RESEARCH ARTICLE

Significance of ATM Gene Polymorphisms in Chronic Myeloid Leukemia - a Case Control Study from India

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Abstract

Background: Development of chronic myeloid leukemia (CML) involves formation of double strand breaks (DSBs) which are initially sensed by the ataxia telangiectasia mutated (ATM) signal kinase to induce a DNA damage response (DDR). Mutations or single nucleotide polymorphisms in ATM gene are known to influence the signaling capacity resulting in susceptibility to certain genetic diseases such as cancers.

Materials and Methods: In the present study, we have analyzed -5144A>T (rs228589) and C4138T (rs3092856) polymorphisms of the ATM gene through polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP) in 925 subjects (476 CML cases and 449 controls).

Results: The A allele of -5144A>T polymorphism and T allele of C4138T polymorphism which were known to be influencing ATM signaling capacity are significantly associated with enhanced risk for CML independently and also in combination (evident from the haplotype and diplotype analyses). Significant elevation in the frequencies of both the risk alleles among high risk groups under European Treatment and Outcome Study (EUTOS) score suggests the possible role of these polymorphisms in predicting the prognosis of CML patients.

Conclusions: This study provides the first evidence of association of functional ATM gene polymorphisms with the increased risk of CML development as well as progression.

Keywords: Chronic myeloid leukemia - ATM-5144A>T - C4138T - EUTOS score - progression

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Introduction

Cells activate a complex, kinase based signaling network to arrest the cell cycle, initiate DNA repair or even induce apoptotic cell death when the integrity of the genome is threatened due to damage by exogenous or endogenous agents. Ataxia telangiectasia mutated (ATM) protein lies at the heart of this signaling network which is collectively referred to as the DNA damage response (DDR). ATM is primarily involved in sensing the DNA damage and in executing the DDR regulated cellular responses. ATM gene was identified in the patients showing high radio sensitivity, a characteristic feature of Ataxia Telangiectasia (AT), using positional cloning approach (Savitsky et al., 1995). It is located on chromosome11 (11q22.3), consists of 66 exons spanning a relatively compact genomic region of about 150kb (Tamar et al., 1996).

ATM deficient cells fail to induce cell cycle check point arrest following DNA damage, resulting in replication of damaged DNA and propagation of errors leading to sustained genomic instability. The molecular event associated with chronic myeloid leukemia (CML) is reciprocal translocation of 9 and 22 chromosomes resulting as a consequence of DNA Double Strand Breaks (DSBs) leading to the generation of Bcr-Abl fusion oncoprotein with constitutive tyrosine kinase activity. ATM was known to recognize DSBs, hence plays significant role in CML pathogenesis. ATM kinase was found to phosphorylate p53 serine20 in a Bcr-Abl independent manner in the CML patients under imatinib treatment (Stiff et al., 2006). Targeting ATM was also suggested to help in the prevention of blast crisis of CML as it was found to enhance the phosphorylation of Nbs1 serine343 in response to genotoxic treatment (Rink et al., 2007).

A rare non-synonymous, missense mutation C4138T (rs3092856) in exon30 of ATM gene results in a non-conservative amino acid substitution from histidine to tyrosine (H1380Y). Constitutive binding of the c-Abl tyrosine kinase with ATM is mediated by the SH3 domain of c-Abl and the proline rich region on ATM

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Materials and Methods

The study was conducted on 476 CML cases recruited from Nizam’s Institute of Medical Sciences (NIMS), Hyderabad after taking informed written consent of the patient. Diagnosis of CML was based on the presence of Bcr-Abl fusion gene and only primary Ph+ve cases in all the three phases of CML were selected for the present study. The clinical characteristics of the patients such as phase of CML, imatinib response etc. were noted from the tumor registry with the help of medical oncologist and used for further analyses. The study was approved by the ethics committee of Osmania University and Nizam’s Institute of Medical Sciences, Hyderabad.

In the present study, we have calculated Sokal (Sokal et al., 1984), Hasford (Hasford et al., 1998) and European Treatment and Outcome Study score (EUTOS score) based on baseline clinical characteristics of the patients such as differential cell count, spleen size etc. and compared with respect to the ATM genotype distribution. The EUTOS score developed recently by Hasford et al., (2011) helps in predicting complete cytogenetic response and subsequent progression free survival of CML patients who are on imatinib treatment. We have also tried to correlate the genotype distribution with the Event Free Survival (EFS) of patients, calculated based on the time interval for CML patients diagnosed in the chronic phase to enter the progressive (accelerated/blast) phase. However, in spite of our sincere attempt to record the data of all patients, few patients were lost for follow up during the course of treatment. 449 age and sex matched healthy controls without any family history of cancers were selected from the local population for the case-control comparison.

