

VAC14 gene-related parkinsonism-dystonia with response to deep brain stimulation

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The authors confirm that the approval of an institutional review board was not required for this work. Informed consent for videotaping was obtained and it is included in the submitted material for review. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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We report a 15-year-old girl with VAC14 gene-related juvenile parkinsonism-dystonia with substantial response to deep brain stimulation to the globus pallidus (GPi-DBS).

The patient was born in a middle-eastern country from consanguineous parents. Her past medical and family histories were unremarkable. At 12 years of age she developed focal dystonia of her left hand, which generalized over 2-1/2 years (**supplementary video 1**). She developed bradykinesia and freezing of gait, with intact cognition. Medical treatment was ineffective.

MRI of the brain demonstrated restricted diffusion of the bilateral corpus striatum, and T2 hypointensity with increased susceptibility of the globus pallidus and substantia nigra consistent with abnormal mineralization (**figure 1**) A clinically available gene panel

evaluating diseases in the spectrum of neurodegeneration with brain iron accumulation (NBIA) was non-diagnostic.

A chromosomal microarray returned with a duplication at 16p13.11 and multiple areas of homozygosity comprising 3% of the genome. The duplication was thought to be an incidental finding, given mismatch between patient and typical phenotype. Upon reviewing the areas of homozygosity, the VAC14 gene stood out as potential candidate based on previous reports.¹⁻³

Sequencing of the VAC14 gene identified a homozygous missense variant of unknown significance (p.Lys651Glu, c.1951A>G). The variant has not been previously described in publicly available databases (gnomAD, Exome Variant Server or 1000 Genomes), and involves a highly conserved amino acid in the protein C-terminal dimerization domain, where previous pathogenic mutations have been located.^{1,4} The alteration is non-conservative from a positively charged amino acid to a negatively charged one. In silico analysis with Mutation Taster predicted it to be disease-causing, but Align GVGD and SIFT predicted the variant to be benign and tolerated.

Patient's skin fibroblasts were analyzed for abnormal endolysosomal morphology, associated with loss of VAC14 function.⁵⁻⁷ Patient cells as well as control human fibroblasts were cultured at equal density in full media for 24 hours. Fields of the cells

were imaged and scored for the presence of visible perinuclear vacuoles. Cell culture – experiments using primary fibroblasts were carried out.¹ Briefly, all images were live cells captured using Leica DMIRB inverted fluorescence microscope. Transfections were carried out using Liofectamine 3000 (ThermoFisher).

The patient's fibroblasts demonstrated evidence of abnormal vacuolization in $76 \pm 2\%$ of cells. In a second experiment, normal VAC14 transfected into patient cells rescued the vacuoles, while GFP alone did not (**supplementary figure 2**).

At 15 years old the patient underwent GPi-DBS, based on literature supporting benefit of pallidal stimulation in early-onset dystonia and brain iron accumulation syndromes.^{8,9}

On initial examination, she had fluctuating tone without rigidity, 1+ hypomimia, 3+ symmetric bradykinesia and generalized dystonia. There was no resting, postural or kinetic tremor. She endorsed fatigue, constipation and joint pain. There was no cognitive change, dysautonomia or REM-sleep behavior disturbance. After 6 months of DBS, there was improvement in facial animation, 2+ bradykinesia and recovery of ambulatory capacity. She required 5 steps to recover from the pull test, with spontaneous retropulsion. Freezing of gait was noted upon turns. Dystonia was much improved. Baseline Burke Fahn Marsden (BFM) motor score was 86.5/120, disability score was 27/30. Within 6 months, motor score improved by 76% (to 21) and disability score improved by 56% (to 12, **supplementary video 2**). The patient also endorsed

improvements in pain and fatigue, but these were not formally measured. Medications and programming settings can be seen in supplementary table 1.

VAC14 encodes a dimeric scaffold protein that binds the lipid kinase PIKFYVE and the phosphatase FIG4. All three components are necessary for the synthesis of PI(3,5)P₂ in the endolysosomal membrane compartment. The mechanism leading to enlarged endolysosomal vacuoles is not known precisely, but it is postulated that decreased levels of PI(3,5)P₂ induce an osmotic effect. Alternatively, it is possible that dysfunction occurs through defects in membrane retrieval or fusion/fission.

