Variant ataxia-telangiectasia presenting as primary-appearing dystonia in Canadian Mennonites

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ABSTRACT

Objective: To compare the phenotype of primary-appearing dystonia due to variant ataxia-telangiectasia (A-T) with that of other dystonia ascertained for genetics research.

Methods: Movement disorder specialists examined 20 Canadian Mennonite adult probands with primary-appearing dystonia, as well as relatives in 4 families with parent-child transmission of dystonia. We screened for the exon 43 c.6200 C>A (p. A2067D) *ATM* mutation and mutations in *DYT1* and *DYT6*. Clinical features of the individuals with dystonia who were harboring *ATM* mutations were compared with those of individuals without mutations.

Result: Genetic analysis revealed a homozygous founder mutation in *ATM* in 13 members from 3 of the families, and no one harbored *DYT6* or *DYT1* mutations. Dystonia in *ATM* families mimicked other forms of early-onset primary torsion dystonia, especially *DYT6*, with prominent cervical, cranial, and brachial involvement. Mean age at onset was markedly younger in the patients with variant A-T (n = 12) than in patients with other dystonia (n = 23), (12 years vs 40 years, $p < 0.05$). The patients with A-T were remarkable for the absence of notable cerebellar atrophy on MRI, lack of frank ataxia on examination, and absence of ocular telangiectasias at original presentation, as well as the presence of prominent myoclonus-dystonia in 2 patients. Many also developed malignancies.

Conclusion: Ataxia and telangiectasias may not be prominent features of patients with variant A-T treated for dystonia in adulthood, and variant A-T may mimic primary torsion dystonia and myoclonus-dystonia. *Neurology*® 2012;78:649–657

GLOSSARY

AFP = α-fetoprotein; **A-T** = ataxia-telangiectasia; **PD** = Parkinson disease.

Ataxia-telangiectasia (A-T) is a rare autosomal recessive disorder due to mutations in the *ATM* gene,[1–3] typically presenting with progressive cerebellar dysfunction and unsteady gait in early childhood and often requiring the use of a wheelchair by age 10. A-T may present in milder variant forms, in which the neurologic features are not as rapidly progressive or as severe. Onset is usually in childhood; however, in variant A-T, ocular telangiectasias may not be prominent, and ataxia is more slowly progressive—only mild to moderately severe by adulthood.[4–8] Movement disorders are usually the presenting feature of variant A-T; up to 40% of patients have tremor by age 12–34.[8] Almost all patients with variant A-T had movement disorders by adulthood, including resting tremor or dystonia (60%) and choreoathetosis (70%).[8] Whereas survival into adulthood is more common than in classic A-T, malignancies remain frequent. Neuropathy is almost always a later emerging feature.[8] Herein, we performed a rigorous cross-sectional analysis of the clinical features of variant A-T in a cohort of adults with a dystonia-

Supplemental data at www.neurology.org

Supplemental Data

Video

From the Department of Neurology (R.S.-P., D.R., K.S., M.S.L., S.B.B.), Beth Israel Medical Center, New York, NY; Departments of Neurology (R.S.-P., S.B.B.) and Radiology (D.L.), Albert Einstein College of Medicine, Bronx, NY; Department of Neurology (A.J.S.), University of British Columbia, Vancouver, Canada; Department of Neurology (D.H.), University of Manitoba, Winnipeg, Canada; Departments of Pathology and Laboratory Medicine and Human Genetics (T.N., R.G.), Geffen School of Medicine, UCLA, Los Angeles, CA; Department of Neurology (S.P.), Columbia University, New York, NY; Department of Neurology (M.S.O.), University of Florida, Movement Disorders Center, College of Medicine, Gainesville; Department of Neurology (R.U.), Mayo Clinic Jacksonville, Jacksonville, FL; Department of Neurology (J.H.), University of Luebeck, Luebeck, Germany; and Departments of Genetics and Genomic Sciences and Neurology (L.J.O.), Mount Sinai School of Medicine, New York, NY.

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predominant phenotype, by comparing these individuals with 23 patients with dystonia without the mutation.

METHODS

Standard protocol approvals, registrations, and patient consents. The internal review boards at Beth Israel Medical Center and Columbia University approved this study.

