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Supporting Data

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A Novel *NPTX1* de novo Variant in a Late-Onset Ataxia Patient

Recently, two missense mutations in *NPTX1* were identified as a cause of autosomal dominant cerebellar ataxia by triggering endoplasmic reticulum stress.¹ The *NPTX1*-encoded protein neuronal pentraxin 1 (NP1) is exclusively expressed in the nervous system with high expression levels in neurons of the cerebellum, cerebral cortex, and hippocampus (Human Protein Atlas²).

In this letter, we report a novel *NPTX1* de novo missense variant identified in a male individual with late-onset, slowly progressive cerebellar ataxia, oculomotor apraxia, choreiform dyskinesias, and cerebellar cognitive affective syndrome. The patient first noticed signs of cerebellar ataxia and dysarthria at the age of 47 years. A first comprehensive examination at the age of 52 years showed moderate ataxia and dysarthria. On follow-up evaluation 2 years later, no subjective deterioration of cerebellar symptoms, except for progressive dysarthria and dysphagia, were reported. Clinical examination additionally demonstrated choreiform dyskinesias and oculomotor apraxia (Table 1, Supporting Information Video S1). Family history concerning movement disorders was negative. Brain magnetic resonance

imaging (MRI) demonstrated cerebellar atrophy with predominantly vermian involvement (Supporting Information Fig. S1). Neuropsychological evaluation showed moderate cognitive impairment characterized by executive dysfunction and attentional deficits, including severely impaired working memory. Further intensive diagnostic workup showed no additional findings (Supporting Information Appendix S1).

Trio exome sequencing, variant calling, annotation, and clinical prioritization were performed on patient's and parental genomic DNA as previously described,³ confirming biological parenthood and identifying a single heterozygous missense variant in exon 1 of *NPTX1* (ENST00000306773.4: c.428G>T, p.R143L), absent from gnomAD and an in-house database. There was no evidence of a putative parental mosaicism in blood (Figures S2 and S3) and carrier testing of the healthy brother showed wild-type sequences. These findings are in line with a de novo occurrence and disease-causal role of the c.428G>T, p.R143L variant in the patient.

The identified c.428G>T variant affects a CG dinucleotide and alters an arginine in NP1 highly conserved across species (Supporting Information Fig. S4) and other proteins of the pentraxin family⁴ (Supporting Information Fig. S5). Accordingly, the change p.R143L is consistently predicted by several in silico tools to be probably damaging or deleterious. Unlike the variants previously identified, p.R143L is not localized in the pentraxin domain but resides within the N-terminal region of NP1.⁵ In silico prediction of protein folding via AlphaFold indicated localization of the p.R143 residue within a coiled-coil domain assumed to be responsible for multimerization.⁶ Substitution of the arginine residue likely disrupts formation of the α -helical secondary structure and tertiary coiled-coil motif, thus possibly affecting homomultimerization and heteromultimerization of NP1.⁷ Misfolding of NP1 could therefore cause aggregation of dysfunctional multimers, explaining the deleterious effect of the p.R143L variant.

Together, our case provides further evidence of pathogenic *NPTX1* variants and highlights the complex neurological phenotype of *NPTX1*-associated disease beyond ataxia. Our patient's clinical phenotype characterized by late-onset, slowly progressive cerebellar ataxia and multiple non-cerebellar symptoms resembles the ones previously described (Table 1).¹ Localization and de novo status of the variant in our patient underline the importance of considering *NPTX1*

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TABLE 1 Summary of genetic findings and clinical features of *NPTX1* cases

