



Published in final edited form as:

*Mov Disord.* 2014 March ; 29(0 3): 344–350. doi:10.1002/mds.25790.

## Cognitive Impairment in Rapid-Onset Dystonia-Parkinsonism

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**Author Disclosures:** Allison Brashear, Jared Cook, Deborah Hill, Beverly Snively, Niki Boggs, and Cynthia Suerken received salary support from NINDS 5R01 NS058949-04

### Author Contributions

Dr. Brashear: Primary investigator, data collector and lead clinician on the study.

Mr. Cook: Analysis and interpretation of the data, drafting and revising the manuscript

Ms. Hill: Data collector and contributed to the drafting of the manuscript.

Dr. Snively and Ms. Suerken performed the statistical analysis of the data.

Ms. Boggs: Data collector and contributed to interpretation of data

Dr. Haq: Reviewed and critiqued manuscript, provided interpretation of the clinical data

Dr. Stacy and Dr. McCall: Reviewed and provided interpretation of the clinical data

Dr. Ozelius and Dr. Swadner: Provided input on the design of the study and interpretation of data.

All had access to the data and contributed to the writing of the manuscript.

### Financial Disclosure for Previous 12 Months:

Dr. Brashear has salary support from NINDS (5R01 NS058949-04), and she consults with Allergan and XenoPort. Her conflict of interest is being managed by Wake Forest University School of Medicine.

Mr. Cook receives salary support from NINDS 5R01 NS058949-04 and The Susanne Marcus Collins Foundation, Inc.

Dr. Snively receives salary support from the following: NINDS R01NS058949, NCCAM R21AT004234, NHLBI NHLBI-WH-11-10, NIA HHSN-271-2011-00004C, NIAID R01AI079226, NICHD P01HD047584, NIDDK R01DK087914.

Ms. Suerken receives salary support from the following: R01AA020629 NIAAA; CADCA, R01HD061010 NICHD, R01HD059855 NICHHD, R01CA141643 NCI; NIDCR, R01AI079226 NIAID, R01NS058949 NINDS, AHFX0006 DOJ; OJJDP.

Dr. Stacy has received a grant/research support from Ceregene, the Michael J. Fox Foundation, NIH, and the Parkinson Study Group. He has acted as a consultant for Allergan, Chelsea, GE, Novartis, Johnson & Johnson, Lilly, Merz, Neuronova, Osmotica, SK Life Sciences, and UCB. He has been on the Protocol Steering Committee for Allergan. He received royalties from Informa Press for Handbook of Dystonia. His conflict of interest is being managed by Duke University. He is a consultant on this project.

Dr. Ozelius receives salary support from NIH [NS058949, NS037409, NS075881, DC011805]; and has received grant support from the Bachmann-Strauss Dystonia and Parkinson Foundation, the Benign Essential Blepharospasm Research Foundation and The Dystonia Medical Research Foundation. She is a current member of the scientific advisory boards of the National Spasmodic Dysphonia Association, the Benign Essential Blepharospasm Research Foundation and Tourette Syndrome Association, Inc., and a past member of the scientific advisory boards of the Bachmann-Strauss Dystonia and Parkinson Foundation and The Dystonia Medical Research Foundation. Dr. Ozelius receives royalty payments from Athena Diagnostics related to patents.

Dr. Swadner has salary support from NINDS [R01 NS058949 (co-investigator), and R21 NS085411] and the DoD [PR100747], and has received research support from the Bachmann Strauss Dystonia and Parkinson Foundation. She has served as an Associate Editor of the *American Journal of Physiology Cell Physiology* and on the Editorial Board of *The Journal of Biological Chemistry*.

Dr. McCall's research has been supported by NIMH, R01 MH095776-01, and by 1U01MH086127-01. He has a scientific advisor for Luitpold Pharmaceuticals. He has received honoraria from Wolters Kluwer Publishing.

Dr. Haq, Ms. Hill and Ms. Boggs have no disclosures for the previous 12 months.

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## Abstract

**Background**—Rapid-Onset Dystonia-Parkinsonism (RDP) is caused by mutations in the ATP1A3 gene. This observational study sought to determine if cognitive performance is decreased in patients with RDP compared with mutation-negative controls.

**Methods**—We studied 22 familial RDP patients, 3 non-motor manifesting mutation-positive family members, 29 mutation-negative family member controls in 9 families, and 4 unrelated RDP patients, totaling 58 individuals. We administered a movement disorder assessment, including the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and Unified Parkinson's Disease Rating Scale (UPDRS), and a cognitive battery of learning, memory, psychomotor speed, attention, and executive function. The cognitive battery was designed to evaluate a wide range of functions; recognition memory instruments were selected to be relatively pure measures of delayed memory, devoid of significant motor or vocal production limitations. Comparisons of standardized cognitive scores were assessed both with and without controlling for psychomotor speed, and similarly for severity of depressive symptoms.

