



The Genetic Relationship of Personality to Major Depression and Schizophrenia

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Since ancient times, dimensions of personality have been linked with the liability to psychiatric illness. In modern times, several research approaches suggest that personality and the liability to psychiatric illness such as schizophrenia and major depression (MD) are influenced by many of the same genes. If this is true, it could shed light on the genetic architecture of psychiatric illness. It could also validate the use of personality measures in unaffected relatives in linkage and association studies of psychiatric illness. This approach could potentially increase statistical power to detect genetic effects. The personality trait neuroticism (N) may be genetically related to MD, while schizotypal traits may be genetically related to schizophrenia. Twin studies have reported that most of the covariation between N and MD is due to shared additive genetic factors. Adoption studies have demonstrated that the biological offspring of schizophrenic mothers are more likely to have schizotypal personality disorder than are children of control mothers. At the current time, only one genome wide scan of N has been published, which does show some overlap in linkage results with genome scans of MD. However, this should be replicated and more rigorously studied. At the present time, there are no established susceptibility genes for MD. When these are established, it will be necessary to assess their relationship with N. Currently, no genome scans of schizotypy have been published. Furthermore, although several putative susceptibility genes for schizophrenia have been reported and replicated, only one - catechol-O-methyltransferase (COMT) - has been tested in schizotypy.

Keywords: Personality; Depression; Schizophrenia; Genetics; Linkage; Twin studies

INTRODUCTION

The relationship between personality and psychiatric illness has been the subject of theory and empirical research since ancient times. Hippocrates theorized that mental illness results from imbalances in four humors, each of which governed a specific personality trait (Jackson, 1986). In the modern era, Kraepelin (1921), Schneider (1958), and Kretschmer (1936) observed personality configurations that were deemed to be substrates of subsequent depressive, manic, or psychotic syndromes.

Personality traits are generally thought to relate to psychopathology in at least four distinct ways, each giving rise to testable hypotheses (reviewed in (Akiskal *et al.*, 1983). First, the causal hypothesis posits that certain dimensions of personality are predisposing factors for psychiatric illness. Second, the scar hypothesis posits that personality pathology is the consequence of previous episodes of illness. Third, the pathoplasty hypothesis posits that personality may influence the clinical features of psychiatric illness but is not necessarily etiologically related to it. Finally, the spectrum, or continuum model posits that personality and psychiatric illness share the same etiological factors, and represent two ends of a single continuum of severity.

In this article, we review the evidence supporting a genetic relationship between personality and two major psychiatric illnesses: major depression and schizophrenia. A genetic relationship between the domains of

personality and psychiatric illness would suggest they arise from similar biological substrates, and would therefore be a subset of the continuum model. In addition, it overlaps with the causal hypothesis. If, for example, the same genes that increase the liability to psychiatric illness also influence personality, personality could potentially be a sensitive index of the risk of illness.

The extent to which the domains of personality and psychiatric illness are genetically related has taken on both nosological as well as genetic significance. This is in part due to the ascendancy of a spectrum concept in the depressive and psychotic disorders that views the state vs. trait dichotomy as less rigid than previously held. For example, the emerging concept of Bipolar IV disorder suggests that some temperaments marked by affective instability may be better conceptualized as mood disorders rather than personality traits (Akiskal and Pinto, 1999).

