

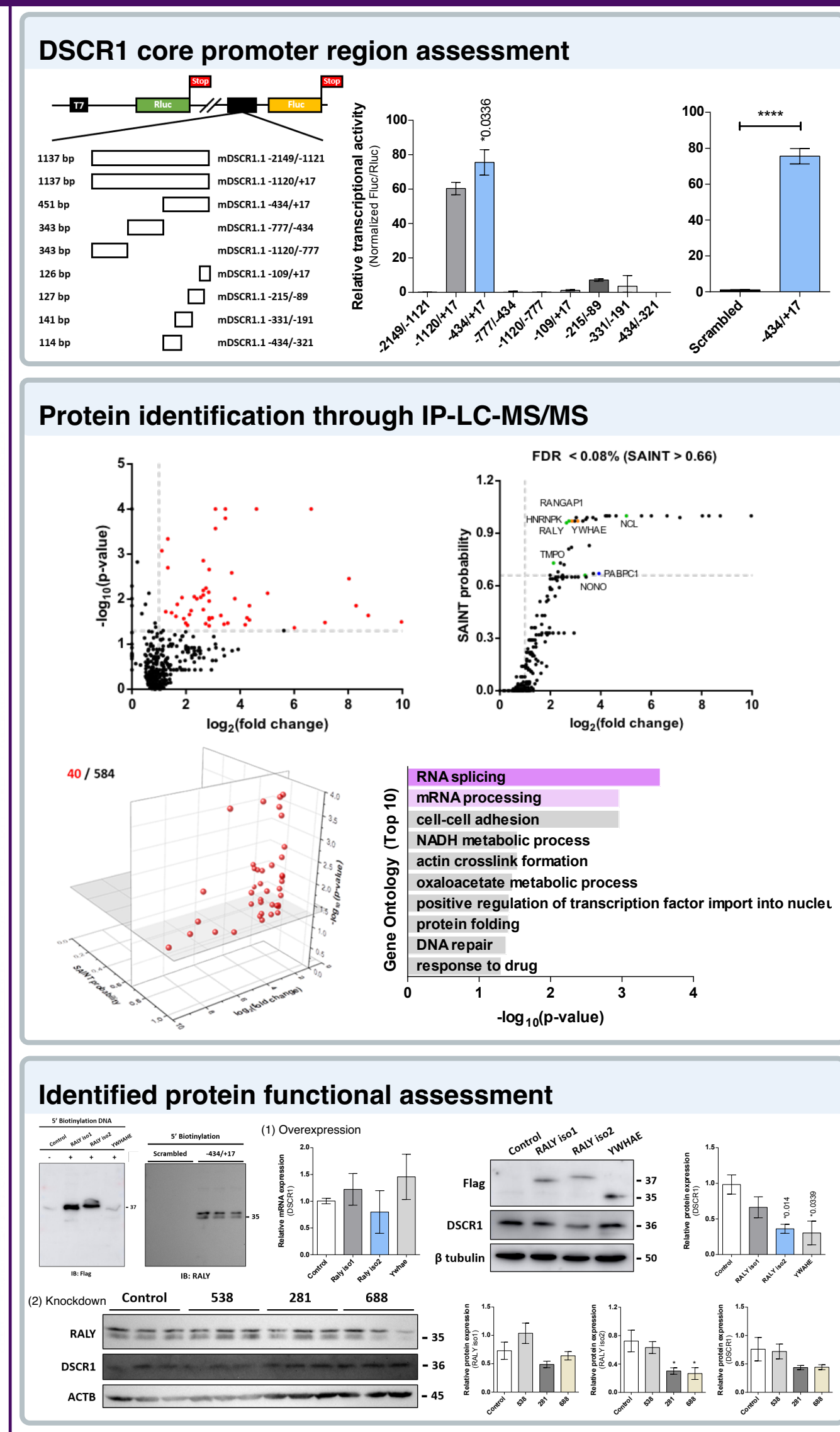
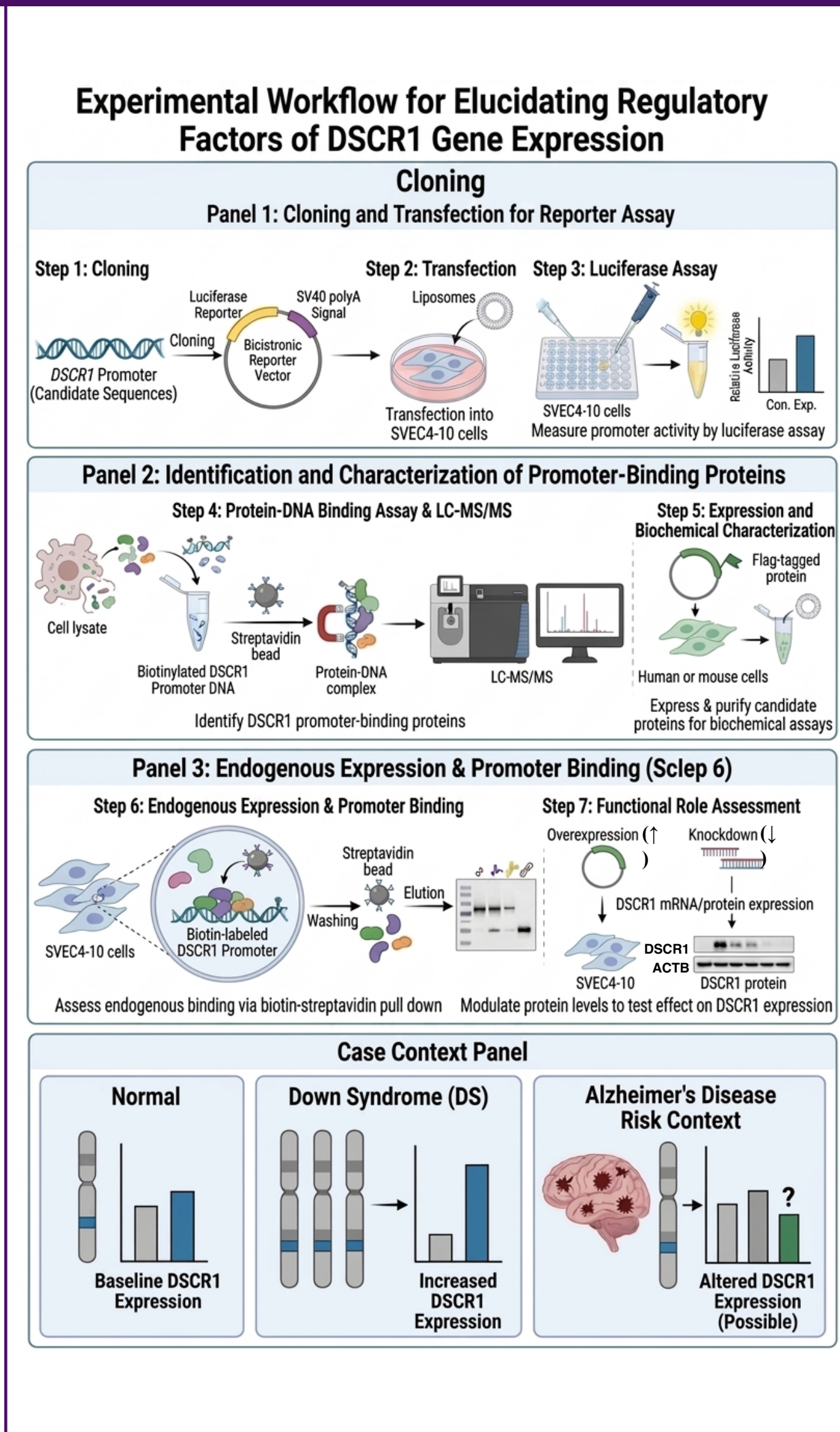
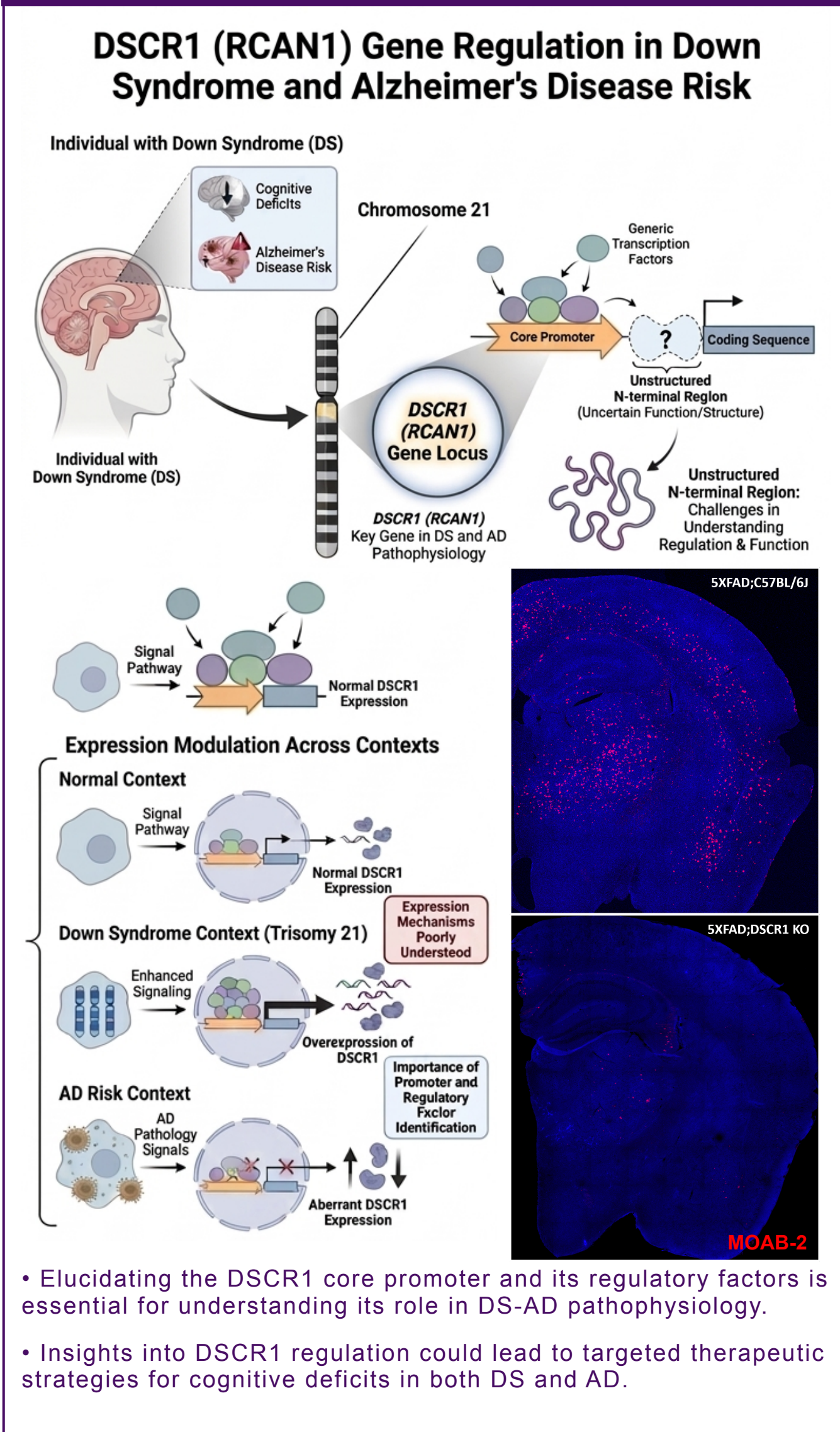
Identification of RALY as a novel regulator of DSCR1 expression with implications for Alzheimer’s Disease

