LINK TO ORIGINAL ARTICLE
LINK TO AUTHOR'S REPLY

Gene-by-environment experiments: a new approach to finding the missing heritability

Marinus H. van IJzendoorn, Marian J. Bakermans-Kranenburg, Jay Belsky, Steven Beach, Gene Brody, Kenneth A. Dodge, Mark Greenberg, Michael Posner and Stephen Scott

For many reasons, tests of the environment, and particularly of gene-by-environment (G×E) interactions, have been left out of genome-wide association (GWA) estimates of genetic main effects. A tutorial on the current study designs for mapping G×E interactions is provided by Duncan Thomas (Gene–environment-wide association studies: emerging approaches. *Nature Reviews Genetics* **11**, 259–272 (2010))[1]. Some[2] have argued that G×E interactions will contribute little to the missing heritability[3] if G×E effects are small or if correlations between gene and environment (rGE) mask genotype-by-genotype (G×G) effects. However, G×E effects may be underestimated in behavioural genetic approaches when it is assumed that environments differ when they are in fact similar. The theoretical challenge is that, in most studies, the environment is self-selected, and so environment effects cannot be distinguished from unmeasured genetic effects. Furthermore, if the environment is poorly assessed, the G×E equation contains two components with highly divergent error variations, creating high risks for type 1 and type 2 errors[4]. Replication of G×E findings is therefore crucially dependent on accurate assessments of the environment[5,6] and on the absence of rGE.

A promising avenue for circumventing the issues that are inherent in correlational G×E studies is the genetically informed experimental intervention[7]. In randomized control trials (RCTs), the environment is manipulated in standard ways, and the randomization breaks the potential rGE. Evidence in support of this approach comes from three pioneering G×E RCTs, all showing that intervention efficacy is genetically moderated by the 7-repeat allele of the dopamine receptor D4 (*DRD4*) gene, which contains 7 copies of a 48 bp tandem repeat. In one randomized experiment, toddlers who carried this allele showed a greater reduction in disruptive behaviour after parenting skill intervention than children who did not carry this allele[7]. In another experiment, preschoolers with the same genotype were more positively affected by being randomly assigned to exposure to computer games that targeted their emerging phoneme awareness skills than those children not carrying this allele were[8]. In a third trial, this one focused on African–American adolescents and their families, teenagers carrying the 7-repeat version of *DRD4* were more positively affected than others by an intervention targeting substance use[9].

These genetically moderated intervention effects are based on rather small samples (157–337 individuals) and need replication. However, they agree with meta-analytic evidence[10] and provide experimental support for the potential importance of G×E[11], suggesting that experimental methods are powerful strategies for examining candidate G×E effects. The observed effects are also consistent with the differential susceptibility claim that individuals differ in the extent to which they are affected — either positively or negatively — by environmental exposures[12,13]. One exciting implication of this perspective is that there should be genetically based heterogeneity in intervention efficacy and, as a corollary, that studies incorrectly estimate intervention efficacy systematically, overestimating it for some (less susceptible) individuals and underestimating it for other (more susceptible) individuals.

GWA studies (GWASs) have documented disappointingly small genetic associations with common human diseases, cognitive abilities and behavioural traits. For example, the first GWASs of reading ability[14] and IQ[15] explained less than 1% of the variance, whereas behavioural genetic (twin) studies have revealed much stronger genetic effects, explaining 50% or more of the variation between individuals[2]. We propose here that one way to bridge this gap — that is, to account for the missing heritability[3] — is through G×E experiments.

Marinus H. van IJzendoorn and Marian J. Bakermans-Kranenburg are at the Centre for Child and Family Studies, Rommert Casimir Institute for Developmental Psychopathology, Leiden University, Wassenaarseweg 52, 2333AK Leiden, The Netherlands.

Jay Belsky is at the Department of Human and Community Development, UC Davis, One Shields Avenue, 1331 Hart Hall, Davis, California 95616, USA.

Steven Beach is at the Institute for Behavioral Research, University of Georgia, 510 Boyd GSRC, Athens, Georgia 30602, USA.

