

SUPPLEMENTAL METHODS

Subject Ascertainment

General Inclusion Criteria for CFSRS

The CFSRS is a 25-year longitudinal study that examined the phenotypic and genetic bases of SSD. This study was approved by the Institutional Review Board of Case Medical Center and University Hospitals. All parents provided written informed consent and children older than 5 years provided assent. Families were ascertained through a proband identified from caseloads of speech-language pathologists (SLPs) in the Greater Cleveland area. Most participants were enrolled at preschool (3-6 years) and followed at school-age (7-11 years) with many followed again at adolescence (12-18 years). Upon entry into the study, a licensed SLP assessed the child to assure that the child met the following inclusion criteria: normal hearing acuity, fewer than 6 episodes of otitis media prior to age 3, monolingual English speaker, and absence of a genetic syndrome or developmental disorder such as autism spectrum disorder other than speech and language disorders. Assessments also were conducted to confirm a performance IQ within normal limits, a speech sound disorder defined as a score less than or equal to the 16th percentile on the Goldman Fristoe Test of Articulation, and oral mechanism exam to ensure that oral structures were within normal limits. At each testing age parents completed a history and developmental questionnaire and the Four Factor Index of Social Class (Hollingshead, 1975) as a measure of SES.

Detailed CAS Phenotyping

A subgroup of children in the CFSRS were diagnosed as CAS by an SLP and/or pediatric neurologist or neuropsychologist. Parent intake questionnaires reported a diagnosis of CAS when the child was between 2 ½ and 5 years of age. Upon entry into the study, the child was re-assessed through direct testing by an SLP on the research team with experience in the

assessment and diagnosis of child speech sound disorders including CAS. Diagnostic criteria for CAS were based on the speech characteristics reported in the literature at the time of diagnosis or the diagnostic criteria described in the CAS Technical Report of the American Speech Language and Hearing Association ¹ (**Supplemental Table 1**). Diagnostic criteria for CAS includes inconsistent speech production, altered prosody, and lengthened transitions. These features are detailed in **Supplemental Table 1** for each participant.

At the initial assessment and follow-up assessment age-appropriate standardized measures were administered to identify LI and RD (See **Supplemental Table 2**). LI was defined as a score < 1 SD below the mean on the Clinical Evaluation of Language Fundamentals, which reflects children with a “marginal disorder / below average” according to the Examiner’s Manual. RD was identified at the school age visit defined as a score <1 SD below the mean on the Word Identification and Word Attack subtests of the Woodcock Reading Mastery Tests.

In addition to classifying children in the study according to the presence or absence of CAS, SSD, LI, and RD as described above, we also conducted a wide range of age-appropriate assessments of articulation, phonological awareness, speeded naming, vocabulary, receptive and expressive language, and literacy (**Supplemental Table 2, Supplemental Figure 1**), as reported in our previous work ²⁻⁶. These quantitative endophenotypes were used to characterize the deficits in children identified with CNVs. Additional clinical manifestations (issues with feeding, delayed language onset, gross/fine motor incoordination, and ADHD) were recorded in the database based on parent interview at each assessment; data abstraction and prior analysis of this data are described elsewhere ³. ADHD was also documented by the ADHD rating Scale ⁷. In addition, we characterized severity of CAS based on membership in clusters

identified through our earlier analysis³; in that analysis, we utilized measures of articulation, vocabulary, and reading to group children with CAS into subgroups of varying severity. Cluster membership is indicated in **Supplemental Table 3**. In addition, psychosocial measures and outcomes were collected from adolescents and young adults on additional surveys, which are described in another paper ⁸; the relevance in this context is that no new medical diagnoses were indicated for the individuals in this study based on those surveys.

