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Cognitive, Linguistic, and Motor Abilities in a Multigenerational Family with Childhood Apraxia of Speech

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Abstract

Objective: This study describes the phenotype in a large family with a strong, multigenerational history of severe speech sound disorder (SSD) persisting into adolescence and adulthood in approximately half the cases. Aims were to determine whether a core phenotype, broader than speech, separated persistent from resolved SSD cases; and to ascertain the uniqueness of the phenotype relative to published cases.
Method: Eleven members of the PM family (9–55 years) were assessed across cognitive, language, literacy, speech, phonological processing, numeracy, and motor domains. Between group comparisons were made using the Mann–Whitney *U*-test ($p < 0.01$). Participant performances were compared to normative data using standardized tests and to the limited published data on persistent SSD phenotypes.
Results: Significant group differences were evident on multiple speech, language, literacy, phonological processing, and verbal intellect measures without any overlapping scores. Persistent cases performed within the impaired range on multiple measures. Phonological memory impairment and subtle literacy weakness were present in resolved SSD cases.
Conclusion: A core phenotype distinguished persistent from resolved SSD cases that was characterized by a multiple verbal trait disorder, including Childhood Apraxia of Speech. Several phenotypic differences differentiated the persistent SSD phenotype in the PM family from the few previously reported studies of large families with SSD, including the absence of comorbid dysarthria and marked orofacial apraxia. This study highlights how comprehensive phenotyping can advance the behavioral study of disorders, in addition to forming a solid basis for future genetic and neural studies.

Keywords: Persistent speech sound disorder; Childhood apraxia of speech; Dyslexia; Expressive language impairment; Familial; Phenotype

Introduction

This study describes an idiopathic speech sound disorder (SSD) phenotype present in a large nuclear family (family PM; $n = 11$) that is unusually severe and persistent in at least half the members, and where SSD aggregates strongly in the extended paternal family. SSD is little studied relative to other verbal trait disorders of language impairment and reading disability (Peterson, McGrath, Smith & Pennington, 2007). Existing SSD research has focused on early childhood forms of the disorder. Burgeoning research into genetic causes of SSD has seen an increase in the number of persistent SSD cases reported in the literature (see reviews in Shriberg, 2010; Turner et al., 2013); however, the quality and extent of phenotypic descriptions vary widely. This study aims to describe the linguistic, cognitive, and motor characteristics of persistent and resolved SSD in the PM family; and determine whether a novel and stable SSD phenotype is present by comparing profiles within the family and to published cases. The study potentially forms a basis for future genetic studies of the PM family.

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SSD Definition and Prevalence

A SSD is present when a child's speech production is below the level expected for their age and developmental stage and is not attributable to a known structural, physical, neurological, or hearing impairment (Diagnostic and Statistical Manual of Mental Disorders 5th ed.; DSM-5; American Psychiatric Association [APA], 2013). It can involve "difficulty with phonological knowledge of speech sounds or the ability to coordinate movements for speech in varying degrees" (APA, 2013, p. 44). Because SSDs are mediated by maturation and environmental influences (Stein et al., 2011, p. 185), prevalence estimates drop from 15.6% of 3-year-old children (Campbell et al., 2003) to 3.8% of 6-year-olds (Shriberg, Tomblin & McSweeny, 1999), excluding children with isolated common clinical distortions (e.g., lisp on /s/, error on /r/). When a SSD persists beyond the age of 8–9 years, it is commonly referred to as persistent SSD (Shriberg et al., 2010; Wren, Roulstone & Miller, 2012); however, the prevalence of SSD in later childhood, adolescence and adulthood has not been established. What is known is that these children often experience academic difficulties in language, reading, and spelling (Lewis, Freebairn, Hansen, Iyengar & Taylor, 2004b; Stackhouse & Snowling, 1992a, 1992b). Clinicians are particularly interested in the behavioral characteristics of persistent SSD and whether persistent status can be reliably predicted in children at a younger age. Information addressing these questions is limited by the focus of research on early childhood SSD.

SSD Heterogeneity and Subtyping

SSDs vary across individuals in severity, persistence, presence of comorbid disorders such as language impairment and reading disability, and outcomes. This heterogeneity has led to the examination of possible SSD subtypes. A number of theoretically driven classification systems for SSDs of unknown origin have been proposed. The most comprehensively studied of these is the Speech Disorders Classification System—Typology (Shriberg et al., 2010). This classification system proposes three broad types of SSD based on current and/or prior speech error patterns: (1) Speech Delay, (2) Motor Speech Disorder, and (3) Speech Errors. Speech Delay is characterized by multiple speech sound substitutions and/or omissions. Motor Speech Disorder features multiple speech sound substitutions, omissions and distortions, and includes childhood apraxia of speech (CAS) and subclinical dysarthria with no neurological diagnosis. Speech Errors consist of common clinical distortion errors that are not associated with poor language or literacy, such as a lisp (Shriberg et al., 2010). The Speech Errors subtype is not the focus of this paper. The Motor Speech Disorder subtype is relevant given CAS is the most frequently diagnosed persistent SSD subtype in published cases and can co-occur with dysarthria (Morgan, Liégeois & Vargha-Khadem, 2010; Stackhouse & Snowling, 1992b; Turner et al., 2015; Velleman & Mervis, 2011; Zaretsky, Velleman & Curro, 2010).

CAS is a disorder of speech motor control in which the motor planning and programming of speech movements is impaired in the *absence* of neuromuscular deficits (i.e., no clinical signs of muscular weakness or abnormal tone/reflexes). The impairment manifests as inaccurate and inconsistent speech sound production, and timing incoordination within and between speech articulators (American Speech Language, Hearing Association, 2007). In contrast, dysarthria is a disorder involving impaired programming and/or execution of the motor movements required for speech due to neuromuscular deficits, such as observed in children with cerebral palsy. In dysarthria, impaired strength, range, rate, or control can affect the multiple physiological subsystems used in speech production including articulation, phonation, respiration, and resonance (Liégeois & Morgan, 2012; Morgan & Vogel, 2009). CAS is estimated to occur in one to two children per thousand (American Speech Language, Hearing Association, 2007). A number of genes have been implicated in CAS (Graham, Deriziotis & Fisher, 2015).

SSD Heritability and Familial Aggregation

SSDs are highly heritable. Behavioral studies, such as familial and twin studies, suggest a strong genetic component. For instance, speech and language disorders were reported in 26% of nuclear family members of probands with SSD, increasing to slightly to 33% when dyslexia or learning disabilities were included (Lewis, 1992). Speech and language disorders were present in at least one nuclear family member of 86% of probands with CAS, although rates of CAS were low (Lewis et al., 2004a). Lewis et al. (2007) found the odds for SSD increased nearly two times for each relative affected by SSD. Twin studies examine the contributions of genetic and environmental influences by investigating differences between monozygotic and dizygotic twins. Such studies report higher group heritability estimates for SSD than language disorders, for example 0.95 for SSD (DeThorne et al., 2006), indicating that differences in speech abilities have a strong genetic component (Hayiou-Thomas, 2008, p. 405).

Although a strong genetic component to SSD is implied by behavioral genetic studies, the underlying molecular mechanisms are not well understood. Families with many affected individuals are of interest because extended pedigrees can offer unique advantages for genetic analyses (Bailey-Wilson & Wilson, 2011; Wijsman, 2012; Wilson & Ziegler, 2011). Sample

selection strategies can enrich the phenotypic data gathered from families and support more targeted genetic analyses (Wilson & Ziegler, 2011). For instance, the selection of multigenerational families with a large number of affected members can result in more powerful linkage analysis and has led to the discovery of high-penetrance risk alleles (Bailey-Wilson & Wilson, 2011). The most influential speech-genetics discovery to date is the *FOXP2* gene identified through detailed phenotyping and molecular genetic analyses of severe and persistent SSD in a single extended pedigree (the KE family) (Lai, Fisher, Hurst, Vargha-Khadem & Monaco, 2001), and confirmed in subsequent cases with similar phenotypes (MacDermot et al., 2005; see summary in Graham & Fisher, 2015). Other selection strategies include recruiting families with severely affected cases or where the phenotype occurs across distributional extremes representing mild to severe cases (Wijsman, 2012; Wilson & Ziegler, 2011).

SSD Phenotyping: Challenges

There are challenges in interpreting the literature on SSD phenotypes. The majority of SSD studies focus on speech data, neglecting the systematic assessment of cognitive, linguistic, and motor domains needed for comprehensive phenotypic descriptions. Information on family members' communication and other skills used to document familial aggregation may not be included and, if present, is usually based on self-report rather than direct assessment. Study interpretation is also affected by methodological factors such as participant heterogeneity in SSD severity and the presence of comorbid language impairment. Furthermore, there is the question of whether assessment methods reliant on speech output are valid for participants with severe to profound SSD (e.g. measures of verbal memory span, verbal working memory, phonological memory, reading accuracy and expressive language).

Most of what is known about the profile of SSD relates to early childhood SSD rather than persistent SSD. Although early childhood cohorts may contain children who go on to have persistent SSD, this is the exception rather than the rule. Where early childhood SSD cohorts were followed into later school age, adolescence, and adulthood, conversational speech errors resolved in the majority of cases (Lewis et al., 2015; Peterson, Pennington, Shriberg & Boada, 2009). Similarities between profiles of some participants with early childhood SSD and persistent SSD would be expected; however, key methodological differences prevent the direct extrapolation of findings from early childhood SSD cohorts to persistent SSD populations. For example, early childhood SSD studies usually recruit groups of children aged 3–6 years with moderate or moderate to severe SSD. In contrast, persistent SSD studies frequently include case studies and familial studies (i.e., where multiple affected family members are recruited) as well as participants with severe or profound SSD, CAS/suspected CAS, diagnosed syndromes, and accompanying genetic investigations (Turner et al., 2015; Vargha-Khadem, Watkins, Alcock, Fletcher & Passingham, 1995). Furthermore, the range of skills that can be assessed in early childhood and persistent SSD differs, for example, reading, spelling, and reading comprehension cannot be assessed in early childhood.

Early Childhood SSD Phenotype

Descriptions of individuals with early childhood SSD vary widely, reflecting diverse participant selection criteria and study methods; however, there are trends. Comorbid verbal trait impairments are common. An estimated 38–62% of children with SSD have comorbid expressive language impairment and 6–21% have comorbid receptive language impairment (Shriberg & Austin, 1998). Children with comorbid SSD and language impairment tend to have difficulties with phonological processing including phonological awareness, phonological memory, and auditory discrimination, as well as subsequent literacy difficulties (Lewis et al., 2015; Nathan, Stackhouse, Goulandris & Snowling, 2004; Raitano, Pennington, Tunick, Boada & Shriberg, 2004). Fine and gross motor differences have been reported in some children with SSD with and without language impairment relative to peers (Newmeyer et al., 2007; Visscher, Houwen, Scherder, Moolenaar & Hartman, 2007), as have lower oral-motor sequencing and rapid sound repetition abilities (Newmeyer et al., 2007; Peter, Button, Stoel-Gammon, Chapman & Raskind, 2013). Some suggest that CAS, specifically, is associated with a global deficit in sequential processing in motor, linguistic, and cognitive domains (Peter et al., 2013).

Among the early childhood SSD studies that exclude cases with comorbid language impairment, findings vary. Johnson and colleagues (1999) report comparable language, cognitive, and academic outcomes for adolescents with a history of SSD and controls. Others report focal weaknesses in phonological awareness and real word decoding relative to controls (Raitano et al., 2004), and in spelling relative to participants' language and reading abilities (Lewis, Freebairn & Taylor, 2000). Neuropsychological abilities are not routinely studied in SSD.

