Chapter 1
Genes and Mental Illness

Contents

1.1 The Evolution of the Concept of Mental Illness

Alienists used to treat mental illness and those afflicted were considered "alienated" or strange. There have been essentially two lines of thought concerning the causes of mental illness: alien and endogenous. The alien causes may be a possession of the gods or the devil, or, more recently, microorganisms such as bacteria and virus. The endogenous causes may be an imbalance of the body fluids – the Hippocratic blood, phlegm, yellow bile, and black bile (thence the term, *melancholia*) or the modern version of an imbalance among serotonin, norepinephrine, and dopamine. It is also generally accepted that severe environmental factors such as extreme heat or cold can cause mental aberrations such as delirium.

Certain types of mental dysfunction, such as maladaptive patterns of behavior and neurosis, have been also attributed to faulty learning or bad modeling. Experimental "neuroses" and "learned helplessness" have been produced in animals by confusing rewards or inescapable punishment (Saunders et al., 1995; Seligman, 1972).

Mental illness is known to run in families. With the advent of biological psychiatry, it was hoped, in the latter part of the twentieth century, that the etiologic genes of mental illness would be discovered. In fact, the diagnostic and statistical manual for mental illness adopted by the American Psychiatric Association in 1980 (DSM III) was based on the research diagnostic criteria (Feighner et al., 1972) that were designed to isolate "pure cultures" of psychiatric illness for biological research.

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At the time DSM III was introduced, the catecholamine theory of affective disorders (Schildkraut, 1965) was the prevailing theory of mood disorders, chlorpromazine the most commonly used antipsychotic, and the Human Genome Project was yet not even a gleam in anyone's eyes. Exciting developments have since occurred in molecular biology and genetics and the Human Genome Project has been completed ahead of schedule (2003). Psychiatric research, at least in part fostered by the rigorous diagnostic criteria of DSM III and its slight modification, DSM IV (1994), has made breathtaking advances, taking full advantage of these and other developments during the *Decade of the Brain*, including neuroimaging techniques. On the strength of these developments, a new theoretical model of psychiatric illness has emerged that is open and evidence based.

Many putative genes that code for vulnerability for psychiatric syndromes are evolutionarily conserved. This explains why schizophrenia which is associated with low fertility rates in the afflicted has not become extinct. Crow (1997a, b, 2000, 2007) and Mitchell and Crow (2005) postulate that vulnerability to schizophrenia may be the price that *Homo sapiens* had to pay for the development of language, i.e., the speciation of humans from their ancestral apes involves the same genes that caused the left hemispheric dominance and language. Crow proposes that there are gradations in the genetic predisposition to psychosis, across diagnostic categories of schizophrenia and bipolar disorder.

Certain genes that endow vulnerability to anxiety, for example, the short allele of the serotonin transporter promoter gene (more of this below), may confer sensitivity to the "smoke detector" of anxiety activation (Nesse, 2001) and be evolutionarily adaptive when humans dwelled in caves in fear of predator animals. In the modern world, however, such sensitivity to anxiety would be dysfunctional for the individual and thus be considered a psychiatric syndrome.

1.2 Gene-Environment Interaction and Brain Morphology and Function

The genes coding for predisposition to various psychiatric syndromes are currently being defined using various techniques including linkage studies and genome scan. As far as psychiatric diagnosis goes, current state of affairs can be summarized as follows: For each diagnostic category, there are many susceptibility genes, and a single gene or a few genes may code for the susceptibility for many different disorders. On the basis of genetic studies, Kendler et al. (1998) proposed that psychosis be reclassified as: (1) classic schizophrenia, (2) major depression, (3) schizophreniform disorder, (4) bipolar-schizomania, (5) schizodepression, and (6) hebephrenia.

What seems clear is that psychiatric disorders are syndromes, phenomenological convergence of a number of different genetic-pathophysiologic pathways. An analogy might be hypertension. Hypertension is a syndrome that has definable signs and complications that can be treated with "antihypertensive" drugs. Hypertension, however, is pathophysiologically heterogeneous – it may be nephrogenic, cardiogenic, neurogenic, endocrine, secondary to familial hyperlipidemia, stress-induced, etc.

