

## CAG Somatic Instability in a Huntington Disease Expansion Carrier Presenting with a Progressive Supranuclear Palsy-like Phenotype

Pathogenic expansions in huntingtin (*HTT*) may present as progressive supranuclear palsy (PSP)/frontotemporal degeneration, or amyotrophic lateral sclerosis (ALS), without chorea.<sup>1</sup> We present the first autopsy report of a PSP-like presentation, with study of somatic CAG expansion. A 68-year-old man presented with falls, cognitive impairment, and speech decline over 2 years. He had vertical supranuclear palsy, paucity of speech with a growling character, reduced verbal fluency, apraxia, mild bradykinesia and rigidity, brisk reflexes, but flexor plantars, and no fasciculations. His parents had died relatively young of unrelated causes. The clinical picture resembled PSP, but MRI brain revealed frontoparietal atrophy, with less prominent midbrain and cerebellar atrophy, and small vessel disease. He did not tolerate levodopa or amantadine and rapidly progressed with mobility loss, dysphagia, visual hallucinations, a sweet tooth, and aggression. *C9orf72* testing was negative. After his son developed chorea and was diagnosed with Huntington's disease (HD), he was tested and had 42 CAG repeats, associated with a mean predicted motor onset age of 52.<sup>2</sup> He died at age 73, without developing chorea. Autopsy revealed typical p62 and 1C2 immunoreactive nuclear inclusions with widespread distribution and severe caudate atrophy (Vonsattel grade 4) and additional limbic TDP43 pathology without motor neuron involvement (Supplementary Fig. S1), in contrast to four ALS-like cases.<sup>1,3</sup> Whole genome sequencing of brain DNA revealed no mutations in 111 genes associated with neurodegeneration,<sup>4</sup> and analysis by ExpansionHunter<sup>5</sup> confirmed the HD expansion (size: 44 repeats) and normal *C9orf72*.

The unusual presentation prompted us to investigate mosaicism because of somatic CAG repeat instability, a well-known phenomenon,<sup>1,6,7</sup> in 17 brain regions. In parallel, we analyzed in a blinded fashion another HD male with 42 repeats, typical

presentation at 55, and mild caudate atrophy (Vonsattel grade 2). We calculated the somatic expansion index,<sup>1,7</sup> which revealed instability in several regions (Fig. 1), and compared this between them and with published reports. The most striking finding in the atypical case was the relative absence of somatic expansion in the caudate, where it was pronounced in the typical case, consistent with previous reports.<sup>1,6-8</sup> The pontine base showed somatic instability in the atypical patient and was relatively spared in the typical and had also been spared in previously reported typical HD and an ALS case.<sup>1</sup> The thalamus and amygdala showed instability in the atypical case, less in typical cases, and were relatively spared in an ALS case. The cerebellum was mildly affected in our atypical case, relatively spared in typical cases, and completely spared in ALS.<sup>1</sup>

Although we cannot fully exclude the possibility of a TDP-43-related phenotype, rather than atypical HD, the clear HD pathology and limited TDP-43 pathology support the latter. Our case suggests that a PSP-like HD presentation may be associated with less detectable somatic CAG instability in the caudate and more in other regions, such as the pons. Because we cannot investigate lost neurons, we cannot determine whether the caudate instability was originally low or appears so because of advanced striatal neuronal loss following somatic expansion.<sup>9</sup> In the latter case, it may be initial increased somatic CAG expansion that underlies a PSP-like phenotype. Detailed studies of typical and atypical HD cases are required to determine whether distinct regional somatic instability patterns or co-existing TDP-43 pathology influence the phenotype. ■

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## Ethics Statement

All participants gave informed consent before donating brains for research. Ethics approval is provided by the UK National Research Ethics Service (07/MRE09/72). All donors had given informed consent for the use of the brains in research. ■

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**Key Words:** Huntington's disease; PSP; CAG repeat; mosaicism; TDP-43; somatic instability

