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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.[1] 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.[2] 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.[1,3] Whole genome sequencing of brain DNA revealed no mutations in 111 genes associated with neurodegeneration,[4] and analysis by ExpansionHunter[5] 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,[1,6,7] 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,[1,7] 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.[1,6-8] 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.[1] 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.[1]

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.[9] 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

*__Correspondence to:__ Prof. Christos Proukakis, Department of Clinical and Movement Neurosciences, Queen Square Institute of Neurology, UCL, Rowland Hill Street, London, NW3 2PF, UK; E-mail: c.proukakis@ucl.ac.uk

Ramita Dewan and Zane Jaunmuktane are joint first authors.

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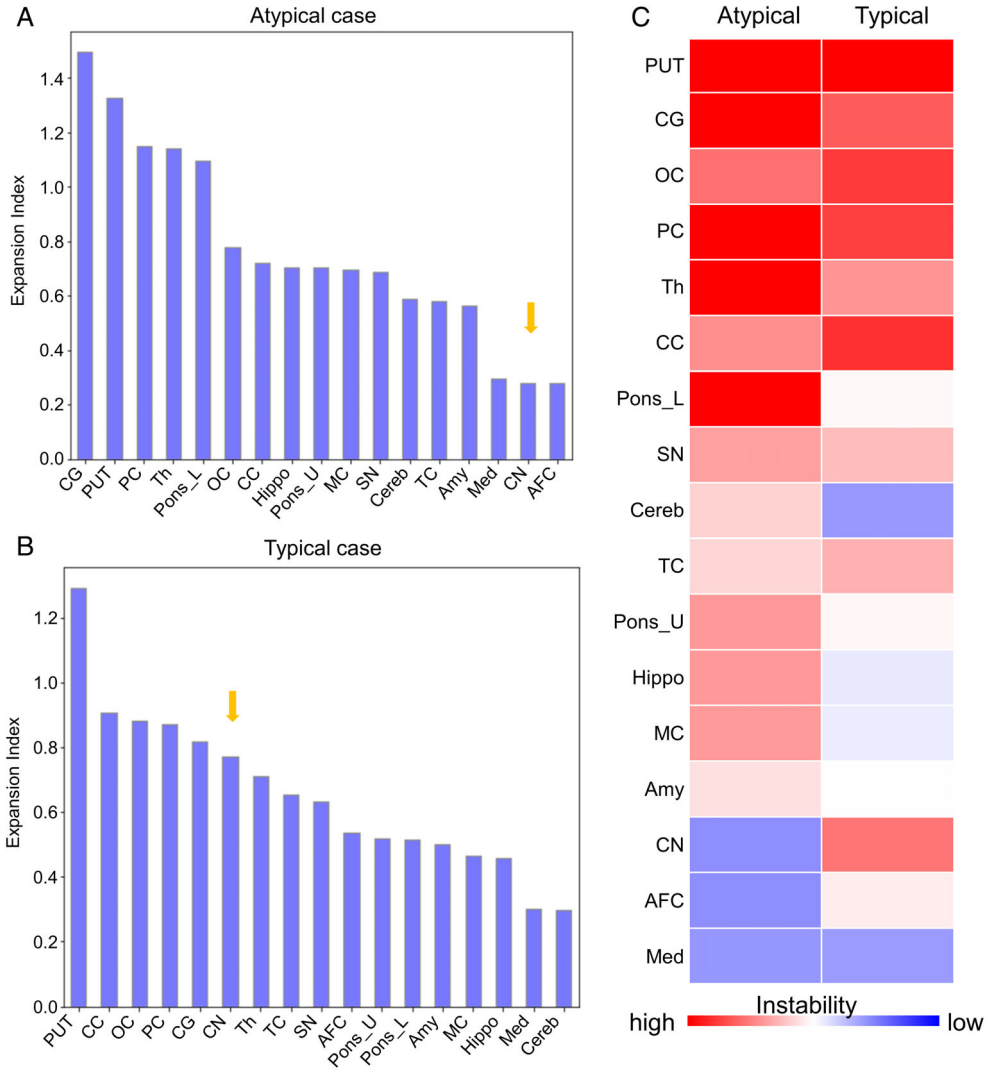

FIG.. 1. Quantitative analysis of somatic CAG instability in an HTT-expansion carrier with atypical presentation and a typical HD patient. (**A,B**) Somatic expansion index in each region of (**A**) the atypical case and (**B**) the typical case. The arrow points to the caudate nucleus. (**C**) Heatmap 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]

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.

Ramita Dewan, MD,[1] Zane Jaunmuktane, MD, FRCPath,[2,3] Monica Emili Garcia-Segura, MSc,[2] Catherine Strand, MSc,[3] Edward Wild, PhD, FRCP,[4,5] Joaquin Villar, PhD, FACMG,[6,7] Clifton L. Dalgard, PhD, CLS,[8,9] Sarah J. Tabrizi, MD, PhD,[4,5,10] Bryan J. Traynor, MD, PhD, FRCPI,[1] and Christos Proukakis, PhD, FRCP[2*]

[1]*Neuromuscular Disease Research Section, Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland, USA*

[2]*Department of Clinical and Movement Neurosciences, Queen Square Institute of Neurology, UCL, London, United Kingdom*

[3]*Queen Square Brain Bank, UCL, London, United Kingdom*

[4]*Huntington's Disease Centre, Queen Square Institute of Neurology, UCL, London, United Kingdom*

[5]*Department of Neurodegenerative Disease, Queen Square Institute of Neurology, UCL, London, United Kingdom*

[6]*Center for Military Precision Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA*

[7]*Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, Maryland, USA*

[8]*Department of Anatomy, Physiology, and Genetics, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA*

[9]*The American Genome Center, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA*

[10]*UK Dementia Research Institute, UCL, London, United Kingdom*

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Supporting Data

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

R.D.: 1B, 1C, 3B
Z.J.: 1B, 1C, 3B
M.E.G.S.: 1C, 3B
C.S.: 1B
E.W.: 1A, 3B
J.V.: 1C
C.L.D.: 1B,1C, 2B
S.J.T.:1A, 3B
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