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Auditory-Perceptual Voice and Speech Evaluation in *ATP1A3* Positive Patients

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Abstract

Introduction: Bulbar symptoms are frequent in patients with rapid-onset dystonia-parkinsonism (RDP). RDP is caused by *ATP1A3* mutations, with onset typically within 30 days of stressor exposure. Most patients have impairments in speech (dysarthria) and voice (dysphonia). These have not been quantified. We aimed to formally characterize these in RDP subjects as compared to mutation negative family controls.

Methods: We analyzed recordings in 32 RDP subjects (male=21, female=11) and 29 mutation negative controls (male=15, female=14). Three raters, blinded to mutation status, rated speech and vocal quality. Dysarthria was classified by subtype. Dysphonia was rated via the GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain) scale. We used general neurological exams and the

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Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) to assess dysarthria, dystonia, and speech/swallowing dysfunction.

Results: The presence of dysarthria was more frequent in RDP subjects compared to controls (72% vs. 17%, $p < 0.0001$). GRBAS voice ratings were worse in the RDP cohort across nearly all categories. Dysarthria in RDP was associated with concordant cranial nerve 9–11 dysfunction (54%, $p = 0.048$), speech/swallowing dysfunction (96%, $p = 0.0003$); and oral dystonia (88%, $p = 0.001$).

Conclusions: Quantitative voice and speech analyses are important in assessing RDP. Subjects frequently experience dysarthria and dysphonia. Dystonia is not the exclusive voice abnormality present in this population. In our analysis, RDP subjects more frequently experienced bulbar symptoms than controls. GRBAS scores are useful in quantifying voice impairment, potentially allowing for better assessments of progression or treatment effects. Future directions include using task-specific diagnostic and perceptual voice evaluation tools to further assess laryngeal dystonia.

Keywords

ATP1A3; rapid-onset dystonia-parkinsonism; RDP; speech; voice

INTRODUCTION

Impairments in speech, voice, and swallowing are frequent comorbidities in RDP. The most common dysfunctions reported are laryngeal dystonia, dysphagia, and dysarthria [1–3]. Dysarthria is a speech disorder characterized by impaired motor execution and/or discoordination of the subsystems involved in speech, including articulation, velopharyngeal function, phonation, and/or respiration [4–5]. Patients with dysarthria may present with weakness or abnormal muscle tone of the speech musculature responsible for articulation, including the lips, palate, and tongue [6]. Figure 1 describe differences in symptomology and evaluation for dysarthria compared to dysphonia, and more specifically, laryngeal dystonia. Different movement disorders have differing degrees of laryngeal dystonia and dysarthria. For example, patients with Parkinson's disease are more likely to report progressively worsening hypokinetic dysarthria and dysphagia, [7] while patients with focal and segmental dystonias may report symptoms of laryngeal dystonia and hyperkinetic dysarthria [8]. Laryngeal dystonia is a specific type of dysphonia, or voice disorder, caused by involuntary spasms of the muscles involved in phonation that results in impaired vocal quality [4–5]. Patients with laryngeal dystonia may describe their voices as hoarse, strained, or characterized by unpredictable voice breaks. Dysarthria, laryngeal dystonia, and dysphagia are thought to commonly occur with *ATP1A3* positive patients due to impairment of the fine motor control that is essential for normal voicing, speech, and/or swallowing.

Impairments of the speech and vocal subsystems alter a patient's ability to communicate and can significantly affect their quality of life [9–10]. These impairments are core features of RDP; the earliest reports of RDP describe dysarthria, dysphagia, mutism, slurred speech, hypophonia, and drooling as among the most frequent symptoms [11–13]. In 2007, Brashear et al examined a cohort of 36 *ATP1A3* mutation-positive Rapid-onset dystonia-parkinsonism (RDP) patients and reported that the majority displayed some degree of dysphagia and/or

dysarthria [14]. To avoid bias and maintain comparability, evaluation of speech abnormalities in these subjects is best accomplished through well-defined and pre-specified algorithms and validated voice and speech measures. However, most studies of patients with *ATP1A3* positive mutations do not quantitate the type and severity of the disorder, or impact of these symptoms on the patient cohort. Speech impairments have also been reported in other *ATP1A3* syndromes, i.e. Alternating Hemiplegia of Childhood (AHC) [15,16] and patients with cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss (CAPOS) syndrome [17,18]. Dysarthria and bulbar symptoms may be a characteristic finding in patients with *ATP1A3* gene mutations.

