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Transmissibility and familiality of NEO personality dimensions in a sample of Korean families with schizophrenia

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Abstract

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 Neuroticism-Extraversion-Openness to experience (NEO) personality dimensions in Korean families with schizophrenic linkage disequilibrium (LD).

We have recruited 204 probands (with schizophrenia) with their parents and siblings whenever possible. We have used NEO questionnaires for measuring personality and symptomatic dimensions. Heritabilities of personality dimensions in total 543 family members were estimated using Sequential Oligogenic Linkage Analysis Routines (SOLAR). Personality dimensions in total family members were compared with those in 307 healthy unrelated controls for measuring the familialities using ANOVA analysis.

Four of the 5 NEO variables were significantly heritable and were included in the subsequent analyses. The 3 groups (control, unaffected first-degree relative, case) were found to be significantly different and with the expected order of average group scores for all heritable dimensions.

Our results show that the aberrations in several personality dimensions could form the complexity of schizophrenic syndrome as a result of genetic–environment coactions or interactions in spite of some limitations (recruited family, phenotyping).

Abbreviations: H2r = heritability, LD = linkage disequilibrium, SOLAR = Sequential Oligogenic Linkage Analysis Routines.

Keywords: dimension, familiality, heritability, personality, schizophrenia

1. Introduction

Schizophrenia is a devastating mental illness that can lead to the deterioration of social and occupational functioning in affected individuals,[1,2] resulting in major costs to society.[3,4] A wide range of studies suggested a genetic schizophrenia component.[5] Thus, a substantial number of studies have been devoted to elucidating the causes of schizophrenia, particularly in relation to basic genetics. However, the complexity of this disorder is consistent with the complexity of the brain in general. Indeed, the advances made so far in understanding schizophrenia and its causes have been meager compared to the amount of research performed to address this illness. A recent study conducted on a large and heterogeneous sample of participants of European ancestry provided discouraging results, 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, further research remains necessary at both the population and molecular levels, before these genes and their implication in schizophrenia can be dismissed. Furthermore, alternative disease phenotypes should be searched. Since there are limitations in categorical phenotypes such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) system, many researchers are exploring comparable quantitative endophenotypes as alternatives to the classical qualitative phenotype that represents schizophrenia.

Mode-of-inheritance studies have suggested the likely involvement of multiple genes in the etiology of schizophrenia. Given that the effect of any single gene is generally modest in schizophrenia, 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 disease and breast cancer. In these cases, families with early onset of the disease led researchers to the identification of associated genes.[7,8]

Several clinical features have been shown to increase the evidence of genetic linkage to chromosomal regions or association with gene variants. Comorbid panic disorder and bipolar II disorder appear to enhance linkage to distinct regions on chromosome 18q.[9,10] In 2 datasets, psychotic features were

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linked to chromosome 13q, while early age at onset was linked to chromosome 21q22 in 2 cohorts.[11,12] It has been reported that mania at onset enhances the linkage to chromosome 16p, while linkage to chromosome 2 was associated with attempted suicide in bipolar disorder.[13] In bipolar disorder, psychotic features, mood-incongruent psychotic features, and persecutory delusions have been associated with dysbindin (DTNBP1), neuregulin (NRG1), and G72 (DAOA), respectively.[14] Based on these early findings, it is suggested that clinical phenomenology can help define the 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] Indeed, as mentioned previously, most of the features that enhance linkage or association signals are familial. However, only a minority of the myriad clinical features of schizophrenia has been studied, mainly because of the time-consuming process of gathering and assembling relevant clinical data in cohorts of sufficient size. Large-scale genetic 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 initiated 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 enable 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] The Epilepsy Phenome–Genome Project was initiated to accomplish similar goals (http://65.175.48.5/epgp/index.htm). Since no such databases currently exist for schizophrenia, we suggest that the aforementioned study on establishing a Bipolar Disorder Phenome Database could be extended to establish a similar Korean Schizophrenia Phenome Database.

