**ATM rs189037 (G>A) polymorphism and risk of lung cancer and head and neck cancer: A meta-analysis**

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**ABSTRACT**

A number of different epidemiological studies have measured the association between the risk of different cancers and polymorphism at promoter region of 5′ untranslated region (5′-UTR) of the Ataxia-telangiectasia mutated (ATM) gene. However the results were contentious rather than conclusive. The current study was aimed at evaluating the association between the SNP (rs189037 G>A) and the risk of head and neck cancer and lung cancer by conducting a meta-analysis. A total of 9 case-control studies were considered for this quantitative analysis. Stats Direct Statistical software (version 2.7.2) was used to evaluate the crude odds ratio (OR) with their 95% confidence interval (CI). The dominant model (GG vs. GA + AA) showed no heterogeneity and the fixed effects pooled OR was found to be significant (OR = 1.14, 95% CI = 1.05–1.25) at p = 0.003. The pooled OR for fixed effects of heterozygote and homozygote mutant allele (GA vs. AA) model was significant (OR = 1.17, 95% CI = 1.04–1.30, p = 0.006) and no heterogeneity was observed for this model. The current meta-analysis manifested that ATM rs189037 G>A genetic polymorphism may contribute increased risk of head and neck and lung cancer. Moreover, the AA mutant allele was found to be related significantly with the prognosis of lung cancer and head and neck cancer.

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**1. Introduction**

Cancer is an aberrant, uncontrolled growth of cells caused by myriad damage or mutations in the genetic material of the cells due to hereditary or environmental factors, which become immune to many signals controlling cellular growth and death often having the potentiality of invading or spreading to varied body parts (Perez-Herrero & Fernandez-Medarde, 2015). DNA double strand breaks (DSBs) are the most injurious among different types of DNA lesions caused by exogenous toxins such as environmental mutagens and chemical carcinogens in conjunction with endogenous sources resulting from reactive oxygen species (ROS) assembly during cellular respiration etc. (Di Domenico et al., 2014; Khalil et al., 2012). It has been proposed that a single unrepaired DSB might be enough to evoke cell death (Bennett et al., 1993) whereas...
misrepaired DSBs can result in loss of genetic information, harmful mutation and chromosomal rearrangements which can lead to cancer development (Weber & Ryan, 2015).

One of the frequently mutated genes in cancer that functions upsteam of TP53 in the DNA damage response (DDR) pathway and conceivably linked to the escape from apoptosis/senescence hallmark is the ataxia-telangiectasia mutated (ATM) located on the long arm of chromosome 11 (11q22–23) and covers around 160 Kb of genomic DNA (Khalil et al., 2012; Macheret & Halazonetis, 2015). The ATM protein is a large 370 kDa serine/threonine kinase that activates over a hundred proteins involved in DDR and other cellular responses like DSB repair, cell cycle regulation, chromatin remodeling, apoptosis etc. and its loss of function contributes to the major features of rare neurodegenerative autosomal recessive disorder ataxia-telangiectasia (AT) including increased cancer risk (Di Domenico et al., 2014; Weber & Ryan, 2015; Chaudhary & Al-Baradie, 2014).

The ATM gene has 66 exons and the first four exons lie in the 5’-UTR which undergo extensive alternative splicing thereby giving rise to different mRNA transcripts with varying sequences and lengths having different regulatory roles via the formation of different secondary structures and varying number of start codons (Khalil et al., 2012; Rotman & Shiloh, 1998). Of the majority of the ATM single nucleotide polymorphisms (SNPs), the rs189037 (G>A), located at the 5’UTR of the promoter region of ATM gene is one of the vital SNPs associated with the risk of several cancers.

Epidemiological studies around the globe confirmed the association between various ATM polymorphisms in different cancer risks (Cancer Genome Atlas Network, 2012; Cancer Genome Atlas Research Network, 2012a; Cancer Genome Atlas Research Network, 2012b; Cancer Genome Atlas Research Network, 2014; Bea et al., 2013; Landau & Wu, 2013). Various articles related to rs189037 SNP in promoter region of the ATM gene and the risk of different cancers have also been published (Liu et al., 2014; Gu et al., 2014a; Shen et al., 2014; Bau et al., 2010; Damiola et al., 2014; Song et al., 2015; Lo et al., 2010; Kim et al., 2006; Hsia et al., 2013). However, the results were not conclusive. In order to evaluate the association between rs189037 SNP and cancer risk, we have performed a meta-analysis from relevant scientific literatures.

2. Materials and methods

2.1. Identification and eligibility of relevant literatures

A range of electronic databases (PubMed, Google Scholar, SNPedia, OMIM, Cochrane library) were searched (last search update was 2015 March) using the search terms ‘ATM’, ‘polymorphism’, ‘cancer’, and ‘rs189037 in ATM’. Manual search of references identified in relevant publication was also performed to find other relevant literatures.

Studies included in our meta-analysis followed the inclusion criteria mentioned below: (1) All were case–control studies related to rs189037 (G>A) polymorphism, (2) Control group were in accordance with Hardy–Weinberg equilibrium, (3) Details of genotype frequencies of ATM rs189037G>A genetic polymorphisms, and (4) Only studies in English literature were considered for this meta-analysis. The major exclusion criteria: (1) No control group, and (2) No details of genotype frequencies of desired polymorphism.

Fig. 1. Flow chart of literature search and relevant study selection. Total 9 case–control studies were included in this meta-analysis.

