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Original Research Article

# Analysis of tumor protein p53 (p53) mutations in eyelid malignancy

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ABSTRACT

**Purpose:** The tumor protein p53 (or p53) gene plays a major role in the maintenance of normal cell growth and differentiation. Alteration in p53 gene is responsible for carcinogenesis. In this study, we evaluated the frequency of p53 mutation and clinicopathological findings in various eyelid malignancies.
**Materials and Methods:** We reviewed a cohort of 20 patients with various eyelid malignancies over one year. The expression of p53protein was analyzed by amplifying the exons 5-9 of p53 gene by conventional Polymerase Chain Reaction (PCR) followed by sequencing to identify mutations.
**Results:** The commonest eyelid malignancies was sebaceous gland carcinoma (SGC;50%) followed by basal cell carcinoma (BCC;45%) and squamous cell carcinoma(SCC; 5%). Study population/patients were mostly elderly (60 %, > 50 years of age) and female (75%). A total of 14 mutations were identified in the p53 genes in 9/20 (45%) patients at different intron or exon. Amongst them 6 patients (66.7%) had SGC and 3 (33.3%) had BCC. Out of the total 14 mutations identified, 8 intronic variation and 6 exonic mutations were identified. Out of 6 exonic variations, 5 caused frame shift mutations due to insertion or deletion of bases and one case was of substitution mutation (D281Y).
**Conclusion:** Sebaceous gland carcinoma (SGC) was found to be most prevalent eyelid cancer in the present study and it most frequent displayed mutation inthe p53 genes among the all eyelid tumors investigated.



## 1. Introduction

Eyelid tumors are the most frequently observed in ophthalmic practices accounting for 5% of all skin tumors.[1] In the United State, Basal cell carcinoma (BCC) is the most common human eyelid cancer accounting for 90% of eyelid tumors.[2,3] Squamous cell carcinoma (SCC) is the second most common malignancy of eyelid in Caucasians accounting for about 10 – 20% of malignant tumors and 5% of the eyelid tumors.[4] Potentially, the sebaceous gland carcinoma(SGC) is more fatal eyelid malignancy accounting for only 1% in the United States. However, in Asia, the sebaceous gland carcinoma is the

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most common malignant eyelid tumor representing about 25 – 40% of all malignant eyelid tumors.[5–7] Malignant melanoma is encountered rarely representing 1% of all eyelid malignancy but contributes a much higher proportion of death.[8] Several studies have been investigated the relationship between the Muir-Torre Syndrome (MTS) and SGC. The Muir-Torre Syndrome (MTS), is an autosomal dominant condition with an association with cutaneous sebaceous neoplasia and internal visceral malignancies (colonic adenocarcinoma).[9,10]

It is a well-known fact that the carcinogenesis starts with the genetic alteration (mutation) in either one of the genes, which are the proto-oncogene, DNA repair genes, and tumor suppressor genes. The tumor protein p53(p53) is a well-known tumor suppressor gene and has been associated with a variety of cancers.[11–13] Human p53 is a highly conserved parallel exon gene that is located on the short arm of chromosome 17, which is about 20 kb in size.[14] The gene was first discovered in 1979.[15] The p53gene is regarded as the guardian of the genome (master regulator and transcription factor), normally kept at low levels in healthy cell but activated by oxidative stress and DNA damage. The p53inducesapoptosis when DNA damage occurs but may lead to the uncontrolled proliferation of cell and genetic instability when it fails. The p53 mutations in SGC, as suggested by its over expression indicate it to have a possible key role in UV radiation exposure and subsequent signal alterations.[16] The Muir-Torre Syndrome has a defect in the DNA mismatch repair (MMR) gene. In MTS, the most commonly MSH2 and less frequently MLH1 DNA mismatch repair proteins are affected.[16] Several mutations and nuclear expression of p53have been reported by different authors in primary malignant tumors.[17–20] However, very few reports have highlighted the role of p53 mutations in eyelid carcinoma.

The present study aimed to determine the frequency of p53 gene mutation in various eyelid carcinomas and to investigate its clinicopathological correlations and prognostic significances in a clinical population comprised of North Indian region.