In this study, fellowship-trained otolaryngologists and speech-language pathologists (SLPs) used standard scales to characterize the voice and speech characteristics of *ATP1A3* positive patients and *ATP1A3* mutation negative family controls. We also recorded neurologist-evaluations of bulbar symptomology in these groups. We performed analyses to compare these groups, and to determine how these symptoms related to the voice and speech outcomes assessed by fellowship-trained otolaryngologists and SLPs. Figure 1 describes the differences in classification and assessment between dysarthria and dysphonia which we used in this study. We were able to detect dysarthria in this patient population but could not sufficiently determine the presence of laryngeal dystonia with the passages recorded, which had not been selected with this need in mind. The study assessments of this cohort were chosen significantly prior to this study and the passages recited did not contain sufficient stimuli (such as contrasting voiced and voiceless phoneme-loaded sentences) to assess the presence of laryngeal dystonia per standard criteria [19–22]. Lastly, our study examined the utility of these assessments in measuring *ATP1A3* positive disease severity.

METHODS

Participants

All participants provided informed consent in accordance with the Declaration of Helsinki and approved by the Wake Forest School of Medicine (WFSM) Institutional Review Board. Based on the current consensus on RDP [23] we adopted minimal criteria to define our cohort. Inclusion criteria were having an *ATP1A3* mutation or being family to someone who did. Families were excluded from this analysis if their first abnormal movement episode occurred before 18 months of age in all affected carriers in the family. Participants and familial controls were drawn from our database of individuals with *ATP1A3* mutations and their family members, comprised of individuals referred to WFSM for suspected *ATP1A3* mutation. On consenting, a buccal or blood sample was obtained from subjects and DNA was extracted using the Puregene procedure (Qiagen systems, Minneapolis MN). The *ATP1A3* gene was Sanger-sequenced using PCR primers and conditions previously described [1]. All carriers discovered were recruited to the database. Family members of carriers were also recruited and tested for *ATP1A3* gene mutations.

Clinical Evaluation

All cohort members underwent a structured interview (consisting of videotaped history-taking session and a subject questionnaire), neuropsychological testing, and a neurologic

exam during which the examiner was blinded to mutation status. The neurological exam included a modified Unified Parkinson Disease Rating Scale Motor subsection (UPDRS-3), [1, 24] and Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) [25]. Bulbar symptoms were assessed by utilizing assessments of cranial nerves 9, 10, and 11 as well as 2 questions from the BFMDRS assessment focusing on speech/swallowing function and oral dystonia.

Voice and Speech Evaluation

Audio recordings were performed on all individuals included in the database. As part of the neurological exam, patients read from the standardized Rainbow Passage [26]. In addition to this, we extracted samples of sustained vowel phonation (/i/) according to the patient's perceived comfortable pitch and levels of loudness, and/or production of several sentences for assessment of connected speech. Any identifying information, such as patient name, sex, time of visit, age, and diagnosis were removed as part of the audio extraction process. Patients were included in this study if they had at least 1 video recording that contained sufficient audio to analyze. Two fellowship-trained otolaryngologists and 2 speech-language pathologists (SLP) served as raters for evaluating patient audio recordings. Raters were blinded to patient diagnosis, age, and time of appointment (i.e. first or repeat appointment) when assessing patient audio recordings. For patients who had more than one audio recording, the most recent audio recording was used for assessment. Audio recordings were presented to the raters in randomized order, and raters were blinded to the source of the audio samples. Each rater assessed audio recordings separately from other raters. Raters first evaluated for the presence or absence of dysarthria, defined as persistently weak and/or uncoordinated musculature critical for speech [27]. As described above, laryngeal dystonia, i.e. involuntary task-specific spasms of the laryngeal muscles, was not assessed for.

