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Microduplications at the 15q11.2 BP1–BP2 locus are enriched in patients with anorexia nervosa

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ABSTRACT

Microduplication at 15q11.2 have been reported in genetic association studies of schizophrenia and autism. Given the potential overlap in psychiatric symptoms of schizophrenia and autism with anorexia nervosa (AN), we were inspired to test the association of this CNV locus with the genetic susceptibility of AN using ParseCNV, a highly quality controlled CNV pipeline developed by our group. The CNV analysis was performed in 1017 AN cases and 7250 controls using the Illumina HumanHap610 SNP arrays data. We uncovered association of the 15q11.2 microduplication with AN with $P = 0.00023$, while no genetic association between the microdeletion of this region and AN was identified. Among four genes in this region that are not imprinted, *NIPA1* has the highest expression in brain and encodes a magnesium transporter protein on early endosomes and the cell surface in neurons. Targeting at Mg^{2+} uptake mediated by *NIPA1* presents an interesting research topic for the explorations of novel therapy for AN and other neurobehavioral diseases, such as schizophrenia and autism.

1. Introduction

Rearrangements of human chromosome 15q11-q14 region have attracted extensive attention due to the critical implications of this locus in human diseases, with six breakpoint regions (BP1-BP6) being described(Pujana et al., 2002). Two extensively studied diseases attributed to genetic variation at this locus are Prader-Willi syndrome (PWS [MIM 176270];) and Angelman syndrome (AS [MIM 105830];).

1.1. Deletions involving 15q11.2

PWS was named after two pediatricians, Andrea Prader and Heinrich Willi, who first described this disease.(Prader and Willi, 1963), which is characterized by hypotonia and feeding difficulties in early infancy, and excessive eating and gradual development of morbid obesity in later infancy or early childhood (Driscoll et al., 1993). It is caused by the deletion of the paternal copy of the imprinted gene region 15q11-q13, while the genes in this region on the maternal copy are virtually inactive through imprinting (Horsthemke and Wagstaff, 2008). The typical deletion is either a larger deletion of BP1-BP3 or a smaller deletion of BP2-BP3(Driscoll et al., 1993). AS was named after the British Pediatrician, Harry Angelman, who first described the disease (Angelman, 1965), which is characterized by developmental delay, intellectual disability, speech impairment, gait ataxia, and a unique inappropriate happy demeanor of frequent laughing and smiling (Dagli et al., 1993). In contrast to PWS, it is commonly caused by a 5- to 7-Mb deletion or imprinting defect of the maternal copy of the gene region 15q11-q13. Like PWS, the deletion is either a larger deletion of BP1-BP3 or a smaller deletion of BP2-BP3(Dagli et al., 1993).

In addition to PWS and AS, a heterozygous microdeletion of approximately 300–500 kb between BP1 and BP2 causes the chromosome 15q11.2 deletion syndrome (MIM 615656), which is associated with developmental and language delay and neurobehavioral disturbances, including autism, attention deficit-hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), seizures, schizophrenia, intellectual impairment such as dyslexia and dyscalculia, and mild dysmorphic features (Burnside et al., 2011; Butler, 2017; Cox and Butler, 2015; Doornbos et al., 2009; Ulfarsson et al., 2017). Four genes are mapped to the microdeletion, tubulin gamma complex associated protein 5(*TUBGCP5*), NIPA magnesium transporter 1(*NIPA1*), NIPA magnesium

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transporter 2(*NIPA2*), and cytoplasmic FMR1 interacting protein 1(*CYFIP1*). Unlike the deletions in PWS and AS, these genes are not imprinted(Chai et al., 2003).