## 2. Materials and Methods

This cross-sectional hospital-based study was conducted over one year (from July2016-June 2017) in the Department of Ophthalmology and Department of Anatomy, Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi, India. The study was conducted following the declaration of the Helsinki principle and approved by the ethical committee of the Institute of Medical Sciences, Banaras Hindu University. All the patients were enrolled after getting the informed written consent. The samples were collected from patients with various eyelid carcinoma with selected according to inclusion and exclusion criteria. Twenty newly diagnosed and histologically confirmed patients with primary eyelid carcinoma without earlier exposure to chemotherapy or radiotherapy were included in the present study. The detailed clinic-radiological findings of all patients were recorded. Tissue samples were taken either by incisional or excisional biopsy. The Haematoxylin and eosin-stained sections were examined to confirm the pathological diagnosis and to find out histopathological differentiation. Fine needle aspiration cytology was done from metastatic lymph node whenever present. The TNM staging was done according to the guidelines of the American Joint Committee on Cancer Classification System (AJCCCS).[21]

### 2.1. Blood sampling and DNA isolation

Three to five-milliliter peripheral venous blood was collected under aseptic precaution from all patients in EDTA-coated vials through venipuncture of antecubital vein. DNA isolation was done following a standard protocol and dissolved in tris-EDTA (TE) buffer. It was followed by measurement of DNA concentration by Nano drop spectrophotometer (Thermo Fisher Scientific, USA)and storage at -20$^{o}$Ctill required.

### 2.2. Mutational analysis and sequencing

Mutation analysis of p53gene of patients (samples)was carried out by amplifying target regions, i,e, exons 5-9 and the intervening intronic using Polymerase Chain Reaction (PCR) and screening of the mutationsby sequencing (Sanger sequencing platform BIGDYE X terminator$^{TM}$). Primers used for PCR amplification of target regions were designed using primer3 software version 0.4.0 (http://frodo.wi.mit.edu/primer 3) for p53 gene axon 5-9 using the sequence from the NCBI gene The primers were used amplified by Thermocycler (Applied Bio-system). In silico PCR analysis and BLAST searches were performed using the UCSC Genome Bioinformatics website (http://genome.ucsc.edu/) .

DNA sequencing was used to screen/verify the candidate gene in the relevant affected individuals. PCR products were first purified by using the EXSOOP protocal. Briefly, PCR amplified DNA fragments were subjected oagarose gel electrophoresis, purified and sequenced using Sanger DNA sequencing method employing BIGDYE X terminator$^{TM}$ dye, on automated sequencer (3130xL Genetic Analyzer, Applied Biosystem). Data analysis was performed by software, Finch TV viewer (http://geospiza.com/ftvdlinfo.html). The gene mutations were verified by sequencing of the complimentary genomic sequences.

The Chi-squared test for equal proportions and Fisher's exact probability test was used for categorical variables. P-value sat less than 0.05 were considered statistically significant. Statistical analysis in the present study was carried out by using the SPSS-19 package for Windows

(SPSS Inc. Chicago, IL, USA).

## 3. Results

In the present study, a cohort of 20 patients, who had reported (IMS, BHU) with various types of eyelid carcinomas were enrolled. Out of these, 25% were male and 75% were of females in the age group of 31-80 years (median 70 years). The maximum case occurrences were noticed in the age group of61-70 years (8/20; 40%). The frequency of eye-lid carcinoma tended to increase with age. The majority of patients belonged to lower socioeconomic status (65%) and rural background (75%). All patients had unilateral involvement - about40% had right eye involvement while about 60% had left eyelid carcinoma which is shown in Table 1.

Histopathological examinations showed distribution of sebaceous gland carcinoma to be the most prevalent (10/20;50%) followed by basal cell carcinoma (9/20, 45%) and squamous cell carcinoma (1/20;5%) (Figures 1 and 2). Surprisingly most of the SGC (40%) observed were in the upper eyelid while BCC (20%) were in the lower lid.