**Results**—Among RDP patients, a majority had onset of motor symptoms by age 25, and had initial symptom presentation in the upper body (face, mouth, or arm). Among patients, the BFMDRS (mean  $\pm$  SD,  $52.1 \pm 29.5$ ) and UPDRS motor subscore ( $29.8 \pm 12.7$ ) confirmed dystonia-parkinsonism. The affected RDP patients performed more poorly, on average, than mutation-negative controls for all learning, memory, psychomotor speed, attention, and executive function scores (all  $P < 0.01$ ). These differences persisted after controlling for psychomotor speed and severity of depressive symptoms.

**Conclusions**—Impaired cognitive function may be a manifestation of ATP1A3 mutation and RDP.

## Keywords

Dystonia; RDP; DYT-12; Rapid-Onset Dystonia-Parkinsonism

## Introduction

Rapid-Onset Dystonia-Parkinsonism (RDP), a rare disease with onset over hours to days, is caused by mutations in the ATP1A3 gene. (1) Motor symptoms occur abruptly and include dysarthria, dysphagia, and slowness of movement with dystonic posturing and postural instability. (2) Motor symptoms remain fixed over time, but second episodes of abrupt worsening have been found. Non-motor symptoms of RDP have recently been reported including psychosis, anxiety, and depression. (3, 4) ATP1A3 mutations also cause alternating hemiplegia of childhood (AHC) where patients have early onset of dystonia with paroxysmal features (before 18 months of age) and often developmental delay. (5) Young children with RDP also present with fluctuating status. (6)

Rodent studies demonstrate ATP1A3 expression in neurons throughout the brain (7, 8) but a high proportion in the basal ganglia and cerebellum, areas involved in higher cognitive processes, (9) suggests a potential pathway for cognitive impairment. We hypothesized that patients with RDP, caused by ATP1A3 mutations, may have additional impairment outside of the dystonia-parkinsonism reported previously. We report the first detailed study of

cognitive status of patients with RDP and suggest that impairment of cognition provides further evidence of effect of ATP1A3 mutations on neuronal networks in the brain.

## Methods

Fifty-eight subjects (29 with *ATP1A3* mutations present and 29 familial control subjects without the mutation) were included in this study. The data reported here are newly collected as part of a broader longitudinal study of RDP. Participants underwent a structured neurologic exam with dystonia and parkinsonism rating scales and a standardized history questionnaire described below. As this is the first cognitive assessment in patients with *ATP1A3* mutations, the neuropsychological battery was designed to gather the most meaningful information across an array of functions. The protocol was designed to be performed in less than two hours, keeping in mind the confounding motor symptoms of RDP and was built upon published work in dystonia. (10, 11)

### Standard Protocol Approvals, Registrations, and Patient Consents

All participants signed an informed consent form approved by the Wake Forest School of Medicine Institutional Review Board before contributing a blood or saliva sample for DNA screen for *ATP1A3* mutations by direct sequencing as described elsewhere. (1)

### Medical History/Movement Disorder Assessment

Standardized, videotaped movement disorder assessments were administered by a neurologist with expertise in dystonia (AB). Measurements included the Unified Parkinson Disease Rating Scale (UPDRS) and Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). Videos were reviewed by a rater (MS) blinded to genotype status to confirm presence of dystonia-parkinsonism. The BFMDRS assessed severity and frequency of dystonia in 9 body areas. (12) Standardized medical history questionnaires were administered to establish family history, age and site of onset, severity of symptoms, report of triggers, second events of symptom onset, and self-reported education history. The Hamilton Rating Scale for Depression (HAM-D) assessed severity of depressive symptoms and the data were published in 2012. (4) The Instrumental Activities of Daily Living (IADL) assessed impact of disease on activities of daily living. Self-report and proxy scores are highly correlated when patients have difficulty responding, making it a useful tool for RDP patients who have communication difficulty. (13)

### Wide Range Assessment of Memory and Learning, Second Edition (WRAML-2)

The WRAML-2 contains subtests encompassing verbal and nonverbal memory domains. (14) Subtests used in this study include: Verbal Learning (Immediate recall, delayed recall, delayed recognition), Picture Memory (Immediate recall and delayed recognition), and Design Memory (Immediate recall). Picture Memory presents the patient with common scenes where as Design Memory presents the patient with an array of geometric figures. WRAML-2 raw scores were converted to scaled scores based on age-specific reference distributions with mean = 10 and standard deviation (SD) = 3. Scaled scores range from 1 to 19, with scores 1 to 4 indicating impairment.

