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VIEWPOINT ARTICLE

Aetiology of childhood apraxia of speech: a clinical practice update for paediatricians

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Abstract

Childhood apraxia of speech (CAS) is a rare disorder of childhood that can leave a watermark of impacts throughout the lifetime. Since first described in the 1950s, aetiological insights have been limited. At a neurobiological level, clinical MRI scans fail to reveal overt neural anomalies in individual cases with CAS, although quantitative MRI methods have revealed subtle brain anomalies at a group level. Dramatic insights have occurred in the past decade however, from the discovery of genetic pathways underlying the phenotype. A number of single genes and copy number variant conditions are now associated with CAS, either in relative isolation as in the case of *FOXP2* variants, or most typically, in association with other neurodevelopmental conditions of epilepsy, intellectual disability, motor impairment and autism. CAS requires careful differential diagnosis from other childhood speech disorders, but when a severe and persistent diagnosis is confirmed, a genetic aetiology should increasingly be pursued.

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Introduction

Speech acquisition is driven biologically, shaped by the environment, and occurs without event in most cases.[1] Yet as many as 1 in 20 preschool children experience difficulty with speech development[2] and paediatricians are often a first port of call for help-seeking parents. Of greatest concern in this group are the 1% of preschool children affected by a severe and striking speech diagnosis, childhood apraxia of speech (CAS).[3,4] CAS is a debilitating disorder that commonly results in lifelong speech impairment. The condition is typically associated with language and literacy impairments[5] with impacts on academic outcomes which potentially limits later employment opportunities. CAS is also known as developmental verbal dyspraxia (DVD) in the United Kingdom[6], and has historically been known as verbal dyspraxia, speech dyspraxia and developmental apraxia of speech.

Symptomatology and diagnosis of CAS

CAS is a complex disorder, defined as a higher-order motor system deficit of motor planning and programming. More specifically, motor planning involves transforming

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abstract sound representations into speech-motor goals or commands, and motor programming involves further specifying the specific movement or acoustic parameters within each articulator for speech production.[7] There is general consensus regarding three core diagnostic features for CAS: (1) inconsistent speech errors (e.g. producing the same syllable or word differently across repetitions of the same word such as "opsa", "upal", "pital" for hospital); (2) lengthened and disrupted co-articulatory transitions (e.g. oral groping during speech; difficulty sequencing sounds and syllables, including frequent omissions of sounds in some cases; marked vowel errors; or hypernasality due to poor on-line planning and programming of velum (palatal) movements for denoting oral/nasal contrasts) and (3) inappropriate prosody (e.g. disrupted rhythm and intonation of speech, such as placing stress on a typically unstressed syllable of a word or placing equal stress across all syllables).[8]

The crux of a CAS diagnosis is based on differentiating the speech presentation from other developmental speech impairments of articulation disorder, phonological disorder, stuttering or dysarthria (Table 1). In 'pure' or isolated idiopathic CAS, children reportedly have the apraxic speech deficit in isolation from any co-occurring neurodevelopmental condition. Isolated CAS is also unrelated to orofacial structural impairments associated with structural articulation deficits such as cleft lip or palate, submucous cleft palate, macroglossia, or a malocclusion (Table 1). Further, isolated CAS is also distinct from dysarthria, i.e. disorder of the central or peripheral nervous system affecting physical strength, tone or range of movement affecting speech production (Table 1). A thorough oral structural and functional

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examination will help identify the presence of oral-structural deficits affecting articulation and will also indicate the presence of disrupted tone or control of neuromuscular movement indicative of dysarthria. A clinical MRI to check for neurological lesions may also be indicated if dysarthria is suspected; children with isolated CAS do not show lesions on routine MRI. Isolated CAS is rare however, and in many cases, children demonstrate one or more of these other developmental speech disorders of articulation, phonology dysarthria, or even stuttering, alongside CAS.[13-16]

Final important considerations of a CAS diagnosis include that (1) features of CAS tend to be less severe with age, with sounds and syllables being co-articulated more clearly and efficiently (although altered prosody remains a hallmark), (2) there is heterogeneity in the severity and specific type of symptomatology across the population, and (3) it is more challenging to provide a reliable CAS diagnosis when it co-occurs with other neurodevelopmental disorders, particularly in children who are largely non-verbal at older age ranges such as often occurs in autism or global developmental delay.

