Investigating Non-Canonical SUMF1 in Alzheimer's Disease with Psychosis

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Introduction

In Alzheimer's disease (AD), genetic factors play a crucial role in the development of psychotic symptoms (delusions and hallucinations), as demonstrated by a recent Genome-Wide Association Studies linking an alternate (non-canonical) transcript of sulfatase modifying factor 1 (*SUMF1*) to AD with psychosis (Figure1)[1]. Mutations impairing the function of canonical *SUMF1* cause multiple sulfatase deficiency, a lysosomal storage disorder associated with neurodegeneration in childhood. The role of non-canonical *SUMF1* in the brain and in the pathogenesis of psychosis in AD patients remains unexplored. This study aims to uncover non-canonical *SUMF1*'s role by studying its expression in HEK293T cells, determining its cellular localization, and exploring its potential involvement in AD with psychosis by analyzing neurons derived from induced pluripotent stem cells (iPSCs).

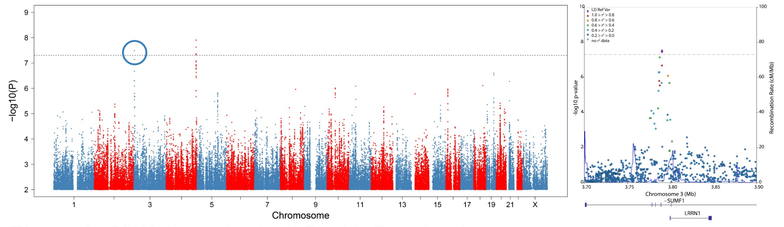

Figure1. GWAS results for AD with Psychosis.

Methods

Non-canonical SUMF1 vector is designed for gene overexpression by introducing the non-canonical *SUMF1* tagged by the green fluorescent protein (GFP).

Lipofection is a genetic transfection technique that uses lipid-based reagents (liposomes) we used to deliver vector containing non-canonical *SUMF1* into HEK293T cells.

Protein extraction and Western Blotting begins with isolating proteins from HEK293 cells and is followed by Western blotting, which detects and analyzes non-canonical *SUMF1* proteins within the samples.

Antisense Oligonucleotides (ASOs) are short DNA or RNA sequences designed to bind to complementary RNA molecules, allowing for gene expression control by inhibiting translation, promoting RNA degradation, or altering splicing patterns.

RNA extraction and qRT-PCR are performed to quantify specific RNA transcripts in the sample.

Generation of neurons form iPS cells involves reprogramming adult cells into induced pluripotent stem cells (iPSCs) and differentiating them into neurons. It enables the creation of patient-specific neurons for various applications, including disease modeling, drug testing, and potential therapies for neurological disorders.

Results

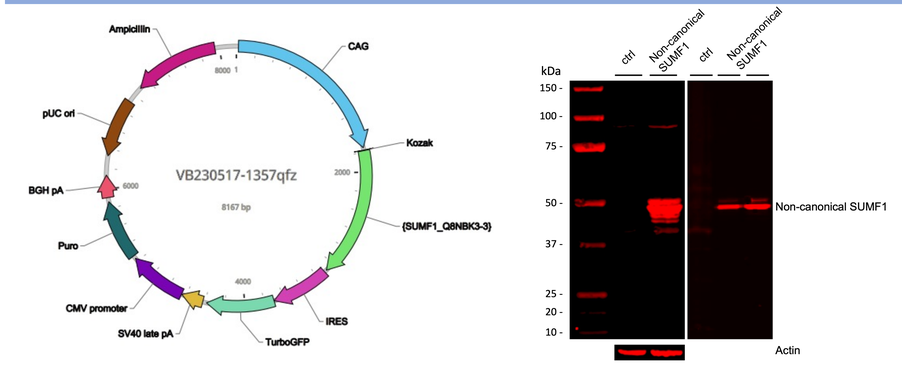

Figure2. Overexpression of non-canonical *SUMF1* in HEK293T cells. Left: Vector Design. Right: Western blotting of non-canonical *SUMF1.*

Figure3. Schematic diagram showing exon structures of canonical and non-canonical SUMF1, and the ASOs tested. Top: Canonical *SUMF1*. Bottom: Non-canonical *SUMF1*.

