**SETBP1 Genetics: Bite-sized Breakthroughs**
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# SETBP1 haploinsufficiency and related disorders clinical and neurobehavioral phenotype study

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**About the Authors:**
The first author of this Bite-Sized Breakthrough is Haley Oyler, (a name you may recognize as she is the SETBP1 Society president and fellow rare disease mama). As the lead principal investigator, Haley Oyler the president of SETBP1 Society drove the project forward with support from Trina Geye and Stephanie Robertson from Tarleton State University to publish the findings from the Searchlight SETBP1 registry. Other SETBP1 specialists helped the paper take shape from their input and expertise, including statistical analysis from Caitlin Hudac from USC, format and targeted publication expertise from Siddharth Srivastava from BCH, and paper review by Wendy Chung from BCH. Additional Searchlight interpretation support from Leeann Synder Greene.

**Background:**
The first step on the path to identifying targeted treatments in any disorder, especially rare ones, is the establishment of a well characterized presentation of a disorder. For many groups, this begins with a natural history and patient registry. Both of these were prioritized early on in the formation of the SETBP1 Society. This paper details the first in-depth phenotype study for both SETBP1 haploinsufficiency disorder (SETBP1-HD) and SETBP1-related disorders (SETBP1-RD). Prior to this publication there was a need for a better understanding of the cognitive and behavior profiles of individuals with SETBP1-HD and SETBP1-RD. The patient data analyzed in this study originated from SETBP1 participants part of the Simons Searchlight. Searchlight is a research initiative hosted by the Simons Foundation Autism Research Initiative (SFARI). Caregivers provide a complete medical history and genetic reports for SETBP1 participants, complete a series of standardized questionnaires, and interview with a genetic counselor (if needed). This paper provides unprecedented education, support, and awareness of the clinical, neurological, and behavioral characteristics of the SETBP1 patient community.

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**Main Findings:**
Germline variants in SETBP1 are associated with three different disorders – Schinzel Giedion Syndrome (SGS), SETBP1-HD, and SETBP1-RD. This research details the neurodevelopmental profile of SETBP1 individuals from Simons searchlight data. Although previous literature has noted subtle facial differences of SETBP1-HD individuals distinct from those with SGS, diagnosis of SETBP1-HD still relies heavily upon genetic testing. This, paired with limited knowledge of the neurodevelopment impact and phenotypic appearances of changes in SETBP1, has hindered patient access to proper diagnoses, adequate care, and better medical management. These prior shortcomings laid the foundations for a deep and longitudinal investigation into SETBP1-HD and SETBP1-RD. This article covers 18 previously unpublished cases of SETBP1-HD and SETBP1-RD from both sexes ranging in age from toddlers to young adults. When comparing SETBP1-HD to SETBP1-RD, distinct orthopedic and gastrointestinal issues were identified in individuals with SETBP1-RD. It is worth noting that no individuals with either disorder reported a diagnosis of cancer, and both cohorts exhibited a unique new clinical observation of high pain tolerance.

Furthermore, both groups had a strong social motivation while exhibiting challenges with repetitive and obsessive behaviors. SETBP1-HD individuals, in particular, demonstrated strengths in interpersonal relations and weaknesses in communication, motor skills, and safe and independent functioning within the community. Previous literature has identified childhood apraxia of speech (CAS), and the findings here concur that 100% of SETBP1-HD and SETBP1-RD individuals over 1 year old reported delays in first words and phrases. In all, this study provides a comprehensive breakdown of previously identified intellectual disability and developmental delay (IDD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and seizures, as well as speech and language delays in addition to a novel comparison of the neurobehavioral presentation of SETBP1-HD and SETBP1-HD.

**What does this mean for SETBP1-HD:**
When asked, SETBP1 Society President Haley Oyler states how proud she is of the work the authors accomplished as a SETBP1 team. For her, “this publication not only shares important phenotype findings for individuals with SETBP1-HD and related disorders but also helps parents better understand the diverse challenges their children face. The dedication of parents—completing medical history interviews, standardized surveys, and annual updates—has come full circle with the release of this paper. This publication stands as both a resource for awareness and a tool for educating medical professionals.” In addition to Haley’s sentiments, this article also underlines the importance of future family participation in data gathering and natural history studies to aid in a continued age-relevant refinement and understanding of SETBP1-HD and SETBP1-RD. This will be even more important as the patient population ages and/or new individuals are identified to complete the most detailed picture of SETBP1 individuals. Future information will aid in more accurate diagnosis, standards of care, and treatment.

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**Accessing the Article:**
The full review article titled “SETBP1 haploinsufficiency and related disorders clinical and neurobehavioral phenotype study” published in *Clinical Genetics* on June 26, 2024, can be accessed here: https://pubmed.ncbi.nlm.nih.gov/38923504/ SETBP1 parents/caregivers can reach out to Haley Oyler for a copy of the publication.

**Other related resources**:
Information on Simons Searchlight: https://www.setbp1.org/registry/

**Bonus Material: The Story Behind the Paper**
The SETBP1 Society has worked closely with Searchlight over the years by serving on their advisory council and providing input to help the Searchlight registry grow with the needs of the neurodiverse genetic community they serve/support. Every year, our community receives registry updates from Simons Searchlight on our SETBP1 registry during virtual and, eventually, in-person meetings. While these updates were very helpful and informative, they were only shared directly with SETBP1 families in attendance. We did not have an effective way of disseminating the results to the entire SETBP1 community or to specialists or medical professionals who could also benefit from the updates.

In 2020, a fellow SETBP1 Society board member, Trina Geye, PhD, who is an associate professor at Tarleton State University, and Haley Oyler hatched an idea to form a partnership between the University and SETBP1 Society to serve as the voice of the SETBP1 Community. In early 2021, the idea took shape as SCoReS (**S**ETBP1 **Co**mmunity **Re**search **S**tudy), community-based participatory research (CBPR), which performs research with the community versus on the community. A 3rd PI, Stephanie Robertson, an associate professor at Tarleton State and director of the Tarleton Center for Child Well-being, joined the study. CBPR is an iterative process where the community is an equal partner in the research, and their needs drive the research direction and priorities.

From the first phase of this partnership, we heard from parents about a need for a better understanding of the neurobehavior profiles of their children with SETBP1-HD and SEBTP1-RD. In direct answer to the concerns of the SETBP1 Community, SCoReS has launched three more phases to better understand the cognitive and behavior profiles of individuals with SETBP1-HD. In parallel, the SETBP1 president thought SCoReS would be the perfect partnership to drive dissemination of the SETBP1 Searchlight registry results to help create broader awareness of the SETBP1-HD and related disorders and education by sharing the findings reported in the Searchlight registry.

Written by: Jordan, Whitlock, PhD, SETBP1 Society Science Coordinator"