Gene–environment interaction and the genetics of depression

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Depression is a group of brain disorders with varied origins, complex genetics and obscure neurobiology. Definitions of clinical phenotypes are not rooted in their neurobiology, and animal models of behavioural despair have considerable limitations. Nevertheless, investigation of subtle alterations in gene expression, of correlations between genotype and brain activity, and of environmental variables interacting with genetic variants have advanced research into the genetics of depression. Although the postgenomic era is still in its infancy, several milestones have already been reached: variation in gene expression has been confirmed to play a predominant role in individual differences; gene–environment interactions have been established in humans and in a nonhuman primate model; gene–phenotype correlations have been substantiated by functional neuroimaging; and the notion of gene networks that control brain development is increasingly recognized. Given the etiologic and psychobiologic complexity of mood disorders, it is not surprising that the identification of specific genetic factors is extremely difficult and continues to be among the last frontiers of gene hunting.

La dépression est un ensemble de troubles cérébraux d'origines variées, dont les caractéristiques génétiques sont complexes et la neurobiologie est mal connue. Les définitions des phénotypes cliniques ne sont pas enracinées dans leur neurobiologie et les modèles animaux de désespoir comportemental ont des limites importantes. Les analyses d'altérations subtiles de l'expression génique, de corrélations entre le génotype et l'activité cérébrale, et de l'interaction entre des variables environnementales et des variantes génétiques ont néanmoins fait progresser la recherche sur les caractéristiques génétiques de la dépression. Même si l'ère postgénomique commence à peine, on a déjà franchi plusieurs étapes marquantes : on a confirmé que la variation de l'expression génique joue un rôle prédominant dans les différences individuelles; on a établi des liens entre les gènes et l'environnement chez les êtres humains et dans un modèle de primate non humain; la neuro-imagerie fonctionnelle a confirmé l'existence de liens entre les gènes et le phénotype et l'on reconnaît de plus en plus le concept de réseaux géniques qui contrôlent le développement du cerveau. Compte tenu de la complexité étiologique et psychobiologique des troubles de l'humeur, il n'est pas étonnant que des facteurs génétiques spécifiques soient extrêmement difficiles à identifier et qu'ils demeurent aux limites extrêmes de la recherche génique.

Introduction

Depression is an etiologically heterogeneous group of brain disorders characterized by a wide range of symptoms that reflect alterations in cognitive, psychomotor and emotional processes. Affected individuals differ remarkably regarding the profile of clinical features, severity and course of illness as well as their response

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to drug treatment and reintegration efforts. Genetic epidemiology has assembled convincing evidence that mood disorders including depression are substantially influenced by genetic factors and that the genetic component is highly complex, polygenic and epistatic. Because the mode of inheritance of depression is complex, it has been concluded that multiple genes of modest effect, in interaction with each other and in conjunction with environmental events, produce vulnerability to the disorder. Investigation of gene–environment interactions in humans and nonhuman primates, as well as gene inactivation studies in mice, have further advanced the identification of genes that are essential for the development and plasticity of brain systems related to depression.

Family studies and gene–environment interaction

Epidemiologic studies of unipolar major depression have revealed a population prevalence of 2%–19% and an age-adjusted risk for first-degree relatives of patients with unipolar major depression of 5%–25%.[1,2] In a meta-analysis of 5 large and rigorously selected family studies of major depression, familiality in this disease was demonstrated by a relative risk of 2.8 for affected subject versus first-degree relative status.[3] Early age of onset and multiple episodes of depression seem to increase the familial aggregation, and different affective disorders are often present in the same family.[4] Relatives of patients with bipolar disorder also have an increased risk of unipolar depression, and affective disorders tend to coexist with anxiety in many families.[5–7]

