

Association of Copy Number Variation of the 15q11.2 BP1-BP2 Region With Cortical and Subcortical Morphology and Cognition

Writing Committee for the ENIGMA-CNV Working Group

[+ Supplemental content](#)

IMPORTANCE Recurrent microdeletions and duplications in the genomic region 15q11.2 between breakpoints 1 (BP1) and 2 (BP2) are associated with neurodevelopmental disorders. These structural variants are present in 0.5% to 1.0% of the population, making 15q11.2 BP1-BP2 the site of the most prevalent known pathogenic copy number variation (CNV). It is unknown to what extent this CNV influences brain structure and affects cognitive abilities.

OBJECTIVE To determine the association of the 15q11.2 BP1-BP2 deletion and duplication CNVs with cortical and subcortical brain morphology and cognitive task performance.

DESIGN, SETTING, AND PARTICIPANTS In this genetic association study, T1-weighted brain magnetic resonance imaging were combined with genetic data from the ENIGMA-CNV consortium and the UK Biobank, with a replication cohort from Iceland. In total, 203 deletion carriers, 45 247 noncarriers, and 306 duplication carriers were included. Data were collected from August 2015 to April 2019, and data were analyzed from September 2018 to September 2019.

MAIN OUTCOMES AND MEASURES The associations of the CNV with global and regional measures of surface area and cortical thickness as well as subcortical volumes were investigated, correcting for age, age², sex, scanner, and intracranial volume. Additionally, measures of cognitive ability were analyzed in the full UK Biobank cohort.

RESULTS Of 45 756 included individuals, the mean (SD) age was 55.8 (18.3) years, and 23 754 (51.9%) were female. Compared with noncarriers, deletion carriers had a lower surface area (Cohen $d = -0.41$; SE, 0.08; $P = 4.9 \times 10^{-8}$), thicker cortex (Cohen $d = 0.36$; SE, 0.07; $P = 1.3 \times 10^{-7}$), and a smaller nucleus accumbens (Cohen $d = -0.27$; SE, 0.07; $P = 7.3 \times 10^{-5}$). There was also a significant negative dose response on cortical thickness ($\beta = -0.24$; SE, 0.05; $P = 6.8 \times 10^{-7}$). Regional cortical analyses showed a localization of the effects to the frontal, cingulate, and parietal lobes. Further, cognitive ability was lower for deletion carriers compared with noncarriers on 5 of 7 tasks.

CONCLUSIONS AND RELEVANCE These findings, from the largest CNV neuroimaging study to date, provide evidence that 15q11.2 BP1-BP2 structural variation is associated with brain morphology and cognition, with deletion carriers being particularly affected. The pattern of results fits with known molecular functions of genes in the 15q11.2 BP1-BP2 region and suggests involvement of these genes in neuronal plasticity. These neurobiological effects likely contribute to the association of this CNV with neurodevelopmental disorders.

Group Information: The writing committee and members of the ENIGMA-CNV Working Group appear at the end of the article.

Corresponding Authors: Ida E. Sønderby, PhD (i.e.sonderby@medisin.uio.no), and Ole A. Andreassen, PhD, MD (o.a.andreassen@medisin.uio.no), Norwegian Centre for Mental Disorders Research, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Kirkeveien 166, Oslo 0407, Norway.

JAMA Psychiatry. 2020;77(4):420-430. doi:10.1001/jamapsychiatry.2019.3779
Published online October 30, 2019.

Copy number variations (CNVs), deletions or duplications of stretches of DNA of more than a kilobase (kb) in size, are an important yet understudied source of genetic variation,¹ covering approximately 12% of the human genome.² There is growing evidence that the complex genetic architecture of brain disorders consists of a combination of both common and rare genetic variation,³ yet the role of CNVs in the etiology of these disorders is quite unclear. There is an increased burden of CNVs in brain disorders, in particular those with a neurodevelopmental component,^{4,5} and several dozen CNVs have been linked to neurodevelopmental processes and pathological behavior in the past decade.⁵⁻⁷ Copy number variations may explain a sizeable portion of the heritability of brain disorders that is missed by genome-wide studies of single-nucleotide polymorphisms and may also potentially provide valuable insights into the underlying neurobiology.

The 15q11.2 genomic region between breakpoint 1 (BP1) and 2 (BP2), which spans from 20.3 Mb to 20.8 Mb (hg18), contains a recurrent CNV approximately 500 kb in size that is present in 0.5% to 1.0% of the population.^{8,9} Four evolutionarily highly conserved genes are located here: *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*.¹⁰ The first 3 of these genes have known roles in neurodevelopment and contain polymorphisms associated with several brain disorders.¹¹⁻¹⁴ Furthermore, their gene expression levels are predictive of behavioral and academic outcomes in individuals with Prader-Willi syndrome,¹⁵ a severe neurodevelopmental disorder caused by deletion of the 15q11.2 to 15q13.1 region.

Symptoms of 15q11.2 BP1-BP2 CNV status vary, and many carriers are not clinically affected.^{16,17} However, the deletion has been unequivocally associated with schizophrenia,^{16,18,19} and in a meta-study of clinical samples,¹⁶ more than half of individuals with a 15q11.2 BP1-BP2 deletion presented with neurobehavioral disturbances. Data from population studies further indicate that deletion carriers unaffected by severe psychiatric and neurodevelopmental disorders have an increased prevalence of dyslexia and dyscalculia.^{8,20} However, the reciprocal duplication has not been convincingly associated with psychiatric or neurodevelopmental disorders, and duplication carriers perform on par with controls on cognitive tests.^{8,20}

Neuroimaging provides a unique opportunity to reveal the neural substrates of CNVs, which can inform our understanding of the functional relevance of the genes involved and identify neurobiological mechanisms underlying abnormal human behavior and cognition. Studies of the neural correlates of 15q11.2 BP1-BP2 variations have reported copy number dose-response effects on brain regions associated with psychosis and dyslexia^{8,21} as well as globally altered white matter diffusion characteristics.²² However, besides using relatively small sample sizes, these prior studies focused only on a subset of brain regions and did not investigate cortical surface area and thickness. These are more specific measures of cortical morphology possibly more sensitive to pathological alterations and differentially associated with cognitive abilities and psychiatric disorders.²³

Here, we present results from, to our knowledge, the largest CNV neuroimaging study to date, investigating the neural correlates of the 15q11.2 BP1-BP2 CNVs in 45 756 individuals gath-

Key Points

Question How does the 15q11.2 BP1-BP2 copy number variation affect cortical and subcortical brain morphology and cognitive performance?

Findings In this genetic association study, using a discovery/replication design with more than 45 000 individuals, a dose response of 15q11.2 BP1-BP2 copy number variations on cortical thickness as well as smaller accumbens and cortical surface area was found for deletion carriers, particularly in frontal brain regions. Further, compared with noncarriers, deletion carriers had poorer cognitive performance.

Meaning These findings point toward altered brain structure for deletion carriers, implicating aberrant cortical morphology, thereby providing an improved understanding of the association of this copy number variation with neurodevelopmental disorders.

ered through the Enhancing Imaging Genetics through Meta-Analysis (ENIGMA) consortium²⁴ and UK Biobank,²⁵ with a replication sample from Iceland.^{8,21} Our primary aim was to identify whether this CNV is associated with global measures of brain morphology (ie, intracranial volume [ICV], mean cortical thickness, and total surface area) and subcortical volumes. We supplemented our primary analyses with investigations of the association of 15q11.2 copy number status with so-far unexplored regional cortical measures and with measures of cognitive performance. Given reported effects on gene expression^{14,15} and the literature on 15q11.2 BP1-BP2,^{8,21} we expected to find 15q11.2 copy number dose effects on the brain measures and poorer cognitive performance for deletion carriers.

Methods

Participants

In total, we included data from 45 756 individuals with neuroimaging data available. For our main sample, we collected data from the ENIGMA-CNV working group and the UK Biobank. We further obtained data from deCODE Genetics²¹ for use as a replication sample. Total sample sizes for the main neuroimaging analyses, split by carrier status, and information on age and sex are given in Table 1. Most cohorts were population-based studies, with a mean of 5.6% of individuals diagnosed as having a brain disorder. eFigure 1 in Supplement 1 and the eTable in Supplement 2 contain information on study design, sample demographic characteristics, and references to articles describing all 37 ENIGMA-CNV working group cohorts, collected up until April 1, 2019. All participants gave written informed consent, and sites involved obtained ethical approvals.

