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# Commentary

## Association of gene polymorphisms with development of cancer risk or their protective role associated with some mutant alleles

Over the past decade, due to the advent of human genome project and its overwhelming success, there has been a great deal of interest in defining genetic polymorphisms and finding their associations with development of disease risks. However, to keep a consistent and balanced growth in this arena, one needs to have an in-depth knowledge about the extent of variations in phenotypes and their potential. Answers must be sought for questions, such as "In their ability to handle and rectify the DNA damage, how much do each individual vary from one another? To what extent do these variations play a role in making any individual susceptible to developing a higher cancer risk? And lastly, but more importantly, how far and to what limit genetic polymorphism can be held responsible for such variations?".

In this issue, Mitra *et al*[1] report the biology of human cancer in relation to genetic polymorphisms. For the first time in 1969, the crucial role played by DNA repair in preventing cancer was conclusively demonstrated by Cleaver[2], when he identified a defect in the pathway of excision repair among patients with Xeroderma Pigmentosum.

With the help of different forms of the enzyme DNA glycosylase, the generic mode of repair the "base excision repair" mechanism, as also supported by the present article[1], is rendered highly specific. These glycosylases perform the initial step in recognizing and removing the altered and damaged base pairs. Similarly, in mammals, one such enzyme, 8-oxoganine DNA glycosylase 1 (hOGG1), mapped to chromosome 3p26.2, is responsible for the removal of 8-oxoguanine, a highly mutagenic agent. Till now, several SNPs in the *hOGG1* gene have been identified, and the repair activities of the variant proteins have been evaluated in many studies like the one on SNP rs1052133 reviewed here[3-6].

This study group[1] consisted of 325 healthy normal unaffected controls and 250 squamous cell carcinomas of the head and neck (SCCHN) affected cases on whom genotype results were obtained for the SNP rs1052133 [*hOGG1*]. They used the method of DNA sequencing analysis, after polymerase chain reaction followed by restriction fragment length polymorphism. This is the first ever case-control based genetic association study to investigate the association of the non-synonymous SNP rs1052133 [Ser326Cys] located in the exonic region of the hOGG1 gene with the risk of SCCHN in the north Indian population and also interestingly the first one to report a protective association of the mutant (G) allele for SCCHN in this subgroup.

Descriptively, the *hOGG1* gene on chromosome 3p26 catalyzes the cleavage of a glycosylic bond between the modified base and a sugar moiety, leaving an abasic apurinic/apyrimidinic site in DNA which is then incised followed by a few successive actions of a phosphodiesterase that completes the repair process with a final function by a DNA polymerase, and a DNA ligase[7,8]. Some studies[9,10] have suggested that a single amino acid change in hOGG1 may affect the catalytic properties of the glycosylase. It is worth mentioning here two different studies by Elahi *et al*[11] and Takezaki *et al*[12] that demonstrated that hOGG1 protein encoded by the wild-type Ser326 allele showed much higher DNA repair activity than the Cys326 allele. The reason cited was that Cys allele being more likely to cause a low activity of the enzyme and the subsequent change of Ser to Cys increases the risk for cancer susceptibility. Also, there have been published data that Ser326Cys has approximately seven-fold higher enzyme activity with 326Ser as compared to the 326Cys protein[13,14]. In view of these findings, many studies[11,12,15-17] like the one by Mitra and colleagues[1] have dwelled into finding any possible correlations between existence of genetic polymorphisms in *hOGG1* and their relation

to tumourigenesis, most of which focused on the single nucleotide polymorphism Ser326Cys to find any possible explanations between its associations with decreased or increased repair activities. One such explanation could be that only under certain conditions of excessive cellular oxidative stress Cys326Cys genotype may be unable to repair the damage done by the free radicals and oxides[9]. Similarly, in a study seeking correlation with these polymorphisms and environmental risk factors like smoking in lung cancer patients, a statistically significant correlation was found between an increased cancer risk and the homogenous Cys/Cys genotype with a dose-dependent effect observed amongst smokers. In addition, an increased risk of orolaryngeal cancer has also been observed among smokers with the Cys/Cys genotype in smokers[17].

