Transcriptome changes and deregulated biological pathways associated with *NF1*-mutated pheochromocytoma

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SUMMARY

Background: *Pheochromocytoma (PHEO) is a rare tumor of intraadrenal sympathetic origin. At least 25-30% of PHEOs have been found to be linked to germline or somatic mutations in the neurofibromin 1 (NF1) gene, which functions as a tumor suppressor. Despite the high frequency of NF1 gene mutations in PHEOs, the exact mechanism underlying the pathogenesis of these tumors has not yet been fully elucidated.*

Methods: *A large-scale analysis of transcriptomic profiles and biological pathways associated with NF1-related PHEOs was conducted utilizing RNA-Seq and miRNA-Seq data from the The Cancer Genome Atlas (TCGA) project. The studied dataset comprised 143 patients with PHEOs.*

Results: *A total of 21 differentially expressed transcripts (14 genes, 3 long noncoding RNAs, and one microRNA) were identified in association with germline and somatic mutations in the NF1 gene. The present study detected a decrease in the mRNA levels of NF1, as well as of its interacting partners, SPRED3 and EZR. A decreased expression of oncogenic microRNA miR-423-3p was also observed. Seven differentially expressed genes (SHC3, SHC1, STAT3, NF1, KSR1, NOS2, and ALDOC) were found to be overrepresented in a number of distinct biological pathways, including those associated with RAS and HIF-1 signaling, the pathway linked to the resistance to the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, and the growth hormone-associated pathway. These findings suggest the deregulation of these pathways in NF1-mutated PHEOs.*

Conclusion: *The results obtained demonstrate the consequences of NF1 gene mutations at the level of the transcriptome. Furthermore, they confirm a change in RAS signaling pathways in NF1-related PHEOs.*

Keywords: *Pheochromocytoma, NF1 mutations, differentially expressed transcripts, RAS signaling pathway*

Arch Oncol 2025;31(2):9-15

https://doi.org/10.2298/AOO250602010S

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Received: **2025-06-02**
Received in revised form: **2025-08-28**
Accepted: **2025-09-12**
Published online: **2025-09-22**

INTRODUCTION

Pheochromocytoma (PHEO) is a rare neuroendocrine tumor that arises from the chromaffin cells of the adrenal medulla. The annual incidence of pheochromocytoma ranges from 0.4 to 9.5 cases per million individuals, depending on genetic risk factors (1). The symptoms of PHEO are primarily the result of excess catecholamine secretion by the tumor. These symptoms include hypertension, headaches, sweating, and tachycardia (2). The diagnosis of PHEO is based on imaging techniques (e.g. computed tomography, magnetic resonance imaging) and biochemical testing of catecholamine metabolites (3). While surgical resection is the standard treatment for these tumors, the procedure carries inherent risks of morbidity and mortality (4).

PHEOs and closely related tumors of sympathetic and parasympathetic paraganglia (extra adrenal paragangliomas) are characterized by an approximate hereditary rate of 40%, with a growing list of susceptibility genes (1,5). Furthermore, somatic mutations in susceptibility genes are detected in 25-30% of tumors (5). The genotype influences the key tumor characteristics, including the anatomical location, secretory function, syndromic presentation, and risks of multifocality and metastasis (6). Up to 6% of PHEOs develop in association with the neurofibromatosis type 1 (NF1) genetic syndrome, which is caused by a hereditary mutation in the *NF1* gene (7). Somatic mutations in the *NF1* gene have been detected in a quarter of sporadic PHEOs (8). Nevertheless, the mechanism underlying the development of *NF1*-related PHEOs remains to be fully elucidated.

In this study, we have investigated the gene expression profiles and changes in biological pathways in PHEOs with mutations in the *NF1* gene. A comprehensive analysis of RNA-Seq and miRNA-Seq data from The Cancer Genome Atlas (TCGA) project has been conducted. We present a list of genes, long noncoding RNAs (lncRNAs), and microRNAs that have been found to exhibit significant expression changes. These changes have the potential to be involved in the pathogenesis of *NF1*-related PHEOs. The results of this study also suggest a pivotal role for RAS signaling in tumor development.