CNV Calls and Validation

Nearly all cohorts had CNVs called in a unified manner using PennCNV,²⁶ as described previously.²⁷ Copy number variants from the Dublin sample were called using Birdseye version 1.5.5 (Birdsuite).²⁸ Samples were filtered based on standardized quality-control metrics,²⁷ and CNVs with at least 40% overlap with the 15q11.2 BP1-BP2 region were identified and

Table 1. Demographic Characteristics of Individuals With Neuroimaging Data Available Used for the Main Analyses

Characteristic	15q11.2 BP1-BP2 CNV Status			Test Statistic ^a	P Value
	Deletion Carriers	Noncarriers	Duplication Carriers		
ENIGMA-CNV and UK Biobank					
Total, No.	146	44 266	192	NA	NA
Female, No. (%)	75 (51.4)	22 912 (51.8)	101 (52.6)	$\chi^2 = 0.06$.97
Age, mean (SD), y	55.4 (19.3)	56.1 (18.4)	55.6 (18.3)	$F = 0.14$.87
deCODE Genetics					
Total, No.	57	981	114	NA	NA
Female, No. (%)	31 (54.4)	565 (57.6)	70 (61.4)	$\chi^2 = 0.90$.64
Age, mean (SD), y	45.2 (13.9)	46.9 (12.0)	46.3 (12.1)	$F = 0.58$.56
Total					
Total, No.	203	45 247	306	NA	NA
Female, No. (%)	106 (52.2)	23 477 (51.9)	171 (55.9)	$\chi^2 = 1.95$.38
Age, mean (SD), y	52.6 (17.9)	55.9 (18.3)	52.2 (16.3)	$F = 9.57$	6.9×10^{-5}

Abbreviations: CNV, copy number variation; NA, not applicable.

^a Inference carried out using χ^2 test for the sex distribution and analysis of variance for the age distribution.

Table 2. Results From the Cognitive Task Performance Analyses^a

Task	15q11.2 BP1-BP2 CNV Status			Deletion Carriers vs Noncarriers		Duplication Carriers vs Noncarriers		Dosage	
	Deletion Carriers, No.	Noncarriers, No.	Duplication Carriers, No.	Cohen <i>d</i> (SE)	P Value ^b	Cohen <i>d</i> (SE)	P Value ^b	β (SE)	P Value ^c
Pairs matching	1790	468 709	2117	-0.05 (0.02)	.02	-0.06 (0.02)	.003	-0.01 (0.02)	.51
Reaction time	1767	464 648	2094	-0.17 (0.02)	2.5×10^{-13}	-0.02 (0.01)	.47	0.07 (0.02)	9.6×10^{-6}
Fluid intelligence	551	154 490	687	-0.28 (0.04)	5.3×10^{-11}	0	.96	0.13 (0.03)	9.6×10^{-6}
Digit span	180	47 569	192	-0.26 (0.07)	.001	0.02 (0.01)	.78	0.14 (0.05)	.009
Symbol substitution	387	111 900	402	-0.17 (0.05)	.001	0	>.99	0.09 (0.04)	.02
Trail making A	342	98 495	352	-0.08 (0.04)	.13	-0.04 (0.02)	.50	0.02 (0.04)	.55
Trail making B	342	98 494	352	-0.24 (0.05)	7.1×10^{-6}	0	>.99	0.12 (0.04)	.002

Abbreviation: CNV, copy number variation.

^a Multiple comparison-corrected significance set at $P < .003$.

^b Inference carried out using *t* tests.

^c Inference carried out using linear regression.

visualized with the iPsychCNV package in R (eFigure 2 in Supplement 1). All 15q11.2 CNVs identified in individuals with neuroimaging data were visually inspected, and no false positives were identified. See eMethods 1 in Supplement 1 for more details on CNV calling and quality control.

Image Acquisition and Processing

The eTable in Supplement 3 lists technical details concerning scanners and acquisition parameters. The brain measures were estimated from T1-weighted magnetic resonance imaging scans, collected and processed at participating sites in accordance with the ENIGMA protocol. This protocol is based on standardized image analysis using FreeSurfer Software Suite version 5.1 to 5.3 (FreeSurfer) and includes harmonized approaches to quality checks (<http://enigma.ini.usc.edu/protocols/imaging-protocols>).

Cognitive Task Performance

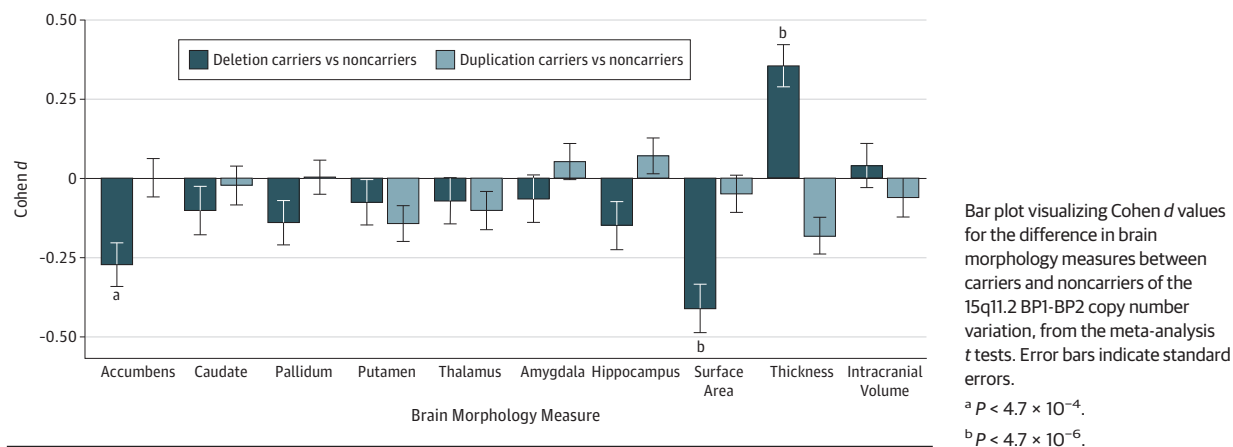
The full UK Biobank study consists of approximately 500 000 participants. The 31 247 UK Biobank participants used for the neuroimaging analyses in the current study are a subset of these. Many UK Biobank participants have also been tested with a neuropsychological test battery.²⁰ Here, we studied performance measures on 7 cognitive tasks, performed by at least

10% of the 500 000 participants, following the approach of Kendall et al.²⁰ This included the pairs matching, reaction time, fluid intelligence, digit span, symbol digit substitution, and trail making A and B tasks. Table 2 lists the sample sizes we used for each task. All measures were recoded so that lower values indicate poorer performance. More details of our approach can be found in eMethods 2 in Supplement 1.

Exclusion and Sensitivity Analyses

Analysis of the imaging data, locally preprocessed at each site, was performed centrally in a mega-analysis with deidentified data. We excluded individuals with a minimum overlap of 40% with genomic regions containing other known pathogenic CNVs (eTable 1 in Supplement 1) and first-degree and second-degree relatives. Only scanner sites with 15q11.2 BP1-BP2 CNV carriers were included. Because of this and varying numbers of missingness, final discovery sample size per primary outcome measure varies, as shown in eTable 2 in Supplement 1. eTables 3-8 and eFigures 3-6 in Supplement 1 list the results of robustness and sensitivity analyses on the primary outcome measures in the discovery sample, including tests that (1) exclude individuals with a known brain disorder diagnosis (2674 [5.4%]), (2) exclude children (3806 [7.8%]), (3) match each carrier with 4 noncar-

Figure 1. Association of the 15q11.2 BP1-BP2 Copy Number Variation With Global and Subcortical Brain Morphology



riers, (4) control for population structure by including 4 genetic principal components as covariates, (5) investigate the role of age in our significant findings by including an interaction term between copy number and age, (6) investigate the role of sex in our significant findings by including an interaction term between copy number and sex, and (7) run the analyses separately for the UK Biobank and ENIGMA-CNV cohorts. Please see eMethods 3 in Supplement 1 for methodological details. Briefly, all results were highly similar to those obtained in the full sample.

Statistical Analyses

All analyses were carried out in R version 3.5.1 (The R Foundation). Prior to the analyses, we regressed out the effects of age, age², and sex from all outcome measures using linear regression. For all brain measures, we included scanner site and ICV in the set of regressed-out variables. We also reran the analyses for our primary brain outcome measures without regressing out ICV (eTable 9 in Supplement 1). Subsequently, for all outcome measures, we applied an inverse normal transformation to the residuals,²⁷ leading to a mean of 0 and SD of 1.

We ran 2 sets of analyses. First, we carried out two 2-sample 2-sided *t* tests, comparing deletion or duplication carriers with noncarriers. Second, we performed dose-response analyses by regressing the outcome measures on 15q11.2 BP1-BP2 copy number, coding deletion carriers as 1, noncarriers as 2, and duplication carriers as 3.

We took into account multiple comparison corrections by calculating the number of independent outcome measures through spectral decomposition of a correlation matrix of the 3 global, 7 subcortical, and 68 regional cortical measures. The estimated equivalent number of independent measures was 35. Given 2 *t* tests and the dosage analyses, we set the significance threshold at a *P* value less than 4.7×10^{-4} ($\alpha = .05/[3 \times 35]$). For the 7 cognitive measures, the number of independent traits was found to be 6, leading to significance at a *P* value less than .003 ($\alpha = .05/[3 \times 6]$).

We further carried out exploratory mediation analyses to couple the imaging findings with the behavioral findings using

the mediation package version 4.4.7 in R. We report the proportion of the total effect of the CNV on cognitive task performance mediated by the brain measures with *P* values calculated through quasi-Bayesian approximation using 5000 simulations.

We list the uncorrected *P* values throughout the article. The effect sizes reported are Cohen *d* values with Hedges correction for *t* tests and β s from the linear regression for the dose response analyses.