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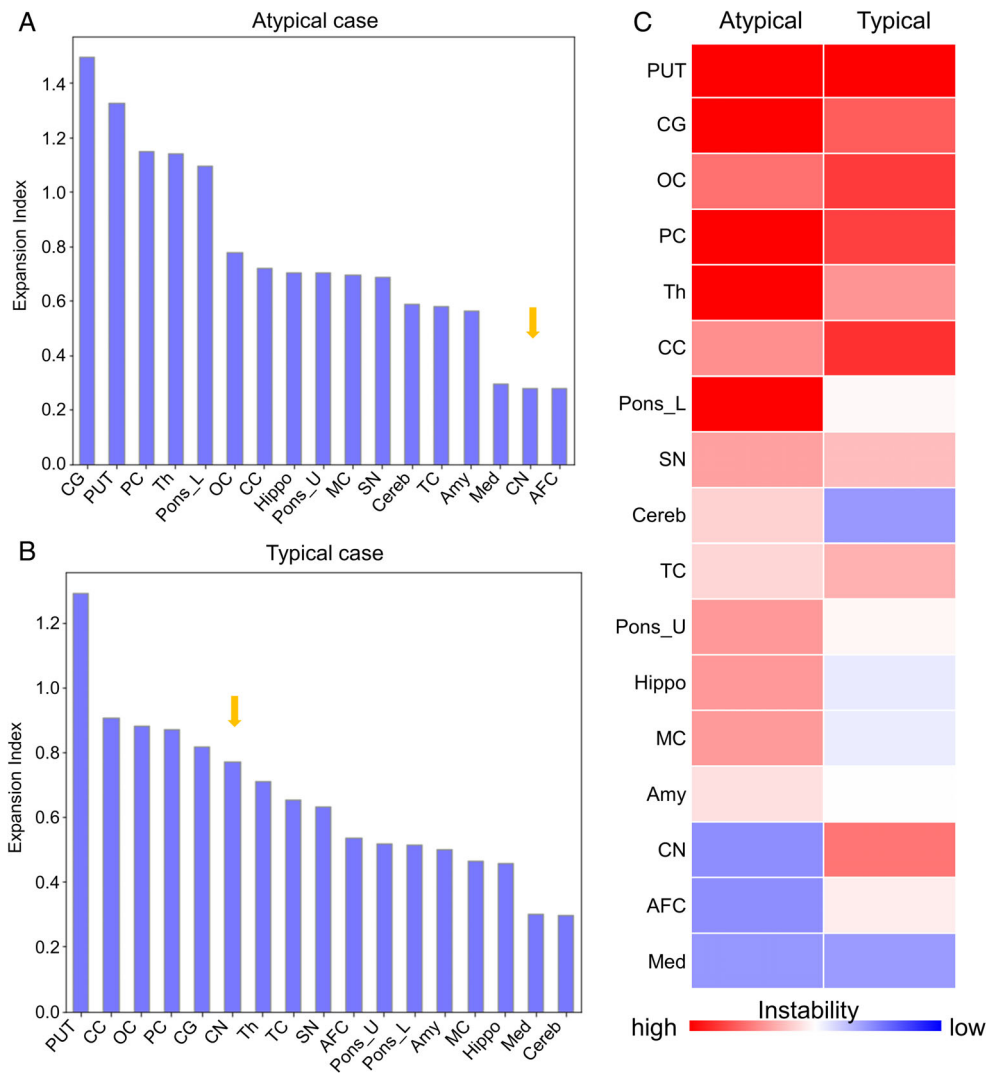
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## Relevant conflicts of interest/financial disclosures:

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**FIG. 1.** Quantitative analysis of somatic CAG instability in an HTT-expansion carrier with atypical presentation and a typical HD patient. **(A,B)** Somatic expansion index in each region of **(A)** the atypical case and **(B)** the typical case. The arrow points to the caudate nucleus. **(C)** Heatmap of the expansion index, arranged in order of mean expansion index for each region, from high to low. PUT = putamen, CG = cingulate gyrus, OC = occipital cortex, PC = parietal cortex, Th = thalamus, CC = corpus callosum, Pons\_L = lower pons, SN = substantia nigra, Cereb = cerebellum, TC = temporal cortex, Pons\_U = upper pons, Hippo = hippocampus, MC = motor cortex, Amy = amygdala, CN = caudate nucleus, AFC = anterior frontal cortex, Med = medulla. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, subject to formal approval by the Queen Square Brain Bank. The data are not publicly available due to privacy or ethical restrictions.