### Controlled Oral Word Association (COWA)

The COWA measures speeded expressive language sensitive to frontal lobe dysfunction. (15) Two verbal fluency scores are obtained. Linguistic fluency requires words beginning with a given letter (F, A, S) to be generated while Semantic fluency requires words fitting a certain category (animals). COWA measurements were rescaled to t-scores based on age,

education level-, gender- and race-specific reference distributions with mean = 50 and SD = 10. (16) T-scores range from 1 to 99, with scores 0 to 39 indicating impairment.

### Symbol Digit Modalities Test (SDMT)

The SDMT is a timed substitution test that requires matching geometric forms to digits 1 through 9. One written and one spoken test is completed. (17) SDMT measurements were rescaled to z-scores based on age- and education level-specific reference distributions with mean = 0 and SD = 1. Z-score values less than -1.0 indicated impairment.

### Trail Making (A&B)

This two-part test provides a measure of visual attention and set shifting ability, as well as psychomotor speed. (18) Trail Making measurements were rescaled to t-scores based on age-, education level-, gender- and race-specific reference distributions with mean = 50 and SD = 10. (16) T-scores range from 1 to 99; with scores 0 to 39 indicating impairment.

### Statistical analysis

Data summaries were reported as means  $\pm$  standard deviations, or counts and percentages. P values for comparison of educational histories between motor manifesting carrier (MMC) and non-carrier (NC) groups were calculated under the generalized linear mixed model using the binomial distribution with logit link, and using a random intercept for family. P values for continuous measures were calculated under the general linear mixed model using a random term for family and family x group interaction. Rates of participants performing in the impaired range are provided (see Table 4), though no formal analysis was performed. Comparisons between the MMC and NC groups were made using independent *t* tests. A value of  $P < .0038$  was considered significant subsequent to Bonferroni correction for multiple comparisons. To control for effects of psychomotor processing time and of severity of depressive symptoms, Trail Making Part A time and HAM-D score, respectively, were used as covariates in the models.  $P < 0.05$  was considered statistically significant. Each comparison was made using complete data only; data records with missing or incomplete results were excluded regardless of reason. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

## Results

Twenty-nine ATP1A3 mutation-positive individuals (25 from 9 families, and 4 unrelated individuals) were examined; 26 exhibited motor symptoms (MMC) and 3 did not exhibit any evidence of movement disorder (non-motor manifesting carriers, NMC). Twenty-nine ATP1A3 mutation-negative participants (NC) from the same families agreed to participate in the study.

Table 1 shows demographic characteristics of participants in the present study. Among motor-manifesting carriers (MMC), a majority had onset of motor symptoms by age 25, and had initial symptom presentation in the upper body (face, mouth, or arm). BFMDRS and UPDRS motor scores confirmed motor complications in MMC patients. Mean scores were poorer in the MMC relative to the NC group. The MMC group also reported greater difficulty in activities of daily living relative to the NC group.

Table 2 shows retrospective self-report of education history across groups. Ninety percent of MMC patients with onset less than 18 years experienced trouble learning in school and were identified with a learning disability as a child while 70% were asked to participate in a special class. Sixty-nine percent of the MMC group with onset at or after 18 years had trouble learning in school while 57% were diagnosed with a learning disorder and 46% were

asked to participate in a special class. To assess whether learning difficulties preceded onset of RDP, proportions with difficulties were compared between MMC patients having later onsets (> 18 years) and NC controls. Between group differences for these MMC patients (69% of the total) and NC controls (26%) did not reach statistical significance ( $p = 0.07$ , two-sided testing). Fifty percent of MMC patients with later onset graduated from high school compared to 89% of the NC group ( $p = 0.07$ , two-sided testing). One NMC participant reported learning problems.

Test results are shown in Tables 3 and 4. The analysis examined performance across cognitive measures. Participants from each group were unable to complete all measures. MMC participants generally were able to complete tasks at a lower rate (68% to 100% among all tests) than were participants from the NC group (96% to 100%), and these rates generally were lower for timed tests (68% to 85% in MMC). Reasons for missing data include motor dysfunction within the MMC group and fatigue or time restrictions across groups.

Table 3 shows cognitive performance across groups. Following correction for multiple comparisons, significant differences were found for all variables between the MMC and NC groups except for WRAML-2 Picture Memory, WRAML-2 Picture Memory Delayed Recognition, and COWA Semantic Verbal Fluency. The NMC group was not analyzed due to inadequate sample size. Whereas contextually based visual memory was relatively preserved, WRAML-2 scores indicate worse performance among MMC participants for retrieval and recognition of visual stimuli free of context (Design Memory, Design Memory Delayed Recognition). MMC participants had greater difficulty with verbal learning (Verbal Learning, Verbal Learning Delayed Recall, Verbal Learning Delayed Recognition). The MMC group performed worse in terms of span, task persistence, psychomotor speed, and mental flexibility (Trail Making Part A, Trail Making Part B). Verbal fluency (COWA) was worse in MMC participants for linguistic categories, though semantic fluency was not found to significantly differ. Coding skills (SDMT) were weaker in MMC participants for written and oral categories. In analyses controlling for psychomotor processing speed (Trail Making Part A time in seconds), all comparisons of WRAML-2, SDMT, COWA, and Trail Making Part B measures remained statistically significant between MMC and NC participants. Similarly, all comparisons of WRAML-2, SDMT, COWA and Trail Making Parts A and B remained statistically significant after controlling for HAM-D scores.

