Schizophrenia genetic variants are not associated with intelligence

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Background. Schizophrenia is associated with lower pre-morbid intelligence (IQ) in addition to (pre-morbid) cognitive decline. Both schizophrenia and IQ are highly heritable traits. Therefore, we hypothesized that genetic variants associated with schizophrenia, including copy number variants (CNVs) and a polygenic schizophrenia (risk) score (PSS), may influence intelligence.

Method. IQ was estimated with the Wechsler Adult Intelligence Scale (WAIS). CNVs were determined from single nucleotide polymorphism (SNP) data using the QuantiSNP and PennCNV algorithms. For the PSS, odds ratios for genome-wide SNP data were calculated in a sample collected by the Psychiatric Genome-Wide Association Study (GWAS) Consortium (8690 schizophrenia patients and 11 831 controls). These were used to calculate individual PSSs in our independent sample of 350 schizophrenia patients and 322 healthy controls.

Results. Although significantly more genes were disrupted by deletions in schizophrenia patients compared to controls (*p* = 0.009), there was no effect of CNV measures on IQ. The PSS was associated with disease status (*R*² = 0.055, *p* = 2.1 × 10⁻⁷) and with IQ in the entire sample (*R*² = 0.018, *p* = 0.0008) but the effect on IQ disappeared after correction for disease status.

Conclusions. Our data suggest that rare and common schizophrenia-associated variants do not explain the variation in IQ in healthy subjects or in schizophrenia patients. Thus, reductions in IQ in schizophrenia patients may be secondary to other processes related to schizophrenia risk.

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Introduction

Schizophrenia is a severe mental disorder with cognitive deficits as a core feature (Kraepelin, 1919; Elvevag & Goldberg, 2000). It has been associated with lower pre-morbid general intelligence (IQ) (Khandaker et al. 2011; Fowler et al. 2012), with cognitive decline prior to illness onset (Reichenberg et al. 2010) and with cognitive decline during the course of the illness (Hedman et al. 2012), although the latter is controversial. Both schizophrenia and IQ are largely determined by genetic factors, with estimated heritabilities of 80% (Cardno et al. 1999) and 70% (Fowler et al. 2012) respectively. Several studies have identified genetic variants that affect these respective phenotypes. For schizophrenia, the findings include an excess of de novo copy number variants (CNVs, genomic micro-deletions or microduplications from 1 kb to multiple Mb in size) (Stefansson et al. 2008; Walsh et al. 2008; Xu et al. 2008) and gene-containing CNV deletions (Buizer-Voskamp et al. 2011). Moreover, 10 individual single nucleotide polymorphisms (SNPs) have been associated with schizophrenia in genome-wide association studies (GWAS) (Ripke et al. 2011), and the combination of many (> 900 000) SNPs captures 23% of the variation in liability to develop schizophrenia (Lee et al. 2012). Similarly, rare CNVs are associated with general intelligence (Yeo et al. 2011) and mental retardation (Guilmot et al. 2009). Although no large GWAS on intelligence in healthy subjects have been reported, the combined effects of multiple SNPs captures 48% of the variation in intelligence in childhood.

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These data suggest that both common and rare alleles contribute to schizophrenia disease susceptibility in addition to general intelligence.

It is likely that subsets of schizophrenia-related SNPs are associated with distinct heritable disease-associated phenotypes. These are called endophenotypes when they are (1) associated with the illness, (2) heritable, (3) primarily state independent and (4) co-segregate with illness in families (Gottesman & Gould, 2003). Brain volume is an example of an endophenotype of schizophrenia, as it is robustly associated with disease (Wright et al. 2000), is highly heritable (van Haren et al. 2012) and co-segregates with illness in families (Boos et al. 2007). It is an objectively assessed quantitative measure. We revealed in a previous study that a combined score of common variants associated with schizophrenia (the polygenic schizophrenia score or PSS) significantly predicts total brain and white matter volume in schizophrenia patients and in healthy subjects (Terwisscha van Scheltinga et al. 2012), suggesting that schizophrenia-associated SNPs may be involved in (normal) white matter development. Thus, novel candidate genes can be identified based on the overlap in high-ranking SNPs associated with schizophrenia and its endophenotypes. IQ is another candidate endophenotype for this approach because of its strong association with disease (Mesholam-Gately et al. 2009), high heritability (Fowler et al. 2012), normally distributed quantitative measures and relatively straightforward assessment.

