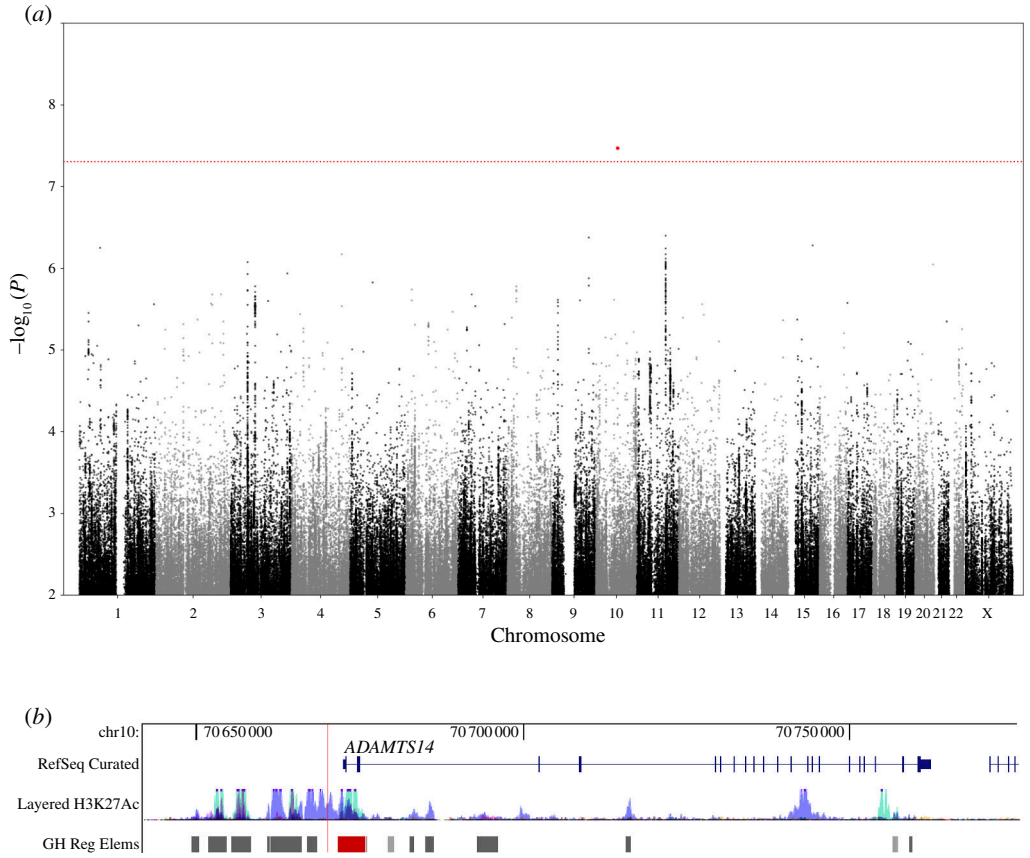

Figure 2. GWAS in the UKB detects a SNP that is significantly associated with OSR. (*a*) Manhattan plot for the GWAS of sex ratio in the UKB. The red dotted line represents the genome-wide significant cutoff ($p = 5 \times 10^{-8}$), and the red dot represents the genome-wide significant signal at rs144724107. (*b*) Genomic context of rs144724107, which is indicated by a red vertical line. RefSeq curated: RefSeq genes from NCBI (blue vertical lines indicate exons); layered H3K27Ac: H3K27Ac marks, which are often found near regulatory elements, in seven cell lines (distinguished by colours) from ENCODE; GH reg elems: GeneHancer regulatory elements (grey: enhancers; red: promoters).

The detected SNP is located 2475 nucleotides upstream of the transcription start site of the ADAMTS14 gene (figure 2*b*). ADAMTS14 belongs to the ADAMTS protein family that encodes multidomain extracellular proteases. Through their roles in extracellular matrix (ECM) remodelling, ADAMTS family members affect multiple steps in animal reproduction, including folliculogenesis, ovulation, implantation, placentation, parturition, testicular development, spermatogenesis and fertilization [45]. For example, experimental data suggest that mouse ADAMTS10 from the sperm acrosome degrades zona pellucida, an ECM surrounding the oocyte, to allow fertilization [46]. This said, the potential role of ADAMTS14 in reproduction is poorly understood [45].

