Finding Suitable Phenotypes for Genetic Studies of Schizophrenia: Heritability and Segregation Analysis

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Background: Schizophrenia is a highly heritable and complex disorder. Multiple genes are likely to be involved, complicating genetic research into the etiology of this disorder. Intermediate phenotypes or endophenotypes may facilitate genetic research if they display a simpler mode of transmission than schizophrenia itself, i.e., if they reflect more closely the underlying genetic effects.

Methods: Twenty-five multigenerational families with multiple members affected with schizophrenia (180 subjects) were administered an extensive neuropsychological, psychophysiological, and personality test battery. Familial correlations were calculated to select heritable traits. Subsequent heritability analysis followed by commingling and segregation analysis were performed to unravel the pattern of transmission and to estimate heritability.

Results: Five traits, including sensorimotor gating, openness, verbal fluency, early visual perception, and spatial working memory, showed moderate familial correlations. Heritability estimates for these traits ranged from 37% to 54%. A major gene model resembling dominant transmission was found for both sensorimotor gating and openness. Verbal fluency, early visual perception, and spatial working memory may be accounted for by polygenic, multifactorial, or environmental effects.

Conclusions: Only 2 of 13 candidate endophenotypes showed a simple mode of transmission useful for successful application in molecular genetic research: sensorimotor gating and openness. To our knowledge, this is the first study to investigate the pattern of transmission for these traits.

Key Words: Heritability, inheritance pattern, neurocognition, personality, psychophysiology, quantitative trait, schizophrenia

Although schizophrenia is highly heritable (~80%) (1) gene-finding studies have reported conflicting results (2). This may be due to the likelihood that schizophrenia is caused by multiple genes interacting with each other and with environmental factors, leading to a complex mode of transmission (3,4). To overcome difficulties such as genetic and phenotypic heterogeneity, the use of endophenotypes may be a promising alternative strategy. Endophenotypes may increase power in quantitative gene mapping by their putative simpler mode of transmission, quantitative nature, and potential to identify the unaffected but potentially gene-carrying relatives (5,6). Indeed, several studies reported stronger linkage findings for the endophenotypic trait than for the clinical diagnosis (7–9).

Meta-analyses have reported abnormalities on numerous characteristics of schizophrenia to accumulate among the unaffected relatives of patients with schizophrenia as compared with the general population (10,11), suggesting a potentially shared genetic etiology between the characteristics and schizophrenia. This is supported by an increasing number of studies reporting substantial genetic contributions to (some of) these candidate endophenotypes (12–15). However, heritability estimates do not provide information on the mode of transmission, i.e., whether the trait is influenced by a single major gene, a small set of genes, or complex interactions. Clearly, using endophenotypes with a complex mode of transmission in genetic research may not provide advantages over the schizophrenia phenotype itself. Ideally, endophenotypes show a mode of transmission that may be caused by few major genetic variants and therefore may provide a simpler means to identify schizophrenia-predisposing variants.

Relatively few studies have examined the mode of transmission of a limited number of schizophrenia-related endophenotypes: oculomotor dysfunction (16,17), P50 ratio (18), P300 latency (19), and spatial working memory, verbal declarative memory, and verbal and visual ability (20). Some of these phenotypes have been mapped to specific genetic loci: 6p21-23 (21–23), 15q14 (24,25), 22q11-q12 (26), 4q21, and suggestive evidence to regions on 1q, 2q, 8q, 9p, 10p, and 15q (8). Interestingly, some of these regions may overlap with schizophrenia loci (27). The strategy of linking endophenotypes with a simple mode of transmission to specific genetic loci has thus been successful. We have therefore studied both heritability and mode of transmission of a selected number of promising (additional) endophenotypes. We selected 13 neuropsychological, psychophysiological, and personality candidate endophenotypes based on previous studies in unaffected relatives and high-risk populations, as well as on the basis of reliability, stability, and heritability estimates if available. First, we calculated familial correlations to select potentially heritable traits. Subsequent heritability analysis followed by commingling and segregation analyses were performed to estimate heritability and to unravel the pattern of transmission. Ultimately, endophenotypes showing a clear pattern of inheritance may result in finding new genes and biological pathways involved in schizophrenia.

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Methods and Materials

Participants

Twenty-five multiplex multigenerational pedigrees of Dutch origin were recruited from the base population through a schizophrenia family member association and through an advertisement in a Dutch daily newspaper. Each pedigree comprised at least two members with a schizophrenia or schizoaffective disorder diagnosis based on the Family Interview for Genetic Studies (FIGS) (28), and at least one member's diagnosis was confirmed by interview. Exclusion criteria for patients and family members were: severe medical or neurological illness; history of closed head injury; loss of consciousness longer than 30 minutes; history of alcohol abuse within the last 6 months; diseases of the central nervous system and history of cerebrovascular accidents (CVAs), dementia, or delirium; aged under 16; or IQ under 70. Specific exclusion criteria for separate tests are given in the relevant method sections. For the personality questionnaire, no exclusion criteria applied. Written informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of the University Medical Center (UMC) Utrecht.

