The phenotypic spectrum of rapid-onset dystonia–parkinsonism (RDP) and mutations in the ATP1A3 gene

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Rapid-onset dystonia–parkinsonism (RDP), also known as DYT12, is characterized by the abrupt onset of dystonia and parkinsonism and is caused by mutations in the ATP1A3 gene. We obtained clinical data and sequenced the ATP1A3 gene in 49 subjects from 21 families referred with ‘possible’ RDP, and performed a genotype–phenotype analysis. Of the new families referred for study only 3 of 14 families (21%) demonstrated a mutation in the ATP1A3 gene, but no new mutations were identified beyond our earlier report of 6. Adding these to previously reported families, we found mutations in 36 individuals from 10 families including 4 de novo mutations and excluded mutations in 13 individuals from 11 families. The phenotype in mutation positive patients included abrupt onset of dystonia with features of parkinsonism, a rostrocaudal gradient, and prominent bulbar findings. Other features found in some mutation carriers included common reports of triggers, minimal or no tremor at onset, occasional mild limb dystonia before the primary onset, lack of response to dopaminergic medications, rare abrupt worsening of symptoms later in life, stabilization of symptoms within a month and minimal improvement overall. In comparing ATP1A3 mutation positive and negative patients, we found that tremor at onset of symptoms, a reversed rostrocaudal gradient, and significant limb pain exclude a diagnosis of RDP. A positive family history is not required. Genetic testing for the ATP1A3 gene is recommended when abrupt onset, rostrocaudal gradient and prominent bulbar findings are present.

Keywords: ATP1A3; dystonia; Na⁺/K⁺-ATPase; parkinsonism; rapid-onset dystonia–parkinsonism; RDP

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Introduction

Rapid-onset dystonia–parkinsonism (RDP) is characterized by the abrupt onset of dystonia and parkinsonism with little response to dopaminergic medications, and is caused by mutations in the Na⁺/K⁺-ATPase alpha three (α3) subunit (Brashear et al., 1998a; Brashear et al., 1997; Brashear et al., 1996; Brashear et al., 1999; de Carvalho...
Aguiar et al., 2004) RDP (DYT12) is an autosomal dominant disorder with variable penetrance, presenting abruptly in the teens to twenties and often striking after a physiological stressor (Dobyns et al., 1993; Pittock et al., 2000; Linazasoro et al., 2002; Kamm et al., 2004; Zaremba et al., 2004; Riley, 2005). Our finding of missense mutations in the ATP1A3 gene as the cause of RDP is the first link of mutations in the α3 subunit of the Na,K-ATPase with human disease.

RDP typically presents with an abrupt onset with limited progression over weeks and little or no improvement thereafter, except in a few patients who have had mild improvement in gait. Several others have had later ‘second’ episodes of abrupt exacerbation (Dobyns et al., 1993).

In 2004, we reported the genetic cause of RDP as one of six novel missense mutations in the ATP1A3 gene in seven families worldwide (de Carvalho Aguiar et al., 2004). Here, we analyse the phenotype in a series of 21 patients and their affected family members (49 total) referred for suspicion of RDP, and compare those with and without mutations of ATP1A3 to identify the clinical features that should aid diagnosis and prompt molecular testing.

Material and methods

Clinical

Patients for this study were referred from neurologists worldwide based on their clinical suspicion of RDP. Subjects were included if their presentation was suggestive of previously reported features of RDP. These included one or more of the following symptoms: abrupt onset of dystonia defined as onset hours to weeks, with stabilization within 30–60 days, prominent bulbar symptoms and/or identifiable triggers (Dobyns et al., 1993). All patients agreed to participate and provided written informed consent. The studies were approved by local institutional review boards. We obtained detailed clinical information regarding age and body site of onset, treatment with dopaminergic medication, affected areas including gait, limb and bulbar symptoms, associated triggers, time to stabilization and any other prominent features as well as a buccal or blood sample. In addition to those patients not seen personally by A.B., S.B.B., W.B.D or A.M., video images were taken of affected individuals and reviewed by the authors most familiar with RDP (A.B., S.B.B., W.B.D.). Videos were reviewed prior to knowledge of mutation analysis but reviewers were aware of RDP as a diagnostic possibility. The clinical data for the subjects with and without identified ATP1A3 mutations were compared.

