Phenotypic diversity of 15q11.2 copy number variants: a case series and review of the literature

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ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY I OCTOBER 3-7, 2022

The proximal region of the long arm of human chromosome 15 (15q) is relatively susceptible to the non-allelic homologous recombination of low copy repeat elements.[1] The clusters of low copy repeats are referred as breakpoint (BP) regions.[2] The six BP regions (BP1-BP6) on the proximal 15q mediate microdeletions and microduplications, which are collectively termed as copy-number variants (CNVs).[2,3] The four highly conserved and non-imprinted genes (NIPA1, NIPA2, CYFIP1 and TUBGCP5) are located in the region between BP1 and BP2 which spans approximately 500 kb.[4] NIPA1, NIPA2, and CYFIP1 are extensively expressed in the central nervous system, whereas TUBGCP5 is more specific to the subthalamic nuclei.[5] These four highly conserved genes have several functions in neuronal connectivity and axonal growth.[6]

OBJECTIVES

Several reports have linked microdeletions and microduplications on the 15q11.2 BP1-BP2 region involving these four genes with behavioural disorders, autism spectrum disorder (ASD), developmental delay, learning disabilities and seizures.[6-14] Moreover, heterogeneous phenotypes from severely affected individuals to healthy carriers suggest incomplete penetrance or variable expressivity of these genes.[14] In the present study, first we report on the phenotypic features of 17 patients with 15q11.2 CNVs. Moreover, we conduct a review of the literature to compare the phenotypic diversity of 15q11.2 CNVs and contribute to the current knowledge from previous case series.

MATERIALS & METHODS

We performed a retrospective case series of the patients with 15q11.2 CNVs who were referred to the Genetic Diagnosis Center of our hospital between January 2015-January 2021. Patient demographics, brain magnetic resonance imaging, electroencephalography, chromosomal microarray results and the clinical data were obtained from the PROBEL hospital information management system. For the interpretation of CNVs, variants were checked in the databases; DGV and DECIPHER, and the phenotypes were compared with the literature and databases such OMIM, ECARUCA, ORPHANET. For the review of the literature, we performed a PubMed search and included all studies reporting the 15q11.2 CNVs between 2007 and 2022 except overlapping studies. After the articles were assessed for eligibility, and data from 15 articles were included. The data were analyzed using the software Statistical Package for Social Science for Windows, version 22.

RESULTS

Of the 17 patients, 65% (n=11) had microduplication and 35% (n=6) had microdeletion in the 15q11.2 BP1-BP2 region. The mean size of the CNVs was 485±165 kb. Patients had a variety of phenotypic features including neurodevelopmental delay (59%), dysmorphic features (41%), epilepsy (41%), cognitive impairment (29%), behavioral problems/psychiatric symptoms (18%), hypotonicity/muscle weakness (18%), scoliosis (12%), neuropathy with liability to pressure palsies (6%), microcephaly (6%), and hydrocephalus (6%). No significant difference was detected between the phenotypic features of microduplication and microdeletion groups (all p>0.05). Results of the other studies reporting the phenotypic features of the patients with 15q11.2 CNVs are summarized in Table 1 and Table 2.

Table 1: Comparison of previously described 15q11.2 microduplication cases with the present study

	Present study	Van der Zwaag et al, 2010	Burnside et al, 2011	Abdelmoity et al, 2012	Picinelli et al, 2016	Mohan et al, 2018	Chu et al, 2021	% Total (present study and literature)
Hypotonicity	1/11 (9%)	0/3	7/49	N/A	1/5	N/A	N/A	9/68 (13.2%)
Neurodevelop-mental delay	7/11 (63%)	2/3	19/49	8/10	5/5	86/215	0/9	127/302 (42%)
Speech impairment	0/11 (0%)	1/3	22/44	N/A	5/5	N/A	0/9	27/72 (37.5%)
Cognitive impairment	3/11 (27%)	N/A	N/A	8/10	4/5	N/A	N/A	15/26 (57.6%)
Epilepsy	4/11 (36%)	0/3	6/49	3/10	0/5	18/215	N/A	31/293 (10.6%)
ADHD	0/11 (0%)	0/3	18/44	0/10	2/5	N/A	N/A	20/73 (27.3%)
Abnormal Brain MRI findings	1/8 (12.5%)	N/A	N/A	2/10	2/5	N/A	1/3	6/26 (23%)
Dysmorphic features	5/11 (45%)	0/3	22/49	4/10	0/5	25/215	1/9	57/302 (18.9%)
Behavioral/ psychiatric symptoms	2/11 (18%)	N/A	19/49	2/10	3/5	30/215	0/9	56/299 (18.7%)