Study design and longitudinal follow-up

Families were ascertained via a proband presenting with SSD and/or CAS as stated above. While the majority of probands were preschool age (~3-5 years old) at the time of ascertainment by virtue of their SSD/CAS diagnosis, siblings in the family could have been older or younger. Children that were older at enrollment (refer to Supplemental Table 3) had a diagnosis of CAS at preschool and were later referred to our study; these children showed persistent CAS. Consequently, the evaluation of siblings was done using assessments appropriate for their age (Supplemental Table 2). In addition, probands and their siblings were re-evaluated every few years, according to the age of the proband, such that the proband was seen at preschool, school-age, and adolescence. Siblings also were also re-evaluated at each of these time points. The aforementioned developmental questionnaire was administered at every visit, so that new medical / neurological issues could be recorded in the data. The clinical and endophenotype data recorded in the Supplemental tables reflects all of the longitudinal data collected for these subjects. Longitudinal assessments were used to characterize persistence ⁹.

Functional annotation

Regulatory disruption score

We annotated our CNVs using a regulatory disruption score, generated using the CNV_FunctionalAnnotation program and methodology ¹⁰. This program uses a simple linear

model, developed using brain samples from the Common Mind Consortium (CMC) study, for predicting expression scores for each gene affected by a given CNV. Han et al. annotated rare CNVs in the gnomAD CNV dataset and examined the regulatory disruption scores in pathogenic variants (overlap of at least 50% of an CNV of the same type and labeled pathogenic for neurodevelopmental disorders (developmental delay, intellectual disability, or autism) in ClinGen) and non-pathogenic variants. They found that pathogenic CNVs in gnomAD had significantly larger regulatory disruption scores in the direction of the dosage change than the non-pathogenic CNVs. Specifically, the mean regulatory disruption score for pathogenic deletions was -5.21, while for non-pathogenic deletions was -0.18, and the mean regulatory disruption score for pathogenic duplications was 12.67 and for non-pathogenic duplications was 0.52.

Population allele frequencies

As an estimate of population frequency for our CNVs we report the max frequency for CNVs observed in the Database of Genomic Variants (DGV) ¹¹, focusing on the DGV gold standard variants. The DGV only reports structural variation found in healthy, control samples. The DGV gold standard variants are a curated set of variants from a select number of studies in DGV, allowing for increased sensitivity and specificity in detecting CNVs, ultimately providing more accurate frequency estimates. High resolution and high quality studies were evaluated for accuracy and sensitivity and included if they passed strict quality filters. Overlapping sample level variants were merged to create variant regions if they shared at least 50% of their length in a reciprocal manner. CNV regions were kept if there was sufficient support from multiple studies and samples indicating a high quality variant region. DGV CNVs considered showed a 30% or greater overlap with our CNV and were of the same type.

Evolutionary constraint

If an CNV affects LoF intolerant genes this may indicate the deleteriousness of that CNV. As an estimate of evolutionary constraint or tolerance to inactivation for the genes affected by our CNVs, we supply gene specific pLI scores, pulled from UCSC tables and the gnomAD database. We report gene and corresponding pLI if the metric was greater than 0.9 (LoF-constrained genes). The pLI score reflects the tolerance of a given gene to the loss of function on the basis of the number of protein truncating variants, that is, the frameshift, splice donor, splice acceptor, and stop-gained variants referenced for this gene in gnomAD database weighted by the size of the gene and the sequencing coverage¹². All of the annotations described above are provided in **Supplemental Table 7**.

