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Authors

Swinford, NA
Prall, SP
Gopalan, S
et al.

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Increased homozygosity due to endogamy results in fitness consequences in a human population

N. A. Swinford[a], S. P. Prall[b], S. Gopalan[c], C. M. Williams[d], J. Sheehama[e], B. A. Scelza[f], and B. M. Henn[a,g,h,1]

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Recessive alleles have been shown to directly affect both human Mendelian disease phenotypes and complex traits. Pedigree studies also suggest that consanguinity results in increased childhood mortality and adverse health phenotypes, presumably through penetrance of recessive mutations. Here, we test whether the accumulation of homozygous, recessive alleles decreases reproductive success in a human population. We address this question among the Namibian Himba, an endogamous agro-pastoralist population, who until very recently practiced natural fertility. Using a sample of 681 individuals, we show that Himba exhibit elevated levels of "inbreeding," calculated as the fraction of the genome in runs of homozygosity (F_{ROH}). Many individuals contain multiple long segments of ROH in their genomes, indicating that their parents had high kinship coefficients. However, we do not find evidence that this is explained by first-cousin consanguinity, despite a reported social preference for cross-cousin marriages. Rather, we show that elevated haplotype sharing in the Himba is due to a bottleneck, likely in the past 60 generations. We test whether increased recessive mutation load results in observed fitness consequences by assessing the effect of F_{ROH} on completed fertility in a cohort of postreproductive women (n = 69). We find that higher F_{ROH} is significantly associated with lower fertility. Our data suggest a multilocus genetic effect on fitness driven by the expression of deleterious recessive alleles, especially those in long ROH. However, these effects are not the result of consanguinity but rather elevated background identity by descent.

mutation load | runs of homozygosity | fertility | bottleneck | endogamy

Significance

Human populations have been shown to differ in their mutation load—the accumulation of mutations in their genomes; the penetrance of these mutations will depend on their recessive, dominant, or additive states. However, most estimates of mutation load are theoretical and have not been associated with evolutionary fitness (i.e., reproductive success). Here, we assess the effect of runs of homozygosity on fitness in a natural fertility population from northern Namibia. As the homozygous fraction of the genome increases, female fertility is significantly reduced. This suggests a multilocus genetic effect on fitness driven by the expression of deleterious recessive alleles. Interestingly, despite a cultural preference for consanguineous marriage in the Himba, we find that such marriages rarely occur between close biological kin.

Through the process of mutation, deleterious alleles constantly arise in a population, and an understanding of how these variants affect phenotype is crucial for the study of human evolution and genetic architecture. Previous work has explored the variance in mutation load among populations, the demographic models that drive those loads, the distribution of fitness effects for new mutations, and the efficacy of selection for removing deleterious variants. However, direct evidence of the consequences of mutation load on fitness in human populations is lacking (1–6). Genetic theory dictates many factors affect a population's mutation load, including founder effects, bottlenecks, small population size, endogamy, and consanguinity. Because a population's mutation load relates to the number of deleterious mutations that have accumulated in its gene pool over time (1), it is thought that an increased mutation load leads to fitness consequences. Further, many deleterious mutations tend to be recessive (2), so processes that increase the level of homozygosity in a genome may result in strong fitness consequences. Evidence for the deleterious effects of recessive mutation load has been shown in multiple species. Increased homozygosity is linked to higher mortality in translocated desert tortoises (7) and decreased fitness in Florida scrub-jays (8) and Soay sheep (9). Decreased fitness has also been observed in *Drosophila* mutation accumulation experiments (10).

In humans, increased homozygosity has been related to decreased height and cardiometabolic disease phenotypes (11, 12). Additionally, it is well known that higher incidences of recessive Mendelian disorders are typically found in founder or endogamous populations (13–15). "Inbreeding" refers to mating between individuals who share one or more common ancestors, and among human populations, it is frequently used to describe consanguineous unions (those between individuals related up to the degree of 2nd cousins) or populations which have experienced recent founder effects (15–17). Here, we reserved the term inbreeding to refer to either the formal process of "inbreeding depression" or close familial unions.

The reduction in fitness associated with an individual's mutation load is dependent on the level of dominance of individual alleles. Previous work has shown that estimates of mutation load can greatly differ under additive versus recessive models (3, 6). Furthermore, there is a relationship between a mutation's level of dominance and deleteriousness—the

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[1]To whom correspondence may be addressed. Email: bmhenn@ucdavis.edu.

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more deleterious a mutation, the more recessive it tends to be. Work in various nonhuman species has also shown that mildly deleterious alleles are often at least partially recessive, with an average dominance level of $h = 0.25$ (2). Szpiech et al. (18) looked at human populations and demonstrated that long runs of homozygosity (ROH) contained disproportionately more deleterious variants than short runs. Additionally, it has been estimated that all human individuals carry at least two recessive pathogenic variants (19) or between 3 and 5 alleles that, if made homozygous, would be lethal (4). Because consanguinity or founder effects increase the likelihood that an individual will inherit identical segments from both parents, resulting in long ROH, inbred individuals would be expected to carry a higher burden of recessive deleterious, and possibly lethal, genotypes. Thus, these processes highlight the impact of recessive mutation load in a population. Levels of inbreeding depression can therefore be calculated as the fraction of the genome in ROH (F_{ROH}) (13, 20).

It is important to note, however, that evidence currently exists for both biological costs and benefits associated with inbreeding depression. These costs include negatively affecting fitness in many species by decreasing offspring viability or reproductive success (8, 15, 21–24) and can exhibit differential intensity based on sex. For example, in Florida scrub-jays and an isolated human population in the Swiss Alps, females were more strongly affected (8, 24). Prior human studies using pedigree data have shown that increased parental relatedness, such as via consanguinity, increases childhood mortality and can decrease the total number of surviving children (17, 23, 24). However, Helgason et al showed that third and fourth-degree cousins have higher fitness than either more closely or more distantly related individuals (i.e., a "Goldilocks" zone) as assessed from Icelandic pedigrees (25). It is unclear from the Icelandic pedigrees whether this reflects biological benefit or whether cultural factors, such as the proximity of nearby kin, increased reproductive success.

Other studies, drawn from cross-cultural anthropology, have demonstrated that there can be important cultural benefits associated with consanguinity, which is common both historically and contemporarily. In order to more fully understand the consequences of inbreeding, the biological effects on fitness must be considered alongside potential social and economic benefits of marriage between kin. Consanguineous marriage, typically among cross-cousins, is currently found among more than 10% of the world's population (26) but occurs at much higher rates in parts of Africa and Asia (27, 28). Consanguineous marriage has been shown to provide many social and economic benefits, including the ability to maintain power and resources within families, and as a strategy for risk reduction (21, 23, 27, 29–31). Societies with more consanguineous marriage tend to have denser, more intensive kinship networks, which help prevent the dilution of material wealth and promote resource-based defense (28). Some studies report higher fertility for consanguineous couples, but these findings may be explained by other factors such as lower age at marriage and first birth or larger ideal family sizes (27).

To assess whether recessive mutation load results in observable fitness consequences in a human population, we combined demographic and genetic data (n = 681) from a community of Himba pastoralists, an endogamous, semi-nomadic population residing in the Kunene region of northwestern Namibia. The Himba are expected to be previously bottlenecked and practice polygyny with a reported first-cousin preference for arranged marriages, but "love matches" exist as well (32). They exhibit an unusually high rate of extra-pair paternity (33), and half-sibling (and other second-degree) relationships constitute a very large proportion of all the relationships among individuals (34), increasing the risk that reproduction could occur between these relatives. Additionally, until recently, they were a natural fertility population and continue to have a pronatalist ideology and fairly short interbirth intervals (between 1 and 3 y) (35). Published genetic studies have used large biobank data to analyze similar phenotypes (16, 36), but power is affected by the use of contraceptives and other social choices that obfuscate the contribution of genetics to fertility. This limitation does not exist in the Himba, making them an ideal population in which to assess a fertility phenotype.

