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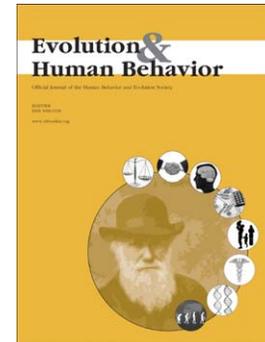
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Genetic analysis of human extrapair mating: Heritability, between-sex correlation, and receptor genes for vasopressin and oxytocin

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Abstract

As in other socially monogamous species, pair-bonded humans commonly engage in sex with a partner other than their primary mate. For men, extrapair mating is straightforwardly explained from an adaptive perspective in terms of the reproductive benefits of multiple mates. For women, whose reproductive output is limited by their reproductive biology rather than by their number of mates, the adaptive benefits of extrapair mating are less obvious. Dominant adaptive explanations focus on women obtaining genetic benefits for their offspring by mating with high-quality extrapair partners. Non-adaptive explanations have rarely been considered in humans, but recent findings in birds suggest that females' predisposition to extrapair mating may result from indirect selection, via direct selection on males and a between-sex genetic correlation. To examine the plausibility of this non-adaptive explanation of extrapair mating in women, we used data on recent extrapair mating in 7,378 Finnish twins and their siblings. Genetic modelling showed within-sex broad-sense heritability – i.e. the percentage of variation in extrapair mating due to genetic variation – of 62% in men and 40% in women. There was no between-sex correlation in extrapair mating, making indirect selection unlikely. Based on previous animal and human findings, we also tested for association of the arginine vasopressin receptor 1A gene (*AVPR1A*) and oxytocin receptor gene (*OXTR*) with extrapair mating. We found gene-based association for *AVPR1A* in women but not in men, and *OXTR* showed no significant association in either sex. Overall, these findings confirm genetic underpinnings of extrapair mating in humans, but do not suggest that women's predisposition to extrapair mating is due to selection on men.

Introduction

In most socially monogamous species (e.g. many birds and some mammals), both male and female members of a pair commonly seek copulations with other individuals (Reichard 1995; Barash and Lipton 2001; Griffith et al. 2002). Males have a low minimal investment to reproduce (i.e. one copulation), so males mating outside the pair can increase their reproductive output; any genes predisposing males to seek extrapair mates would be adaptive (in the absence of strong countervailing selective pressures). However, females' reproductive potential is constrained by their biological capacity to reproduce, so females do not necessarily increase their reproductive potential by extrapair mating— in addition, females may also incur direct costs from extrapair copulations, such as disease transmission and withdrawal of paternal investment into offspring of uncertain paternity (Arnqvist and Kirkpatrick 2005; Albrecht et al. 2006). As such, it is not clear why females in socially monogamous species have evolved such that they mate outside the pair (Forstmeier et al. 2014).

There have been proposed a number of adaptive explanations for female extrapair mating, along with challenges to the traditional theoretical and empirical basis for the expectation of sex-differentiation in adaptation for extrapair mating (Gowaty et al. 2012; Gowaty 2013). The dominant explanation of female extrapair mating has been that it can be adaptive if females are able to obtain extrapair mates of higher genetic quality than their social mates, thereby increasing the genetic quality of their offspring and increasing their number of grandoffspring (Jennions and Petrie 2000; Neff and Pitcher 2005). However, reviews of the empirical evidence in socially monogamous birds suggest that the genetic benefits to offspring of extrapair matings are generally very weak or nonexistent, and are likely to be outweighed by direct costs (Arnqvist and Kirkpatrick 2005; Akçay and

Roughgarden 2007). While there was debate as to the correct interpretation of these results (Griffith 2007; Eliassen and Kokko 2008), several more recent studies directly testing for such indirect benefits in birds suggest that offspring of extrapair matings actually have lower lifetime fitness and genetic value than offspring of within-pair matings (Reid and Sardell 2012; Sardell et al. 2012; Hsu et al. 2014; though see Gerlach et al. 2011), which poses a major challenge to this as a general adaptive explanation of female extrapair mating. As such, alternative explanations need to be considered.