To validate the detected GWAS signal, we examined an independent sample—14 590 individuals of European ancestry from the Women's Health Initiative (WHI) [47]. The WHI includes the information of the number of daughters and sons of each (woman) participant. However, the SNP of interest (rs144724107) was not included in the dataset, probably because the A allele is too rare among WHI participants of European ancestry and its imputation did not meet the quality standard. We were forced to abort this validation. Given the rarity of the A allele at rs144724107 and the lack of association signals of SNPs in the vicinity of this SNP (figure 2*a*), the detected association could be spurious, and therefore future verification of our finding is desired.

Given the special role of sex chromosomes in sex determination, one might expect OSR-associated SNPs to be enriched on sex chromosomes relative to autosomes. To test this hypothesis, we examined independent, significant SNPs in the UKB-based GWAS, where independence was ensured using plink2 (indep-pairwise 500 kb 0.2), and significance was determined by various nominal *p*-value cutoffs. However, we did not find evidence for the hypothesis, because the fraction of independent, significant SNPs do not differ significantly between X and autosomes (p = 0.21, 0.23 and 0.69, respectively, with significance defined by nominal $p < 0.01$, 0.001 and 0.0001; Fisher's exact test).

(d) Gene-based analyses detect two OSR-associated genes

When multiple SNPs in a gene each have a relatively small effect on a trait, a gene-based GWAS may detect the associated gene that an SNP-based GWAS cannot [48]. We thus performed two gene-based association analyses of OSR in the UKB. First, we summarized the SNP-based GWAS summary statistics for each gene using the package sumFREGAT [49] (see §4). However, this analysis detected no OSR-associated genes with a false discovery rate smaller than 5% (electronic supplementary material, figure S3a). Second, we employed a gene-based burden test for rare missense variants (MAF < 1%) using the UKB exome data [50] (see §4). This analysis identified two genes, *RLF* and *KIF20B*, to be associated with OSR with a false discovery rate smaller than 5% ($p = 8.23 \times 10^{-7}$ and $p = 2.24 \times 10^{-6}$, respectively) (electronic supplementary material, figure S3b). *RLF*

encodes a zinc finger protein predicted to have a DNA-binding transcription activator activity (provided by Alliance of Genome Resources [51], April 2022), but it has no known function in spermatogenesis or fertilization. *KIF20B* encodes a kinesin-like protein in the kinesin-6 family and plays an essential role in cytokinesis [52]. Kinesin-like proteins are generally functional during spermatogenesis [53,54]. Consistently, *KIF20B* is highly expressed in testis [55]. Additionally, *KIF20B* is expressed in the human ovary, suggesting a potential role in oocyte meiosis [56]. Because part of the oocyte meiosis occurs after fertilization, *KIF20B* may influence OSR by affecting the success rate of oocyte meiosis based on the genotype of the fertilizing sperm.

ADAMTS14 is not significantly associated with OSR in the sumFREGAT test (nominal $p = 0.15$) or the burden test (nominal $p = 0.67$). *BRCA1* and *BRCA2*, the previously debated OSR-associated genes [34–36], are not significantly associated with OSR in either test (nominal $p = 0.72$ and 0.92 for *BRCA1* and nominal $p = 0.57$ and 0.57 for *BRCA2*, respectively).

Additionally, genes that are sexually differentially expressed in early human embryonic development [57] do not show significantly different p values when compared with all other genes considered in the above two gene-based association analyses ($p = 0.24$ and 0.55, respectively, two-tailed Mann–Whitney U test). Similarly, autosomal genes with haploid-biased expressions in sperm do not show significantly different p values when compared with other autosomal genes expressed in sperm [58] ($p = 0.48$ and 0.85, respectively, two-tailed Mann–Whitney U test).

(e) Imprecise measurement of OSR can explain its non-significant heritability estimate

After surveying genetic variants and genes that are potentially associated with human OSR, we used linkage disequilibrium score regression (LDSC) [59] to estimate the heritability of human OSR. From the UKB-based GWAS, we estimated that the SNP-based heritability of OSR is −0.00055, with a 95% confidence interval of [−0.00147, 0.00038]. We further used the UKB data to infer the family based heritability from between-relative correlations in offspring sex (see §4), which yielded 0.0032 [−0.081, 0.092]. The virtually zero heritability estimates of OSR from the UKB are in line with Zietsch *et al*. estimate from Swedish people [37].

