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Decoding the Genetic Alterations in Genes of Fibroblast Growth Factor Family and Their Possible Association with HNSCC

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: HNSCC is a type of cancer in the oral and pharynx region. Several mutations/variations are observed in these cancer phenotypes. Fibroblast growth factor belongs to the family of heparin binding growth factors. *FGF*s are multifunctional proteins with a wide variety of effects; they are most commonly mitogens. Their expression pattern correlates with invasion of HNSCC.
Aim: To assess the genetic alterations in genes of the fibroblast growth factor family and their association with HNSCC.
Materials and Methods: The demographic data and samples of 528 HNSCC patients was collected from the cBioportal database. Oncoprint analysis was done to assess the amplification and genetic alterations of the members of the *FGF* gene family. String analysis was performed to evaluate the protein-protein interaction. The information about previous reported mutation and correlation with novel and reported mutation was obtained using GnomAD analysis.

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Results and Discussion: *FGF3,4* and *19* genes showed maximum variation (25%). *FGF4* and *FGF19* genes showed maximum amplification in addition to deletion mutation. Excitingly *FGF3*, *FGF4* and *FGF19* genes showed similar amplification patterns in most of the HNSCC patients. Statistical significant difference in the gene expression of *FGF3* 9.578 x 10-3 observed between normal and primary tumour. S. Findings showed many novel mutations and also 4 reported mutations ie:*FGF1*, *FGF12, FGF20, FGF21*

Conclusion: Our present study concludes that more evidence is required to confirm their association with HNSCC.

Keywords: Amplification; fibroblast growth factor; head and neck squamous cell carcinoma; novel; variants.

1. INTRODUCTION

Head and neck squamous cell carcinoma(HNSCC) includes cancer in lip, oral cavity,oropharynx, nasopharyngeal and laryngeal regions. Incidence is nearly 7,00,000 new cases and more than 3,80,000 deaths per annum worldwide [1]. Squamous cells are protective cells which are seen in the outermost layers of skin and mucous membranes [2]. Head and squamous cell carcinoma mostly develops in mouth and throat regions. Survey conducted in 2018 by GLOBOCAN concludes that higher prevalence rates are grouped in asian countries [3]. Head and squamous cell carcinoma mainly caused due to alterations in DNA or specific genes. Other exogenous factors like heavy alcohol consumption, tobacco chewing and smoking [4]. Neoplasm can be treated by surgery, radiation, chemotherapy and hormonal therapy. Long term treatment causes major side effects like nausea, vomiting, bone-marrow suppression, paraesthesias, and reversible hair loss [5]. Incidence of carcinoma is more among male than females [6].

Fibroblast growth factor(*FGF*s) belongs to the family of heparin binding growth factors. These growth factors are generally extracellular in origin, but they will activate the cell surface receptors [7]. Mostly they will bind heparin and its metabolites. They are released only upon injury or tissue remodelling. Fibroblast growth factors are a vast family which contains nearly 22 individual members. They are structurally designed as signaling molecules. Members include *FGF1, FGF2, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGF10, FGF11, FGF12, FGF13, FGF14, FGF16, FGF17, FGF18, FGF19, FGF20, FGF2, FGF22, FGF23*. There is no human *FGF15*. Fibroblast growth factor has 4 receptors *FGFR1, FGFR2, FGFR3, FGFR4. FGF 1-10* binds to the receptors. *FGF1* is known as acidic fibroblast growth factor and *FGF2* is known as basic fibroblast growth factor [8]. *FGF18* is identified to possess cell development and morphogenic properties. Fibroblast growth factor helps in mesoderm induction, limb development and wound healing processes. *FGF*s secreted by hypoblasts play a role in stimulating a *Wnt* signalling pathway during avian gastrulation. Our team has extensive knowledge and research experience that has translate into high quality publications[9–13].

Previous studies have concluded in the diagnosis of subtypes of *RCC, FGFR2* isoform testing can be used. The tissue-specific discovery of a prevalent isoform switch of *FGFR2* holds promise for the potential development of *FGFR2-IIIc* as a separate biomarker of early detection and therapeutic target for *ccRCC* [14]. Formalin fixed, paraffin embedded tumours compared with frozen neoplasm, described the feasibility of comprehensive gene profiling [15]. Various studies have been done regarding the etiology of HNSCC, but none of them is precise. Our aim of the study is to decoding the genetic alterations in fibroblast growth factor and assessing its interrelationship with HNSCC.