Twin and family-based studies have accrued considerable evidence that a complex genetic mechanism is involved in vulnerability to depressive disorders.[8,9] Compared with the general population, first-degree relatives of depressed individuals have a nearly 3-fold increase in their risk of developing a major depressive disorder. In general, twin studies of depressive adults suggest that genes and specific environmental factors are critical and that shared environmental factors, although important in less severe subtypes of depression, are possibly of less significance.[10–13] The heritability of unipolar depression appears to be remarkable, with estimates between 40% and 70%. Depression-associated genetic factors are largely shared with generalized anxiety disorder, whereas environmental determinants seem to be distinct.[14–16] This notion is consistent with recent models of emotional disorders, which view depression and anxiety as sharing common vulnerabilities but differing in dimensions including, for instance, focus of attention or psychosocial liability. Although life events may precipitate depression, examination of familial liability along with social adversity reveals that environmental effects tend to be contaminated by genetic influences.[16,17] The predisposition to suffer life events is likely to be influenced by shared family environment, and some events may be associated with genetic factors.

Whereas genetic research has typically focused either on depression-related traits or on major depressive disorders, with few investigations evaluating the genetic and environmental relation between the two, it is crucial to identify whether a certain quantitative trait pathogenetically influences the disorder or whether the trait is a syndromal dimension of the disorder. The concept of traits influencing disease liability also supports the hypothesis that a genetic predisposition, coupled with early life stress in critical stages of development, may result in a phenotype that is neurobiologically vulnerable to stress and may lower an individual's threshold for developing depression on additional exposure to stress.

Molecular genetics

Linkage analysis of extended pedigrees is a practical approach to identifying disease genes for monogenic diseases that display a mendelian mode of inheritance. In these studies, highly polymorphic genetic markers that are present throughout the genome allow the identification of the chromosomal region containing the disease-relevant genetic variation. Despite meiotic recombination events, marker alleles that remain close to the disease-causing variant tend to cosegregate with the disease within a family. Because mood disorders, including depression, are believed to be heterogeneous in origin, different susceptibility genes may be operative in different families. As large families with monogenic inheritance of depressive disorders are rare, they are unlikely to be representative of the majority of cases. Although a rare disease-causing mutation in a single gene would not explain most cases, identification of such a major gene effect may facilitate the investigation of the poorly understood pathophysiology of mood disorders.

Differential psychopathologic ascertainment aimed

at the delineation of distinct clinical subtype (e.g., early age of onset, stress reactivity, suicidality) may increase the probability of identifying a truly monogenic family. In addition to the mode of inheritance, the analysis requires assumptions to be made regarding the penetrance of the variant and the frequency of the susceptibility allele in the general population. For affective disorders, as well as for many other complex diseases, these parameters are not known. Therefore, nonparametric methods, such as the affected pedigree member method, which investigates pairs of affected relatives, in most cases siblings, are preferred. Because siblings share on average 50% of their alleles, pairs of siblings affected by the same disorder will have increased allele sharing for markers close to the disease gene. This method is independent of whether the disease is dominant, recessive or nonmendelian.

Bipolar disorder, a serious affective disorder with a lifetime risk of about 1%, in which individuals suffer from episodes of extreme depression and mania, is by far the most frequently studied mood disorder using linkage analysis. In most families, bipolar disorder is now thought to be influenced by multiple genes, as well as environmental influences.[18,19] Gene–gene and gene–environment interactions therefore complicate attempts to understand the cause of this complex disorder. Locus heterogeneity is also thought to be present, in which several distinct genes contribute to the disorder, perhaps even within the same family.

