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Identification of the phenotype in psychiatric genetics

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Summary. Statistical procedures and molecular genetic techniques have attained a fine degree of resolution. Their ability to find disease genes has revolutionized medicine and raised hopes for breakthroughs in psychiatry. However, such breakthroughs may require an equally discriminating nosology. A psychiatric genetic nosology seeks to classify patients into categories that correspond to distinct genetic entities by addressing the problem of diagnostic accuracy: the degree to which a diagnosis correctly classifies people with and without a putative genetic illness. We review methods that deal with misclassification in genetic studies. These are clinical and epidemiological approaches that deal directly with how to define the observable manifestation of a putative genotype. We discuss two groups of methods: those that use known phenotypes and those that design new phenotypes.

Key words: Genetics – Nosology – Methodology – Linkage analysis

Introduction

A century of research into the genetic basis of psychopathology has opened new vistas for research and new hopes for treatment. For many psychiatric disorders we have a sturdy foundation of genetic epidemiological data that posits genes as etiological agents (Faraone and Tsuang 1985; Tsuang and Faraone 1990; Tsuang et al., in press). Upon this foundation, the new tools of molecular and statistical genetics promise to build an enduring theoretical and empirical structure that will house solutions to many questions of etiology, pathophysiology, diagnosis and treatment. However, the geneticist and the statistician will not succeed without continued advances by psychiatric epidemiologists and clinical investigators. Indeed, the failures to replicate linkage findings in schizophrenia (Sherrington et al. 1988; Gurling 1992), and mood disorders (Egeland et al. 1987; Kelsoe et al. 1989) suggest that methods that are routinely successful for simple Mendelian illnesses will not fare well with psychiatric disorders.

As others have documented, the clinical and epidemiological features of psychiatric disorders raise many questions for genetic studies (Diehl and Kendler 1989; Merikangas et al. 1989; Elston and Wilson 1990; Gershon 1990; Green 1990; Matthysse 1990; Morton 1990; Ott, 1990a, 1990b; Risch 1990a; Suarez et al. 1990; Weeks et al. 1990; Spence et al. 1992). In this article we focus on one of these questions: how do we define genetically meaningful diagnostic categories?

Goals of a psychiatric genetic nosology

Kendler (1990) introduced the term "scientific nosology" to describe nosological systems that are created by formulating and testing hypotheses. We use the term "psychiatric genetic nosology" to refer to a scientific nosology created from psychiatric genetic data. A psychiatric genetic nosology seeks to classify patients into categories that correspond to distinct genetic entities. We do not suggest that such a nosology will be useful for clinicians or that it should replace DSM-IV or ICD-10. Our point is simply that psychiatric genetics need not rely on diagnostic contructs created for other purposes.

A psychiatric genetic nosology should address the key measurement issues in psychiatric genetics. Each of these issues, in different guises, confronts the problem of diagnostic accuracy. We used the word "accuracy" to indicate the degree to which a diagnosis correctly classifies people with and without a putative genetic illness. When dealing with a categorical diagnosis, the fundamental types of inaccuracy are false-positives and false-negatives. False-positives refer to subjects who are incorrectly diagnosed as ill. False-negatives refer to sub-

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jects incorrectly diagnosed as well. The application of these concepts to genetic studies requires subtle modifications to our concept of diagnostic accuracy. A genetic perspective focuses on two threats to diagnostic accuracy: etiological heterogeneity and reduced penetrance.

Etiological heterogeneity occurs when several genetic and non-genetic factors can independently cause disease. In this situation, although we might accurately discriminate people with and without the disease, it may be difficult to discriminate etiological subtypes. Although seemingly not parsimonious, etiological heterogeneity cannot be ignored as a reasonable possibility. For example, researchers have implicated four genetic loci as independent causes of Alzheimer's disease: two on chromosome 21 (St. George-Hyslop et al. 1987; Tanzi et al. 1987; Van Broeckhoven et al. 1988; Goate et al. 1989, 1991; Chartier-Harlin et al. 1991; Naruse et al. 1991; van Duijn et al. 1991) one on chromosome 14 (Schellenberg et al. 1992; Nechiporuk et al. 1993; Mullan et al., in press; St. George-Hyslop et al., in press; Van Broeckhoven et al., in press) and one on chromosome 19 (Pericak-Vance et al. 1991). Furthermore, many familial cases are not linked to any of these genes and many cases of Alzheimer's disease are probably caused by non-genetic factors.

From a measurement perspective, etiological heterogeneity creates a second class of false-positives: subjects who are correctly classified as having an illness but incorrectly classified as having a genetic subform of the illness. For example, some patients diagnosed as having Alzheimer's disease do not have the diagnosis confirmed on autopsy; these correspond to the traditional definition of a false-positive. Among all patients who have the disease at autopsy, all will be true-positives for the illness, but false-positives for all but one subform (e.g. a patient with a chromosome-21 mutation would be a false-positive in studies of the chromosome-14 variant). Thus, there are two types of false-positives and both make it difficult to detect genes for etiologically heterogeneous disorders. Put simply, false-positives diminish statistical power and reduce evidence for linkage (Ott 1992). Fortunately, genetic research in Alzheimer's and other diseases shows that these problems are not insurmountable.

