Published in final edited form as:
*Parkinsonism Relat Disord*. 2012 July ; 18(6): 737–741. doi:10.1016/j.parkreldis.2012.03.020.

# New triggers and non-motor findings in a family with rapid-onset dystonia-parkinsonism

**Richard L. Barbano**[a], **Deborah F. Hill**[b], **Beverly M. Snively**[c], **Laney S. Light**[c], **Niki Boggs**[d], **W. Vaughn McCall**[d], **Mark Stacy**[e], **Laurie Ozelius**[f,g], **Kathleen J. Sweadner**[h], and **Allison Brashear**[b,*]

[a]Department of Neurology, University of Rochester School of Medicine, Rochester, NY, USA

[b]Department of Neurology, Wake Forest School of Medicine, Wake Forest University Baptist Medical Center, Winston Salem, NC 27157, USA

[c]Department of Public Health Sciences, Wake Forest School of Medicine, Wake Forest University Baptist Medical School, Winston Salem, NC, USA

[d]Department of Psychiatry, Wake Forest School of Medicine, Wake Forest University Baptist Medical Center, Winston Salem, NC, USA

[e]Department of Neurology, Duke University School of Medicine, Durham, NC, USA

[f]Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, NY, USA

[g]Department of Neurology, Mount Sinai School of Medicine, NY, USA

[h]Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

## Abstract

**Background—**A woman from Italy presented with dystonic leg symptoms at the age of 59. Rapid-onset dystonia-parkinsonism (RDP) was not suspected until 3 affected children (2 male, 1 female) with presentations consistent with the disorder were recognized.

**Methods—**The mother and four of her children (3 with and 1 without dystonia) were evaluated with an extensive battery including standardized history questionnaire and rating scales. In addition, all four children had cognitive testing and three of the four children had psychiatric interviews.



*Corresponding author. Tel.: +1 336 716 3545; fax: +1 336 716 9489. abrashea@wakehealth.edu (A. Brashear).

**Authors roles:** Drs. Barbano and Brashear, Ms. Hill and Ms. Boggs were primary data collectors and lead clinicians on the study. Drs. McCall and Stacey were reviewers of the clinical data. Dr. Snively and Ms. Light performed the statistical analysis. Dr. Sweadner and Dr. Ozelius provided input on the design of the study. All had access to the data and contributed to the writing of the manuscript.

Financial disclosure: Dr. Barbano has participated in research trials sponsored by Allergan and Merz, and consults for Allergan. Dr. Barbano participates in the University Of Rochester Conflict Of Management Of Interest Management Plan.

Dr. Stacy performs research for Ceregene, IMPAX, Neuraltus, Novartis, Schering-Plough, and the Parkinson Study Group and consults for Allergan, Biogen, General Electric, Novartis, Osmotica, TEVA and Synosia. He has received honoraria from Allergan, Boeringher-Ingelheim, Novartis, TEVA and serves on safety monitoring boards for Biogen, and Neurologix. His conflict of interest is being managed by Duke University Medical School. He is a consultant on this project.

Dr. Brashear has salary support from this study from NIH (R01-NS058949).She performs research for Allergan, Merz, and Ipsen, and consults for Allergan, Merz and Ipsen. She does not do speaker's bureaus. Her conflict of interest is being managed by Wake Forest University School of Medicine. She has also received honorarium for consulting for Wemove.org and speaking honorarium from the American Academy of Neurology. She is on the Dystonia Medical Research Foundation scientific advisory board.

**Results—**In this family, a T613M mutation in the ATP1A3 gene was confirmed, the most common mutation present in patients with RDP. The proband's limb dystonia was atypical of RDP, symptoms of the others affected included dysarthria, asymmetric limb dystonia, and dysphagia more consistent with RDP. The two sons developed dystonia-parkinsonism in adolescence after consuming large amounts of alcohol. All 3 of those with psychiatric interviews reached diagnosable thresholds for mood disorder (bipolar or dysthymia) and some form of anxiety disorder.

