EDITORIAL

Gene–environment interactions in *Molecular Psychiatry*

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Individuals experiencing the same catastrophe or the same loss can react very differently: some develop psychiatric symptoms that evolve to full blown psychiatric disorders such as major depression or post-traumatic stress disorder, while others stay symptom-free. Such disparate responses might be due to variations in genetic substrates. Likewise, no single genetic variation will always cause the same degree of psychiatric symptoms. Our field, which is now so focused on the identification of genetic substrates, will eventually move to the understanding of penetrance, which is likely to be highly variable in psychiatry. Penetrance can be affected by the effects of other genes as well as by the environment. The challenge to contemporary psychiatry is to dissect the components of genomic and environmental substrates, to understand gene–gene and gene–environment interactions, and to develop treatment strategies that optimally impact on environmental and genomic substrates. Articles in *Molecular Psychiatry* increasingly address gene–environment interactions.

The concept of environment has become broader. Earlier epidemiological work was focused on environmental factors such as toxins, chemicals, and pollutants. However, we now conceptualize environment as everything that is extrinsic to the individual. This includes diet, exercise, and family structure. In 1999 we published a landmark article on the impact of an environmental factor, namely early parental loss, on psychiatric disorders. That study, from Bernard Lerer's group in Jerusalem, showed that loss of a parent before age 9 (loss of mother being worse than loss of father and divorce worse than death) was highly significantly associated with psychiatric disorders in adulthood, particularly major depression.¹ It is important to notice that not all those who suffered early parental loss become depressed — this suggests that biological (and genomic) substrates contribute to phenotypic outcome. Nevertheless, the environmental effect can be profound.

In our previous issue we published a highly interesting article² describing the findings that monkeys with deleterious early rearing experiences, consisting of early maternal separation and rearing by peers, were differentiated by genotype in cerebrospinal fluid (CSF)

concentrations of 5-hydroxyindoleacetic acid (5-HIAA), where monkeys reared normally by their mothers were not. Specifically, peer-raised monkeys with two copies of the long variant of the serotonin transporter regulatory region (l/l), which was shown to be associated with higher transcriptional activity, had higher levels of CSF 5-HIAA than those with one copy of the long variant and one copy of the short one (l/s). Those differences in CSF 5-HIAA levels were not seen in mother-reared monkeys. These data illustrate how gene–environment interactions cause a specific biochemical phenotype.

The genome is incredibly complex and genes for psychiatric disorders remain elusive. The umbrella of environmental contributions encompasses a wide range of elements, including but not restricted to climate, nutrition, physical activity, infectious agents, drugs, socio-economic status, and family structure. How can we possibly begin to understand complex interactions between broad categories such as genome and environment?

Useful starting points might be gene–drug and gene–diet interactions. Drug response is a highly variable phenotype that emerges as the result of the exposure of genomic substrates to drugs, including therapeutic drugs, drugs of abuse, and alcohol. Such a phenotype can be dissected at the neuroanatomical and genetic levels. In this issue, Loewenstein (pages 129–131 and Image section, page 128), discusses the biology of tremor induced by alcohol and identifies a possible role of olivary gap-junctions in the generation of physiological and pathological tremors. Schinka *et al* (pages 224–228) identify a functional polymorphism within the opioid receptor gene as a *general* risk gene for substance dependence. Substance abuse and dependence are phenotypes that emerge only after exposure to the environment. In a totally abstemious society such phenotypes would not emerge and it would not be possible to conduct this type of study. In contrast the exposure of individuals to drugs raises a host of important questions that can be addressed with functional and genomic tools: What are the effects of the drug on brain substrates resulting in symptoms such as tremor? What are the genetic substrates that lead some but not all individuals to become addicted to drugs to which they are exposed?

Another phenotype that occurs in response to the environment is that of treatment relapse in depressed patients who ingest a tryptophan-depleting diet. This type of nutritional intervention can cause rapid relapse of depressed symptoms, particularly in patients treated with selective serotonin reuptake inhibitors. Moreno *et al* (pages 213–216) show a significant association

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between a serotonin transporter regulatory region polymorphism and mood response during tryptophan depletion. Their data indicate that individuals whose genotype predicted increased serotonin transporter activity are more susceptible to depressive changes in response to diet-induced perturbations in serotonin.

While the fundamental biology of psychiatric disorders represents an enormous challenge, it might be at this point more feasible to ascertain the genetic contribution to specific environmentally triggered events. Those may be less heterogeneous and therefore more approachable from a genetic perspective than the major psychiatric disorders.

Does this mean that research should move away from the major disorders? Not at all. Both areas of genetics of complex disorders and gene–environment interactions will experience growth and enrich each other. The genetics of psychiatric disorders is well represented in this issue, particularly in bipolar disorder. Bennett *et al* (pages 189–200) present the first stage report of the Wellcome Trust UK–Irish bipolar affective disorder sibling-pair genome screen. The authors identified 19 points across the genome where the minimum linkage

score exceeded a value set for follow-up in second-stage screening. Some points overlapped with previous linkage reports, both within bipolar affective disorder and other psychiatric illnesses. The article by Massat *et al* (pages 201–207) reports a multicentric association study that shows an excess of a specific allele for $\alpha 3$ subunit GABA receptor gene (GABRA3) in bipolar patients. The authors suggest that the GABRA3 polymorphism may confer susceptibility to or may be in linkage disequilibrium with another gene involved in the genetic etiology of bipolar disorder.

These articles provide an excellent illustration of the search for genes and for gene–environment interactions that is now being reported in *Molecular Psychiatry*.

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