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CLINICAL REPORT

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BCL11A frameshift mutation associated with dyspraxia and hypotonia affecting the fine, gross, oral, and speech motor systems

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We report the case of a 7-year-old male of Western European origin presenting with moderate intellectual disability, severe childhood apraxia of speech in the presence of oral and manual dyspraxia, and hypotonia across motor systems including the oral and speech motor systems. Exome sequencing revealed a de novo frameshift protein truncating mutation in the fourth exon of *BCL11A*, a gene recently demonstrated as being involved in cognition and language development. Making parallels with a previously described patient with a 200 kb 2p15p16.1 deletion encompassing the entire *BCL11A* gene and displaying a similar phenotype, we characterize in depth how BCL11A is involved in clinical aspects of language development and oral praxis.

KEYWORDS
BCL11A, childhood apraxia of speech, exome sequencing, intellectual disability, language delay

Abbreviations: ADI-R, autism diagnostic interview-revised; ADOS, autism diagnostic observation schedule; DTVP, developmental test of visual perception; ELO, «Evaluation du langage oral»; FSIQ, Full scale intelligence quotient; IQ, Intelligence quotient; MABC, Movement assessment battery for children; PIQ, Performance intelligence quotient; VIQ, Verbal intelligence quotient; WIPPSI, Wechsler preschool and primary scale of intelligence.

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1 | INTRODUCTION

Numerous genetic factors contribute to speech and language development and impairment (Barnett & van Bon, 2015; Graham & Fisher, 2015). In the most recent analysis of the Deciphering Developmental Disorders (DDD) study (Deciphering Developmental Disorders Study, 2015), the extent of speech delay in patients with developmental disorders has been shown to statistically increase the likelihood of finding a damaging de novo mutation (Deciphering Developmental Disorders Study, 2017). Most of these mutations have a global, unspecific impact on speech development. However, some have an effect on specific aspects of language such as *FOXP2* (Morgan, Fisher, Scheffer, & Hildebrand, 2016; Reuter et al., 2017) or *GRIN2A* (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001; Myers & Scheffer, 2016; Turner et al., 2015) anomalies, which lead to childhood apraxia of speech, oral motor dyspraxia, and dysarthria, or *SETBP1* encompassing 18q12.3 deletions which seems to impact expressive language, while preserving receptive language (Filges et al., 2011; Marseglia et al., 2012).

The B-cell lymphoma/leukemia 11A (*BCL11A*) gene encodes a C2H2 zinc-finger transcription factor highly expressed in the brain and the adult erythroid lineage (Avram, Fields, Senawong, Topark-Ngarm, & Leid, 2002; Leid et al., 2004; Nakamura et al., 2000), and is part of the murine BAF swi/snf chromatin remodeling complex (Kadoch et al., 2013). BCL11A has been shown to be a critical modulator of hemoglobin switching and HbF silencing (Basak et al., 2015; Funnell et al., 2015; Guda et al., 2015; Xu et al., 2013). In the murine brain, *Bcl11a* controls cell polarity, radial migration of upper cortical neurons, axon branching, and dendrite outgrowth (Kuo, Chen, & Hsueh 2010; Kuo, Hong, & Hsueh, 2009; Kuo, Hong, Chien, & Hsueh, 2010b; Wiegreffe et al., 2015). The DDD project (Deciphering Developmental Disorders Study, 2015; Dias et al., 2016) demonstrated that *BCL11A* haploinsufficiency causes intellectual disability and language delay (OMIM #617101). Patients with *BCL11A* mutations have global developmental delay, intellectual disability, which is moderate in most cases, and language delay of variable severity, with the occurrence of first words ranging from 16 months (mild) to only two words at the age of 6 years (severe). Microcephaly, autism spectrum disorder, and mild dysmorphism can be present and the level of fetal Hb is raised. In addition, *BCL11A* is included in most CNVs reported as the 2p15-p16.1 microdeletion syndrome (OMIM #612513), characterized by developmental delay, intellectual disability, hypotonia, poor verbal skills, craniofacial and skeletal features, digital anomalies, and fetal hemoglobin persistence (Basak et al., 2015; Funnell et al., 2015). When described, patients with 2p15p16 microdeletion encompassing *BCL11A* show delayed receptive and expressive language skills (Hancarova et al., 2013; Piccione et al., 2012; Rajcan-Separovic et al., 2007), language delay (Balci, Sawyer, Davila, Humphreys, & Dyment, 2015; Felix, Petrin, Sanseverino, & Murray, 2010), language restricted to a few single words and signing (Florisson et al., 2013), or absence of language (Florisson et al., 2013; Hucthagowder et al., 2012). Apart from Peter, Matsushita, Oda, and Raskind, (2014), who described a 200 kb 2p15p16.1 deletion encompassing the entire *BCL11A* gene (plus 50 kb of non-coding sequence but no other known coding or non-coding gene) in a patient with mild intellectual disability, childhood apraxia of speech, dysarthria, and oral and motor dyspraxia, language anomalies have not been extensively studied in patients with mutations or microdeletions affecting *BCL11A*.