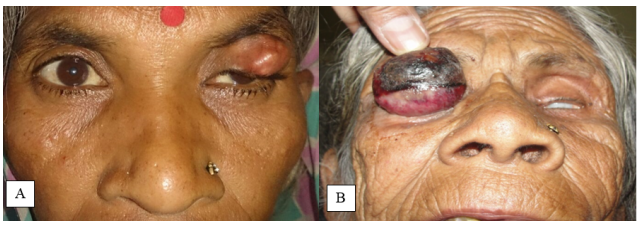


**Fig. 1:** Clinical photograph of **(A)** Middle aged female patient showing multi nodular Sebaceous Gland Carcinoma Left Upper eyelid. **(B)** One eyed old female patient having ulcero-nodular Squamous Cell Carcinoma of right eye upper lid.

PCR amplified exons 5-9 of the p53 gene were. separated on 2% agarose gel (Figures 3 and 4) and sequenced. The multiple sequence alignment found no sequence variation in exon 5, 6 and 9 of the p53gene. The G>T transversions were identified in the exons 7 and 8offour out of 8 patients.

The study indicated that the p53gene was frequently mutated (45%) in the total eyelid carcinomas observed in the test population. Analysis of the direct sequencing revealed a total of fourteen (14) mutations in different exons and introns of the p53 gene of 9 patients(45%). Here we have observed a total of 8novel polymorphic intronic variations and 6 exonic variations dispersed in coding sequence of exons 7 and 8. Interestingly, in all cases evaluated, there was not a single case of genetic variation in exon 5, 6 and 9 of the p53 gene. To analyze the mutational status of p53 gene of patients displaying eyelid malignancies. Out of 6 exonic variation,5 specimen displayed frameshift mutation due to insertion or deletion of amino acid (Tables 1 and 2 ins A, delGG, 2 ins C) and one was of substitution mutation (D281Y0.Chromatograms displaying sequencing result for

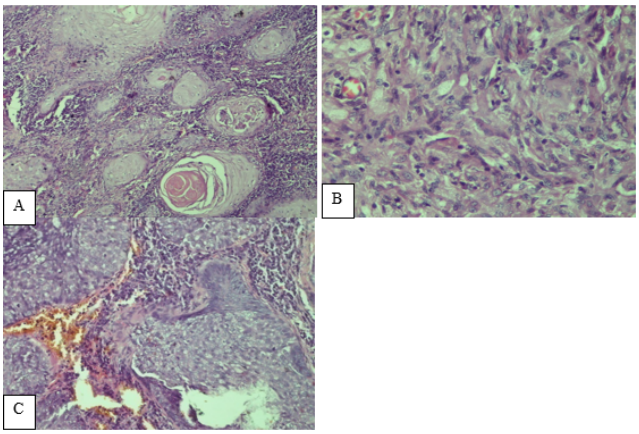


**Fig. 2:** Microphotograph of different histological section stained (Hematoxylin and Eosin x 100 X) showing **(A)** Squamous cell carcinoma showing keratin pearls, numerous malignant cells and mitotic figure.**(B)** Sebaceous gland carcinoma moderately differentiated showing lobules of malignant cells with sebaceous differentiation.**(C)** Basal cell carcinoma showing nests of pigment liden atypical basal cells with peripheral palisading & mitotic figures.

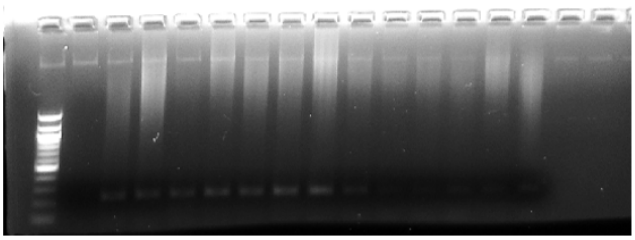

**Fig. 3:** PCR product of exon 5 and 6 in agarose gel viewed through ultraviolet light.

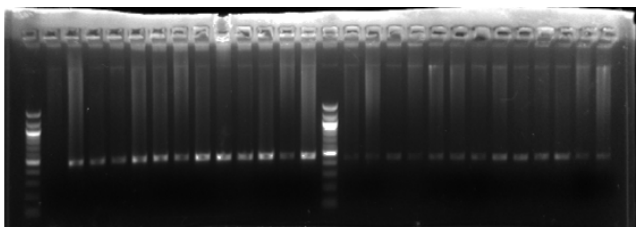

**Fig. 4:** PCR product of exon7, 8 and 9 in agarose gel viewed through ultraviolet light.

mutation identified in exon 5,6,7,8 and 9 are provided in Figures 5, 6, 7, 8 and 9. Further, we have concluded under 9 patients 6(66.7%0 patients having SGC and 3 (33.3%) having BCC observed mutation. No mutation was found in normal cases of various eyelid skin. The genetic variation of different patients is presented in Table 2.