**Conclusions—**The phenotype and age of onset is broader than previously reported in RDP, suggesting that it could be under-reported. Prior to this study, neuropsychologic symptoms associated with RDP were under-appreciated. Those patients who are at risk or suspected of having RDP should be cautioned to avoid excessive alcohol intake. Further study is needed to assess if the cognitive and psychiatric features are part of a broader RDP phenotype and this may have implications for future research into genetic susceptibility for psychiatric disease.

### Keywords

Dystonia; RDP; DYT-12; Rapid-onset dystonia-parkinsonism

## 1. Introduction

Rapid-onset dystonia-parkinsonism (RDP) is an autosomal dominant movement disorder caused by a variety of missense mutations in the ATP1A3 gene and typically presenting with abrupt onset and prominent speech and swallowing difficulties [1–3]. Onset often occurs within hours and progresses over a few days to a week. In addition to dystonia, classic manifestations of parkinsonism including postural instability, bradykinesia, masked facies, and hypomimia can be present. While symptoms may begin in any region of the body, they often progress to other areas [3]. Age of onset of RDP is usually in teens to early adulthood, at times associated with triggers such as heat or stress, but phenotypic variance has been reported [1]. Symptoms present with variable distribution for the months and years following onset. Many patients report improvement of symptoms without any specific therapy [3]. We describe the first report of a family of Italian heritage with an unusual leg presentation and late age of onset, newly reported triggers, and prominent neuropsychologic symptoms not previously described in RDP. The finding of the most common recurrent mutation, T613M, in this family further suggests a broader phenotype of ATP1A3 mutations.

## 2. Methods

Participants signed an informed consent form approved by Wake Forest University School of Medicine and/or University of Rochester Institutional Review Board. The patients contributed a blood or saliva sample (buccal swab) for DNA screen for ATP1A3 mutations by direct sequencing as described previously [4]. The participants underwent a detailed, systematic analysis used in other patients with RDP, described below.

### 2.1. Medical history/movement disorder assessment

A standardized history questionnaire including onset of symptoms, report of triggers, and second events was administered in addition to a standardized, videotaped, movement disorder assessment. Measures included the Unified Parkinson's Disease Rating Scale (UPDRS) [5], and the Burke Fahn Marsden Dystonia Scale (BFMS) [6]. The movement disorder assessment was reviewed and scored by a movement disorder expert blinded to mutation status (M.S.).

Supplementary video associated with this article can be found, in the online version, at doi: 10.1016/j.parkreldis.2012.03.020.

### 2.2. Psychiatric assessment

The Composite International Diagnostic Interview (CIDI-Auto version) was previously used in a study of psychiatric comorbidity in patients with DYT1 [7,8]. The CIDI is a fully structured interview developed by the World Health Organization and the former United States Alcohol, Drug Abuse and Mental Health Administration to serve as a standardized method of establishing diagnoses according to ICD-10 and DSM-IIIR definitions. It was intended to minimize clinical judgment and interviewer bias in establishing diagnoses. The CIDI-Auto is the computerized version of the CIDI items and scoring algorithms. For the present study, the interview was conducted by a trained rater while being videotaped.

Using the videotaped CIDI-Auto interview, the rater then completed a paper-and-pencil Structured Clinical Interview for DSM-IV Disorders (SCID-I) [9]. The SCID-I is an appropriate tool for assessing current and lifetime psychiatric diagnoses in medical patients and family members provided they are cognitively able to understand and respond to questions. It is a reliable and valid semi-structured interview useful for identifying psychotic symptoms, psychotic disorders, mood disorders, substance use disorders, and anxiety/adjustment disorders. After generating diagnoses from both instruments, the data were reviewed by a psychiatrist blinded to mutation status. In the event of a discrepancy in diagnosis, the psychiatrist reviewed the videotapes to resolve diagnostic questions between the two instruments and established final diagnoses (reported in Table 2). Discrepancies were generally more prominent in cases where multiple diagnoses were given using both instruments.

### 2.3. Cognitive/memory assessment

This battery was designed to gather information across an array of functions without unduly tiring the patients, while building on work in other studies of genetic forms of dystonia [10,11]. To assess verbal and non-verbal memory, subtests from the Wide Range Assessment of Memory and Learning (WRAML) were employed [12]. The Verbal Learning and Recall subtests (which require verbal production), and the Picture Memory test (which can employ a simple pointing response) were both administered and their respective recognition memory subtests (all of which can employ a simple yes/no gesture) served as delayed memory measures. Only the recognition memory findings are reported here in order to have relatively pure measures of delayed memory, devoid of significant motor or vocal production limitations.