	This Report	Coutelier et al. (2021) ¹
General information		
No. of patients	1 patient	17 patients from 6 families
Sex	Male	6 male, 11 female
<i>NPTX1</i> variants	c.428G>T, p.R143L	c.1165G>A, p.G389R (16) c.980A>G, p.E327G (1)
Age at onset (y)	47	50.7 ± 7.9 (range 34–71)
Age at first examination (y)	52	58.7 ± 10.8 (range 40–79)
Symptoms		
Cerebellar ataxia	Moderate SARA score 14	Mild (11), moderate (3), severe (1), asymptomatic (1), NA (1) Mean SARA score 8 ± 5.0 (available in only 7/17 patients)
Dysphagia	+	+ (1), – (15)
Hearing loss	–	+ (3), – (13)
Urinary symptoms	–	– (12), mild incontinence (2), mild urgency (1), incontinence (1)
Neurological examination and imaging		
Predominant sign	Ataxia with oculomotor apraxia, handicap 2 of 7	Ataxia (12), ataxia with oculomotor apraxia (2), tremor (1), diplopia (1), asymptomatic (1), mean handicap 3 ± 1.5 of 7 (assessed in 15/17 patients)
Ocular signs	Hypometric saccades, oculomotor apraxia	Nystagmus (14), saccades (6), diplopia (4), square waves (2), ptosis (2), upward gaze limitation (2), oculomotor apraxia (1)
Reflexes	Increased	Increased (7), normal (5), decreased (4)
Vibration sense on ankles	Normal	Normal (12), mildly decreased (2), severely decreased (1), abolished (1)
Choreiform dyskinesias	+	+ (1), – (15)
Myoclonus	–	+ (3), – (13)
Tremor	–	+ (7), – (9)
Neuropsychological evaluation	Executive dysfunction, attention deficit	None (7), attention deficit (2), executive dysfunction (1), apraxia (2), memory impairment (2), frontal syndrome (1), NA (2)
Brain MRI	Cerebellar atrophy, predominantly vermian	Cerebellar atrophy (5), vermian atrophy (3), white matter changes (2), hypophysis adenoma (1), normal (2), NA (5)

NA, not assessed or not available; SARA, Scale for the Assessment and Rating of Ataxia; MRI, magnetic resonance imaging.




mutations beyond the mutations in the pentraxin domain not only in familial autosomal dominant cerebellar ataxia but also in sporadic cases of late-onset ataxia.

Detailed information on additional diagnostic workup, trio exome analysis, and applied in silico tools are included in Supporting Information Appendix S1. ●

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Supporting Data

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Conversion to Hybrid Deep Brain Stimulation System to Enable Multi-Contact Fractionation Can be Therapeutic

For more than 25 years since its inception, a single-source programmable implantable pulse generator (IPG) was the mainstay technology of modern deep brain stimulation (DBS) systems used for medication-refractory movement disorders.¹ However, multiple independent current control (MICC) was a recent innovation in IPG design, which was approved by the United States Food and Drug Administration. MICC attempts to control current fluctuations and enhance precision delivery by using an independent current source directed

to each contact on the electrode lead.^{2,3} Current-control should also allow for the delivered therapy to remain more stable, at least in relation to fluctuations in impedance.² Stimulation-induced side effects are commonly reported and these may be related to inherent DBS device limitations. This often leads to the dilemma of administering suboptimal stimulation parameters to avoid side effects.⁴ Hence, we postulated that converting a precursor, optimized system with an MICC-ready DBS IPG would be feasible and yield additional therapeutic benefits.

This retrospective chart review consisted of 50 adult Parkinson's disease and essential tremor patients, from which three additional study subsamples were statistically analyzed. All patients presented with single-source, voltage-controlled Medtronic IPG devices and subsequently underwent single conversion to a hybrid DBS system with a Boston Scientific MICC-enabled IPG. Differences in side-effect thresholds (SETs) were retrospectively assessed using Wilcoxon signed-rank tests and Shapiro–Wilk tests were used to test normality assumptions.⁵ Statistical significance was determined using an alpha of 0.05 (two-tailed).

All conversions were successfully undertaken with no surgical complications (eg, infections, reoperations, hardware malfunctions) or complications related to reprogramming. Moreover, there was no adverse effect (eg, unexpected pain, cosmetic deformity, infection, hematoma, wound erosion) in any patient following conversion.

Among the Study Subsample patients, there was a statistically significant median difference in SETs at the first postoperative clinic visit compared to before conversion (median 11 days after conversion; left electrode: median 4.0 mA vs. 3.7 mA, $P = 0.017$; right electrode: 4.2 mA vs. 3.7 mA, $P = 0.030$; Fig. 1). Nearly 91% of patients received fractionation at the first postoperative visit. Approximately 68% of patients improved in at least one symptom or adverse event at the first postoperative visit. The accompanying supplemental information provides additional details regarding the study methodology, results, and limitations. Among the limitations of our study are the retrospective design and lack of objective movement disorder scales (eg, Unified Parkinson's Disease Rating Scale), which may have introduced bias. Additionally, the possible restrictions to magnetic resonance imaging of hybrid DBS systems, a possible increase in study-wide error rate, use of a convenience sample at one clinical site, and the unintentional lack of Black/African American patients in our study may have further biased our findings.

Our study preliminarily demonstrated that conversion from a single-source system to a hybrid DBS system using an MICC-enabled IPG is safe and feasible. The most common reason for conversion was battery depletion. Some patients desired a rechargeable DBS system, which was achievable with the MICC-enabled device. Improvements in SETs evidenced in our

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