## Genome studies must account for history-Response

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LETTERS

*Edited by* **Jennifer Sills**

## Retraction

The online Research Article "Insular cortex processes aversive somatosensory information and is crucial for threat learning" used optogenetic methods in mice to conclude that insular cortex is involved in auditory cued fear learning (*1*). A reanalysis of the data performed by the authors in October 2019 showed, however, that the mouse behavior data reported in Figs. 1C, 3C, 3F, and 6B, and the corresponding data in supplementary figures, had been manipulated. The reanalysis showed that data points from many individual mice had been moved, with the effect that the difference between optogenetic silencing groups and control groups became larger than in the real data. Thus, in the reanalyzed data, the statistical significance disappears for many datasets of Figs. 1, 3, and 6, and these experiments need to be reestablished in future work. The first author, who performed these measurements, has admitted to having committed the data falsification. No other coauthors were involved in the data manipulation, and thus their data (Figs. 2 and 5 and supplementary figs. S2, S4–S6, S11, and S15–S18) remain valid. Because the data manipulations affect important conclusions of the paper, the authors retract the Research Article. We apologize to the readership of *Science*.

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### REFERENCES AND NOTES

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## Genome studies reveal flaws in broad consent

In their Research Article "Large-scale GWAS reveals insights into the genetic architecture of same-sex sexual behavior" (30 August, p. eaat7693), A. Ganna *et al.* found that same-sex sexual behavior is influenced by many genes. The study used data and genetic information from a number of sources, including UK Biobank. UK Biobank participants gave broad consent between 2006 and 2010 to the use of their data, health records, and bodily materials for "health-related research purposes" (*1*, *2*). Ganna *et al.*'s study reveals the ethical problems with using broad consent from participants for biobank research.

**Is it time to reconsider broad consent models for biobank research?**

There are three ways in which studying the genetic architecture of same-sex sexual behavior can be claimed to be health-related. First, it would be health-related if same-sex and/or different-sex behavior were in themselves states of health or illness. However, homosexuality has long been removed from disease classifications, and making such a claim would be normatively problematic in implying that one or both of these behaviors signified disease. Second, the study would be health-related if persons who engage in one of these behaviors are on aggregate more or less likely to experience particular health outcomes. Yet this justification vastly increases the scope of the term "health-related." Any behavior can have a link to health outcomes. For example, voting behavior has such a link (*3*, *4*), but it would be odd to classify a hypothetical study of the genetic architecture of voting behavior as health-related. Third, the study would be health-related if all research that improves our understanding of human biology were health-related. This again leads to a massive expansion of the scope of the term, collapsing the distinction between health-related research and basic molecular biology research.

The understanding of what qualifies as health-related research is likely to change over time, but the restriction on allowable research is governed by the meaning the term had for participants at the time they gave their consent (*5*, *6*). Broad consent was developed at a time when it was difficult to keep in contact with research participants after their initial consent, but keeping that contact is now much easier and cheaper. We should consider implementing more interactive consent models, such as dynamic or meta-consent, that allow participants to vary their consent preferences as the science progresses and societal values change (*7*, *8*).

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**COMPETING INTERESTS**

S.H. is a former member of the UK Biobank Ethics and Governance Council.

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# Genome studies must account for history

In their Research Article "Large-scale GWAS reveals insights into the genetic architecture of same-sex sexual behavior" (30 August, p. eaat7693), A. Ganna *et al.* found that prevalence of same-sex experience in the UK Biobank population increased four-fold across study participants' birth years, and prevalence in the younger, self-selecting 23andMe consumer population was 6 times that of UK Biobank. The authors treat single nucleotide polymorphisms identified in these populations as ahistorical components of the "architecture of same-sex sexual behavior." We question the generalizability of their findings.