Furthermore, understanding the genetic relationship between personality and psychiatric illness could shed light on the genetic architecture of both, as well as potentially suggest ways of improving our ability to identify susceptibility genes. The genetic architecture of psychiatric traits has long been described as complex. This usually denotes the presence of mechanisms such as genetic heterogeneity, pleiotropy, variable expressivity, reduced penetrance, and phenocopies not seen in Mendelian diseases. Most complex traits are thought to be polygenic (Falconer and Mackay, 1996). This usually implies multiple thresholds of liability, whereby subjects with the core phenotype often have relatives with milder manifestations of the same underlying genetic etiology (Reich *et al.*, 1972). Statistical modeling has supported the multiple-threshold paradigm in the psychotic disorders (Kendler *et al.*, 1995b; Baron and Risch, 1987). Some personality traits appear to be qualitatively similar, but quantitatively less severe than characteristics of the illnesses with which they are correlated. It is therefore intuitively plausible that personality traits in healthy individuals are influenced by susceptibility alleles for psychiatric illness. Including the personalities of relatives in linkage and association studies of psychiatric illness may increase the power to detect genetic effects. The utility of this approach has been supported. Personality traits as endophenotypes improved power to detect linkage to alcoholism in one study (Czerwinski *et al.*, 1999), while the inclusion of schizophrenia-related personality disorders in the definition of affection in some linkage studies of schizophrenia have resulted in higher LOD scores (Riley and McGuffin, 2000).

In this review, we focus on two of the more thoroughly studied genetic relationships between personality and psychiatric illness: that between neuroticism and major depression, and that between schizotypy and schizophrenia. These illustrate the progress and insights that have been achieved in this field as well as the limitations of various study methods to address questions.

NEUROTICISM AND MAJOR DEPRESSION

Hans Eysenck introduced an influential theory that attempted to parsimoniously explain individual differences in personality using three factors: neuroticism (N), extraversion (E), and psychoticism (Eysenck and Eysenck, 1985). N was defined by Eysenck as the vulnerability to neurotic breakdown under stress (Eysenck and Eysenck, 1985), and represents the predisposition to experience negative emotions. Nearly all subsequently developed frameworks of personality theories have incorporated N or N-like traits. Clinical, epidemiological, family, and twin studies have demonstrated quite robust relationships between N and MD. In prospective studies, high N predicted the future onset of MD in individuals who had previously never experienced episodes of MD (Nystrom and Lindegard, 1975; Boyce *et al.*, 1991; Kendler *et al.*, 1993b), suggesting a causal relationship. An acute episode of MD, however, may induce higher levels of reported N (Coppin, 1965; Kerr *et al.*, 1970; Hirschfeld *et al.*, 1983; Farmer *et al.*, 2002). This is sometimes called the "state" effect, and may be confounded with a true trait effect of N on MD in within-person studies.

Despite these relationships, correlation does not imply causation. One of the most compelling causal links has been that of shared familial factors influencing both N and MD. This would predict higher N in the relatives of subjects with MD who themselves have never had a depressive episode. Several studies have demonstrated that the healthy relatives of depressed probands had higher N scores than healthy relatives of controls (Wetzel *et al.*, 1980; Krieg *et al.*, 1990; Maier *et al.*, 1992; Lauer *et al.*, 1997). Family studies, however, cannot truly test hypotheses about genetic factors shared between two traits. This is because the covariation of traits can just as well be explained by common environmental factors that are also shared by them (Neale and Cardon, 1992). These factors may include prenatal or perinatal events, nutrition, infection, education, social class, and parenting factors. Twin studies, on the other hand, are well suited to differentiating

genetic from common environmental factors influencing single traits or the covariation between traits. In two twin studies, the covariation between N and MD was largely due to additive genetic effects common to both (Jardine *et al.*, 1984; Kendler *et al.*, 1993b; Fanous *et al.*, 2002). This supports the notion that N and the liability to MD are influenced by many of the same allelic variants.

Twin studies use as their raw materials only the correlations for traits, or for the liability to illness, within twin pairs. Genetic effects are inferred from differences in these correlations between monozygotic twin pairs, who share all their genes, and dizygotic pairs, who on average share half their genes (Neale and Cardon, 1992). A genetic relationship between two phenotypes is inferred from the pattern of cross-twin, cross-trait correlations. These are the correlation between one trait in the first member of a twin pair and the other trait in the second member of the pair. If the cross-twin, cross-trait correlation is significantly higher in MZ than DZ twins, a genetic relationship between the two traits is supported (Neale and Cardon, 1992). Twin correlations, however, are themselves the products of the aggregate effects of many genes, and contain no information about how many and which specific genes are responsible.

