Morbidity and mortality from ataxia-telangiectasia are associated with *ATM* genotype

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Background: Ataxia-telangiectasia (A-T) is a rare genetic disease caused by germline biallelic mutations in the ataxia-telangiectasia mutated gene *(ATM)* that result in partial or complete loss of ATM expression or activity. The course of the disease is characterized by neurologic manifestations, infections, and cancers.

Objective: We studied A-T progression and investigated whether manifestations were associated with the *ATM* genotype.

Methods: We performed a retrospective cohort study in France of 240 patients with A-T born from 1954 to 2005 and analyzed *ATM* mutations in 184 patients, along with neurologic manifestations, infections, and cancers.

Results: Among patients with A-T, the Kaplan-Meier 20-year survival rate was 53.4%; the prognosis for these patients has not changed since 1954. Life expectancy was lower among patients with mutations in *ATM* that caused total loss of expression or function of the gene product (null mutations) compared with that seen in patients with hypomorphic mutations because of earlier onset of cancer (mainly hematologic malignancies). Cancer (hazard ratio, 2.7; 95% CI, 1.6-4.5) and respiratory tract infections (hazard ratio, 2.3; 95% CI, 1.4-3.8) were independently associated with mortality. Cancer (hazard ratio, 5.8; 95% CI, 2.9-11.6) was a major risk factor for mortality among patients with null mutations, whereas respiratory tract infections (hazard ratio, 4.1; 95% CI, 1.8-9.1) were the leading cause of death among patients with hypomorphic mutations.

Conclusion: Morbidity and mortality among patients with A-T are associated with *ATM* genotype. This information could improve our prognostic ability and lead to adapted therapeutic strategies. (J Allergy Clin Immunol 2011;128:382-9.)

Key words: *Cancer, genetics, leukemia, lymphoma, inherited, DNA repair*

Ataxia-telangiectasia (A-T) is a rare genetic disorder with autosomal-recessive inheritance characterized by progressive neurologic impairment with cerebellar syndrome, oculocutaneous telangiectasia, defects in B and T cell–mediated immunity,

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Abbreviations used
A-T: Ataxia-telangiectasia
ATM: Ataxia-telangiectasia mutated gene
CEREDIH: French National Reference Center for Primary Immunodeficiencies
IQR: Interquartile range
RTI: Chronic upper or lower respiratory tract infection
IR: Incidence rate

and increased susceptibility to malignancies (mainly lymphoid neoplasms).[1] No curative strategy for this disease is currently available.

A-T is caused by biallelic mutations in the ataxia-telangiectasia mutated gene *(ATM)*, which is located at 11q22.3.[2,3] *ATM* encodes a Ser/Thr protein kinase that is expressed in a wide range of tissues. ATM regulates a complex signaling cascade involved in the detection and repair of DNA double-strand breaks and activation of cell-cycle checkpoints.[4] The prevalence of patients with A-T in Europe is estimated to be 1 in 150,000.[5]

Patients present with variable symptoms, and therefore the diagnosis of A-T can be made by pediatric neurologists, immune hematologists, or geneticists. The French National Reference Center for Primary Immunodeficiencies (CEREDIH) was created in 2005 and has set up a national registry to include all patients with primary immune deficiencies by using the European Society for Immunodeficiencies database.[6] From January 2006 to March 2008, more than 3000 patients were registered in the CEREDIH database, including 240 patients with A-T; older patients were given diagnoses based on clinical and laboratory features (before *ATM* sequence analysis and cytogenetic application availabilities), whereas younger patients were given diagnoses based on cytogenetic analysis of lymphocytes and sequence analysis of *ATM*.[7] A-T is characterized by chromosomal instability and translocations that involve genes that encode members of the immunoglobulin superfamily; translocations in 7p14, 7q35, 14q11, and 14q32 are found in at least 4% of lymphocytes in metaphase analysis. Patients with A-T were registered in the CEREDIH database, regardless of the presence or absence of immunodeficiency. We aimed to describe the main characteristics of A-T and its complications (disability, infections, lung disease, and malignancies), identify risk factors for mortality, and associate *ATM* mutations with morbidities and mortality. To our knowledge, this is the largest cohort of patients with A-T examined and the first study to make associations between cancer, infections, and *ATM* genotypes.

METHODS

Diagnosis

ATM was genotyped in patients with 3 or more of the following: ataxia, oculocutaneous telangiectasia, recurrent infections, low serum levels of IgA, high serum levels of α-fetoprotein (≥10-fold the upper limit of normal), or A-T karyotype abnormalities (≥4% of metaphase lymphocytes with translocations at 7p14, 7q35, 14q11, 14q32, 2p12, or 22q11, as described in 1982).[8] When no blood samples were available from pediatric patients or their parents, making analysis of *ATM* impossible, A-T was diagnosed based only on clinical and laboratory criteria. The clinical definition of A-T was ataxia with at least 2 of the other criteria listed above, and the molecular definition was a loss-of-function mutation (a stop codon, large deletion, or other missense mutation that would prevent gene-product function) in at least 1 allele of the *ATM* gene.

