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

Paraskevi Tziortzouda, Ludo Van Den Bosch and Frank Hirth

In their correspondence on our Review (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], Lanznaster et al. query our statement that TDP43 aggregates are not a major hallmark of familial ALS caused by mutations in *SOD1* (Lanznaster, D., Hergesheimer, R., Vourc'h, P., Corcia, P. & Blasco, H. TDP43 aggregates: the 'Schrödinger's cat' in amyotrophic lateral sclerosis. *Nat. Rev. Neurosci.* https://doi.org/10.1038/s41583-021-00477-1 (2021))[2]. We remain convinced that our statement is correct and not falsified by the post-mortem data currently available.

The philosopher Karl Popper conceptualized falsification as a tool to apply logic in scientific discovery[3], illustrating his argument with the famous statement that "no matter how many instances of white swans we may have observed, this does not justify the conclusion that all swans are white"[3]. Correspondingly, our statement that TDP43 aggregates have not been found in familial ALS caused by mutations in *SOD1* can be considered falsified if one familial ALS case caused by *SOD1* mutations is found that contains TDP43 aggregates. The correspondence of Lanznaster et al. suggests that this is indeed the case, pointing to four case reports of TDP43 pathology in patients with mutations in *SOD1*[2]. But are these seemingly rare exceptions to the rule, indeed, 'swans'? In other words, is it certain that the reported cases are from familial ALS patients with a disease-causing *SOD1* mutation? One of the cited studies itself concluded that a heterozygous D91A mutation in *SOD1* is not a disease-causing mutation and unrelated to the observed TDP43 pathology typical for sporadic ALS[4]. It is even recommended that patients carrying this mutation should not be included in a clinical trial targeting *SOD1* with antisense oligonucleotides[4].

The three other papers referred to by Lanznaster et al. show TDP43-positive staining in isolated ALS patients without a clear family history of the disease. The 41-year-old man in the case report of Okamoto et al. had no family history of neurodegenerative disorders and should therefore be considered to be a sporadic ALS patient[5]. The only patient in the Sumi et al. paper showing TDP43 staining carries the rare C111Y mutation and it remains uncertain whether this is the disease-causing *SOD1* mutation[6]. The same remark applies to the study of Jeon et al.[7]: the only post-mortem sample in this study is from a patient for which there is no information on the family history and who carries the very rare G86S mutation in *SOD1*. In conclusion, in our view, all of these patients can be regarded as having suffered from sporadic ALS in the absence of any proof that the various *SOD1* mutations are indeed the underlying cause of their disease.

By contrast, the report by Sumi et al. also shows the results of TDP43 staining in post-mortem samples from five other ALS patients with *SOD1* mutations linked to familial ALS (G37R, 2 × L126S, 2 × 126 2 bp deletion), all of which were negative for TDP43 pathology[6]. This is in line with a systematic study performed, using post-mortem tissues of 15 well-characterized familial ALS patients with different *SOD1* mutations, none of which showed TDP43 pathology[8].

Taken together, it remains unproven that the patients referred to by Lanznaster et al. are familial ALS cases caused by mutations in *SOD1*. Or, in Popper's terminology, there is no evidence to deduce that these are 'swans', let alone 'black swans'. We therefore conclude that our statement cannot be considered falsified.

Paraskevi Tziortzouda[1,2], *Ludo Van Den Bosch*[1,2]✉ *and Frank Hirth*[3]✉

[1]*Department of Neurosciences and Leuven Brain Institute (LBI), KU Leuven, Leuven, Belgium.*
[2]*Laboratory of Neurobiology, VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium.*
[3]*Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.*
✉*e-mail: ludo.vandenbosch@kuleuven.be; frank.hirth@kcl.ac.uk*

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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. Lanznaster, D., Hergesheimer, R., Vourc'h, P., Corcia, P. & Blasco, H. TDP43 aggregates: the "Schrödinger's cat" in amyotrophic lateral sclerosis. *Nat. Rev. Neurosci.* https://doi.org/10.1038/s41583-021-00477-1 (2021).
3. Popper, K. *Logik der Forschung* (Springer-Verlag GmbH, 1935). English translation available in Popper, K. *The Logic of Scientific Discovery* (Routledge, 1959).
4. 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).
5. Okamoto, Y. et al. An autopsy case of SOD1-related ALS with TDP-43 positive inclusions. *Neurology* **77**, 1993–1995 (2011).
6. 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).
7. Jeon, G. S. et al. Pathological modification of TDP-43 in amyotrophic lateral sclerosis with SOD1 mutations. *Mol. Neurobiol.* **56**, 2007–2021 (2019).
8. Mackenzie, I. R. A. et al. Pathological TDP-43 distinguishes sporadic amyotrophic lateral sclerosis from amyotrophic lateral sclerosis with SOD1 mutations. *Ann. Neurol.* **61**, 427–434 (2007).

Competing interests
The authors declare no competing interests.