

ARTICLE

Childhood Apraxia of Speech (CAS) in two patients with 16p11.2 microdeletion syndrome

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We report clinical findings that extend the phenotype of the ~550 kb 16p11.2 microdeletion syndrome to include a rare, severe, and persistent pediatric speech sound disorder termed Childhood Apraxia of Speech (CAS). CAS is the speech disorder identified in a multigenerational pedigree ('KE') in which half of the members have a mutation in *FOXP2* that co-segregates with CAS, oromotor apraxia, and low scores on a nonword repetition task. Each of the two patients in the current report completed a 2-h assessment protocol that provided information on their cognitive, language, speech, oral mechanism, motor, and developmental histories and performance. Their histories and standard scores on perceptual and acoustic speech tasks met clinical and research criteria for CAS. Array comparative genomic hybridization analyses identified deletions at chromosome 16p11.2 in each patient. These are the first reported cases with well-characterized CAS in the 16p11.2 syndrome literature and the first report of this microdeletion in CAS genetics research. We discuss implications of findings for issues in both literatures.

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INTRODUCTION

The 16p11.2 microdeletion syndrome

The 16p11.2 microdeletion syndrome is a contiguous deletion syndrome which can be transmitted from a parent to a child in a dominant manner, although the majority of cases are *de novo*.¹ The estimated population prevalence is 0.5%,^{2,3} with a prevalence of 0.3–0.7% in large cohorts of patients with intellectual disability and other developmental and behavioral problems.⁴

The 16p11.2 microdeletion syndrome was initially described in patients from several developmental backgrounds, including developmental delay and mild cognitive impairment,⁵ Asperger syndrome,⁶ autism spectrum disorder,^{2,7} dyslexia,² and individuals with aggression, hyperactivity, schizophrenia, bipolar disorder, and symptoms of obsessive-compulsive disorder.⁷ More recently, the 16p11.2 microdeletion phenotype was broadened to include speech-language impairment,^{1,4,8} motor delay, dysmorphologies, and seizures.¹ The syndrome has variable expressivity and incomplete penetrance, with reports including descriptions of healthy carriers and mildly-to-severely affected patients. The microdeletions of most 16p11.2 patients are ~550 kb in size and extend from genomic location 29.5–30.1 Mb (NCBI Build 36.1; hg18;⁸ genomic glossaries and standards are available at the University of California, Santa Cruz genome browser: <http://genome.ucsc.edu/>). The deletion is flanked by two low-copy repeats of ~147 kb, suggesting that the pathogenesis is mediated by non-allelic homologous recombination.⁷

A number of reports provide information on the prevalence of speech-language impairments in 16p11.2 microdeletion syndrome. One study reported that 'speech/language delay and cognitive impairment' (p.332) were the most common clinical deficits in 17

patients with 16p11.2 microdeletions and 10 with 16p11.2 duplications.¹ Another study reported 'speech retardation' (p.85) in 19 of 20 (95%) patients with 16p11.2 deletions.⁸ Other studies have found speech and language deficits in 17 of 18 (94%) patients with 16p11.2 deletions,⁹ and language deficits in 18 of 21 (86%) patients.⁴ In a study reporting developmental milestones for speech-language acquisition in 9 patients with 16p11.2 deletions, 6 (67%) patients had significant delays in age of single word acquisition, 7 (78%) had delays in age of phrase development, and all 9 (100%) had deficits in reciprocal conversation.⁴

A significant research problem with reports indicating speech impairment in patients with 16p11.2 microdeletion syndrome is the lack of phenotypic specificity. Only a few studies have included standardized perceptual measures of speech production, and no studies reviewed have used acoustic measures for fine-graded description and classification of speech, prosody, and voice impairment. Lacking such measures, speech findings in the 16p11.2 microdeletion literature have not been informative on the subtype(s) of speech sound disorder associated with deficits in cognitive-linguistic and/or neuromotor processes, with attendant constraints on descriptive-explanatory accounts of genomic and neuromotor causal substrates.

