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Scott F. Stoltenberg

Margit Burmeister

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Recent Progress in Psychiatric Genetics—Some Hope but No Hype

Scott F. Stoltenberg and Margit Burmeister

Department of Psychiatry, Mental Health Research Institute and Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA

Corresponding author – Margit Burmeister, 1026 MHRI 0720, 205 Zina Pitcher Place, Ann Arbor, MI 48109-0720, USA, telephone +1-734-647-2186, fax +1-734-647-4130, email margit@umich.edu

Abstract

The reputation of the field of psychiatric genetics has recently become tarnished in the view of many human geneticists. Too many linked loci were claimed and withdrawn, too many association studies published and not confirmed, and, more recently, too many new and different chromosomal regions have been implicated for the same disorder. Here, we summarize recent trends, focusing on research that moves away from traditional linkage studies. Some promising strategies include psychopharmacogenetics and consideration of endophenotypes such as neurophysiological and behavioral markers in addition to the clinical diagnosis. Utilization of rapid and automated methods for scoring genetic variants in large-scale association studies followed by multivariate analyses, which include environmental as well as genetic data, will likely fare better than traditional linkage analysis in disentangling the complex genetics of psychiatric disorders. Some notable areas of recent progress include quantification of the genetic complexity of autism, identification of genetic variants protecting individuals from alcoholism, and the description of several polymorphisms likely to be relevant to behavior and psychiatry. The most notable example may be a common variant that affects the transcription rate in the promoter for the serotonin transporter gene that may be relevant for individual differences in the response to common antidepressants.

Introduction

Recent advances in molecular genetics and the unprecedented developments in biotechnology have inspired tremendous optimism that we will soon know a few genes involved

in susceptibility to psychiatric disorders and individual differences in normal human behavior. Nevertheless, in contrast to some other complex disorders, no susceptibility loci for psychiatric disorders have been unambiguously identified. This is especially disappointing given the overwhelming epidemiological evidence that susceptibility to psychiatric disorders has a substantial genetic component. Concordance rates among monozygotic (MZ) twins for schizophrenia, bipolar disorder (also known as manic depression), alcoholism, and Tourette syndrome are ~50%. Short reviews of the epidemiological and genetic data for the most common psychiatric disorders are given in a recent summary prepared by a National Institute of Mental Health working group (1). Here we discuss the reasons for this relative lack of progress, including diagnostic problems and genetic complexity, and outline novel approaches likely to bemore successful. Since animal models will be discussed elsewhere in this issue (2), we will not discuss them here, although they are likely to have a key role in identifying interesting candidate genes.

Epistatic Interaction of Genes and Multigenic Inheritance

The transmission patterns of psychiatric disorders are undeniably complex. It is likely that a variety of genetic as well as environmental pathways can increase one's susceptibility to a given psychiatric disorder. This is the concept of equifinality, where different initial conditions can lead to the same endpoint (3). Although genetic heterogeneity is generally accepted to be a complicating issue for psychiatric disorders, it is not an insurmountable problem for gene identification. An instructive example is that of hearing loss, where >50 loci have been mapped and about a dozen have been identified (4,5).

In addition to heterogeneity, it is anticipated that to increase risk for many complex disorders, multiple deleterious genetic variants are required in combination. This is called multiplicative, epistatic, oligogenic, or multigenic inheritance (6–8). Such inheritance is indicated when the risk to very close relatives of those affected is high but decreases rapidly in more distant relatives, as is observed in both schizophrenia (7) and bipolar disorder (9). To date, autism provides the best evidence for this type of multigenic inheritance. The MZ twin concordance rate for autism is close to 100%, yet the dizygotic rate is only 2–10%, suggesting that more than three interacting genes are involved [see also the review on the genetics of autism in this issue (10)]. Risch et al. (11) conducted a genome scan on sibs with autism and came to the stunning conclusion that increased allele sharing is observed over virtually every chromosomal region. These data are best explained if autism is caused by the interaction of >20 different loci, each with a minor effect. Such loci will be extremely difficult to identify and are expected to be quite common, such that everyone probably carries a few "autism alleles."