Past linkage studies in unipolar depression suffered from poor design and included only a small number of families,[20,21] whereas 2 state-of-the-art genome-wide linkage scans have recently been published and several others are presently in progress. Zubenko et al[22] have reported several chromosomal loci that may influence the development of recurrent major depressive disorder in 81 families. The highest maximum logarithm of the odds ratio (LOD) score observed occurred at marker D2S2321 (205 cM), located 121 kb proximal to the cyclic adenosine monophosphate (AMP) response element binding protein 1 (CREB1), a ubiquitous nuclear transcription factor.[23] Nineteen chromosomal regions contained linkage peaks that reached genome-wide statistical significance. Six linkage peaks were revealed after an analysis of covariance controlled for the effects of gender and epistatic interaction with the CREB1 locus. Based on a systematic analysis of candidate genes located in the linked chromosomal regions, it is concluded that gene products derived from these genes participate in cellular signalling pathways that converge on CREB and that allelic variants of downstream target genes of CREB may affect the susceptibility of mood disorders. Because CREB is a pivotal regulatory protein in many cell types, additional spatiotemporally specific (protein) factors are likely to contribute to the genetic risk, in order to specify the depression-associated endophenotypes that constitute a clinically relevant depressive syndrome. The next level of complexity will be reached with the identification of those genetic factors that modify the disease mechanism (as well as treatment response and long-term course of illness) in individual patients with a disorder of the depressive spectrum.

Abkevich et al[24] conducted a genome-wide scan in 1890 individuals from 110 pedigrees with a strong family history of major depression and provided strong evidence for the existence of a sex-specific disposition locus for major depression on chromosome 12q22–12q23.2. Interestingly, a previous linkage analysis for quantitative trait loci (QTLs) influencing variation in the neuroticism personality trait also identified a gender-specific locus on chromosome 12q23.1.[25] Although the findings of these 3 linkage analyses require rigorous replication, they confirm previous evidence that 1 or more genes involved in psychiatric diseases are present on chromosome 12q.

A considerable number of linkage studies have been published, suggesting a number of candidate regions on different chromosomes, including 1q, 4p, 10p, 12q, 13q, 18p, 18q, 21q, 22q and Xq, but no bipolar disorder susceptibility gene has been identified yet.[26,27] A recent meta-analysis of all reported genome scans found the strongest evidence for bipolar susceptibility loci on 13q and 22q.[28] The same regions were also implicated in schizophrenic spectrum disorders, suggesting sharing of susceptibility genes. Additional loci, including regions on chromosomes 2p, 4q, 6q, 7q, 8q, 9q, 10q, 14q, 16p and 17q,[29–32] have also been linked to bipolar disorder but have yet to be replicated by independent studies. However, although some of these chromosomal regions meet strict criteria for significant evidence of linkage, narrowing the linkage regions and identifying candidate genes have proved difficult, and no genes have yet been conclusively demonstrated to affect risk for bipolar disorder. The inconsistencies appear to result from still widely underestimated genetic heterogeneity and insufficient statistical power to detect loci with smaller effects.

On the other hand, the clinical (categorial) diagnosis, no matter how carefully assessed, does not reflect neurobiologic (dimensional) processes and may, therefore, not be the appropriate phenotype for genetic analysis. The definition of more homogeneous disease phenotypes or clinical subtypes, such as the presence of catatonic features or response to antibipolar treatment, or functional neuroimaging-derived endophenotypes with less genetic complexity, preferably biologically measurable but not necessarily exclusive for the disease, is a prerequisite, if not an absolute requirement, for future study designs.[33] Chromosomal rearrangements, such as the balanced translocation of chromosomes 1 and 11 that is associated with schizophrenic and affective disorders or other chromosomal aberrations, such as the 22q11 microdeletion, may also have the potential to identify the chromosomal location of a candidate gene.[34] Last, population isolates may be used to increase the probability of all affected individuals having the same disease alleles.

