Chapter 15

A neurodevelopmental framework for research in childhood apraxia of speech

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Abstract

We describe rationale, methods, and genetic findings for a neurodevelopmental framework for research in Childhood Apraxia of Speech (CAS). The proposed framework is motivated by the consensus perspective that despite considerable research and clinical attention, the core speech processing features of idiopathic CAS and its clinical signs remain unknown. The goal of the research framework is to obtain this information from comparative studies of adults with acquired apraxia of speech (AOS), children with CAS as a sequelae of a neurological disorder, children with CAS secondary to complex neurodevelopmental disorders, and the putative clinical entity—children suspected to have CAS of unknown (i.e., idiopathic) origin. Discussion begins with an overview of terms and issues underlying CAS as a speech sound disorder, followed by rationale and methods for the proposed research framework. The final section summarizes findings and issues from 18 studies reporting CAS in the context of genetically based neurodevelopmental disorders.

15.1 Etiological subtypes of speech sound disorders

15.1.1 Terms

Speech Sound Disorders (*SSD*), a classification term recently adopted by the American Speech-Language-Hearing Association, provides a welcome solution to the nosological challenges associated with prior attempts to classify children's speech disorders based on *articulatory* versus *phonological* explanatory processes. *Speech* subsumes all articulatory and phonological mechanisms, *sound* separates this class of speech disorder from speech fluency disorders, and *disorder* is the public health construct required for access to diagnostic and treatment services. Thus, SSD provides a unified term for research and clinical practice in childhood SSD of both known origin (e.g., cleft palate, Down syndrome) and of currently unknown origin, the latter historically termed *functional*, *developmental*, or *idiopathic* speech disorders. Elsewhere, *Speech Delay* (*SD*) and *Speech Errors* (*SE*) are delineated as cover terms for two subordinate classifications of SSD of currently unknown origin (Shriberg 2009). In comparison to children with SE, for whom transient or persistent speech sound distortions may be of negligible to moderate socio-educational significance, children with SD have speech processing deficits that place them at risk for literacy,

Table 15.1 Working terms, distal origins, and proximal processes affected in five putative subtypes of SD

Working Term	Abbreviation	Primary origin	Processes affected
Speech Delay–Genetic	SD-GEN	Polygenic/environmental	Cognitive-linguistic
Speech Delay–Otitis media with effusion	SD-OME	Polygenic/environmental	Auditory-perceptual
Speech Delay–Developmental psychosocial involvement	SD-DPI	Polygenic/environmental	Affective-temperamental
Speech Delay–Apraxia of speech	SD-AOS	Monogenic? Oligogenic?	Speech-motor control
Speech Delay–Dysarthria	SD-DYS	Monogenic? Oligogenic?	Speech-motor control

learning, social, and vocational challenges. The subtype of SD termed Childhood Apraxia of Speech (CAS), one of five proposed subtypes of SD and the focus of this paper, clearly places a child at elevated risk for such challenges (ASHA 2007b).

Table 15.1 is a list of five subtypes of SD posited to have different etiological (*distal*) origins, with each origin having implications for speech processing (*proximal*) constraints. For research needs, a set of working terms and their abbreviations are used to reference children whose SD may be caused or significantly mediated by one or more of these five proposed distal-proximal constraints. As listed in Table 15.1, the five proposed subtypes of SD are defined by (a) cognitive-linguistic processing constraints associated with genetic risk factors (*SD-GEN*); (b) auditory-perceptual processing constraints due to mild-moderate fluctuant conductive hearing loss consequent to early recurrent otitis media with effusion (*SD-OME*); (c) affective, temperamental constraints associated with developmental psychosocial involvement (*SD-DPI*); (d) speech motor planning/programming deficits consistent with apraxia of speech (*SD-AOS*; elsewhere termed *CAS* or Developmental Verbal Dyspraxia [*DVD*]); and (e) speech motor execution constraints consistent with subtypes of dysarthria (*SD-DYS*). For clinical concerns, these five proximal speech-processing constraints presumably are associated with prognosis and treatment, with each constraint comprising a potential focus of treatment. It is important to underscore that the division of SD into these five interim classifications and their abbreviated working terms is used as a heuristic for research. A significant proportion of children who have SD likely have involvement in more than one putative subtype.