In this report, we describe a boy with a single base de novo deletion in exon 4, causing a frameshift protein truncating mutation of *BCL11A*. The patient presents with a phenotype strikingly similar to the patient described by Peter et al. (2014), as it combines severe childhood apraxia of speech, gross and fine motor impairment, and moderate intellectual delay.

1.1 | Clinical report

The patient is the second of two children born to a non-consanguineous couple of Western European origin with no family history of neurodevelopmental disorders. He was born after an uneventful pregnancy and a normal delivery. Birth parameters were normal (weight 3,300 g, head circumference 33.5 cm, length 49 cm) and no congenital anomaly was observed. Growth parameters evolved within normal limits except for progressive mild microcephaly (50 cm at 7 years old, 1st Centile, −2.32 SD). He had global developmental delay: he sat unsupported at 11 months, walked at 24 months of age, and had an important language delay.

Parents first sought specialized medical care when the patient was 13 months old. At that time, physical examination was normal apart from discrete facial dysmorphism consisting of bilateral epicanthi, sparse eyebrows, a wide mouth with full lips, full tip of the nose, discrete retrognathia, fine hair with high frontal and posterior hairline, and a frontal upsweep, everted upper part of the ears, prominent antihelix, deep fossa, and small attached ear lobe (Figures 1b and 1c). Neurological examination revealed axial and oral hypotonia with excessive drooling. The patient had good social competences, smiling often and presenting good eye contact.

Physical and speech therapy was initiated at the age of 3; at that time the patient's vocabulary was limited to three words. At the age of four and a half he was able to make full sentences, still producing “me”/“I” substitutions occurring in the French equivalents of these words. The patient was having difficulties when conjugating verbs. He could count to three, but was unable to recognize colors. He was placed in a special education program.

Full cognitive testing was performed at the age of 5. General intellectual ability was evaluated using the French version of the Wechsler preschool and primary scale of intelligence (WPPSI-III) (Wechsler, 2002) resulting in an intelligence quotient of 53 with substantial inhomogeneity between subtests. The patient achieved relatively good scores in logical reasoning (score of 8), picture concepts (score of 5), and word reasoning (score of 5), but had very low scores in information and vocabulary (both a score of 1), block design (testing visual perception, organization, and visual-motor coordination; score of 1), and coding (testing visual-motor processing speed and short-term memory; score of 2) (for details, see Table 1).

