Contribution of copy number variations to the risk of severe eating disorders

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Aim: Eating disorders (EDs) are complex, multifactorial psychiatric conditions. Previous studies identified pathogenic copy number variations associated with NDDs (NDD-CNVs) in ED patients. However, no statistical evidence for an association between NDD-CNVs and EDs has been demonstrated. Therefore, we examined whether NDD-CNVs confer risk for EDs.

Methods: Using array comparative genomic hybridization (aCGH), we conducted a high-resolution CNV analysis of 71 severe female ED patients and 1045 female controls. According to the American College of Medical Genetics guidelines, we identified NDD-CNVs or pathogenic/likely pathogenic CNVs in NDD-linked loci. Gene set analysis was performed to examine the involvement of synaptic dysfunction in EDs. Clinical data were retrospectively examined for ED patients with NDD-CNVs.

Results: Of the samples analyzed with aCGH, 70 severe ED patients (98.6%) and 1036 controls (99.1%) passed our quality control filtering. We obtained 189 and 2539 rare CNVs from patients and controls, respectively. NDD-CNVs were identified in 10.0% (7/70) of patients and 2.3% (24/1036) of controls. Statistical analysis revealed a significant association between NDD-CNVs and EDs (odds ratio = 4.69, \( P = 0.0023 \)). NDD-CNVs in ED patients included 45,X and deletions at KATNAL2, DIP2A, PTPRT, RBFOX1, CNTN4, MACROD2, and FAM92B. Four of these genes were related to synaptic function. In gene set analysis, we observed a nominally significant enrichment of rare exonic CNVs in synaptic signaling in ED patients (odds ratio = 2.55, \( P = 0.0254 \)).

Conclusion: Our study provides the first preliminary evidence that NDD-CNVs may confer risk for severe EDs. The pathophysiology may involve synaptic dysfunction.

Keywords: anorexia nervosa, copy number variations, eating disorders, synapses.

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focused on severe subgroup of patients because patients with severe symptoms or treatment-resistance are more likely to carry rare deleterious variants of large effect.\textsuperscript{6} We found the first preliminary evidence for an association between NDD-CNVs and severe EDs. The findings from NDD-CNVs and gene set analysis suggest that the pathophysiology of these disorders may involve synaptic dysfunction.

**Methods**

**Participants**

This study was approved by the ethics committee of Nagoya University Graduate School of Medicine, and written informed consent was obtained from participants. All participants were Japanese females and recruited in the center of main island of Japan. We studied 71 severe ED patients (mean age 29.2 \pm 9.4 years) and 1045 controls (mean age 37.9 \pm 13.6 years). All patients required hospitalization in the psychiatric ward of Nagoya University Hospital and had a lifetime minimum BMI <15 kg/m\(^2\) (median: 11.3 kg/m\(^2\); range: 8.0–14.9 kg/m\(^2\)). They had a clinically diagnosed history of AN restrictive type (AN-R; \(n = 29\)), AN binge-eating/purging type (AN-BP; \(n = 36\)), or avoidant/restrictive food intake disorder (ARFID) (\(n = 6\)) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). The mean age of onset was 19.5 years. Controls were selected from the general population and had no history of psychiatric disorders based upon responses to questionnaires or self-reporting.

**CNV analysis**

We performed CNV analysis using array comparative genomic hybridization (aCGH): Agilent SurePrint G3 human CGH 400k (Agilent, Santa Clara, CA). We generated CNV calls for all subjects with Nexus Copy Number software v9.0 (BioDiscovery, El Segundo, CA) using the Fast Adaptive States Segmentation Technique 2 algorithm. The following log2 ratio thresholds were set to detect CNVs in the Agilent arrays: 10–500 kb: –0.6 (deletion) and 0.4 (duplication), >500 kb: –0.4 (deletion) and 0.3 (duplication). These thresholds are much more stringent than the default thresholds of \(\alpha = 0.71\) for aCGH data. The significance threshold to adjust the sensitivity of the segmentation algorithm was set at \(1 \times 10^{-6}\) and at least three contiguous probes were required for CNV calls. A noise-reduction algorithm for aCGH data was used for the systematic correction of artifacts caused by GC content and fragment length.

