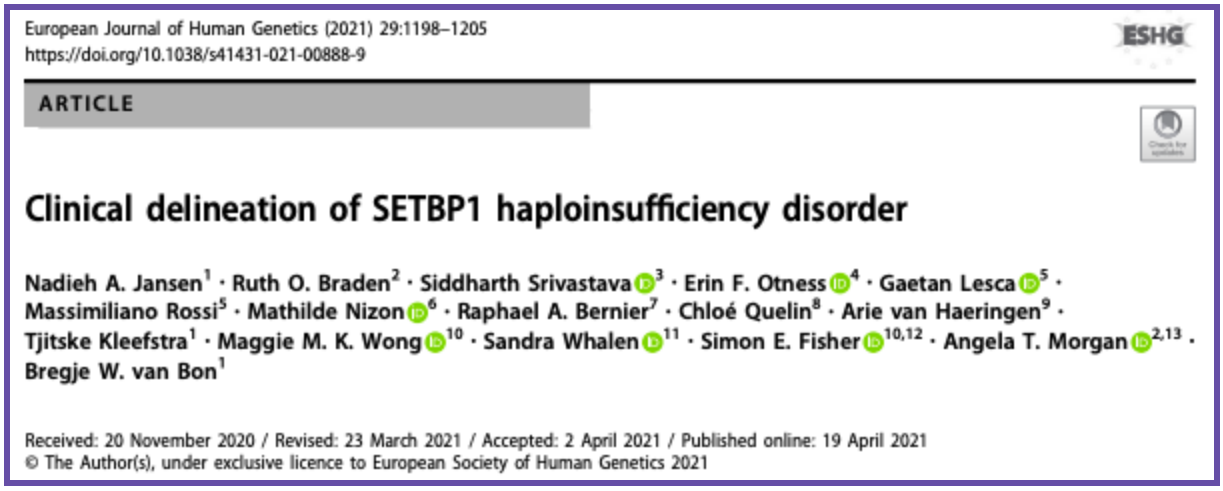

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ARTICLE

Clinical delineation of SETBP1 haploinsufficiency disorder

Nadieh A. Jansen[1] · Ruth O. Braden[2] · Siddharth Srivastava[3] · Erin F. Otness[4] · Gaetan Lesca[5] · Massimiliano Rossi[5] · Mathilde Nizon[6] · Raphael A. Bernier[7] · Chloé Quelin[8] · Arie van Haeringen[9] · Tjitske Kleefstra[1] · Maggie M. K. Wong[10] · Sandra Whalen[11] · Simon E. Fisher[10,12] · Angela T. Morgan[2,13] · Bregje W. van Bon[1]

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About the Authors:
This time, we are looking back at a breakthrough article published in the *European Journal of Human Genetics* in 2021 by Nadieh Jansen, MS, located at Radboud University Medical Center for our "SETBP1 Genetics: Bite-sized Breakthrough". In collaboration with multiple co-authors, including Dr. Bregje van Bon, Dr. Siddharth Srivastava, Dr. Simon Fisher, and Dr. Angela Morgan, all members of our SETBP1 Alliance Collaboration, this article highlights an international research effort between Australian, American, and European scientists. In 2010, some of these same researchers were responsible for identifying de-novo, otherwise referred to as a spontaneous, gain-of-function variants in SET Binding Protein 1 (*SETBP1*), and this work is a continuation of that through its clinical delineation of the loss-of-function *SETBP1* haploinsufficiency disorder.

Background:
Before the publication of this work, the scientific and clinical field has not systematically evaluated the major features and presentation of *SETBP1* haploinsufficiency disorder (SETBP1-HD). SETBP1-HD, also referred to as Mental Retardation Dominant 29 (MRD29), is the result of a heterozygous deletion resulting in a loss-of-function variant in the *SETBP1* gene. Haploinsufficiency of *SETBP1* means that having only one functioning copy of a gene is insufficient to produce the required amount of protein for normal cellular processes. In the case of SETBP1-HD, the variants introduced are expected to produce incomplete mRNA transcripts of *SETBP1* that are flagged for degradation in a process called nonsense-mediated decay therefore preventing the production of incomplete or abnormal SETBP1 protein. Overall, individuals with SETBP1-HD present with a milder phenotype than gain-of-function variants in *SETBP1* that cause Schinzel-Giedion Syndrome. This article delineates the clinical difference between SETBP1-HD and other SETBP1-associated syndromes.