The raters next assessed each consecutive audio recording using the GRBAS scale, a well-established otolaryngological assessment of voice quality [28]. The GRBAS scale consists of 5 categories (Grade, Roughness, Breathiness, Asthenia, and Strain) with each rater assessing a single audio recording from 0–3 (0 indicating normalcy, 1 indicating a slight degree of severity, 2 indicating a medium degree, and 3 indicating highest degree) for each GRBAS category. The Grade portion of the scale measures the overall degree of the voice disorder as a whole. The Roughness aspect assesses irregularities in vocal fold vibrations, which may be perceived as a rough or coarse quality. The Breathiness aspect measures the perceived degree of vocal turbulence. Asthenia describes the degree of vocal weakness resulting in reduced vocal ability and power. Finally, the Strain aspect of this scale measures the presence of vocal tension, which may be perceived as a tight and strained quality.

Statistical Analysis

Descriptive statistics were used to report the characteristics for positive *ATP1A3* mutation patients and healthy familial controls. The associations between presence of dysarthria from the neurology and otolaryngology/SLP exam, BFMDRS sub-scores, and cranial nerve dysfunction were assessed using a Fisher's Exact Test. Due to the absence of normality in the GRBAS variables, the Mann-Whitney test was conducted to determine significant differences in voice evaluation GRBAS scores between the positive *ATP1A3* mutation cohort and the healthy familial control cohort, and Spearman's correlations were used to

determine if there was a correlation between BFMDRS scores and GRBAS voice evaluation scores. Cohen's Kappa coefficient was used to measure dysarthria agreement between the neurology assessment and the otolaryngologist/SLP assessment.

RESULTS

Of the total cohort, 5 *ATP1A3* mutation positive subjects were unable to provide analyzable recordings. Thirty-two *ATP1A3* positive patients (males=21, females=11) and 29 healthy family controls (males=15, females=14) were evaluated in a blinded manner by 1 otolaryngologist and 2 SLP's. Additionally, 35 (males=24, females=11) *ATP1A3* positive patients and 27 healthy controls (males=15, females=12) were independently examined by a fellowship-trained movement disorder neurologist to assess presence of dysarthria, and overall dystonia, speech/swallowing dysfunction, and oral dystonia assessed by the BFMDRS. Two mutation negative subjects and 1 mutation positive subject did not have the necessary neurological data for inclusion in the analysis. Figure 2 depicts the organization of the study and the number of patients within each group. Each independent family had at least one proband per family. The characteristics of positive *ATP1A3* mutation patients and mutation negative familial controls are shown in Table 1.

Association of Dysarthria with *ATP1A3* Positive Mutation Status

Five patients with RDP were excluded due to their impairment being so severe that they could not phonate or due to their audio not being recorded. Of the 32 patients with RDP, 23 (72%) were diagnosed with dysarthria by the otolaryngologist/SLPs, and out of the 29 healthy familial controls, 5 (17%) were diagnosed as having dysarthria. A dysarthria diagnosis was significantly higher in patients with RDP as compared to healthy familial controls ($p < 0.0001$).

Dysarthria classification: For patients who were diagnosed as having dysarthria, their dysarthria was further classified by the SLPs. Of the 23 patients with concurrent dysarthria diagnosed and positive *ATP1A3* mutation status, 3 patients presented with symptoms consistent with hyperkinetic dysarthria; 5 patients had symptoms consistent with hypokinetic dysarthria; 5 patients had symptoms consistent with flaccid dysarthria; 3 patients had symptoms consistent with ataxic dysarthria; and 7 patients had symptoms consistent with mixed dysarthria indicating the presence of 2 dysarthria subtypes. The spastic dysarthria subtype was not present individually in any of the patients examined but was identified in 4 of the patients with mixed dysarthria. No patient presented with both hypokinetic and hyperkinetic dysarthria, or flaccid and hyperkinetic dysarthria.