1.2. Duplications involving 15q11.2

Proximal chromosomal 15q are enriched with segmental duplications (Bailey et al., 2002; Zody et al., 2006). Maternal duplications of the Prader-Willi/Angelman Critical Region (PWACR) within Chr15q11.2-q13.1 causes 15q Duplication Syndrome, characterized by hypotonia, ataxia, intellectual disability, autism spectrum disorder (ASD), and epilepsy(Finucane et al., 1993) (Bundey et al., 1994) (Coppola et al., 2013). Paternal duplications of the PWACR may have less deleterious effect on development, but are associated with variable phenotypes, such as parasomnia or ASD(Finucane et al., 1993) (Urraca et al., 2013). Compared to microdeletion of BP1-BP2, microduplication of BP1-BP2 may have milder phenotypes including cognitive impairment, speech delay and developmental delay(Benitez-Burraco et al., 2017; Burnside et al., 2011; Menten et al., 2006), as well as high inter-individual variability of neurodevelopmental disorders(Picinelli et al., 2016).

1.3. Microduplication of BP1-BP2 and anorexia nervosa

Using the Illumina HumanHap610 single nucleotide polymorphism (SNP) arrays with ~610,000 markers, our group performed a copy number variation (CNV) analysis in a population sample of anorexia nervosa (AN), including 1033 cases and 3773 controls(Wang et al., 2011). The CNV calls were generated using the PennCNV software, which is based on an integrated hidden Markov model and incorporates signal intensity of each SNP, the distance between neighboring SNPs, and the allele frequency(Wang et al., 2007). A microduplication locus at 15q11.2 was suggested of genetic association with AN with nominal significance ($P = 0.036$), whereas it did not pass correction for multiple testings(Wang et al., 2011). However, a recent case-only study including 1983 cases of AN did not identify this microduplication locus, while genotyping data of the Illumina 660W-Quad SNP arrays(Boraska et al., 2014) and PennCNV were used for the CNV analysis (Yilmaz et al., 2017).

Previously, microduplication of BP1-BP2 at 15q11.2 has been reported to be associated with both schizophrenia(Kirov et al., 2012) and autism(Burnside et al., 2011; van der Zwaag et al., 2010). Schizophrenia and AN are two related diseases. There is a high prevalence of comorbidity of the two diseases and AN has been reported to coexist in 1%–4% of schizophrenia patients(Kouidrat et al., 2014). The symptoms of AN may precede the onset of schizophrenia, whereas psychotic symptoms may also occur in the process of AN(Morylowska-Topolska et al., 2017). GWA studies have suggested the two diseases may share common genetic factors. For example, the A-kinase anchoring protein 6 gene (*AKAP6*), highly expressed in brain(Fagerberg et al., 2014), was identified in genetic association studies of both AN and schizophrenia (Goes et al., 2015; Li et al., 2017; Wang et al., 2011). The SOX2 overlapping transcript gene (*SOX2-OT*), producing alternatively spliced long non-coding RNAs with tissue-specific expression in brain(Fagerberg et al., 2014), was identified in genetic association studies of both AN and schizophrenia(2014; Boraska et al., 2014; Goes et al., 2015; Li et al., 2017). Autism spectrum disorder and AN are also closely related (Westwood and Tchanturia, 2017). Previous studies have shown over-representation of autism spectrum disorder in AN(Huke et al., 2013; Westwood et al., 2016). The family with *FAM155A*signal of tissue-specific expression in brain(Fagerberg et al., 2014) was identified in genetic association of both AN and autism(2013; Wang et al., 2011).

Based on the above evidence, the microduplication of BP1-BP2 presents an interesting candidate for impacting the genetic susceptibility of AN. Further understanding of this locus may help to understand the molecular mechanism of AN, as well as its overlap and genetic sharing with other mental disorders. Here, we used our optimized CNV algorithm (ParseCNV) and focused on the CNV analysis of the BP1-BP2 locus. ParseCNV was developed by our group as a robust CNV analytical tool (Glessner et al., 2013), uncovering an interesting association signal at the microduplication locus, BP1-BP2, at 15q11.2.