Childhood Apraxia of Speech (CAS)

The present focus on patients with 16p11.2 microdeletions concerns Childhood Apraxia of Speech (CAS), a rare (<0.01%), severe, and persistent subtype of pediatric speech sound disorder.¹⁰ Whereas the proximal causes of Speech Delay, the most common subtype of

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speech sound disorders,¹¹ is a deficit in forming linguistic representations of sounds, syllables, and words, the proximal cause of CAS¹² is in transcoding linguistic representations into the articulatory gestures that produce speech.¹³ The neural substrates of both Speech Delay and CAS include deficits in cortical processes, with CAS also associated with deficits in cerebellar and basal ganglia regions and pathways.¹⁰

The genomic origins of CAS have begun to be studied in the past 2 decades. The most significant finding, to date, has been the identification of a mutation in the forkhead-box P2 (*FOXP2*) gene as the source of CAS in approximately half of the widely cited, multigenerational 'KE' pedigree.^{14,15} Detection of additional affected individuals with translocations affecting the *FOXP2* locus and point mutations in the coding sequence of the gene have confirmed its role in speech^{16–19} and language²⁰ impairment. Mice that carry heterozygous mutations equivalent to those in affected members of the KE family have deficits in learning rapid motor sequences, as well as impaired synaptic plasticity in corticostriatal and cerebellar circuits.^{21,22}

A primary constraint in CAS-genetics and other CAS research—the need for a diagnostically conclusive assessment method—has recently been addressed.²³ The goal of the present study was to use contemporary methods in speech and genetics, to add to the literature the first report of co-occurring 16p11.2 microdeletion syndrome and CAS in two patients.

CLINICAL REPORT

Patients 1 and 2 (P1 and P2, respectively; ages and sex not specified for anonymity) were recruited and consented for a study of pediatric motor speech disorders approved by institutional review boards at the data collection and data analyses institutions. The patients were assessed by the same examiner using the Madison Speech Assessment Protocol (MSAP), a 2-h protocol developed for research in speech sound disorders across the lifespan, including CAS.²³ The MSAP includes 15 measures that provide a range of speaking conditions for age-sex standardized scores that profile a speaker's speech processing and speech production competence, precision, and stability. Competence variables index severity of involvement, precision variables index phonetic accuracy, and stability variables index variability within a sample (ie, coefficient of variation). The assessment protocol also includes measures of intellectual function, receptive and expressive language, oral mechanism structure and function, oral nonverbal motor function, and parental information on a patient's developmental, educational, and behavioral histories. Digital recordings of responses to the MSAP speech tasks were processed using computer-aided methods for perceptual and acoustic analyses.

Table 1 provides examples from Patient 1 of the unique deficits in the precision and stability of speech due to deficits in planning/programming the articulatory gestures subserving speech. The right-most column in Table 1 includes the characteristic deletion, substitution, and distortion errors in speakers with CAS, coded in narrow phonetic transcription for computer analyses together with wave form displays of the acoustic signal. Readers unfamiliar with CAS can find additional information in a technically accessible tutorial on the types of motor speech disorders in idiopathic and complex neurodevelopmental contexts, including CAS.²⁴

Table 2 is a summary of the assessment findings for P1 and P2 that follow, including information in six domains associated with the CAS phenotype.

Table 1 Some examples of Patient 1's transcoding (planning/programming) errors on a challenging multisyllabic word repetition task

	Stimulus		Trial	Repetition	
	Orthographic	Phonetic		Orthographic	Phonetic
caterpillar		kætəpɪlə	1	calapider	kæləpɪtə
			2	calpiller	kælpɪlə
sympathize		sɪmpəθaɪz	1	simpasize	sɪmpəˌsɑɪz
			2	simpafise	sɪmpɪfəɪz
especially		əspɛʃəli	1	espeshuhly	əspɛʃəli
			2	ekspeshly	əkspɛʃ_lɪ
peculiar		pəkʃuljə	1	buhtilperler	p_tɪl_pəl_ə
			2	puhtiguyhler	pət_ɪg_jəl_ə
municipal		m_junɪsəpəl	1	muhnisyuhble	m_ʌnɪs_jəbəl
			2	muhnisyuble	m_ʌnɪs_jʊbəl

Each of the five stimulus words spoken by an adult male was presented on an audio recording that included two tokens each of 25 randomized multisyllabic words.

