# Reported associations between receptor genes and human sociality are explained by methodological errors and do not replicate

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Using a sample of 757 British individuals, Pearce et al. (1) tested 24 single-nucleotide polymorphisms (SNPs) in six candidate genes for association with eight social behavior traits. For each SNP for each trait, five genotypic model tests were reported (except the androgen receptor gene, for which two model tests were reported), resulting in 936 reported tests. Of these, 44 (4.7%) were significant at $P < 0.05$, a proportion of significant associations that would be expected by chance if there was no true association between the SNPs and the traits measured in this dataset.

Pearce et al. allude to having corrected for multiple testing using the *mperm* option in Plink. However, they do not report corrected *P* values, but instead report in the *SI Appendix* that "genotypic model significance levels did not always survive correction for multiple tests using *mperm*." It is unclear how many tests, if any, did survive multiple testing correction. The authors dismiss the usefulness of multiple testing corrections because they "fail to account for dependence between tests due to linkage disequilibrium," but in fact *mperm* does enable correction for such dependence.

Pearce et al. argue that individual SNP–behavior associations are less interesting than "the overall pattern exhibited across the behavioural domains by the individual neuropeptides." To test for nonrandom distribution of SNP effects across social domains, they used a contingency table comprising counts of the number of SNPs in each gene that exhibit at least one association ($P < 0.05$) with at least one variable within each behavioral domain. A highly significant $\chi^2$ test of independence is reported. This test is invalid because several of its assumptions are violated (2). Most importantly, nonoccurrences (i.e., the number of SNPs in each gene that did not exhibit any association with any variable within each behavioral domain) were not included. If nonoccurrences are included (Table 1, based on Pearce et al.'s table S2), the $\chi^2$ test of independence is not significant ($\chi^2 = 24.27$, df = 25, $P = 0.503$), suggesting a random pattern of SNP/gene effects across domains.

The above is consistent with the significant effects reported in Pearce et al. being false positives. We had available a sample (3) more than four times the size of Pearce et al.'s that enabled testing for replication of eight of the reported significant SNP associations with the Sociosexual Orientation Inventory (the variable with the most reported associations in their data). None of the associations were significant in our data (Table 2).

Candidate gene association studies are viewed with skepticism in the genetics community because of their poor record of replication, and many journals no longer generally consider them for publication (e.g., see ref. 4). Genome-wide association studies with six-digit sample sizes (e.g., refs. 5–8) show that true SNP effects on behavioral traits are miniscule and rarely found in a priori hypothesized candidate genes. When interpreted as an underpowered study with null findings, Pearce et al.'s results are consistent with what we know from genome-wide association studies.

## Acknowledgments

This research was made possible by Grants 138291, 274521, and 284385 from the Academy of Finland (to P.J.). B.P.Z. is supported by an ARC Future Fellowship (FT160100298).

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Author contributions: B.P.Z. designed research; P.J. performed research; P.J., K.J.H.V., and F.K.B. analyzed data; and B.P.Z. wrote the paper.

The authors declare no conflict of interest.



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**Table 1. Number of SNPs in each gene that did and did not exhibit at least one association with a variable within each behavioral domain**

| | Disposition | | Dyadic relationships | | Wider network | |
|---|---|---|---|---|---|---|
| Receptor gene | Any significant | None significant | Any significant | None significant | Any significant | None significant |
| Testosterone | 1 | 3 | 0 | 2 | 0 | 2 |
| β-Endorphin | 6 | 14 | 2 | 8 | 1 | 9 |
| Vasopressin | 1 | 7 | 0 | 4 | 0 | 4 |
| Oxytocin | 2 | 38 | 9 | 11 | 2 | 18 |
| Dopamine | 1 | 15 | 1 | 7 | 3 | 5 |
| Serotonin | 0 | 8 | 0 | 4 | 1 | 3 |

The above counts for oxytocin (disposition) and dopamine (disposition, dyadic relationships, and wider network), based on Pearce et al.'s table S2, and cross-checked with statistics reported in text, do not match the proportions reported in Pearce et al.'s figure 2. The proportions reported in Pearce et al. for these cells appear incorrect.

**Table 2. Replication of associations between SNPs and the Sociosexual Orientation Inventory**

| | Pearce et al. (1), $n = 757$ | | GSA data [Johansson et al. (3)], $n = 3{,}466$–$3{,}498$ |
|---|---|---|---|
| SNP | Model | *P* | *P* |
| rs237887 | add x sex | 0.014 | 0.963 |
| rs4686302 | add x sex | 0.047 | 0.255 |
| rs2254298 | geno_2df | 0.046 | 0.715 |
| rs53576 | domdev | 0.035 | 0.146 |
| rs237897 | domdev x sex | 0.034 | 0.857 |
| rs2268490/rs2268493* | geno_2df | 0.046 | 0.060 |
| rs265981/rs4532* | domdev | 0.039 | 0.194 |
| | domdev x sex | 0.039 | 0.110 |

Data were analyzed in Plink, version 1.90, using covariates sex and age with the *–genotypic* option and were corrected for nonindependence (family clustering) using the *–family* option; a random member of each monozygotic twin pair in the GSA sample was dropped as is standard in Plink. None of the effects is significant if all monozygotic twins are retained.

*The rs2268490 and rs265981 SNPs are not available in the Genetics of Sexuality and Aggression (GSA) dataset but are in complete linkage disequilibrium with rs2268493 and rs4532, respectively; thus, the latter two SNPs were used as proxies for replication.


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