Mutation analysis

DNA was extracted from white blood or buccal cells using the Puregene procedure (Gentra Systems Inc., Minneapolis, MN). The samples were analysed in a stepwise manner, first testing for the six known ATP1A3 mutations. When this analysis was negative, the remainder of the coding portion of the ATP1A3 gene was sequenced to ensure that no other mutations were present. The 23 exons of the ATP1A3 gene were amplified using previously specified primers and conditions (de Carvalho Aguiar et al., 2004). The PCR products were sequenced using the standard dideoxy nucleotide method. Five hundred control chromosomes from individuals of Northern European ancestry were screened for each mutation by denaturing high performance liquid chromatography (DHPLC) using the WAVE® Nucleic Acid Fragment Analysis System (Transgenomic, Omaha, NE) as previously described (de Carvalho Aguiar et al., 2004).

Statistical analysis

Baseline characteristics between mutation positive and negative individuals were compared using Student’s t-tests or Mann–Whitney tests for continuous variables and χ² or Fisher’s exact tests for categorical variables. Statistical analyses were performed using Stata 9.0 software (College Station, TX).

Results

Forty-nine subjects were referred because of suspected RDP. Mutations in the ATP1A3 gene were found in 36 individuals from 10 families (Table 1), including 26 individuals from seven families reported previously (de Carvalho Aguiar et al., 2004). In the remaining 13 subjects from 11 families (Table 2), no mutations in the ATP1A3 gene were found (de Carvalho Aguiar et al., 2004). We identified mutations in 3 of the 14 new families analysed. In all three of the new mutation positive families, one of the six previously identified mutations in the ATP1A3 gene was found. The three new cases included one familial and one de novo patient with the T613M mutation, and one ‘possible’ de novo patient with an E277K mutation (Table 1). The latter was labelled possible as only one parent was available for testing. The fourth de novo subject was previously reported. These recurrent mutations most likely represent mutational hotspots in important functional residues (de Carvalho Aguiar et al., 2004). For the mutation positive group, the specific mutation and most consistent clinical manifestations are listed in Table 1 with further details added in Supplementary Table 1, available online. Similar data for patients referred for possible RDP, but in whom no mutations were detected, are provided in Table 2. Overall, we found many consistent features from the history and examination among mutation positive individuals, and significant differences among most mutation negative individuals that should help distinguish true RDP from overlapping disorders. However, no consistent clinical differences were seen between patients carrying different mutations and patients within a family or across families with the same mutation exhibited variable expressivity.

Pattern of presentation of RDP

The pattern of presentation of RDP was remarkably consistent across the entire group of mutation positive patients. The primary onset of RDP consists of the abrupt onset of bulbar and limb dystonia with features of parkinsonism. These striking episodes were sometimes preceded by vague antecedent symptoms, and were rarely followed by later exacerbations or ‘secondary’ onsets.
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mutation</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>n</td>
<td>Nucleotide sequence</td>
</tr>
<tr>
<td>1 (Kamphuis et al., 2005)</td>
<td>1</td>
<td>c.821T → C</td>
</tr>
<tr>
<td>2 (de Carvalho Aguiar et al., 2004)</td>
<td>1d</td>
<td>c.829G → A</td>
</tr>
<tr>
<td>3 (Linazasoro et al., 2002)</td>
<td>1d</td>
<td>c.1838C → T</td>
</tr>
<tr>
<td>4 (Zaremba et al., 2004)</td>
<td>13</td>
<td>c.1838C → T</td>
</tr>
<tr>
<td>5 (de Carvalho Aguiar et al., 2004)</td>
<td>13</td>
<td>c.2273T → G</td>
</tr>
<tr>
<td>6 (de Carvalho Aguiar et al., 2004)</td>
<td>1</td>
<td>c.2338T → C</td>
</tr>
<tr>
<td>7 (de Carvalho Aguiar et al., 2004)</td>
<td>1</td>
<td>c.2401G → T</td>
</tr>
<tr>
<td>8 (Pittock et al., 2000)</td>
<td>8</td>
<td>c.1838C → T</td>
</tr>
<tr>
<td>9 (new report)</td>
<td>1d</td>
<td>c.1838C → T</td>
</tr>
<tr>
<td>10 (Riley, 2005)</td>
<td>1</td>
<td>c.829G → A</td>
</tr>
</tbody>
</table>