Genetic linkage studies can not only provide direct evidence of the presence of genetic factors underlying traits or illnesses, but can also implicate specific chromosomal regions. In complex behavioral phenotypes, this method has been validated by the subsequent identification and replication of specific susceptibility genes within genomic regions that were originally linked to schizophrenia, such as chromosomes 6p and 8p (Harrison and Owen, 2003). To date, very few genome-wide linkage scans have been performed in either N or MD, although MD is often a part of broad phenotypes used in genetic analyses of bipolar disorder. A recent genome scan using extremely discordant and concordant sibling pairs identified loci linked to N on chromosomes 1q, 4q, 7p, 12q, and 13q with genome wide significance (Fullerton *et al.*, 2003). Nurnberger *et al.* (2001) reported linkage to a region on chromosome 1q, overlapping substantially with the region linked to N (Fullerton *et al.*, 2003), of a phenotype characterized as the presence of either alcoholism or MD (Nurnberger *et al.*, 2001). Abkevich *et al.* (2003) recently reported significant linkage, in males only, of MD to a locus on 12q22-q23 overlapping with the 12q linkage to N. Although the overlap of these results are encouraging, it will be necessary to use more rigorous methods to test for significant similarity in evidence of

genetic linkage to N and MD. Evidence could also be provided if greater statistical power to detect linkage is obtained if N and MD are analyzed jointly in the same sample.

Nevertheless, similarities in genetic linkage peaks cannot provide absolute proof that the same gene is involved in two different traits for three reasons. First, there is considerable stochastic variation in the location of a linked region (Roberts *et al.*, 1999). Second, multiple genes can occur in the same linked region. Third, linkage operates at the level of the family. Therefore, not all affected *individuals* in linked families have necessarily inherited the mutation in the gene responsible for the linkage. This would be especially true in more common diseases. It will therefore ultimately be necessary to demonstrate association between both N and MD and the same susceptibility gene(s).

Most association studies of MD have focused on genes involved in the serotonergic system. Associations between serotonergic genes and affective disorder have face validity based on evidence from several domains linking serotonin with depression. This includes a reduced number of platelet serotonin binding sites (Ellis and Salmond, 1994), blunted prolactin response to L-tryptophan and fenfluramine (Heninger *et al.*, 1984; Siever *et al.*, 1984), and increased density of serotonin receptors in the frontal lobes of suicide victims or depressed patients (Arora and Meltzer, 1989; Arango *et al.*, 1990; D'haenen *et al.*, 1992), as well as depressive mood induced by depletion of tryptophan (Delgado *et al.*, 1994). Genes in serotonergic pathways are therefore natural candidates for association studies of N. The vast majority of these studies have been of a length polymorphism in the serotonin transporter or 5-HTTLPR. Four large-scale studies reported associations between high N and the short allele (Murakami *et al.*, 1999; Greenberg *et al.*, 2000; Melke *et al.*, 2001; Sen *et al.*, 2004), while three did not (Gelernter *et al.*, 1998; Jorm *et al.*, 1998; Flory *et al.*, 1999). The data from association studies between this polymorphism and MD have also been equivocal, as in a recent meta-analysis of European studies in which no significant effect was found (Mendlewicz *et al.*, 2004).

SCHIZOTYPY AND SCHIZOPHRENIA

Writers from a variety of theoretical perspectives have noted that relatives of schizophrenic patients frequently have odd personalities (reviewed by Kendler, 1985). Some of the traits seen in these individuals are attenu-

ated forms of schizophrenic symptoms, and include odd speech, magical thinking, illusions, social isolation, and ideas of reference. Several of these traits correctly differentiated the relatives of schizophrenics from the relatives of controls in the Copenhagen sample of the Danish Adoption Study of Schizophrenia (Kety *et al.*, 1975), and were subsequently incorporated into DSM-III criteria for Schizotypal Personality Disorder (Spitzer *et al.*, 1979).