Reduced penetrance means that not all carriers of a pathogenic genotype will become ill. A key point is that penetrance is a descriptive statement (e.g. 10% of gene carriers will become ill), not a causal mechanism. As such, it is a statement of diagnostic inaccuracy, as it indicates that some gene carriers will be misclassified because they do not express the illness. Low penetrance may be a common characteristic of psychiatric illness. For example, when one member of a monozygotic twin pair has schizophrenia (Gottesman and Shields 1982), bipolar disorder (Tsuang and Faraone 1990), major depression (Tsuang and Faraone 1990) or panic disorder (Crowe 1990), the probability of the co-twin being ill is well below 100%. Although this could indicate etiological heterogeneity (some cases may not be genetic), it also suggests a role for reduced penetrance. From a measurement perspective, reduced penetrance means that there is a second type of false-negative: subjects who carry the gene but are correctly diagnosed as not having the disease.

Table 1. Measurement/genetic level classification outcomes

True-status	Gene carriers		Not gene carriers	
	Diagnostic status		Diagnostic status	
	Ill	Well	Ill	Well
Diseased	TP/TP	FN/FN	**TP/FP**	**FN/TN**
Non-diseased	**FP/TP**	**TN/FN**	FP/FP	TN/TN

Note: TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative
Entries indicate measurement/genetic-level outcomes. Boldface type indicates where one level of analysis results in correct classification but the other level results in misclassification

In summary, a genetic nosology must overcome two levels of diagnostic inaccuracy. At the measurement level, our diagnostic and neurobiological assessment measures may incorrectly classify subjects with and without the disorder being studied. At the genetic level, our diagnoses will misclassify subjects as having (or not having) the gene being studied. Table 1 shows the eight possible outcomes from these two levels of classification. The four outcomes emphasized in boldface type are cases where one level of analysis results in correct classification but the other level results in misclassification. For example, when we diagnose a non-diseased gene carrier as ill, this person is a false-positive from the measurement perspective, but a true-positive from the genetic perspective. In contrast, someone with the disease who is diagnosed as ill is a true-positive from both perspectives. Since measurement and genetic level outcomes are not identical, researchers have developed special strategies for resolving misclassification error at the genetic level.

Methods for psychiatric genetic nosology

This section provides a brief overview of methods put forth as solutions to the problems of misclassification in genetic studies. We do not discuss purely statistical methods such as linkage analysis with affected members (Weeks and Lange 1988) or model parameterizations that include reduced penetrance and etiological heterogeneity (Ott 1992). These are effective statistical solutions, but they do not directly address issues of nosology. In contrast, clinical and epidemiological approaches deal directly with how to define the observable manifestation (phenotype) of a putative genotype. Our review of the literature identified several different epidemiological approaches to the problem of genetic nosology. These fall into two groups: methods that use known phenotypes and those that design new phenotypes.

Methods that use known phenotypes

This first group of methods seeks to solve the nosological problems of genetic studies by starting with known psychiatric or neurobiological categories and reorganizing

them in a fashion that maximizes the usefulness of family data for genetic linkage studies.

Decreasing false-negatives. When the genotype that causes a psychiatric disorder has variable manifestations, we say that the genotype has variable expressivity. Whereas penetrance describes the probability that the genotype will be manifested as a specific illness, expressivity indicates that the occurrence of the clinical phenotype is not an all-or-none phenomenon: there may be quantitative gradations of being affected or qualitative differences in gene expression. The variable expressivity of genotypes for psychiatric disorders may produce a "spectrum" of both clinical and non-clinical phenomena.

Variable expression appears to be a common feature of familial psychiatric disorders. The schizophrenia genotype may produce schizoaffective disorder (Faraone and Tsuang 1985), schizotypal personality and atypical psychotic disorders (Tsuang et al. 1991b, in press). The biological relatives of bipolar patients are at high risk for major depressive and bipolar II disorders (Tsuang and Faraone 1990). The familial predisposition for panic disorder appears to express itself in childhood anxiety disorders and laboratory measures of inhibited behavior (Rosenbaum et al. 1988). Obsessive-compulsive disorder and chronic tics are alternate manifestations of Tourette's syndrome (Pauls et al. 1986). The genotype for attention deficit hyperactivity disorder may express itself as major depressive (Biederman et al. 1991b; Biederman et al. 1992) or conduct and antisocial personality disorders (Faraone et al. 1991; Biederman et al. 1992).

Although additional psychiatric phenotypes may be useful for linkage analyses, it seems unlikely that there will be a one-to-one correspondence between genetically influenced processes in the brain and the clinical phenomena that we observe. Since psychiatric signs and symptoms may be relatively remote effects of the genotype, linkage studies might be more fruitful if they focus on more direct measures of brain function. This strategy may be a necessity if more than one gene causes the illness. To paraphrase Matthysse (1990), minor genes for schizophrenia might be major genes for some index of central nervous system dysfunction. If this is so, then these latter neurobiologic phenotypes may prove to be extremely useful for linkage analysis.

For example, the search for neurobiologic expressions of the schizophrenia genotype has uncovered several excellent candidates. These include smooth-pursuit eye movement dysfunction (Holzman et al. 1974; Iacono 1983; Clementz and Sweeney 1990; Clementz et al. 1990, 1992; Iacono et al. 1992), the auditory P300-evoked potential (Blackwood et al. 1991a), visual sustained attention (Neuchterlein and Dawson 1984; Erlenmeyer-Kimling et al. 1991), and neuropsychological impairment (Faraone et al. 1992; Kremen et al., in press).

