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Convergent and Divergent Cerebellar Alterations in 22q11.2 Copy Number Variants

Hoki Fung, Kathleen P. O'Hora, Rune Boen, Haley R. Wang, Carolyn M. Amir, Charles H. Schleifer, Leila Kushan-Wells, Blake A. Miranda, Elizabeth K. Bondy, Paul J. Mathews, and Carrie E. Bearden

ABSTRACT

BACKGROUND: Copy number variants (CNVs) at 22q11.2 confer substantial risk for neurodevelopmental and psychiatric disorders. Both the 22q11.2 deletion (22qDel) and 22q11.2 duplication (22qDup) are associated with increased risk for autism spectrum disorder and intellectual disability. In contrast, while 22qDel markedly increases risk for schizophrenia, 22qDup may be protective. Prior neuroimaging work has focused primarily on the cerebrum, leaving cerebellar contributions understudied, despite growing evidence for their relevance to cognition and psychopathology. Here, we characterized regional cerebellar structure and examined multivariate cerebellar-behavior associations in individuals with reciprocal 22q11.2 CNVs.

METHODS: We analyzed 514 structural magnetic resonance imaging scans from 315 participants (mean age = 16.4 ± 8.8 years; 52% female), comprising 22qDel carriers (n = 111), 22qDup carriers (n = 37), and typically developing (TD) control participants (n = 167). The cerebellum was parcellated into 28 subregions using ACAPULCO. Group differences in total and regional cerebellar volumes were examined using linear mixed-effects models with false discovery rate correction. Multivariate brain-behavior associations were assessed using partial least squares correlation (PLSC).

RESULTS: Relative to TD control participants, 22qDel carriers showed widespread cerebellar volume reductions, whereas alterations in 22qDup were milder and regionally selective. Vermis VII was reduced in both 22q11.2 CNVs, indicating a shared site of anatomical vulnerability. PLSC identified domain-specific cerebellar patterns, with posterior regions—most prominently bilateral lobule VIIIA—associated with cognitive and social functioning and bilateral crus II and medial regions associated with psychosis-risk symptoms.

CONCLUSIONS: Reciprocal 22q11.2 CNVs showed shared and divergent cerebellar alterations, with distinct subregions contributing to different behavioral domains, underscoring the cerebellum's multifaceted role in neurodevelopment and psychiatric disease risk.

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Copy number variants (CNVs) (i.e., deletions or duplications) at the 22q11.2 locus have a profound impact on neurodevelopment and clinical outcomes, encompassing a wide range of cognitive, psychiatric, and socioaffective symptoms (1–3). 22q11.2 deletion (22qDel), a hemizygous deletion of ~1.5 to 2.6 megabases on the long arm of chromosome 22, is the most common contiguous gene deletion syndrome, occurring in ~1 in 3700 live births (4). Along with craniofacial abnormalities, congenital heart defects, and other medical conditions, 22qDel confers greatly increased likelihood of developmental neuropsychiatric disorders including autism spectrum disorder (ASD), intellectual disability (ID), attention-deficit/hyperactivity disorder (ADHD), and anxiety disorders (1). Notably, 22qDel is one of the strongest known genetic risk factors for schizophrenia, with ~1 in 10 carriers meeting diagnostic criteria (5) and approximately one-third exhibiting clinically significant subthreshold psychosis symptoms (6,7).

The 22q11.2 duplication (22qDup) is the reciprocal of the 22qDel, occurring at the same locus and typically of comparable size (8). It affects many of the same bodily systems and may also be associated with developmental delays, craniofacial abnormalities, cardiovascular defects, and other congenital abnormalities (9). Common neurobehavioral features include learning difficulties, motor impairment, attention deficits, and social and behavioral problems (10). Clinical and behavioral manifestations are generally milder and more heterogeneous than in 22qDel, and many individuals appear clinically unaffected (4). Consistent with this, the 22qDup is often underascertained clinically and may be more common in the general population than 22qDel, with an estimated prevalence of ~1 in 1600 live births (4). Despite its overall milder presentation, 22qDup is associated with elevated risk for several neurodevelopmental and psychiatric conditions, including ASD, ID, ADHD, and anxiety disorders, at levels

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comparable to 22qDel (4,11,12). In contrast, 22qDup does not confer the same elevated risk for schizophrenia and may even be associated with reduced risk relative to the general population (4,13,14). Together, this combination of shared neurodevelopmental features and divergent psychosis risk positions reciprocal 22q11.2 CNVs as a powerful genetics-first model for dissecting neurobiological mechanisms underlying shared and divergent cognitive, socioaffective, and psychiatric vulnerabilities.

Despite this compelling premise, neuroimaging data on 22qDup carriers remain scarce; nevertheless, our recent findings indicate that copy number variation at the 22q11.2 locus is associated with systematic differences in brain morphology across a number of metrics (7,15–21). Across studies, two general patterns have emerged. First, 22qDel carriers consistently exhibit widespread reductions across multiple brain metrics, including intracranial, gray, and white matter volumes, on average, relative to control participants (15–17,22). Second, structural findings in 22qDup carriers are generally subtler and more heterogeneous, with many measures resembling typically developing (TD) control individuals and only a subset exhibiting opposing effects relative to 22qDel carriers. For example, 22qDel is associated with reduced cortical surface area, increased cortical thickness, smaller hippocampal volume, larger corpus callosum volume, and higher fractional anisotropy assessed via diffusion-weighted imaging, whereas 22qDup carriers show the opposite pattern (15,19,20). Together, these findings provide initial evidence that copy number–dependent effects at the 22q11.2 locus are selective rather than uniformly symmetric across brain measures, underscoring the need for targeted characterization of neural systems relevant to cognition, autism-related traits, and psychosis risk.