Although schizophrenia and IQ are phenotypically correlated and are both largely determined by genetic factors, these factors do not necessarily overlap. To what extent IQ-related genetic variants explain variation in schizophrenia is still unclear. A twin study in a sample of schizophrenia and healthy twins (n = 263 subjects) found that IQ measured after disease onset explained 37% of the variation in disease status (Toulopoulou et al. 2007). Shared genetic influences accounted for 92% of this phenotypic correlation. However, a large Swedish population cohort study of twins and sib pairs (n = 374,199 subjects) found that the broader phenotype of psychosis explained a much smaller amount (1%) of variation in pre-morbid intelligence at age 18, although this phenotypic correlation was also largely determined by shared genetic influences (for 91%). However, because the correlation was small, the genetic variance for pre-morbid IQ shared with psychosis was only 7% (Fowler et al. 2012). This suggests that, of all genetic variants associated with pre-morbid IQ, few will influence psychosis, and vice versa. However, no studies have yet investigated the predictive value of measured genetic variants.

The pre-morbid cognitive deficits in schizophrenia patients were reported to be largest in the domains of problem solving, working memory and processing speed (Reichenberg et al. 2010). It is possible that schizophrenia-associated genetic factors influence these specific cognitive functions rather than general intelligence. However, previous studies indicate that IQ and working memory have a similar high heritability and a comparable genetic overlap with schizophrenia (Toulopoulou et al. 2007; Aukes et al. 2009). None of the cognitive subtests indicated a significantly better schizophrenia endophenotype than total IQ. Therefore, we used total IQ as our main outcome measure.

The aim of the current study was therefore to investigate the relationship between IQ and two distinct types of schizophrenia-related genetic variants: CNVs and common SNPs. There are several possible scenarios. The first option is that these genetic variants are associated with IQ in both patients and healthy controls. If so, this would imply that novel schizophrenia risk genes could be identified using population-based samples with IQ data. A second option is that these variants affect IQ in schizophrenia patients only, which would suggest that schizophrenia genes affect processes involved in cognition. Finally, if disease-associated variants do not predict IQ in schizophrenia patients or in healthy subjects, this could indicate that the cognitive deficits in patients are secondary to other processes related to the risk for schizophrenia, for example environmental factors such as the use of cannabis or stress. Alternatively, the cognitive deficits may be related to indirect genetic effects, for example by genes influencing early brain development, which in turn affects cognition.

Method

Subjects and IQ measurements

The study was approved by the Medical Ethical Committee of the University Medical Center Utrecht. The sample consisted of 350 patients (90% with schizophrenia and 10% with schizo-affective disorder) and 322 controls. Clinical diagnosis was determined using the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al. 1992). Unaffected controls had no history of psychiatric illness except for three subjects who had a history of anxiety disorder, obsessive–compulsive disorder and adjustment disorder respectively. None of the control subjects had first-degree family members with psychotic illness.

Total IQ was estimated with the Wechsler Adult Intelligence Scale (WAIS; Stinissen et al. 1970). Four out of 11 subtests of WAIS versions III (n = 97) and IIIR
Sets of SNPs with disease, including both true risk alleles and stochastic
of the odds ratio for that particular variant. 'Risk
(carried (0, 1 or 2) was multiplied by the logarithm
each SNP, the number of 'risk variants' an individual
p
cut-offs for effect on schizophrenia (\(p = 0.018\), \(p = 0.0008\), for \(p_{\text{cut-off}} = 0.3\) as
disease status and a CNV × disease status interaction as factors and total IQ as the dependent variable in the
total sample. All analyses were repeated for deletions and duplications separately.

