Update on psychiatric genetics

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Genetic factors play a fundamental role in the genesis of many mental disorders. The identification of the underlying genetic variation will therefore transform parts of psychiatry toward a neuroscience-based discipline. With the sequence of the human genome now available, the majority of common variations identified, and new high-throughput technologies arriving in academic research laboratories, the identification of genes is expected to explain a large proportion of the risk of developing mental disorders. So far, a number of risk genes have been identified, but no major gene has emerged. The majority of these genes participate in the regulation of biogenic amines that play critical roles in affect modulation and reward systems. The identification of genetic variations associated with mental disorders should provide an approach to evaluate risk for mental disorders, adjust pharmacotherapy on the individual level, and even allow for preventive interactions. New targets for the development of treatment are anticipated to derive from results of genetic studies. In this review, we summarize the current state of psychiatric genetics, underscore current discussions, and predict where the field is expected to move in the near future. ***Genet Med* 2007:9(6):332–340.**

Key Words: *Psychiatric genetics, complex disease, linkage analysis, association study*

INTRODUCTION

Many psychiatric conditions have a strong heritability, but major genes have not yet been identified. This comes as a surprise given that medicine is discovering new genes on a weekly basis. Psychiatry is based on an intricate system of classification that is accepted and practiced around the world and should be able to provide the accurate and detailed clinical phenotyping on which successful genetic studies depend. Funding by the National Institute of Mental Health (NIMH) is at a peak, and there has never been more spending in absolute numbers for genetic psychiatric studies. Thomas Insel, the NIMH director, optimistically suggests referring to the current decade as the "decade of discovery."[1]

The field of psychiatric genetics has not yet lived up to these high expectations. The reasons for this range from an especially complex entanglement of multiple genetic and environmental factors to the impracticality of the current clinical phenotyping system for genetic studies. It is important to realize that genetics for complex diseases has limitations and might never be able to deliver a binary diagnosis for an illness such as schizophrenia. Nonetheless, genetic effects have been established for a number of genes, mostly from monoamine pathways. Some of these genetic variations have been confirmed in different studies, and they no doubt contribute to the risk of psychiatric disease.

New approaches in psychiatric genetics, including enhanced expression studies, metabolomics, and brain imaging, might provide alternative or complementary means of phenotyping for future genetic studies. The available genomic tools have improved dramatically over the last few years, with tagging SNP-based association studies now a standard and whole genome association studies within the reach of many academic laboratories.

In this review, we aim to provide a concise overview of the current state of psychiatric genetics, ongoing issues, and future developments that are expected to significantly enhance our ability to identify major genes. First, we present an overview regarding psychiatric diagnoses and the complexity of mental illness. Second, we provide a summary of the genetic contribution to specific mental illnesses, including depression, schizophrenia, and other psychiatric disorders. In each section, the evidence for specific disorders is reviewed by research approach, including linkage studies, candidate gene identification, and chromosomal aberrations. Third, we review promising methodologies being used to identify the genetic contribution to psychiatric disorders.

PSYCHIATRIC DIAGNOSTIC CLASSIFICATION RECONSIDERED

With the establishment of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) as the standard diagnostic

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reference during the last 25 years, the field of psychiatry has attracted the interest of neuroscientists, geneticists, and brain imagers. A standardized nomenclature is the foundation of comparative empiric experimentation and promises the identification of biomarkers, genes, or structural brain equivalents for disease. However, at least for genetics, the high expectations have not revealed substantial gene identifications. This is at least one reason for a renewed discussion on psychiatric classification. The DSM has been criticized for failing to identify what underlies the symptomatic expression of a condition.[2] Rather than organizing psychiatric diseases around etiopathies (neoplastic, infectious, vascular, etc.), the DSM is appearance-driven, acknowledging commonalities between phenomenological features. Of course, the neuroscience of psychiatric disease simply does not yet allow for a different approach, but the resulting phenotypes might not represent the involved genotypes well enough, which is a huge burden for any genetic study. The field has developed a validated series of instruments for psychiatric phenotyping, such as the Diagnostic Interview for Genetic Studies (DIGS) and Family Interview for Genetic Studies (FIGS), but these and others can be cumbersome to administer. The more subtle phenotypes of individuals may be difficult to assign accurately. Intelligible principles as to why certain mental disorders share characteristics with some disorders but not with others cannot be derived from the current classification system. The discussion has focused on the question of whether a nominalist or essentialist approach would serve psychiatry better as a neuroscience discipline.[3] McHugh has suggested that a psychiatric disorder should be defined by more fundamental characteristics, and he proposed that mental disorders be separated into four comprehensive clusters.[2] Others have argued that it might be premature to adopt this approach.[3] Regardless, identification of strong genetic effects has the potential to deliver new information for this discussion.