- Table 1 -

Embracing complexity in the CAS phenotype

Cases with isolated idiopathic CAS have received the most research interest, arguably limiting our understanding of cases with more complex co-morbid profiles. Most recently however, the identification of single genes or related biological pathways

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associated with CAS has encouraged application of broader phenotyping approaches in the field. This phenotyping encompasses not only speech symptomatology, but also other neuropsychological, neurobiological, morphological, behavioural and medical symptoms, embracing the heterogeneity and co-morbidity more representative of the broader CAS population.

Neurobiology of CAS

In terms of neurological involvement, routine clinical MRI scans are not currently sensitive enough to identify neural anomalies or correlates for individual children with isolated idiopathic CAS, even when the phenotype or clinical presentation is severe. A handful of reports exist on overt clinical MRI findings in children with known causes of CAS that come with medical or neurodevelopmental co-morbidities such as galactosaemia due to disruption to *GALT1*, creatine transporter deficits, and rolandic epilepsy for example.[17] To date however, the most comprehensive quantitative MRI work in this area has been conducted in CAS associated with *FOXP2* mutation.[18-23] As for most linguistic phenotypes, studies of *FOXP2*-associated speech and language deficits, including CAS, suggest the phenotype is associated with a broad neural network, but is most commonly characterised by anomalies of the inferior frontal cortices, rolandic cortices, basal ganglia and cerebellum.[17,21] There is some variability in the neural phenotype however, even in cases with similar genotypes, e.g. neural correlates across individuals with *FOXP2* variants. [21]

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Genetic bases of CAS

The discovery that variants of *FOXP2* were associated with a rare and monogenic form of CAS[24] catalysed the study of further genes for speech and language disorders. More than 15 years on from the *FOXP2* discovery, microarray and next generation technologies now enable rapid and relatively cost-efficient genetic testing and have led to a proliferation of further discoveries of gene pathways associated with CAS.[13-16,25,26]

To highlight the rapidly growing aetiological knowledge in this field, and the presence of significant neurodevelopmental co-morbidity for many cases with CAS, we will illustrate genotype-phenotype associations for a handful of single gene variants and copy number variant conditions associated with CAS (Table 2). It was beyond the scope of this article to provide an exhaustive summary of all neurogenetic syndromes, copy number variant conditions or even chromosomal rearrangements associated with CAS, however CAS has been associated with conditions such as Floating Harbor syndrome[27], Cri du chat syndrome[28], galactosaemia[29], 6q25.3 deletion[16], 7q11.23 duplication[26] and chromosomal translocations.[30,31] Moreover, we have not covered recently identified genes for CAS, where replication or further evidence of the relevance of these candidates to the broader population of CAS is not yet clear.[25]

- Table 2 -

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FOXP2/7q31.1 deletion

FOXP2 was the first gene implicated in a monogenic form of CAS[24] occurring in the absence of frank neurological lesion, intellectual impairment or other overt neurodevelopmental conditions. Both *de novo* and inherited forms of the heterozygous *FOXP2* mutations pathogenic for CAS have been reported.[24, 32, 33] Penetrance for CAS is high, close to 100% based on reported cases.[34] Individuals with intragenic mutations disturbing *FOXP2* may be categorised as having '*FOXP2*-only' related speech and language disorders, whereas cases with *FOXP2* disruption via translocation, deletion or other complex variants such as pericentromeric inversion or uniparental disomy may be referred to as '*FOXP2*-plus' related speech and language disorders.[34]

Cases with the underlying genetic alteration of '*FOXP2*-only,' typically have preserved performance intelligence quotient (IQ) compared to verbal IQ, appropriate social abilities, and typical fine and gross motor skills alongside CAS. Although mild cognitive impairment, mild motor impairments, autistic features (but not a formal autism spectrum disorder (ASD) diagnosis) and even mild dysmorphology (e.g. narrow palpebral fissures, mild finger pads, horizontal eyebrows, large ears) have recently been reported in some cases with *FOXP2*-only mutations.[32,34]

By contrast, individuals with *FOXP2*-plus genetic aberrations are more likely to have global developmental and behavioural issues with oral-motor deficits, global developmental delay, and ASD alongside CAS.[34] These additional phenotypes may

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relate to disruptions of other genes neighbouring *FOXP2* in that region of chromosome 7.