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## References

- Dewan R, Chia R, Ding J, et al. Pathogenic huntingtin repeat expansions in patients with frontotemporal dementia and amyotrophic lateral sclerosis. *Neuron* 2021;109(3):448–460.e4.
- Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR, International Huntington's Disease Collaborative Group. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin Genet* 2004; 65(4):267–277.
- Tada M, Coon EA, Osmand AP, et al. Coexistence of Huntington's disease and amyotrophic lateral sclerosis: a clinicopathologic study. *Acta Neuropathol* 2012;124(5):749–760.
- Blauwendraat C, Faghri F, Pihlstrom L, et al. NeuroChip, an updated version of the NeuroX genotyping platform to rapidly screen for variants associated with neurological diseases. *Neurobiol Aging* 2017; 17(57):247.e9–247.e13.
- Dolzhenko E, Deshpande V, Schlesinger F, et al. ExpansionHunter: a sequence-graph-based tool to analyze variation in short tandem repeat regions. *Bioinformatics* 2019;35(22):4754–4756.
- Telenius H, Kremer B, Goldberg YP, et al. Somatic and gonadal mosaicism of the Huntington disease gene CAG repeat in brain and sperm. *Nat Genet* 1994;6(4):409–414.
- Mouro Pinto R, Arning L, Giordano JV, et al. Patterns of CAG repeat instability in the central nervous system and periphery in Huntington's disease and in spinocerebellar ataxia type 1. *Hum Mol Genet* 2020;29(15):2551–2567.
- Kono Y, Agawa Y, Watanabe Y, Ohama E, Nanba E, Nakashima K. Analysis of the CAG repeat number in a patient with Huntington's disease. *Intern Med* 1999;38(5):407–411.
- Kennedy L, Evans E, Chen C-M, Craven L, Detloff PJ, Ennis M, Shelbourne PF. Dramatic tissue-specific mutation length increases are an early molecular event in Huntington disease pathogenesis. *Hum Mol Genet* 2003;12(24):3359–3367.

## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

## Assessment of GGC Repeat Expansion in *GIPC1* in Patients with Parkinson's Disease

The cause of Parkinson's disease (PD) is still unclear, and it is thought to be caused by a combination of aging, genetic and environmental risk factors. Mutations of more than 20 genes

have been identified to cause PD.<sup>1</sup> Short tandem repeat (STR) expansions have been found to be associated with PD (eg, CAG expansions in several spinocerebellar ataxia genes, the expanded GGC (A trinucleotide repeat GGC expansion) repeat in Notch 2 N-Terminal Like C gene (*NOTCH2NLC*)).<sup>2,3</sup>

In this study, we aimed to explore the role of tandem repeat expansions in the pathogenesis of PD. Initially, 85 unrelated Chinese patients with PD were performed with whole-genome long-read sequencing (LRS) on the Oxford Nanopore PromethION platform (see [Appendix S1](#)). Based on the STR detection with LRS data, we found two patients with PD (PD-1 and PD-2) harboring pathologic GGC repeat expansions (larger than 70 repeats) in the 5' untranslated region of PDZ domain containing family member 1 gene (*GIPC1*) (Fig. 1A,B), which was identified as a frequent cause of Oculopharyngodistal myopathy (OPDM).<sup>4,5</sup> Repeat-primed polymerase chain reaction (RP-PCR) and GC-rich polymerase chain reaction (GC-PCR) were conducted to confirm the LRS results. The electropherogram demonstrated a sawtooth pattern in both cases, and the sizes of the detected expansion were 101 repeats and 85 repeats, respectively (Fig. 1C,D). Next, we screened GGC repeat expansion in *GIPC1* in a larger cohort of 2419 unrelated patients with PD using RP-PCR and GC-PCR (Table S1). We found that another 16 sporadic patients with PD also carried expanded GGC repeats in *GIPC1* (Fig. S1). Together, there were a total of 18 patients with PD who harbored GGC repeat expansions in *GIPC1*, and the GGC repeat sizes ranged from 70 to 401. A careful review of the clinical features of the patients carrying the pathogenic *GIPC1* GGC expansion confirmed the diagnosis of PD, and none of them manifested any OPDM phenotype (Figs. S2 and S3, Table S2; see [Appendix S1](#)).

Moreover, our study investigated the allelic distribution of *GIPC1* GGC repeat in the healthy population. Intriguingly, eight of 1631 Chinese healthy control subjects also showed *GIPC1* GGC repeat expansions (Fig. S4). Although the carrier rate of the pathogenic *GIPC1* GGC repeat expansions was higher among patients with PD than that among healthy individuals (0.72% vs. 0.49%, respectively) (Fig. 1E), no significant difference was observed in the distribution of pathogenic *GIPC1* GGC repeat between patients with PD and controls (Fisher's exact test  $P$  value = 0.42; odds ratio, 1.46; 95% confidence interval, 0.6060–3.9136).

In agreement with previously reported observations in OPDM,<sup>4,5</sup> we did note that the incomplete penetrance was presented in the family with PD (Figs. S5 and S6). Our finding, for

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