Persistent SSD Phenotype

Most published cases of persistent SSD with multiple sound errors describe current or historical SSD in the severe to profound range. CAS or CAS-like symptoms are frequently reported (Lewis et al., 2004b; Zaretsky et al., 2010). However, the type of persistent SSD and inter-rater reliability on diagnosis are often not reported, and the differentiation of CAS and dysarthria has proved challenging. For example, in two multigenerational families with CAS (Scheffer et al., 1995; Vargha-Khadem et al., 1995), a diagnosis of CAS plus dysarthria was only subsequently reported, affecting interpretation of findings from earlier studies of the affected cases (Morgan, Liégeois & Vargha-Khadem, 2010; Turner et al., 2015). Although both conditions represent a motor speech disorder, they affect different components of the motor speech system: CAS involves motor planning and programming, and dysarthria involves motor programming and execution. They also have some shared and some unique symptoms and can require different intervention approaches.

Comorbid dysarthria has been reported with moderate frequency among persistent SSD cases with a genetic correlate (Fedorenko et al., 2015; Peter, Matsushita, Oda & Raskind, 2014; Rice et al., 2012; Turner et al., 2013; Velleman & Mervis, 2011). In published cases without accompanying genetic studies, a definitive diagnosis of comorbid dysarthria is rare (Zaretsky et al., 2010); however, subtle oromotor issues such as mild dysphagia or drooling have been suggested in some cases (Stackhouse, Pascoe & Gardner, 2006). Where assessed, orofacial praxis has been identified in only some cases: Of note, it is a strong feature of the large multigenerational family studies of CAS (Kugler et al., 2008; Saleeby, Hadjian, Martinosky & Swift, 1978; Turner et al., 2015; Vargha-Khadem et al., 1995). With regard to fine and gross limb motor skills, systematic assessment is rare (Rice et al., 2012). Limb motor difficulties have frequently been noted or suspected suggesting more widespread motor involvement (Lewis et al., 2004b; Stackhouse & Snowling, 1992b; Zaretsky et al., 2010).

Relatively few studies of primary persistent SSD report comprehensive data on domains other than speech. Such studies include participants with persistent SSD of unknown origin or with an identified genetic cause, and the majority show deficits across multiple verbal traits. Where speech, expressive language, literacy, and/or phonological processing were systematically assessed, they were impaired (Lewis et al., 2004b; Speake, Stackhouse & Pascoe, 2012; Stackhouse & Snowling, 1992a, 1992b; Turner et al., 2013; Zaretsky et al., 2010). Receptive language abilities were variable (Lewis et al., 2004b; Stackhouse & Snowling, 1992a) and often reported as stronger than expressive language (Lewis et al., 2004b; McLaughlin & Kriegsmann, 1980; Rice et al., 2012; Turner et al., 2013). Reading comprehension was rarely assessed, but a qualitative examination of data in two papers showed it to be stronger than phonological decoding skills (Lewis et al., 2004b, Table 6, p. 129; Zaretsky et al., 2010, p. 62). In two studies, receptive and expressive language skills were within the average range (Ballard, Robin, McCabe & McDonald, 2010, $n = 3$; Kenney, Barac-Cikoja, Finnegan, Jeffries & Ludlow, 2006, $n = 9$): Notably, expressive language was not fully assessed by Kenney and colleagues, literacy was not assessed in either study, and participants either ceased treatment before 9 years of age or had not received treatment during childhood, suggesting relatively mild cases. The interpretation of other small group studies suggesting language and/or literacy skills within the normal range is hindered by lack of information on SSD subtype (Cleland, Scobbie & Wrench, 2015; Redle et al., 2015).

Cognition has been minimally described with data usually limited to estimates of overall intellectual functioning (Cumley & Swanson, 1999; Peter et al., 2014), nonverbal intelligence (Fedorenko et al., 2015; Lewis et al., 2004b), or both verbal and nonverbal intellect (Raca et al., 2013). Several case studies have suggested general deficits in working memory (Turner et al., 2013; Zaretsky et al., 2010). Rice et al. (2012) compared the IQ results of three families with *FOXP2* abnormalities (two duos and the KE family) and concluded that core features were "constraints in the cognitive processing domains underlying performance on these WAIS-III subtasks—attention, short-term memory, and speed of processing" (p. 180).

Large family studies. There have been a handful of large families studied with high levels of aggregation of persistent SSD. The most well-known family is KE in which half the members of the three-generations studied were affected by a mutation in the *FOXP2* gene along with severe and persistent SSD (Lai et al., 2001; Vargha-Khadem et al., 1995). Symptom severity varied. However, compared to unaffected family members, all affected members show marked orofacial apraxia (OFA); comorbid CAS and dysarthria; expressive and receptive language problems with expressive more severely affected; and difficulties with spelling, reading, and rhythm perception and production (Alcock, Passingham, Watkins & Vargha-Khadem, 2000; Morgan et al., 2010; Vargha-Khadem et al., 1995, 1998; Watkins, Dronkers & Vargha-Khadem, 2002). The mean verbal and nonverbal IQ of the affected group were significantly lower than the unaffected group and population norms. Nonetheless, their borderline to high average nonverbal IQ (71–111, mean = 75) indicated no frank intellectual disability.

Reports of other multigenerational families contain limited detail (Saleeby et al., 1978) or included some family members who were syndromal (McLaughlin & Kriegsmann, 1980) or had other conditions such as seizures (Kugler et al., 2008;

Scheffer et al., 1995). For example, Saleeby et al. (1978) reported a family with 34 of 66 members diagnosed with CAS but only a conference abstract is available.

In summary, persistent SSD cases with multiple sound errors frequently present with a more complex profile of concomitant cognitive, linguistic, and motor impairments. Persistent SSD has been both less studied than early childhood SSD and more frequently associated with positive genetic findings. The comprehensive testing of persistent cases has potential to define phenotypic profiles more accurately; suggest associated characteristics for further study and, potentially, contribute to the study of specific genotype–phenotype relationships.

Aims

This study aimed to gather speech, language, and neuropsychological data from 11 nuclear family members (PM family) within a multigenerational pedigree who either had a history of SSD ($n = 5$) or current persistent SSD ($n = 6$) of unknown origin. Characteristics unique to the PM family provided a rare opportunity to advance the phenotypic, and potentially genotypic, study of SSD—particularly those SSDs severe enough to persist into adolescence and adulthood. This included a high level of familial aggregation of SSD, the presence of distributional extremes of SSD, multiple severely affected cases, the large family size, and family members over 9 years of age. The latter characteristic permitted the assessment of persistent SSD in all cases: This provided a degree of diagnostic stability, partially countering challenges posed by developmental changes in the SSD phenotype. Data were used to determine whether the phenotype was unique to this family or comparable to phenotypes described in published familial or singleton SSD research. The findings from this study contribute to understanding of familial SSDs, as well as the characteristics of individuals with severe SSDs that still affect speech intelligibility after the age of 9 years. It was hypothesized that:

(1) Speech, language, and neuropsychological testing would identify a core phenotype in the PM family, potentially broader than speech, that differentiated the persistent SSD cases from the resolved cases.
(2) The core phenotype associated with the persistent SSD cases in the PM family would be similar to strongly familial cases of persistent SSD described in the literature.

Method

Participants

The PM family included nine siblings (i.e., Siblings 1–9; seven males) aged 9–28 years, the mother (51 years) and the father (55 years) (Table 1). The parents were non-consanguineous. Comprehensive case history information was obtained via parent/self-report and clinical files available for Siblings 4, 5, 6, 7, 8, and 9. Based on these sources, all nine siblings had been diagnosed with SSD characterized by multiple sound errors in the preschool years. The father and four of his ten siblings had a reported history of SSD persisting into adulthood in multiple cases. The mother reported mild SSD in early childhood with no therapy or family history of verbal trait disorder. The parents' siblings were unavailable for testing. The 11 PM family members were separated into resolved and persistent SSD groups based on the presence of SSD and receipt of speech treatment for multiple sound errors beyond 9 years of age (Shriberg et al., 2010; Wren et al., 2012). The persistent SSD group ($n = 6$, 9–55 years) included the father and Siblings 4, 5, 7, 8, and 9; and the resolved SSD group ($n = 5$, 13–51 years) included the mother and Siblings 1, 2, 3, and 6.

The study was approved by the local institutional review board for ethics in human research and thus conformed to the Declaration of Helsinki (BMJ 1991; 302: 1194) guidelines on research involving human subjects.

Procedures

All family members completed assessments of cognition, language, literacy, phonological processing, oral structure and function, speech, motor skills, and numeracy. Standardized assessments were used where possible (Box 1). Speech accuracy was calculated on narrow phonetic transcription of conversational speech, multisyllabic words, and nonwords using Percentage of phonemes correct (PPC) which counts deletions, substitutions, and distortions of consonants and vowels as errors (Shriberg, Austin, Lewis, McSweeny & Wilson, 1997).

Table 1. Individual demographic and case history information

Characteristic	Mum	Dad	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9
SSD grouping	Resolve	Persist	Resolve	Resolve	Resolve	Persist	Persist	Resolve	Persist	Persist	Persist
Sex	F	M	F	M	M	M	M	M	F	M	M
Age at testing (years/months)	51;7	55;7	28;0	24;0	20;11	16;5	17;5	15;11	13;5	10;11	9;5
Years of education	11	8	16	13	13	9	9	11	9	7	5
Medical-developmental											
Hypertension in pregnancy											
Prematurity											
Borderline low birth weight											
Difficulty breast feeding											
Referral to Feeding Clinic											
Cardiac history[a]											
Ear and hearing history[b]											
Gross motor delay											
Occupational therapy ref[c]											
Social-emotional history											
Psychological referral											
Psychological treatment[d]											
Self-conscious of speech											
Academic history											
Poor school attendance											
Specialist high school[e]											
Learning support required											
SSD history											
History of SSD											
Adult sibling/s with SSD											
Received therapy for SSD											
Limited preschool therapy											
Previous diagnosis of CAS											
Intelligibility at age 5 years		v. poor			poor	v. poor	v. poor	poor	v. poor	v. poor	v. poor
Intelligibility at age 9 years		v. poor				v. poor	v. poor		fair	poor	v. poor
Rate of progress		v. slow				v. slow	v. slow		fair	v. slow	v. slow
Communication device use[f]											

Note: SSD = speech sound disorder. Shaded = yes/affected. v. = very.

[a]Sibling 3—high blood pressure and tachycardia diagnosed at 16 years; Sibling 8—congenital variant systemic venous anatomy with normal cardiac function; Sibling 4—high blood pressure attributed to anxiety and a slight functional heart murmur; Sibling 1—mild functional heart murmur diagnosed aged 2 years and a pulmonary embolism at 16 years.

[b]Sibling 1—ear infections in preschool; Sibling 4—occasional intermittent wax; father—recent, bilateral mild-moderate noise induced hearing loss but adequate for speech in a quiet environment.

[c]Teacher/therapist referred to occupational therapy for handwriting and tying laces but none tested.

[d]Sibling 4 accessed regular mental health support in late adolescence; Sibling 9—multiple referrals, minimal contact.

[e]Sibling 4 attended high school for children with learning disabilities and/or emotional-behavioral difficulties.

[f]Sibling 4 uses an electronic communication device outside home; Sibling 9 trialling a device to supplement speech.

Box 1. Test Battery

Cognition

(1) Wechsler Intelligence Scale for Children IV (WISC-IV) (Wechsler, 2005) or Wechsler Adult Intelligence Scale III (WAIS-III) (Wechsler, 1997a): Perceptual Reasoning Index, Verbal Reasoning Index, Processing Speed Index, Working Memory Index, and Full Scale Intelligence Quotient.
(2) Wechsler Memory Scale III (WMS-III) (Wechsler, 1997b) or the Wechsler Intelligence Scale for Children III—Processing Instrument (WISC-III-PI) (Kaplan, Fein, Kramer, Delis & Morris, 1999): Spatial span subtest evaluating spatial working memory.

Language

(1) Clinical Evaluation of Language Fundamentals-4 (CELF-4) (Semel et al. 2006): Expressive Language Index, Receptive Language Index, Language Content Index, Language Memory Index, and Core Language Score.
(2) Peabody Picture Vocabulary Test-4 (PPVT-4) (Dunn & Dunn, 2007) assessing receptive vocabulary.