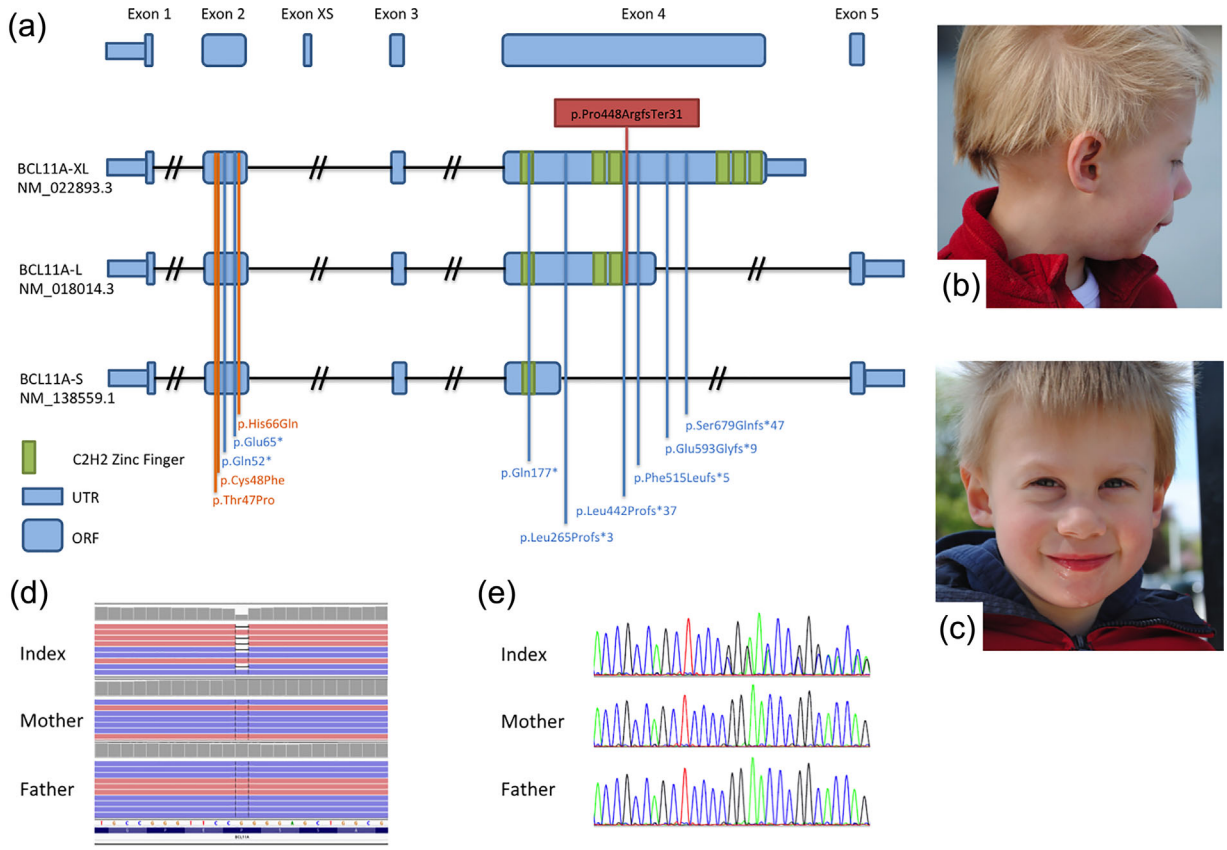

FIGURE 1 (a) Figure adapted from Dias et al. (2016). Schematic representation of the three major isoforms of BCL11A. Mutations are represented on and annotated according to the BCL11A-XL isoform (NM_022893.3); the mutation of our patient is represented by a red frame, the mutations represented by blue and orange lines are the ones described in Dias et al. (Orange: missense mutation; Blue: nonsense mutation). (b,c) Clinical features of our patient showing the high posterior hairline (b) and excessive drooling (c). (d) de novo cytosine deletion (c.1343delC) in exon 4 of the *BCL11A* gene visualized in IGV. This mutation is leading to a premature stop codon, p.Pro448Argfs*31. (e) Presence of the mutation in the child but none of the parent was confirmed by Sanger sequencing.[Color figure can be viewed at wileyonlinelibrary.com]

When the patient was 7 years old, orofacial praxis (non speech articulatory postures), speech, and language assessments were performed using the following French batteries: the Hénin–Dulac scale (Henin, 1978) for orofacial praxis, EXALang 5–8 (Thibault, Helloin, & Croteau, 2003) for speech and ELO (Khomsi, 2001) for language (see methods and Table 1).