**Table 1:** Distribution of Clinicopathological Characteristics of study of the subject

| **Parameters** | | **No (n=20 )** | **%** |
|---|---|---|---|
| **Sex** | Male | 5.0 | 25.0 |
| | Female | 15.0 | 75.0 |
| **Age** (Years) | 31-40 | 2.0 | 10.0 |
| | 41-50 | 5.0 | 25.0 |
| | 51-60 | 4.0 | 20.0 |
| | 61-70 | 8.0 | 40.0 |
| | >70 | 1.0 | 5.0 |
| **Residence** | Urban | 1.0 | 5.0 |
| | Semi-urban | 4.0 | 20.0 |
| | Rural | 15.0 | 75.0 |
| **Pathological Diagnosis** | Basal Cell Carcinoma | 9.0 | 45.0 |
| | Sebaceous Gland Carcinoma | 10.0 | 50.0 |
| | Squamous Cell Carcinoma | 1.0 | 5.0 |
| **Laterality** | Right Eye | 8.0 | 40.0 |
| | Left Eye | 12.0 | 60.0 |
| **Anatomical Location** | Upper lid | 12.0 | 60.0 |
| | Lower lid | 6.0 | 30.0 |
| | Medial Canthus | 1.0 | 5.0 |
| | Lateral canthus | 1.0 | 5.0 |

**Table 2:** Distribution of patients based on genetic variation

| **Genomic position** | **Exon** | **Patient ID** | **Pathological Diagnosis** | **Amino Acid Change** | **Database Status** |
|---|---|---|---|---|---|
| 13377C>A | Intronic Variation | BHU ID 10/17<br>BHU ID 75/17 | BCC SGC | Intronic Variation | Novel Polymorphic Variant |
| 13874A>G | Intronic Variation | BHU ID 09/17 | SGC | Intronic Variation | Novel Polymorphic Variant |
| 14082T>G | Intronic Variation | BHU ID 09/17<br>BHU ID 30/17 | BCC SGC | Intronic Variation | Novel Polymorphic Variant |
| 13430C>T | Intronic Variation | BHU ID 09/17<br>BHU ID 30/17 | SGC SGC | Intronic Variation | rs12947788 |
| 13724_13725insC | Coding sequence | BHU ID 20/17 | BCC | Frameshift Mutation | Novel Variant |
| 13760G>T | Coding sequence | BHU ID 181/17 | BCC | D281Y | HGMD ID CM076566 |
| 13856G>T | Intronic Variation | BHU ID 181/17 | SGC | Intronic Variation | Novel Polymorphic Variant |
| 13859G>C | Intronic Variation | BHU ID 181/17<br>BHU ID 141/17 | SGC SGC | Intronic Variation | Novel Variant |
| 13870G>T | Intronic Variation | BHU ID 181/17<br>BHU ID 141/17 | SGC SGC | Intronic Variation | Novel Variant |
| 13894G>T | Intronic Variation | BHU ID 75/17 | SGC | Intronic Variation | Novel Variant |
| 13713_13714insC | Coding sequence | BHU ID 20/17<br>BHU ID 181/17 | SGC SGC | R267T frameshifts | HGMD ID CD004355 |
| 13702_13703insA | Coding sequence | BHU ID 141/17 | SGC | G262R frameshift | Novel Variant |
| 13703_13704delGG | Coding sequence | BHU ID 20/17 | SGC | G262 frameshift | Novel Variant |
| 13708_13709insA | Coding sequence | BHU ID 141/17 | SGC | L264T frameshift | Novel Variant |