Both the ATM gene polymorphisms were analyzed through PCR-RFLP (Restriction Fragment Length Polymorphism) technique. 5ml of blood sample was collected into EDTA vacutainer from all the cases and control subjects and used for the isolation of DNA by salting-out/non enzymatic method (Lahiri and Nurnberger., 1991). Sequence specific primers (BIOSERVE) were used for the amplification of promoter and exon30 of ATM gene to include the regions containing -5144A>T (Wang et al., 2011) and C4138T (Mel0 et al., 2001) polymorphisms respectively. The primer sequences were as given below;

ATM (promoter) F: 5’-CCGCCAGTCTCAACTCGTAA-3’
ATM (promoter) R: 5’-TGGTGTCTGGTGTGGTT-3’
ATM (exon30) F: 5’-TGAAACAAACTTTTAAA
ATM (exon30) R: 5’-AGAAGGAATGTTCTATTATT
AACTCA-3’

The PCR master mix was composed of 50 ng DNA, 25 mM dNTP mix, 25pM of each forward and reverse primer, and 0.25-0.5 U Taq polymerase (Bangalore Genei) within a total volume of 10 µl. PCR reactions were performed at annealing temperatures of 55°C for 30 sec and 54°C for 45 sec for amplifying -5144A>T and C4138T polymorphisms respectively. The amplified PCR products of sizes 195bp and 220bp were treated with restriction enzyme FokI (NEW ENGLAND BIOLABS) and MnlI (NEW ENGLAND BIOLABS) for genotyping -5144A>T and C4138T polymorphisms respectively and the band pattern was analyzed on 3% agarose gel. About 98% of samples (including both cases and controls) were genotyped perfectly. Few randomly selected samples were re-genotyped by other person from the laboratory and the results were found to be concordant. Statistical analyses were performed through SPSS (IBM SPSS statistics20) and SNPSTAT online tool.

Results and Discussion

Association of ATM (-5144A>T) polymorphism with the pathogenesis of CML

In the present study, we have observed a significant elevation in the frequency of AA genotype among CML cases under all models of inheritance with consistent increase in the frequency of A allele in CML group (70.32%) when compared to controls (62.88%) (Table1) suggesting a strong association of A allele with CML development. This finding was in contrast to the earlier reports by Lee et al, (2005) and Koren et al, (2006) where the variant allele (T) was found to be more prevalent and associated with breast cancer. Study conducted by Sarika et al, 2014 (data yet to be communicated) in our lab also revealed significant association of T allele with enhanced risk of breast cancer. DNA repair capacity (DRC) was found to be reduced in case of TT genotype and T allele due to altered ATM signaling while the DRC was shown to be progressively increased for AT and AA genotypes (Shin et al., 2008; Wang et al., 2011). The association with A allele observed in our study could be attributed to the highly increased DRC capacity which might activate the error prone NHEJ repair pathway, particularly in hematopoietic lineage, resulting in the accumulation of mutations and leukemia development.

Genotype frequencies of -5144A>T polymorphism were consistent with the Hardy Weinberg Equilibrium. Allele frequencies for the -5144A>T polymorphism were shown to be varied for different populations in HapMap (Figure1) (International HapMap project-dbSNP). In this study, frequency of A allele was much higher and that of T allele was reduced when compared to other populations in both cases and controls.

Interestingly, the frequencies of AA genotype (Table2) and A allele (Figure2) were significantly increased in the high risk group of CML patients under EUTOS score (57.5%) when compared to the low risk group (40.1%) (Chi square p = 0.01). Moreover, frequencies of
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AA genotype (Table 3) and A allele (Figure 2) exhibited an increasing but insignificant trend among patients diagnosed in the advanced phases indicating that A allele might confer risk in CML patients for progression. Conversely, the polymorphism did not show any association with imatinib response and with respect to the risk groups under Sokal and Hasford scores except for the reduction in A allele frequency in the intermediate Sokal risk group. The survival analysis of Kaplan-Meier curves revealed insignificant association of the polymorphism with median EFS and 4-year OS of the patients diagnosed in chronic phase (Figure 3a & 3b).

