Gene-Environment-Wide Interaction Studies in Psychiatry

Rates of psychiatric disorders, including schizophrenia, vary across regions and demographic groups, suggesting widespread environmental influences. However, reported "environmental" effects are misleading, for in reality they represent the effect of the environmental exposure as expressed in relationship to all the genetic influences that render an individual more sensitive to it. Genetic control of sensitivity to the environment is known as gene-environment interaction (G×E). Because study populations always contain a mix of genetically susceptible and nonsusceptible individuals, associations between environmental exposures and psychiatric outcomes will be shifted toward the null if there is underlying G×E. The article by Clarke and colleagues in this issue (1) nicely illustrates this effect. In this study, maternal pyelonephritis during pregnancy was the identified environmental factor. This infection, by itself, did not increase the subsequent rate of schizophrenia in the offspring of affected women. However, in the presence of genetic liability, for example, a father who had schizophrenia, a significant association with maternal pyelonephritis became apparent. The results were indicative of a gene-environment interaction, as the two risk factors—family history and maternal infection—were more than additive, such that the risk for the two factors in combination was greater than the sum of their individual effects.

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Gene × Environment Approaches

Quantitative Genetic Epidemiology

Clarke and colleagues' elegant study demonstrates that traditional epidemiological designs examining environmental exposures can be enriched by modeling genetic variation as a traditional risk factor in hypothesis-based epidemiological analyses. Genetic risk can be indexed by proxy variables such as a positive family history (as used by Clarke and colleagues), intermediary phenotypes (2), sibling correlations on a behavioral trait (3), or the quantification of genetic contribution to a trait using structural equation modeling in twin or extended family data (4). Even though measures such as family history induce a high rate of false negative misclassification, and direct molecular genetic information can now be easily incorporated in epidemiological analyses (see below), there is still considerable scope for analyses using indirect measures of genetic risk. This is because quantitative genetic epidemiology in theory provides the possibility of modeling the net total genetic contribution to a trait, including all unspecified gene-gene interactions as well as unmeasured gene-environment interactions that might contribute to differential susceptibility to the exposure of interest. This clearly represents an advantage over molecular genetic measures of genetic variation contributing to a trait, as even genome-wide association studies with the most densely posi-

tioned marker information in the largest of samples are currently able to explain only a fraction of the total heritability of the trait under examination.

Hypothesis-Based Molecular Genetic G×E Using Candidate Genes

Traditional epidemiological analyses may also model G×E using direct molecular genetic variation in hypothesis-based candidate genes. One example is the hypothesized interaction between variation in the gene encoding the serotonin transporter and life stress in depression. The initial report of such a finding (5) generated much interest, but the most recent meta-analysis examining the body of work attempting to replicate it concluded that there was no evidence to support a gene-environment interaction. One reason for this may be that the prior probability of any G×E hypothesis based on a single measure of molecular genetic variation is so low that only a fraction of the studies reporting a p value <0.05 are likely to have a research hypothesis that is true. This is unlikely, however, given the fact that meta-analysis of experimental gene-environment interaction studies investigating emotional stimuli affecting amygdala activation does suggest moderation by the same serotonin transporter polymorphism (6), in agreement with experimental animal research (7). Similar examples exist in research on psychotic disorders, where an initial observational study suggested an interaction between cannabis use and the $COMT^{Val158Met}$ polymorphism (8). Although a later study using a case-only design could not replicate this finding (9), an experimental study did provide evidence for the same gene-environment interaction (10). In combination, the findings suggest that experimental human and animal studies will be of major importance for follow-up of necessarily "noisy" observational findings of G×E.

Agnostic Molecular Genetic G×E Using GWAS: GEWIS

Undoubtedly the greatest challenge in the years to come is to combine the agnostic, previously much berated but very recently reinvigorated, mass-marker approach of genomic interrogation on the one hand with the hypothesis-based approach of epidemiology and neurobiology on the other. Genome-wide association studies (GWAS) have brought about a revolution in the search for molecular genetic variation underlying psychiatric disorders. While it is not likely that every genetic variant relevant for psychiatry will be found through the hypothesis-free genome-wide approach of GWAS, fears of yet more inconclusive "fishing expeditions" have been refuted as GWAS of large samples have detected associations with common single-nucleotide polymorphisms and rare copy-number variants. This development is important for G×E research for two reasons. The first is that findings from GWAS will yield genetic variation for candidate approach G×E analysis with a much higher prior probability than was hitherto the case. The second is that GWAS identify associations that misleadingly are interpreted as "genetic" but in reality also include all underlying gene-environment interactions. This creates the challenge to enrich GWAS with environmental information so that gene-environment-wide interaction studies (GEWIS) (11) may be conducted. GEWIS obviously pose formidable conceptual and epidemiological challenges. Traditional epidemiological tools and methodologies are not equipped for the mass-marker agnostic approach of GWAS, and the scale, cost, and precision of environmental measurements differ radically from those used in molecular genetics. In addition, new statistical approaches need to be developed beyond interaction as departure from additive or multiplicative joint effects while guarding against noninterpretable flooding of false positive signals from GEWIS. In order to meet these challenges, new multidisciplinary collaborations need to be formed, ethical implications need to be examined, and novel statistical approaches need to be developed. GEWIS are therefore poised in the years to come to produce replicable gene-environment interactions.

References

1. Clarke MC, Tanskanen A, Huttunen M, Whittaker JC, Cannon M: Evidence for an interaction between familial liability and prenatal exposure to infection in the causation of schizophrenia. Am J Psychiatry 2009; 166: 1025–1030
2. Weiser M, van Os J, Reichenberg A, Rabinowitz J, Nahon D, Kravitz E, Lubin G, Shmushkevitz M, Knobler HY, Noy S, Davidson M: Social and cognitive functioning, urbanicity, and risk for schizophrenia. Br J Psychiatry 2007; 191:320–324
3. Wichers M, Myin-Germeys I, Jacobs N, Peeters F, Kenis G, Derom C, Vlietinck R, Delespaul P, van Os J: Genetic risk of depression and stress-induced negative affect in daily life. Br J Psychiatry 2007; 191:218–223
4. Wichers MC, Purcell S, Danckaerts M, Derom C, Derom R, Vlietinck R, van Os J: Prenatal life and postnatal psychopathology: evidence for negative gene-birth weight interaction. Psychol Med 2002; 32:1165–1174
5. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR: Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA 2009; 301:2462–2471
6. Munafo MR, Brown SM, Hariri AR: Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. Biol Psychiatry 2008; 63:852–857
7. Suomi SJ: Risk, resilience, and gene × environment interactions in rhesus monkeys. Ann NY Acad Sci 2006; 1094:52–62
8. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW: Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-*O*-methyltransferase gene: longitudinal evidence of a gene × environment interaction. Biol Psychiatry 2005; 57:1117–1127
9. Zammit S, Spurlock G, Williams H, Norton N, Williams N, O'Donovan MC, Owen MJ: Genotype effects of CHRNA7, CNR1, and COMT in schizophrenia: interactions with tobacco and cannabis use. Br J Psychiatry 2007; 191:402–407
10. Henquet C, Rosa A, Krabbendam L, Papiol S, Fananas L, Drukker M, Ramaekers JG, van Os J: An experimental study of catechol-*O*-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. Neuropsychopharmacology 2006; 31:2748–2757
11. Khoury MJ, Wacholder S: Invited commentary: from genome-wide association studies to gene-environment-wide interaction studies: challenges and opportunities. Am J Epidemiol 2009; 169:227–230

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