The cerebellum is of particular relevance in this context. The cerebellum contains up to 80% of all neurons in the human brain, despite only representing 10% of total brain mass (23). While traditionally viewed as a motor structure, the cerebellum has become of increasing interest as a critical hub for cognitive, affective, and social processing, with rapidly growing evidence for altered development in neuropsychiatric and neurodevelopmental disorders, including schizophrenia and ASD (24). Neuroimaging studies have revealed a topographic organization of the cerebellum, with motor functions localized to the anterior lobe and part of lobules IV and VIII; cognitive functions localized to the posterior lobe, primarily lobule VII; and affective processes localized to the posterior vermis and adjacent regions (25–27). Reduced cerebellar gray matter volume has been consistently reported in idiopathic schizophrenia, with widespread reductions across multiple cerebellar lobules. These reductions are most pronounced in posterior regions linked to higher-order cognitive networks, while anterior, motor-related regions appear relatively less affected (28). Findings in idiopathic ASD have been less consistent, with reports of both increased and decreased total cerebellar volumes, but converging evidence implicates cerebellar regions that support social and cognitive functions (29,30).

Within this framework, genetically defined CNV populations offer a unique opportunity to examine cerebellar contributions to behavioral features and clinical risks in a more etiologically homogeneous manner. In 22qDel, reduced total cerebellar volume has been consistently observed across cross-sectional studies conducted during childhood, adolescence, and adulthood (31–36), but regional characterization remains limited, with only one study to date reporting widespread lobular reductions at fine anatomical resolution (37). In contrast, cerebellar structure has not been systematically examined in 22qDup. Consequently, it is unknown whether cerebellar alterations are present in 22qDup, whether they overlap with or diverge from those observed in 22qDel, and how such patterns may relate to shared versus distinct neurobehavioral phenotypes across the two CNVs.

Addressing this gap is particularly important given accumulating evidence that individuals with 22qDup exhibit clinically meaningful impairments in cognition and social functioning (12), despite the absence of elevated psychosis risk. Therefore, direct comparison of cerebellar structure in 22qDel and 22qDup provides a critical opportunity to disentangle cerebellar alterations associated with shared neurodevelopmental vulnerabilities from those that may contribute to divergent psychiatric outcomes, including psychosis.

Here, we investigated volumetric differences in the cerebellum and its subregions across individuals with 22qDel, individuals with 22qDup, and TD control participants, leveraging the largest structural magnetic resonance imaging (MRI) dataset of 22qDup currently available. Guided by prior work, we hypothesized that cerebellar volumes would differ across CNV groups, with both shared and CNV-specific patterns revealed through direct comparison of 22qDel and 22qDup. We addressed these aims using ACAPULCO, a novel deep learning–based cerebellar parcellation method (38), applied to the largest MRI sample of reciprocal 22q11.2 CNVs available to date. To assess functional relevance, we used partial least squares correlation (PLSC), a data-driven multivariate approach, to examine patterns of covariation between cerebellar volumes and behavioral and clinical measures. We hypothesized that cerebellar regions associated with cognitive functioning and autism-related traits would be distinct from those associated with psychosis-risk symptoms.

METHODS AND MATERIALS

Participants and Study Design

In this study, we collected 524 longitudinal structural MRI scans from 317 unique individuals across 3 groups: 22qDel, 22qDup, and TD control. Participants with molecularly confirmed 22qDel or 22qDup were recruited as part of an ongoing longitudinal study at the University of California Los Angeles (UCLA). Recruitment occurred through clinical referrals, community outreach, and research registries. TD control participants were recruited from the same communities as CNV carriers. All participants underwent cognitive testing, clinical assessments, and structural MRI scanning across 1 to 6 annual visits (mean number of visits per participant = 1.63). Written informed consent (or assent with parental consent for minors) was obtained from all participants. All procedures were approved by the Institutional

Review Board at UCLA. Additional recruitment and exclusion details are provided in Supplemental Methods.

Behavioral and Clinical Measures

Cognitive ability was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) or WASI-II (39,40). Autism-related traits were measured with the Social Responsiveness Scale, Second Edition (41). Psychosis-risk symptoms were evaluated using the Structured Interview for Psychosis-Risk Syndromes (42). Full descriptions of each instrument, scoring procedure, and the number of available observations are provided in Supplemental Methods.

MRI Acquisition, Image Processing, and Harmonization

Structural MRI data were acquired at UCLA using three 3T Siemens scanners (Trio and Prisma) with standardized T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequences (43). Images were visually inspected for quality, and estimated total intracranial volume (eTIV) was determined using FreeSurfer (version 5.3/version 6.0) (44). Cerebellar parcellation was performed using ACAPULCO (version 3.0) (38), a state-of-the-art deep learning–based method that automatically segments the cerebellum from raw T1-weighted images into 28 anatomically defined subregions using two cascaded convolutional networks (see Table S2 for the full list of regions). Volumes were harmonized across scanners using Longitudinal ComBat (45). Detailed acquisition parameters, preprocessing steps, and quality control procedures are provided in Supplemental Methods.

Statistical Analysis

Group differences in total and regional cerebellar volumes were examined using linear mixed-effects models with fixed effects for group, sex, mean-centered age (linear and quadratic), and eTIV, with a random intercept for participant. False discovery rate (FDR) correction was applied across 28 subregions. Sensitivity analyses assessing robustness to current psychotropic medication use and age stratification, along with model specifications, data transformations, and visualization methods, are described in Supplemental Methods.

To examine multivariate brain-behavior associations, we used PLSC to identify latent components (LCs) capturing shared covariance between regional cerebellar volumes and neurobehavioral measures (46,47). Guided by prior evidence of convergent alterations in cognition and social functioning (12) and gene dosage–dependent differences in psychosis risk in 22q11.2 CNVs (13,14), we specified two separate PLSC models: one examining cognitive ability and reciprocal social functioning and another examining psychosis-risk symptoms. PLSC analyses were conducted on harmonized cerebellar volumes and relevant behavioral and clinical measures, with statistical significance assessed using permutation testing. Full methodological details, including the complete list of measures included in each PLSC model, are provided in Supplemental Methods.

RESULTS

Participant Characteristics

The full sample included 317 unique participants and 524 MRI sessions. Following parcellation quality control, 10 scans were excluded due to poor-quality cerebellar segmentations, resulting in a final analytic sample of 514 sessions from 315 participants: 111 with 22qDel, 37 with 22qDup, and 167 TD control. Baseline demographic and behavioral characteristics of the study sample, along with group comparison statistics, are summarized in Table 1. Briefly, groups were comparable in sex and age. Both CNV groups showed lower IQ and elevated autism-related traits compared with the TD control group. Psychosis symptoms were elevated in the 22qDel group compared with both the 22qDup group and the TD control group. These patterns are consistent with a previous cross-sectional characterization of phenotypic features of 22q11.2 CNVs in a subset of this cohort (12).