Table 4 shows percentages of participants with scores falling in the impaired range. Impaired scores occur more often among MMC participants across cognitive variables. Rates of impairment appear especially high in the MMC group for executive functioning (COWA and Trail Making B) as well as psychomotor speed and attention (SDMT and Trail Making A). In the study sample overall, we observed poorer cognitive test scores with both decreased psychomotor speed (increased time for Trail Making Part A) and increased severity of depressive symptoms as measured by the HAM-D.

No participants from the NMC group were impaired on measures of memory. One NMC participant performed in the impaired range for Trail Making B, SDMT (Written and Oral), and COWA Semantic Verbal Fluency. Two NMC participants performed in the impaired range on COWA Linguistic Verbal Fluency.

To examine the effects of RDP severity, Spearman correlations were calculated across cognitive and disease severity measures (UPDRS, BFMDRS, and IADL). Significant positive correlations were found between IADL scores and standardized scores for SDMT-Written ( $p = 0.043$ ), Trail Making Part A ( $p = 0.019$ ) and Trail Making Part B ( $p = 0.004$ ). As activities of daily living (ADL) ratings decreased, so did scores on these cognitive



measures. Significant negative correlations were found between UPDRS scores and scores for SDMT-Oral ( $p = 0.05$ ) and Trail Making Part B ( $p = 0.010$ ) as well as between BFMDRS scores and Trail Making Part B ( $p = 0.020$ ). As disease severity increased, performance on these cognitive measures decreased. Similar analyses were completed for cognitive measures and duration of illness for MMC participants. No significant relationship was found.

## Discussion

Our findings of significantly worse cognitive performance in RDP motor manifesting patients when compared to an unaffected, mutation-negative control group of family members support our hypothesis that cognitive impairment may be a part of the RDP phenotype. After correction for multiple comparisons, semantic verbal fluency and visual memory with a contextual component did not significantly differ between RDP patients and controls. RDP patients regularly performed in the impaired range for attention, verbal fluency, and coding tasks. Impairment rates among RDP patients are less robust, though still notable, for both visual memory and verbal learning tasks.

### Cognitive performance in RDP families

Shared environment amongst MMC, NMC and NC participants, who were recruited from the same families, diminishes the potential influence of environmental factors over differences in cognitive status for these patients. However, the onset of motor symptoms in RDP is often related to the interaction of a genetic mutation with a physiological stressor, such as running, childbirth or psychological stress. There was no similar stressor or abrupt onset reported for the cognitive impairment.

Participants in this study represent a broad range of ages across the adult spectrum. Though scores on cognitive measures are derived from normative samples controlling for age, degenerative conditions unrelated to RDP could influence cognitive performance for study participants advanced in age.

Interpretation of results for RDP patients could be limited by the timed speech requirements of some tests (SDMT-Oral, COWA). Increased disease severity correlated with poorer performance on SDMT-Oral for MMC participants. Dysarthria has been shown to predict poorer scores on the SDMT-Oral in patients with multiple sclerosis, though the same study did not find any relationship between dysarthria and performance on linguistic COWA. (19) The current study may over-estimate impairment to attention and psychomotor speed as measured by SDMT-Oral. Oral-motor tasks that also measure executive functioning and language (linguistic and semantic forms of the COWA), however, may not have the same susceptibility to dysarthria. Other research has shown a modest relationship between myoclonus severity and performance on a semantic verbal fluency task, though no other differences on speed of motor reactions, in light of mild cognitive impairments for myoclonus-dystonia sufferers with genetic mutation. (20)

Increased disease severity and decreased ADL ratings were related to poorer performance on written, timed measures (Trail Making Parts A and B, and SDMT-Written). These findings suggest some influence of motor impairment on the performance of these particular tests. However, a prior study found no difference between performance on Trail Making Parts A and B between a healthy control group and myoclonus-dystonia sufferers without a genetic mutation. (20) The same study did find poorer performance on executive functioning tasks (including Trail Making Part B) between myoclonus-dystonia patients with genetic mutation and healthy controls.

Three participants in the current study were identified with ATP1A3 gene mutations without motor symptoms. Further investigation of such individuals, with increased sample size, could further understanding of the impact of ATP1A3 mutations on cognitive functioning.