Diagnostic Problems and Pleiotropy: What a Microdeletion Syndrome Can Reveal about Psychiatric Disorders

Although diagnoses for psychiatric disorders are obtained by clinical interview rather than by laboratory tests, they are not completely subjective. Psychiatrists have for decades used structured algorithms to aid in diagnosis. These algorithms are described in Diagnostic

and Statistical Manuals (DSMs) that have been extensively tested and revised to improve their reliability and validity, with DSM-IV being the current version (12,13). These structured diagnostic criteria were developed to provide homogeneous groups for both biological and treatment studies. However, in the context of psychiatric genetics, it is not clear that these diagnostic categories have any relationship to genetic etiology. For example, a debate continues on whether bipolar disorder and schizophrenia are clearly distinct disorders or part of a spectrum, and recent latent class analysis suggests that the reality is more complex than either view (14).

Co-morbidity is another important complicating issue. Many psychiatric disorders often co-occur, such as substance-abuse disorders with mood and anxiety disorders (15). Such relationships among disorders may be explained by: (i) one of the disorders causing the other secondarily (e.g., depression → alcoholism, or vice versa); or (ii) one biological system affecting both traits [pleiotropy, e.g., dependence on marijuana, alcohol, and nicotine (16)]. An illustrative and rather sobering example of how diagnostic categories may not accurately reflect the underlying genetic condition is velocardiofacial syndrome (VCFS). This syndrome is usually caused by a specific deletion of ~3 Mb on chromosome 22q11 and is associated with severe cognitive and behavioral problems (17). Individuals with VCFS are often diagnosed with a co-morbid psychiatric disorder, such as schizophrenia, bipolar disorder, major depression, attention deficit hyperactivity disorder (ADHD), or even autism (18–20).We can conclude that at least some genetic defects predispose to forms of psychiatric illness that do not fall neatly into a clearly defined DSM-IV category. In a few patients with schizophrenia lacking other hallmark features of VCFS, 22q11 deletions have been detected (21,22). Therefore, 22q11 is actively studied worldwide, and some positive linkage findings for schizophrenia and bipolar disorder have been reported (23–25).

One gene in the critical 22q interval deleted in VCFS deserves special mention: *COMT*, which codes for catechol-*O*-methyltransferase, an enzyme involved in neurotransmitter metabolism. There are two forms of the enzyme differing at amino acid 158: one has high enzymatic activity, the other low. These two variants are found at about equal frequencies in Caucasians (26) and have been studied in patient samples with a variety of psychiatric disorders (Table 1). If hemizygosity for *COMT* was responsible for some of the psychiatric features of VCFS, having the low-activity form of *COMT* opposite a deletion would be predicted to be the most detrimental. Indeed, several studies support the involvement of *COMT* in rapid cycling bipolar disorder in VCFS patients (27,28).

Linkage Studies for Psychiatric Disorders Continue to Be Confusing

Because of their power to localize loci for classic Mendelian disorders, linkage studies have been the workhorse of disease gene-mapping studies. Loci for many complex disorders, such as Alzheimer's disease or many cancers, have first been pinpointed by linkage analysis (29,30). Based on these successes, both traditional and sib-pair linkage studies for psychiatric disorders have been performed, both in larger populations and in many different isolated populations in which there may be less heterogeneity due to a founder effect. These studies have recently been extensively reviewed and are not discussed further here (25,31–33). The more consistent, although not uncontested, loci are on chromosomes 6, 8,

13, and 22 for schizophrenia, and 4, 18, 21, and X for bipolar disorder. However, as discussed by Gershon (8), even when linkage is not initially replicated, the positive result does not need to be discarded: if the statistical power to find one particular locus under realistic assumptions is only ~5–10%, most studies of similar size should not be expected to replicate a correct original linkage. This fact makes the existing body of linkage results difficult to judge because many of the nonreplications may be due to insufficient statistical power, not because the linkage was not real.