Literacy and Numeracy

(1) Wechsler Individual Achievement Test II, (WIAT-II) (Wechsler, 2002): Word Spelling, Word Reading, Pseudoword Decoding (i.e., nonword reading), Written Expression, and Numerical Operations. The Written Expression subtest yields separate Spelling, Punctuation, and Holistic Written Expression scores based on a written paragraph or essay.
(2) Woodcock Johnson, Academic Battery III (Woodcock, McGrew & Mather, 2001): Passage Comprehension subtest.

Phonological Processing

(1) Comprehensive Test of Phonological Processing (CTOPP): Nonword Repetition subtest (Wagner, Torgesen & Rashotte, 1999)—repetition of 1–6 syllable-length strings with varying consonants and vowels, e.g., *"chaseedoolid"*.
(2) Madison Speech Assessment Protocol (MSAP): Syllable Repetition Task (Shriberg, Lohmeier, Strand & Jakielski, 2012)—repetition of 2–4 syllable-length strings with varying consonants only, e.g., *"banada"*.
(3) Auditory Discrimination Task 2-Complex Nonwords (Stackhouse 1989 in Stackhouse, Vance, Pascoe & Wells, 2007): 40 complex non-word pairs differing in either place of articulation, voicing, cluster sequence, metathesis, e.g., are these the same or different—*wesp/weps, bikut/bituk*.
(4) Auditory Lexical Discrimination Task 2-Without Pictures (Constable, Stackhouse, & Wells, 1987 in Stackhouse et al., 2007), e.g., is this word said correctly—*hostipal, mifrocone*.

Oromotor

(1) Orofacial Examination Task in the Madison Speech Assessment Protocol (MSAP) (Shriberg et al., 2010).
(2) Oral Structure-Function-Praxis Examination in the MSAP (Shriberg et al., 2010).

Speech

(1) Conversational speech—100 different words. Percentage of phonemes correct (PPC) measure calculated.
(2) Multisyllabic Words Task, repetition of 3–5 syllable-length words (MSAP; Shriberg et al., 2010)[a]: PPC.
(3) Nonword speech sample from the Nonword Repetition subtest (CTOPP; Wagner, Torgesen & Rashotte, 1999): PPC calculated.
(4) Diadochokinesis Task (MSAP; Shriberg et al., 2010), e.g., rapid repetition of sequences "*papapa*", "*pataka*".

Motor

(1) Neuropyschological Assessment II (NEPSY II) (Korkman, Kirk & Kemp, 2007): Finger Tapping, Imitating Hand Positions, Manual Motor Sequences subtests to evaluate fine motor speed and coordination.
(2) Activities for Examining Practic Function checklist (Lezak, Howieson, Loring, Hannay & Fischer, 2004, p. 639), assesses buccofacial, upper and lower limb, and body praxis, e.g., pretend to flip a coin, sweep the floor.

Hearing

(1) Tympanometry, pure tone audiometry, and otoacoustic emission tests on participants with incomplete historical documentation of hearing status. Auditory brainstem evoked response audiometry was conducted on Sibling 9.

Note: For participants outside the normative data age range, raw scores were compared to the oldest available normative data: 21.11 years (CELF-4); 24.11 years (CTOPP); 19.11 years (WIAT-II Written Expression subtest); 12.11 years (NEPSY-II motor tasks); 7.11 and 8.11 years for lexical and nonword discrimination tasks, respectively.

[a]The first author recorded MSAP stimuli in Australian-English with the author's consent. All 15 MSAP tasks were administered: Perceptual analyses are reported on two tasks in this paper.

Two 2.5 hr assessment sessions were conducted. Previous standardized cognitive and language assessments results were used where administered within a 2-year and 12-month period, respectively. Sibling 4 did not complete all assessments due to anxiety and SSD severity: In this case, some historical clinical data are used and explicitly referenced. Assessments were video and audio recorded in a quiet room with a high quality digital recorder and external microphone placed 8 inches from the participant's mouth. The first author (BC), a speech-language pathologist (SLP), gathered case history data and assessed language, speech, phonological processing, and oromotor skills. The second author (LP), a neuropsychologist, assessed cognition, literacy, numeracy, fine and gross motor abilities. BC scored word and nonword reading tasks to avoid penalizing consistent speech error patterns. Audiological evaluations were conducted by an audiologist.

A verbal reasoning index score, referred to as verbal IQ in this paper, was derived from at least the Vocabulary and Similarities subtests of the Wechsler Intelligence Scale for Children IV (WISC-IV) or Wechsler Adult Intelligence Scale III (WAIS-III). A perceptual reasoning index, referred to as nonverbal IQ in this paper, was based on the Block Design, Matrix Reasoning, and Picture Completion/Picture Concepts subtests of the WISC-IV or WAIS-III. Processing speed (PSI) and working memory (WMI) index scores were calculated from core subtests of the WISC-IV or WAIS-III, including Coding and Symbol Search, and Digit Span and Letter-Number Sequencing, respectively. All the individual subtest scores available were prorated to calculate a full scale intelligence quotient giving an overall estimate of cognitive ability.

Reliability

Intra and inter-rater reliability between two authors (BC and EB/KB) were calculated for 15% of phonetically transcribed multisyllabic words, and 100% of oromotor function and praxis responses and diadochokinetic sound sequences. Intra and inter-rater reliability rates based on point-by-point agreement were comparable to published levels (Lewis et al., 2015) at 94% and 87% for broad transcription and 91% and 82.5% for narrow transcription, respectively. Oromotor and diadochokinesis tasks were independently rated using test scoring criteria: Raters unanimously judged the presence/absence of dysarthria and orofacial praxis. For CAS diagnosis and severity rating, inter-rater reliability was established across three raters (BC, EB, KB): Two published CAS feature lists (American Speech-Language-Hearing Association, 2007; Shriberg, Potter & Strand, 2011) were applied across four speech tasks per participant, and historical file notes were used to supplement judgements. Raters were unanimous in assignment of presence/absence of CAS and assigned severity ratings.

Table 2. Cognitive test results: comparison of persistent and resolved SSD groups

Measure	Persistent SSD			Resolved SSD			*p*	*Z*	r_{spb}
	n	*Mdn*(*IQR*)	Range	*n*	*Mdn*(*IQR*)	Range			
Full scale IQ	6	80 (75–92)	71–97	5	103 (98–108)	90–106	0.017*	2.39	0.75
Nonverbal IQ	6	91 (84–101)	79–106	5	99 (91–106)	89–109	0.234	1.19	0.38
Verbal IQ	6	80 (69–83)	57–88	5	107 (96–118)	96–124	**0.006****	2.75	0.87
Working memory	6	88.50 (77–97)	68–107	5	99 (97–104)	94–107	0.118	1.56	0.49
Processing speed	6	89.50 (75–109)	73–104	5	96 (96–100)	88–103	0.521	0.64	0.20
Similarities	6	5.50 (5–6)	3–8	5	11 (10–14)	9–15	**0.006****	2.75	0.87
Vocabulary	6	6 (4–7)	1–8	5	12 (8–13)	8–14	0.010*	2.59	0.82
Block design	6	7.50 (6–9)	5–9	5	10 (8–11)	6–11	0.140	1.47	0.47
Matrix reasoning	6	10.50 (7–11)	5–13	5	10 (10–13)	10–13	0.508	0.66	0.21
Digit span	6	8 (7–10)	4–10	5	10 (8–11)	8–13	0.139	1.48	0.47
Letter-number[a]	6	8.50 (7–10)	5–10	5	10 (10–10)	10–11	0.029*	2.19	0.69
Coding	6	8 (7–12)	5–14	5	9 (9–9)	8–10	0.457	0.74	0.24
Symbol search	6	9 (5–11)	3–11	5	10 (10–11)	8–11	0.348	0.94	0.30
Spatial span[b]	6	10.50 (10–13)	9–14	5	11 (10–12)	8–17	0.926	0.09	0.03
Spatial span fwd	6	11.50 (10–13)	10–13	5	9 (9–11)	7–15	0.231	1.20	0.38
Spatial span bwd	6	10 (9–12)	7–14	5	12 (12–13)	9–15	0.229	1.20	0.38

Note: SSD = speech sound disorder. See Box 1 for test details. Values are group median (interquartile range), absolute range, Mann–Whitney *U*-test *p* and *Z* scores, effect size (r_{spb} = nonparametric point biserial correlation). First five measures are composite scores: Standard score, *M*(*SD*) = 100(15); remainder are subtest scaled scores, *M*(*SD*) = 10(3).

[a]Letter-Number Sequencing subtest.

[b]Average of Spatial Span Forwards and Spatial Span Backwards subtests.

**Significant at $p < 0.01$ (bold); *Significant at $p < 0.05$.

Table 3. Language test results: comparison of persistent and resolved SSD groups

Measure	Persistent SSD			Resolved SSD			*p*	*Z*	r_{spb}
	n	*Mdn*(*IQR*)	Range	*n*	*Mdn*(*IQR*)	Range			
PPVT-4	6	79 (76–81)	75–83	5	97 (93–97)	91–103	**0.006****	2.75	0.87
Expressive language[a]	5	55 (55–61)	49–70	5	95 (93–101.50)	93–110	**0.009****	2.63	0.88
Receptive language[a]	5	88 (71–88)	63–92	4	99.50 (94–102)	91–102	0.026*	2.22	0.79
Language content[a]	5	66 (66–76)	61–83	4	96 (91–99.50)	87–102	0.014*	2.46	0.87
Language memory[a]	5	68 (56–73)	56–78	4	92.50 (87–100)	85–104	0.014*	2.46	0.87

Note: SSD = speech sound disorder. Standard scores, *M*(*SD*) = 100(15). PPVT-4 = Peabody Picture Vocabulary Test-4th ed.
[a]Clinical Evaluation of Language Fundamentals-4th ed. index scores: Reduced *n* explained by Sibling 4's difficulty completing verbal subtests; the administration of only core subtests to Sibling 1, and age restrictions of some subtests.
**Significant at $p < 0.01$ (bold); *Significant at $p < 0.05$.

Table 4. Literacy and numeracy test results: comparison of persistent and resolved SSD groups

Measure	Persistent			Resolved			*p*	*Z*	r_{spb}
	n	*Mdn*(*IQR*)	Range	*n*	*Mdn*(*IQR*)	Range			
Word reading	5	58 (51–59)	51–77	5	96 (92–101)	81–103	**0.009****	2.62	0.87
Nonword reading	5	67 (66–70)	55–74	5	97 (94–103)	84–103	**0.009****	2.62	0.87
Word spelling	6	62 (55–67)	50–82	5	92 (92–100)	84–101	**0.006****	2.74	0.87
Written expression									
Holistic[a] (0–6)[a]	6	1 (1–1)	0–2	5	4 (3–4)	3–4	**0.005****	2.80	0.89
Spelling[b] (0–4)[b]	6	0.00 (0–1)	0–2	5	1 (0–2)	0–2	0.364	0.91	0.29
Punctuation (0–4)[b]	6	0.50 (0–1)	0–1	5	1 (1–2)	1–3	0.035*	2.11	0.67
Passage comprehension	6	74 (69–78)	67–85	5	96 (94–98)	78–108	0.022*	2.29	0.72
Numerical operations	6	85 (85–86)	73–89	5	88 (81–91)	80–94	0.464	0.73	0.23

Note: SSD = speech sound disorder. See Box 1 for test details. Standard scores, *M*(*SD*) = 100(15), unless stated.
[a]Qualitative criterion based ranking system.
[b]Quartile scores but bottom 5% assigned a score of 0.
**Significant at $p < 0.01$ (bold); *Significant at $p < 0.05$.