Keefe et al. (1991) discussed the use of non-clinical phenotypes (e.g., biological, laboratory measures) to refine the definition of affection status for genetic studies. They described three types of indicators. Diagnostic indicators are neurocognitive deficits that are more common among individuals with a disease compared with controls. These are not secondary to exogenous factors (e.g., medication) and are not state-dependent. They are called diagnostic indicators because they are associated with the diagnosis. They may not be useful for genetic studies since they could be sequelae of the nongenetic factors that cause disease expression. Spectrum indicators meet the criteria for diagnostic indicators, but are also found in subjects with disorders believed to be genetically related to the disease. Thus, spectrum indicators are likely to reflect the effects of the genotype that causes the disease. Phenotypic indicators meet the criteria for diagnostic indicators, but also show evidence for genetic transmission; they are found among relatives of diseased probands (even if the relatives do not have the disease). Phenotypic indicators are especially useful for linkage analyses because they identify affected family members who cannot be classified as affected by psychiatric measures alone.

Phenotypic indicators must be used cautiously for two reasons. One problem arises when many are available for a single disease. Consider the example of schizophrenia. As we have discussed above, we already know of several clinical and neurobiological, phenotypic indicators. When a linkage study collects several of these, it becomes possible to test for linkage using many different definitions of who is and is not affected. This increases the risk that a positive linkage finding will be due to chance alone. There are statistical solutions to this problem (Goldin 1990; Green 1990; Ott 1990a), but each of these is accompanied by some loss in statistical power.

Thus, if linkage analysis is to benefit from phenotypic indicators, they must be used judiciously. One approach to the problem of multiple disease definitions is to define a diagnostic hierarchy prior to linkage analyses (Merikangas et al. 1989; Weeks et al. 1990). The top level of the hierarchy includes the core definition of the illness. Subsequent levels use increasingly broader definitions. For example a schizophrenia linkage study could include at its top level schizophrenia and schizoaffective disorder, depressed. At the second level, psychotic disorder NOS and schizotypal personality disorder could be added. A third level could add individuals who exhibit oculomotor, attentional or neuropsychological impairments. The first level minimizes the likelihood of false-positive diagnoses. As lower levels are included, the sensitivity will be increased, but there is an associated decrement in specificity (i.e., the false-positive rate increases).

Baron, Endicott, and Ott (1990) described a hierarchical approach for linkage studies of bipolar disorder. Their first level comprised bipolar I disorder, manic episode, and schizoaffective disorder, manic. Their second level added bipolar II disorder (with major depression), recurrent unipolar depression, and recurrent schizoaffective disorder, depressed. Their third level added bipolar II disorder (with minor or intermittent depression), single episode of schizoaffective disorder, depressed, cyclothymia, and hypomania.

A second problem hampers the use of phenotypic indicators: it is possible for such an indicator to be useless,

even though its prevalence among relatives of diseased subjects is statistically greater than the prevalence in a control group. Phenotypic indicators are helpful because they decrease the false-negative rate (i.e. they increase penetrance). However, this decrease in the false-negative rate is usually accompanied by an increase in the false-positive rate (i.e. the phenotypic indicators are usually more prevalent among controls than the disease under study). For example, the rate of oculomotor dysfunction among relatives of schizophrenic patients ranges from 14 to 50% (Holzman et al. 1974, 1977, 1984; Blackwood et al. 1991b; Clementz et al. 1992; Iacono et al. 1992). Since this is greater than the 10% rate of schizophrenia and related psychoses (Gottesman and Shields 1982), oculomotor dysfunction decreases the false-negative rate. But this ignores a key point: although rates of oculomotor impairment are statistically greater among relatives of schizophrenic patients compared with controls, the rate among controls is not negligible (2–8%) (Holzman et al. 1974, 1977, 1984; Blackwood et al. 1991b; Clementz et al. 1992; Iacono et al. 1992). This suggests that the use of oculomotor measures as a phenotypic indicator may increase false-positives.

How do we know if the trade-off between false-negatives and false-positives makes a phenotypic indicator more or less useful? Risch's (1990b, c) work suggests a simple method. He shows that the power of an affected relative pair linkage study is directly related to the ratio of two prevalences: the prevalence among relatives of ill probands and the prevalence in the general population. The greater the ratio, the more power. Thus, one way to increase the statistical power of linkage analysis is to define a phenotype that is highly prevalent among relatives of ill probands but rare in the general population. It follows that a phenotype indicator will be most useful if it increases the prevalence ratio. If it maintains the same ratio, it may be useful by increasing the number of pedigrees informative for linkage analysis. For example, families with two or more cases of schizophrenia are rare; their ascertainment is a difficult, time-consuming and expensive process (Pulver and Bale 1989; Chen et al. 1992). Many more families would be informative if we use phenotypic indicators to designate affection.

Decreasing false-positives. Greenberg (1992) suggested that a phenotype definition strategy used for epilepsy might be useful for psychiatric illness. For a linkage study, he and his colleagues decide to sample families via a specific type of proband – one with juvenile myoclonic epilepsy (JME). However, since previous research had indicated that some clinically normal relatives of JME patients had abnormal electroencephalograms (EEGs), they decided to use JME or the presence of an abnormal EEG to define the affected phenotype among family members. When individuals with abnormal EEGs were classified as affected, the lod score (i.e. the evidence for linkage) was statistically significant at 3.8, nearly quadruple the non-significant value obtained when abnormal EEGs were considered unaffected.