One such alternative (nonadaptive) explanation is the between-sex genetic correlation hypothesis, which is that genetic variants predisposing males to male extrapair mating (and hence putatively selected for) might also predispose females to extrapair mating (Arnqvist and Kirkpatrick 2005; Forstmeier et al. 2011; Forstmeier et al. 2014). That is, female extrapair mating behaviour is maintained as a byproduct of selection for this behaviour in males. A recent finding of genetic correlations between measures of male and female extrapair mating behaviour in zebra finches (Forstmeier et al. 2011) is consistent with this hypothesis. While this finding does not in itself invalidate adaptive hypotheses in this or other species, it does warrant the consideration of between-sex genetic correlation as a plausible alternative to adaptive explanations of female extrapair mating.

This has important implications for evolutionary research into human mating; socially monogamous partnerships are the most common form of marriage even among forager societies in which other arrangements (e.g. polygyny, polyandry, promiscuity) are also common (Marlowe 2003). As in other species, extrapair copulation is common in humans across cultures (Greiling and Buss 2000; Marlowe 2000), and nonpaternity rates are non-zero in all societies that have been studied (Anderson 2006) and are quite high (9% and 17%) in the two small-scale natural-fertility (i.e. similar to ancestral) populations in which this has been carefully investigated (Neel and Weiss 1975; Scelza 2011) – this rate is comparable to

an estimated average rate of extrapair paternity among bird species (11%; Griffith et al. 2002).

The dominant evolutionary theories of human mating strategies (e.g. sexual strategies theory (Buss and Schmitt 1993); strategic pluralism (Gangestad and Simpson 2000), dual mating strategies (Fisher 1992)) regard both men and women as having evolved distinct psychological mechanisms adapted for both long-term and short-term (including extrapair) mating strategies. Pillsworth and Haselton (2006) specifically propose that women are endowed with suites of adaptations that function to form a social partnership with a man she judges to be a reliable investing partner while surreptitiously seeking good genes (for her offspring) from another man through extrapair sexual encounters. While there is indirect evidence from a variety of sources consistent with this hypothesis (reviewed in Gangestad 2006; Pillsworth and Haselton 2006), there is no direct evidence to this effect (e.g. there is no evidence that offspring of extrapair matings are fitter than offspring of within-pair matings). Given this and the aforementioned recent findings in socially monogamous birds, which suggest that extrapair offspring are less fit than within-pair offspring (Reid and Sardell 2012; Sardell et al. 2012; Hsu et al. 2014) and that there is substantial cross-sex correlation in extrapair mating behaviours (Forstmeier et al. 2011), it is worthwhile investigating the plausibility of the between-sex genetic correlation as an alternative explanation for female extrapair mating in humans. Previously, this alternative explanation has barely been considered.

There is evidence from studies of identical and nonidentical twins that sociosexuality (i.e. orientation towards short- or long-term mating strategy) is heritable in both men and women. Bailey et al. (2000) estimated that genetic factors account for 26% and 43% of the variance in men and women, respectively, although it should be noted that the male genetic variance did not reach statistical significance. Furthermore, there was a significant between-

sex correlation, consistent with the between-sex genetic correlation hypothesis. However, the sociosexuality score was made up of a variety of measures, most of which did not pertain to extrapair mating per se (i.e. copulating with others while in a pair-bond relationship). There has been one twin study specifically on extrapair mating, but only in women (Cherkas et al. 2004); in that study, 41% of the variance in female infidelity was estimated to be accounted for by genetic factors. It remains unknown as to what extent genetic factors influence men's extrapair mating behaviour and whether they are the same genetic factors as influence women's extrapair mating behaviour. This knowledge is crucial in weighing the relative merits of adaptationist and genetic-constraint explanations of female extrapair mating in humans.

Here we conduct two studies investigating potential genetic influences on male and female extrapair mating, and whether the same genetic factors influence the behaviour in both sexes. Study 1 uses the classical twin design to estimate the proportion of variation in extrapair mating that can be attributed to genetic differences in general, while Study 2 tests variation in two specific genes (oxytocin and vasopressin receptor genes) for association with extrapair mating.

Study 1

In Study 1 we used data from 7,378 twins and siblings who are in long-term relationships to estimate within-sex heritability and test for a between-sex correlation in recent extrapair copulation in order to assess the plausibility of the between-sex genetic correlation explanation of female extrapair mating in humans.