2. MATERIALS AND METHODS

2.1 Data Source

The present study is in retrospective study design Source of information (ie): patients data were procured from cBioportal database [16]; [17]. cBioportal genomics integrates an exhaustive collection of molecular lines. The database is user friendly. Epigenetic and proteomic collections were registered. Information about different cohorts was collected. The sample data set contains 528 tumour samples of head and squamous cell carcinoma. The samples harboured copy number variations and mutation data. The demographic details of patients with head and squamous cell carcinoma

dataset were tabulated (Table 1). User defined questions queries regarding genes submitted on cBioportal database.

2.2 Oncoprint Analysis

The oncoprint data provides information on the probabilities of specific gene alterations, the type of alterations, changes in protein that codes for amino acids, and genes of amplification, deletion, insertion, frameshift, mutation, and so on. This information is used to derive a putative relation between the disease phenotype and genotype, assess the variation in less understood pathways or genes, differentiate the novel and previously reported variations associated with disease phenotype.

2.3 Protein Network Analysis

STRING is one of the first projects, and it focuses on high coverage, ease of use, and a consistent scoring system to set itself apart. The STRING database incorporates data from a variety of sources, including experimental data, numerical prediction methods, and publicly available text collections. It is open to the public and is maintained on a regular basis. Using a variety of functional classification schemes such as GO, Pfam, and KEGG, the resource also highlights functional enrichments in user-provided protein lists. The advanced version of string contains approximately 24.5 million proteins from 5000 organisms [18].

2.4 GNOMAD Analysis

A resource created by an international consortium of researchers, the genome aggregation database(GnomAD) aims to collect and harmonise both exome and genome sequencing data from a wide range of large scale sequencing projects and to make summary data accessible to the broader scientific community. The data set provided on this website unrelated individuals sequenced as part of various different diseases. These sample sequences were collected based on public consent, consortium, permission, exome data quality and lack of relatedness with other samples [19].

2.5 Gene Expression and Survival Analysis

The expression of the gene presenting with highest frequency of gene alteration in HNSCC was analysed using the UALCAN (http://ualcan.path.uab.edu/cgi-bin/TCGA-survival) database. Survival curve analysis based on the tumor grade and expression profile was performed to demonstrate the putative role of FGF family of genes with HNSCC. Combined survival effect analysis of gene expression and other clinical parameters such as race, gender, tumor grade, cancer subtypes were assessed using log-rank test that generated a p value which was further used to indicate statistical significance of survival correlation between groups [20].

3. RESULTS

Primary database used from cBioportal. Several dataset collected from TCGA, firehouse legacy. Only selected samples were used in the present study. TCGA gave information about 528 HNSCC patients. From the (Table:1) demographic data, male and female ratio was found to be 193:71 of diagnostic age ranging from 19-90 years. The number of individuals having a history of smoking was found to be 97% (515 individuals). The percentage of patients with HNSCC who consume alcohol is 66% (352 individuals). The datas were collected from different geographic populations, white 85% (452 individuals), africans 9% (48 individuals), asian 2% (11 individuals), american indian 0.3% (2 individuals). The distribution of patients based on histological grading of tumour 58% of patients had grade-II tumour.

Oncoprint analysis performed to analyse the genetic mutation and alterations of the fibroblast growth factor family. Here gene *FGF3,FGF4* and *FGF19* are observed to have higher percentages of alteration (Fig. 1). Oncoprint analysis reveals that 14 genes underwent amplification, In which genes like *FGF3, FGF4* and *FGF19* showed 25% of gene alteration. Genes *FGF1, FGF2, FGF4, FGF5, FGF7, FGF8, FGF9, FGF10, FGF11, FGF13, FGF14, FGF19, FGF21* and *FGF23* have undergone genetic alteration. A shift in DNA that causes a protein to terminate or terminate its translation earlier than expected is stop mutation. This is a common type of mutation that causes a shortened or non-functional protein to be expressed in humans and other animals. Genes have undergone stop mutation or termination mutation ie): *FGF1, FGF12.* Genes like *FGF3, FGF4 and FGF19* harboured the highest number of variations/ mutations among the gene identified alteration (Table 2). Several splice mutations and missense mutations of unknown significance were documented (Fig 1). Genetic alterations in the genes associated with