Since this positive linkage finding has been independently replicated (Weissbecker et al. 1991), we cannot attribute it to the play of chance. As Greenberg discussed, the implications for psychiatric research are straightforward: select probands using a very circumscribed phenotype, but use a broader definition of phenotypes for family members. For example, a schizophrenia linkage project might select families by starting with probands who have Kraepelinian schizophrenia – which is defined by a 5-year history of illness and complete dependence on others (Keefe et al. 1987). However, the criteria for affection status could then be broadened to include other cases of schizophrenia, other disorders and phenotypic indicators according to a prespecified diagnostic hierarchy.

Greenberg's approach should decrease false-positives to the extent that the proband ascertainment criterion selects a genetically homogeneous subgroup. In selecting JME, he and others surmised that phenotypic expression provided clues to genotypic subtypes of epilepsy. Unfortunately, owing to the variable expression of genotypes, divergence at the phenotypic level does not always correspond to divergence at the genotypic level. So, how do we differentiate phenotypic variability due to variable expression from that caused by etiological heterogeneity?

Pauls et al. (1986) suggested that data from family studies could answer this question. In their studies of Tourette's syndrome (TS) and obsessive-compulsive disorder (OCD) they posited the following. If OCD is a variable expression of TS, then the relatives of TS probands should have elevated rates of OCD, whether or not the proband also had OCD. If OCD is found only among relatives of those probands having both TS and OCD, then there are two possibilities. TS and OCD may be independently transmitted disorders or TS with OCD may be a genetic subtype of TS. If the latter is the case, then TS and OCD should not be independently transmitted in the families of probands with both disorders. That is, in these families relatives with TS should have higher rates of OCD than relatives without TS.

The approach advocated by Pauls et al. (1986) is in some ways an essential phase of analysis because so many psychiatric disorders occur comorbidly with other disorders (Boyd et al. 1984). For example, attention deficit hyperactivity disorder is associated with conduct disorder, major depression, anxiety disorders and learning disabilities (Biederman et al. 1991c). A series of family-genetic analyses suggests that the presence of conduct disorder signals a discrete subtype of the disorder, major depression is a variable expression of the disorder, but anxiety and learning disabilites appear to be independently transmitted from ADHD (Biederman et al. 1991a, 1992; Faraone et al. 1991, in press). Such findings provide useful guides for genetic studies of ADHD: stratify probands based on the presence of conduct disorder and count major depression – but not anxiety or learning disabilities – as a spectrum indicator.

Fine tuning the false-positive and false-negative rates. Tsuang et al. (1991c) proposed a simple method of fine tuning the false-positive and false-negative rates of diagnosis. They noted that the measurement level error in

Table 2. Sensitivity and specificity of four diagnostic rules under four conditions

Four diagnostic rules	Condition 1		Condition 2		Condition 3		Condition 4	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
1. Obtain one diagnosis and use it as the final diagnosis	0.60	0.60	0.60	0.90	0.90	0.60	0.90	0.90
2. Obtain two diagnoses. Record the final diagnosis as ill if both diagnostician 1 AND diagnostician 2 diagnose the subject as ill	0.36	0.84	0.36	0.97	0.80	0.84	0.80	0.97
3. Obtain two diagnoses. Record the final diagnosis as ill if diagnostician 1 OR diagnostician 2 diagnose the subject as ill	0.84	0.36	0.84	0.80	0.97	0.36	0.97	0.80
4. Use three diagnosticians and record the majority opinion as the final diagnosis	0.64	0.64	0.64	0.96	0.96	0.64	0.96	0.96

Note: The sensitivities and specificities for one diagnostician (Rule 1) are assumed. These are used to compute results for rules 2–4

Table 1 is difficult to handle because, for psychiatric illnesses, we have no gold standard to define who is and is not affected. Thus, the two traditional indices of diagnostic accuracy, sensitivity (the probability that an affected subject is diagnosed as affected) and specificity (the probability that an unaffected subject is diagnosed as unaffected) are difficult, if not impossible, to compute. Fortunately, even when these indices cannot be computed, it is still possible to apply known epidemiological methods to fine tune the unknown values.

This is possible because, as extensive literature in epidemiology and biostatistics shows, the sensitivity and specificity of a diagnostic procedure changes in predictable ways when we combine the results of multiple diagnostic procedures in a systematic fashion (Quade et al. 1980; Politser 1982; McClish and Quade 1985; Gastwirth 1987; Lau 1989, 1991). To illustrate this phenomenon, we computed the sensitivities and specificities of four different diagnostic rules. These rules are defined in Table 2.

The first, and simplest, diagnostic rule is to use the diagnosis of one diagnostician as the final diagnosis. We do not concern ourselves here with exactly how the diagnosis is made. It may be based on clinical interviews, medical records or reports from informants. The key point is that only a single individual renders a diagnostic decision. We form the second rule by obtaining two diagnoses. We record the final diagnosis as ill if both diagnosticians diagnose the subject as ill. For the third rule, we also obtain two diagnoses, but we record the final diagnosis as ill if either diagnostician diagnoses the subject as ill. The fourth rule requires three diagnosticians. The final diagnosis is recorded as ill if a majority of the three conclude that the subject is ill.