For replication of the primary results, the Icelandic data were processed and analyzed as described above. We meta-analyzed the results from the discovery and replication cohorts through the metaphor package version 2.0.0 in R, as described previously.²⁷

Results

Global Morphology and Subcortical Volumes

Deletion carriers had significantly lower total surface area, thicker cortices, and lower nucleus accumbens volume than noncarriers in the discovery sample. The group difference between deletion carriers and noncarriers in surface area was also significant in the replication sample, while the association with mean cortical thickness did not surpass the multiple comparisons-corrected threshold (eTable 10 in Supplement 1). Meta-analysis of the 2 samples showed the same pattern, with significant differences between deletion carriers and noncarriers on surface area, cortical thickness, and the nucleus accumbens (Figure 1) (Table 3). The pattern of results remained very similar when not correcting for ICV (eTable 9 in Supplement 1).

As can be seen in Figure 1, compared with noncarriers, deletion carriers showed higher cortical thickness while duplication carriers showed lower cortical thickness. This is reflected in a significant copy number dose response (Table 3). eTable 10 in Supplement 1 lists the full results from the linear regression analyses separately for the discovery and replication sample.

Table 3. Meta-analysis Results on Each of the Primary Brain Morphology Measures^a

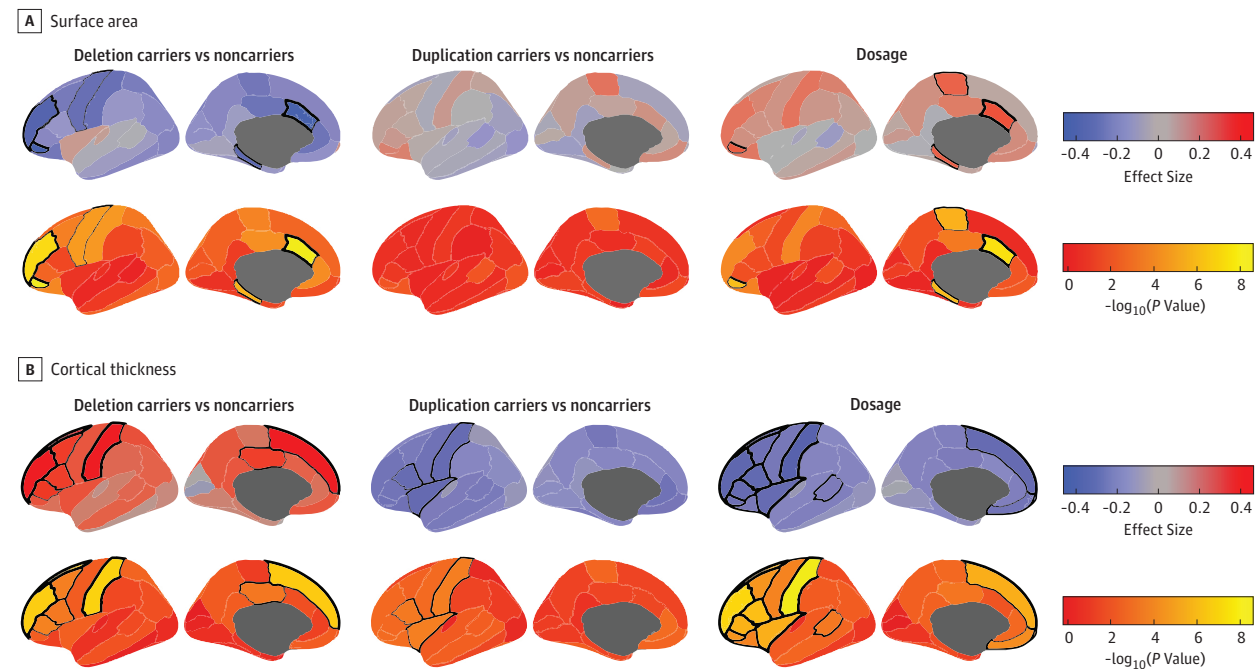
Brain Morphology Measure	Deletion Carriers vs Noncarriers		Duplication Carriers vs Noncarriers		Dosage	
	Cohen <i>d</i> (SE)	<i>P</i> Value ^b	Cohen <i>d</i> (SE)	<i>P</i> Value ^b	β (SE)	<i>P</i> Value ^c
Accumbens	-0.27 (0.07)	7.3×10^{-5}	0 (0.06)	.99	0.12 (0.05)	.02
Caudate	-0.10 (0.08)	.18	-0.02 (0.06)	.70	0.03 (0.05)	.59
Pallidum	-0.14 (0.07)	.04	0 (0.05)	.96	0.06 (0.05)	.19
Putamen	-0.08 (0.07)	.28	-0.14 (0.06)	.01	-0.04 (0.05)	.42
Thalamus	-0.07 (0.07)	.32	-0.10 (0.06)	.09	-0.02 (0.05)	.61
Amygdala	-0.07 (0.07)	.38	0.05 (0.06)	.35	0.07 (0.05)	.17
Hippocampus	-0.15 (0.08)	.05	0.07 (0.06)	.23	0.10 (0.05)	.03
Surface area	-0.41 (0.08)	4.9×10^{-8}	-0.05 (0.06)	.39	0.14 (0.05)	.005
Thickness	0.36 (0.07)	1.3×10^{-7}	-0.18 (0.06)	.002	-0.24 (0.05)	6.8×10^{-7}
Intracranial volume	0.04 (0.07)	.57	-0.06 (0.06)	.30	-0.04 (0.05)	.46

^a Multiple comparison-corrected significance set at $P < 4.7 \times 10^{-4}$.

^b Inference carried out using *t* tests.

^c Inference carried out using linear regression.

Figure 2. Association of the 15q11.2 BP1-BP2 Copy Number Variation With Regional Cortical Brain Morphology



Results from *t* tests and linear regression of 15q11.2 BP1-BP2 copy number variation on regional surface area (A) and cortical thickness (B). The effect sizes in the deletion carriers vs noncarriers and duplication carriers vs noncarriers columns are Cohen *d* values, and the effect sizes in the dosage columns are

β coefficients. Black demarcations around a brain region indicates it passes the multiple comparisons-corrected significance threshold of $P < 4.7 \times 10^{-4}$, with thicker lines indicating more significant findings.

Regional Cortical Morphology

Following up on the significant association of the 15q11.2 BP1-BP2 CNVs with total surface area and mean cortical thickness, we investigated regional measures. Here, we found a clear pattern of consistently smaller surface area and thicker cortices for deletion carriers compared with noncarriers, particularly across the frontal lobe, the anterior cingulate, and precentral and postcentral gyri (Figure 2). There were also dose responses in these same regions; duplication carriers showed

an opposite pattern, with larger surface area and thinner cortices than noncarriers, albeit with absolute Cohen *d* values of about half of those observed for the pairwise comparisons between deletion carriers and noncarriers. For the full results per brain region, see eTable 11 in Supplement 1.

Cognitive Function

The deletion carriers differed from the 2 other groups on the measures of cognition, with lower performance on all tasks,

reaching multiple comparison-corrected significance for 5 of 7 tasks. In contrast, duplication carriers performed similarly to noncarriers on all tasks.

Larger ICV and total surface area were associated with higher performance on nearly all tasks (eAppendix 1 in Supplement 1). Generally, frontal cortical surface regions were associated with task performance, particularly for the fluid intelligence and trail making B tasks. Further, in the exploratory mediation analyses, there was significant mediation only on 2 tasks; total surface area accounted for 4% of the lower fluid intelligence task results of deletion carriers, while mean cortical thickness accounted for -2% of this (eAppendix 1 in Supplement 1). For the trail making B task, total surface area and the nucleus accumbens accounted for 10% and 4%, respectively, of the lower performance of deletion carriers. The regional cortical measures indicated localization of the mediation to frontal and cingulate regions. For the full results, please see the eAppendix 1 in Supplement 1.

Discussion

Here, we report results from, to our knowledge, the largest study to date assessing associations of the 15q11.2 BP1-BP2 CNV with brain structure and cognitive function. We found that deletion carriers have widespread aberrant brain morphology and poorer cognitive performance.

Most notably, we found smaller surface area and thicker cortices for deletion carriers compared with duplication carriers and noncarriers, as well as a clear copy number dose effect on thickness. Surface area and cortical thickness are 2 complementary morphometric features of the cortex, thought to capture mostly distinct neurodevelopmental and aging processes²⁹ and to be genetically independent of each other.^{30,31} Increasing surface area combined with apparent cortical thinning, often termed *cortical stretching*, is a phenomenon primarily observed during neurodevelopment.³²⁻³⁴ It may reflect an important optimization process, as areal expansion appears a more efficient way to improve brain connectivity than increasing cortical thickness.³⁵ This is thought to result from a combination of mechanisms, including synaptic pruning and dendritic arborization leading to flattening of the cortex^{34,36} as well as increases in myelination and axon caliber causing it to stretch tangentially to the surface.³⁷ Additionally, differences in myelination may influence magnetic resonance imaging contrast and thereby cortical thickness estimates, with greater myelination leading to apparent cortical thinning by shifting the gray/white matter boundary deeper into the cortex.³⁸ In line with this, rats with *CYFIP1* haploinsufficiency, one of the genes within the 15q11.2 region, have lowered myelination.³⁹ On the other hand, a 2019 study²² reported a negative dose response of this CNV on white matter diffusion measures in humans, with deletion carriers having higher fractional anisotropy. Therefore, future neuroimaging studies of this CNV may particularly focus on white matter microstructure and the gray/white matter boundary.