Because the power of linkage analysis to detect small gene effects is quite limited, at least with realistic cohort sizes, molecular genetic research in depression has primarily relied on association analysis using DNA variants in or near candidate genes with etiologic or pathophysiologic relevance. Gene variants with a significant impact on the functionality of components of brain neurotransmission, such as the serotonin (5-HT) system, are a rational starting point. Based on converging lines of evidence that 5-HT and serotonergic gene expression are involved in a myriad of processes during brain development, as well as synaptic plasticity in adulthood, depression-related temperamental predispositions and behaviour are likely to be influenced by genetically driven variability of 5-HT function. Consequently, the contribution of genetic variants of the 5-HT transporter (5-HTT), a protein critically involved in the control of 5-HT function, to the risk of mood disorders, including depression and bipolar disorder, has been explored in several independent population-based and family-based studies.[35,36] Moreover, evidence is accumulating that a repeat polymorphism in the 5′-flanking transcriptional control region of the 5-HTT gene (*5HTTLPR*), resulting in allelic variation of 5-HTT expression and function, is associated with personality traits of negative emotionality including anxiety, depression and aggressiveness (neuroticism and agreeableness).[37,38] The short and long *5HTTLPR* variants differentially modulate transcriptional activity of the 5-HTT gene promoter, 5-HTT protein concentration, 5-HT uptake activity in lymphoblastoid cells, mRNA concentrations in the raphe complex of the human brain post mortem, platelet 5-HT uptake and content, 5-HT system responsivity elicited by pharmacologic challenge tests, mood changes following tryptophan depletion and in-vivo single-photon emission computed tomography (SPECT) imaging of human brain 5-HTT, with the short variant being associated with lower 5-HTT expression and function.[39]

Depression-related traits

A growing body of evidence implicates personality traits, such as neuroticism or the anxiety-related cluster, in the comorbidity of mood disorders.[6,14,40] The dimensional structure of neuroticism comprising fearfulness, depression, negative emotionality and stress reactivity has been delineated by systematic research. As indexed by the personality scale of neuroticism, general vulnerability is likely to overlap genetically with both anxiety and depression. Separation of depression from depression-related personality disorders in current consensual diagnostic systems has therefore enhanced interest in the link between temperament, personality and mood disorders as well as the impact of this interrelation on the heterogeneity within diagnostic entities, prediction of long-term course and treatment response. This concept may predict that when a QTL, such as *5HTTLPR*, is found for neuroticism, the same QTL should be associated with symptoms of anxiety and depression.[40] Anxiety and mood disorders are, therefore, likely to represent the extreme end of variation in negative emotionality. The genetic factor contributing to the extreme ends of dimensions of variation commonly recognized as a disorder may be quantitatively, not qualitatively, different from the rest of the distribution. This vista has important implications for identifying genes for complex traits related to distinct disorders.

However, the effect sizes for *5HTTLPR*–personality associations indicate that this polymorphism has only a moderate influence on these behavioural predispositions that corresponds to less than 5% of the total variance, based on estimates from twin studies using these and related measures that have consistently demonstrated that genetic factors contribute 40%–60% of the variance in neuroticism and other related personality traits.[38] The associations represent only a modest share

of the genetic contribution to depression-related and anxiety-related traits. An additive contribution of comparable size or epistatic interaction has, in fact, been found in studies of other quantitative traits. Thus, the results are consistent with the view that the influence of a single, common polymorphism on continuously distributed traits is likely to be modest, if not minimal.

A modulatory effect of allelic variation of 5-HTT function on cortical activity provided the first evidence that genotype–phenotype correlations may be accessible by functional imaging of the brain. Recently, Hariri et al[41] reported that individuals with 1 or 2 copies of the low-activity short *5HTTLPR* variant exhibit greater amygdala neuronal activity, as assessed by functional magnetic resonance imaging (fMRI), in response to fearful stimuli compared with individuals homozygous for the high-activity long allele. These findings confirm that genetically driven variation of serotonergic function contributes to the response of brain regions underlying human emotional behaviour and indicate that differential excitability of the amygdala to emotional stimuli may contribute to increased fear and anxiety-related responses.

Variants that change the structure of the 5-HTT protein are rare and their potential to alter 5-HT uptake activity remains to be determined.[42–45] Most of these variants have yet to be explored with respect to a functional effect on transport activity or association with a behavioural phenotype or disorder. Nevertheless, 2 nonsynonymous single nucleotide polymorphisms (SNPs) that change the coding sequence of the 5-HTT gene were found to segregate with complex serotonergic dysfunction-related phenotypes including obsessive–compulsive disorder (OCD) and other 5-HT spectrum disorders or were associated with severe depression. OCD is characterized by either obsessions or compulsions that cause marked distress and are time consuming or significantly interfere with an individual's normal routine or functioning. Obsessions are recurrent and persistent ideas, thoughts, impulses or images that an individual attempts to ignore or suppress, whereas compulsions are repetitive, purposeful and intentional behaviours performed in response to an obsession to neutralize or prevent discomfort, worry and anxiety or some dreaded event. OCD often co-occurs with other disorders, including depression.

