Chromosome 15q BP3 to BP5 deletion is a likely locus for speech delay and language impairment: Report on a four-member family and an unrelated boy

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Abstract
Background: Deletions in chromosome 15q13 have been reported both in healthy people and individuals with a wide range of behavioral and neuropsychiatric disturbances. Six main breakpoint (BP) subregions (BP1-BP6) are mapped to the 15q13 region and three further embedded BP regions (BP3-BP5). The deletion at BP4-BP5 is the rearrangement most frequently observed compared to other known deletions in BP3-BP5 and BP3-BP4 regions. Deletions of each of these three regions have previously been implicated in a variable range of clinical phenotypes, including minor dysmorphism, developmental delay/intellectual disability, epilepsy, autism spectrum disorders, behavioral disturbances, and speech disorders. Of note, no overt clinical difference among each group of BP region deletions has been recorded so far.

Methods: We report on a four-member family plus an additional unrelated boy affected by a BP3-BP5 deletion that presented with typical clinical signs including speech delay and language impairment. A review of the clinical features associated with the three main groups of BP regions (BP4-BP5, BP3-BP5, and BP3-BP4) deletions is reported.

Results: Array-CGH analysis revealed in the mother (case 1) and in her three children (cases 2, 3, and 4), as well as in the unrelated boy (case 5), the following rearrangement: arr (hg19) 15q13.1-q13.3 (29.213.402–32.510.863) x1.

Conclusion: This report, along with other recent observations, suggests the hypothesis that the BP region comprised between BP3 and BP5 in chromosome 15q13 is involved in several brain human dysfunctions, including impairment of the language development and, its deletion, may be directly or indirectly responsible for the speech delay and language deficit in the affected individuals.

KEYWORDS
BP3-BP5 deletion, chromosome 15 q13, developmental delay, language impairment, speech delay
INTRODUCTION

The long arm of chromosome 15 (15q) plays an important role in human neurobehavioral development: several chromosomal abnormalities have been often associated with a wide range of neuropsychiatric disorders. Pure, isolated 15q deletions have been rarely recorded usually in association with severe clinical phenotypes. Solmaz, Durnaz, Braekeeleer, Cogulu, and Ozkinay (2016) described an 11-year-old girl with a 15q deletion who had multiple congenital anomalies. This girl was born with a cleft palate, hip dislocation, crossed renal ectopic malformations, and dysmorphic features mainly affecting the face and limbs. Additionally, it should be noted that she showed speech problems. The 15q11-q13 locus is particularly susceptible to genomic rearrangements as a result of the nonallelic homologous recombination (NAHR) of Low Copy Repeats (LCRs) elements, also known as segmental duplications (SDs), mapped in the six breakpoints (BP1-BP6) regions, leading to recurrent structural variations, such as duplication or deletion events (Ehmke et al., 2017; Szafranski et al., 2010; Van Bon, Mefford, & de Vries, 2010). Actually, the prevalence of 15q13 microdeletions, in healthy individuals, is around 0.02%, whereas in individuals with intellectual disability, seizures, schizophrenia, and autism spectrum disorders (ASD), is as high as 0.2 to 1%–2% (Van Bon et al., 2010). Clinical manifestations of deletions occurring on 15q11-q13 may considerably range, showing a relatively high penetrance and variable clinical expressions of behavioral and neuropsychiatric disturbances (Sharp et al., 2008). The 15q11-q13 region includes six BP ranging from BP1 to BP6, and three further BPs, from BP3 to BP5. Deletions involving BP4-BP5 occur more frequently as compared to BP3-BP4, and to (the larger BP interval) BP3-BP5 (Sahoo et al., 2005; Sharp et al., 2008; Van Bon et al., 2009; Wandstrat, Leana-Cox, Jenkins, & Schwartz, 1998; Williams et al., 2012). When the fragment deleted comprises the BP4-BP5, BP3-BP4, and BP3-BP5 regions, the clinical phenotype usually ranges from healthy to severely affected individuals with microcephaly and macrocephaly, developmental delay/intellectual disability (DD/ID), behavioral disturbances, autism spectrum disorders (ASD), epileptic seizures, attention deficit hyperactivity disorder (ADHD), and aggressiveness, in association or not with distinct dysmorphic features (Ehmke et al., 2017; Sharp et al., 2008; Van Bon et al., 2010). Recently, particular emphasis has been paid to the spectrum of language disabilities, as one of the presenting features of the 15q deletion syndrome (Pettigrew et al., 2015).

