


REPLY TO LETTER

Reply: Genetic heterogeneity of neuronal intranuclear inclusion disease. What about the infantile variant?Wai Yan Yau¹ , Zhongbo Chen^{1,2} , Roisin Sullivan¹ , Jana Vandrovcova¹ & Henry Houlden^{1,3}¹Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom²Department of Neurodegenerative Diseases, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom³Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, London, United Kingdom**Correspondence**

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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.

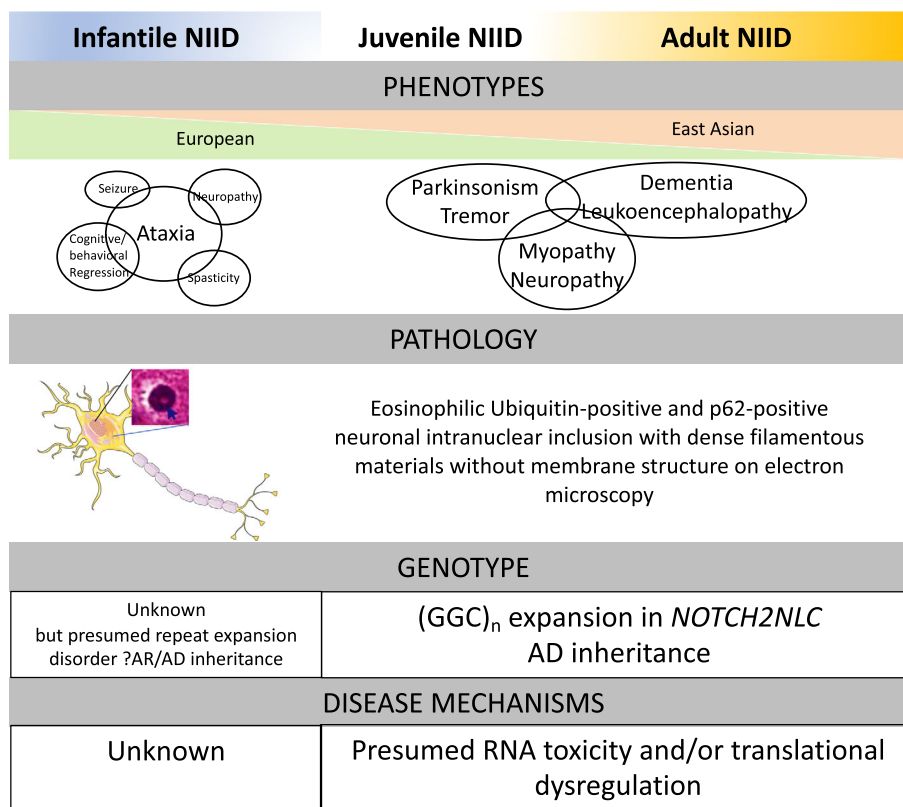


Figure 1. An overview of current understanding in the clinico-pathologico-genetic correlation of infantile-, juvenile- and adult-onset NIID.

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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.

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