Childhood apraxia of speech and dysarthria in rare monogenic disorders

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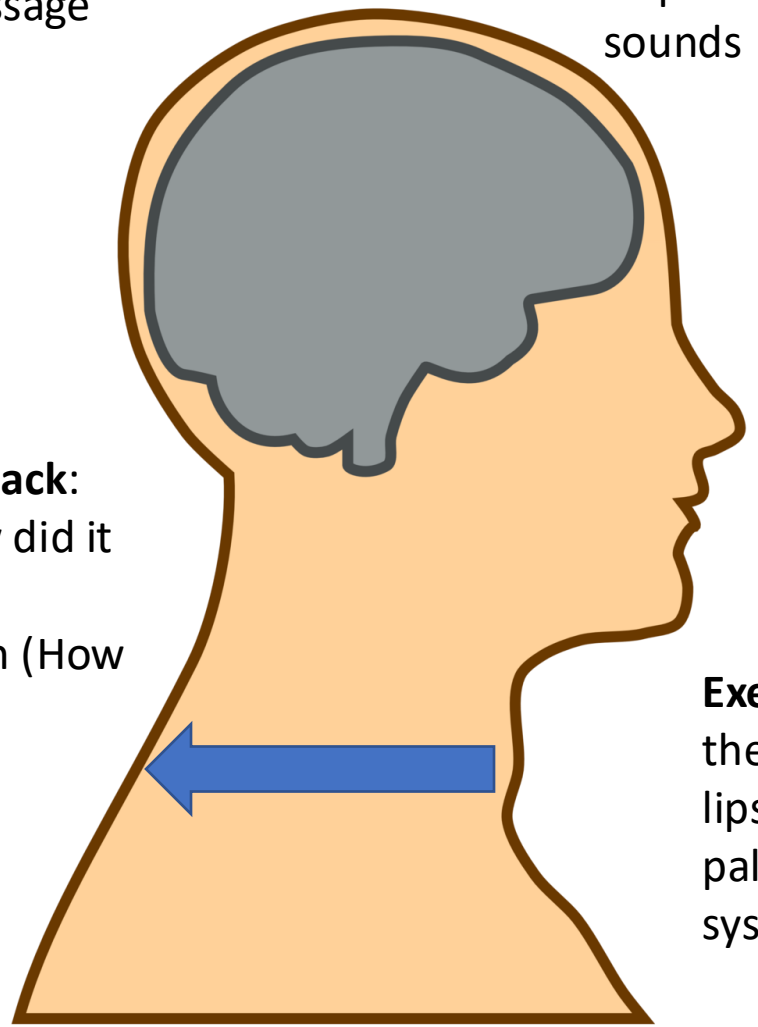
Overview

- What are motor speech disorders (MSDs)?
- Rare monogenic disorders identified through clinical exome sequencing among children with MSDs
- MSDs in MED13L-related disorder

What are motor speech disorders?

Cognitive linguistic stage: Decide to communicate and formulate message

Transcoding: Plan and program the sequence of motor movements required to produce sounds