Our study differs from prior work on fertility by a) utilizing genome-wide data rather than pedigree-based inference of inbreeding coefficients, b) assessing the effect of recessive deleterious mutations in unions which span a range of kinship coefficients rather than consanguineous unions, c) incorporating data from a natural fertility population (i.e. no hormonal contraceptive use), and d) modeling the background levels of genetic drift in the population.

Results

We find elevated levels of homozygosity in the Himba as measured by F_{ROH} for three different minimum length thresholds: 500 kb, 1,500 kb, and 5,000 kb (Fig. 1). The lengths of ROH segments reflect the time since a common ancestor, where shorter ROH result from events occurring in the more distant past and longer ROH result from more recent events. In an idealized outbred population, the F_{ROH} expectation for the offspring of first cousins would be 0.0625, and F_{ROH} calculated using a minimum threshold of 1,500 kb to call ROH is comparable to a pedigree estimate of inbreeding (14). The mean F_{ROH} 1,500 of 2.6% observed in the Himba, and first reported in Swinford et al. (37), is therefore between the values expected for the offspring of second cousins and offspring of first cousins in an outbred population (15). However, this measure is not applicable to a population like the Himba who have elevated levels of IBD sharing (see below). Therefore, to estimate the F_{ROH} expectation for the offspring of Himba first cousins, we added 0.0625 to the average amount of background relatedness in the population resulting from more distant demographic history. To calculate this background level of inbreeding, we set a low (500 kb) threshold to call ROH and calculated F_{ROH} for all individuals. We then filtered out the individuals with F_{ROH} levels greater than 0.0625 and calculated the average level of F_{ROH} in the remaining individuals (0.0420). This background F_{ROH} level was then summed with 0.0625, resulting in an expectation of $F_{ROH} = 0.1045$ for the offspring of Himba first cousins. Only one individual met this expectation (individual 14 in Fig. 5). Interestingly, this individual's parents share IBD consistent with that of Himba first cousins; however, they are not genealogical first cousins themselves (*IBD Sharing between Couples*). Although a first-cousin preference in arranged marriages has been reported, we did not find any *parental* pairs that were first-cousin relatives. Regardless, the presence of long (>5,000 kb) ROH segments in many individuals and the distribution of F_{ROH} values resulting from these long ROH segments alone suggests an effect of recent demographic changes.

Inferring a Population Bottleneck. Elevated levels of homozygosity can also result from a population bottleneck. Based on knowledge of historical events, we hypothesized that Himba experienced a recent bottleneck within the past ~6 generations (38). These historical events included heavy cattle raiding beginning in the second half of the 1800s, forcing many Himba out of northern Namibia. In 1897, a severe rinderpest epidemic decimated up to 90% of livestock herds. Contagious Bovine Pleuropneumonia

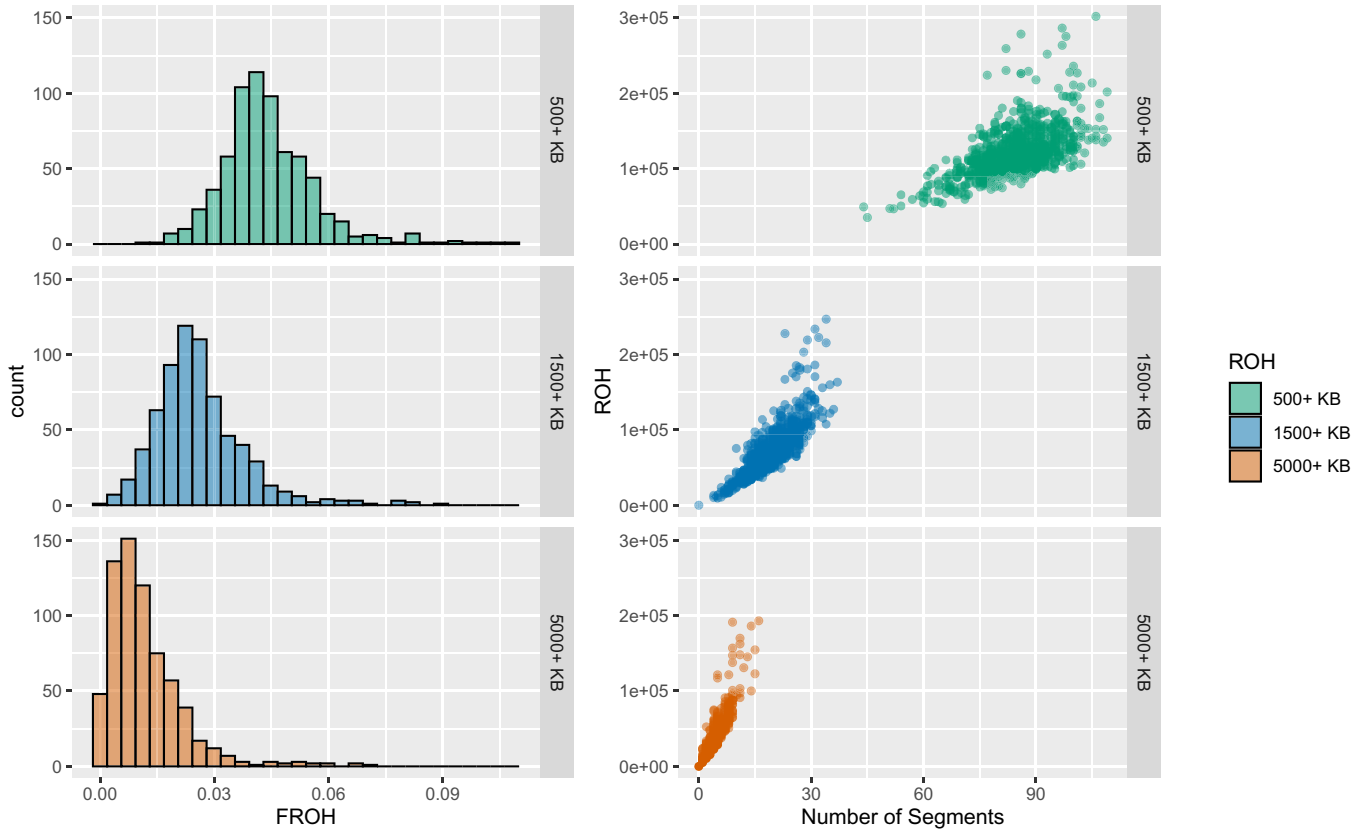

Fig. 1. F_{ROH} distributions for varying thresholds to call ROH and the relationship between the number of ROH segments and the total amount of ROH for all Himba (n = 681). The *Top* panel displays individuals' measurements resulting when F_{ROH} is calculated using a minimum threshold of 500 kb to call ROH, and the *Middle* and *Bottom* panels are the values calculated using minimum thresholds of 1,500 kb and 5,000 kb, respectively, to call ROH.

also caused devastating cattle losses in the 1930s and continued to impact herds for at least the next 50 y. Several severe droughts have also occurred throughout the 20th century. Additionally, in the first two decades of the 20th century, the Himba experienced the pressures of genocide, harsh taxes, and decreased mobility and isolation (38, 39). To test this hypothesis of recent bottleneck, we selected 120 unrelated individuals and estimated the effective population size (N_e) for the last 100 generations using a nonparametric method that uses inferred identical-by-descent (IBD) segments between pairs of individuals (40). We optimized the parameters used to infer IBD with a pipeline described by Gopalan et al. (41) (*Materials and Methods* and *SI Appendix*, Methods).

Our estimation of N_e through time indicates that a bottleneck has occurred throughout approximately the past 60 generations, reaching a minimum effective population size of approximately 450 individuals 12 generations ago (ga) (Fig. 2*A*). Himba exhibit elevated levels of total ROH in the genome compared to other African populations, including representatives from eastern, southern, and western regions: Bench, Zulu, Igbo, and Mandinka. Instead, their distribution is more similar to that of the Chabu foragers from Ethiopia. The Chabu, who are currently experiencing a bottleneck that is estimated to have begun slightly more recently than 60 generations ago (41), have a higher mean value of total ROH but exhibit a range of values similar to those in the Himba (Fig. 2*B*).