The large estimation error of OSR due to the small number of offspring per person renders the phenotypic variance of OSR substantially overestimated and heritability substantially underestimated. To assess the impact of the OSR measurement error on the estimated heritability, we simulated a hypothetical human sample where the genetic architecture of OSR is identical to that of the standing height, a trait known to be highly heritable [60]. Briefly, for each UKB participant of European ancestry, we set his/her hypothetical OSR by dividing his/her standing height by twice the average standing height of all UKB participants of European ancestry (figure 3*a*; see §4). The hypothetical OSR has a mean of 0.5 and a coefficient of variation (CV) equal to that of the standing height. The potential effects of common GWAS covariates on the hypothetical OSR were subsequently removed statistically (figure 3*a*). We then conducted a GWAS on the hypothetical OSR and calculated its SNP-based heritability. As expected, the SNP-based heritability is as high as that of the standing height: 0.43 with a 95% confidence interval of [0.395, 0.465] (figure 3*b*).

We then generated the sexes of a participant's offspring by binomial sampling based on the hypothetical OSR and the true number of siblings. The simulated dataset allowed us to conduct a GWAS and calculate the SNP-based heritability of the estimated (hypothetical) OSR (figure 3*a*). The SNP-based heritability of the estimated (hypothetical) OSR is only 6.73×10^{-4}, with a 95% confidence interval of [-1.82×10^{-4}, 1.53×10^{-3}] (figure 3*b*). We repeated the simulation 20 times. The mean SNP-based heritability of the estimated (hypothetical) OSR is 6.9×10^{-4}, and none of the 20 estimates are significant at the 5% level after a Bonferroni correction for multiple testing (figure 3*b*). Clearly, even when the heritability of OSR is as high as that of the standing height, the heritability of the estimated OSR is almost zero because of the large error in measuring OSR.

(f) The observed genetic architecture of human OSR does not contradict Fisher's principle

We detected only one SNP and two genes that are significantly associated with the human OSR in the UKB and found the estimated heritability of OSR to be indistinguishable from 0. While these observations can be explained by the enormous measurement error of OSR, it remains unclear whether these observations are consistent with the expectations of an evolving population governed by Fisher's principle. To address this question, we used SLiM 3 [61] to perform population genetic simulations of human sex ratio evolution under Fisher's principle, followed by a comparison between OSR's genetic architecture observed in the simulated population with that observed in the UKB. We separately considered two evolutionary scenarios: stabilizing selection and directional selection.

In the first scenario, the optimal PSR was set at 0.5. Evolution started with a genetically homogenous population having an effective population size (N_e) of 7310 (following the estimated ancestral human population size [62]) and an OSR of 0.5. Fisher's principle will operate as the population undergoes sexual reproduction and propagates, favouring alleles that increase the proportion of offspring with the rarer sex when PSR deviates from 0.5, thereby creating a scenario of stabilizing selection. Mutations altering the OSR followed an exponential size distribution. They entered the population and were subjected to drift and selection. We first simulated the evolution of this population till it reached the mutation-drift-selection equilibrium. We then set this time to be 800 000 years before present and started the evolutionary simulation of mutation, drift and selection along with a model of human demographic history [62] until present. Briefly, this demographic model represents a relatively constant ancestral human population in Africa, followed by an out-of-Africa migration and a split between European and Asian populations, which subsequently experienced rapid expansions. At the end of the simulation, we examined the European population for the number of OSR-influencing genetic variants segregating in the population, the number of detectable OSB-influencing SNPs in a sample resembling the UKB, and the estimated heritability of OSR.