THE COMPLEXITY OF MENTAL DISORDERS

Mental disorders are considered genetically complex with many genes involved, possibly acting in an additive manner. Twin studies and epidemiological research indicate that environmental factors modulate the genetic vulnerability toward the development of a mental illness. Derived from genetic studies in neurodegenerative disorders (such as Alzheimer, Parkinson, or motor neuron disease), it is likely that dozens of genes are involved in psychiatric disorders. The detection of a significant effect for a minor gene and interaction between several genes requires a large sample of patients and controls. This is still a difficult task to manage with today's technology. The high rate of findings not confirmed in other studies is at least in part attributable to factors such as sample size, differences in genomic structure (population stratification), environmental exposures (e.g., culture), and diagnostic criteria.

Given the many reports that mental illness is overrepresented in families, it is striking that no gene has been identified as causing disease in a classic monogenetic trait (e.g., autosomal dominant). An exception to this is that a first gene might have recently been identified for Tourette's syndrome and obsessive compulsive disorder (see following).[4,5] Such genes would likely contribute to only a small proportion of mental disorders, but much could be gained by identifying new molecular pathways. For example, in Alzheimer disease, early-onset forms are mostly caused by mutations in three different genes, presenilins 1 and 2, and amyloid beta precursor protein. Animal models based on these genes have now been developed, and these models have benefited the understanding of late-onset Alzheimer disease, which is presumably more genetically complex.

REVIEW OF PSYCHIATRIC DISORDERS: CURRENT STATE OF THE EVIDENCE

The genetics of depression

Depression is characterized by disturbance of mood, thinking, sleep, appetite, and motor activity, and suicidal thoughts and attempts.[6] A wide range of phenotypic heterogeneity exists, but two major forms are the focus of genetic studies: major (unipolar) depressive disorder (MDD) and bipolar disorder (BPD). For MDD, a lifetime prevalence of 16.7% has been estimated, with women affected twice as often as men. Heritability is between 33% and 45%.[7] A meta-analysis of MDD twin studies confirmed additive genetic effects, with an estimated heritability of 37%.[8] For BPD, the lifetime prevalence is approximately 1% to 1.5% in the United States.[9] The heritability has been estimated at 85% in a sample of monozygotic and dizygotic twin pairs.[10] Morbidity risk for first-degree relatives ranges from 3% to 15% in different studies.[11]

Linkage analysis

In a genome wide linkage study of 110 families with MDD, Abkevich et al. identified a quantitative trait locus on chromosome 12q.[12] The locus was only significant for men, but it overlaps with a locus independently identified in BPD studies.[13,14] Fullerton et al. linked chromosome 12q to the personality trait neuroticism with opposite gender effects.[15] This study also reported significant evidence for linkage on chromosomes 1q, 4q, 7q, 8p, 11q, 12q, and 13q. Holmans et al. performed a genome scan on a large sample of patients with recurrent MDD with onset before age 31 years for probands or age 41 years for other affected family members. They identified linkage to chromosome 15q.[16]

For BPD, a large number of presumptive chromosomal loci have been reported, including 2p, 4p, 4q, 6q, 8q, 11p, 12q, 13q, 16p, 16q, 18p, 18q, 21q, 22q, and Xq. A meta-analysis by Bader and colleagues found strongest evidence for linkage at chromosomes 13q and 20q.[17] Another meta-analysis that included more studies and innovative statistical approaches concluded that the most significant areas of linkage were at 9p, 10q, and 14q.[18]

Despite these many positive findings and the availability of some large family studies, no gene has yet been conclusively reported. The reasons might lie in relatively small effects for

each of these loci, unusual mutation mechanisms (such as chromosomal microdeletions or amplifications), interactions between genes or between genes and environment, or false-positive and -negative linkage findings.