Our follow-up analyses mapping the association of the 15q11.2 BP1-BP2 CNV with regional measures of cortical sur-

face area and thickness indicated localization to the frontal and cingulate cortices as well as the precentral and postcentral gyri. The frontal and cingulate regions are key regions for cognitive control, as also suggested by our brain to cognition analyses, and linked to brain disorders. The involvement of the precentral and postcentral gyri is in line with a 2019 diffusion tensor imaging study of 15q11.2 BP1-BP2 CNV carriers,²² finding the strongest effects in the posterior limb of the internal capsule, a key sensorimotor relay area implicated in schizophrenia and autism spectrum disorder, which may explain some of the motor delays associated with this CNV. As such, our findings add to reports of a 15q11.2 BP1-BP2 copy number dose response on the structure of brain regions associated with cognition and brain disorders.⁸ It should be noted that our findings of thicker cortices in deletion carriers is contrary to the cortical thinning generally observed in individuals with some brain disorders, such as schizophrenia,⁴⁰ suggesting at least partly differing neural mechanisms. This may contribute to the incomplete penetrance of this CNV and the variation in clinical profile of deletion carriers.

Altered gene expression due to 15q11.2 structural variation may affect the mechanisms underlying cortical morphology and myelination in a dose-dependent manner. Carriers of 15q11.2 BP1-BP2 duplication have 70% higher mRNA levels of all 4 genes in this region compared with noncarriers, and of these 4, *CYFIP1* and *NIPAI* are highly expressed in the developing brain.¹⁴ These 2 genes are also key players in a number of processes contributing to brain plasticity, including axon outgrowth and dendritic spine formation.⁴¹⁻⁴³ Experimentally induced low expression of *CYFIP1*, a known actin regulator, leads to a reduction in the number of mature oligodendrocytes and lower myelination,³⁹ while overexpression leads to an increase in dendritic complexity and an increased immature spine number.⁴⁴ Furthermore, common *CYFIP1* polymorphisms that influence its expression levels have been linked to variation in cortical surface area.⁴⁵ Of note, rodents with lower or higher expression of *CYFIP1* show behavioral inflexibility and poor social interaction, which may correspond partly to the observed social difficulties of some 15q11.2 BP1-BP2 CNV carriers.^{39,46}

For subcortical regions, we found that deletion carriers had significantly smaller relative volume of the nucleus accumbens compared with noncarriers. This replicates the findings on 15q11.2 BP1-BP2 of a 2019 UK Biobank magnetic resonance imaging study of CNVs associated with schizophrenia⁴⁷ using a sample that is 5-fold larger. This structure is central in behavioral adaptation on the basis of experience-dependent synaptic plasticity.^{48,49} *CYFIP1*-haploinsufficient mice show reduced gene expression specifically in the nucleus accumbens, together with compulsive-like behavior.⁵⁰ Furthermore, altered dendritic morphology of both the nucleus accumbens and frontal brain regions results in behavioral and cognitive abnormalities analogous to those seen in schizophrenia.⁵¹ Lowered gene expression leading to reduced axon outgrowth and dendritic spine formation, influencing cortical morphology, may therefore also contribute to smaller volume of the accumbens for 15q11.2 BP1-BP2 CNV deletion carriers and lead to psychopathology.

In line with the results from the brain morphology analyses, we found deletion carriers to perform worse on the tasks measuring cognitive ability. This is the same pattern as reported previously for the 15q11.2 BP1-BP2 CNV, with only deletion carriers having reduced performance and duplication carriers not performing differently from noncarriers.⁸ We find that cognitive ability is broadly affected, with the largest effect size found for the fluid intelligence task. The digit span task, reliant on working memory, and the trail making B task, testing visual attention, were further among the most strongly affected. The broader effect compared with previous studies may be due to our larger sample size, enabling differences observed in this study to reach significance; indeed, the effect sizes here are in the same range as previously reported.⁸ Our findings of widespread differences in brain morphology, particularly across the frontal cortex, attest to broadly affected cognitive ability, as also supported by our follow-up analyses of the association of the brain measures with cognition. This is consistent with the behavioral profile of associated neurodevelopmental disorders and previous findings of links between CNVs and levels of intelligence.⁵²

Despite significant dose responses on cortical measures, duplication carriers performed similarly to noncarriers on the cognitive tasks. The 15q11.2 BP1-BP2 duplication has been linked to neurodevelopmental disturbances in clinical populations,^{14,19} yet not in population samples,⁸ while the UK Biobank sample consists of older individuals (older than 45 years) with a significant healthy volunteer bias⁵³ and a strong underrepresentation of neurodevelopmental disorders. Further, the interactome of *CYFIP1* is highly enriched for genes implicated in neurological disorders,⁴¹ and there are strong indications that the effects of CNVs involve complex genetic interactions.⁵⁴ Therefore, the effect on pathological brain development and brain disorders may be dependent on other risk factors, contributing to the lack of significant results for cognition in duplication carriers as well as the clinical variability of this CNV.

Limitations

This study has limitations. Several interesting findings did not pass the multiple comparisons-corrected significance threshold in the replication sample, which may have been because

of its relatively small size. In addition, in this exploratory study, we made use of cross-sectional samples containing few young children, preventing any claims about whether the observed effects are neurodevelopmental in nature. Therefore, more focused studies are needed to confirm and follow up on our findings, ideally with longitudinal data, to investigate when this CNV exerts the identified effects. Confirmation of the CNV calls was based on visual inspection, not at the DNA level, which allows for the possibility of false negatives. However, it should be noted that the observed frequency of carriers is in line with previous studies and that the results are consistent across different single-nucleotide polymorphism arrays. Future studies should aim to include other imaging measures, such as white matter microstructure and cerebrospinal fluid, and strive to identify resilience mechanisms involved in protecting a subset of CNV carriers.

Conclusions

To conclude, we found a significant association of the 15q11.2 BP1-BP2 CNV with brain structure and cognitive performance of its carriers, improving our understanding of the nature of its association with brain disorders. To our knowledge, we report for the first time how the 15q11.2 BP1-BP2 deletion affects cortical structures in humans in a large sample. The observed effects are consistent across cohorts. Our well-powered sample enabled the discovery of a distinct pattern of lower surface area and thicker cortices of brain regions underlying high-level cognitive functions in deletion carriers. This suggests plausible biological mechanisms that might contribute to disorders associated with this CNV, not influenced by reverse causation and treatment effects. We further provided evidence that 15q11.2 BP1-BP2 deletion broadly affects cognition in a population sample, stressing the importance of incorporating CNV research in our understanding of public health.⁵⁵ Our findings fit with the known molecular functions of the genes covered by this CNV and are consistent with reports of their behavioral correlates. This work has potential clinical utility insofar as it contributes to evaluation and stratification that in time may allow for more optimal intervention.

ARTICLE INFORMATION

Accepted for Publication: September 26, 2019.

Published Online: October 30, 2019.

doi:10.1001/jamapsychiatry.2019.3779

Writing Committee for the ENIGMA-CNV

Working Group: Dennis van der Meer, PhD; Ida E. Sønderby, PhD; Tobias Kaufmann, PhD; G. Bragi Walters, BSc; Abdel Abdellou, PhD; David Ames, MD; Katrin Amunts, PhD, MD; Micael Andersson, MSc; Nicola J. Armstrong, PhD; Manon Bernard, BSc; Nicholas B. Blackburn, PhD; John Blangero, PhD; Dorret I. Boomsma, PhD; Henry Brodaty, DSc, MD; Rachel M. Brouwer, PhD; Robin Bülow, MD; Wiepke Cahn, PhD, MD; Vince D. Calhoun, PhD; Svenja Caspers, PhD, MD; Gianpiero L. Cavalleri, PhD; Christopher R. K. Ching, PhD; Sven Cichon, PhD; Simone Ciufolini, PhD, MD; Aiden Corvin, PhD, MD; Benedicto Crespo-Facorro, PhD, MD; Joanne E.

