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Gene Expression Profiling of *URGCP* and *NTRK1-3*/MAPK Pathway Genes in Soft Tissue Sarcomas

Zeliha Akdağ,[1] Ferda Bir,[2] Emel Kılıçarslan,[2] Lale Şatıroğlu Tufan,[3] Yavuz Dodurga[1]

[1]Department of Medical Biology, Pamukkale University, Faculty of Medicine, Denizli, Türkiye
[2]Division of Medical Pathology, Department of Surgical Sciences, Pamukkale University, Faculty of Medicine, Denizli, Türkiye
[3]Department of Forensic Medicine, Forensic Genetics Lab, Ankara University, Faculty of Medicine, Ankara, Türkiye

ABSTRACT

Objective: Sarcoma is a heterogeneous malignant cancer of mesenchymal origin, and approximately 80% of cases are soft tissue sarcomas (STSs). *NTRK* genes play roles in nerve cell development, while the MAPK signaling pathway contributes to tumor cell migration, invasion, and metastasis. *URGCP* is an oncogene involved in tumor development in many cancers; however, its role and molecular mechanism in STS remain unknown. This study aimed to investigate the expression and correlations of the *NTRK1*, *NTRK2*, and *NTRK3* genes, MAPK signaling pathway genes, and the *URGCP* oncogene in STS subtypes.

Materials and Methods: RNA was isolated from formalin-fixed, paraffin-embedded (FFPE) tissue samples obtained from 80 patients with STS. The expression levels of *NTRK1*, *NTRK2*, *NTRK3*, *MEK1*, *MEK2*, *ERK1*, and the *URGCP* oncogene were analyzed using quantitative real-time PCR (qPCR). Correlations among these genes and their associations with STS were evaluated.

Results: The analyses did not reveal statistically significant correlations between *NTRK* genes and genes involved in the MAPK signaling pathway. In addition, no statistically significant association was observed between *URGCP* expression and STS.

Conclusion: This study demonstrates for the first time the association of *URGCP* with soft tissue sarcoma and reveals a link between *NTRK* genes and the MAPK signaling pathway in STS.

Keywords: MAPK signaling pathway, *NTRK1*, *NTRK2*, *NTRK3*, sarcoma, soft tissue sarcoma, *URGCP*.

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Address for correspondence:
Yavuz Dodurga.
Department of Medical Biology, Pamukkale University, Faculty of Medicine, Denizli, Türkiye
Phone: +90 505 713 09 49
E-mail: ydodurga@pau.edu.tr

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INTRODUCTION

Sarcoma is a rare type of cancer of mesenchymal origin, accounting for approximately 1% of all malignant cancers and arising in connective tissues such as bone, muscle, and adipose tissue. It has more than 100 subtypes, 20% of which originate from bone and 80% from soft tissue.[1–4] Soft tissue sarcomas (STSs) are malignant tumors of mesenchymal origin comprising numerous histological subtypes, particularly those arising from connective tissue, and account for only 1% of all malignant cancers.[2,4] In our study, 12 subtypes of soft tissue sarcoma were investigated.

Malignant peripheral nerve sheath tumors (MPNSTs) constitute approximately 10% of all soft tissue tumors and have a high tendency to metastasis.[5–7] Inflammatory myofibroblastic tumor is a very rare tumor of intermediate grade because of its low recurrence risk and metastatic potential.[8,9] Dedifferentiated liposarcoma is the most heterogeneous of all sarcomas, with a wide variety of histological patterns. It is a high-grade and aggressive disease, and high rates of local and metastatic recurrence are associated with very high mortality.[10,11] Myxofibrosarcoma is a mesenchymal fibrous soft tissue sarcoma that can range from low to high grade, typically occurs in the extremities of older individuals, and is characterized by a high local recurrence rate, with metastases predominantly involving the lungs and bones.[12–14] Leiomyosarcoma is one of the most common subtypes, accounting for approximately 20% of soft tissue sarcoma cases. It has substantial intrinsic aggressiveness and is one of the sarcoma subtypes with the highest risk of distant recurrence and reduced disease-specific survival.[15,16] Synovial sarcoma is the best-defined "translocation-associated sarcoma," characterized by the presence of a translocation involving the SS18 gene on chromosome 18 and one of several synovial sarcoma X genes on chromosome X. It is a high-grade sarcoma with an aggressive course and a high potential for early metastasis.[17,18] Undifferentiated pleomorphic sarcoma is one of the most common soft tissue sarcomas. It is a high-grade, aggressive sarcoma previously known as malignant fibrous histiocytoma.[19] Fibrosarcoma is a malignant neoplasm consisting of fibroblasts that may exhibit varying amounts of collagen production and a "herringbone" architecture. It is a rare, highly malignant tumor of mesenchymal cell origin.[20] Fibromatosis does not metastasize; however, particularly deep-seated lesions exhibit a destructive growth pattern by infiltrating the surrounding soft tissues.[21] Extraskeletal mesenchymal chondrosarcoma is a rare malignant soft tissue tumor of chondroprogenitor cell origin. It is a high-grade malignancy with a high tendency for distant metastasis.[22] Myofibroblastic sarcoma is a rare tumor composed of malignant myofibroblasts. In addition to having a high recurrence potential, metastasis is less common.[23]