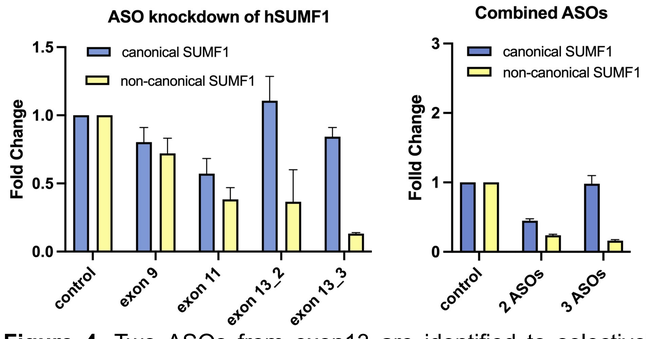

Figure 4. Two ASOs from exon13 are identified to selectively knock down the non-canonical *SUMF1* while not affecting the canonical form. Left: Knockdown of non-canonical *SUMF1* with separate ASOs targeting exon 9, 11, and 13. Right: Knockdown of non-canonical *SUMF1* with combined ASOs. 2 ASOs: exon 13_2 and 13_3. 3 ASOs: exon 11, 13_2, and 13_3.

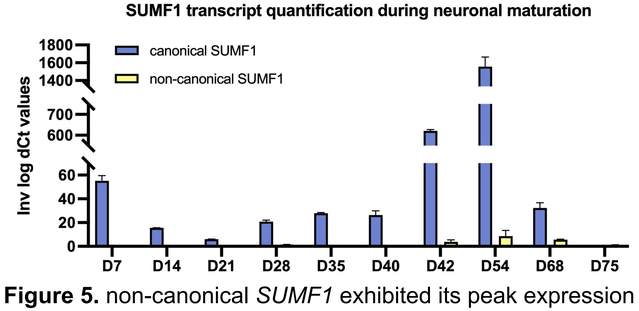

Figure 5. non-canonical *SUMF1* exhibited its peak expression around day 54 in iPSCs.

Conclusions

The study successfully confirmed the presence of non-canonical *SUMF1* in HEK293T cells (Figure 2), suggesting that it is indeed expressed in relevant cell lines, laying the groundwork for further investigations.

The design and optimization of ASOs targeting non-canonical SUMF1 mRNA highlight the feasibility of selectively modulating the expression of this specific transcript without affecting the canonical form (Figure3, 4). This demonstrates the controllability of non-canonical *SUMF1* expression.

The study observed distinct expression patterns of non-canonical *SUMF1* during neuronal maturation from iPSCs. Notably, peak expression occurred around day 54 (Figure 5), which may have implications for understanding the temporal dynamics of AD pathogenesis.

Overall, this study has shed light on the role of non-canonical *SUMF1* in the context of Alzheimer's disease (AD) with psychotic symptoms, offering a promising avenue for further research and potential therapeutic interventions.

Future Directions

Functional Significance of Non-Canonical *SUMF1*: While the study establishes the presence and controllability of non-canonical *SUMF1*, its functional significance in AD with psychotic symptoms remains unclear. Future studies should focus on elucidating the precise role of non-canonical *SUMF1* in the brain, particularly how its overexpression or downregulation may contribute to the development of psychotic symptoms in AD.

Interactions with Canonical *SUMF1*: Investigating whether non-canonical *SUMF1* interacts with the canonical form of *SUMF1* and how this interaction affects *SUMF1*'s function is crucial. This could provide insights into the mechanisms underlying *SUMF1*-related pathways and their impact on neurodegenerative processes in AD.

Animal Models and In Vivo Studies: To validate the relevance of the findings in a more biologically complex setting, further research should involve animal models of AD or humanized mouse models that can recapitulate the disease's complexity. In vivo experiments can provide a better understanding of the implications of non-canonical *SUMF1* modulation.

References

1.DeMichele-Sweet, Mary Ann A et al. “Genome-wide association identifies the first risk loci for psychosis in Alzheimer disease.” *Molecular psychiatry* vol. 26,10 (2021): 5797-5811. doi:10.1038/s41380-021-01152-8