Comparison of GRBAS Voice Evaluation between *ATP1A3* Mutation Positive and Negative Cohorts

When comparing the voice evaluation using the GRBAS scale conducted by the otolaryngologist/SLPs, it was found that patients with RDP had select significantly higher GRBAS scores, indicating that certain aspects of their voice were worse compared to controls (Figure 3). The Grade, Roughness, Asthenia, and Strain scores were higher, and therefore worse in severity, in the *ATP1A3* mutation positive cohort compared to the healthy

familial controls (Grade mean $\pm$ SD: 1.2 ± 0.73 , 0.44 ± 0.71 , $p < 0.0001$; Roughness 0.53 ± 0.58 , 0.2 ± 0.46 , $p = 0.005$; Asthenia 0.58 ± 0.74 , 0.21 ± 0.48 , $p = 0.015$; Strain 0.93 ± 0.61 , 0.37 ± 0.52 , $p = 0.0003$). There were no significant differences in the Breathiness voice scores between the RDP cohort and the healthy familial controls (0.26 ± 0.48 , 0.26 ± 0.56 , $p = 0.553$).

Correlation Between GRBAS Scores and BFMDRS Scores: BFMDRS scores from *ATP1A3* mutation positive and negative cohorts were assessed to determine if there was a correlation between dystonia severity evaluation assessments by the BFMDRS and voice evaluation assessed by the GRBAS evaluation. Though there were positive correlations between BFMDRS total scores and Grade ($r = 0.19$), Breathiness ($r = 0.22$) and Asthenia ($r = 0.22$) scores, these were not significant.

Comparison of Dysarthria Assessed by Neurology and Otolaryngology/SLPs

As part of the routine neurology evaluation, neurologists evaluate presence of dysarthria within the *ATP1A3* mutation positive and negative cohorts. Out of the 35 RDP patients, 26 (74%) were judged by neurologists to have dysarthria, and none of the 27 mutation negative familial controls. A neurologist diagnosing dysarthria was significantly associated with positive *ATP1A3* mutation status ($p < 0.0001$). When examining the total number of *ATP1A3* mutation positive and negative patients that were agreed upon as having or not having dysarthria between the neurology exam and the otolaryngology/SLP exam, the agreement was substantial ($k = 0.694$); however, it was important to also determine the number of specific individuals that were agreed upon as having dysarthria from both the neurology and otolaryngology/SLP exam. When analyzing the individual evaluations of patients to determine the number of individual *ATP1A3* mutation positive and negative patients who were agreed upon as having or not having dysarthria between the neurology exam and the otolaryngology/SLP exam, the agreement was fair ($k = 0.330$).

Association of Dysarthria Assessed by Neurology with Bulbar Symptom Dysfunction

Within the cohort of neurologist-diagnosed dysarthric RDP subjects consisting of 35 patients with *ATP1A3* mutations, we evaluated the association with cranial nerve 9, 10, and 11 dysfunction. Of 26 subjects, 14 (54%) had concordant cranial nerve 9–11 dysfunction. The association was significant ($p = 0.048$). Within this same cohort, we also evaluated the association with BFMDRS sub-scores evaluating mouth dystonia, and speech/swallowing dysfunction. Of the neurologist-diagnosed dysarthric RDP subjects, 25 (96%) had difficulty on the speech/swallowing sub-question of the BFMDRS scale and 23 (88%) were defined by the neurologists as having oral dystonia on this sub-question of the BFMDRS scale. Neurologist-diagnosed dysarthria was significantly associated in this sub-cohort with BFMDRS speech/swallowing dysfunction ($p = 0.0003$) and BFMDRS oral dystonia ($p = 0.001$).