In particular, many chromosomal translocations are associated with malignant diseases.[24] Neurotrophic tropomyosin receptor kinases (NTRKs), arising from gene fusions belonging to the tropomyosin receptor kinase (TRK) family, are important factors in the development and differentiation of neural cells, as well as in maintaining neuronal homeostasis and regulating synapse formation and plasticity.[25,26]

Mitogen-activated protein kinases (MAPKs), which comprise multiple modules, constitute one of the most highly conserved signaling pathways and have functions in cell proliferation, apoptosis, tumor growth, metastasis, and drug resistance.[27,28]

KEY MESSAGES

- This study evaluated the expression of NTRK1/2/3, MAPK pathway genes (MEK1, MEK2, ERK1), and URGCP in soft tissue sarcoma (STS) subtypes.
- No statistically significant correlations were identified between NTRK genes and MAPK signaling components, and no molecular link suggesting MAPK pathway activation in STS could be demonstrated based on the present data.
- No statistically significant association was observed between URGCP expression and STS; therefore, no definitive evidence of its oncogenic relevance in soft tissue sarcoma could be established in this study.

Previous studies have revealed that ERK/MAPK, the most extensively studied signaling pathway, is more effective in proliferation and differentiation.[29–31]

Cell proliferation upregulated gene 4 (*URGCP*/*URG4*), an oncogene, was identified by Dodurga et al.[32] as a novel gene induced by the X antigen encoded by hepatitis B virus. *URGCP* is located on chromosome 7 (7p13) and promotes cell proliferation through signaling pathways such as MAPK. It is involved in tumor development and formation in many cancer types, including hepatocellular carcinoma, osteosarcoma, and glioblastoma. Previous studies have shown that patients with high *URGCP* expression have shorter survival. Although *URGCP* is known to contribute to tumor formation by interacting with various signaling pathways, its effect on soft tissue sarcomas and its molecular mechanism remain unknown.[33]

The present study aimed to investigate the mRNA expression levels of the *NTRK1*, *NTRK2*, *NTRK3*, *MEK1*, *MEK2*, *ERK1*, and *URGCP* genes in formalin-fixed, paraffin-embedded sarcoma tissue samples using quantitative real-time PCR. Furthermore, the study sought to evaluate the potential associations between the expression profiles of these genes and the clinicopathological characteristics of sarcoma cases, thereby providing insight into the molecular mechanisms underlying sarcoma development and progression.

MATERIALS AND METHODS

Collection of Study Samples

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (Approval Number: 01, Date: 10.01.2023). A total of 80 cases diagnosed with sarcoma at the Pamukkale University Department of Pathology and archived as

formalin-fixed, paraffin-embedded (FFPE) tissue blocks were included in the study. In addition, five non-tumoral FFPE tissue samples were included as a control group and used as the reference group for gene expression normalization analyses. Patients aged 18–70 years with a histopathologically confirmed diagnosis of soft tissue sarcoma were included in the study. Due to the rarity of this tumor group, strict exclusion criteria were not extensively applied to ensure an adequate sample size. Tissue samples (FFPEs) embedded in paraffin blocks and fixed with 10% formaldehyde solution were used in the study. H&E-stained and different types of immunohistochemically stained sections from all cases were re-evaluated for diagnostic and prognostic parameters. The sections that best represented the tumor tissue and contained the least necrosis, hemorrhage, inflammatory cells, and stromal elements were selected. For RNA isolation from the paraffin blocks of these sections, consecutive serial sections were cut at a thickness of 20 µm using a microtome (Leica RM2125RT, Germany).

Total RNA Isolation, cDNA Synthesis, and mRNA Expression Detection by Real-Time PCR Assay

Prior to RNA isolation, FFPE sections were deparaffinized using xylene followed by ethanol washing, as recommended in the Qiagen miRNeasy FFPE Kit protocol. The Qiagen miRNeasy FFPE Kit (Cat. No. 217504) was used for total RNA isolation from paraffin-embedded samples. RNA isolation was performed by deparaffinization followed by spin-column purification according to the kit protocol. The concentration of the isolated RNA was determined, and all RNA samples were adjusted to 380 ng/µL to ensure standardization before cDNA synthesis. cDNA synthesis was performed using the WIZScript™ cDNA Synthesis Kit (REF: W2211) according to the procedure specified by the manufacturer. The mRNA expression changes of seven genes, including *NTRK1*, *NTRK2*, *NTRK3*, *MEK1*, *MEK2*, *ERK1*, and *URGCP*, were determined. GAPDH was used as the housekeeping gene for normalization. The reverse and forward sequences of the genes are given in Table 1. Reactions were prepared using SYBR® Green Master Mix and the Sugenomics qPCR SybrMaster Kit (Catalog No. PCR01C263), and quantitative real-time PCR was performed using a Qiagen Rotor-Gene device.