Total Cerebellar Volume

A linear mixed-effects model revealed significantly smaller total cerebellar volume in the 22qDel group compared with the TD control group ($B = -16{,}072.03$, $p < .001$), while the 22qDup group showed no significant difference from the TD control group ($B = 1579.76$, $p = .46$) (see Table S1 for full model output). Direct comparison between the two CNV groups indicated that total cerebellar volume was significantly smaller in 22qDel relative to 22qDup.

Regional Cerebellar Volume

To characterize regional cerebellar volume differences across groups, we conducted region-wise analyses across 28 anatomically defined regions. When TD control participants were used as the reference group (Figure 1A), individuals with 22qDel showed widespread cerebellar volume reductions, with 25 of 28 regions (except bilateral lobule IV and left lobule V) significantly smaller after FDR correction ($q < .05$). Non-thresholded beta estimates are displayed on a cerebellar flatmap in Figure 2A, and full model results are provided in Table S2.

In contrast, individuals with 22qDup showed a more heterogeneous pattern of regional volume differences relative to TD control participants (Figure 1A). Although beta estimates suggested larger volumes in some regions and smaller volumes in others (Figure 2B), effect sizes were generally smaller. Only vermis VII was significantly smaller in individuals with 22qDup compared with TD control participants after FDR correction ($B = -100.05$, $q < .05$). At the nominal threshold ($p < .05$), right lobule VIIIA ($B = -358.09$, $p = .047$, $q = .36$) was smaller and vermis IX ($B = 61.02$, $p = .041$, $q = .36$) was larger in individuals with 22qDup relative to TD control participants. See Table S2 for full model results.

Direct comparisons between the two CNV groups, implemented by reparameterizing the original models with 22qDel as the reference group (Figure 1B), revealed significantly larger regional volumes in the 22qDup group relative to the 22qDel group across most cerebellar regions (20 of 28). The largest group differences were observed in vermis IX ($B = 229.48$,

Table 1. Participant Characteristics at Baseline by Group

Measure	TD Control, n = 167	22qDel, n = 111	22qDup, n = 37	Group Comparisons[a]
Age, Years	16.2 (6.9)	16.2 (9.4)	18.2 (13.5)	KW $\chi^2_2 = 1.79$, $p = .408$
Age Range, Years	6–45	5–55	5–49	–
Sex, Female	51.5%	55.0%	48.6%	$\chi^2_2 = 0.55$, $p = .758$
eTIV, mm^3	1,541,862 (159,072)	1,429,772 (179,795)	1,543,068 (162,409)	$F_{2,312} = 16.25$, $p < .001$; 22qDel < TD ≈ 22qDup
FSIQ	112.12 (19.64)	79.34 (12.36)	97.32 (17.24)	KW $\chi^2_2 = 86.8$, $p < .001$; 22qDel < 22qDup < TD
SRS-2 Total T-Score	47.5 (10.3)	70.5 (14.3)	66.8 (16.2)	KW $\chi^2_2 = 66.88$, $p < .001$; TD < 22qDel ≈ 22qDup
SIPS-P Total Score	1.24 (1.84)	5.99 (6.54)	2.62 (3.09)	KW $\chi^2_2 = 38.4$, $p < .001$; TD ≈ 22qDup < 22qDel

Values are presented as mean (SD), range, and %. Baseline demographic, cognitive, and clinical characteristics of TD control participants, individuals with 22qDel, and individuals with 22qDup. Group comparison statistics are reported for all measures. The 3 groups were comparable in sex and age distributions at baseline. FSIQ was lower in both CNV groups. SRS-2 total T-scores, reflecting autism-related traits, were elevated in both CNV groups relative to the control group. SIPS-P total scores, reflecting psychosis severity, were higher in individuals with 22qDel relative to both TD control participants and individuals with 22qDup, with no significant difference between TD control participants and individuals with 22qDup. eTIV was lower in the 22qDel group compared with both the TD control and 22qDup groups.

ANOVA, analysis of variance; CNV, copy number variant; eTIV, estimated total intracranial volume; FSIQ, Full Scale IQ; HSD, honestly significant difference; KW, Kruskal-Wallis; 22qDel, 22q11.2 deletion; 22qDup, 22q11.2 duplication; SIPS-P, Structured Interview for Psychosis-Risk Syndromes Positive Symptoms; SRS-2, Social Responsiveness Scale, Second Edition; TD, typically developing.

[a]Group differences in continuous variables were tested using 1-way ANOVA (eTIV) or KW tests (age, FSIQ, SRS-2 total T-score, SIPS-P total score), depending on normality and variance. χ^2 tests were used for categorical variables (sex). Post hoc pairwise comparisons used Tukey's HSD test (ANOVA) or Wilcoxon rank-sum tests with Bonferroni correction (nonparametric).

$p < .001$), left lobule VIIIB ($B = 660.72$, $p < .001$), right crus II ($B = 1228.06$, $p < .001$), and the corpus medullare ($B = 2098.59$, $p < .001$). Full model results are provided in Table S3.

To distinguish regions showing shared versus CNV-specific patterns of alterations, we integrated TD-referenced and 22qDel-referenced results. At the FDR-corrected level