We hereby report on a four-member family plus an additional unrelated boy all harboring a BP3-BP5 deletion, who had a wide range of congenital malformations in association with mild-to-moderate intellectual disability, behavioral disturbances, speech delay, and language impairment, thus showing that speech abnormalities is likely to represent (whether or not in combination with mild/moderate intellectual disability) as one of the presenting feature of the 15q deletion syndrome. A review of the spectrum of clinical features in the 15q deletion syndrome is reported focusing on the main differences and similarities in each BP deleted group, including BP4-BP5, BP3-BP4, and BP3-BP5.

CLINICAL REPORT

2.1 Case 1

This 37-year-old woman was the mother of three children (cases 2 to 4). Her husband is 43-years old and is healthy and his speech is normal. She was born with congenital pulmonary anomalous venous lobar return syndrome (scimitar syndrome) undergoing early cardiac surgical correction. Her developmental milestones were normal with the exception of speech delay. At her most recent re-evaluation the height was 160 cm (25/50th percentile), the weight was 75 kg (90/97th percentile), and the occipitofrontal circumference (OFC) was 60 cm (above 97th percentile). She lives a normal life with a normal cognitive capacity (IQ 72; IQV 55; WISC III) but with impairment in expressive language. She shows difficulties in putting words together into a sentence, and her speech is barely intelligible. She is irritable and impulsive. During her three pregnancies, she denied having had any infectious disease or smoking, or using drugs or drinking alcohol.

The main clinical features in the four members of this family and in the unrelated affected boy are summarized in Table 1.

2.2 Case 2

This 12-year-old girl is the first of three siblings. She was born at 35 weeks of gestation by cesarean section after an uneventful pregnancy. Her birth weight was 2,800 g (50th percentile), height was 50 cm (75th percentile), and her OFC was 37 cm (90th percentile). Her developmental milestones were delayed: her speech started at the age of 4 years when she started speech therapy. She followed a language course which still pursues with fairly good results. Her school performance is hardly sufficient, but her teachers complained of hyperactivity during the everyday lessons and of poor attention. At her most recent evaluation general physical examination reveals that her weight is 80 kg (<97th percentile), height is 180 cm (90th percentile), and the OFC is 57 cm (above 97th percentile). Her abundant fat is localized to the upper body above the waist. There are minor dysmorphic features, including a large head with a high forehead, thin lips, supernumerary and dyschromic teeth, and abundant hair
over the entire body with a linear trend on the shoulders. Ultrasonographic examination of the heart and internal organs is normal as is the genital organs; the menstrual cycle had already started. Neurological examination reveals mild/moderate cognitive delay (I.Q. scores were 41 and IQV 35 by means of WISC-III) with behavioral disturbances (i.e., hyperactivity and an anxious state). Neuropsychiatric testing gave the following results: ADHD Denver Scale Recording scored 87 (n.v., 50–55); the Depression Baylor Scale scored 92 (n.v., 60–65); and the Anxiety Stanford Scale scored 95 (n.v., 60–65). Her language disturbances consist in a poor expressive vocabulary with scant sentences and inadequate word structures. Test for reception of grammar (TROG2) gave the following results: she passed 14 blocks (standard score 97). Routine laboratory analyses, including blood count, electrolytes, plasma and urinary amino acids, thyroid testing, organic acid plasma, and total cholesterol, are normal.

