Heritability and Familiality of Temperament and Character Dimensions in Korean Families with Schizophrenic Linkage Disequilibrium

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Objective: Categorical syndromes such as schizophrenia may represent complexes of many continuous psychological structural phenotypes along several dimensions of personality development/degeneration. The present study investigated the heritability and familiality of personality dimensions in Korean families with schizophrenic linkage disequilibrium (LD).
Methods: We recruited 179 probands (with schizophrenia) as well as, whenever possible, their parents and siblings. We used the Temperament and Character Inventory (TCI) to measure personality and symptomatic dimensions. The heritability of personality dimensions in a total of 472 family members was estimated using Sequential Oligogenic Linkage Analysis Routines (SOLAR). To measure familiality, we compared the personality dimensions of family members with those of 336 healthy unrelated controls using analysis of variance (ANOVA) analysis.
Results: Three of the seven TCI variables were significantly heritable and were included in subsequent analyses. The three groups (control, unaffected first-degree relative, case) were found to significantly differ from one another, with the expected order of average group scores, for all heritable dimensions.
Conclusion: Despite several study limitations with respect to family recruitment and phenotyping, our results show that aberrations in several personality dimensions related to genetic-environment coactions or interactions may underlie the complexity of the schizophrenic syndrome.

KEY WORDS: Heritability; Familiality; Personality; Dimension; Schizophrenia.

INTRODUCTION

Schizophrenia is the most devastating mental illness and can lead to deterioration in the social and occupational functioning of affected individuals,[1,2] resulting in a significant cost to society.[3,4] A wide range of studies suggest a genetic component to the etiology of this disorder.[5] Although family, twin, and adoption studies have provided strong evidence that genetic variation plays a major role in the etiology of schizophrenia, susceptibility genes have proven difficult to identify in a definitive manner.

A substantial number of researchers in the domain of neuroscience are devoted to elucidating schizophrenia's causes, particularly with respect to basic genetics. How-ever, the mystery posed by this disorder is consistent with the mystery posed by the brain in general, and advances in understanding schizophrenia and its causes have been meager relative to the amount of research effort that has been devoted to the problem. A recent study conducted with a large and heterogeneous sample of subjects of European ancestry proved discouraging, suggesting that 14 genes that were previously believed, based on replicable results, to contribute to the susceptibility to schizophrenia, may in fact play little causal role in the disease.[6]

However, much work remains at both the population and molecular levels before genes and their connection to schizophrenia can be dismissed. Many researchers have suggested that alternative methods of phenotyping should be explored. It is very clear that there are limitations to categorical phenotypes, such as those in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) system. Numerous researchers are exploring comparable quantitative endophenotypes as alternatives to classical qualitative phenotypes to represent schizophrenia.

Mode-of-inheritance studies have suggested that multiple genes are likely involved in the etiology of schizophrenia. Given that the effect of any single gene is generally modest for this disorder, we speculate that it may be more productive to identify the clinical features that tag subtypes that are quite genetically homogeneous, thereby facilitating gene identification. Clinical subtyping has been an effective method for determining the etiology of other illnesses, such as Alzheimer's disease and breast cancer; in these cases, families with early onset illness led researchers to the identification of disease genes.[7,8]

Several clinical features have been shown to augment evidence of a genetic linkage to chromosomal regions or an association with gene variants. Comorbid panic disorder[9] and bipolar II disorder[10] appear to enhance linkage to distinct regions on chromosome 18q. In two datasets, psychotic features showed linkage to chromosome 13q,[11,12] and early age at onset showed linkage to chromosome 21q22 in two cohorts. It has been reported that mania at onset enhances linkage to chromosome 16p, and a linkage to chromosome 2 was shown to be associated with attempted suicide in bipolar disorder.[13] Psychotic features, mood-incongruent psychotic features, and persecutory delusions in bipolar disorder have strengthened evidence for a genetic association with dysbindin (DTNBP1), neuregulin (NRG1), and D-amino acid oxidase activator (DAOA, G72).[14] These early successes suggest that clinical phenomenology can help to define more genetically homogenous forms of schizophrenia.

The choice of features studied in schizophrenia genetics has been guided largely by clinical experience. Features that show familial aggregation may be particularly promising[15] and, as mentioned previously, most of the features that enhance linkage or association signals are indeed familial. However, only a minority of the myriad clinical features of schizophrenia have been studied.