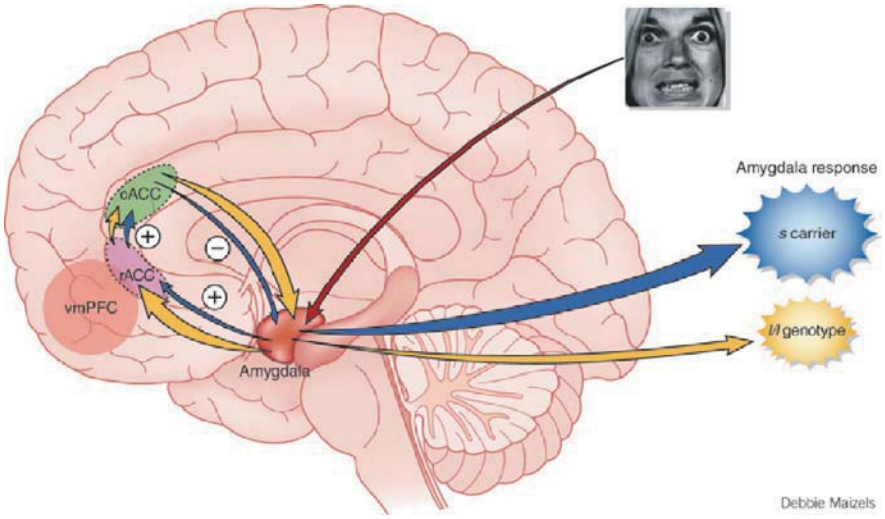
1.3 Gene–Environment Interaction: Serotonin Transporter Gene as an Exemplar

A single gene that codes for the vulnerability to multiple psychiatric (and medical) conditions is the serotonin transporter gene (SERT) and its promoter region polymorphism (5-HTTLPR). SERT is highly evolutionarily conserved and regulates the entire serotoninergic system and its receptors via modulation of extracellular fluid serotonin concentrations. DNA screens of patients with autism, ADHD, bipolar disorder, and Tourette's syndrome have detected signals in the chromosome 17q region where SERT is located (Murphy et al., 2004). 5-HTTLPR polymorphism consists of short (s) and long (l) alleles, and the presence of the short allele tends to reduce the effectiveness and efficiency of SERT. The short allele has been identified as the underlying variation for the risk for the above disorders as well as anxiety, increased neuroticism scales, smoking oticism, smoking behavior, negative mood, social behavior, especially to reduce negative mood and feel stimulated, difficulty in quitting smoking, social phobia, major depression, and irritable bowel syndrome (Hu et al., 2000; Lerman et al., 2000; Lotrich and Pollock, 2004; Yeo et al., 2004).

Why does a single gene code for so many vulnerabilities? One simple answer may be that the gene codes for one or more basic evolutionarily adaptive predispositions that, in combination with other factors, may determine the development and severity of a psychiatric syndrome. When we look at the list of vulnerabilities above, it seems clear that there is a continuum, from anxiety to adaptive/maladaptive behavior to phobia to major depression, and/or to physical symptoms. The concept of endophenotype is useful in understanding traits associated with syndromes (e.g., eye-tracking abnormality in schizophrenics and relatives) (Gottesman and Gould, 2003) and might provide clues to a genotypic diagnosis.

Pezawas et al. (2005) showed that the short allele carriers show reduced gray matter in limbic regions critical for processing of negative emotion, particularly perigenual cingulate and amygdala. Functional MRI studies of fearful stimuli show a tightly coupled feedback circuit between the amygdala and the cingulate, implicated in the extinction of negative affect. Short allele carriers showed relative uncoupling of this circuit and the magnitude of coupling inversely predicted almost 30% of variation in temperamental anxiety. They also show increased amygdala activation to fearful stimuli (Bertolino et al., 2005; Hariri et al., 2002). Thus, this gene seems to increase the affected individual's brain's sensitivity to negative affect and anxiety (Gross and Hen, 2004). What other factors, then, may further predispose the individual for a major depression?