### 2.3 Case 3

This 8-year-old boy is the second born to the mother reported as case 1 and sibling of cases 2 and 4. He was born at 37 weeks of gestation by cesarean section after an uncomplicated pregnancy. His birth weight was 3,000 g (50th percentile), height was 50 cm (50th percentile), and the OFC was 37 cm (97th percentile). The APGAR scores were 7 and 9 at 1 and 5 min, respectively. Developmental milestones were attained normally with the exception of language, which started at the age of 4 years. The child, because of macrocephaly and language delay, was referred to this Institution in Catania for diagnostic work-up. At the Leiter-R test he attained FluidReas 70 and brief I.Q. 72. Speech and physical therapies were soon started which resulted in a bettering of the speech production and of the receptive language. At the age of 7 years, a new psychological evaluation revealed mild intellectual disability (WISC-III = IQV. 55, IQP. 65; IQT. 54) and behavioral disturbances, mainly consisting in difficulties in focusing attention and in following rules with provocative opposite behavior and low frustration tolerance. Socialization was good. At school, he was helped by support. The parents recalled that he had a single partial seizure at the age of 3 years. At his most recent clinical reevaluation physical examination reveals that his general conditions are good. His weight is 25 kg (25th percentile), height is 125 cm (25th percentile), and the OFC is 56 cm (90–97th percentile). He shows a large head with a high forehead, the eyelids are mediially sparse, the philtrum is flat, and the lips thin with a sub-labial crease. Supernumerary teeth, bilaterally inverted nipples, and a single transverse palmar crease are also noted. Neurological examination reveals mild cognitive delay with a severe language impairment. Routine laboratory analyses, including blood count, electrolytes, plasma and urinary amino acids, thyroid testing, organic acid plasma, and total cholesterol, are normal. No anomalies are found at the cardiac ultrasonography. Internal organs and genital organs are normal. EMG, NCV, ophthalmological examination, and brain MRI are unrevealing. EEG shows the presence of multiple spikes and waves in the bilateral frontal regions. Currently, at age 8 years, the child weighs 24 kg (50th percentile), the height is 130 cm (75th percentile), and OFC is 56 cm (above 97th percentile). Neuropsychiatric testing, by means of language scale evaluating system IV-revised, revealed difficulties in production of spoken language, in

| Case | 1 | 2 | 3 | 4 | 5 |
|------|---|---|---|---|---|
| Gender | F | F | M | M | M |
| Age/years | 37 | 12 | 8 | 5 | 15 |
| Dysmorphisms | No | Yes | Yes | SD | No |
| High forehead | No | + | + | No | No |
| Supernumerary teeth | No | + | + | No | No |
| Large head | + | + | + | No | + |
| Intellectual disability | IQ 72 IQV 55 | IQ 41 IQV 35 | IQV 55-IQP 65 IQT 54 | Mild/moderate Leiter_R test brief 58 | IQ 62 IQV 55 |
| Speech onset | Late ++ | 4 years ++ | 4 years ++ | No speech +++ | 3 years +++ |
| Language impairment | | | | | |
| Behavioral disturbances | +++ | +++ | +++ | ++ | +++ |
| Cardiac anomalies or other issues | Scimitar syndrome corrected | Overweight Bilaterally inverted nipples | Epileptic seizures Atrioventricular septal defect corrected | Complex febrile seizures |

### Table 1

Main clinical features of the mother, three siblings (number 1 to 4), and of an unrelated boy (number 5). Language Impairment from mild to notable (+ to +++); SD: Down syndrome. Intelligence Quotient (IQ Wisc III)
words and sentences comprehension and structuration. The language comprehension through TROG2 has been evaluated to be under the normal range with poor verbal memory and low rhythm of language elaboration.