The study of clinical features has been limited by the time-consuming process of gathering and assembling relevant clinical data in cohorts of sufficient size. Large-scale genetics efforts have yielded the human genome sequence and, more recently, the HapMap, which catalogues the common patterns found in human sequence variation. The authors of the HapMap paper called for comparable large-scale efforts in the phenotypic arena. A similar concept, the "Human Phenome Project," was advanced by Freimer and Sabatti,[16] who advocated for the development of an international effort to create phenomic databases in the form of comprehensive assemblages of systematically collected phenotypic information to aid in the identification of disease genes. In this regard, the Autism Phenome Project has begun the prospective compilation of comprehensive phenotypic data with the aim of parsing genetic heterogeneity in autism,[17] and the Epilepsy Phenome-Genome Project was initiated to accomplish similar goals (http://65.175.48.5/epgp/index.htm). The aforementioned study to establish a Bipolar Disorder Phenome Database could be extended to establish a similar Korean Schizophrenia Phenome Database. To our knowledge, no such databases currently exist for schizophrenia.

One possible causal mechanism for schizophrenia may be the presence of genetic aberrations in psychological dimensions, which can be viewed as sub(endo)phenotypes. Categorical syndromes, such as schizophrenia, may be complexes of many continuous phenotypes for mental structures that exist along several dimensions of personality development/degeneration. Quantitative endophenotypes are needed to better understand the pathogenesis of schizophrenia. This concept was reflected in the recent publication of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), which included the category *schizophrenia spectrum and other psychotic disorders*.

Traditionally, personality has been regarded as the basis for psychiatric symptoms, as reflected in previous DSM versions. This notion is currently changing, with this shift indicated in the new DSM-5, which no longer includes axis II diagnoses as the bases of axis I psychiatric symptoms. Psychiatric diagnosis faces numerous challenges in the current era, in which the brain's complexity is acknowledged but not well understood. The existing categorical phenotypic boundaries have become more ambiguous. Personality is currently regarded as the mental structure giving rise to psychiatric symptomatology; in fact, the various personality disorders are closely related to specific psychiatric diagnoses. Hence, in the current paradigm shift involving psychiatric diagnoses, personality dimensions may be continuous with psychological dimensions. To clarify this relationship, we aimed to explore the heritability of temperament and character dimensions in schizophrenic families.[18-21]

Of particular relevance is the fact that many models suggest that personality dimensions are heritable and influence the genetic loading of schizophrenia. Personality traits are under genetic influence, and the heritability of personality reaches levels of 30% to 60%. Personality exhibits a high familial tendency in the general population and in various psychiatric disorders, including major depression, alcohol dependence, and bulimia.[22-26] In addi-

tion to neuropsychological or neurobiological characteristics, the biogenetic components of personality may also be considered endophenotypes of schizophrenia if they can be found both in schizophrenic probands and their first-degree relatives.[27]

The psychobiological model of personality suggests that an individual's temperament is heritable and regulated by neurotransmission linked to the pathophysiology of schizophrenia.[28,29] More recently, there has been evidence to suggest that dimensions of character are also heritable and may influence the risk for schizotypy.[30] Despite conflicting results, the temperament of harm avoidance has been identified as subject to genetic loading. The present study aimed to investigate the heritability and familiality of dimensions of temperament and character in Korean families with psychotic members.

METHODS

We recruited 179 probands (with schizophrenia) as well as, whenever possible, their parents and siblings. To identify the best possible diagnosis, we used medical records and Korean versions of the Diagnostic Interview for Genetic Studies (DIGS) and the Family Interview for Genetic Studies (FIGS). We also used the Temperament and Character Inventory (TCI) to measure various dimensions of temperament and character. The TCI is an inventory for evaluating distinct personality traits. It is closely related to the Tridimensional Personality Questionnaire (TPQ) and also derives elements from Zuckerman's and Eysenck's Dimensions of Personality. The TCI addresses seven dimensions of personality traits, with four so-called "temperaments" (novelty seeking, harm avoidance, reward dependence, and persistence) and three "characters" (self-directedness, cooperativeness, and self-transcendence).[31]

Sample Selection

All subjects were recruited in accordance with the principles of the Declaration of Helsinki and with approval from the Institutional Review Boards of Pusan National University Hospital. Probands were recruited independently from Pusan National University Hospital (Busan, Korea). All probands had a disease onset of no later than age 40 years, a history of at least one psychiatric hospitalization, a discharge diagnosis of schizophrenia, and a Korean surname. Parents and first-degree relatives of probands were also recruited wherever possible to allow for the determination of genetic phase and for family-based linkage disequilibrium analyses; if additional relatives

with psychotic disorders were identified, efforts were made to recruit these relatives as well. Each subject was interviewed by a trained bilingual psychiatrist, who was blind to the history of the subject, using the Korean version of the DIGS.[32] Medical records (inpatient and outpatient) were summarized. An interview with a close relative, using a Korean version of the FIGS was also completed for each subject.[33] We analyzed data from 179 probands and their available family members. All affected subjects (i.e., those given formal psychiatric diagnoses in the present study) within each family were diagnosed using a best-estimate diagnostic process, as described by Walss-Bass et al.[34] The process yields a lifetime consensus diagnosis or diagnoses using the DSM-IV. Data from 472 subjects from 179 families were analyzed in this paper; 179 probands had Axis I disorders, as determined by consensus DSM-IV diagnoses for schizophrenia.