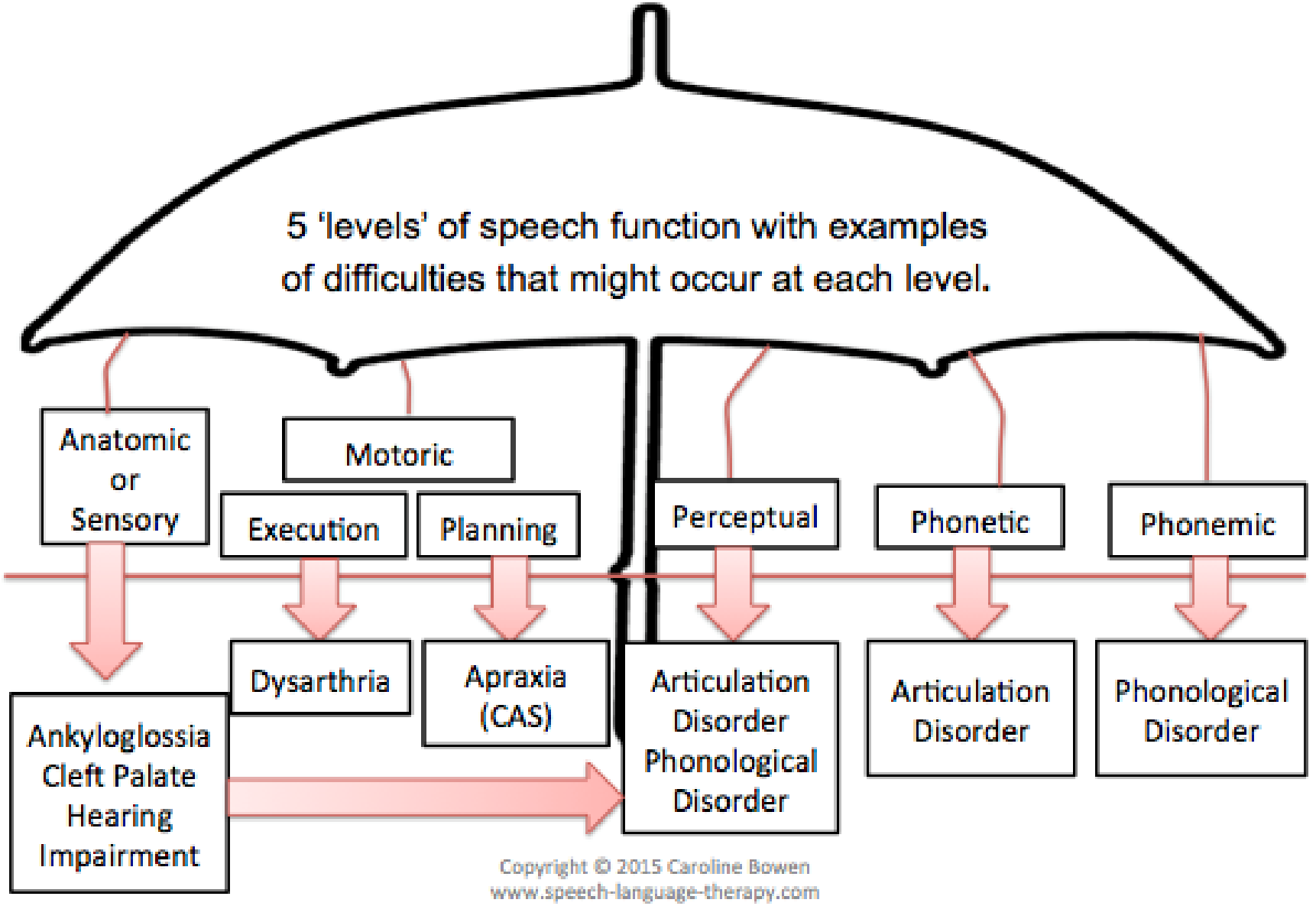


How does speech happen?

Sensory feedback: Auditory (How did it sound?) Proprioception (How did it feel?)

Execution: Carry out the motor plan using lips, tongue, jaw, soft palate, respiratory system

Children's Speech Sound Disorders



Motor speech disorders (MSDs)

- Speech sound disorders (problems with articulation) caused by deficits in **motor planning/programming** or **execution**
  - Childhood apraxia of speech (CAS)
  - Dysarthria
  - Speech motor delay/ Motor speech disorder-NOS

- Low population prevalence (~1 in 1000 children ages 4-8)

- More common in certain populations:
  - Complex neurodevelopmental disorders
  - Certain genetic disorders (16p11.2 deletions, 22q11.2 deletions, *SETBP1*-related disorder; *FOXP2* LoF variants)

Rare monogenic disorders identified through clinical exome sequencing among children with MSDs

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Objectives

- Leverage clinical exome sequencing (ES) data for largest cohort of children with MSDs to date in order to:
  - Identify new genes associated with MSDs
  - Determine whether certain genes are statistically over-represented among children with MSD phenotype compared to others undergoing clinical ES
  - Evaluate the molecular diagnostic yield of ES as a function of sex and neurodevelopmental comorbidity

Participants

- Participants were 2,004 children with apraxia or dysarthria, ages 2-21, who underwent clinical exome sequencing with CNV detection
- Participants with hearing impairment or absent speech excluded
- Further categorized by co-morbid neurodevelopmental diagnosis (GDD or ID, ASD, motor impairment, seizures)

Methods

- Pathogenicity of variants evaluated using ACMG/AMP guidelines
- Multivariable logistic regression models used to estimate associations between comorbid neurodevelopmental diagnoses and presence of positive genetic finding
- Gene-based burden analysis compared frequency of pathogenic variants in MSD group (N=2,004) to frequency of pathogenic variants in a general clinical exome sequencing referral cohort (N=65,790)
  - To identify genes with the highest likelihood of association with MSD phenotype