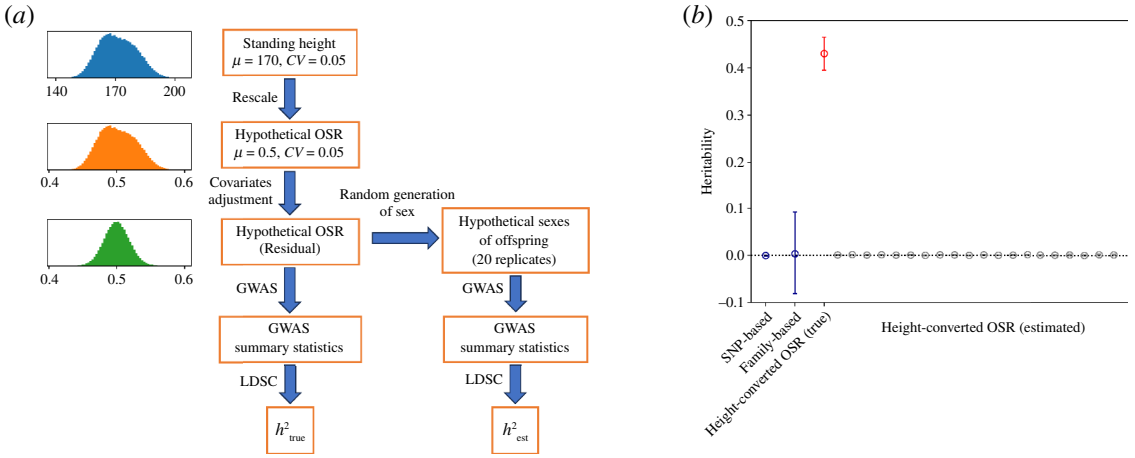

Figure 3. Heritability of human sex ratio and estimated sex ratio if the genetic architecture of sex ratio equals that of human standing height. (*a*) Procedure of generating the hypothetical sex ratio from standing height and estimating two heritabilities (h^2_{true}: heritability of hypothetical OSR; h^2_{est}: heritability of estimated hypothetical OSR). (*b*) Heritability of OSR. SNP-based: SNP-based estimate of OSR heritability; family based: family based estimate of OSR heritability; height-converted OSR (true): SNP-based heritability of hypothetical OSR when the genetic architecture of OSR is assumed to equal that of standing height; height-converted OSR (estimated): SNP-based heritability of estimated hypothetical OSR. Error bars represent 95% confidence intervals. A circle is shown in red when the heritability is significantly greater than zero ($p < 0.05$).

The results of the simulation varied depending on OSR's mutation rate per genome per generation (μ) and mean mutation size ($\bar{\beta}$) assumed (figure 4*a–c*). Many combinations of μ and $\bar{\beta}$ yielded simulation results consistent with the empirical estimate of the OSR heritability, whose 95% confidence interval is shown by the shaded area in figure 4*a*. For example, when $\mu \leq 10^{-5}$ per genome per generation, equivalent to a mutational target size of ≤ 833 nucleotides under a human mutation rate of 1.2×10^{-8} per nucleotide per generation [63], almost any reasonable value of $\bar{\beta}$ would yield a result compatible with the observed heritability of human OSR (figure 4*a*). However, when μ is larger, relatively small $\bar{\beta}$ values are required to produce results compatible with the observed heritability estimate. For instance, if $\mu = 10^{-4}$, equivalent to a mutational target site of 8333 nucleotides, $\bar{\beta}$ has to be ≤0.01. Similarly, many combinations of μ and $\bar{\beta}$ produced simulation results consistent with the detectability of 0 to 1 OSR-associated SNP in the UKB (shaded area in figure 4*b*). The number of OSR-influencing genetic variants present in the simulated population increases with μ but is virtually independent of $\bar{\beta}$ (figure 4*c*). When μ is between 10^{-5} and 10^{-4}, for example, 10–100 causal variants are expected (figure 4*c*), but the vast majority are undetectable in a sample like the UKB (figure 4*b*).