Genetics and molecular methods. In all the multiplex families, dystonia was present in 2 generations and was consistent with a dominant mode of transmission with reduced penetrance (although there was consanguinity in 2 of the families); therefore, testing for mutations in *DYT6* and *DYT1* was performed. No individuals had ataxia or telangiectasia, and the diagnosis of A-T was not considered until a distant relative in one family was diagnosed with A-T after poor outcome from irradiation of a lymphoid malignancy that began at 3 years of age. He had early balance and walking difficulties, which subsequently improved, as well as dystonia.[9] We then determined that the homozygous exon 43 c.6200 C>A (p. A2067D) *ATM* mutation found in this relative was the etiology for the dystonia in the proband of one of the families and therefore screened the other individuals from this family, as well as all other patients and family members to determine whether they shared this A-T mutation. For *ATM* testing, DNA was extracted using the Puregene procedure (Qiagen, Valencia, CA), followed by targeted screening of the mutation c.6200 C>A (p. A2067D).[10] A 345-bp product encompassing exon 43 was amplified using the following intronic primers: forward 5′-cacccagctgatattttggga-3′ and reverse 5′-tgtttagaatgaggagagaggc-3′. The c.6200 C>A mutation was detected by digestion with *Hae*III followed by agarose gel electrophoresis. Sanger sequencing verified all homozygous genotypes and a representative sample of heterozygous carriers. Probands were also screened for mutations in *DYT1* and *DYT6*, as described previously.[11,12] Radiosensitivity assays and screening for ATM levels were performed in C:301, C:302, and D:301 using methods described previously.[13,14]

Participants and clinical methods. In our study, initially undertaken to identify the *DYT6* gene in Amish and Mennonites with dystonia,[15,16] 20 probands with dystonia and with Canadian Mennonite heritage (4 from the multiplex families and 16 others) were ascertained through referring movement disorder neurologists and response to research advertisements. Probands and available family members were interviewed and examined in person at family homes or medical centers and videotaped according to previously published protocols[17] from 1998 to 2010. Blood for DNA extraction was obtained.

Movement disorder neurologists who were blinded to genotype information made final decisions regarding the presence of definite, probable, possible, and no dystonia after considering the evaluations of on-site examiners, video review examiners, and any additional information available from medical records.[17] Information regarding other movement disorders (e.g., myoclonus, chorea, and parkinsonism) was also noted in the video review.

A total of 156 family members had clinical information and DNA available for analysis, and 35 were definitely affected with dystonia, including 19 individuals from 4 multiplex Canadian Mennonite families (figure 1) and 16 others. All examinations and video reviews were completed as part of dystonia studies before the determination that dystonia was due to a founder A-T mutation in 3 of the families.

Variant A-T. After determination that A-T was the causative disease in families A, B, and C, reports of telangiectasias and malignancies were ascertained from medical records and follow-up, and 2 individuals from family C had α-fetoprotein (AFP) assessed (C:301 and C:303) and video rereview to assess chorea. Brain pathology reports were available for one subject (family A) and 2 previously deceased family members (from family C). C:301 had extensive testing after the diagnosis of A-T, including neuro-ophthalmologic examination and quantitative motor physiology testing (tremor analysis[18] and spiral analysis[19]).

Statistical analysis. Clinical features of individuals with dystonia homozygous for the *ATM* c.6200 C>A mutation were compared with those of mutation-negative individuals, using generalized estimating equation models for dichotomous variables and random effects models for continuous or ordinal variables (STATA8; StataCorp, College Station, TX).