In terms of quality control (QC), scores were calculated for each sample based on the statistical variance of the probe-to-probe log ratios. These QC scores showed the quality of the sample and experiment, with lower QC scores indicating higher quality results. We excluded samples with QC \(>0.2\), gender mismatch, and excessive autosomal CNV calls (Subject QC). Next, we excluded CNV calls <10 kb, those with low probe density (<1 probe/30 kb), >70% overlap with segmental duplications, >10% overlap with CpG islands, and Call P-value \(>1 \times 10^{-10}\), and those on the Y chromosome. Then, we filtered out common CNVs (\(\pm 1\)% of the total sample). Finally, we obtained high-quality rare (<1%) CNVs for all subjects. All genomic locations were given in hg18 coordinates. In our previous study, we confirmed that rare CNVs from Agilent arrays are highly accurate with a validation rate >99%.\textsuperscript{6}

The Wilcoxon rank-sum test was used to compare the number and size of rare CNVs between ED patients and controls.

**Identification of NDD-CNVs**

We aimed to identify NDD-CNVs in our sample. For this purpose, we preselected 867 loci (826 risk genes and 41 CNV loci) that are linked to NDDs (Supplementary Table 1a and b). The NDD-linked genes were selected from the SFARI database (category 1–3) and Developmental Brain Disorder Gene Database (Tier 1–3). The association between these genes and NDDs were supported by strong genetic evidence from rare variant studies (e.g., the identification of \textit{de novo} variants). The NDD-linked CNV loci were selected based on our previous study.\textsuperscript{7} Then, we identified pathogenic or likely pathogenic CNVs in these loci according to the American College of Medical Genetics guidelines.\textsuperscript{10,11} Briefly, pathogenic/likely pathogenic CNVs in the NDD-linked genes included intragenic deletions and duplications overlapping with at least one exon of such genes, which would affect protein structure and function. Conversely, intronic CNVs, intragenic CNVs involving only the 3' end of genes, and intragenic duplications overlapping with the first or last exon were not considered to be pathogenic. Intragenic duplications overlapping with the first or last exon are often not deleterious because functional gene structure may be preserved.\textsuperscript{12} NDD-CNVs identified in patients were validated with quantitative real-time PCR.

The sample size of patients was relatively small, and genetic heterogeneity of EDs was assumed to be high. Therefore, we explored an association between all NDD-CNVs combined and EDs. The statistical significance of the association was calculated using the two-tailed Fisher’s exact test.

**Gene set analysis**

To examine the involvement of synaptic dysfunction in the pathophysiology of EDs, we performed a gene set analysis using synaptic gene sets. Specifically, we evaluated whether rare exonic CNVs (both deletions and duplications) intersecting genes within a synaptic gene set are enriched in ED patients. Two synaptic gene sets were taken from SynGO\textsuperscript{13} and used for this analysis: synapse organization (GO:0050808, 306 genes) and synaptic signaling (GO:0099536, 193 genes). SynGO is a knowledge base that focuses on synapse-specific ontologies, and its annotations are based on published, expert-curated evidence.\textsuperscript{13} In SynGO, the selected gene sets are positioned as representative sets related to synaptic function. Two-tailed Fisher’s exact tests were used for statistical analysis. The significance level \(\alpha\) was determined by dividing 0.05 by the number of tests for Bonferroni correction \((\alpha = 0.05 / 2 = 0.025): P\)-values below 0.025 were considered significant, while \(P\)-values between 0.025 and 0.05 were considered nominally significant.

**Phenotypic assessment**

We obtained longitudinal clinical data for patients with NDD-CNVs from medical records. The data included developmental history, age at onset, psychiatric symptoms, number of admissions, psychiatric comorbidities, premorbid IQ (JART scores), and brain imaging findings. Comorbid psychiatric disorders were assessed based on the developmental and current history and other available information obtained by interviews from patients and their families. Diagnosis was made according to the DSM-5.

**Results**

**Identification of CNVs**

Of the 71 severe ED patients and 1045 controls analyzed with aCGH, 70 patients (98.6%) and 1036 controls (99.1%) passed our quality control filtering. The lifetime minimum BMI in ED patients was 11.4 kg/m\(^2\) (range: 8.0–14.9 kg/m\(^2\)). We identified 2728 rare CNVs (<1%) in all subjects and their characteristics are shown in Table 1. Of these CNVs, 38% and 62% were <50 kb and <100 kb in size, respectively. There was no significant difference in the number and size of rare CNVs between ED patients and controls (number: \(P = 0.38\), size: \(P = 0.71\)).