In the second scenario, when the population reached the mutation-drift-selection equilibrium aforementioned, we altered the expected equilibrium PSR from the default value of 0.500 to 0.524 and set that time to be 800 000 years before present. We then started the simulation of mutation, drift and selection along with the consideration of the human demographic history mentioned. As in the simulation of the first scenario, we observed many combinations of μ and $\bar{\beta}$ that yielded results consistent with empirical observations of the OSR heritability and number of detectable OSR-influencing SNPs (figure 4*d,e*). In fact, given μ and $\bar{\beta}$, the simulation results under the two scenarios (figure 4*a–f*) are quite similar, suggesting that it would be difficult to distinguish between the two scenarios based solely on the present-day data. We further examined the adaptive shift of PSR in our simulation under the second scenario, finding that a low μ (e.g. $\leq 10^{-5}$ per genome per generation) coupled with a low $\bar{\beta}$ (e.g. ≤0.0025) would not be sufficient for the PSR to move from its original optimum (0.500) to the new optimum (0.524) in 0.8 million years (figure 4*g*). However, the adaptive shift in PSR is expected under $\mu \geq 10^{-5}$ and $\bar{\beta} \geq 0.01$ (figure 4*g*). Note that upon reaching the new optimum, PSR is expected to be under stabilizing selection again. Together, our simulations demonstrate that the empirically observed genetic architecture of human OSR is compatible with the expectation from Fisher's principle.

3. Discussion

We reasoned that, because of the enormous measurement error of human OSR as a result of the small number of offspring per person, the statistical power in detecting OSR heritability or identifying OSR-associated genetic variants is low. Indeed, our simulation confirmed that previous large-scale genetic analyses of human OSR were underpowered. We then conducted a more powerful GWAS in the UKB and identified a rare allele at rs144724107 that is associated with a 19% reduction in OSR, meaning that the probability that a birth yields a daughter rises from 0.480 for individuals not carrying this allele to 0.577 for individuals heterozygous for this allele. While the causal effect of this SNP on OSR and the potential mechanism involved are unknown, the SNP's genomic location upstream of *ADAMTS14*, a member of the *ADAMTS* extracellular protease family that has been implicated in spermatogenesis and fertilization [45], is tantalizing. Notwithstanding, the lack of association of SNPs in the vicinity of rs144724107 with OSR (figure 2*a*) and the nonsignificant result for *ADAMTS14* in two gene-based tests suggest that the detected association at rs144724107 could be spurious and therefore requires validation in independent samples (given that our attempted validation in the WHI was aborted due to its lack of information about rs144724107). The validation could be challenging because, at rs144724107, the MAF is only 0.25% in individuals of European ancestry. Note that because our