MATERIALS AND METHODS

Datasets

The RNA-Seq and miRNA-Seq public datasets collected from the Pheochromocytoma and Paraganglioma (PCPG) - The Cancer Genome Atlas (TCGA) project (https://portal.gdc.cancer.gov/projects/TCGA-PCPG) were used in the study. The data for patients with PHEOs were selected from these datasets and were analyzed. The obtained data for 143 patients with PHEOs were divided into two groups according to their *NF1* gene mutational status. The *NF1*-mutated group includes 21 PHEOs with germline or somatic mutations in the *NF1* gene (Table 1); the *NF1*-wild-type group consists of 122 PHEOs without mutations in the corresponding gene. Experimental procedure of mutation analysis described in TCGA's study of PCPG (9).

Table 1. A list of *NF1* mutations in patients with PHEOs (metadata derived from the PCPG-TCGA project).

NF1 mutation	Mutation origin	Sex	Age	Metastasis / Recurrence
p.R440X	Germline	F	42	No
p.D1537fs		M	52	
p.F894S		F	30	
p.585_586del		F	44	
p.R1306X		F	28	
p.A2079fs		F	59	
No data	Somatic	F	51	
p.S1754fs		F	66	
p.Arg997Thr		F	71	
p.Q400*		F	43	
p.W784R		F	70	
p.A188fs		F	69	
p.V1531fs		M	58	
p.S413*		F	47	
p.KIDAV428fs		M	59	
p.L492fs		M	76	
p.K874fs		M	39	
p.K583N		F	45	
p.S2309fs		M	37	
p.TV2409fs		F	73	
p.KFFHAI1345fs		M	57	

F, female; M, male.

Differential expression analysis

Downloaded RNA-Seq and miRNA-Seq data were transferred into the R environment. The differential expression of genes (DEGs) and miRNAs was analyzed using the edgeR Bioconductor package (10). The trimmed mean of M-values (TMM) method with counts per million (CPM) calculations was used to normalize the obtained data. The F-criterion of quasi-likelihood (QLF) and the Mann-Whitney U-criterion (MW) were applied to assess the reliability of changes. The Benjamini-Hochberg correction was used to calculate the expected false discovery rate (FDR). The significance of the fold change between the compared groups (Log-2FC) and the overall expression level of transcripts in the cohort (Log2CPM) were calculated. The mRNA annotation was performed using the biomaRt Bioconductor package (11), and the multiMiR Bioconductor package was used for microRNA annotation (12). The pathway enrichment analysis was performed across a set of differentially expressed genes using the over-representation analysis (ORA) approach and the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (13). The STRING database was utilized in order to facilitate the analysis of predicted protein interactions (14). The correlation matrix was created using Pearson correlation.

RESULTS AND DISCUSSION

Differently expressed genes and miRNAs associated with *NF1*-mutated PHEOs

RNA-Seq data analysis identified seventeen genes (*SHC3, SPRED3, NOS2, PLXNB1, NF1, NAGLU, SH3KBP1, ALDOC, NEK8, TMEM99, GMPR, TESC, EDIL3, EZR, RBPMS2, TSKU,* and *TSPAN6*) and three lncRNAs (AC092378.1, LINC00639, and AC015922.3) with significant changes (more than 2-fold) in the expression level in *NF1*-mutated PHEOs (Log2CPM≥1, Log2FC≥1≤-1, FDR≤0.05 by QLF and MW tests) (Table 2, Figure 1).

LncRNAs AC092378.1 and LINC00639, as well as *SHC3*, *SPRED3*, *NOS2*, and *PLXNB1* genes were characterized by increased expression levels, while other genes demonstrated decreased expression levels. The correlation matrix showed a moderate positive correlation (r=0.5–0.7) between the expression levels of the following DEGs: *TSKU–EZR* (r=0.57), *TSPAN6–EZR* (r=0.7), *TSPAN6–GMPR* (r=0.56), *SPRED3–SHC3* (r=0.57), and *TSPAN6–TSKU* (r=0.65) (p≤0.05) (Figure 2). The majority of these genes are implicated in the regulation of critical signaling pathways, including RAS/MAPK, Wnt, and NF-κB, and are potential participants in a comprehensive tumor-associated regulatory network.

Table 2. Differently expressed genes, lncRNA, and miRNA in *NF1*-mutated PHEOs.

