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ORIGINAL ARTICLE

Identification of Single-nucleotide Alterations in MAP3K8 Gene in a Turkish Head and Neck Squamous Cell Carcinoma Patient Group

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OBJECTIVE

The MAP3K8 protooncogene participates in the MEK-1, MKK-6, SAPK, NFAT, and NF-kB signaling pathways. HNSCC was shown to have overexpressed the MAP3K8 gene and chromosomal duplications; however, to the best of our knowledge, no study has linked MAP3K8 SNPs to HNSCC susceptibility in the Turkish population. In this study, it was aimed to determine whether single-nucleotide changes in the MAP3K8 gene are risk factors in the Turkish HNSCC patient group.

METHODS

Sixty-one HNSCC patients and 30 healthy volunteers from Türkiye were included in this study. Genomic DNA isolation was performed from peripheral blood samples. The MAP3K8 chromosome gene region 10:30451254-30451972 was amplified by PCR reaction and sequencing was carried out by Sanger sequencing protocol.

RESULTS

In the chromosome 10:30451254-30451972 region of MAP3K8 gene, 203 SNP codes were scanned. Among them, rs303426 polymorphism was found as statistically significant between HNSCC patient and control group. The results indicated that people who carry A allele either as being homozygote or heterozygote have more risk in developing HNSCC.

CONCLUSION

MAP3K8 mutations are extremely rare in HNSCC. The results of this study may be important by showing the relationship between this rare MAP3K8 SNP with the risk of HNSCC in Turkish patient group.

Keywords: HNSCC; MAP3K8 gene; polymorphism; Turkish patient group.

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INTRODUCTION

Squamous cell carcinoma (SCC) is a common type of head and neck cancer, corresponding to approximately 90% of cases.[1] Alterations in the genomic DNA structure are the main reason for developing head and neck squamous cell carcinoma (HNSCC) and various chromosomal aberrations and/or mutations in proto-oncogenes are responsible for disease development.[2]

High-throughput approaches have been used in a variety of studies to examine the genomic landscape of HNSCC. These studies have revealed substantial single-nucleotide polymorphisms and copy number changes in some genes including DKN2A, NOTCH1, PIK3CA, FAT1, HRAS, CASP8, and PTEN.[3,4] Since HNSCC carcinogenesis involves different pathways; the identification of genetic variations in important signaling pathways could help disease susceptibility, and also personal differences in terms of treatment response and prognosis.[5]

MAP3K8 (COT or TPL-2) is one of the MAP3Ks identified in mammals. The MAP3K8 protooncogene is a member of serine/threonine protein kinase family and is involved in MEK-1, MKK-6, SAPK, NFAT, and NF-kB signaling pathways.[6,7] Mutations and overexpression of the MAP3K8 gene have been shown to play a role in various types of cancer, including thymoma, lymphoma, breast, prostate, papillary thyroid cancer, Hodgkin's disease, and nasopharyngeal carcinoma.[8–13] In head and neck cancer, it was shown that MAP3K8 gene expression is upregulated in the erlotinib-resistant SCC-25 cell line compared to the drug-sensitive version.[14] In addition, it was noted that in HNSCC lymphatic metastasis, there were duplications in the 10p11–22 chromosome region where the MAP3K8 gene is located, compared to primary tumor cells.[15]

The most prevalent type of genetic variation is single-nucleotide polymorphism (SNP), which makes it a perfect genetic susceptibility marker.[16] Therefore, the evaluation of MAP3K8 polymorphisms that may cause the development of HNSCC may be important in the early diagnosis and prognosis of the disease. MAP3K8 gene overexpression and duplications in the chromosomal region were shown in HNSCC; however, up to our knowledge, there are no report which shows the relationship between MAP3K8 SNPs and the susceptibility of HNSCC in Turkish population. In the present study, we aimed to screen for single-nucleotide changes in chromosome 10:30451254–30451972 region of MAP3K8 gene in a Turkish head and neck cancer patient group. This region includes exon 6; thus, an alteration in this region may affect the proper functioning of the kinase protein.