2. Methods

2.1. CNV analysis

The CNV analysis was done in 1033 AN cases (1009 females and 24 males) and 7529 controls based on the Illumina HumanHap 550 and 610 SNP arrays data. The AN samples were collected in North America and Europe by an international, multisite group with experienced academic collaborators in assessing eating-disordered individuals, while consistent behavioral assessment procedures across sites were established (Kaye et al., 2000; Wang et al., 2011). All cases met an unequivocal lifetime core diagnosis of AN by DSM-IV criteria, waiving the single criterion of amenorrhea because some cases were treated with exogenous hormone replacement, thus without amenorrhea(Kaye et al., 2000). All cases were diagnosed of AN by age 25 and for at least 3 years(Kaye et al., 2000). Structured interview of anorexia nervosa and bulimic syndromes (SIAB) was used for an assessment of eating disorder symptoms and course of illness(Fichter et al., 1998). The inclusion criteria for the research subjects and the genotyping method were described elsewhere(Wang et al., 2011). Population stratification was examined using the principal component analysis (PCA) analysis (supplementary Fig.1), and outliers were removed. There were 1017 AN cases and 7250 controls after the quality control process. The CNV was called and tested for genetic association by the software, ParseCNV (Glessner et al., 2013). The latter software presents a major improvement in the CNV calling pipeline given the built-in comprehensive QC analysis component which scrutinizes CNV calls with multiple lines of evidence, including CNV call overlap profiles, genomic context, number of probes supporting the CNV call and single probe intensities(Glessner et al., 2013).

2.2. Validation of the CNV locus by quantitative polymerase chain reaction

Five available DNA samples from AN were used for the validation of the CNV locus using quantitative polymerase chain reaction (qPCR). Probes and primer sequences were selected using the ProbeFinder v2.49 software (Roche, Indianapolis, IN) from the Universal Probe Library (UPL, Roche, Indianapolis, IN). The probe and primers used in this study are: the probe #27, cat.no. 04687582001; the left primer sequence 5′-ctcaatcgagcacaactactgc-3’; the right primer Sequence 5′-gagtcgagagtttccattcca-3’; Amplicon Sequence 5′-ctcaatcgagcacaactactgcttcgacaggcagcttactggaatggaaactctcgactc-3’. The probe is in the *NIPA2* gene. The qPCR was performed on an ABI Prism™ 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Each sample reaction was done in triplicate, in 10 μl of reaction mixture containing 10 ng genomic DNA, 100 nM of the UPL probe, 400 nM of each PCR primer, and 1 × TaqMan Gene Expression Master Mix containing UDG and ROX (Life Technologies, Carlsbad, CA). Two samples of reference genomic DNA with normal copy number (Promega, Madison, WI) were included in the assay as normal controls. Data were collected using the Sequence Detection Software v2.4 (Applied Biosystems, Foster City, CA), and analyzed by the ΔΔCT method.

3. Results

Using the ParseCNV pipeline, heterozygous microduplication at the 15q11.2 BP1–BP2 locus was called in 13 out of 1017 cases and 24 out of 7250 controls (Table 1). Among the 13 patients, 5 cases are of the binge–purge type, 5 cases are restrictive type, and 3 cases have no subtype information of the AN phenotype. The plots of B-allele

Table 1
The 15q11.2 BP1–BP2 microduplication in anorexia nervosa.

CNV	total	Heterozygote[a] (n)	Normal copy number (n)	Fisher's Exact Test *P* value	OR (95% CI)
Microduplication		**Copy number ≥ 3**	**Copy number = 2**		
Cases[b]	1017	13 (1.28%)	1004 (98.72%)	0.00023	3.90 (1.98, 7.68)
Controls	7250	24 (0.33%)	7226 (99.67%)		
Microdeletion		**Copy number = 1**	**Copy number = 2**		
Cases[c]	1017	3 (0.29%)	1014 (99.71%)	1	–
Controls	7250	24 (0.33%)	7226 (99.67%)		

[a] Heterozygous microduplication or hemizygous microdeletion.
[b] Among the 13 patients, 5 cases are binge–purge type, 5 cases are restrictive type, and 3 cases have no subtype information of the AN phenotype.
[c] Among these 3 cases, 2 cases are binge–purge type and 1 case has no subtype information of the AN phenotype.