Chronic upper or lower respiratory tract infections (RTIs) were defined by the presence of chronic sinusitis, chronic bronchitis, recurrent bacterial pneumonia, or bronchiectasis.

Enrollment

This study was conducted under the auspices of CEREDIH. Pediatric neurologists, pediatric and adult immunologists, and geneticists in teaching hospitals throughout France were invited to participate in the study. Patients with or without immunodeficiency were included in the study. Informed consent of living patients was obtained directly from adult patients with A-T or from the parents of patients younger than 18 years. The following data were collected from medical records: sociodemographic characteristics, neurologic signs, telangiectasia, infections, bronchiectasis, malignancies (also validated from the pathology report), and *ATM* mutations. Data analysis of the CEREDIH database was approved by the French Commission Nationale de l'Informatique et des Libertés.

ATM mutation detection

Techniques for detecting *ATM* mutations evolved from 1997 (when *ATM* gene analysis became available in France) to 2007. Restriction endonuclease fingerprinting, the protein truncation test, fluorescence-assisted mismatch analysis, DNA HPLC, and direct sequencing of cDNA were used in succession. More recently, direct sequencing of genomic DNA has been performed. The entire coding exons and an average of 30 nucleotides that spanned each exon-intron junction were analyzed. When no point mutation, no small mutation, or only 1 of 2 expected mutations was identified, the search for large gene rearrangements was performed by means of semiquantitative PCR with the SALSA MLPA kit P041/P042 ATM (MRC-Holland, Amsterdam, The Netherlands). The mRNA consequences of suspected splicing mutations were analyzed at the cDNA level. When no cDNA was available, *in silico* algorithms (Splice Site Prediction by Neural Network, Splice Site Finder, Max EntScan) were used.[9] All missense mutations with unknown biological effects were considered to have a likely pathogenic effect when at least 2 of the following criteria were present: carrier frequency of less than 1% in a series of controls, location in a domain of *ATM* that is required for function (especially the phosphatidylinositol 3-kinases or domains FRAP-ATM-TRRAP), or a high score from the Align-GVGD algorithm, which quantifies amino acid changes and their conservation among species.[10]

ATM mutation classification

All identified mutations were classified according to the expected functional activity of the *ATM* product as either complete loss of expression or activity (class A or null) or reduced expression or some residual activity (class B or hypomorphic). Polymorphisms were not included in this classification. Class A mutations, which cause production of a truncated product or complete lack of protein after nonsense-mediated mRNA decay, included frameshift mutations that arose from small deletions of nucleotides or insertions in the coding sequence, nonsense mutations, splice-site mutations, or large deletions of the gene. Class B mutations cause reduced expression or protein activity and included known or likely pathogenic missense mutations, splice-site mutations, or deletions that did not alter the reading frame.

Associating morbidity and mortality with genotype

Patients were assigned to 1 of 3 groups based on the combination of *ATM* mutations identified and their expected effect on the activity of the gene product to analyze morbidity and mortality and associate them with genotype. Group 0 included patients with class A mutations in each allele, group 1 included patients with at least 1 class B mutation in 1 allele and 1 class A or class B mutation in the other, and group 2 included patients with a class A mutation in only 1 allele. Group 2 patients were excluded from morbidity, mortality, and genotype analyses because gene-product activity could not be determined.

Statistical analysis

Continuous variables are expressed as medians and interquartile ranges (IQRs [Q1-Q3]) or means and SDs. Life expectancy was estimated from birth.

TABLE I. Demographic characteristics of the patients with A-T

	Total (n = 240)
Male/female (sex ratio)	118/122 (0.97)*
Median age at diagnosis (y [IQR])	5.3 (2.9-8.0)†
Median time to diagnosis (y [IQR])	2.8 (1.3-6.0)‡
Known consanguinity	66/230 (28.7%)
Familial cases	85/237 (35.9%)
Brother or sister	64
Cousin or uncle	5
Unknown relationship	16
Status: age	
Death; median age of death (y [IQR]); range	93 (38.8%); 15.6 (10.0-21.6); 3.8-44.5
Alive; median age (y [IQR]); range	107 (44.6%); 11.6 (7.9-17.5); 2.6-47.0
Lost to follow-up; median age (y [IQR]); range	40 (16.7%); 11.6 (7.5-16.4); 2.3-41.7

*Sex ratio of the French population younger than 25 years: 1.04.
†N = 236.
‡N = 197.