The term schizotypy was originally coined by Rado (1953), who intended it to refer to personality traits in individuals who carried high-risk genotypes for schizophrenia, but did not manifest cardinal features of the illness. This remains an apt definition with heuristic value, as it is important not only to determine etiological continuities between schizotypy and schizophrenia, but discontinuities as well in understanding the genetic architecture of both conditions. For example, it has been suggested that biological endophenotypes that are shared between schizophrenia and schizotypy are more specific indicators of underlying genetic factors, while those specific to schizophrenia may index environmental factors (Cannon *et al.*, 2002). If this is true, it could aid in identifying susceptibility genes for schizophrenia, as schizotypal traits may lay closer in the causal pathways leading from gene expression to psychotic illness without the complexity of the illness itself that is introduced by phenocopies, reduced penetrance, etc.

The most basic issue to address in establishing a genetic relationship between schizotypy and schizophrenia is whether the family members of schizophrenics have higher levels of schizotypy than the relatives of controls. Several studies have reported a higher risk of schizotypal personality disorder (SPD) in the first-degree relatives of schizophrenics (Baron *et al.*, 1985; Levinson and Mowry, 1991; Kendler *et al.*, 1993a). Moreover, the presence of SPD can differentiate the offspring of schizophrenic mothers from the offspring of controls (Parnas *et al.*, 1993; Erlenmeyer-Kimling *et al.*, 1995). A genetic etiology common to both is supported by an increase risk of SPD in adoptees with biological mothers with schizophrenia compared to adoptees with low risk biological mothers, as reported in a recent Finnish adoption study (Tienari *et al.*, 2003). However, we are not aware of any studies examining the prevalence of SPD in the monozygotic co-twins of schizophrenic probands compared to their dizygotic co-twins. If the prevalence in MZ's were significantly higher, this would augment available evidence suggesting that the familial relationship between schizotypy and schizophrenia is in fact genetic.

Using factor analysis, the clinical features of SPD can

be decomposed into several dimensions, the most salient of which qualitatively resemble positive symptoms (e.g., magical thinking and illusions) and negative symptoms (e.g., social isolation and odd speech) (Kendler *et al.*, 1995a; Gruzelier and Doig, 1996; Nuechterlein *et al.*, 2002). Another approach to studying the relationship between schizophrenia and personality has been to use these dimensions instead of operationalized diagnostic criteria (such as those for SPD) as the personality phenotype of interest. This could lead to increased power, as individuals carrying no personality disorder diagnosis would be available for analysis. High levels of these traits, even in individuals that do not meet criteria for SPD, predict schizophrenia and other psychotic disorders in relatives (Kendler *et al.*, 1995a).

These dimensions are not only etiologically related to schizophrenia susceptibility in general, but are also likely to be influenced by the same genetic factors that influence corresponding dimensions of schizophrenic psychopathology. In a population-based family study from Ireland, positive symptoms in psychotic probands predicted positive schizotypal symptoms in non-psychotic relatives, while negative symptoms predicted negative schizotypal symptoms in relatives (Fanous *et al.*, 2001). This was evidence of the etiological continuity of the clinical features of schizophrenia across the line of demarcation between psychotic and non-psychotic subjects and further validates the dimensions of schizotypy. Several population-based twin studies have demonstrated that these dimensions are not only familial, but also substantially heritable (Hay *et al.*, 2001; MacDonald *et al.*, 2001; Linney *et al.*, 2003). These studies again provide no information, however, about specific genomic regions.