RESULTS

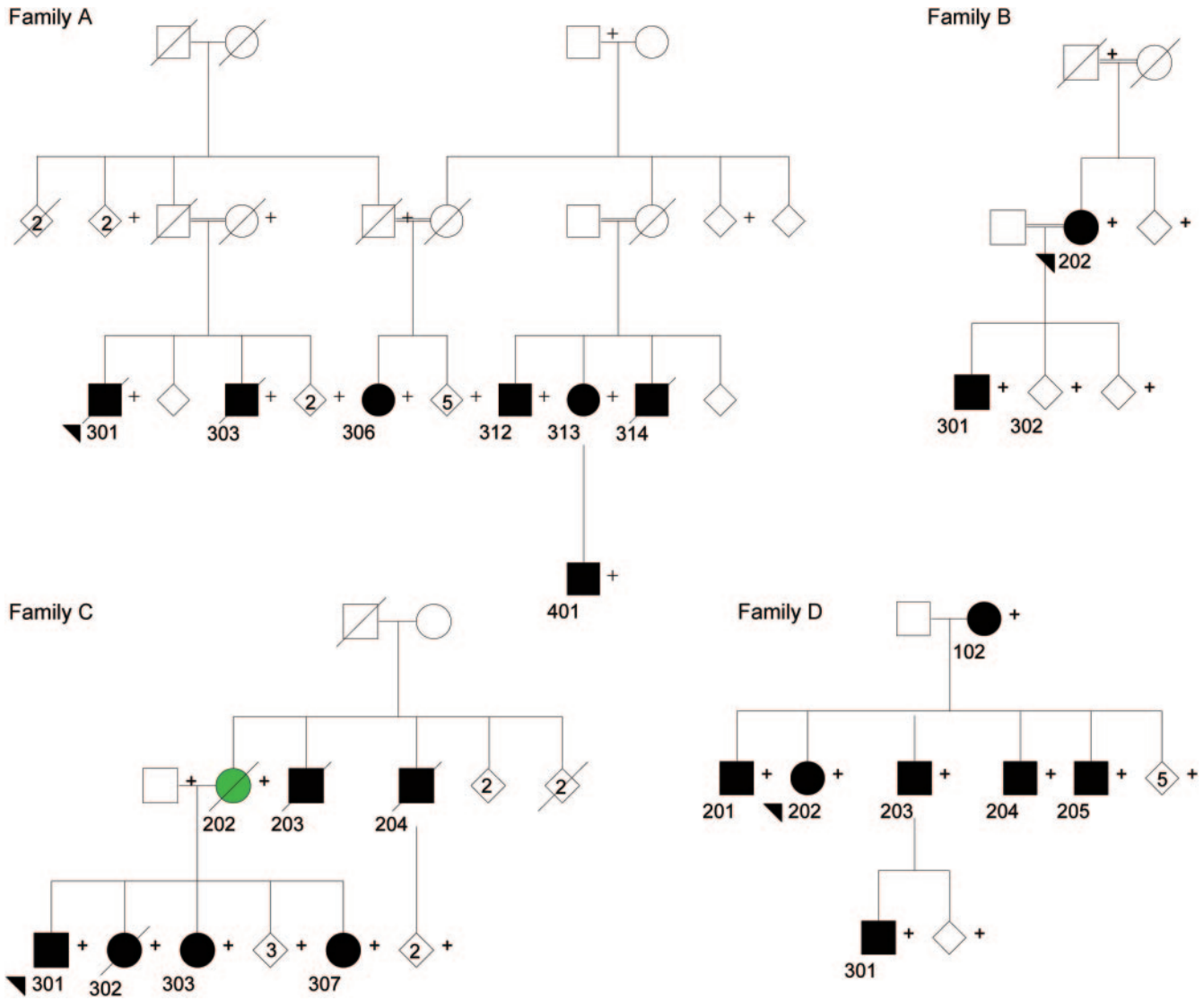
A total of 35 individuals from 20 families of Canadian Mennonite background with definite dystonia were identified. Nineteen of the individuals with definite dystonia were from 4 multiplex families. The remaining 16 individuals did not have an affected relative examined, although 7 reported a family history suggestive of dystonia.

No individuals harbored either a *DYT1* or *DYT6* mutation. Twelve subjects with definite dystonia from families A–C harbored homozygous 6200 C>A *ATM* mutations. Twenty-three others with dystonia were noncarriers (family D and all other affected individuals) (table 1). There was only one additional homozygous carrier among the family members with possible or no dystonia. She had possible right leg dystonia, minimal balance problems, and normal tandem gait on examination at age 8. In addition, her family had noted swaying of her trunk while sitting at 13 months that improved with age. Two families were determined to be related; the third was not.

Clinical features. Among the subjects with dystonia with the 6200 C>A *ATM* mutation, most had early age at onset with slowly progressive dystonia and irregular tremor, and some had myoclonus (table 2 and video [on the *Neurology*® Web site at www.neurology.org]). Movements were compatible with a highly active lifestyle in all. Although some had clumsy gait, none were described as ataxic (table 2). Two mutation-positive subjects reported ataxia in early childhood that remitted.

