TDP43 aggregates: the 'Schrödinger's cat' in amyotrophic lateral sclerosis

Débora Lanznaster, Rudolf Hergesheimer, Patrick Vourc'h, Philippe Corcia and Hélène Blasco

A recent Review by Tziortzouda et al. (Tziortzouda, P., Van Den Bosch, L. & Hirth, F. Triad of TDP43 control in neurodegeneration: autoregulation, localization and aggregation. *Nat. Rev. Neurosci.* 22, 197–208 (2021))[1] provided a comprehensive overview of TDP43's physiological functions and described how small dysfunctions in its intrinsic control system might eventually lead to TDP43 pathology. TDP43 protein aggregation is a key element in amyotrophic lateral sclerosis (ALS) as it has a major impact on motor neuron degeneration. However, the statement that all ALS patients present TDP43 abnormalities except for two genetic-related ALS cases is misleading; the only way of determining if TDP43 pathology is there or not is by looking into the 'sealed box'.

The presence of TDP43 aggregates is not the only culprit of neurodegeneration in ALS, as they are not found in roughly 3–5% of ALS patients and, as mentioned by Tziortzouda and co-authors, TDP43 pathology was not demonstrated in patients carrying *FUS* mutations. The authors claimed that ALS patients carrying *SOD1* mutations also have no TDP43 abnormalities; however, this information is controversial. While several studies have indeed reported an absence of these aggregates, four case reports have demonstrated the occurrence of TDP43 pathology in patients with diverse *SOD1* mutations, specifically D91A (REF.[2]), G86S (REF.[3]), C111Y (REF.[4]) and I112T (REF.[5]) mutations. Furthermore, TDP43 alterations were also shown in mouse models in which *Sod1* is mutated and in fibroblasts or hiPSC-derived motor neurons from patients with *SOD1* mutations[6]. In this regard, it is misleading to affirm that TDP43 abnormalities are not found in SOD1-ALS cases.

A growing body of evidence gathered in recent years supports a cross-talk between SOD1 and TDP43 in physiological and pathological conditions. For example, one study showed that TDP43 regulates *SOD1* RNA[7] but another study did not replicate this finding[8]. Evidence for TDP43's interaction with *SOD1* RNA was found in spinal cord lysates from one patient with ALS (SOD1-A4T)[9] and TDP43 was shown to physically interact with mutated SOD1-G93A protein but not the wild-type protein[10].

So far, it is not possible to distinguish a pattern for these interactions or for the occurrence of TDP43 pathology in individuals with certain mutations in *SOD1*. One interesting consideration is that the post-mortem studies that demonstrated TDP43 pathology in ALS cases linked to *SOD1* mutations found these abnormalities in motor neurons from the lumbar spinal cord, while the majority of studies that did not find TDP43 pathology analysed the motor cortex, brainstem or other non-specified sections of the spinal cord. Could this suggest that the presence of TDP43 abnormalities is a matter of location in distinct subsets of patients? By focusing TDP43 analysis to a single area in the motor system, we could be missing important information regarding the pathological mechanisms taking place in the larger scenario. Even worse, could the 'presence or absence' conundrum of TDP43 pathology be a simple by-product of the limited techniques used to demonstrate such abnormalities? After all, performing histological analysis of the complete motor system for every single ALS patient would be an insurmountable amount of work.

Furthermore, the dogma that all (other) cases of ALS present TDP43 pathology needs to be approached with caution. In a Review published two years ago, we reviewed 30 genes linked to genetic ALS and we found that, so far, TDP43 pathology was demonstrated in post-mortem analysis from cases bearing mutations in 17 genes (including *SOD1* mutations)[6]. For two other genes (*CHCHD10* and *CCNF*) TDP43 pathology was demonstrated in cell culture or animal models. At that time, the absence of TDP43 pathology was demonstrated for mutations in other four genes (*FUS*, *CHMP2B*, *SPG11* and *TUBA4A*). Importantly, for the remaining seven genes (*ALS2*, *C21orf2*, *ELP3*, *FIG4*, *NEFH*, *NEK1* and *VABP*) there were no studies investigating TDP43 pathology[6]. These observations preclude one from making strong affirmations about the presence or absence of TDP43 pathology in all ALS patients.