Table 2 Phenotype information for two patients assessed with the Madison Speech Assessment Protocol (MSAP)

Domain	Sub-domain	Patient 1	Patient 2
Intellectual function ²⁵		(+)	(+)
	Nonverbal		+
	Verbal		
	Composite		+
Language ²⁶		(+)	(+)
	Listening comprehension		
	Oral expression		+
	Oral composite		+
Speech		(+)	(+)
	Processing ¹³	+	+
	Production ⁴⁴	+	+
Oral Mechanism ²³	Structure		
	Function		
Motor	Gross	(+)	(+)
	Oral-nonverbal ²³		+
Development	Medical		
	Psychosocial	(+)	

Plus '+' indicates impairment on the test administered; '(+)' indicates history of impairment by parent report, and a blank cell indicates test performance or reported history within typical limits.

Intellectual function

Intellectual function was tested at assessment using the Kaufman Brief Intelligence Test, Second Edition.²⁵ P1's parental report indicated that intellectual function tested lower than typical at earlier developmental periods. On assessment, however, P1's standard nonverbal score (108) based on completion of matrices, and standard verbal performance score (96) based on verbal knowledge and answers to riddles yielded a composite IQ of 103, within typical limits. P2's nonverbal standard score (79) and verbal performance score (90) yielded a composite IQ of 82, below typical limits.

Language

In addition to receiving speech services since preschool, both children have received special school services at various ages for expressive language impairment, reading impairment, and spelling and writing difficulties. Language assessment was completed using The Oral and Written Language Scales.²⁶ P1's standard scores were 100 and 92 for the Listening Comprehension and Oral Expression scales, respectively, with a score of 95 on the Oral Composite scale within typical limits. P2's standard scores of 96, 71, and 82 on the three scales, respectively, yielded a language expression composite below typical limits.

Speech

Speech processing was assessed using the Syllable Repetition Task (SRT), a nonword repetition task developed specifically to assess speakers with speech errors.¹³ In addition to an overall competence score on the ability to repeat nonsense words (one of the endophenotypes co-segregating with the *FOXP2* mutation in the KE family), the SRT provides standard scores on auditory-perceptual encoding, memory, and transcoding processes. Both P1 and P2 had standard scores below typical limits on three of the four SRT measures (encoding scores were within typical limits). They also had standard scores below typical limits on the Percentage of Consonants Correct-Revised (PCCR), a measure of speech competence obtained from conversational speech.²³ Thus, both patients' histories and their profiles of persisting speech impairment meet contemporary research criteria for CAS.¹³

Oral mechanism

Neither of the patients had histories of sucking, drooling, or swallowing problems. Oral structures and functions were assessed using an unpublished task developed by the sixth author to classify and quantify the presence of structural and functional deficits in patients referred to the Mayo Clinic Neurology Department. For both patients, there were no obvious dysmorphologies, and structural findings were negative for anomalies of the lips, mandible, dental occlusion, tongue, frenum, and hard palate. Both patients were normal in measures of tactile sensation, proprioception, muscle tone, velar elevation, phonatory function, and phonatory quality.

Motor

No gross motor tests were administered, but at various ages, both patients had received physical therapy and occupational therapy services in the schools. Findings on a task assessing nonverbal oral apraxia were negative for P1. P2 had mild groping and other errors consistent with nonverbal oral apraxia.

Developmental

Each of the patient's medical histories included illnesses and events (eg, concussions, seizures) that could plausibly be risk factors for the neurologic substrates of motor speech disorder, but there are no strong associations in the literature.¹⁰ There were no obesity concerns²⁷ with either patient. P1 was on antidepressant medication and has reportedly experienced social difficulties. P2 was on medication for Attention-deficit/hyperactivity disorder and behavioral issues.

Summary

It is useful to summarize case history and assessment findings for the two patients with CAS in relation to phenotype reports, to date, for children with chromosome 16p11.2 microdeletion syndrome. Similar to prior findings in this syndrome, one or both patients had histories

and/or test findings indicating intellectual disability, persistent expressive language impairment, persistent reading and other verbal trait disorders, gross motor concerns, and psychosocial issues. Unlike findings reported for at least some individuals with 16p11.2 microdeletion, neither patient is obese, is on the autism spectrum, has an obvious dysmorphology, has a history of hypotonia, or has signs of schizophrenia, bipolar disorder, or obsessive-compulsive disorder.