Association of ATM (C4138T) polymorphism with the pathogenesis of CML

In silico analysis of the ATM C4138T (H1380Y) revealed insignificant association of the polymorphism with median EFS and 4-year OS of the patients diagnosed in chronic phase (Figure 3a & 3b).

**Table 1. Genotype and Allele Frequency Distribution of ATM -5144A>T and C4138T Polymorphisms**

| Model of inheritance | Genotype | Controls | CML | Odds Ratio@ (95%CI) | P* |
|----------------------|----------|----------|-----|---------------------|----|
| -5144A>T (rs228589) |          |          |     |                     |    |
| N=427/470 (controls/CML cases) |          |          |     |                     |    |
| Co dominant | AA | 164 (38.4) | 229 (48.7) | 1.00 (ref) |    |
| | AT | 209 (49.0) | 203 (43.2) | 0.68 (0.51-0.90) | 0.001** |
| | TT | 54 (12.7) | 38 (8.1) | 0.46 (0.29-0.74) |    |
| Dominant | AA | 164 (38.4) | 229 (48.7) | 1.00 (ref) |    |
| | AT+TT | 263 (61.6) | 241 (51.3) | 0.63 (0.48-0.83) | 9e-04** |
| Recessive | AA+AT | 373 (87.3) | 432 (91.9) | 1.00 (ref) |    |
| | TT | 54 (12.7) | 38 (8.1) | 0.57 (0.36-0.89) | 0.012* |
| Over dominant | AA+TT | 218 (51.0) | 267 (56.8) | 1.00 (ref) |    |
| | AT | 209 (49.0) | 203 (43.2) | 0.79 (0.60-1.02) | 0.075# |
| Alleles | A | 537 (62.88) | 661 (70.32) | 1.00 (ref) |    |
| | T | 317 (37.12) | 279 (29.68) | 0.72 (0.59-0.87) | 0.001** |
| HWEp | 0.35 | 0.51 |    |                     |    |

| Model of inheritance | Genotype | Controls | CML | Odds Ratio@ (95%CI) | P* |
|----------------------|----------|----------|-----|---------------------|----|
| C4138T (rs3092856) |          |          |     |                     |    |
| N=438/475 (controls/CML cases) |          |          |     |                     |    |
| Co dominant | CC | 394 (90.0) | 410 (86.3) | 1.00 (ref) |    |
| | CT | 43 (9.8) | 60 (12.6) | 1.36 (0.89-2.06) | 0.09# |
| | TT | 1 (0.2) | 5 (1.1) | 5.19 (0.60-44.87) |    |
| Dominant | CC | 394 (90.0) | 410 (86.3) | 1.00 (ref) |    |
| | CT+TT | 44 (10.0) | 65 (13.7) | 1.44 (0.96-2.17) | 0.08# |
| Recessive | CC+CT | 437 (99.8) | 470 (99.0) | 1.00 (ref) |    |
| | TT | 1 (0.2) | 5 (1.0) | 5.01 (0.58-43.31) | 0.09# |
| Over dominant | CC+TT | 395 (90.2) | 415 (87.4) | 1.00 (ref) |    |
| | CT | 43 (9.8) | 60 (12.6) | 1.34 (0.88-2.04) | 0.17 |
| Alleles | C | 831 (94.86) | 880 (92.63) | 1.00 (ref) |    |
| | T | 45 (5.14) | 70 (7.37) | 1.14 (1.00-1.16) | 0.05# |
| HWEp | 1 | 0.16 |    |                     |    |

@Odds ratios adjusted by age and sex; £chi-square p value; **p<0.01; *p<0.05; #p<0.10, HWEp Hardy Weinberg Equilibrium p value