A missense mutation resulting in a conserved Ile-425-Val substitution in the 5-HTT gene was detected in 2 affected individuals and their family members with OCD and related disorders.[46] Six of 7 family members with the variant had OCD or OC personality disorder. In addition, the affected individuals and their immediate family members carrying the Ile-425-Val variant met diagnostic criteria for other disorders including autism, social phobia, anorexia nervosa, tic disorder, depression and alcohol abuse or dependence. The evolutionary conserved Ile-425-Val substitution is located in transmembrane domain 8 (TMD8) and may modify the α-helical secondary structure of the 5-HTT protein and, consequently, transport function. Studies of the expression of the mutant 5-HTT gene cDNA in human cells demonstrated a gain of function through constitutive activation of 5-HT transport in a nitric oxide-stimulated pathway resulting in a 2-fold increase in 5-HT uptake.[47] Taken together, these findings strongly indicate that gain-of-function mutations associated with coding sequence may contribute to the expression of psychopathology related to serotonergic dysfunction in some families.

Interestingly, 2 brothers from one of the families with OCD and autism who carried the Ile-425-Val variant also had the long/long *5HTTLPR* genotype that was previously found to be associated with or preferentially transmitted in both OCD[48,49] and autism.[50,51] Moreover, a conservative Leu-255-Met substitution located in TMD4 was detected in a patient with delusional depression, who was also found to carry a short/short *5HTTLPR* genotype, which is implicated in anxiety-related and depression-related traits.[43] Possibly, low 5-HTT gene expression in interaction with the Leu-255-Met variant, which is highly conserved among various species, could additively perturb 5-HTT function or regulation. These 2 examples of co-occurrence and possible cooperativity of allelic variation in gene expression and protein structure might represent a "double hit" with functional consequences in the same gain-of-function and loss-of-function direction for both of these 5-HTT gene variations.[52]

Analogous to the 5-HTT gene and its allelic variation of expression, a functional SNP (C-1019G) in the transcriptional control region of the gene for the 5-HT_{1A} receptor (*HTR1A*) is associated with anxiety-related and depression-related personality traits,[53] as well as depression and suicidality. In-vitro experiments demonstrated that the G variant displays differential binding efficiency of transcriptional regulators (repressors/enhancers) that may lead to allelic variation of 5-HT_{1A}

receptor expression and function.[54] The agoraphobic subtype of panic disorder also appears to be associated with *HTR1A*.[55] These findings further support multiple lines of evidence that implicate the 5-HT_{1A} receptor in the pathophysiology of anxiety and depression, as well as in the mode of action of anxiolytic and antidepressant drugs. Patients with panic disorder and depression exhibit an attenuation of 5-HT_{1A} receptor-mediated hypothermic and neuroendocrine responses, reflecting dysfunction of both presynaptic and postsynaptic 5-HT_{1A} receptors.[56,57] Likewise, a decrease in ligand binding to 5-HT_{1A} receptors, as assessed by positron emission tomography, has been shown in forebrain areas and in the raphe of depressed patients.[58,59] Downregulation and hyporesponsivity of $5HT_{1A}$ receptors in patients with major depression are not reversed by antidepressant drug treatment,[59–61] thus further supporting the notion that low receptor function is a trait and, therefore, a pathogenetic mechanism of the disease.