In a study by Paz-Elizur and colleagues[18], it was found that there existed a significantly lower enzymatic activity in hOGG1 in patients with non-small-cell lung cancer and their respective healthy age and gender matched controls. A year later, in another study on 37 SCCHN patients compared with 93 controls they reported a reduced OGG activity in patients with SCCHN. Eighteen of these SCCHN patients were disease-free following three years of treatment and on re-assessment of the OGG activity at that time they found no changes since the diagnosis, suggesting that the lower OGG activity in these patients might not be a result of the cancer they had suffered. Thus, there always exists a possibility that this kind of effects are a result rather than a cause of the disease, adding to one of the limitations to such case-control studies. A recent study on human lymphocytes by Janssen *et al*[20] found DNA repair activity of *hOGG1* to be independent of the Ser326Cys variant. Also, in comparison with *in vitro* studies, there is not much known about the *in vivo* enzymatic activity associated with Ser326Cys variant in normal human cells. In congruence with the results conceived by such studies, Zhang and group[21] also failed to observe an association between the variant Ser326Cys and HNSCC, and represented sufficient power for detecting odds of 1.6. In view of the functional effects of Ser326Cys on the enzyme activity of *hOGG1* and concentrating on the related studies, a review article summarizing results of 14 studies showed that nine of these studies found no difference in activity by the polymorphism[22]. However, there are two reports suggesting a functional importance of Ser326Cys. One by Aka and colleagues[23] showed a lower enzymatic activity-for-repair in the *OGG1* variants Ser/Cys and Cys/Cys genotypes than the Ser/Ser genotype. On a multivariate analysis the repair capacity was found to be influenced by the OGG1 polymorphism in the control population. On the other hand, Luna *et al*[24] commented on the location and transportation of the gene and demonstrated that a subcellular localization brought about by a phosphorylation of the Ser-326 causes the difference in the mutation suppressive ability between the two polymorphic variants.

Amongst a few other limitations such as a small number of subjects for the subgroup analyses followed by a further reduction in the magnitude of statistical power, there is an increased potential for random error[1]. Although we are convinced with the strong association evident from the odds ratios and significant *P* values, the power of the test would have been much higher if they had larger sample size. The authors could match cases vs. controls by at least 1:2 ratios if their budget could allow. Besides a small sample size one of the strengths that this study highlights is the uniqueness of the Indian population suggesting that in order to minimize the effects the population stratification any epidemiological study based on understanding the genetic association in the north Indian population should be conducted within sub-populations divided by ethnicities. It should be noted that head and neck squamous cell carcinoma is a tobacco-related cancer with strong data on its incidence increasing linearly depending on the number of cigarettes smoked[25]. As mentioned by the authors, matched controls for ethnicities were selected from populations living in the northern States of India who may be affected for diseases other than cancer. However, aiming to minimize chances of bias, even though being recruited from the general population it may just represent a sample of ill-defined reference population, and selection bias sometimes cannot be avoided, especially if genotyping data were associated with possible disease conditions controls had.

What can be said about the discordant results from all these studies on association of cancer risk and gene polymorphisms or their protective role associated with some mutant alleles, so far? Some studies have shown a significant effect of the Ser326Cys polymorphism in *OGG1* on enzyme activity while a few others using the same methods and gene fragmenting/sequencing techniques demonstrated a disagreement to the existence of any such association. The picture seems mixed. Also, with regards to age, there are conflicting reports of positive, negative, or no association with

repair capacity. Conclusively, there is an unidentified range of complex biologic factors that may be involved in generating oxidative stress causing damage to the genotype and in those that are functional in its repair. In view of the complexity of the aetiology of head and neck cancer in which multiple factors are involved, a panel of susceptibility biomarkers (including genetic polymorphisms) in other DNA repair pathways is also warranted to define subjects at high risk of developing such cancers because we feel that there is no single genetic marker that may predict risk adequately in such multifactorial diseases.

This study by Mitra and colleagues[1] will be a very good framework for future studies on association of the SNPs in various subgroups of Indian population. Probably in future if we get similar results from other studies, the SNP500 Cancer database of the Cancer Genome Anatomy Project will have to be redesigned, considering the enormous diversity of the Indian population. For confirmation of the present findings as reported here, additional studies with larger number of subjects and thus more statistical power should be encouraged.

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