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Title of Thesis: **P53 mutation detection in Urinary Bladder Cancer in Kashmiri Population**

ABSTRACT

Cancer is a clonal disorder, composed of malignant cells of several distinguishable characteristics such as immortality, faster growth, unable to establish cell-cell interaction, propensity to invade, metastasize and grow in an abnormal cellular environment. Molecular pathways that lead to malignant transformation of normal cells are different in different types of neoplasm's, even in different tissues and even in different types of pathology. There are six hallmark features of cancer cell phenotype: disregard of signals to stop proliferation or of signals to differentiate; capacity of sustained proliferation; evasion of apoptosis; sustained angiogenesis; tissue invasion and metastasis (*Hanahan and Weinberg, 2000).*

Bladder Cancer is the fourth most common malignancy among men and eight most frequent among women. An average of 2,60,000 cases of urinary bladder cancer are diagnosed worldwide every year. Approximately 90% cancers are of "Transitional Cell Carcinoma" (TCC) type, originating in the epithelial cells (the internal lining) of the bladder wall. When the tumor is limited to this layer, it is called "superficial" bladder cancer. This superficial cancer tends to recur despite surgery or treatment. A tumor that penetrates more deeply into the muscular layer of the urinary bladder is called "invasive" urinary bladder cancer. Genetic etiology of bladder cancer in patients from Kashmir valley is was not known. Since *TP53* is one of the major checkpoint gene found mutated in most human cancers, it will be speculative to see the role of this gene too in over all bladder cancer development.Therefore the present study had been, designed to characterize *TP53* gene mutations in bladder cancer patients of Kashmir and to correlate these mutations with Bladder cancer. We have done the study from the epidemiological point of view,as ours is a neglected population and has not been studied yet, and this is the first report. The focus of our study was to determine the incidence of mutations in the *TP53* gene in patients with bladder TCC analyzing the characteristics of the mutations, their locations and importance with respect to various clinicopathological characteristics in Kashmir population.

The frequency of *TP53* gene mutations in patients with urinary bladder carcinoma from the Kashmir is comparatively same as that shown in reports from other countries. Mutations of the *TP53* gene in this study were detected in the advanced histopathological stages of the disease. Mutation of the *TP53* gene is thus one of the

commonest genetic changes in the development of human bladder cancer. The high frequency of *TP53* gene mutations implicates *TP53* as a predominant factor for bladder cancer in high risk ethnic Kashmiri population. However, the group under investigation is too small to be considered for epidemiological conclusion. Further, the wild type samples reflect the involvement of different etiological factors which need to be evaluated in further studies in bladder cancer patients of ethnic Kashmiri population

TP53 mutation /alteration may be an important biological event in bladder tumorigenesis, detection of these changes may provide fundamental information about the natural history of the disease and may eventually provide useful information in making therapeutic decision. The next stage will be to determine in clinical trials whether the use of this information can favorably influence treatment options to result in overall improved clinical outcome. The research will require clinicians to focus on and understand some of the basic science and molecular biology relevant to bladder cancer.

- We studied mutations in exons 5-8(DNA binding domain) of the tumor suppressor gene *TP53* in 60 bladder cancer cases of kashmiri population.

- PCR-SSCP followed by direct sequencing analysis of exons 5-8 of gene *TP53* revealed the presence of mutations in 19 out of 60 (31.6%) bladder cancer cases.

- Significant amount of mutations were found in exon 5 (16.6%), exon 6 (27.7%), exon 7 (16.6%) and exon 8 (38.9%) respectively.

- (16.6%) of the *TP53* mutations were detected at hotspot codon 245 and but no mutations were detected at other hotspot codon 175, 248, 273, 196 and 282. A non sense mutation at codon 280 in bladder cancer (Arg > Stop) was found in two sample.

- The most commonly mutated codons in our study were 280, 199, 163 and 245: these findings support the notion that codon 280 is a hotspot in bladder cancer because it is mutated in 4% of bladder tumors versus 1% of tumors from all sites

- Double silent mutations was also found in one sample with two mutations in exon 8 in codon 283 and 284.

- Four mutations (26.3%) were G: C > A: T transitions which could more possibly be due to endogenous formation of urinary N-nitroso compounds that leads to O6-alkylguanine formation and G: C > A:T transitions. Interestingly in our study we found in two case G >T transversions at codon 202 suggesting that a tobacco carcinogen may be responsible for this mutation .