Female gene flow stratifies Hindu castes

Scientists have long been interested in understanding how social processes modulate evolutionary forces. A good example of this is the intensively studied Hindu caste system, which governs the mating practices of nearly one-sixth of the world’s population. However, there is controversy concerning the effect of social stratification on the genetic structure of caste communities. Here we show that differences in social rank between castes correspond to mitochondrial DNA (mtDNA) distances between castes but not genetic distances estimated from Y-chromosome data.

Hindu populations are stratified into five varna, each of which is associated with a ‘status’. Ranked from lowest to highest status, these are Panchama, Sudra, Vysya, Kshatriya and Brahmin. There are approximately 2,000 castes in contemporary India, roughly grouped into these varna. Religious rites, access to material resources and education, and occupational specialization are directly related to caste status. Marriages between individuals of equal status are preferred. Matings between a man from a higher varna and a woman from a lower varna are permissible under certain circumstances, in which case the offspring tend to attain a status similar to that of their father. In contrast, marriage of a woman from a higher varna to a man of a lower varna is strongly discouraged. This suggests that women have limited but upward social mobility, whereas men have very little.

To test the effects of this mating system on genetic variation, we analysed mtDNA and Y-chromosome variation in 250 individuals from 12 Telugu-speaking caste populations from northeastern Andhra Pradesh in southern India. Castes and varna were ranked by status into upper (Brahmin, Kshatriya and Vysya), middle (Kapu, Yadava, Jarali and Wadabahija), and lower (Relli, Madiga and Mala) groups.

We identified 182 unique mtDNA haplotypes, four of which are shared among upper, middle and lower castes, seven between lower and middle castes, and three between middle and upper castes. No haplotypes are shared exclusively between upper and lower castes. This suggests that haplotype sharing between castes is limited by social rank. The genetic distance between upper and lower castes (0.00054) is similar to that between the upper and middle castes (0.00062), and larger than that between middle and lower castes (0.00005). Thus, caste status is not associated with Y-chromosome genetic distance.

A statistical comparison of the genetic distances based on mtDNA and Y-chromosome data reveals a low, non-significant correlation ($r = 0.14, P > 0.3$) by the Mantel permutation test. There are several possible explanations for this lack of concordance.

First, there may not be enough Y-chromosome STRs to reveal a meaningful pattern, although a comparison of a distance matrix based on the Y-chromosome SNPs with the matrix based on STRs yields a significant positive correlation ($r = 0.68, P < 0.0025$). This high degree of consistency would not be expected if the STR distances were due to insufficient data.

Second, the lack of correlation between social rank and Y-chromosome distance might be produced by random male movement between castes. This explanation is unlikely because the Y-chromosome data show greater differentiation between groups than the mtDNA data: the proportion of genetic variation attributable to differences between groups for Y-chromosome STRs is 0.10 ($P < 0.001$), whereas that based on mtDNA data is only 0.015 ($P < 0.002$). This result is consistent with females having greater inter caste gene flow than males, and agrees with historical evidence that males were less likely to change castes.

A third possible explanation is that the discordance is caused by differences in mutation rates between the Y-chromosome and mtDNA systems. However, the greatest observed difference in mutation rates is between the Y-chromosome STRs and the Y-chromosome SNPs, yet these two data sets are highly concordant.

The remaining explanation for the discordance, and the one most consistent with the historical data, is that systematic female gene flow among castes produced a correlation between social rank and mtDNA distances. A relative lack of male gene flow resulted in no correlation between social rank and Y-chromosome distances, and supports the idea that the pattern of Y-chromosome variation is largely the result of mutation and genetic drift. This indicates that mobility between castes of different status has been higher for females than males, as predicted from ethnographic records. We therefore conclude that genetic stratification of the Hindu caste system is driven by the social mobility of women.

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Effects of progesterone or neuroactive steroid?

Smith et al. reported some interesting results about the effects of progesterone treatment and withdrawal on the gene encoding the GABA_A receptor α4 subunit, a constituent of receptors for the neurotransmitter GABA (γ-amino butyric acid). However, we disagree with their conclusion that the effects of progesterone withdrawal are mediated by reduced levels in the brain of the GABA_A receptor active neurosteroid 3α-OH-5α-pregnan-20-one (3α,5α-THP, or allopregnanolone). The ability of indomethacin to reverse the effects of progesterone was interpreted as evidence that the effects of progesterone were mediated by 3α,5α-THP. Smith et al. did not provide direct evidence that levels of 3α,5α-THP were reduced by indomethacin (which reversed the effects of progesterone), or that progesterone levels were not altered by indomethacin. In some cases, indomethacin can increase progesterone levels directly, which may explain why indomethacin can reverse the effects of progesterone withdrawal.