Gene-expression profiling

Large-scale, high-throughput, cDNA microarray technology now allows the identification of altered gene expression patterns in the human postmortem brain of patients with neuropsychiatric disorders including depression, bipolar disorder and schizophrenia, which is an important step in understanding gene function in these complex disorders. Changes in expression of a number of genes have been reported in bipolar disorder. A meta-analysis of studies using microarrays and other techniques has identified modifications in the expression of genes related to neurotransmission, survival of neuronal and glial cells, and signal transduction.[62,63] Depression, bipolar disorder and schizophrenia seem to share a number of changes in gene expression. Whereas bipolar disorder is associated with low expression of several genes and more closely resembles schizophrenia in the overall pattern of changes, depression shows the smallest number of modifications. Intriguingly, decreased glial fibrillary acidic protein levels and numbers of oligodendrocytes were observed in depression, bipolar disorder and schizophrenia, which suggests that glial dysfunction may be a common substrate for all of these disorders. These observations match the increasing number of reports that describe glial abnormalities in neuropsychiatric disorders. Because glial cells are central to homeostatic and regulatory processes that affect neuronal development, plasticity and survival, this concept suggests that glial regulation of nitric oxide, glutamate, dopamine or serotonin neurotransmission, or calcium homeostasis may have special importance for these disorders. Finally, profiling of gene-expression patterns associated with clinically effective drugs in cell systems and in the animal model represents a complementary approach and may provide new insights into understanding drug mechanisms.[64–66]

Animal models

Quantitative genetic research on animal models consists primarily of inbred strain and selection studies. Whereas comparisons between different inbred strains of mice expose remarkable differences in measures of depression-related and anxiety-related behaviour, differences within strains can be attributed to environmental influences. Inbred and recombinant inbred strain studies are highly efficient in dissecting genetic influences, for investigating interactions between genotype and environment, and for testing the disposition–stress model.

Mice strains that have been selectively bred to display a phenotype of interest are currently being used to identify genetic loci that contribute to behavioural traits, including fearfulness, emotionality and behavioural despair. However, linkage analyses provide only a rough chromosomal localization, whereas the next step, identifying the relevant genes by positional cloning, remains a challenging task. Because mice and humans share many orthologous genes mapped to syntenic chromosomal regions, it is conceivable that individual genes identified for one or more types of murine fear-related behaviour may be developed as animal models for human anxiety. Following chromosomal mapping of polymorphic genes and evaluation of gene function using genetically engineered mice, behavioural parameters are investigated. As an example, findings in mice with a targeted inactivation of the 5-HTT gene emphasize the relevance of adaptive 5-HT uptake function and 5-HT homeostasis in the developing human brain as well as molecular processes underlying anxiety-related traits,[67–72] in addition to 5-HT spectrum disorders including depression and bipolar disorder.[36] Despite growing evidence for a potential role of 5-HTT in the integration of synaptic connections in the rodent, nonhuman primate and human brain during critical periods of development, adult life and

old age, knowledge of the molecular mechanisms involved in these fine-tuning processes remains fragmentary.[66,72] Thus, the combination of elaborate genetic and behavioural analyses may lead to the identification of many genes with effects on the variation and development of murine depression-related and anxiety-related behaviour.

Finally, recent advances in conditional knockout and knockin (and overexpression) techniques in mice increasingly affect our understanding of the neurobiologic basis and the neurodevelopmental processes of depression-related and anxiety-related behaviour.[72] However, the majority of neural substrates and circuitries that regulate emotional processes or cause mood disorders remain remarkably elusive. Among the reasons for the lack of progress are several conceptional deficiencies regarding the psychobiology of emotionality and behavioural despair, which make it difficult to develop and validate reliable models of depression. The clinical presentation of mood disorders and the lack of consensus on clinical categories further complicates the development of mouse models for depressive disorders. The dilemma that no single paradigm mimics the diagnostic entities or treatment response of mood disorders may reflect the inadequacy of classification rather than failure to develop valid mouse models.

Gene–environment interaction in humans and in the nonhuman primate model

Because the genetic basis of present-day temperamental and behavioural traits may reflect selective forces among our remote ancestors, research efforts have recently been focused on nonhuman primates, especially rhesus macaques. In this primate model, environmental influences are probably less complex, can be more easily controlled for and are thus less likely to confound associations between behaviour and genes. All forms of emotionality in rhesus monkeys (major categories are anxiety and aggression) appear to be modulated by environmental factors, and marked disruptions to the mother–infant relationship probably confer increased risk.