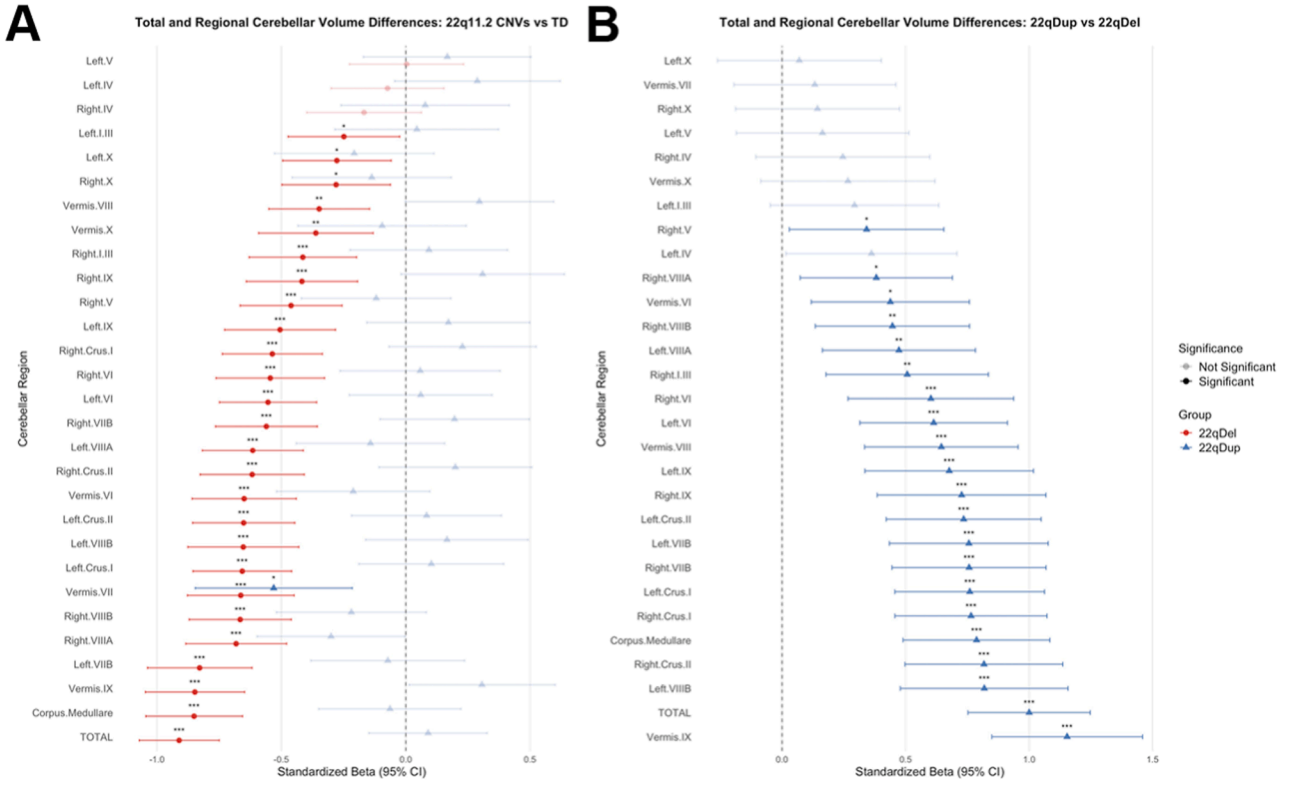

Figure 1. Group differences in total and regional cerebellar volumes. **(A)** Standardized beta coefficients and 95% CIs are shown for 22qDel and 22qDup groups relative to the TD control group. **(B)** Standardized beta coefficients and 95% CIs for the 22qDup group relative to the 22qDel group. Results in both panels were derived from the same linear mixed-effects model specification, with group reference levels varied to estimate the relevant contrasts. Models included fixed effects of sex, mean-centered age (linear and quadratic), and estimated intracranial volume, with participant-level random intercepts to account for repeated measures. Asterisks indicate significance after FDR correction for regional volumes: *$q < .05$, **$q < .01$, ***$q < .001$. TOTAL refers to total cerebellar volume and is shown with the uncorrected p value, as it was not included in the FDR correction. 22qDel, 22q11.2 deletion; 22qDup, 22q11.2 duplication; CNV, copy number variant; FDR, false discovery rate; TD, typically developing.