Several additional measures, sensitive to frontal lobe dysfunction, were administered, including Controlled Oral Word Association (COWA) [13], a test of speeded expressive language, and Trail Making A & B [14]. The COWA generates two scores, one for the number of words beginning with a given letter (linguistic fluency) and the other for the number of words fitting a category (semantic fluency –animals in this case) that can be generated in 1 min. The Trail Making A task measures psychomotor speed (requiring patients to connect circles in order by number) while part B (also timed) requires patients to alternate between digits and letters, a measure of mental flexibility.

Published normative data were used to ascertain dysfunction with the COWA and Trail Making measures [15]. IQ estimate was derived using Raven's Progressive Matrices (RPM) [16], a visual test of inductive reasoning requiring only a pointing response. In some instances, subjects were unable to complete all items due to fatigue or time constraints. In those cases, scores were prorated to derive an estimated total correct score. The total correct

scores were compared to norms generated by a standardization study completed in Des Moines, IA and published in the test manual [16].

## 3. Results

After obtaining informed consent, we examined 5 family members. A professional interpreter was employed to assist in evaluation of the proband, who spoke minimal English. The proband completed a patient history questionnaire and motor exam but not the cognitive or psychiatric assessment. The 4 offspring completed the cognitive assessment, and 3 offspring completed the psychiatric interview. Of the 5 individuals evaluated, 4 had definite dystonia-parkinsonism on examination and one did not (Table 1). Genotyping results showed T613M mutation in all 5 individuals.

### 3.1. Medical history/movement disorder assessment

**3.1.1. Age of onset—**The age of onset of the proband (59 years of age) was older than that of her three affected children, all of whom had motor symptom onset in adolescence (Table 1).

Prodromal symptoms: Two of the 4 affected with motor symptoms describe mild limb cramping at 6–12 months before onset of motor symptoms. The proband was initially thought to have restless leg syndrome. The proband described onset overnight of “numbness” and problems with walking associated with less severe problems in arms and mild swallowing and speech difficulties. Patient II.2 described mild limb cramping in the right arm and leg one year before the abrupt onset overnight of dystonic symptoms. The limb cramping was mild, persistent but he could still write and walk but was “different”. The other two patients denied any prodromal limb symptoms.

**3.1.2. Triggers—**The proband described abrupt onset overnight of problems with walking, including weakness and numbness. She reported gradual worsening of symptoms over 3 years, then stabilization of symptoms with minimal bulbar findings. This family has similar triggers described in other families with RDP but two had a new trigger, alcohol use, associated with RDP that may have impact on preventing disease in at risk individuals.

**3.1.3. Alcohol as a trigger—**Two of the three children (II.2, II.3) reported onset of dystonic symptoms within 24 h of drinking excessive amounts of alcohol. In both children, the alcohol exposure was not new, and both had evidence of alcohol abuse noted on the CIDI interview. Both admitted to drinking excessive amounts of alcohol (more than the usual) the night before, and both confirm the onset of symptoms the next day. Patient II.2 meets criteria for alcohol dependence and reports first noticing symptoms of dependence at age 15. Patient II.3 did not meet alcohol dependence on the CIDI. After the initial onset of RDP he abstained from drinking, but approximately 2 years later after a second drinking episode, he developed sensations of burning and weakness in the limbs. This resolved and he has not used alcohol since. Prior to RDP onset he reported consuming 1 drink, 1–2 times a week. The other child had continued to drink alcohol regularly at the time of exam and has not had any change in his symptoms.

**3.1.4. Distribution of dystonia—**The proband had predominately lower extremity dystonia whereas the 3 children presenting with symptoms more characteristic of RDP, such as dysarthria, swallowing, and dystonic hand postures. All four had dystonia-parkinsonism diagnosed by the blinded rater.