**Identification of NDD-CNVs**

Table 2 shows the identified NDD-CNVs in the present study. We found eight NDD-CNVs in seven ED patients (three AN-R, three AN-BP, and one ARFID): 45X and deletions at KATNAL2, DIP2A, PTPRT, RBFOX1, CNTN4, MACROD2, and FAM92B. These deletions affected at least one exon of NDD genes (Fig. 1). The NDD-CNVs identified in ED patients affected four synaptic genes (i.e., PTPRT, DIP2A, RBFOX1, and CNTN4). One AN-BP patient (Case 3) had two NDD-CNVs (deletions at DIP2A and PTPRT). In controls, we identified 24 NDD-CNVs: 17 CNVs disrupting NDD
genes and seven large recurrent CNVs. Thus, 10.0% (7/70) of ED patients and 2.3% (24/1036) of controls carried one or two NDD-CNVs. Statistical analysis showed a significant excess of these CNVs in ED patients compared to controls (odds ratio = 4.69, \( p = 0.0023 \)).

**Gene set analysis**

The results of gene set analysis are shown in Table 3. We found a nominally significant enrichment of rare exonic CNVs in synaptic signaling in ED patients (odds ratio = 2.55, \( P = 0.0254 \)).

### Table 1. Characteristics of rare CNVs

| Diagnosis | ED patients | CONT | Total |
|-----------|-------------|------|-------|
| Sample size (after QC) | 70 | 1036 | 1106 |
| Total number of rare CNVs | 189 | 2539 | 2728 |
| Mean number of rare CNVs per subject | 2.70 | 2.45 | 2.47 |
| Proportion of deletions | 0.54 | 0.54 | 0.54 |
| Proportion of <100 kb | 0.6 | 0.62 | 0.62 |
| Proportion of <50 kb | 0.35 | 0.38 | 0.38 |
| Median CNV size (kb) | 74.1 | 69.6 | 69.6 |

Abbreviations: CNV, copy number variation; CONT, control; ED, eating disorder.

### Table 2. List of NDD-CNVs identified in the present study

| Sample ID | Diagnosis | CNV regions (hg18) | CNV size (kb) | NDD-CNVs |
|-----------|-----------|--------------------|---------------|----------|
| Case 1 | AN-R | chrX:239315–154882257 | 154643 | 45,X |
| Case 2 | AN-BP | chr18:42803418–42850905 | 47 | KATNAL2 del |
| Case 3 | AN-BP | chr20:4071367–40755445 | 42 | PTPRT del |
| Case 4 | AN-BP | chr16:6729807–674172 | 144 | RBFOX1 del |
| Case 5 | AN-R | chr3:2249529–2272390 | 23 | CNNT4 del |
| Case 6 | ARFID | chr20:14512172–14984703 | 473 | MACROD2 del |
| Case 7 | AN-R | chr16:83647246–83979767 | 151 | FAM92B del |
| Control 1 | CONT | chr16:74896665–74925155 | 28 | CNNTAP4 dup |
| Control 2 | CONT | chr2:50871072–51045009 | 174 | NRXN1 del |
| Control 3 | CONT | chr22:7882326–8885747 | 62 | TNR6B del |
| Control 4 | CONT | chr15:23748243–23561947 | 84 | ATPI10a dup |
| Control 5 | CONT | chr3:31663373–31824111 | 161 | DMO del |
| Control 6 | CONT | chr11:98640950–98771710 | 131 | CNNT5 dup |
| Control 7 | CONT | chr15:20194004–20751393 | 557 | 15q11.2 (NPH1) del |
| Control 8 | CONT | chr16:1501188–16701937 | 1671 | 16p13.11 (NDE1, MYH11) dup |
| Control 9 | CONT | chr22:49223470–49258901 | 62 | SBF1 del |
| Control 10 | CONT | chr11:99236699–99319332 | 83 | CNNT5 del |
| Control 11 | CONT | chr4:92011820–92091768 | 80 | CCSER1 dup |
| Control 12 | CONT | chr15:2858517–30241239 | 1656 | 15q13.3 (CHRNA7, FAN1) dup |
| Control 13 | CONT | chr11:99095140–10562141 | 6586 | 11q22.1–q23.3 (CNNT5, TRPC6) del |
| Control 14 | CONT | chr5:11422713–11441999 | 19 | CNNTN2 del |
| Control 15 | CONT | chr6:16719401–167252680 | 59 | RPS6K2A2 del |
| Control 16 | CONT | chr22:172721966–19961412 | 2689 | 22q11.21 (velocardiofacial syndrome region) dup |
| Control 17 | CONT | chr16:21753133–22445650 | 693 | 16p12.1 (EEF2K, CDR2) del |
| Control 18 | CONT | chr20:14905262–15154939 | 250 | MACROD2 del |
| Control 19 | CONT | chr11:99319332–99414236 | 95 | CNNT5 dup |
| Control 20 | CONT | chr10:56120554–56328279 | 208 | PCDH15 del |
| Control 21 | CONT | chr15:20194004–20987146 | 793 | 15q11.2 (NPH1) del |
| Control 22 | CONT | chrX:6571854–7935080 | 1363 | Xp22.31 (X-linked ichthyosis region, STS) del |
| Control 23 | CONT | chr9:119081759–119111496 | 30 | ASTN2 dup |
| Control 24 | CONT | chr1:53259586–53292991 | 33 | SCP2 del |