TABLE II. Age of diagnosis and time to diagnosis according to birth date or years of cytogenetic and *ATM* analyses

	Age at diagnosis (y; n = 197),* median (IQR)	*P* value	Time to diagnosis (y; n = 197),* median (IQR)	*P* value
Date of birth				
<1980 (n = 62)	6.4 (3.9-8.3)	.0003†	4.1 (1.6-6.3)	.02
1980-1990 (n = 47)	5.3 (2.9-8.6)		3.0 (1.3-7.1)	
1991-2000 (n = 65)	4.6 (2.7-6.7)		2.2 (1.0-5.0)	
>2000 (n = 23)	3.3 (2.3-4.8)		2.0 (1.2-3.5)	
Cytogenetic analysis and *ATM* sequence analysis				
≤1982 (n = 78)	6.4 (3.6-8.5)	$<10^{-4}$	3.8 (1.5-6.4)	.03
1982-1997 (n = 83)	5.3 (2.7-8.3)		2.6 (1.1-6.1)	
>1997 (n = 36)	3.7 (2.4-4.9)		2.1 (1.3-3.4)	

*Age at diagnosis and time to diagnosis were both available for 197 patients.
†Kruskal-Wallis test.

Variables were compared across groups by using the Mann-Whitney *U* test for continuous variables and the χ^2 or Fisher exact test for categorical variables. The Kruskal-Wallis test was used to compare continuous variables in more than 2 groups. Incidence rates (IRs) were calculated per 100 patient-years. Kaplan-Meier curves were used to estimate the survival probability of patients. A Cox regression was used to estimate mortality risk factors during follow-up. Patients lost to follow-up were censored at the date of the last visit. For all analyses, statistical significance was defined as a *P* value of less than .05. Statistical analyses were performed with SAS 8.02 software (SAS Institute, Inc, Cary, NC).

RESULTS

Diagnosis and sociodemographic characteristics

From June 2006 to September 2007, 242 diagnoses of A-T were confirmed according to the described diagnostic criteria; 240 patients born from 1954 to 2005 were enrolled in the cohort (2 patients declined to participate). A-T was diagnosed based on clinical, laboratory, and molecular criteria for 76.7% (184/240) of the patients and based on clinical and laboratory criteria for only 23.3% (56/240) of the patients. In the latter group, in addition to ataxia, 96.4% (54/56) of the patients presented with telangiectasia, and 87.5% (49/56) had recurrent infections. The 2 patients without telangiectasia had low serum levels of IgA and recurrent infections. High serum levels of α-fetoprotein, low serum levels of IgA, and cytogenetic abnormalities were present in 100% (34/34), 79.3% (46/58), and 94.0% (47/50) of the patients, respectively, for whom this information was available.

The patients' demographic characteristics are summarized in Table I. The median age at diagnosis was 5.3 years (IQR, 2.9-8.0; range, 0.6-41.9 years) and the median time to diagnosis was 2.8 years (IQR, 1.3-6.0; range, 0-27.9 years). Age and time to diagnosis decreased among patients born more recently, as presented in Table II. In families with multiple cases, the median age at diagnosis was 8.3 years (IQR, 4.3-11.5) and 4.3 years (IQR, 1.8-7.3) for the first and second cases, respectively ($P = .001$).

Clinical events and outcomes

The main clinical events and ages at onset are reported in Table III.

Neurologic disorders. The main clinical feature of cerebellar syndrome, ataxia, was present in all but 3 patients, who were 3.4, 3.8, and 11.6 years old, respectively, at their last examination. Cerebellar syndrome and drooling were the first neurologic signs observed in patients and occurred at mean ages of 4.4 years (SD, 4.2 years) and 6.7 years (SD, 5.4 years), respectively. Oculomotor apraxia (reported in 77.9% [134/172] of cases) and dysarthria (reported in 82.4% [108/131] of cases) were first observed at mean ages of 7.3 years (SD, 4.0 years) and 9.1 years (SD, 5.0 years), respectively. Loss of ability to walk occurred at a mean age of 10.2 years (SD, 4.6 years). Cerebellar imaging was available for 66 patients, 65 of whom had cerebellar atrophy (mean age, 9.5 years; SD, 6.3 years).

Telangiectasia. Telangiectasia were observed in 91.0% (201/221) of patients, with ocular involvement in 173 patients, and occurred at a mean age of 6.6 years (SD, 4.9 years).

Cancers. Cancers developed in 22.1% (53/240) of the patients (mean age, 14.0 years [SD, 9.8 years]); their mean life expectancy was 14.9 years (SD, 9.9 years). The Pearson correlation coefficient between age at cancer diagnosis and age of death was 0.98 ($P < 10^{-4}$). Forty-seven patients had hematologic malignancies, and there were 6 carcinomas (breast tumors in 2 patients, including 1 male patient; stomach tumors in 2 patients; thyroid cancer in 1 patient; and unknown primary site in 1 patient). The mean age of carcinoma diagnosis was 33.7 years, and the mean age of diagnosis of hematologic malignancy was 11.4 years ($P = .007$).