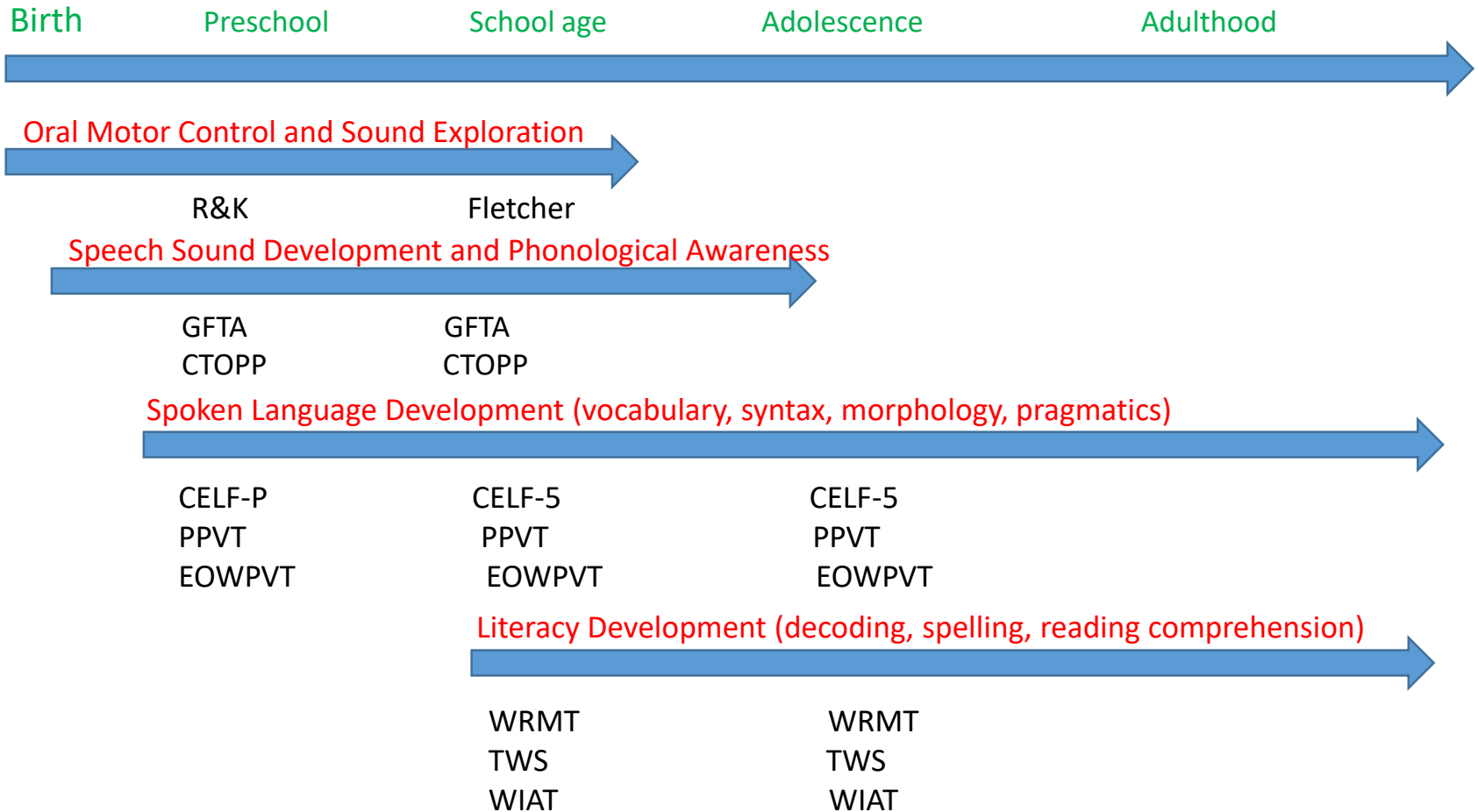
Dosage sensitivity

Recent work has shown that deletions and duplications not only affect clinical outcome due to their effect on coding (exonic) regions, but dosage sensitivity as a whole is important ^{13,14}. In fact, some regions may not contain genes, but the deletion of these regions can still have a phenotypic impact. Recent work has evaluated the probability of phenotypic implications of deletions (pHaplo) and duplications (pTriplo) at a gene level ¹⁴ and also categorization of CNV effects for regions of the genome ¹⁵. We utilized the supplemental data provided by Collins et al. and CNV-ClinViewer to examine the potential impact of deletions and duplications on coding genes and entire regions, respectively. These results are included in **Table 3**.