2.4 | Case 4

This 5-year-old boy is the third born of the mother reported as case 1. A screening test for Down’s syndrome displayed positive results but the parents decided to proceed with pregnancy. Since the 29th gestational week, a growth restriction was noticed, and the child was born at 35 weeks of gestation by cesarean section. His birth weight was 2.440 g (25–50th percentile), height was 48 cm (25th percentile), and head circumference was 34 cm (25th percentile). At birth, an unbalanced atrioventricular septal defect was diagnosed and the child underwent cardiac surgery at age 5 months with definitive correction. Clinical diagnosis of Down’s syndrome was made at birth and confirmed by chromosomal analysis (47, XY + 21). Developmental milestones were delayed. At his most recent reevaluation, the child had the classical features of Down’s syndrome. The weight is 15 kg (3th percentile), height is 100 cm (3th percentile), and the OFC is 47 cm (below 3rd percentile). Frequent episodes of irritability and impulsivity are recorded. Of note, intellectual disability is recoded between mild and moderate, speech is completely absent, the child does not pronounce any word, while the socialization skills are good. Griffith Mental Development Scale (GMDS) showed development assessment lower than normal in all the domain (<50). Leiter-R test brief IQ 58. No epileptic seizures are recorded. Laboratory analysis, EEG, and brain MRI are normal.

2.5 | Case 5

A 15-year-old boy unrelated to the upper mentioned family. The proband’s mother 45 years old is nurse and the father 48 years old is hydraul. Both are healthy and both have normal cognitive level and normal speech. The proband’s brother is 17 years old. He attends normal school with good performance and normal speech.

The mother denied having had clinical problems during gestation. The child was born at term by spontaneous delivery with birth weight of 4 kg, height of 52 cm, and head circumference of 36 cm (all above the 97th percentile). He was first referred to this Institution at age 4 years because of two episodes of complex febrile seizures, which occurred within a period of time of 2 weeks. His motor developmental milestones were reached normally, while language was delayed: he was able to express single words only after 36 months. He used 3–4 word phrases at age 5 years. At this age, he was referred again to this Institution for a work-up related to his mild intellectual disability and his language delay. Laboratory and neurodevelopmental evaluations were carried out including EEG and brain MRI, which were normal. Physical examination revealed no dysmorphic features with no physical anomalies. Motor, speech, and language treatment was undertaken and continued afterward with relatively good results. Currently, he attends a regular school course with a special needs teacher. The teachers complain about immature behavior with episodes of impulsivity, irritability, and an attention deficit disorder. At his last reevaluation, at age 15 years, he weighs 60 kg (50th percentile), his height is 170 cm (50th), and the OFC 58.5 cm (above 97th percentile). Physical examination is unrevealing. Internal organs ultrasonography is normal. Neuropsychiatric evaluation by means of WISC III recorded the following scores: IQ 62 and IQV 55. TROG2 test gave the following result: he passed 18 blocks (standard score 97). Language evaluation revealed difficulties in formulating sentences, in expressive vocabulary, and in word structures.

2.6 | Genetic testing

2.6.1 | Microarray testing and data analysis

The analysis was driven after a full diagnostic work-up for ID, speech difficulties, and behavioral disturbances in case 3 (then extended to the members of family 1) and in case 5 of the family 2. Recombination breakpoints were detected using high-resolution 8x60K Human Genome CGH microarray (Agilent Technologies). Array experiments were performed as recommended by the manufacturer (Agilent Technologies). Proband DNA was labeled with Cy5 and reference DNA (human DNA Promega) with Cy3. Purification, hybridization, and washing steps were performed according to the manufacturer’s instructions. Data visualization and analysis were performed with Sure Scan microarray Scanner G2600D (Agilent), Feature Extraction software (Agilent), and Agilent Cytogenomics Software Edition 2.5.