Statistical Analysis

mRNA expression levels were quantified using the $2^{-\Delta\Delta Ct}$ method. Relative gene expression analyses were performed using the RT^2 Profiler™ PCR Array Data Analysis software (Qiagen). (https://www.qiagen.com/tr/shop/genes-and-pathways/data-analysis-centeroverview-page/) Each qPCR reaction was performed in technical triplicate, and the mean Ct value was used for subsequent analyses. Patient demographic and clinicopathological characteristics were summarized using descriptive statistics. Categorical variables were presented as frequencies and percentages. Data are presented as fold-change values calculated using the $2^{-\Delta\Delta Ct}$ method. p-values >0.05 indicate no statistical significance. N/A: not applicable (statistical analysis could not be performed due to insufficient sample size in some subgroups).

Table 1. Forward and reverse primer sequences of the genes used in the study

Gene name	Gene sequence
*MEK1*_F	5′-GGTGTTCAAGGTCTCCCACAAG-3′
*MEK1*_R	5′-CACGATGTACGGCGAGTTGCAT-3′
*MEK2*_F	5′-GTGGTCACCAAAGTCCAGCACA-3′
*MEK2*_R	5′-CCACGATGTACGGAGAGTTGCA-3′
*ERK1*_F	5′-TGGCAAGCACTACCTGGATCAG-3′
*ERK1*_R	5′-GCAGAGACTGTAGGTAGTTTCGG-3′
*URGCP*_F	5′-CTTCATCCTGAGTCCCTACCG-3′
*URGCP*_R	5′-GCCGTTCTGCTGCATTCG-3′
*NTRK1*_F	5′-CACTAACAGCACATCTGGAGACC-3′
*NTRK1*_R	5′-TGAGCACAAGGAGCAGCGTAGA-3′
*NTRK2*_F	5′-ACAGTCAGCTCAAGCCAGACAC-3′
*NTRK2*_R	5′-GTCCTGCTCAGGACAGAGGTTA-3′
*NTRK3*_F	5′-CCGACACTGTGGTCATTGGCAT-3′
*NTRK3*_R	5′-CAGTTCTCGCTTCAGCACGATG-3′
*GAPDH*_F	5′-GTCTCCTCTGACTTCAACAGCG-3′
*GAPDH*_R	5′-ACCACCCTGTTGCTGTAGCCAA-3′

RESULTS

The subtype data of the Sarcoma Patient Group were obtained from 80 paraffin-embedded block samples diagnosed as different types of "SARCOMA" by the Pamukkale University Department of Pathology and retained as archived material in paraffin blocks. Among 80 patients with soft tissue sarcoma, 12 different subtypes were identified in FFPE tissue samples. The subtypes and patient numbers are given in Table 2. In addition, a scatter plot is shown in Figure 1.

Of the 80 patient samples, 8 were malignant peripheral nerve sheath sarcoma (MPNSTs), 7 were dedifferentiated liposarcoma (DDLS), 9 were synovial sarcoma (SS), 7 were fibrosarcoma, 8 were undifferentiated pleomorphic sarcoma (UPS), 12 were inflammatory myofibroblastic tumor (IMT), 10 were myxofibrosarcoma (MFS), including low grade myxofibrosarcoma (2/10), 2 were extraskeletal mesenchymal chondrosarcoma, 1 was fibromatosis, 14 were leiomyosarcoma (LMS), 2 were myofibroblastic sarcoma.

When the distribution of patients with STS according to sex was analyzed, 57% (n=46) of the patients were male and 43% (n=34) were female (Fig. 2). Most of the patients were between the ages of 50–59 and 60–69 years (Fig. 2, 3).

mRNA Expression Changes in the Sarcoma Patient Group

The mRNA expression changes of seven genes in total, including *NTRK1*, *NTRK2*, *NTRK3*, *MEK1*, *MEK2*, *ERK1*, and the *URGCP* oncogene, which are downstream genes of the MAPK signaling pathway, were detected using real-time PCR. Gene expression changes among patients were evaluated using Ct (threshold cycle) values determined from the patient groups as a result of PCR reactions. *GAPDH* was used as the housekeeping gene for normalization purposes.

Expression changes were determined as shown in Table 3. Fold increases in the mRNA expression of the genes and p values obtained as a result of statistical evaluation are shown in Table 3.