A central concept in the classification system proposed in Table 15.1 is that both genetic and environmental sources confer risk and protective elements to the expression, severity, and persistence or normalization of each subtype of SD. As shown in the third column, genetic sources are divided into contributions from *monogenic* (one), *oligogenic* (a few), or *polygenic* (many) genes or genomic regions. For SD-GEN, estimated to be the most prevalent subtype of SD and predicted to have polygenic/environmental origins, *susceptibility loci* (regions of interest) have been reported on four autosomes: chromosomes 1, 3, 6, and 15 (Lewis et al., 2006). The Lewis et al. review of speech-genetic studies includes discussion of the candidate genes within each susceptibility locus that have been linked to verbal trait disorders (i.e., impairments in language, reading, and spelling). Reports by two research groups indicate that at least part of the association of SSD with reading disability is likely due to common genes in regions of interest on chromosomes 5p22 and 15q21 (Smith et al., 2005) and in the centromeric region of chromosome 3 (Stein et al., 2004).

As indicated in Table 15.1, polygenic and environmental origins are posited for SD-OME and SD-DPI. For the subtypes of SD with the working terms SD-AOS and SD-DYS, however, their

considerably lower prevalence, marked severity of expression, and involvement of specific motor systems suggest monogenic or oligogenic, rather than polygenic origins, with few or no significant environmental contributions. The third section of this paper returns to genetic issues and findings for SD-AOS in non-idiopathic contexts.

15.1.2 Differential diagnosis of CAS

The classification terms in Table 15.1, together with an additional term for speakers with normal or normalized speech (*Typical Speech, TS*), provide three diagnostic challenges for research and practice in CAS (i.e., SD-AOS). The following classification challenges are made more or less difficult as mediated by a child's age (toddler, preschooler, school-age, adolescent) and relative severity of expression (mild, moderate, severe) of CAS.

Differentiate CAS from Typical Speech (TS). The earliest diagnostic/prognostic challenge for children suspected to have CAS occurs before two years of age when a child with moderate to severe CAS may be producing a limited amount of speech. Unlike the histories of children with the other four subtypes of SD in Table 15.1, case histories of children suspected to have CAS indicate that they are late to begin talking. With only limited speech output to evaluate, it is difficult to determine if the delayed onset of speech in such children is due entirely or partially to cognitive-language constraints (i.e., a *Late-Talker*) or to a deficit in *praxis*, the construct from which CAS takes its name. The latter may be suspected if excessive articulatory efforts are apparent in a child's attempt to imitate speech models, compared to the absence of such difficulties in well-practiced, spontaneous speech forms (Velleman 2002).

Differentiate CAS from SD-GEN, SD-OME, and SD-DPI. Once a child of any age is producing a sufficient amount of speech for perceptual, acoustic, and other types of instrumental analyses, the assessment challenge is to differentiate CAS from three of the four other subtypes of SD listed in Table 15.1. Differential diagnosis requires quantitative analyses of SE patterns, including close description of prosodic and vocal features. As noted previously, a primary constraint on such analyses is the lack of research consensus on the speech, prosodic, and vocal signs that are pathognomonic (definitive) for CAS. A Position Statement on CAS by the American Speech-Language-Hearing Association (ASHA 2007a) includes the following three signs for which, as concluded in the position paper, there is consensus in both the adult AOS and child CAS communities: '(a) inconsistent errors on consonants and vowels in repeated productions of syllables or words, (b) lengthened and disrupted coarticulatory transitions between sounds and syllables, and (c) inappropriate prosody, especially in the realization of lexical or phrasal stress' (p. 2). Notice that such behaviours provide only the starting point for development of the methods and quantitative criteria required to translate such observations into reliable diagnostic markers that meet psychometric requirements for research and clinical decision-making.

Differentiate CAS from SD-DYS. Differentiating CAS from SD-DYS, a third diagnostic specificity need, is less widely discussed in the CAS literature than in the adult AOS literature. At present, the criterial speech and non-speech signs of childhood dysarthria draw heavily from the descriptions available in research on acquired dysarthria in adults (e.g., Duffy 2005). Other than descriptions of speech in subtypes of cerebral palsy, there is a notably sparse literature on clinical or subclinical childhood dysarthria. As with SD-AOS, SD-DYS is often a provisional diagnosis (i.e., '*suspected* to have dysarthria' or '*dysarthria cannot be ruled out*') in children who do not have a frank neuromotor disorder.