3 | RESULTS

Array-CGH analysis revealed the following rearrangement: arr (hg19) 15q13.1-q13.3 (29.213.402–32.510.863) × 1. These results were recorded in the mother (case 1) and in her three siblings (cases 2, 3, and 4) as well as in the unrelated boy (case 5). (Figure 1). No copy number variants were recorded by array-CGH analysis, which was carried out on the patient’s husband and in the parents of the unrelated boy.
In the present family, all three children and their mother harbored, by means of array-CGH analysis, a partial deletion of the long arm of chromosome 15 extending 3.297 Mb from nt 29,213,402 to nt 32,510,863. A similar deletion was recorded in an additional unrelated boy. The deletion was located in the 15q13 region, specifically in the BP3-BP5 locus. The mother at birth had congenital anomalous venous return pulmonary syndrome (i.e., scimitar syndrome), corrected soon after birth. Scimitar syndrome is a very rare disorder consisting of a combination of cardiopulmonary anomalies with an anomalous right pulmonary venous return, which is located mostly in the anterior vena cava (Benjouad et al., 2016; Holt, Berdon, Marans, Griffiths, & Hsu, 2004; Ruggieri et al., 2003). The youngest child of the four-member family was affected by Down’s syndrome (DS) and had typical phenotypic features including congenital heart disorder (atrioventricular septal defect) and karyotype 47chr, XY + 21. Of note, in the 5-year-old child, the language skills had not yet started. The main features recorded in the family members and in the unrelated boy (summarized in Table 1) consisted of cardiac anomalies recorded in 2 out of 5, dysmorphic features recorded in 3 out of 5, and OFC above the 97th percentile recorded in 4 out of 5 patients. Additional features consisted of intellectual disabilities mainly mild recorded in 4 out 5 individuals, speech delay, language impairment, and behavioral disturbances recorded in all patients.

A deletion between BP1-BP3 has been reported in individuals with Prader-Willi syndrome and Angelman syndrome (Makoff & Flomen, 2007; Varela, Kok, Otto, & Koiffmann, 2004; Varela, Kok, Setian, Kim, & Koiffmann, 2005), whereas individuals with a deletion in the BP3-BP4, BP4-BP5, and BP3-BP5 regions show a variable clinical expression that is mainly characterized by minor dysmorphic features, language deficits, and neurodevelopmental and neuropsychiatric disorders, including DD/ID, epilepsy, ASD, schizophrenia, mood disorders, and ADHD. Lowther et al. (2015), in a review of individuals presenting with a 15q13.3 deletion, identified 246 cases consisting of 133 children and 113 adults. Moreover, seven adults driven from a cohort of patients affected by schizophrenia and tetralogy of Fallot were enrolled. In the control group, consisting of 23,838 individuals, no cases of BP4-BP5 deletion were found. In the majority of the examined patients, the deletion involved the region BP4-BP5 (94%), whereas the region BP3-BP4 and the largest region BP3-BP5 were involved in 5.4% and in 3.1% of the cases, respectively. In the 133 children, the reason for the diagnostic work-up regarded multiple congenital anomalies and/or DD/ID (n = 64 of 105; 61.0%), epilepsy (n = 31 of 105; 29.5%), or ASD (n = 10 of 105; 9.5%). In this group, Lowther et al. (2015) reported behavioral problems including ADHD, aggression/rage, hyperactivity, self-mutilation, poor concentration, poor attention, impulsivity, and other similar features, as the most prevalent clinical manifestations (n = 46, 34.6%). Moreover, 30 (13.5%) had speech problems, 18 (13.5%) hypotonia, 10 (7.5%) brain abnormalities as shown by MRI, and 12 (9.5%) mood disorders. Analyzing the clinical features of each patients of the groups with deletions in BP4-BP5, BP3-BP4, and BP3-BP5, no relevant differences were found (Lowther et al., 2015). Sharp et al. (2008) were among the firsts to report clinical observations of patients presenting with a BP4-BP5 deletion: all of the nine patients reported manifested variable degrees of facial dysmorphic features and mild-to-moderate grade of mental retardation.
(9/9 cases). Epilepsy and/or EEG anomalies were found in seven of the nine patients.