METHODS

Patient 1

A saliva sample for P1 was collected using the Oragene DNA OG-500 kit (DNA Genotek Inc., Kanata, Ontario, Canada) and standard collection procedures. Genomic DNA purified using the PureGene DNA extraction kit reagents (Qiagen, Valencia, CA, USA) was used for array comparative genomic hybridization testing (aCGH). aCGH was performed with custom designed high-density oligonucleotide-based arrays (Roche NimbleGen Systems Inc., Madison, WI, USA) that can detect small genomic imbalances (deletions and duplications) at the resolution of individual genes (~30 kb). The custom arrays contain 385 000 isothermal, 45–85-mer oligonucleotide probes that are synthesized directly on a silica surface using light-directed photochemistry (<http://www.nimblegen.com>). They provide increased coverage for the regions previously associated with CAS (*FOXP2*) and other candidate loci from prior studies combined with a median interprobe distance of ~6 kb for the rest of the genome. DNA labeling, hybridization, post-hybridization washes and array scanning were performed according to the manufacturer's recommendations (Roche NimbleGen Systems Inc.). Data were extracted using NimbleGen's NimbleScan software and viewed with NimbleGen's SignalMap data browser software.

Patient 2

A blood sample for P2 was collected using standard sampling procedures. aCGH was performed using a 180-K custom oligonucleotide microarray (Agilent Technologies, Santa Clara, CA, USA) representing a uniform design developed through an academic laboratory consortium.²⁸

RESULTS

aCGH testing for P1 identified a 562-kb deletion of chromosome 16p11.2, with breakpoints at 29 537 669–30 099 8220 (NCBI Build 36.1; hg18). Additional findings include a small (310 kb) duplication at 13q13.3 (genomic coordinates 36 204 182–36 514 838, NCBI Build 36.1; hg18), affecting the genes *RFXAP*, *SMAD9*, *ALG5*, *EXOSC8* and *FAM48*, and a small (~120 kb) deletion at 14q23.2 (genomic coordinates 62 065 906–62 185 755, NCBI Build 36.1; hg18) which did not contain any known genes. The genes in the 13q13.3 region have not been associated with neurodevelopmental disorders. *RFXAP* has been associated with the bare lymphocyte syndrome type II,²⁹ *SMAD9* has been associated with pulmonary artery hypertension;³⁰ *ALG5*, *EXOSC8* and *FAM48* have not been associated with any human hereditary diseases. Although the clinical significance of the additional copy number variants (CNVs) in P1 is uncertain, owing to their small size and the absence of genes implicated in neurological functions, we assume it parsimonious to ascribe the CAS phenotype to neurodevelopmental consequences of the 16p11.2 microdeletion (see Letter to the Editor³¹). Parental samples were unfortunately not available to determine whether either of the parents carries the 16p11.2 deletion detected in P1; however, previous studies indicate that the majority of the reported cases of the 16p11.2 microdeletion syndrome are *de novo*.³²

aCGH testing for P2 identified an interstitial deletion of 8 oligonucleotide probes at 16p11.2, spanning ~517 kb. Metaphase fluorescent *in-situ* hybridization (FISH) studies using a probe within the deleted interval (RP11-114A14) confirmed the deletion:

arr 16p11.2 (29 581 455–30 098 069) × 1 dn [hg18]. Parental FISH studies indicated that this deletion was not inherited from either parent. As above, because this microdeletion is classified as ‘pathogenic’ in the International Standards for Cytogenomic Arrays (ISCA) database (<https://www.iscaconsortium.org/>), with an estimated penetrance of 0.96 in a recent large-scale comparative study reporting statistically significant association with a wide array of complex neurodevelopmental disorders,³³ this *de novo* deletion likely is causal to this patient’s abnormal phenotype.