Table 5. Phonological processing and speech production results: comparison of persistent and resolved SSD groups

Measure	Persistent SSD			Resolved SSD			*p*	*Z*	r_{spb}
	n	*Mdn*(*IQR*)	Range	*n*	*Mdn*(*IQR*)	Range			
Phonological processing									
Nonword discrimination %	6	71 (70–75)	65–78	5	95 (93–95)	88–95	**0.006****	2.77	0.88
Nonword repetition SS[a]	5	1 (1–2)	1–2	5	4 (4–4)	4–5	**0.006****	2.74	0.91
Syllable repetition %[b]	5	58 (58–76)	56–86	5	84 (80–96)	76–96	0.057	1.90	0.63
Lexical discrimination	6	93 (83–97)	80–97	5	97 (90–100)	90–100	0.266	1.11	0.35
Speech production									
Conversation PPC %	5	86 (71.11–87.63)	60–88	5	93 (92.71–98.66)	91–99	**0.009****	2.61	0.87
Multisyllabic words PPC %	6	60.5 (43–65)	18–73	5	93 (92–95)	86–95	**0.006****	2.74	0.87
Nonword repetition PPC %	5	46 (39–50)	36–61	5	80 (63.50–80.50)	63–84	**0.009****	2.61	0.87

Note: SSD = speech sound disorder. See Box 1 for test details. PPC = percentage phonemes correct (i.e., consonants *and* vowels correct) counting sound deletions, substitutions, and distortions as errors.
[a]SS = scaled score, *M*(*SD*) = 10(3): Scored as correct/incorrect and distortions errors not penalized, as per test specifications.
[b]Percentage of consonants correct-revised (i.e., distortion errors not penalized).
**Significant at $p < 0.01$ (bold).

Data Analyses

Developmental, socio-emotional and academic background extracted from the case histories and parent/self-report are described. Due to the small sample size for the resolved and persistent groups in this family, between group comparisons were made using the Mann–Whitney *U*-test with a conservative alpha level ($p < 0.01$) to adjust for multiple comparisons.

Median, interquartile range, and absolute range are reported. Effect size was determined using nonparametric point biserial correlation (r_{spb}) where > 0.80 was considered a strong effect size.

Results

Results are presented in two sections: Case history information (Table 1) followed by comparisons between resolved versus persistent SSD groups (Tables 2–5). Individual participants' performance on key measures are in *Appendix A* (see Supplementary material online).

Case History Information

Developmental history. Members of the PM family were non-syndromal with no developmental diagnoses, such as Intellectual Disability, Attention Deficit disorder or Autism Spectrum Disorder, and no history of childhood hearing impairment. All children had seen a pediatrician. No clear familial medical history patterns existed (Table 1). Seven of nine children were diagnosed with CAS or suspected CAS by multiple SLPs at preschool age according to case file notes of Siblings 4, 5, 6, 7, 8, 9 and parent recollection of Sibling 3 (file unavailable). The mother reported speech clarity was the primary presenting issue in all cases but did not confidently recall early communication milestones. Timely acquisition of gross motor skills was reported, with the exception of slow head control acquisition in Sibling 4. There was variability in SSD severity, receipt of speech pathology services, and response to intervention. In the preschool years, the father and all nine children received limited therapy due to relatively late referral (i.e., only Siblings 4 and 8 were referred prior to age 4 years), frequent non-attendance of therapy appointments, and restricted public speech pathology services. At age 5 years, the father and seven of nine children (Siblings 3, 4, 5, 6, 7, 8, 9) required therapy; at 9 years, the father and five children (Siblings 4, 5, 7, 8, 9) required therapy. At school age, the youngest three children (Siblings 7, 8, 9) had greater access to therapy services than older siblings due to changes in local service provision.

Socio-emotional history. All family members who received therapy for SSD (i.e., all except mother) reported lasting self-consciousness about their speech. Even when errors had completely or largely resolved, participants identified particular words or sounds requiring effort, and/or described avoiding words and some speaking situations such as speaking in front of the class or at work meetings. Teasing and bullying related to speech were reported in more impaired family members (father and Siblings 4, 5, 7, 8, 9). Severe, persisting anxiety about speaking to non-family members since early primary school years, as well as distress and frustration when misunderstood, was reported in the two family members with lowest speech intelligibility (Siblings 4 and 9): Both were diagnosed with social anxiety disorder. Psychological referral was recommended for Siblings 3, 4, 7, 8, and 9, primarily for anxiety-related presentations.

Academic history. All attended mainstream primary school. The father and Siblings 4, 5, 7, 8, and 9 required formal learning support throughout primary and high school. The youngest four siblings still attended school; the father and Siblings 4 and 5 completed eight to 9 years of formal education; Siblings 1, 2, 3, completed 13 to 16 years; and the mother completed 11 years. At the time of study, Sibling 4 returned to a technical college to complete his school certificate with learning support. All who participated in mandatory foreign language learning volunteered it was their most difficult subject.

Test Results

First, results of the non-parametric Mann–Whitney *U*-test comparing the resolved and persistent SSD groups are presented. This is followed by a description of each group's results (Tables 2–5). Key individual participant scores are presented in *Appendix A* (see Supplementary material online).

Cognition. Verbal IQ was the only cognitive measure showing significant between-group differences and the effect size was large ($Z = 2.74$, $r_{spb} = 0.87$). Verbal IQ was significantly lower in the persistent SSD group than the resolved SSD group. Between-group differences were not significant for full scale IQ, nonverbal IQ, WMI, or PSI, with median scores for both groups within the average range (Table 2).

Resolved SSD group Nonverbal IQ and verbal IQ were in the average range for all cases (nonverbal IQ: *Mdn* = 99, range 89–109; verbal IQ: *Mdn* = 107, range 96–124). Verbal IQ was a relative strength and significantly higher than nonverbal IQ in three of five resolved cases (Siblings 1, 2, 3: verbal IQ > nonverbal IQ, $p < 0.01$).

Persistent SSD group Nonverbal IQ was within 1 *SD* of the mean for four of six persistent cases, and 1.0 and 1.4 *SD* below the mean in the remaining two cases (*Mdn* = 91, range 79–106). Verbal IQ was more than 1 *SD* below the mean in five of six persistent cases (*Mdn* = 80, range 57–88). Verbal IQ was significantly lower than nonverbal IQ in three of six cases (father, Siblings 4 and 9, $p < 0.01$). A fourth member (Sibling 7) displayed a magnitude of discrepancy that, although not statistically significant (at $p < 0.01$), occurred in only 24% of the normal population.

Language. There were significant group differences with large effect sizes on single word receptive vocabulary and expressive language tests (i.e., Peabody Picture Vocabulary Test-4: $Z = 2.75$, $r_{spb} = 0.87$; Clinical Evaluation of Language Fundamentals-4 Expressive Language Index [ELI]: $Z = 2.63$, $r_{spb} = 0.88$; see Table 3). The persistent SSD group performed well below the resolved SSD group. Between-group differences were not significant on measures of overall receptive language, semantic content, and memory dependent language abilities (i.e., Receptive Language Index [RLI], Language Content Index, and Language Memory Index, respectively).

Resolved SSD group Expressive and receptive language scores were in the average range for all cases on the Peabody Picture Vocabulary Test-4 (PPVT-4) and all Clinical Evaluation of Language Fundamentals-4 (CELF-4) index scores (PPVT-4: *Mdn* = 97, range 91–103; ELI: *Mdn* = 95, range 93–110; Language Content Index: *Mdn* = 96, range 87–102; Language Memory Index, *Mdn* = 92.50, range 85–104; RLI: *Mdn* = 99.50, range 91–102). No cases had a statistically significant discrepancy between expressive and receptive language. No cases met DSM-5 criteria for Language Disorder (APA, 2013).

Persistent SSD group Language scores were in the impaired range for all cases on the PPVT-4 and all CELF-4 language index scores except the RLI (PPVT-4: *Mdn* = 79, range 75–83; ELI: *Mdn* = 55, range 49–70; Language Content Index: *Mdn* = 66, range 61–83; Language Memory Index, *Mdn* = 68, range 56–78). RLI scores ranged widely (*Mdn* = 88, range 63–92). Five of six cases had a statistically significant discrepancy between expressive and receptive language (ELI < RLI, $p < 0.01$). The sixth case (father) displayed a magnitude of discrepancy that, although not statistically significant, occurred in only 7.5% of the normal population. All had an ELI at least 2 *SD* below the mean and at least 1.5 *SD* below nonverbal IQ. All met DSM-5 criteria for Language Disorder in the expressive domain (APA, 2013), except for the criterion of presence of a motor speech disorder (see Speech results).

Literacy. There were significant group differences with large effect sizes on tests of word reading and spelling accuracy, nonword reading, and written expression (Word Reading: $Z = 2.62$, $r_{spb} = 0.87$; Pseudoword Decoding: $Z = 2.62$, $r_{spb} = 0.87$; Word Spelling: $Z = 2.74$, $r_{spb} = 0.87$; Written Expression-Holistic: $Z = 2.80$, $r_{spb} = 0.89$; see Table 4). The persistent SSD group performed well below the resolved SSD group. Between-group differences were not significant on Passage Comprehension or punctuation and spelling measures derived from a time limited written expression sample. However, comparisons on the latter measures were limited because persistent SSD group members wrote little (maximum 1 paragraph), restricting output to words they could spell; resolved SSD group members wrote several paragraphs (minimum) and displayed spelling weaknesses not evident on the single word spelling task.

Resolved SSD group Word and nonword reading were within 1 *SD* of the mean for all but the mother (Word Reading: −1.25 *SD;* *Mdn* = 96, range 81–103; Pseudoword Decoding: −1.0 *SD*; *Mdn* = 97, range 84–103). Word Spelling and Passage Comprehension were within 1 *SD* of the mean for all but Sibling 6 (Word Spelling: −1.0 *SD*; *Mdn* = 92, range 84–100; Passage Comprehension: −1.5 *SD*; *Mdn* = 96, range 78–108). On the Written Expression task, holistic written expression rankings ranged from 3 to 4 (maximum = 6), spelling quartiles were ≤2, and punctuation quartiles ranged from 1 to 3. Each resolved case had a statistically significant discrepancy ($p < 0.01$) between verbal IQ and at least one standardized literacy measure.

Persistent SSD group Word reading, word spelling, and nonword reading were impaired in all persistent cases (Word Reading: *Mdn* = 58, range 51–77; nonword reading: *Mdn* = 67, range 55–74; Word Spelling: *Mdn* = 62, range 50–82). Passage Comprehension was >1 *SD* below the mean in all but one case (*Mdn* = 74, range 67–85; father, Siblings 4 and 8 = −1.0 to −1.5 *SD* < mean; Siblings 5, 7, and 9 = −2.0 to −2.25 *SD* < mean). Written Expression skills were reduced: Holistic written expression rankings ranged from 0–2 (maximum = 6), punctuation quartiles from 0 to 1, and spelling quartiles were ≤2. Each persistent case showed a statistically significant discrepancy ($p < 0.01$) between verbal IQ and Word Reading and nonword reading; and four of six cases had a discrepancy between verbal IQ and Word Spelling ($p < 0.01$).

Each persistent SSD group member met criteria for a diagnosis of Specific Learning Disorder (SLD) with impairment in reading (or dyslexia) and written expression: This was based on literacy results relative to age and, where applicable, grade expectations (DSM-5, APA, 2013). Discrepancies in literacy performances relative to intellectual estimates were considered in determining SLD eligibility. Of note, Sibling 7's Word Spelling was −1*SD* below the mean; however, diagnosis was

further supported by bottom 5th percentile spelling performance on the Written Expression task and a previous diagnosis of dyslexia in clinical records.

Phonological Processing. There were significant group differences with large effect sizes on measures of nonword repetition and complex auditory nonword discrimination (nonword repetition: $Z = 2.74$, $r_{spb} = 0.91$; complex auditory nonword discrimination: $Z = 2.77$, $r_{spb} = 0.88$; see Table 5). The persistent SSD group performed well below the resolved SSD group. There were no significant group differences on the syllable repetition or lexical discrimination tasks.