Diagnostic Assessment

Each family was screened using the FIGS conducted by telephone with a family member. Patients were diagnosed by DSM-IV criteria based on the Comprehensive Assessment of Symptoms and History (CASH), a semistructured diagnostic interview (29), and by retrieving medical records. A master's level clinician (M.F.A.) conducted the interview and discussed the results with a psychiatrist (J.-P.S.). Lifetime experienced psychiatric episodes in relatives were assessed (by M.F.A.) using the Mini-International Neuropsychiatric Interview-Structured (MINI-Plus), a clinical interview for DSM-IV Axis I disorders (30).

Cognitive Measures

An extensive neuropsychological and psychophysiological test battery, conducted in the same order for every participant at the UMC Utrecht, lasted about 4 hours, excluding a sufficient number of breaks. Personality questionnaires were completed beforehand. We selected 13 measures on the basis of fulfilling as many criteria as possible for candidate endophenotypes (5,31) (Table 1; Supplement 1). The following five measures were selected on the basis of familial correlation (see below) and are described here in detail.

Table 1. Parent-Offspring and Sib-Sib Correlations of All Endophenotypes

Test	Concept	n_{PO}	$\rho_{PO} \pm SE$	n_{SS}	$\rho_{SS} \pm SE$
PPI	Sensorimotor gating	78	.38 ± .10	98	.01 ± .11
Openness	Personality: Openness to experience	115	.32 ± .13	138	.33 ± .13
Backward Masking					
Location	Early visual perception, global	75	.22 ± .15	81	.23 ± .14
Identification	Early visual perception, local	74	.04 ± .10	83	−.10 ± .10
Spatial Span					
Forward	Spatial attention	98	.22 ± .10	112	.14 ± .12
Total	Spatial working memory	98	.21 ± .12	112	.22 ± .13
Backward	Spatial working memory	98	.16 ± .13	112	.21 ± .13
Verbal Fluency					
Categories	Semantic fluency	94	.17 ± .10	106	.34 ± .14
Letters	Phonemic fluency	87	.05 ± .14	109	.29 ± .13
CPT-IP	Continuous performance				
logB verbal	Conservative response bias (verbal)	81	.16 ± .10	94	−.01 ± .11
d′ verbal	Level of attention (verbal)	81	−.06 ± .11	94	−.08 ± .10
d′ spatial	Level of attention (spatial)	81	.03 ± .11	94	−.03 ± .10
logB spatial	Conservative response bias (spatial)	81	−.14 ± .11	94	.01 ± .11
P50					
P50 ratio (S2/S1)	Sensory gating	76	.13 ± .12	86	−.03 ± .10
P50 difference (S1-S2)	Sensory gating	83	.07 ± .13	102	.00 ± .10
N100 (S2/S1)	Sensory gating	80	−.10 ± .11	99	−.05 ± .09
Neuroticism	Personality: Neuroticism	114	.13 ± .08	135	−.02 ± .08
Digit Span					
Forward	Verbal attention	92	.13 ± .10	108	.03 ± .10
Total	Verbal working memory	92	.10 ± .10	108	−.02 ± .09
Backward	Verbal working memory	92	−.01 ± .09	108	−.13 ± .07
CVLT					
Immediate recall	Immediate verbal memory	91	.12 ± .11	108	.09 ± .11
Short delay recall	Short delay verbal memory	92	.11 ± .13	108	.09 ± .11
Delayed free recall	Delayed verbal memory	92	−.02 ± .13	108	.06 ± .11
Facial Recognition Test	Facial recognition	95	.09 ± .13	108	.16 ± .13
Purdue Pegboard	Psychomotor dexterity	85	.04 ± .11	91	.23 ± .14
Trail Making (B-A)	Set shifting	97	−.00 ± .12	109	.04 ± .10

Note: Bold type are the measures selected for further analyses (see text); for each selected measure, we used the variable with the highest PO and SS correlations.

CVLT, Californian Verbal Learning Task; CPT-IP, Continuous Performance Test-Identical Pairs; n_{PO}, number of parent-offspring pairs; n_{SS}, number of sib-sib pairs; ρ_{PO}, parent-offspring correlation; ρ_{SS}, sib-sib correlation; PPI, prepulse inhibition; S1, stimulus 1; S2, stimulus 2; SE, standard error.