GRIN2A

The identification of a role for *GRIN2A* in CAS has a long history, beginning 60 years ago with the discovery of epilepsy-associated speech and language disorders or 'aphasias'.[35] Further clinical enquiry into children with epilepsy since this time has revealed a broad spectrum of epilepsy aphasias which represents an association between epilepsy, speech (including CAS) and language disorders and the EEG signature of centro-temporal spikes.[36] In recent years, mutations or very small deletions in *GRIN2A* have been identified in patients with focal epilepsy and speech and language dysfunction.[37] Variable epilepsy and linguistic phenotypes may be associated with the *GRIN2A* genotype but, in relation to speech, CAS, dysarthria and oral motor impairments have been consistently reported across families regardless of the associated form of epilepsy.[38] The speech phenotype may also occur in the absence of a seizure disorder, suggesting an important role for *GRIN2A* in speech-motor function or CAS,[38] and not only in the epilepsy aphasias.

SETBP1

Germline *de novo* mutations in *SETBP1* have been identified as the cause of Schinzel-Giedion Syndrome, a rare and severe developmental disorder of seizures, midface hypoplasia, cardiac defects and skeletal abnormalities and with a link to somatic events seen in myeloid malignancies.[39] Yet recent reports of germline chromosomal

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deletions and truncating mutations in *SETBP1* show that loss-of-function mutations cause a markedly different and less severe phenotype with impaired expressive speech, relatively intact receptive language abilities, decreased fine motor skills, hyperactivity/ADHD, autistic traits and subtle dysmorphism.[40,41] Most recently the phenotype was expanded to specify two cases with CAS with a *SETBP1* frameshift mutation and de novo LoF mutation respectively.[25]

BCL11A and 2p15p16.1 microdeletion

Microdeletions of *BCL11A* have been reported in association with CAS, dysarthria, hypotonia and general oral and gross motor dyspraxia alongside the usual constellation of features associated with the 2p15p16.1 microdeletion syndrome,[14,42,43] namely a broad intellectual disability (ID) profile with concomitant poor expressive language, growth retardation, autism, craniofacial and skeletal dysmorphic traits, internal organ defects, abnormal muscle tone and gross motor delays.[44]

KANSL1 or 17q21.31 microdeletion

Koolen de Vries syndrome (KdVS) is a rare multi-system disorder associated with developmental delay, intellectual disability, hypotonia, and facial dysmorphism. Epilepsy and brain anomalies are also common, whereas cleft palate and hearing loss occur infrequently. KdVS is caused by haploinsufficiency of *KANSL1*, either due to a 17q21.31 microdeletion or intragenic variant.[45] Speech development is a core challenge for children with KdVS, particularly in the preschool period. Early history includes hypotonia, feeding difficulties and delayed onset of first words, occurring

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between 2.5 to 3.5 years of age.[14] Almost all children with KdVS receive a diagnosis of CAS, often co-morbid with dysarthria and additional articulation and phonological errors.[14] The presence of CAS with co-occurring speech diagnoses is seen in other genetic conditions, such as Floating Harbour Syndrome,[27] 7q11.23 duplication syndrome,[26] 16p11.2 deletion[13] and *2p15p16.1* microdeletion.[15]

ELKS/ERC1 and 12p13.33 deletion

Thevenon and colleagues[46] identified nine participants across six families with rare deletions at 12p13.33. *ELKS/ERC1* was the only gene consistently deleted across affected family members hence the authors hypothesised this gene was key to expression of the phenotype. Delayed first words (36 to 42 months), delayed walking, and prominent ear lobes were common features.[46] Five of the nine participants were reported to have CAS. Language and reading difficulties were reported in some. The participants also had a broader profile of neuro-developmental disorder beyond speech and language, including intellectual impairment (5/9), psychiatric manifestations (5/9), behavioural difficulties (7/9), ADHD (6/9) and ASD (2/9).[46] Overall, it appears that deletions of 12p13.33 may be responsible for variable phenotypes including CAS, associated with a broader neurobehavioural syndrome.