- 1 American-Speech-Language-Hearing-Association. *Childhood Apraxia of Speech [Technical Report]*, 2007).
- 2 Benchek, P., Igo, R. P., Jr., Voss-Hoyne, H., Wren, Y., Miller, G., Truitt, B. *et al.* Association between genes regulating neural pathways for quantitative traits of speech and language disorders. *NPI genomic medicine* **6**, 64, doi:10.1038/s41525-021-00225-5 (2021).

- 3 Stein, C. M., Benchek, P., Miller, G., Hall, N. B., Menon, D., Freebairn, L. *et al.* Feature-driven classification reveals potential comorbid subtypes within childhood apraxia of speech. *BMC pediatrics* **20**, 519, doi:10.1186/s12887-020-02421-1 (2020).
- 4 Lewis, B., Freebairn, L. & Taylor, H. Follow-up of children with early expressive phonology disorders. *Journal of Learning Disabilities* **33**, 433-444 (2000).
- 5 Lewis, B. A., Avrich, A. A., Freebairn, L. A., Hansen, A. J., Sucheston, L. E., Kuo, I. *et al.* Literacy outcomes of children with early childhood speech sound disorders: impact of endophenotypes. *J Speech Lang Hear. Res* **54**, 1628-1643 (2011).
- 6 Lewis, B. A., Avrich, A. A., Freebairn, L. A., Taylor, H. G., Iyengar, S. K. & Stein, C. M. Subtyping Children With Speech Sound Disorders by Endophenotypes. *Top Lang Disord* **31**, 112-127 (2011).
- 7 DuPaul, G. P., TJ; Anastopoulos, AD; Reid, R. (Guilford Press, 1998).
- 8 Lewis, B. A., Benchek, P., Tag, J., Miller, G., Freebairn, L., Taylor, H. G. *et al.* Psychosocial Comorbidities in Adolescents With Histories of Childhood Apraxia of Speech. *Am J Speech Lang Pathol* **30**, 2572-2588, doi:10.1044/2021_ajslp-21-00035 (2021).
- 9 Lewis, B. A. M., G; Iyengar, SK; Stein, CM; Benchek, P. Long-term Outcomes for Individuals with Childhood Apraxia of Speech. *Journal of Speech, Language, and Hearing Research* (in press).
- 10 Han, L., Zhao, X., Benton, M. L., Perumal, T., Collins, R. L., Hoffman, G. E. *et al.* Functional annotation of rare structural variation in the human brain. *Nature communications* **11**, 2990, doi:10.1038/s41467-020-16736-1 (2020).
- 11 MacDonald, J. R., Ziman, R., Yuen, R. K., Feuk, L. & Scherer, S. W. The Database of Genomic Variants: a curated collection of structural variation in the human genome. *Nucleic Acids Res* **42**, D986-992, doi:10.1093/nar/gkt958 (2014).
- 12 Lek, M., Karczewski, K. J., Minikel, E. V., Samocha, K. E., Banks, E., Fennell, T. *et al.* Analysis of protein-coding genetic variation in 60,706 humans. *Nature* **536**, 285-291, doi:10.1038/nature19057 (2016).
- 13 Rice, A. M. & McLysaght, A. Dosage-sensitive genes in evolution and disease. *BMC biology* **15**, 78, doi:10.1186/s12915-017-0418-y (2017).
- 14 Collins, R. L., Glessner, J. T., Porcu, E., Lepamets, M., Brandon, R., Lauricella, C. *et al.* A cross-disorder dosage sensitivity map of the human genome. *Cell* **185**, 3041-3055.e3025, doi:10.1016/j.cell.2022.06.036 (2022).
- 15 Macnee, M., Pérez-Palma, E., Brünger, T., Klöckner, C., Platzer, K., Stefanski, A. *et al.* CNV-ClinViewer: enhancing the clinical interpretation of large copy-number variants online. *Bioinformatics* **39**, doi:10.1093/bioinformatics/btad290 (2023).