DISCUSSION

Assessing the voice and speech outcomes for patients with any movement disorder with prominent bulbar symptoms is important for two reasons: these deficits can be as disabling

as limb and gait dysfunction, and greater granularity of assessment allows for clearer assessment of improvement or decline [29]. To our knowledge, no previous study has examined voice and speech outcomes in patients with positive *ATP1A3* mutation status via formal otolaryngological/SLP evaluation. We believe evaluation is important in the assessment of RDP given the prominence of bulbar dysfunction for these patients, and the need to better characterize an expanding and evolving phenotype [30]. Though the literature reports low vocal loudness, decreased speech intelligibility, and labored speech in patients with RDP, [11, 31] researchers have not addressed the prevalence, characterization, or accuracy of dysarthria diagnoses. The question of whether the area of expertise of the rater (i.e. neurology versus speech pathology) affects the diagnosis has also not been addressed.

Consistent with our understanding of RDP's phenotype we observed a significant association between RDP status and speech dysfunction, specifically the presence of dysarthria. As would be expected, dysarthria in our cohort was significantly associated with neurologist-rated cranial nerve 9–11 dysfunction, and dystonia identified on the speech/swallowing and oral dystonia sub-questions of the BFMDRS. Patients with RDP have impairments in vocal quality, specifically in the Grade, Roughness, Asthenia, and Strain components of their voices. Our results suggest that the identification of dysarthria and dysphonia are a critical portion of care for this patient population given the high prevalence and symptom severity we observed. Moreover, our findings support the perception that patients with dystonia and dystonia-plus syndromes may be more likely to experience voice and speech perturbations, as well as bulbar symptoms involvement. Therefore, it is essential for patients with dystonia and dystonia-plus syndromes to be accurately evaluated to ensure that their speech and voice is being monitored to detect changes over time or as a result of treatment. Given how significantly speech and voice symptoms affect a patient's quality of life for patients with movement disorders, [32] it is important for physicians to be aware of the prevalence and severity of these symptoms in this patient cohort, and more generally, in patients with dystonia or another dystonia-plus syndrome, to assist patients in seeking the appropriate treatment.

Our study provides quantitative insight into the most common speech and voice disorders that patients with positive *ATP1A3* mutation status can experience so that patients and families can be properly educated about these symptoms and potentially obtain a referral to otolaryngology and speech-language pathology if necessary. Further evaluation may be appropriate for this patient population due to the fact that the BFMDRS scale may not be able to completely capture important aspects of voice/speech. However, further studies are needed to evaluate if voice and speech analyses are superior to routine dysarthria evaluation in terms of evaluating treatment effect, and improvements or worsening of symptoms over time, specifically as it relates to activities of daily living, in patients with voice and speech dysfunction.

Though our study contains the largest cohort of *ATP1A3* mutation-positive patients with voice and speech analysis to date, RDP is a very rare condition. The exact prevalence of RDP has not been reported, but due to the rarity of the condition, our sample size is relatively small. Furthermore, we employed a retrospective design, limiting us to protocols that were not designed with detailed voice capture in mind. The perceptual assessment and

identification of the subtype of dysarthria was limited due to the brevity of the connected speech sample and lack of additional perceptual, oral motor, and standardized assessments. The recordings also did not contain sufficient connected speech tasks contrasting voiced vs voiceless phoneme-loaded sentences to identify vocal characteristics of laryngeal dystonia. For example, task-specific laryngeal spasms associated with Adductor Spasmodic Dysphonia (ADSD) may be more easily detected by having the patient read sentences consisting of voiced phonemes, and the abnormally extended duration of voiceless phonemes characteristic of Abductor Spasmodic Dysphonia (ABSD) may be perceived when the patient reads sentences consisting of voiceless phonemes. We also did not capture how the patients felt their daily living was impacted by their speech and/or voice impairments. However, we plan to modify our examination protocol to include more comprehensive voice recording, and will institute the standardized, validated Voice Handicap Index – 10 (VHI-10) [33] and Eating Assessment Tool – 10 [34] to capture patient-reported symptoms of dysphonia and dysphagia respectively. The mechanism of dysphagia deserves further evaluation and should be addressed in further studies. The question of whether dyspraxia plays a role in speech and swallowing dysfunction in these patients will also be an important point to address in future investigations.