Gene/lncRNA/miRNA	Log2CPM	Log2FC	FDR (QLF)	FDR (MW)	Function
AC092378.1	1.47	2.29	0.05	0.03	LncRNA
SHC3	5.18	1.57	0.001	0.004	Signaling pathway of the transmembrane receptor protein tyrosine kinase
LINC00639	2.12	2.49	0.0001	0.009	LncRNA
SPRED3	4.3	1.08	0.05	0.03	Negative regulation of the RAS/MAPK signaling pathway
NOS2	4.62	1.65	0.02	0.04	Production of nitric oxide, inflammatory response
PLXNB1	7.54	1.17	0.02	0.02	Negative regulation of cell adhesion, regulation of cell morphology, the semaphorin-plexin signalling pathway
NF1	6.21	-1.37	0.000008	0.003	Negative regulation of the RAS signaling pathway
AC015922.3	2.45	-1.49	0.0002	0.005	LncRNA
NAGLU	5.58	-1.04	0.0006	0.01	Metabolism of glycosaminoglycans and heparan sulfate/heparin
SH3KBP1	5.33	-1.35	0.02	0.02	Apoptosis, cell adhesion, regulation of clathrin-dependent endocytosis
ALDOC	7.43	-1.16	0.025	0.05	Glycolysis and gluconeogenesis
NEK8	1.84	-1.06	0.001	0.009	Cell cycle
TMEM99	3.51	-1.12	0.0001	0.006	A transmembrane protein with unexplored function
GMPR	3.31	-1.57	0.002	0.01	Nucleotide metabolism
TESC	3.92	-2.67	0.01	0.04	Negative regulation of cell proliferation, regulation of gene expression and differentiation
EDIL3	5.19	-1.93	0.02	0.03	Angiogenesis
EZR	6.93	-1.14	0.04	0.04	Cell adhesion and migration
RBPMS2	2.88	-2.14	0.006	0.02	Alternative splicing, negative regulation of the BMP signalling pathway
TSKU	3.08	-1.89	0.01	0.05	Negative regulation of the Wnt signalling pathway
TSPAN6	3.17	-1.15	0.02	0.04	Regulation of the NF-kappaB signalling pathway
miR-423-3p	6.29	-0.61	0.002	0.003	Regulation of cell cycle, apoptosis, PI3K-Act, FoxO, ErbB, P53, Jak-STAT, and HIF-1 signalling pathways

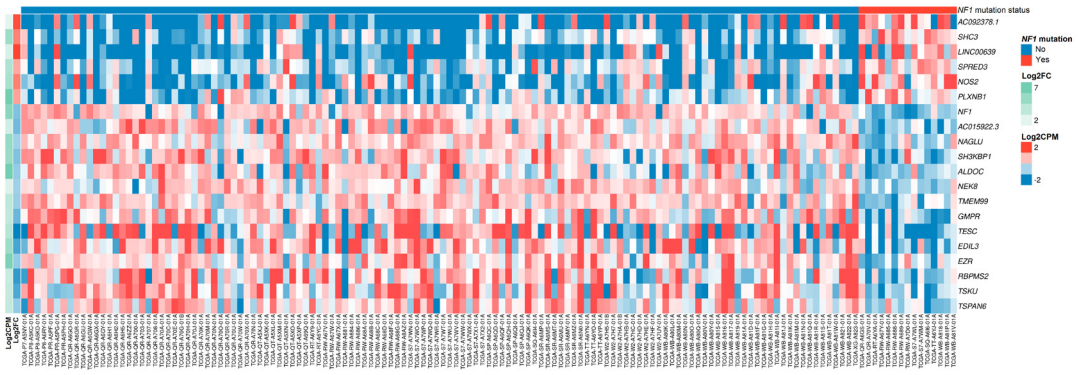

Figure 1. Heatmap of differentially expressed genes and lncRNAs associated with *NF1*-mutated PHEOs.