Methods

Participants

The full Finnish community-based twin-sibling sample consisted of 13,092 individuals aged from 18 to 49 ($M=29.2$, $SD=7.3$) from 7,737 families (see Johansson et al. 2013); for analysis we used the subset of individuals who had been in a relationship for at least the last year (see Measures for details), which consisted of 7,378 individuals aged from 18 to 49 ($M=29.8$, $SD=6.4$). Families with only one participating member who was in a relationship were retained because those data help to stabilise the group means, even though they do not contribute to the correlations between family members. Twins of unknown zygosity were excluded from analysis. A maximum of three siblings were retained per family, because models including more siblings were unstable due to the small number of larger sibships. Number of pairs of each type are included in Table 1.

Measures

Relationship status

In the first wave of data collection, participants were asked their relationship status [Divorced; Not seeing anybody at the moment; Never had a sexual relationship; Widowed; Engaged, Living together; Seeing only one person; Married, Registered partnership; Seeing several persons]. In the second wave of data collection participants were instead asked firstly: Do you have a steady sexual partner? [Yes/No] and secondly: For how long have you been in a relationship with this partner? [Less than a month; For a month or more, but less than 6 months; 6-12 months; 1-3 years; 4-10 years; More than 10 years]. Participants who were married (wave 1) or had a steady sexual partner for at least a year (wave 2) were regarded as

having been in a relationship for the last year and were included for analysis; others were excluded.

Extrapair mating

In a separate section of the survey, participants were asked how many different sexual partners they had had in the last 12 months. Participants were coded as positive (1) for extrapair mating if they reported more than one sexual partner in the last year, and otherwise were coded as negative (0).

Analyses

Analyses were performed on raw dichotomous data, where it is assumed that thresholds delimiting the two categories (i.e. extrapair mater vs. not) overlay a normally distributed continuum of liability (i.e. likelihood of engaging in extrapair mating). Twin/sibling tetrachoric correlations and their 95% confidence intervals were determined using maximum likelihood modelling in Mx (Neale et al. 2006), which is standard for twin-family designs because it accounts for the pseudo-independence of multiple twin and sibling pairs within families by explicitly incorporating their inter-relationship into the models. Age was modelled as a covariate with a separate age effect for males and females, effectively partialling out age from the twin/sibling correlations – this prevents age from acting as a confound, since twin pairs are always the same age.

Mx was also used to estimate the proportions of variation accounted for by additive genetic (A), nonadditive genetic (D), and residual (E) variation, as per standard twin-sibling analysis (Neale and Cardon 1992; Posthuma et al. 2003). This can be achieved because MZ twins share all their genes, while DZ twins and siblings share on average only half their segregating genes. Additive genetic variation results from the sum of allelic effects within

and across genes. Non-additive genetic variation includes that due to dominance and epistasis: allelic interactions within and across genes, respectively. Residual variation includes measurement error and environmental influences that are not shared between twin pairs, such as idiosyncratic experiences. *A*, *D*, and *E* influences predict different patterns of twin correlations, and modelling is used to determine the combination of *A*, *D*, and *E* that best fit the observed correlations. Family (shared) environmental effects can be estimated with twin-sibling data, but not concurrently with nonadditive genetic effects; very low same-sex twin correlations suggested negligible shared environmental effects, so as per standard practice in these cases, nonadditive effects were estimated with shared environmental effects assumed to be zero (Neale and Cardon 1992; Posthuma et al. 2003). Variance components were estimated separately for each sex. Further details of twin analysis can be found elsewhere (Neale and Cardon 1992; Posthuma et al. 2003).

Results

Preliminary testing

Of the individuals who had been in a relationship for at least the last year, 9.8% of men and 6.4% of women reported two or more sexual partners in the last year, indicating extrapair mating. Age effects on extrapair mating were not significant.

Corresponding DZ twin and sibling correlations were equated (i.e. male DZ/sibling pairs; female DZ/sibling pairs; opposite-sex DZ/sibling pairs) without loss of model-fit ($\chi^2_3=3.28, p=.35$), consistent with the equal genetic similarity of DZ and sibling pairs.

