ATM germline heterozygosity does not play a role in chronic lymphocytic leukemia initiation but influences rapid disease progression through loss of the remaining *ATM* allele

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ABSTRACT

Ataxia telangiectasia patients, with constitutional bi-allelic *ATM* mutations, have a marked risk of lymphoid tumors and *ATM* mutation carriers have a smaller risk of cancer. Sporadic *ATM* mutations occur in 10-20% of chronic lymphocytic leukemia and are often associated with chromosome 11q deletions which cause loss of an *ATM* allele. The role of constitutional *ATM* mutations in the pathogenesis of chronic lymphocytic leukemia is unknown. Here we investigated the frequency of constitutional *ATM* mutations in either of two chronic lymphocytic leukemia cohorts, those with and without a chromosome 11q deletion. We found that in comparison to controls, constitutional pathogenic *ATM* mutations were increased in patients with chromosome 11q deletions (6 of 140 *vs.* 0 of 281, P=0.001) but not in those without 11q deletions (2 of 178 *vs.* 0 of 281, P=0.15). These results suggest that *ATM* germline heterozygosity does not play a role in chronic lymphocytic leukemia initiation but rather influences rapid disease progression through *ATM* loss.

Key words: sickle cell disease, nephropathy, hemolysis, kidney.

Citation: Skowronska A, Austen B, Powell JE, Weston V, Oscier DG, Dyer MJS, Matutes E, Pratt G, Fegan C, Moss P, Taylor MA, and Stankovic T. ATM *germline heterozygosity does not play a role in chronic lymphocytic leukemia initiation but influences rapid disease progression through loss of the remaining* ATM *allele. Haematologica 2012;97(1):142-146. doi:10.3324/haematol.2011.048827*

Introduction

Ataxia telangiectasia (AT) results from bi-allelic constitutional mutations in the *Ataxia Telangiectasia Mutated* (*ATM*) gene on chromosome 11q23. AT is characterized by a 200-fold increased risk of lymphoid tumors[1] and carriers are also at an increased risk of cancer development albeit at a much lower level.[2] Sporadic *ATM* mutations have been detected in tumor cells in patients with various lymphoid malignancies including B-cell chronic lymphocytic leukemia (CLL).[3-5] The ATM protein signals cellular responses to DNA damage in the form of DNA double strand breaks (DSBs) and prevents accumulation of potentially tumorigenic cells with unrepaired DNA DSBs.[1]

The diagnosis of CLL requires a B-cell clone of more than 5×10^9 cells/L of blood with characteristic cell surface markers. Individuals with a CLL clone of less than 5×10^9/L and no additional pathological features are classified as having the pre-malignant condition monoclonal B-cell lymphocytosis (MBL).[6,7] CLL shows marked clinical heterogeneity and prognostic markers associated with a poor outcome include deletions of chromosomes 17p and 11q, leading to loss of *TP53* and *ATM* alleles, respectively.[8] Mutations in *ATM* are linked to poor prognosis and are commonly, but not exclusively, associated with a chromosome 11q23 deletion. We found that 36% of CLLs with an 11q deletion carry a mutation in the remaining *ATM* allele resulting in bi-allelic *ATM* defects.[3,4]

Instances of familial occurrence are recognized in CLL[9] and registry studies confirm that first degree relatives of CLL patients have a 7-fold increased risk of developing CLL.[10] Relatives are also at an increased rate of MBL.[11] Within CLL pedigrees there are no consistent patterns of leukemic development suggesting involvement of multiple low risk alleles rather than a single high-risk locus.[9] Recent genome wide association studies provide evidence for low penetrance risk alleles that together may increase an individual's risk of developing CLL.[12,13]

ATM mutations occur at different stages of CLL development and in occasional cases an *ATM* mutation is present in a patient's germline.[3,4,14] In one previous study, *ATM* mutations were not found to be responsible for CLL familial clustering;[15] however, the role of constitutional pathogenic *ATM* muta-

The online version of this article has a Supplementary Appendix.
**AS and BA contributed equally to the study.*
Acknowledgments: we thank Maria Podinovskaya, Clemency Hawksley and Ian Edwards for technical support.
Funding: this work was supported by the Leukaemia Lymphoma Research UK and Cancer Research UK.
Manuscript received on June 3, 2011. Revised version arrived on August 23, 2011. Manuscript accepted on September 8, 2011.
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tions in the pathogenesis of CLL remains unknown. In this study, we have addressed the role of *ATM* carrier status in two CLL cohorts. We compared the frequency of constitutional *ATM* mutations in 140 CLL patients with an 11q deletion, where *ATM* mutation is a frequent genetic event,[4] and 178 CLL patients with no 11q deletion, where *ATM* mutations are rare,[3] with 281 healthy controls.