Fig. 2. CASP scores for 9 eligible studies for the relationship between ATM rs189037 polymorphism and susceptibility to lung, head and neck cancer.
2.2. Data extraction & quality assessment

Data were carefully extracted from all eligible publications independently by two of the authors, according to the inclusion criteria mentioned above. The data were collected from each relevant study according to the following details: the first author’s full name, publication year, ethnicity of studied population, design of study, genotyping methods, genotype frequencies etc. The critical appraisal skills program (CASP) for case–control studies (http://www.casp-uk.net/) was performed for quality assurance of the selected eligible studies considered for the quantitative analysis. The scoring pattern for the CASP criteria is as follows: the study addresses a clearly focused issue (CASP1); an appropriate research design answers the research problem (CASP2); the selection of cases was inscribed acceptably (CASP3); the controls were selected acceptably (CASP4); the measurement for exposure factors is selected acceptably (CASP5); the potential confounding factors are considered in the study design/analysis (CASP6); the research results are accomplished (CASP7); the research results are considered (CASP8); the selected cases were inscribed acceptably (CASP9); the measurement for exposure factors is considered (CASP10); the selection of cases was inscribed acceptably (CASP11); and the measurement for exposure factors is considered acceptably (CASP12). The study successfully identified 42 studies from different database and manual searches. After reviewing the titles and abstracts, we excluded 4 studies. Out of 38 remaining studies, 29 were excluded further. Finally, 9 case–control studies containing of 4507 cancer patients and 4778 control subjects, met our inclusion criteria for quantitative data analysis (Fig. 1). Overall, the studies were carried out among 8 Asians and 1 Caucasian population according to the inclusion criteria. CASP scores and the characteristics of all the studies are summarized in Table 2. The pooled OR was considered to be significant at p < 0.05.

3. Results

3.1. Characteristics of studies

Initially we identified total 42 studies from different database and manual searches. After reviewing the titles and abstracts, we excluded 4 studies. Out of 38 remaining studies, 29 were excluded further. Finally, 9 case–control studies containing of 4507 cancer patients and 4778 control subjects, met our inclusion criteria for quantitative data analysis (Fig. 1). Overall, the studies were carried out among 8 Asians and 1 Caucasian population according to the inclusion criteria. CASP scores and the characteristics of all the studies are summarized in Table 2. The pooled OR was considered to be significant at p < 0.05.

3.2. Meta-analysis result

The pooled ORs for ATM rs189037G–A and cancer risk is listed in Table 2. The homozygote model (GG vs. AA) showed significant heterogeneity (p = 0.01, I² = 63.6%) and the random effects pooled OR was 1.23 (95% CI = 1.00–1.51) at p = 0.053. The dominant model (GG vs. GA + AA) showed no heterogeneity and the fixed effects pooled OR was found to be significant (OR = 1.14, 95% CI = 1.05–1.25) at p = 0.003. On other hand recessive model (GG + GA vs. AA) showed significant heterogeneity (p = 0.01, I² = 60.7%) and the random effects

| Genotype rs189037 G–A | OR     | 95% CI    | p² value | p value for Cochran Q test | I²   | Combination method |
|----------------------|--------|-----------|----------|--------------------------|------|--------------------|
| GG vs. AA            | 1.23   | 1.00–1.51 | 0.053    | 0.01                     | 63.6%| Random effect      |
| GG vs. (GA + AA)     | 1.14   | 1.05–1.25 | 0.003    | 0.17                     | 31.6%| Fixed effect       |
| (GG + GA) vs. AA     | 1.17   | 1.00–1.40 | 0.068    | 0.01                     | 60.7%| Random effect      |
| G vs. A              | 1.11   | 1.00–1.23 | 0.046    | 0.01                     | 63.7%| Random effect      |
| GG vs. GA            | 1.08   | 1.00–1.20 | 0.066    | 0.06                     | 0%   | Fixed effect       |
| GA vs. AA            | 1.17   | 1.04–1.30 | 0.006    | 0.03                     | 45.8%| Fixed effect       |

p² value > 0.05 indicates control group is in Hardy-Weinberg equilibrium.
pooled OR did not show any significant result (OR = 1.17, 95% CI = 1.00–1.40) (p = 0.068). The association between A allele and the risk of developing cancer relative to the allele G revealed significant heterogeneity (p = 0.01, I² = 63.7%) but the random effects pooled OR did not show significant result (OR = 1.11, 95% CI = 1.00–1.23, p = 0.046). Homozygote wild and heterozygote alleles (GG vs. GA)
showed no heterogeneity and the pooled OR for fixed effects was not significant ($\text{OR} = 1.09, 95\% \text{ CI} = 1.00–1.20, p = 0.066$). However, the pooled OR for fixed effects of heterozygote and homozygote mutant allele ($\text{GA vs. AA}$) model was significant ($\text{OR} = 1.17, 95\% \text{ CI} = 1.04–1.30, p = 0.006$) and no heterogeneity was observed for this model (Fig. 3).

Sensitivity test was assigned to check the influence of each studies on overall pooled OR. Begg–Mazumdar’s funnel plot (Fig. 4) did not show any publication asymmetry which was confirmed by Egger's test. There was no publication bias for $\text{ATM rs189037G}$-$\text{A}$ (Homozygote model: $\tau = -0.11, p = 0.24$; Dominant model: $\tau = -0.11, p =$
Conflict of interest
None declared.

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