Examining the overlap of specific genomic regions that are linked to both schizophrenia and schizotypy would provide more substantial evidence that these traits represent the expression of common genes. This could also identify genomic regions where fine mapping and association studies of schizophrenia susceptibility genes would benefit from jointly including personality and other traits in non-psychotic individuals. We recently performed a genome-wide scan of schizotypy in the non-psychotic members of 270 Irish high-density schizophrenia families. No genomic regions were suggestively linked using criteria set forth by Lander and Kruglyak (1995). This does not, however, preclude the presence of small but true genetic effects. Nevertheless, the LOD scores observed were highly significantly correlated, genome-wide, with LOD scores achieved in a genome scan of narrowly defined

schizophrenia (Fanous *et al.*, unpublished data). Consistent with this was a linkage study of 10 moderately large Canadian schizophrenia families (Brzustowicz *et al.*, 1997). In this study, the traditional linkage method using a categorical phenotype resulted in no significant evidence of linkage. However, using a quantitative trait based in the positive subscale of the Positive and Negative Syndrome Scale, in which both affected and unaffected relatives were coded, did provide significant evidence. This suggests that personality-based phenotypes in non-psychotic individuals are influenced by susceptibility alleles for schizophrenia.

Very few genetic association studies have been performed in schizotypy. This is perhaps because attention is focused primarily on schizophrenia and identifying susceptibility genes for it. However, if greater statistical power is to be achieved, it will be important to explore the potential role of schizotypy in non-psychotic individuals. An important premise of the utility of schizotypy is that schizophrenia susceptibility genes also influence schizotypy. In a Greek sample, the val allele of catechol-*O*-methyltransferase (COMT) was significantly overrepresented in individuals with high levels of self-reported schizotypy (Avramopoulos *et al.*, 2002). This gene has been associated with schizophrenia in several samples (Shifman *et al.*, 2002; Glatt *et al.*, 2003; Wonodi *et al.*, 2003). However, in the ISHDSF, in which both DTNBP1 (Straub *et al.*, 2002) and COMT (Chen *et al.*, unpublished results) are associated with schizophrenia, neither of these genes was associated with schizotypy (Fanous *et al.*, unpublished results). Taken together with the results of the genomewide correlation in LOD scores, this suggests that heretofore unidentified schizophrenia susceptibility genes in this sample also influence personality in non-psychotic relatives. It will be important to test whether other newly identified putative susceptibility genes such as neuregulin-1, G-72, D-aminoacid oxidase (DAAO), regulator of G-protein signalling-4 (RGS4), and proline d-hydrogenase (PRODH2) influence schizotypal features in non-psychotic individuals (Harrison and Owen, 2003).

CONCLUSIONS

At the present time there is a substantial body of evidence, from a variety of research perspectives, that both personality and the liability to psychiatric illness are influenced by variation in the same genes. Most of this evidence comes from indirect methods, such as family and twin studies. For N and MD, most of this indirect evidence comes mostly from twin studies. For

schizotypy and schizophrenia, the most compelling evidence comes from adoption studies. Genetic linkage studies of N are in their infancy at this time, with only one published genome scan (Fullerton *et al.*, 2003). The overlap of the results of this study with those of two linkage studies of major depression (Nurnberger *et al.*, 2001; Abkevich *et al.*, 2003) is encouraging, but must be replicated. To date, there are no published genome scans of schizotypy, however, while there is only one published association study of schizotypy and a susceptibility gene for schizophrenia (Avramopoulos *et al.*, 2002).

Future studies should rigorously examine the overlap of genetic linkage results between genome scans of N and MD, and genome scans of schizotypy and schizophrenia. Furthermore, when strongly supported putative susceptibility genes for MD are available, it will be necessary to test their effects on N. This is currently possible with schizotypy but has only begun. It will also be important to jointly use N and schizotypy in joint linkage analyses with MD and schizophrenia, respectively. If greater statistical power is achieved, this could pave the way for the use of linkage, followed by association studies, of personality in population-based samples to detect and identify genes for psychiatric illness. This could have substantially greater statistical power than current methods. However, much work remains to be done to validate this approach.

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