One possible mechanism underlying schizophrenia may be the genetic aberrations in mental dimensions as subphenotypes (endophenotypes). A categorical syndrome like schizophrenia may be a complex of many continuous mental structure phenotypes including several personality development/degeneration dimensions. Quantitative endophenotypes are needed to better understand the pathogenesis of schizophrenia. This concept was reflected in a recent publication of DSM-5 through the 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 being indicated in the new DSM-5, which no longer includes axis II diagnoses as the basis 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; indeed, the various personality disorders are closely related to specific psychiatric diagnoses. Hence, in the current paradigm shift involving psychiatric diagnoses, personality dimensions, and psychological dimensions may be continuous.[18–22]

In particular, many models suggested that personality dimensions are heritable and influence the genetic loading of schizophrenia. Personality traits can be influenced by the genetics of the individual, and the heritability of personality reaches 33% to 65%. Personality has a high familial tendency in the general population, as well as in the cases of individuals with various psychiatric disorders including major depression, alcohol dependence, and bulimia. In addition to neuropsychological or neurobiological characteristics, the biogenetic components of personality may also be considered as endophenotypes of schizophrenia, if they can be found both in probands with schizophrenia and their first-degree relatives.[23–29] To clarify this relationship, we aimed to explore the heritability and familiarity of Neuroticism-Extraversion-Openness to experience (NEO) personality dimensions in Korean families with schizophrenia.

2. Methods

A total of 204 probands with schizophrenia were recruited, along with their parents and siblings whenever possible. For a better estimation of the diagnosis, we used the medical records and a Korean version of Diagnostic Interview for Genetic Studies (DIGS) and Family Interview for Genetic Studies (FIGS). We also used NEO questionnaires for measuring the personality dimensions (Table 1).

This test complements the NEO Personality Inventory, Revised (NEO PI-R), which is a psychological personality inventory assessment developed by Paul T. Costa Jr. and Robert R. McCrae for adult men and women. The NEO PI-R includes 5 major personality domains (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness), as well as 6 subscales that further define each domain.[30–32]

Table 1

Demographic characteristics of the pedigree members, probands with schizophrenia, unaffected first-degree relatives, and control subjects as recruitment.

	Number of subjects		Age Mean (SD/SEM)		Sex Male N (%)/female N (%)	
Pedigree members						
Probands with schizophrenia	543	204	44.3 (15.8/0.7)	35.0 (11.8/0.8)	255 (47.0)/288 (53.0)	102 (50.0)/102 (50.0)
Unaffected first-degree relatives		339		50.3 (15.2/0.9)		153 (45.1)/186 (54.9)
Control members						
Unrelated subjects	307	307	28.7 (2.9/0.2)	28.7 (2.9/0.2)	159 (51.8)/148 (48.2)	159 (51.8)/148 (48.2)
Statistics	NA		$t=14.6$	$F=242.1$	$\chi^2=1.8$	$\chi^2=3.0$
P			$<.001$	$<.001$	.2	.2

NA = not applicable, SD = standard deviation, SEM = standard error of the mean.

2.1. Sample selection

All participants 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. All probands had a disease onset of no later than age 40, a history of at least one psychiatric hospitalization, a discharge diagnosis of schizophrenia, and a Korean surname. The parents and first-degree relatives of the probands were also recruited wherever possible to allow for the determination of the genetic phase and for family-based linkage disequilibrium (LD) analyses. If additional relatives with psychotic disorders were identified, efforts were made to recruit these relatives as well. Using the Korean version (2.0) of DIGS, each participant was interviewed by a trained bilingual psychiatrist, who was blinded to the participant's history. The inpatient and outpatient medical records were summarized. An interview with a close relative, using the Korean version (2.0) of FIGS was also completed for each participant.[33–35] We used a diagnostic inventory that is specific for genetic studies because we are planning a subsequent genetic analysis including genome-wide association analysis (GWAS) and whole exome sequencing study (NGS) based on the recruited pedigrees and estimated personality endophenotypes. We analyzed data from 204 probands and their available family members. All affected participants (i.e., those given formal psychiatric diagnoses in the present study) within each family were diagnosed using a best-estimate diagnostic process.[36] A "best-estimate" diagnosis is made by expert clinicians on the basis of diagnostic information from direct interview conducted by another clinician plus information from medical records and from reports of family members. Two psychologists independently diagnosed the same participant by applying the best-estimate procedure. The process yields a lifetime consensus diagnosis or diagnoses using the DSM-IV. Data from 543 participants from 204 families were analyzed in this study; 204 probands had axis I disorders, as determined by consensus DSM-IV diagnoses for schizophrenia.