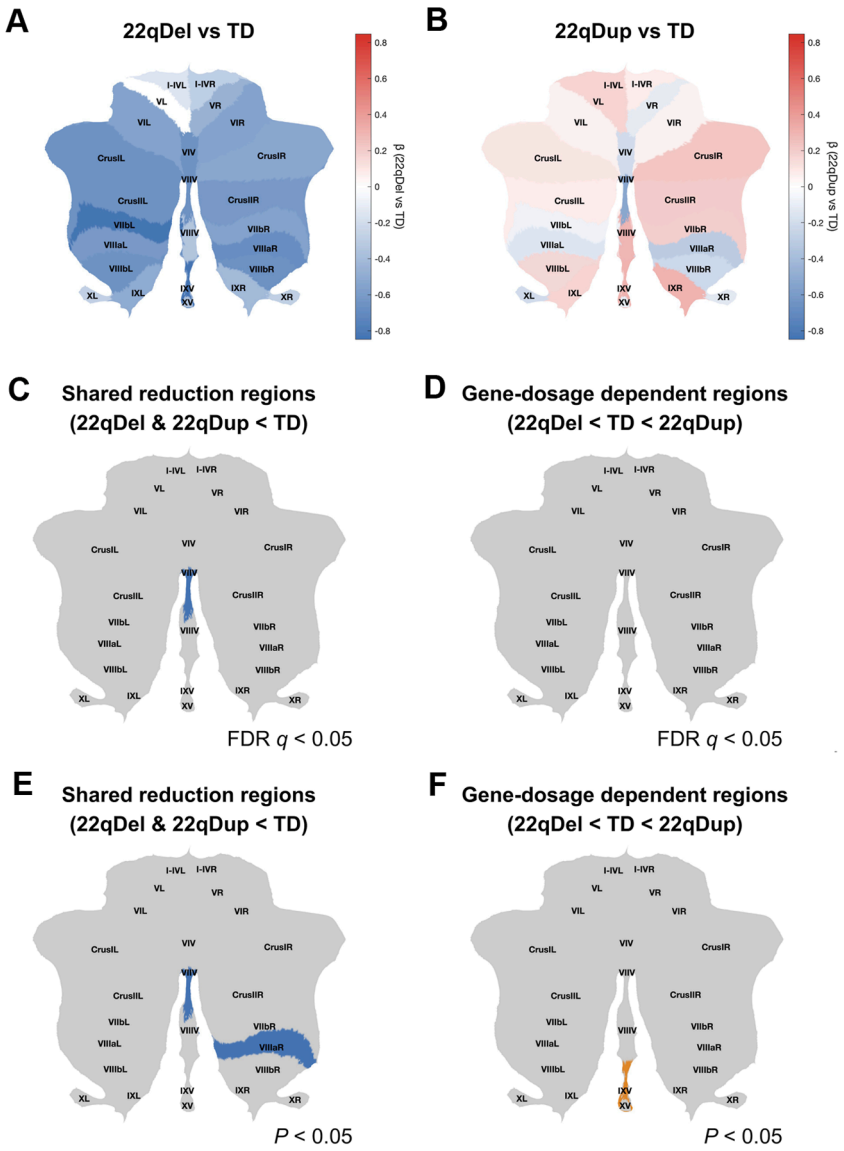

Figure 2. Flatmap visualizations of cerebellar volume differences across 22q11.2 copy number variants. **(A)** Flatmap indicating widespread cerebellar volume reductions in individuals with 22qDel compared with TD control participants, particularly in midline and lateral posterior regions. **(B)** Flatmap indicating more subtle and heterogeneous volume differences in individuals with 22qDup compared with TD control participants, including both increases and reductions across subregions. **(C)** Binary map highlighting regions with convergent volume reductions in 22qDel and 22qDup at $q_{FDR} <$ .05 (vermis VII). **(D)** Binary map highlighting regions with monotonic gene dosage effects (22qDel < TD < 22qDup) at $q_{FDR} <$ .05 (no regions). **(E)** Binary map highlighting regions with convergent volume reductions in 22qDel and 22qDup at uncorrected $p <$ .05 (vermis VII, right lobule VIIIA). **(F)** Binary map highlighting regions with monotonic gene dosage effects (22qDel < TD < 22qDup) at uncorrected $p <$ .05 (vermis IX). Regional volumes were derived using the ACAPULCO cerebellar parcellation and mapped to SUIT-defined anatomical regions for visualization. Beta values reflect standardized group effects from linear mixed-effects models, displayed without *p*-value thresholding on a symmetric scale (blue = negative, red = positive). To align with SUIT's anatomical scheme, beta values of lobule I to III and lobule IV from ACAPULCO were averaged to create a single lobule I to IV region. The corpus medullare was not visualized in these maps. Binary maps show regions where both the 22qDel and 22qDup groups differed significantly from the TD control group at the indicated threshold; gray regions indicate regions that did not meet this criterion. See Table S2 for full model results. 22qDel, 22q11.2 deletion; 22qDup, 22q11.2 duplication; FDR, false discovery rate; L, left; R, right; SUIT, spatially unbiased infratentorial template; TD, typically developing.

(Figure 2C, D), vermis VII was significantly smaller in both 22q11.2 CNV groups relative to the TD control group and did not differ significantly between the 22qDel and 22qDup groups ($B = 24.93$, $p = .43$), indicating a convergent reduction of comparable magnitude across CNVs (22qDel ≈ 22qDup < TD). At the nominal level, right lobule VIIIA was smaller in both CNV groups relative to the TD control group (Figure 2E) but showed significantly larger volume in the 22qDup group than in the 22qDel group ($B = 454.53$, $p = .02$), consistent with a graded effect (22qDel < 22qDup < TD). In contrast, vermis IX exhibited a distinct gene dosage–dependent pattern across groups (22qDel < TD < 22qDup) (Figure 2F).

Sensitivity Analyses

Adjusting for current medication use (antipsychotics, antidepressants, psychostimulants, and any psychotropic medication) and repeating analyses separately in pediatric (<18 years) and adult (≥18 years) subgroups did not alter the overall pattern or interpretation of total or regional cerebellar volume differences. Detailed results are provided in Supplemental Results) (Tables S4–S6).

Associations Between Cerebellar Volume and Neurobehavioral Outcomes

PLSC: Cognitive Ability and Autism-Related Traits. PLSC analysis identified a single significant LC ($q_{FDR} <$ .05) capturing 95.3% of the covariance between cerebellar regional volumes and measures of cognitive ability and reciprocal social behavior. Cerebellar and behavioral composite scores were significantly correlated across all participants ($r = 0.41$, $p <$ .001) (Figure 3A), indicating a robust multivariate association between

