Uncovering Regulatory Mechanisms in FET Protein Knockout Cells via ISMARAmotif Analysis

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Abstract:

The molecular functions of FET proteins (FUS, EWSR1, and TAF15) in transcriptional regulation and RNA metabolism remain only partially understood. Here, we investigate the regulatory changes induced by the knockout (KO) of individual FET proteins in SH-SY5Y cells, focusing on the integration of ISMARA motif activity response analysis (ISMARAmotif) (Piotr J. Balwierz, 2014) and differential gene expression analysis.

By applying ISMARAmotif analysis, which infers transcription factor activity from computationally predicted binding sites leveraging transcriptomic data, to RNA-seq datasets derived from human cell lines (four conditions: wild-type (WT) and knockouts for EWSR1, FUS, and TAF15, each with three biological replicates), we identified key transcriptional regulators underlying FET protein-associated gene expression patterns.

Singular value decomposition (SVD) (James Bisgard, 2021) of the inferred ISMARAmotif activities allowed us to identify transcription factor motifs whose activity changes significantly in response to each FET protein KO. By focusing on these key motifs, we revealed distinct transcriptional regulators associated with each KO condition. Enrichment analysis of the identified motifs further highlighted the biological processes most impacted by these regulatory changes, shedding light on the pathways disrupted by the loss of individual FET proteins, including processes related to cell cycle regulation and stress response.

Our study applies the established combination (Raphaëlle Luisier, 2014) of ISMARAmotif analysis and SVD to decipher the complex effects of FET protein knockouts, providing mechanistic insights into their function and role in cellular biology. These findings build on previous work and offer a foundation for further exploration of FET protein involvement in disease pathogenesis.

References:

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