Guilt by association - does *SCAF8* haploinsufficiency lead to a neurodevelopmental disorder?

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Abstract

Heterozygous loss-of-function (LOF) variants in *SCAF4* are associated with an autosomal dominant neurodevelopmental disorder (NDD), also known as Fliedner-Zweier syndrome[1,2]. This disorder is characterized by mild developmental delay, including speech impairment, seizures, and behavioral issues such as attention-deficit/hyperactivity disorder, autism spectrum disorder, and increased aggression[3,4].

The *SCAF4* and *SCAF8* genes are paralogs that are thought to have arisen via a gene duplication that occurred in vertebrates, and both encode mRNA anti-terminator proteins required for correct gene expression. The encoded proteins have significant sequence homology (38% identity and 50% similarity), and both contain a carboxyl-terminal domain (CTD)-interaction domain, characteristic of transcription termination factors, as seen in their yeast orthologs. Functional studies have demonstrated that the lethal *SCAF4/SCAF8* double knockout human cell line can be rescued by either SCAF4 or SCAF8, supporting a common and essential function of these proteins[5]. The *SCAF4* and *SCAF8* genes are both constrained against LOF variants (pLi = 1) and have similar ubiquitous gene expression profiles. However, to date, there is no published data associating *SCAF8* haploinsufficiency with a human phenotype[6].

Case Presentation

The aim of the University of North Carolina's (UNC) Genetic Determinants of Neurological and Developmental Disorders (GDNDD) IRB-approved study is to identify novel genetic variants via genome sequencing. One GDNDD participant was a 6-year-old male with speech delay, ADHD, impulsivity, behavioral aggression, and intractable focal-onset epilepsy. MRI was unremarkable. Prior clinical genetic testing included an epilepsy gene panel which reported four heterozygous variants of uncertain significance in genes associated with autosomal recessive conditions (*ALDH7A1, GLDC, PTPN23,* and *SZT2).*

Genome Sequencing at UNC

Trio short-read genome sequencing was generated at Flagship Biosciences, and the data analyzed by the UNC clinical genomic analysis (GENYSIS) core facility[7] to identify single nucleotide, copy number, and structural variants (using Delly2[8] and annotated using AnnotSV[9]). A heterozygous *de novo* frameshifting variant in the *SCAF8* gene was identified that is predicted to lead to nonsense-mediated decay and haploinsufficiency (see **Figure 1**): NM_014892.5:c.1891del; p.(Ala631GlnfsTer24).

Results

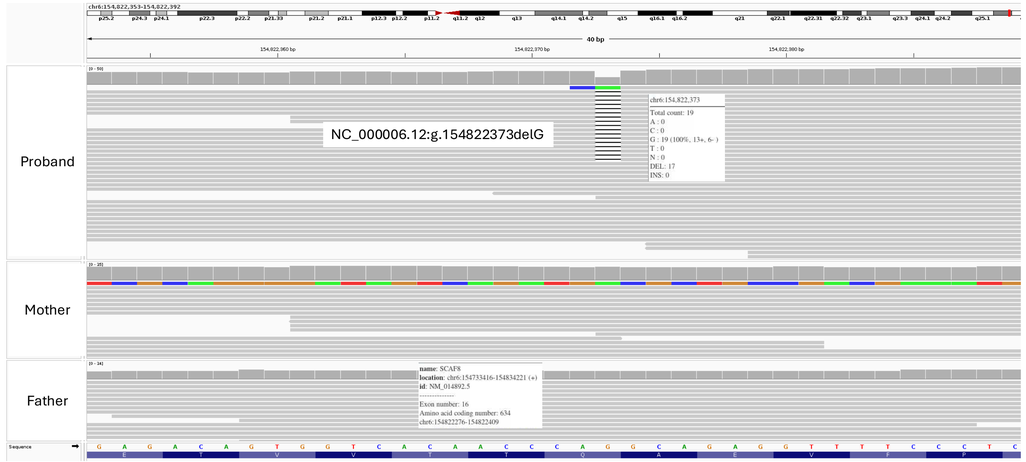

Figure 1: Integrated Genomics Viewer[10] (IGV) screenshot highlighting the *de novo* single base deletion in exon 16 of the *SCAF8* gene of the GDNDD proband (NC_000006.12:g.154822373delG).

Help build a cohort of NDD patients with *SCAF8* LOF variants for RNA-seq analysis

Got a *SCAF8* LOF variant?

Summary

Given the overlapping structure and function of the SCAF4 and SCAF8 proteins, and the association of *SCAF4* with a known neurodevelopmental disorder, we propose that the *de novo SCAF8* c.1891del, p.(Ala631GlnfsTer24), LOF variant is responsible for the neurodevelopmental phenotypes seen in our GDNDD patient. As such, the variant was confirmed by Sanger sequencing and DNA fingerprinting of proband and parental clinical samples. However, due to the limited evidence supporting a role for *SCAF8* in human disease, the variant was reported in the participant's medical record and submitted to ClinVar (Accession: SCV006555116) as a variant of uncertain significance.

As it has been previously demonstrated by RNA-sequencing (RNA-seq) that NDD patients with *de novo SCAF4* LOF variants exhibit differential gene expression and splicing compared to controls[3,] we applied for and were awarded funds by GeneWiz from Azenta Life Sciences[11] for RNA-seq and analysis of 15 *SCAF8* LOF probands and control RNA samples. It is hoped that by deep phenotyping patients and demonstrating differential gene expression and splicing via RNA-seq analysis, that a new gene-disease relationship can be defined.

The *SCAF8* variant has been submitted to GeneMatcher[12] and we are actively seeking additional patients and collaborations to further investigate this potential new gene-disease relationship. **If you have an NDD patient with a *SCAF8* LOF variant, please contact us at GDNDD@neurology.unc.edu to discuss enrollment in our *SCAF8* study: https://go.unc.edu/GDNDD**

References

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