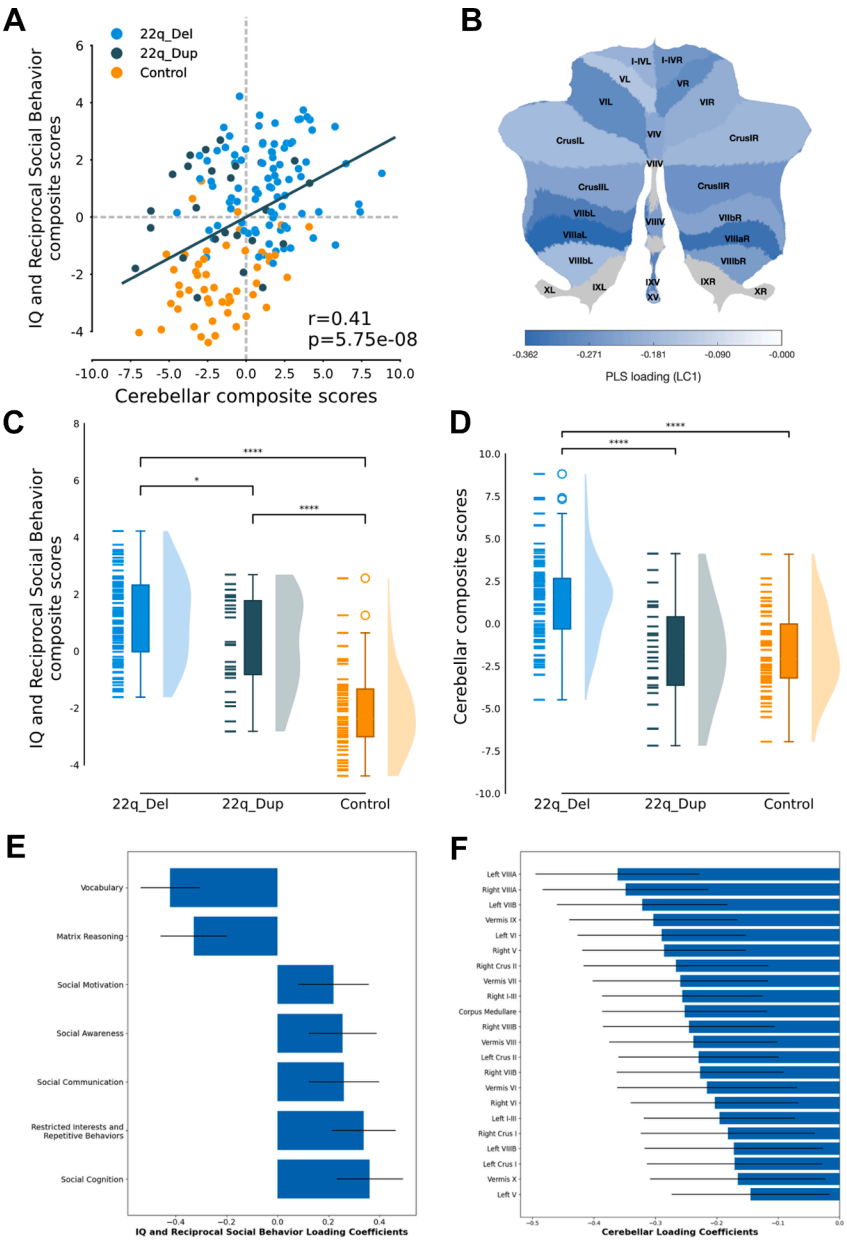

Figure 3. Multivariate associations between cerebellar volume and cognitive and social functioning. PLS correlation identified a single significant LC (false discovery rate–corrected $q < .05$) explaining 95.3% of the covariance between cerebellar regional volumes and measures of cognitive ability and reciprocal social behavior. **(A)** Cerebellar and behavioral composite scores were significantly correlated across participants ($r = 0.41$, $p < .001$). **(B)** Cerebellar loadings showed a distributed pattern of lower volumes across posterior cerebellar regions. **(C, D)** Behavioral and cerebellar composite scores differed across groups. **(E, F)** Loadings indicated that the strongest contributions were from posterior cerebellar regions, including the bilateral lobule VIIIA, left lobule VIIB, and vermis IX, associated with lower cognitive ability and greater autism-related social difficulties. $^{*}p < .05$, $^{****}p < .0001$. 22q_Del, 22q11.2 deletion; 22q_Dup, 22q11.2 duplication; L, left; LC, latent component; PLS, partial least squares; R, right.

cerebellar structure and cognitive and social functioning. To characterize the nature of this association, we examined the LC loadings (Figure 3E, F). These loadings indicate that higher LC scores reflect smaller cerebellar volumes across multiple regions, lower cognitive ability, and greater autism-related social difficulties. Cerebellar contributions were the strongest in posterior regions (Figure 3B), including the left lobule VIIIA ($r = -0.36$), right lobule VIIIA ($r = -0.35$), left lobule VIIB ($r = -0.32$), vermis IX ($r = -0.30$), and left lobule VI ($r = -0.29$). Together, these findings suggest that multiregional cerebellar volume reduction, particularly in lobule VIIIA, is associated with lower cognitive ability and greater social functioning impairments across groups.

Group comparisons of LC composite scores revealed differences across groups; behavioral composite scores (i.e., reflecting lower cognitive ability and greater autism-related social difficulties) were higher in CNV groups relative to the TD control group (Figure 3C), whereas cerebellar composite scores (i.e., reflecting smaller multiregional cerebellar volumes) were higher in the 22qDel group compared with both the TD control and 22qDup groups (Figure 3D). Detailed results, including within-group correlations and the full set of cerebellar and behavioral measures contributing to LC, are provided in Supplemental Results.

PLSC: Psychosis-Risk Symptoms. PLSC analysis identified a single significant LC ($q_{FDR} < .05$) capturing 94.0% of the covariance between cerebellar regional volumes and psychosis-risk symptoms. Cerebellar and behavioral composite scores were significantly correlated across all participants included in the analysis ($r = 0.28$, $p < .001$) (Figure 4A), indicating a robust multivariate association between cerebellar structure and psychosis-risk symptom severity. To characterize the nature of this association, we examined the LC loadings (Figure 4E, F). Higher LC scores are characterized by smaller cerebellar volumes across multiple regions and greater severity of positive psychosis-risk symptoms. Cerebellar contributions were the strongest in the left crus II ($r = -0.27$), right crus II ($r = -0.27$), the corpus medullare ($r = -0.26$), and vermis IX ($r = -0.24$) (Figure 4B). Together, these findings suggest that multiregional cerebellar volume reduction, particularly in crus II, is associated with greater severity of positive psychosis-risk symptoms across groups.

Group comparisons of LC composite scores revealed differences across groups. Psychosis-risk behavioral composite