To determine the potential utility of these rules, we simulated their sensitivities and specificities. To do so, we needed to assume values for the sensitivity and specificity of a single diagnosis. For diagnostic rules using more than one diagnostician, we then computed sensitivity and specificity using the method of McClish and Quade (1985). The results are presented in Table 2. The four conditions (in separate columns) assume different values for the sensitivity and specificity of a single diagnostician. These values are given in the first row of Table 2.

Table 2 shows that, compared with a single diagnosis, using two diagnosticians (Rules 2 and 3) can increase either sensitivity or specificity but not both. For example, under condition one, if we require two "ill" diagnoses, the sensitivity decreases from 0.60 to 0.36 and the specificity increases from 0.60 to 0.84. We see the reverse trend if we require only one of the two diagnoses to conclude that the subject is ill. To improve both sensitivity and specificity we must use more than two diagnosticians. However, as the table shows, when we use a tiebreaker to resolve disagreements between two diagnosticians, the gains are modest compared with the results of a single diagnostician.

The four conditions in Table 2 (which vary the assumed sensitivity and specificity of a single diagnostician) illustrate three features of multiple testing procedures. First, the direction of change produced by each rule is invariant across conditions (i.e. the columns of the table). For example, requiring two positive diagnoses (Rule 2) always increases specificity, but decreases sensitivity. In contrast, requiring only one of two diagnoses to be positive (Rule 3) always increases sensitivity, but decreases specificity.

Table 2 also shows that the "best" diagnostic rule depends upon the sensitivity and specificity of a single diagnostician. If these are poor (e.g. condition one where both equal 0.6), then it is not feasible for multiple diagnoses to create a phenotype definition that will be useful for linkage analyses. In contrast, when either or both are large (0.9), it becomes possibles to construct a very accurate phenotype definition. For example, when the sensitivity is 0.6 and the specificity 0.9 (condition two), the use of three diagnosticians achieves a specificity of 0.96 (which is nearly perfect).

Of course, as is true for all areas of medical decision making (Kraemer 1992), the choice of a diagnostic rule

cannot be divorced from its goals. Since false-positives can mask the presence of linkage (Greenberg 1992; Ott 1992), a psychiatric genetic nosology should seek maximum specificity while maintaining reasonable levels of sensitivity. This goal would favor Rule 2, since this can dramatically increase specificity. Further work in this area needs to examine the gains to diagnostic accuracy that might be afforded by more than three diagnosticians.

We present the results in Table 2 to illustrate the features of multiple testing procedures, not to provide definitive guidelines for linkage analysis. Indeed, several limitations may constrain their utility for some linkage studies. First, we have assumed that the multiple diagnosticians used for each rule have the same sensitivity and specificity and that these are invariant across samples. This is, at best, an approximation. Second, we have assumed that the diagnoses are independent (i.e. one diagnostician's diagnosis does not influence another's). Thus, diagnosticians cannot discuss cases or make their diagnosis at "consensus" conferences.

Finally, our calculations assume knowledge of the "true" sensitivity and specificity of a single diagnostician. If we do not know these values, it is difficult to choose the best rule. For example, the quest for specificity could become counterproductive is we apply the second rule to a diagnosis that has perfect specificity (1.0). In this case, we cannot improve specificity, but requiring two positive diagnoses, we will reduce sensitivity.

This latter problem is a thorny one because, to directly compute the sensitivity and specificity of a single diagnostician, we need a gold standard that tells us the true illness state of our subjects (Kraemer 1992). Fortunately, we can indirectly estimate these values by using latent structure analysis (Lazarsfeld and Henry 1968; Lord and Novick 1969) or a variety of other methods that infer true illness status from clinical features known to be associated with the illness (Hui and Walter 1980; Henkelman et al. 1990; Schulzer et al. 1991; Rice et al. 1992).

Methods that define new phenotypes

The second group of methods moves one step closer to a true psychiatric genetic nosology. Instead of using predefined categories, these methods attempt to define new phenotypes that maximally correspond to the genetic component of psychiatric illnesses. They each struggle with the key problem of Table 1: we never know a subject's true disease status or their true genetic status. Thus, methods of genetic nosology have sought out meaningful characteristics of genetic epidemiological data that provide some leverage on these unobserved features of psychiatric illness.

"Caseness" and the Quantification of Uncertainty. The official diagnostic nomenclature used by clinicians and most researchers treats diagnoses as discrete, binary entities: the patient is either ill or not ill. In contrast, measurement approaches in the psychological literature (Lord and Novick 1968) focus on dimensional traits that can take on a range of values. The concept of "caseness" lies between these two extremes. Put simply, caseness is a dimensional measure of the degree to which we believe that a subject is truly ill.

Caseness has an intuitive appeal that conforms to the realities of diagnosis that face both clinicians and researchers. Some patients clearly have a disorder, others certainly do not. Many more fall between the extremes of diagnostic clarity. It is sensible to associate each of these uncertain cases with an index of caseness that expresses the probability that they truly have the disorder. Although such an index would not necessarily deal with the genetic level of diagnostic error, it should facilitate genetic analyses to the degree that it corresponds to the true (but unobservable) illness status of the subject.

Ott (1991) shows how any index of caseness can be used in a linkage analysis. His method assumes that subjects are assigned weights indicating the probability that they are affected. These weights can be subjective probability judgments made by diagnosticians, or predictions made by mathematical models of disease expression. In a linkage algorithm, these weights can be used to determine the penetrance of each genotype for diagnoses made with varying degrees of certainty.