ADHD, attention deficit hyperactivity disorder; MRI, magnetic resonance imaging; N/A, not applicable.

Table 2: Comparison of previously described 15q11.2 microdeletion cases with the present study

	Present study	Murthy et al, 2007	Doornbos et al, 2009	von der Lippe et al, 2011	Burnside et al, 2011	Sempere Pérez et al, 2011	Madrigal et al, 2012	Abdelmoity et al, 2012	Cafferkey et al, 2014	Vanlerberghe et al, 2015	Hashemi et al, 2015	Mohan et al, 2018	Han et al, 2021	Chu et al, 2021	% Total (present study and literature)
Microcephaly	1/6 (16%)	N/A	N/A	N/A	N/A	N/A	2/2	4/16	N/A	10/42	3/22	N/A	0/3	N/A	20/91 (22%)
Hypotonicity	2/6 (33%)	N/A	N/A	N/A	N/A	N/A	N/A	2/15	N/A	9/41	2/22	N/A	3/3	N/A	18/87 (20.7%)
Neurodevelop-mental delay	3/6 (50%)	1/1	8/9	3/7	20/56	1/1	2/2	N/A	65/77	18/41	19/22	91/262	3/3	5/10	239/497 (48%)
Speech impairment	1/6 (16%)	1/1	8/8	7/7	44/49	1/1	2/2	N/A	37/77	35/41	4/22	N/A	3/3	2/10	145/227 (63.9%)
Cognitive impairment	2/6 (33%)	1/1	N/A	N/A	11/49	1/1	2/2	13/16	N/A	28/41	N/A	N/A	3/3	N/A	61/118 (51.7%)
Epilepsy	3/6 (50%)	0/1	2/8	1/7	14/56	0/1	0/2	2/15	13/83	9/48	3/22	27/262	1/3	N/A	75/514 (15%)
ADHD	1/6 (16%)	1/1	2/8	1/7	16/49	1/1	0/2	7/12	N/A	20/41	6/22	N/A	0/3	N/A	55/152 (36.2%)
Abnormal Brain MRI findings	1/2 (50%)	0/1	1/4	1/2	N/A	N/A	N/A	N/A	N/A	12/31	6/16	N/A	0/3	1/5	22/63 (34.9%)
Dysmorphic features	2/6 (33%)	N/A	6/9	N/A	27/56	1/1	N/A	N/A	28/83	30/42	8/19	44/262	0/3	1/10	147/491 (30%)
Behavioral/ psychiatric symptoms	1/6 (16%)	0/1	0/9	1/7	N/A	0/1	N/A	N/A	35/73	0/40	4/22	25/262	0/3	0/10	66/434 (15.2%)

ADHD, attention deficit hyperactivity disorder; MRI, magnetic resonance imaging; N/A, not applicable.

CONCLUSIONS

The 15q11.2 BP1-BP2 region has been suggested to be a “susceptibility” locus for neurodevelopmental and neuropsychiatric disorders since the phenotypic variability and low penetrance.[14] The associated phenotypes of CNVs on BP1-BP2 region range from normal phenotypes to neurodevelopmental delay, behavioral problems, seizures, dyslexia, dyscalculia, mild dysmorphic features, anorexia, neuropsychiatric conditions such as schizophrenia, ASD, and attention deficit/hyperactivity disorder.[7-21] We believe that greater understanding of the possible influences of the CNVs in this susceptibility locus will aid in our clinical approach in the future.

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