fibroblast growth factor families were documented. Alteration of each gene is noted and checked whether it is a novel mutation or previously reported mutation. Interestingly patients with *FGF19* mutation also had *FGF3* and *FGF4* genes mutated. Arranging the gene based on high degree of amplification *FGF3, FGF4, FGF19* followed by *FGF12, FGF10, FGF6* and *FGF23.*

Oncoprint analysis of samples showed mostly no alterations in most of the genes. More than 20% of the gene has undergone amplification. Some genes showed truncating mutation, as a change in DNA that can truncate or shorten protein seen in *FGF1, FGF2, FGF12, FG21, FG22* and *FGF23*. Splice mutation is also genetic mutation that inserts, deletes, changes the number of nucleotides at specific sites, splicing occurs during processing from precursor messenger RNA to mature messenger RNA. Only gene showing splice mutation is *FGF11*. statistically significant difference in the gene expression of FGF3 9.578 x 10-3 observed between normal and primary tumour. Total of 4 reported variant have been identified by GnomAD analysis viz., *FGF1*(rs770592235), *FGF12*(rs7685097171), *FGF20*(rs765043985) and *FGF21*(rs781670890). Differential expression of gene in normal versus primary tumour for *FGF3* only showed statistical significance value. Protein network interaction of *FGF3* (Fig. 2).

Differential expression of genes in Normal vs Primary tumor

- *FGF3* - 9.578 x 10-3 (Statistically significant)
- *FGF4* - 1.172 x 10-1
- *FGF19* - 5.165 x 10-2

4. DISCUSSION

Fibroblast growth factors(*FGFs*) are generally secreted small proteins which act by binding to receptors of transmembrane tyrosine kinase(FGFRs). Activation of FGFRs will activate the multiple cytoplasmic cascades that lead to cell behaviour changes [21]. In a number of developmental and physiological processes, *FGF*s play a critical role [22]. *FGF* gene family composed of eight subfamilies. Evolutionary history of the *FGF* gene family is characterized by gene duplication and gene losses [23]. Humans have 18 *FGF* ligands in the whole body and four FGFR receptors (FGFR1, FGFR2, FGFR3, FGFR4). *FGF* ligands are growth factors of polypeptides that influence several processes of development including cell proliferation, differentiation, migration, morphogenesis and patterning [24]. In order to build an axial and craniofacial skeleton, *FGF-FGFR* signalling is also important [25]. In particular, intramembranous ossification of cranial bone and suture has been implicated in signalling cascade [26]. In adults *FGF* and FGFRs are used in tissue repair. *FGF* signalling follows one of the three signalling pathways of transduction: *RAS/MAP* kinase, *P13/AKT* or *PLCY* [27].

Table 1. Represents the demographics details of the HNSCC patients collected from cBioportal

Gender	Male (n = 386)
	Female (n = 142)
Mutation count	6-3181
Diagnosis age	19-90 years
Smoking status	Smokers: 515
	Data not available: 12
	Unknown: 1
Alcohol history	Yes – 352
	No – 165
	Data not available: 11
Neoplasm Histologic grade	Grade 1: 63
	Grade 2: 311
	Grade 3: 125
	Grade 4: 7
	Grade GX: 18
	Data not available: 4
Race category	White: 452
	African: 48
	Asian: 11
	American Indian or Alaska native: 2
	Data not available: 15

Table 2. Gene alterations in fibroblast growth factor 1 gene family as assessed from the Oncoprint data