CONCLUSION

In this study, we report that patients with positive *ATP1A3* mutation status are likely to have dysarthria and dysphonia. The dysarthria that this patient population presents with may be a subset of the bulbar symptoms that are commonly observed in this patient population. When present, bulbar symptoms are often moderate or severe [11], and quantitative voice analysis will typically not be necessary to determine speech therapy needs or provide insight into whether a patient is experiencing any limitation of function. However, quantitative speech analysis could be helpful in determining whether speech is spasm-restricted and might be ameliorated by botulinum toxin injections. It also offers another potential outcome measure for any future treatment trial. Further research will be required to delineate its sensitivity in this regard.

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References:

- [1]. Brashear A, Sweadner KJ, Cook JF, Swoboda KJ, & Ozelius L (2007). ATP1A3-Related Neurologic Disorders, GeneReviews®. University of Washington, Seattle.
- [2]. Roubergue A, Roze E, Vuillaumier-Barrot S, Fontenille M-J, Méneret A, Vidailhet M, ... Nicole S The multiple faces of the ATP1A3 -related dystonic movement disorder, *Mov. Disord.* 28 (2013), 1457–1459. [PubMed: 23483595]
- [3]. Sasaki M, Ishii A, Saito Y, & Hirose S Intermediate form between alternating hemiplegia of childhood and rapid-onset dystonia-parkinsonism, *Mov. Disord.* 29 (2014), 153–154. [PubMed: 24123283]
- [4]. Stachler RJ, Francis DO, Schwartz SR, Damask CC, Digoy GP, Krouse HJ, ... Nnacheta LC Clinical Practice Guideline: Hoarseness (Dysphonia) (Update), *Otolaryngol. Head Neck Surg.* 158 (2018), S1–S42. [PubMed: 29494321]
- [5]. Sapienza C, & Hoffman-Ruddy B (2009). *Voice Disorders*. San Diego, CA: Plural Publisher.
- [6]. Lansford KL, & Liss JM Vowel Acoustics in Dysarthria: Speech Disorder Diagnosis and Classification, *J. Speech Lang. Hear Res.* 57 (2014), 57. [PubMed: 24687467]
- [7]. Martens H, Van Nuffelen G, Wouters K, & De Bodt M Reception of Communicative Functions of Prosody in Hypokinetic Dysarthria due to Parkinson's Disease, *J. Parkinson's Dis.* 6 (2016), 219–229. [PubMed: 26889630]
- [8]. Barkmeier-Kraemer JM, & Clark HM *Speech-Language Pathology Evaluation and Management of Hyperkinetic Disorders Affecting Speech and Swallowing Function, Tremor and Other Hyperkinetic Movements*, New York, 2017
- [9]. Cohen SM, Dupont WD, & Courey MS Quality-of-Life Impact of Non-Neoplastic Voice Disorders: A Meta-Analysis, *Ann. Oto. Rhinol. Laryngol.* 115 (2006), 128–134.
- [10]. Ramig LO, Sapir S, Fox C, & Countryman S Changes in vocal loudness following intensive voice treatment (LSVT) in individuals with Parkinson's disease: A comparison with untreated patients and normal age-matched controls, *Mov. Disord.* 16 (2001), 79–83. [PubMed: 11215597]
- [11]. Haq I, Snively B, Sweadner K, Suerken C, Cook J, Ozelius L, et al. Revising rapid-onset dystonia-parkinsonism: Broadening indications for ATP1A3 testing, *Mov. Disord.* 48 (2019), 1528–1536.
- [12]. Dobyns WB, Ozelius LJ, Kramer PL, Brashear A, Farlow MR, Perry TR, ... Breakefield XO Rapid-onset dystonia-parkinsonism, *Neurol.* 43 (1993), 2596–2602.
- [13]. Kramer PL, Mineta M, Klein C, Schilling K, De Leon D, Farlow MR, ... Brashear A Rapid-onset dystonia-parkinsonism: Linkage to chromosome 19q13, *Ann. Neurol.* 46 (1999), 176–182. [PubMed: 10443882]
- [14]. Brashear A, Dobyns WB, de Carvalho Aguiar P, Borg M, Frijns CJM, Gollamudi S, ... Ozelius LJ The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the ATP1A3 gene, *Brain*, 130 (2007), 828–835. [PubMed: 17282997]
- [15]. Capuano A, Garone G, Tiralongo G, Graziola F Alternating Hemiplegia of Childhood: Understanding the Genotype-Phenotype Relationship of ATP1A3 Variations, *Appl Clin Genet*, 13 (2020), 71–81. [PubMed: 32280259]
- [16]. Panagiotakaki E, Doummar D, Nogue E, Nagot N, Lesca G, Riant F, ... Roubertie A Movement disorders in patients with alternating hemiplegia: Soft and Still at the Same Time, *Neurol*, 94 (2020), e1378-e1385.
- [17]. Demos M, van Karnebeek C, Ross C, Adam S, Shen Y, Zhan S, ... Forge Canada Consortium. A novel recurrent mutation in ATP1A3 causes CAPOS syndrome, *Orphanet J Rare Dis*, 9 (2014), 15. [PubMed: 24468074]
- [18]. Maas R, Schieving J, Schouten M, Kamsteeg E, van de Warrenburg B The Genetic Homogeneity of CAPOS Syndrome: Four New Patients With the c.2452G>A (p.Glu818Lys) Mutation in the ATP1A3 Gene, *Pediatr Neurol*, 59 (2016), 71–75. [PubMed: 27091223]
- [19]. Nash EA, & Ludlow CL Laryngeal Muscle Activity During Speech Breaks in Adductor Spasmodic Dysphonia, *Laryngoscope*. 106 (1996), 484–489. [PubMed: 8614226]
- [20]. Roy N Differential Diagnosis of muscle tension dysphonia and spasmodic dysphonia. *Curr Opin Otolaryngol Head Neck Surg.* 18 (2010), 165–70. [PubMed: 20389245]