Abbreviations: AN-BP, anorexia nervosa binge-eating/purging type; AN-R, anorexia nervosa restrictive type; ARFID, avoidant/restrictive food intake disorder; CONT, control; del, deletion; dup, duplication; NDD, neurodevelopmental disorder.
Severe eating disorders and CNVs

Phenotypic assessment
Table 4 summarizes clinical data for patients with NDD-CNVs. Age of onset of EDs was 15–23 years, and lifetime lowest BMI ranged from 10.6 to 14.6 kg/m². Case 1 with 45,X had a history of language delay. Case 4 with RBFOX1 deletion had mild intellectual disability and alcohol use disorder. Her full-scale IQ, verbal IQ, and performance IQ were 75, 64, and 74, respectively. Although these results showed borderline intelligence, she was clinically determined to have mild intellectual disability based on the information of her developmental, educational, and life history. Two other patients (Case 5 with CNTN4 deletion and Case 6 with MACROD2 deletion) had a comorbidity of major depressive disorder. Three of seven patients showed cortical atrophy on brain MRI. We compared clinical variables between patients with (N = 7) and without (N = 63) NDD-CNVs. No significant difference in age of onset, number of admissions, or premorbid IQ (p > .05) was found.

Discussion
We provide the first evidence for an association between NDD-CNVs and severe EDs (odds ratio = 4.69, P = 0.0023). This highlights an important role for CNVs in the risk for severe EDs. The NDD-CNVs identified in patients included 45,X and deletions at KATNAL2, PTPRT, DIP2A, RBFOX1, CNTN4, MACROD2, and FAM92B. These genes were associated with risk of autism spectrum disorder and/or other NDDs by identification of de novo (loss-of-function) variants.14–19 In addition, two NDD-CNVs (CNTN4 deletion and 45,X) were also reported in ED patients. Both deletion and duplication disrupting CNTN4 were observed in AN patients.9 In a recent population-based study, females with 45,X (Turner syndrome) were found to have twice the risk of EDs.20 These findings are consistent with studies showing shared genetic factors between EDs and NDDs.3,21 Phenotypic data also showed a high rate (43%) of developmental problems in patients with NDD-CNVs, including language delay, cognitive delay, and low birth weight. Three AN patients
Table 4. A brief summary of clinical data for ED patients with NDD-CNVs

| NDD-Patient CNVs Diagnosis | Family history of psychiatric disorders | Developmental history | Age at Onset (years) | Severe dietary restriction | Disturbed body image | Fear of gaining weight | Binge-eating/purging | Lifetime lowest BMI (kg/m²) | Psychiatric comorbidity | Brain MRI |
|---------------------------|----------------------------------------|-----------------------|----------------------|--------------------------|---------------------|------------------------|----------------------|--------------------------|-----------------------|----------|
| Case 1 45,X AN-R | – | Language delay | 23 | + | + | + | 12.0 | – | Cortical atrophy | NA |
| Case 2 KATNAL2 deletion | AN-BP | – | Normal | 20 | + | + | + | 12.2 | – | Cortical atrophy | NA |
| Case 3 DIP2A deletion PTPRT deletion | AN-BP | – | Normal | 22 | + | + | + | 11.0 | – | Cortical atrophy | NA |
| Case 4 RBFOX1 deletion | AN-BP | + | Cognitive delay | 15 | + | + | + | 10.6 | Mild ID; alcohol use disorder | Cortical atrophy |
| Case 5 CNTN4 deletion | AN-R | NA | Normal | 16 | + | + | + | 14.6 | MDD | Normal |
| Case 6 MACROD2 deletion | ARFID | – | Low birth weight | 20 | + | + | + | 11.0 | MDD | NA |
| Case 7 FAM92B deletion | AN-R | + | Normal | 15 | + | + | + | 13.6 | – | Arachnoid cyst of middle cranial fossa | |