Resolved SSD group Nonword repetition was impaired in all cases falling 1.7–2 *SD* below the mean (subtest scaled score: *Mdn* = 4, range 4–5). Nonword discrimination scores were within 1.0 *SD* from the mean (percent discriminated: *Mdn* = 95%, range 88–95%) using age limited normative data (7–8 year olds: *M* = 90.66%, *SD* = 7.5, Stackhouse et al., 2007, p. 61).

Persistent SSD group Nonword repetition was impaired in all persistent cases falling 2.6–3 *SD* below the mean (subtest scaled score: *Mdn* = 1, range 1–2). Nonword discrimination scores were >1.5 *SD* below the mean (percent accurate *Mdn* = 71%, range 65–78%).

Oral Structure and Function. Performance on oromotor tasks did not discriminate between persistent and resolved groups.

Oral structure No major oral structural abnormalities were present. All family members had crowded, crooked teeth. The parents had some missing teeth. Six family members had a mildly less prominent mandible relative to maxilla (resolved group: mother and Siblings 1, 2, 3; persistent group: Siblings 4, 5), including an overbite in the mother and Sibling 5.

Orofacial praxis OFA ranging from minimal to mild was observed in three of 11 family members (persistent group: father, Sibling 8; resolved group; Sibling 3) and self-reported by persistent case, Sibling 4, who had historically documented OFA (see Supplementary material online, *Appendix A*). Four other siblings scored within the normal range, although subtle hesitations were queried on between one and three OFA tasks (persistent group: Sibling 9; resolved group: Siblings 1, 2, 6). The hesitations were deemed too subtle by assessors to reliably rate as affected.

Oromotor function Non-speech oromotor functions were unremarkable in all family members (e.g., lateral tongue movements, lip retraction/protrusion). Regarding speech-like maximum performance motor tasks, three persistent SSD cases could not sustain the vowel /ah/ longer than 10 s (Siblings 5, 7, 8, range = 7–8 s), and all family members had minimal to severe difficulty sustaining /z/ with consistent voicing. Specifically, the father and Siblings 8 and 9 could not initiate a /z/ sound, and remaining cases showed minimal to mild fluctuations in voicing during the task (mother, Siblings 1, 5, 7: <10 s; Siblings 2, 3, 6: >10 s). Sibling 4 was too anxious to participate, but historical records document a normal ENT exam, no dysarthria, and difficulty sequencing sounds in diadokokinesis (DDK) tasks.

DDK was affected in seven of 11 family members (persistent group: father, Siblings 4, 7, 8, 9; resolved group: Sibling 3, 6; see Supplementary material online, *Appendix A*). Severity in observed cases ranged from minimal to moderate, but was mostly mild. DDK errors related to one or more of the following: Sound sequencing, interrupted rhythm, delayed voice onset time, imprecise speech sounds or inconsistent accuracy of speech sounds. The sixth persistent case (Sibling 5) had equivocal, inconsistent sound distortions and was conservatively rated as unaffected.

Speech. There were significant group differences with large effect sizes for the phoneme accuracy measure in conversational speech, multisyllabic words and nonwords (PPC: conversation $Z = 2.61$, $r_{spb} = 0.87$; multisyllabic words $Z = 2.74$, $r_{spb} = 0.87$; nonwords $Z = 2.61$, $r_{spb} = 0.87$. See Table 5). The persistent SSD group performed well below the resolved SSD group. No family member displayed frank dysarthria.

Resolved SSD group Median PPC was 93% for conversation and multisyllabic words (range 91–99% and 86–95%, respectively) and 80% for nonwords (range 63–84%). No resolved case met criteria for CAS, and ratings of overall SSD severity in conversational speech ranged from within normal limits to minimal (i.e., distortion errors).

Persistent SSD group Median PPC was 86% for conversational speech (range 60–88%), 60.5% for multisyllabic words (range 18–73%), and 46% for nonwords (range 36–61%). The most speech impaired participant, Sibling 4, could not provide conversational and nonword samples. A CAS diagnosis was unanimously assigned to all persistent cases with the most mildly affected member of this group, Sibling 7, meeting criteria on historical rather than current data. SSD severity ratings of conversational speech ranged from mild to moderate-severe in five cases and severe in the sixth (Sibling 4): Sibling 4's severity rating is supported by clinical records, parent reports of poor speech intelligibility and use of an electronic communication device.

Motor Skills. There were no significant differences between groups on Finger Tapping-Repetition Combined scores (ie left and right hands combined) score, Finger Tapping Sequences Combined score, Imitating Hand Positions Combined, or

Manual Motor Sequences (see Supplementary material online, *Appendix B*). Nor were there significant differences on the Coding subtest of the WISC-IV/WAIS-III, a core processing speed subtest reliant on efficient fine motor output. All family members passed all items on the Examining Practic Function checklist, except most could not whistle.

All family members performed in the normal range with dominant and non-dominant hands on Fingertip Tapping Repetition and Finger Tapping Sequences, except the mother on the latter task (FTS SS = 5). Six family members scored at or below the 25th percentile on Manual Motor Sequences (resolved cases: mother, persistent cases: Siblings 4, 5, 7, 8, 9), and seven scored below the 25th percentile on Imitating Hand Positions (resolved cases: mother, Sibling 3; persistent cases: father, Siblings 4, 7, 8, 9).

Numeracy. There were no significant group differences on Numerical Operations (resolved cases: *Mdn* = 88, range 80–94; persistent cases: *Mdn* = 85, range 73–89). Scores for the resolved group were within 1 *SD* from the mean in three cases and 1.3 *SD* below the mean for two members. Four of six persistent cases were also within the average range and two cases were 1.1 *SD* and 1.8 *SD* below the mean (Table 4).

Discussion

The purpose of this paper was to comprehensively describe the phenotype in a large nuclear family with a high aggregation of persistent multigenerational SSD. It was hypothesized that a core phenotype in the PM family, potentially broader than multiple persistent speech errors, would differentiate the persistent SSD cases from the resolved cases; and that this core phenotype would share characteristics with strongly familial persistent SSD cases reported in the literature. A unique opportunity to study a familial SSD phenotype as well as characteristics of persistent SSD cases that included adolescent and adult participants was provided by the distinctive combination of family characteristics. This included the high familial aggregation of SSD, the presence of severe and persistent SSD, all participants over 9 years of age, and a large family size. Findings of this study also form a basis for future phenotype–genotype studies.

Persistent SSD Phenotype

In support of the first hypothesis, the six persistent SSD cases (father, Siblings 4, 5, 7, 8, 9, aged 9–18 years) shared a core pattern of impairment that clearly differentiated them from the five resolved SSD cases (mother, Siblings 1, 2, 3, 6, aged 15–28 years). This core pattern of impairment was characterized by a multiple verbal trait disorder. There were significant differences between the two groups with large effect sizes and no overlap in score distributions on measures of speech accuracy (multisyllabic words, nonwords, and conversational speech), verbal IQ, receptive vocabulary, expressive language, word reading, word spelling, nonword reading, nonword repetition, nonword discrimination, and written expression. There were no significant group differences on measures of overall IQ, nonverbal IQ, working memory, processing speed, motor skills, or numerical operations. Descriptively, persistent cases were characterized by (1) CAS currently ranging from severe to mild; (2) language disorder in the expressive domain (APA, 2013) with standardized scores ≥ 2 *SD* below the mean; (3) a discrepancy between receptive language and expressive language (expressive < receptive); (4) impaired single word receptive vocabulary; (5) lower verbal IQ than resolved cases; (6) impaired reading and spelling meeting criteria for SLD with impairment in reading (or dyslexia) and written expression (DSM-5, APA, 2013); (7) severely impaired phonological memory (as measured by nonword repetition); (8) impaired nonword discrimination; and (9) academic difficulties requiring formal learning support through to the high school years. Historical documentation showed speech intelligibility among persistent cases at 9 years of age ranged from fair to very poor, and progress in therapy ranged from fair to very slow.

Comparisons with Published Cases. In relation to the second hypothesis, persistent PM family cases are first compared to the most similar of the large families studied, the KE family (Vargha-Khadem et al., 1995), then to the broader body of published persistent SSD cases. Many reported cases are not directly comparable to the PM family on account of features such as frank intellectual disability, dysmorphisms, and neurodevelopmental diagnoses (see reviews in Palka et al., 2012; Shriberg, 2010). In relation to comparisons with published cases of primary persistent SSD, caution is required: Similarities and differences may be masked by variations in assessment protocols, genetic analyses, level of family information obtained, and immutable factors such as family size. For example, a genetic cause could be subsequently identified in currently idiopathic cases, singletons in case and group studies may have unreported familial aggregation of SSD, and small family size may limit the expression of familial aggregation.

Consistent with the KE family, the most salient feature of the persistent SSD phenotype in the PM family is prominently disordered speech. Both families share unusually high levels of familial aggregation of CAS; severe presentations of CAS persisting into adolescence/adulthood and necessitating alternative communication systems in some cases; a phenotype characterized by a multiple verbal trait disorder affecting speech, language, and literacy; and broadly similar nonverbal IQ (PM—persistent cases: median = 91, range = 79–106; KE—affected cases: mean=86, range 71–111; Vargha-Khadem et al., 1995). Difficulty with sequential manual tasks requiring complex motor programming was present in all affected KE family members (Vargha-Khadem, 2011) and the majority of persistent PM family cases, although neither family had difficulty with simple limb praxis tasks such as pretending to brush hair (Watkins et al., 2002).

Notable phenotypic differences between persistent cases in PM and KE families were the absence of dysarthria and lack of consistent and marked OFA in the PM family. There were no significant differences in the nonverbal IQ (including the Coding subtest) of persistent and resolved cases in the PM family as seen in affected versus unaffected members of the KE family (Watkins et al., 2002). Critically, unlike the KE family, the PM family lacked any completely unaffected members: Resolved cases had a history of SSD. Early speech and language development of unaffected KE family members was retrospectively reported as normal (Hurst, Baraitser, Auger, Graham & Norell, 1990); however, "there was considerable overlap between the two groups on most tests" (Vargha-Khadem, Gadian, Copp & Mishkin, 2005, p. 132) leaving to question whether some unaffected KE members may have had a history of subtle verbal trait disorders.

Cognitive profile Among reported cases with persistent SSD and cognition in the borderline to average range, cognitive profiles are broadly similar to persistent PM family cases. The commonly reported pattern of relatively stronger nonverbal than verbal intellect (Palka et al., 2012; Speake et al., 2012; Zaretsky et al., 2010) was found in three of six persistent cases in the PM family. Although the remaining three cases did not have a statistically significant discrepancy in IQ, the trend of relatively stronger nonverbal than language skills held with specific expressive language testing results 1–2 *SD* below nonverbal IQ.

Comparisons of other cognitive measures are limited by a lack of information on published persistent SSD cases. However, in contrast to previously published studies, persistent PM family cases did not demonstrate core deficits in generic working memory (Turner et al., 2013; Zaretsky et al., 2010) or the cognitive processes underlying attention, short-term memory, and speed of processing tasks on the WAIS-III (Rice et al., 2012, p. 180). Persistent cases in the PM family typically displayed intact spatial short-term memory span, spatial working memory, auditory-verbal short-term memory span, and auditory-verbal working memory: Moreover, there were no significant group differences on these measures suggesting they were not core deficits. In contrast, all persistent cases were severely impaired on a recognized measure of phonological memory (nonword repetition, SS range = 1–2) despite a range in SSD severity. This suggests a specific difficulty arising from vulnerability within the phonological system as opposed to impairments within more general attentional or higher-level working memory domains.

There are legitimate concerns that nonword repetition tasks index speech accuracy in participants with SSD (Shriberg et al., 2009). Nonetheless, findings suggest phonological processing of nonword information was particularly challenging for the PM family. Although the increased motor programming load required for production of a novel nonword sequence contributes to performance on these tasks, persistent cases were also impaired on a complex nonword discrimination in the presence of adequate performance on a lexical discrimination task. Furthermore, even the persistent case with mild CAS (Sibling 7) achieved the lowest nonword repetition score (SS = 1). Complex nonword repetition tasks are known to be sensitive to a range of behavioral phenotypes such as language impairment and reading disability without SSD (Shriberg et al., 2009). However, the finding that all resolved PM family cases also had impaired nonword repetition (SS range = 4–5)—despite normalized/near normalized speech, average language abilities, and most standardized literacy measures in the normal range—suggests the familial predisposition to difficulty on this task may be related to the SSD.