16p11.2 deletion

The 16p11.2 deletion represents one of the most well-studied CNVs in neurodevelopmental disorders. These deletions are relatively common, occurring in

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around 1 per 5000 individuals, and occurring in either *de novo* or inherited forms.[47] Moderate ID, ASD, poor cognitive and language ability (as great as 2 SD below familial non-carriers), epilepsy, macrocephaly (apparent by age 2 years), brain abnormalities such as Chiari Type 1 malformations or cerebellar ectopia, and obesity are associated with 16p11.2 deletion.[47] A number of studies have also confirmed the high penetrance of CAS in children with 16p11.2 deletions.[13,48] Other speech profiles have also been reported in 16p11.2 deletion in addition to CAS, including articulation and phonological disorders, dysarthria, minimal verbal output, and even typical speech in some.[13]

Conclusion

The paediatric evaluation of a child with CAS should clarify whether the speech disorder is consistent with a diagnosis of CAS and whether there are co-existing problems with speech (e.g. dysarthria). The clinician should look for evidence for co-morbid neurodevelopmental disorders such as intellectual disability or autism. An oral examination should be performed as well as a neurological examination. In children who have abnormal neurological findings or in whom there is evidence of dysarthria, an MRI of the brain could be considered. In most children, a Comparative Genomic Hybridisation (CGH) microarray should be performed. Furthermore, if the child has epilepsy or if they have a speech disorder which shows considerable fluctuation then a sleep EEG should be considered (abnormal in *GRIN2A* associated CAS).

Evidence is increasingly suggesting CAS is a genetic disorder, yet the genetic

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landscape is complex and is not fully understood. Mutations of *FOXP2*-only have been associated with a relatively homogeneous phenotype of CAS and language disorder in the absence of ID, but this has been the only candidate gene to date to show a selectivity of this kind. Other genotypes associated with CAS to date generally lead to broader ID syndromes (e.g., *BCL11A, KANSL1*) and/or significant medical comorbidities such as epilepsy (e.g., *GRIN2A*) or autism (16p11.2 deletion), where CAS may occur as part of the broader spectrum of the condition.

The potential clinical implications for refining the aetiology of CAS are clearly significant in terms of personalised medicine, with the prospect of optimised diagnosis, genetic and prognostic counselling and targeted therapeutics. For the moment, where CAS appears persistent and severe, a genetic aetiology should be increasingly pursued.

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References

1. Levelt WJM. *Speaking: From intention to articulation*. MIT Press, Cambridge, MA, 1989.

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Author Manuscript

2. Eadie P, Morgan A, Ukoumunne OC, Ttofari-Eecen K, Wake M, Reilly S. Speech sound disorder at 4 years: prevalence, comorbidities, and predictors in a community cohort of children. *Dev. Med. Child Neurol*. 2015; ***57***: 578-84.

3. Morley ME. *The development and disorders of speech in childhood* (3rd ed.). Williams and Wilkins, Baltimore, 1972.

4. Yoss KA. *Developmental apraxia of speech in children: Familial patterns and behavioral characteristics*. Paper presented at the ASHA North Central Regional Conference, Minneapolis, MN, 1975.

5. Gillon GT, Moriarty BC. Childhood apraxia of speech: children at risk for persistent reading and spelling disorder. *Semin. Speech Lang*. 2007; **28** :48-57.

6. Royal College of Speech Language Therapists (RCSLT). Policy statement: Developmental Verbal Dyspraxia. 2011. Available at: https://www.ndp3.org/documents/rcslt2011dvdPolicyStatement.pdf (accessed 18.6.18).

7. Morgan A, Murray E. Chapter 5. Clinical management of motor speech disorders. In Dodd B, Morgan A, eds. *Intervention case studies of child speech impairment*. J&R Press, London, UK, 2017; 75-94.

8. American Speech-Language-Hearing Association (ASHA). (2007). *Ad Hoc Committee on Childhood Apraxia of Speech*. Rockville (MD), Available from: http://www.asha.org/policy/PS2007-00277/ (accessed 18.6.18).