**3.1.5. Other illnesses—**No history of epilepsy is reported in the family. Participant II.1 reports a history of seizures starting at age 40. Seizures were associated with a meningioma that was later resected. Participants I.1, II.1 and II.4 all report a history of headaches accompanied by nausea, light sensitivity and an interference with daily activities. Patient II.2 reports a history of headaches accompanied by sensitivity to light and interference with daily activities but no nausea is reported. Patient II.3 denies any history of migraine-like headaches.

### 3.2. Psychiatric assessment

All of the offspring of the proband examined in this study had some symptoms or a diagnosis of psychiatric disease. The psychiatric interview data (Table 2) demonstrated disorders of mood and anxiety in all three of the mutation positive children who were interviewed. Two received diagnoses of panic disorder and bipolar disorder, one of whom acknowledged having been treated for depression and anxiety in the past. These same two siblings also received diagnoses of obsessive compulsive disorder and substance abuse disorders. The third sibling reached diagnostic threshold for dysthymia. She had a prior diagnosis of schizophrenia with psychosis, occurring after the motor symptoms. The family history was significant for psychotic symptoms and in fact, there were psychotic symptoms reported by one offspring during the present interview, although they did not reach diagnostic thresholds. At least two of the children have a history of suicidal ideation in the past. All psychotic symptoms appear to have occurred after the abrupt onset of motor symptoms. In addition, it is worth noting that two of the children carried childhood diagnoses of conduct disorder. The unaffected carrier did not participate in the psychiatric assessment.

### 3.3. Cognitive/memory assessment

Only one individual exhibited any evidence of amnestic impairment, and then on only one measure. The most striking cognitive findings were the impairments in verbal fluency and executive functioning tasks (Table 3). All four individuals who completed the cognitive assessments exhibited moderate impairment on the linguistic verbal fluency task, and two of those also exhibited deficits on the semantic fluency task. Although these results should be interpreted with caution given the oromotor symptoms in the affected patients, observations suggest that these results reflect more than could be attributed to lower facial dystonia alone. Specifically, the unaffected sibling also exhibited a linguistic fluency deficit and one of the more severely affected siblings failed to exhibit a semantic fluency deficit.

Results of the Trail Making tests indicated significant impairments on the Trail Making B task in three individuals, while performance on the Trail Making A task was generally within normal limits (with one exception). Again, the pattern of deficits suggest that dystonia cannot entirely account for these findings as the Trail Making A task is a more pure measure of psychomotor speed. Therefore, relatively normal scores on this measure suggest adequate speed, and that deficits in mental flexibility most likely account for the reduced Trail Making B scores. The unaffected sibling, likewise, exhibited the same pattern of findings, with average Trail Making A and significantly impaired Trail Making B scores. Impairment in inductive reasoning was documented in two individuals.

## 4. Discussion

The results of the study of this new family identify several new and important clinical features of RDP associated with ATP1A3 mutations including: 1) the proband's late age of onset and presentation with dystonia in the leg; 2) the role of alcohol as a potential trigger with at least 2 of the 4 confirmed affected individuals identifying alcohol as trigger; and 3)

prominent neuropsychiatric and cognitive features present in 4 of 4 individuals studied with these batteries and demonstrating impairments in the verbal fluency and executive functioning tasks in several mutation carriers with and without motor symptoms.

The T613M mutation of ATP1A3 has been previously reported in two large families and three other unrelated patients [4,17,18]. This report brings the total confirmed cases of this mutation to 9 total families and/or individuals: 3 families, 3 confirmed *de-novo* cases, and 3 others that are unconfirmed *de-novo*[19].

The association with triggers including heat exposure, psychological stress and childbirth [1,3,20], has been common but not absolute for all those with dystonic features and ATP1A3 mutations. This family adds a new potential trigger, the excessive use of alcohol. This has led to a more detailed on-going analysis of the role of alcohol as a trigger in RDP, within our larger longitudinal study across all families with RDP, suggesting a role of alcohol as at least one of the triggers in 40% of affected patients [21]. In spite of these triggers, all family members except for II.3 report a history of headaches with migraine symptoms. Worsening of RDP symptoms after alcohol use has occurred in an unrelated mildly affected individual with the T613M mutation (Brashear unpublished observations). Further study of the role of alcohol in RDP is needed in animal models.