On possible differences associated with the sizes of P1 and P2 deletions, the literature indicates that 16p11.2 microdeletion is mediated by non-allelic homologous recombination between flanking 147 kb low-copy repeat sequences with 99.5% sequence identity. The unique sequence that is deleted is between the flanking repeats, and is identical between patients. There could be slight difference in the breakpoint location within the repeats, but that is considered clinically irrelevant. In addition, difference in array design (exact localization of individual probes on each array) may have led to slightly different determination of the breakpoints. Relative to the question of possible additive phenotypic effects associated with genomic findings for P1, Table 2 findings and additional speech analyses did not indicate more severe involvement for P1 than P2.

DISCUSSION

We hypothesized that as has been found for a number of complex neurodevelopmental disorders (eg, autism),^{6,34} intellectual disability,^{35,36} and schizophrenia,³⁷ rare CNVs in genomic DNA may be associated with increased risk for CAS. Consistent with this hypothesis, array comparative genomic hybridization analyses identified 16p11.2 deletions in two patients with CAS in the same approximate region as reported for other patients with this syndrome. Methods to identify CAS included a standardized assessment protocol and well-developed, computer-aided perceptual and acoustic methods for diagnostic classification. To our knowledge, there are no other published CNV studies of CAS using comparable contemporary methods.

Although speech and language delays have been described as one of the predominant features of 16p11.2 microdeletion, this is the first report to document persistent CAS in this syndrome (see also Letter to the Editor in this volume³¹). As discussed below, extension of the phenotype of the 16p11.2 syndrome to include CAS has implications for genotype–phenotype research in other complex neurodevelopmental disorders and for best practices in clinical genetics and speech pathology.

One research implication is the need to study possible causal pathway associations among three heretofore distinct complex neurodevelopmental disorders—16p11.2 microdeletion, CAS, and epilepsy. Emerging genomic studies have begun to report that speech impairment consistent with CAS is associated with several genes and loci for epilepsy, including *FOXPI*,^{34,38} *FOXG1*,³⁹ *ELP4*,³⁶ and *RAI1*.⁴⁰ CAS and epilepsy may have common neurogenetic substrates associated with 16p11.2 deletions or they may co-segregate as separate traits.^{38,41}

Another research direction is the possibility of common causal pathways among 16p11.2 microdeletion syndrome, CAS, and autism. The 16p11.2 deletion alters dosage for 25 genes, 2 of which, *SEZ6L2* and *DOC2A*, have been implicated in autism disorder.⁷ A recent study tested the hypothesis that comorbid CAS in autism explains, at least in part, the unusual speech, prosody, and voice behaviors reported in children with verbal autism.²⁴ Findings from a study of 46 patients with verbal autism whose genetic backgrounds were not assessed,

did not support the hypothesis, with continuing studies focusing on the potential causal role of CAS in nonverbal autism. Clearly, such studies should include speech, prosody, and voice profiling of children with 16p11.2 microdeletions disrupting *SEZ6L2* and *DOC2A* and possibly other deleted genes in the 16p11.2 deletion syndrome.

Last, we speculate that 16p11.2 deletions may have a considerably higher attributable risk for CAS than mutations in *FOXP2*. In a study of 49 probands with suspected CAS obtained from many sites, a *FOXP2* mutation was identified in only one proband (ie, ~2% of the sample) and two of his nuclear family members.¹⁶ The parent study of the present patients with well-characterized CAS is pursuing this question. Literature reviews suggest that CAS rates are notably higher in syndromic neurodevelopmental disorders than in idiopathic contexts.⁴² In one recent study of 33 youth with classic galactosemia and a history of speech disorders, CAS was documented in 8 (24.2%) of patients.⁴³ Such findings suggest that patients with CAS should be considered for aCGH testing to look for 16p11.2 deletions or other genomic CNVs associated with increased risk for speech and language impairments. Similarly, referrals for speech assessment for undiagnosed CAS may be appropriate for children with 16p11.2 deletions and significant speech sound disorder. As illustrated in Table 1, signature perceptual signs of CAS (ie, signs that differentiate it from Speech Delay and do not require acoustic analyses) in preschool, primary school, and adolescent children are imprecise and unstable speech sound errors, linguistically inappropriate pauses, and slow rate of speech.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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