Measures assessed for Speech and Language Development across the Lifespan



Legend, Supplemental Figure 1. Measures assessed for Speech and Language Development across the Lifespan. The figure provides a timeline for the assessment of oral and written language development. As shown first, the systemic mapping of oral motor movements with acoustic targets begins in infancy and forms the basis of speech sound production (phonemes), corresponding with the child's native language. Assessments of oral motor control (R & K, Fletcher) and speech sound production (GFTA) provide information about these early developing skills. By preschool age, children are beginning to develop oral language that will eventually match an adult model. Measures of receptive vocabulary (PPVT) and expressive vocabulary (EOWPVT), language processing and production (CELF-P and CELF-5) and phonological awareness (CTOPP) provide information about a child's developmental trajectory towards mature oral communication skills. Oral language skills form the foundation for written language and are measured by decoding (WRMT), spelling (TWS), and reading comprehension (WIAT). R & K = Robbins and Klee Oral and Speech Motor Control Protocol; Fletcher = Fletcher Time-by-Count Test of Diadochokinetic Syllable Rate; GFTA = Goldman-Fristoe Test of Articulation; CTOPP = Comprehensive Test of Phonological Processing; PPVT = Peabody Picture Vocabulary; EOWPVT = Expressive One-Word Picture Vocabulary Test; CELF-P = Clinical Evaluation of Language Fundamentals, Preschool; CELF-5 = Clinical Evaluation of Language fundamentals-Fifth Edition; TWS = Test of Written Spelling; WRMT = Woodcock Reading Mastery Test; WIAT = Wechsler Individual Achievement Test, Reading Comprehension

Supplemental Table S1.

Inclusion Criteria for CAS by Participant

	50	70	107	135	207	410	434	1013	1018	1025	1092	1124	1128 [^]	1159
Inconsistent Speech Production														
Inconsistency or variability of errors	+	+	+	+	+	+	+	+	+	+	+	+		+
Variability in use of syllable shapes		+	+	+			+	+	+	+	+	+		+
Variability in the use of consonant types and errors	+	+	+	+	+	+	+	+	+	+	+			+
Variability of errors increases with increasing length of utterance	+	+		+	+	+	+	+	+	+	+	+	+	+
Variability may occur in the repeated production of the same lexical item	+		+	+		+	+			+	+			
Altered Prosody														
Prosodic disturbances	+					+		+				+	+	
Equal Stress or Lexical Stress Errors	+													
Prolongation errors	+				+	+	+	+						
Vowel Errors/Distortions	+						+		+					+
Altered characteristics of rate, pitch and loudness which may alter intelligibility	+		+	+		+	+		+	+		+	+	+
Lengthened Transitions														
Slowed DDK rates and/or disrupted DDK sequence	+	+	+	+		+	+	+	+	+	+		+	+
Difficulty sequencing phonemes and syllables	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Voicing errors	+	+	+			+	+	+	+	+	+			
Nonphonemic productions (glottal plosives)						+					+			
Errors increase with word length and phonological complexity	+	+		+	+	+	+	+	+	+	+	+	+	+
Difficulty maintaining syllable integrity		+		+	+	+	+	+	+	+	+	+		+
Nasality issues and/or nasal emission			+										+	+

Note. [^]Initial research assessment was between 7;4 and 14;3 years of age.