Orofacial praxis was severely impaired (under 2nd percentile for all subtests), characterized by either very weak or impossible imitation, the occurrence of many facial synkinesia (e.g., raising eyebrows when asked to rise up the tongue) and frequent automatic-voluntary dissociation of oro-facial gestures (e.g., being unable to use tongue on demand but able to protrude tongue in the context of natural observation), clearly supporting the hypothesis of impaired motor programming.

Speech was characterized by inaccurate speech sound production (under 1st percentile); in particular, we observed the frequent occurrence of errors of resonance (nasalization/oralization), devoicing phenomenon, and final consonant deletion within the word. The patient produced vowels accurately in isolation but not always in the context of connected speech. On a dynamical point of view, there was an inconsistency of production, with the occurrence of multiple inaccurate speech sound productions within a same word, the latest being more frequently observed in the context of a directed task rather than during natural speech (automatic-voluntary dissociation), and the occurrence of increased error rates in longer and/or more complex word shapes. The phonetic inventory was still reduced. In isolation, the patient could not produce fricatives phonemes (more precisely [ʃ], [ʒ], [s] in French). Instead, he produced a substitutive interdental sound. In connected speech, when a fricative phoneme was the last syllable of a word, the substitutive interdental sound was not produced, annulling the last syllable. Furthermore, voice sounded breathy and weak and was characterized by a high vocal pitch, and intermittent hyper nasality, resulting in low speech intelligibility. Such voice could result from weakness of phonatory gesture suggesting dysarthria. The global linguistic profile (lexicon at 16th percentile and morphosyntax at 4th percentile) was characterized by a homogeneous moderate deficit, similar to the one observed in terms of the child's developmental age.

From the patient's phenotype, the following signs/symptoms are consistent with childhood apraxia of speech as described in the American Speech Language Hearing Association (ASHA) technical

TABLE 1 Summary of the cognitive, linguistic, praxic, social, and communication evaluation

IQ (age of 5)	Raw scores	Standard scores	Percentiles	Age equivalent (years)
Cognitive functions evaluated and tests used				
WPPSI III		Mean = 100(SD = 15)		
FSIQ	53*			
VIQ	50*			
PIQ	63*			
Subtests		Mean = 10 (SD = 3)		
Information	1*			
Vocabulary	1*			
Word reasoning	5			
Block design	1*			
Matrix (logical) reasoning	8			
Pictures concept	5			
Coding	2*			
Recepetive vocabulary	6			
Non-speech oral motor testing (orofacial praxis de Hénin, age of 7)				
Lips	2.85/10*		0.01	
Tongue	3.5/10*		0	
Cheeks and mandibula	2.85/10*		0.02	
Eyes and forehead	2/10*		0.02	
Speech testing (logatome repetition, EXALang, age of 7)	3/16*		0	
Language testing (ELO, age of 7)				
Lexical stock passive	13/20		15.87	
Syntaxic comprehension	6/21		3.4	
Syntaxic expresssion	12/25		15.87	
Motor/visual perception skills testing (age of 7)				
MABC (2nd edition)				
Manual dexterity	40*		<5	<3
Aiming and catching, and balance skills	40*		<5	<3
Balance skills	40*		<5	<3
Developmental test of visual perception (DTVP-2)				
Eye-hand coordination	97*		2	4.3
Position in space	4*		1	<3
Copying	5*		2	<3
Spatial relations	3*		2	4.1
Autism spectrum disorder testing (age of 7)		**ASD cut-off score**		
Autism diagnostic observation schedule (ADOS Module 2)				
Commmunication	2	3		
Social interaction	3	4		
Restrcited and repetitive behaviors	1	–		
Autism diagnostic interview-revised (ADI-R)				
Social interaction	5	10		
Communication and language behavior	6	8		
Restricted and repetitive behaviors	2	3		