9. Morgan AT, Günther T. Chapter 2. Clinical management of articulation impairment in children. In Dodd B, Morgan A, eds. *Intervention case studies of child speech impairment*. J&R Press, London, UK, 2017; 9-29.

10. Dodd B. Chapter 9. Clinical Management of Phonological Impairment in Children. In Dodd B, Morgan A, eds. *Intervention case studies of child speech impairment*. J&R Press, London, UK, 2017; 161-179.

11. Morgan AT, Masterton R, Pigdon L, Connelly A, Liégeois FJ. Functional magnetic resonance imaging of chronic dysarthric speech after childhood brain injury: reliance on a left-hemisphere compensatory network. *Brain*. 2013; **136**: 646-57.

12. Reilly S, McKean C, Morgan A, Wake M. Identifying and managing common childhood language and speech impairments. *BMJ*. 2015; **350**: h2318.

This article is protected by copyright. All rights reserved.

Author Manuscript

13. Mei C, Fedorenko E, Amor DJ, et al. Deep phenotyping of speech and language skills in individuals with 16p11.2 deletion. *Eur. J. Hum. Genet*. 2018; *26*: 676-86.

14. Morgan AT, Haaften LV, van Hulst K, et al. Early speech development in Koolen de Vries syndrome limited by oral praxis and hypotonia. *Eur. J. Hum. Genet*. 2018; **26**: 75-84.

15. Peter B, Matsushita M, Oda K, Raskind W. De novo microdeletion of *BCL11A* is associated with severe speech sound disorder. *Am. J. Med. Genet. A*. 2014*;* **164A**: 2091-6.

16. Peter B, Lancaster H, Vose C, et al. Two unrelated children with overlapping 6q25.3 deletions, motor speech disorders, and language delays. *Am. J. Med. Genet. A*. 2017; **173**: 2659-2669

17. Liégeois FJ, Morgan AT. Neural bases of childhood speech disorders: lateralization and plasticity for speech functions during development. *Neurosci. Biobehav. Rev*. 2012; **36**: 439-58.

18. Belton E, Salmond CH, Watkins KE, Vargha-Khadem F, Gadian DG. Bilateral brain abnormalities associated with dominantly inherited verbal and orofacial dyspraxia. *Hum. Brain Map.* 2003; **18**: 194-200.

19. Liégeois F, Baldeweg T, Connelly A, Gadian DG, Mishkin M, Vargha-Khadem, F. Language fMRI abnormalities associated with FOXP2 gene mutation. *Nat. Neurosci.* 2003; **6**: 1230-7.

20. Liégeois F, Morgan AT, Connelly A, Vargha-Khadem F. Endophenotypes of *FOXP2*: dysfunction within the human articulatory network. *Eur. J. Paed. Neuro*. 2011; **15**: 283-8.

21. Liégeois FJ, Hildebrand MS, Bonthrone A, et al. Early neuroimaging markers of *FOXP2* intragenic deletion. *Sci. Rep*. 2016; **6**: 35192.

22. Vargha-Khadem F, Watkins KE, Price CJ, et al. Neural basis of an inherited speech and language disorder. *Proc. Nat. Acad. Sci. USA (PNAS)*. 1998; **95**: 12695-700.

23. Watkins KE, Vargha-Khadem F, Ashburner J, et al. MRI analysis of an inherited speech and language disorder: structural brain abnormalities. *Brain*. 2002; **125**: 465-78.

This article is protected by copyright. All rights reserved.

Author Manuscript

24. Lai CS, Fisher SE, Hurst JA, Vargha-Khadem F, Monaco AP. A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature.* 2001*;* **413**: 519-23.

25. Eising E, Carrion-Castillo A, Vino A, et al. A set of regulatory genes co-expressed in embryonic human brain is implicated in disrupted speech development. *Mol. Psychiatry*. 2018 Feb 20. doi: 10.1038/s41380-018-0020-x.

26. Velleman SL, Mervis CB. Children with 7q11.23 Duplication Syndrome: Speech, Language, Cognitive, and Behavioral Characteristics and their Implications for Intervention. *Perspect. Lang. Learn Educ*. 2011; **18** :108-16.