### Comparisons to other diseases

ATP1A3 mutations may be an independent risk factor for cognitive impairment. ATP1A3 mutations are causative for AHC, where at least 74% of the known cases are do novo mutations. (5) Features of AHC include paroxysmal attacks of hemiplegia or quadriplegia and between these attacks patients demonstrate dystonia, ataxia and choreoathetosis, and may also have cognitive impairment and developmental delay. (21–23) In the 2009 study of 103 patients diagnosed with AHC (23) all were reported to have cognitive impairment with many also having ataxia (96%), and hemiplegic, tonic, or dystonic episodes (50%). There is one case report from 2005 of detailed neuropsychological testing in a child with AHC (without genetic testing) (24) demonstrating impaired academic, intellectual, attention and executive function, similar to this large group of RDP patients. We propose that ATP1A3 mutations in AHC likely contribute to cognitive impairment. Quantitative assessment of older AHC patients with mutations in ATP1A3 using the battery employed here might show more severe cognitive impairment related to the earlier onset of disease in AHC.

The data presented here adds to previous literature describing cognitive impairment as part of the phenotype in other forms of genetic dystonia. Patients with primary dystonia have been identified with attentional-executive cognitive deficits as measured by the Cambridge Neuropsychological Test Automated Battery. (10) In a different study, no differences were found between symptomatic DYT1 mutation carriers and controls for cognitive tests evaluating verbal and nonverbal abstract abilities, attention, information psychomotor speed, and spatial organization. (11) However, the symptomatic groups showed increased verbal memory retroactive interference. Other patients with primary dystonia showed no differences from controls on measures of executive functioning and working memory. (25) Varying cognitive profiles in patients with dystonia illustrate the need for further study of associated non-motor symptoms for dystonia.

### Significance of cognitive impairment in RDP

The role of Na,K-ATPase in neuronal networks is just now being explored in human brain, mouse models and imaging. Widespread distribution of ATP1A3 in the brain suggests that the timing of onset or the trigger may affect the phenotype that results. ATP1A3 is present in neurons in the basal ganglia and cerebellum. These interconnected regions (26, 27) have increasingly been implicated in functions beyond simple motor control (28) particularly with respect to attention, language, and learning. (29) Though discussion of mechanism is speculative, it is interesting that cerebellar cognitive affective syndrome (CCAS) (28, 29) has been identified in individuals with cerebellar damage, consisting of executive dysfunction (30), impaired visuospatial cognition (31, 32), and language processing/production deficits. (33) This resembles the cognitive deficits seen in our patients. ATP1A3 is also prevalent in the hippocampus, (8) and some of our patients' deficits may involve these more anterior memory-processing pathways. Mouse studies suggest that deficiencies in Na,K-ATPase are linked to impaired memory and learning, consistent with current findings in RDP-manifesting ATP1A3 gene mutation carriers. (34)

Results of this study of 22 patients from 9 families and 4 unrelated RDP cases with ATP1A3 mutations and their mutation-negative family members suggests that cognitive impairment occurs in those with ATP1A3 mutations and motor manifestations. The study is limited in that most of the patients studied had motor symptoms at the time of the assessment, but our results, together with the recent reports of ATP1A3 causing AHC, suggest that cognitive

impairment may be an independent manifestation of ATP1A3 mutations. Those who care for patients with cognitive impairment, particularly in families with a history of dystonia or parkinsonism, may consider ATP1A3 mutations as a possible contributor to these deficits. Na, K-ATPase in the central nervous system profoundly affects neuronal excitability (35) and our findings suggest that the impact of a defective pump may give rise to additional clinical symptoms beyond dystonia-parkinsonism.