Caspi et al. (2002, 2003) have shown, in an elegant longitudinal study, that stress during the most recent 2 years in adulthood and maltreatment in childhood interacted with the 5-HTTLPR status. Individuals with two copies of the short allele who also had the stressors had greatest amount of depressive symptoms and suicidality than heterozygous individuals, and those with only the long alleles had the least amount of depression. The short allele carriers have been shown to have more neuroticism scores on Eysenck personality inventory, and those with both short allele



Differences in processing of emotional stimuli between *s* allele carriers (*darker arrows*) and homozygous *l* allele carriers (*lighter arrows*). Negative emotional stimuli are evaluated by the amygdale after preliminary analysis in the ventral visual pathway (not shown). Carriers of the *s* allele have markedly reduced positive functional coupling between the rostral anterior cingulate (rACC) and the amygdala, which results in a net decrease in inhibitory feedback from the caudal anterior cingulate (cACC), via connections between rACC and cACC (*short upward arrows*). Brain volume was also substantially reduced in *s* allele carriers in the rACC and, to a lesser extent, the cACC and amygdala. The consequence of these genotype-based alterations is an emotional hyperresponsivity to negative affective stimuli in *s* allele carriers (*large dark cloud*) compared with individuals lacking this allele (*small light cloud*), which may be related to an increased risk of developing depression. As found in a previous study, functional coupling between the vmPFC (*light circle on left*) and the amygdala was also increased in *s* allele carriers. (From Hamann, 2005, reprinted with permission)

and high neuroticism were at higher risk of developing lifetime depression (Munaro et al., 2005).

Studies in monkeys have shown that the anxiety-enhancing effect of the short allele is mitigated with good mothering in infancy (Barr et al., 2004; Suomi, 2003, 2005).

5-HTTLPR may also determine response to drugs. Depressed individuals with the short allele were found to respond better to antidepressants that are both serotonergic and noradrenergic (i.e., mirtazapine) rather than serotonin-specific reuptake blockers. On the other hand, individuals with the long allele may have more side effects with exactly those drugs that are more effective for those with the short allele (Murphy et al., 2004). Diet deficient in the serotonin precursor, tryptophan, has been shown to induce depression in healthy women with the 5-HTTLPR s/s regardless of family history of depression, while those l/l were resistant to depression regardless of family history of depression. Those with l/s without family history of depression were intermediate between l/l and s/s in depressive mood with tryptophan depletion,

while l/s with family history of depression showed depressive response like the s/s (Neumeister, 2003; Neumeister et al., 2006, 2002, 2004a, b).

Thus, 5-HTTLPR short allele, in conjunction with childhood stress, confers an individual with the trait to respond to later stress with increased anxiety and neuroticism, which, in turn, predisposes the individual for later major depression, suicidality, and psychophysiologic disorders. Other gene–environment interactions predisposing to trait and disorder have been reported, including type 4 dopamine receptor gene (D4DR) and novelty seeking and ADHD (Ebstein et al., 1997; Keltikangas-Jarvinen et al., 2003), monoamine oxidase A (MAOA) and antisocial personality (Caspi et al., 2002; Craig, 2005), and dopamine transporter gene (DAT1) and ADHD (Brookes et al., 2006). The Val66Met allele of the brain-derived neurotrophic factor (BDNF) gene causes reduced dendritic branching in hippocampus, impaired contextual fear conditioning, and increased anxiety that is less sensitive to antidepressant treatment. There are alleles of the glucocorticoid receptor gene found in the normal population, which confer a higher sensitivity to glucocorticoids for both negative feedback and insulin reponsiveness or glucocorticoid resistance and an association with an increased likelihood of depression in several alleles and increased response to antidepressants in one of them (McEwen, 2007).

FKBP5 polymorphism (a glucocorticoid receptor-regulating gene) has also been shown to interact with childhood abuse in increasing the risk of PTSD in an urban general hospital population (Binder et al., 2008).

1.4 Emerging Model of Mental Illness: Gene × Meme Interaction

It seems clear, then, that modern model of psychiatric and medical illness must be based on *gene* × *environment interaction*. This model posits that the "vulnerability gene" has evolutionarily adaptive function as evidenced by its very conservation. It holds that there are critical interactions between the genotype and early environment in forming a personality trait which may in turn be adaptive or maladaptive at the individual level, e.g., anxiety-prone, exploratory, attention fluctuating, hypervigilant, etc. Kandel showed how environment (and learning) modifies gene expression (Kandel, 1979, 1998).