Age at onset of dystonia was younger in the A-T group (median 12 years, range 1–20 years) than in the group without A-T (median 40, range 9–59 years) ($p < 0.001$) (figure 2). Site of onset of dystonia did not differ between the 2 groups, with neck onset being most common for both homozygous

Figure 1 Pedigrees for multiplex families



Families A–C harbored the mutation; family D did not. + demarcates individuals examined. A shaded circle or square designates an individual with dystonia. No + indicates individuals affected by history.

mutation carriers and noncarriers. In contrast, final distribution of dystonia varied markedly among groups ($p = 0.03$) with that in the mutation group more likely to be generalized (58.3% vs 13%) and 92% of the homozygous mutation carriers having brachial dystonia, whereas only 26.1% of noncarriers had arm involvement. Leg dystonia was more frequent in the mutation-positive group, although there was limited functional impairment, as only one individual used a walking aid, and none used a wheelchair.

Cranial involvement was common in both groups (66.7% in the AT group and 52.2% in the noncarrier group), but tongue and jaw involvement were different, with 58.3% of homozygous individuals having dystonia in these sites, compared with only 21.7% of the noncarriers. Speech was rated as abnormal in 91.7% of the patients with A-T but in only in 35% of the noncarrier patients. Because definite laryngeal, jaw, or tongue dystonia was not noted in all patients with speech involvement, we cannot fully exclude the possibility that, in addition to dystonia, there may be a cerebellar component.

Although dystonia was the primary movement in all patients, nondystonic features were also noted in some and more frequently in the patients with A-T than in the noncarriers. Two of the 12 *ATM* homozygotes had a phenotype consistent with myoclonus-dystonia, whereas none of the mutation-negative subjects did. Facial choreiform movements were also noted in the patients with A-T, although these could also be seen in *DYT6* dystonia (video).

Additional clinical features. In all 3 A-T mutation families, there was at least one family member who

Table 1 Clinical features: Comparison of clinical features in *ATM* mutation and nonmutation dystonia cases

	ATM mutation cases (n = 12)	Mutation-negative (n = 23)	*p* Value[a]
Women, %	50	69.6	0.260
Age at examination, y, median (range)	51.5 (12–64)	52.0 (23–84)	0.129
Age at onset, y, median (range)	12 (1–20)	40 (9–59)	<0.01
Site onset, %[b]			
Arm	25	8.7	0.208
Leg	16.6	4.3	0.248
Cranial	8.3	37.5	0.105
Face	0	21.7	
Tongue/jaw	0	0	
Larynx	8.3	4.4	1.000
Cervical	58.3	60.9	0.884
Sites affected, %			
Arm	91.7	34.78	0.003
Leg	50.0	13.4	0.025
Cranial	66.7	52.2	0.413
Face	66.7	47.8	0.476
Tongue/jaw	58.3	21.7	0.059
Larynx	41.7	8.7	0.033
Cervical	83.3	73.9	0.532
Distribution, %			0.017
Focal	16.6	43.5	0.126
Segmental	25.0	43.5	0.289
Generalized/multifocal	58.3	13.0	0.009
Speech affected, %	91.7	26.1	0.008

[a] All positive vs negative.
[b] Some individuals had more than one site of onset.

reported unsteady gait in early childhood that spontaneously improved. None of the individuals examined complained of persistent walking problems in adulthood. Frank ataxia was not noted in any of the affected individuals with the exception of inability to tandem in C:301 at age 59 along with sensory neuropathy. However, among the A-T mutation carriers with dystonia, several had clumsy or lumbering gait not solely attributable to dystonia.

Neuropathy occurred in 3 individuals (table 2). One noncarrier had apraxia of eyelid opening, but this did not occur in mutation carriers. After the discovery that C:301's dystonia was due to A-T, he had a formal neuro-ophthalmologic evaluation, which did not demonstrate ocular dysmetria or ocular motor apraxia; he had slightly saccadic pursuits and occasional 2-step saccades, without nystagmus or square wave jerks. In C:302, no telangiectasias were noted initially, although after the diagnosis of A-T, telangiectasias on the inner lower lip were discovered.