Design and Methods

CLL and control cohorts

CLL cohorts were taken from patients treated on the UK CLL4 Trial and at Birmingham, Bournemouth and Leicester hospitals. All were diagnosed according to standard criteria and had had fluorescence *in situ* hybridization (FISH) performed with the *ATM* (11q23) probe. Controls included a volunteer research subgroup (n=71) and anonymous blood donors (n=210). Ethical approval was obtained from South Birmingham Ethics Committee (ref. O4/Q2709/25).

Mutational analysis of the ATM gene

Genomic DNA was extracted from mononuclear cells, as previously described.[3,4] Screening for *ATM* sequence changes was performed using denaturing high-performance liquid chromatography (DHPLC).[3,4] DHPLC is able to detect mutations present in just 5-10% of the total cell population.[16] The PCR products were sequenced whenever variant chromatogram patterns were detected.[3,4] Sequence changes were compared to published results[17,18] and *ATM* databases (*http://chromium.liacs.nl/LOVD2/home.php*). To exclude consideration of rare polymorphisms, sequence changes were classified as *pathogenic mutations* only if they were previously reported as causative mutations in AT patients or were predicted to cause protein truncation. When an *ATM* mutation was detected in the leukemic cells from a CLL case, subsequent analysis of constitutional DNA was performed on either buccal cells or peripheral blood (PB) granulocytes. When PB granulocytes were used, we adopted a strategy to ensure changes were genuine germline mutations and not due to contamination with leukemia cells. Mutations were classified as *acquired* if the heteroduplex peak area representing mutation in the CLL DNA was either absent from the granulocyte DNA or represented less than 40% of the peak area observed in the corresponding tumor DNA. Mutations were classified as *germline* if the peak area in the granulocyte DNA represented more than 90% of that seen in the CLL DNA. To validate this approach, we amplified clonal VDJ recombinations from representative paired samples (*Online Supplementary Figure S1A and B*).

Analysis of immunoglobulin gene usage and class switch recombination (CSR)

Immunoglobulin heavy chain (*IGH*) VDJ rearrangements were amplified using primers corresponding to the consensus sequences of the framework 1 (FR1) and joining (J6) region. Nucleotide sequences were analyzed as previously described.[19] *IGHV* genes were classified as unmutated if there was 98% or more homology with the parent sequence. Analysis of CSR involved amplification of the Sμ–Sα and Sμ–Sγ switch joints, as previously described.[20] The amplified sequences were aligned using Basic Local Alignment Search Tool database (*http://www.ncbi.nlm.nih.gov/BLAST/*).

Statistical analysis

Fisher's exact t-test was used for comparisons of parameters and the Kaplan-Meier method was used to determine survival outcomes.

Results and Discussion

ATM sequence changes in CLL patients and controls

We analyzed the *ATM* coding region in 318 CLL patients (140 with a chromosome 11q deletion and 178 with no 11q deletion) and 281 controls. Altogether, 85 unique sequence changes were detected in CLL patients, which included 19 changes that were also found in control individuals and 66 changes that were only observed among CLL patients. Sixty of these CLL-specific changes were identified in just one CLL patient, and 6 were identified in more than one CLL case. Thirty-one changes were classified as pathogenic *ATM* mutation using our stringent criteria. The remaining changes represented 27 known poly-

Table 1. Pathogenic *ATM* mutations within the CLL patients.

