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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

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, age^2, 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 (β = −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.

Supplemental content

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

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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 gathered through the Enhancing Imaging Genetics through Meta-Analysis (ENIGMA) consortium[24] 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.

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.

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 Genetics[21] 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 15p11.2 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 *d* (SE)	*P* Value[b]	Cohen *d* (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).

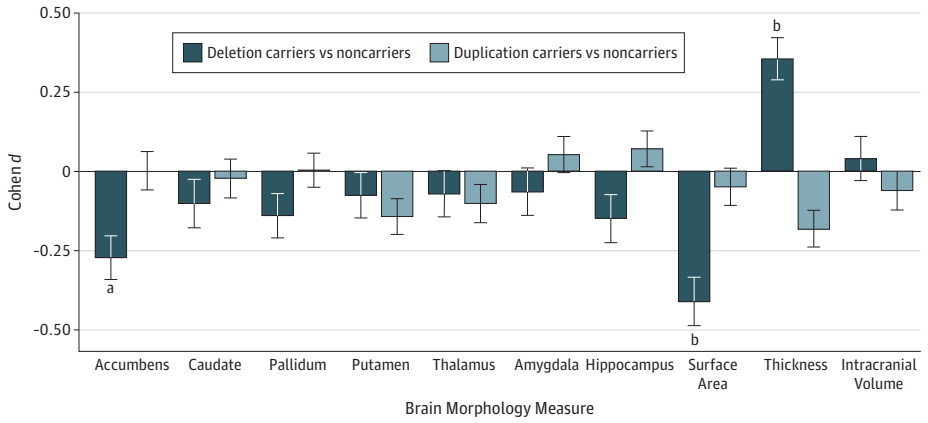
Cognitive Task Performance

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



Bar plot visualizing Cohen *d* values for the difference in brain morphology measures between carriers and noncarriers of the 15q11.2 BP1-BP2 copy number variation, from the meta-analysis *t* tests. Error bars indicate standard errors.

[a] $P < 4.7 \times 10^{-4}$.

[b] $P < 4.7 \times 10^{-6}$.

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, age^2, 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 βs 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]

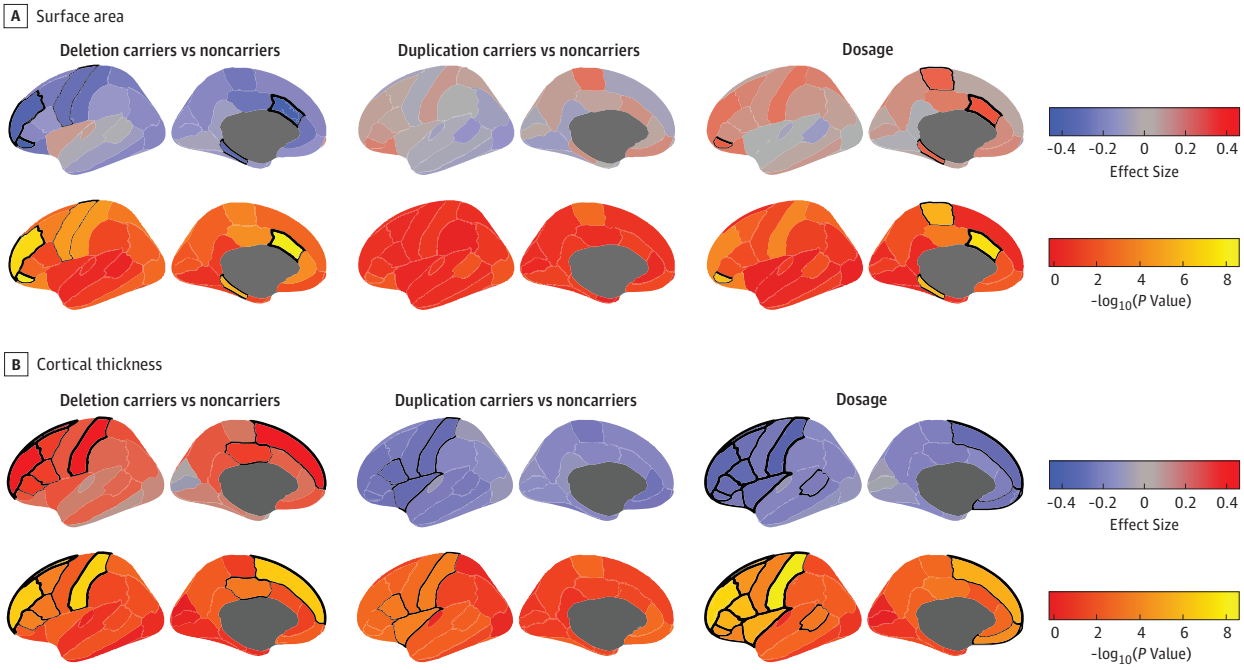
	Deletion Carriers vs Noncarriers		Duplication Carriers vs Noncarriers		Dosage	
Brain Morphology Measure	Cohen *d* (SE)	*P* Value[b]	Cohen *d* (SE)	*P* Value[b]	β (SE)	*P* Value[c]
Accumbens	−0.27 (0.07)	7.3×10^{-5}	0 (0.06)	.99	0.12 (0.05)	.02
Caudate	−0.10 (0.08)	.18	−0.02 (0.06)	.70	0.03 (0.05)	.59
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 processes[29] 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 study[22] 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 surface 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 *NIPA1* 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 schizophrenia[47] 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 bias[53] 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

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