Political context and stigmatization of homosexuality affects whether people engage in and/or report same-sex behavior (*1*, *2*). Historical conditions such as decriminalization of homosexuality in 1967 and legalization of marriage equality in 2013 and 2014 instigated substantial shifts in reporting of same-sex orientations (*3*, *4*). Sampling based on voluntary surveys that limited the cohorts to cis-gender people of white-European descent could exaggerate these dynamics. Furthermore, many sexual minorities are unsampled due to the HIV/AIDS epidemic in the 1980s and 1990s (*5*). Centering the analysis around the variable of birth year and interpreting findings in relation to historical, social, and legal context might alter the study's conclusions (*6*).

Ganna *et al.*'s conjecture that "genetic and sociocultural influences on sexual behavior might interact" does not resolve these concerns. This approach implies that it is acceptable to issue claims of genetic drivers of behaviors and then lay the burden of proof on social scientists to perform post-hoc socio-cultural analysis. Given the epistemic authority of the molecular biosciences and the potential consequences for those with vulnerable social identities, damage caused by these studies is hard to repair. As socio-genomic GWAS studies proliferate, we call for community standards for research design that acknowledge the historical, political, and social context of phenotypes under study.

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## Response

Our genome-wide association study (GWAS) on same-sex sexual behavior, which used data from the UK Biobank (*1*), was reviewed and approved by the UK Biobank Access Sub-Committee. We also sought stakeholder input from allies and advocates for the LGBTQIA+ community, as has been done in the past (*2*, *3*). Despite these efforts, Holm and Ploug contend that broad biobank consent is insufficient. They argue that our study only tenuously qualifies as "health-related" and thus stretches the bounds of the participants' consent.

We agree with Holm and Ploug that same- or different-sex sexual behaviors are not states of disease or health; same-sex sexual behavior is a natural part of normal human variation, and we in no way condone othering of members of the LGBTQIA+ community. However, we disagree that our study is related only indirectly to health. Same-sex sexual behavior intersects with health care in a variety of ways. For example, sexual behavior and history are used to guide recommendations of whether to take preexposure prophylaxis medication (*4*). Sexual minorities experience stigma, microaggressions, and prejudice, which have been shown to relate to the higher rates of anxiety and depression (*5*). These connections help contextualize the higher rates of suicidality, mood and anxiety disorders, and alcohol and substance use seen in sexual minorities (*6*–*8*). The genetic correlation analyses in our Research Article add to our understanding about how sexual behavior relates to health outcomes, and publicly available summary statistics from our GWAS may be used by other researchers to better understand genetic and environmental influences on sexual behavior, facilitating a fuller understanding of human health.

Holm and Ploug argue that participants may not have given consent for our study based on the information they had about the potential use of their data. We believe that when broad biobank consent is used, institutional bodies (such as the UK Biobank's Board and its Access Sub-Committee) must take responsibility for approving specific research requests rather than expecting participants to understand all such details for possible research projects. We also point out that participants had more options and information than Holm and Ploug describe. The UK Biobank pamphlet (*9*) emphasizes that participants can skip or select "prefer not to answer" for any question; an additional message underlining this option was presented before the section with sexuality-related questions. The UK Biobank's consent and information forms also explained its intention to "support a diverse range of research" including "the promotion of health throughout society," and it stated that health "is affected by [people's] lifestyle, environment, and genes" (*9*). Given this full context, the genetic study of sexual behavior is both health-related and consistent with the consent of the participants.

Richardson *et al.* discuss the issue of selective sampling and comment that the social and historical context of the participants may affect our findings. We acknowledged both the limits of our samples and the importance of sociocultural context in our Research Article. We agree with Richardson *et al.* that analyzing the data according to birth year and taking into account cultural factors would be fascinating. Indeed, we did attempt some preliminary analyses to evaluate whether this line of inquiry was feasible. Unfortunately, fine-grained analyses stratified by birth year require extremely large

samples to detect the relevant effects, and statistical power analyses indicated that the current sample size was insufficient to yield meaningful results (we reported some sensitivity analyses in table S5). As GWAS sample sizes continue to grow, more analyses will become more feasible, and we look forward to contributing to these investigations. We join others (*10*–*12*) in calling for greater diversity in these samples.

