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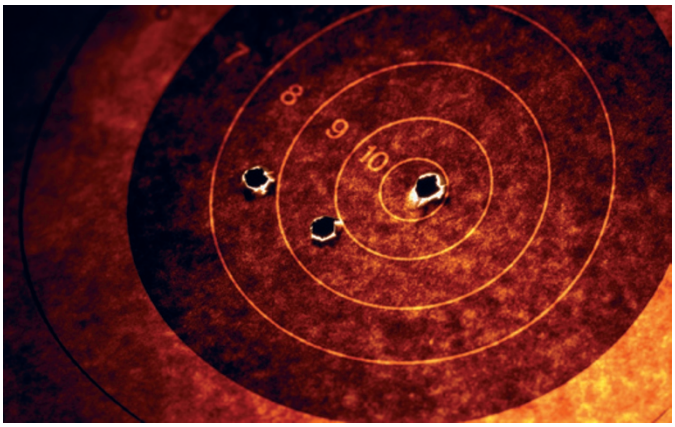
NEURODEGENERATIVE DISEASE

A target map for TDP43

Cytoplasmic aggregation of TAR DNA-binding protein 43 (TDP43), and mutations in the gene that encodes it, have been linked to frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis, bringing it to the forefront of neurodegeneration research. The contribution of TDP43 to the disease processes is unclear; however, two recent papers bring us closer to an understanding of its functional roles by characterizing its RNA targets in the brain.

Although several RNA targets of TDP43 are known, a more comprehensive catalogue of its brain targets was lacking. To address this issue, the new studies used UV irradiation-induced cross-linking of protein–RNA interactions, followed by immunoprecipitation of TDP43 and analysis of the RNA sequences to which it is bound. Polymenidou *et al.* discovered TDP43 binding sites in pre-mRNAs encoded by more than 6,000 genes in the adult mouse brain. Both studies found TDP43 binding sites to be particularly enriched in introns containing multiple repeat clusters of the ribonucleic acids uracil and guanine.



To determine which of these RNAs are actually regulated by TDP43, Polymenidou *et al.* injected antisense oligonucleotides against *TDP43* into the striatum of mice. TDP43 depletion affected the levels of the mRNAs encoded by 601 genes, and resulted in changes in 965 alternative splicing events. Similarly, Tollervey *et al.* observed more than 200 altered splicing events upon TDP43 knockdown in human neuroblastoma cells. They also studied the TDP43–RNA interactions in post-mortem brains of individuals with FTLD, discovering increased interactions with specific long non-coding RNAs.

Characterization of the mRNAs regulated by TDP43 revealed that many have important roles in synaptic function and neuronal development. Furthermore, a number of proteins previously linked to neurodegenerative disease are regulated by TDP43, including progranulin, sortilin and RNA-binding protein FUS (also known as TLS).

These results demonstrate a role for TDP43 in regulating the levels and splicing of many RNAs in the brain, suggesting that loss of TDP43 from the nucleus as it accumulates in the cytoplasm might have important implications for nervous system function. The work provides a useful starting point for future studies to pin down the contribution of TDP43 to neurodegenerative disease more precisely.

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ORIGINAL RESEARCH PAPERS Tollervey, J.R. *et al.* Characterizing the RNA targets and position-dependent splicing regulation by TDP-43. *Nature Neurosci.* **14**, 452–458 (2011) | Polymenidou, M. *et al.* Long pre-mRNA depletion and RNA missplicing contribute to neuronal vulnerability from loss of TDP-43. *Nature Neurosci.* **14**, 459–468 (2011).

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