+, present; –, absent; psych, psychological stress; unk, unknown. aRDP score: 0, unaffected; 1, limb dystonia only; 2, arm and bulbar dystonia with normal gait; 3, same as 2 with leg involvement but walking unassisted; 4, same as 2 walking with walker or in wheelchair. bF > A > L gradient: rostrocaudal gradient of face > arm > leg (Brashear et al., 1996, 1997, 1999). cGait score: 1, unaffected; 2, affected walks independently; 3, walks with assistance; 4, unable to walk (Brashear et al., 1997; Brashear et al., 1996; Brashear et al., Zaremba et al., 2004). dDe novo mutation. eOnset was abrupt.
Antecedent symptoms
Before the primary onset of RDP, several patients had vague symptoms of dystonia that usually involve the hands and arms. In almost all subjects this was mild and confined to the distal arm or leg. Generalized or truncal dystonia was never reported as an antecedent symptom. For example, the patient from family 10 had mild progressive limb dystonia over about 9 years that was followed by two acute episodes of abrupt worsening over several days. The first of these involved hand symptoms only that improved, while the second consisted of dystonia in all extremities. This is opposite to the pattern found in other early onset dystonia (Kamphuis et al., 2005).

Primary onset
The primary onset in mutation positive patients was always abrupt. Many patients reported specific triggers consisting of either physical or psychological stress. The symptoms rarely improved after the primary onset, although we documented mild improvement in leg symptoms in four patients. The bulbar and arm symptoms never improved.

The age of primary onset ranged from 8 to 55 years, although a young adult onset was most common and onset after age 40 years was rare. Among the 36 affected individuals studied, we found an age of onset before 20 years in 17 patients (47%), between 21 and 30 years in 14 (39%), between 31 and 40 years in 3 (8%) and after 40 years of age in the remaining 2 patients (6%). However, the ages of onset of the mutation positive and the mutation negative groups were not significantly different.

The bulbar symptoms in RDP are striking. Patients are typically dysarthric and hypophonic with mild to moderate dysphagia. Pseudobulbar features are not seen. The speech and swallowing symptoms appear to be related to the rostrocaudal gradient. Those with more profound facial involvement have more speech and swallowing difficulties. In addition, investigators note that the facial features are unique to RDP such that individuals from different families harbouring different mutations have strikingly similar facial features (J.Z., G.L. and S.B.B., personal communication).

The involuntary movements are characterized by generalized or segmental dystonia with superimposed parkinsonian features, primarily bradykinesia and postural instability. All subjects lacked other features, such as pill-rolling tremor, diurnal fluctuation and response to standard medications for parkinsonism. We observed a consistent rostrocaudal gradient of the dystonia and parkinsonism, such that bulbar symptoms were more severe than arm symptoms and arm symptoms more severe than leg symptoms in all mutation positive patients. This is opposite to the pattern found in other early onset dystonia.