Results: ES Yield and Comorbidity Analysis

- Positive diagnostic result in 527 of 2004 (26.3%)
- Significantly higher for females (31.8%) than males (22.8%)
- No significant difference in diagnostic yield between CAS (26.7%) and dysarthria (26.0%) [p>.99]
- Individuals with co-morbid NDDs 58% more likely to have positive genetic finding

Results: Genomic Findings

- Out of 527 with positive genomic findings, 495 (94%) had sequence variants and 32 (6%) had CNVs

- Pathogenic/likely pathogenic variants detected in 262 genes
  - 102 genes with variants in 2 or more
  - 24 genes with variants in 5 or more

- 29 unique CNVs
  - 5 cases of 16p11.2 deletion

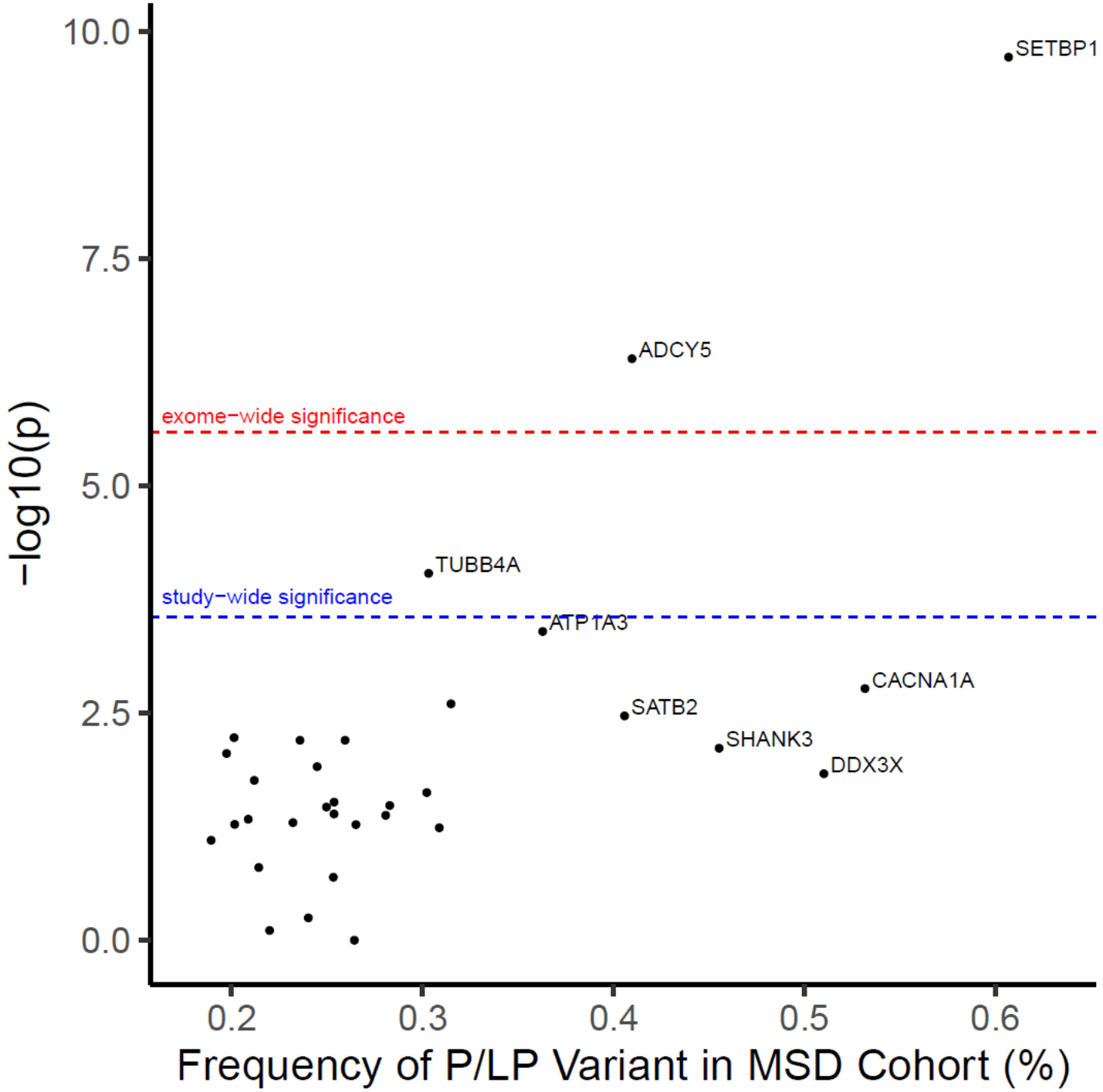
Frequency of MSD Phenotype for Genes with P/LP Variants in ≥6 Cases

