LETTER to the EDITOR

Absence of the TP53 Poly-A Signal Sequence Variant rs78378222 in Oral, Cervical and Breast Cancers in South India

Asian Pac J Cancer Prev, **15 (21)**, 9555-9556

Dear Editor

With recent advancements in genomics, rare genetic variants attract the attention of cancer researchers as they represent one among the many diverse mechanisms that determine cancer risk and outcome. One such rare variant is the Single Nucleotide Polymorphism rs78378222 that alters the polyadenylation signal (AATAAA to AATACA) of TP53. Initially identified in Caucasian population, the variant 'C' allele was associated with an increased risk for prostate cancer, brain cancer and colorectal adenoma but not with colorectal cancer, breast cancer and melanoma (Stacey et al., 2011). Further, the risk allele impaired the proper termination of TP53 resulting in 'cancer promoting' longer mRNA transcripts that hindered p53 expression and its downstream functions in apoptosis (Stacey et al., 2011; Li et al., 2013). Simultaneously it was reported that rs78378222 increased the risk of esophageal cancer in Han Chinese population (Zhou et al., 2012). A similar study based on Caucasian population, showed that the rare variant was associated with risk for glioma and also significantly improved survival in patients (Egan et al., 2012). However, the association to survival was not observed in glioma patients of Northern European ancestry although it increased glioma risk (Enciso-Mora et al., 2013). A recent study showed that the heterozygous 'AC' genotype was not associated with melanoma and lung cancer, but had a protective role against squamous cell carcinoma of head and neck in non-Hispanic whites (Guan et al., 2013).

Given the multitude of effects of rs78378222 in cancer patients of different ethnicity and on account of paucity of information on 'C' allele frequency in Indian population, we genotyped 439 genomic DNA samples from oral (108), cervical (96) and breast (235) cancer patients of Indian ethnicity. Blood samples were collected from Government Royapettah Hospital & Government Kasturba Gandhi Hospital for Women and Children, Chennai and clinical information from subjects was undertaken with informed consent and relevant ethical review board approval was accorded. We adopted the PCR-RFLP methodology described by Zhou et al (2012), with a single base mismatch in reverse primer creating a *Hind III* recognition site when the wild type A allele is present (Figure 1). The RFLP results were confirmed by direct sequencing of 10% of case/control samples chosen at random (Figure 2). We found that the 'C' allele was totally absent in cancer samples. We also genotyped 504 healthy controls and found only AA genotype in all samples. In contrast to the studies that reported the occurrence of the 'C' allele in heterozygous condition (AC genotype) in up to 4% of cancers, we observed 100% AA genotype in both cancer and control samples. Several possibilities may account for the absence of 'C' allele. First, the rs78378222 occurs in 3' untranslated region (polyadenylation site) of TP53, the guardian of the genome, and hence may be under purifying selection. And secondly, the risk allele may be exclusive to certain geographical locations, and it was reported that the frequency declined with each population's distance from Iceland (Stacey et al., 2011).

Despite these considerations, our study has certain limitations that warrant any further conclusions. Apart from the three types of cancers analysed in the present study, the absence of the variant allele in other tumor types cannot be ruled out. Nevertheless, the absence of the heterozygous 'AC' genotype in the 439 cancer cases and 504 controls clearly indicates that rs78378222 is very rare

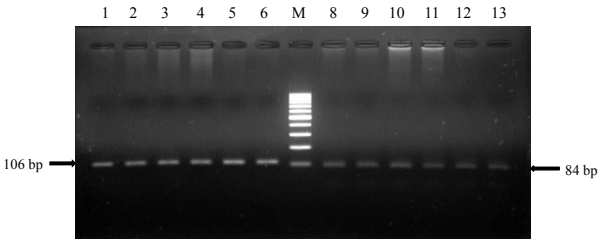

Figure 1. Analysis of TP53 rs78378222 A>C Polymorphism. Representative picture of agarose gel showing PCR-RFLP analysis of TP53 rs78378222 genotypes by *Hind III* digestion. M: 100 bp DNA ladder, Lane 1-6: Undigested PCR fragments 106 bp in length, L 8-13: *Hind III* digested PCR fragments (84bp) showing AA genotype

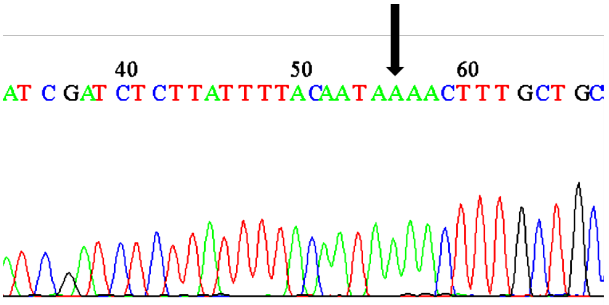

Figure 2. Sequencing of the PCR Fragment for Detection of rs78378222 Genotype Confirming Wild Type Poly-A Signal Sequence

among oral, cervical and breast cancers of Indian origin, especially of southern region. Further, the SNP may be under purifying selection leading to non-existence in the studied regional population. Owing to the controversial findings in different population, the prognostic relevance of this particular SNP may be of importance to specific ethnicity. To the best of our knowledge, this is the first study from India to report on the SNP rs78378222 and future studies from different parts of India are warranted to arrive at conclusions.

Acknowledgements

This work was supported by grants from Department of Biotechnology, New Delhi, India (Grant No.BT/PR10023/AGR/36/27/2007) and Department of Atomic Energy, Board of Research in Nuclear Sciences, Mumbai, India (Grant No.35/14/10/2014-BRNS/0210), sanctioned to AKM. The infrastructural facilities of our Department were offered by University Grants Commission and Department of Science and Technology, through UGC-SAP and DST-FIST grants respectively. AKDMR, VV, MM and KA are supported by individual research fellowship from the Council of Scientific and Industrial Research, New Delhi. SR and GA are supported by individual research fellowship from the University Grants Commission, New Delhi.

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