Table 2 Clinical characteristics in 13 patients without ATP1A3 mutations

<table>
<thead>
<tr>
<th>Family</th>
<th>Number affected</th>
<th>Age of onset (years)</th>
<th>Reported triggers</th>
<th>Rapid onset</th>
<th>Time to stabilize</th>
<th>RDP score</th>
<th>Bulbar Gradient</th>
<th>Gait score</th>
<th>Tremor</th>
<th>Other unique features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>8</td>
<td>None</td>
<td>+</td>
<td>Slow progression</td>
<td>3</td>
<td>F &gt; A &gt; L 2</td>
<td>+</td>
<td>Cerebellar atrophy</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>20–34</td>
<td>None</td>
<td>Unk</td>
<td></td>
<td>3</td>
<td>F &gt; A &gt; L 2</td>
<td>−</td>
<td>Arm dystonia with pain, limited upgaze, ocular apraxia foot pain, foot posture; sphincter dysfunction</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>54</td>
<td>+</td>
<td>Unk</td>
<td></td>
<td>1</td>
<td>L &gt; A 2</td>
<td>+</td>
<td>Hemidystonia; dysmorphic; cognitive delay; ocular apraxia; migraine HA</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>2</td>
<td>Psy +</td>
<td>Gradual progression</td>
<td>3</td>
<td>F &gt; A &gt; L 2</td>
<td>+</td>
<td>Partially L-dopa responsive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>2</td>
<td>Teens–22</td>
<td>None</td>
<td>Unk</td>
<td></td>
<td>3</td>
<td>F = A &gt; L 2</td>
<td>+</td>
<td>Positive anticholinergics</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>1</td>
<td>38</td>
<td>Psych</td>
<td>1 day</td>
<td>2</td>
<td>2</td>
<td>A &gt; L &gt; F 1</td>
<td>−</td>
<td>Intermittent fluctuating cervical/cranial dystonia and slow parkinsonism</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>1</td>
<td>8</td>
<td>None</td>
<td>+</td>
<td>2–3 days</td>
<td>2</td>
<td></td>
<td>−</td>
<td>Cervical</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>1</td>
<td>32</td>
<td>Stress, HA</td>
<td>6 months</td>
<td></td>
<td>3</td>
<td>F &gt; A &gt; L 2</td>
<td>+</td>
<td>Cervical, later migraine HA</td>
<td></td>
</tr>
</tbody>
</table>

+ present; −, not present. F, face; A, arm; cervical, cervical dystonia; HA, headache; L, leg; N, neck; NA, not applicable; Psych, psychological stress; Unk, unknown; WC, writer’s cramp. See legend to Table 1 for description of F > A > L, RDP and gait scores.
syndromes such as DYT1-associated dystonia and dopa-responsive dystonia (DRD), both of which present with more severe leg involvement (Heiman et al., 2004). Although unusual, presentation with isolated arm dystonia has been reported in some families with DYT1, particularly those from Japan (Matsumoto et al., 2001).

The parkinsonian findings in RDP include slowness of movement and postural instability. With the exception of the single case reported by Kamphuis et al. (2005), the parkinsonism has been limited to bradykinesia, postural instability and the hypophonia described earlier. The typical stooped gait, tremor and gradual decline seen in idiopathic Parkinson’s disease (PD) have not been reported. It is important to note that our referrals are from movement disorder experts seeking a diagnosis of a patient with atypical dystonic symptoms and patients with atypical PD have not been screened for mutations.

**Secondary onset**

A few patients reported later episodes of abrupt worsening of symptoms, occurring 1–9 years after the initial onset. These resembled the primary onsets, with worsening of bulbar, arm and leg symptoms over a similar time course.

**Non-motor features**

While more difficult to recognize, several mutation positive patients have had symptoms beyond the involuntary movements, which is also typical of other dystonia syndromes (Heiman et al., 2004; Klein and Ozelius, 2002). For example, psychiatric disorders including depression and social phobia were reported in several affected individuals from family 8 (Pittock et al., 2000). Several individuals from families 5 and 7 reported similar psychiatric disorders in themselves or affected relatives, but we were unable to obtain detailed evaluations. Seizures are not part of the RDP phenotype at presentation, but three individuals with mutations from families 2, 5 and 7 developed seizures several years later; all responded to medications.

**RDP-like disorders differ from RDP**

We next compared the clinical features between mutation positive (Table 1) and negative (Table 2) patients, and summarize key differences in Table 3. Most notably, patients without mutations typically lacked the expected rostrocaudal gradient, but reported tremor and pain. Most had onset in the legs, which was never seen in mutation positive RDP. In addition, two mutation negative patients had abrupt onset of isolated cervical dystonia that remained isolated to the neck.

A statistical analysis of the mutation positive group (Table 1) and mutation negative group (Table 2) notes that abrupt onset, rostrocaudal gradient and bulbar symptoms are all differentiating features of the mutation positive subjects (Table 3).