Candidate gene approach

With the limited availability of large and clinically well-defined families, many studies chose the candidate gene approach and association analysis in case/control settings. Much of the work has concentrated on the pathways of monoamines that are targets for antidepressant drugs, especially the serotonin neurotransmitter system, which has important implications for the pathophysiology of affective disorders.[19,20] The protein that regulates serotonin uptake into cells, *5-hydroxytryptamine transporter* (5-HTT) or SLC6A4, is localized in dendrites of serotonin-releasing neurons but is also found in platelets and is thus accessible for functional studies. Meltzer et al. demonstrated that the serotonin uptake velocity in platelets is inherited and is low in patients with MDD and BPD and in patients with schizoaffective depression.[21,22] Later, an insertion/deletion polymorphism in the promoter region of 5-HTT was shown to be associated with personality traits such as anxiety, depression, and aggressiveness.[23] The shorter "S" variant causes less 5-HTT expression than the long "L" allele.[24] In a 2003 article, Caspi et al. reported their longitudinal study about how life stresses precipitate depression depending on the inherited 5-HTT alleles.[25] In their study, they determined whether subjects had undergone stressful life events and whether they had experienced a major depressive episode. The effects of life events on depressive symptoms were significantly stronger among SS and SL subjects than among LL subjects. The authors pointed out that 5-HTT might not be directly associated with depression but may work via the gene by environment interaction.[25] Studies in mice and rhesus macaques, and imaging studies in humans supported the connection between 5-HTT alleles and stress.[26–28] For BPD, however, a recent review and meta-analysis concluded a detectable but very small effect of 5-HTT.[29] Other candidate genes that showed modest effects for BPD were *monoamine oxidase A* (MAOA) and *catechol-O-methyl transferase* (COMT).[30,31] The rationale is that MAOA and COMT catabolize noradrenalin, and the noradrenergic system is thought to be involved in aggressive behavior.[32]

Recently, loss-of-function variations in the *tryptophan hydroxylase 2* (TPH2) gene have been reported to be overrepresented in MDD.[33] TPH2 is primarily expressed in the brain, where it plays a fundamental role in serotonin synthesis.[34] However, other groups had difficulty confirming these findings.[35] Regardless, a recent study identified the association of a risk haplotype block in TPH2 with suicide attempts and MDD in four populations.[36]

Another interesting candidate gene that has been studied is *brain-derived neurotrophic factor* (BDNF). BDNF promotes survival and differentiation of neurons and is located at chromosome 11p13, a locus that has been implicated in linkage studies of BPD. A common variation in BDNF (VAL66Met) showed significant association in three Caucasian bipolar samples.[37–39] No association has been found for BDNF and mood disorders in a large European nonclinical community sample and for BDNF in a Japanese schizophrenia study.[40,41]

Genetics of schizophrenia

Clinically schizophrenia is characterized by delusions, hallucinations, disorganized thinking and speech, catatonic behavior, and social withdrawal. A phenotypic overlap with bipolar disorder, which is often accompanied by psychotic features and cognitive changes, is supported by family studies and genetic findings. Approximately 1% of the world's population has schizophrenia.[42–44] Schizophrenia has been subject to many detailed epidemiologic and genetic studies. The heritability has been repeatedly estimated as 80% to 85%.[45–47] Moldin reviewed family and twin studies published between 1920 and 1987 and showed recurrence risk ratios, as defined by the risk in siblings divided by the risk of the general population: 48 for monozygotic twins, 11 for first-degree relatives, 4.25 for second-degree relatives, and 2 for third-degree relatives.[48]

Linkage studies

Numerous studies have attempted to identify chromosomal loci for schizophrenia, and a large number of presumptive regions have been reported, including 1q21, 1q42, 5q, 6p, 6q, 8p, 10p, 10q, 13q, 17p, and 22q.[49] A meta-analysis of whole-genome linkage scans of BPD and schizophrenia by Badner and Gershon supported chromosomes 8p, 13q, and 22q.[17] Another study by Lewis that used different methods favored 2q but also supported a number of additional chromosomes, including 8p and 22q.[50] A chromosomal locus on 18p has been independently identified in linkage analysis studies of bipolar and schizophrenia samples.[51] There is now repeated evidence for a number of schizophrenia loci, and some interesting genes have emerged from these regions.

