



Published in final edited form as:

Psychophysiology. 2014 December ; 51(12): 1329–1330. doi:10.1111/psyp.12354.

Hunting genes, hunting endophenotypes

GREGORY A. MILLER^{a,b}, PETER E. CLAYSON^a, and CINDY M. YEE^{a,b}

^aDepartment of Psychology, University of California, Los Angeles, Los Angeles, California, USA

^bDepartment of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, California, USA

Abstract

Identifying specific genetic contributions to psychopathology has proved to be much more difficult than anticipated. In pursuit of this goal, Iacono and colleagues provide a remarkable set of studies that are important for the methods showcased as well as the findings reported. The immediate yield of positive findings is somewhat limited, but such an outcome is in fact quite informative. These papers will inspire further innovation and ambition in efforts to identify causal pathways to psychopathology and more specifically will increase emphasis on endophenotypes, a perspective highly compatible with the NIMH Research Domain Criteria RDoC initiative.

Descriptors

Psychopathology; Endophenotype; Genome; RDoC; GWAS; Gene × environment interaction

Fifty-two years after Meehl (1962) proposed a substantial role for genes in schizophrenia, we know that genes make major contributions to psychopathology, but we still do not know which genes play which roles. Waves of findings about candidate genes have crashed on the rocky coast of replication. Many more such findings will undoubtedly follow. Surely some will eventually replicate, but the recent assumption has been that the effects are small. If an effect size is small, one condition for successful replication is very large *N*s. The studies in the present issue of the journal represent such efforts but also pursue rare genetic patterns that may have quite large effects.

The genetic and environmental combinations that control how the genome is operationalized are a moving target: both one's environment and one's genome shift over time (Charney, 2012). Whereas simple Mendelian models of genetic influence have been established for some biological phenomena, "it is possible for behavioral phenotypes to be heritable in the absence of any specific genetic etiology. ... the causal chain linking the physical [biochemical] units to complex human behavior is, for most practical purposes, infinitely complex ..." (Kendler, 2005; Turkheimer, 1998, p. 790).

In this special issue, Iacono and colleagues address this challenge by undertaking a remarkable project to identify genes associated with psychophysiological phenomena that

are well established as endophenotypes for psychopathology, rather than attempting to relate individual genes to manifest psychopathology. Endophenotypes are quantifiable psychological or biological phenomena intermediate in the causal chain between genes and phenotypic manifestation (Gottesman & Gould, 2003; Gottesman & Shields, 1972; Iacono & Lykken, 1979), and thus they are potentially more tractable for identification and intervention (Lenzenweger, 2010; Miller & Rockstroh, 2013). Furthermore, endophenotypes can be pursued without naively reductionistic assumptions about the relationships between biological and psychological phenomena (Lilienfeld, 2007; Miller, 1996, 2010; Turkheimer, 1998). One of the innovations of the present set of studies is the assessment of genetic contributions to a wide variety of endophenotypes within a single sample, an existence proof that such comprehensive projects are possible.

Whereas the total genetic impact on psychopathology is quite large, identification of individually small effects would require sufficient *N*s and continuing advances in methods before providing insights into the biochemical mechanisms to which they contribute. Then comes an even tougher challenge: how to model the relationships among the hundreds (thousands?) of biochemical pathways that the genetic associations point to, and, more importantly, how to model their relationships with the psychological phenotypes that are the fundamental phenomena of psychopathology?

Another possibility, much less widely recognized but an innovation that the present studies begin to realize, may prove much more tractable. Causal factors that even in aggregate contribute a trivial amount to overall variance in a population may nevertheless contribute quite substantially when they converge. A detection protocol composed of indicators that are uncorrelated in the general population will have a very low coefficient alpha yet may succeed quite well in finding rare cases of convergence (Golden & Meehl, 1979). Based on the results of their work on genetic contributions to electroencephalogram (EEG) power spectrum components such as those considered as endophenotypes in this special issue, Lykken, Tellegen, and Iacono (1982; see also Lykken, McGue, Tellegen, & Bouchard, 1992) proposed the concept of “emergence,” a phenomenon in which a trait with a large genetic contribution does not run in families because the trait depends on a rare convergence of specific alleles. Such a convergence may produce large genetic effects. Although large *N*s may be needed to detect such rare contributions in a population, the genetic contribution may be decisive, perhaps even both necessary and sufficient. Such phenomena will be difficult to find but extremely generative. Furthermore, the relevant biochemical mechanisms and their environmental drivers may be relatively straightforward. That, in turn, would provide promising guidance for the development of psychological and biological treatments that target their biochemistry.

Short of such discoveries, a central challenge that remains is to identify the mechanisms by which environmental factors contribute to psychopathology. Traits are not heritable in some general sense. Heritability is defined for a given population in a given environment. The same gene in a different population or a different environment may show much higher or much lower heritability. Even highly heritable traits can be strongly manipulated by environmental factors (Johnson, Turkheimer, Gottesman, & Bouchard, 2009), yet we lack an adequate map of the environment, parallel to the genome.