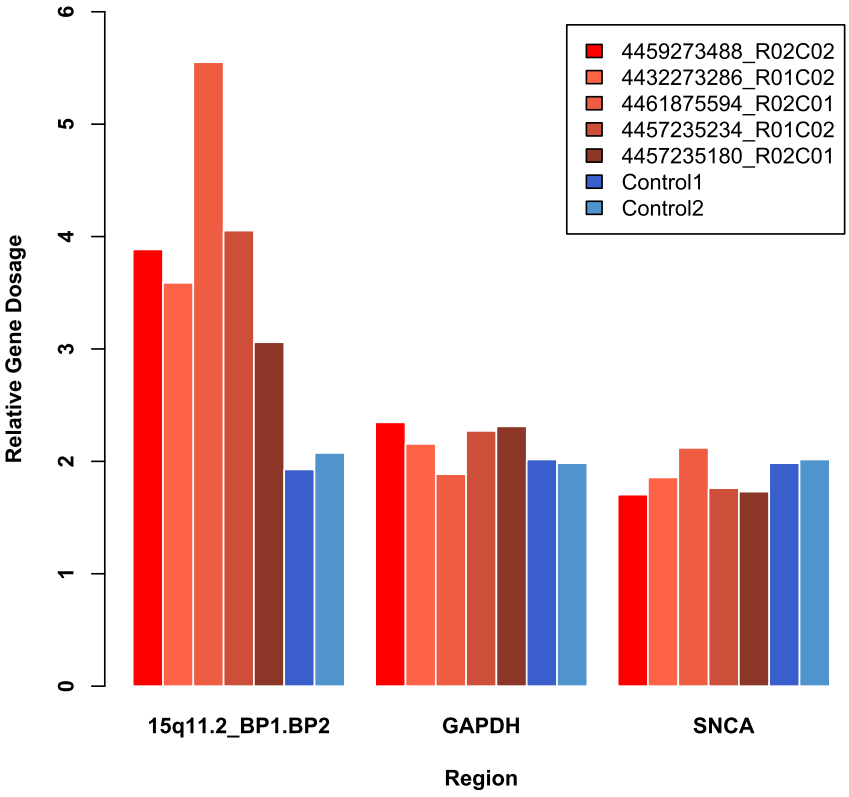

Fig. 1. The CNV locus confirmation by qPCR. The probe is in the *NIPA2* gene. In details, it is Probe #27 (cat.no. 04687582001, Sigma-Aldrich, St. Louis, MO). For the amplification, Left Primer: ctcaatcgagcacaactactgc; Right Primer: gagtcgagagtttccattcca; the Amplicon Sequence: ctcaatcgagcacaactactgcttcga-caggcagcttactggaatggaaactctcgactc; the Amplicon Length: 60bp; chromosome position: chr15:23033527–23033586 (hg19). Each individual with the microduplication showed higher gene dosage than two control individuals, while two control genes with normal copy number, *GAPDH* and *SNCA*, showed no difference across different individuals.

frequency (BAF) and Log R Ratio (LRR) in the cases are shown in Supplementary Fig.2. In addition, we confirmed the CNV locus by qPCR (Fig. 1) in five individuals with available DNA, i.e., all five individuals with the microduplication showed higher gene dosage than two control individuals, while two control genes with normal copy number showed no difference across different individuals. Thus, we could only do the confirmation in five AN cases with the microduplication as the other eight AN cases with the microduplication did not have DNA available. Shown by our results, the 15q11.2 BP1–BP2 microduplication is significantly enriched in the case group with $P = 0.00023$, OR(95% CI) = 3.90 (1.98, 7.68). In contract, the 15q11.2 BP1–BP2 microdeletion has no difference between cases and controls.

4. Discussion

AN is an eating disorder and a complex disease associated with significant morbidity and mortality, and notably more common in females (Diagnostic, 2000). While the etiology of AN remains largely unknown, there is evidence to suggest a strong genetic component in the susceptibility to AN. The relative risk of first-degree female relatives of individuals with AN are > 10 times higher than in the reference population(Strober et al., 2000). Twin studies demonstrate heritability of about 56%(Bulik et al., 2006; Wade et al., 2000).