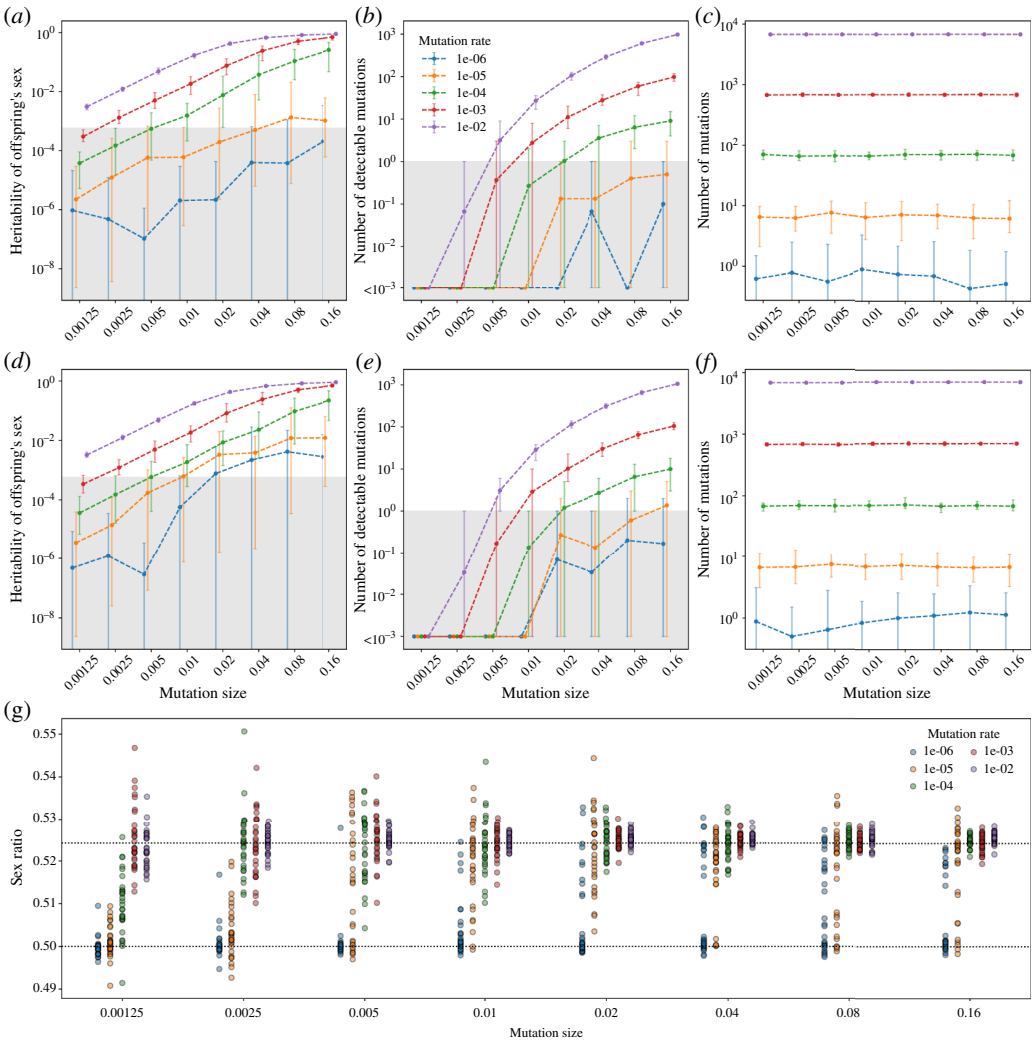

Figure 4. Key statistics at the end of simulation of human sex ratio evolution under Fisher's principle. (*a–c*) Heritability of OSR (*a*), number of detectable OSR-influencing SNPs (*b*) and number of segregating OSR-influencing variants (*c*) at the end of the simulated human sex ratio evolution under stabilizing selection. (*d–g*) Heritability of OSR (*d*), number of detectable OSR-influencing SNPs (*e*), number of segregating OSR-influencing variants (*f*) and population sex ratio (*g*) at the end of the simulated human sex ratio evolution under directional selection from the original population sex ratio of 0.500 to the new equilibrium of 0.524. In (*a–f*), error bars represent the maximum and minimum values from 30 simulation replications, shaded area represents the 95% confidence interval of the empirically estimated heritability (*a,d*) or the range of the number of empirically detected OSR-associated SNPs (between 0 and 1) (*b,e*). In (*g*), the lower dotted line represents the initial population sex ratio while the upper dotted line represents the equilibrium population sex ratio. Mutation rate refers to the number of mutations per generation per genome that affect OSR. Mutation size refers to the mean effect of mutations on OSR.

GWAS associated a participant's genotype with sibling's sex, we cannot distinguish whether the potential effect of rs144724107 is maternal or paternal.

Our gene-based tests found two genes, *RLF* and *KIF20B*, to be significantly associated with OSR. While the potential mechanism by which *RLF* influences OSR is unclear, *KIF20B* functions in cytokinesis [52] and is likely involved in spermatogenesis and oocyte meiosis [53,54,56], which could influence OSR. Further research is needed to validate the potential effects of these genes on OSR. Neither *BRCA1* nor *BRCA2*, whose potential impacts on OSR have been debated [34–36], are associated with OSR in our gene-based tests.

Despite the identification of an OSR-associated SNP in the UKB, the SNP is rare and the estimated heritability of human OSR is not significant. We found that, because of the large measurement error of human OSR, even if the genetic architecture of OSR equals that of human standing height, which has one of the highest heritabilities of all human polygenic traits [44], we would not have observed OSR's heritability to be significant. In other words, the seeming lack of heritability of human OSR can be explained by OSR's large measurement error. Given the above finding and the fact that almost all human quantitative traits exhibit significant heritability [38], the simplest and most plausible interpretation is not that human OSR is immune to mutation but that the extreme imprecision of human OSR estimation hinders the detection of its heritability.