Chromosomal aberrations

Interestingly, a number of chromosomal aberrations have been identified in patients with schizophrenia, and some of the best candidate genes are associated with these loci. Several studies have reported that 22q11 deletions are associated with risk of schizophrenia.[52] Thus, genes located at 22q11 are promising candidates for schizophrenia. Current results favor the genes COMT, *proline dehydrogenase* (PRODH), and *DHHC-type containing 8 zinc finger* (ZDHHC8) (Table 1). COMT is a well-studied candidate because of its crucial role in the dopamine pathway. Most studies on COMT have focused on a common Val158Met polymorphism that confers higher activity and thermal stability.[53] This SNP has also been associated with reduced performance in tests of frontal lobe function.[54,55] Shifman et al. identified a highly significant COMT haplotype association with schizophrenia.[56] A recent meta-analysis concluded that the 158Val allele comprises a small but reliable risk factor for schizophrenia for people of European ancestry, but the influence of this polymorphism on risk in Asian populations remains unclear.[57] Thus, the negative replication reports

Table 1
Examples of psychiatric genes extensively discussed in recent years

Phenotype	Gene	Protein	Proposed function
Schizophrenia	COMT (22q11)	Catechol-O-methyltransferase	O-methylation and degradation of neurotransmitters dopamine, epinephrine, and norepinephrine
	PRODH (22q11)	Proline dehydrogenase (oxidase) 1	Mitochondrial proline dehydrogenase
	ZDHHC8 (22q11)	DHHC-type containing zinc finger 8	Knock-out mice showed repulse inhibition, exploratory activity in a new environment, and decreased sensitivity to dizocilpine
	DISC1 (1q42)	Disrupted in schizophrenia 1	Involved in neurite outgrowth and cortical development
	Dtnbp1 (6p22)	Dysbindin/dystrobrevin binding protein 1	May play a role in organelle biogenesis
	NRG1 (8p21)	Neuregulin 1	Induces growth and differentiation of epithelial, neuronal, glial, and other types of cells
	PDE4B (1p31)	Phosphodiesterase 4B	Second messenger that regulates and mediates cellular responses to extracellular signals, such as hormones, light, and neurotransmitters
	RGS4 (1q23)	Regulator of G-protein signaling 4	GTPase-activating protein for heterotrimeric G proteins
Mood disorders	BDNF (11p13)	Brain-derived neurotrophic factor	Necessary for survival of striatal neurons, synaptic integrity
	5HTT (SLC6A4)	5-hydroxytryptamine transporter	Membrane protein and member of the sodium:neurotransmitter symporter family that transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons
	MAOA (Xp11.3)	Monoamine oxidase A	Localizes to the mitochondrial outer membrane; degrades amine neurotransmitters, such as dopamine, norepinephrine, and serotonin; Brunner syndrome
	G72/DAAO (13q34)	D-amino acid oxidase activator/ D-amino-acid oxidase	Degrades gliotransmitter D-serine, a potent activator of *N*-methyl-d-aspartate type glutamate receptor
OCD	SLITRK1 (13q31)	SLIT and NTRK-like protein 1	Expressed predominantly in neural tissues, membrane protein, neurite-modulating activity
Anxiety, PTSD	DRD2 (11q23)	Dopamine receptor D2	G-protein coupled receptor; inhibits adenylyl cyclase activity
	DRD4 (11p15)	Dopamine receptor D4	G-protein coupled receptor; inhibits adenylyl cyclase activity
	5HTT (SLC6A4)	5-hydroxytryptamine transporter	
Substance abuse	DBH (9q34)	Dopamine beta-hydroxylase	Present in the synaptic vesicles of postganglionic sympathetic neurons and converts dopamine to norepinephrine
	DRD2 (11q23)	Dopamine receptor D2	
	COMT (22q11)	Catechol-O-methyltransferase	

might be the result of sample size issues in the situation of a small gene affect or ethnicity.[44] For PRODH, a complete deletion of the gene and rare heterozygous missense mutations were detected in few patients with schizophrenia, and those sequence alterations were associated with hyperprolinemia.[58] Almost all of these mutations were also identified in a relatively small number of controls. It is conceivable that some mutations confer an exclusive risk for a small portion of patients with schizophrenia, but additional studies have not yet confirmed these findings. The gene is also supported by a mouse model that reported behavioral abnormalities in sensory motor gating that are analogous to those observed in subjects with schizophrenia.[59] Finally, ZDHHC8 contains a SNP (rs175174) that has been reported to confer risk for schizophrenia, but only in women.[60] The sexually dimorphic effects have also been shown in ZDHHC8 knockout mice, with only female mice exhibiting deficits in prepulse inhibition and decreased exploratory activity. These findings are awaiting confirmation in more population-based studies, but negative reports have already emerged.[44,61,62]