Biallelic mutations in the VAC14 gene have been associated with three allelic disorders: childhood striatonigral degeneration, juvenile parkinsonism-dystonia and Yunis-Varon-like syndrome¹ Precise genotype-phenotype correlation is lacking, although it appears that truncating variants are associated with more severe phenotypes. Mouse models present with neurodegeneration and enlarged endolysosomal vacuoles, recapitulating the neuropathologic findings from human subjects.^{6,7,10} In the few patients reported so far, age of onset seems to range from 1.5 to 13 years with onset of dystonia in a limb with rapid generalization affecting gait.^{1,3,10} Imaging may demonstrate diffusion restriction in the striatum and susceptibility-weighted hypointensity in the pallidum and substantia nigra.¹ **(supplementary table 2).**

We believe that VAC14-related parkinsonism dystonia should be considered in the differential diagnosis of NBAs, especially if available genetic panels are negative. To our knowledge, there is no effective treatment. Our patient experienced substantial improvement in dystonia with GPi-DBS, but it is unclear whether benefit will be sustained. GPi-DBS may be considered if there is failure of medical therapy.

Author roles:

- 1. Research project: A. Conception; B. Organization, C. Execution**
- 2. Statistical analysis: A. Design, B. Execution, C. Review and Critique**
- 3. Manuscript preparation: A. Writing of the first draft, B. Review and Critique**

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Edward Yang: 1C, 3B

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Figure legends:

Figure 1. Axial SWI (A,B, E, F), FLAIR (C,G), and diffusion trace (D,H) sequences for the VAC14 proband at 14 years of age (A-D) and an age/sex matched control evaluated for headache (E-H). SWI imaging demonstrates abnormal susceptibility in the globus pallidus internus (arrows, A) and substantial nigra (arrows, B) as well as subtle diffusion abnormality in the corpus striatum (arrows, D). There was no convincing T2/FLAIR hyperintensity in the basal ganglia or substantia nigra (C).

Figure 2. Vacuolization of patient fibroblasts is rescued with VAC14. A) Live cell image of representative perinuclear vacuolization (arrow) seen in patient skin fibroblasts. B) Patient fibroblast vacuolization rescued by cotransfection of VAC14 and GFP. C) Quantification of vacuolization in patient and control fibroblasts as well as rescue of vacuolization following VAC14 transfection. (Scale bars, 50 μm ; Error bars, standard deviation)

Video legends:

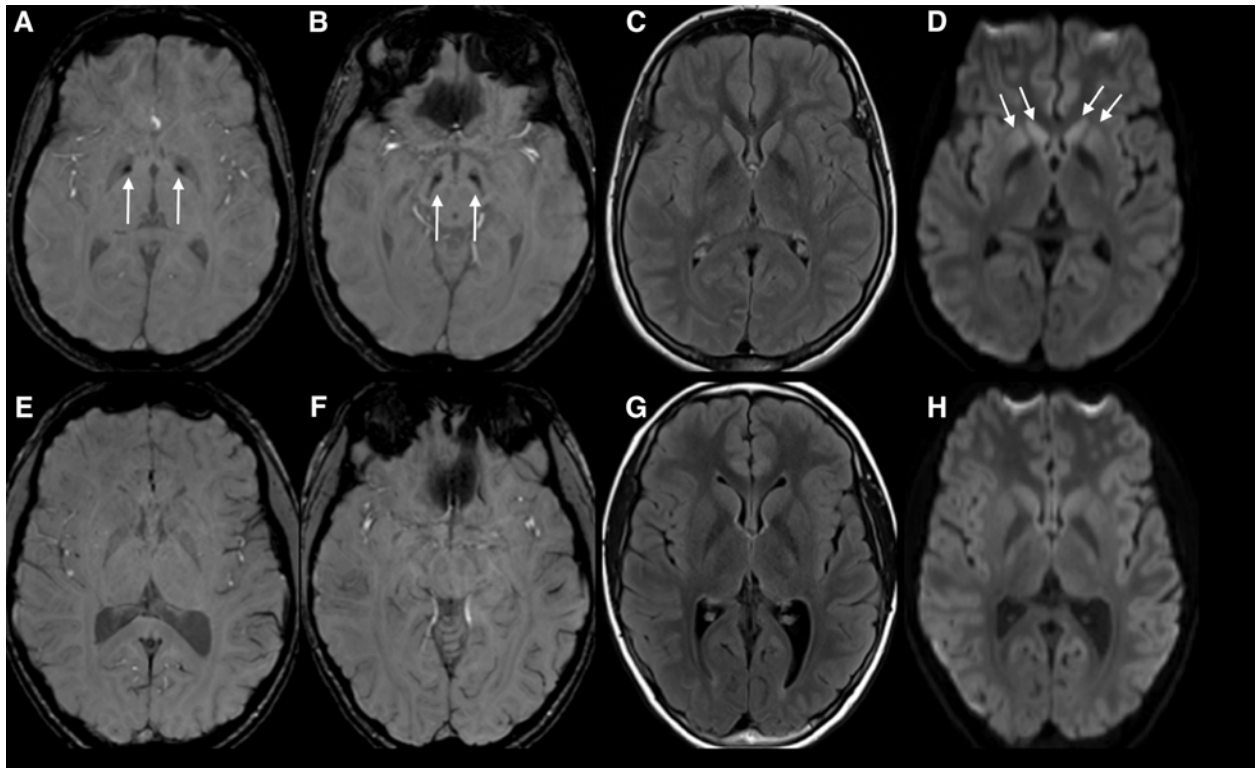
Video 1: Baseline. The patient is non-ambulatory, with severe generalized dystonia affecting the neck, trunk and extremities. Bradykinesia is noted on repeated finger tapping.