Language and literacy profile Consistent with findings in singleton and familial persistent SSD literature, persistent PM family cases displayed impairment across multiple verbal traits of language, spelling, reading, and phonological processing (Lewis et al., 2004b, 2015; Stackhouse & Snowling, 1992a, 1992b), including stronger receptive than expressive language (Lewis et al., 2004b; Turner et al., 2013; Vargha-Khadem et al., 2005). Impaired single word receptive vocabulary was present in all persistent PM family cases within a narrow score range, even though receptive language abilities ranged widely from severely impaired to average. This suggests support for the proposal that cascading effects of impaired phonological processing in children with SSD affect the quality of phonological representations; in turn affecting the completeness of lexical representations and thus vocabulary, language, and literacy (Rvachew & Grawburg, 2006; Zaretsky et al., 2010). In relation to CAS specifically, it has been further hypothesized "phonological impairment is a by-product of atypical motor learning or sequencing, and that this ultimately leads to disrupted development of phonological representations" (Liegeois, Morgan & Vargha-Khadem, 2007, p. 183).

Reading comprehension was reduced relative to age expectations in the majority of persistent PM family cases but less impaired than phonologically based decoding skills (Table 5): This is consistent with limited published data (Lewis et al., 2004b; Zaretsky et al., 2010). Unlike word/nonword reading and spelling accuracy tasks, reading comprehension is supported by other language based skills and general knowledge. The increased difficulty in spelling than reading reported by Lewis and colleagues (2004b) was not replicated in persistent PM family cases, although all described spelling as more difficult than reading. In summary, findings of this study support a multiple deficit account of literacy (Raitano et al., 2004, p. 833 for discussion).

Speech and oromotor profile The finding that all persistent cases in the PM family had CAS was consistent with published research where CAS/suspected CAS is the most frequently diagnosed persistent SSD subtype (Lewis et al., 2004b; Turner et al., 2013). Severity levels were also similar (Lewis et al., 2004b; Speake et al., 2012)—although very few studies report cases without intellectual disability who used augmentative and alternative communication systems (Cumley & Swanson, 1999; McLaughlin & Kriegsmann, 1980; Vargha-Khadem et al., 1995). The high level of familial aggregation of CAS in the PM family, however, is unusual given the rarity of CAS in the normal population (<0.01%; ASHA, 2007) and the low rates in nuclear family members of probands with CAS (Lewis et al., 2004a).

The absence of dysarthria in persistent PM family cases contrasts with published persistent SSD cases that frequently report comorbid dysarthria (Fedorenko et al., 2015; Morgan et al., 2010; Peter et al., 2014; Rice et al., 2012; Turner et al., 2015) or subtle oromotor issues (Stackhouse et al., 2006; Zaretsky et al., 2010). Where assessed, OFA is inconsistently identified in published cases of persistent SSD: This accords with the minimal to mild levels of OFA found in only some PM family members but contrasts other large family studies where OFA is a strong feature (Kugler et al., 2008; Saleeby et al., 1978; Scheffer et al., 1995; Vargha-Khadem et al., 1995). The effects of age, task complexity, and comorbid dysarthria on the diagnosis of OFA are worthy of consideration and highlight the need for standard assessments of oromotor structure, function, and praxis across the lifespan. As an example, the OFA tasks used in the KE family studies included more complex sequences than used here or elsewhere (i.e., 11 sets of three-part oromotor movements performed simultaneously then sequentially; Vargha-Khadem et al., 1998), and the diadokochinetic sequences contained consonant clusters ("pla-kra-ta"; Morgan et al., 2010, p. 97, rather than typically used "pa-ta-ka").

Motor profile The below average performance by the majority of persistent PM family cases on manual motor programming tasks is consistent with prior research that has queried motor difficulties in persistent SSD cases (Cumley & Swanson, 1999; Stackhouse & Snowling, 1992b; Zaretsky et al., 2010) or reported differences relative to controls on challenging motor tasks (Redle et al., 2015).

In summary the second hypothesis was partially supported: Persistent PM family cases displayed greater phenotypic similarity to published idiopathic singleton cases than strongly familial cases. There were similarities to the KE family in terms of phenotype, levels of familial aggregation, severity, and persistence of SSD into adulthood; however, the absence of dysarthria and marked orofacial praxis in the PM family were key differences.

Resolved SSD Phenotype

There are strong similarities among the profiles of resolved PM family cases and reports of adolescents/adults with early childhood SSD without comorbid language impairment (Johnson et al., 1999; Lewis et al., 2015). In contrast to persistent PM family cases, all resolved cases were in the normal range on tests of verbal IQ, nonverbal IQ, receptive and expressive language. Speech ranged from within normal limits to minimal distortion errors on multisyllabic words and in conversation in Sibling 3, consistent with existing literature (Johnson et al., 1999; Lewis et al., 2015). Resolved cases were overwhelmingly in the average range on standardized literacy measures. However, subtle residual literacy vulnerabilities were suggested by the statistically significant discrepancy between verbal IQ and at least one standardized literacy measure, and lower than expected performance on aspects of the written expression task. All resolved PM family cases were impaired on the nonword repetition task. Although it remains unclear whether this task presents unique challenges to speech production for resolved SSD cases or reveals phonological memory difficulties (or both), impaired phonological memory and subtle literacy weakness have been previously reported (Lewis & Freebairn, 1992; Lewis et al., 2015). The subtle motor control problems for speech and manual tasks noted in some resolved PM family cases is consistent with published cases (Lewis et al., 2015; Peter & Raskind, 2011).

Findings of this study support the critical role language plays in outcomes for children with SSD (Lewis & Freebairn, 1992; Rvachew, 2007). Resolved PM family cases with the strongest literacy skills (Siblings 1, 2, 3) also had the strongest language abilities: Not only did they achieve the highest scores on all tests of language and verbal intellect, they were the only three family members with statistically significantly higher verbal than nonverbal IQ. This is despite Sibling 3 being the

only resolved case to retain subtle speech distortion errors. Conversely, resolved cases with the lowest language scores (mother and Sibling 6) - albeit still in the average range - had the lowest literacy abilities. Two possible interpretations of these findings have been discussed in the literature (Rvachew, 2007). First, language impairment is an additive risk factor for reading disorder alongside the risk already associated with SSD (Raitano et al., 2004). Alternatively, strong language skills may be one of a range of factors protecting against reading disorder in children with an underlying phonological processing deficit (Snowling, Bishop & Stothard, 2000).

Discrete or Continuous Phenotype?

Statistically significant differences between persistent and resolved groups on 11 key measures and differences in historical variables provide strong support for the presence of discrete persistent and resolved SSD phenotypes. Findings suggest the persistent SSD phenotype primarily affects verbal traits of speech, language, literacy, and phonological processing and broadly affects learning and academic outcomes. Support for this dichotomous view includes that (a) the two phenotypes held for age and severity; (b) there was no overlap of individual scores on any of 11 key measures that significantly separated the groups; and (c) all persistent cases were individually impaired on speech, language, literacy, and phonological processing tasks. This finding is noteworthy given that in the KE family there was a high degree of overlap among individual scores (Vargha-Khadem et al., 1998), and each affected member was individually impaired on only 3 of 28 tasks (i.e., word repetition, nonword repetition, and simultaneous and sequential orofacial movements). Critically, however, in the KE family, significant group differences were present on many tasks and a mutation in the *FOXP2* gene segregated perfectly with affected status (Lai et al., 2001; Vargha-Khadem et al., 1995).

An alternate interpretation of the current data is the presence of a continuous familial SSD phenotype in the PM family. Support for this view includes the identification of several traits common to all family members, and the presence of a range of abilities within the two groups. All family members shared a history of preschool SSD, impaired phonological processing abilities, at least Verbal or Nonverbal IQ in the normal range, a statistically significant discrepancy between Verbal IQ and at least one standardized literacy measure, and a degree of specific difficulty coordinating respiratory and phonatory systems when sustaining /z/ production. Additionally, the father and all nine children shared a history of treatment for SSD, had at least one adult sibling affected by severe and persistent SSD, and retained a degree of self-consciousness about their speech. With regard to the range of abilities within the groups, Sibling 7 in the persistent group was more mildly affected across literacy, language, and speech areas than other persistent cases; and Siblings 3 and 6 in the resolved group were diagnosed with severe CAS in the preschool years. Descriptively, there were familial trends to below average performance on diadochokinesis and manual motor planning tasks, and psychological referral for anxiety-related presentations. Future genetic testing may provide insight into the presence of a discrete versus continuous phenotype in the PM family.

Study Implications

This study has implications for the management of children diagnosed with severe to profound SSD in particular, CAS. No member of the PM family with significant speech sound errors past 9 years of age avoided language impairment, dyslexia, and phonological processing impairment. This is not to suggest speech production alone indexes the degree of impairment to the phonological system: The most severely speech impaired member (Sibling 4) had stronger literacy and language abilities than the father despite similar nonverbal IQ. However, it suggests that in individuals with a profile similar to persistent PM family cases, there may be a tipping point for SSD severity beyond which a multiple verbal trait disorder is difficult to avoid. This is supported by research showing multiple verbal traits were affected in children diagnosed with severe or profound SSD in early childhood who had significant speech errors after age 9 years (see review in introduction). Studies comparing children with isolated SSD and children with comorbid SSD and language impairment have reported more severe SSD in the latter group. Furthermore, Lewis and colleagues (2015) found higher rates of comorbid reading disability and language impairment in adolescents with persistent SSD relative to no-SSD and resolved SSD groups.

It is unclear to what degree a multiple verbal trait disorder co-occurs with persistent SSD or is due to the downstream effects of SSD on development of phonological representations and thus language and literacy. Severe and persistent forms of language impairment and dyslexia occur independent of SSD; but there is limited evidence that severe and persistent SSD occurs in the absence of these disorders. Findings of this study suggest that children with severe CAS in particular require comprehensive assessments of speech, language, literacy, cognitive, and motor systems because multiple domains are likely affected. Such information enables interventions to be individually tailored and may inform prognosis. It is likely that purely motor based treatments for CAS cannot sufficiently address associated language and literacy difficulties, and

that data gathered from the measurement of outcomes across multiple domains are required to determine the most effective and efficient interventions. The need to develop literacy and language skills in addition to intelligible speech is highlighted in cases where children do not become fully intelligible and require strong literacy skills to use alternative electronic communication devices (Carrigg et al., 2015). A further implication of this study is the early consideration of the socio-emotional health of children with severe and profound SSD, given the trend to anxiety-related presentations in persistent PM family cases.

Limitations and Future Directions

Caution needs to be exercised in interpreting study findings due to the small sample size and potential lack of generalizability beyond this one family. Further limitations include the absence of genetic and neuroimaging data, lack of assessment of the father's extended family, the inability to definitively identify the SSD subtype in resolved cases had in their early years (i.e., Speech Delay or CAS), and challenges subtyping older individuals with childhood speech disorders. Numeracy was insufficiently assessed to draw conclusions about mathematical abilities, and additional speech perception tasks may have been informative. Factors other than severity could also affect the persistence of SSD, such as the timing, amount and type of treatment received, which were not explored in this study. Although the effect of reduced school attendance on test results is unknown, it was not considered to influence the core phenotype: Attendance was equally poor for all family members and was not a point of difference. Despite reduced school attendance, the resolved SSD cases performed in the normal range on measures of academic achievement. Furthermore, the residual phonological processing impairment and relative literacy weaknesses observed in resolved cases are also documented in similar cases without reported school attendance issues.