In C:301, quantitative physiologic analysis revealed a low-frequency tremor varying from 3 to 7 Hz, irregular postural, and action tremors of his head and hands, worse on the right side, driven by short and long duration (100–500 msec) proximal neck and cocontracting forearm antagonist EMG bursts. There were infrequent short-duration (25–50 msec) cocontracting EMG bursts in the right forearm antagonists consistent with myoclonus. Computerized spiral analysis revealed mild to moderate overall degrees of severity, worse on the right, with low-frequency 4–5 Hz irregular multiaxial tremors. Spiral executions were of normal speed, without evidence for micrographia but with mildly increased loop width variability. MRI and transcranial sonography imaging for C:301 is shown in figure 3.

Four of the *ATM* homozygotes had improvement of spasms and pain with cervical botulinum toxin A injections. Improvement occurred with anticholinergics (1 subject) and diazepam (3 subjects). No response occurred to baclofen (Lioresal) (1 subject), tetrabenazine (2 subjects), or carbidopa/levodopa (3 subjects).

Evaluation of heterozygous carriers. Among the family members in the dystonia families, 37 individuals (mean ± SD age 44 ± 24 years, range 8–86 years) carried one copy of the founder mutation. None of the heterozygous carriers demonstrated definite dystonia. One carrier had definite parkinsonism and was subsequently treated with levodopa with improvement. C:201, an obligate carrier, died at the age of 82 without evidence of parkinsonism.

Historical information in families with *ATM* mutations. C:204 died of a sarcoma at age 51, at which time movements interfered with ambulation. Autopsy did not show cerebellar or brainstem degeneration. C:203 had movements that slowly but progressively worsened with age. Speech was normal until the later phases of illness, and just before death he could walk with great difficulty but was able to drive a car. It is not clear whether the gait difficulty was secondary to neuropathy or ataxia. He died at age 51 from a malignancy of unknown type, and autopsy showed atrophy of the olivary nucleus and a reduction of large Betz cells in the motor cortex. A:314 had arm and neck movements. Of 5 unexamined siblings of C:201 (an obligate carrier) who survived to adulthood, one brother reportedly had levodopa-responsive Parkinson disease (PD) diagnosed at age 42 and died at age 77, another had parkinsonism with prominent postural instability, and a sister had PD and died at age 77.

DISCUSSION Our data suggest that dystonia, especially early-onset dystonia with cervical and brachial

Table 2 Clinical and testing features in all *ATM* carriers affected with dystonia

Family	Sex	Age exam, y	Age onset, y	Site onset	Sites affected[a]	Myoclonus/ jerky dystonia	Chorea	Symptomatic neuropathy	Malignancy (age, y)	Cellular markers of A-T: protein assay and radiosensitivity[b]	AFP
A											
301[c]	M	64	13	Arm	UFNAMRGL	N	Cranial		Stomach (56)		
									Prostate (64)		
303	M	56	16	Neck	UFJTNAM		Cranial		Renal (51)		
306	F	43	1	Both legs	UFLNAMKRG	N	Neck, arm		Myeloid leukemia (57)		
312	M	53	Unknown	Arm	A				Stomach (36)		
313	F	52	Unknown	Unknown	AMRG		Cranial				
401	M	26	15	Arm	NAMRG	FAM	Cranial				
B											
202	F	40	20	Neck	UFNA	A	Cranial				
301	M	12	11	Neck	N						
C											
301	M	60	1	Neck, legs	LUFNAMK	N	Cranial, neck, arms	Sensorimotor	Prostate (59)	ATM trace radiosensitivity	22.6 μg/L (normal <6.1)
302[a]	F	53	12	Neck	LUFTNAG	N	Arm		Stomach (58)	ATM lacking radiosensitivity	84 μg/L (normal <11)
303	F	51	12	Neck	UFTNAMR	AN	Cranial	Sensorimotor[d]			
307[e]	F	42	4	Neck, larynx	UFLNAMR	AUFN	Cranial, arm	Sensorimotor (after vincristine)	Lymphoma (40)		

Abbreviations: AFP = α-fetoprotein; A-T = ataxia-telangiectasia; A = right arm; F = lower face; G = left leg; J = tongue; K = trunk; L = larynx; N = neck; M = left arm; R = right leg; U = upper face.

[a] Medical conditions also included Sjögren syndrome, polyclonal gammopathy, history of leukopenia, positive rheumatoid factor, protein S deficiency and deep vein thrombosis, and renal tubular acidosis.