More recently the reports of *de-novo* mutations and familial cases occurring worldwide have suggested that RDP may be more common and that the phenotypic pattern may be more variable [1,4]. Our family adds to this data as the first family of Italian descent with a mutation and because leg onset and a later age of onset are both unusual [2] thus stressing the importance of considering a diagnosis of RDP in atypical case.

The description of this family suggests that ATP1A3 may have a role in psychiatric, cognitive and motor disorders in the brain. This is supported by studies in both humans and mice. Association between polymorphisms in the Na, K-ATPase genes and bipolar disorder have been reported [22,23]. A 2009 study of 126 subjects with bipolar disease from 118 families identified an association with an SNP in the 3′ untranslated region of ATP1A3 [22]. In a 1998 study of Irish patients with bipolar disease and 85 matched controls, the authors demonstrated an association between bipolar disease and a dinucleotide repeat polymorphism within the first introns of the ATP1A3 gene ($p = 0.022$) that increased in significance when considering only the subset of patients presenting with a depressive episode ($p = 0.001$) [23]. ATP1A3 has been further implicated in patients with depression and suicide using expression profiling in brain tissue from these patients [24]. Finally, the heterozygote knock-out model of Atp1a3 is hyperactive and has learning and memory deficits [25].

The characterization of humans with RDP is usually complicated by the presence of motor symptoms at the time of testing. While this family has one gene carrier without motor symptoms and with cognitive findings, the number is too small to draw definitive conclusions. However, the predominant finding of psychiatric symptoms in those with motor symptoms supports our hypothesis that ATP1A3 mutations may present with a wide spectrum of features, motor and non-motor. These results are supported by previous reports of depression, anxiety and schizophrenia in individuals with motor manifesting ATP1A3 mutations [18,20,26]. The findings in this family, particularly the psychiatric disease, support the hypothesis that as in other forms of genetic dystonia [7,8], the genetic abnormality in RDP affects more than motor pathways.

RDP remains an untreatable genetic form of dystonia-parkinsonism, known to occur both in families and in sporadic cases with d*e-novo* mutations. The report of this family indicates that ATP1A3 mutations affect multiple areas of the brain rather than producing an isolated

motor syndrome and also raises the possibility that alcohol may be an avoidable trigger in those known to be at risk.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

This study was supported by NINDS 5R01NS058949-03 (AB).

Ms. Hill salary support from this study from NIH grant R01-NS058949 Dr. Snively received support for this study from NIH grant R01-NS058949.

Ms. Light receives salary support from this study from NIH grant R01-NS058949.

Ms. Boggs receives salary support from this study from NIH grant R01-NS058949.

Dr. McCall receives research support from: Sealy and Cephalon and serves on advisory boards for Sealy, Merck and Sepracor. Dr. McCall is on the speaker's bureau for Sepracor and Merck.

Dr. Ozelius has grants from the Bachmann-Strauss Dystonia and Parkinson Foundation, The Dystonia Medical Research Foundation and NIH NS046340, NS058949, NS037409, RR026123. She is a current member of the scientific advisory boards of the National Spasmodic Dysphonia Association and the Benign Essential Blepharospasm Research Foundation 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 a patent. Athena has supported one Grand Rounds given by Dr. Ozelius.

Dr. Sweadner has salary support from NINDS (R01 NS050696 (PI) and R01-NS058949 (co-investigator)); receives research support from the Bachmann-Strauss Dystonia and Parkinson Foundation; and serves as an Associate Editor of the *American Journal of Physiology Cell Physiology* and on the Editorial Board of *The Journal of Biological Chemistry*.