Twin correlations

Table 1 shows the intraclass tetrachoric correlations for different twin/sibling pairs. Female MZ twin pairs correlated significantly more strongly than did female DZ twin/sibling pairs ($\chi^2_1= 3.88, p=.049$), indicating a significant genetic component to variation in extrapair mating in females. Similarly, male MZ twin pairs correlated significantly more strongly than did male DZ twin/sibling pairs ($\chi^2_1= 8.22, p=.004$), indicating a significant genetic component to variation in extrapair mating in males.

DZ twin/sibling pairs did not correlate significantly in male pairs, female pairs, or opposite-sex pairs. Given the substantial correlations in MZ pairs, these very low DZ correlations suggest nonadditive genetic influences, although the wide confidence intervals warrant caution. This does not support the hypothesis that women's propensity to mate outside the social pair is due to positive selection for this behaviour in men. Indeed if we take the twin correlations at face value (i.e. ignoring the wide confidence intervals), there appears to be very little additive genetic variation even within sex, hence limiting the potential for the trait to respond to selection.

Genetic modelling

Table 2 shows estimates of the proportion of variation in extrapair mating accounted for by genetic (additive (A) and nonadditive (D)) and residual (E) factors. As can be seen, much of the variation is due to nonadditive genetic factors, whereas additive genetic factors appear not to play a role. However, there is little statistical power to distinguish between A and D , so the confidence intervals for their individual estimates include zero. Dropping D did not lead to a significant drop in model fit for males ($\chi^2_1= 82.91, p=.09$), females ($\chi^2_1= 2.01, p=.16$), or overall ($\chi^2_1= 2.96, p=.09$). However, the total genetic effect ($A+D$) is clearly non-zero in both males and females and is estimated to account for 63% and 40% of the variation, respectively.

Study 2

In Study 2 we tested whether some of the genetic variation in extrapair mating identified in Study 1 might be due to specific genes that have previously been associated with pair-bonding behaviour. Arginine vasopressin and oxytocin are hormones found in most mammals. A substantial body of work on monogamous and non-monogamous species of voles implicates these hormones and their receptor genes – arginine vasopressin receptor 1A gene (*AVPR1A*) and oxytocin receptor gene (*OXTR*) – in the striking differences in pair-bonding behaviour between these closely related species (see Insel 2010 for a review). This work has led to research in humans which has suggested that between-individual variation in *AVPR1A* and *OXTR* may be associated with individual differences in social behaviour (see Ebstein et al. 2012 for a review). Most relevantly, variation in social pair-bonding behaviour in human couples (e.g. marital stability and affiliative behaviour) has been associated with variation in both *AVPR1A* (Walum et al. 2008) and *OXTR* (Walum et al. 2012), though extrapair mating was not assessed in these studies. The only study that has tested for a link between *AVPR1A* and extrapair mating found no link; however, only one microsatellite (highly variable genetic marker) was genotyped (Cherkas et al. 2004), whereas the standard for later studies was to genotype multiple loci in a gene.

Here we performed gene-based tests (Liu et al. 2010) of multiple single nucleotide polymorphisms (SNPs) in the *AVPR1A* and *OXTR* genes for association with extrapair mating. The investigated SNPs are located in, as well as up- and downstream of the *OXTR* or *AVPR1A*, respectively, and they have all been associated with human social behaviours in previous reports (Ebstein et al. 2012; Westberg and Walum 2014). The gene-based analysis the p-values of SNPs in and around each gene as a group and tests whether those p-values are overall lower than would be expected by chance, given the number of SNPs in the gene and

taking into account their intercorrelation. We also tested two microsatellites (highly variable genetic markers) in the promoter region of *AVPR1A* for association with extrapair mating.