[b] Protein assay and radiosensitivity: C:302: cells were found to be lacking in ATM protein and were radiosensitive; C:301: lymphoblastoid cells showed radiosensitivity of 19 (normal range 50 ± 13; radiosensitive range 14 ± 7) and Western blot of ATM protein showed only a trace amount (<5 of wild-type controls on same blots) of ATM protein. For D:301 (no c.6200 C>A mutation), activity was in the normal range.

[c] Autopsy showed mild loss of Purkinje cells in cerebellum.

[d] Impaired vibration and joint position sense as well as lower extremity areflexia. EMG/NC at age 43 was reported to be normal and at age 51 showed reduced sensorineural action potentials in the sural, median, and superficial peroneal nerves with normal sensory distal latencies and conduction velocities. There were normal compound muscle action potentials in median and extensor digitorum brevis muscle, but slightly reduced tibial, consistent with axonal sensor-motor polyneuropathy.

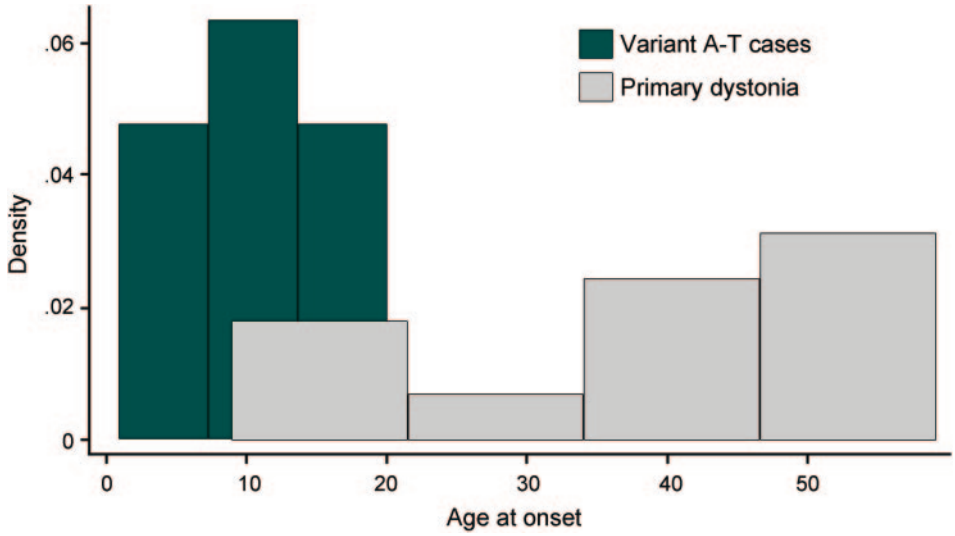
[e] Surgery for congenital shortening of the forearm bones (Keinbock disease).

onset and prominent cranial involvement, is a major feature of variant A-T; it may occur without frank ataxia and may be misdiagnosed in adults with primary-appearing dystonia. Both the age at onset and frequency of cranial involvement in the variant A-T group overlap with that seen in *DYT6* dystonia[18]: median age 12 years vs 14 years and 67% vs 70% of individuals with variant A-T and *DYT6*, respectively.[16] The phenotype also overlaps with myoclonus-dystonia.

Our subjects differ from those with classic A-T in their overall preserved gait in adulthood and absence of prominent telangiectasias, oculomotor apraxia, and ataxia.[3,8,20–25] However, ataxia that was present in early childhood and spontaneously remitted was present in 2 individuals, and some individuals had clumsy gait that was not solely attributed to dystonia. Therefore, absence of ataxia does not exclude a diagnosis of variant A-T, but mild clumsiness, possible ataxic features, childhood history of a remitting ataxia, and family history, even in a dominant-appearing transmission pattern, could support a variant A-T diagnosis. Because no subjects had ocular telangiectasias, but oropharyngeal telangiectasias were noted in our subject and in another subject with mild A-T, examination should include thorough evaluation for oropharyngeal telangiectasias, and their presence should heighten the suspicion of A-T.