Another chromosomal abnormality linked with schizophrenia and BPD, a balanced translocation, has been reported on chromosome t(1;11)(q42;q14.3).[63] Independently, Ekelund et al. linked the same locus to schizophrenia in a Finnish sample.[64] The gene DISC1 is located within this region, and there is evidence that DISC1 might contribute to schizophrenia by affecting neuronal functions such as neuronal migration, neurite architecture, mitochondrial function, and intracellular transport.[65,66] The Ser704Cys change in DISC1 has also been associated with hippocampal structure and cognitive function.[67,68] So far, positive and negative association results between DISC1 and schizophrenia and BPD have emerged, and the findings suggest distinct significance of DISC1 in different populations.[69,70] Recently, an alternative translocation t(1;11) (q42;q14) has been identified in a small Scottish family that co-segregated with schizophrenia. This chromosomal ab-

erration disrupted phosphodiesterase 4B (PDE4B), a gene that has been shown to cause behavioral changes in mice and fruit flies.[71] Moreover, Millar et al. showed physical and functional interaction with DISC1.[71] Additional studies are necessary to assess the significance of this report.

Candidate genes

A number of candidate genes located within schizophrenia linkage regions have been studied. *Dysbindin* (DTNBP1) on chromosome 6p was first reported by Straub et al., and significant association was confirmed by 10 subsequent studies.[44,72] These studies found, however, different risk alleles and haplotypes in dysbindin associated with schizophrenia. No causative sequence variant has been identified, but dysbindin expression levels were reduced in postmortem brain from patients with schizophrenia.[44,73]

In the Icelandic population, *neuregulin 1* (NRG1) on chromosome 8p is associated with schizophrenia. The same haplotype was subsequently confirmed in a Scottish sample and a British sample.[74] More positive and some negative studies have emerged, but not all studies identified the original Icelandic haplotype.[44,75] Two recent meta-analyses supported NRG1 as a susceptibility gene for schizophrenia.[76,77] Despite detailed resequencing, a specific sequence variation has not been identified. Nevertheless, there is support from animal models, expression studies, and functional studies that NRG1 is an interesting candidate gene for schizophrenia.[78–80]

D-Amino-acid oxidase (DAAO) and *D-amino-acid oxidase activator* (DAOA or G72) are located at chromosome 13q, and association with schizophrenia has been reported in a number of studies.[81,82] As for dysbindin and NRG1, there is no consensus on a specific sequence variation or haplotype between these studies. Both genes encode functionally interacting proteins expressed in the caudate and amygdala. Interestingly, G72/DAAO is also implicated in BPD.[83–85]

The gene *regulator of G-protein signaling* (RGS4) on chromosome 1q has been reported by several groups as a susceptibility gene for schizophrenia.[86–88] However, the level of statistical support varied, and the evidence for a role of RGS4 in schizophrenia is considered weak at this point.[44,89] RGS4 is a negative regulator of G protein-coupled receptors, and expression was decreased in the schizophrenic brain. There is evidence that RGS4 modulates activity at certain serotonergic and metabotropic glutamatergic receptors, and RGS4 might interact with NRG1 via its receptor ErbB3.

Taken together, there is increasing evidence by replicate studies for positive linkage and association with a number of genes involved in schizophrenia. The lack of a specific sequence variation in any of the reported genes so far prevents its use in the identification of at-risk individuals.