Chronic upper and lower RTIs and other infections. Ninety-seven (40.4%) patients with A-T had RTIs. Six patients had opportunistic infections: 2 had varicella zoster virus–induced pneumonia, 2 had invasive aspergillosis (at the ages of 23.8 and 26.7 years), 1 had *Pneumocystis jiroveci*–induced pneumonia at the age of 0.9 years, and 1 had a *Candida* species bloodstream infection. Eighty-two (34.8%) of the 236 patients for whom information was available received immunoglobulin replacement therapy; 75.6% (31/41) of the patients with bronchiectasis received immunoglobulin replacement therapy.

Pneumothorax occurred in 14 of 128 (10.9%) patients (mean age, 16.8 years [SD, 8.6 years]) and occurred significantly more frequently in female than male patients (11/64 [17.2%] vs 3/64

TABLE III. Clinical characteristics of patients and age of onset of complications

	Total, n = 240 (%)*	Mean age (y [SD])
Neurologic manifestations		
Cerebellar syndrome	213/216 (98.6)	4.4 (4.2)
Ataxia	204/204 (100)	
Dysmetria	96/129 (74.4)	
Dysarthria	108/131 (82.4)	9.1 (5.0)
Moderate	101	
Severe	7	
Oculomotor apraxia	134/172 (77.9)	7.3 (4.0)
Loss of ability to walk	112/162 (69.1)	10.2 (4.6)
Needs a wheelchair	85/132 (64.4)	11.7 (5.3)
Drooling	51/123 (41.5)	6.7 (5.4)
Pyramidal signs	25/109 (22.9)	7.5 (6.2)
Hypotonic face	17/111 (15.3)	9.4 (4.0)
Abnormal swallowing	25/109 (22.9)	13.7 (5.6)
Abnormal movement	27/91 (29.7)	11.7 (4.8)
Cancer	53 (22.1)†	14.0 (9.8)
Hematologic malignancies	47	11.4 (6.7)
Lymphoma	40	
Non-Hodgkin		27
Hodgkin		9
Burkitt		4
Leukemia	7	
Acute lymphoblastic	6	
T-cell prolymphocytic	1	
Carcinoma	6	33.7 (8.2)
Infections and consequences		
RTI	97 (40.4)	
Chronic sinusitis/bronchitis	53 (22.1)	5.4 (3.9)
Bacterial pneumonia	65 (27.1)	
Single	44	8.0 (6.4)
Recurrent	21	7.7 (6.9)
Bronchiectasis	43 (17.9)	9.3 (6.1)
Other manifestations		
Telangiectasia	201/221 (91.0)	6.6 (4.9)
Postural disorders	117/148 (79.1)	4.6 (4.9)
Scoliosis	34/125 (27.2)	13.7 (3.6)
Pneumothorax	14/128 (10.9)	16.8 (8.6)
No. of episodes		
2	5	
1	9	
Glucose intolerance	6/116 (5.2)	

*Data are not available for all patients.
†At the time of the last visit.

[4.7%], $P = .02$). However, the mean age at onset in female patients (18.2 years [SD, 9.1 years]) was greater than in male patients (11.6 years [SD, 4.0 years], $P = .02$).

Phenotypes by age group

The IR of cerebellar syndrome increased until patients were a mean age of 12 years and then decreased. Cerebellar syndrome was associated with the highest IR for loss of ability to walk in the group of patients 6 to 11 years of age (IR, 10.4 per 100 patient-years; Table IV). The IR for telangiectasia was highest in the patients 6 to 11 years of age (IR, 18.5 per 100 patient-years). The IR for pneumothorax was highest in the group of patients 12 to 17 years of age. The IR of the first episode of bacterial pneumonia tended to decrease with age, and the incidence of bronchiectasis detection was constant among age groups. Cancer IRs increased continuously in each age group until patients were 12 to 17 years of age. Mortality almost doubled after the age of 12 years, reaching an IR of 5.1 per 100 patient-years, and continued to increase in older patients.

TABLE IV. Incidence rates of the main phenotypic features and complications

	Age group (y)			
	0-5	6-11	12-17	≥18
Cerebellar syndrome	17.3	18.7	6.9	2.7
Loss of ability to walk	0.4	10.4	7.4	1.3
Telangiectasia	9.3	18.5	8.6	4.0
First episode of bacterial pneumonia	2.4	2.0	1.8	1.4
Bronchiectasis	1.1	1.8	1.1	1.1
First episode of pneumothorax	0	0.3	1.2	0.8
Cancer	0.7	1.6	2.4	2.5
Mortality	0.5	2.0	5.1	6.9

Values represent the IR for 100 patients per year.

Life expectancy

The Kaplan-Meier 20-year survival rate was 53.4%. There were no statistically significant differences between patients with cancer or RTIs or in familial cases between the first and subsequent cases. The survival rate was not significantly associated with any year of birth from 1954 to 2005 ($P = .3$, log-rank test; see Fig E1 in this article's Online Repository at www.jacionline.org).