Alcoholism is another psychiatric disorder that continues to be the subject of substantial genetic analysis. For example, Lappalainen et al. (34) found both linkage and association of a rather narrowly defined alcoholism phenotype (with early onset and antisocial behavior) in a population isolate in Finland to an allele of the serotonin receptor *HTR1B*. Perhaps the most ambitious effort to map alcoholism susceptibility genes is the Collaborative Study on the Genetics of Alcoholism (COGA). Initiated in 1989 by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), COGA involves six research centers across the USA. The COGA group recently published a very large (>900 individuals) sib-pair linkage study on alcohol dependence (35). Although this is by far the most extensive study, the linkage results have been somewhat disappointing; although linkage to chromosomes 1, 7, and possibly 2 and 4 was implicated, none of these loci reached a truly convincing single locus *P* value. However, another group (36) studying a southwestern American Indian population found evidence for linkage on 4p overlapping the region identified in the COGA study near the *ADH* gene cluster, discussed later as a candidate gene.

Endophenotypes or Trait Markers—Are They Better than Clinical Diagnosis?

Concordance for psychiatric illness among MZ twins is usually ~50%, indicating a substantial role for the environment or chance. In addition, as discussed earlier, many psychiatric disorders are caused by multiple genes that interact. Both facts predict that having just one predisposing allele does not imply high risk; in fact, the majority of carriers are not expected to express any clinical phenotype. How, then, can carriers for genetic linkage studies be identified? Some predisposing alleles might be found through a definable intermediate domain, e.g., neurophysiology. The basic idea of endophenotypes, or trait markers, is to find a trait that is more common in affected individuals than in the general population but also displayed often by unaffected relatives, marking these individuals as carriers of one of the predisposing alleles. Such a trait should be heritable, frequent in "high-risk" subjects (parents, siblings, or offspring), stable over one's lifetime, and unaffected by medication use (37). Several potential traits have recently been identified. A low response to alcohol is common in offspring of alcoholics and is predictive of future alcoholism (38). Holzman et al. (39) have long advocated that a deficit in smooth pursuit eye tracking—present in 50–80% of patients with schizophrenia, 40% of their first-degree relatives, but also 8% of the general population—is a marker for schizophrenia susceptibility genes. Recently, tentative linkage to this trait has been found on 6p, near a region previously implicated for schizophrenia (40). Freedman et al. (41) have described an electrophysiological deficit, decreased P50 inhibition, that is common (~10%) in the general population but is associated with schizophrenia in ~50% of patients. Linkage of this P50

or a related deficit in families with schizophrenia has been reported on chromosomes 15 and 22 (41,42), with greater LOD scores than with schizophrenia alone. A different electrophysiological trait marker is the amplitude of the event-related potential called P3 or P300, which is associated with alcoholism (43), conduct problems (44), and other psychiatric illnesses (45). The fact that this particular trait is not specific to alcoholism or schizophrenia does not disqualify it for genetic studies—since there is diagnostic overlap and co-morbidity, some alleles are expected to be more general predisposing factors. Linkage analysis of the P3 amplitude in families with alcoholism resulted in significant linkage on other chromosomal regions than when alcoholism alone was considered (35,46). Variance component analysis, in which both alcoholism and P3 amplitude were considered jointly, improved the evidence for linkage to a chromosomal region, 4p, known to contain protective candidate genes (47).

Behavioral traits, such as temperament, appear to be another set of potential markers of interest in psychiatric genetics. Although these traits are further removed from the genetic level than are physiological measures, they are easily testable and quantifiable, and there is a vast amount of literature linking temperament to biology (48). Cloninger et al. (49) argue that different personality disorders are associated with unique profiles of temperament traits. Similarly, anxiety and neuroticism scores are higher in depressed individuals than in the general population (50). A variety of studies also suggest that milder, nonpathological abnormalities in behavior are present in the parents of autistic children and thus may be markers for some of the many predisposing genes for autism (51). In the case of ADHD, a segregation analysis indicates that ADHD is best viewed as the extreme of a continuum, rather than a distinct disorder (52). Furthermore, genetic predisposition to a point on this continuum may be more or less pathological when expressed in different contexts. For example, an individual with hyperactive traits and a short attention span may excel if he or she is on a stand-up comedy stage but may not in a standard chemistry lecture.

Candidate Genes—The More the Merrier?