Video 2: First segment: 3 months after DBS. There is improvement in truncal and appendicular dystonia. Segment 2: 6 months after DBS. Further improvement in dystonia is noted. The patient can walk independently.

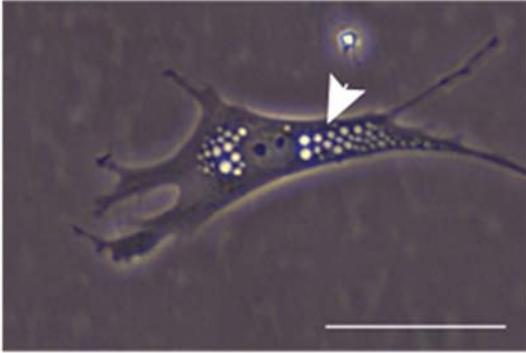
Supplementary material legends:

Supplementary Table 1: Deep Brain Stimulation settings, Burke-Fahn Marsden scale and medications

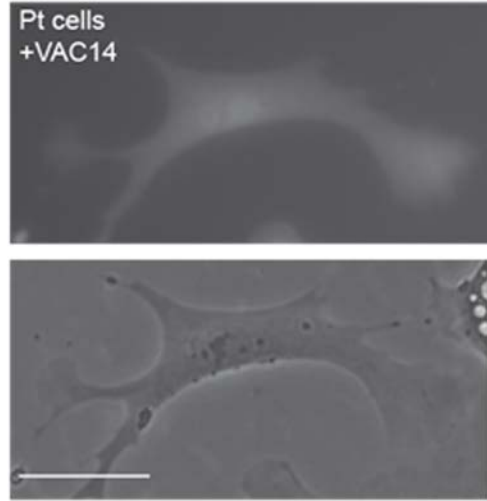
Supplementary Table 2: Published reports of VAC14-related gene disorders, at the time of manuscript submission. Table includes genetic and clinical characteristics. Papers are referenced in the bibliography section of the main manuscript.