A total of 204 participants 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 participant's lifetime: hallucinations, delusions, grossly disorganized thought processes, or grossly disorganized behavior. This definition of psychosis corresponds to 4 of the 5 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 participant, 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 DSM-IV criteria.[36]

Our study also included 307 Korean control participants who were psychiatrically normal. Participants with potentially biasing conditions were excluded from the study. Participants were also excluded if they had been receiving corticoid, estrogen, androgen, or triiodothyronine (T3)–thyroxine (T4) therapy, or if they received diphenylhydantoin, vitamin D, bisphosphonate, calcitonin, fluoride, thiazide diuretics, or barbiturates for more than 6 months. Because it was impossible to obtain a population-based register for technical and legal reasons, control participants meeting the inclusion/exclusion criteria were recruited from volunteers (students and hospital workers) at the hospital (Fig. 1).

2.2. Statistical analysis

The heritability of personality dimensions was estimated in a total of 543 family members using Sequential Oligogenic Linkage Analysis Routines (SOLAR).[37] The SOLAR is an extensive, flexible software package for genetic variance components analysis, including linkage analysis, quantitative genetic analysis, single-nucleotide polymorphisms (SNP) association analysis (QTN, QTLD, and MGA), and covariate screening. Operations are included for calculation of marker-specific or multipoint identity-by-descent (IBD) matrices in pedigrees of arbitrary size and complexity, and for linkage analysis of multiple quantitative traits and/or discrete traits that may involve multiple loci (oligogenic analysis), dominance effects, household effects, and interactions. Heritability represents the portion of the phenotypic variance accounted for by the total additive genetic variance. Genetic variance is the portion of phenotypic variance due to pedigree relationships rather than environmental factors or error. Indices with stronger covariance between genetically more similar individuals rather than between genetically less similar individuals have higher heritability. Within the SOLAR program, this is assessed by contrasting the observed covariance matrices for a trait with the covariance matrix predicted by kinship. Only NEO variables with significant heritability, corrected for multiple comparison at a 5% false discovery rate (FDR), were included in subsequent analyses. Personality dimensions in all the family members were compared with those in 307 healthy unrelated controls for measuring the familiarities using analysis of variance (ANOVA). Scheffe post hoc test, widely used for considering contrast, was applied instead of Tukey-Kramer of Student–Newman–Keuls tests. Genetic/environmental correlations with symptomatic dimensions for significant personality dimensions aggregated in families were also investigated using SOLAR. Although differences in the NEO measures between unaffected first-degree relatives and controls that rule out effects secondary to disease in the affected individuals are indicative of genetic vulnerability, they could also be due to environmental factors shared by individuals with schizophrenia and their unaffected relatives. To determine whether NEO personality and liability for schizophrenia have common genetic or environmental influences, mixed discrete/continuous trait bivariate analyses were conducted. These analyses decompose phenotypic correlations into genetic (g) and environmental (e) correlations between the 2 traits. If the genetic correlation is significantly different from 0, then the traits are considered to be influenced by the same genetic factors. If the environmental correlation is significantly different from 0, then the traits are considered to be influenced by the same environmental factors. The significance (5% FDR) of these correlations was tested by comparing the natural log (ln) likelihood for 2 restricted models (with g or e constrained to equal 0.0) against the ln likelihood for the model in which these parameters were estimated. Finally, we performed multivariate analyses on those NEO traits that were genetically correlated with schizophrenia to determine whether these traits represent independent risk factors. All statistical analyses were performed using the SPSS system, version 11.5. The significance level required was set at 5%.

3. Results

3.1. Heritability

Four of the 5 NEO variables (extraversion, conscientiousness, neuroticism, openness) were significantly heritable and were