In conclusion, it is true to ascertain that TDP43 pathology is not systematically found in all *SOD1*-mutated ALS cases and has so far only reported in single case reports – but this ultimately reveals how far we are from fully understanding ALS pathology. The utter disregard of TDP43 pathology in *SOD1* cases can affect the management of this subset of patients in the advent of a therapeutics targeting TDP43 aggregates or produce biased results when these patients are included in clinical trials for *SOD1* antisense therapy[2]. The development of imaging techniques to identify TDP43 pathology in the different regions of the motor system in live patients would shed light on this matter and help us solve this puzzle. Until then, we should consider that TDP43 pathology is both there and not there until we open the box to finally find out.

There is a reply to this letter by Tziortzouda, P., Van Den Bosch, L. & Hirth, F. *Nat. Rev. Neurosci.* https://doi.org/10.1038/s41583-021-00478-0 (2021).

Débora Lanznaster ✉, Rudolf Hergesheimer, Patrick Vourc'h, Philippe Corcia and Hélène Blasco
UMR1253 iBrain, University of Tours, Tours, France.
✉*e-mail: debora.lanznaster@univ-tours.fr*

https://doi.org/10.1038/s41583-021-00477-1

1. Tziortzouda, P., Van Den Bosch, L. & Hirth, F. Triad of TDP43 control in neurodegeneration: autoregulation, localization and aggregation. *Nat. Rev. Neurosci.* **22**, 197–208 (2021).
2. Feneberg, E., Turner, M. R., Ansorge, O. & Talbot, K. Amyotrophic lateral sclerosis with a heterozygous D91A SOD1 variant and classical ALS-TDP neuropathology. *Neurology* **95**, 595–596 (2020).
3. Jeon, G. S. et al. Pathological modification of TDP-43 in amyotrophic lateral sclerosis with SOD1 mutations. *Mol. Neurobiol.* **56**, 2007–2021 (2019).
4. Sumi, H. et al. Nuclear TAR DNA binding protein 43 expression in spinal cord neurons correlates with the clinical course in amyotrophic lateral sclerosis. *J. Neuropathol. Exp. Neurol.* **68**, 37–47 (2009).
5. Okamoto, Y. et al. An autopsy case of SOD1-related ALS with TDP-43 positive inclusions. *Neurology* **77**, 1993–1995 (2011).
6. Hergesheimer, R. C. et al. The debated toxic role of aggregated TDP-43 in amyotrophic lateral sclerosis: a resolution in sight? *Brain* **142**, 1176–1194 (2019).
7. Somalinga, B. R., Day, C. E., Wei, S., Roth, M. G. & Thomas, P. J. TDP-43 identified from a genome wide RNAi screen for SOD1 regulators. *PLoS One* **7**, e35818 (2012).
8. Polymenidou, M. et al. Long pre-mRNA depletion and RNA missplicing contribute to neuronal vulnerability from loss of TDP-43. *Nat. Neurosci.* **14**, 459–468 (2011).
9. Volkening, K., Keller, B. A., Leystra-Lantz, C. & Strong, M. J. RNA and protein interactors with TDP-43 in human spinal-cord lysates in amyotrophic lateral sclerosis. *J. Proteome Res.* **17**, 1712–1729 (2018).
10. Higashi, S., Tsuchiya, Y., Araki, T., Wada, K. & Kabuta, T. TDP-43 physically interacts with amyotrophic lateral sclerosis-linked mutant CuZn superoxide dismutase. *Neurochem. Int.* **57**, 906–913 (2010).

Competing interests
The authors declare no competing interests.