According to our results, *NTRK1*, *NTRK2*, and *NTRK3* gene expression was significantly increased in some soft tissue sarcoma patient groups. In synovial sarcoma, NTRK1 expression increased 8.85-fold, *NTRK2* expression increased 3.07-fold, and *NTRK3* expression increased 7.11-fold; in fibrosarcoma, *NTRK1* expression increased 10.15-fold and *NTRK3* expression increased 7.86-fold; in undifferentiated pleomorphic sarcoma, *NTRK2* expression increased 4.40-fold; in inflammatory myofibroblastic sarcoma, *NTRK2* expression increased 2.26-fold;

Table 2. Soft tissue sarcoma subtypes and number of patients

Soft tissue sarcoma subtype	Number of patients
Malignant peripheral nerve sheath tumor (MPNST)	8
Dedifferentiated liposarcoma (DDLS)	7
Synovial sarcoma (SS)	9
Fibrosarcoma	7
Undifferentiated pleomorphic sarcoma (UPS)	8
Inflammatory myofibroblastic tumor (IMT)	12
Myxofibrosarcoma (MFS)	8
Extraskeletal mesenchymal chondrosarcoma	2
Fibromatosis	1
Leiomyosarcoma (LMS)	14
Myofibrosarcoma	2
Low-grade myxofibrosarcoma	2

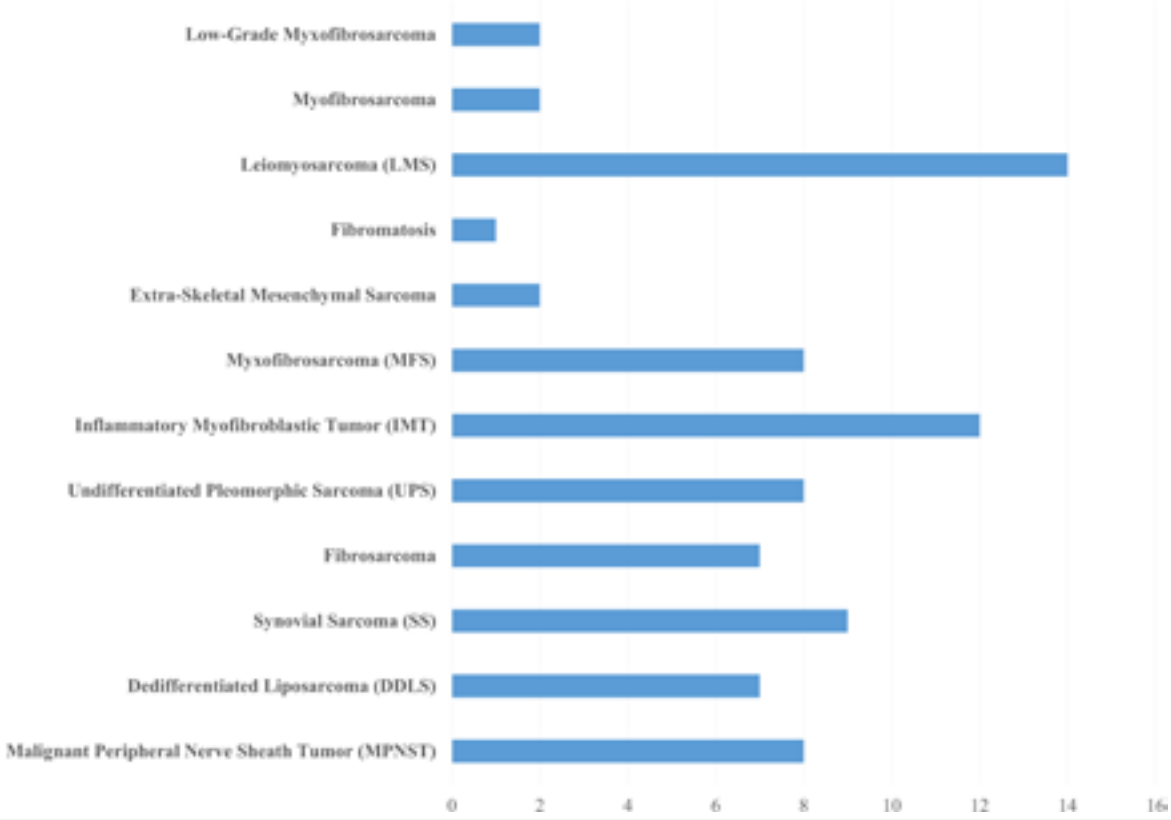

Figure 1. Distribution of soft tissue sarcoma subtypes.

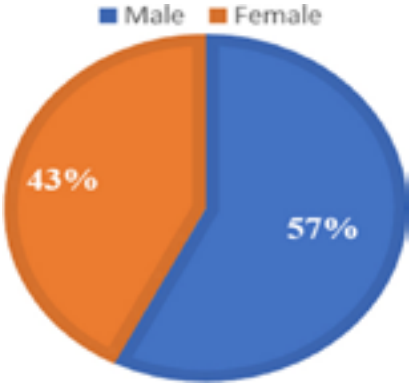

Figure 2. Distribution of soft tissue sarcoma cases according to sex.