In order to validate our inferences of effective population size history, we used two additional methods to estimate changes in effective population size and founder events. HapLD is a recently developed method that relies on patterns of linkage disequilibrium to infer N_e through time (42). The results are similar to those obtained using IBDNe. Although the absolute estimates of N_e vary, they display the same overall shape, indicating that a bottleneck began approximately 87 generations ago and reached a minimum 18 generations ago (Fig. 2*C*). Because the Himba and the Zulu are both southern African populations of the Bantu expansion, we compared N_e trajectory results for the two populations. The Zulu share a similar ancestral N_e as the Himba until approximately 38 generations ago and then begin rapid growth while the Himba N_e continues to decline (Fig. 2*D*).

Our bottleneck estimates are also consistent with results obtained from ASCEND, a method that infers the timing and strength of founder events by looking at the correlation between pairs of SNPs and compared to an outgroup to account for ancestral allele sharing (43). ASCEND estimates that a founding event occurred in the Himba 16 to 17 generations ago with an intensity (calculated as the duration of the bottleneck divided by twice the effective population size during the bottleneck) between 2.5% and 2.7% (*SI Appendix*, Fig. S1). This level of intensity is greater than those experienced by the Jewish populations analyzed by Tournebize et al. (43). The estimated timing of this founder event is thus similar among all three analyses, ranging between 12 and 18 generations ago. Taken together, these results support the occurrence of a recent bottleneck in the Himba, but this event predates recorded epidemics and warfare.

We also used simulation to help validate the results of our inferred bottleneck, we simulated two bottlenecks under different scenarios using msprime and compared the IBDNe and F_{ROH} distribution results of the simulations with the actual Himba data. The simulated bottlenecks specified a beginning N_e of 4,000 and final N_e of 450 to roughly reflect the starting and minimum N_e values inferred from the 120 unrelated Himba individuals. In the

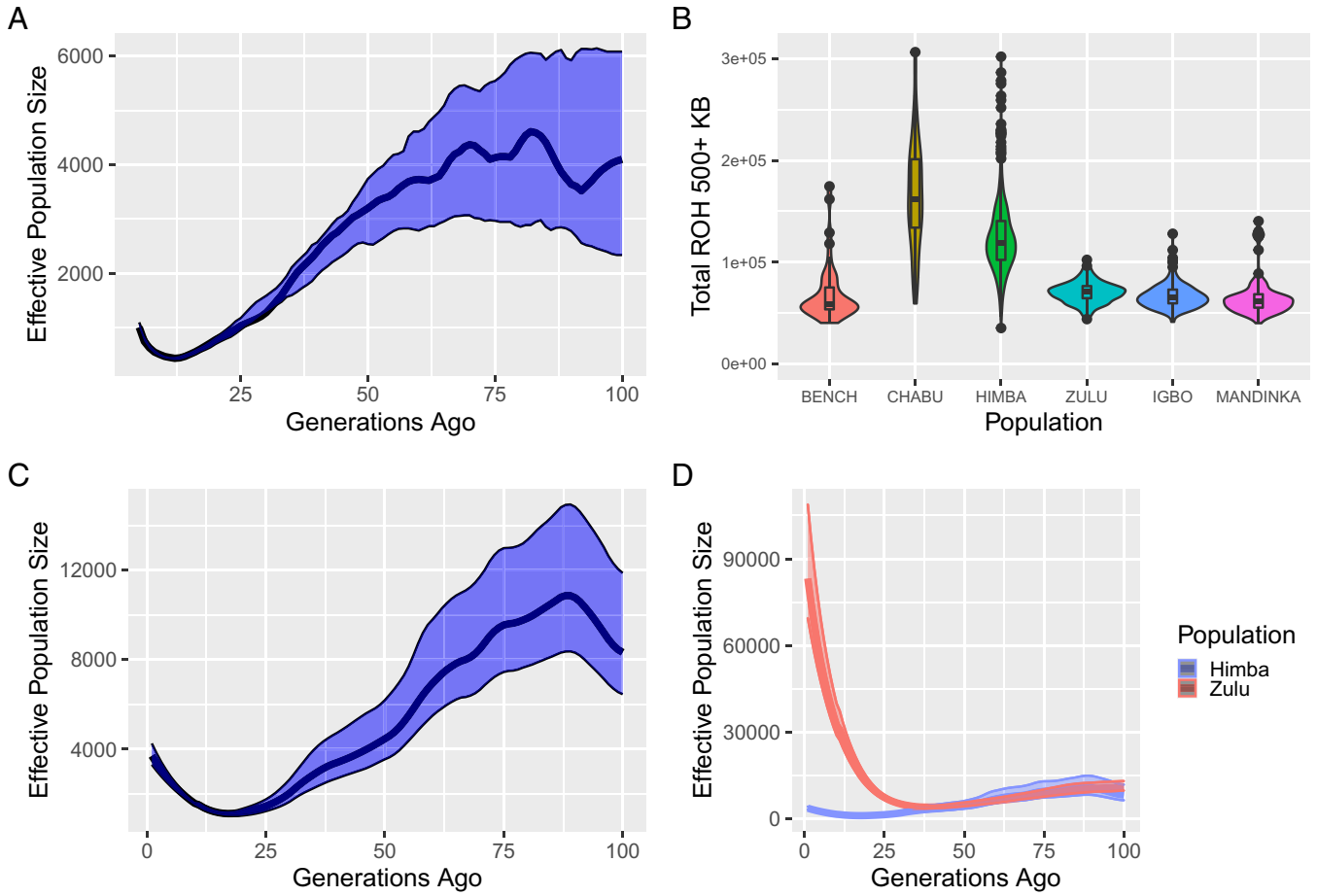

Fig. 2. Identical by Descent Segments indicate a recent population bottleneck for the Himba. (*A*) Effective population size through time was estimated for a sample of unrelated Himba individuals (n = 120) using IBDNe. The 95% CI shown in blue. (*B*) To understand whether ROH resulting from IBD sharing in the Himba was unusual, we contrasted them with two Ethiopian populations (Bench and Chabu), two western African populations (Igbo and Mandinka), and the Bantu-speaking Zulu from South Africa. The distribution of total amount of ROH in individuals' genomes for ROH segments 500 kb and longer is depicted as a violin plot. The Himba are comparable to the Chabu, an Ethiopian hunter-gatherer population which has also experienced recent population decline (Gopalan et al.). Strikingly, they have much higher ROH than the Zulu. (*C*) Bottleneck inference results from HapLD for unrelated Himba individuals (n = 120). 95% CI are shown in blue. (*D*) Himba (blue) and Zulu (red) bottleneck inference results from HapLD with 95% CI.

two scenarios, the starting N_e value was set to begin declining at either 60 or 6 generations ago. We find the IBD inferred from the simulated bottleneck beginning 60 ga more closely matches our real data than the one inferred from the simulated bottleneck beginning 6 ga (*SI Appendix*, Fig. S2). We also calculated the F_{ROH} 1500 distributions for both sets of simulated individuals as well as for our subset of 120 unrelated Himba individuals. We find the F_{ROH} distribution of our 120 unrelated Himba individuals more closely matches the F_{ROH} distribution of our simulated individuals experiencing a bottleneck beginning 60 ga (*SI Appendix*, Fig. S3). The mean F_{ROH} 1500 value for the simulated individuals is 0.013 and 0.026 for the 6 and 60 ga simulations, respectively, compared to a value of 0.036 in the set of unrelated Himba. However, both distributions of F_{ROH} values for simulated individuals differ from the distribution of values for unrelated Himba (6 ga bottleneck: P = 2.2e-16, 60 ga bottleneck: P = 0.004).

To further investigate the cause of ROH, we looked at the relationship between F_{ROH} 1500, which has been shown to be comparable to a pedigree estimate of the inbreeding coefficient (14), and F_{IS} (*SI Appendix*, Fig. S4). F_{IS} represents the departure from random mating in the population, where F_{IS} = 0 indicates random mating, F_{IS} < 0 indicates inbreeding avoidance, and F_{IS} > 0 indicates consanguinity (36, 44). We find that the population average is equal to −0.0035 and not significantly different than zero (P = 1.343e-10) and 67% of people have a negative F_{IS}. Additionally, F_{ROH} 1500 was greater than F_{IS} for all individuals. In contrast, populations with high rates of consanguinity lie on the diagonal where $F_{ROH} = F_{IS}$. These findings suggest that, while some consanguinity is still present (*IBD Sharing between Couples*), it is low N_e that is more responsible for higher homozygosity.