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- The underlying mechanism that makes individuals with Down syndrome (DS) more susceptible to developing Alzheimer’s disease (AD) remains unclear.
- RALY is a newly identified repressor of Down Syndrome Critical Region 1 (DSCR1), directly binding its promoter to limit transcription.
- RALY isoform 2 binds to the DSCR1 promoter and lowers DSCR1 protein levels, acting as a regulator of DSCR1 homeostasis.
- The RALY-DSCR1 regulatory axis provides a mechanistic clue to how DSCR1 dysregulation may contribute to AD pathology in DS.

INTRODUCTIONMETHODSRESULTSCONCLUSIONSREFERENCES



- A 450-bp region surrounding the DSCR1 transcription start site was identified as the core promoter using bicistronic reporter mapping.
- Biotin-DNA pull-down and LC-MS/MS revealed a focused set of promoter-binding proteins, with 40 high-confidence candidates enriched after stringent filtering.
- RALY isoform 2 showed specific and endogenous binding to the DSCR1 promoter, validating it as a bona fide interactor.
- Overexpression of RALY isoform 2 reduced DSCR1 protein levels without altering mRNA levels, suggesting a post-transcriptional or translational regulatory mechanism.
- These findings support a model in which RALY isoform 2 acts as a context-dependent regulator, buffering DSCR1 protein abundance to maintain cellular homeostasis.

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