Mutations

ATM gene mutation analysis was performed in 184 patients from 154 families. We analyzed DNA samples from children with A-T in 139 families, from both parents of children with A-T in 11 families (because samples from the patients were not available), and from mothers of children with A-T in 4 families. In one family 2 of the 4 parents of 2 first cousins with A-T were not related; thus 3 different *ATM* mutations were expected to be detected in this family, 1 from sisters who each had a child with A-T and 2 from unrelated parents of patients.

Among the 305 alleles of *ATM* analyzed, 292 mutations were identified, indicating a mutation detection rate of 96%. We identified 167 different mutations, confirming the large mutation spectrum of *ATM*. All mutations identified are listed in Table E1 in this article's Online Repository at www.jacionline.org; a summary is presented in Table V.

The mutations most frequently identified were class A mutations: 214 (73%) of 292 characterized alleles, usually corresponding to frameshift mutations because of a small nucleotide insertion or deletion and resulting in complete loss of ATM protein. In one family, 01-38983A, 2 class A mutations were identified in the same allele, and a third pathogenic mutation was identified in the other allele (c.3712_3716del5 and c.3187_3191del5).

Class B mutations were identified in 78 (27%) alleles; most were missense mutations, and 32 likely pathogenic missense mutations were found in 27 (17%) families. A homozygous mutation was detected in 4 families. Only 2 mutations, each detected in a different family, were associated with an align-GVGD score of less than C25 and were therefore not predicted to affect *ATM* function (c.8748T>A/p.Asp2916Glu and c.6998C>A/

TABLE V. *ATM* mutations identified in 154 families affected by A-T

Mutations	No. of mutated alleles (n = 292)	Families with ≥1 allele, no. (%)	Different mutations (n = 167)	Most frequent mutation (no. of families)
Class A				
Frameshift	109*	80 (52)	58	c.3712_3716del5;p.Leu1238_Leu1239>LysfsX6 (10)
				c.3802delG;p.Val1268stop (9)
Nonsense	68	52 (34)	38	c.5644C>T;p.Arg1882stop (6)
				c.103C>T;p.Arg35stop (5)
Splicing	31	24 (16)	20	IVS21+1G>A(c.2839_2921del83);p.Tyr947_Ser974>GlnfsX9 (3)
				IVS38-2A>C(c.5496_5556del61); p.Val1833_Gln1853>GlufsX64 (3)
Large gene deletion	6	5 (3)	4	Exon 64-65 deletion (2)
Class B				
Pathogenic missense	23	21 (14)	10	c.6679C>T;p.Arg2227Cys (7)
Likely pathogenic missense	32	27 (17)	20	c.8731G>T;p.asp2913Tyr (4)
Splicing	16	14 (9)	13	IVS40-2A>C;p.Pro1922_Arg1973del, p.Pro1922AsnfsX4 (2)
				c.3576G>A(c.3403_3576del174;p.Ser1135_Lys1192del (2)
Small in-frame deletions	4	4 (3)	2	c.8461_8463delATG;p.Met2821del (3)
Large in-frame deletions	3	2 (1)	2	Exon 7 deletion (1)
				Exon 46-47 deletion (1)

*Two mutations in 1 allele and a third mutation in the other allele were identified in family 01-38983A001: c.3712_3716del5 and c.3187 _3191del5. Therefore in this table 2 mutations are reported in only 1 allele.

p.Thr2333Lys). In these 2 families a class A mutation was identified, and no other mutation was identified. No statistically significant difference in the proportions of familial cases was observed between patients with null mutations (group 0, 31.1%) and patients with hypomorphic mutations (group 1, 40.8%).

Morbidity, mortality, and genotype analyses

Biallelic mutations, either homozygous or compound heterozygous, were identified in 172 patients. A monoallelic mutation was identified in 12 patients, which was a class B mutation in 4. One hundred two of the 184 patients studied were classified in group 0 (2 class A mutations), 74 in group 1 (≥1 class B mutation and 1 class A or class B mutation), and 8 in group 2 (only 1 null mutation identified). Patients in group 2 were excluded from the analysis of morbidity, mortality, and genotype because residual protein activity was not known.