The Effects of F_{ROH} on Fertility. To assess the effects of F_{ROH} on fertility, we identified postreproductive women in our sample, which we defined as all women greater than 47 y old—as this was the oldest age recorded at which a woman gave birth in this community—and performed a regression fit to a Poisson distribution using year of birth (YOB) and number of marriages (NM) as covariates. We used a proxy measure of reproductive success, defined as the number of children who survived to a minimum age of five. We ran two versions of the model, one including all women regardless of parity, and the other excluding nulliparous women. Many biological conditions, unrelated to recessive load, can affect fertility. In addition to untreated venereal disease (45, 46), conditions such as polycystic ovarian syndrome and endometriosis can affect a woman's ability to become pregnant (47, 48).

F_{ROH} predicts the total number of children surviving to age five for all three minimum thresholds of ROH in models that contain

only women who have given birth (n=65, Pr[β<0] > 99%) (Figs. 3 and 4). Our sample of all postreproductive women included four seemingly infertile women (i.e., women who have had zero births). Because we lack medical records that could confirm diagnoses for reduced fertility or sterility, we ran the models again with the addition of the four seemingly sterile women to avoid possible bias. When all women are included in the model, the signal is attenuated, but F_{ROH} continues to have a negative effect on completed fertility for all three minimum thresholds of ROH (n = 69, Pr[β<0] > 98%) (Figs. 3 and 4). Examination of potential outliers flagged one individual with high Pareto k values (>0.5) in two models; however, removal of this individual did not alter model results nor the influence of F_{ROH} on model outcomes (Pr[β<0] > 95%).

IBD Sharing between Couples. While cousin marriage is preferred among the Himba, especially for arranged marriages, "love matches" are also common, particularly following the first marriage (49). Additionally, it is common and socially acceptable for both husbands and wives to take additional partners (50). Children born outside of marital unions, either through concurrency or out-of-wedlock, are referred to as *omoka*. When a woman is married to a man, he becomes the social father of all her children, regardless of biological paternity. Despite this, Himba recognize distinctions between social and biological paternity (51). To assess the effect of different relationships on the distribution of F_{ROH} values, we analyzed the distributions of IBD sharing between different categories of parental couples in a subset of trios (n = 105) for whom we had marriage data, self-reported kinship for married couples, and were able to verify genetic paternity of offspring. Conditional on a couple having confirmed biological offspring together, trios were divided into three categories: A. married couples self-reported to be unrelated (n = 7), and B. married couples self-reported to be related (*Materials and Methods*) (n = 26). C. mothers and boyfriends (n = 72). Of these self-reported related couples in "B", 15 were described as first cousins, 3 were described as first cousins once removed, 1 was described as avuncular, 1 was described as avuncular once removed, and the other 6 were described as more distantly related.

We found no significant difference (P > 0.085) between the distributions of IBD sharing between couples within each category (average IBD between biological parents of *omoka* children = 291 cM, average IBD between unrelated married couples = 347 cM, and average IBD between related married couples = 284 cM). Among married couples purported to be related, the majority of relationships were described as first cousins or first cousins once removed. The average IBD sharing between first-cousin pairs (n = 291 pairs) and half-cousin pairs (n = 957) in the Himba, identified using PONDEROSA (34), is 1,157 cM and 725 cM, respectively. Thus, while we have many examples of first cousins in the dataset, we observe much lower levels of IBD sharing between married couples. Despite reported relationships, individuals do not appear to marry biologically close kin. However, this does not preclude higher IBD sharing in some couples.

In fact, the parental couples with the highest IBD sharing in our dataset are extra-pair relationships (boyfriend/girlfriend) in which one couple shares a total of 1,038 cM (individuals 9 and 11 in Fig. 5) and the other shares a total of 1,074 cM (individuals 9 and 10 in Fig. 5). These couples have IBD consistent with a third-degree relationship but, after reconstructing their pedigree (*Materials and Methods*), they are not first-cousins. Rather, they are related through multiple distant relationships. The women (individuals 10 and 11) are paternal half-siblings. They are both half-cousins with the man (individual 9) through their fathers (individuals 4 and 7). Additionally, woman 11 shares a fourth-degree relationship with the man's paternal grandfather, and the man shares a fourth-degree relationship with woman 11's mother. Woman 10's mother also shares a cryptic relationship with the man's father (Fig. 5). This type of pedigree, where two individuals are connected through multiple distant relationships or "reticulations," is common within the Himba.

To help quantify this, we analyzed close reticulations only. Many Himba relative pairs exhibit high levels of IBD2 sharing that indicate that they are related through both parents. There are several confirmed cases: double cousins (co-co), double half-cousins (hco-hco), half-siblings/half-cousins (hs-hco), half-siblings/cousins (hs-co), cousin/half-cousin (co-hco), and even double half-avuncular pairs (hav-hav). There are 22 of these relationships confirmed (*SI Appendix*, Fig. S6), but there are likely more as these can only be confirmed in families with four generations of genotyped individuals. Additionally, we only considered close reticulations here, but more distant reticulations have been observed in the data. Focusing on half-siblings, we took simulated hs, hs-co, hs-hco, and half-sibling/second-cousins and used them to train a linear discriminant analysis classifier, which we used to classify real Himba half-siblings as hs only, hs-co, hs-hco, or hs-sco. We classified 34 of the 835 half-siblings as being either hs-co (n = 7) or hs-hco (n = 11) or hs-sco (n = 16) (*SI Appendix*, Fig. S7). As we only analyzed half-sibling pairs, this suggests that a minimum of 4% of pairs are closely related through both parents.

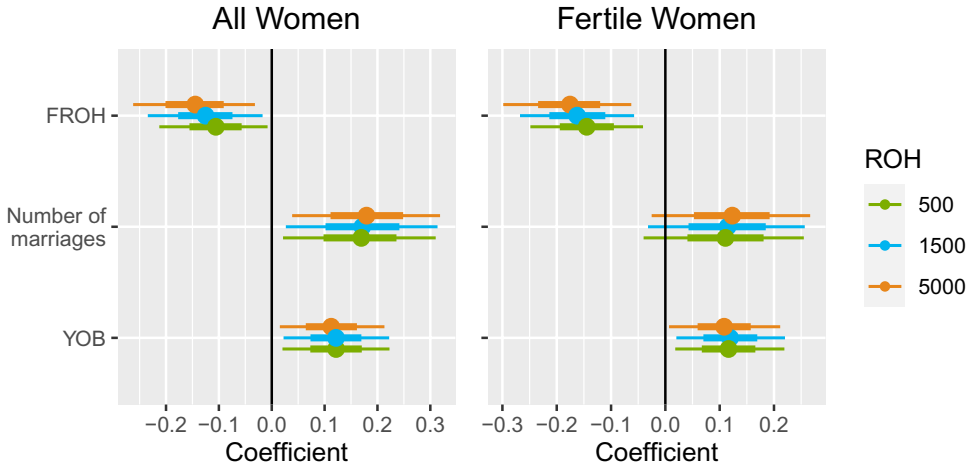

Fig. 3. Effects of predictors for fertility models. Posterior distributions (posterior median with 66% (thick line) and 95% (thin line) credible intervals) for variables used to predict completed fertility.