The effect of indomethacin blockade of 3α-hydroxysteroid oxidoreductase activity is dependent on the relative levels of 3α,5α-THP and its immediate precursor 5α-dihydroprogesterone. When 3α,5α-THP concentrations are raised after progesterone infusion or stress, indomethacin would block the oxidation of 3α,5α-THP, increasing its concentration. Using the same dose regimen as ref. 1 we find that stress-induced elevation of 3α,5α-THP levels in the brain are increased by pretreatment with indomethacin (Fig. 1). Blockade of this enzyme with fluoxetine has also been shown to raise 3α,5α-THP levels in the rat brain. The omission of 3α,5α-THP and progesterone levels in the report by Smith et al. therefore raises concerns about the conclusion that 3α,5α-THP mediates the effects of progesterone withdrawal.

Manipulation of progesterone levels in female rats is likely to influence the expression of many genes as well as the levels of numerous steroids other than 3α,5α-THP. Therefore, even if 3α,5α-THP levels are reduced by indomethacin, this does not demonstrate that the effects of progesterone withdrawal on GABA_A receptors are mediated by 3α,5α-THP. Correlational evidence, although suggestive, does not establish a causal relationship.

The effects of progesterone and ethanol withdrawal on GABA_A receptor α4 subunit gene expression are similar. However, cross-tolerance between ethanol and 3α,5α-THP does not occur in vivo. Indeed, chronic ethanol administration produces cross-tolerance to benzodiazepines, but also results in sensitization to both behavioural and neurochemical responses to 3α,5α-THP. Moreover, this effect is greater in female than male rats, suggesting that the higher progesterone levels in female rats are associated with greater sensitization to 3α,5α-THP. This sensitization is probably due to intrinsic changes in GABA_A receptors, as concentrations of 3α,5α-THP are not altered after chronic ethanol administration. Although the effects of ethanol and progesterone on GABA_A receptor α4 gene expression are known, there is no direct evidence that 3α,5α-THP alters the expression of this gene.

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Smith et al. reply — Morrow et al. are incorrect to state that we did not provide direct evidence that 3α-OH-5α-pregnan-20-one (3α,5α-THP, or allopregnanolone) levels were reduced by indomethacin. We pointed out that our previous studies showed that indomethacin administration concomitant with progesterone reduced the level of 3α,5α-THP in the central nervous system from 8.2 ± 1.3 ng per g to 2.3 ± 0.35 ng per g without altering levels of 5α-DHP or progesterone. This treatment, which prevented the withdrawal of 3α,5α-THP that normally accompanies progesterone withdrawal, completely prevented the withdrawal effects of progesterone we observed, including acceleration in the decay of GABA-gated current and upregulation of the GABA_A receptor α4 subunit.

We have shown that direct withdrawal of 3α,5α-THP, in the absence of progesterone withdrawal, also results in faster decay of GABA-gated current in association with upregulation of the α4 subunit. In this case, withdrawal from the GABA-modulatory metabolite 3α,5α-THP was accomplished with the use of a 5α-reductase inhibitor to block 3α,5α-THP formation without altering progesterone levels. Taken together, these results establish 3α,5α-THP as the active agent that exhibits withdrawal properties. In contrast, Morrow et al. administered indomethacin 20 minutes before ethanol stress, which would prevent direct conversion of 3α-DHP to 3α,5α-THP. The indomethacin-induced increases in 3α,5α-THP levels they report after ethanol stress can be explained only by stress-induced effects on the degradation of 3α,5α-THP.

We further disagree with the suggestion by Morrow et al. that our findings are purely correlational. Indomethacin is a highly selective blocker of 3α-hydroxysteroid oxidoreductase activity, and so reduces 3α,5α-THP levels specifically, without altering levels of other hormones such as 5α-DHP or progesterone. This is therefore the most definitive procedure to determine the role of the 3α,5α-THP metabolite in the upregulation of the α4 subunit we observe after progesterone withdrawal. Direct administration of 3α,5α-THP would be a less convincing model because back-conversion to 5α-DHP can occur. Furthermore, systemic administration of progesterone best mimics physiological conditions in our animal model of premenstrual syndrome, in which circulating progesterone is converted in the CNS to 3α,5α-THP.

Earlier results from Morrow et al. indicate that sensitivity to 3α,5α-THP is increased after ethanol withdrawal. We are intrigued by this finding because recent data from our laboratory indicate that withdrawal of 3α,5α-THP also increases ethanol potentiation of GABA-gated current in CA1 hippocampus by 71.2 ± 5.4% over control levels. This result is consistent with reports of increased alcohol consumption in women during the premenstrual period. Both of these findings clearly distinguish the effects of ethanol from those of benzodiazepines, which exhibit reduced GABA-modulatory effects.