The presence of parkinsonism in a heterozygous family member as well as in 3 siblings of an obligate carrier and prior reports of rest tremor in variant A-T,[8] raise the question of whether parkinsonism may be part of a motor phenotype in heterozygous and homozygous A-T mutation carriers. There is selective loss of dopaminergic nigrostriatal neurons in ATM-deficient mice,[26] and substantia nigra Lewy bodies occurred in a 31-year-old individual with A-T.[27] Although no nigral cell loss was reported in

Figure 2 Age at onset in individuals with variant ataxia-telangiectasia (A-T) compared with those with nonmutation primary dystonia



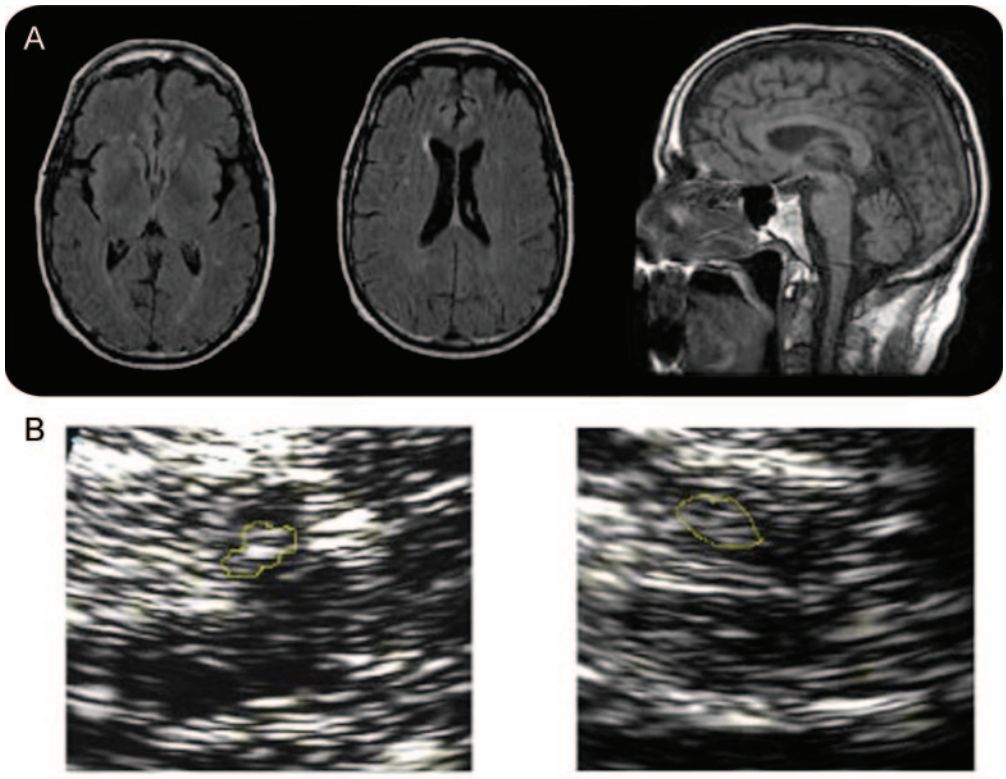
any of the autopsies, there was nigral hyperechogenicity on transcranial sonography in C:301, a nonspecific marker present in >90% of individuals with PD that may represent nigral iron deposition.[28] Substantia nigra hyperechogenicity is also increased in *DYT6* dystonia,[29] although it may be present in 10% of controls. Parkinsonism in the heterozygous relatives cannot be specifically attributed to abnormalities in *ATM*, as DNA was not available, and PD is a common disorder. Therefore, it is not clear whether PD relates to the heterozygous *ATM* mutation, a PD gene segregating in this family, or a chance association.

The etiology of dystonia in both classic and variant A-T is not well understood. Classic A-T is usually caused by null *ATM* alleles that truncate or severely destabilize the ATM protein, resulting in a lack of functional ATM.[30,31] ATM protein kinase is a major regulator of multiple signaling cascades that react to and repair DNA strand breaks, and lower levels of ATM may lead to a failure of activation of cellular checkpoints. Consequently, some hypothesize that the clinical presentation may result from faulty DNA repair.[5,32] The postulated mechanism of variant A-T is that it is due to mutations that result in higher residual levels of ATM protein than those that cause classic A-T.[8,31] Hence, for homozygous mutations with higher ATM activity, the milder phenotype would tend to segregate within families, and the family as a whole may present with movement disorders rather than ataxia as the primary feature. The pA2067D missense mutation identified in these families (personal communication, T. Nakamura, The Gatti Laboratory, UCLA, 2009) was reported in the heterozygote state in a German patient with A-T (Ae003),[10] and in the homozygous state in Canadian Mennonites.[5,9] Although our families support the idea that variant A-T has a milder phenotype that segregates within families, our data do not fully support the proposed mechanism of milder etiology, because ATM enzyme activity was either very low or nonexistent in the 2 cases studied.