## Acknowledgments

**Study Funding:** This study was supported by NINDS 5R01NS058949-04 (AB)

## Reference List

- de Carvalho AP, Sweadner KJ, Penniston JT, et al. Mutations in the Na<sup>+</sup>/K<sup>+</sup> -ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. *Neuron*. 2004 Jul 22;43:169–175. [PubMed: 15260953]
- Dobyns WB, Ozelius LJ, Kramer PL, et al. Rapid-onset dystonia-parkinsonism. *Neurology*. 1993 Dec;43:2596–2602. [PubMed: 8255463]
- Barbano RL, Hill DF, Snively BM, et al. New triggers and non-motor findings in a family with rapid-onset dystonia-parkinsonism. *Parkinsonism Relat Disord*. 2012 Jul;18:737–741. [PubMed: 22534615]
- Brashear A, Cook JF, Hill DF, et al. Psychiatric disorders in rapid-onset dystonia-parkinsonism. *Neurology*. 2012 Sep 11;79:1168–1173. [PubMed: 22933743]
- Heinzen EL, Swoboda KJ, Hitomi Y, et al. De novo mutations in ATP1A3 cause alternating hemiplegia of childhood. *Nat Genet*. 2012 Sep;44:1030–1034. [PubMed: 22842232]
- Brashear A, Mink JW, Hill DF, et al. ATP1A3 mutations in infants: a new rapid-onset dystonia-parkinsonism phenotype characterized by motor delay and ataxia. *Dev Med Child Neurol*. 2012 Nov;54:1065–1067. [PubMed: 22924536]
- McGrail KM, Sweadner KJ. Immunofluorescent localization of two different Na,K-ATPases in the rat retina and in identified dissociated retinal cells. *J Neurosci*. 1986 May;6:1272–1283. [PubMed: 3012013]
- Bottger P, Tracz Z, Heuck A, Nissen P, Romero-Ramos M, Lykke-Hartmann K. Distribution of Na/K-ATPase alpha 3 isoform, a sodium-potassium P-type pump associated with rapid-onset of dystonia parkinsonism (RDP) in the adult mouse brain. *J Comp Neurol*. 2011 Feb 1;519:376–404. [PubMed: 21165980]
- Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Brain Res Rev*. 2000 Mar;31:236–250. [PubMed: 10719151]
- Scott RB, Gregory R, Wilson J, et al. Executive cognitive deficits in primary dystonia. *Mov Disord*. 2003 May;18:539–550. [PubMed: 12722168]
- Balas M, Peretz C, Badarny S, Scott RB, Giladi N. Neuropsychological profile of DYT1 dystonia. *Mov Disord*. 2006 Dec;21:2073–2077. [PubMed: 17013905]
- Krystkowiak P, du Montcel ST, Vercueil L, et al. Reliability of the Burke-Fahn-Marsden scale in a multicenter trial for dystonia. *Movement Disorders*. 2007; 22:685–689. [PubMed: 17274034]
- McCall WV, Dunn AG, Rosenquist P, Hughes D. Proxy validation of patient self-reports of ADL and IADL function before and after electroconvulsive therapy. *J ECT*. 2002 Jun;18:74–79. [PubMed: 12195134]
- Sheslow, D.; Adams, W. *Wide Range Assessment of Memory and Learning*. Second Edition. Lutz, Florida: Wide Range Inc; 2007.
- Spree, O.; Strauss, EA. *Compendium of Neuropsychological Tests*. New York: Oxford University Press; 1998.
- Heaton, RK.; Miller, W.; Taylor, MJ.; Grant, I. *Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults*. Psychological Assessment Resources, Inc; 2004.



17. Smith, A. Symbol Digit Modalities Test: Manual. Los Angeles: Western Psychological Services; 2007.
18. Washington DC- Adjutant General's Office WD. Army Individual Test Battery. Manual of directions and scoring. 1944
19. Smith MM, Arnett PA. Dysarthria predicts poorer performance on cognitive tasks requiring a speeded oral response in an MS population. *J Clin Exp Neuropsychol*. 2007 Nov.29:804–812. [PubMed: 18030632]
20. van Tricht MJ, Dreissen YE, Cath D, et al. Cognition and psychopathology in myoclonus-dystonia. *J Neurol Neurosurg Psychiatry*. 2012 Aug.83:814–820. [PubMed: 22626943]
21. Ozelius LJ. Clinical spectrum of disease associated with ATP1A3 mutations. *Lancet Neurol*. 2012 Sep.11:741–743. [PubMed: 22857851]
22. Panagiotakaki E, Gobbi G, Neville B, et al. Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults. *Brain*. 2010 Dec. 133:3598–3610. [PubMed: 20974617]
23. Sweney MT, Silver K, Gerard-Blanluet M, et al. Alternating hemiplegia of childhood: early characteristics and evolution of a neurodevelopmental syndrome. *Pediatrics*. 2009 Mar.123:e534–e541. [PubMed: 19254988]
24. Shafer ME, Mayfield JW, McDonald F. Alternating hemiplegia of childhood: a study of neuropsychological functioning. *Appl Neuropsychol*. 2005; 12:49–56. [PubMed: 15788223]
25. Jahanshahi M, Marsden CD. Psychological functioning before and after treatment of torticollis with botulinum toxin. *J Neurol Neurosurg Psychiatry*. 1992:55.
26. Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. *Proc Natl Acad Sci U S A*. 2010 May 4.107:8452–8456. [PubMed: 20404184]
27. Bostan AC, Strick PL. The cerebellum and basal ganglia are interconnected. *Neuropsychol Rev*. 2010 Sep.20:261–270. [PubMed: 20811947]
28. Allen G, Buxton RB, Wong EC, Courchesne E. Attentional activation of the cerebellum independent of motor involvement. *Science*. 1997 Mar 28.275:1940–1943. [PubMed: 9072973]
29. Schmahmann JD, Caplan D. Cognition, emotion and the cerebellum. *Brain*. 2006 Feb.129:290–292. [PubMed: 16434422]
30. Gottwald B, Wilde B, Mihajlovic Z, Mehdorn HM. Evidence for distinct cognitive deficits after focal cerebellar lesions. *J Neurol Neurosurg Psychiatry*. 2004 Nov.75:1524–1531. [PubMed: 15489381]
31. Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci*. 2004; 16:367–378. [PubMed: 15377747]
32. Schmahmann JD, Ko R, MacMore J. The human basis pontis: motor syndromes and topographic organization. *Brain*. 2004 Jun.127:1269–1291. [PubMed: 15128614]
33. Ravizza SM, McCormick CA, Schlerf JE, Justus T, Ivry RB, Fiez JA. Cerebellar damage produces selective deficits in verbal working memory. *Brain*. 2006 Feb.129:306–320. [PubMed: 16317024]
34. Moseley AE, Williams MT, Schaefer TL, et al. Deficiency in Na,K-ATPase alpha isoform genes alters spatial learning, motor activity, and anxiety in mice. *J Neurosci*. 2007 Jan 17.27:616–626. [PubMed: 17234593]
35. Benarroch EE. Na<sup>+</sup>, K<sup>+</sup>-ATPase: functions in the nervous system and involvement in neurologic disease. *Neurology*. 2011 Jan 18.76:287–293. [PubMed: 21242497]