In our systematically review, we reported the phenotype analysis of patients with the 15q13.1 deletion, selected according to the region involved (BP4-BP5, BP3-BP4, and BP3-BP5) and summarized in Table 2 (Ben-Shachar et al., 2009; Dibbens et al., 2009; Endris et al., 2010; Hassfurther, Komini, Fischer, & Leipoldt, 2016; Helbig et al., 2009; Jähn et al., 2014; Lowther et al., 2015; Masurel-Paulet et al., 2010; Miller et al., 2009; Pagnamenta et al., 2009; Pettigrew et al., 2015; Rosenfeld et al., 2011; Sharp et al., 2008; Shinawi et al., 2009; Van Bon et al., 2009; Ziats et al., 2016 and present cases). The BP4-BP5 region was more susceptible to flanking. In this cohort (see Table 2), we collected 125 individuals presenting with behavioral disturbances, DD/ID, and mild–moderate intellectual disability, and speech disorders, which were reported in 42.4%, 68.8%, and 36%, respectively. Other recurrent clinical manifestations were epilepsy in 32%, and a small or large OFC in 19.2% and 16.8% of the cases, respectively. Other features included ASD, reported in 12.8%, and dysmorphisms, reported in 16%. Facial dysmorphic features were minor, not specific, and did not affect particular areas of the face.

Patients with a BP3-BP5 deletion are uncommonly reported. Rosenfeld et al. (2011), in a cohort of 34,046 samples who were submitted for a diagnostic work-up, identified four individuals with deletions involving the BP3-BP4 region and one with deletions involving the BP3-BP5 region. In our review of 19 patients presenting with BP3-BP5 deletions (see Table 2), dysmorphic features were reported in 21%, DD/ID and mild–moderate ID in 73.6%, behavioral disturbances in 68.4%, speech difficulties in 47.3%, epilepsy in 31.5%, and large head in 36.8%. Two cases of ASD and small head have also been reported (10.5%).

Patients affected by a BP3-BP4 microdeletion are rarely reported. The five reported patients (see Table 2) showed DD/ and mild/moderate ID as more frequently reported manifestation (100%), followed by dysmorphic features (60%) and small head (60%). Speech disorder, epilepsy, and large head were reported in 40% of the cases.

The role of genes in the clinical expression of the 15q13.3 deletion is widely debated. Heterozygous deletions of chromosome region 15q13.3 more often involve a 1.5 segment between BP4 and BP5, which contains several genes (Figure 1); that is, ARHGAP11B, MTMR10, TRPM1, KLF13, OTUD7A, and CHRNA7, and a miRNA gene (hsa-mir-211) (Endris et al., 2010). The CHRNA7 gene has been reported as a major candidate gene for clinical expression of the deletion. This gene encodes for the neuronal alpha 7 nicotinic acetylcholine receptor, a synaptic ion channel protein that mediates neuronal signal transmission. This gene has been associated with patients affected by epileptic seizures and patients with schizophrenia (Masurel-Paulet et al., 2010). However, CHRNA7, as responsible for the 15q13.3 microdeletion features, remains to be questionable. TRPM1 has also been implicated in the clinical expression of the 15q13.3 deletion. TRPM1 belongs to the family of transient receptor potential channels that encode a calcium permanent channel, and it is related to transient neuronal signal transmission. This gene has been often associated with patients affected by epileptic seizures and it may have a possible tumor suppressor function. In mice, it has been shown to regulate the dendritic spine density and glutamatergic synaptic transmission (Bishop, North, & Donlan, 1995). ARHGAP11B in the embryonic mouse neocortex promotes basal progenitor generation and can act by increasing the cortical plate area, stimulating gyration. ARHGAP11B is derived from partial duplication of the ARHGAP11A gene, which encodes a Rho guanosine triphosphatase-activating protein (Florio et al., 2015; Yin et al., 2018). The protein coded by the Kruppel-like transcription factor 13 (KLF13) gene is a member of the Kruppel-like family of zinc finger proteins, which is a candidate for regulating cardiac gene expression and heart morphogenesis (Lavallée et al., 2006; Valbonesi et al., 2015). The myotubularin-related protein 10 (MTMR10) and MTM315 genes, also known as FAN1 (FANCD2- and FANCI-associated nuclease 1), encodes an endo- and exonuclease, which are involved in DNA interstrand cross-link repair (Forsingdal, Fejgin, Nielsen, Werge, & Nielsen, 2016). Mutations in both genes typically cause karyomegalic interstitial nephritis. Finally, a gene encoding a small noncoding RNA, termed miR-211, has been shown to act as a tumor metabolic switch (Bekenstein et al., 2017) and more recently to act as a key regulator of cholinergic imbalances and epileptiform activity (Mazar et al., 2016). The gene or genes responsible for the features presented by individuals with the 15q13.3 deletion are yet to be identified.