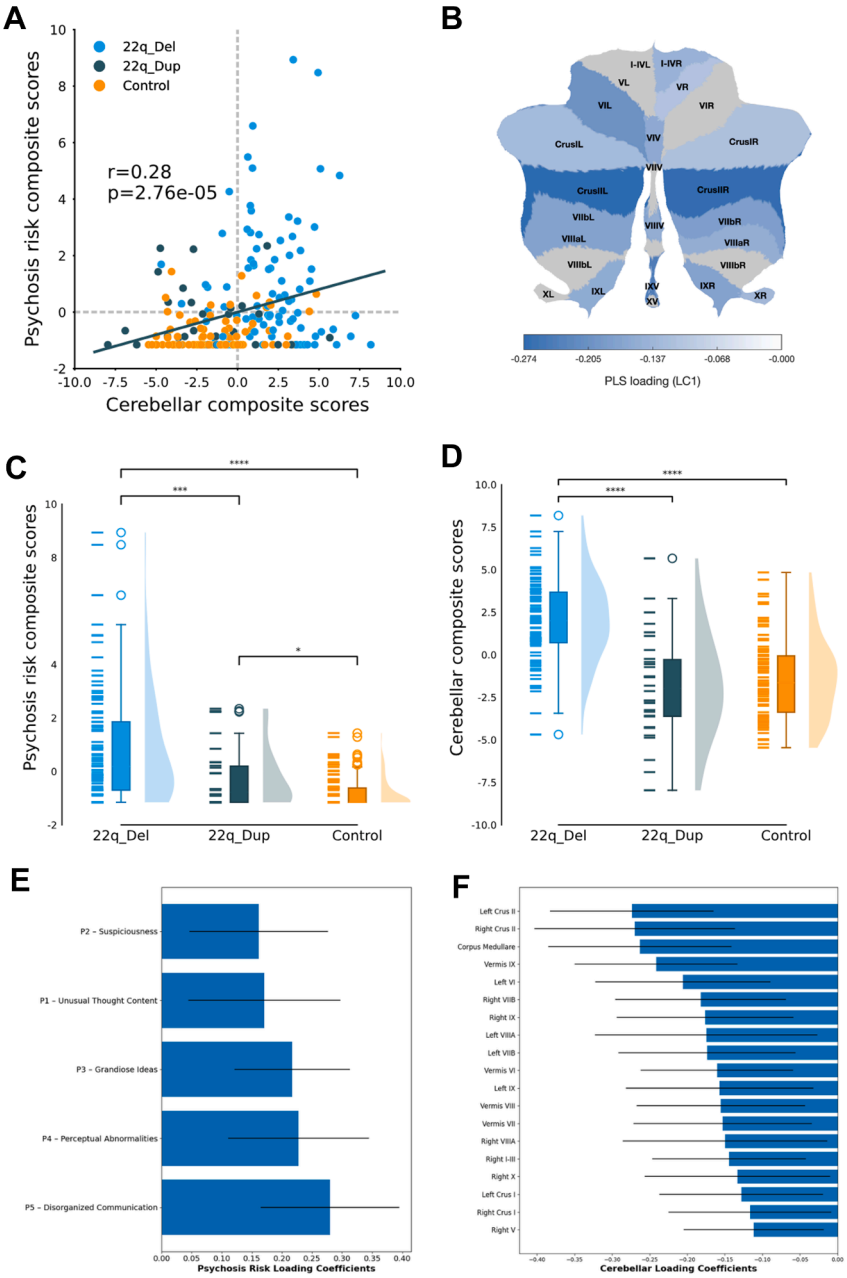

Figure 4. Multivariate associations between cerebellar volume and psychosis-risk symptoms. PLS correlation identified a single significant LC (false discovery rate–corrected $q < .05$) explaining 94.0% of the covariance between cerebellar regional volumes and psychosis-risk symptoms. **(A)** Cerebellar and behavioral composite scores were significantly correlated across participants ($r = 0.28$, $p < .001$). **(B)** Cerebellar loadings showed a distributed pattern of lower volumes across medial and hemispheric regions. **(C, D)** Behavioral and cerebellar composite scores differed across groups. **(E, F)** Loadings indicated that the strongest contributions were from the bilateral crus II, corpus medullare, and vermis IX, associated with greater severity of positive psychosis-risk symptoms. $^{*}p < .05$, $^{***}p < .001$, $^{****}p < .0001$. 22q_Del, 22q11.2 deletion; 22q_Dup, 22q11.2 duplication; L, left; LC, latent component; PLS, partial least squares; R, right.

scores (i.e., reflecting greater psychosis-risk symptom severity) were highest in the 22qDel carriers, intermediate in the 22qDup carriers, and lowest in the TD control group (Figure 4C). Cerebellar composite scores (i.e., reflecting smaller multiregional cerebellar volumes) were higher in individuals with 22qDel relative to both individuals with 22qDup and TD control participants (Figure 4D). Detailed results, including within-group correlations and the full set of cerebellar and psychosis-risk clinical measures contributing to LC, are provided in Supplemental Results.

DISCUSSION

In this study, we examined cerebellar volumetric alterations and their behavioral relevance in individuals with reciprocal 22q11.2 CNVs using high-resolution structural MRI data and lobule-specific parcellation. Extending prior reports of reduced cortical and cerebellar volume in 22qDel carriers (15–17,22), we found that cerebellar involvement in 22q11.2 copy number variation is not characterized by simple reciprocal gene dosage effects. While individuals with 22qDel showed widespread reductions in total and regional cerebellar volume, alterations in 22qDup were relatively subtle and heterogeneous, with preserved global volume but focal regional deviations. This pattern reveals a previously unrecognized, regionally selective architecture of cerebellar vulnerability, comprising both shared and CNV-specific effects rather than a uniform 22qDel $<$ TD $<$ 22qDup gradient. Notably, vermis VII—implicated in motor learning and coordination and cognitive-affective functions (48,49)—was significantly reduced in both CNV groups, reflecting a shared locus of cerebellar vulnerability. Multivariate brain-behavior analyses identified two robust, domain-specific cerebellar covariance patterns, with posterior cerebellar regions, including bilateral lobule VIIIA, contributing most strongly to cognitive-social functioning and bilateral crus II to psychosis-risk symptoms. Together, these findings highlight selective and region-specific cerebellar involvement in 22q11.2 CNVs and provide the first lobule-level characterization of cerebellar volume alterations in individuals with 22qDup.

Cerebellar Alterations in 22qDup

A central contribution of this study is the comprehensive characterization of cerebellar morphology in individuals with 22qDup, enabling direct comparison with 22qDel carriers. Unlike the widespread hypoplasia observed in deletion carriers, the 22qDup was associated with regionally specific alterations, including a significant reduction in vermis VII and nominal trends toward reduction of right lobule VIIIA but enlargement of vermis IX. The absence of a group-level difference in total cerebellar volume may reflect this bidirectional regional pattern, in which local increases and decreases offset one another at the global scale. These findings indicate that 22qDup does not represent simply the inverse of 22qDel but instead exerts subtler, spatially selective effects on cerebellar development. This asymmetry is consistent with prior reports in cortical and subcortical systems, in which deletions—both at 22q11.2 and more broadly—show large, pervasive effects, whereas duplications exhibit lower penetrance and more heterogeneous neuroanatomical consequences (15,19,50). Together, these results underscore the importance of regionally resolved analyses for detecting duplication-related effects that may be obscured by global measures.

Multivariate Cerebellar-Behavior Relationships: Insights From PLSC

Using PLSC, we identified robust multivariate associations between cerebellar regional volumes and neurobehavioral outcomes across all participants, with patterns that were specific to behavioral domains. For cognitive ability and autism-related social traits, reduced volumes across a broad set of cerebellar regions, particularly within the posterior cerebellum, were associated with lower cognitive performance and greater social impairment. These results are consistent with accumulating evidence for the cerebellum's role in higher-order cognitive and socioaffective processes (25,26,51). Bilateral lobule VIIIA, along with lobules VI and VIIB, contribute to cognitive functions (25,52), with lobule VIIb/VIIIa specifically serving as a node within the dorsal attention network and supporting visual working memory representations (53–55). The cerebellar vermis has been implicated in emotional processing (51,56,57) and shows consistent structural abnormalities in idiopathic ASD (58–60). These findings support the hypothesis that cerebellar dysfunction contributes to cognitive and social deficits observed in both 22q11.2 CNV carriers and idiopathic ASD.