15.1.3 Definitional alternatives

The diversity of definitional perspectives in CAS has been deliberated most recently at an international research symposium (Shriberg and Campbell 2003), at the miniseminar that included the

present chapter, and in an American Speech-Language-Hearing Association position paper and accompanying technical report (ASHA, 2007a, b). Rationale for the definitional perspectives outlined in the present paper is based on an affirmative answer to each of the following questions:

Should apraxia of speech be defined by one or more core speech processing features (i.e., as identified by behavioural markers) that are generally similar:

(1) in congenital and acquired forms?

(2) in idiopathic versus non-idiopathic forms?

(3) at all levels of severity?

(4) in the same speaker at different points in development?

On the first question, there are many reasons to suspect that the core speech processing deficit in CAS – constraints in the planning of gestures that subserve speech – might differ in congenital compared to acquired forms. Although both forms have praxis impairment, relevant sensorimotor processes likely vary considerably in children developing speech compared to those with an acquired disorder. Notwithstanding differences in genetic and epigenetic expression and other risk factors that may mediate error severity and error topography, it is parsimonious to posit a common core deficit in speech processing. From a similar perspective, we take the position on the second question that the core speech processing features of idiopathic CAS and non-idiopathic CAS (i.e., whether apraxia occurs as the sole disorder or as a secondary sign in complex neurodevelopmental disorders) should be similar or generally equivalent.

The third and fourth questions above clearly seem to require affirmative answers because severity of expression at any one or more developmental period is a secondary rather than core feature of disease and disorder. Again, a parsimonious view would posit that although severity of expression may be significantly attenuated over time, hopefully with appropriate treatment, core praxic features of CAS as manifest in their behavioural signs and age/severity adjusted diagnostic markers should be stable over even long time periods.

15.2 A neurodevelopmental framework for research in CAS

15.2.1 Rationale and description

Figure 15.1 illustrates a four-phase neurodevelopmental framework for research in CAS. Rationale for this proposal is that the only way to obviate the 'circularity' (Guyette and Diedrich 1981) or 'tautology' (McNeil et al., 1997) problem in subject selection for research in idiopathic CAS is by programmatic study of CAS occurring in forms with known neurogenic origins. Accordingly, the first of the four phases depicted in Fig. 15.1 is to conduct studies to identify and validate the linguistic domains (e.g., vowels, consonants, prosody) in which the core speech processing features of CAS can be quantified as they occur in adult AOS, in children following a neurological disorder (e.g., infection, trauma), and in complex neurodevelopmental disorders. Some examples of complex neurodevelopmental backgrounds reporting CAS as a secondary disorder include the autism spectrum, chromosome translocations, Coffin-Sirus syndrome, Down syndrome, Fragile X syndrome, Joubert syndrome, galactosemia, Rett syndrome, Rolandic epilepsy, Russell-Silver syndrome, Velocardiofacial syndrome, and duplication of the Williams-Beuren locus. As indicated in Fig. 15.1, this phase is increasingly being informed by knockout, knockdown, and knockin avian and mammalian studies of FoxP2 and other genes (e.g., the FMRP gene in Fragile X syndrome).

In the second phase, findings from the studies of non-idiopathic CAS and children suspected to have idiopathic CAS can be used to inform the inclusional/exclusional criteria to classify

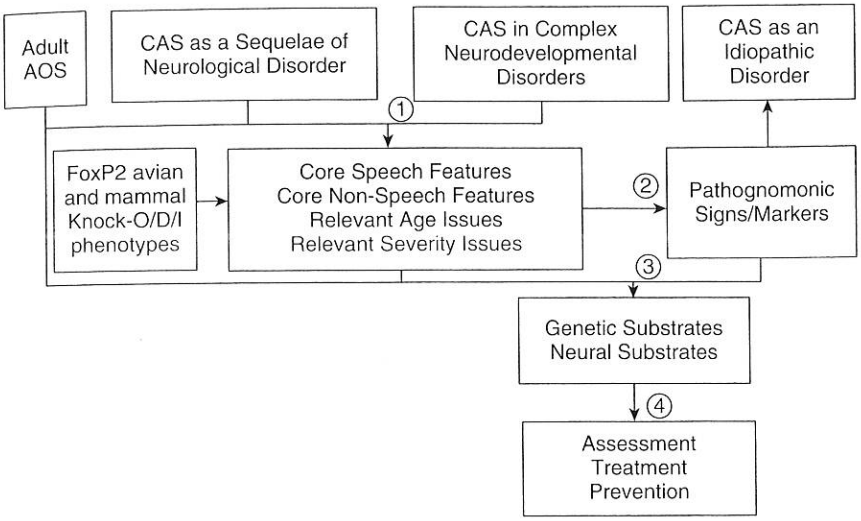

Fig. 15.1 A neurodevelopmental framework for research in CAS.