**Andrea Ganna[1,2,3,4]*, Karin J.H. Verweij[5]*, Michel G. Nivard[6], Robert Maier[1,2,3], Robbee Wedow[1,3,7,8,9,10,11], Alexander S. Busch[12,13,14], Abdel Abdellaoui[5], Shengru Guo[15], J. Fah Sathirapongsasuti[16], 23andMe Research Team[16], Paul Lichtenstein[4], Sebastian Lundström[17], Niklas Långström[4], Adam Auton[16], Kathleen Mullan Harris[18,19], Gary W. Beecham[15], Eden R. Martin[15], Alan R. Sanders[20,21], John R.B. Perry[12]*, Benjamin M. Neale[1,2,3]*, Brendan P. Zietsch[22]*†**

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## COMPETING INTERESTS

J.F.S. is an employee of MedGenome, Inc. B.M.N. is a member of the scientific advisory board at Deep Genomics and consultant for Camp4 Therapeutics, Takeda Pharmaceutical, and Biogen.

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## TECHNICAL COMMENT ABSTRACTS

### Comment on "Demographic dynamics of the smallest marine vertebrates fuel coral reef ecosystem functioning"

**Jacob E. Allgeier and Timothy J. Cline**

Brandl *et al.* (Reports, 21 June 2019, p. 1189) report that cryptobenthic fishes underpin coral reef ecosystem function by contributing ~60% of "consumed fish" biomass and ~20% of production. These results are artifacts of their simulation. Using their data and model, we show that cryptobenthic species contribute less than 4% to fish production, calling into question the extent to which they contribute to the high productivity of coral reefs.

**Full text:** dx.doi.org/10.1126/science.aay9321

### Response to Comment on "Demographic dynamics of the smallest marine vertebrates fuel coral reef ecosystem functioning"

**Simon J. Brandl, Renato A. Morais, Jordan M. Casey, Valeriano Parravicini, Luke Tornabene, Christopher H. R. Goatley, Isabelle M. Côté, Carole C. Baldwin, Nina M. D. Schiettekatte, David R. Bellwood**

Allgeier and Cline suggest that our model overestimates the contributions of cryptobenthic fishes to coral reef functioning. However, their 20-year model ignores the basic biological limits of population growth. If incorporated, cryptobenthic contributions to consumed fish biomass remain high (20 to 70%). Disturbance cycles and uncertainties surrounding the fate of large fishes on decadal scales further demonstrate the important role of cryptobenthic fishes.

**Full text:** dx.doi.org/10.1126/science.aaz1301

## ERRATA

**Erratum for the Report: "The STAT3-Binding Long Noncoding RNA lnc-DC Controls Human Dendritic Cell Differentiation" by P. Wang *et al.*, *Science* 366**, eaba5539 (2019). Published online 20 December 2019; 10.1126/science.aba5539

**Erratum for the Report: "Aging increases cell-to-cell transcriptional variability upon immune stimulation" by C. P. Martinez-Jimenez *et al.*, *Science* 366**, eaba3487 (2019). Published online 20 December 2019; 10.1126/science.aba3487

# Genome studies must account for history—Response

Andrea Ganna, Karin J.H. Verweij, Michel G. Nivard, Robert Maier, Robbee Wedow, Alexander S. Busch, Abdel Abdellaoui, Shengru Guo, J. Fah Sathirapongsasuti, 23andMe Research Team, Paul Lichtenstein, Sebastian Lundström, Niklas Långström, Adam Auton, Kathleen Mullan Harris, Gary W. Beecham, Eden R. Martin, Alan R. Sanders, John R.B. Perry, Benjamin M. Neale and Brendan P. Zietsch

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