**Table 3 Statistical analysis of key characteristics in those with and without ATP1A3 mutations**

| Characteristics | Mutation+ group | Mutation− group | P-value
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset</td>
<td>36/36 (100%)</td>
<td>7/11 (63.6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>F &gt; A &gt; L</td>
<td>36/36 (100%)</td>
<td>1/3 (77%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bulbar symptoms</td>
<td>36/36 (100%)</td>
<td>7/11 (53.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prominent</td>
<td>0/36 (0%)</td>
<td>4/13 (30.7%)</td>
<td>0.003</td>
</tr>
<tr>
<td>pain</td>
<td>0/36 (0%)</td>
<td>2/11 (18.2%)</td>
<td>0.051</td>
</tr>
</tbody>
</table>

*Fisher’s exact for categorical data, t-test for continuous data.

Tremor was not reported at the onset in patients with mutations, but was noted in 5 of the 13 subjects without mutations. Similarly, intractable burning pain was reported in 2 of 11 mutation negative patients and non-specific limb pain was reported in several others, whereas pain was not reported in any of the mutation positive patients. The presence of pain and tremor in patients who did not carry mutations makes this an important differentiating feature between the two populations. However, family members reported tremor developing later in life in a few affected individuals in RDP families 4 and 5.

**Discussion**

RDP is a unique autosomal dominant movement disorder that typically presents in teens and young adults with abrupt onset of dystonia and parkinsonism. Our discovery of missense mutations in the ATP1A3 gene in affected individuals from 10 families with RDP allowed us to perform detailed genotype–phenotype comparison in the largest series of patients with mutations in ATP1A3 to date.

**RDP phenotype and diagnostic criteria**

The patients suspected of having RDP and sent for mutation analysis of the ATP1A3 gene came from all over the world. Typically referrals were made because these patients had some disease features that overlapped with the disease phenotype described in the original family (i.e. rapid onset, triggering event, orofacial dystonia, etc.). Due to referral bias the group of 49 patients in this report represents a highly selected group of dystonia patients. Despite significant bias in ascertainment of these patients toward an RDP-like phenotype, we found several characteristics that distinguished mutation positive from mutation negative ATP1A3 patients, which can be used as the basis for neurological diagnosis.

Based on our experience in the 10 mutation positive families, we propose that the minimal diagnostic criteria for RDP should include: (i) abrupt onset of dystonia with features of parkinsonism over a few minutes to 30 days, (ii) a clear rostrocaudal (face>arm>leg) gradient of
involvement and (iii) prominent bulbar findings. In this highly selected group we noted the rostrocaudal gradient to be a hallmark of RDP. In our series we found that all of mutation positive patients met all three of the above minimal diagnostic criteria. In addition three cases without a mutation (A, D and F, Table 2) met these criteria. Those with these findings should be referred for RDP testing.

In addition, there are other features suggestive of RDP which include (iv) minimal or no tremor at onset, (v) occasional mild limb dystonia prior to the primary onset of RDP, (vi) common reports of triggers associated with the abrupt onset of symptoms, (vii) rare ‘second onsets’ or abrupt worsening of symptoms later in life, (viii) stabilization of symptoms within a month and (ix) minimal improvement overall but with limited improvement in gait in a few patients. In this highly selected group, when comparing all ATP1A3 mutation positive and negative patients, we found that the presence of tremor at onset of symptoms, a reverse of the rostrocaudal gradient (leg more affected than arm more affected than face) and significant limb pain exclude a diagnosis of RDP. When these additional features are considered, only case F (Table 2) cannot be eliminated and appears to be a phenocopy.

**Non-motor features**

Since it is an exclusively neuronal protein, defects in the Na,K-ATPase could lead to problems with neuronal function beyond motor control. Because α3-expressing neurons are present throughout the nervous system, we suspect that our findings of non-motor symptoms in several patients, namely psychological symptoms such as depression or social phobias, or seizures may represent part of the phenotype of ATP1A3 mutations. These symptoms may have a biochemical basis considering our prior findings of abnormal dopamine, serotonin and norepinephrine metabolites in cerebrospinal fluid of affected individuals and asymptomatic carriers (Brashear et al., 1998a; Brashear et al., 1998b). However, these symptoms probably do not differentiate RDP from other genetic dystonias. Recurrent major depression has been proposed as part of the DYT1 phenotype, although it is independent of the motor symptoms as mood disorders were also observed in non-manifesting DYT1 gene carriers (Heiman et al., 2004). In addition, obsessive compulsive disorder has been reported in both symptomatic and asymptomatic carriers of myoclonus–dystonia (Saunders-Pullman et al., 2002). The presence of psychological symptoms and seizures fits with the localization of α3 in neurons and suggests, as noted in myoclonus–dystonia and DYT1, that some genetic movement disorders have a phenotype beyond motor findings.