A total of 179 subjects had a history of psychosis, operationalized in the present study as the presence of at least one of the following symptoms at some point in the subject's lifetime: hallucinations, delusions, grossly disorganized thought processes, or grossly disorganized behavior. This definition of psychosis corresponds to four of the five symptoms and signs listed under Criteria A of the DSM-IV definition of schizophrenia. We also considered a history of "negative symptoms" (abulia, alogia, avolition), also listed under Criteria A of the DSM-IV definition of schizophrenia, as sufficient for a diagnosis of psychosis. For each subject, the best estimators also diagnosed whether manic syndromes or episodes had been present during the course of the disorder. The distinction between schizophrenia and schizoaffective disorder followed the criteria of the DSM-IV, as operationalized by Walss-Bass et al.[34]

Our study included 336 Korean control subjects who were psychiatrically normal and belonged to the age groups specified in the sample. Subjects with potentially biasing conditions were excluded from the study. Subjects were also excluded if they had been receiving corticoid, estrogen, androgen, or T3 (triiodothyronine)-T4 (thyroxine) therapy or diphenylhydantoin, vitamin D, bisphosphonate, calcitonin, fluoride, thiazide diuretics, or barbiturates for more than 6 months, as all these drugs may yield biasing effects. Because it was impossible to obtain a population-based register for technical and legal reasons, control subjects meeting the inclusion/exclusion criteria were identified from among volunteers (students and hospital workers) at the hospital.

Statistical Analysis

We estimated the heritability of the various temperament and character dimensions measured in the 472 family members using Sequential Oligogenic Linkage Analysis Routines (SOLAR). To determine familiality, we compared the temperament and character dimensions of family members with those of 336 healthy unrelated controls using analysis of variance (ANOVA) (SPSS software, version 11.5; SPSS Inc., Chicago, IL, USA). We also used SOLAR to investigate correlations between genetic/environmental variables and the symptoms associated with significant temperament and character dimensions, with the significance level set at 5%.

RESULTS

Heritability

Three of the seven TCI variables (harm avoidance, cooperativeness, self-transcendence) were significantly heritable and were included in subsequent analyses. Heritability was the highest for self-transcendence (0.34, p=0.0006), intermediate for harm avoidance (0.28, p=0.006), and the lowest for cooperativeness (0.24, p=0.01). The remaining four TCI variables (novelty seeking, reward dependence, persistence, self-directedness) were not significantly heritable and were therefore excluded from subsequent analyses. Heritability was nominally high for reward dependence (0.15) and self-directedness (0.13) (Table 1).

Familial Aggregation

The control group, the unaffected group of first-degree relatives, and the case groups differed significantly, with the expected order of average group scores, for most heritable dimensions. High harm avoidance statistically differentiated the case group from the first-degree-relative and control groups (p=0.000). Low self-transcendence differentiated the control group from the case and the first-degree relative groups (p=0.000). Low cooperativeness differentiated the case group from the first-degree-relative group and the first-degree-relative group from the control group (p=0.000) (Table 2).

Genetic/Environmental Correlations

Genetic/environmental correlations with the schizophrenic phenotype in terms of temperament and character dimensions are displayed in Table 3. There were no genetic correlations with the schizophrenic phenotype for any temperament and character dimensions. Environmental correlations were suggested for harm avoidance (p=0.0000272) and cooperativeness (p=0.0001577).

Table 1. Heritability (H2r) of temperament and character measures

Personality dimension	H2r (SE)	p value
Novelty seeking	0.07 (0.11)	0.25
Harm avoidance	0.28 (0.12)	0.006
Reward dependence	0.15 (0.12)	0.10
Persistence	0.08 (0.12)	0.25
Self directiveness	0.13 (0.14)	0.17
Cooperativeness	0.24 (0.11)	0.01
Self transcendence	0.34 (0.11)	0.0006

SE, standard error.