Numbers with an asterisk (*) indicate scores significantly below the mean (below 2 SDs) or reaching/exceeding the cut-off (for ASD tests).

report: severely impaired orofacial praxis, consonant inventory too limited given child age, vowel errors, inconsistency of speech sound productions, increased errors with increased word complexity, and errors of resonance (nasalization, oralization) and intermittent hyper nasality consistent with motor programming deficits for velar movements. Motor signs/symptoms consistent with oral muscular hyptonia included a weak and breathy voice and excessive drooling (American Speech Language Hearing Association (ASHA), 2007).

The patient experienced difficulty with both gross and fine motor skills. He had a delay in developing new motor skills, for example, bike riding, ball catching, handling a knife and fork, and buttoning. Activities requiring bimanual coordination (e.g., cutting with scissors), drawing and handwriting (even with the help of models) were extremely difficult to perform. He also had substantial difficulties in organizing his desk, homework, and space on a page. Impairment in the performance of motor skills, and visual-spatial skills were completed with the Movement Assessment Battery for Children 2nd edition (Henderson, Rose, & Henderson, 1992), and DTVP2 systematically showing very weak scores (far below the 5th percentile) for the proposed tasks (Table 1). According to the ASHA technical report, deficits in motor learning and motor coordination in the fine and gross motor domains are seen in many children with childhood apraxia of speech, providing further evidence for this diagnosis.

Neither the Autism Diagnostic Interview™ Revised (ADI™-R), nor the Autism Diagnostic Observation Schedule (ADOS) rating scales reached threshold for one of the three domains of socialization, communication and stereotyped behaviors, thereby ruling out autism spectrum disorder (ASD).

Brain MRI (1.5 Tesla), overnight EEG monitoring, auditory evoked potentials, all performed at the age of 3 years, were normal. Brain MRI (3 Tesla) was normal at the age of 7 years. Metabolic testing, including plasma amino acids, sialotransferrin, urinary organic acids, oligo- and mucopolysaccharides did not reveal any abnormality. CGH-array detected only known polymorphisms.

Whole exome sequencing, performed in trio, revealed a de novo cytosine deletion (c.1343delC) in exon 4 of the *BCL11A* gene (NM_022893 [BCL11A_i001]), confirmed by Sanger sequencing (Figures 1d and 1e). This deletion induces a frameshift predicted to lead to a premature stop codon, p.Pro448Argfs*31. Deep amplicon sequencing revealed no mosaicism in the parents at coverage of more than 4000x. Because of the known role of BCL11A on hemoglobin switching and HbF silencing, hemoglobin electrophoresis and quantification were performed, which detected elevated HbF at 4.4% and 4.5% (Normal <1.5%) on two successive measures (6 months interval) without any other hematological abnormalities (Hb: 12.7 g/dl; vitamin B12, ferritin: normal).

2 | METHODS

The parents gave written consent for them and written permission for the patient to participate in the ADrESSE exome sequencing study and blood sampling being performed for DNA extraction (approved by local Hôpital Erasme and HUDERF Children Hospital Ethical committees under P2013/206 reference).

Orofacial praxis (non speech articulatory postures) was formally examined using the Hénin–Dulac scale, during which the patient is asked through a verbal order and imitation to mobilize sequentially tongue, lips, cheek, mandible, eyelid, and finally forehead (Henin, 1978). Speech was evaluated using EXALang 5–8 (Thibault et al., 2003), involving the child in a speaking task that requires single postures versus sequences of postures (at syllable, single-word, bisyllable, multisyllable levels). Language was evaluated with the batterie ELO (Examen du Langage Oral) (Khomsi, 2001). Voice quality has been subject to perceptual judgment by an expert clinician. Intermittent hypernasality was objectified by the use of a mirror held beneath the nose while the child pronounced vowels (mirror fogging because of nasal air escape).

