ANNALS of Clinical and Translational Neurology
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AMERICAN NEUROLOGICAL ASSOCIATION

LETTER

No evidence supports the genetic heterogeneity of Neuronal intranuclear inclusion disease

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Funding information
This work was supported by the grants from the National Key R&D Program of China (2017YFE0103700 and 2019YFA0802600), the National Science Foundation of China (81771454 and 81974244), and Jiangsu Province's Key Discipline of Prenatal Diagnosis (FXK201746).

Received: 28 August 2012; Accepted: 15 February 2013

Annals of Clinical and Translational Neurology **2020; 7(12): 2542–2543**

doi: 10.1002/acn3.51223

Dear Editor,

We read with great interest the recently published article by Chen et al. titled neuronal intranuclear inclusion disease is genetically heterogeneous.[1] In this study, the authors examined the GGC repeat expansion of the *NOTCH2NLC* gene in the patients with the clinical diagnosis of neuronal intranuclear inclusion disease (NIID). They found that only one patient had abnormal GGC repeat expansion of *NOTCH2NLC* in 12 patients diagnosed with NIID, and concluded that NIID is genetically heterogeneous. Although we believe that there is a possibility for this conclusion, we do not agree with the authors' inference without evidence.

First, the authors did not propose a new genetic mutation as the pathogenic genes of NIID. At present, the published literature shows that *NOTCH2NLC* is the only causative gene reported for the genetic diagnosis of NIID.[2,3] Although the authors did not find expanded GGC repeats in the *NOTCH2NLC* gene in 11 patients clinically diagnosed with NIID in the European population, we think it is inappropriate to infer the genetic heterogeneity without evidence of new causative genes for NIID.

Second, the clinical manifestations and pathological results caused by *FMR1* mutation[4] are very similar to those of *NOTCH2NLC* mutation, and it is a possible heterogeneous gene that causes NIID. However, *FMR1* repeated CGG expansion results in a disease called fragile X-associated tremor/ataxia syndrome (FXTAS) in clinical diagnosis, it is not NIID.[4] At the same time, the authors also considered them to be two different diseases in their own diagnostic criteria, denying the possibility that *FMR1* is a heterogeneous gene. Therefore, even if other genes cause similar pathophysiological processes and clinical manifestations, they may be two completely different diseases. In the authors' own diagnostic criteria, only *NOTCH2NLC* repeat expansion causes NIID, as does not reflect the view that NIID has genetic heterogeneity.

Finally, the author's diagnosis of NIID mainly relies on pathological results, but intranuclear eosinophilic ubiquitinated inclusions also have been reported in a variety of neurodegenerative diseases besides NIID.[4,5] Although the authors had demonstrated this point, the conclusion is that *NOTCH2NLC* expansion is not the only driver for diseases with neuronal intranuclear inclusions (NIIs), and it is not a supplement to the conclusion that NIID is genetically heterogeneous. In addition, the authors should also provide more evidence to prove the correctness of the diagnosis in their patients, such as imaging results.

In conclusion, we believe that there was no evidence to support the genetic heterogeneity of NIID so far.

Conflict of Interest

All authors report no disclosures.

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