Association studies with candidate genes remain conceptually the simplest genetic studies. They are popular because specific biological hypotheses can be tested in a design similar to a classical case-control study. However, a few caveats must be considered when interpreting the results of these seemingly simple studies. First, any attractive candidate gene is studied by a large number of laboratories, and there is clearly publication bias toward positive findings. Secondly, population stratification can result in false-positive associations that persist even when larger samples are studied. To overcome this problem, newer statistical tests have been developed, most of which use family (parents or discordant siblings) rather than population controls. These tests have recently been reviewed (53–55). Currently, the best candidate alleles (since we all carry the same genes, it is the different alleles that are candidates) fulfill at least two criteria: (i) the variant has been shown to be functional (at the transcription or enzyme activity level, for example); and (ii) the variant has a high likelihood of being biologically relevant. Table 1 presents some currently studied candidate genes; not all of them are functional.

Table 1. Candidate genes of recent interest in psychiatric genetics

Gene	Variant(s)	Disorder (or endophenotype)	Citations
5-HT transporter SLC6A4	Promotor VNTR (5-HTTLPR), 2nd intron VNTR	Bipolar, MDD, OCD, compulsive buying, temperament, substance dependence, schizophrenia, anxiety, Alzheimer's, SAD, psychoses, generalized social phobia, alcohol tolerance	61,84–102
Tryptophan 5-mono-oxygenase (TPH; EC 1.14.16.4)	Intronic RFLP	Bipolar, MDD	90,103,104
Monoamine oxidase (MAO; EC 1.4.3.4)	*Eco*RV RFLP, promoter-VNTR	Tourette syndrome, substance abuse, OCD, mood disorders	105–107
5-HT receptor 1B (HTR1B)	*Hin*cII RFLP	Antisocial alcoholism	34
5-HT receptor 2A (HTR2A)	*Hpa*II RFLP102T/C promotor	MDD, Alzheimer's, schizophrenia, generalized social phobia	90,98,100,108
5-HT receptor 2C (HTR2C)	Cys23Ser	MDD, Alzheimer's	90,98
5-HT receptor 6 (HTR6)	267C/T	Schizophrenia	109
5-HT receptor 7 (HTR7)	2nd intron C/T	Autism	110
DA-β-hydroxylase (DBH; EC 1.14.17.1)	Ala304Ser	Bipolar I, schizophrenia	111,112
DA receptor D1 (DRD1)	RFLP	Bipolar	113
DA receptor D2 (DRD2)	Ser311Cys	Bipolar, schizophrenia, alcoholism	88,113–115
DA receptor D3 (DRD3)	*Msp*I RFLP, *Bal*I RFLP, *Msc*I RFLP	Tourette syndrome, substance dependence, schizophrenia, bipolar	93,113,116–118
DA receptor D4 HUMD4C (DRD4)	VNTR, 48 bp direct repeat	Temperament, bipolar, MDD, schizophrenia, psychoses	84,88,90,119,120
DA receptor D5 (DRD5)	Microsatellite (DRD5-M), $(TC)_n$ promotor repeat	Schizophrenia, bipolar	121
DA transporter (SLC6A3)	DAT1 VNTR in 3′-untranslated region	Bipolar, MDD, alcohol withdrawal, ADHD	88,90,122,123
Tyrosine hydroxylase (TH; EC 1.14.16.2)	VNTR intron I	Alcohol-withdrawal delirium, bipolar	124,125
Catechol-*O*-methyl-transferase (COMT; EC 2.1.1.6)	158G/A	ADHD, schizophrenia, MDD, OCD, bipolar	90,106,126–131
NE transporter (pSLC6A2)	1287G/A	MDD, Tourette syndrome	132,133
γ-aminobutyric acid, $GABA_A$ receptor $\alpha 1$	GABRA1	Mood disorders	120,134
μ-opioid receptor (OPRM1)	118A/G	Alcohol dependence, alcohol withdrawal	135–138
δ-opioid receptor (OPRD1)	921T/C	Substance dependence	139

Table 1. *Continued*

Gene	Variant(s)	Disorder (or endophenotype)	Citations
Cytochrome P-450 (CYP2E1)	RFLP	Excessive alcohol consumption	140,141
KCNN3, SCA1, SCA6, hSKCa3	Trinucleotide expansions	Schizophrenia	142–149