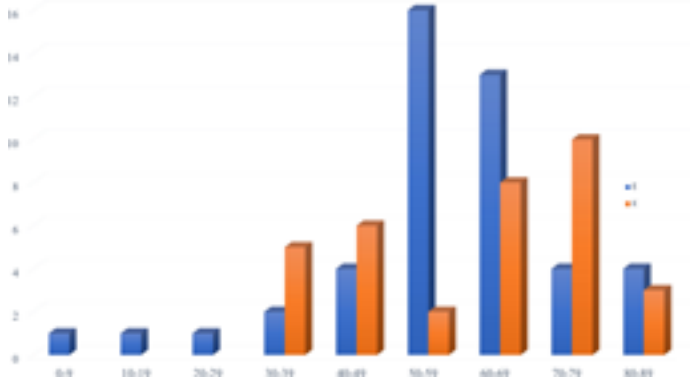

Figure 3. Age and sex distribution of soft tissue sarcoma cases.

in myxofibrosarcoma, *NTRK2* expression increased 7.47-fold; in extraskeletal mesenchymal chondrosarcoma, *NTRK2* expression increased 3.35-fold; in fibromatosis, *NTRK2* expression increased 199.81-fold and *NTRK3* expression increased 14.07-fold; and in leiomyosarcoma, *NTRK2* expression increased 3.58-fold. A trend toward increased mRNA expression of *NTRK1*, *NTRK2*, and *NTRK3* was observed; however, the differences were not statistically significant (p>0.05). In the groups diagnosed with extraskeletal mesenchymal chondrosarcoma, fibromatosis, myofibroblastic sarcoma, and low-grade myxofibrosarcoma, p values were not provided because the number of patients was less than 3. In addition, in malignant peripheral nerve sheath sarcoma, *NTRK1* expression decreased 10.94-fold, *NTRK2* expression decreased 10.61-fold, and *NTRK3* expression decreased 6.06-fold; in undifferentiated pleomorphic sarcoma, *NTRK1* expression decreased 3.22-fold and *NTRK3* expression decreased 3.36-fold; in inflammatory myofibroblastic sarcoma, *NTRK1* expression decreased 9.44-fold and *NTRK3* expression decreased 7.16-fold; in myxofibrosarcoma, *NTRK1* expression decreased 2.30-fold and *NTRK3* expression decreased 2.33-fold; in extraskeletal mesenchymal sarcoma, *NTRK1* expression decreased 4.65-fold and *NTRK3* expression decreased 5.50-fold; in fibromatosis, *NTRK1* expression decreased 32.84-fold; in leiomyosarcoma, *NTRK1* expression decreased 4.91-fold and *NTRK3* expression decreased 7.13-fold; in myofibroblastic sarcoma, *NTRK1* expression decreased 179.46-fold, *NTRK2* expression decreased 4.22-fold, and *NTRK3* expression decreased 95.34-fold; and in low-grade myxofibrosarcoma, *NTRK1* expression decreased 51.89-fold, *NTRK2* expression decreased 3.44-fold, and *NTRK3* expression decreased 35.38-fold. These decreases were not statistically significant (p>0.05). Since the number of patients in the groups diagnosed with extraskeletal mesenchymal chondrosarcoma, fibromatosis, myofibroblastic sarcoma, and low-grade myxofibrosarcoma was less than 3, no p value was provided.

When we evaluated the expression of *MEK1*, *MEK2*, and ERK1, genes involved in the MAPK signaling pathway that are thought to be related to soft tissue sarcomas, in our patient groups, *ERK1* expression was found to be 3.32-fold higher in dedifferentiated liposarcoma and 3.32-fold higher in synovial sarcoma; in synovial sarcoma, *MEK1* expression increased 6.24-fold, *MEK2* expression increased 7.20-fold, and *ERK1* expression increased 25.77-fold; in fibrosarcoma, *MEK1* expression increased 8.85-fold, *MEK2* expression increased 11.62-fold, and *ERK1* expression increased 24.11-fold; and in fibromatosis, *MEK1* expression increased 16.00-fold, *MEK2* expression increased 16.34-fold, and *ERK1* expression increased 8.74-fold. However, none of these changes were statistically significant (p>0.05).

Regarding the mRNA expression changes of the *URGCP* gene, which is known as a novel oncogene, in soft tissue sarcoma patient groups, a 5.43-fold increase was observed in synovial sarcoma, a 9.09-fold increase in fibrosarcoma, and an 11.45-fold increase in fibromatosis; however, these changes were not statistically significant (p>0.05).

