LETTER

Reply to Drury and Theall: No evidence of population stratification

We appreciate the opportunity to address the five critiques raised by Drury and Theall in their letter (1) concerning our recent article (2). First, Drury and Theall explain that previous studies used saliva to measure telomere length (TL), and they provide two examples in the literature. We indicate that this is the case in our paper [for example, we state that "Our study validates other work showing that multiple tissues, including saliva, can be used to measure TL. . ." (2)]. We also provide two references following this statement, including one to a paper by Theall et al., which they also referred to in their letter (3). Our study differed in providing a comparison between saliva and mononuclear cell TL (figures S2 and S3 in ref. 2). Second, Drury and Theall point to two other studies using African American children, one of which we also cite (3). One of these two studies (4) did not include an exclusively African American sample, the other (3) did, and we regret the oversight. Third, and most important, Drury and Theall are concerned that we overlook significant differences in allele frequencies between the two extreme groups. However, the authors appear to have treated table S1 in our report (2) as containing cell counts instead of percentages. So doing would grossly overestimate the significance of any apparent difference. In Table 1 we provide the χ^2 tests of harsh vs. nurturing environment by gene using cell count (test 1 in Table 1). None is significant. Fourth, Drury and Theall are correct that we did not supply estimates of similarity to African American population or Hardy–Weinberg Equilibrium (HWE). Although HWE is straightforward to estimate (see test 2 in Table 1), comparing our 40-person sample to what is expected of the African American population is more difficult. In test 3 of Table 1 we provide a χ^2 test of our 40-person sample to the African American sample in the larger, population-based Fragile Families study (n = 1,393). We have also compared the minor allele frequency of the entire Fragile Families African American sample to estimates available in HapMap and found them to be generally in accord. Finally, the fifth concern was that there was no statistical evidence of differential susceptibility, only visual. As we note in our report (see especially figure 1 of ref. 2), dopaminergic pathway genes do not fit this pattern; however, the serotonergic pathway genes may. Moreover, although we do not indicate that our data confirm the differential susceptibility hypothesis—only that it is consistent with it—the observation that the TL is longest in advantaged subjects with the 2+ sensitizing genotype is inconsistent with the diathesis-stress model. Further statistical testing will await the analysis of many more subjects, which is currently underway. In sum, we feel our results are correct and appreciate the opportunity to provide additional information to support this conclusion.

ACKNOWLEDGMENTS. Funding for this study was provided by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01 HD076592) and the Penn State Clinical and Translational Science Institute (UL1 TR000127). In addition, this work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development through Grants R01HD36916, R01HD39135, and R01HD40421.

***Colter Mitchell*[a] *and Daniel Notterman*[b,c,1]**

[a]*Survey Research Center and Population Studies Center, University of Michigan, Ann Arbor, MI 48104;* [b]*Departments of Pediatrics, and Biochemistry and Molecular Biology, College of Medicine, Pennsylvania State University, Hershey, PA 17033; and* [c]*Department of Molecular Biology and Woodrow Wilson School, Princeton University, Princeton, NJ 08544*

1 Drury S, Theall K (2014) Carefully thinking about telomeres. *Proc Natl Acad Sci USA* 111:E2441.
2 Mitchell C, et al. (2014) Social disadvantage, genetic sensitivity, and children's telomere length. *Proc Natl Acad Sci USA* 111(16): 5944–5949.
3 Theall KP, Brett ZH, Shirtcliff EA, Dunn EC, Drury SS (2013) Neighborhood disorder and telomeres: Connecting children's exposure to community level stress and cellular response. *Soc Sci Med* 85:50–58.
4 Asok A, Bernard K, Roth TL, Rosen JB, Dozier M (2013) Parental responsiveness moderates the association between early-life stress and reduced telomere length. *Dev Psychopathol* 25(3):577–585.

Author contributions: C.M. and D.N. designed research, performed research, contributed new reagents/analytic tools, analyzed data, and wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence should be addressed. E-mail: dan1@princeton.edu.

Table 1. Three χ^2 tests of harsh vs. nurturing environment, HWE, and comparison with the Fragile Families African American sample

	Test 1: Harsh vs. nurturing cell counts		Test 2: Hardy–Weinberg Equilibrium		Test 3: Comparison with rest of Fragile Families African American sample (n = 1,393)	
Genotype	χ^2 statistic	P value (2 df)	χ^2 statistic	P value (1 df)	χ^2 statistic	P value (2 df)
DRD4	2.7	0.26	0.06	0.81	0.5	0.79
DRD2	2.5	0.28	1.02	0.31	1.5	0.47
DAT1	2.5	0.29	0.13	0.72	0.2	0.89
COMT	0.9	0.63	0.55	0.46	1.8	0.40
5-HTTLPR	3.3	0.20	3.52	0.06	4.6	0.11
Stin2	1.8	0.41	0.00	0.98	0.1	0.96
TPH2a	3.1	0.21	0.06	0.80	0.1	0.93
TPH2b	0.9	0.63	1.11	0.29	3.1	0.21

www.pnas.org/cgi/doi/10.1073/pnas.1407451111