participants as true positives for idiopathic CAS. Findings from these four forms of CAS can provide the information base needed for third-phase studies of the genetic and neural substrates underlying the pathophysiology of apraxia. Last, in the fourth phase, investigators from a number of disciplines can use aggregate findings to develop optimum methods for assessment, treatment, and ultimately, prevention.

15.2.2 Method

The second element required for the research framework shown in Fig. 15.1 is a lifespan assessment protocol for each of the four contexts for CAS. Table 15.2 is an overview of the assessment and analysis framework. As shown in the two left-hand columns, speech targets are organized by three linguistic domains (vowels/diphthongs, consonants, prosody-voice), each subordinated under three analytic constructs reflecting a participant's speech competence, precision, and stability. For each of these nine domains, prior studies in our laboratory and elsewhere have suggested segmental and suprasegmental indices (i.e., signs) that may meet accuracy criteria as diagnostic markers of apraxia, one of several subtypes of dysarthria, or for a classification termed motor speech disorder-not otherwise specified (i.e., a cover term non-specific for apraxia or dysarthria).

Potential diagnostic markers for apraxia (e.g., *unstable planar area, unstable vowel duration, overstressed lexical stress*) are interrogated using a high-throughput computer platform for acoustic-aided transcription and transcription-aided acoustics (Shriberg 2008). Multiple data sources are used to examine contextual influences on each index obtained from a 1-hour assessment protocol that includes 15 speech tasks (e.g., vowel repetition tasks, challenging word tasks, conversational sample). Comparison databases are used to derive age x sex z-scores for each index/variable from each speech task. As shown in Table 15.2, clinical classification information on the resulting profiles of z-scores is consolidated and tabulated within a 27-cell matrix. Shriberg (2008) summarizes findings from four studies of CAS in complex neurodevelopmental disorders using the matrix in Table 15.2.

Table 15.2 Assessment and analyses framework of perceptual and acoustic findings from speakers' responses to the Madison Speech Assessment Protocol. All analyses, including perceptual coding for the Prosody-Voice Screening Profile (PVSP), are completed in the PEPPER environment (Shriberg 2008)

Assessment and analyses framework		Clinical classification		
Construct	**Domain**	**Apraxia**	**Dysarthria**	**Motor speech disorder – not otherwise specified**
Competence	Vowels/diphthongs			
	Consonants			
	Prosody-Voice			
Precision	Vowels/diphthongs			
	Consonants			
	Prosody-Voice			
Stability	Vowels/diphthongs			
	Consonants			
	Prosody-Voice			

15.3 Genetic research in childhood apraxia of speech

Table 15.3 is a summary of findings from 18 studies reporting behaviours consistent with CAS in the context of genetically based, complex neurodevelopmental disorders. Entries in Table 15.3 were restricted to those appearing in peer-reviewed, English language publications; additional case studies have been reported at conferences and on internet forums. As shown in the source information column, three research groups have provided data for 41 of the 55 (75%) cases of reported CAS included in Table 15.3, with affected members of the KE family (Lai et al., 2001) accounting for 15 (27%) of the cases. Only 5 of the 18 (28%) studies include data for more than one affected family member. Although most reports lack detailed or even basic information on how CAS was assessed, the thesis is that these studies provide the precedent literature for programmatic study of CAS in genetically based neurodevelopmental disorders. Space constraints prohibit discussion of methods and speech findings in each study. The following sections briefly contrast trends in these genetic case reports with those reported for idiopathic CAS (e.g., ASHA 2007b).