MATERIALS AND METHODS

Study Groups and DNA Isolation

Sixty-one unrelated Turkish HNSCC patients, clinically diagnosed at Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Otorhinolaryngology and 30 unrelated healthy volunteers from different geographic regions of Türkiye, were included in this study. Control group was selected to match the patients in terms of demographic data including age and gender. All individuals in the study groups gave informed consent and approval of the Local Ethics Committee was obtained from Dışkapı Yıldırım Beyazıt Training and Research Hospital (November 12, 2018, #56/22). The study was conducted in accordance with guidelines of the Declaration of Helsinki. Clinicopathological parameters of HNSCC patients and control groups are shown in Table 1.

Genomic DNA isolation was performed with QIAamp® DNA Blood Kit (Qiagen, Germany) by taking 3–4 mL of peripheral blood samples from both patient and control groups into EDTA-K3 containing tubes. The purity and concentration of the DNA samples were determined by spectrophotometric analyses at 260/280 nm (AlphaSpec™ µL Spectrophotometer/ Alpha Innotech Corp.).

Table 1 Clinicopathological parameters of HNSCC patients and control groups

	Control group (n=30)	Patient group (n=61)
Gender		
Male	25	51
Female	5	10
Age, median (range)	57 (40–73)	60 (42–79)
Tumor type	–	Larynx (40) Tongue (5) Hypopharynx (4) Buccal (3) Lip (3) Auricular (1) Oral (2) Paranasal sinus (1) Nasopharynx (1) Parotis (1)
Tumor stage	–	T1: 11 T2: 16 T3: 27 T4: 7

HNSCC: Head and neck squamous cell carcinoma

Genotyping

The MAP3K8 chromosome gene region 10:30451254–30451972 was amplified by polymerase chain reaction (PCR) method using specific primers. Amplification of chromosome 10:30451254–30451972 region of MAP3K8 was carried out on a ThermoPCR system in a 50 µl reaction mixture Easytag (TransGen Biotech, China) containing 10 pmol of forward (5'-AGTGGCACAACTTTCACTGG-3') and reverse (5'-TTCCCCTTCTTTGTCCTTCGT-3') primers and 50 ng DNA. The PCR cycling conditions consisted of an initial denaturation step at 95°C for 5 min, followed by 35 cycles of 94°C for 1 min, 59°C for 1 min, 72°C for 1 min, and final extension step at 72°C for 5 min.

PCR products (556 bp) were visualized by agarose gel electrophoresis using an imaging system (BioRAD). PCR products were purified and sequencing was carried out by Sanger sequencing protocol of BM Laboratory Systems, Türkiye. Sequences were analysed by MITOMAP and compared with MAP3K8 NCBI reference sequences. SNP codes scanned in the chromosome 10:30451254–30451972 region were rs1165786690, rs992106145, rs1428294268, rs916397740, rs969226709, rs1389767633, rs1310273711, rs1588784059, rs1588784070, rs1588784076, rs1588784084, rs1588784091, rs528684092, rs1588784084, rs1588784091, rs528684092, rs1476531728, rs1460272230, rs750643003, rs1198270171, rs199659350, rs303426, rs1269607437, rs561885103, rs1047055406, rs762978091, rs1273420722, rs938490212, rs1056914097, rs912586791, rs1269607437, rs561885103, rs1047055406, rs762978091, rs1273420722, rs938490212, rs1056914097, rs912586791, rs944289256, rs1039952018, rs1441905915, rs886298297, rs899982207, rs944289256, rs1039952018, rs1441905915, rs886298297, rs899982207, rs1004746048, rs1011707949, rs112402171, rs1043419351, rs903602091, rs1004746048, rs1011707949, rs112402171, rs1043419351, rs903602091, rs1305549502, rs1408363348, rs1370298679, rs770580895, rs1375013768, rs1305549502, rs1408363348, rs1370298679, rs770580895, rs1375013768, rs1223867729, rs371032502, rs1408267915, rs1470229486, rs112249809, rs748215392, rs1356919636, rs145319860, rs773454053, rs763277014, rs533325307, rs774511606, rs1588784392, rs371032502, rs1408267915, rs1470229486, rs112249809, rs748215392, rs1356919636, rs145319860, rs773454053, rs763277014, rs533325307, rs774511606, rs1588784392, rs1373499805, rs760131672, rs1324968516, rs1200373560, rs768122949, rs776345267, rs1216536649, rs761372768, rs1588784392, rs1373499805, rs760131672, rs1324968516, rs1200373560, rs768122949, rs776345267, rs1216536649, rs761372768, rs764843243, rs1191283360, rs1431157160, rs1294907660, rs764843243, rs1191283360, rs1431157160, rs1294907660, rs1204969252, rs750107886, rs1029129071, rs954461874, rs960674093, rs1204969252, rs750107886, rs1029129071, rs954461874, rs960674093, rs373977741, rs1564370920, rs139293295, rs766203908, rs751299982, rs1019779505, rs1397742363, rs1305400973, rs754968500, rs373977741, rs1564370920, rs139293295, rs766203908, rs751299982, rs1019779505, rs1397742363, rs1305400973, rs754968500, rs1350423859, rs781104573, rs779977265, rs748268594, rs1357627827, rs1350423859, rs781104573, rs779977265, rs748268594, rs1357627827, rs867629514, rs1285357490, rs552197626, rs1415074739, rs1269803880, rs374471102, rs1157068245, rs867629514, rs1285357490, rs756197619, rs552197626, rs1415074739, rs1269803880, rs374471102, rs1157068245, rs1197852938, rs1375880577, rs1471537566, rs1471108707, rs1158768197, rs1411155958, rs919792786, rs1471072981, rs1471246335, rs1209036466, rs989465189, rs149199668, rs1197852938, rs1375880577, rs1471537566, rs1471108707, rs1158768197, rs1411155958, rs919792786, rs1471072981, rs1471246335, rs1209036466, rs989465189, rs149199668, rs190602161, rs561019825, rs534855846, rs944056598, rs980139999, rs1377479761, rs73247425, and rs1419173388.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 16.0 software was used for statistical analysis. The frequencies of MAPK8 rs303426 SNP alleles and genotypes were obtained by direct count and departure from the Hardy–Weinberg equilibrium was evaluated by Chi square analysis. p value smaller than 0.05 was considered as statistically significant. Odd ratios (OR) and 95% confidence intervals (CI) were also calculated.