Now that we have the genome (tellingly, a phrase one hears much less often now than some years ago), we realize that we need far more than the genome to understand mental illness, which is, after all, mental and not physical; psychological, not biological. Continued study of gene \times environment interactions, gene-environment correlations, and epigenetic factors controlled by genes and environment will contribute to a mechanistic account of various psychopathologies. With luck, we will find that possibly diverse etiological pathways converge onto relatively few endophenotypes such as those studied in these papers and others yet to be identified. We can hope for a many-to-few mapping of genes to endophenotypes, as well as a few-to-many mapping of endophenotypes to DSM/ICD diagnoses. Thus, a relatively limited set of endophenotypes may be crucial in mental illness, fostering detection, prevention, and treatment.

We may come to understand such key endophenotypes with a framework descended from the National Institute of Mental Health Research Domain Criteria (RDoC) proposal (Cuthbert & Kozak, 2013; Insel et al., 2010). We may retain DSM/ICD diagnoses to categorize traditionally conceived clinical syndromes, or we may develop clinical characterizations more similar to RDoC (which encourages though does not require dimensional constructs). Perhaps our next diagnostic system should foreground psychological and biological endophenotypes, rather than traditional symptoms, as the core characterization of most mental illnesses and as the primary target of research and intervention.

We need studies such as those provided in this special issue in order to find those key endophenotypes. The goal of research on genetic factors in psychopathology is not a list of interesting genes, nor of interesting psychological and biological endophenotypes. The goal is an understanding of the environmentally mediated biochemical pathways by which genes collectively manifest in endophenotypes and clinical phenomena. The studies in this issue are an impressive and innovative effort in that direction.

Acknowledgments

Preparation of this manuscript was supported in part by Center grant P50 MH066286 from the National Institute of Mental Health, Bethesda, MD.

References

- Charney E. Behavior genetics and postgenomics. *Behavioral and Brain Sciences*. 2012; 35:331–358. [PubMed: 23095378]
- Cuthbert BN, Kozak MJ. Constructing constructs for psychopathology: The NIMH research domain criteria. *Journal of Abnormal Psychology*. 2013; 122:928–937. [PubMed: 24016027]
- Golden RR, Meehl PE. Detection of the schizoid taxon with MMPI indicators. *Journal of Abnormal Psychology*. 1979; 88:217–233. [PubMed: 500949]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Gottesman, II.; Shields, J. *Schizophrenia and genetics: A twin study vantage point*. Academic Press; New York, NY: 1972.
- Iacono WG, Lykken DT. Eye tracking and psychopathology: New procedures applied to a sample of normal monozygotic twins. *Archives of General Psychiatry*. 1979; 36:1361–1369. [PubMed: 573993]

- Insel TR, Cuthbert BN, Garvey M, Heinssen R, Pine DS, Quinn K, Wang P. Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*. 2010; 167:748–751. doi: 10.1176/appi.ajp.2010.09091379. [PubMed: 20595427]
- Johnson W, Turkheimer E, Gottesman II, Bouchard TJ. Beyond heritability: twin studies in behavioral research. *Current Directions in Psychological Science*. 2009; 18:217–220. [PubMed: 20625474]
- Kendler KS. “A gene for ...”: The nature of gene action in psychiatric disorders. *American Journal of Psychiatry*. 2005; 162:1243–1252. [PubMed: 15994704]
- Lenzenweger, MF. Schizotypy and schizophrenia: The view from experimental psychopathology. Guilford Press; New York, NY: 2010.
- Lilienfeld SO. Cognitive neuroscience and depression: Legitimate versus illegitimate reductionism and five challenges. *Cognitive Therapy and Research*. 2007; 31:263–272.
- Lykken DT, McGue M, Tellegen A, Bouchard TJ. Emergenesis: Genetic traits that may not run in families. *American Psychologist*. 1992; 47:1565–1577. [PubMed: 1476327]
- Lykken DT, Tellegen A, Iacono WG. EEG spectra in twins: Evidence for a neglected mechanism of genetic determination. *Physiological Psychology*. 1982; 10:60–65.
- Meehl PE. Schizotaxia, schizotypy, schizophrenia. *American Psychologist*. 1962; 17:827–838.
- Miller GA. How we think about cognition, emotion, and biology in psychopathology. *Psychophysiology*. 1996; 33:615–628. [PubMed: 8961782]
- Miller GA. Mistreating psychology in the decades of the brain. *Perspectives on Psychological Science*. 2010; 5:716–743. [PubMed: 21949539]
- Miller GA, Rockstroh B. Endophenotypes in psychopathology research: Where do we stand? *Annual Review of Clinical Psychology*. 2013; 9:177–213. doi: 10.1146/annurevclinpsy-050212-185540.
- Turkheimer E. Heritability and biological explanation. *Psychological Review*. 1998; 105:782–791. [PubMed: 9830379]