SETBP1 Genetics: Bite-sized Breakthroughs
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SETBP1 variants outside the degron disrupt DNA-binding, transcription and neuronal differentiation capacity to cause a heterogeneous neurodevelopmental disorder

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About the Authors:
This international study was led by Maggie Wong, with key contributions from Rosalie Kampen and Ruth Braden. The senior and corresponding authors were Simon E. Fisher, Bregje van Bon and Angela Morgan. The research took place across many centers and was mainly carried out at the Max Planck Institute of Psycholinguistics and Radboud University Medical Center in the Netherlands, with support from clinical genetics, speech and language researchers, and neuroscience teams across Europe, Australia, and the United States.

What was the study about?
Researchers wanted to learn whether SETBP1 missense variants and an in-frame deletion found outside the Schinzel-Giedion syndrome “degron” hotspot (positions 868–871 on the protein) could cause a neurodevelopmental disorder. They also wanted to understand how these variants change the way SETBP1 works inside cells.

What did the researchers do?
The team studied 18 individuals with missense variants located outside the degron hotspot and an in-frame deletion variant in SETBP1. To understand how these variants affect people and cells, the researchers used:

- Detailed clinical evaluations
- Laboratory studies using patient-derived cells
- Tests of SETBP1 protein stability, DNA-binding, and transcription activity
- Experiments that looked at how neurons grow and develop
- Gene expression analysis (RNA-seq)

This comprehensive approach allowed them to understand both the clinical features and the biological mechanisms behind these variants.

Main Findings:

1. **A distinct SETBP1-related neurodevelopmental profile**

People with these variants shared a wide range of developmental, learning, and medical features. Their symptoms overlapped with—but were not the same as—SETBP1 haploinsufficiency disorder (SETBP1-HD) or Schinzel-Giedion syndrome (SGS). This suggests a third group within the SETBP1 spectrum, which the authors call SETBP1-related disorders (SETBP1-RD).

2. **The variants disrupt SETBP1's function, not just protein levels**

Across both the missense variants and the in-frame deletion, the researchers found:

- Reduced or altered DNA-binding ability
- Impaired transcriptional regulation (how SETBP1 helps control gene activity)
- Defects in neuronal differentiation and maturation
- Widespread changes in gene expression

Importantly, these problems happened even when SETBP1 protein levels looked normal or were higher than expected. This tells us that the protein amount is not the main issue.

This is different from

- SETBP1-HD, where the body has too little SETBP1
- SGS, where the body has too much SETBP1

Both of those conditions are caused mainly by problems with protein quantity, while this new group is caused by problems with protein function.

3. **A loss-of-function mechanism**

These variants appear to cause a partial or full loss of SETBP1's normal activity, which helps explain many of the neurological and developmental differences seen in individuals with SETBP1-RD.

Why is this important?

This study expands our understanding of SETBP1 by showing that missense variants outside the degron, including an in-frame deletion, cause a meaningful, clinically distinct neurodevelopmental disorder. These findings highlight:

- The broader clinical and molecular spectrum of SETBP1-related conditions

- The importance of testing how the protein works, not just how much of it the body makes
- The need to recognize these variants in medical and genetic evaluations

Accessing the Article:
The full review article titled “SETBP1 variants outside the degron disrupt DNA-binding, transcription, and neuronal differentiation capacity to cause a heterogeneous neurodevelopmental disorder,” published in *Nature Communications* on October 10, 2025, can be accessed here: https://pmc.ncbi.nlm.nih.gov/articles/PMC12514306/.

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