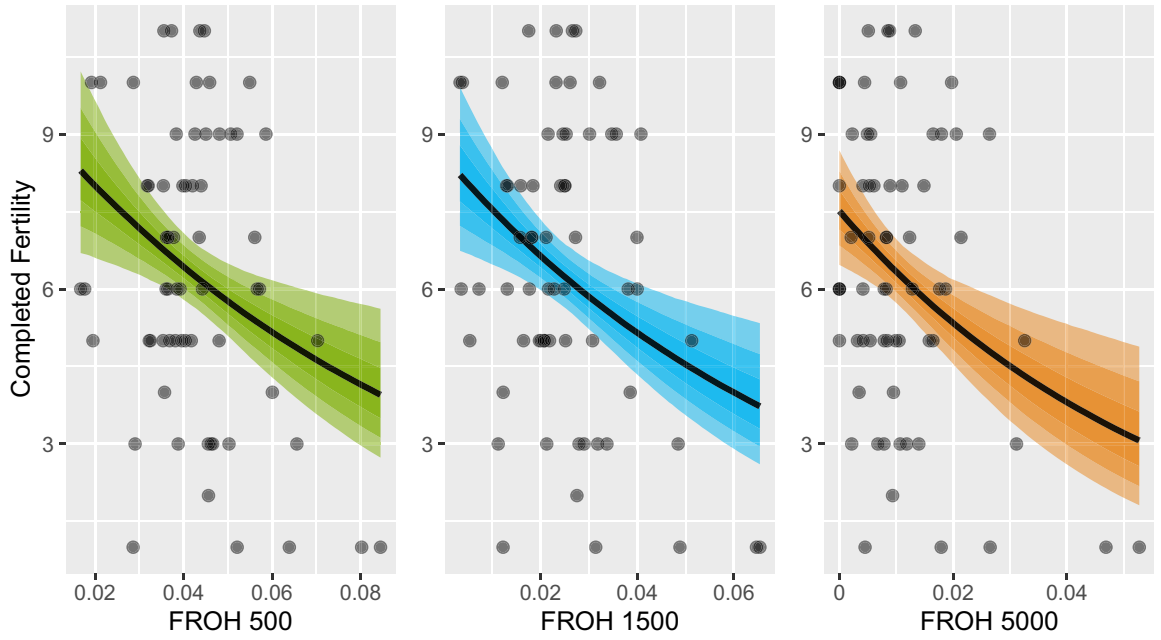

Fig. 4. F_{ROH} predicts lower fertility. Posterior predictions of Bayesian Poisson regression models predicting fertility in fertile women are shown with 50, 80, and 95% intervals. The line indicates the posterior median. Raw data are also shown.

Discussion

Long runs of homozygosity in human populations can be generated by consanguinity as well as strong founder effects (14, 52–54). Using a minimum threshold of 1,500 kb to call ROH, the average fraction of the Himba genome in long runs of homozygosity is 2.6%. Although we observe that elevated levels of F_{ROH} 1500 and Himba social norms promote consanguineous marriage (55), we do not observe any first-cousin parental pairs in our dataset even among married couples who report consanguinity. Rather, our results indicate that the Himba of northern Namibia experienced a population bottleneck that reached its minimum effective population size between approximately 12 and 18 generations ago. Although historical data suggest a more recent bottleneck (within the past six generations), we were unable to detect such a bottleneck here regardless of the method used. This may be due to a lack of actual genetic bottlenecking during this time or the difficulty of the IBDNe program to estimate accurate effective population sizes for the most recent generations. The bottleneck could trace back to the Bantu expansion across southern Africa over the 2,000 y. However, total ROH in the genome is much higher in Himba than in Zulu, a southern African population derived from the Bantu expansion (56), and the Zulu exhibit a different N_e trajectory compared to the Himba.

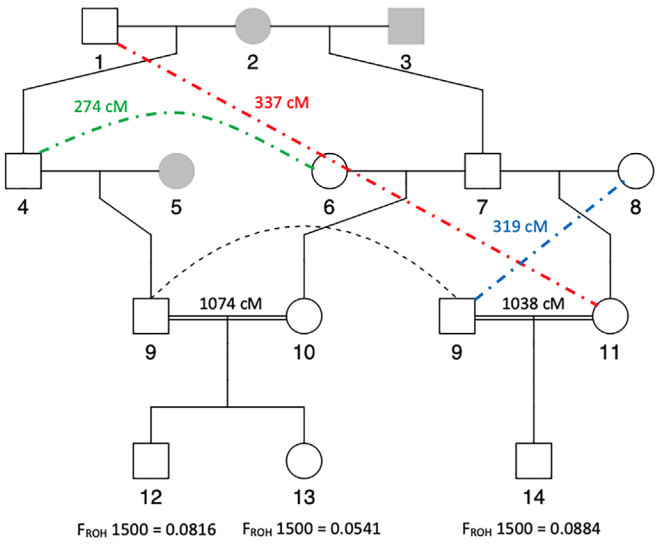

Fig. 5. Partial pedigree reconstruction for a couple with high IBD sharing. To parse the relationship between parental couples with high IBD sharing, we reconstructed their pedigrees. Parents 9 and 11, as well as 9 and 10, are half-cousins through their fathers, individuals 4 and 7. Unsampled individuals are shown in gray. The pairwise shared IBD for additional cryptic relationships are represented with colored dashed lines and corresponding values. Additional offspring, siblings, and partners are not shown for the individuals represented here. Individual 9 is represented twice (connected by a black dashed line) for clarity in the representation of the pedigree.

Our results suggest that bottleneck and endogamy are more responsible for elevated F_{ROH} than consanguinity. The average F_{IS} value for the population is negative but near zero, suggesting that the Himba exhibit random mating ($F_{IS} = 0$) or inbreeding avoidance ($F_{IS} < 0$). This is consistent with the Himba practice of concurrency which more closely resembles random mating than do practices in other cultures. However, mating among the Himba is not completely random. In addition to any mate preference and sexual selection variables that may be at play, interviews reveal that the Himba do avoid close inbreeding by alerting paternal half-siblings of their relatedness so that they know not to take each other as a girlfriend or boyfriend. The relationship between F_{ROH} and F_{IS} indicates that increased ROH is due to low N_e resulting from bottlenecks or founder events rather than from frequent consanguinity, and our bottleneck simulations indicate that bottleneck can produce F_{ROH} distributions similar to what we observe in the Himba. However, some consanguinity is present in the Himba. This is illustrated in the reconstructed pedigree, where individual 9 has extra-pair relationships with two half-cousins [#10, #11] who themselves are half-siblings. We estimate that approximately 4% of half-siblings have an additional recent (second cousin or closer) reticulation. Thus, while consanguinity does occur, our results suggest that bottleneck and endogamy have contributed most to elevated F_{ROH} even in the presence of random mating or inbreeding avoidance.

Among married couples in our sample, half reported that their partner was a second- or third-degree relative. However, after reconstructing genetic pedigrees, we observed low levels of IBD sharing among married couples who are purported to be related. There are several possible explanations for the discrepancy between social and biological relatedness among consanguineous couples. First, errors in the demographic interviews could account for some differences, if individuals reported spouses as a first cousin, when in fact they were a more distant relation. However, another likely explanation is that a high rate of extra-pair paternity has led to an untethering of social and biological relatedness. Himba have a strong cultural tradition of sexual concurrency, with most adults having both marital and nonmarital partners (50), and previous analyses have shown that Himba have an extra-pair paternity rate of 48% (33). Concurrency is presumed to be a longstanding practice, as it was written about in the first ethnographies of this group in the early 20th century (57–59). This means that if a man marries his cross-cousin (e.g., his mother's brother's daughter), there is only about a 50/50 chance she is his biological cousin, assuming that the brother is the mother's full sibling. There is a less than 50% chance given that the brother may have a different father, and then, he may also not be the biological father of the woman the man is marrying. With successive generations of concurrency and extra-pair paternity, the chance of relatedness reduces even further. Over time, this could lead to the results we show here. This interplay between concurrency and a preference for consanguinity may thus allow Himba to reap the benefits of a densely connected kin network, while minimizing the costs of higher mutation load that might typically come with consanguineous marriage.