Curran, PhD; Shareefa Dalvie, PhD; Paola Dazzan, PhD; Eco J. C. de Geus, PhD; Greig I. de Zubicaray, PhD; Sonja M. C. de Zwart, MSc; Norman Delanty, MD; Anouk den Braber, PhD; Sylvane Desrivieres, PhD; Marta Di Forti, PhD, MD; Joanne L. Doherty, PhD; Gary Donohoe, PhD; Stefan Ehrlich, PhD, MD; Else Eising, PhD; Thomas Espeseth, PhD; Simon E. Fisher, DPhil; Tormod Fladby, PhD, MD; Oleksandr Frei, PhD; Vincent Frouin, MSc; Masaki Fukunaga, PhD; Thomas Gareau, PhD; David C. Glahn, PhD; Hans J. Grabe, MD; Nynke A. Groenewold, PhD; Ómar Gústafsson, PhD; Jan Haavik, PhD, MD; Asta K. Haberg, PhD, MD; Ryota Hashimoto, PhD, MD; Jayne Y. Hehir-Kwa, PhD; Derrek P. Hibar, PhD; Manon H. J. Hillegers, PhD, MD; Per Hoffmann, PhD; Laurena Holleran, PhD; Jouke-Jan Hottenga, PhD; Hilleke E. Hulshoff Pol, PhD; Masashi Ikeda, PhD, MD; Sébastien Jacquemont, MD; Neda Jahanshad, PhD; Christiane Jockwitz, PhD; Stefan

Johansson, PhD; Erik G. Jönsson, PhD, MD; Masataka Kikuchi, PhD; Emma E. M. Knowles, PhD; John B. Kwok, PhD; Stephanie Le Hellard, PhD; David E. J. Linden, DPhil; Jingyu Liu, PhD; Arvid Lundervold, PhD, MD; Astri J. Lundervold, PhD; Nicholas G. Martin, PhD; Karen A. Mather, PhD; Samuel R. Mathias, PhD; Katie L. McMahon, PhD; Allan F. McRae, PhD; Sarah E. Medland, PhD; Torgeir Moberget, PhD; Clara Moreau, PhD; Derek W. Morris, PhD; Thomas W. Mühleisen, PhD; Robin M. Murray, MD; Jan E. Nordvik, PhD; Lars Nyberg, PhD; Loes M. Olde Loohuis, PhD; Roel A. Ophoff, PhD; Michael J. Owen, PhD, FRCPsych; Tomas Paus, PhD, MD; Zdenka Pausova, MD; Juan M. Peralta, MSc; Bruce Pike, PhD; Carlos Prieto, PhD; Erin Burke Quinlan, PhD; Céline S. Reinbold, PhD; Tiago Reis Marques, PhD, MD; James J. H. Rucker, PhD, MD; Perminder S. Sachdev, PhD, MD; Sigrid B. Sando, PhD, MD; Peter R. Schofield, PhD, DSc;

Andrew J. Schork, PhD; Gunter Schumann, MD, PhD; Jean Shin, PhD; Elena Shumskaya, PhD; Ana I. Silva, MSc; Sanjay M. Sisodia, PhD, FRCP; Vidar M. Steen, PhD, MD; Dan J. Stein, PhD, MD; Lachlan T. Strike, PhD; Christian K. Tamnes, PhD; Alexander Teumer, PhD; Anbupalam Thalamuthu, PhD; Diana Tordesillas-Gutiérrez, PhD, MSc; Anne Uhlmann, PhD; Magnús Ó. Úlfarsson, PhD; Dennis van 't Ent, PhD; Marianne B. M. van den Bree, PhD; Evangelos Vassos, PhD, MD; Wei Wen, PhD; Katharina Wittfeld, PhD; Margaret J. Wright, PhD; Tetyana Zayats, PhD, MD; Anders M. Dale, PhD; Srdjan Djurovic, PhD; Ingrid Agartz, PhD, MD; Lars T. Westlye, PhD; Hreinn Stefánsson, PhD; Kári Stefánsson, PhD, MD; Paul M. Thompson, PhD; Ole A. Andreassen, PhD, MD.

Affiliations of Writing Committee for the ENIGMA-CNV Working Group: Norwegian Centre for Mental Disorders Research, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway (van der Meer, Sørnderby, Kaufmann, Frei, Jönsson, Moberget, Tamnes, Agartz, Westlye, Andreassen); School of Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands (van der Meer, Linden); deCODE Genetics, Reykjavík, Iceland (Walters, Gústafsson, Úlfarsson, H. Stefánsson, K. Stefánsson); Faculty of Medicine, University of Iceland, Reykjavík, Iceland (Walters, K. Stefánsson); Department of Psychiatry, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands (Abdellaoui); Department of Biological Psychology and Netherlands Twin Register, VU University Amsterdam, Amsterdam, the Netherlands (Abdellaoui, Boomsma, de Geus, den Braber, Hottenga, van 't Ent); University of Melbourne Academic Unit for Psychiatry of Old Age, Kew, Australia (Ames); National Ageing Research Institute, Parkville, Australia (Ames); Institute of Neuroscience and Medicine, Research Centre Juelich, Juelich, Germany (Amunts, Caspers, Cichon, Jockwitz, Mühleisen); C. and O. Vogt Institute for Brain Research, Medical Faculty, Heinrich Heine University Duesseldorf, Duesseldorf, Germany (Amunts, Mühleisen); JARA-BRAIN, Juelich-Aachen Research Alliance, Juelich, Germany (Amunts, Caspers); Umeå Centre for Functional Brain Imaging, Umeå University, Umeå, Sweden (Andersson, Nyberg); Department of Integrative Medical Biology, Umeå University, Umeå, Sweden (Andersson, Nyberg); Mathematics and Statistics, Murdoch University, Perth, Australia (Armstrong); Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada (Bernard, Pausova, Shin); South Texas Diabetes and Obesity Institute, Department of Human Genetics, School of Medicine, University of Texas Rio Grande Valley, Brownsville (Blackburn, Blangero, Curran, Peralta); Amsterdam Neuroscience, Amsterdam, the Netherlands (Boomsma, de Geus, den Braber, Hottenga, van 't Ent); Amsterdam Public Health Research Institute, VU Medical Center, Amsterdam, the Netherlands (Boomsma, de Geus, Hottenga); Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, Australia (Brodaty, Mather, Sachdev, Thalamuthu, Wen); Dementia Centre for Research Collaboration, School of Psychiatry, University of New South Wales, Sydney, Australia (Brodaty); Department of Psychiatry, UMC Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands (Brouwer,

Cahn, de Zwart, Hulshoff Pol); Department of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Greifswald, Germany (Bülow); Altrecht Science, Utrecht, the Netherlands (Cahn); Tri-institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, Emory University, Atlanta (Calhoun, Liu); The Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque (Calhoun); Institute for Anatomy I, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany (Caspers); The School of Pharmacy and Biomolecular Sciences, The Royal College of Surgeons in Ireland, Dublin, Ireland (Cavalleri); The SFI FutureNeuro Research Centre, Dublin, Ireland (Cavalleri, Delanty); Interdepartmental Neuroscience Program, University of California, Los Angeles (Ching); Imaging Genetics Center, Mark and Mary Stevens Institute for Neuroimaging and Informatics, University of Southern California, Los Angeles (Ching, Jahanshad, Thompson); Department of Biomedicine, University of Basel, Basel, Switzerland (Cichon, Mühleisen, Reinbold); Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland (Cichon, Reinbold); Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (Ciufolini, Dazzan, Reis Marques); Department of Psychiatry and Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland (Corvin); University Hospital Marqués de Valdecilla, IdahoIVAL, Centre de Investigación Biomédica en Red Salud Mental (CIBERSAM), Santander, Spain (Crespo-Facorro); University Hospital Virgen del Rocío, IBI, Centre de Investigación Biomédica en Red Salud Mental (CIBERSAM), Sevilla, Spain (Crespo-Facorro); Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, Western Cape, South Africa (Dalvie, Groenewold, Stein, Uhlmann); Faculty of Health and Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia (de Zubicaray); Beaumont Hospital, Dublin, Ireland (Delanty); Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, VU Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands (den Braber); Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (Desrivieres, Di Forti, Murray, Rucker, Vassos); MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, United Kingdom (Doherty, Linden, Owen, van den Bree); Cardiff University Brain Research Imaging Centre School of Psychology, Cardiff University, Cardiff, United Kingdom (Doherty, Silva); Centre for Neuroimaging and Cognitive Genomics, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Galway, Ireland (Donohoe, Holleran, Morris); Psychological and Social Medicine, Faculty of Medicine, Dresden University of Technology, Dresden, Germany (Ehrlich); Language and Genetics Department, Max Planck Institute for Psycholinguistics, Nijmegen, the Netherlands (Eising, Fisher); Department of Psychology, University of Oslo, Oslo, Norway (Espeseth, Reinbold, Westlye); Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands (Fisher,

Shumskaya); Akershus University Hospital, Lorenskog, Norway (Fladby); University of Oslo, Lorenskog, Norway (Fladby); Neurospin, Le Commissariat à l'énergie atomique et aux énergies alternatives, Université Paris-Saclay, Gif-sur-Yvette, France (Frouin, Gareau); Division of Cerebral Integration, National Institute for Physiological Sciences, Okazaki, Japan (Fukunaga); Department of Life Science, Sokendai, Hayama, Japan (Fukunaga); Boston Children's Hospital, Boston, Massachusetts (Glahn, Knowles, Mathias); Institute of Living, Hartford, Connecticut (Glahn); Harvard Medical School, Boston, Massachusetts (Glahn, Knowles, Mathias); Department of Psychiatry and Psychotherapy, Greifswald, Germany (Grabe, Wittfeld); German Center of Neurodegenerative Diseases (DZNE), Rostock/Greifswald, Greifswald, Germany (Grabe, Wittfeld); Department of Biomedicine, University of Bergen, Bergen, Norway (Haavik, A. Lundervold, Zayats); Division of Psychiatry, Haukeland University Hospital, Bergen, Norway (Haavik); Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway (Haberg, Sando); St Olav's Hospital, Department of Radiology and Nuclear Medicine, Trondheim, Norway (Haberg); Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Japan (Hashimoto); Osaka University, Osaka, Japan (Hashimoto); Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands (Hehir-Kwa); Genentech, San Francisco, California (Hibar); Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC-Sophia's Children's Hospital, Rotterdam, the Netherlands (Hillegers); Institute of Human Genetics, University of Bonn Medical School, Bonn, Germany (Hoffmann); Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland (Hoffmann); Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Japan (Ikeda); Sainte Justine Hospital Research Center, Montreal, Quebec, Canada (Jacquemont, Moreau); Department of Pediatrics, University of Montreal, Montreal, Quebec, Canada (Jacquemont); Department of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen University, Medical Faculty, Aachen, Germany (Jockwitz); Department of Clinical Science, University of Bergen, Bergen, Norway (Johansson); Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway (Johansson, Agartz); Centre for Psychiatric Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (Jönsson); Department of Genome Informatics, Graduate School of Medicine, Osaka University, Osaka, Japan (Kikuchi); The University of Sydney Central Clinical School, Sydney, Australia (Kwok); School of Medical Sciences, University of New South Wales, Sydney, Australia (Kwok, Schofield); Norwegian Centre for Mental Disorders Research, Department of Clinical Science, University of Bergen, Bergen, Norway (Le Hellard, Steen, Djurovic); Dr Einar Martens Research Group for Biological Psychiatry, Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway (Le Hellard, Steen); Mohn Medical Imaging and Visualization Centre, Department of Radiology, Haukeland University Hospital, Bergen, Norway (A. Lundervold); Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway

(A. J. Lundervold); Genetic Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, Australia (Martin); Neuroscience Research Australia, Randwick, Australia (Mather); Herston Imaging Research Facility and School of Clinical Sciences, Queensland University of Technology, Brisbane, Australia (McMahon); Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia (McRae); Queensland Brain Institute, The University of Queensland, Brisbane, Australia (McRae, Strike, Wright); Psychiatric Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia (Medland); Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Montreal, Quebec, Canada (Moreau); The CatoSenteret Rehabilitation Center, Son, Norway (Nordvik); Department of Radiation Sciences, Umeå University, Umeå, Sweden (Nyberg); Center for Neurobehavioral Genetics, University of California, Los Angeles (Olde Loohuis, Ophoff); Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, Ontario, Canada (Paus); Physiology and Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada (Paus, Pausova, Shin); Department of Radiology, University of Calgary, Calgary, Alberta, Canada (Pike); Bioinformatics Service, Nucleus, University of Salamanca, Salamanca, Spain (Prieto); Centre for Population Neuroscience and Precision Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (Quinlan, Schumann); Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Imperial College London, London, United Kingdom (Reis Marques); Neuropsychiatric Institute, The Prince of Wales Hospital, Sydney, Australia (Sachdev); Department of Neurology, University Hospital of Trondheim, Trondheim, Norway (Sando); Neuroscience Research Australia, Sydney, Australia (Schofield); Institute for Biological Psychiatry, Roskilde, Denmark (Schork); Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands (Shumskaya); Neuroscience and Mental Health Research Institute, Cardiff, United Kingdom (Silva); Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology and Chalfont Centre for Epilepsy, London, United Kingdom (Sisodiya); South African Medical Research Council Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa (Stein); PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway (Tamnes); Department of Psychiatry, Diakonhjemmet Hospital, Oslo, Norway (Tamnes, Agartz); Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany (Teumer); Neuroimaging Unit, Technological Facilities, Valdecilla Biomedical Research Institute, IdahoVAL, Santander, Spain (Tordesillas-Gutiérrez); Faculty of Electrical and Computer Engineering, University of Iceland, Reykjavik, Iceland (Úlfarsson); School of Medicine, Cardiff University, Cardiff, United Kingdom (van den Bree); National Institute for Health Research, Mental Health Biomedical Research Centre, South London and Maudsley National Health Service Foundation Trust and King's College London, London, United Kingdom (Vassos); Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston (Zayats);

Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Boston, Massachusetts (Zayats); Center for Multimodal Imaging and Genetics, University of California, San Diego (Dale); Department of Medical Genetics, Oslo University Hospital, Oslo, Norway (Djurovic).

Author Contributions: Drs van der Meer and Sønderby had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs van der Meer and Sønderby contributed equally to this work.

Study concept and design: van der Meer, Sønderby, Ames, Corvin, Crespo-Facorro, Glahn, Grabe, Hibar, Jahanshad, Ophoff, Paus, Sando, Dale, Agartz, Thompson, Andreassen.

Acquisition, analysis, or interpretation of data: van der Meer, Sønderby, Kaufmann, Walters, Abdellaoui, Ames, Amunts, Andersson, Armstrong, Bernard, Blackburn, Blangero, Boomsma, Brodaty, Brouwer, Bülow, Cahn, Calhoun, Caspers, Cavalleri, Ching, Cichon, Ciufolini, Crespo-Facorro, Curran, Dalvie, Dazzan, de Geus, de Zubicaray, de Zwarte, Delanty, den Braber, Desrivieres, Di Forti, Doherty, Donohoe, Ehrlich, Eising, Espeseth, Fisher, Fladby, Frei, Frouin, Fukunaga, Gareau, Glahn, Grabe, Groenewold, Gústafsson, Haavik, Haberg, Hashimoto, Hehir-Kwa, Hibar, Hillegers, Hoffmann, Holleran, Hottenga, Hulshoff Pol, Ikeda, Jacquemont, Jahanshad, Jockwitz, Johansson, Jönsson, Kikuchi, Knowles, Kwok, Le Hellard, Linden, Liu, A. J. Lundervold, A. J. Lundervold, Martin, Mather, Mathias, McMahon, McRae, Medland, Moberget, Moreau, Morris, Mühleisen, Murray, Nordvik, Nyberg, Olde Loohuis, Owen, Paus, Pausova, Peralta, Pike, Prieto, Quinlan, Reinbold, Reis Marques, Rucker, Sachdev, Sando, Schofield, Schork, Schumann, Shin, Shumskaya, Silva, Sisodiya, Steen, Stein, Strike, Tamnes, Teumer, Thalamuthu, Tordesillas-Gutiérrez, Uhlmann, Úlfarsson, van 't Ent, van den Bree, Vassos, Wen, Wittfeld, Wright, Zayats, Dale, Djurovic, Agartz, Westlye, H. Stefánsson, K. Stefánsson, Thompson, Andreassen.

Drafting of the manuscript: van der Meer, Sønderby, Walters, Fukunaga, Gústafsson, Haberg, Hibar, Hottenga, Hulshoff Pol, Knowles, Mathias, Prieto, Úlfarsson, Andreassen.

Critical revision of the manuscript for important intellectual content: van der Meer, Sønderby, Kaufmann, Abdellaoui, Ames, Amunts, Andersson, Armstrong, Bernard, Blackburn, Blangero, Boomsma, Brodaty, Brouwer, Bülow, Cahn, Calhoun, Caspers, Cavalleri, Ching, Cichon, Ciufolini, Corvin, Crespo-Facorro, Curran, Dalvie, Dazzan, de Geus, de Zubicaray, de Zwarte, Delanty, den Braber, Desrivieres, Di Forti, Doherty, Donohoe, Ehrlich, Eising, Espeseth, Fisher, Fladby, Frei, Frouin, Fukunaga, Gareau, Glahn, Grabe, Groenewold, Haavik, Haberg, Hashimoto, Hehir-Kwa, Hibar, Hillegers, Hoffmann, Holleran, Ikeda, Jacquemont, Jahanshad, Jockwitz, Johansson, Jönsson, Kikuchi, Kwok, Le Hellard, Linden, Liu, A. J. Lundervold, A. J. Lundervold, Martin, Mather, McMahon, McRae, Medland, Moberget, Moreau, Morris, Mühleisen, Murray, Nordvik, Nyberg, Olde Loohuis, Ophoff, Owen, Paus, Pausova, Peralta, Pike, Quinlan, Reinbold, Reis Marques, Rucker, Sachdev, Sando, Schofield, Schork, Schumann, Shin, Shumskaya, Silva, Sisodiya, Steen, Stein, Strike, Tamnes, Teumer, Thalamuthu, Tordesillas-Gutiérrez, Uhlmann, van 't Ent, van den Bree, Vassos, Wen, Wittfeld,

Wright, Zayats, Dale, Djurovic, Agartz, Westlye, H. Stefánsson, K. Stefánsson, Thompson, Andreassen. **Statistical analysis:** van der Meer, Sønderby, Walters, Abdellaoui, Andersson, Armstrong, Bernard, Blackburn, Calhoun, Cichon, Ciufolini, de Zwarte, Eising, Frei, Gareau, Glahn, Gústafsson, Hehir-Kwa, Hibar, Holleran, Hottenga, Ikeda, Kikuchi, Knowles, Martin, Mathias, McRae, Medland, Moberget, Olde Loohuis, Reinbold, Shin, Shumskaya, Teumer, Thalamuthu, Tordesillas-Gutiérrez, Wen, Wittfeld, Zayats, Westlye, H. Stefánsson. **Obtained funding:** Ames, Blangero, Boomsma, Brodaty, Cavalleri, Corvin, Crespo-Facorro, Dazzan, de Geus, de Zubicaray, Desrivieres, Doherty, Donohoe, Espeseth, Fisher, Fladby, Glahn, Haavik, Haberg, Martin, Nordvik, Nyberg, Ophoff, Owen, Paus, Pausova, Sachdev, Schumann, van den Bree, Djurovic, Agartz, Westlye, Thompson, Andreassen. **Administrative, technical, or material support:** Sønderby, Kaufmann, Ames, Andersson, Brouwer, Bülow, Caspers, Ching, Cichon, Crespo-Facorro, Curran, Dalvie, de Zwarte, Desrivieres, Espeseth, Fladby, Grabe, Groenewold, Hashimoto, Hibar, Hoffmann, Hottenga, Jahanshad, Johansson, Jönsson, Liu, Mather, McMahon, Medland, Murray, Nordvik, Ophoff, Paus, Pike, Quinlan, Reinbold, Reis Marques, Sachdev, Shumskaya, Stein, Strike, Tamnes, van 't Ent, van den Bree, Dale, Agartz, K. Stefánsson, Thompson, Andreassen. **Study supervision:** Sønderby, Walters, Ames, Amunts, Boomsma, Ching, Cichon, de Geus, Desrivieres, Fisher, Grabe, McMahon, Ophoff, Owen, Paus, Djurovic, K. Stefánsson, Andreassen.