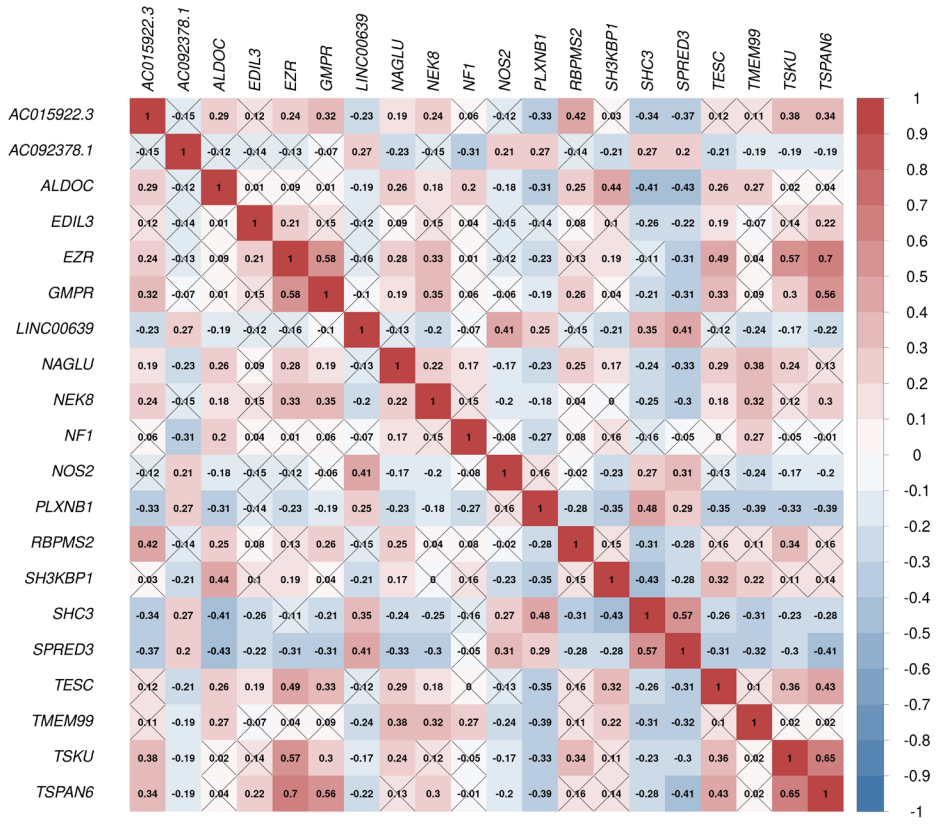

Figure 2. Correlation matrix of the DEG co-expression analysis. Heatmap showing Pearson's correlation coefficient (r). Crossed-out cells indicate a P>0.05.

The most significant increase in expression (more than 5-fold) was observed for lncRNAs AC092378.1 and LINC00639. The *TESC* and *RBPMS2* genes exhibited a substantial decrease in expression of 6 and 4 times, respectively. It is important to note that the *NF1* gene was identified among the genes with a significantly reduced expression in *NF1*-mutated PHEOs. *NF1* is a tumor suppressor gene that requires the loss of both gene alleles to promote tumorigenesis. Recent studies have reported a frequent loss of *NF1* heterozygosity (LOH) in *NF1*-related hereditary PHEOs, as well as LOH at the *NF1* gene locus and low mRNA expression in sporadic PHEOs with somatic *NF1* mutations (15,16). Consequently, the identification of decreased *NF1* mRNA expression may signify the loss of *NF1* heterozygosity in the studied PHEOs.

From the list of identified genes, the interacting partners of neurofibromin 1 are SPRED3 and EZR proteins. The SPRED3 protein belongs to the SPRED family of proteins that are able to bind to NF1 (17). This protein in complex with neurofibromin 1 negatively regulates the RAS/MAPK signaling pathway. The STRING database revealed the existence of coexpression between neurofibromin 1 and EZR proteins.

Furthermore, microRNA miR-423-3p was identified to be differentially expressed between the studied groups (Log2CPM≥1, FDR≤0.05 by QLF and MW tests) (Table 2). The microRNA miR-423-3p has been found to be aberrantly expressed in a multitude of tumor types; it has been determined that this microRNA is an oncogenic (18).

Deregulated biological pathways in *NF1*-mutated PHEOs

KEGG pathway enrichment analysis was conducted on a non-filtered set of significantly DEGs (P≤0.05). Following a comprehensive analysis, four pathways were identified as being significantly enriched (FDR≤0.05) in *NF1*-mutated PHEOs (Table 3, Figure 3).

Table 3. Significantly deregulated biological pathways in *NF1*-mutated PHEOs..

KEGG ID	Pathway	Gene ratio	FDR	Gene
hsa01521	EGFR tyrosine kinase inhibitor resistance	4/19	0.002	*SHC3, SHC1, STAT3, NF1*
hsa04014	RAS signaling pathway	4/19	0.03	*KSR1, SHC3, SHC1, NF1*
hsa04066	HIF-1 signaling pathway	3/19	0.03	*NOS2, ALDOC, STAT3*
hsa04935	Growth hormone synthesis, secretion and action	3/19	0.04	*SHC3, SHC1, STAT3*

Neurofibromin plays a major role in the regulation of the RAS signaling pathway in both health and disease. The *NF1* deficiency has been demonstrated to result in increased RAS activity and cell hyperproliferation (19).