There was no difference in the duration of follow-up between patients in group 0 (14.5 years [SD, 7.7 years]) and group 1 (16.7 years [SD, 9.9 years]). The mean age at diagnosis of A-T was less in group 0 (5.9 years) than in group 1 (8.0 years, $P = .03$). The mean ages of onset of cerebellar syndrome and loss of ability to walk were slightly lower in group 0 than in group 1 ($P = .09$). The Kaplan-Meier 20-year survival rates did not differ significantly between group 0 (54.7%) and group 1 (64.1%; $P = .3$, log-rank test; Fig 1, *A*). Mutation data were available from 36 of 53 patients who had malignancies. Of patients in group 0 or group 1, 18.6% (19/102) and 23.0% (17/74), respectively, had a malignancy (no statistical difference). However, on the basis of the Kaplan-Meier analysis, cancer occurred earlier in patients in group 0 (50% of cancers occurred before the age of 9.4 years) than in group 1 (50% of cancers occurred before the age of 18.9 years; $P = .01$, log-rank test; Fig 1, *B*). The mean age at death was less in group 0 (15.9 years [SD, 6.5 years]) than in group 1 (20.4 years [SD, 10.9 years], $P = .04$, Table VI). Among the patients who died after a diagnosis of cancer, the incidence of hematologic malignancies was greater in group 0 than in group 1 (17/17 [100%] vs 10/15 [66.7%], $P = .015$).

In a multivariate analysis that was stratified for the type of *ATM* mutation (or estimated activity of ATM), cancer was strongly and independently associated with mortality in group 0 (hazard ratio, 5.8; 95% CI, 2.9-11.6), whereas cancer was marginally associated with death for group 1 (hazard ratio, 1.8; 95% CI, 0.8-3.9; Table VI).

DISCUSSION

We have associated morbidity and mortality from A-T with the type of mutation in *ATM* using data from 240 patients. Analysis of this cohort indicated that time to diagnosis decreased from 1954 to 2007, possibly because of increasing knowledge about the disease and the availability of karyotype analysis in 1982 and *ATM* sequence analysis in 1997. Despite these advances and the fact that patients are almost always given a diagnosis of A-T at teaching hospitals because of the rarity and complexity of the disease, survival time has not changed since 1954; A-T remains a severe and untreatable genetic disease. The overall survival time of the cohort analyzed in this study was similar to that reported by Crawford et al.[11] In our study cerebellar syndrome was the first sign of A-T, which is consistent with published data,[12,13] and the age of loss of ability to walk was comparable with that reported by Woods et al.[14,15]

One limitation of the study was the fact that genotype data were available for only 35 (66.0%) of the 53 patients with cancer because many patients were evaluated in the 1960s, when *ATM* sequence analysis was not available. It was also a challenge to classify mutations as null or hypomorphic because missense mutations and in-frame deletions can lead to loss of kinase or other important activities of the gene product.[16-18] We associated morbidity and mortality from cancer and RTIs with *ATM* genotype; associations were affected by age at diagnosis, age of onset of cancer, and life expectancy. The mean age at death was less among patients with biallelic null mutations (group 0), as previously described by Li and Swift.[19] In these patients cancer was the main factor associated with death; they developed cancers (mainly lymphomas) earlier than patients with hypomorphic mutations. Morell et al[20] reported a similar rate of cancer (19.8%)