Figure 1. HapMap of ATM -5144A>T Polymorphism for Different Populations

Figure 4. HapMap of ATM C4138T Polymorphism for Different Populations
Table 2. Distribution of ATM -5144A>T and C4138T Genotypes with Respect to the Risk Scores

| VARIABLE          | AA n (%) | AT n (%) | TT n (%) | p²      | VARIABLE          | CC n (%) | CT n (%) | TT n (%) | p²      |
|-------------------|----------|----------|----------|---------|-------------------|----------|----------|----------|---------|
| **Sokal score**   |          |          |          |         | **Sokal score**   |          |          |          |         |
| Low risk          | 34 (57.6)| 21 (35.6)| 4 (6.8)  |         | Low risk         | 49 (83.1)| 9 (15.3)| 1 (1.7)  |         |
| Moderate risk     | 50 (43.1)| 51 (44.0)| 15 (12.9)|         | Moderate risk     | 106 (89.1)| 13 (10.9)| 0 (0)    |         |
| OR (95%CI)        | 1.00 (ref)| 1.62    | 2.09     | 0.21    | OR (95%CI)        | 1.00 (ref)| 0.62    | NA       | 0.62    |
| High risk         | 78 (51.0)| 65 (42.5)| 10 (6.5) |         | High risk         | 133 (86.9)| 19 (12.4)| 1 (0.7)  |         |
| OR (95%CI)        | 1.00 (ref)| 1.30    | 0.84     | 0.21    | OR (95%CI)        | 1.00 (ref)| 0.71    | 0.31     | 0.02-6.29|
| **Hasford score** |          |          |          |         | **Hasford score** |          |          |          |         |
| Low risk          | 31 (53.4)| 21 (36.2)| 6 (10.3) |         | Low risk         | 50 (84.7)| 9 (15.3)| 0 (0)    |         |
| Moderate risk     | 61 (43.3)| 67 (47.5)| 13 (9.2) |         | Moderate risk     | 128 (89.5)| 15 (10.5)| 0 (0)    |         |
| OR (95%CI)        | 1.00 (ref)| 1.63    | 1.04     | 0.4     | OR (95%CI)        | 1.00 (ref)| 0.65    | NA       | 0.19    |
| High risk         | 35 (51.5)| 30 (44.1)| 3 (4.4)  |         | High risk         | 54 (79.4)| 13 (19.1)| 1 (1.5)  |         |
| OR (95%CI)        | 1.00 (ref)| 1.30    | 0.30     | 0.4     | OR (95%CI)        | 1.00 (ref)| 1.33    | NA       |         |
| **EUTOS score**   |          |          |          |         | **EUTOS score**   |          |          |          |         |
| Low risk          | 85 (40.1)| 104 (49.1)| 23 (10.8)| 0.01    | Low risk         | 194 (90.2)| 20 (9.3)| 1 (0.5)  |         |
| High risk         | 80 (57.5)| 50 (36.0)| 9 (6.5)  |         | High risk         | 114 (82.0)| 23 (16.6)| 2 (1.4)  | 0.08#   |
| OR (95%CI)        | 1.00 (ref)| 0.52    | 0.42     | 0.01    | OR (95%CI)        | 1.00 (ref)| 1.97    | 3.43     |         |

@Odds ratios adjusted by age and sex; χ²-square p value; *p<0.05; #p<0.10

**Figure 2. Risk Allele Frequency with Respect to the Clinical Variables (-5144A>T)**

The genotype distribution Table 1 revealed elevation in the frequencies of CT and TT genotypes among CML cases compared to controls under co-dominant and dominant models of inheritance. The TT genotype frequency was also elevated under recessive model with border-line significance. The allele frequencies of ATM (C4138T) polymorphism did not deviate from the Hardy Weinberg Equilibrium among both cases and controls.

HapMap frequency of the variant allele for different populations (International HapMap project-dbSNP) (Figure4) revealed it as a very low penetrant allele with Global minor (T) allele frequency 0.034 (Ensembl). However, the frequency of variant allele was considerably higher in our population when compared to other populations (Table1). This polymorphism was first screened by Melo et al., (2001) among CML patients diagnosed in blast crisis, where the frequency of mutant allele was found to be almost similar in both cases (0.7)
The results on distribution of ATM (C4138T) polymorphism recommended that the variant T allele, associated with impaired Abl interaction with ATM, could interfere with pro-apoptotic signaling in response to DNA-DSB damage, hence associated with CML development.

With respect to the risk scores, the CT genotype and T allele frequencies were elevated significantly among high risk group (16.6%, 9.71% respectively) under EUTOS score when compared to low risk group (9.3%, 5.12% respectively) (Table2, Figure5) suggesting that T allele might confer high risk for progression in CML patients which might predict poor treatment outcome. However, the genotype and allele distribution did not show variation with respect to low and high risk groups under Sokal and Hasford risk scores.