CGH-array was performed on a 4 × 44 K ISCA array (Bluegnome, Cambridge, United Kingdom) and analyzed with BlueFuse Multi software (Bluegnome). Exome sequencing was performed at the Brussels Interuniversity Genomics High Throughput core (BRIGHT-core, Brussels, Belgium). Exome capture was achieved using the SeqCap EZ Human Exome Library v3.0 60 Mb (NimbleGen, Madison, WI). Samples were subsequently sequenced in a paired-end 125 bp run on a HiSeq 1500 instrument (Illumina, San Diego, CA). Sequences were aligned to the reference genome (hg19) and variants were called using a BWA-mem Unified Genotyper GATK pipeline. Filtering of the variants was accomplished using Highlander (http://sites.uclouvain.be/highlander). Details on pipeline and filtering are available on request. To assess for mosaicism in the parents, we used targeted deep sequencing. Fragments of 210 bp surrounding the position of the identified mutation were PCR-amplified, barcoded and sequenced on a MiSeq using standard V2 chemistry with 2 × 250 bp cycles (Illumina). Primer sequences are available on request.

3 | DISCUSSION

Up to now, 11 patients with missense or loss-of-function (LoF) mutations of *BCL11A* have been reported (see OMIM #617101 and Dias et al. [2016] for review), and a *BCL11A* haploinsufficiency related Intellectual Disability—Language Delay Disorder has been fully validated, in vivo, and in vitro (Dias et al., 2016).

Our patient harbors a de novo cytosine deletion (c.1343delC) in exon 4 of the *BCL11A* gene (NM_022893 [BCL11A_i001]) leading to a premature stop codon (p.Pro448Argfs*31) at the same amino acid (479) as the c.1325_1325del (p.Leu442Profs*37) reported in a cohort of patients with ASD (De Rubeis et al., 2014). Reported LoF mutations are scattered throughout the gene, whereas the pathological missense variants described so far are all located in the N-terminal domain, necessary for dimerization of BCL11A isoforms and interaction with nucleosome remodeling complexes (Dias et al., 2016) (Figure 1A). A few LoF variants are also reported in the ExAC cohort (Lek et al., 2016): two at the very C-distal portion of the BCL11A-XL isoform (hg19, chr2:

g.60687611G>C (p.Tyr812*); chr2:g.60687571G>A (p.Arg826*)), and one in the fifth exon of isoforms BCL11A-L and- S (chr2: g.60679767delC, NM_018014.3:p.Arg756Glufs*22, NM_138559.1: p.Arg222Lysfs*17).

Patients with missense and LoF variants of *BCL11A* described by Dias et al. (2016) have global developmental delay, mostly moderate intellectual disability, and speech and language delay, as observed in our patient. Other signs include microcephaly (5/9) and mild facial dysmorphism. Many of the dysmorphic features present in our patient (epicanthi, full tip of the nose, protruding philtrum, full lower lip, high frontal hairline and frontal hair upsweep, mild retrognathia) are also observed in the Dias et al. (2016) series. In addition, our patient had a marked posterior and lateral receding hairline at 3 years of age that improved at 7 years of age (Figure 1b).

Consistent with murine models and *BCL11A* mutated patients described by Dias et al. (2016), our patient has progressive microcephaly, with a head circumference at the 1st percentile (−2.32 SD). Repeated brain MRI at 1.5 and 3 Tesla failed to demonstrate any CNS structural anomaly, similar to patients with missense and LoF mutations of *BCL11A* (Dias et al., 2016), but dissimilar to patients with the 2p15-p16.1 microdeletion syndrome, for which at least three genes have been shown to participate to the brain malformation phenotype in zebrafish models (Bagheri et al., 2016). Our patient did not meet the diagnostic criteria of ASD, concordant with the low frequency of ASD in the 11 reported patients (Dias et al., 2016). Our patient had manual dyspraxia, a feature scarcely reported in patients with microdeletions encompassing *BCL11A* (Basak et al., 2015).