Conflict of Interest Disclosures: Dr Brodaty is an advisory board member for Nutricia Australia and has received research funding from the European Union Joint Programme Neurodegenerative Disorders and the National Health and Medical Research Council of Australia. Dr Brouwer has received grants from the Netherlands Organization for Scientific Research (MagW and Brain and Cognition) and Utrecht University. Dr Caspers has received grants from the Initiative and Networking Fund of the Helmholtz Association and the European Union Horizon 2020 Research and Innovation Program under Grant Agreement 785907. Dr Ching has received research support from Biogen. Dr Crespo-Facorro has received personal fees from Janssen-Cilag, Otsuka Pharmaceutical, and Lundbeck. Dr Desrivieres has received grants from the Medical Research Council, Medical Research Foundation, NIHR Biomedical Research Centre, and National Institutes of Health. Dr Di Forti has received personal fees from Janssen Pharmaceutica. Dr Doherty has received grants from the Wellcome Trust. Dr Fladby has received grants from the Norwegian Research Council and the European Union Joint Programme Neurodegenerative Disorders. Dr Fukunaga has received grants from the Japan Society for the Promotion of Science and Japan Agency for Medical Research and Development. Dr Grabe has received grants from the German Research Foundation (DFG), German Ministry of Education and Research (BMBF), the DAMP Foundation, the European Union Joint Programme Neurodegenerative Disorders, and the European Social Fund as well as grants and personal fees from Fresenius Medical Care; personal fees from Neuraxpharm and Janssen-Cilag. Dr Haavik has received grants from Stiftelsen Kristian Gerhard Jebsen and personal fees from Eli Lilly and Co, Shire, and Biocodex.

Dr Hehir-Kwa has received grants from the Netherlands Organization for Scientific Research. Dr Hillegers has received grants from the National Alliance for Research on Schizophrenia and Depression Brain and Behavior Foundation and Netherlands Organisation for Health Research and Development. Dr Jacquemont has received grants from Brain Canada, Canada Research Chair, and Canadian Institutes of Health Research. Dr Jahanshad has received grants from the National Institutes of Health and Biogen. Dr Linden has received grants from the Wellcome Trust and book royalties from the Oxford University Press and Palgrave Macmillan. Dr Liu has received grants from the National Institutes of Health. Dr Astri Lundervold has received personal fees from Shire. Dr Mather has received grants from the National Health and Medical Research Council of Australia and Australian Research Council. Dr Moberget has received grants from the Southern and Eastern Norway Regional Health Authority. Dr Owen has received grants from the Medical Research Council, Wellcome Trust, and Takeda Pharmaceuticals. Dr Reis Marques has received personal fees from Lundbeck, Janssen Pharmaceutica, Astellas Pharma, and Angelini. Dr Rucker has received grants from the Wellcome Trust and NIHR Biomedical Research Centre. Dr Sachdev has received grants from the National Health and Medical Research Council of Australia, Australian Research Council, National Institute of Aging, Holden Foundation, Wicking Trust, Vincent Fairfax Family Foundation, and Yulgilbar Foundation as well as personal fees from Biogen. Dr Schofield has received grants from the National Health and Medical Research Council of Australia paid to Neuroscience Research Australia. Dr Steen has received grants from the Research Council of Norway. Dr Stein has received personal fees from Lundbeck and Sun Pharmaceutical Industries. Dr Thalamuthu has received grants from the National Health and Medical Research Council of Australia. Dr van den Bree has received grants from Takeda Pharmaceuticals. Dr Dale is a founder of, holds equity in, and serves on the scientific advisory board of CorTechs Lab; is a member of the scientific advisory board of Human Longevity; has received grants from GE Healthcare; and is a member of the Alzheimer's Disease Genetics Consortium (ADGC), Enhancing Imaging Genetics through Meta-Analysis (ENIGMA), Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL), and Psychiatric Genomics Consortium (PGC) groups. Dr Westlye has received grants from the Research Council of Norway, Southern and Eastern Norway Regional Health Authority, and European Research Council. Dr Thompson has received grants from Biogen. Dr Andreassen has received grants from the Research Council of Norway, Stiftelsen Kristian Gerhard Jebsen, Southern and Eastern Norway Regional Health Authority, and National Institutes of Health; personal fees from Lundbeck; and serves as a consultant for HealthLytix. No other disclosures were reported.

Funding/Support: This study is supported in part by grants U54 EB20403, R01MH116147, and R56AG058854 from the National Institutes of Health, grant 609020 from the European Union Seventh Framework Programme, and grants 223273 and 276082 from the Research Council Norway. Part of this work was performed using the Service for Sensitive Data (TSD), which is

developed and operated by the TSD Service Group and owned by the University of Oslo. Additional funding details can be found in eAppendix 2 in Supplement 1.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

- Cheng Z, Ventura M, She X, et al. A genome-wide comparison of recent chimpanzee and human segmental duplications. *Nature*. 2005;437(7055):88-93. doi:10.1038/nature04000
- Redon R, Ishikawa S, Fitch KR, et al. Global variation in copy number in the human genome. *Nature*. 2006;444(7118):444-454. doi:10.1038/nature05329
- Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nat Rev Genet*. 2012;13(8):537-551. doi:10.1038/nrg3240
- Girirajan S, Brkanac Z, Coe BP, et al. Relative burden of large CNVs on a range of neurodevelopmental phenotypes. *PLoS Genet*. 2011;7(11):e1002334. doi:10.1371/journal.pgen.1002334
- Cooper GM, Coe BP, Girirajan S, et al. A copy number variation morbidity map of developmental delay. *Nat Genet*. 2011;43(9):838-846. doi:10.1038/ng.909
- Watson CT, Marques-Bonet T, Sharp AJ, Mefford HC. The genetics of microdeletion and microduplication syndromes: an update. *Annu Rev Genomics Hum Genet*. 2014;15:215-244. doi:10.1146/annurev-genom-091212-153408
- Rees E, Kendall K, Pardiñas AF, et al. Analysis of intellectual disability copy number variants for association with schizophrenia. *JAMA Psychiatry*. 2016;73(9):963-969. doi:10.1001/jamapsychiatry.2016.1831
- Stefansson H, Meyer-Lindenberg A, Steinberg S, et al. CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature*. 2014;505(7483):361-366. doi:10.1038/nature12818
- Crawford K, Bracher-Smith M, Owen D, et al. Medical consequences of pathogenic CNVs in adults: analysis of the UK Biobank. *J Med Genet*. 2019;56(3):131-138.
- Chai JH, Locke DP, Grealis JM, et al. Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. *Am J Hum Genet*. 2003;73(4):898-925. doi:10.1086/378816
- Goytain A, Hines RM, El-Husseini A, Quamme GA. *NIPA1*(SPG6), the basis for autosomal dominant form of hereditary spastic paraplegia, encodes a functional Mg²⁺ transporter. *J Biol Chem*. 2007;282(11):8060-8068. doi:10.1074/jbc.M610314200
- Goytain A, Hines RM, Quamme GA. Functional characterization of *NIPA2*, a selective Mg²⁺ transporter. *Am J Physiol Cell Physiol*. 2008;295(4):C944-C953. doi:10.1152/ajpcell.00091.2008
- Napoli I, Mercedo V, Boyd PP, et al. The fragile X syndrome protein represses activity-dependent translation through *CYFIP1*, a new 4E-BP. *Cell*. 2008;134(6):1042-1054. doi:10.1016/j.cell.2008.07.031
- van der Zwaag B, Staal WG, Hochstenbach R, et al. A co-segregating microduplication of chromosome 15q11.2 pinpoints two risk genes for autism spectrum disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2010;153B(4):960-966. doi:10.1002/ajmg.b.31055
- Bittel DC, Kibiryeva N, Butler MG. Expression of 4 genes between chromosome 15 breakpoints 1 and 2 and behavioral outcomes in Prader-Willi syndrome. *Pediatrics*. 2006;118(4):e1276-e1283. doi:10.1542/peds.2006-0424
- Cox DM, Butler MG. The 15q11.2 BP1-BP2 microdeletion syndrome: a review. *Int J Mol Sci*. 2015;16(2):4068-4082. doi:10.3390/ijms16024068
- Mohan KN, Cao Y, Pham J, et al. Phenotypic association of 15q11.2 CNVs of the region of breakpoints 1-2 (BP1-BP2) in a large cohort of samples referred for genetic diagnosis. *J Hum Genet*. 2019;64(3):253-255. doi:10.1038/s10038-018-0543-7
- Stefansson H, Rujescu D, Cichon S, et al. Genetic Risk and Outcome in Psychosis. Large recurrent microdeletions associated with schizophrenia. *Nature*. 2008;455(7210):232-236. doi:10.1038/nature07229
- Burnside RD, Pasion R, Mikhail FM, et al. Microdeletion/microduplication of proximal 15q11.2 between BP1 and BP2: a susceptibility region for neurological dysfunction including developmental and language delay. *Hum Genet*. 2011;130(4):517-528. doi:10.1007/s00439-011-0970-4
- Kendall KM, Rees E, Escott-Price V, et al. Cognitive performance among carriers of pathogenic copy number variants: analysis of 152,000 UK Biobank subjects. *Biol Psychiatry*. 2017;82(2):103-110. doi:10.1016/j.biopsych.2016.08.014
- Ulfarsson MO, Walters GB, Gustafsson O, et al. 15q11.2 CNV affects cognitive, structural and functional correlates of dyslexia and dyscalculia. *Transl Psychiatry*. 2017;7(4):e1109. doi:10.1038/tp.2017.77
- Silva AI, Ulfarsson MO, Stefansson H, et al. Reciprocal white matter changes associated with copy number variation at 15q11.2 BP1-BP2: a diffusion tensor imaging study. *Biol Psychiatry*. 2019;85(7):563-572. doi:10.1016/j.biopsych.2018.11.004
- Winkler AM, Greve DN, Bjuland KJ, et al. Joint analysis of cortical area and thickness as a replacement for the analysis of the volume of the cerebral cortex. *Cereb Cortex*. 2018;28(2):738-749. doi:10.1093/cercor/bhx308
- Thompson PM, Stein JL, Medland SE, et al. Alzheimer's Disease Neuroimaging Initiative, EPIGEN Consortium, IMAGEN Consortium, Saguenay Youth Study (SYS) Group. The ENIGMA consortium: large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging Behav*. 2014;8(2):153-182. doi:10.1007/s11682-013-9269-5
- Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779
- Wang K, Li M, Hadley D, et al. PennCNV: an integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. *Genome Res*. 2007;17(11):1665-1674. doi:10.1101/gr.6861907