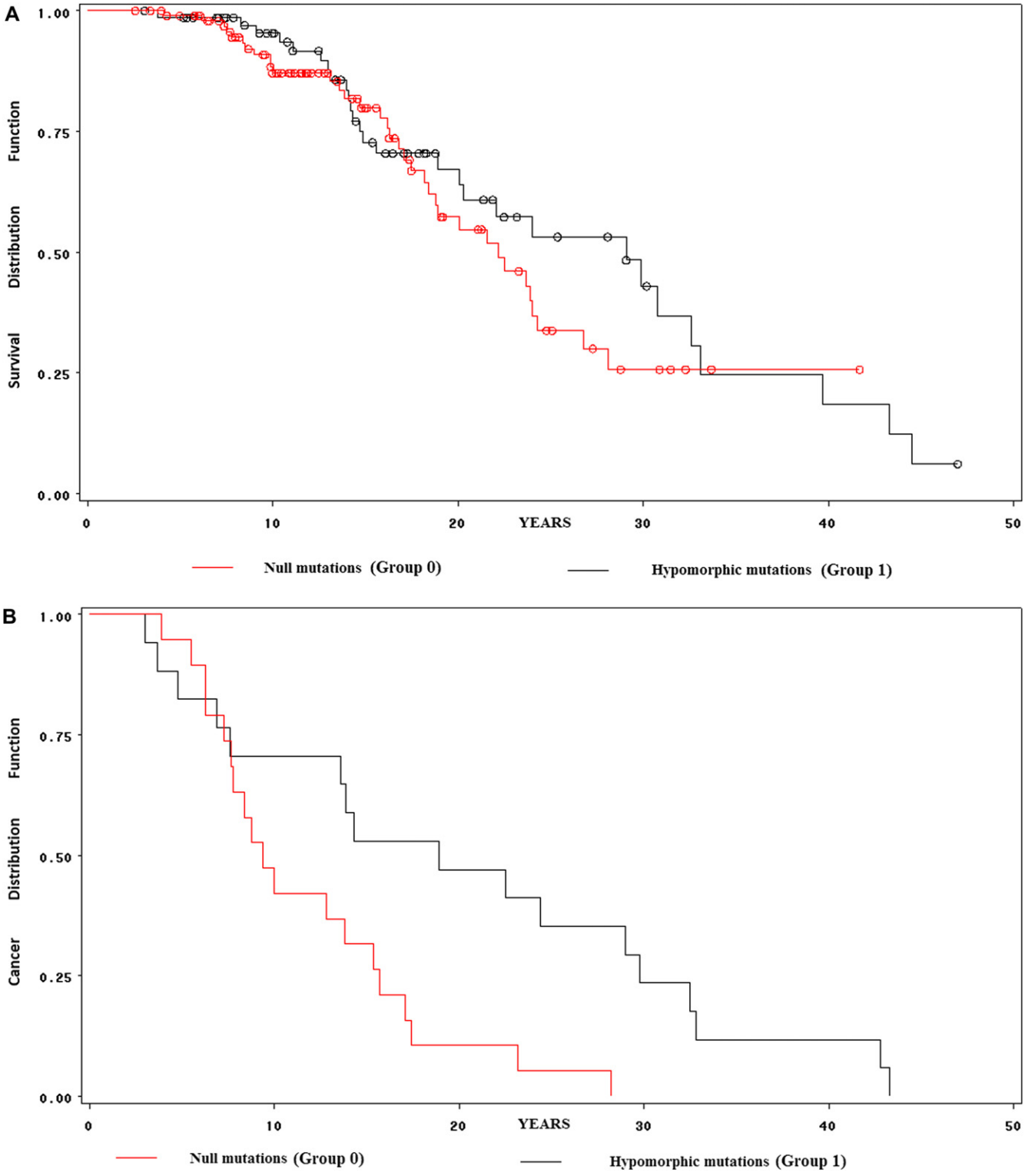

FIG 1. Life expectancy of patients with A-T based on *ATM* mutation. **A**, Survival in 102 patients in group 0 (biallelic null mutations, *red curve*) and 74 patients in group 1 (≥1 hypomorphic mutation, *black curve*; $P = .3$, log-rank test). The Kaplan-Meier 20-year survival rates were 54.7% for patients in group 0 and 64.1% for patients in group 1. **B**, Onset of cancer in groups 0 and 1 ($P = .01$, log-rank test). The mean age at onset of cancer was 11.8 ± 6.4 years in group 0 and 20.2 ± 13.2 years in group 1.

TABLE VI. Complications and univariate and multivariate analyses of factors that affect mortality

	Mutations		
	Null (n = 102)	Hypomorphic (n = 74)	*P* value
Mean age (y [SD])			
Diagnosis*	5.9 (5.4)	8.0 (7.3)	.03
Cerebellar syndrome	4.0 (4.2)	5.1 (4.7)	.09
Loss of ability to walk	9.7 (2.6)	11.6 (7.2)	.09
First episode of bacterial pneumonia	8.2 (7.1)	9.2 (7.4)	
Bronchiectasis	8.2 (5.9)	10.7 (8.2)	
Cancer	11.8 (6.4)	20.2 (13.2)	.01†
Death	15.9 (6.5)	20.4 (10.9)	.04
Hazard ratio (Cox model [95% CI])‡			
Cancer (univariate)	6.2 (3.2-12.1)	1.7 (0.8-3.8)	
Cancer (multivariate)	5.8 (2.9-11.6)	1.8 (0.8-3.9)	
RTI (univariate)	1.8 (0.9-3.7)	3.9 (1.8-8.7)	
RTI (multivariate)	1.4 (0.7-2.9)	4.1 (1.8-9.1)	

Note: The Cox model was used to evaluate data from patients with biallelic null (group 0, n = 102) or hypomorphic (group 1, n = 74) mutations in *ATM*.
*The median age at diagnosis is less in patients with null mutations (5.3 years; IQR, 2.5-7.3 years) compared with that in patients with hypomorphic mutations (6.0 years; IQR, 3.7-8.7 years; $P = .02$, Wilcoxon test).
†Log-rank test.
‡In the multivariate analysis modeling the risk of death according to the presence of cancer and the presence of RTI, the reference value for these 2 variables is absence of the disease.

among patients with A-T, mostly hematologic malignancies and particularly non-Hodgkin lymphomas. Strikingly, compared with hematologic malignancies, carcinomas occurred later in life and appeared to have a similarly poor prognosis. Mortality among patients with carcinomas or hematologic malignancies did not differ significantly (83.3% vs 90%). The median time of survival after diagnosis was also similar for each cancer type: 0.6 years (IQR, 0.1-1.2 years) versus 0.3 years (IQR, 0.1-1.7 years), respectively.

RTIs appeared to be the main risk factor for mortality among patients with hypomorphic mutations in *ATM*; it would be interesting to determine whether they have a specific type of immune deficiency. Neurologic impairment (loss of ability to walk and abnormal swallowing), immune deficiency, and severe scoliosis probably predispose patients to RTIs and occur before cancer is diagnosed in this group. The fact that RTIs increased mortality in group 1 compared with group 0 can probably be explained by the later onset of cancer in group 1.