Future studies aiming to predict persistent multiple verbal trait disorder in young children with SSD could consider factors such as a family history of persistent SSD with multiple verbal trait disorder; a preschool diagnosis of severe or profound CAS affecting intelligibility at school entry; multiple speech errors at age 9 years; and very slow to fair therapy progress. Other factors to examine include concomitant severe expressive language impairment; poor phonological processing, including nonword discrimination; impaired receptive vocabulary, even in the presence of average receptive language; and literacy difficulties, specifically in phonological decoding. Limb motor coordination difficulties and anxiety-related presentations also warrant attention in future studies. A multivariate analysis in a larger persistent SSD cohort or longitudinal study of a prospective at-risk cohort may reveal how variables interact in the persistent SSD profile.

Future studies could also investigate genetic and neural correlates in the PM family. The neural basis for CAS remains poorly understood and minimally studied (Liégeois & Morgan, 2012, p. 439). The little that is known relates primarily to CAS associated with epilepsy, metabolic disorders, syndromes, and/or comorbid dysarthria—none of which were found in the PM family members. In a review of the neural basis of childhood speech disorders, Liégeois and Morgan (2012) examined 12 studies: They conclude: "The few studies reporting on childhood apraxia of speech converged towards morphological, structural, metabolic or epileptic anomalies affecting the basal ganglia, perisylvian and rolandic cortices bilaterally" (p. 439). Future neuroimaging data on the PM family, who are without comorbid medical conditions, may serve as a point of comparison in the sparse literature on the neural correlates of CAS.

Conclusions

Rapid advances in speech genetics have not been matched by the development of well-defined phenotypes for SSD. Here, the comprehensive assessment of a large multigenerational family revealed a core phenotype characterized by a multiple verbal trait disorder that distinguished persistent from resolved SSD cases. The phenotype bore greater resemblance to published idiopathic singleton cases than those in large family studies, given the absence of comorbid dysarthria or marked OFA. The phonological memory impairment and subtle literacy weakness present in resolved PM family cases resembled published reports.

This study responds to calls for carefully defined speech and language phenotypes (Grigorenko, 2009), the use of protocols sensitive to different SSDs (Shriberg, Jakielski & El-Shanti, 2008), the direct assessment of siblings and parents (Lewis et al., 2004a), and the investigation of SSD in families with multigenerational histories (Peter & Raskind, 2011). Comprehensive phenotyping can advance the study of SSD. The identification of cognitive, linguistic, and motor profiles associated with persistent SSD may increase the precision of subtyping, improve cross-study comparisons of phenotypically similar participants, and facilitate the discovery of genetic and neural correlates.

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Conflict of Interest

None declared.

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References

Alcock, K. J., Passingham, R. E., Watkins, K., & Vargha-Khadem, F. (2000). Pitch and timing abilities in inherited speech and language impairment. *Brain and Language*, *75* (*1*), 34–46. doi:10.1006/brln.2000.2323.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders*. (5th ed.) Washington, D.C: American Psychiatric Publishing.

American Speech-Language-Hearing Association. (2007). Childhood apraxia of speech [Technical Report]. Available from www.asha.org/policy.

Bailey-Wilson, J. E., & Wilson, A. F. (2011). Linkage analysis in the next-generation sequencing era. *Human Heredity*, *72* (*4*), 228.

Ballard, K. J., Robin, D. A., McCabe, P., & McDonald, J. (2010). A treatment for dysprosody in childhood apraxia of speech. *Journal of Speech Language and Hearing Research*, *53* (*5*), 1227.

Campbell, T. F., Dollaghan, C. A., Rockette, H. E., Paradise, J. L., Feldman, H. M., Shriberg, L. D., … Kurs-Lasky, M. (2003). Risk factors for speech delay of unknown origin in 3-year-old children. *Child development*, *74* (*2*), 346–357.

Carrigg, B., Baker, E., Parry, L., & Ballard, K. J. (2015). Persistent speech sound disorder in a 22-year-old male: Communication, educational, socio-emotional, and vocational outcomes. *SIG 16 Perspectives on School-Based Issues*, *16* (*2*), 37–49.

Cleland, J., Scobbie, J. M., & Wrench, A. A. (2015). Using ultrasound visual biofeedback to treat persistent primary speech sound disorders. *Clinical Linguistics and Phonetics*, *29* (*8–10*), 575–597. doi:10.3109/02699206.2015.1016188.

Cumley, G., & Swanson, S. (1999). Augmentative and alternative communication options for children with developmental apraxia of speech: three case studies. *Augmentative and Alternative Commuication*, *15* (*2*), 110–125. doi:10.1080/07434619912331278615.

DeThorne, L. S., Hart, S. A., Petrill, S. A., Deater-Deckard, K., Thompson, L. A., Schatschneider, C., Davison, M. D. (2006). Children's history of speech-language difficulties: Genetic influences and associations with reading-related measures. *Journal of Speech Language and Hearing Research*, *49* (*6*), 1280–1293. doi:10.1044/1092-4388(2006/092).

Dunn, L. M., & Dunn, D. M. (2007). *Peabody Picture Vocabulary Test* (4th ed.). Bloomington, MN: Pearson.

Fedorenko, E., Morgan, A., Murray, E., Cardinaux, A., Mei, C., Tager-Flusberg, H., … Kanwisher, N. (2015). A highly penetrant form of childhood apraxia of speech due to deletion of 16p11. 2. *European Journal of Human Genetics*, *24* (*2*), 302–306.

Graham, S. A., Deriziotis, P., & Fisher, S. E. (2015). Insights into the genetic foundations of human communication. *Neuropsychology Review*, *25* (*1*), 3–26.

Graham, S. A., & Fisher, S. E. (2015). Understanding language from a genomic perspective. *Annual Review of Genetics*, *49*, 131–160.

Grigorenko, E. L. (2009). Speaking genes or genes for speaking? Deciphering the genetics of speech and language. *Journal of Child Psychology and Psychiatry*, *50* (*1–2*), 116–125. doi:10.1111/j.1469-7610.2008.02006.x.

Hayiou-Thomas, M. E. (2008). Genetic and environmental influences on early speech, language and literacy development. *Journal of Communication Disorders*, *41* (*5*), 397–408.

Hurst, J. A., Baraitser, M., Auger, E., Graham, F., & Norell, S. (1990). An extended family with a dominantly inherited speech disorder. *Developmental Medicine and Child Neurology*, *32* (*4*), 352–355.

Johnson, C. J., Beitchman, J. H., Young, A., Escobar, M., Atkinson, L., Wilson, B., … Lam, I. (1999). Fourteen-year follow-up of children with and without speech/language impairments: Speech/language stability and outcomes. *Journal of Speech Language and Hearing Research*, *42* (*3*), 744–760.

Kaplan, E., Fein, D., Kramer, J., Delis, D. C., & Morris, R. (1999). *WISC-III as a process instrument*. San Antonio, TX: The Psychological Corporation.

Kenney, M. K., Barac-Cikoja, D., Finnegan, K., Jeffries, N., & Ludlow, C. L. (2006). Speech perception and short-term memory deficits in persistent developmental speech disorder. *Brain and Language*, *96* (*2*), 178–190.

Korkman, M., Kirk, U., & Kemp, S. (2007). *NEPSY (2nd ed.): A developmental neuropsychological assessment*. San Antonio: TX: The Psychological Corporation.

Kugler, S. L., Bali, B., Lieberman, P., Strug, L., Gagnon, B., Murphy, P. L., … Pal, D. K. (2008). An autosomal dominant genetically heterogeneous variant of rolandic epilepsy and speech disorder. *Epilepsia*, *49* (*6*), 1086–1090.

Lai, C. S. L., Fisher, S. E., Hurst, J. A., Vargha-Khadem, F., & Monaco, A. P. (2001). A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature*, *413* (*6855*), 519–523.

Lewis, B. A. (1992). Pedigree analysis of children with phonology disorders. *Journal of Learning Disabilities*, *25*, 586–597.

Lewis, B. A., & Freebairn, L. (1992). Residual effects of preschool phonology disorders in grade school, adolescence, and adulthood. *Journal of Speech Language and Hearing Research*, *35* (*4*), 819–831.

Lewis, B. A., Freebairn, L., Tag, J., Ciesla, A. A., Iyengar, S. K., Stein, C. M., Taylor, H. G. (2015). Adolescent outcomes of children with early speech sound disorders with and without language impairment. *American Journal of Speech-Language Pathology*, *24* (*2*), 150–163. doi:10.1044/2014_AJSLP-14-0075.

Lewis, B. A., Freebairn, L. A., Hansen, A., Gerry Taylor, H., Iyengar, S., & Shriberg, L. D. (2004a). Family pedigrees of children with suspected childhood apraxia of speech. *Journal of Communication Disorders*, *37* (*2*), 157–175.

Lewis, B. A., Freebairn, L. A., Hansen, A. J., Iyengar, S. K., & Taylor, H. G. (2004b). School-age follow-up of children with childhood apraxia of speech. *Language, speech, and hearing services in schools*, *35* (*2*), 122–140. doi:10.1044/0161-1461(2004/014).

Lewis, B. A., Freebairn, L. A., Hansen, A. J., Miscimarra, L., Iyengar, S. K., & Taylor, H. G. (2007). Speech and language skills of parents of children with speech sound disorders. *American Journal of Speech-Language Pathology*, *16* (*2*), 108–118.

Lewis, B. A., Freebairn, L. A., & Taylor, H. G. (2000). Follow-up of children with early expressive phonology disorders. *Journal of Learning Disabilities*, *33* (*5*), 433–444.

Lezak, M., Howieson, D., Loring, D., Hannay, J., & Fischer, J. (2004). *Neuropsychological assessment* (4th ed.). New York: Oxford University Press.

Liegeois, F., Morgan, A., & Vargha-Khadem, F. (2007). Neurocognitive correlates of developmental verbal and orofacial dyspraxia. In Coch, D., Fischer, K. W., & Dawson, G. (Eds.) *Human behavior, learning, and the developing brain: Typical development* (pp.168–186). New York: Guilford Press.

Liégeois, F. J., & Morgan, A. T. (2012). Neural bases of childhood speech disorders: Lateralization and plasticity for speech functions during development. *Neuroscience & Biobehavioral Reviews*, *36* (*1*), 439–458. doi:http://dx.doi.org/10.1016/j.neubiorev.2011.07.011.

MacDermot, K. D., Bonora, E., Sykes, N., Coupe, A. M., Lai, C. S. L., Vernes, S. C., … Fisher, S. E. (2005). Identification of FOXP2 truncation as a novel cause of developmental speech and language deficits. *American Journal of Human Genetics*, *76* (*6*), 1074–1080.

McLaughlin, J. F., & Kriegsmann, E. (1980). Developmental dyspraxia in a family with X-linked mental retardation (Renpenning syndrome). *Developmental Medicine and Child Neurology*, *22* (*1*), 84–92. doi:10.1111/j.1469-8749.1980.tb04308.x.

Morgan, A., Liégeois, F., & Vargha-Khadem, F. (2010). Motor speech profile in relation to site of brain pathology: A developmental perspective. In Maassen, B. , & Lieshout, P. V. (Eds.) *Speech motor control: New developments in basic and applied research* (pp.95–115). Oxford: Oxford University Press.

Morgan, A., & Vogel, A. (2009). A Cochrane review of treatment for dysarthria following acquired brain injury in children and adolescents. *European Journal of Physical and Rehabilitation Medicine*, *45* (*2*), 197–204.

Nathan, L., Stackhouse, J., Goulandris, N., & Snowling, M. J. (2004). The development of early literacy skills among children with speech difficulties: A test of the "critical age hypothesis". *Journal of Speech Language and Hearing Research*, *47* (*2*), 377–391.

Newmeyer, A. J., Grether, S., Grasha, C., White, J., Akers, R., Aylward, C., … deGrauw, T. (2007). Fine motor function and oral-motor imitation skills in preschool-age children with speech-sound disorders. *Clinical Pediatrics*, *46* (*7*), 604–611. doi:10.1177/0009922807299545.