Sequence change	Amino acid change	Chromosome 11q deletion	Previously observed in AT patients
a) Pathogenic germline *ATM* mutations			
c.1066-6T>G	splicing site exon 11	Yes	Yes
c.2720_2723delGTGT	p.(Cys907fs)	Yes	Yes
c.3712_3716delTTATT	p.(Leu1238fs)	Yes	Yes
c.5228C>T **	p.(Thr1743Ile)	Yes	Yes
c.7638_7646del9	p.(Arg2547_Ser2549del)	Yes	Yes
c.8977C>T	p.(Arg2993X)	Yes	Yes
c.1058_1059delGT	p.(Cys353fs)	No	No
c.8266A>T	p.(Lys2756X)	No	Yes
b) Pathogenic acquired *ATM* mutations			
c.1120C>T	p.(Gln374X)	Yes	Yes
c.1402delAA	p.(Lys468fs)	Yes	Yes
c.2308G>T	p.(Glu770X)	Yes	No
c.3651delG	p.(Leu1217fs)	Yes	No
c.3720_3736del17	p.(Asn1240fs)	Yes	No
c.4591C>T	p.(Gln1531X)	Yes	No
c.5006-2A>G	splicing site exon 36	Yes	No
c.6375insT	p.(Glu2126fs)	Yes	Yes
c.6815delA	p.(Glu2272fs)	Yes	No
c.6989_6995del7	p.(Leu2330fs)	Yes	No
c.7883_7887del5	p.(Ile2628fs)	Yes	Yes
c.8246_8252del7insT	p.(Lys2749_Thr2751delinsIle)	Yes	No
c.8672-1G>T	splicing site exon 62	Yes	No
c.9023G>A	p.(Arg3008His)	Yes	Yes
c.2466+2T>G	splicing site exon 18	No	No
c.4095_4109+4del19	p.(Lys1365fs)	No	No
c.5228C>T	p.(Thr1743Ile)	No	Yes
c.8834_8867del34	p.(Lys2945fs)	No	No
c.9022C>T	p.(Arg3008Cys)	No	Yes
c) Pathogenic *ATM* mutations with unknown germline status			
c.478_482delTCTCA	p.(Ser160fs)	Yes	No
c.3883_3885delCTT	p.(Lys1295del)	Yes	No
c.8672G>A	p.(Gly2891Asp)	Yes	Yes
c.9139C>T	p.(Arg3047X)	Yes	Yes
c.2193delC	p.(Tyr731fs)	No	No

Table 2. Clinical and biological characteristics of CLL in ATM germline mutation carriers.

Germline *ATM* mutation	Age at diagnosis (years)	Presence of 11q deletion	Stage at diagnosis	VDJ profile	CSR joint profile	TTFT (mths)	OS (mths)
c.1058_1059delGT	61	No	B	V1-2/D21-9/J4 UM	NA	0	90
c.2720_2723delGTGT	65	Yes	B	V1-69/D3/J6 UM V3-13/D3/J6 UM	NA	0	93+
c.3712_3716delTTATT	71	Yes	B	V3-30/D3/J6 UM	NA	1	43
c.5228C>T	66	Yes	A	VH3-11/D3/J4 UM	cNHEJ	9.5	78+
c.7638_7646del9	68	Yes	C	V4-4/D3/J6 UM	NA	0	1
c.8266A>T	52	No	B	V3-15/D4/J3 M	NA	1	95+
c.8977C>T	51	Yes	B	V1-18/D3/J4 M	cNHEJ	0	59.5
c.1066-6T>G	60	Yes	B	V1-69/D3/J6 UM	NA	69	104

UM-VH gene is unmutated, M-VH gene is mutated. NK: not known; CSR: class switch recombination; NA-CSR joint not amplified; cNHEJ-classical non-homologous end joining; TTFT: time to first treatment in months; OS: overall survival from diagnosis in months; +: indicates censored patient at time of analysis.