## References

1. Brashear A, Dobyns WB, de Carvalho AP, Borg M, Frijns CJ, Gollamudi S, et al. The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the ATP1A3 gene. Brain. 2007 Mar; 130(Pt 3):828–35. [PubMed: 17282997]
2. Brashear A, Farlow MR, Butler IJ, Kasarskis EJ, Dobyns WB. Variable phenotype of rapid-onset dystonia-parkinsonism. Mov Disord. 1996 Mar; 11(2):151–6. [PubMed: 8684384]
3. Dobyns WB, Ozelius LJ, Kramer PL, Brashear A, Farlow MR, Perry TR, et al. Rapid-onset dystonia-parkinsonism. Neurology. 1993 Dec; 43(12):2596–602. [PubMed: 8255463]
4. de Carvalho AP, Sweadner KJ, Penniston JT, Zaremba J, Liu L, Caton M, et al. Mutations in the Na +/K+ – ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. Neuron. 2004 Jul 22;43(2):169–75. [PubMed: 15260953]
5. The unified Parkinson's disease rating scale [UPDRS]: status and recommendations. Mov Disord. 2003 Jul; 18(7):738–50. [PubMed: 12815652]
6. Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology. 1985 Jan; 35(1):73–7. [PubMed: 3966004]
7. Heiman GA, Ottman R, Saunders-Pullman RJ, Ozelius LJ, Risch NJ, Bressman SB. Increased risk for recurrent major depression in DYT1 dystonia mutation carriers. Neurology. 2004 Aug 24; 63(4): 631–7. [PubMed: 15326234]
8. Hess CW, Raymond D, Aguiar PC, Frucht S, Shriberg J, Heiman GA, et al. Myoclonus-dystonia, obsessive-compulsive disorder, and alcohol dependence in SGCE mutation carriers. Neurology. 2007 Feb 13; 68(7):522–4. [PubMed: 17296918]

9. First, MB.; Spitzer, RL.; Williams, JBW.; Gibbon, M. Structured clinical interview for DSM-IV [SCID]. Washington, DC: American Psychiatric Association; 1995.
10. Balas M, Peretz C, Badarny S, Scott RB, Giladi N. Neuropsychological profile of DYT1 dystonia. Mov Disord. 2006 Dec; 21(12):2073–7. [PubMed: 17013905]
11. Scott RB, Gregory R, Wilson J, Banks S, Turner A, Parkin S, et al. Executive cognitive deficits in primary dystonia. Mov Disord. 2003 May; 18(5):539–50. [PubMed: 12722168]
12. Sheslow, D.; Adams, W. Wide range assessment of memory and learning. 2nd. Lutz, Florida: Psychological Assessment Resources; 2007.
13. Spreen, O.; Strauss, E. A compendium of neuropsychological tests. New York: Oxford University Press; 1998.
14. Smith, A. Symbol digit modalities test. Los Angeles: Western Psychological Services; 2007.
15. Heaton, RK.; Miller, W.; Taylor, MJ.; Grant, I. Revised comprehensive norms for an expanded halstead-reitan battery: demographically adjusted neuro-psychological norms for African American and Caucasian adults. Psychological Assessment Resources, Inc; 2004.
16. Raven, JC. Raven's progressive matrices and coloured progressive matrices with research supplement. San Antonio: Harcourt Assessment; 2000.
17. Zaremba J, Mierzewska H, Lysiak Z, Kramer P, Ozelius LJ, Brashear A. Rapid-onset dystonia-parkinsonism: a fourth family consistent with linkage to chromosome 19q13. Mov Disord. 2004 Dec; 19(12):1506–10. [PubMed: 15390049]
18. McKeon A, Ozelius LJ, Hardiman O, Greenway MJ, Pittock SJ. Heterogeneity of presentation and outcome in the Irish rapid-onset dystonia-parkinsonism kindred. Mov Disord. 2007 May 21.
19. Brashear A, Hill DF, Snively B, Sweadner KJ, Ozelius L. De novo and recurrent mutations in ATP1A3 are common in rapid-onset dystonia-Parkinsonism. Neurology. Feb 3.2010 74(Suppl. 2):A204.
20. Brashear A, DeLeon D, Bressman SB, Thyagarajan D, Farlow MR, Dobyns WB. Rapid-onset dystonia-parkinsonism in a second family. Neurology. 1997 Apr; 48(4):1066–9. [PubMed: 9109901]
21. Brashear A, Hill DF, Snively B, Sweadner KJ, Ozelius L. New triggers in rapid-onset dystonia-parkinsonism [RDP]. Neurology. 2010; 74(Suppl. 2):A205.
22. Goldstein I, Lerer E, Laiba E, Mallet J, Mujaheed M, Laurent C, et al. Association between sodium- and potassium-activated adenosine triphosphatase alpha isoforms and bipolar disorders. Biol Psychiatry. 2009 Jun 1; 65(11):985–91. [PubMed: 19058785]
23. Mynett-Johnson L, Murphy V, McCormack J, Shields DC, Claffey E, Manley P, et al. Evidence for an allelic association between bipolar disorder and a $Na^+$ $k^+$ adenosine triphosphatase alpha subunit gene [ATP1A3]. Bio Psychiatry. 1998 Jul 1; 44(1):47–51. [PubMed: 9646882]
24. Tochigi M, Iwamoto K, Bundo M, Sasaki T, Kato N, Kato T. Gene expression profiling of major depression and suicide in the prefrontal cortex of postmortem brains. Neurosci Res. 2008 Feb; 60(2):184–91. [PubMed: 18068248]
25. Moseley AE, Williams MT, Schaefer TL, Bohanan CS, Neumann JC, Behbehani MM, 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(3):616–26. [PubMed: 17234593]
26. Pittock SJ, Joyce C, O'Keane V, Hugle B, Hardiman MO, Brett F, et al. Rapid-onset dystonia-parkinsonism: a clinical and genetic analysis of a new kindred. Neurology. 2000 Oct 10; 55(7): 991–5. [PubMed: 11061257]