DISCUSSION

Soft tissue sarcoma is a rare cancer with a prevalence of approximately 1% among all malignant tumor types. Soft tissue sarcomas occur in various age groups but are more common in middle-aged patients. There are more than 100 subtypes, including those occurring in adults, young adults, and pediatric patients. The incidence of soft tissue sarcomas, from most to least common, is highest in the lower extremities, followed by the upper extremities, retroperitoneum, and head and neck.[2,33,34]

With the development of molecular diagnostic technologies for solid tumors, gene expression-based predictive approaches have increased considerably in recent years. The NTRK gene family is a biomarker that may be useful in the diagnosis and treatment of soft tissue sarcomas. The NTRK gene family

Table 3. mRNA expression changes in *NTRK1*, *NTRK2*, *NTRK3*, *MEK1*, *MEK2*, *ERK1*, and *URGCP* among soft tissue sarcoma subtypes

Soft tissue sarcoma subtype	Gene	Fold change	p	Soft tissue sarcoma subtype	Gene	Fold change	p
Malignant peripheral nerve sheath tumor	*NTRK1*	-10.94	0.281633	Myxofibrosarcoma	*NTRK1*	-2.30	0.206836
	NTRK2	-10.61	0.18192		*NTRK2*	7.47	0.605382
	NTRK3	-6.06	0.249364		*NTRK3*	-2.33	0.224951
	MEK1	-6.92	0.196281		*MEK1*	-3.95	0.199838
	MEK2	-3.66	0.683821		*MEK2*	-1.19	0.276038
	ERK1	-2.32	0.753324		*ERK1*	-1.38	0.504707
	URGCP	-6.94	0.34875		*URGCP*	-3.45	0.212101
Dedifferentiated liposarcoma	*NTRK1*	-1.42	0.333208	Extraskeletal mesenchymal chondrosarcoma	*NTRK1*	-4.65	N/A
	NTRK2	1.37	0.884828		*NTRK2*	3.35	N/A
	NTRK3	-1.28	0.397838		*NTRK3*	-5.50	N/A
	MEK1	-1.07	0.434377		*MEK1*	-7.29	N/A
	MEK2	-1.07	0.561547		*MEK2*	-3.10	N/A
	ERK1	3.32	0.500875		*ERK1*	-1.15	N/A
	URGCP	-1.19	0.397512		*URGCP*	-5.11	N/A
Synovial sarcoma	*NTRK1*	8.85	0.823855	Fibromatosis	*NTRK1*	-32.84	N/A
	NTRK2	3.07	0.676786		*NTRK2*	199.81	N/A
	NTRK3	7.11	0.872715		*NTRK3*	14.07	N/A
	MEK1	6.24	0.856598		*MEK1*	16.00	N/A
	MEK2	7.20	0.883655		*MEK2*	16.34	N/A
	ERK1	25.77	0.33401		*ERK1*	8.74	N/A
	URGCP	5.43	0.971169		*URGCP*	11.45	N/A
Fibrosarcoma	*NTRK1*	10.15	0.740549	Leiomyosarcoma	*NTRK1*	-4.91	N/A
	NTRK2	1.73	0.539956		*NTRK2*	3.58	N/A
	NTRK3	7.86	0.714319		*NTRK3*	-7.13	N/A
	MEK1	8.85	0.59401		*MEK1*	-5.14	N/A
	MEK2	11.62	0.523597		*MEK2*	-2.08	N/A
	ERK1	24.11	0.310417		*ERK1*	-5.35	N/A
	URGCP	9.09	0.673954		*URGCP*	-6.96	N/A
Undifferentiated pleomorphic sarcoma	*NTRK1*	-3.22	0.219797	Myofibroblastic sarcoma	*NTRK1*	-179.46	N/A
	NTRK2	4.40	0.623485		*NTRK2*	-4.22	N/A
	NTRK3	-3.36	0.257268		*NTRK3*	-95.34	N/A
	MEK1	-2.27	0.984675		*MEK1*	-47.18	N/A
	MEK2	-2.35	0.379809		*MEK2*	-36.63	N/A
	ERK1	-3.68	0.337059		*ERK1*	-61.71	N/A
	URGCP	-8.04	0.243411		*URGCP*	-104.51	N/A
Inflammatory myofibroblastic tumor	*NTRK1*	-9.44	0.100646	Low-grade myxofibrosarcoma	*NTRK1*	-51.89	N/A
	NTRK2	2.26	0.629345		*NTRK2*	-3.44	N/A
	NTRK3	-7.16	0.125581		*NTRK3*	-35.38	N/A
	MEK1	-13.09	0.095242		*MEK1*	-49.69	N/A
	MEK2	-4.21	0.152371		*MEK2*	-21.19	N/A
	ERK1	-3.49	0.450555		*ERK1*	-165.13	N/A
	URGCP	-11.95	0.10455		*URGCP*	-44.55	N/A

consists of three genes, *NTRK1*, *NTRK2*, and *NTRK3*. Each encodes a tropomyosin receptor kinase that interacts with downstream signaling pathways. They are important components of downstream signaling pathways involved in various processes such as cellular survival, differentiation, and growth.[26,35]