- [21]. Roy N, Mauszycki SC, Merrill RM, Gouse M, Smith ME Toward improved differential diagnosis of adductor spasmodic dysphonia and muscle tension dysphonia. *Folia Phoniatr Logop.* 59 (2007) 83–90. [PubMed: 17337898]
- [22]. Cannito MP, Chorna LB, Kahane JC, Dworkin JP Influence of Consonant Voicing Characteristics on Sentence Production in Abductor Versus Adductor Spasmodic Dysphonia. *Journal of Voice.* 28 (2014) 394.e13–e22.
- [23]. Rosewich H, Sweney MT, DeBrosse S, Ess K, Ozelius L, Andermann E, ... Swoboda K Research conference summary from the 2014 International Task Force on ATP1A3 -Related Disorders, *Neurol. Genet.* 3 (2017), e139. [PubMed: 28293679]
- [24]. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, ... Seidl L Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: Status and recommendations from The Movement Disorder Society Task Force on rating scales for Parkinson's disease. *Mov. Disord.* 19 (2004), 1020–1028. [PubMed: 15372591]
- [25]. Comella CL, Leurgans S, Wu J, Stebbins GT, & Chmura T Rating scales for dystonia: A multicenter assessment, *Mov. Disord.* 18 (2003), 303–312. [PubMed: 12621634]
- [26]. Fairbanks G, Voice and articulation drill book, New York: Harper & Row 1960.
- [27]. Webb WG, Adler, Richard, Neurology for the speech-language pathologist, 6th edition Missouri: Mosby 2016.
- [28]. Hirano M. Psycho-acoustic evaluation of voice Arnold, Winckel, Wyke(Eds.), Disorders of Human Communication, 5, Clinical Examination of Voice, Springer-Verlag, New York and Wien, 1981.
- [29]. Burgos R, Bretón I, Cereda E, Desport JC, Dziewas R, Genton L, ... Bischoff SC, ESPEN guideline clinical nutrition in neurology, *Clin. Nutr.* 37 (2018) 354–396. [PubMed: 29274834]
- [30]. Rosewich H, Ohlenbusch A, Huppke P, Schlotawa L, Baethmann M, Carrilho I, ... Maris S (2014). The expanding clinical and genetic spectrum of ATP1A3-related disorders, *Neurol.* 82 (2014).
- [31]. Termsarasab P, Yang AC, & Frucht SJ Intermediate Phenotypes of ATP1A3 Mutations: Phenotype-Genotype Correlations, Tremor Other Hyperkinet. Move. 5 (2015).
- [32]. Finger ME, Madden LL, Haq IU, McLouth CJ, & Siddiqui MS Analysis of the prevalence and onset of dysphonia and dysphagia symptoms in movement disorders at an academic medical center, *J. Clin. Neurosci.* 64 (2019) 111–115. [PubMed: 30948311]
- [33]. Rosen C, Lee A, Osborne J, Zullo T, & Murry T, Development and Validation of the Voice Handicap Index-10, *Laryngoscope.* 114 (2004) 1549–1556. [PubMed: 15475780]
- [34]. Belafsky P, Mouadeb D, Rees C, Pryor J, Postma G, Allen J, & Leonard R, Validity and Reliability of the Eating Assessment Tool (EAT-10), *Ann Otol Rhinol Laryngol.* 117 (2008) 919–924. [PubMed: 19140539]

