ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

REPLY TO LETTER

Reply: Genetic heterogeneity of neuronal intranuclear inclusion disease. What about the infantile variant?

Wai Yan Yau[1], Zhongbo Chen[1,2], Roisin Sullivan[1], Jana Vandrovcova[1] & Henry Houlden[1,3]

[1]Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom
[2]Department of Neurodegenerative Diseases, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom
[3]Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, London, United Kingdom

Correspondence
Wai Yan Yau, Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom. Tel: +44 (0)203 4484249; E-mail: wai.yau.17@ucl.ac.uk

Funding Information
W.Y.Y. receives a PhD studentship from Ataxia UK and Rosetree Trust and funding from a Nicholas Blair MDSANZ traveling fellowship. R.S. receives funding from MRC. Z.C. is supported by a clinical fellowship from the Leonard Wolfson Foundation. We are grateful to the Medical Research Council (MRC), The Wellcome Trust Synaptopathies award, MRC Centre grant (G0601943), Ataxia UK, The Rosetrees Trust, Brain Research UK, UCL ODA/LMIC award, The MSA Trust, MDUK, The Muscular Dystrophy Association (MDA). This research was also supported by the UCL/UCLH National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Received: 11 February 2021; Accepted: 11 February 2021
Annals of Clinical and Translational Neurology **2021; 8(4): 1002–1004**

doi: 10.1002/acn3.51330

We thank Sikora et al. for their interest in our work and their letter that highlighted the distinctive clinical manifestations and disease trajectory of infantile neuronal intranuclear inclusion disease (iNIID).[1] The authors provided a summary of all published cases of iNIID and has demonstrated that iNIID is a rapidly progressive neurodegenerative disorder across different ethnicities with complex phenotypes; the unifying features in these patients were ataxia and cerebellar atrophy. None of the patients lived beyond ten years old. In comparison, dementia, neuropathy, myopathy, leukoencephalopathy and other movement disorders are more common clinical manifestations of juvenile and adult-onset NIID carrying the GGC repeat expansion in *NOTCH2NLC* and their disease course usually spans decades.[2,3] Although neuronal intranuclear inclusions were found throughout tissues in the nervous system and other organs, patients with iNIID do not have typical MRI findings of hyperintensity in the corticomedullary junction on diffusion-weighted sequences and typical NIIs on skin biopsy.

We concede that our study and algorithm predominantly focused on juvenile and adult-onset NIID, partly due to the rarity of reported iNIID.[4] The report of the European infant with iNIID who was also tested negative for the *NOTCH2NLC* GGC repeat expansion strengthens our proposal that NIID is a genetically heterogeneous disease.[5] NIID patients of European descent likely carry the same trinucleotide repeat at a different genetic locus, analogous to the recent discovery of a pentanucleotide expansion in six different genetic loci responsible for benign adult familial myoclonic epilepsy in different ethnic populations.[6] Inherent attributes of repeat expansion disorders may also explain the difference in the phenotypes between infantile and juvenile/adult-onset NIID. We hypothesize that iNIID patients may carry a much larger repeat expansion or they may carry biallelic expansions of the same repeat. The clinical disease heterogeneity can be seen in other repeat expansion disorders such as spinocerebellar ataxia 3: a larger CAG repeat expansion manifests with childhood-onset spasticity and parkinsonism without ataxia whilst a shorter repeat allele causes ataxia and peripheral neuropathy at a later age.[7,8] However, we agree with Sikora et al that iNIID may also be a distinct genetic disorder to juvenile and adult-onset NIID. Figure 1 provides a simplified overview of current understandings in different forms of NIID. Future collaboration and analysis of mutation-negative cases of NIID will be paramount in solving this genetic conundrum and help patients achieve a genetic diagnosis.