15.3.1 Age and sex

Patient age in Table 15.3 ranged from three years to older adults, compared with the idiopathic CAS literature which is almost exclusively limited to preschool and school-aged children, with some follow-up studies of adolescents (ASHA 2007b). The nearly equal (0.9:1) ratio of males-to-females in these 18 studies also differs from the sex ratios for idiopathic CAS reported in case-control studies. The latter have routinely reported considerably higher boys-to-girls ratios, approximating 100% boys in some literature reviews (e.g., Hall et al., 1993; Shriberg et al., 1997). Such sex ratio differences in idiopathic CAS compared to CAS in known neurodevelopmental contexts may have significant implications for genetic transmission models. Notice that many cases of reported CAS in Table 15.3 were based on sporadic genetic events (e.g., chromosome translocations), rather than from polymorphisms segregating in families, as is the case in the KE family.

Table 15.3 Patient information, phenotype summaries, and genetic findings for 18 papers providing molecular genetic information for 55 children and adults reported to have speech impairments consistent with CAS

Source		Case information			Phenotype summaries[a]				Genetic findings		
Authors	**Group[b]**	**Case(s)**	**Age (yrs)**	**No. of cases**	**Orofacial Apraxia**	**Cognitive impairment**	**Language impairment**	**Dysmorphology**	**Description**	**Loci**	**Gene**
Sarda et al. (1988)	–	Boy	7	1		X	X	X	Interstitial deletion	7q31.2-q32.3	*FOXP2*
Weistuch and Shiff-Myers (1996)	–	Boy	5	1	X	X	X		Balanced translocation	1q;2q	
Tan-Sindhunata et al. (2000)	–	Boy Girl Mother	4 3 37	3		X		X	Supernumerary ring chromosome	r (7)	
Lai et al. (2000)	A	'CS' boy	5	1	X	X	X		Balanced translocation	5q22; 7q31.2	*FOXP2*
Lai et al. (2001)	A	'KE' 6 males; 9 females	3 generations	15	X	X	X		Point mutation	7q31	*FOXP2*
Liégeois et al. (2001)	A	'AA' Man		1	X	X	X		Deletion	7q31	*FOXP2*
Velagaleti et al. (2002)	–	Boy	12	1		X	X	X	Supernumerary ring chromosome	r (7)	
Tyson et al. (2004)	B	Boy	14	1		X	X	X	Deletion	7q31	*FOXP2*
MacDermot et al. (2005)	A	1 boy; 1 girl; Mother	4 2	3	X	X	X		Point mutation	7q31	*FOXP2*

[a] Patients reported as 'affected' in each report differ in the type and severity of impairments, and for reports with multiple patients, the number of affected patients for each of the three phenotypes. Data are based on varying levels of observational and clinical data. Blank cells typically indicate no information.

[b] Location of research group with two or more table entries: A: London-Oxford; B: Toronto; C: Madison: Other

(*Continued*)

Table 15.3 (Cont.) Patient information, phenotype summaries, and genetic findings for 18 papers providing molecular genetic information for 55 children and adults reported to have speech impairments consistent with CAS

Source		Case information			Phenotype summaries[a]				Genetic findings		
Authors	**Group[b]**	**Case(s)**	**Age (yrs)**	**No. of cases**	**Orofacial Apraxia**	**Cognitive impairment**	**Language impairment**	**Dysmorphology**	**Description**	**Loci**	**Gene**
Somerville et al. (2005)	B	Boy		1		X	X	X	Duplication	7q11.23	(Williams-Beuren locus)
Lichtenbelt et al. (2005)	–	Girl	4	1		X	X		Supernumerary ring chromosome	7q	
Zeesman et al. (2006)	B	Girl	5	1	X	X	X	X	Interstitial deletion	7q31.2-q32.2	*FOXP2*
Shriberg et al. (2006)	C	'TB' Mother; daughter	50 19	2		X	X		Balanced translocation	7q;13q	*FOXP2* (*RFC3*)
Feuk et al. (2006)	B	4 males; 8 females (1 no information)	children	13	X	X	X		Paternal deletion (5); translocation (1); maternal uniparental disomy (7)	7q31	*FOXP2*
Lennon et al. (2007)	–	Boy	7	1		X	X	X	Deletion	7q31	*FOXP2*
Cody et al. (2007)	–	3 boys; 2 girls	2–7	5		X	X	X	Interstitial deletions	18q	
Battini et al. (2007)	–	Boy	9	1	X	X	X		de novo mutation	X-linked	*SLC6A8*
Shriberg et al. (2008)	C	1 boy; 2 girls	11–17	3		X	X	X	Unbalanced translocation	4q;16q	