The presence of long ROH is particularly important in assessing the effects of mutation load on fertility. Increased risk for complex diseases has been shown in populations where IBD sharing is elevated or consanguinity is common, suggesting a causal role for multiple recessive mutations throughout the genome (13). Furthermore, long ROH have been shown to be enriched for deleterious nonsynonymous homozygous derived genotypes (9, 18, 52). Therefore, it has been suggested that fitness could be reduced via gene knockouts within long ROH (52). Although our study was limited in its sample size of postreproductive women, we found F_{ROH} to have a significant effect on completed fertility. Our results show a trend of increasing effect size of F_{ROH} on fertility when longer and longer runs of homozygosity are analyzed. This result is consistent with longer tracts carrying greater numbers of deleterious mutations or more damaging mutations such as gene knockouts. Additional variance in phenotypic effect may be caused by varying placement of ROH within the genome. Specific genomic regions may be especially harmful to reproduction if deleterious variants disrupt genes critical to proper reproductive function (60, 61). Overall, our results suggest a multilocus effect on fitness driven by the expression of deleterious recessive alleles, especially those harbored in long ROH.

Our results are consistent with earlier self-reported pedigrees studies which considered the effect of consanguinity on fertility. Chagnon et al. (23) analyzed the South American Yanomamö group and reported that children whose parents were more closely related (i.e. children who would be expected to have higher F_{ROH}) had significantly lower fertility themselves. Similarly, Postma et al. (24) used town records to reconstruct genealogies for individuals from a small Swiss village and reported inbreeding depression for fertility among women. Our results strengthen these findings by demonstrating this pattern in another human population using molecular genetic measurements rather than pedigree estimates of relatedness. We caution that self-reported pedigrees may not always reflect biological kinship coefficients, as discussed above.

Variance in fertility within our cohort of postreproductive women is not solely due to recessive genetic effects; our models explain 16.3 to 18% of the variance indicating fertility is affected by other factors. Secondary sterility resulting from untreated venereal disease, such as gonorrhea, may be a factor in this population (45, 46, 62). Pennington and Harpending (45) have suggested that, prior to the 1960s, venereal disease caused lower fertility in the Namibian Herero, a population closely related to the Himba. They argue that women born after ~1945 would be at low risk for sterility due to venereal disease since antibiotics would have been available by the time they became sexually active, and women born prior to ~1915 would be at the greatest risk since antibiotics would not have been available until after they reached menopause (45). In our sample, nine women were born prior to 1945, including one of the four infertile women, and none of the women in our sample were born prior to 1915. However, more recent work by Hazel et al. (62) has shown the continued prevalence of gonorrhea infection along with low levels of treatment among Kaokaoland pastoralists, including Himba. Furthermore, this study suggests that these infections may be limiting fertility, but it is unclear to what extent, if any, this is occurring as no official measurements or analyses of the effects of gonorrhea on fertility have been made. A lack of medical records in our Himba sample makes it impossible to know whether there are other exogenous medical conditions that could be affecting fertility as well.

Our results are important for understanding the architecture of complex traits in human populations by suggesting that recessive mutation load may play a key role in fitness. A recent study by Szpiech et al. (63) noted that ROHs from different ancestries had different proportions of damaging homozygotes. This is thought to be due to differing population histories, resulting in haplotypes from high heterozygosity populations (such as African populations) containing more strongly deleterious variants than those found on haplotypes from lower-heterozygosity populations, and thus being more severely damaging when found in ROH. The effects of F_{ROH} on fertility and other polygenic traits may then differ between populations. Thus, this work should ideally be replicated in several populations of varying demographic histories. Future work pertaining to the effects of F_{ROH} on fertility should also annotate variants found in ROH to assess their level of deleteriousness. In conclusion, this work is especially important in demonstrating how differences in mutation loads, especially when considered under a recessive model, may affect differences in evolutionary fitness.

Materials and Methods

Study Population. The Himba are a small Bantu-speaking population that resides in Kunene Region, northwestern Namibia. They are a seminomadic agro-pastoralist group who practice polygyny with a reported first-cousin preference for arranged marriages; however, "love matches" are also common. Additionally, it is common and socially accepted for both husbands and wives to take additional partners (32). Within the past 200 y, the Himba have experienced many factors that have likely contributed to population decline, including genocide, climate change, severe drought, and rinderpest epidemics that decimated cattle resources (38).

Ethical Approval. The data in this study were collected following ethical approval granted by the University of California, Los Angeles (IRB-10-000238) and the State University of New York, Stony Brook (IRB-636415-12). The study was also approved by the Namibian Ministry of Home Affairs and supported by the University of Namibia Office of Academic Affairs and Research, and local community approval of the study was granted by Chief Basekama Ngombe. These data were collected as part of the Kunene Rural Health and Demography Project, which has been working in the community since 2010. Community leaders were actively involved in discussions regarding the research, including who could access the genetic data and what it could be used for, prior to data collection (with initial consultation in 2013 by BMH, BAS, followed by subsequent consultation after

DNA collection in 2016). All data and samples were collected with informed consent and parental assent for minors.

Genetic Data. Individuals were genotyped on either the MEGAex or H3Africa SNP array. Quality control and filtering proceeded as documented in dbGaP phs001995.v1.p1 as part of Scelza et al. (33), which included using PLINK to filter for missingness greater than 5%, a minor allele frequency less than or equal to 1%, and a Hardy–Weinberg equilibrium exact test with a *P*-value below 0.0001. We obtained genetic data from three more individuals on the H3Africa array and added them to the dataset after initial QC steps by filtering for SNPs common between the original dataset and the three new individuals. Both datasets were filtered to contain autosomes only to avoid X-chromosome interference in F_{ROH} estimates for males. Genotype data from the H3Africa array were thinned using PLINK2/1.9 to match the SNP density of the MEGAex array, therefore ensuring consistency when calling ROH and allowing for higher SNP density than would be present after merging the datasets due to missingness across platforms. The final H3Africa dataset contained 504 individuals and 755,660 SNPs, and the final MEGAex dataset contained 177 individuals and 755,423 SNPs.

We performed a test to ensure that randomly thinning the SNP density did not affect the estimation of an individual's F_{ROH}. To do this, we thinned the H3Africa dataset 10 separate times, identified ROH in each set as before with a minimum segment length threshold of 1,500 kb, and recalculated F_{ROH} in each set. We then calculated the absolute value of the differences between the F_{ROH} values in each new thinned set and in the original thinned set for each individual. We averaged the 10 values for differences between tests for each individual, resulting in an average difference for F_{ROH} calculated from differently thinned SNP array data for each individual, and used these values to calculate a root-mean-square error (RMSE) of 0.00058, confirming no significant difference between tests.

Measures of Inbreeding. We identified ROH and calculated FROH as in Swinford et al. (37). To calculate F_{ROH}, we first calculated the length of the genome tested in the SNP arrays by summing the lengths between the first and last SNPs genotyped on each chromosome. We then identified ROH in each individual using PLINK2/1.9 with a scanning window of 50 SNPs and allowing for a maximum of 2 missing SNPs and 1 heterozygote. We identified ROH for each of three different minimum length thresholds–500 kb, 1,500 kb, and 5,000 kb–and then calculated F_{ROH} for each of the three thresholds by dividing the total length of the genome found to be in ROH by the total length of the genome tested in the SNP array. These calculations were done separately for both platforms and then combined in R, resulting in F_{ROH} estimates for a total of 681 Himba individuals. We also used PLINK/1.9 to calculate F_{IS} separately for both platforms and then combined the datasets as was done for identifying ROH. We used a one-sample t-test in R to determine whether the average F_{IS} of the population was significantly different from zero.

Measure of Reproductive Success. Reproductive success was measured as the number of children a woman had who survived to a minimum age of five years old and these data were collected during interviews. In populations where infant and child mortality are high, survival to age five is used as a proxy for likelihood of survival to adulthood. In addition, still births and infant mortality are sensitive topics, which women were often reticent to report. Thus, a measure of fitness based on the number of births alone is both less reliable and less pertinent to overall reproductive success than number of children surviving to age five.

Linear Modelling and Statistical Analysis. To assess the effects of F_{ROH} on fertility, we performed a Bayesian Poisson regression in R, fitted using the *brms()* package (64). We assessed the effects of F_{ROH} on fertility for three different standardized measurements of F_{ROH} (using minimum thresholds of 500 kb, 1,500 kb, and 5,000 kb to call ROH) and used the measure of total number of children surviving to age five as the response variable. Standardized YOB and NM were used as covariates in the modelling process. Regularizing priors were used for all predictors. Pareto-smoothed importance sampling cross-validation (PSIS) was used to evaluate the impact of potential outliers in the data by calculating and flagging Pareto k values (65). When Pareto k values were above 0.5, the data in question were removed and model rerun. Where necessary, we report the probability of a positive or negative effect for predictors ($Pr[\beta < \text{or} > 0]$).