Our simulation of human sex ratio evolution under Fisher's principle demonstrated that the observed genetic architecture of human sex ratio is compatible with Fisher's principle. Specifically, the empirical observation is compatible with the scenario of stabilizing selection as well as the scenario of directional selection acting on human sex ratio; without additional information, it would be difficult to distinguish between the two scenarios. Our simulation further suggests the plausibility of segregating OSR-influencing genetic variants in humans, the number and size of which depend on mutation rate and size. However, because the past and present genetic analyses would have identified most large-effect variants and most common, intermediate-effect variants (figure 1), the undetected genetic variants, if they exist, likely have small effects or have intermediate effects

and are rare. This is consistent with the findings from our evolutionary simulation that OSR mutations have either a small target size, a small effect size, or both to be compatible with the observed genetic architecture of human OSR (figure 4). Our power analysis suggests that, when the sample size increases to eight times that of the UKB, even some extremely rare, intermediate-effect SNPs (MAF < 1% and $\beta > 0.02$) could be detected (electronic supplementary material, figure S1). However, extremely rare, small-effect SNPs (MAF < 1% and $\beta < 0.01$) would be difficult to detect even in such large samples (electronic supplementary material, figure S1). This said, if genes controlling OSR are conserved across animals, a more powerful strategy in identifying such genes would be to use species that have many more offspring than humans do, because of the higher precision in measuring OSR in such species.

While our study focused on human OSR and the forces governing the evolution of human OSR, we note that identifying genes and mutations that impact OSR can potentially revolutionize animal husbandry. In agriculture, one sex is often of substantially larger economic value (mostly females) than the other (e.g. hens for egg production and cows for milk production), and individuals of lower economic value (mostly males) are usually killed soon after birth. Finding genetic variants in farm animals with effects as large as that computed for human rs144724107 would likely bring huge profits and contribute to animal welfare.

Our results also highlight the importance of considering phenotyping errors in assessing heritability and identifying genetic variants of phenotypic traits, because there are conceivably other traits that are as difficult to measure precisely as OSR (e.g. propensity for divorce).

4. Material and methods

(a) Study samples

We limited the analysis to individuals of European ancestry to avoid population stratification that could generate spurious results in GWAS. The UKB data [43] analysed included 452 557 participants of European ancestry aged between 40 and 70 (245 509 females and 207 048 males recruited from the UK). European ancestry was determined by self-reported ethnic background (data-field 22009) and by clustering (K-means with $K = 4$) the first four genetic principal components (data-field 21000). An individual was included in the analysis only when s/he self-reported as 'white' and was genetically clustered with most of other 'white' individuals. Individuals with genotype missing rate greater than 0.02 were excluded. To prevent double counting of siblings, we further removed 20 822 participants whose full siblings had already been counted as participants, resulting in a final sample size of 431 735 participants with sex information for a total of 873 715 full siblings. Our study was approved by the UKB (#177030).

Our analysis of the WHI data [47] included 14 590 individuals of European ancestry aged between 50 and 79 (all postmenopausal females recruited from the USA). European ancestry was determined by self-reported ethnic background (RACE = 'white'). Additional quality control on genotyped cohort is described in the WHI GWAS Harmonization and Imputation Project [64]. We aimed to use the WHI data to validate the OSR-associated SNP identified from the UKB. Our project was approved by the WHI (#33897).

(b) Variant screening

For genetic variants in the UKB, genotyping, imputation and preliminary quality control were conducted by the UKB [43]. We excluded SNPs that satisfy any of the following conditions: (i) MAF < 0.1%, (ii) imputation quality INFO < 0.8, (iii) genotyping missing rate > 20% and (iv) Hardy–Weinberg equilibrium rejected at $p = 10^{-10}$. In the end, 13 562 115 SNPs on autosomes and in the non-pseudoautosomal region of the X chromosome were used.

The WHI data consist of six GWAS studies: Hip Fracture GWAS (HIPFX), SHARe, GARNET, WHIMS+, GECCO and MOPMAP, although participants of SHARe are non-Europeans so they were not included in our analysis. Each study performed cohort recruitment, genotyping, and initial quality control independently. Data harmonization and imputation were then conducted jointly for the six GWAS studies by WHI GWAS Harmonization and Imputation Project (see [64] for detailed descriptions). We merged the five harmonized datasets using Canary [65], and excluded SNPs that have low imputation quality (Rsq < 0.8) or have MAF < 1% (rs144724107 was absent even before the above filtering). In the end, 6 263 078 SNPs remained. SNPs on the X chromosome were not imputed, so they were not included.