15.3.2 Cognitive-language impairment

Unlike the idiopathic CAS literature, which frequently reports children whose only sign is a significant speech involvement, all 18 of the studies in Table 15.3 report cognitive-language involvement ('X') in at least one patient. As indicated previously, most of the studies in Table 15.3 provide little information on the assessment procedures and criteria used to classify patients as positive for cognitive, language, or speech impairment, orofacial apraxia, or dysmorphisms. Some of these cases are likely false positives, including patients who have (a) typical speech, (b) SD due to a non-motor etiology (SD-GEN, SD-OME, SD-DPI), or (c) a different motor speech disorder (SD-DYS). Such sensitivity/specificity constraints notwithstanding, the routine finding of language and especially cognitive impairments in these cases compared to findings in the idiopathic CAS literature warrants close research examination.

15.3.3 Orofacial apraxia, dysmorphisms, and dysarthria

Approximately half of the cases reported in Table 15.3 were classified as having orofacial apraxia. This total is heavily weighted by the 15 affected members of the KE family for whom orofacial apraxia was the basis for classifying family members as affected (Vargha-Khadem et al., 1998; see also Chapter 6 Morgan et al., this volume). Again, many studies provide only minimal methodological information and not all studies appear to have reported information for this variable. Of considerable interest is the finding that orofacial apraxia was not found in many cases of *FOXP2* impairments, including two family members whose speech and non-speech characteristics were tested with an extensive battery of speech and non-speech measures (Shriberg et al., 2006). Orofacial apraxia is also reported for only some cases of idiopathic CAS, with implications for an eventual understanding of pathophysiological substrates.

A variety of craniofacial and other dysmorphisms were also reported in approximately half of the cases in Table 15.3. By definition, such findings do not appear in the idiopathic CAS literature. Of interest is an observation in Zeesman et al. (2006), indicating that their patient had dysmorphic features similar to those described in the child reported in both Sarda et al. (1988) and the patient described in Lai et al. (2000). Similarly, Somerville et al. (2005, p. 1700) reported a 'subtle but recognizable facial phenotype' in their patient similar to the phenotype described in Lichtenbelt et al. (2005), Tan-Sindhunata et al. (2000), and Chantot-Bastaraud et al. (2004).

Finally, as shown in Table 15.3, several studies report speech behaviours consistent with dysarthria, whereas few studies of idiopathic CAS report signs of dysarthria. An important research question is whether there may be genomic loci that confer shared risk for either or both of these sensorimotor speech disorders.

15.3.4 Genetic findings

The most frequent genetic finding in Table 15.3 is a disruption in regions of interest or genes on chromosome 7 within or near the *FOXP2* gene. Emphasis on chromosome 7 and *FOXP2* in Table 15.3 is, of course, in part a consequence of the widespread influence of the genetic findings for the KE family, with its implications for study of the neurological substrates and evolutionary biology of speech (see Morgan et al., Chapter 6, this volume). The number of case reports implicating *FOXP2* deficits in Table 15.3 in addition to affected members of the KE family increases its attributable risk for CAS. As noted at the outset of this discussion, however, the KE family remains the only pedigree in which reported CAS has been associated with a point mutation segregating in a large, multigenerational family (Tomblin et al., 2009). In contrast, most of the reports in Table 15.3 are associated with sporadic cytogenetic events in one or a few family members in which copy number variations (i.e., deletions and duplications of genomic material)

resulted from chromosome translocations. As chromosome translocations have been associated with a large number of neurodevelopmental syndromes, they would appear to be a productive source for research addressing the genetic origins of CAS.

15.4 Research directions

The entries in Table 15.3 sample only some of the possible contexts in which research in genetically based neurodevelopmental disorders can be informative for apraxia of speech. This chapter has suggested that advances in identifying the core motor control processes, speech signs, and diagnostic markers of the idiopathic form of CAS may be possible using a comparative research framework. Some emerging examples of this framework include Shriberg and Potter (2008), Shriberg et al. (2006), Shriberg et al. (2008). Studies in process will focus on genotype-phenotype associations in CAS, with the potential of eventually identifying a biomarker for the early detection of this challenging childhood SSD.

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