

REPLY TO LETTER

Reply to: No evidence supports genetic heterogeneity of neuronal intranuclear inclusion disease

Zhongbo Chen¹ , Mina Ryten¹ & Henry Houlden²¹Department of Neurodegenerative Disease, Queen Square Institute of Neurology, University College London (UCL), London, UK²Department of Neuromuscular Disease, Queen Square Institute of Neurology, UCL, London, UK**Correspondence**

Zhongbo Chen, Department of Neurodegenerative Disease, Queen Square Institute of Neurology, University College London, London WC1N 3BG, UK. Tel: +44(0)203 4484249; Fax: +44 (0)20 3448 4723; E-mail: zhongbo.chen@ucl.ac.uk

Funding information

ZC was funded by a Leonard Wolfson Clinical Research Training Fellowship.

Received: 22 September 2020; Accepted: 28 September 2020

Annals of Clinical and Translational Neurology 2020; 7(12): 2544–2545

doi: 10.1002/acn3.51222

We appreciate Li and colleagues' interest¹ in our work which did not identify associated *NOTCH2NLC* CGG expansion after screening a large pathologically confirmed cohort of European neuronal intranuclear inclusion disease (NIID) and additional cases with other brain intranuclear inclusions.² Given that over 90% of East Asian NIID patients have *NOTCH2NLC* expansion,^{3,4} our findings show that this is an uncommon cause of European NIID.

Li *et al.* argue that we have not provided evidence for NIID being genetically heterogeneous given that: (i) we do not identify an alternative causative variant in these individuals and (ii) question the validity of diagnosis in our pathologically confirmed cases.¹ While we are still striving to identify the genetic cause within our *NOTCH2NLC*-negative cases, genetic heterogeneity has become the rule rather than the exception for neurological diseases,⁵ forming a major bottleneck to diagnosis in most rare genetic disorders.⁶ This is exemplified in familial amyotrophic lateral sclerosis (FALS), in which, for many years, there was only one known associated gene (*SOD1*) in a small proportion of cases.⁷ Despite this, FALS was still viewed as genetically heterogeneous in the remainder.^{7,8} FALS is one example among many complex and Mendelian neurological disorders that follow this trend. Likewise, it seems most probable that NIID also exhibits genetic heterogeneity. In fact, genetic heterogeneity is already being recognized in studying independent NIID cohorts, as exemplified by the recently reported case of *NOTCH2NLC* expansion-negative infantile-onset NIID.⁹

Furthermore, we remain confident of our findings since all our NIID cases have received stringent neuropathological characterization from brain banks globally and

incorporate established and published cases with high confidence including the initial case coining the term NIID;¹⁰ and a case series that highlighted the differences between NIID and fragile X-associated tremor/ataxia syndrome (FXTAS)¹¹ among others.^{12,13} Additionally, cases have been screened for the FXTAS *FMRI* premutation and an FXTAS case was used as a negative control (cases 2-11, Table 11²). Nonetheless, Li and colleagues suggest that our pathologically confirmed cases would benefit from radiological data to affirm diagnosis, although no consensus NIID diagnostic criteria using imaging currently exist. In fact, our review of published cases highlights the lack of typical imaging findings in European patients ($P = 1.098 \times 10^{-17}$) and only ~70% of Japanese NIID have MRI DWI changes (Figure 1c²).

Therefore, these findings lead us to conclude that European NIID cases are most likely to represent a distinct clinical and genetic disease entity, which, when explained, could provide important insights into underlying pathological mechanisms.

Conflict of Interest

The authors declare no competing interests.

References

1. Li H, Sun M, Wan B, Xu X. No evidence supports genetic heterogeneity of Neuronal intranuclear inclusion disease. *Ann Clin Transl Neurol* 2020; In press.
2. Chen Z, Yan Yau W, Jaunmuktane Z, et al. Neuronal intranuclear inclusion disease is genetically heterogeneous.

- Ann Clin Transl Neurol 7: 1716–1725. <https://doi.org/10.1002/acn3.51151>
- Ishiura H, Shibata S, Yoshimura J, et al. Noncoding CGG repeat expansions in neuronal intranuclear inclusion disease, oculopharyngodistal myopathy and an overlapping disease. *Nat Genet* 2019;51:1222–1232.
 - Sone J, Mitsuhashi S, Fujita A, et al. Long-read sequencing identifies GGC repeat expansions in NOTCH2NLC associated with neuronal intranuclear inclusion disease. *Nat Genet* 2019;51:1215–1221.
 - Warman Chardon J, Beaulieu C, Hartley T, et al. Axons to exons: the molecular diagnosis of rare neurological diseases by next-generation sequencing. *Curr Neurol Neurosci Rep* 2015;15:64.
 - Boycott KM, Hartley T, Biesecker LG, et al. A diagnosis for all rare genetic diseases: the horizon and the next frontiers. *Cell* 2019;177:32–37.
 - Al-Chalabi A, Jones A, Troakes C, et al. The genetics and neuropathology of amyotrophic lateral sclerosis. *Acta Neuropathol* 2012;124:339–352.
 - Roggenbuck J, Quick A, Kolb SJ. Genetic testing and genetic counseling for amyotrophic lateral sclerosis: an update for clinicians. *Genet Med* 2017;19:267–274.
 - Jedlickova I, Pristoupilova A, Hulkova H, et al. NOTCH2NLC CGG repeats are not expanded and skin biopsy was negative in an infantile patient with neuronal intranuclear inclusion disease. *J Neuropathol Exp Neurol* 2020;79:1065–1071.
 - Haltia M, Somer H, Palo J, Johnson WG. Neuronal intranuclear inclusion disease in identical twins. *Ann Neurol* 1984;15:316–321.
 - Gelpi E, Botta-Orfila T, Bodi L, et al. Neuronal intranuclear (hyaline) inclusion disease and fragile X-associated tremor/ataxia syndrome: a morphological and molecular dilemma. *Brain* 2017;140:e51–e51.
 - O’Sullivan JD, Hanagasi HA, Daniel SE, et al. Neuronal intranuclear inclusion disease and juvenile Parkinsonism. *Movement Dis* 2000;15:990–995.
 - Kimber TE, Blumbergs PC, Rice JP, et al. Familial neuronal intranuclear inclusion disease with ubiquitin positive inclusions. *J Neurol Sci* 1998;160:33–40.