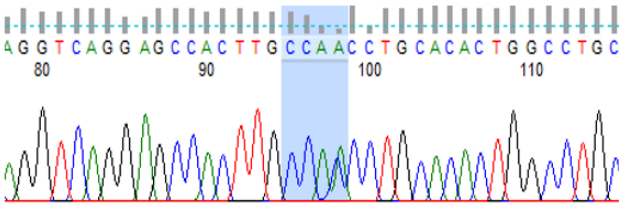


**Fig. 5:** Chromatogram show g.13377C >A variation in exon 7 of P53 gene

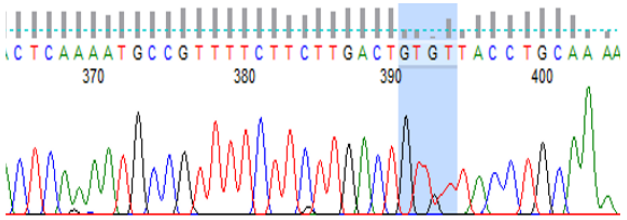


**Fig. 6:** Chromatogram show g.14082T>G variation in exon 7 of P53 gene

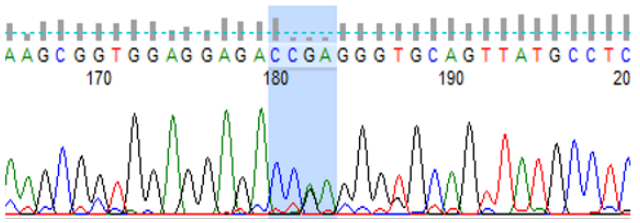


**Fig. 7:** Chromatogram show g.13874A>G variation in exon 8 of P53 gene

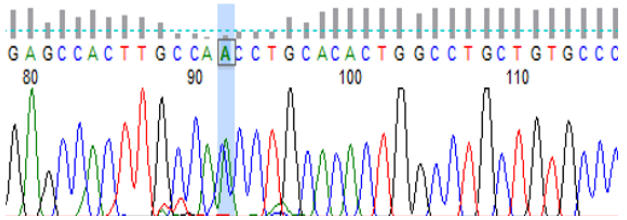


**Fig. 8:** Chromatogram show g.13377C >A variation in exon7 of P53 gene

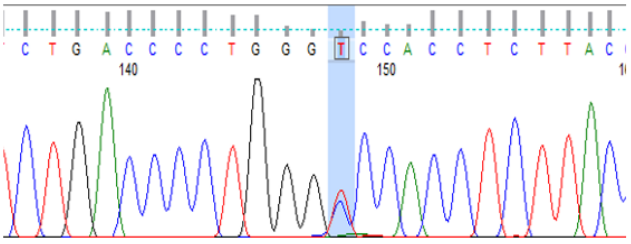


**Fig. 9:** Chromatogram show g.13430C>T variation in exon7 of P53 gene

## 4. Discussion

In present study we encountered three types of eyelid malignancies in patients, namely, SGC (10/20, 50%), BCC (9/20, 45%) and SCC (1/20, 5%). Our findings were consistent with a previously reported clinicopathological.[2] A study by Ramya et al had found sebaceous gland carcinoma (47.7%) to be the commonest malignant tumor of all, followed by BCC (26.8%) and SCC (21.9%).[22] Almost similar finding was noted by Sihota et al; SGC (32.56%), BCC (29.77%) and SCC (28.08%) when they performed study over 313 Indian patients.[23] We have observed that most of the eyelid malignancies occurred in $6^{th}$-$7^{th}$ decades of life, predicting that with the advancement of age the chances of the occurrence of malignancies increase. This finding is in agreement with previously mentioned studies.[22–24] Vitaliano and Urbach (1980),[24] who had also indicated age as an important risk factor in non-melanoma skin tumors. Gender wise females (75%) outnumbered males with females more likely to develop sebaceous eyelid tumors than males. We assume this may be the result of rural female being more exposed to smoke, dust, UV exposure, etc, in this part of India which could be predisposing them to more of these eyelid malignancies. This finding was in agreement with reported findings from a study by Shields JA.[25]