Gene	Number of cases with P/LP variant in MSD cohort (N = 2004)	CAS	Dysarthria
SETBP1	12	11	1
CACNA1A	11	4	8
DDX3X	10	9	2
SHANK3	9	6	3
ADCY5	8	0	8
SATB2	8	7	1
ATP1A3	7	1	6
ADNP	6	4	2
CTNNB1	6	0	6
GNAO1	6	0	6
MED13L	6	6	0
POGZ	6	3	3
TUBB4A	6	1	5

Results: Gene-Based Burden Analysis

- Used case-referent analysis to examine if any genes statistically more likely to harbor P/LP variants in MSD group (cases) compared to the remainder of the ES cohort (referent)

Gene	Frequency in MSD Cohort (N=2004)	Frequency in Larger ES Cohort (N=65790)	Odds Ratio
MED13L	6 (0.25%)	80 (0.12%)	2.47
CTNNB1	6 (0.25%)	87 (0.13%)	2.27


10.0
7.5
5.0
2.5
0.0
−log10(p)
SETBP1
ADCY5
exome−wide significance
TUBB4A
study−wide significance
ATP1A3
CACNA1A
SATB2
SHANK3
DDX3X
0.2
0.3
0.4
0.5
0.6
Frequency of P/LP Variant in MSD Cohort (%)

Conclusions

- High genetic diagnostic rate overall (26.3%), with higher rate among females and those with NDDs
- First study to examine genetic underpinnings of MSDs other than CAS; found similar diagnostic yield between CAS and dysarthria
  - Variants in the same gene typically detected in individuals with different MSDs, consistent with well-documented variable expressivity of variants associated with NDDs
- Many new genes implicated in MSDs
- *MED13L and CTNNB1* were prevalent findings in MSD cohort and may be overrepresented among individuals with MSDs compared to other children undergoing clinical ES

Motor speech disorders in MED13L

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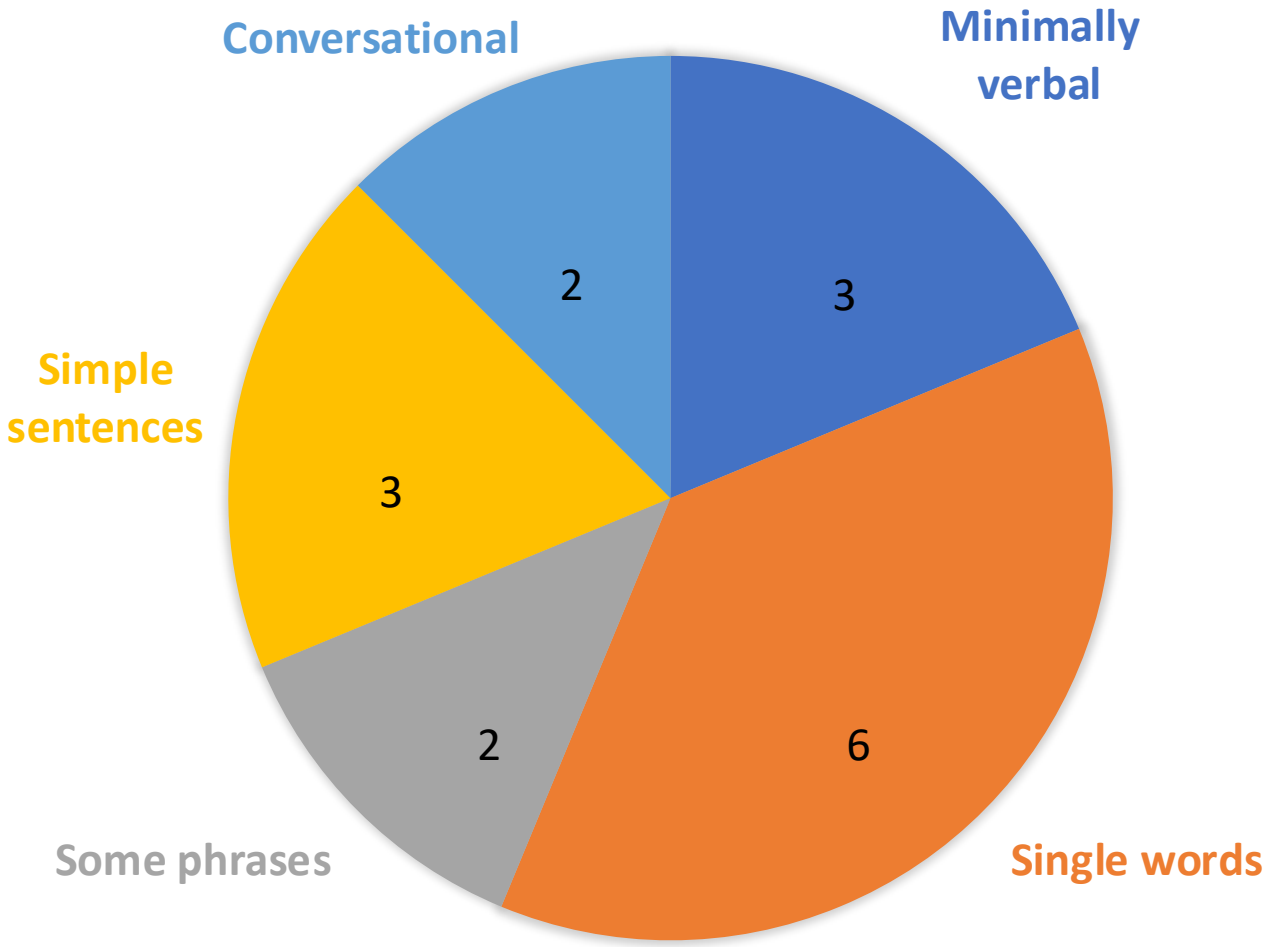
MED13L-related disorder associated with severe motor speech impairment phenotype