**Table 1**

Demographic and phenotypic Characteristics.

| Pedigree number | Age at onset | Age at exam | Burke Fahn Marsden | UPDRS motor | Triggers | Presentation |
|---|---|---|---|---|---|---|
| I.1 [Parent] | 59 | 64 | 36 | 27 | Heat | Leg cramping 6 months prior to sudden onset dystonia with left foot incoordination, progressing over years to bilateral limb involvement, facial grimacing |
| II.1 [Child] | N/A | 44 | 0 | 0 | N/A | Asymptomatic |
| II.2 [Child] | 18 | 38 | 58 | 34 | Alcohol stress | Intermittent limb cramping over one year prior to sudden onset [overnight] dysarthria and asymmetric limb dystonia [R > L] and dysphagia |
| II.3 [Child] | 18 | 39 | 41 | 18 | Alcohol heat physical activity | Sudden onset [overnight] of dysarthria, progressing to asymmetric limb dystonia [R > L] and dysphagia over three weeks |
| II.4 [Child] | 19 | 36 | 70.5 | 42 | Heat stress | Sudden onset [overnight] asymmetric limb dystonia [L > R] followed by dysarthria, drooling, and generalized dystonia over several hours. |

**Table 2**

Final psychiatric diagnoses.

| | Mood | Anxiety | Substance |
|---|---|---|---|
| Patient II.2 | Bipolar | Obsessive compulsive disorder | Alcohol abuse |
| | | Panic disorder | Alcohol dependence |
| | | Post traumatic stress disorder | Cannabis abuse |
| | | | Cannabis dependence |
| Patient II.3 | Bipolar | Obsessive compulsive disorder | Alcohol abuse |
| | | Panic disorder | |
| Patient II.4 | Dysthymia | Post traumatic stress disorder | |

**Table 3**

Cognitive functions.

| | Reasoning | Memory | | Verbal fluency | | Executive functions | |
|---|---|---|---|---|---|---|---|
| | Raven's[a] | WRAML[b] | | COWA[c] | | Trail Making[d] | |
| | Matrices | Picture memory delayed | Verbal memory delayed | Linguistic | Semantic | Part A | Part B |
| Patient II.1 | 1* | 7 | 8 | 27* | 43 | 48 | 19* |
| Patient II.2 | 5 | 7 | 3* | 31* | 56 | 41 | 23* |
| Patient II.3 | 10 | 8 | 9 | 28* | 30* | 46 | 45 |
| Patient II.4 | 1* | 7 | 10 | 28* | 27* | 30* | 23* |

Note 1: Patient II.1 has no motor findings.

Note 2: * Impaired.

[a] Raven's Progressive Matrices percentile scores.

[b] Wide Range Assessment of Memory and Learning; mean = 10, standard deviation = 3.

[c] Controlled Oral Word Association; *T* scores with mean = 50, standard deviation = 15.

[d] *T* scores with mean = 50, standard deviation = 15.

*Parkinsonism Relat Disord*. Author manuscript; available in PMC 2013 August 26.