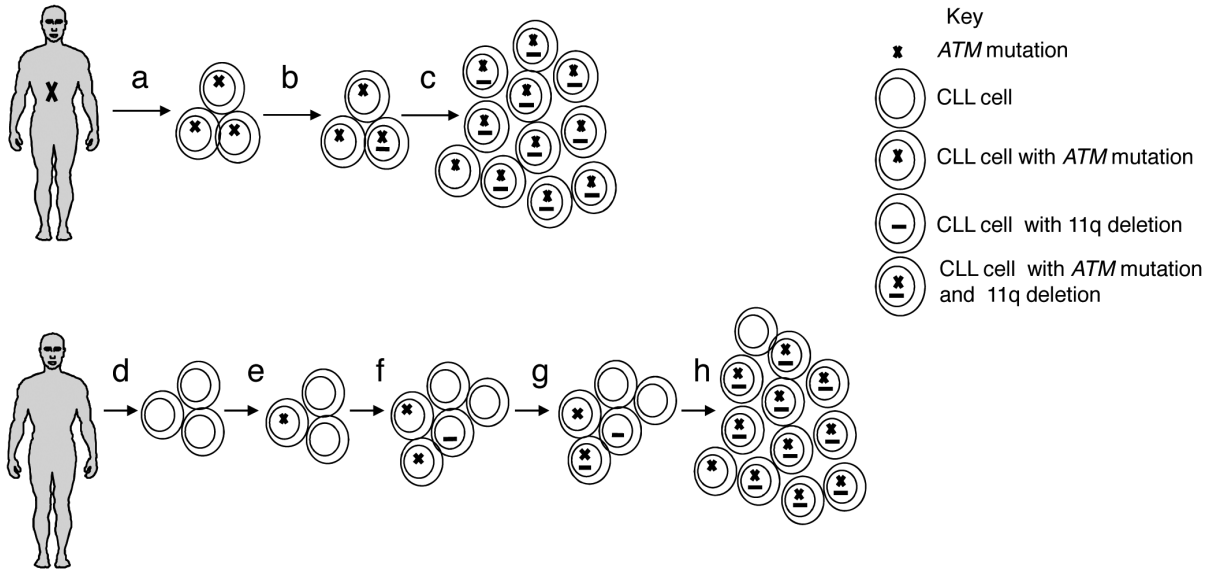

Figure 1. Model for CLL development in *ATM* mutation carriers. The upper panel represents a model for CLL pathogenesis in an *ATM* germline mutation carrier. CLL clonal initiation occurs independently of the germline *ATM* mutation but all cells within the clone will carry the *ATM* mutation because this is present in all body cells (a). Subsequent loss of chromosome 11q in any CLL cell (b) will lead to loss of *ATM* function resulting in apoptotic resistance and a selective pressure for rapid clonal expansion and disease progression (c). By comparison, the lower panel represents a model of CLL pathogenesis with wild-type germline *ATM*. Following clonal initiation (d), subsequent development of an acquired *ATM* mutation or chromosome 11q deletion might be expected to initially exert limited selective pressure (e,f). Only if both defects are acquired within a cell does loss of *ATM* function occur and rapid clonal expansion (g,h). Loss of *ATM* function will occur less frequently and over a more prolonged time course in this model than in the germline *ATM* mutation model and here development of alternative genetic events may influence disease progress rather than *ATM*/11q defects (not illustrated).

morphisms and 27 missense 'sequence variants', where the pathogenecity of the specific sequence change has not been proven. In total, 35 unique sequence changes were detected in controls including the 19 changes that were common to both CLLs and controls. Twenty-nine changes were known polymorphic variants, 6 were classified as sequence variants and no changes fulfilled our criteria for a pathogenic *ATM* mutation (*Online Supplementary Tables S1 and S2*).

Pathogenic constitutional ATM *mutations*

The pathogenic *ATM* mutations occurred in 24 CLLs with an 11q deletion and 8 CLLs without an 11q deletion (Table 1). Amongst CLLs with an 11q deletion, 6 mutations were of germline origin, 14 were acquired in leukemic DNA and 4 remained of unknown origin due to lack of germline material. Amongst CLLs without a chromosome 11q deletion, 2 mutations were constitutional, 5 were acquired and one of unknown origin. In cases with

an 11q deletion, 3 germline mutations were predicted to lead to a truncated protein (c.2720_2723delGTGT, c.3712_3716delTTATT, c.8977C>T), one to an amino acid substitution (c.5228C>T [p.T1743I]), one to an in-frame deletion (c.7638_7646del9 [p.R2547_S2549del]) and one to altered splicing (skipping of exon 11) (c.1066-6T>G). In non-11q deleted CLLs, both constitutional mutations (c.1058_1059delGT, c.8266A>T) were predicted to lead to premature termination of the protein. Seven out of 8 of the constitutional mutations have been previously reported in AT families.[17,18] Consideration of the two separate CLL cohorts demonstrated that in comparison to controls, constitutional pathogenic *ATM* mutations are significantly more common in CLL patients who develop a chromosome 11q deletion (6 of 140 *vs*. 0 of 281, *P*=0.001) but not in those who do not subsequently acquire this deletion in their leukemic clone (2 of 178 *vs.* 0 of 281, *P*=0.15).