RESULTS

In the chromosome 10:30451254–30451972 region of MAP3K8 gene, 203 SNP codes were scanned. Among them, the results indicated that the genotype frequencies of MAP3K8 polymorphism (rs303426) were statistically significant between HNSCC patient and control group. This polymorphism results in substitution of an adenine nucleotide instead of guanine. Figure 1 shows the electropherograms representing homozygote wild, heterozygote, and homozygote rare genotypes.

MAP3K8 gene polymorphism (rs303426) in HNSCC patients and control group subjects is listed in Table 2. Among the HNSCC patients, 21% were found to

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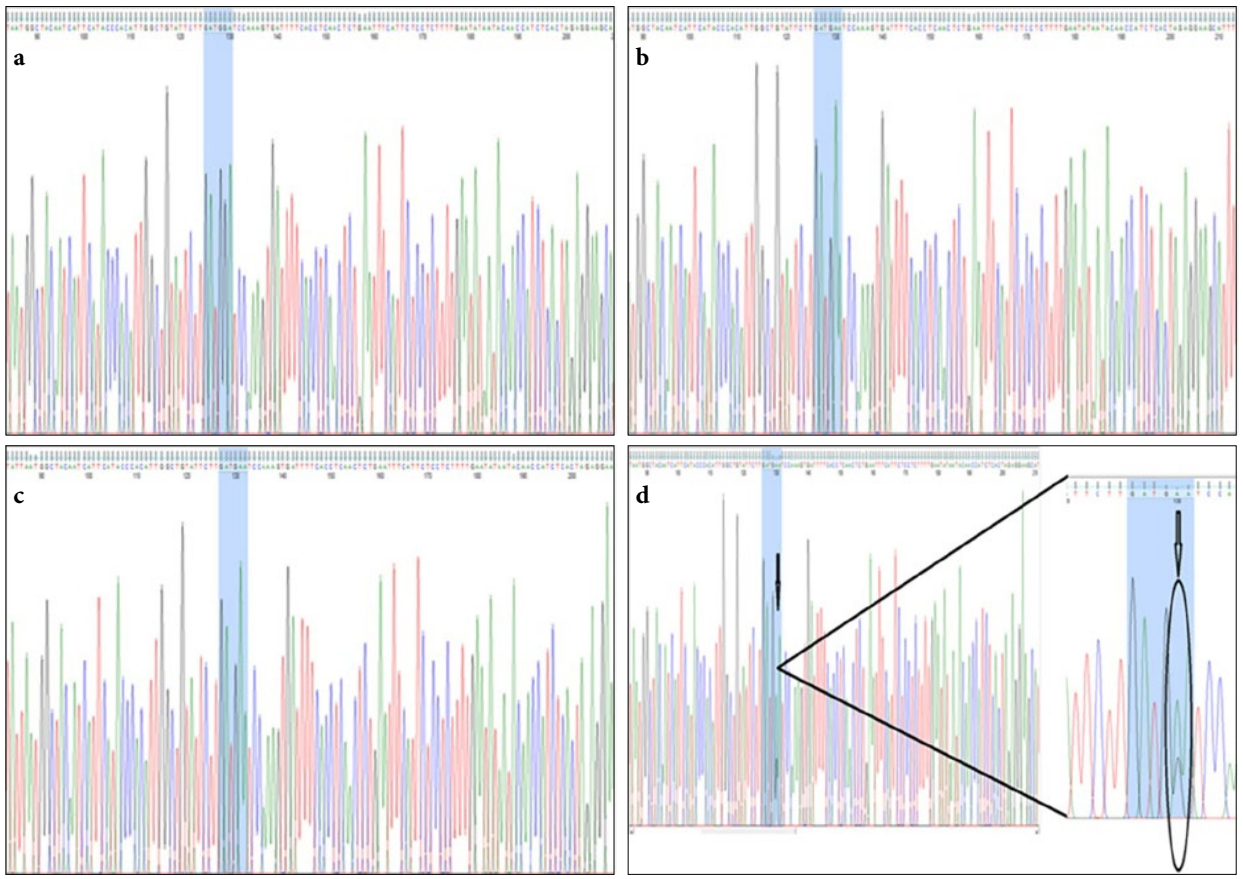