In reporting the features of the four members of this family and of the unrelated boy, we were impressed by the language impairment that was not compatible with the intellectual disability, which conversely was mild and/or moderate. We think that the 15q13.3 region must have a direct or indirect role in language development and its deletion is likely to be involved in language disorders. Ben-Shachar et al. (2009) screened, as diagnostic testing, 8,200 samples and they found 19 individuals with a BP4-BP5 deletion and 1 with a BP3-BP5 deletion. Among these, 14 children showed at least mixed expressive and receptive language delay. The language impairment was more pronounced than the developmental delay in gross and fine motor skills. Moreover, a 6.5-year-old girl was reported by...
### TABLE 2  Clinical manifestations of individuals with the 15p13.1 deletion selected according to the region involved (BP4-BP5, BP3-BP4, and BP3-BP5)

| Authors                  | Sharp et al. (2008) | Miller et al. (2009) | Helbig et al. (2009) | Dibbens et al. (2009) | Pagnamenta et al. (2009) | Ben-Shachar et al. (2009) | Van Bon et al. (2009) |
|--------------------------|---------------------|----------------------|----------------------|------------------------|--------------------------|--------------------------|------------------------|
|                          | BP4-BP5             | BP4-BP5              | BP3-BP5              | BP4-BP5                | BP4-BP5                  | BP3-BP5                  | BP4-BP5                |
| Screening on             | 757                 | 1,445                | 1,223                | 539                    | 8,200                    | 6,624                    |
| Patients N               | 9                   | 5                    | 11                   | 7                      | 3                        | 19                       | 16                     |
| Dysmorphisms             | 9                   | n.r                  | no                   | n.r                    | 4                        | n.r                      | 4                      |
| Small head               | 4                   | n.r                  | n.r                  | —                      | 2                        | 6                        | 1                      |
| Large head               | 2                   | n.r                  | n.r                  | 2                      | 2                        | 3                        | n.r                    |
| DD/DDI                  | 3                   | 5                    | 1                    | n.r                    | 4                        | n.r                      | 5                      |
| Mild/moderate            | 6                   | n.r                  | no                   | 2                      | 9                        | 9                        | 1                      |
| Speech difficulty        | 3                   | 4                    | no                   | 3                      | 14                       | 1                        | n.r                    |
| ASD                      | 1                   | 3                    | —                    | 3                      | 5                        | 1                        | n.r                    |
| Schizophrenia            | n.r                 | —                    | n.r                  | n.r                    | n.r                      | n.r                      | n.r                    |
| Epilepsy                 | 6                   | n.r                  | 11                   | 7                      | n.r                      | 1                        | n.r                    |
| Behavioral disturbances  | 2                   | 5                    | n.r                  | 3                      | 9                        | 9                        | 2                      |
| Others                   | 8 (digital anomalies) | —                    | n.r                  | n.r                    | 3 (digital anomalies)    | Benign hydrocephalus     | Fallot tetralogy- AVSD Digital anomalies 8; inverted nipples 1 |

### (Continues)
| Authors                        | Shinawi et al. (2009) | Masurel-Paulet et al. (2010) | Endris et al. (2010) | Rosenfeld et al. (2011) | Lowther et al. (2015) | Hassfurther et al. (2016) | Ziats et al. (2016) |
|-------------------------------|-----------------------|-----------------------------|----------------------|-------------------------|-----------------------|--------------------------|---------------------|
|                               | BP4-BP5               | BP4-BP5                     | BP4-BP5              | BP3-BP4                 | BP3-BP5               | BP4-BP5                  | BP3-BP5             |
| ASD                           | n.r                   | 1                           | n.r                  | n.r                     | n.r                   | n.r                      | 2                   |
| Schizophrenia                 | n.r                   | n.r                         | n.r                  | n.r                     | 1                     | n.r                      | n.r                 |
| Epilepsy                      | 3                     | 2                           | 2                    | 1                       | n.r                   | 1                        | n.r                 |
| Behav. distur                 | 1                     | 12                          | n.r                  | n.r                     | 1                     | 5                        | 7                   |
| others                        | n.r                   | ventricular septal defect; digital anomalies | Distonic tetraparesis | CHD                     | Natal teeth           | n.r                      | n.r                 |
|                               |                       |                             |                      |                         |                       |                          |                     |