Characteristics of the pathogenic ATM *mutation carriers*

We compared patients' characteristics between those with constitutional *ATM* mutations, acquired *ATM* mutations, *ATM* sequence variants (with no additional *ATM* mutation) and those with *ATM* wild-type or known *ATM* polymorphisms (Table 2, *Online Supplementary Table S3*). Overall there was no difference in stage at diagnosis or *VH* mutations status between the 4 categories, but notably amongst patients with constitutional *ATM* mutations, 7 of 8 were advanced stage at diagnosis and 6 of 8 had unmutated *VH* genes. There was a significant difference in overall survival between these groups (*P*=0.005). Patients with constitutional and acquired *ATM* pathogenic mutations and those with *ATM* sequence variants all had inferior survival compared to those with wild-type *ATM*.

The ATM protein ensures fidelity of CSR and prevents use of non-classical non-homologous end joining (NHEJ).[21] We investigated CSR and VDJ profiles in CLL cells of *ATM* mutant carriers.[22] Both CLLs analyzed were found to have normal CSR joints. Two patients had a CLL clone carrying the V1-69/D3/J6 segment pattern[22] and the remaining cases showed a range of V segments (Table 2).

Acquired defects in *ATM* are common in CLL and their impact on cellular phenotype and clinical prognosis has already been established.[3,4] Constitutional *ATM* mutations have rarely been identified in CLL patients but their contribution to the pathogenesis of CLL is unknown.[18,19] Here we show that, in comparison to controls, a significantly increased frequency of constitutional pathogenic *ATM* mutant alleles occurs specifically within the subset of CLL patients who subsequently develop a deletion of chromosome 11q in their leukemic cells.

In this study, we used highly stringent criteria to classify pathogenic *ATM* mutations. Classification of missense changes is difficult and although features such as occurrence within functional domains and acquisition within cancer cells suggest pathogenecity, the only way to prove functional consequences is by mutation modeling. Given our focus in this study on constitutional changes, where classification can be more difficult, we used more stringent criteria than in previous publications. Consequently, certain changes previously classified as mutations were here labeled as sequence variants. The poor survival outcome observed in the 'sequence variant' group is interesting and suggests many of these changes may indeed be exerting functional consequences.

Control and CLL cohorts were not age matched but there was no reason to indicate imposed bias. If controls were younger than patients, then some individuals could develop CLL in later life. Given an incidence of CLL of 4 per 100,000, this would be a rare event.[6] It is possible that the number of pathogenic germ-line *ATM* mutations was higher among CLL patients than we were able to demonstrate. In 4 patients with and one without a chromosome 11q deletion, pathogenic *ATM* mutations were identified but constitutional material was not available. Thus, the frequency of *ATM* mutation carriers in CLL patients could have been underestimated; but even if all of these 5 cases carried constitutional *ATM* mutations it would not alter the significance of our findings.

The finding of a significantly increased frequency of *ATM* carriers only amongst the 11q deleted CLL subgroup suggested that the principal effect of a germline *ATM* mutation might be on progression rather than leukemia initiation. Several lines of evidence support this interpretation. First, there is no evidence of an increased frequency of CLL among AT family members.[2] Second, chromosome 11q deletion in leukemic cells is generally considered a late event in CLL pathogenesis suggesting that complete loss of ATM function occurs after initial clonal proliferation.[23] Finally, here we observed no evidence for the effect of ATM loss on cellular processes, such as CSR and VDJ segment usage, that might be associated with CLL initiation.[24] Thus, we propose a model whereby *ATM* germline mutations do not contribute to CLL initiation but rather predispose to rapid disease progression through acquired chromosome 11q deletions, loss of ATM activity and clonal expansion (Figure1). In keeping with this model, we found that most *ATM* mutant carriers were already high stage at diagnosis. Furthermore, although our entire CLL cohort was biased for patients with advanced disease, via selection for 11q deletion and inclusion of CLL4 trial patients, carriers of *ATM* mutations still demonstrated short overall survival.

Many cases of CLL are preceded by an asymptomatic MBL and studies suggest a prevalence of MBL of 3.5% and a transformation rate to CLL of 1% per annum.[7] Given this prevalence, it is likely that occasional *ATM* mutation carriers will develop MBL by chance during their lifetime and in such individuals there will be selective pressure for the loss of a second *ATM* allele by 11q deletion leading to an aggressive leukemia phenotype characterized by impaired DNA damage induced apoptosis and genomic instability.[1,4] This explanation is in keeping with our finding of an excess of *ATM* carriers amongst the CLL cohort who had a chromosome 11q deletion.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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