Palka, C., Alfonsi, M., Mohn, A., Cerbo, R., Franchi, P. G., Fantasia, D., … Zori, R. (2012). Mosaic 7q31 deletion involving FOXP2 gene associated with language impairment. *Pediatrics*, *129* (*1*), e183–e188.

Peter, B., Button, L., Stoel-Gammon, C., Chapman, K., & Raskind, W. H. (2013). Deficits in sequential processing manifest in motor and linguistic tasks in a multigenerational family with childhood apraxia of speech. *Clinical Linguistics and Phonetics*, *27* (*3*), 163–191.

Peter, B., Matsushita, M., Oda, K., & Raskind, W. (2014). De novo microdeletion of BCL11A is associated with severe speech sound disorder. *American Journal of Medical Genetics A*, *164* (*8*), 2091–2096.

Peter, B., & Raskind, W. H. (2011). Evidence for a familial speech sound disorder subtype in a multigenerational study of oral and hand motor sequencing ability. *Topics in Language Disorders*, *31* (*2*), 145–167.

Peterson, R. L., McGrath, L. M., Smith, S. D., & Pennington, B. F. (2007). Neuropsychology and genetics of speech, language, and literacy disorders. *Pediatric Clinics of North America*, *54* (*3*), 543–561. doi:10.1016/j.pcl.2007.02.009.

Peterson, R. L., Pennington, B. F., Shriberg, L. D., & Boada, R. (2009). What influences literacy outcome in children with speech sound disorder? *Journal of Speech Language Hearing Research*, *52* (*5*), 1175–1188. doi:10.1044/1092-4388(2009/08-0024).

Raca, G., Baas, B. S., Kirmani, S., Laffin, J. J., Jackson, C. A., Strand, E. A., … Shriberg, L. D. (2013). Childhood apraxia of speech (CAS) in two patients with 16p11. 2 microdeletion syndrome. *European Journal of Human Genetics*, *21* (*4*), 455–459.

Raitano, N. A., Pennington, B. F., Tunick, R. A., Boada, R., & Shriberg, L. D. (2004). Pre-literacy skills of subgroups of children with speech sound disorders. *Journal of Child Psychology and Psychiatry*, *45* (*4*), 821–835.

Redle, E., Vannest, J., Maloney, T., Tsevat, R. K., Eikenberry, S., Lewis, B., … Holland, S. K. (2015). Functional MRI evidence for fine motor praxis dysfunction in children with persistent speech disorders. *Brain Research*, *1597*, 47–56.

Rice, G. M., Raca, G., Jakielski, K. J., Laffin, J. J., Iyama-Kurtycz, C. M., Hartley, S. L., … Shriberg, L. D. (2012). Phenotype of FOXP2 haploinsufficiency in a mother and son. *American Journal of Medical Genetics A*, *158* (*1*), 174–181.

Rvachew, S. (2007). Phonolgical processing and reading in children with speech sound disorders. *American Journal of Speech-Language Pathology*, *16* (*3*), 260–270. doi:10.1044/1058-0360(2007/030).

Rvachew, S., & Grawburg, M. (2006). Correlates of phonological awareness in preschoolers with speech sound disorders. *Journal of Speech Language Hearing Research*, *49* (*1*), 74–87.

Saleeby, N. C., Hadjian, S., Martinosky, S. J., & Swift, M. R. (1978). Familial verbal dyspraxia: a clinic study. Conference Proceedings (Abstract). *American Speech Language Hearing Association Conference*, San Francisco, CA, 20, p. 816.

Scheffer, I. E., Jones, L., Pozzebon, M., Anne Howell, R., Saling, M. M., & Berkovic, S. F. (1995). Autosomal dominant rolandic epilepsy and speech dyspraxia: A new syndrome with anticipation. *Annals of Neurology*, *38* (*4*), 633–642.

Semel, E., Wiig, E., & Secord, W. (2006). *Clinical Evaluation of Language Fundamentals (4th ed.). Australian Standardized Edition*. Sydney, NSW: Harcourt Assessment.

Shriberg, L. D. (2010). *A neurodevelopmental framework for research in childhood apraxia of speech.* Speech motor control: New developments in basic and applied research (pp.259–270). New York: Oxford University Press Inc.

Shriberg, L., & Austin, D. (1998). Comorbidity of speech-language disorder: Implications for a phenotype marker for speech delay. In Paul, R. (Ed.) *Exploring the speech-language connection* (pp.73–117). London: Paul H. Brookes.

Shriberg, L. D., Austin, D., Lewis, B. A., McSweeny, J. L., & Wilson, D. L. (1997). The percentage of consonants correct (PCC) metric: Extensions and reliability data. *Journal of Speech Language Hearing Research*, *40* (*4*), 708–722.

Shriberg, L. D., Fourakis, M., Hall, S. D., Karlsson, H. B., Lohmeier, H. L., McSweeny, J. L., … Tilkens, C. M. (2010). Extensions to the speech disorders classification system (SDCS). *Clinical Linguistics and Phonetics*, *24* (*10*), 795–824.

Shriberg, L. D., Jakielski, K. J., & El-Shanti, H. (2008). Breakpoint localization using array-CGH in three siblings with an unbalanced 4q;16q translocation and childhood apraxia of speech (CAS). *American Journal of Medical Genetics A*, *146A* (*17*), 2227–2233. doi:10.1002/ajmg.a.32363.

Shriberg, L. D., Lohmeier, H. L., Campbell, T. F., Dollaghan, C. A., Green, J. R., & Moore, C. A. (2009). A nonword repetition task for speakers with misarticulations: The syllable repetition task (SRT). *Journal of Speech Language Hearing Research*, *52* (*5*), 1189–1212. doi:10.1044/1092-4388(2009/08-0047).

Shriberg, L. D., Lohmeier, H. L., Strand, E. A., & Jakielski, K. J. (2012). Encoding, memory, and transcoding deficits in childhood apraxia of speech. *Clinical Linguistics and Phonetics*, *26* (*5*), 445–482.

Shriberg, L. D., Potter, N. L., & Strand, E. A. (2011). Prevalence and phenotype of childhood apraxia of speech in youth with galactosemia. *Journal of Speech Language Hearing Research*, *54* (*2*), 487–519.

Shriberg, L. D., Tomblin, J. B., & McSweeny, J. L. (1999). Prevalence of speech delay in 6-year-old children and comorbidity with language impairment. *Journal of Speech Language Hearing Research*, *42* (*6*), 1461–1481.

Snowling, M., Bishop, D., & Stothard, S. E. (2000). Is preschool language impairment a risk factor for dyslexia in adolescence? *Journal of Child Psychology and Psychiatry*, *41* (*05*), 587–600.

Speake, J., Stackhouse, J., & Pascoe, M. (2012). Vowel targeted intervention for children with persisting speech difficulties: Impact on intelligibility. *Child Language Teaching and Therapy*, *28* (*3*), 277–295.

Stackhouse, J., Pascoe, M., & Gardner, H. (2006). Intervention for a child with persisting speech and literacydifficulties: A psycholinguistic approach. *International Journal of Speech-Language Pathology*, *8* (*3*), 231–244.

Stackhouse, J., & Snowling, M. (1992a). Barriers to literacy development in two cases of developmental verbal dyspraxia. *Cognitive Neuropsychology*, *9* (*4*), 273–299.

Stackhouse, J., & Snowling, M. (1992b). Developmental verbal dyspraxia II: A developmental perspective on two case studies. *International Journal of Language and Communication Disorders*, *27* (*1*), 35–54.

Stackhouse, J., Vance, M., Pascoe, M., & Wells, B. (2007). *Compendium of auditory and speech tasks: Children's speech and literacy difficulties 4 with CD-ROM*. Chichester, England: John Wiley & Sons.

Stein, C. M., Lu, Q., Elston, R. C., Freebairn, L. A., Hansen, A. J., Shriberg, L. D., … Iyengar, S. K. (2011). Heritability estimation for speech-sound traits with developmental trajectories. *Behavior Genetics*, *41* (*2*), 184–191.

Turner, S. J., Hildebrand, M. S., Block, S., Damiano, J., Fahey, M., Reilly, S., … Morgan, A. T. (2013). Small intragenic deletion in FOXP2 associated with childhood apraxia of speech and dysarthria. *American Journal of Medical Genetics A*, *161* (*9*), 2321–2326.

Turner, S. J., Mayes, A. K., Verhoeven, A., Mandelstam, S. A., Morgan, A. T., & Scheffer, I. E. (2015). GRIN2A An aptly named gene for speech dysfunction. *Neurology*, *84* (*6*), 586–593.

Vargha-Khadem, F. (2011). *The gift of speech: FOXP2 gene and the KE family*. Paper presented at the Paediatric Clinical Neuropsychology Course, University College London Institute of Child Health, & Great Ormond Street Hospital for Children, London, UK.

Vargha-Khadem, F., Gadian, D. G., Copp, A., & Mishkin, M. (2005). FOXP2 and the neuroanatomy of speech and language. *Nature reviews Neuroscience*, *6* (*2*), 131–138. doi:10.1038/nrn1605.

Vargha-Khadem, F., Watkins, K., Alcock, K., Fletcher, P., & Passingham, R. (1995). Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder. *Proceedings of the National Academy of Sciences*, *92* (*3*), 930–933.

Vargha-Khadem, F., Watkins, K. E., Price, C. J., Ashburner, J., Alcock, K. J., Connelly, A., … Passingham, R. E. (1998). Neural basis of an inherited speech and language disorder. *Proceedings of the National Academy of Sciences U.S.A*, *95* (*21*), 12695–12700.

Velleman, S. L., & Mervis, C. B. (2011). Children with 7q11. 23 duplication syndrome: Speech, language, cognitive, and behavioral characteristics and their implications for intervention. *SIG 1 Perspectives on Language Learning and Education*, *18* (*3*), 108–116.

Visscher, C., Houwen, S., Scherder, E. J., Moolenaar, B., & Hartman, E. (2007). Motor profile of children with developmental speech and language disorders. *Pediatrics*, *120* (*1*), e158–e163.

Wagner, R., Torgesen, J., & Rashotte, C. (1999). *Comprehensive test of phonological Processing*. Austin, TX: Pro-Ed.

Watkins, K. E., Dronkers, N. F., & Vargha-Khadem, F. (2002). Behavioural analysis of an inherited speech and language disorder: Comparison with acquired aphasia. *Brain*, *125*, 452–464.

Wechsler, D. (1997a). *Wechsler adult intelligence scale* (3rd ed.). San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997b). *Wechsler memory scale* (3rd ed.). San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2002). *Wechsler individual achievement test* (2nd ed.). Sydney, NSW: Pearson Assessment, Australian Standardised Edition.

Wechsler, D. (2005). *Wechsler intelligence scale for children* (4th ed.). Sydney, NSW: Harcourt Assessment, Australian Standardised Edition.

Wijsman, E. (2012). The role of large pedigrees in an era of high-throughput sequencing. *Human Genetics*, *131* (*10*), 1555–1563. doi:10.1007/s00439-012-1190-2.

Wilson, A. F., & Ziegler, A. (2011). Lessons learned from genetic analysis workshop 17: Transitioning from genome-wide association studies to whole-genome statistical genetic analysis. *Genetic Epidemiology*, *35* (*S1*), S107–S114.

Woodcock, R. W., McGrew, K., & Mather, N. (2001). *Woodcock-Johnson tests of achievement* (3rd ed.). Itasca, IL: Riverside Publishing.

Wren, Y., Roulstone, S. E., & Miller, L. L. (2012). Distinguishing groups of children with persistent speech disorder: Findings from a prospective population study. *Logopedics, phoniatrics, vocology*, *37* (*1*), 1–10.

Zaretsky, E., Velleman, S. L., & Curro, K. (2010). Through the magnifying glass: Underlying literacy deficits and remediation potential in childhood apraxia of speech. *International Journal of Speech Language Pathology*, *12* (*1*), 58–68. doi:10.3109/17549500903216720.