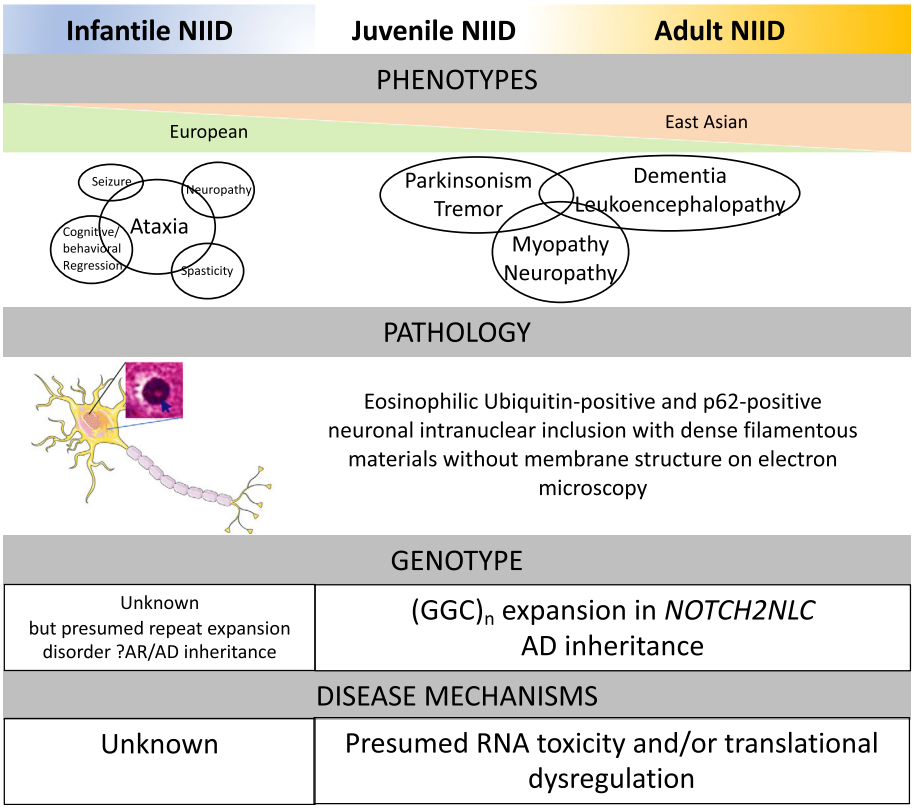

Figure 1. An overview of current understanding in the clinico-pathologico-genetic correlation of infantile-, juvenile- and adult-onset NIID.

Acknowledgments

W.Y.Y. receives a PhD studentship from Ataxia UK and Rosetree Trust and funding from a Nicholas Blair MDSANZ traveling fellowship. R.S. receives funding from MRC. Z.C. is supported by a clinical fellowship from the Leonard Wolfson Foundation. We are grateful to the Medical Research Council (MRC), The Wellcome Trust Synaptopathies award, MRC Centre grant (G0601943), Ataxia UK, The Rosetrees Trust, Brain Research UK, UCL ODA/LMIC award, The MSA Trust, MDUK, The Muscular Dystrophy Association (MDA). This research was also supported by the UCL/UCLH National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Authors' Contributions

WYY, ZC, RS, JV and HH contributed to drafting the text, preparing the figures and critical review of the final manuscript.

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

Not applicable.

References

1. Sikora J, Jedličková I, Přistoupilová A, et al. Genetic heterogeneity of neuronal intranuclear inclusion disease. What about the infantile variant? Ann Clin Transl Neurol 2021. https://doi.org/10.1002/acn3.51222
2. 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.
3. 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.
4. Chen Z, Yan Yau W, Jaunmuktane Z, et al. Neuronal intranuclear inclusion disease is genetically heterogeneous. Ann Clin Transl Neurol 2020;7:1716–1725.
5. 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.

6. Ishiura H, Tsuji S. Advances in repeat expansion diseases and a new concept of repeat motif-phenotype correlation. Curr Opin Genet Dev 2020;65:176–185.
7. Lu CS, Chang HC, Kuo PC, et al. The parkinsonian phenotype of spinocerebellar ataxia type 3 in a Taiwanese family. Parkinsonism Relat Disord 2004;10: 369–373.
8. Riess O, Rub U, Pastore A, et al. SCA3: neurological features, pathogenesis and animal models. Cerebellum 2008;7:125–137.

