Ultrarare Coding Variants and Cognitive Function in Schizophrenia

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IMPORTANCE Impaired cognitive function in schizophrenia is associated with poor functional outcomes, but the role of rare coding variants is unclear.

OBJECTIVE To determine whether ultrarare constrained variants (URCVs) are associated with cognition in patients with schizophrenia.

DESIGN, SETTING, AND PARTICIPANTS Linear regression was used to perform a within-case genetic association study of URCVs and current cognition and premorbid cognitive ability. A multivariable linear regression analysis of the outcomes associated with URCVs, schizophrenia polygenic risk score, polygenic risk score for intelligence and schizophrenia associated copy number variants on cognitive ability was performed. Exome sequencing data from 802 participants with schizophrenia were assessed for current cognition using the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery and for estimated premorbid IQ using the National Adult Reading Test. Individuals were recruited from clinical and voluntary mental health services in the UK. Those with a diagnosis of intellectual disability or a neurological disorder known to affect cognition were excluded. Data collection occurred between 2007 and 2015. Data were analyzed between April 2020 and March 2022.

MAIN OUTCOMES AND MEASURES Association between URCVs, current cognition, and current cognition adjusted for premorbid IQ.

RESULTS Of the 802 participants, 499 (62%) were men and 303 (38%) were women; mean (SD) age at interview was 43.36 (11.87) years. Ultrarare constrained variants (n = 400) were associated with lower current cognition scores (β = −0.18; SE = 0.07; P = .005). In the univariable analysis, premorbid IQ was associated with URCVs (β = −0.12; SE = 0.05; P = .02) and partly attenuated the association with current cognition (β = −0.09; SE = 0.05; P = .08). Multivariable analysis showed that measured genetic factors combined accounted for 6.2% of variance in current cognition, 10.3% of variance in premorbid IQ, and supported outcomes of URCVs associated with current cognition independent of premorbid IQ (β = −0.10; SE = 0.05; P = .03).

CONCLUSIONS AND RELEVANCE The findings of this study suggest that URCVs contribute to variance in cognitive function in schizophrenia, with partly independent associations before and after onset of the disorder. Although the estimated effect sizes were small, future studies may show that the effect sizes will be greater with better annotation of pathogenic variants. Genomic data may contribute to identifying those at particularly high risk of cognitive impairment in whom early remedial or preventive measures can be implemented.

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Key Points

Question Are ultrarare constrained variants (URCVs) associated with reduced cognitive function in individuals diagnosed with schizophrenia?

Findings In this within-case genetic association study of 802 individuals with schizophrenia who had undergone exome sequencing and cognitive testing, significantly reduced cognitive function was found in individuals carrying URCVs.

Meaning This study found that URCVs were associated with reduced general cognitive function in schizophrenia; with better annotation of pathogenic variants, genomic data may contribute to identifying those with schizophrenia at particularly high risk of cognitive impairment in whom early remedial or preventative measures can be implemented.

Methods

Sample and Phenotype Description
We included 873 participants prior to quality control (QC) from the Cardiff Cognition in Schizophrenia cohort, which consists of patients with a clinical diagnosis of schizophrenia.

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chizophrenia displays considerable variation in clinical features, course, and outcome. It is also associated with variable impairments in cognitive function, and IQ is lower by approximately 1 SD relative to the general population. The nature of the association between cognitive function and schizophrenia is poorly understood but is of importance because there is a large body of evidence that cognitive impairment is associated with poor functional outcomes in work, independent living, and social integration.

Schizophrenia is typically first diagnosed when psychosis becomes manifest, usually in late adolescence or early adulthood, but premorbid impairments in cognition frequently occur. People with schizophrenia have an average premorbid IQ of 0.5 SD lower than controls. The association of schizophrenia with various premorbid developmental deficits, including cognitive impairment, together with evidence for association with environmental exposures in utero and in early childhood, and, more recently, genetic evidence, support the idea that schizophrenia is, at least in part, a neurodevelopmental disorder. There is also evidence for a further decline in cognitive function after diagnosis, but it is not clear whether this decline reflects ongoing processes intrinsic to the pathophysiology of schizophrenia or secondary factors such as medication effects, comorbid physical illness, substance misuse, or ascertainment bias.

Schizophrenia is highly heritable and polygenic, with risk conferred by alleles across the frequency spectrum including common risk alleles, rare copy number variants (CNVs), and rare damaging coding variants. There is also evidence that the CNVs and genes associated with schizophrenia through both common and rare coding variants overlap with CNVs and genes implicated in childhood-onset neurodevelopmental disorders (NDDs).