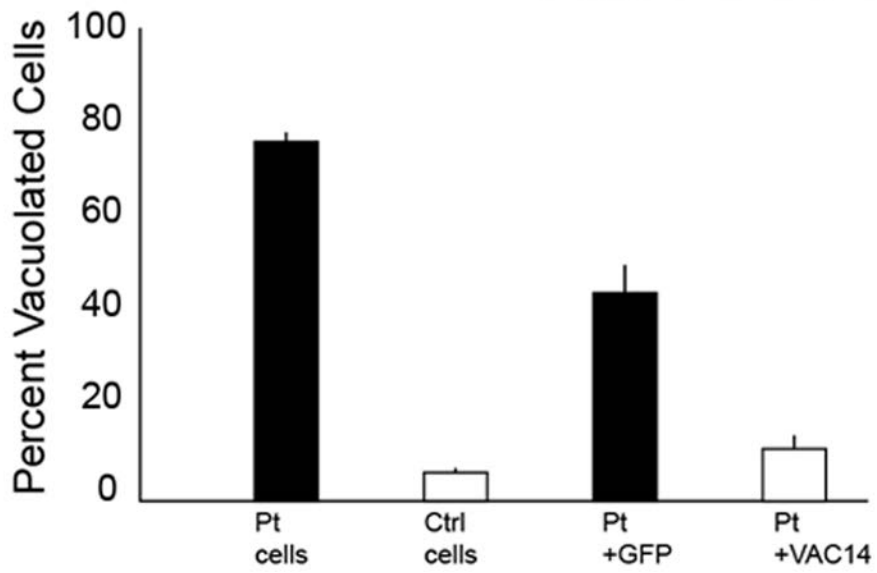
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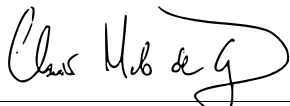
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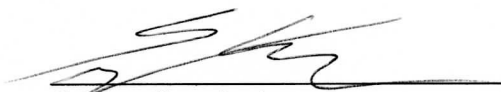