Methods

DNA Extraction and Genotyping

From saliva samples, 12 SNPs were genotyped in the *OXTR* gene, and 7 SNPs in the *AVPR1A* gene. In addition, two microsatellites in the promoter region of *AVPR1A* (RS1, which is a (GATA)₁₄ tetranucleotide repeat; and RS3, a complex (CT)₄-TT-(CT)₈-(GT)₂₄ repeat, both upstream from the transcription start site) were genotyped. Saliva samples were collected using the OrageneTM DNA (DNA Genotek, Inc.) self-collection kits that were posted to the participants and returned by mail. The participants were instructed to follow the manufacturer's instructions in collecting the samples and to deposit approximately 2 ml of saliva into the collection cup. When an adequate sample was collected, the cap was placed on the cup and closed firmly. The collection cup is designed so that a stabilizing solution from the cap is released when closed. This solution mixes with the saliva and stabilizes the saliva sample for long-term storage at room temperature or in low-temperature freezers. Genotyping of SNPs was performed by LGC Genomics in the United Kingdom (www.lcggenomics.com) using the KASPar chemistry, a competitive allele-specific PCR SNP genotyping system performed with FRET quencher cassette oligos. The RS3 microsatellite was amplified with primers 5'-TCCTGTAGAGATGTAAGTGC-3' (forward) and 5'-GTTTCTTTCTGGAAGAGACTTAGATGG-3' (reverse), and the RS1 microsatellite with primers 5'-AGGGACTGGTTCTACAATCTGC-3' (forward) and 5'-ACCTCTCAAGTTATGTTGGTGG-3' (reverse) (Kim et al. 2002; Wassink et al. 2004). The

fluorescently labelled DNA fragments were analysed by size with automated capillary electrophoresis by using an ABI PRISM 3730 Genetic Analyzer (Applied Biosystems).

Around 120 other SNPs and three other microsatellites in or near genes other than *AVPR1A* and *OXTR* were also genotyped, but none had hypothesised associations with extrapair mating. Genomewide SNP data were not available.

Statistical Analyses

For the analyses of SNP data, we estimated gene-based p -values based on the individual p -values for each SNP in the gene using the VEGAS software (Liu et al. 2010). Firstly, the Generalized Estimating Equations (GEE) procedure in SPSS 21.0 (SPSS, Inc.) was used to compute a Wald χ^2 p value for the association between each SNP and the dependent variable (i.e. whether the person had engaged in sexual activity outside the relationship or not). The GEE procedure appropriately controls for between-subjects dependence, which was necessary because the sample consisted of twin and sibling pairs. In all these analyses, age was inserted as a covariate. We fitted a binary logistic model to the data, as the dependent variable was dichotomous. Next, the Wald χ^2 p values for the association between each SNP and the dependent variable (extrapair mating) were analysed with VEGAS, which estimates linkage disequilibrium patterns for each gene using the HapMap release 22 CEU population as reference before estimating a gene-based p value for the association between the gene and the dependent variable. Analyses including genotype data were conducted in three steps: for the whole sample, and then separately for men and women.

Microsatellites were analysed separately. The RS3 microsatellite was analysed comparing 334-repeat allele carriers against individuals who carried no 334 repeat based on results from previous research (Walum et al. 2008). The RS1 microsatellite was divided by the median number of repeats into long (L) and short (S) alleles. Thus, both microsatellites

were subsequently analysed as biallelic loci with three possible genotypes: 0, 1 or 2 copies of the 334 repeat allele (RS3); and L/L, S/L, and S/S (RS1). These were analysed using the GEE procedure as described above, using age as a covariate.

Results

Descriptive Statistics

Genotype data were available for a subset of individuals ($n = 2483$ - 2527 , the exact sample size varying between different loci due to individual occurrences of genotyping error) from the second data collection of the GSA sample (Johansson et al. 2013). The allele frequencies and genotype distributions for the SNPs can be seen in Table 3 (data for men and women presented together). On average, SNP data were available for 946 men (range = 933-953) and 1564 women (range = 1550-1579).

A standard test for possible genotyping error is to compare the observed genotype distributions (common homozygote : heterozygote : rare homozygote) to those expected from observed allele frequencies under Hardy-Weinberg equilibrium (i.e. in the absence of evolutionary influences such as selection and non-random mating). Only one SNP (*OXTR* rs11720238) deviated significantly from Hardy-Weinberg equilibrium after controlling for multiple comparisons. We retained this SNP for analysis in the absence of any other indications of genotyping problems.

Genotype Analyses

Individual SNP and microsatellite association tests are shown in the Supplementary Table. For males, no SNP associations with extrapair mating were nominally significant ($p < .05$). For women, no SNPs in the *OXTR* gene showed nominally significant associations, but five out

of seven SNPs were associated with extrapair mating at $p < .05$. Neither the RS3 nor the RS1 microsatellites were significantly associated with extrapair mating in men or women.