Aim: To characterize the speech, language, motor, cognitive, and adaptive phenotype of individuals with *MED13L*-related disorder.

Cohort (N)	Domain	Assessment Protocol (n)
In-Person (17)	Speech	GFTA-3 (12)
		DEMSS (4)
		ProCAD (14)
	Language	PPVT-5 (14)
		EVT-3 (13)
	Cognition	MSEL (3)
		DAS-2 (6)
		KBIT-2 (6)
	Visual Motor	Beery VMI (15)
Virtual (67)	Medical and Developmental	Medical history interview (59)
		Seizure survey (65)
		Developmental history interview (67)
		EHR review (1)
	Adaptive	VABS-3 (47)
	Behavior	CBCL 1.5-5 years (31)
		CBCL 6-18 years (25)

Results: In-Person Cohort (N=17)



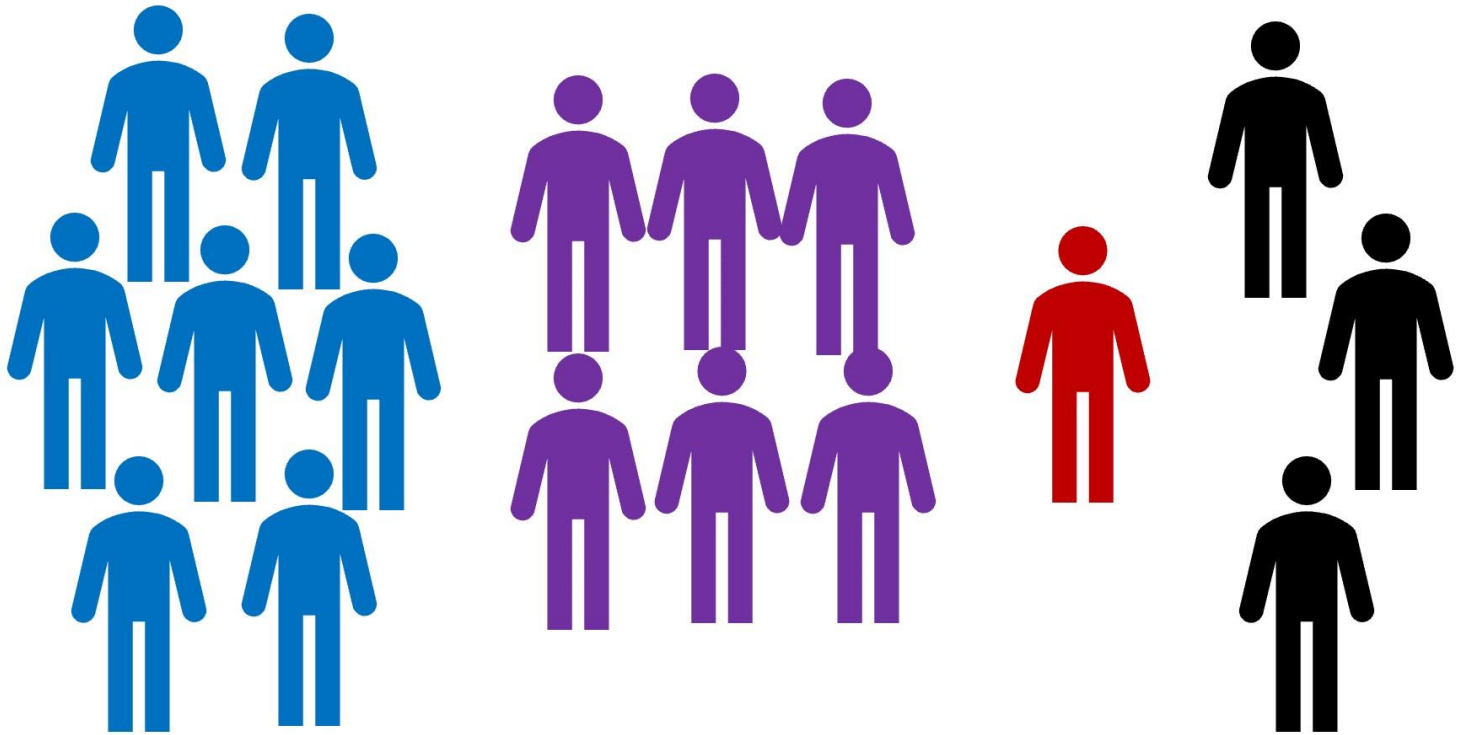
7 (41%) use some form of AAC

- 6 speech-generating devices
- 1 sign language

9 (53%) report oral-motor dysfunction

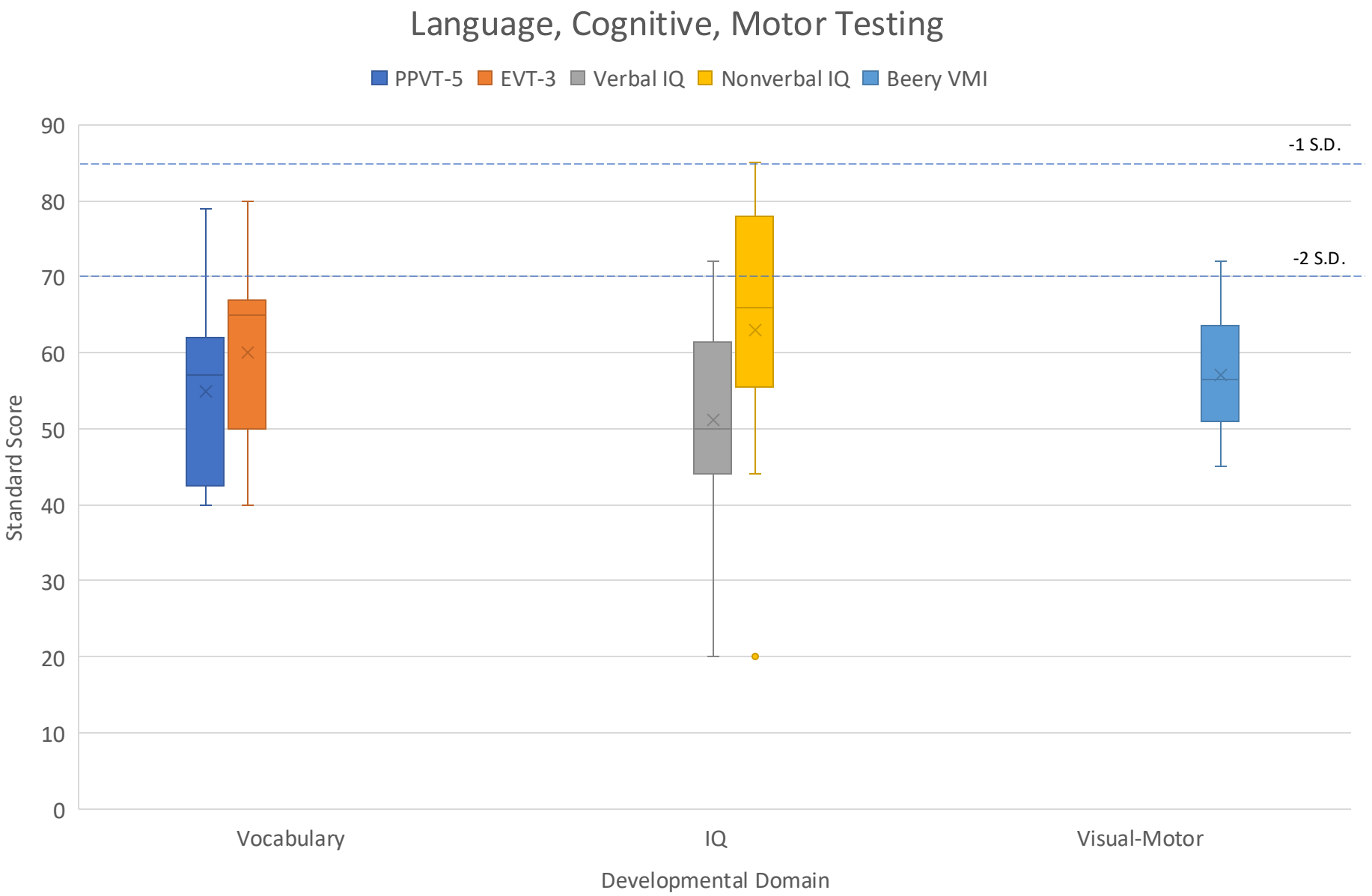
- 6 difficulty feeding in infancy
- 4 drooling in later childhood
- 2 open-mouth posture