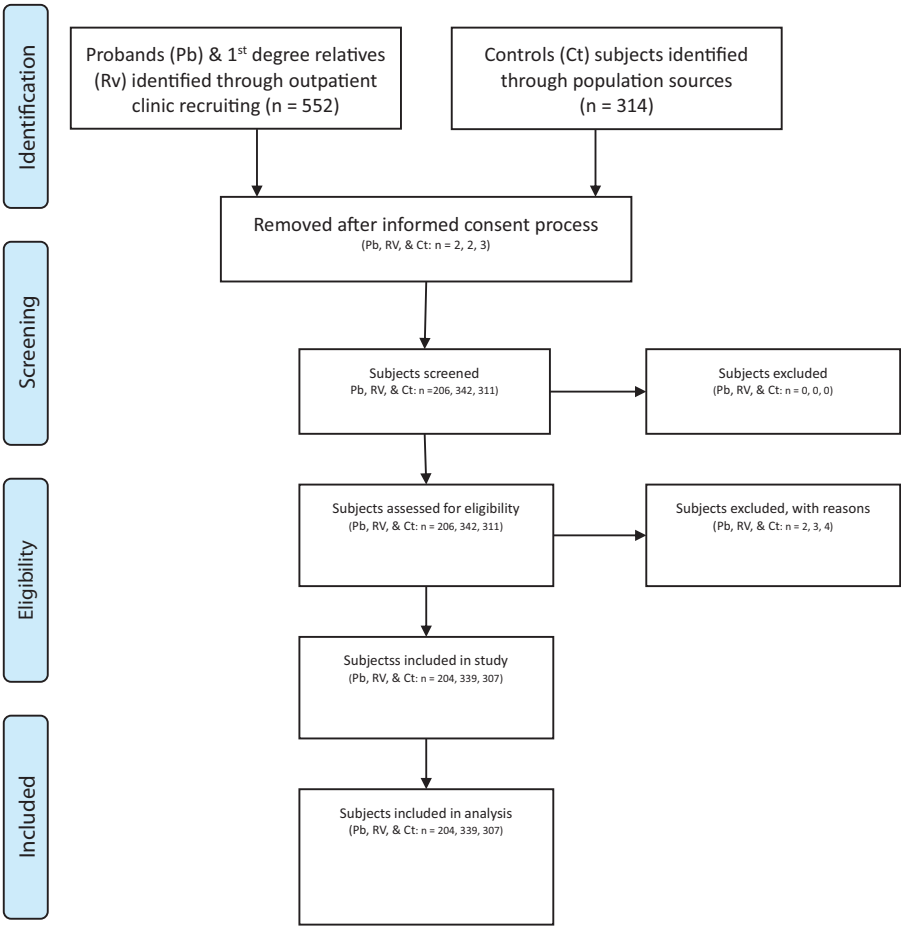

Figure 1. Flowchart for recruitment of the pedigree members, probands with schizophrenia, unaffected first-degree relatives, and control subjects.

included in subsequent analyses. Heritability was the highest for conscientiousness (0.30, $P=.008$) and neuroticism (0.30, $P=.01$), intermediate for openness (0.29, $P=.009$), and lowest for extraversion (0.24, $P=.01$). One NEO variable (agreeableness) was not significantly heritable (0.03, $P=.40$), and was thus excluded from subsequent analyses (Table 2).

3.2. Familial aggregation

The controls, unaffected first-degree relatives, and case groups were significantly different and had the expected order of average group scores for most heritable dimensions. Low extraversion and low conscientiousness differentiated the case group from the first-degree relatives and controls ($P<.001$). High neuroticism and openness differentiated the control group from the first-degree relatives and case group ($P<.001$; Table 3).

Table 2

Heritability (H2r) of NEO personality measures.

Personality dimensions	H2r	H2r (SEM)	*P*
Extraversion	0.24	0.11	.01
Agreeableness	0.03	0.11	.40
Conscientiousness	0.30	0.13	.008
Neuroticism	0.30	0.12	.01
Openness	0.29	0.13	.009

SEM = standard error of the mean.

3.3. Genetic/environmental correlations

The genetic/environmental correlations with the schizophrenic phenotype are displayed in Table 4. There were no genetic correlations with the schizophrenic phenotype for any NEO personality dimensions. In contrast, environmental correlations were suggested for the 4 dimensions.

4. 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. One key to making data valuable to the community is to provide public access. Value could be added to the schizophrenia phenome database by incorporating data from additional studies. It is also worth considering combining these clinical data with physiological data from brain imaging, hypothalamic–pituitary–adrenal axis, evoked potential, and neuropsychological studies. Further steps that could be added to the existing dataset include data reduction through techniques such as factor analysis. These

Table 3

Familial aggregation of personality measures.