Some SNPs were not included in the gene-based tests. One *OXTR* SNP, rs53567, was not included in the HapMap 22 database (CEU population), and could therefore not be analysed in the gene-based tests. Due to its extremely low allelic variation, the rs3759292 SNP in *AVPR1A* was dropped from all subsequent analyses. Due to insufficient phenotypic variance resulting from rare genotypes, or otherwise incomputable distributions in the single-SNP association tests, three *OXTR* SNPs (rs2254298, rs1488467, and rs4564970) were dropped from the gene-based test for women, and three *AVPR1A* SNPs (rs3021529, rs1587097, and rs11174811) from the gene-based tests for men. Thus, 6 *AVPR1A* SNPs and 11 *OXTR* SNPs were included in gene-based testing for the whole sample combined (6 *AVPR1A* SNPs and 8 *OXTR* SNPs for women, and 3 *AVPR1A* and 11 *OXTR* SNPs for men).

Gene-based test results (Table 4) show that the *AVPR1A* gene was significantly associated with extrapair mating when women and men were combined, but only in women when the sexes were analysed separately. Bonferroni correction for 12 tests (male/female/full sample for two genes and two microsatellites) would result in $\alpha = .0042$ for the significance test, in which case only the association in women between the *AVPR1A* gene and extrapair mating would remain significant. No association was detected between extrapair mating and the *OXTR*. In addition to the gene-based analysis we also analysed each SNP separately (see Supplementary Table).

Discussion

There are several novel findings from these two studies. First, we found significant genetic influences accounting for around half the variation in extrapair mating in both sexes, confirming biological underpinnings to the behavior. Second, we found a near-zero cross-sex correlation in extrapair mating – that is, 697 brother-sister pairs showed no similarity in likelihood of having extrapair mates. A near-zero cross-sex correlation means that extrapair mating in females is unlikely to be strongly affected by correlated response to selection on extrapair mating in males. Third, we found a significant gene-based association between SNP variation in the *AVPR1A* gene and extrapair mating in women, providing some support for a role in humans analogous to the gene's apparent role in differentiating the behaviour of monogamous and non-monogamous vole species.

While genetic influences on human individual differences are pervasive, the magnitude of the genetic contribution (63% in men and 40% in women) to variation in extrapair mating over a one-year period is perhaps surprising, given that such behaviour depends not only on the individual but on the availability of willing extrapair partners, circumstantial opportunity, intensity of the social partner's mate guarding, and so on. Variation in realised mate choice, for example, which similarly depends on the reciprocal choices of other individuals, exhibits near-zero heritability (Zietsch et al. 2011). Nevertheless, our findings in men and women roughly accord with the findings of Cherkas et al. (2004) in British women; in that study, genes were estimated to account for 50% of the variation in women's lifetime extrapair mating. Our results also accord with results from the British female sample in terms of the large proportion of nonadditive genetic effects relative to additive effects, though this is even more exaggerated in our results. A large proportion of

nonadditive relative to additive genetic effects can reflect strong past selection on a trait (because selection is more efficient at winnowing additive than nonadditive genetic variation; Merila and Sheldon 1999), though it need not necessarily be the case; moreover, we had little power to distinguish additive and nonadditive genetic effects in this study, so their relative proportions should be interpreted cautiously.

We found a nonsignificant, near-zero cross-sex correlation ($r=.03$) – however, because the same-sex nonidentical twin/sib pair correlations were also near-zero, we do not know whether the near-zero cross-sex correlation is because different genes influence males and females, or simply that there is negligible additive genetic variation (i.e. males and females could be influenced by the same nonadditive genetic influences). In either case, the near-zero cross-sex correlation means that any selection for extrapair mating in males is unlikely to yield a substantial correlated response to selection in females, since additive genetic cross-sex covariance is the only mechanism by which this could occur.