The MAPK signaling pathway is a signaling cascade that plays an important role in cell proliferation, apoptosis, and differentiation. Abnormal activation of the MAPK signaling pathway caused by various mechanisms, such as receptor tyrosine kinases and gene mutations, is involved in tumor formation and progression by contributing to processes such as cell growth, survival, invasion, and metastasis.[31,36]

Oncogenes are genes with important roles in apoptosis, proliferation, and the cell cycle. These genes, which play a role in carcinogenesis and cancer progression, are numerous, and increasing numbers of oncogenes are being discovered every year. One of these oncogenes is cell proliferation upregulated gene 4. The *URGCP* oncogene was first found to contribute to hepatocarcinogenesis. In later studies, it was found to be upregulated in cancer types such as gastric cancer and osteosarcoma. For this reason, the *URGCP* gene is likely to be an important molecular target for cancer treatment, considering its effects on cell cycle regulation.[32,37,38]

Song et al.[39] investigated the relationship between various fusion genes and the clinicopathological features of 242 cases of seven types of soft tissue tumors using one-step RT-PCR. The study included patients from 1999 to 2021. The samples included cases of rhabdomyosarcoma (RMS), synovial sarcoma (SS), pediatric peripheral primitive neuroectodermal tumor (pPNET), alveolar soft part sarcoma (ASPS), dermatofibrosarcoma protuberans (DFSP), myxoid liposarcoma (MLPS), and soft tissue angiofibroma (AFST). By examining the relationship between fusion gene status and clinicopathological parameters, they revealed that fusion gene status was associated with age and location but not with sex or tumor diameter. Similarly, in our study, we think that fusion genes could not be associated with sex and tumor diameter but may be associated with age. In particular, an increased frequency was observed in patients aged 30 years and older.

NTRK fusions can be found in many different tumors, and on a molecular basis, *NTRK3* is the most common, followed by *NTRK1* and *NTRK2* expression. In a study by Siozopoulou et al.,[40] 70 FFPE-fixed soft tissue and bone tumor cases were evaluated. As a result of the study, the rate of sarcomas with expression was determined to be approximately 2.8% of the total population. In addition, the prognosis of *NTRK1*- and *NTRK3*-related sarcomas in relation to histomorphology was investigated, and it was found that sarcomas with *NTRK1* fusion may exhibit low- or high-grade histomorphology. At the same time, morphologically high-grade tumors containing *NTRK1* may show an aggressive course, while low-grade tumors may exhibit a more favorable clinical course. On the other hand, sarcomas with *NTRK3* fusion are more aggressive neoplasms. However, contrary to this finding, a very low-grade tumor containing an *NTRK3* fusion was reported in the study. Likewise, in our study, particularly the *NTRK3* fusion gene was expected to be detected in high-grade tumors, but it did not reach statistical significance.

In a study conducted by Solomon et al.,[41] a total of 38,095 samples were obtained from 33,997 patients, and *NTRK1*, *NTRK2*, and *NTRK3* fusion gene detection was performed. Only 13 cases among 87 tumors and tumor types with 1,915 molecular diagnoses were associated with NTRK genes. In addition, only 3 of 17 inflammatory myofibroblastic tumors were associated with NTRK genes.

The MAPK signaling pathway plays an important role in various molecular mechanisms, such as proliferation, differentiation, and apoptosis, in normal cells. The signaling pathway can be overactivated due to mutations, amplifications, and translocations in genes responsible for the regulation of cell fate, survival, and genome integrity. This can lead to cancer and tumor formation. In a study conducted by Arconada-Luque et al.,[42] the relationship between the MAPK signaling pathway and sarcomagenesis was investigated. They compared the expression levels of different MAPKs using cell lines and mouse models and found no difference in ERK2 expression in tumor samples. Similarly, we did not find any difference in ERK expression levels in our study. In addition, Gu et al.[24] examined the relationship with the MAPK signaling pathway using a MEK inhibitor in malignant peripheral nerve sheath tumors. They confirmed the overactivation of the MAPK signaling pathway in malignant peripheral nerve sheath tumors. In our study, no difference was observed in the expression changes of the MAPK signaling pathway.

Cell proliferation upregulated gene 4 is an oncogene involved in various types of cancer. In leukemia and prostate cancer, overexpression of the *URGCP* gene is involved not only in tumor development but also in metastasis and recurrence. The molecular mechanism of the *URGCP* oncogene in soft tissue sarcomas is not yet known.