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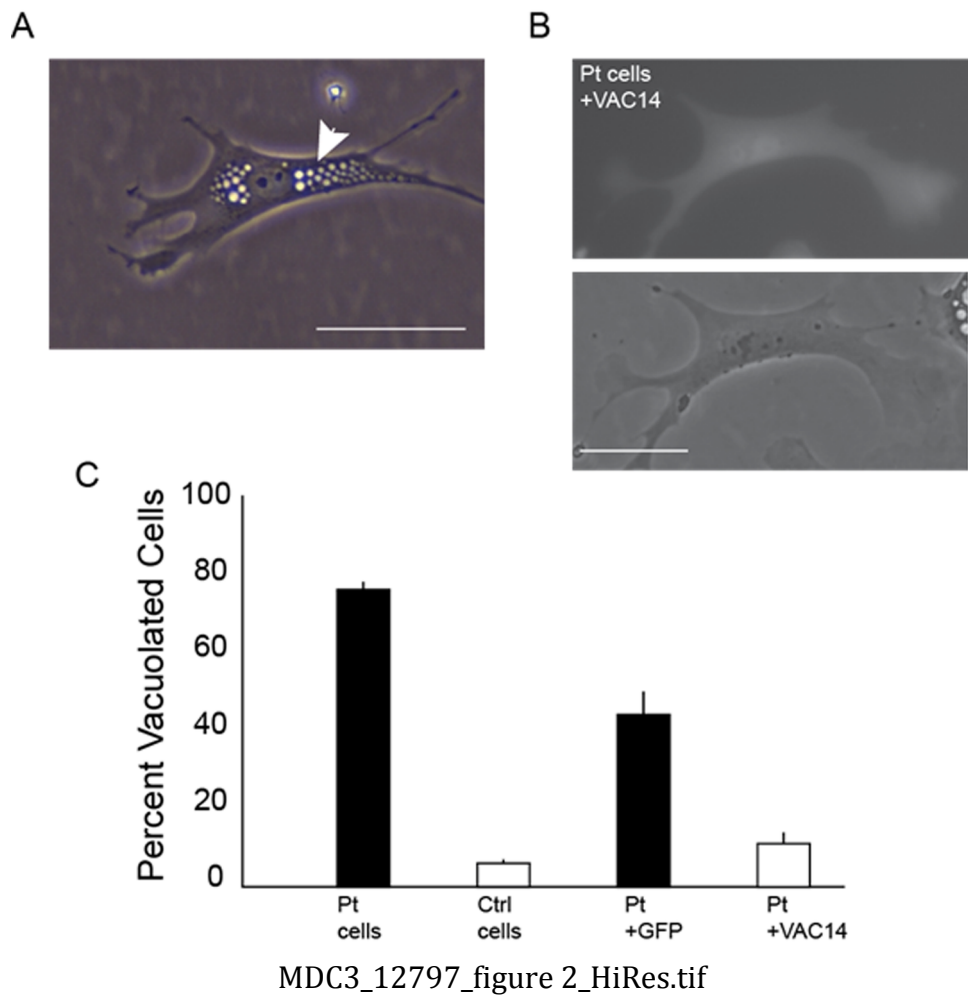
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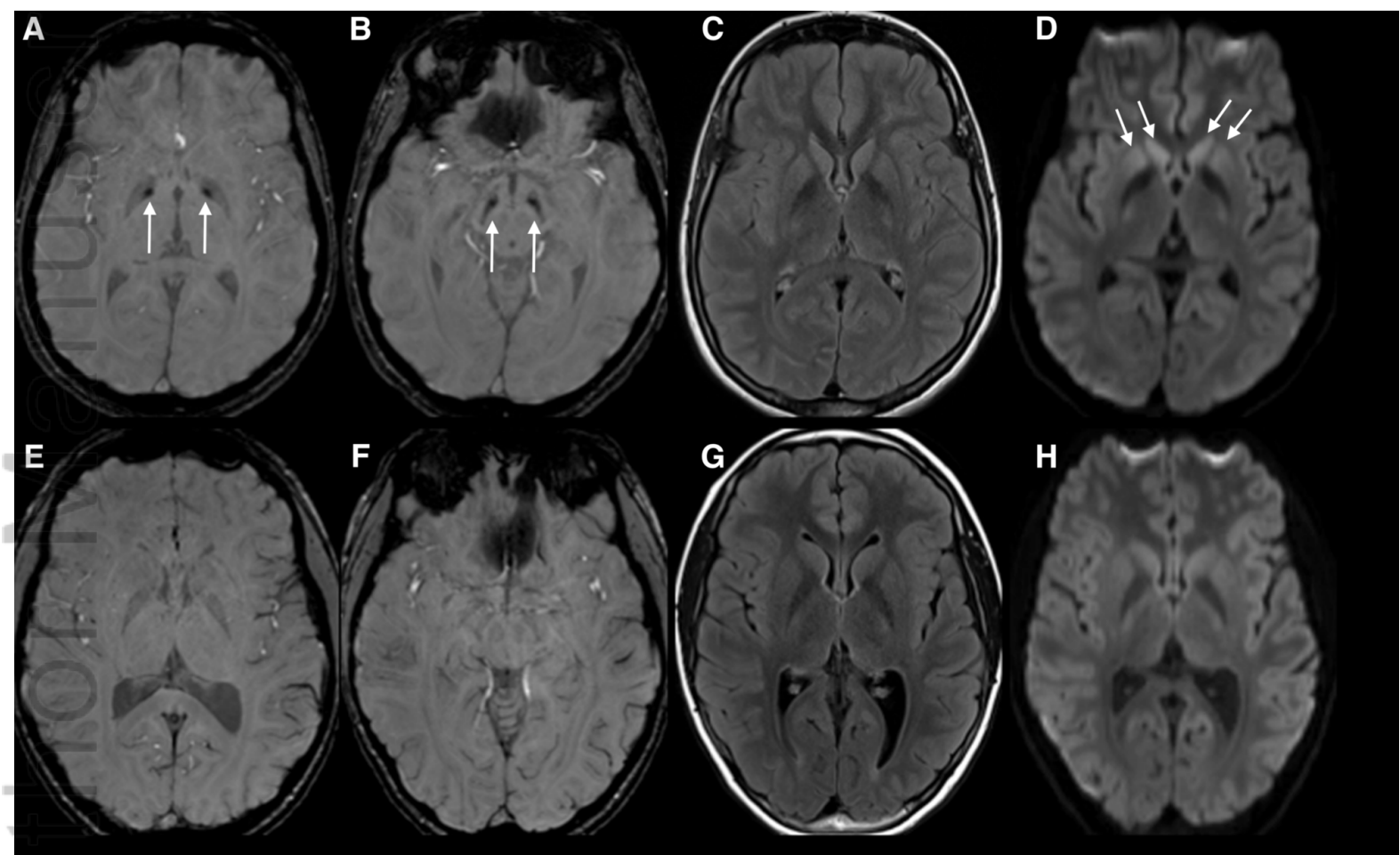
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