One appeal of caseness measures is that they can be used to summarize the multiple sources of diagnostic and neurobiological data that bear on the definition of psychiatric phenotypes. Instead of conducting several analyses that test linkage to a hierarchy of conditions, each condition can be assigned a weight that indicates the probability that a subject with the condition has the genotype of interest. For example, in a schizophrenia linkage study, a schizophrenic subject might be given a weight of 1, a subject with schizotypal personality and oculomotor dysfunction a weight of 0.8 and a subject with either schizotypal personality or oculomotor dysfunction a weight of 0.6.

Rice et al. (1987, 1992) showed how an index of caseness could be derived from stability data. They reasoned that diagnoses that are stable over time are more likely to reflect a true underlying illness than diagnoses that are not stable. To define an index of caseness based on stability, they used clinical measures from patients with mood disorder diagnoses (e.g. number of symptoms, number of episodes) to predict who would and would not report a lifetime history of the disorder 6 years later. The result of this procedure is a logistic regression equation that uses the clinical measures to compute the probability that a case will be stable over a 6-year period. This probability is an index of caseness inasmuch as stability over time reflects the subjects true illness status.

For example, in their analysis of major depression, the caseness index ranged from a low of 0.46 for subjects having three symptoms and no history of treatment to 1.0 for those who had eight symptoms and a history of treatment (Rice et al. 1992). These analyses confirmed an intuitive sense of how severity should be related to caseness and diagnostic stability.

Although a caseness index based on stability may deal with measurement level error, it may not reflect genetic level misclassification. For example, it is possible

that genetic subtypes or genetic and non-genetic forms of depression do not differ on the severity variables that constitute Rice et al.'s caseness index. Methods that use information about genetic relationships may be needed to define a genetic level of caseness.

The familial-sporadic distinction. Ideally, a psychiatric genetic nosology would discriminate between genetic and non-genetic forms of an illness. Some day, when we know which mutations cause psychiatric disorders, it may be possible to specify exact diagnostic criteria for genetic and non-genetic subforms. In the meantime, it may be worthwhile to use the familial-sporadic distinction as a "proxy" for the genetic-non-genetic distinction. We say that a patient has a familial form of disease if at least one relative also has the disease (or a genetically related disorder). Otherwise, we say that the patient has a sporadic form. Thus, the familial-sporadic strategy attempts to distinguish cases of illness that are more likely to be of the genetic type from those that are more likely to be of the sporadic type.

This strategy uses the psychiatric status of the relatives of the patient and could be termed positive-versus-negative family history. The method assumes that patients having one or more ill relatives are more likely to have a genetic form of schizophrenia; they are designated as familial cases. Patients having no ill relatives are assumed to be more likely to have an environmental form of schizophrenia; they are designated as sporadic cases. We emphasize that the designations "familial" and "sporadic" are imperfect indicators of the probability of membership in the latent, unobservable categories of "genetic" and "environmental".

As Lewis et al. (1987) pointed out, the classification of cases as familial or sporadic is a research strategy not an etiological model. If clinical or neurobiological measures discriminate these groups, we can learn something about the relative importance of genetic and environmental factors in subgroups defined by these factors. Also, comparisons between familial and sporadic subgroups can help us develop criteria that identify a more homogeneously familial form of the illness. As discussed above, the creation of homogeneous groups should facilitate linkage analysis. Of course, the familial/sporadic strategy cannot determine the mechanism of familial aggregation (e.g. single gene vs. multigene vs. environmental transmission). We must base such inferences on other information (e.g. twin, segregation analysis and linkage studies).

A powerful version of the familial-sporadic strategy involves the comparison of concordant and discordant MZ twins. Because MZ twins share identical genotypes, an illness having complete genetic determination should be observed in both twins. Thus, it is useful to separate MZ twin pairs that both have the disease (concordant pairs) from pairs where only one has the disease (discordant pairs). Clearly, genetic factors should be more prominent in the concordant than the discordant pairs.

One serious problem with the familial-sporadic method is misclassification. Several factors contribute to inaccuracies in the assignment of "true genetic" cases to the familial category and "true environmental" cases to the sporadic category. First, the method is insensitive to differences in the size and age structure of families (Kendler and Hays 1982; Kendler 1987a). For example, a patient with ten relatives available for study is more likely to have an ill relative than a patient with only one relative. Therefore, the availability of relatives for study can influence the accuracy of classification.

However, Lyons, et al. (1989a) suggested that, under some conditions, even a modest relationship between the familial-sporadic and genetic-non-genetic distinctions might be useful. They conducted a power analysis employing a Monte Carlo simulation procedure based on the rates of misclassification determined by Kendler (1987a, b). They concluded that for a sample size of 175, statistical power was moderate to good for effect sizes greater than or equal to one SD unit. Put simply, the utility of the familial-sporadic strategy depends on the size of the samples studied (the larger the better) and the size of the true, unobservable differences between the genetic and nongenetic forms of illness.