For the PSS, we performed linear regressions using the PSS as predictor and the total IQ estimates as
the outcome measure. Ten population stratification
dimensions, an inbreeding coefficient, the number
of SNPs used for scoring and the number of CNVs
were used as covariates (for details see Terwisscha
van Scheltinga et al. 2012b). Similar to the previous
analysis, we performed secondary analyses while in-
cluding effects for disease status and PSS × disease
status interactions. The association of the PSSs with
disease status was analyzed using logistic regression.
The variance explained, adjusted for the number of
predictors in the model (\(R^2\)), was used as the main
outcome parameter. \(p\) values were Bonferroni cor-
corrected for multiple comparisons with \(\alpha = 0.008\) [0.05/6
(because there are three ‘independent’ genetic mea-
tures (two CNV and one PSS) × 2 tests: main effect and
interaction effect)]. Post-hoc we analyzed the associ-
between the PSS and the four subtests of the
WAIS-IIIR separately.

Results
As shown in Table 1, there were significantly more
males in the patient group than in the control group
(78% v. 49%, \(p < 0.0001\)). The groups did not differ in
age and parental education. The years of education
and estimated IQ were significantly lower in the
schizophrenia patients.

Table 2 shows that there was a trend towards
more deletions in schizophrenia patients compared to
healthy controls \(p = 0.09\), whereas significantly more
genes were affected by deletions in patients \(p = 0.009\).
Neither of the CNV measures showed a significant
association with IQ.

The PSS significantly predicted disease status in the
current sample (\(R^2 = 0.055\), \(p = 2.1 \times 10^{-3}\), for \(p_{\text{cut-off}} = 0.3\). A significant association was found between the
PSS and IQ (\(R^2 = 0.018\), \(p = 0.0008\), for \(p_{\text{cut-off}} = 0.3\) as
shown in Fig. 1. The results for the other \(p_{\text{cut-off}}\) are also
shown in Fig. 1. However, after correction for disease
status the association was no longer significant
\(p_{\text{PSS}} = 0.97\), \(p_{\text{PSS} \times \text{disease status}} = 0.17\). Furthermore, no
association of the PSS with IQ was found within the

\(n = 575\) were used (WAIS-III: block design, compre-
hension, vocabulary and picture arrangement; WAIS-
IIIR: block design, information, symbol search and arithmetic). Raw scores were multiplied by 11/4 to
obtain an estimate of total IQ. Because of adjustment of the norm scores, mean IQ measures were significantly
lower in the newer version compared to the older
version. Therefore, IQ scores were corrected for ver-
sion, by taking the unstandardized residual in a linear
regression, with the newer version (IIIIR) as reference.
Estimated IQ scores were normally distributed both
before and after correction for version.

Genotyping, CNV and PSS measurements
Subjects were genotyped at the University of Califor-
nia, Los Angeles (UCLA) Neurosciences Genomics
Core (UNGC) using the Illumina HumanHap550
beadchip. CNVs were determined from SNP data
using the QuantiSNP and PennCNV algorithms as
described previously (Buizer-Voskamp et al. 2011;
Terwisscha van Scheltinga et al. 2012a). In brief, de-
viations in log R ratios (a measure of the magnitude of
the combined fluorescent signals from both sets of
probes) and B allele frequencies (relative ratio of the
fluorescent signals from one allelic probe to the other)
for 10 consecutive SNPs were regarded as CNVs. Re-
seq genes within 50 kb of the CNV borders were
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First, the difference in the two CNV measures (the
total number of CNVs and the total number of genes
affected by CNVs) between patients and controls was
calculated using a \(t\) test. Second, the two CNV
measures were used as factors in ANOVAs together
with disease status and a CNV × disease status inter-
action as factors and total IQ as the dependent variable
in the total sample. All analyses were repeated for
deletions and duplications separately.