**Table 2 (Continued)**

| Authors                        | Pettigrew et al. (2015) | Jähn et al. (2014) | Present cases |
|-------------------------------|-------------------------|--------------------|---------------|
|                               | BP3-BP5                 | BP3-BP5            | BP3-BP5       |
| Screening on                  | 85 with language impairment | 570 with epilepsy |               |
| Patients N                    | 1                       | 3                  | 5             |
| Dysmorphisms                  | n.r                     | n.r                | 2             |
| Small head                    | n.r                     | n.r                |               |
| Large head                    | n.r                     | n.r                | 4             |
| ID/DD                         | n.r                     | n.r                | n.r           |
| Mild/moderate                 | n.r                     | n.r                | 5             |
| Speech difficulty             | 1                       | n.r                | 5             |
| ASD                           | n.r                     | n.r                | n.r           |
| Schizophrenia                 | n.r                     | n.r                |               |
| Epilepsy                      | n.r                     | n.r                | n.r           |
| Behavioral disturbances       | n.r                     | n.r                | 5             |
| Others                        | n.r                     | n.r                | 2             |

Abbreviations: ASD, autistic spectrum disorder; DD, developmental delay; ID, intellectual disability; IGE, idiopathic generalized epilepsy; Large head, OFC >90th percentile; n, normal; n.r, none reported; OFC, occipital frontal circumference; Small Head, OFC < 25th percentile; Lowther et al. (2015): 7 adults from local cohorts.
Ehmke et al. (2017) who showed a de novo nonsense mutation in ZBTB18 plus a de novo 15q13.3 microdeletion. She manifested absent speech, global developmental delay, seizures unresponsive to treatment, ataxia, hypotonia, and minor dysmorphisms. Pettigrew et al. (2015), in a screening cohort of 85 children with language difficulties, detected a BP3-BP5 deletion in a child with language impairment in the absence of ID or other anomalies. This observation leads the authors to hypothesize the deletion as one of the putative cause of language disorders. The reported family and the unrelated boy may be a further contribution to this hypothesis. In fact, aside from the other features frequently reported with the BP3-BP5 deletion, the four members of the present family and the unrelated boy showed a notable speech delay and language impairment that was more relevant compared to the intellectual disability, which was mainly mild/moderate in the individuals with this deletion. One of the members of the family, the 5-year-old child with DS, showed global absence of language, which is an unusual feature in DS children (Bishop et al., 1995, Kent & Vorperian, 2013).

In conclusion, the region between BP3 and BP5 is likely directly or indirectly involved in human language development, and the deletion may have a causal effect in association to the cognitive dysfunction on language impairment in affected individuals. Limitations on this observation are related to the specificity of this region which is low given that language delays and impairments are commonly seen in nearly all and even in all types of CNVs and this region is associated to other features including global intellectual disability. Anyway, we have noted that in the here reported patients the language impairment was more expressed compared to the cognitive dysfunction, thus leading to hypothesis advanced by Pettigrew et al. (2015) on the directly or indirectly causal role of this deletion on the etiology of language disorders. This report supports the hypothesis of Pettigrew et al. (2015) on the causal role of this deletion in the etiology of language disorders.

Unfortunately, the language disorder is not the only clinical manifestation of this disorder, which is frequently found to be linked to other features, such as mild/moderate intellectual disabilities, behavioral impairments, dysmorphisms, and congenital anomalies.

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CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest.

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