Gene	Protein encoded	Cytogenetic loci	Alteration	% of alteration	Variant allele frequency	gnomAD frequency
FGF1	Fibroblast growth factor 1	5q31.3	Deep deletion	0.8	0.12	Novel
			Q142*		0.27	rs770590235
			R137W		0.74	rs764725960
			L150M			
FGF2	Fibroblast growth factor 2	4q28.1	Deep deletion	0.8		
			I176F		0.27	Novel
			R124Pfs*60		0.33	Novel
FGF3	Fibroblast growth factor 3	11q13.3	Amplification	25	0.43	Novel
			V137E			
FGF4	Fibroblast growth factor 4	11q13.3	Amplification	25	-	-
			Deep deletion			
FGF5	Fibroblast growth factor 5	4q21.21	Amplification	1.4		
			Deep deletion			
			L9F		0.04	Novel
			F11L		0.43	Novel
			A143G		0.30	Novel
FGF6	Fibroblast growth factor 6	12p13.32	Amplification	3	0.21	
			G64V			Novel
FGF7	Fibroblast growth factor 7	15q21.2	Amplification	0.6	0.06	
			Deep deletion			
			N149S			Novel
FGF8	Fibroblast growth factor 8	10q24.32	Deep deletion	0.8		
			A170V		0.20	Novel
			T183M		0.14	Novel
FGF9	Fibroblast growth factor 9	13q12.11	Amplification	1.6	0.17	
			Deep deletion			
			T81S			Novel
FGF10	Fibroblast growth factor 10	5p12	Amplification	6		
			Deep deletion			
			K137E		0.19	Novel
			D149N		0.12	Novel
FGF11	Fibroblast growth factor 11	17p13.1	Amplification	1.4	0.45	
			Deep deletion			
			V203=			Novel
FGF12	Fibroblast growth factor 12	3q28-q29	Amplification	20		
			P89T		0.24	Novel
			R165H		0.04	rs768509717
			R64W		0.12	Novel

Gene	Protein encoded	Cytogenetic loci	Alteration	% of alteration	Variant allele frequency	gnomAD frequency
			H88Y		0.06	Novel
			R114H		0.34	Novel
			*244Lext*53		0.10	Novel
FGF13	Fibroblast growth factor 13	Xq26.3-q27.1	Amplification	3		
			Deep deletion			
			G91D		0.19	Novel
			D211N		0.74	Novel
			P139T		0.60	Novel
FGF14	Fibroblast growth factor 14	13q33.1	Amplification	1.6	0.25	
			Deep deletion			
			K21E			Novel
FGF16	Fibroblast growth factor 16	Xq21.1	Deep deletion	0.6	-	-
FGF17	Fibroblast growth factor 17	8p21.3	Deep deletion	3		
			L12V		0.41	Novel
			R164H		0.58	Novel
FGF18	Fibroblast growth factor 18	5q35.1	-	0		-
FGF19	Fibroblast growth factor 19	11q13.3	Amplification	25		
			Deep deletion			
			A86T		0.21	Novel
			D129V		0.03	Novel
			D119N		0.37	Novel
FGF20	Fibroblast growth factor 20	8p22	Deep deletion	3	0.25	
			E131D			rs765043985
FGF21	Fibroblast growth factor 21	19q13.33	Amplification	0.6		
			G95Efs*100		0.19	Novel
			S191L		0.14	rs781670890
FGF22	Fibroblast growth factor 22	19p13.3	Deletion	1		
			R150Gfs*?		0.29	Novel
			Q137H		0.19	Novel
FGF23	Fibroblast growth factor 23	12p13.32	Amplification	4		
			R198W		0.19	Novel
			G237Wfs*25		0.19	Novel
			C206F		0.30	Novel
			R176Gfs*15		0.42	Novel
			R143T		0.38	Novel
			P203T		0.38	Novel
			M199I		0.09	Novel
			A47G		0.10	Novel