**Possible second RDP locus (RDP2)**

A kindred with eight individuals affected by RDP was recently reported in whom no mutations of ATP1A3 were found (Kabakci et al., 2005). The proband presented at 6 years with overnight onset of dysphonia, dysphagia, orofacial dystonia and dystonia of all four limbs, which meets our RDP diagnostic criteria. Five of the affected individuals in this family had concurrent renal disease consisting of hypoplasia, cysts or fatal renal failure with no details available, which were never observed in RDP patients with ATP1A3 mutations. The most likely explanation for lack of a mutation in ATP1A3 is a second RDP locus. A non-coding mutation of ATP1A3 is presumably possible, although we view this as less likely given that all mutations found to date in ATP1A3 (and ATP1A2) are missense changes in specific regions of the protein.

**Potential benefit of criteria: positive family history not required**

The benefits of using the suggested criteria of abrupt onset, a rostrocaudal gradient, and prominent bulbar findings broaden the suggestive diagnostic criteria for RDP. In prior reports, we considered a positive family history necessary for diagnosis. Using these criteria and testing for ATP1A3 mutations, we now report four patients with mutation positive RDP and normal results of mutation analysis in one (one patient) or both (three patients) parents. Based upon lack of a family history and the absence of ATP1A3 mutations in one or both parents, the mutations found in these four individuals most likely represent spontaneous mutations in ATP1A3. Our finding of four individuals with de novo mutations underscores the need to consider RDP in patients with atypical presentations of dystonia or parkinsonism, and the potential usefulness of genetic testing.

**Could RDP phenotype be broader similar to ATP1A2 mutations?**

While RDP is the first human disease to be associated with mutations of ATP1A3, three neurological diseases have been associated with mutations in the ATP1A2 subunit: infantile seizures, familial hemiplegic migraine (FHM) and more recently familial common migraine (Terwindt et al., 1998; Vanmolkot, 2003a; Vanmolkot, 2003b; De Fusco et al., 2004; Estevez and Gardner, 2004). The dominant characteristics of patients presenting with diseases caused by mutations in ATP1A3 and ATP1A2 are consistent with what is known about the major cell-type distribution of α3 and α2 in the brain (de Carvalho Aguiar et al., 2004). The Na,K-ATPase converts metabolic energy by moving Na out of the cell and K into the cell, restoring the ion gradients of the cell reduced by the activity of ion channels and Na\(^{+}\)-dependent
carriers (McGrail et al., 1991). The Na,K-ATPase has three subunits, α, β, γ with the α representing the catalytic component of the enzyme. The α3 isof orm is expressed exclusively in neurons in the CNS and given the highly regulated structure of α3 is reasonable to postulate that defects in ATP1A3 would cause neurological disease beyond dystonia. The phenotype of ATP1A2 mutations continues to broaden with the recent report of Todt et al., implicating mutations in the ATP1A2 gene in familial common migraine (Todt et al., 2005). The broad and varied phenotype of ATP1A2 mutations is important to consider when evaluating the non-motor findings in patients with ATP1A3 mutations.

Will mutations of ATP1A3 be found in other phenotypes?

Although we observed subtle antecedent motor symptoms and non-motor symptoms such as depression, social phobias and late-onset seizures in several patients with RDP, we do not yet know whether these should be considered part of the typical RDP phenotype. However, we suspect that they are related considering the reported findings with ATP1A2. Were the same phenomenon to be seen with mutations of ATP1A3, the candidate phenotypes might include mood or other mental disorders, seizures, or less severe forms of dystonia or parkinsonism, such as oromandibular dystonia or atypical parkinsonism. More detailed evaluations in ‘asymptomatic’ ATP1A3 mutation carriers without RDP may provide important clues regarding which more common disorders are worthy of study. Thus, the association of RDP and the ATP1A3 gene opens the door for new research directions to understand (and possibly treat) dystonia as well as other neurological and psychological disorders.

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