When the data was stratified with respect to the phase of CML and imatinib response, the genotype (Table3) and allelic (Figure5) distribution did not show any association. However, we could not detect any TT homozygous mutants among advanced phase and Imatinib poor responders. The median EFS and relative 4year OS reduced for the patients with TT genotype. This report is in agreement with earlier report wherein overall survival was significantly elevated among the CML cases (7.37%) when compared to controls (5.14%) with adjusted OR 1.14 (1.00-1.16; p=0.05). This result suggested that T allele of the ATM (C4138T) polymorphism might result in defective ATM signaling to repair DSB leading to CML development.

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Table 4. Haplotype and Diplotype Analyses of ATM Single Nucleotide Polymorphisms

| Haplotypes | Controls | Cases | OR@ (95% CI) | P   |
|------------|----------|-------|--------------|-----|
| A-C        | 0.588    | 0.632 | 1.00 (Ref)   | --  |
| T-C        | 0.361    | 0.294 | 0.71 (0.58-0.88) | 0.002** |
| A-T        | 0.041    | 0.071 | 1.61 (0.98-2.65) | 0.062# |
| T-T        | 0.01     | 0.003 | 0.24 (0.02-2.47) | 0.23 |

Global haplotype association p value 0.0006**

| Diplotypes | Controls | Cases | OR@ (95% CI) | P   |
|------------|----------|-------|--------------|-----|
| T-C_T-C    | 56 (53.3%) | 38 (36.89%) | 1.00 (ref) | --  |
| T-C_A-T    | 29 (27.62%) | 22 (21.36%) | 1.12 (0.56-2.23) | 0.75 |
| A-C_A-T+   | 19 (18.10%) | 39 (37.86%) | 3.02 (1.52-6.01) | 0.002** |
| T_T_A-T    | 4 (4.00%) | 5 (4.80%) | 5.89 (1.63-17.03) | 0.12 |

@Odds ratios adjusted by age and sex; **p<0.01; #p<0.05

Elevated ATM haplotype distribution between cases and controls revealed global haplotype association p value 0.0006 (Table 4). Haplotype (A-T) with A allele at -5144 position and T allele at 4138 position of ATM gene was elevated among CML cases when compared to that of controls with a borderline significance. This association could be attributed to the presence of two risk alleles which might be ensuing defective ATM signaling. These results were in accordance with the earlier reports on ATM -5144A>T polymorphism, where the polymorphism was shown to confer risk in combination with haplotypes of different ATM SNPs (Lee et al., 2005; Koren et al., 2006). Captivatingly, the haplotype T-C with alleles other than risk alleles of both the SNPs (T allele of -5144A>T polymorphism and C allele of C4138T polymorphism) was significantly elevated among controls indicating protective role for these allele combination against CML.

Additionally, the combined analysis of haplotype pairs (diplotypes) (Table 4) showed that frequency of diplotype with A-T haplotype (risk haplotype) was increased among cases when compared to controls. Significant association of A-T haplotype with CML was observed particularly for the A-C_A-T and T-T_A-T diplotype, which has 50% chances of producing the risk haplotype, indicating combination of AA (-5144A>T) + CT (C4138T) and AT (-5144A>T) + TT (C4138T) genotypes as the risk conferring ATM genotypes in CML implying the effect of heterozygotes also. Frequency of A-T_A-T diplotype (representing 100% risk haplotype) was also increased among CML cases even though significant p value could not be observed due to small sample size of the particular combination. These results demonstrated that deregulation and defective signaling of ATM gene might get enhanced in the presence of both risk alleles/genotypes of -5144A>T and C4138T polymorphisms which might contribute to the eminent threat for CML.

In conclusion, The risk alleles of functionally
significant SNPs in the ATM gene (-5144A>T and -4138T) (A and T respectively) were found to be associated with deregulated ATM signaling and DNA repair capacity while might contribute to the elevated risk of CML. Haplotype and diplotype analyses revealed that combination of risk alleles may further enhance the risk. Even though we could not observe specific trend in the distribution of these SNPs with phase of CML, imatinib response and EFS or 4-year OS, elevation in the frequencies of risk alleles among the high risk group of CML patients under EUTOS score demonstrated that analyses of ATM SNPs might also assist to envisage poor treatment outcome in CML patients.

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