Inclusion Criteria for CAS by Participant

	1171 [^]	1174 [^]	1188	1200	1209	1220	1229 [^]	1293 [^]	1302	1315	1317	1361	1394 [^]	1398
Inconsistent Speech Production														
Inconsistency or variability of errors		+	+	+	+	+		+	+		+	+	+	+
Variability in use of syllable shapes		+	+	+	+				+		+	+	+	+
Variability in the use of consonant types and errors		+	+	+	+	+		+			+	+	+	+
Variability of errors increases with increasing length of utterance		+	+	+	+	+	+	+	+		+	+	+	+
Variability may occur in the repeated production of the same lexical item		+	+				+						+	+
Altered Prosody														
Prosodic disturbances				+	+			+				+	+	
Equal Stress or Lexical Stress Errors		+			+									+
Prolongation errors		+												
Vowel Errors/Distortions		+	+	+	+	+	+	+	+		+	+		
Altered characteristics of rate, pitch and loudness which may alter intelligibility			+	+	+		+	+			+	+	+	+
Lengthened Transitions														
Slowed DDK rates and/or disrupted DDK sequence	+	+	+	+	+	+	+	+	+		+	+	+	+
Difficulty sequencing phonemes and syllables	+	+	+	+	+	+	+	+	+		+	+	+	+
Voicing errors		+	+	+					+		+	+	+	+
Nonphonemic productions (e.g., glottal plosives)				+							+	+	+	+
Errors increase with word length and phonological complexity		+	+	+	+	+	+	+	+		+	+	+	+
Difficulty maintaining syllable integrity		+	+	+	+				+		+	+	+	+
Nasality issues and/or nasal emission							+							

Note. [^]Initial research assessment was between 7;4 and 14;3 years of age.

Supplemental Table S2. Measures¹ of Endophenotypes and Core Symptom Domains at Early Childhood and School Age		
Domain	Time 1 Measures (Early Childhood, ages 3-6)	Time 2 and 3 Measures (School-age (age 7-11) /Adolescent (age 12+))
Speech sound articulation	GFTA; Speech sample Multisyllable Real and Non-Word Repetition	GFTA; Speech sample Multisyllable Real and Non-Word Repetition
Motor Speech Skills <i>Oral Motor Function</i> <i>Syllable Sequencing</i>	Robbins & Klee Oral Motor Protocol	The Fletcher time-by-count test of diadochokinetic syllable rate
Receptive and Expressive Spoken Language	CELF-P or TOLD-P	CELF
Receptive and Expressive Vocabulary	PPVT (Receptive); EOWPVT (Expressive)	PPVT (Receptive); EOWPVT (Expressive)
Literacy	Not assessed at Time 1	WRMT (Word Attack and Word ID); TWS; TOWRE; WIAT
Phonological Awareness	CTOPP Elision	CTOPP Elision
Rapid Automatized Naming	CTOPP Rapid Color Naming	CTOPP Rapid Color Naming
ADHD	DuPaul Pre-school scale	DuPaul scale
Other clinical outcomes (fine motor, etc)	Developmental History Questionnaire	Developmental History Questionnaire
Note: ¹ For all measures the most current edition of the test was administered at each assessment. CTOPP=Comprehensive Test of Phonological Processing; PPVT=Peabody Picture Vocabulary Test; EOWPVT=Expressive One Word Picture Vocabulary Test; GFTA=Goldman Fristoe Test of Articulation; CELF-P=Clinical Evaluation of Language Fundamentals-Preschool; CELF=Clinical Evaluation of Language Fundamentals; WRMT=Woodcock Reading Master Test; TWS=Test of Written Spelling; TOWRE=Test of Word Reading Efficiency; WIAT=Wechsler Individual Achievement Test.		

Supplemental Table S3.