Bottleneck Inference. To determine the effective population size through time, we first identified a subset of unrelated individuals (n = 120) and ran IBDNe (40) specifying a minimum centimorgan length of 4 cM and limited the number of generations before present to calculate N_e for to 100 (gmax 100). The output was graphed in R. Our msprime simulations followed Gopalan et al. (41) and specified a starting N_e of 4,000, a final N_e in the present of 450, the generation at which to begin the bottleneck (60 or 6 ga), the number of haploid individuals to simulate (n = 120), and a mutation rate of 1e-8. We simulated 120 individuals and identified IBD in the output using hap-ibd and then ran IBDNe to reconstruct inferred N_e through time. Additionally, we ran HapLD on our 120 unrelated Himba and on 99 unrelated Zulu for comparison (42). We also ran ASCEND to estimate the timing of a founder event in the Himba, using the Zulu as an outgroup (43). Additional information on methods, procedures, and parameters can be found in supplement.

Paternity Identification and Marriage Data. *Omoka* status was determined and confirmed with genetic paternity analysis as described in Scelza et al. (33). Children were described as *omoka* if their biological father was not their mother's husband at the time of their birth. Information regarding marital unions and the descriptions of married couples' relatedness were collected in interviews and then translated into a specific category of relatedness. For example, a description of "mother's brother's daughter" was translated to the category of first cousins, while descriptions such as "father's brother's daughter's daughter" or "the husband's mother is from the wife's paternal uncle" were translated to the category of first cousins once removed. One couple was described to be related in two different ways, as both first cousins once removed and possibly as third cousins once removed as well. However, it was unclear to what extent these two connections were independent or overlapping so they were included in the category of the closer of the two relationships (i.e., first cousins once removed).

Pedigrees. For pedigree reconstruction, we used PONDEROSA, an algorithm that infers pedigree relationships and is especially suited for populations with elevated IBD sharing (34) to identify all pedigree relationships in the data. To estimate the prevalence of close reticulations, we used Ped-Sim (66) to simulate many multirelationship types and then trained a linear discriminant analysis classifier, which we used to classify the types on consanguinity in the pedigrees of Himba half-siblings. Additional information and parameters can be found in supplement.

Data, Materials, and Software Availability. SNP array data for the Himba are available via dbGaP, accession phs001995.v1.p1. Genomic data for the Zulu are available via EGA, accession: EGAS00001000960 (67). Other data, code, and materials are available on GitHub: https://github.com/hennlab/Himba_Fertility_Demography (68).

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Author affiliations: [a]Department of Anthropology, University of California Davis, Davis, CA 95616; [b]Department of Anthropology, University of Missouri, Columbia, MO 65211; [c]Department of Evolutionary Anthropology, Duke University, Durham, NC 27708; [d]Center for Computational Molecular Biology, Brown University, Providence, RI 02912; [e]Department of Human, Biological and Translational Medical Sciences, School of Medicine University of Namibia, Oshakati 10005, Namibia; [f]Department of Anthropology, University of California Los Angeles, Los Angeles, CA 90095; [g]Center for Population Biology, University of California Davis, Davis, CA 95616; and [h]Genome Center, University of California Davis, Davis, CA 95616

1. M. Lopez *et al.*, The demographic history and mutational load of African hunter-gatherers and farmers. *Nat. Ecol. Evol.* **2**, 721–730 (2018).
2. B. M. Henn, L. R. Botigué, C. D. Bustamante, A. G. Clark, S. Gravel, Estimating the mutation load in human genomes. *Nat. Rev. Genet.* **16**, 333–343 (2015).
3. B. M. Henn *et al.*, Distance from sub-Saharan Africa predicts mutational load in diverse human genomes. *Proc. Natl. Acad. Sci. U.S.A.* **113**, E440–E449 (2016).
4. K. E. Lohmueller *et al.*, Proportionally more deleterious genetic variation in European than in African populations. *Nature* **451**, 994–997 (2008).