(c) Sex ratio

The UKB does not record participants' numbers of daughters and sons, but instead provides their numbers of full sisters and full brothers. The relevant UKB survey question is 'How many sisters/brothers do you have? (Please include those who have died, and twin sisters/brothers. Do not include half-sisters/half-brothers, step-sisters/step-brothers or adopted sisters/brothers.)' Hence, the answer to this question precisely tells the sex ratio at birth for the participant's full siblings. The information was collected only from those participants who indicated that they were not adopted as a child. We utilized the numbers of full brothers and sisters of a participant (i.e. the OSR of the participant's parents) in the GWAS to identify OSR-associated SNPs. Note that we did not consider the sex of the participant in the GWAS because of the known participation difference between the two sexes [66]. The logic behind the GWAS on the sibling sex ratio is that, if an allele is associated with the birth of a boy,

that allele would be overrepresented in families with a male-biased sibling sex ratio. That is, an individual carrying that allele is likely to have more brothers than sisters. Therefore, the allele is expected to be identified by the GWAS on the sibling sex ratio.

The WHI has records of the numbers of daughters and sons of a participant. The relevant WHI survey questions are 'Have you had any daughters/sons?' and 'How many daughters/sons?'.

(d) GWAS

Details of GWAS are described in electronic supplementary material.

(e) Statistical power analysis

To evaluate the statistical power of the present GWAS and two previous large-scale genetic analyses of sex ratio [33,37], we conducted computer simulations, with the detailed procedures described in electronic supplementary material.

(f) Correcting the observed odds ratio in the UKB-based GWAS

Because our GWAS in the UKB measured the association between a participant's genotype and his/her sibling's sex, which was an indirect association analysis of OSR, the actual effect of an allele on OSR was underestimated. Because the genetic relatedness between a person and his/her parent is twice that between the person and his/her sibling, the actual effect size (log odds ratio) on OSR is expected to be twice the inferred effect size on the sibling sex ratio. To ensure rigor and minimize potential biases from empirical measurement errors, we estimated the actual effect of the significant allele by simulation. Specifically, we simulated sexes of the siblings of the UKB participants following the preceding section by assuming a true odds ratio of the allele of interest. The true odds ratio ranged from 0.55 to −0.82 in our simulation, and the allele frequency was fixed at 0.0025. The allele's effect was assumed to be paternal. As in the GWAS, we conducted a logistic regression, using the sibling sex as the dependent variable and the participant's genotype as the independent variable, to estimate the observed odds ratio. The simulation was replicated 1000 times to calculate the mean and 95% confidence interval of the observed odds ratio. The relationship between the true odds ratio and the observed odds ratio (electronic supplementary material, figure S1) was used to correct the observed odds ratio. As expected, the true odds ratio is about twice the observed odds ratio in the log scale.

(g) Heritability estimation

SNP-based and family-based heritabilities of sex ratio were estimated, with the detailed procedures described in electronic supplementary material.

(h) Gene-based association analyses

We performed two gene-based association analyses, with the details described in electronic supplementary material.

(i) Simulating the genetic architecture of sex ratio following that of standing height

To simulate the genetic architecture of sex ratio following that of human standing height, we obtained the hypothetical sex ratio of a participant of European ancestry in the UKB through four steps described in electronic supplementary material.

(j) Simulations of human sex ratio evolution

We used SLiM 3 [61] to simulate sex ratio evolution in humans, with the detailed procedure described in electronic supplementary material.

Ethics. This work was approved by the University of Michigan Institutional Review Boards (HUM00227418).

Data accessibility. The UKB and WHI data used are available at the respective databases (applications required for access). Custom code can be downloaded from Dryad [67].

Supplementary material is available online [68].

Declaration of AI use. We have not used AI-assisted technologies in creating this article.

Authors' contributions. S.S.: conceptualization, data curation, formal analysis, investigation, methodology, writing—original draft, writing—review and editing; J.Z.: conceptualization, funding acquisition, methodology, project administration, resources, supervision, writing—original draft, writing—review and editing.

Both authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. We declare we have no competing interests.

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