Speech Phenotype (N = 17)

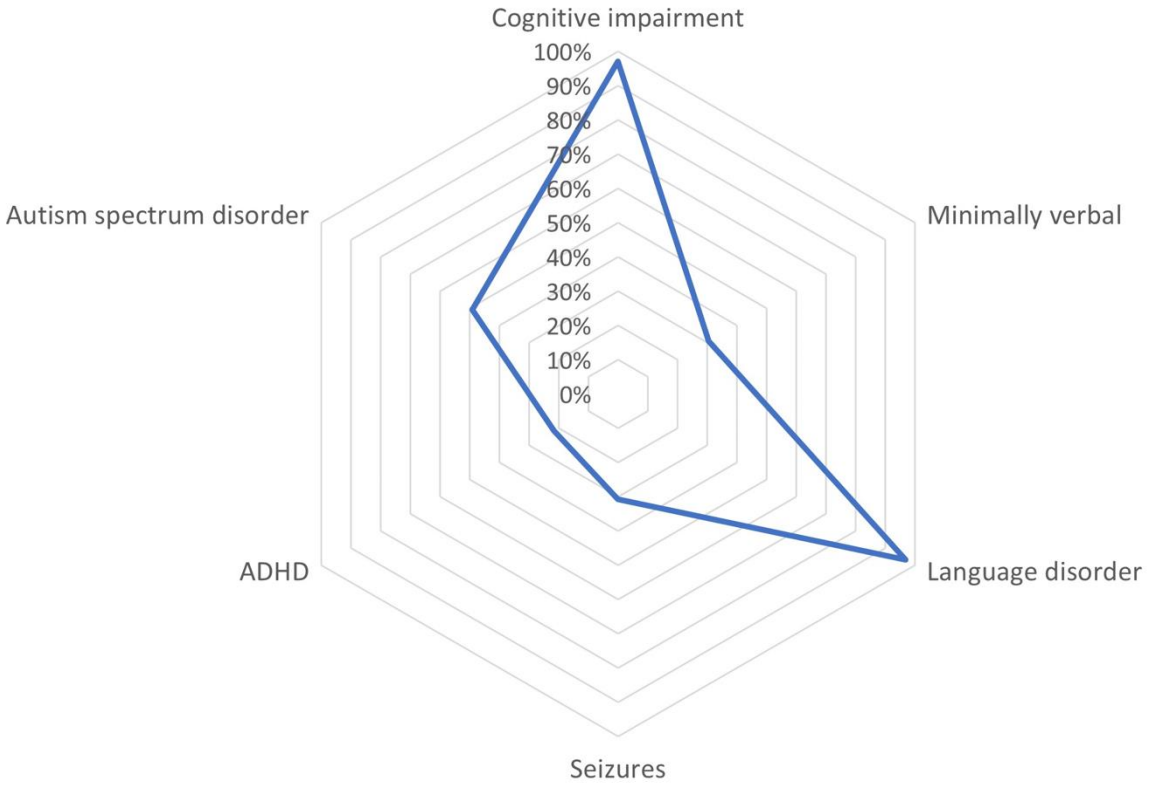


CAS only = 7. CAS + Dysarthria = 6. Dysarthria only = 1.