5. Y. B. Simons, M. C. Turchin, J. K. Pritchard, G. Sella, The deleterious mutation load is insensitive to recent population history. *Nat. Genet.* **46**, 220–224 (2014).
6. C. E. T. Pedersen *et al.*, The effect of an extreme and prolonged population bottleneck on patterns of deleterious variation: Insights from the Greenlandic Inuit. *Genetics* **205**, 787–801 (2017).
7. P. A. Scott, L. J. Allison, K. J. Field, R. C. Averill-Murray, H. Bradley Shaffer, Individual heterozygosity predicts translocation success in threatened desert tortoises. *Science* **370**, 1086–1089 (2020).
8. N. Chen, E. J. Cosgrove, R. Bowman, J. W. Fitzpatrick, A. G. Clark, Genomic consequences of population decline in the endangered Florida Scrub-Jay. *Curr. Biol.* **26**, 2974–2979 (2016).
9. M. A. Stoffel, S. E. Johnston, J. G. Pilkington, J. M. Pemberton, Mutation load decreases with haplotype age in wild Soay sheep. *Evol. Lett.* **5**, 187–195 (2021).
10. A. Eyre-Walker, P. D. Keightley, The distribution of fitness effects of new mutations. *Nat. Rev. Genet.* **8**, 610–618 (2007).
11. R. McQuillan *et al.*, Evidence of inbreeding depression on human height. *PLoS Genet.* **8**, e1002655 (2012).
12. F. C. Ceballos *et al.*, Autozygosity influences cardiometabolic disease-associated traits in the AWI-Gen sub-Saharan African study. *Nat. Commun.* **11**, 5754 (2020).
13. R. McQuillan *et al.*, Runs of homozygosity in european populations. *Am. J. Hum. Genet.* **83**, 359–372 (2008).
14. F. C. Ceballos, P. K. Joshi, D. W. Clark, M. Ramsay, J. F. Wilson, Runs of homozygosity: Windows into population history and trait architecture. *Nat. Rev. Genet.* **19**, 220–234 (2018).
15. A. H. Bittles, M. L. Black, The impact of consanguinity on neonatal and infant health. *Early Hum. Dev.* **86**, 737–741 (2010).
16. L. Yengo, N. R. Wray, P. M. Visscher, Extreme inbreeding in a European ancestry sample from the contemporary UK population. *Nat. Commun.* **10**, 1–11 (2019).
17. L. E. Dorsten, L. Hotchkiss, T. M. King, The effect of inbreeding on early childhood mortality: Twelve generations of an Amish settlement. *Demography* **36**, 263–271 (1999).
18. Z. A. Szpiech *et al.*, Long runs of homozygosity are enriched for deleterious variation. *Am. J. Hum. Genetics* **93**, 90–102 (2013).
19. H. Fridman *et al.*, The landscape of autosomal-recessive pathogenic variants in European populations reveals phenotype-specific effects. *Am. J. Hum. Genet.* **108**, 608–619 (2021).
20. G. Alvarez, C. Quinteiro, F. C. Ceballos, "Inbreeding and genetic disorder" in *Advances in the Study of Genetic Disorders*, K. Ikehara, Ed. (InTech, 2011), pp. 21–44.
21. G. Alvarez, F. C. Ceballos, C. Quinteiro, The role of inbreeding in the extinction of a European royal dynasty. *PLoS One* **4**, 1–7 (2009).
22. D. H. Bailey, K. R. Hill, R. S. Walker, Fitness consequences of spousal relatedness in 46 small-scale societies. *Biol. Lett.* **10**, 20140160 (2014).
23. N. A. Chagnon, R. F. Lynch, M. K. Shenk, R. Hames, M. V. Flinn, Cross-cousin marriage among the Yanomamö shows evidence of parent-offspring conflict and mate competition between brothers. *Proc. Natl. Acad. Sci. U.S.A.* **114**, E2590–E2597 (2017).
24. E. Postma, L. Martini, P. Martini, Inbred women in a small and isolated Swiss village have fewer children. *J. Evol. Biol.* **23**, 1468–1474 (2010).
25. A. Helgason, S. Pálsson, D. F. Guojartsson, P. Kristjánsson, K. Stefánsson, An association between the kinship and fertility of human couples. *Science* **319**, 813–817 (2008).
26. A. H. Bittles, M. L. Black, Consanguineous marriage and human evolution. *Annu. Rev. Anthropol.* **39**, 193–207 (2010).
27. A. H. Bittles *et al.*, Reproductive behavior and health consanguineous marriages. *Science* **252**, 789–794 (1991).
28. R. S. Walker, D. H. Bailey, Marrying kin in small-scale societies. *Am. J. Hum. Biol.* **26**, 384–388 (2014).
29. N. F. Anderson, Cousin marriage in Victorian England. *J. Fam. Hist.* **11**, 285–301 (1986).
30. A. L. Hughes, Preferential first-cousin marriage and inclusive fitness. *Ethol. Sociobiol.* **1**, 311–317 (1980).
31. K. Charsley, Risk, trust, gender and transnational cousin marriage among British Pakistanis. *Ethn. Racial. Stud.* **30**, 1117–1131 (2007).
32. B. A. Scelza, Female choice and extra-pair paternity in a traditional human population. *Biol. Lett.* **7**, 5–7 (2011).
33. B. A. Scelza *et al.*, High rate of extrapair paternity in a human population demonstrates diversity in human reproductive strategies. *Sci. Adv.* **6**, eaay6195 (2020).
34. C. M. Williams *et al.*, A rapid, accurate approach to inferring pedigrees in endogamous populations. bioRxiv [Preprint] (2020). https://doi.org/10.1101/2020.02.25.965376 (Accessed 2 October 2020).
35. B. A. Scelza, J. B. Silk, Fosterage as a system of dispersed cooperative breeding: Evidence from the Himba. *Hum. Nat.* **25**, 448–464 (2014).
36. D. W. Clark *et al.*, Associations of autozygosity with a broad range of human phenotypes. *Nat. Commun.* **10**, 4957 (2019).
37. N. Swinford *et al.*, Examination of runs of homozygosity in relation to height in an endogamous Namibian population. *Am. J. Biol. Anthropol.* **180**, 207–215 (2022).
38. M. Bollig, "Risk and risk minimisation among Himba Pastoralists in Northwestern Namibia". *Nomad. People.* **1**, 66–89 (1997).
39. M. Bollig, The colonial encapsulation of the north-western Namibian pastoral economy. *Africa* **68**, 506–536 (1998).
40. S. R. Browning, B. L. Browning, Accurate non-parametric estimation of recent effective population size from segments of identity by descent. *Am. J. Hum. Genet.* **97**, 404–418 (2015).
41. S. Gopalan *et al.*, Hunter-gatherer genomes reveal diverse demographic trajectories during the rise of farming in Eastern Africa. *Curr. Biol.* **32**, 1852–1860 (2022).
42. R. Fournier, D. Reich, P. F. Palamara, Haplotype-based inference of recent effective population size in modern and ancient DNA samples. bioRxiv [Preprint] (2022). https://doi.org/10.1101/2022.08.03.501074 (Accessed 29 January 2023).
43. R. Tournebize, G. Chu, P. Moorjani, Reconstructing the history of founder events using genome-wide patterns of allele sharing across individuals. *PLoS Genet.* **18**, e1010243 (2022).
44. F. C. Ceballos, S. Hazelhurst, M. Ramsay, Runs of homozygosity in sub-Saharan African populations provide insights into complex demographic histories. *Hum. Genet.* **138**, 1123–1142 (2019).
45. R. Pennington, H. Harpending, Infertility in Herero pastoralists of southern Africa. *Am. J. Hum. Biol.* **3**, 135–153 (1991).
46. A. Hazel, *Sexually Transmitted Diseases Among Pastoralists in Kaokoland, Namibia: Epidemiology, Ecology, and Behavior* (University of Michigan, 2012).
47. P. Vercellini, P. Viganò, E. Somigliana, L. Fedele, Endometriosis: Pathogenesis and treatment. *Nat. Rev. Endocrinol.* **10**, 261–275 (2014).
48. J. Bellver *et al.*, Polycystic ovary syndrome throughout a woman's life. *J. Assist. Reprod. Genet.* **35**, 25–39 (2018).
49. S. Prall, B. Scelza, The effect of mating market dynamics on partner preference and relationship quality among Himba pastoralists. *Sci. Adv.* **8**, eabm5629 (2022).
50. B. A. Scelza, S. P. Prall, Only death will separate us: The role of extramarital partnerships among Himba Pastoralists. *Arch. Sex Behav.* **52**, 1355–1363 (2023).
51. S. P. Prall, B. A. Scelza, Why men invest in non-biological offspring: Paternal care and paternity confidence among Himba pastoralists. *Proc. R Soc. B Biol. Sci.* **287**, 20192890 (2020).
52. J. A. Mooney *et al.*, Understanding the hidden complexity of latin American population isolates. *Am. J. Hum. Genet.* **103**, 707–726 (2018).
53. M. Kirin *et al.*, Genomic runs of homozygosity record population history and consanguinity. *PLoS One* **5**, 1–7 (2010).
54. B. M. Henn *et al.*, Hunter-gatherer genomic diversity suggests a southern African origin for modern humans. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 5154–5162 (2011).
55. B. Scelza, S. Prall, K. Starkweather, The role of spousal separation on norms related to gender and sexuality among himba pastoralists. *Soc. Sci.* **10**, 174 (2021).
56. D. J. Rowold, D. Perez-Benedico, O. Stojkovic, R. Garcia-Bertrand, R. J. Herrera, On the Bantu expansion. *Gene* **593**, 48–57 (2016).
57. G. Viehe, "Die Ovaherero" in *Rechtsverhältnisse von Eingeborenen Völkern in Afrika Und Ozeanien* (Springer, Berlin Heidelberg, 1903), pp. 294–312.
58. E. Dannert, *Zum Rechte der Herero, insbesondere über ihr Familien-und Erbrecht* (D. Reimer, 1906).
59. G. D. Gibson, Herero Marriage. *Rhodes-Livingstone J.* **24**, 1–37 (1958).
60. L. C. Layman, The genetic basis of female reproductive disorders: Etiology and clinical testing. *Mol. Cell Endocrinol.* **370**, 138–148 (2013).
61. H. Valdes-Socin *et al.*, Reproduction, smell, and neurodevelopmental disorders: Genetic defects in different hypogonadotropic hypogonadal syndromes. *Front. Endocrinol. (Lausanne)* **5**, 1–8 (2014).
62. A. Hazel, S. Ponnaluri-Wears, G. S. Davis, B. S. Low, B. Foxman, High prevalence of Neisseria gonorrhoeae in a remote, undertreated population of Namibian pastoralists. *Epidemiol. Infect.* **142**, 2422–2432 (2014).
63. Z. A. Szpiech *et al.*, Ancestry-dependent enrichment of deleterious homozygotes in runs of homozygosity. *Am. J. Hum. Genet.* **105**, 747–762 (2019).
64. P. C. Bürkner, brms: An R package for Bayesian multilevel models using Stan. *J. Stat. Softw.* **80**, 1–28 (2017).
65. A. Vehtari, A. Gelman, J. Gabry, Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. *Stat. Comput.* **27**, 1413–1432 (2017).
66. M. Caballero *et al.*, Crossover interference and sex-specific genetic maps shape identical by descent sharing in close relatives. *PLoS Genet.* **15**, e1007979 (2019).
67. The African Genome Variation Project, APCDR AGV Project: Whole genome sequencing of 3 African populations. European Genome-Phenome Archive (EGA). https://ega-archive.org/studies/EGAS00001000960. Accessed 16 January 2023.
68. N.A. Swinford, Himba_Fertility_Demography. GitHub. https://github.com/hennlab/Himba_Fertility_Demography. Deposited 3 September 2023.