Personality dimensions	Control	Unaffected first-degree relative	Case	P
Extraversion	60.2±10.0 (0.6)	60.3±8.7 (0.5)	53.5±10.8*,† (0.8)	<.001
Conscientiousness	67.6±10.1 (0.6)	70.8±10.0* (0.6)	63.0±11.9*,† (0.8)	<.001
Neuroticism	65.4±10.5 (0.6)	62.2±10.4* (0.6)	57.5±12.7*,† (0.9)	<.001
Openness	63.6±8.8 (0.5)	59.0±9.0* (0.5)	55.3±11.6*,† (0.8)	<.001

Values are presented as mean±standard deviation (standard error of the mean).

* Compared to controls by Scheffe test.

† Compared to first-degree relatives by Scheffe test.

Table 4

Bivariate analysis between affection status and personality measures.

	Schizophrenic phenotype			
	Genetic correlation		Environmental correlation	
Personality dimensions	ρg (SEM)	P	ρe (SEM)	P
Extraversion	1 (NC)	.5055186	−0.4100373 (0.9963981)	7.24485e−08
Conscientiousness	−1 (NC)	.8564175	−0.2853066 (0.1055013)	.0029093
Neuroticism	−1 (NC)	.4439460	−0.1944272 (0.0890034)	.0439697
Openness	1 (NC)	.7106446	−0.3386749 (0.2521358)	.0000266

ρe = environmental correlation coefficient, ρg = genetic correlation coefficient, NC = not computable, SEM = standard error of the mean.

factors could then be tested for familiarity, and the factor scores could be used as phenotypes for genetic studies.

Although difficult, it is important to recruit sufficient numbers of control participants who are carefully matched for age and sex. Although they were recruited from the general population, the normal controls in the present study may be excessively normal samples, which is one of the study's limitations. We could not recruit age/sex matched controls in the present study due to the numerous limitations involved in the recruitment process. We are currently designing a recruiting method to enable the acquisition of 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 suggested that aberrations in several dimensions pertaining to NEO personality that are attributable to genetic–environment coactions or interactions may underlie the complexity of schizophrenia. Four of the 5 NEO variables (extraversion, conscientiousness, neuroticism, openness) were significantly heritable and were included in subsequent analyses. Two endophenotypes, namely low extraversion and low conscientiousness, enabled the differentiation of the probands from their first-degree relatives and normal controls. Another 2 endophenotypes, namely neuroticism and openness, differentiated all 3 groups, exhibiting the expected order of average group scores. There were no genetic correlations with the schizophrenic phenotype for any temperament or character dimension. An environmental correlation was suggested for 4 dimensions.

The present findings corroborated previous results indicating that some personality dimensions may be heritable and familial in families with schizophrenia, thus offering promising endophenotypic markers for schizophrenia. However, several limitations involving the recruitment of families and phenotyping should be acknowledged.[38–40] These endophenotypic NEO personality markers will serve as important coefficients in solving the mysterious equations that determine schizophrenia.[41] However, the usefulness of most types of positional genetic variations and environmental factors to serve as loaded variables in equations describing the causes of schizophrenia remains to be clarified.

Low degrees of extraversion may plausibly result in negative symptoms because some patients with schizophrenia show a tendency towards abulia, alogia, and avolition. On the other hand, low conscientiousness may promote abundant impulsivity and violence. At its pathological extreme, low openness may leave patients isolated in an autistic and closed world, leading to psychotic fantasies. Psychotic patients often exhibit eventually low neuroticism in social settings, which reflect the neurosis–psychosis continuum. They frequently lose their jobs due to such ineffectiveness in social contexts, which results in their overall deterioration.

The human psychopathology of psychosis emerges as anxiety, a state of mental disequilibrium. Men become depressed when their anxieties are not resolved. Psychopathologically, psychosis and mania are deviations from reality in which depressed patients fall, and addiction is the final defense beyond psychosis, thereby leading to comorbidity. The comorbidity of psychosis and addiction is very clear from a psychopathologic perspective. Clinically, addictive symptoms are prevalent among patients with schizophrenia and bipolar disorder. The close interrelationship between psyche and soma has been studied. For understanding the mechanisms underlying the psychiatric symptoms, the comorbidity of psychosis and addiction needs to be analyzed genetically from the perspectives of several broad processes, including personality, memory, and cognition. The genetic regulation of these processes may explain the methamphetamine addiction leading to psychosis.[42–46]

Future targeted genotyping, genome-wide linkage, and association studies with extensive pedigrees are required that will help in performing sequencing analyses in families with probands with subtyped schizophrenia in relation 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 challenge that currently confronts psychiatrists.

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