27. White SM, Morgan A, Da Costa A, et al. The phenotype of Floating-Harbor syndrome in 10 patients. *Am. J. Med. Genet. A*. 2010; **152A**: 821-9.

28. Elmakky A, Carli D, Lugli L, et al. A three-generation family with terminal microdeletion involving 5p15.33-32 due to a whole-arm 5;15 chromosomal translocation with a steady phenotype of atypical cri du chat syndrome. *Eur. J. Med. Gen.* 2014*;* **57**: 145-50.

29. Potter NL, Nievergelt Y, Shriberg LD. Motor and speech disorders in classic galactosemia. *J. Inherited Metabolic Dis. Rep*. 2013; **11**: 31-41.

30. Weistuch L, Schiff-Myers NB. Chromosomal translocation in a child with SLI and apraxia. *J. Speech Hear. Res*. 1996; **39** :668-71.

31. Shriberg LD, Jakielski KJ, El-Shanti H. Breakpoint localization using array-CGH in three siblings with an unbalanced 4q;16q translocation and childhood apraxia of speech (CAS). *Am. J. Med. Genet A*. 2008; **146A**: 2227-33.

32. Reuter MS, Riess A, Moog U, et al. FOXP2 variants in 14 individuals with developmental speech and language disorders broaden the mutational and clinical spectrum. *J. Med. Genet*. 2017; **54**: 64-72.

33. Turner SJ, Hildebrand MS, Block S, et al. Small intragenic deletion in FOXP2 associated with childhood apraxia of speech and dysarthria. *Am. J. Med. Genet. A*. 2013; **161A**: 2321-6.

34. Morgan A, Fisher SE, Scheffer I, Hildebrand M. (2017). *FOXP2*-Related Speech and Language Disorders. In: Pagon RA, Adam MP, Ardingerm HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K. (Eds). SourceGeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

This article is protected by copyright. All rights reserved.

Author Manuscript

35. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. *Neurology*. 1957; **7**: 523-30.

36. Turner SJ, Morgan AT, Perez ER, Scheffer IE. New genes for focal epilepsies with speech and language disorders. *Current Neuro. Neurosci. Rep.* 2015a; **15**: 35.

37. Carvill GL, Regan BM, Yendle SC, et al. GRIN2A mutations cause epilepsy-aphasia spectrum disorders. *Nature Genet.* 2013; **45**: 1073-6.

38. Turner SJ, Mayes AK, Verhoeven A, Mandelstam SA, Morgan AT, Scheffer IE. *GRIN2A*: an aptly named gene for speech dysfunction. *Neurology*. 2015b; **84**: 586-93.

39. Acuna-Hidalgo R, Deriziotis P, Steehouwer M, et al. Overlapping SETBP1 gain-of-function mutations in Schinzel-Giedion syndrome and hematologic malignancies. *PLoS Genet*. 2017;**13**:e1006683.

40. Coe BP, Witherspoon K, Rosenfeld JA, et al. Refining analyses of copy number variation identifies specific genes associated with developmental delay. *Nat. Genet*. 2014; **46**: 1063-71.

41. Marseglia G, Scordo MR, Pescucci C, et al. 372 Kb microdeletion in 18q12.3 causing SETBP1 haploinsufficiency associated with mild mental retardation and expressive speech impairment. *Eur. J. Med. Genet*. 2012; **55**: 216–21

42. Dias C, Estruch SB, Graham SA, et al. *BCL11A* Haploinsufficiency Causes an Intellectual Disability Syndrome and Dysregulates Transcription. *Am. J. Med. Genet.* 2016*;* **99:** 253-74.

43. Soblet J, Dimov I, Graf von Kalckreuth C, et al. *BCL11A* frameshift mutation associated with dyspraxia and hypotonia affecting the fine, gross, oral, and speech motor systems. *Am. J. Med. Genet. A*. 2018; **176**: 201-8.

44. Lévy J, Coussement A, Dupont C, et al. Molecular and clinical delineation of 2p15p16.1 microdeletion syndrome. *Am. J. Med. Genet. A*. 2017; **173**: 2081-7.

45. Koolen DA, de Vries BBA. (2016). KANSL1-Related Intellectual Disability Syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.