5-HT, serotonin; DA, dopamine; NE, norepinephrine; OCD, obsessive-compulsive disorder; MDD, major depressive disorder; SAD, seasonal affective disorder; ADHD, attention deficit and hyperactivity disorder

Since its discovery in 1996 (56), a serotonin transporter promoter polymorphism (5-HTTLPR) has been cited in >100 publications searching for association with traits ranging from compulsive buying through depression to alcoholism (Table 1). The alleles are caused by a 44 bp insertion/deletion ~1 kb upstream of the serotonin transporter gene (SLC6A4), with homozygosity for the short variant resulting in less transcript and less protein expression (56,57). Low levels of serotonin degradation products in the cerebrospinal fluid of aggressive and/or suicidal men or monkeys is among the most replicated physiological findings in psychiatry. Furthermore, some mutations in components of the serotonin pathway cause impulsive-aggressive behavior in patients or mice (reviewed in refs 58–60). Figure 1 presents a diagram of a serotonergic synapse containing several components that have genetic variants thought to be likely candidate genes for psychiatric disorders. Although most findings of associations with 5-HTTLPR to date, including an initial association with the personality trait neuroticism (57), have not been replicated (61–63), studies are continuing under the assumption that such a biologically relevant variant is likely to have some behavioral correlates.

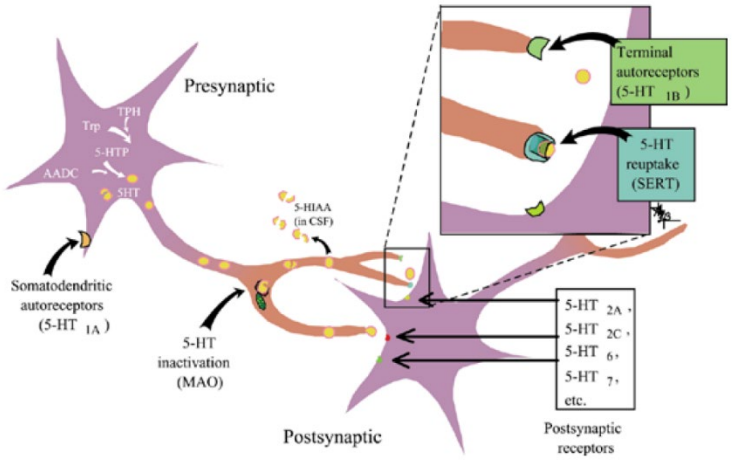

Figure 1. A serotonergic synapse showing components that have genetic variants thought to be likely candidate genes for psychiatric disorders. The first important step in serotonin (5-HT) synthesis is the uptake of tryptophan (Trp) into the presynaptic cell. The conversion of Trp to 5-hydroxytryptophan (5-HTP) is catalyzed by tryptophan hydroxylase (TPH). Aromatic amino acid decarboxylase (AADC) then converts 5-HTP to 5-HT, which

is subsequently released into the synapse. Once released, 5-HT may bind to post-synaptic receptors (e.g., 5-HT2A, 5-HT2C) or pre-synaptic autoreceptors (5-HT1B, 5-HT1A) or be removed from the synapse via the 5-HT transporter (SERT). Following re-uptake, 5-HT may be inactivated by monoamine oxidase (MAO) and then further oxidized to 5-hydroxy-indoleacetic acid (5-HIAA). Measures of 5-HIAA in the cerebrospinal fluid (CSF) are often used to index serotonergic system function.

In addition to 5-HTTLPR and COMT discussed earlier, DRD4 deserves a special mention. This dopamine receptor binds clozapine, a widely used medication for the treatment of schizophrenia. A highly variable 48 bp (16 amino acid) repeat is present in 2–10 copies at the C-terminal, cytoplasmic end of this G-protein-coupled receptor (64). Two studies reported that the longer forms are associated with higher "novelty/sensation seeking" scores (65,66), but these findings have not been replicated (67–69). However, given that even within each repeat there are several variants, perhaps only certain ones are associated with novelty seeking (70).

