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ARTICLE

Speech and language deficits are central to *SETBP1* haploinsufficiency disorder

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About the Authors:
In the SETBP1 Society's April edition of Bite-sized Breakthroughs, we highlight Angela Morgan's work on speech and language deficits in SETBP1 haploinsufficiency disorder (SETBP1-HD), published in the European Journal of Human Genetics in 2021. This paper is a cornerstone for ongoing international efforts to investigate expressive communication impairment in the SETBP1-HD community.

Background:
Before this publication speech and language deficits were only reported in small case series studying independent cohorts containing heterozygous loss of function (LoF) variants in *SETBP1* with childhood apraxia of speech. While *SETBP1* had previously been proposed as a candidate gene for expressive speech disorder, the additional support in the literature to confirm these suspicions was lacking, as the main focus in the SETBP1-HD research field had largely been focused on the neurodevelopmental presentation of affected individuals. This paper examined the nature of speech deficits in SETBP1-HD as the specifics of apraxia in individuals with *SETBP1* LoF variants remained unclear. While additional previous genome-wide association studies have reported associations between *SETBP1* and differences in the mean length of sentences and use of complex sentence structures (see Caglayan et al. in resources) as well as altered phonological working memory (see Perdue et al. in resources) the extent of these differences and their link to speech and language deficits observed in affected individuals is still under investigation in the SETBP1-HD community.

Main Findings:
Most papers before this one have relied on retrospective examinations of medical records from a handful of individuals, whereas Morgan's work provides an in-depth examination of speech and language abilities across 31 individuals ranging from infancy to adulthood with variants and deletions in the *SETBP1* gene. To be included in the study, participants had to have a genetic diagnosis of a heterozygous *SETBP1* variant or an 18q12.3 deletion accompanied by a referral

from a physician. The final cohort for this study had 24 new cases that had not been previously reported.

To investigate the broader phenotypic profile of individuals with SETBP1-HD outside of neurodevelopment, the researchers focused on core features involving speech, language (expressive, receptive, written, and social), and adaptive behavior (language relative to daily functioning, social, and motor skills). Using a combination of surveys paired with clinical phonological, communication, and development profiles, they reveal that speech and language deficits are central to SETBP1-HD. A detailed outline of the specific categories investigated is detailed in the paper. The findings in this article expand the phenotype of SETBP1-HD beyond the previous neurodevelopmental profile to include expressive speech difficulties. Their findings indicate that “articulatory, spoken and written language (reading, writing) deficits are distinctive features of the broader neurodevelopmental profile.”

It is important to remember that there could be some clinical bias in subjective assessments of language comprehension as it is difficult to evaluate minimally verbal children and separate how the brain can process language from the motor contributions of some individuals. Additionally, a large portion of children in the study had autistic features but lacked a formal ASD diagnosis however; there was limited evidence in this study for an ASD signature associated with SETBP1 LoF variants.

What does this mean for SETBP1-HD:
The evidence provided in this article helps to strengthen the SETBP1 gene’s position as a speech impairment gene from its previous role as a suspected candidate. As a result, SETBP1 should be considered a strong candidate for speech and language disorders, and additional research in this area has been underway since 2021.

Morgan’s work emphasizes a need for regular speech surveillance to enable targeted speech therapy for particular age groups within SETBP1-HD. In addition, it highlights a previously unrecognized potential benefit for including early speech intervention as a critical new standard of clinical care for SETBP1-HD in the first year of life. Furthermore, incorporating sign language or communication devices could aid in language before speech development. Finally, this research is paving the way for future clinical trials of intensive speech therapies in individuals with SETBP1 LOF variants.

Accessing the Review article:
The full review article titled “*Speech and language deficits are central to SETBP1 Haploinsufficiency disorder*” published in the *European Journal of Human Genetics* on April 27, 2021, can be accessed here: https://www.nature.com/articles/s41431-021-00894-x.pdf

Other related resources:
Caglayan AO, et al. Genome-wide association and exome sequencing study of language disorder in an isolated population. Pediatrics. 2016;137:e20152469. https://pubmed.ncbi.nlm.nih.gov/27016271/

Perdue MV, Mascheretti S, Kornilov SA, Jasińska KK, Ryherd K, Mencl WE, et al. Common variation within the SETBP1 gene is associated with reading-related skills and patterns of functional neural activation. Neuropsychologia 2019;130:44–51. https://pubmed.ncbi.nlm.nih.gov/30009840/

What are genome-wide association studies: https://medlineplus.gov/genetics/understanding/genomicresearch/gwastudies/

Conditions associated with genes for childhood apraxia: https://www.geneticsofspeech.org.au/genes/conditions-associated-with-candidate-genes-for-childhood-apraxia-of-speech/setbp1/

SETBP1 Speech Tracker Study: https://www.setbp1.org/speechtracker/

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