Main Findings:
Before this article, only 10 cases with loss-of-function variants in *SETBP1* have been noted in the literature and the majority of the clinical data was not the main focus of these previous works. This study analyzed clinical data from 34 patients with a confirmed molecular diagnosis of SETBP1-HD. Only individuals with heterozygous loss-of-function variants or SETBP1 gene deletions in the coding region that did not cover adjacent genes were included to ensure a clearly defined phenotype. This work excluded any individuals with a potential secondary clinically relevant variant in another gene aside from *SETBP1*. In this article, Jansen categorizes the SETBP1-HD phenotype focusing on psychomotor development, growth parameters, behavior, neurology, dysmorphisms, congenital anomalies, and other clinical features. The authors' analysis reveals that the main clinical features of SETBP1-HD include mild to moderate developmental delay, a wide range of intellectual disability, seizures, and hypotonia with an absence of major motor problems at later ages. In addition, speech impairment, which has not previously been emphasized, was present in almost all children diagnosed. The main childhood behavior problems reported involved hyperactivity and attention deficit. Furthermore, less than half of individuals (48%) reported vision impairment. Notably, the lack of a recognizable, consistent facial gestalt across the SETBP1-HD cohort distinguishes these individuals from those with SGS.

What does this mean for SETBP1-HD:
This article is the first time anyone has focused on describing SETBP1-HD from a genotype-driven perspective. While the largest phenotypic study of SETBP1-HD thus far, this study consists of data from a rather small number of patients (34), and it will be interesting to see how the findings might evolve if a similar study was to be repeated with more subjects. The research reveals that the phenotypic spectrum of individuals with SETBP1-HD is more variable than previously thought. Additionally, with only 18% of individuals formally diagnosed with ADHD in this study, neuropsychological assessments could benefit a subset of children with SETBP1-HD as this could provide opportunities for specific personalized guidance at home and in schools. Additionally, the use of infants and preschoolers in this study provides a future opportunity to specifically look at ADHD phenotypes in older SETBP1-HD kids. Due to subtle overlapping facial dysmorphisms, most clinicians often diagnose patients with SETBP1-HD using whole exome sequencing or gene panels. While the researchers hoped to uncover a genotype-phenotype correlation, they noted instead that individuals with severe clinical presentations have variants throughout the *SETBP1* gene. The lack of a cluster or phenotypic hotspot allows future research to uncover how the location of specific variants leads to distinct clinical presentations within individuals. Future studies will need to focus on the potential underlying mechanism driving the difference in phenotype between SETBP1-HD and SGS individuals and the severity of clinical presentation between different variants within SETBP1-HD. While we know that SETBP1 is a transcriptional regulator that binds different promoter regions of the genome, its mechanisms at the molecular level that go awry in SETBP1-HD remain largely unknown. Jansen's 2021 article provides a foundation for the community to expand upon as researchers work to capture the entire presentation of SETBP1-HD. While SETBP1-HD is ultra-rare, this work most likely does not include all

individuals currently diagnosed with SETBP1-HD and emphasizes the need for future participation in similar studies to expand our clinical understanding of SETBP1-HD.

Special note: 20 of the participants in this study also participated in a separate investigation that delves deeper into the speech and language development of SETBP1-HD, which will be featured in an upcoming Bite-Sized Breakthrough.

Accessing the Review article:
The full review article titled "*Clinical delineation of SETBP1 haploinsufficiency disorder*" published in the *European Journal of Human Genetics* on April 19, 2021, can be accessed here: https://www.nature.com/articles/s41431-021-00888-9

Other related resources:
De novo mutations of SETBP1 cause Schinzel-Giedion syndrome. Nat Genet. 2010 https://doi.org/10.1038%2Fng.581

Speech and language deficits are central to SETBP1 haploinsufficiency disorder https://www.nature.com/articles/s41431-021-00894-x.pdf

ADHD Diagnostic Guidelines https://publications.aap.org/pediatrics/article/144/4/e20192528/81590/Clinical-Practice-Guideline-for-the-Diagnosis

Written by: Jordan Whitlock, PhD, member of the SETBP1 Society MSAB