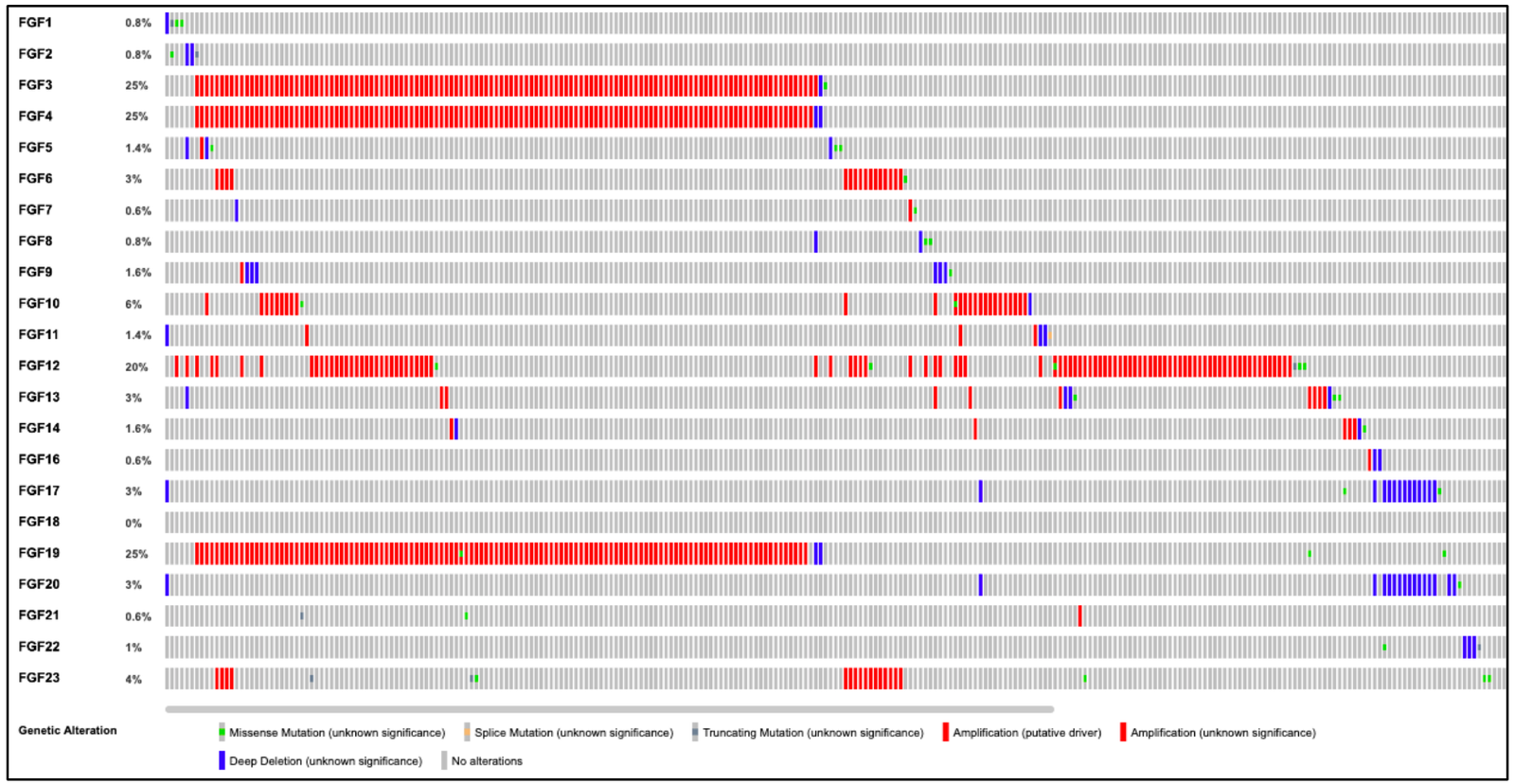

Fig. 1. Oncoprint data depicting the genetic alterations in fibroblast growth factor family 1