The most robust of all reported allelic variations relevant for psychiatric disorders is the association between the *ADH*/*ALDH* cluster on 4p and alcoholism. In linkage studies in two different populations, independent evidence for 4p was found (see above), and association was found both in an Asian (71) and a European (72) population. The biological relevance of this genetic influence of variation in the alcohol metabolism pathway on drinking behavior has been known for many years. Following ingestion, alcohol is converted, in the liver, by alcohol dehydrogenase (ADH) to acetaldehyde, which is then converted by aldehyde dehydrogenase (ALDH) to acetate. Genetic variants that have a protective effect on the development of alcoholism include a high-activity isoform of ADH (ADH2*2) and a low-activity isoform of ALDH (ALDH2*2) (71). For individuals with ALDH2*2 (especially homozygotes, primarily people of Asian descent), ingestion of alcohol produces a "flushing" response that is characterized by increased blood flow to the skin of the face, neck, and chest and may include nausea, tachycardia, hypotension, and headache. These effects are thought to be due to a build-up of acetaldehyde in the blood.

Initially, reports of candidate gene association studies consisted of testing the effects of alleles one at a time. More recently, potential epistatic interactions have been explicitly examined by testing for the effects of two markers and their statistical interaction. In these analyses, diagnoses are not the phenotypes of interest; rather, some continuously distributed endophenotype such as temperament is the dependent variable (73,74). This kind of analysis makes sense when the markers studied are known to belong to interacting systems and when the phenotype is thought to be oligogenic. Novel techniques such as single nucleotide polymorphisms (SNPs) scored on DNA chips are likely to revolutionize association studies by allowing for simultaneous testing of possibly thousands of candidate genes (75–77). Of course, the number of comparisons made must be considered, but this does not represent an insurmountable problem (78). In addition, it must be appreciated that the statistical power to detect interaction effects with a given sample size is much less than the power to detect main effects (79), so large samples are required for such analyses.

Psychopharmacology Informed by Genetics?

One of the primary goals of psychiatric genetics is to further the development of psychopharmacological agents. Psychopharmacogenetics may improve patient care by helping the clinician to individualize a patient's treatment plan based on the individual's genotype at some informative genetic marker (80,81). For example, individuals suffering from major depression, obsessive-compulsive disorder, or several other psychiatric disorders respond favorably to selective serotonin reuptake inhibitors (SSRIs) (e.g., Prozac). However, ~30% of patients do not improve on SSRIs. Two reports from Italy suggest that nonresponders may be individuals who are homozygous for the low-activity form of 5-HTTLPR (82,83). If confirmed, and this is an important "if," genetic testing of millions of patients may become reality soon. Since many psychiatric conditions are associated with an increased suicide rate, effective treatment matching may well save lives.

Summary

As we enter the new millennium, the field of psychiatric genetics is experiencing a paradigm shift. Linkage analyses continue to be largely disappointing—even though some loci can be confirmed, positional cloning is considered an unlikely route to identify genes involved in most psychiatric disorders. Co-morbidity and diagnostic uncertainties continue to plague the field. The realization that many susceptibility alleles will be common variants rather than rare mutations makes necessary new approaches to the design, analysis, and interpretation of psychiatric genetic studies. Two new directions emerge from these facts: (i) the genetic study of endophenotypes, i.e., phenotypes associated with a psychiatric illness that are more quantifiable, more common, and often associated across a wider spectrum of disorders; and (ii) genetic studies that are candidate gene driven rather than disorder driven. Candidate genes are surveyed for variants, and when a promising gene variant is identified that is both biologically relevant and has proven functional significance, it is tested across the whole spectrum of psychiatric illness and endophenotypes, and for psychopharmacogenetic relevance. With new emerging techniques such as SNP analysis on DNA chips, these types of studies are predicted to increase. Although in this review we have barely touched on recent advances in statistical analyses, they are the lenses through which we examine heredity-behavior relationships. The inclusion of covariates and the examination of interactions, both gene-gene and gene-environment, will be necessary in the development of a more complete understanding of the etiology of psychiatric disorders. Although there is a tremendous amount of work ahead, we remain cautiously optimistic that genetic studies will clarify the complex roles of genes and environment in the etiology of psychiatric disorders.

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