Recent and current stress may play the role of tipping the balance from a trait to a syndrome that has a course of its own.

How do environment and stress affect the genes exactly? To be precise, except in a few extreme cases of physical stress, environment and stress affect human beings only when they are perceived. As we have seen, the serotonin transporter promoter gene polymorphism may affect *how* the same stimulus may be perceived – as threatening or non-threatening – and may in turn result in activation or deactivation of genes. The fact that a recent meta-analysis failed to show a significant interaction between the serotonin transporter promoter polymorphism (5-HTTLPR) and stress in the risk of depression (Risch et al., 2009) highlights that the interaction is not a simple gene × stress, but rather mediated by the individual *traits and percepts*.

When a sensation from a sensory organ reaches the brain, it is processed against existing templates formed by both genetic predisposition and memory, the output of this process constitutes perception. The templates and the percept are memes as we will discuss in the next chapter. In sum, environment affects and interacts with genes through memes in the course of development, and mental health and mental illness are the outcomes of this interaction.

References

Barr, C. S., Newman, T. K., Lindell, S., et al. (2004) Interaction between serotonin transporter gene variation and rearing condition in alcohol preference and consumption in female primates. *Arch Gen Psychiatry*, **61**, 1146–1152.

Bertolino, A., Arciero, G., Rubino, V., et al. (2005) Variation of human amygdala response during threatening stimuli as a function of 5′HTTLPR genotype and personality style. *Biol Psychiatry*, **57**, 1517–1525.

Binder, E. B., Bradley, R. G., Liu, W., et al. (2008) Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA*, **299**, 1291–1305.

Brookes, K. J., Mill, J., Guindalini, C., et al. (2006) A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. *Arch Gen Psychiatry*, **63**, 74–81.

Caspi, A., McClay, J., Moffitt, T. E., et al. (2002) Role of genotype in the cycle of violence in maltreated children. *Science*, **297**, 851–854.

Caspi, A., Sugden, K., Moffitt, T. E., et al. (2003) Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, **301**, 386–389.

Craig, I. W. (2005) The role of monoamine oxidase A, MAOA, in the aetiology of antisocial behaviour: The importance of gene-environment interactions. *Novartis Found Symposium*, **268**, 227–237; discussion 237–241, 242–253.

Crow, T. J. (1997a) Is schizophrenia the price that Homo sapiens pays for language? *Schizophr Res*, **28**, 127–141.

Crow, T. J. (1997b) Temporolimbic or transcallosal connections: Where is the primary lesion in schizophrenia and what is its nature? *Schizophr Bull*, **23**, 521–523.

Crow, T. J. (2000) Schizophrenia as the price that homo sapiens pays for language: A resolution of the central paradox in the origin of the species. *Brain Res Brain Res Rev*, **31**, 118–129.

Crow, T. J. (2007) How and why genetic linkage has not solved the problem of psychosis: Review and hypothesis. *Am J Psychiatry*, **164**, 13–21.

Ebstein, R. P., Nemanov, L., Klotz, I., et al. (1997) Additional evidence for an association between the dopamine D4 receptor (D4DR) exon III repeat polymorphism and the human personality trait of Novelty Seeking. *Mol Psychiatry*, **2**, 472–477.

Feighner, J. P., Robins, E., Guze, S. B., et al. (1972) Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*, **26**, 57–63.

Gottesman, I. I., Gould, T. D. (2003) The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry*, **160**, 636–645.

Gross, C., Hen, R. (2004) The developmental origins of anxiety. *Nat Rev Neurosci*, **5**, 545–552.

Hamann, S. (2005) Blue genes: wiring the brain for depression. *Nat Neurosci*, **8**, 701–703.

Hariri, A. R., Mattay, V. S., Tessitore, A., et al. (2002) Serotonin transporter genetic variation and the response of the human amygdala. *Science*, **297**, 400–403.

Hu, S., Brody, C. L., Fisher, C., et al. (2000) Interaction between the serotonin transporter gene and neuroticism in cigarette smoking behavior. *Mol Psychiatry*, **5**, 181–188.

Kandel, E. R. (1979) Psychotherapy and the single synapse. The impact of psychiatric thought on neurobiologic research. *N Engl J Med*, **301**, 1028–1037.