OTHER PSYCHIATRIC DISORDERS

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is a classic example of environmental factors leading to the development of a psychiatric disease.[90] Despite evidence supporting the presence of a dose-response relationship between the severity of trauma exposure and PTSD, the fact remains that most individuals with trauma exposure do not develop the disorder.[91,92] PTSD is not the only negative mental health outcome resulting from trauma exposure. Higher rates of major depression, panic, and substance abuse have all been documented among individuals with trauma exposure.[93]

Empirical evidence supports the transmission of PTSD within families. In a twin study, True et al. reported estimated heritabilities for PTSD among Vietnam War-era American veterans ranging from 13% to 30% for re-experiencing symptoms, 30% to 34% for avoidance and numbing symptoms, and 28% to 32% for arousal symptoms.[94] As reviewed by Radant et al., persons with a family history of anxiety disorder have a risk of developing PTSD that is 2.4 to3.0 times higher than that of controls, a family history of psychosis that is associated with a relative risk of PTSD of 3.89, and a family history of personality disorder with a 2.4- to 3-fold increased risk of developing PTSD.[95]

Several candidate genes were considered as risk factors for PTSD, including BDNF, DRD2, and SLC6A4.[96–98] Results from different studies produced conflicting results and suffered from a small sample size or included comorbidity of alcohol abuse.[99,100]

Other anxiety disorders

Family and twin studies demonstrated the importance of genetic factors as major determinants of anxiety disorders including general anxiety disorder and panic disorder.[101–103] Panic disorder and its spectrum have the strongest magnitude of familial clustering and genetic underpinnings. Studies of offspring of parents with anxiety disorders demonstrate an increased risk of mood and anxiety disorders, but there is far less specificity of the manifestations of anxiety among children and young adolescents.[104] Monozygotic twins have been shown to be twice as prone to general anxiety disorder and panic disorder as dizygotic twins.[105] Generalized anxiety disorder and stressful life events are established risk factors for MDD.[106] In a larger data set of 1033 female same-sex twins, a heritability of approximately 30% was reported for general anxiety disorder.[107]

Cloninger et al. studied human personality traits in 758 sibling pairs from 177 nuclear families and reported a locus on chromosome 8p21 associated with harm avoidance, a measure of anxiety proneness.[108] Several candidate genes have been studied, including 5-HTT, which has been found associated with the anxiety-related trait neuroticism. A meta-analysis of 26 studies confirmed the importance of the promoter polymorphism in 5-HTT for anxiety-related personality traits.[109,110] The dopamine receptors DRD2, DRD3, and DRD4 have been studied, with most support coming from DRD4 polymorphisms.[111] However, a substantial genetic finding to explain a larger portion of the studied traits has not yet been identified.

Obsessive compulsive disorder spectrum

Obsessive compulsive disorder (OCD) comprises a spectrum of disorders characterized by significant intrusive ideations, obsessions, ritualistic behaviors associated with anxiety, and compulsions. Twin studies, family studies, and segregation analyses have shown that heritability is between 33% and 66%.[112] First-degree relatives are 3 to 12 times more likely to develop OCD symptoms.[113]

Linkage studies identified chromosomal loci on 9p and 19q, with the latter producing a LOD score of only 1.73.[114] However, given the broad clinical spectrum of OCD, more narrowly defined phenotypes will likely produce additional loci, as shown for Tourette's syndrome.[115] Several candidate genes have been implicated in OCD, including COMT, 5-HTT, and MAO.[113] All these genes have been studied in several other psychiatric disorders, as previously described. This exemplifies the broad overlap of disease concepts in molecular psychiatry but is also an indicator of the lack of a more convincing chromosomal locus that would provide new candidate genes as available for schizophrenia.

In that light, a recent *Science* article by Abelson et al. identified a chromosomal translocation in a patient with Tourette's syndrome and subsequently studied the gene *slit and trk like 1* (SLITRK1).[4] In addition to the translocation, they identified a family with a frame-shift mutation and two other pedigrees with a micro-RNA target site mutation. All these changes were extremely rare and would not have been identified by association studies. This article was celebrated by *Science* as one of the top 10 scientific breakthroughs in 2005. In a sample of patients with trichotillomania, we recently identified additional missense mutations that were absent in a very large control sample.[5]

Substance abuse/dependence

Epidemiologic studies provide evidence that genetic factors play a significant role in predisposition to abuse of addictive substances. Nurnberger et al. analyzed data from the Collaborative Study on the Genetics of Alcoholism and reported a lifetime risk of alcohol dependence, as defined by the DSM-IV, among relatives of probands to be 28.8%, versus 14.4% among relatives of controls.[116] The results of many twin studies have concluded that cocaine use and dependency is highly heritable.[117] The heritability for the initiation of smoking is 56%, and nicotine dependency has a heritability of approximately 70%.[118]