As previously reported,[21-23] we observed that RTIs were the main infectious complication among patients with A-T. For some patients, these infections were related to immune deficiency, which was detected in 61.4% of 70 patients with A-T in the British Isles.[14] In other studies the presence of immune deficiency has not been associated with RTIs.[24] Factors such as recurrent pulmonary aspiration and muscle weakness can contribute to RTIs. We did not associate RTIs with *ATM* mutations, which is in contrast to the study by Staples et al.[25] This single-center study included a smaller number of patients, and infection was defined as the presence of recurrent sinopulmonary infections. Because RTI affects patient survival and is an independent risk factor for mortality, antibiotic prophylaxis (effective against encapsulated bacteria, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*)[26-28] and immunoglobulin replacement therapy should be considered at early stages in the management of these patients.

In summary, patients with biallelic mutations in *ATM* that cause total loss of expression or gene-product function have a higher risk for cancer (mainly hematologic malignancies) at younger ages than patients with 1 hypomorphic mutation in *ATM*, who have greater mortality from RTIs. These associations between morbidity, mortality, and *ATM* genotype provide a basis to develop and adapt therapies. Prospective studies should be performed to determine the outcomes of various chemotherapy protocols and prophylactic antibiotic and immunoglobulin replacement therapies, as well as to prevent neurologic impairments, in patients with A-T.

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Clinical implications: Early diagnosis of hematologic malignancies, especially in patients with null mutations in *ATM*, could improve treatment. Clinicians should be aware of the importance of primary prevention of respiratory tract infections in patients with hypomorphic mutations.

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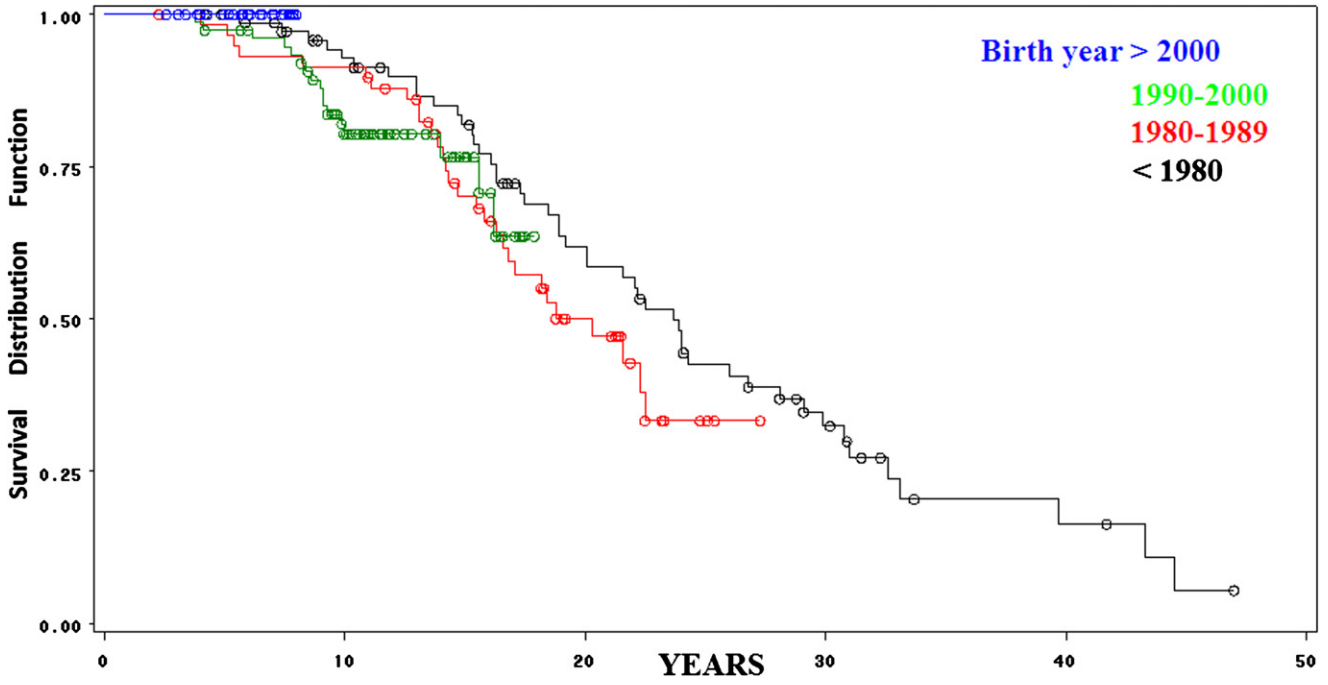

FIG E1. Survival of 240 patients with A-T. As a function of the year of birth ($P = .3$, log-rank test), the Kaplan-Meier 20-year survival rate was 58.9%.