One of the most replicated findings in psychobiology is the observation of lower 5-HIAA, the major metabolite of 5-HT, in the brain and cerebrospinal fluid (CSF) in impulsive aggression and suicidal behaviour. In rhesus monkeys, brain 5-HT turnover, as measured by cisternal CSF 5-HIAA concentrations, shows a strong heritable component and is trait-like, with demonstrated stability over an individual's lifetime.[73–75] Early experiences have long-term consequences for the function of the central 5-HT system, as indicated by robustly altered CSF 5-HIAA levels, as well as anxiety, depression and aggression-related behaviour, in rhesus monkeys deprived of their mother at birth and raised only with peers. This model of maternal separation was therefore used to study gene–environment interaction by testing for associations between central 5-HT turnover and the polymorphism in the transcriptional control region of the 5-HTT gene (*rh5HTTLPR*).[76] The findings suggest that the *rh5HTTLPR* genotype is predictive of CSF 5-HIAA concentrations in rhesus monkeys, but that early experiences make unique contributions to variation in later 5-HT system function, which provides evidence of an environment-dependent association between the 5-HTT gene and a direct measure of brain 5-HT turnover and thus, ultimately, function. The consequences of deleterious early experiences of maternal separation seem consistent with the notion that *5HTTLPR* may influence the risk for mood disorders.

The interactive effect of the *rh5HTTLPR* genotype and early rearing environment on social play and aggression was also explored.[77] Infant rhesus monkeys homozygous for the long variant were more likely to engage in rough play than were individuals with the long/short variant, with a significant interaction between the *5-HTT* genotype and rearing condition. Peer-reared infants carrying the short variant were less likely to play with peers than those homozygous for the long allele, whereas the *rh5HTTLPR* genotype had no effect on the incidence of social play among mother-reared monkeys. Socially dominant mother-reared monkeys were more likely than their peer-reared counterparts to engage in aggression. In contrast, peer-reared but not mother-reared monkeys with the low-activity short allele exhibited more aggressive behaviours than their long/long counterparts. This genotype by rearing interaction for aggressive behaviour indicates that peer-reared subjects with the short allele, while unlikely to win in a competitive encounter, are more inclined to persist in aggression once it begins. Moreover, high composite scores for alcohol intake and alcohol-elicited aggression are associated with the low-activity short *rh5HTTLPR* variant in male rhesus monkeys, which provides a potential model for type II alcoholism.[78]

Taken together, these findings provide evidence of an environment-dependent association between allelic variation of 5-HTT expression and central 5-HT function, and they illustrate the possibility that specific genetic factors play a role in 5-HT-mediated behaviour in primates. Because rhesus monkeys exhibit temperamental and behavioural traits that parallel anxiety, depression and aggression-related personality dimensions observed in humans with the low-activity *5HTTLPR* variant, it may be possible to search for evolutionary continuity in the genetic mechanism for individual differences. Nonhuman primate studies may also be useful in helping to identify environmental factors that either compound the vulnerability conferred by a particular genetic makeup or, conversely, act to improve the behavioural outcome associated with a distinct genetic makeup.

Consequently, it is increasingly accepted that much of the impact of genes on emotionality, including anxiety and depression, depends on interactions between genes and the environment. Such interactions would lead to the expression of environmental effects only in the presence of a permissive genetic background. Not unexpectedly, a recent study by Caspi et al[79] robustly confirmed that individuals with 1 or 2 short versions of *5HTTLPR* are up to 2 times more likely to get depressed after stressful events such as bereavement, romantic disasters, illnesses or losing their job. Moreover, childhood maltreatment significantly increased the probability of developing depressive syndromes in later life in individuals with the low-activity short allele of *5HTTLPR*. These results further support the notion that a combination of genetic disposition and specific life events may interact to facilitate the development of mental illness. What went largely unconsidered, though, were its implications for the relevance of studying the genetics of personality. Depression is strongly associated with anxiety-related and depression-related traits, the personality dimensions that have been linked to allelic variation of 5-HTT function. Given the high comorbidity between anxiety and depression and the evidence for their modulation by common genetic factors,[80] it is likely that predisposition to mood disorders will also be determined by environmental influences whose impact on the brain is under genetic control.