Speech, Language, and Literacy Measures by CAS Participant

	50	70	107	135	207	410	434	1013	1018	1025	1092	1124	1128 [^]	1159
Speech Measures														
Speech sound articulation	+	+		+		+	+	+	+	+	+	+		+
Multisyllable real word repetition	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Multisyllable nonword repetition	+	+	+	+	+	+	+	+	+	+	+		+	+
Oral motor function/Syllable Sequencing	+	+		+		+	+	+	+	+	+		+	+
Persistence of speech sound errors at the last assessment (older than 8;5 years)	+		+	+		+	+			+		+	+	+
Language Measures														
Receptive Language	+		+	+		+	+				+		+	
Expressive Language	+	+	+	+		+	+	+	+	+			+	+
Total Language	+		+	+		+	+		+				+	
Receptive vocabulary	+						+						+	
Expressive vocabulary	+											+	+	+
Literacy Measures														
Single real word decoding			+				+			+		+	+	+
Single nonword decoding	+		+				+		+				+	
Single word fluency	+	–	+	–			–		–		–		+	+
Reading Comprehension	+	–	+	+			+		–		–	+	+	+
Phonological Awareness							+		+			+	+	+
Rapid Automatized Naming	+					+					+		+	+
Spelling	+		+			+	+		+	+			+	+
Cluster analysis derived severity	1	NA	2	2	3	2	1	3	2	3	3	1	1	1

Note. All assessment data was taken from the earliest time point available except persistence data which was measured when the participant was older than 8;5 years; + indicates a score $\leq 1\ SD$ (85); – indicates missing data; ^7;4 – 14;3 years. Cluster severity 1 indicates most severe; 2 moderately severe; 3 mild in severity; NA missing data.

CNV SUPPLEMENTAL INFORMATION

Speech, Language and Literacy Measures for CAS by Participant

	1171	1174	1188	1200	1209	1220	1229 [^]	1293 [^]	1302	1315	1317	1361	1394 [^]	1398
Speech Measures														
Speech sound articulation		+	+	+	+		+		+		+	+	+	+
Multisyllable real word repetition	+	+	+	+	+	+	+		+	+		+	+	+
Multisyllable non-word repetition		+	+	+	+	+			+	+		+	+	+
Oral motor function/Syllable Sequencing		+	+	+	+	+	+	+	+		+	+	+	+
Persistence of speech sound errors at the last assessment (older than 8;5)		+	+	+	+	+	+	+	U				+	+
Language Measures														
Receptive Language	+	+		+				+			+			
Expressive Language	+	+	+	+				+			+	+		+
Total Language	+	+	+	+				+			+			
Receptive vocabulary	+		+	+				+						
Expressive vocabulary		+	+	+									+	
Literacy Measures														
Single real word decoding	+		+	+	+	+		+	-				+	
Single nonword decoding	+		+	+		+		+	-				+	
Single word decoding fluency	-		+		+	+		+	-				+	-
Reading Comprehension	+		+	+	+			+	-				+	-
Phonological Awareness	+		+	+	+			+	-				+	
Rapid Automatized Naming	+				+			+					+	+
Spelling	+		+	+	+	+		+	-				+	
Cluster analysis derived severity	1	3	1	1	2	2	3	1	NA	NA	3	3	2	2

Note. All assessment data was taken from the earliest time point available except persistence data which was measured when the participant was older than 8;5 years; + indicates a score $\leq 1 SD$ (85); - indicates missing data; ^7;4 – 14;3 years; U = unknown. Cluster severity 1 indicates most severe; 2 moderately severe; 3 mild in severity; NA missing data.

Supplemental Table 4. CNVs that do not segregate with binary trait within family						
Family no.	Patient no.	Relationship (sex)	Copy no.	Genome Co-ordinates (hg 19)	Traits ⁺	
F0033	P0135	Proband (M)	3	7:88339640-89933766	Apraxia, Speech, Lang,	
	P0138	Sibling (M)	2	7:88339640-89933766	Speech, Stutter	
	P0433	Sibling (F)	3	7:88339640-89933766	Speech	
	P0137	father	2	7:88339640-89933766		
F8025	P1092	Proband (F)	3	4:113373779-113750065	Apraxia, Speech, Lang	
	P1093	Sibling (F)	3	4:113373779-113750065	Speech	
	P1094	Sibling (F)	2	4:113373779-113750065	Speech, Lang	
	P1095	Sibling (M)	2	4:113373779-113750065		
	P5072	mother	2	4:113373779-113750065		
	P5073	father	3	4:113373779-113750065		
F0048	P0207	Proband	1	18:1903069-1969519	Apraxia, Speech	
	P0210	Sibling	1	18:1903069-1969519	Speech, Lang	
	P0211	Sibling	2	18:1903069-1969519	Speech, Lang	
	P209	Father	2	18:1903069-1969519		
	P208	Mother	1	18:1903069-1969519		