The relationship between decreased ATM activity and prominent dystonia in variant A-T is unclear. Classic A-T occurs with cerebellar and extracerebellar pathology[33,34] and imaging abnormalities,[35–37] with cerebellar granular and Purkinje cell loss being the most consistent feature.[35] MRI examinations in classic A-T revealed, in 1 of 2 patients with prominent movement disorders, obvious basal ganglia pathology[37]; 1 patient with prominent dystonia had a unilateral putaminal hyperintensity on T2-weighted images and bilateral decreased striatal [^{123}I]iodobenzamine binding with SPECT imaging.[24] It is unlikely that dystonia in variant A-T can be attributed solely to cerebellar atrophy, because this feature was not prominent on MRI in any of our subjects, and in another subject with variant A-T with prominent early-onset dystonia, nonspecific cerebellar atrophy without a cerebellar functional correlate was present.[22] Thus, although the phenotype suggests primary basal ganglia dysfunction with a paucity of cerebellar features, with minimal or no cerebellar atrophy on MRI, the etiology remains uncertain as pathologic findings suggest at least some of the cerebellar involvement noted in classic A-T. With the exception of nigral hyperechogenicity, markers of striatal pathology were also not present on structural imaging in our subjects nor were they noted on autopsy.

Even though neurologic disease is milder overall in variant A-T than in classic A-T, the burden of

Figure 3 Brain MRI (A) and transcranial ultrasonography (B) images



(A) 1.5-T nonenhanced and enhanced MRI of the brain (for C:301) at age 59 revealed several small unidentified bright objects in the white matter of the cerebral hemispheres bilaterally as well as minimal dilatation of the ventricles and subarachnoid spaces consistent with aging, but was otherwise normal, without cerebellar atrophy. After the radiologist was informed of the diagnosis, possible vermian atrophy was noted on rereview. (B) Transcranial sonography of the midbrain: image results for a patient with Parkinson disease (left) and C:301 (right). Yellow encircling demarcates area of hyperechogenicity. In C:301 there was hyperechogenicity compared with laboratory controls.[29]

malignancy remains high. It is therefore imperative to make the diagnosis of variant A-T, because malignancies occur frequently and may be triggered by radiation exposures that might be avoided. Screening for AFP should be considered, and it is elevated (greater than 10 ng/mL) in 95% of individuals with classic A-T. AFP was abnormal in our subjects and a relative,[9] but at a much lower range than that in classic A-T. Although normal AFP levels can be seen in variant A-T,[20] AFP may be a useful low-cost screening tool with excellent sensitivity for A-T and could be followed by immunoblotting for ATM protein and a radiosensitivity assay.[5,8,30] Gene mutation studies, although supportive, are not necessary for the diagnosis, because mutations are not identified in all patients, and the causality of many missense DNA changes is often elusive.[38–40] Therefore, AFP screening should be considered in patients with early-onset dystonia, even with normal eye movements and without ataxia or telangiectasia. Our data suggest that not only should A-T be included in the differential diagnosis of early-onset primary-appearing dystonia but also the non-neurologic oncologic disease burden, which may be worsened by radiation, warrants screening for early identification.

AUTHOR CONTRIBUTIONS

Study design and conceptualization: Dr. Saunders-Pullman, D. Raymond, Dr. Ozelius, Dr. Bressman. Analysis and interpretation of the data: Dr. Saunders-Pullman, D. Raymond, Dr. Stoessl, Dr. Hobson, Dr. Nakamura, Dr. Pullman, Dr. Lefton, Dr. Okun, Dr. Uitti, Dr. Sachdev, K. Stanley, Dr. San Luciano, Dr. Hagenah, Dr. Gatti. Statistical analysis: Dr. Saunders-Pullman. Drafting and revision of the manuscript: Dr. Saunders-Pullman. Revision of the manuscript: D. Raymond, Dr. Stoessl, Dr. Hobson, Dr. Nakamura, Dr. Pullman, Dr. Lefton, Dr. Okun, Dr. Sachdev, Dr. San Luciano, Dr. Hagenah, Dr. Gatti, Dr. Ozelius, Dr. Bressman.

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DISCLOSURE

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