The tumor protein p53(p53) is tumor suppressor genes located on chromosome 17 of humans is consider as a caretaker of genome. A high frequency of mutation in p53 has been implicated in the pathogenesis of various solid tumors.[16] Current study observed a high prevalence ofp53 gene is mutation in the majority of total eyelid carcinoma cases being reported (9/20, 45%). Previously, high prevalence of p53gene mutations had been also reported in many carcinomas including those of ovary (47.8%), colorectum (43.2%), lung (38.6%), stomach (32.0%) and breast (25.1%) (http://www.p53.iarc.fr).[26–28] However, in the development of cancers, the pathologic implication of p53mutations has not been fully explored and established. In prostate and breast cancer, it is often observed that early detection of mutation is rare and tends to be more frequently detected at an advanced stage, suggesting mutation of p53 might occur at an advanced stage of tumor progression.[28] Out of the total 14 mutations identified in the current study, 8 were intronic variation, which is novel polymorphic variation. It is commonly present in the general population and does not produce disease. However, it may be speculated that in adverse conditions, it may be contributing to the disease condition. In two patient each of SGC and BCC, we found a common mutation of the p53 gene inthe region (13430C>T)position cause disease in normal population which is often seenC–T transition on dipyrimidine or CC–TT mutations produced due to DNA lesion aregenerally result of UV exposure ofskinaredisease-causing mutation.

OInterestingly, our study identifiedhigh prevalence of p53 mutation (6/9SGC patients as compared to others, which are common in the Asian-Indian population. However, this is in contrast with several other studies that report more incidence of sebaceous gland carcinoma as compared to others mainly because of different geographical factors involved in the etiology of thep53alteration in ocular SGC, which varied between 50-67%.[29] Kiyosaki et al dictated, based upon a small series of SGC cases,p53 gene (10/1567%)p53 mutation followed by Rb gene where 6/16 (37.5%) cases using next-generation sequencing technique (NGS). In the analyzed group of tumors two cases of SGC have been shown variation in exons 7 and 8 respectively at 13713_13714insC genomic position cause disease associated with Li-Fraumani syndromethat have beenreportedby others. Moreover, most of the mutationsSGC and BCC but did not observed in SCC. However, the l should be noted as well e.g., which may be partially responsible for the observance of differential outcome with regard to prevalence of p53 mutation in our samples, e.g., limited number of samples absence of patients with melanoma and absence of p53 mutation in other mentioned eyelid carcinomas

## 5. Conclusion

Most of the tumors appeared in the latter part of life, i.e., $6^{th}$ – $7^{th}$decades of life, mainly to those who work in the exposed area. Our mutation profiling shows that aberrant p53 could play a major role in various eyelid malignancies in which the sebaceous gland carcinoma could selectively be one of the preferred targets of p53 mutation. Our results indicate that in various eyelid malignancies p53 gene could be taken as a prognostic biomarker. Studies with a greater number of samples to validate the p53 mutations and its correlation with the clinicopathological condition/outcomes of various eyelid carcinoma are warranted. Followings are key massage:

The alterations in Tumor Protein p53 (TP53 or p53), a key tumor suppressor protein involved in the maintenance of normal cell growth and differentiation, are frequently observed in different cancers (5-50%) including the eyelid cancers.

In the North Indian study cohort, eyelid malignancies were more prevalent in elderly (>50 years) females (75%) with sebaceous gland carcinoma (SGC) being the most frequent (50%),followed by the basal cell carcinoma (BCC; 45%) and the squamous cell carcinoma (SCC; 5%).

45% of the eyelid carcinomas (9/20) harbored mutation(s) in the p53 gene (8 intronic + 6 exonic; 11 novels), with SGCs comprising 2/3 cases (66.7%) and BCCs comprising about 1/3 (33.3%) cases, indicating the prominent role of p53 mutations in eyelid carcinomas esp. SGC.

## 6. Author Contributions

RPM, VPS, -designed the Study; SKB, RS -procured the samples and performed the experiments; VPS- provided critical input; AK-designed and performed the statistical analyses, RS-interpreted the results; RPM, VPS, SS-wrote the first draft of the manuscript with inputs from all co-authors; POL - critical appraisal of the manuscript; All authors reviewed and approved the final version of the manuscript prior to submission.

## 7. Conflict of Interest

The authors declare no potential conflicts of interest.

## 8. Funding support

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