27. Sønderby IE, Gústafsson Ó, Doan NT, et al; 16p11.2 European Consortium, for the ENIGMA-CNV working group. Dose response of the 16p11.2 distal copy number variant on intracranial volume and basal ganglia [published online October 3, 2018]. *Mol Psychiatry*. doi:10.1038/s41380-018-0118-1
28. Morris DW, Pearson RD, Cormican P, et al; International Schizophrenia Consortium, SGENE+ Consortium; Wellcome Trust Case Control Consortium 2. An inherited duplication at the gene p21 protein-activated kinase 7 (*PAK7*) is a risk factor for psychosis. *Hum Mol Genet*. 2014;23(12):3316-3326. doi:10.1093/hmg/ddu025
29. Lemaitre H, Goldman AL, Sambataro F, et al. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? *Neurobiol Aging*. 2012;33(3):617.e1-617.e9. doi:10.1016/j.neurobiolaging.2010.07.013
30. Panizzon MS, Fennema-Notestine C, Eyler LT, et al. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex*. 2009;19(11):2728-2735. doi:10.1093/cercor/bhp026
31. Winkler AM, Kochunov P, Blangero J, et al. Cortical thickness or grey matter volume? the importance of selecting the phenotype for imaging genetics studies. *Neuroimage*. 2010;53(3):1135-1146. doi:10.1016/j.neuroimage.2009.12.028
32. Hogstrom LJ, Westlye LT, Walhovd KB, Fjell AM. The structure of the cerebral cortex across adult life: age-related patterns of surface area, thickness, and gyrification. *Cereb Cortex*. 2013;23(11):2521-2530. doi:10.1093/cercor/bhs231
33. White T, Su S, Schmidt M, Kao C-Y, Sapiro G. The development of gyrification in childhood and adolescence. *Brain Cogn*. 2010;72(1):36-45. doi:10.1016/j.bandc.2009.10.009
34. Tamnes CK, Herting MM, Goddings A-L, et al. Development of the cerebral cortex across adolescence: a multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness. *J Neurosci*. 2017;37(12):3402-3412. doi:10.1523/JNEUROSCI.3302-16.2017
35. Murre JMJ, Sturdy DPF. The connectivity of the brain: multi-level quantitative analysis. *Biol Cybern*. 1995;73(6):529-545. doi:10.1007/BF00199545
36. Raznahan A, Shaw P, Lalonde F, et al. How does your cortex grow? *J Neurosci*. 2011;31(19):7174-7177. doi:10.1523/JNEUROSCI.0054-11.2011
37. Seldon HL. Does brain white matter growth expand the cortex like a balloon? hypothesis and consequences. *Laterality*. 2005;10(1):81-95. doi:10.1080/13576500342000310
38. Natu VS, Gomez J, Barnett M, et al. Apparent thinning of visual cortex during childhood is associated with myelination, not pruning [published online July 13, 2018]. *bioRxiv*. doi:10.1101/368274
39. Silva AI, Haddon JE, Ahmed Syed Y, et al. *CYFIP1* haploinsufficient rats show white matter changes, myelin thinning, abnormal oligodendrocytes and behavioural inflexibility. *Nat Commun*. 2019;10(1):3455. doi:10.1038/s41467-019-11119-7
40. Rimol LM, Hartberg CB, Nesvåg R, et al. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biol Psychiatry*. 2010;68(1):41-50. doi:10.1016/j.biopsych.2010.03.036
41. De Rubeis S, Pasciuto E, Li KW, et al. *CYFIP1* coordinates mRNA translation and cytoskeleton remodeling to ensure proper dendritic spine formation. *Neuron*. 2013;79(6):1169-1182. doi:10.1016/j.neuron.2013.06.039
42. Schenck A, Bardoni B, Langmann C, Harden N, Mandel J-L, Giangrande A. *CYFIP/Sra-1* controls neuronal connectivity in *Drosophila* and links the Rac1 GTPase pathway to the fragile X protein. *Neuron*. 2003;38(6):887-898. doi:10.1016/S0896-6273(03)00354-4
43. Wang X, Shaw WR, Tsang HTH, Reid E, O'Kane CJ. *Drosophila* spichthyn inhibits BMP signaling and regulates synaptic growth and axonal microtubules. *Nat Neurosci*. 2007;10(2):177-185. doi:10.1038/nrn1841
44. Pathania M, Davenport EC, Muir J, Sheehan DF, López-Doménech G, Kittler JT. The autism and schizophrenia associated gene *CYFIP1* is critical for the maintenance of dendritic complexity and the stabilization of mature spines. *Transl Psychiatry*. 2014;4:e374. doi:10.1038/tp.2014.16
45. Woo YJ, Wang T, Guadalupe T, et al. A common *CYFIP1* variant at the 15q11.2 disease locus is associated with structural variation at the language-related left supramarginal gyrus. *PLoS One*. 2016;11(6):e0158036. doi:10.1371/journal.pone.0158036
46. Nakatani J, Tamada K, Hatanaka F, et al. Abnormal behavior in a chromosome-engineered mouse model for human 15q11-13 duplication seen in autism. *Cell*. 2009;137(7):1235-1246. doi:10.1016/j.cell.2009.04.024
47. Warland A, Kendall KM, Rees E, Kirov G, Caseras X. Schizophrenia-associated genomic copy number variants and subcortical brain volumes in the UK Biobank [published online January 24, 2019]. *Mol Psychiatry*. doi:10.1038/s41380-019-0355-y
48. Rinaldi A, Oliverio A, Mele A. Spatial memory, plasticity and nucleus accumbens. *Rev Neurosci*. 2012;23(5-6):527-541. doi:10.1515/revneuro-2012-0070
49. Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nat Rev Neurosci*. 2006;7(9):697-709. doi:10.1038/nrn1970
50. Babbs RK, Ruan QT, Kelliher JC, et al. *CYFIP1* haploinsufficiency increases compulsive-like behavior and paternally inherited palatable food intake: implications for Prader-Willi Syndrome [published online February 14, 2018]. *bioRxiv*. doi:10.1101/264846
51. Flores G, Alquicer G, Silva-Gómez AB, et al. Alterations in dendritic morphology of prefrontal cortical and nucleus accumbens neurons in post-pubertal rats after neonatal excitotoxic lesions of the ventral hippocampus. *Neuroscience*. 2005;133(2):463-470. doi:10.1016/j.neuroscience.2005.02.021
52. Huguet G, Schramm C, Douard E, et al; IMAGEN Consortium. Measuring and estimating the effect sizes of copy number variants on general intelligence in community-based samples. *JAMA Psychiatry*. 2018;75(5):447-457. doi:10.1001/jamapsychiatry.2018.0039
53. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186(9):1026-1034. doi:10.1093/aje/kwx246
54. Jensen M, Girirajan S. An interaction-based model for neuropsychiatric features of copy-number variants. *PLoS Genet*. 2019;15(1):e1007879. doi:10.1371/journal.pgen.1007879
55. Männik K, Mägi R, Macé A, et al. Copy number variations and cognitive phenotypes in unselected populations. *JAMA*. 2015;313(20):2044-2054. doi:10.1001/jama.2015.4845