For the PSS, we performed linear regressions using
the PSS as predictor and the total IQ estimates as
the outcome measure. Ten population stratification
dimensions, an inbreeding coefficient, the number
of SNPs used for scoring and the number of CNVs
were used as covariates (for details see Terwisscha
van Scheltinga et al. 2012b). Similar to the previous
analysis, we performed secondary analyses while in-
cluding effects for disease status and PSS × disease
status interactions. The association of the PSSs with
disease status was analyzed using logistic regression.
The variance explained, adjusted for the number of
predictors in the model (\(R^2\)), was used as the main
outcome parameter. \(p\) values were Bonferroni cor-
corrected for multiple comparisons with \(\alpha = 0.008\) [0.05/6
(because there are three ‘independent’ genetic mea-
tures (two CNV and one PSS) × 2 tests: main effect and
interaction effect)]. Post-hoc we analyzed the associ-
between the PSS and the four subtests of the
WAIS-IIIR separately.

Statistical analyses
As shown in Table 1, there were significantly more
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status the association was no longer significant
\(p_{\text{PSS}} = 0.97\), \(p_{\text{PSS} \times \text{disease status}} = 0.17\). Furthermore, no
association of the PSS with IQ was found within the
The combined score of schizophrenia-associated SNPs was associated with disease status, indicating that a PSS can predict disease in an independent sample. The PSS was also significantly associated with IQ in the entire sample of patients and controls. However, after correcting for disease status, this association disappeared. The PSS does not predict IQ within the patient and control groups. This result may seem puzzling at first sight, but can be explained by assuming that both IQ and the PSS are independently associated with schizophrenia.

Another possibility is that schizophrenia-associated genetic factors influence specific cognitive functions rather than general intelligence. Therefore, we repeated the analyses post-hoc for each of the four subtests of the WAIS-IIIIR separately. Similar results were found as for the total IQ scores: the PSS explained some of the variation in the subtest in the whole sample but the association disappeared after correction for disease status. We estimated that we had 80% power to detect a significant effect with \( \alpha = 0.008 \) when the PSS explained 1.8% or more of the variance in IQ. Thus, if there is any effect of schizophrenia-related SNPs on total IQ or one of the cognitive subdomains, this effect is likely to be small.

The findings are in agreement with the small (7%) genetic variance for psychosis shared with pre-morbid IQ (Fowler et al. 2012). Thus, although there is a robust association between schizophrenia and intelligence, this may not be due mainly to shared genetic factors. Instead, the cognitive deficits in schizophrenia patients may be secondary to other processes. We showed previously, in a partly overlapping sample, that the variance in total brain and white matter volume explained by the PSS is much larger (4.8 and 5.1%) (Terwisscha van Scheltinga et al. 2012b).
This effect was found in schizophrenia patients and also in healthy controls. Hence, the cognitive deficits in schizophrenia patients could be a result of a generalized effect of schizophrenia genes on early brain growth and maturation, perhaps in interaction with the effects of disease-related environmental factors.

There are several other factors that may have influenced the results and that should be acknowledged as potential limitations of this study. First, IQ measurements in patients could be influenced by the presence of psychotic symptoms, or the use of medication or illicit drugs, which could have partly masked the genetic effects. Second, total IQ was estimated by four out of 11 WAIS subtests, which is less precise than an estimate based on all 11 subtests, although the shortened version is more widely used (Fowler et al. 2012). Furthermore, the lack of effect of global CNV measures on IQ does not exclude an effect of individual CNVs at specific chromosomal locations on schizophrenia susceptibility and IQ. However, because CNVs at specific locations are usually rare, these are likely to go unnoticed in the current sample.

To conclude, rare and common schizophrenia-related genetic variants do not predict variation in IQ in healthy subjects or within the schizophrenia patient group. This suggests that cognitive deficits and the risk for schizophrenia cannot be attributed to shared genes. The cognitive dysfunction in schizophrenia patients is therefore more likely to be secondary to other processes related to schizophrenia risk. Thus, although we did not investigate this directly, our study suggests that population-based studies aiming to identify schizophrenia candidate genes by investigating the association of genetic variants with IQ may not be fruitful.

Appendix

The Schizophrenia Psychiatric GWAS Consortium


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Declaration of Interest

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Schizophrenia SNPs do not predict IQ

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