Gene Brody is at the Center for Family Research, University of Georgia, 1095 College Station Road, Athens, Georgia 30605, USA.

Kenneth A. Dodge is at the Center for Child and Family Policy, Duke University, Durham, North Carolina 27708, USA.

Mark Greenberg is at the Prevention Research Center, Pennsylvania State University, Henderson Building South, University Park, Pennsylvania 16802, USA.

Michael Posner is at the Department of Psychology, University of Oregon, 1227 University of Oregon Straub Hall, 15th and Onyx Street, Eugene, Oregon 97403, USA.

Stephen Scott is at King's College London, Institute of Psychiatry, de Crespigny Park, London SE5 8AF, UK.

Correspondence to M.H.v.IJ., M.J.B. and J.B.
e-mails: vanijzen@fsw.leidenuniv.nl; bakermans@fsw.leidenuniv.nl; jbelsky@ucdavis.edu

doi:10.1038/nrg2764-c1
Published online 18 November 2011

1. Thomas, D. Gene–environment-wide association studies: emerging approaches. *Nature Rev. Genet.* **11**, 259–272 (2010).
2. Plomin, R. Child development and molecular genetics: 13 years later. *Child Dev.* (in the press).
3. Maher, B. Personal genomes: The case of the missing heritability. *Nature* **456**, 18–21 (2008).
4. Wachs, T. D. & Plomin, R. *Conceptualization and Measurement of Organism–Environment Interaction.* (American Psychological Association, Washington, DC, 1991).
5. Caspi A. *et al.* Influence of life stress on depression: moderation by a polymorphism in the *5-HTT* gene. *Science* **301**, 386–389 (2003).
6. McGuffin, P., Alsabban, S. & Uher, R. The truth about genetic variation in the serotonin transporter gene and response to stress and medication. *Br. J. Psychiatry* **198**, 424–427 (2011).
7. Bakermans-Kranenburg, M. J., van IJzendoorn, M. H., Pijlman, F. T. A., Mesman, J. & Juffer, F. Experimental evidence for differential susceptibility: dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behaviour in a randomized trial. *Dev. Psychol.* **44**, 293–300 (2008).
8. Kegel, C. A. T., Bus, A. G. & van IJzendoorn, M. H. Differential susceptibility in early literacy instruction through computer games: the role of the dopamine D4 receptor gene (*DRD4*). *Mind Brain Educ.* **5**, 71–78 (2011).
9. Beach, S. R. H., Brody, G. H., Lei, M. K. & Philibert, R. A. Differential susceptibility to parenting among African American youths: testing the DRD4 hypothesis. *J. Fam. Psychol.* **24**, 513–521 (2010).
10. Bakermans-Kranenburg, M. J. & van IJzendoorn, M. H. Differential susceptibility to rearing environment depending on dopamine-related genes: new evidence and a meta-analysis. *Dev. Psychopathol.* **23**, 39–52 (2011).
11. Rutter, M. *Genes and Behaviour: Nature–Nurture Interplay Explained.* (2006, Oxford, Blackwell).

12. Belsky, J., Bakermans-Kranenburg, M. J. & van IJzendoorn, M. H. For better and for worse: differential susceptibility to environmental influences. *Curr. Dir. Psychol. Sci.* **16**, 300–304 (2007).
13. Belsky, J *et al.* Vulnerability genes or plasticity genes? *Mol. Psychiatry* **14**, 746–754 (2009).
14. Meaburn, E. L., Harlaar, N., Craig, I. W., Schalkwyk, L. C. & Plomin, R. Quantitative trait locus association scan of early reading disability and ability using pooled DNA and 100K SNP microarrays in a sample of 5,760 children. *Mol. Psychiatry* **13**, 729–740 (2008).
15. Davis, O. S. P. *et al.* A three-stage genome-wide association study of general cognitive ability: hunting the small effects. *Behav. Genet.* **40**, 759–767 (2010).

Acknowledgements
The authors were supported by the Jacobs Foundation.

Competing interests statement
The authors declare no competing financial interests.