Cognitive function is moderately heritable in the general population and, similar to schizophrenia, is highly polygenic and affected by alleles across the frequency spectrum including common variants, CNVs and rare coding variation. Many of the common alleles that influence liability to schizophrenia also influence IQ in the general population, although it is unclear whether they also influence cognitive function in people with schizophrenia perhaps reflecting the modest samples sizes and power of these studies, differences in duration of illness at the time of testing and the nature of the cognitive tests used. Nevertheless, common alleles that are associated with higher intelligence in the general population are associated with better cognitive ability in individuals with schizophrenia.

At the rare variant level, cognitive function in people with schizophrenia who are carriers of CNVs is, on average, approximately 0.5 to 1.0 SDs below that of noncarriers. Within people with schizophrenia, de novo protein truncating variants (PTVs) are more common in those with relatively poor school performance while the incidence of rare PTVs is higher in those with comorbid intellectual disability. Together, these findings are consistent with the hypothesis that rare coding variants may be associated with a higher risk of cognitive impairment in schizophrenia, although no study to date has investigated this in individuals with schizophrenia who have undergone quantitative assessment of cognitive function.

Given the association between cognitive function and functional outcome, it is important to understand the timing of, and mechanisms behind, cognitive impairment in schizophrenia to inform the design and implementation of interventions. Two recent studies of schizophrenia have examined genetic risk factors and timing, specifically premorbid and postonset cognitive function (referred to as current cognition hereafter). The first showed CNV carrier status was associated with substantially impaired current and premorbid cognitive function. The second found that common variant liability for IQ was associated with both current cognition and premorbid IQ, but the association with current cognition was largely explained by premorbid effects. In contrast, schizophrenia liability was associated only with current cognitive ability, and this association was independent of premorbid IQ. These findings suggest that common genetic variation that influences IQ in the general population and rare pathogenic CNVs contribute to premorbid cognitive impairment in schizophrenia, and that common schizophrenia risk alleles may be associated with further impairment after onset.

In the present study, we sought to assess whether rare coding variants are associated with current cognitive function in patients with schizophrenia, and to investigate the timing of any observed outcomes with respect to onset of the disorder. Unlike previous studies, we were able to examine cognition quantitatively across the range of cognitive abilities. Moreover, we also had estimates of premorbid IQ, allowing us to study for the first time to date the timing relative to disease onset at which genetic factors are apparent. In addition to exome sequencing data, we had CNV and single-nucleotide variations array data, which allowed us to investigate the combined and independent cognitive outcomes in schizophrenia associated with rare coding variants, CNVs, and common variants.

Methods

Sample and Phenotype Description
We included 873 participants prior to quality control (QC) from the Cardiff Cognition in Schizophrenia cohort, which consists of patients with a clinical diagnosis of schizophrenia.
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We performed a within-case genetic association study of the association between the incidence of rare coding variants and cognitive ability. Recent studies have reported that evidence of selective constraint, at either the variant or gene level, is a feature associated with rare coding variants that contribute to impaired cognition in people with schizophrenia or autism spectrum disorder, as well as in the general population. Thus, in the current study, we postulated that ultrarare constrained variants (URCVs), defined as either PTVs in LoF1 genes (genes with gnomAD probability of loss-of-function intolerance scores ≥0.94) or damaging-missense variants (MPC ≥2)42 that are observed once in our sample and are not present in the gnomAD nonneuro data set, are associated with lower measures of current cognition in people with schizophrenia (eMethods 5 in the Supplement). We next investigated URCVs in terms of estimated premorbid IQ to assess whether these outcomes explained the associations between URCVs and current cognition.

Statistical Analysis
Linear regression was used to test for association between cognition and the number of URCVs carried by each individual. We covaried for sex, age at interview, sequencing site, principal components 1 through 10, and the exome wide incidence of ultrarare synonymous variants. R², which represents the proportion of phenotypic variance explained by the relevant models, was estimated from the multivariable linear models and univariable linear models. Statistical significance was determined as 2-sided P < .05. Further details of statistical analysis and study design are available in eMethods 7 in the Supplement.