There are several caveats to this finding. One is that, despite the large sample size, the estimate of the cross-sex correlation has wide confidence intervals. This is largely because of the rarity of reported extrapair mating in the previous year, which reduces the precision of tetrachoric twin/sibling pair correlations. A lifetime measure of extrapair mating would reduce this problem (albeit potentially increasing other problems involving retrospective recall/reporting biases), but such a measure was not available in this sample. Another important caveat is that the implications of the lack of cross-sex correlations apply to the possibility of current indirect selection, but not necessarily to ancestral indirect selection. For example, a positive cross-sex correlation in extrapair mating may have been present in ancestral populations, allowing indirect selection for female extrapair mating (via males) – subsequently, different selection pressures acting directly on females may have eroded this correlation but not eliminated the nonadditive genetic predisposition to extrapair mating.

The finding of a significant association of variation in *AVPR1A* with variation in extrapair mating is broadly consistent with the gene's apparent role in differentiating the mating behaviour of monogamous and non-monogamous vole species (Insel 2010), and with findings in humans linking a SNP within the gene with a pair-bonding measure tapping marital difficulties and degree of affiliative behaviour in couples (Walum et al. 2008). However, it should be well noted that our results do not directly replicate previous results in humans. Whereas Walum et al. (2008) found association in men (but not women) of a single polymorphism (RS3) with scores on the aforementioned social pair-bonding measure, we find no association of RS3 with extrapair mating (a related but different measure), and indeed our gene-based association was only significant in women, not in men. Furthermore, we find no evidence of an association of extrapair mating with *OXTR* (or the specific SNP rs7632287), which had been previously associated with pair-bonding behaviours in women (Walum et al. 2012). We also did not see any associations between extrapair mating and the two SNPs rs53576 and rs2254298, which have been suggested to be two promising candidate variants in *OXTR*. This is in line with a recent meta-analysis reporting no detectable effect of these two *OXTR* SNPs on human social behaviours (Bakermans-Kranenburg and van Ijzendoorn 2013), but other variants in *OXTR* have not been as thoroughly examined in past studies and may still warrant further investigation. Problems with the replicability of candidate-gene associations for behavioural traits are well documented (e.g. Bosker et al. 2011; Verweij et al. 2012), and high-powered direct replications are of paramount importance (Duncan and Keller 2011). Our *AVPR1A* association is neither a direct nor high-powered replication, and so should be regarded as tentative until subjected to rigorous replication, with publication of both positive and negative findings.

Notwithstanding these cautionary notes, the present study makes several advances in our understanding of extrapair mating in humans. We find strong (nonadditive) genetic

effects on extrapair mating in women and, for the first time, in men. We also find for the first time that there is no substantive cross-sex familial correlation in extrapair mating, which suggests that selection pressures for male extrapair mating would not yield a correlated response in female extrapair mating, rendering unlikely this nonadaptive evolutionary explanation of female extrapair mating. Finally, we find association of a plausible candidate gene with extrapair mating in women, which may give insight into the biology of extrapair mating in humans and warrants further investigation.

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Table 1

Intraclass tetrachoric correlations (and 95% confidence intervals) for extrapair mating.

	Tetrachoric correlations (95% CI)
Identical twin females (N pairs=370)	.43 (.17, .64)
Identical twin males (N pairs=101)	.67 (.32, .88)
Identical twins all (N pairs=471)	.50 (.30, .67)
Nonidentical twin/sibling females (N pairs=973)	.08 (-.16, .32)
Nonidentical twin/sibling males (N pairs=239)	-.07 (-.33, .30)
Opposite-sex twin/siblings (N pairs=697)	.03 (-.21, .26)
Nonidentical twins/siblings all (N pairs=1909)	.04 (-.12, .19)

Table 2. Proportion of variation in extrapair mating accounted for by genetic (additive (A) and nonadditive (D)) and residual (E) factors, with 95% confidence intervals in brackets. Estimates are provided for males and females separately, as well as for males and females equated (i.e. 'All').

	Male	Female	All
Additive genetic (A)	.00 (.00, .82)	.00 (.00, .48)	.00 (.00, .53)
Nonadditive genetic (D)	.62 (.00, .86)	.40 (.00, .61)	.53 (.00, .69)
Total genetic ($A+D$)	.62 (.26, .86)	.40 (.14, .61)	.53 (.34, .69)
Residual (E)	.38 (.14, .74)	.61 (.39, .86)	.47 (.31, .66)

Table 3

Allele frequencies and genotype distributions for arginine vasopressin receptor 1A (*AVPR1A*) and oxytocin receptor (*OXTR*) gene-linked single nucleotide polymorphisms for men and women combined.