Highlights

- Patients with RDP are more likely to experience dysarthria than familial controls.
- Patients with RDP are more likely to experience voice dysfunction than controls.
- Dysarthria in RDP was associated with concordant cranial nerve 9–11 dysfunction.
- Dysarthria in RDP was associated with BFMDRS speech dysfunction and oral dystonia.
- Quantitative speech assessment may have potential as an outcome to detect change over time or treatment effect in RDP.

Figure 1.

Overview of symptomology and corresponding voice or speech diagnosis. This flow chart highlights the differences in symptomology between patients experiencing dysarthria compared to dysphonia or laryngeal dystonia. This chart also identifies differences in voice characteristics that can be used to help further delineate types of dysphonia, including adductor spasmodic dysphonia, abductor spasmodic dysphonia, and muscle tension dysphonia.

Footnote:

* A thorough voice evaluation by a medical professional is needed to determine the underlying cause of dysphonia. Symptoms of spasmodic dysphonia can be difficult to detect. Some patients may compensate for their voice breaks by increasing laryngeal muscle tension to dampen the intermittent muscle spasms. The continuous strain and effortful vocal characteristics of muscle tension dysphonia can be mistaken for spasmodic dysphonia.

Figure 2.

Schematic identifying the process used to evaluate patients involved in this study and number in each group. As depicted in the figure, some patients' speech was too impaired to analyze by the otolaryngologist or speech pathologists. Missing neurological data also prevented the inclusion of some subjects in our analyses.

Figure 3.

Average GRBAS scores of patients with *ATP1A3* mutations compared to average scores of healthy familial controls. This bar graph shows that the Grade, Roughness, Asthenia, and Strain scores were higher, indicating more severe dysfunction in the *ATP1A3* mutation cohort compared to healthy familial controls. * $p < 0.0001$; ** $p = 0.005$; *** $p = 0.015$; **** $p = 0.0003$.

Table 1.

Characteristics of the ATP1A3 mutation positive and negative cohorts

	ATP1A3 mutation positive	ATP1A3 mutation negative	Total
Number of Subjects	37	29	66
Sex	Males 65% Females 35%	Males 52% Females 48%	Males 59% Females 41%
Average age at exam $\pm$ SD (years)	41.68 $\pm$ 16.54	38.1 $\pm$ 19.42	40 $\pm$ 17.87
Average age at motor symptom onset $\pm$ SD (years)	-	21.61 $\pm$ 13.2	-
Average BFMDRS Score $\pm$ SD	42.74 $\pm$ 31.36	0.41 $\pm$ 0.94	24.16 $\pm$ 31.52
Duration of motor symptoms $\pm$ SD (years)	-	18.03 $\pm$ 12.46	-

SD: standard deviation; BFMDRS: Burke Fahn Marsden Dystonia Rating Scale