Results
Ultrarare Constrained Variants
Of the 802 participants, 499 (62%) were men and 303 (38%) were women; mean (SD) age at interview was 43.36 (11.87) years. Consistent with our primary hypothesis, the incidence of URCVs was associated with lower current cognitive ability (Table 1), each variant associated with a reduction in performance of 0.18 SDs (current cognition: β = −0.18; SE = 0.07; P = .005; current cognition conditioned on premorbid IQ: β = −0.09; SE = 0.05; P = .08; and premorbid IQ: β = −0.12; SE = 0.05; P = .02). Effect sizes were robust to controlling for primary DSM-IV diagnosis (eResults and eTable 3 in the Supplement), or excluding PTVs considered low confidence by LOFTEE44 (eTable 4 in the Supplement). To explain this primary association signal, we tested the effect sizes on cognition conferred separately by ultrarare damaging missense variants (MPC ≥2) and ultrarare PTVs in LoF1 genes, but found no differences between the 2 classes of mutation (eTable 5 in the Supplement).

Timing and Cognition
After covarying for premorbid IQ, the effect size for URCVs and current cognition was substantially attenuated (β = −0.09; SE 0.05; P = .08) (Table 1). Similar results were obtained in a multivariable analysis that considered other classes of genetic variation (β = −0.10; SE 0.05; P = .03). The outcome of URCVs as-
The results suggest that URCVs are factors in cognitive function after the onset of illness or have only premorbid outcomes, but these may affect cognitive domains indexed by MCCB but...
not NART. To examine the latter hypothesis, we investigated URCVs and MCCB domains but found similar effect sizes across all domains, the exception being social cognition in which no effect size was apparent (eTable 7 in the Supplement). Moreover, the domain that had the highest Pearson correlation coefficient with NART (ie, working memory) was also the current cognition domain that had the highest effect size with URCVs. Together these findings may counter the suggestion of URCVs having restricted premorbid effects on domains of cognition that are not indexed by NART (eTable 7 in the Supplement).

URCVs in NDD Genes and Non-NDD Genes
As an exploratory analysis, we compared cognitive ability in schizophrenia with URCVs in NDD genes with those in genes not associated with NDD (non-NDD genes), recognizing that the latter group will contain genes that have yet to be implicated in NDDs. While the point estimates of the effect sizes were substantially greater for URCVs in NDD genes than in non-NDD genes, the differences were not statistically significant (Table 2).

URCVs, CNVs, Schizophrenia PRS, IQ PRS, and Cognitive Function
In addition, we performed multivariable analyses on a subset of 648 individuals who had data on URCVs, CNVs (eTable 8 in the Supplement), SZ PRS, and IQ PRS. The estimated effect sizes (Table 3) were similar to those obtained from the univariable models (eTable 9 in the Supplement) (for example, in the multivariable analysis, the URCV effect size on premorbid IQ was β = −0.14; SE, 0.05; P < .01; in the univariable analysis, the URCV effect size on premorbid IQ was β = −0.12; SE, 0.05; P = .02), which is broadly consistent with the different classes of variant acting independently on cognition. After conditioning on premorbid IQ, all effect sizes on current cognition were attenuated except for the SZ PRS (for example, in the multivariable analysis the URCV effect size on current cognition without covarying for premorbid IQ was β = −0.19; SE = 0.07; P = .005; in the multivariable analysis the URCV effect size on current cognition when covarying for premorbid IQ was β = −0.10; SE = 0.05; P = .03) (Table 3 and Table 4).

All measured genetic factors accounted for 6.2% of the variance in current cognition and 10.3% of the variance in premorbid IQ (Table 4). After controlling for premorbid IQ, all measured genetic factors accounted for 1.6% of the variance in current cognition.

Discussion
We have investigated the contribution of genetics to variation in cognitive ability in individuals with schizophrenia. We focused primarily on URCVs, a class of mutation that contributes to risk of schizophrenia,13-15 and which is particularly enriched in people with schizophrenia who have poor school performance14 and comorbid intellectual disability.14 We found that URCVs contribute more generally to variance in current cognitive function in schizophrenia rather than simply being enriched in patients with intellectual disability. Our finding that cognitive function in schizophrenia rather than simply being affected by other genetic factors is consistent with previous reports16 and suggests that URCVs may have a general role in cognitive development.

The baseline covariates that are included in each model were age at interview, sex, sequencing site, synonymous variants, and principal components 1 through 10. Premorbid IQ is included in the baseline for all analyses as indicated.