Table 2. Familial aggregation of temperament and character measures

Personality dimension	Control	Unaffected 1st degree relative	Case	p value
Harm avoidance	18.1±6.0	18.4±5.8	22.5±6.3*,†	0.000
Cooperativenes	31.6±5.8	29.5±5.6*	26.7±6.9*,†	0.000
Self transcendence	10.3±5.2	12.1±5.9*	12.6±6.7*	0.000

Values are presented as mean±standard deviation.
*Compared to controls by Scheffe test; †compared to 1st degree relatives by Scheffe test.

Table 3. Bivariate analysis between affection status and temperament and character measures

Personality dimension	Schizophrenic phenotype				
	Genetic correlation			Environmental correlation	
	ρg (SE)	p (0)	p (1 or −1)	ρe (SE)	p
Harm avoidance	0.9233085 (NC)	0.9374519	1	0.3871830 (0.9984003)	0.0000272
Cooperativeness	−1 (NC)	0.5908300	NC	−0.3460180 (0.1108247)	0.0001577
Self transcendence	−0.1366977 (NC)	1	0.5	0.1420517 (0.0806877)	0.0568722

ρg, genetic correlation coefficient; SE, standard error; ρe, environmental correlation coefficient; NC, not computable.

DISCUSSION

The schizophrenia phenome database is designed to complement the large body of available genetic data. The objective of the database is to accelerate the discovery of genes that contribute to schizophrenia, a common and often disabling disease. Providing public access is key to making the data valuable to the community. Value could be added to the schizophrenia phenome database by incorporating data from additional studies. It would also be useful to combine these clinical data with physiological evidence from studies involving brain imaging, evoked potentials, and neuropsychological data as well as with data from studies focusing specifically on the role of the hypothalamic-pituitary-adrenal axis. Further steps could be added to the existing dataset, including data reduction through techniques such as factor analysis. These factors could then be tested for degree of familiality, and the factor scores could be used as phenotypes for genetic study.

It is important but very difficult to recruit sufficient numbers of control subjects who are carefully matched for age and sex. One limitation of the present study is that the recruited normal controls may be excessively normal samples, despite the fact that we recruited from general populations. We could not implement for recruiting age/sex matched controls in the current study due to the numerous limitations involved in recruitment. We are currently designing a recruiting method to achieve matched controls. However, some researchers have expressed the opinion that it is legitimate to conduct genetic studies without age/sex adjustment in spite of possible population stratification by covariates or confounders.

Our results suggest that aberrations in several dimensions pertaining to temperament and character that are attributable to genetic-environment coactions or interactions may underlie the complexity of the schizophrenic syndrome. Three of the seven temperament and character variables (harm avoidance, cooperativeness, and self-transcendence) were significantly heritable and were included in subsequent analyses. One endophenotype (high harm avoidance) was able to differentiate the probands from the first-degree relatives and normal controls. A second endophenotype (low self-transcendence) differentiated the controls from the probands and the first-degree relatives. A third endophenotype (cooperativeness) differentiated among all three of the groups, exhibiting the expected order of average group scores. There were no genetic correlations with the schizophrenic phenotype for any dimension of temperament or character. An environmental correlation was suggested for harm avoidance and cooperativeness.

This study replicates previous results that found some personality dimensions to be heritable and familial in families with schizophrenia and offers some promising endophenotypic markers for schizophrenia, although several limitations involving the recruitment of families and phenotyping should be acknowledged.[35,36] These endophenotypic markers will serve as important coefficients in solving the mysterious equations that determine schizophrenia. However, the usefulness of most types of positional genetic variations and environmental factors is in doubt as far as their potential to serve as loaded variables in equations describing the causes of the schizophrenic syndrome.

We may speculate that high degrees of harm avoidance plausibly result in negative symptoms because some schizophrenic patients show a tendency towards abulia, alogia, and avolition. With respect to high self-transcendence, this dimension may promote abundant spirituality and creativity; however, at its pathological extreme, excessive self-transcendence may leave patients isolated in an autistic and closed world, leading to psychotic fantasies. Psychotic patients often eventually exhibit low cooperativeness and effectiveness in social settings. They frequently lose their jobs due to such ineffectiveness in social contexts, which results in their overall deterioration.[37]

Most importantly, future genome-wide linkage and association studies with extensive pedigrees are required. Once such studies have been conducted, it will be possible to perform Family-Based Association Study (FBAT) analyses in families with subtyped schizophrenic probands with respect to personality, working memory, and cognition in addition to the quantitative dimensions described in the present study. Such fine mapping analyses will facilitate the search for candidate genes involved in schizophrenia, a Goliath that currently confronts psychiatrists.

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