Uhl et al. reviewed the literature and identified as many as 15 chromosomal loci, most with only moderate significance, that might harbor candidate genes for the vulnerability of substance abuse.[119] Located in the linked region on chromosome 9 is the *dopamine beta hydroxylase* (DBH) gene, whereas the *dopamine D2 receptor* (DRD2) gene is located within the chromosome 11 linkage region. The COMT gene, also involved in dopamine metabolism, was not reproduced in genomic linkage screens but has been implicated in a number of association studies with related phenotypes.[120,121] The dopaminergic system has been favored in most studies because it stimulates the mesocorticolimbic circuits of the brain that are thought to be important in behavioral reward and reinforcement.[122] However, no significant gene has been identified yet.

CONVERGING METHODOLOGIES FOR THE STUDY OF GENETICS AND PSYCHIATRIC DISORDERS

Imaging

The consequences of genetic variation on brain structure and function is becoming accessible with modern imaging techniques. For example, Bookheimer et al. used functional magnetic resonance imaging (MRI) to study memory processes in people with and without genetic risk factors for dementia.[123] Healthy elderly individuals who carried the epsilon 4 allele of the apolipoprotein E gene (APOE-4), which is associated with an increased risk of developing Alzheimer's disease, showed increased activation of the hippocampus, the parietal cortex, and prefrontal cortex structures implicated in memory function. When a subgroup of subjects was tested 2 years later, their decline in memory performance correlated with the degree of baseline brain activation. These results suggest that functional MRI can detect subtle neural changes even before the development of clinically apparent memory deficits.[123]

Volumetric neuroimaging in MDD suggests abnormalities in the frontal lobe, basal ganglia, cerebellum, and hippocampus/amygdala complex. In bipolar disorder, abnormalities in the third ventricle, frontal lobe, cerebellum, and possibly the temporal lobe are noted.[124] Anatomically abnormal orbital frontal regions and basal ganglia have been reported in OCD, temporal lobe was found to be reduced in size in panic disorder, and abnormal hippocampus shrinkage was shown in PTSD.[125] MRI studies often have limited sample sizes and a cross-sectional design. Longitudinal MRI studies accompanied by genetic studies of larger sample sizes will provide more powerful tools.

Metabolomics

Metabolomics is a relatively new and fast-growing field. Metabolomics allows for measurement of global metabolite profiles in organic samples. Metabolites are the result of the interaction of the system's genome with its environment and are not merely the end product of gene expression; they also form part of the regulatory system in an integrated manner.[126] An early metabolomics study in schizophrenia used human brain tissue and showed that half of the altered proteins were associated with mitochondrial function and oxidative stress responses.[127] Cluster analyses of transcriptional alterations were able to differentiate 90% of patients with schizophrenia from controls and confounding drug effects could be excluded. Metabolomic studies are expected to identify signatures of disease and could provide alternative or additive means of stratifying samples into less heterogeneous subsets.

Systems biology

Systems biology is a new field that seeks to integrate different levels of information to understand how biological systems function (e.g., gene and protein networks involved in cell signaling, metabolic pathways). By studying the relationships and interactions between various biological datasets, it is hoped that a model of a whole system can be developed and studied in silico. Originally introduced in cancer biology, systems biology is expected to gain a more prominent role in unraveling the causes of genetically complex diseases.[128,129] Future large-scale gene, protein, and metabolite studies will potentially accelerate hypothesis generation and testing in disease models. Computer simulations integrating knowledge on different levels will help to prioritize targets for detailed studies.[130]

CONCLUSION

Although psychiatric genetics is characterized by unprecedented efforts to identify the underlying genetic basis, very few candidates have been accepted as definite risk genes. No genes that explain a major portion of the respective psychiatric disorder have emerged. Genes with a major effect might not exist; rather, increased risk for psychiatric conditions could result from a large number of small gene effects. The availability of new methods for genetic analysis on the genome level now allows for studies that were unimaginable a few years ago. It remains to be seen whether these new approaches will translate into real success. Whether psychiatric illness is especially "complex" or the current clinical classification system does not represent the underlying pathology well, current and future efforts are likely to eventually succeed in specifically identifying the genetic contribution to psychiatric illness.

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