Kandel, E. R. (1998) A new intellectual framework for psychiatry. *Am J Psychiatry*, **155**, 457–469.

Keltikangas-Jarvinen, L., Elovainio, M., Kivimaki, M., et al. (2003) Association between the type 4 dopamine receptor gene polymorphism and novelty seeking. *Psychosom Med*, **65**, 471–476.

Kendler, K. S., Karkowski, L. M., Walsh, D. (1998) The structure of psychosis: Latent class analysis of probands from the Roscommon Family Study. *Arch Gen Psychiatry*, **55**, 492–499.

Lerman, C., Caporaso, N. E., Audrain, J., et al. (2000) Interacting effects of the serotonin transporter gene and neuroticism in smoking practices and nicotine dependence. *Mol Psychiatry*, **5**, 189–192.

Lotrich, F. E., Pollock, B. G. (2004) Meta-analysis of serotonin transporter polymorphisms and affective disorders. *Psychiatr Genet*, **14**, 121–129.

McEwen, B. S. (2007) Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiol Rev*, **87**, 873–904.

Mitchell, R. L., Crow, T. J. (2005) Right hemisphere language functions and schizophrenia: The forgotten hemisphere? *Brain*, **128**, 963–978.

Munaro, M., Clark, T., Roberts, K., et al. (2005) Neuroticism mediates the association of the serotonin transporter gene with lifetime major depression. *Neuropsychobiology*, **24**, 1–8.

Murphy, G. M., Jr., Hollander, S. B., Rodrigues, H. E., et al. (2004) Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. *Arch Gen Psychiatry*, **61**, 1163–1169.

Murphy, D. L., Lerner, A., Rudnick, G., et al. (2004) Serotonin transporter: Gene, genetic disorders, and pharmacogenetics. *Mol Interv*, **4**, 109–123.

Nesse, R. M. (2001) The smoke detector principle. Natural selection and the regulation of defensive responses. *Ann NY Acad Sci*, **935**, 75–85.

Neumeister, A. (2003) Tryptophan depletion, serotonin, and depression: Where do we stand? *Psychopharmacol Bull*, **37**, 99–115.

Neumeister, A., Hu, X. Z., Luckenbaugh, D. A., et al. (2006) Differential effects of 5-HTTLPR genotypes on the behavioral and neural responses to tryptophan depletion in patients with major depression and controls. *Arch Gen Psychiatry*, **63**, 978–986.

Neumeister, A., Konstantinidis, A., Stastny, J., et al. (2002) Association between serotonin transporter gene promoter polymorphism (5HTTLPR) and behavioral responses to tryptophan depletion in healthy women with and without family history of depression. *Arch Gen Psychiatry*, **59**, 613–620.

Neumeister, A., Nugent, A. C., Waldeck, T., et al. (2004a) Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. *Arch Gen Psychiatry*, **61**, 765–773.

Neumeister, A., Young, T., Stastny, J. (2004b) Implications of genetic research on the role of the serotonin in depression: Emphasis on the serotonin type 1A receptor and the serotonin transporter. *Psychopharmacology (Berl)*, **174**, 512–524.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., et al. (2005) 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nat Neurosci*, **8**, 828–834.

Risch, N., Herrell, R., Lehner, T., et al. (2009) Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. *JAMA*, **301**, 2462–2471.

Saunders, B., Wilkinson, C., Phillips, M. (1995) The impact of a brief motivational intervention with opiate users attending a methadone programme. *Addiction*, **90**, 415–424.

Schildkraut, J. J. (1965) The catecholamine hypothesis of affective disorders: A review of supporting evidence. *Am J Psychiatry*, **122**, 509–522.

Seligman, M. E. (1972) Learned helplessness. *Annu Rev Med*, **23**, 407–412.

Suomi, S. J. (2003) Gene-environment interactions and the neurobiology of social conflict. *Ann NY Acad Sci*, **1008**, 132–139.

Suomi, S. J. (2005) Aggression and social behaviour in rhesus monkeys. *Novartis Found Symposium*, **268**, 216–222; discussion 222–216, 242–253.

Yeo, A., Boyd, P., Lumsden, S., et al. (2004) Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut*, **53**, 1452–1458.