**Table 1**

Demographics and disease characteristics.

	<b>Motor Manifesting Carriers (N=26)</b>	<b>Non-Motor Manifesting Carriers (N=3)</b>	<b>Non-Carrier Family Members (N=29)</b>
Female	7 (27%)	3 (100%)	15 (52%)
Age at cognitive testing	40 ± 15	65 ± 20	46 ± 15
Duration of RDP (years)	17.0 ± 12.4	NA	NA
Age at RDP onset (years)	23.0 ± 13.0	NA	NA
<18	10 (38%)	NA	NA
18–25	10 (38%)	NA	NA
26–39	2 (8%)	NA	NA
40+	4 (15%)	NA	NA
RDP severity score			
1	3 (12%)	NA	NA
2	2 (8%)	NA	NA
3	12 (46%)	NA	NA
4	9 (35%)	NA	NA
Symptoms started			
Face	1 (4%)	NA	NA
Mouth (speech)	10 (38%)	NA	NA
Arm	9 (35%)	NA	NA
Leg	5 (19%)	NA	NA
Trunk	1 (4%)	NA	NA
UPDRS-III	29.8 ± 12.7	1.7 ± 2.1	0.4 ± 0.9
BFMDRS	52.1 ± 29.5	0.0 ± 0.0	0.1 ± 0.4
IADL	24.4 ± 7.4	27.7 ± 5.8	30.6 ± 0.9

Abbreviations: BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale, total score; IADL = Instrumental Activities of Daily Living, 8-item total score; RDP = Rapid-onset dystonia-parkinsonism; UPDRS-III = Unified Parkinson's Disease Rating Scale, motor subscore.

RDP severity score descriptors are: 0 = unaffected, 1 = limb dystonia only including writer's cramp, 2 = affected arm and bulbar muscles with normal gait, 3 = same as 2 with legs affected but walking unassisted, and 4 = same as 2 with legs affected but walking with walker or in a wheelchair.

Values are mean ± standard deviation or count (%).

**Table 2**

Educational histories.

	Motor Manifesting Carriers		Non-Motor Manifesting Carriers (N = 3)	Non-Carrier Family Members (N = 29)	P Value
	Onset <18y (N = 10)	Onset 18y (N = 16)			
Trouble learning in school	9 (90%)	11 (69%)	1 (33%)	6 (22%)	0.06
History of learning disability as a child	9 (90%)	8 (57%)	0 (0%)	5 (19%)	0.09
Asked to join a special class to learn better	7 (70%)	6 (46%)	0 (0%)	4 (15%)	0.12
At least one of 3 above	9 (90%)	11 (69%)	1 (33%)	7 (26%)	0.07
High school graduate+	7 (70%)	8 (50%)	1 (33%)	25 (89%)	0.07

P values are for comparison of educational histories in adult-onset ( 18y) manifesting carriers versus non-carrier family members calculated under the generalized linear mixed model using the binomial distribution with logit link, and using a random intercept for family.

Values are count (%).

**Table 3**

Neuropsychological testing.