SNP rs number	Location	Alleles	Minor allele frequency (%)	Common homozygotes	Heterozygotes	Rare homozygotes	HWE χ^2
<i>Arginine Vasopressin Receptor 1A Gene (AVPR1A) SNPs</i>							
rs10877970	5'	C/T	C: 738 (14.7%)	1844 (73.3%)	602 (23.9%)	68 (2.7%)	4.86 *
rs3759292 ^a	5'	G/A	G: 11 (0.4%)	2505 (99.6%)	11 (0.4%)	0 (0.0%)	0.01
rs10877969	5'	C/T	C: 709 (14.3%)	1838 (74.0%)	581 (23.4%)	64 (2.6%)	4.82 *
rs3021529	5'UTR	A/G	A: 512 (10.1%)	2041 (80.8%)	460 (18.2%)	26 (1.0%)	<0.01
rs1042615	Exon 1	G/A	A: 2042 (40.6%)	901 (35.8%)	1186 (47.2%)	428 (17.0%)	1.25
rs11174811	3'	A/C	A: 504 (10.0%)	2028 (80.9%)	456 (18.2%)	24 (1.0%)	0.09
rs1587097	3'	C/T	T: 337 (6.7%)	2193 (87.2%)	309 (12.3%)	14 (0.6%)	0.75
<i>Oxytocin Receptor Gene (OXTR) SNPs</i>							
rs75775	5'	G/T	T: 1207 (24.0%)	1436 (57.2%)	941 (37.5%)	133 (5.3%)	1.75
rs1488467	5'	C/G	C: 197 (3.9%)	2326 (92.4%)	187 (7.4%)	5 (0.2%)	0.37
rs4564970	5'	C/G	C: 235 (4.7%)	2280 (90.9%)	219 (8.7%)	8 (0.3%)	1.24
rs4686302	Exon 3	C/T	T: 672 (13.5%)	1865 (74.7%)	590 (23.6%)	41 (1.6%)	0.53
rs237897	Intron 3	G/A	A: 2493(49.8%)	643 (25.7%)	1277 (51.1%)	581 (23.2%)	1.19
rs53576	Intron 3	G/A	A: 2064 (41.4%)	862 (34.6%)	1198 (48.1%)	433 (17.4%)	0.23
rs2254298	Intron 3	G/A	A: 400 (8.0%)	2122 (84.8%)	362 (14.5%)	19 (0.8%)	0.67
rs2268493	Intron 3	C/T	C: 1951 (38.9%)	957 (38.2%)	1151 (45.9%)	400 (15.9%)	2.99
rs237887	Intron 3	G/A	G: 2046 (40.8%)	903 (35.8%)	1190 (47.2%)	428 (17.0%)	1.13
rs1042778	3' UTR	G/T	T: 1999 (39.7%)	915 (36.3%)	1209 (48.0%)	395 (15.7%)	0.02
rs7632287	3'	G/A	A: 1434 (28.6%)	1281 (51.1%)	1016 (40.5%)	209 (8.3)	0.14

rs11720238 3' G/T T: 587 (11.7%) 1985 (78.8%) 479 (19.0%) 54 (2.1%) 14.67***

Note. SNP = Single Nucleotide Polymorphism; HWE = Hardy-Weinberg equilibrium (Rodriguez et al. 2009); A = adenine, C = cytosine, G = guanine, T = thymine. ^a = excluded from gene-based testing due to extremely low minor allele frequency; ^b = not included in the HapMap 22 CEU population database and therefore excluded from gene-based testing. * = $p < .05$; *** = $p = .000064$

Table 4

Gene-based associations between extrapair mating and the genes coding for the arginine vasopressin 1A and oxytocin receptors. (Number of markers in brackets.)

Gene	Gene-based p for men	Gene-based p for women	Gene-based p for men + women combined
<i>AVPR1A</i>	.22 (3)	.0002 (6)	.007 (6)
<i>OXTR</i>	.07 (11)	.21 (8)	.23 (11)

NB: *AVPR1A* = arginine vasopressin receptor 1A gene, *OXTR* = oxytocin receptor gene.