Abbreviations: AN-BP, anorexia nervosa binge-eating/purging type; AN-R, anorexia nervosa restrictive type; ARFID, avoidant/restrictive food intake disorder; ASD, autism spectrum disorder; BMI, body mass index; ID, intellectual disability; MDD, major depressive disorder; MRI, magnetic resonance imaging; NA, not available; NDD, neurodevelopmental disorder.

showed cortical atrophy on brain MRI. This was possibly caused by severe dehydration due to malnutrition.\textsuperscript{22}

The NDD-CNVs identified in ED patients affected four synaptic genes (PTPRT, DIP2A, RBFOX1, and CNTN4). This finding is noteworthy because few studies have linked synaptic dysfunction to the pathophysiology of EDs. PTPRT encodes protein tyrosine phosphatase receptor type T, is exclusively expressed in the central nervous system, and regulates synaptic formation and function.\textsuperscript{23,24} Specifically, PTPRT regulates the expression of AMPA receptors, membrane trafficking of GluR2, GABAergic synaptic functions, and neurogenesis in the dentate gyrus. Interestingly, Ptprt knockout mice show reduced food intake with less body fat and are resistant to high-fat diet-induced obesity.\textsuperscript{25} Dip2a is involved in the synthesis of acetylated coenzyme A and is primarily expressed in the brain. Dip2a-deficient mice exhibit abnormal spine morphogenesis, reduced synaptic transmission, and autism-like behavior.\textsuperscript{26} RBFOX1 is a splicing factor that plays an important role in the regulation of the alternative splicing of large neuronal gene networks involved in brain development.\textsuperscript{27} Rbfox1 plays a critical role in shaping excitatory and inhibitory synaptic function and neuronal connectivity.\textsuperscript{28} CNTN4 has an important function related to synaptic plasticity and associative learning.\textsuperscript{29} Cntn4-deficient mice show increased fear conditioning, which is a potential underlying mechanism of AN.\textsuperscript{30}

In gene set analysis, we observed a nominally significant enrichment of rare exonic CNVs in synaptic signaling in ED patients. This result further suggests the possible involvement of synaptic dysfunction in severe EDs. This synaptic function was also implicated in other psychiatric disorders.\textsuperscript{22,27}

Our study has both strengths and limitations. The strengths of this study are to focus on the severe subgroup of EDs. In many complex genetic disorders, individuals with severe symptoms or treatment-resistance are more likely to carry pathogenic variants of large effect.\textsuperscript{31,32} Another strength is the use of high-resolution aCGH. This allowed us to detect small CNVs (< 50 kb) including three NDD-CNVs (deletions at KATNAL2, PTPRT, and CNTN4) in ED patients. The limitation is the small sample size, especially for ED patients. Therefore, our findings should be replicated in future studies with larger samples. Another limitation is that we could not confirm the inheritance pattern of NDD-CNVs because genomic DNA from parents of ED patients was not available.

In conclusion, our study suggests that NDD-CNVs may confer risk for severe EDs. The pathophysiology may involve synaptic dysfunction.

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Author contributions
I.K. and N.O. designed the study. I.K., B.A., and H.K. performed the experiments. I.K. and M.N. analyzed the data. M.I., S.T., and T.O. recruited the participants and/or collected DNA samples or phenotype data. I.K. wrote the first draft of the manuscript, and the other authors commented on and refined the manuscript. All authors carefully read the manuscript and approved the final version for submission.

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Supporting information
Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Supplementary Table 1a. 826 genes linked to NDDs

Supplementary Table 1b. 41 CNV loci linked to NDDs