Speech and language delay is recognized as a key feature of the *BCL11A* LoF and missense mutations, and *BCL11A* encompassing 2p15p16 microdeletion syndromes (see introduction). But except for one report (Peter et al., 2014) and the present case, it has only been briefly depicted. Peter et al. (2014) reported an 11 year old boy with a 203 kb 2p16.1 microdeletion encompassing only the *BCL11A* gene (NCBI36: chr2:60.7–60.8). Peter's patient and ours present a strikingly similar speech disorder: both patients presented phonemic alterations, with deletion of consonants and syllables, phonemic substitutions (our patient), vowels errors increasing with phonetic complexity (both), and low speech intelligibility (both), all consistent with childhood apraxia of speech.

On a mechanistic point-of-view, we noticed that both patients presented with oral-motor dysfunction, excessive drooling (also reported in the patient of Rajcan-Separovic et al. (2007), difficult chewing, weak articular contact, and a breathy speech, all suggestive of dysarthria. In addition, intermittent hypernasality was observed in both patients. BCL11A is a known interactor of COUP-TF1 and COUP-TF1 knockout in mice results in malformations of the glossopharyngeal ganglion (Avram et al., 2000, 2002; Qiu et al., 1997). In humans the glossopharyngeal nerve and ganglion are responsible for motor (stylopharyngeal) and sensory innervation of the upper pharynx, and parasympathetic innervation of the parotid gland (Sarrazin, Toulgoat, & Benoudiba, 2013). Hence, the hypothesis of BCL11A mediating a dysfunction of the glossopharyngeal nerve could, at least partially, explain the oro-praxic and phonological deficits and excessive drooling present in the described patients.

BCL11A has been recently suggested by a proteomics study to be part of the BAF swi/snf chromatin remodeling complex (Kadoch et al., 2013). Dias et al. (2016) showed differential expression of BAF swi/snf related genes in the hippocampus of *Bcl11a* haploinsufficient mice, suggesting that *BCL11A* is a BAFopathy gene. In this context, it is noticeable that, before performing research exome sequencing, the unique gene we selected for clinical Sanger sequencing, based on dysmorphology criteria present in our patient, was *ARID1B*, a classic BAFopathy gene (Hoyer et al., 2012).

BCL11A is known to be a repressor of fetal hemoglobin expression. Patients with missense and LoF mutations (Dias et al., 2016), or *BCL11A* encompassing 2p15p16 microdeletions (Basak et al., 2015; Funnell et al., 2015) were shown to have elevated fetal hemoglobin levels, ranging from 3.1% (Dias et al., 2016) to 29.7% (Basak et al., 2015). Our patient value of 4.5% of HbF is thus in accordance with reported cases and constitutes additional evidence for the pathogenic nature of the LoF variant observed in our patient. As the neurodevelopmental deleterious effects of *BCL11A* haploinsufficiency are now established, marked caution should be applied in the evaluation of BCL11A inhibitors as therapeutic options for hemoglobinopathies such as sickle-cell disease or thalassemia (Bauer, Kamran, & Orkin, 2012).

In conclusion, our case and the one of Peter et al. (2014) demonstrate a strikingly similar phenotype of dysarthria and childhood apraxia of speech associated with *BCL11A* haploinsufficiency. While Peter's patient had a deletion of *BCL11A* and 50 kb of non-coding sequence, our case is a LoF mutation, strongly suggesting that *BCL11A* haploinsufficiency is responsible for the language phenotype of both patients. In-depth language description of more patients with *BCL11A* missense and LoFs variants is needed to assess whether these speech disorder phenotypes are major components of the *BCL11A* related syndrome, or anecdotic features present in a minority of patients. Excessive drooling reported in at least three patients does suggest that dysarthria and oro-praxic symptoms could also be specific to *BCL11A* haploinsufficiency, possibly through glossopharyngeal nerve dysfunction.

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