Fig. 1. Electropherograms from (a) a control, (b) a HNSCC patient with homozygote wild genotype (GG); (c) a HNSCC patient with homozygote rare genotype (AA); (d) a HNSCC patient with heterozygote genotype (GA).
HNSCC: Head and neck squamous cell carcinoma; GG: Homozygote wild genotype; AA: Homozygote rare genotype; GA: Heterozygote genotype.

be homozygote for wild (GG) type, 56% were heterozygote (GA), and 23% were homozygote rare (AA) type. On the other hand, these ratios were as 43%, 27% and 30% for GG, GA and AA genotypes in control group, respectively. The results indicate that the genotype frequencies of MAP3K8 polymorphism were statistically significant between the cancer cases and control group ($p<0.05$). In addition, we performed an analysis of carrying A allele on the risk of developing HNSCC (Table 3). The results indicated that people who carry A allele either as being homozygote (A/A) (OR 2,824; 95% CI 1,095–7,280) or heterozygote (G/A) (OR 4,25; 95% CI 1,432–12,618) have more risk in developing HNSCC compared to homozygote G/G genotype.

DISCUSSION

Identification of the molecular mechanisms for the development of HNSCC is necessary not only for understanding the pathogenesis of the disease but also for improving early detection and therapeutic biomarkers. Consequently, it is vital to determine a non-invasive method for the prediction of the early disease.

MAPK pathway mutations affect one-fifth of HNSCC cases.[17] MAPK signalling pathway leads to activation of MEK/ERK and it has a central role in regulating cell survival in different types of cancers. MEK/ERK is the major signalling pathway downstream of MAP3K8 and MEK is a direct substrate for MAP3 kinases including MAP3K8.[18] Therefore, alterations in the genomic sequence of MAP3K8 gene can be related to the disease outcome. However, genetic sequence analyses showed that MAP3K8 mutation is very rare, eventhough there are altered expression levels and abnormal activation in human cancers.[19–21]

Altered expression levels of MAP3K8 in tumor development are highly contraversial.[13] In some of the studies,[19,21] overexpression of MAP3K8 is associ-

Table 2 Genotype frequencies of MAP3K8 rs303426 polymorphism in HNSCC patients and controls

