



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

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Complete List of Authors:	Chen, Zhongbo; UCL Institute of Neurology, Department of Neuromuscular Diseases; UCL Institute of Neurology, Department of Neurodegenerative Diseases Ryten, Mina; UCL Institute of Neurology, Department of Molecular Neuroscience; King's College London , Department of Medical & Molecular Genetics Houlden, Henry; Institute of Neurology, Department of Molecular Neuroscience
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Abstract:	

Reply to: “No evidence supports genetic heterogeneity of Neuronal intranuclear inclusion disease”

Running title Reply to: No evidence supports genetic heterogeneity of NIID

Zhongbo Chen¹, Mina Ryten¹, Henry Houlden²

1. Department of Neurodegenerative Disease, Queen Square Institute of Neurology, University College London (UCL), UK
2. Department of Neuromuscular Disease, Queen Square Institute of Neurology, UCL, UK

Correspondence

Dr 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

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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 inclusions². 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 cases¹. 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 diseases⁵, forming a major bottleneck to diagnosis in most rare genetic disorders⁶. 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 cases⁷. 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 recognised in studying independent NIID cohorts, as exemplified by the recently-reported case of *NOTCH2NLC* expansion-negative infantile-onset NIID⁹.

Furthermore, we remain confident of our findings since all our NIID cases have received stringent neuropathological characterisation from brain banks globally and incorporate established and published cases with high confidence including the initial case coining the term NIID¹⁰; and a case series that highlighted 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 (Case 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 exists. In fact, our review of published cases highlights 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.

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