The analysis conducted by Lyons et al. (1989a) assumed that the genetic form of the disorder is due to a single major genetic locus. Eaves et al. (1986) conducted a power analysis of the familial-sporadic distinction, assuming a multifactorial polygenic process in which there is a normally distributed liability to illness that is due to numerous genes and environmental factors acting in an additive fashion. They concluded that large samples of probands and first-degree relatives are required to detect etiological heterogeneity with "substantial probability." In contrast, studies of MZ twins could attain high levels of statistical power with samples that were 85% smaller than those required for first-degree relatives. Thus, these authors concluded that use of MZ twins is a much more powerful approach.

Since power analyses show that the familial-sporadic strategy has low statistical power for non-twin samples, it is notable that, even with small samples, this method has produced positive results. For example, sporadic cases of schizophrenia are more likely to have had perinatal complications and brain abnormalities by computed tomography. Familial cases are more likely to have attentional deficits (Lyons et al. 1989b). We are far from having diagnostic criteria for "familial" schizophrenia, but the available data suggest that this is a possibility.

A familial index of caseness. Recently, Blacker and Tsuang (1992, 1993) showed how an extension of the familial non-familial strategy could be used as a basis for creating a familial index of caseness. They were concerned with the problem of how one classifies cases of major depression among members of bipolar pedigrees. Although bipolar disorder shares genetic causes with some cases of major depression, some cases of major depression are not genetic and others may have a genetic etiology unrelated to bipolar disorder (Tsuang and Faraone 1990).

To create a caseness index, Blacker and Tsuang proposed comparing cases of depression observed in families of bipolar probands to cases of depression observed

in families of depressed probands. Any feature that discriminates the two groups could be used in such comparisons. However, for the problem of bipolarity in depressed patients, these authors chose to focus on features shown by the phenomenology of depression in bipolar patients and in depressive patients who subsequently had a bipolar episode. They showed how logistic regression might be used to create a measure of caseness that indexed the probability that the depressed subject was a potential bipolar case.

Diagnostic efficiency and genetic nosology. Faraone et al. (1993) presented a method of phenotype definition that combined measurement level information with genetic level information. At the mesurement level they proposed to sharpen the accuracy of diagnoses for DSM-III attention deficit disorder by using the "diagnostic efficiency" of diagnostic criteria to form a more efficient diagnosis. In this context, "diagnostic efficiency" means the degree to which individual criteria correctly discriminate cases from non-cases.

As Widiger et al. (1984) cogently argued, actuarial prediction and decision theory provide a useful framework for evaluating the diagnostic efficiency of individual criteria. In pursuing the validity of individual symptoms, these methods eschew the demonstration of statistically different criteria rates between diagnostic groups, because such differences will hold for symptoms that are not useful for the diagnostician (Meehl and Rosen 1955). Instead, the focus is on a conditional probability analysis which computes the sensitivity, specificity, positive predictive power and negative predictive power of symptoms and combinations of symptoms as predictors of diagnoses. In epidemiological contexts, these statistics have been pivotal for the demonstration of descriptive validity (Burke and Regier 1988). More recently, researchers have demonstrated their utility for the development of diagnostic algorithms and the demonstration of divergent validity for psychiatric disorders (Spitzer et al. 1990).

Kraemer (1992) has shown that sophisticated conditional probability analyses can be performed within the mathematical framework of signal detection theory and receiver operating characteristic (ROC) methodology (Swets and Pickett 1982). Although originally developed for applications in engineering and experimental psychology, ROC analysis is emerging as a useful tool for assessing the diagnostic efficiency of the signs, symptoms and laboratory tests used in psychiatry (Hsiao et al. 1989). These methods can summarize the information from a conditional probability analysis in a manner that allows for the manageable determination of symptom combinations that best discriminate cases from non-cases (Siegel et al. 1989, 1990).

The signal detection framework provides a comprehensive approach to assessing the sensitivity and specificity of diagnostic algorithms. The ROC graph summarizes these measures by plotting sensitivity against (1 – specificity). In diagnostic applications it is convenient to plot sensitivity against specificity for ease of interpretation. Kraemer (1992) has shown that the diagnostic efficiency of each symptom can be more easily grasped from a transformation of the ROC curve called the quality ROC curve (QROC). The QROC adjusts the sensitivity (SE) and specificity (SP) for the base rate of the symptom (Q) by plotting the kappa coefficient for specificity, $\kappa_{SP} = \frac{SP - (1 - Q)}{Q}$, against the kappa coefficient for sensitivity, $\kappa_{SE} = \frac{SE - Q}{1 - Q}$.

Faraone et al. (1993) used a modified verison of Kraemer's (1992) ROC-based method to a sample of 73 attention deficit disorder (ADD) patients, 26 psychiatric control patients, 26 normal controls and all available first-degree relatives of these index children. Each patient had been diagnosed by an expert clinician and had also been rated on the presence or absence of 21 signs and symptoms of ADD. Using QROC-based methods, a new diagnostic algorithm was created. Put simply, by estimating κ_{SE} and κ_{SP} for each item, this procedure found the combination of items that yielded the best discrimination of the ADD and control probands. The QROC-based diagnosis was more diagnostically efficient than diagnoses created with other procedures.

To see if this psychometric crafting of diagnostic categories had implications for familial transmission, Faraone et al. diagnosed all probands and family members with their QROC-based diagnosis of ADD. Although the QROC-based diagnosis had been formulated using data on the probands, information from relatives had not been used in its development. Thus, this analysis provided a quasi-cross-validation of the method. The QROC-based diagnosis was more familial than either the DSM-III diagnosis or simple diagnoses based on the number of positive diagnostic criteria. These results suggest that reducing measurement level error (by increasng diagnostic efficiency) can yield phenotypes that are more informative for genetic analyses.