In this study, we used ParseCNV(Glessner et al., 2013), which is a QC-enriched version of PennCNV(Wang et al., 2007) also developed in our laboratory. We uncovered association of the susceptibility of AN for the candidate genetic locus, at 15q11.2 BP1–BP2, harboring a microduplication, which has been previously extensively highlighted for its roles in neurobehavioral disorders (Wang et al., 2011). The association of the 15q11.2 BP1–BP2 microduplication is for the first time shown with AN. The 15q11.2 BP1–BP2 locus contains four genes that are not imprinted, i.e. *TUBGCP5, NIPA1, NIPA2,* and *CYFIP1*(Chai et al., 2003). In addition, our results show that it is the duplication, but not deletion, of this region, which is associated with the susceptibility to AN. What have been observed in PWS is that deletion in this region is associated with the phenotype of excessive eating. This is in line with what we have found in the current study, i.e. microdeletion is not associated with anorexia nervosa, but in contrast to deletion causing excessive eating, microduplication in this region is associated with the genetic susceptibility of AN.

The function of these four genes remains unclear. Previous reports indicate that mutations in *NIPA2* may result in haploinsufficiency of the gene that are associated with childhood absence epilepsy(Jiang et al., 2012), but controversy remains(Hildebrand et al., 2014). All four genes

are ubiquitously expressed in different tissues, however, *NIPA1* has the highest expression in brain among different tissues(Fagerberg et al., 2014). As a magnesium transporter, the NIPA1 protein associates with early endosomes and the cell surface in a variety of neuronal and epithelial cells, and mediates Mg^{2+} uptake(Goytain et al., 2007). Dominant negative mutations of *NIPA1* cause spastic paraplegia-6 (APG6) (Chen et al., 2005; Rainier et al., 2003; Reed et al., 2005). As shown by our study, haploinsufficiency from hemideletion of *NIPA1* is not associated with AN. However, the 15q11.2 BP1–BP2 microduplication may lead to a gain-of-function of *NIPA1*, while abnormal intracellular Mg^{2+} may have inhibitory influence on neurons and decreases neuronal survival(Dribben et al., 2010). Previous studies show that Mg^{2+} functions to block NMDA receptors(Pittaluga et al., 2000), and NMDA receptors have been suggested to play a role in a female patient with anti-NMDA receptor encephalitis presenting as atypical AN(Perogamvros et al., 2012). Therefore, further study on *NIPA1* in AN is needed as this gene may turn out to be a potential drug target for the treatment of AN and other neurobehavioral diseases as it has also shown association with schizophrenia(Kirov et al., 2012) and autism(Burnside et al., 2011; van der Zwaag et al., 2010). In addition, according to a previous microarray study on gene expression in the prefrontal cortex in 15 cases with eating disorders (ED, including 7 bulimia nervosa, 2 anorexia nervosa, binge–purge type, 3 AN, and 3 eating disorder not otherwise specified) and 102 nonpsychiatric controls, the expression of *CYFIP1* shows a trend of higher expression in ED cases with $P = 0.06$ (Supplementary Fig. 3, the Gene Expression Omnibus accession GSE60190) (Jaffe et al., 2014). It should be noted that among these patients, only 5 of them have confirmatory evidence of being AN cases. The GSE60190 dataset is lack of phenotype information to enable further analysis of ED subtypes (Jaffe et al., 2014). On the other hand, it is known that different ED subtypes may share same mechanisms(Schulte et al., 2016). Therefore, there might be an association of increased *CYFIP1* gene dosage by the 15q11.2 microduplication with AN. The different expression of *CYFIP1* could also be a component of a series of changes, regulated by a transcription factor or an epigenetic mechanism. The role of *CYFIP1* in AN warrants further study. As a limitation of this study, the *in silico* results presented in this paper could not be verified in a majority of the cases by wet lab approach because of the unavailability of any more DNA material, thus the new CNV findings should be validated in an independent sample in a future study.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.01.021.

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