46. Thevenon J, Callier P, Andrieux J, et al. 12p13.33 microdeletion including ELKS/ERC1, a new locus associated with childhood apraxia of speech. *Eur. J. Hum Gen*. 2013; **21**: 82-8.

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Author Manuscript

47. Miller DT, Chung W, Nasir R, et al. 16p11.2 Recurrent Microdeletion. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. 2015. Seattle (WA): University of Washington, Seattle; 1993-2018.

48. Fedorenko E, Morgan A, Murray E, et al. A highly penetrant form of childhood apraxia of speech due to deletion of 16p11.2. *Eur. J. Hum. Genet*. 2016; **24**: 302-6.

Table 1: Clinical diagnoses of Childhood Speech Sound Disorders

Speech Diagnosis		**Definition**
Articulation	**Functional disorder**	Inability to consistently produce a perceptually acceptable form of one or more speech sounds, in isolation or in words.[9] Speech disorder exists in absence of hearing impairment, orofacial structural deficits or other identifiable cause.[9]
	Structural disorder	Inability to consistently produce a perceptually acceptable form of one or more speech sounds, in isolation or in words.[9] Occurs due to orofacial structural impairment such as a cleft lip or palate, macroglossia or malocclusion of the mandible or maxilla).[9]
Phonological	**Delay**	Child is delayed, relative to peers, in understanding and correctly using the speech sounds of their language to contrast meaning, e.g., substituting 't' for 's' in horse is a typical phonological error in children aged 3 years, but should be resolved by 4 years. Persistence of this error at age 4 years would denote a delay in phonology.[10]
	Disorder	Child fails to understand and correctly use speech sounds of their language to contrast meaning. Child uses atypical speech errors used by < 10% of normative population, such as a sound preference substitution where a favourite sound is used in place of the correct phoneme (e.g., 'd' for 'k' in cup, 'd' for 'n' in knife, and 'd' for 'sh' in shoe).[10]
Childhood apraxia of speech		Disorder of speech motor programming/planning characterized by errors of speech consistency (e.g., different productions of 'copta', 'upa', 'opta' for same target word helicopter), co-articulation (e.g., oral groping, difficulty sequencing sounds and syllables) and prosody (e.g., equal stress across words).[7,8]
Dysarthria		A speech disorder resulting from a disorder of the central or peripheral nervous system that impairs neuromuscular control and tone resulting in spasticity, ataxia, fluctuating tone or inco-ordinated and involuntary movements which in turn leads to deficits across one or more subdomains of speech (i.e., phonation, articulation, prosody, or resonance).[11]
Stuttering		A disorder of speech fluency characterized by repetitions of sounds, syllables, words or phrases, or prolongation of sounds, or hesitations and blocks (i.e., when a child tries to speak but no sound comes out).[12]

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Table 2: Examples of broader neurodevelopmental phenotypes in children seen with CAS associated with specific gene pathways

Genetic condition	Dysmorphology	Epilepsy	Intellectual disability	ASD	ADHD	Motor deficits	Language deficits	Oromotor disorder/praxis	CAS	Dysarthria
FOXP2-only	+ subtle	-	-/borderline	-	-	-	+	+	+	+
FOXP2-plus (7q31.1 deletion)	+ subtle	-	+ mild-mod	+	-	+	+	+	+	+
GRIN2A	+ subtle	+	+	-	-	-	+	+	+	+
SETBP1	+ subtle	-	?/borderline	-	+	+	+	?	+	?
BCL11A/2p15p16.1 microdeletion	+	-	+	+	-	+	+	+	+	+
ELKS/ERC1/12p13.33 microdeletion	+ subtle	-	+	+	+	-	+	+	+	-
KANSL1/17q21.31 microdeletion	+	+	+ mild-mod	-	-	-	+	+	+	+
16p11.2 deletion	+ subtle	+	+	+	-	-	+	+	+	+ mild

^ Phenotypic heterogeneity is common, hence this table is intended to provide a representative summary of features often seen in association with the genotype in question; - denotes feature is typically absent; + denotes feature is typically present; ? unknown; mod denotes moderate; mild-mod denotes a range between mild to moderate; ADHD: Attention deficit hyperactivity disorder; ASD: autism spectrum disorder; CAS: childhood apraxia of speech.

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