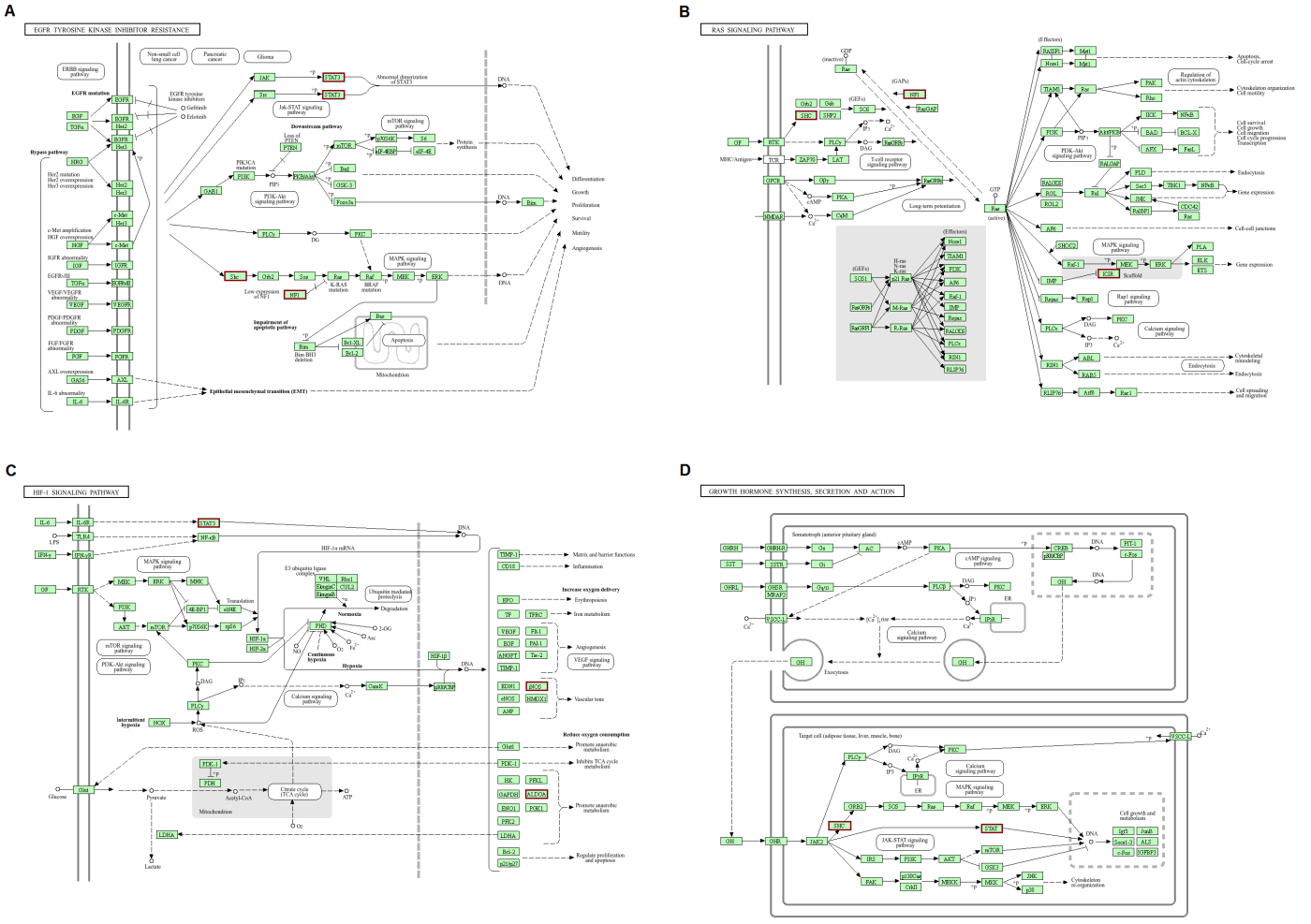

Figure 3: Visualization of KEGG pathways potentially associated with *NF1*-mutated PHEOs. A; EGFR tyrosine kinase inhibitor resistance pathway, B; RAS signaling pathway. C; HIF-1 signaling pathway. D; EGFR tyrosine kinase inhibitor resistance pathway. The components of the pathways that are significantly enriched with DEGs (P≤0.05) are indicated by red bold frames.