	<b>Motor Manifesting Carriers</b>	<b>Non-Motor Manifesting Carriers</b>	<b>Non-Carrier Family Members</b>	<b>P Value</b>
<b>Memory and Learning</b>				
WRAML Picture Memory	7.2 ± 2.9 [n=26]	9.5 ± 2.1 [n=2]	9.7 ± 2.4 [n=29]	0.010
WRAML Picture Memory Delayed Recognition	7.9 ± 3.2 [n=25]	7.5 ± 0.7 [n=2]	11.0 ± 3.3 [n=29]	0.008
WRAML Design Memory	6.3 ± 2.2 [n=22]	8.5 ± 4.9 [n=2]	10.5 ± 3.1 [n=22]	0.001
WRAML Design Memory Delayed Recognition	6.2 ± 2.6 [n=21]	6.5 ± 2.1 [n=2]	11.4 ± 3.0 [n=22]	<0.001
WRAML Verbal Learning	6.1 ± 2.8 [n=23]	10.0 ± 3.6 [n=3]	9.9 ± 3.1 [n=29]	<0.001
WRAML Verbal Learning Delayed Recall	6.1 ± 3.1 [n=21]	11.0 ± 5.3 [n=3]	9.7 ± 2.8 [n=29]	<0.001
WRAML Verbal Learning Delayed Recognition	7.3 ± 3.7 [n=23]	10.7 ± 3.1 [n=3]	10.2 ± 2.7 [n=29]	0.002
<b>Psychomotor Speed and Attention</b>				
Trail Making Test Part A	38.7 ± 9.4 [n=23]	64 ± 22.6 [n=2]	51.7 ± 11.9 [n=29]	<0.001
SDMT-Written	-2.4 ± 0.9 [n=22]	-1.0 ± 2.9 [n=2]	0.4 ± 0.9 [n=29]	<0.001
SDMT-Oral	-1.9 ± 1.2 [n=19]	-1.0 ± 2.4 [n=2]	0.4 ± 0.9 [n=28]	<0.001
<b>Executive Functioning</b>				
Trail Making Test Part B	36.7 ± 9.8 [n=21]	37.5 ± 26.2 [n=2]	51.1 ± 11.7 [n=29]	<0.001
COWA Semantic Verbal Fluency	35.2 ± 13.3 [n=18]	45.0 ± 11.1 [n=3]	50.9 ± 9.3 [n=29]	0.005
COWA Linguistic Verbal Fluency	32.9 ± 7.5 [n=17]	39.0 ± 13.1 [n=3]	47.7 ± 10.0 [n=29]	<0.001

Abbreviations: WRAML = Range Assessment of Memory and Learning, Second Edition (WRAML-2); SDMT = Symbol Digit Modalities Test; COWA = Controlled Oral Word Association; n = number of participants able to complete each test.

P values are for comparison of neuropsychological test scores in manifesting carriers versus non-carrier family members calculated under the general linear mixed model using random terms for family and family x genotype-phenotype group.

Values are mean ± standard deviation [n].

**Table 4**

Percent impaired on neuropsychological testing.

	<b>Motor Manifesting Carriers</b>	<b>Non-Motor Manifesting Carriers</b>	<b>Non-Carrier Family Members</b>
<b>Memory and Learning</b>			
WRAML Picture Memory	5 (19%) [n=26]	0 (0%) [n=2]	0 (0%) [n=29]
WRAML Picture Memory Delayed Recognition	4 (16%) [n=25]	0 (0%) [n=2]	1 (3%) [n=29]
WRAML Design Memory	3 (14%) [n=22]	0 (0%) [n=3]	0 (0%) [n=22]
WRAML Design Memory Delayed Recognition	5 (24%) [n=21]	0 (0%) [n=3]	0 (0%) [n=22]
WRAML Verbal Learning	6 (26%) [n=23]	0 (0%) [n=3]	1 (3%) [n=29]
WRAML Verbal Learning Delayed Recall	7 (33%) [n=21]	0 (0%) [n=3]	0 (0%) [n=29]
WRAML Verbal Learning Delayed Recognition	5 (22%) [n=23]	0 (0%) [n=3]	0 (0%) [n=29]
<b>Psychomotor Speed and Attention</b>			
Trail Making Test Part A	11 (48%) [n=23]	0 (0%) [n=2]	6 (21%) [n=29]
SDMT-Written	20 (91%) [n=22]	1 (50%) [n=2]	2 (7%) [n=29]
SDMT-Oral	15 (79%) [n=19]	1 (50%) [n=2]	0 (0%) [n=28]
<b>Executive Functioning</b>			
Trail Making Test Part B	15 (68%) [n=21]	1 (50%) [n=2]	4 (14%) [n=29]
COWA Semantic Verbal Fluency	12 (67%) [n=18]	1 (33%) [n=3]	2 (7%) [n=29]
COWA Linguistic Verbal Fluency	16 (94%) [n=17]	2 (67%) [n=3]	6 (21%) [n=29]

Abbreviations: WRAML = Range Assessment of Memory and Learning, Second Edition (WRAML-2); SDMT = Symbol Digit Modalities Test; COWA = Controlled Oral Word Association; n = number of participants able to complete each test.

All cutoffs for impairment are controlled for age; SDMT cutoffs also control for education (years), and Trail Making and COWA for education (years), gender, and race.

Values are count (%) [n].