NOTCH2NLC Intermediate-length Repeat Expansion and Parkinson's Disease in Patients of European Descent

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Out of 1011 sporadic Parkinson's Disease (PD) patients of Chinese ethnicity, Shi et al. identified 11 patients with intermediate-length GGC repeat expansions (41-64 repeats) in *NOTCH2NLC*[1]. Interestingly, the skin samples in 2 of these patients demonstrated phospho-alpha-synuclein deposition rather than the typical inclusion bodies of neuronal intranuclear inclusion disease. We aimed to validate the association between this intermediate-length repeat expansions and PD in an ethnically different cohort.

We estimated the *NOTCH2NLC* GGC allele sizes in 825 PD patients of European descent—in whom pathogenic repeat expansions were previously excluded[2]—by amplifying the genomic DNA region containing the repeat using polymerase chain reaction primers specific for *NOTCH2NLC*[3]. The genomic DNA of all patients were from the National Institute of Neurological Disorders and Stroke Human Genetics and Cell Line Repository, United States. The study was approved by the joint ethics committee of University College London Queen Square Institute of Neurology and National Hospital for Neurology and Neurosurgery, United Kingdom (UCL: 19/LO/1796).

In our PD cohort, we did not identify any patient with intermediate-length repeat expansions. The estimated repeat sizes ranged from 10 to 38 in our patients (Figure 1). Our study is limited by a lack of a control group. In addition, use of long-read sequencing may also achieve better estimates of GGC repeat sizes and ascertain the presence of repeat interruption. However, these factors should not impact on the result of this study.

Despite of the negative screen in our cohort, another case-control study in 1000 Chinese sporadic PD patients identified that 1% of them carried intermediate-length GGC repeat expansions in *NOTCH2NLC*[4]. Furthermore, gray-zone GGC alleles (41-54 repeats) at *FMR1*—another neurodegenerative disease caused by polyglycine expansions—are also associated with increased risk of PD in women[5]. Shi et al. posited *NOTCH2NLC* protein upregulation and autophagy dysfunction as the potential pathomechanism in PD patients with intermediate-length GGC repeat expansions[1]. Therefore, the role of intermediate-length GGC in *NOTCH2NLC* as a genetic risk factor of PD remains to be confirmed and requires further studies with larger longitudinal clinic-pathological cohorts.

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Author contributions

WYY, RS, NWW and HH contributed to conception and design of the study; WYY, RS, CR, EC and JV contributed to the acquisition and analysis of data; WYY and RS contributed to drafting the text and preparing the figures.

Potential conflicts of interest

The authors declare no competing interests.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Figure legend

Figure 1. Distribution of the GGC repeat length of *NOTCH2NLC* in the 825 Parkinson's disease patients of European descent.

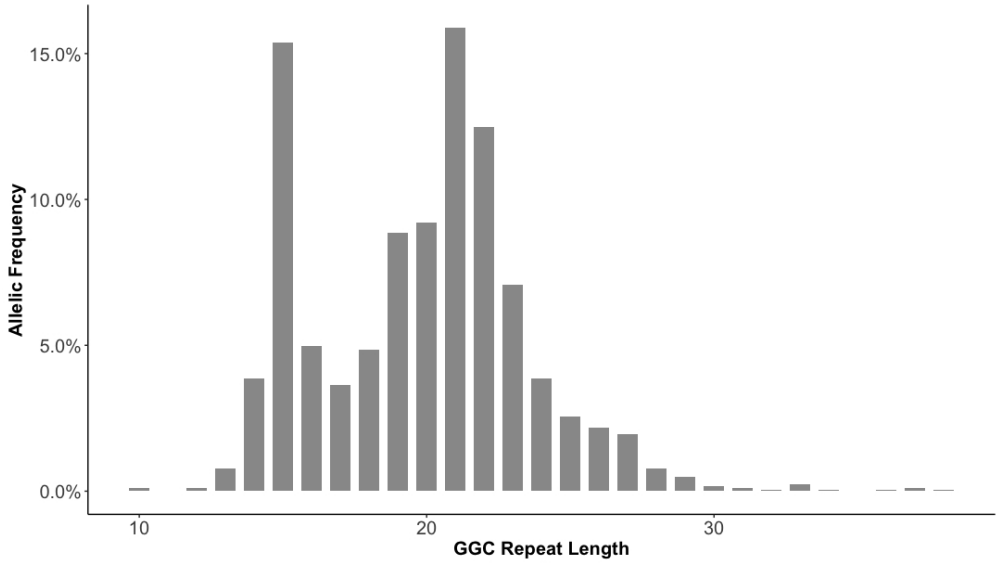

Figure 1. Distribution of the GGC repeat length of NOTCH2NLC in the 825 white patients with Parkinson's Disease.

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