Polymorphism	Observed frequency of Genotypes and Alleles		Predicted frequency by Hardy-Weinberg equilibrium		Allel Frequences	p
	n	%	n	%		
Control						0.024*
Homozigote genotype (GG)	13	43	9.63	29.19		
Heterozygote genotype (GA)	8	27	14.73	44.64		
Rare Homozygote genotype (AA)	9	30	5.63	17.06		
G allel	34	56.6	–	–	0.5667	
A allel	26	43.4	–	–	0.4333	
Patients						
Homozigote genotype (GG)	13	21	14.75	24.18		
Heterozygote genotype (GA)	34	56	30.49	49.99		
Rare Homozygote genotype (AA)	14	23	15.75	25.82		
G allel	60	49.18	–	–	0.4918	
A allel	62	50.82	–	–	0.5082	
Total						
Homozigote genotype (GG)	26	29	24.27	26.67		
Heterozygote genotype (GA)	42	46	45.45	49.95		
Rare Homozygote genotype (AA)	23	25	21.27	23.37		
G allel	94	51.64	–	–	0.5165	
A allel	88	48.36	–	–	0.4835	

*: p<0.05. The allele frequencies in all subjects were consistent with Hardy-Weinberg equilibrium (p<0.05). HNSCC: Head and neck squamous cell carcinoma; GG: Homozygote wild genotype; GA: Heterozygote genotype; AA: Homozygote rare genotype

Table 3 Risk analysis of allele frequencies between HNSCC patients and controls

Gene	Allele and genotype	OR (95% CI) p				Total
		Allele	GA	GG	AA	
MAP3K8 rs303426	G/A GG/GA/AA	1.351 (0.726–2.517) 0.342	4.25 (1.432–12.618) 0.00726*	1.556 (0.499–4.848) 0.44521	2.824 (1.095–7.280) 0.0288*	OD: (1.272) 0.359

*p value <0.05 is considered significant, %95 CI that did not include unity is statiscally significant. HNSCC: Head and neck squamous cell carcinoma; OR: Odds ratio; CI: Confidence interval; GA: Heterozygote genotype; GG: Homozygote wild genotype; AA: Homozygote rare genotype; G/A: G allele/A allele

ated with increased tumorigenesis and poor prognosis, whereas there are other studies [22,23] which show that reduced MAP3K8 expression is related to poor prognosis and tumor aggressiveness. Jeong et al.,[13] showed that MAP3K8 is upregulated in androjen depletion-independent (ADI) prostate cancer and plays a critical role in the promotion of disease progression. MAP3K8 expression is also upregulated in human breast cancer and ovarian carcinoma.[10,24] On the other hand, reduced MAP3K8 expression was found as related to tumor aggressiveness in non-small cell lung cancer.[22] MAP3K8 has a complicated role in cancer, and it is probable that each cancer type has its own set of biomarkers and genetic background.

Several DNA sequence alterations were identified in HNSCC upto now. These include frequent mutations in several genes such as TP53, EGFR, CCND1, NOTCH1, MET, and PIK3CA.[3,4] However, MAP3K8 mutations are extremely rare in cancer with respect to BRAF or its upstream regulator KRAS.[25] Clark et al.,[26] identified an activating mutation of human MAP3K8 occuring in lung cancer. The frequency of MAP3K8 gene

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alterations and their relationship with the progression of HNSCC has not been clearly demonstrated yet. In the present study, we have identified a SNP (rs303426) which is related to HNSCC development in a Turkish patient group. The results indicated that people who carry A allele either being homozygote (A/A) or heterozygote (G/A) have more risk in developing the disease.

Although somatic mtDNA alterations are the main targets in the diagnosis and prognosis of different cancers because they are only present in tumor tissue, the difficulties in handling the conventional mode of cancer diagnostics have required a shift into finding new areas that explore biomarkers that are less or non-invasive with readily available samples such as blood, urine, and saliva. [27] In this study, we have concentrated on germline MAP3K8 SNPs that may be connected to the emergence of HNSCC in a Turkish patient population. The significance of testing blood samples from HNSCC patients for germline mutations is to find a potential marker utilizing a less invasive technique instead of using biopsy samples.

Limitations of the Study

Our study still has some limitations. The patient and control numbers should be increased, and also, haplotype analysis linking to MAP3K8 expression level in both blood samples and tumor tissues is rather necessary.

CONCLUSION

The results of this study may be important since to the best of our knowledge, there is no study in the literature showing the relationship between this rare MAP3K8 SNP with the risk of HNSCC. According to our data, carrying A allele for rs303426 polymorphism of MAP3K8 gene could be a potential marker for early detection of the disease.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (no: 56/22, date: 12/11/2018).

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