Abbreviations: CNV, copy number variant; IQ PRS, IQ polygenic risk score; NA, not applicable; SZ PRS, schizophrenia polygenic risk score; URCVs, ultrarare constrained variants.

a R² from both the multivariable linear models and univariable linear models represents the proportion of phenotypic variance explained by the relevant models including baseline in 648 samples. The proportions of variance of the cognitive measure after correction for the baseline variables explained by each genetic component are their values in the Table divided by (1−R² [baseline]).

b Model refers to the linear regression model.

c Variance explained of the genetic component is the R² of the relevant model minus the R² of the model containing the baseline covariates alone.

d The baseline covariates that are included in each model were age at interview, sex, sequencing site, synonymous variants, and principal components 1 through 10. Premorbid IQ is included in the baseline for all analyses as indicated.

The distribution of premorbid IQ and current cognition scores in URCV carriers largely overlaps that of noncarriers (eFigure 7 in the Supplement) supports this conclusion. Each URCV was associated on average with 0.18 SD lower current cognitive performance as indexed by the Measurement and Treatment Research to Improve Cognition in Schizophrenia composite score.

Those who develop schizophrenia frequently exhibit impairments in cognition before diagnosis.2,3 These deficits appear to have their origins in childhood,3,43-45 and which is clearly not a consequence of manifest disorder and, together with associations with other premorbid developmental deficits and environmental exposures, support the idea that schizophrenia is an early-onset disorder with a genetic etiology.
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Research Original Investigation

Conclusions

Results of this study suggest that URCVs were associated with cognitive impairment in schizophrenia, and we found evidence they may independently exert effects after onset of the disorder as well as premorbidly. In our study, the estimated effect sizes were small, but future studies may find that the effect sizes will be greater with better annotation of pathogenic

Strengths and Limitations

To our knowledge, this study is first to evaluate the association between URCVs and quantitative measures of current cognition in people with schizophrenia and to examine timing of the outcomes in the context of all known relevant classes of genomic variation. Limitations are that NART is an indirect measure of premorbid IQ, although this limitation is mitigated somewhat by work showing it to be strongly correlated with direct measures of premorbid IQ. Our study was focused on individuals of European ancestry because sufficient samples from cases of individuals with non-European ancestry were not available, but we expect the findings from URCVs and CNVs in terms of cognition in schizophrenia are more likely to generalize to individuals with non-European ancestries than the outcomes associated with IQ PRS, which was generated from European ancestry-based IQ genome-wide association study data.

At a population level, variance explained allows for an assessment of the contribution of different classes of variant that considers differences in allele frequencies and effect sizes. The multivariable model indicated that the genetic factors measured in this study account for a total of 10.3% of the variance in premorbid IQ and 6.2% of the variance in current cognition, the latter decreasing to 1.6% of the variance after conditioning on premorbid IQ (Table 4).

Each URCV was associated with a 0.18 SD lower MCCB composite score, equivalent to a reduction of only 2.7 in IQ points. When considering this in relation to the effect sizes found with the other classes of mutation on cognition, it is important to note that the discovery of potentially relevant rare variation is at an early stage, and studies of much larger samples are warranted. Moreover, in the case of URCVs, the estimated effect sizes of alleles of true effect will have been reduced by the inclusion of many alleles that have no effect on either schizophrenia liability or cognition. Consistent with this idea, URCVs that are likely to be enriched for those with true effects by virtue of being located in genes associated with neurodevelopmental disorders yielded a larger point estimate for their effect size than the same classes of mutations in non-NDD genes (Table 2) and were similar in effect size to those for IQ PRS. We acknowledge the estimated effect size of URCVs in NDD genes was not significantly greater than variants in the non-NDD set, possibly reflecting the relatively small number of URCVs in NDD genes, but these findings support the idea that better annotation and classification of pathogenic URCVs will increase the estimated effect size of this class of alleles, while more complete discovery will increase its contribution to the variance explained. This situation may suggest that, although URCVs are by definition uncommon, it may be possible to use them to identify a small subgroup of individuals with early signs of schizophrenia or with increased risk of schizophrenia, who are at higher risk of subsequent cognitive decline and in whom early remedial or preventative measures can be implemented. The discovery of rare risk alleles associated with cognitive decline might also help to illuminate areas of biology that are important in the impairments in cognitive function that are seen more generally in schizophrenia and which affect functional outcomes.

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genetic variants. As findings from other studies accrue, we can expect them to inform the use of genomic data for identifying those individuals with, or at high risk of developing, schizophrenia who are particularly likely to develop subsequent cognitive impairment and in whom early remedial or preventative measures can be implemented.

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Concept and design: Rees, Walters, O'Donovan, Owen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Creeth, Rees, O'Donovan, Owen.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Creeth, Rees, Holmans.
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