Pedigree discriminant analysis. Although temporal stability, familial transmission and psychometric considerations each provide a means of defining caseness, they do not capitalize on a key feature of illness in pedigrees: the pattern of familial transmission. Ideally, we could compile diagnostic and neurobiological data into a phenotype that exhibited Mendelian transmission. All other things being equal, a phenotype that exhibits Mendelian transmission should be more suitable for linkage analysis than a phenotype that does not.

Pedigree discriminant analysis solves this problem by estimating a linear function of phenotypic variables that maximizes the likelihood of pedigree data under a single-gene hypothesis (Zlotnik et al. 1983). The procedure starts with measures that are expressions of the genotype of interests. For a schizophrenia study, these could be measures of psychosis, negative symptoms, oculomotor dysfunction or neuropsychological impairment. It then creates a weighted sum of these variables that, compared with all possible weighted sums, provides the most evidence for Mendelian transmission.

Goldin et al. (1980) showed that pedigree discriminant analysis using several indices of von Willebrand dis-

ease provided evidence for Mendelian transmission, even though each of the measures taken one at a time could not. Amos et al. (1986) demonstrated the utility of the method for detecting genes relevant to coronary heart disease. They also show that the method is useful in controlling for familial correlations induced by environmental factors.

Although we know of no application to psychiatric illness, it may be useful for two reasons. First, segregation analyses of psychiatric disorders usually do not yield simple Mendelian models of illness (Faraone and Tsuang 1985; Faraone et al. 1990). It may be that multiple indicators of psychiatric genetic syndromes will conform to single-gene transmission. Indeed, as discussed above, the diagnostic categories designed for clinical use may not be optimal for the detection of genes that predispose to psychiatric illness.

Second, psychiatric disorders may be caused by the simultaneous action of more than one gene. Pedigree discriminant analysis could conceivably create several linear combinations of measures, such that each combination was maximally sensitive to a different gene. This might give linkage analysts a more powerful means of detecting several genes relevant to a single disorder.

Discussion

Developments in psychiatric nosology may be the rate-limiting step in the search for psychiatric disease genes. If so, the improvement and application of methods discussed in this article may be necessary to avoid detours to non-replication and quicken the pace of discovery.

Of course, we will not know if these methods are necessary until after the next wave of linkage studies have completed their analyses of standard diagnostic categories. Indeed, Alzheimer's disease researchers have found, and replicated, linkage to four different loci (Tsuang et al., in press). Moreover, these findings have led to the discovery of etiologically significant mutations (Citron et al. 1992). These successes show that clinical neuropsychiatric disease categories can be effective in linkage analysis.

It is likely that some psychiatric genes will be found using traditional diagnostic categories but that the discovery of others will require a genetic nosology. If methods of genetic nosology lead to the detection of linkage, we will then face the question of relevance: will a gene that is linked to some complicated function of putative disease gene indicators have any relevance for psychiatric disease? For example, the detection and replication of linkage for the DSM-III-R diagnosis of schizophrenia has face valid implications for the syndrome that afflicts patients. In contrast, what would it mean to detect linkage for a weighted sum of negative symptoms, attentional deviance and oculomotor dysfunction?

Unfortunately, we cannot know the clinical relevance of contrived phenotypes until they lead to mutations of pathophysiological significance. A replicated linkage would be encouraging, but will not tell us if the locus detected contains a gene of clinical significance or one that is of interest only from a behaviour genetic perspective. To increase the likelihood that a contrived phenotype will lead to clinically meaningful genes researchers should choose measures that have previously been validated as indicators of the genotype of interest.

Guidelines for validating such indicators have periodically been presented in the literature (Reider and Gershon 1978; Gershon and Goldin 1986; Garver 1987; Keefe et al. 1991; Kremen et al. 1992). These provide some guidance for choosing measures with which to design phenotypes for linkage analysis. Six specific guidelines are as follows.

1. Specificity: the indicator is more strongly associated with the disease of interest than with other psychiatric conditions. 2. State independence: the indicator is stable over time and not an epiphenomenon of the illness or its treatment. 3. Heritability: the indicator shows familial transmission. 4. Familial association: the indicator is more prevalent among the relatives of ill probands compared with an appropriate control group. 5. Co-segregation: the indicator is more prevalent among the ill relatives of the ill probands compared with the well relatives of ill probands. 6. Biological and clinical plausibility: The indicator bears some conceptual relationship to the disease: even if shoe size met other criteria, it would be suspect as a valid indicator due to its lack of biological or clinical plausibility. Clinical plausibility might be demonstrated by showing that the indicator resembles the clinical phenomenology of the illness. For example, negative symptoms are a prominent feature of schizophrenia that may be an expression of the genotype among relatives of schizophrenic patients (Tsuang et al. 1991a). Neurodiagnostic indicators will have some biological plausibility if they assess brain regions believed to be impaired by the disorder (Kremen et al., in press).

Statistical procedures and molecular genetic techniques have attained a fine degree of resolution. Their ability to find disease genes has revolutionized medicine and raised hopes for breakthroughs in psychiatry. However, such breakthroughs may require an equally discriminating psychiatric nosology – a nomenclature than can more validly discriminate genetic and non-genetic subtypes of illness (and genetic subtypes as well).

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