In contrast, psychosis-risk symptoms were associated with a distinct cerebellar pattern characterized by prominent contributions from bilateral crus II and vermis IX, with reduced volumes linked to greater positive symptom severity regardless of genetic diagnosis. Widespread posterior cerebellar reductions, particularly in crus I/II, are consistent structural signatures of schizophrenia and psychosis (28,61,62). These structural abnormalities are consistent with the cognitive dysmetria framework, which proposes that impaired cerebello-thalamo-cortical circuitry underlies psychotic symptomatology (63–66). The cerebellar vermis shows consistent structural abnormalities across the psychotic-affective spectrum (67,68) and has been implicated in emotional processing (51,56,57), supporting cerebellar dysfunction as a core feature of emerging psychosis (28,69,70).

Together, these cerebellar-behavior associations indicate that distinct cerebellar subregions contribute differentially to cognitive-social functioning and psychosis-related dimensions, reinforcing the cerebellum's multifunctional role in neurodevelopment and psychiatric risk. Importantly, these multivariate associations reflected shared brain-behavior covariance across participants, with diagnostic groups differing in expression rather than in the underlying latent structure, highlighting the value of multivariate approaches for disentangling domain-specific brain-behavior relationships from diagnostic contrasts.

Focal Anatomical Vulnerability and Distributed Brain-Behavior Associations

Across analyses, vermis VII emerged as the most consistent site of convergent anatomical reduction across both CNV groups. As part of the posterior limbic cerebellum, vermis VII has been implicated in emotional processing (51,56,57) and

cognitive functions (25,49,71). Structural reductions in vermal lobules VI and VII have been consistently reported in ASD (29,30,60) and are consistent with the social and cognitive deficits observed in these conditions. Notably, vermis VII contributed to both multivariate brain-behavior models examined in this study but was not among the strongest regional contributors to either. This dissociation suggests that while vermis VII represents a shared site of anatomical vulnerability, cerebellar influences on behavioral outcomes are not driven by a single region in isolation. In contrast, vermis IX showed nominal copy number–dependent volumetric differences (22qDel < TD < 22qDup) and emerged as a stronger contributor across both multivariate models, highlighting it as a potential locus through which 22q11.2 copy number variation differentially shapes cerebellar contributions to multiple behavioral domains. More broadly, these findings underscore that cerebellar risk in 22q11.2 CNVs is best understood through distributed multivariate patterns that integrate both shared and divergent regional effects rather than single-region abnormalities alone.

Limitations

Several limitations of the current study should be noted. Although our sample is the largest to examine cerebellar morphology in 22q11.2 CNVs, statistical power remains limited for duplication carriers. Accordingly, findings involving 22qDup should be interpreted as providing a first, foundational characterization of cerebellar features that motivates future replication and extension. The wide age range of the sample represents both a strength and a limitation: It enables examination of cerebellar structure across a broad developmental window but also introduces heterogeneity. Although age was modeled flexibly and supported by sensitivity analyses, developmental trajectories could not be fully examined within the scope of the current study. Finally, while the multivariate analyses revealed stable, data-driven cerebellar-behavioral associations consistent with prior literature, interpretation should consider the relatively young sample, characterized by low endorsement of positive psychosis-risk symptoms compared with other clinically ascertained cohorts, as well as the effective sample size being constrained to participants with complete multivariate data. Therefore, the brain-behavior findings should be viewed as complementary and intended to inform future hypothesis-driven studies.

Implications and Future Directions

Using a genetics-first approach, we found that reciprocal 22q11.2 CNV carriers—both associated with elevated ASD risk—share a focal cerebellar vulnerability, with vermis VII emerging as the most consistently reduced region. This convergence with findings in idiopathic ASD positions the cerebellum as a common neural substrate across genetic and nongenetic forms of risk. At the same time, nominal effects in the right lobule VIIIA (22qDel < 22qDup < TD) and vermis IX (22qDel < TD < 22qDup) reveal regional heterogeneity, indicating that beyond shared vulnerabilities, cerebellar alterations diverge in a region-specific and copy number–dependent manner. Furthermore, multivariate analyses show that cognitive-social functioning and psychosis risk are associated with distinct distributed cerebellar profiles rather than isolated focal abnormalities. High-resolution lobular parcellation was key to detecting these effects, emphasizing the need for fine-grained brain-behavior mapping across CNV types.

Future studies with larger, longitudinal samples will be critical for increasing power to detect group differences and for examining developmental changes in cerebellar structure across 22q11.2 CNVs. As cerebellum-specific, developmentally resolved gene expression resources continue to mature (72,73), future work will be well positioned to more directly integrate regional neuroimaging findings with temporospatial patterns of gene expression relevant to 22q11.2 CNVs and their clinical expression. In addition, complementary approaches incorporating functional parcellation, cerebellar functional connectivity, transcriptomics, and detailed behavioral phenotyping will further clarify cerebellar mechanisms in 22q11.2 CNVs. Finally, direct comparisons with clinically and behaviorally defined high-risk groups and other neuropsychiatric CNVs (e.g., 3q29 and 16p11.2 CNVs) will help delineate shared and unique cerebellar mechanisms across neurodevelopmental disorders.

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ARTICLE INFORMATION

From the Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, California (HF, KPO, RB, HRW, CMA, CHS, LK-W, EKB, CEB); Neuroscience Interdepartmental Program, University of California, Los Angeles, Los Angeles, California (HF, KPO, CMA, CHS, BAM); Department of Psychology, University of California, Los Angeles, Los Angeles, California (HRW, BAM, CEB); Department of Neurology, UCLA, Los Angeles School of Medicine, Los Angeles, California (PJM); and The Lundquist Institute, Harbor-UCLA Medical Center, Torrance, California (PJM).

Address correspondence to Carrie E. Bearden, Ph.D., at cbearden@mednet.ucla.edu.

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