According to the data obtained in our study, the primary reason for the statistically nonsignificant mRNA expression changes is the insufficient number of patients in the study population. Since soft tissue sarcoma types are rare cancers, an equal and sufficient patient population could not be provided for each group. Therefore, no statistical significance could be

established in the study. We think that stress, inflammation, death receptor activation, oxidative stress, and therapeutic agents may influence the NTRK genes and MAPK signaling pathway during the clinical follow-up of patients included in the study and therefore contribute to changes in mRNA expression. According to the pathology results, *NTRK1*, *NTRK2*, and *NTRK3* gene expression was reported to be negative on immunohistochemical staining in our cases, which was similar to the findings of our study. After the *URGCP* oncogene, which we used in our study, was found to play a role in various cancer types, such as gastric cancer and hepatocellular cancer, it was thought that it might also have an effect on soft tissue sarcomas. However, no negative or positive effect was found in our results. For this reason, we think that it may serve as a basis for future research incorporating larger patient populations, disease prognosis, and a wider range of examinations. The discrepancy between mRNA expression levels and immunohistochemistry findings may be explained by post-transcriptional and post-translational regulatory mechanisms, including microRNA-mediated regulation, differences in protein stability, translational efficiency, and protein degradation. In addition, technical limitations of immunohistochemistry, particularly its sensitivity in detecting low-abundance proteins in formalin-fixed, paraffin-embedded (FFPE) tissues, may also contribute to this inconsistency.

Soft tissue sarcomas, which are rare among all cancer types, have more than 100 subtypes, and these subtypes are themselves rare malignant tumors. Therefore, the detection and prognosis of the disease have not been fully elucidated. Detection of NTRK genes is a promising marker, particularly for the detection of STS. In our study, we examined the expression levels of NTRK genes using real-time PCR. However, we think that real-time PCR should be supported by immunohistochemical staining. In addition, we anticipate that more accurate studies can be conducted with the support of next-generation sequencing (NGS), which has become widespread in recent years. We also believe that increasing the study cohort will improve the results and may provide a basis for further studies.

CONCLUSIONS

The correlation between the expression levels of the *NTRK1*, *NTRK2*, and *NTRK3* genes and the MAPK signaling pathway in STS was investigated for the first time, and their relationship with the *URGCP* oncogene was revealed for the first time. The molecular mechanism of the *URGCP* oncogene in STS has not been determined.

In this study, we observed increased NTRK2 gene expression in synovial sarcoma, undifferentiated pleomorphic sarcoma, inflammatory myofibroblastic tumor, myxofibrosarcoma (except low grade myxofibrosarcoma) extraskeletal mesenchymal chondrosarcoma, fibromatosis, and leiomyosarcoma; increased *NTRK3* gene expression in synovial sarcoma, fibrosarcoma, and fibromatosis; and increased *NTRK1* gene expression in synovial sarcoma and fibrosarcoma. In addition, decreased *NTRK1* gene fusion was observed in malignant peripheral nerve sheath sarcoma, undifferentiated pleomorphic sarcoma, inflammatory myofibroblastic tumor, myxofibrosarcoma (including low grade myxofibrosarcoma), extraskeletal mesenchymal chondrosarcoma, fibromatosis, leiomyosarcoma, myofibroblastic sarcoma, decreased *NTRK3* gene fusion was observed in malignant peripheral nerve sheath sarcoma, undifferentiated pleomorphic sarcoma, inflammatory myofibroblastic tumor, myxofibrosarcoma (including low grade myxofibrosarcoma), extraskeletal mesenchymal chondrosarcoma, leiomyosarcoma, myofibroblastic sarcoma, and decreased *NTRK2* gene fusion was observed in malignant peripheral nerve sheath sarcoma, myofibroblastic sarcoma, and low-grade myxofibrosarcoma.

In dedifferentiated liposarcoma, synovial sarcoma, fibrosarcoma, and fibromatosis, *ERK1* of the MAPK signaling pathway was increased, while *MEK1* and *MEK2* were increased in synovial sarcoma, fibrosarcoma, and fibromatosis. The *URGCP* oncogene was also increased in synovial sarcoma, fibrosarcoma, and fibromatosis. The observed fluctuations in expression levels did not reach statistical significance ($p>0.05$). In addition, p values could not be obtained because the numbers of patients with fibromatosis, myofibroblastic sarcoma, and low-grade myxofibrosarcoma were less than 3 and 3, respectively. A limitation of the present study is the heterogeneous distribution of soft tissue sarcoma subtypes and the small sample sizes in several rare subgroups, which may have reduced the statistical power of the analyses and limited the ability to detect statistically significant differences. Therefore, larger multicenter studies including greater numbers of patients are needed. Furthermore, additional investigations incorporating protein-level validation methods such as immunohistochemistry, Western blotting, and proteomic analyses would further strengthen the biological interpretation of the observed mRNA expression changes. Our results were similar to those reported in the literature and were consistent with the pathological findings.

Ethics Committee Approval: Ethics committee approval was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee (Approval Number: 01, Date: 10.01.2023).

Informed Consent: Due to the retrospective design and the use of archived formalin-fixed paraffin-embedded (FFPE) tissue samples, the requirement for written informed consent was waived by the Ethics Committee.

Conflict of Interest: The authors have no conflicts of interest to declare.

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