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Psychophysiology. Author manuscript; available in PMC 2015 May 11.

Published in final edited form as:

Psychophysiology. 2014 December ; 51(12): 1327–1328. doi:10.1111/psyp.12362.

The missing heritability of behavior: The search continues

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Abstract

Genetic variation altering behavior is elusive. This commentary discusses implications for the search for "missing heritability" posed by a unified series of studies from the Minnesota Center for Twin and Family Research. Endophenotypes are measured in a longitudinal cohort including twins, analyzed for heritability and genetically mapped via genome-wide association and genome sequencing. The genes identified account for a fraction of the heritability, but the manner in which the studies were conducted points to explanations other than methodology. The MCTFR data are an unprecedented addition to the research information commons. Other gene discoveries will follow when they are analyzed in new ways and in combination with other studies. Even larger samples may be needed. Alternatively or in addition, locus identification, especially rare alleles, may require the study of families and population isolates with founder characteristics.

Descriptors

Genome-wide association; Heritability; Endophenotype; Intermediate phenotype; Founder population; Rare allele; Polygenicity; Minnesota Center for Twin and Family Research

In this issue of *Psychophysiology* is an event unprecedented in human genetics, the simultaneous publication of genome-wide association (GWA) and sequencing in a single sample, namely, 4,905 individuals from the Minnesota Center for Twin and Family Research (MCTFR). By estimating heritability and performing GWA and deep sequencing in the same sample, the investigators who contributed to the MCTFR have more incisively addressed the riddle of the "missing heritability" in GWA studies, and the nature of genetic influences on behavior. Tending to validate what they have done, but as will not otherwise be the focus of this commentary, significant evidence was discovered for involvement of several genes, adding to the small complement of genes that have been identified in prior research and that are thought to influence behavior.

Why endophenotypes?

Appropriately for *Psychophysiology*, the focus of the MCTFR studies is on intermediate phenotypes that, by virtue of heritability and disease relationship, meet the definition of "endophenotype." Intriguingly, the first successful GWA (Klein et al., 2005) associated

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complement Factor H to macular degeneration, a disease that frequently leads to blindness in the elderly and that is diagnosed via a specific neural endophenotype, namely, changes in retinal blood vessels. As compared to the negligible effect of complement Factor H on blindness, the gene has a large effect on macular degeneration enabling successful GWA in only 96 cases and 50 controls. Other traits, which are more etiologically discrete and perhaps measured as intermediate phenotypes, are also more likely to be linkable to functional variants. For example, several loci for electroencephalogram (EEG) spectral power were identified in a relatively small GWA performed in a population isolate (Hodgkinson et al., 2010). A critic can easily observe that not all intermediate phenotypes are created equal for genetic linkage studies, but in some instances, such as a functional polymorphism at neuropeptide Y (*NPY*), it is possible to trace the dilution of allele effect from molecule (neuropeptide) to intermediate phenotypes (neuroimaging responses to emotion and pain) to complex behavior (Zhou et al., 2008). MCTFR's endophenotypes, including P300 amplitude, electrodermal activity, startle eye blink, antisaccade error, and electroencephalographic spectral characteristics, are hopefully a harbinger of GWA using measures of brain function.

Integrative analyses in the information commons

It is difficult to overestimate the importance of the availability of MCTFR data for researchers worldwide who would never have the resources to generate such a research asset, or who can analyze their own rich datasets, whether from humans or model organisms, to search for convergences and replications. Because MCTFR has measured multiple endophenotypes in the same individuals whose genomes were characterized, the MCTFR dataset is a rich resource for integrative analyses to understand pathways of causality. Many of the most important insights may only emerge over time and as phenotype, genotype, and sequence are used in combination and together with other information on gene function and expression, evolutionary conservation, and linkage to related phenotypes.

The missing heritability in GWA

It has been estimated that GWA can explain at least 30% of heritability of common diseases, but for most complex diseases, including psychiatric diseases, geneticists have fallen fall short of this target. Given that it will take years to analyze and integrate MCTFR data in these other contexts, and this study—large as it is—remains underpowered to detect many genetic effects, it is not surprising that the MCTFR study has not explained most of the heritable variance of the phenotypes it targeted. However, because heritability and gene effects were measured in the same sample, and because of the focus on endophenotypes discussed earlier, some of the most facile answers to the riddle of the missing heritability are less tenable. Part of the explanation may be methodological. To accumulate the numbers requisite for GWA, samples are usually collected across multiple sites and countries, leading to site-to-site variation and less precise measurement. Heterogeneity between cases and controls and among cases can also arise due to differences in population of origin or exposures. However, the MCTFR study, which has none of these methodologic defects, indicates the genes may be elusive for other reasons.

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Due to gene-gene interactions, additive inheritance of complex traits may be less than has been estimated (Zuk et al., 2014). For most psychiatric disorders and, for example, addictive disorders for which monozygotic/dizygotic concordance ratios are close to the perfect 2:1, resemblance between relative pairs is proportionate to degree of relationship, apparently providing strong evidence of additivity (Goldman, Oroszi, & Ducci, 2005). However, Zuk et al show circumstances under which such patterns *can* be compatible with epistasis. MCTFR's analysis of polygenic contributions of genes may be taken to support this view because, in several cases, the polygenic variance was remarkably consistent with measured heritability. This is extremely interesting, but caution is in order for several reasons. The polygenic patterns are unreplicated. As discussed in the MCTFR papers, there is a substantial confidence interval around estimates of polygenic inheritance, and altering the assumptions in the analyses can substantially affect the estimates. Furthermore, effects of other types of functional loci, including variable number of tandem repeat polymorphisms and rare variants, would not be captured by the arrays used for the GWA. Therefore, the polygenic components that were detected are unexpectedly high, even if one accepts that the statistical methodology is robust. Probably we have a better understanding of the strengths and pitfalls of twin-based heritability analyses than we have of the estimation of polygenic inheritance from GWA. Proving that combinations of genes alter these traits will be difficult, and will ultimately require the identification of at least some of the functional loci and the study of their interaction.

Lastly, an important explanation for missing inheritance is rare variants of the single nucleotide type (SNVs) that are not captured by GWA. Although Zuk et al. (2014) estimated that discovery samples of at least 25,000 cases are required, with substantial replication samples, MCTFR's whole genome sequencing of 1,325 individuals is an important step forward. Without larger samples or the context of large families or founder populations, it may be difficult to securely connect the rare alleles detected by sequencing to the behavior. Both families and founder populations are tools for identifying the effects of rare variants, as illustrated by identification of an *HTR2B* stop codon that contributes to impulsivity and alcoholism in Finns, but that is absent in other populations (Bevilacqua et al., 2010). It would also be interesting to sequence some of the phenotypically discordant identical twins in the MCTFR study, searching for de novo mutations. However, the availability of the MCTFR database provides a comparison sample that could be immediately used by anyone performing studies in founder populations or families, or searching for de novo mutations. Also, it can be queried for genes identified in model organisms. Any investigator studying the relationship of rare and uncommon alleles to behavior will find in the MCTFR database a trove of comparative data.

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