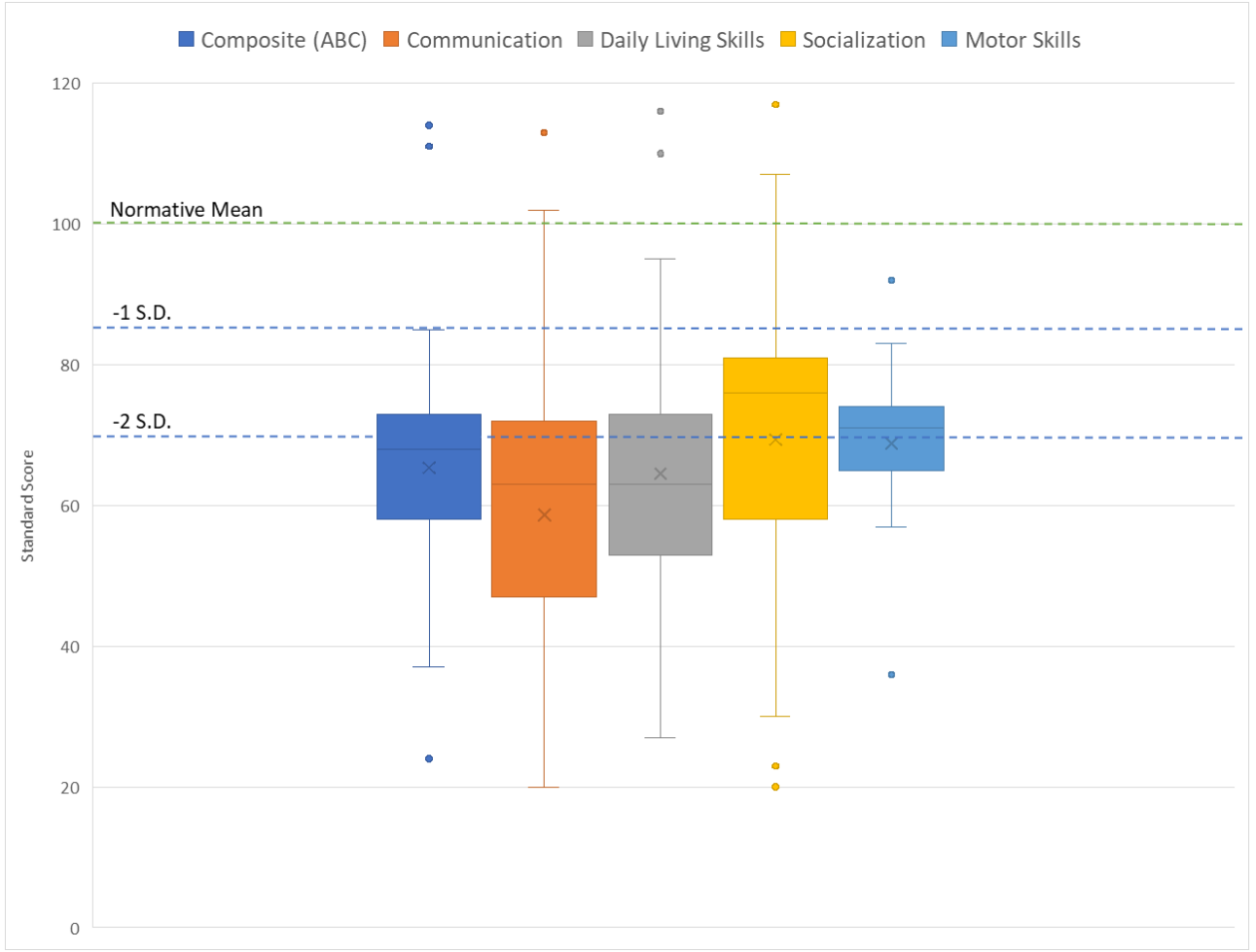
Minimally Verbal = 3.


Language, Cognitive, Motor Testing
PPVT-5
EVT-3
Verbal IQ
Nonverbal IQ
Beery VMI
90
80
70
60
50
40
30
20
10
0
Standard Score
-1 S.D.
-2 S.D.
Vocabulary
IQ
Visual-Motor
Developmental Domain

Results: Virtual Cohort (N=67)



Neurodevelopmental Diagnoses



Vineland Adaptive Behavior Scale

Conclusions

- All individuals who completed in-person phenotyping met criteria for a diagnosis of MSD (CAS, dysarthria, or both)
- Commensurate receptive and expressive language impairment
- Better nonverbal compared to verbal IQ
- Significant global motor impairment common

Clinical Implications

- Children with known P/LP variants in *MED13L* would benefit from early referrals to speech therapy

- Low threshold for suspicion of MSDs in children with *MED13L*-related disorder
  - Evidence-based motor learning techniques should be incorporated
  - High frequency and intensity of therapy

- AAC strategies, including use of speech-generating devices, should be carefully considered during initial assessment

Questions?

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Thank you to all our participating families! We couldn’t do it without you!