Another finding by Caspi et al,[79] that early trauma inflicted by childhood maltreatment interacts with allelic variation of 5-HTT function increases vulnerability to development of mood disorders, is particularly interesting. A remarkable body of evidence suggests that emotionality and stress reactivity can be influenced by experiences early in life, and it has long been supposed that severe early life trauma may increase the risk for anxiety and affective disorders.[81] For example, adults who experience 4 of a list of 7 severe early traumatic events showed a more than 4-fold increased risk of depressive symptoms and about a 12-fold increased risk of attempted suicide.[82] No direct correlation between any specific childhood trauma and a specific adult anxiety or mood disorder could be made, however, suggesting that other, possibly genetic, factors determine the precise pathology that is precipitated by the traumatic event. The observation that individuals are particularly susceptible to adverse environmental influences during early developmental stages is confirmed by animal studies that have demonstrated the influential effects of the quality of maternal care on lifelong emotional behaviour and brain functioning.

Conclusion

Although monoaminergic dysfunction is likely to occur in depression, pathogenetic mechanisms continue to be inadequately understood at the neuronal and molecular level. A complementary approach to genetic studies of depression and related disorders involves investigation of genes (i.e., construction of transcriptome maps) and their protein products (i.e., application of proteomics) implicated in the brain neurocircuitries of emotionality and behavioural despair in animal models. Based on converging lines of evidence that genetically driven variability of expression and function of proteins that regulate the function of brain neurotransmitter systems (e.g., receptors, ion channels, transporters, enzymes) are associated with complex behavioural traits, research is now giving emphasis to the molecular basis of depression-related and anxiety-related behaviours in rodents and, increasingly, nonhuman primates.

More functionally relevant polymorphisms in genes within a single neurotransmitter system, or in genes that constitute a functional unit in their concerted actions, need to be identified and assessed in both large population-based and family-based association studies to avoid stratification artifacts and to elucidate complex interactions of multiple loci. Even pivotal regula-

tory proteins of neurotransmission, such as receptors, transporters and modifying enzymes, will have only a modest impact, whereas noise from nongenetic mechanisms may seriously obstruct identification of relevant genes. Although current methods for the detection of gene–environment interaction in behavioural genetics are largely indirect, the most relevant consequence of gene identification for behavioural traits related to depression may be that it will provide the tools required to systematically clarify the effects of gene–environment interaction.

Although depression confronts geneticists with similar challenges to other complex medical diseases, such as hypertension or diabetes, it is unique in that it is a consequence of the dysfunctional master control organ, the brain. Although the postgenomic era is still in its infancy, several milestones have already been reached (Box 1): variation in gene expression has been confirmed to play a predominant role in individual differences; gene–environment interactions have been established in humans and in a nonhuman primate model; gene–phenotype correlations have been substantiated by functional neuroimaging; and the notion of gene networks that control brain development is increasingly recognized. Given the psychobiologic complexity of depressive disorders, it is not surprising that the identification of specific genetic factors is extremely difficult and continues to be among the last frontiers of gene hunting. Future research will take advantage of the completion of the sequencing of the human and mouse genome coinciding with the revolution in bioinformatics. Integration of these emerging technologies for genetic analysis will provide the basis for gene identification and functional studies in depression.

Box 1: Genetics of depression in the postgenomic era

- Variation in gene expression is confirmed to play a predominant role in individual differences in depression-related traits
- Gene–environment interactions are established in humans and in a nonhuman primate model
- Gene–phenotype correlations are substantiated by functional neuroimaging
- Concept of gene networks that control brain development is increasingly recognized

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