If parent not listed, parent was not genotyped (DNA unavailable)

* Predicted duplication in this family, was confirmed in another family

⁺ Phenotypes determined by direct testing of children. Parents were not directly tested.

Supplemental Table S5.

Sibling Phenotypes

Family (FID)	FID0033		FID8008	FID8107		FID0074		FID8055	FID8061		FID8025			FID8066		FID8060		FID8049		
Sibling ID	138	433	1019	1303	1304	411	415	1158	1175	1176	1093	1094	1095	1189	1190	1172	1173	1127	1129	1130
Speech Sound Measures																				
Speech sound articulation		+		+	+					+	+	+		+						#
Multisyllable real word repetition	+	+		+	+	+	+	+				+	+	+	+	+	+			
Multisyllable non word repetition	+	+		+	+	+	+	+			+	+	+	+	+	+	+			
Oral motor function/Syllable sequencing		+			+					+					+					
Fluency	#																			
Language Measures																				
Receptive Language						+	+	+					+	+	+	+	+			
Expressive Language					+	+	+	+					+			+	+			
Total Language						+	+	+					+	+		+	+			
Receptive vocabulary																	+			
Expressive vocabulary																	+			
Literacy Measures																				
Single real word decoding					*	+									+		+			
Single non-word decoding					*	+						+	+	+	+		+			
Single word fluency	—	—	—	—	—	+					—	—	+		+	—	—	—	—	—
Reading Comprehension					*	+							+		+		+			—
Phonological Awareness					*	+						+	+		+		+			
RAN					*	+									+					
Spelling	+				*	+	+	+				+	+	+	+		+			—

Note. All assessment data was taken from the earliest time point available; + indicates a score $\leq$ SD 85; — indicates missing data; * = too young to assess; # speech disorder reported by parent; RAN = Rapid Automatized Naming

Supplemental Table S6.

Clinical Manifestations by Parent Report by Participant

	50	70	107	135	207	410	434	1013	1018	1025	1092	1124	1128	1159
Clinical Manifestations														
Problems with Feeding/Eating/Oral Motor	+					+	+					+	+	+
Delayed language onset				+			+	+	+	+				+
Gross motor incoordination				+			+			+			+	+
Fine motor incoordination	+		+	+		+	+	+	+				+	
ADHD	+		+		+		+		+			+		+

	1171	1174	1188	1200	1209	1220	1229	1293	1302	1315	1317	1361	1394	1398
Clinical Manifestations														
Problems with Feeding/Eating/Oral Motor			+		+				+					+
Delayed language onset		+	+	+	+	+	+	+	+	+	+	+	+	
Gross motor incoordination			+		+	+					+		+	
Fine motor incoordination			+	+	+			+			+		+	
ADHD	+	+	+	+				+		+	+		+	+

Note. + indicates parent reported clinical manifestation.

Supplemental Table 7. Replication of CNVs in probands in microarray data

Locus	Number of children with type of variant		Phenotypes of children		
	Deletion	Duplication	CAS	SSD+LI	SSD only
2:97735774-97804498	2			1	1
2:132718104-132979733	2	2	1	3	
4:168808644-168993082		1		1	
4:189241227-189512452	3			2	1
5:59,710570-59769304		1		1	
8:137680264-137735693	6		2	2	2
10:45208524-45336137		1			1
16:29581236-30197928	1			1	