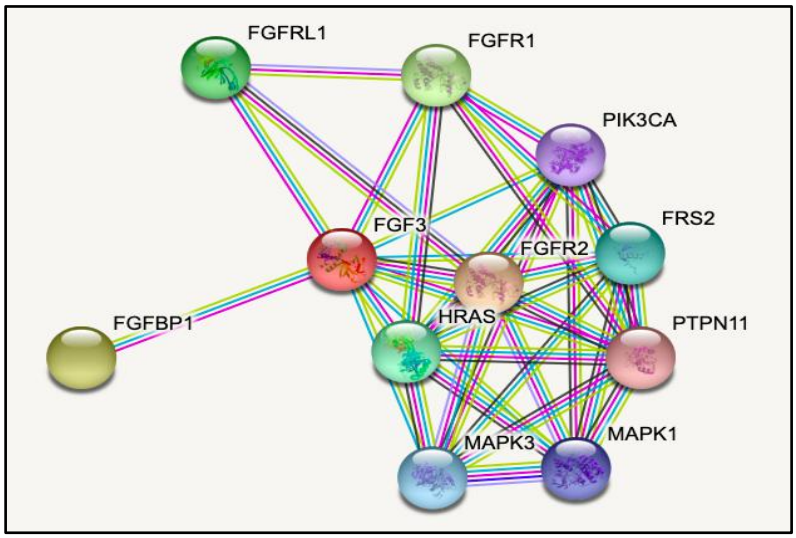

Fig. 2. Protein network interaction of *FGF3* as assessed using STRING database

More than 35% of head and squamous cell carcinoma occurs due to amplification and rearrangement [28]. Higher incidence of HNSCC was observed in African and American populations [4]. Saliva serves as a diagnostic tool/ medium for early detection of HNSCC [29] [30]. Until now smoking seems to be a major etiology of head and neck squamous cell carcinoma. Hence saliva can be used as a diagnostic marker for smoking related cancer other than gene markers [31]. Fibroblast growth factor (FGFR1) receptor 1 serves as a putative driver for tumour progression. It was identified in patients by targeted sequencing [32]. Previous studies suggest that FGFR1 receptor amplification and overexpression was around (9-17%) and (8-12%). Former study reported that a high degree of polymorphism (35-54%) was observed in *FGFR4* in which glycine was replaced by arginine at 388 position. But amplification and overexpression of individual genes have no role in determining the survival rate of infected individuals [33]. High amplification of *FGF19* may lead to head and neck squamous cell carcinoma due to increase in autocrine FGF19 secretion [34]. Amplification of *FGF19* will cause constitutive activation of FGF receptor (*FGF9*)-dependent activation. *FGF19* proved to promote cell proliferation [35]. Similar to our present study, previously many articles about genetic alteration in the family of *SPARC* gene [36] and regarding the antioxidant gene association with HNSCC have been done [37].

Multiple studies have reported that proliferation, differentiation, mineralisation may depend on the *FGF2* signalling pathway. But a unique inhibitor will inhibit the whole lineage from FGFR1, FGFR2, FGFR3 and FGFR4. On an interesting note, *FGF2* plays a major role in differentiation of oligodendrocytes and inhibits the formation of myelin [38]. From Fig 2 *FGF3* gene has been connected to variety of tumour related proteins like *HRAS, MAPK*, *MAPK3, FGFR1, FGFR2, FRS2, FGFRL1, FGFBP11* and *PTPN11*. *HRAS* protein is involved in activation of Ras protein signalling transduction pathway. *HRAS* and *FGF3* gene correlation with bladder cancer has been proved. Increases or decreases in *HRAS* gene cause huge variation in *FGF3* gene [39]. Mitogen activated protein kinase 3 (*MAPK3*) acts as essential components of the MAP kinase signaling transduction pathway. Reduction in *ERK1/2(P44/P42)* phosphorylation has relation with tumour growth in oral cell carcinoma[40]. Phosphatidylinositol 4,5 bisphosphate 3-kinase catalytic subunit alpha isoform, plays a key role by recruiting its domain-containing protein to the membrane including *AKT1* and *PDPK1*, involved in cell growth, proliferation., motility and morphology. Expression of *PIK3CA* was increased in case of oral cell carcinoma [41]. Limitations of this study, sampling is done in particular populations. Several studies conducted by the authors employing computational methods had aided us in developing the study design for the present study [42-52]. The *in silico* methods can be used to identify mutations which can act as potential drivers of the tumorigenesis process [53], [54][23,55], [56]. Our research team has conducted several studies related to identification of molecular targets and variants in genes which show a direct or indirect association with cancer [57,58,59,60,42,49,50,52,61].

5. CONCLUSION

In our present study, brief genetic alterations of the members of fibroblast growth factors was discussed. Not all the genes showed significant mutations. Only a few of the genes showed higher amplifications. To derive an association between genetic alterations and HNSCC, markers found in this study screened in specific populations. This will pave the way for upcoming research in pathogenesis, early diagnosis and therapy. Further experimental confirmation is required for the results to confirm the correlation factor.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline Patient's consent and ethical approval has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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