Consequently, it was hypothesized that impaired RAS proto-oncogene regulation might be responsible for the spectrum of clinical manifestations, including tumorigenesis, caused by loss-of-function *NF1* mutations. In the present study, the deregulation of the RAS signaling pathway was detected in PHEOs with pathogenic mutations in the *NF1* gene. However, the set of overrepresented genes did not include either direct protein targets of neurofibromin (HRAS, NRAS, KRAS) or other RAS-regulated proteins. This pathway includes four genes for which differential expression has been observed: *KSR1* (Log2FC=-0.81, FDR (QLF/MW)≤0.01) and *NF1* (Log2FC=-1.37, FDR (QLF/MW)≤0.003), both of which are involved in the regulation of the RAS/MAPK cascade; *SHC3* (Log2FC=1.57, FDR (QLF/MW)≤0.004) and *SHC1* (Log2FC=0.87, FDR (QLF/MW)≤0.01), which are implicated in various signal networks including RAS cascade activation (20,21). The present findings at the transcriptome level indicate an important role for RAS cascade deregulation in *NF1*-realted PHEO development. Deregulated pathways such as 'EGFR tyrosine kinase inhibitor resistance' and 'growth hormone synthesis, secretion and action' have been identified as being involved with *SHC3*, *SHC1* and *NF1*, as well as the *STAT3* gene, which has been shown to have a decreased mRNA expression (Log2FC=-0.73, FDR (QLF/MW)≤0.01). The correlation between *NF1* mutations and diminished *NF1* expression with the EGFR inhibitor resistance in cancer cells has been supported by several studies (22-24). It has been hypothesized that the molecular mechanism underlying the *NF1*-related resistance to anti-EGFR therapy is attributable to the aberrant activation of the RAS/MAPK signaling pathway, consequent to *NF1* loss (24). In PHEOs, the differential expression of genes participating in both biological pathways was detected, thereby confirming their connection and association with *NF1* mutations in tumorigenesis.

Growth hormone excess has been observed in approximately 10% of individuals with *NF1* mutations, predominantly in cases of optic pathway gliomas (25). The molecular mechanism underlying growth hormone excess remains to be elucidated; however, it has been hypothesized that the loss of somatostatinergic inhibi-

tion and the overexpression of GHRH and GPR101 proteins are the primary drivers (26). Conversely, growth hormone deficiency has been documented in children diagnosed with neurofibromatosis type 1 (27). As demonstrated in several studies, there is a concomitant secretion of the growth hormone-releasing hormone (GHRH) by pheochromocytoma and acromegaly (28, 29). Consequently, the mechanisms underlying growth hormone pathway deregulation in PHEOs can be associated with *NF1* loss.

The deregulation of the HIF-1 signaling pathway was found to be associated with alterations in the expression levels of *NOS2* (Log2FC=1.65, FDR (QLF/MW)≤0.03), *ALDOC* (Log2FC=-1.16, FDR (QLF/MW)≤0.04), and *STAT3* genes in *NF1*-mutated PHEOs. The study by Rad et al. demonstrated a close interconnectedness of STAT3 and HIF in *NF1*-related MPNST cell lines, with these pathways being implicated in cell migration, invasion, and tumor formation (30). The deregulation of the HIF-1 signaling pathways can be achieved through the inhibition of the RAS cascade (31). Consequently, inactivating *NF1* mutations may potentially induce metabolic changes that could lead to the tumor growth.

CONCLUSION

In *NF1*-related PHEOs, a significant deregulation of the RAS signaling pathway was identified, which is a major target of neurofibromin. The alterations in the EGFR tyrosine kinase inhibitor resistance pathway and HIF-1 signaling pathway, which were also identified, could be considered as downstream consequences of RAS cascade deregulation.

NF1-mutated PHEOs exhibited a decline in *NF1* mRNA levels, which may be indicative of the loss of heterozygosity. Furthermore, the diminished expression of the *SPRED3* gene, which encodes the neurofibromin 1 interaction partner and is a negative regulator of RAS/MAPK signaling, was potentially facilitated by the deregulation of this pathway.

ACKNOWLEDGMENTS

This research was funded by the Program of Fundamental Research in the Russian Federation for the 2021–2030 period (project No. 124032100001-1) and the Russian Science Foundation (grant no. 24-14-00439). The study was performed using the computational power of EIMB RAS "Genome" center (https://www.eimb.ru/ru1/ckp/ccu_genome_c.php).

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