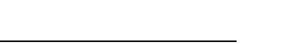

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RESEARCH ARTICLE

Long noncoding RNA expression analysis in Crimean Congo hemorrhagic fever patients

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Abstract

Crimean Congo hemorrhagic fever (CCHF) is an acute viral infection that can cause death. The detection of host transcriptome is important for understanding differences in the pathogenesis of the disease. Long noncoding RNAs (lncRNAs) regulate gene expression in different biological processes. They have also emerged as key molecules for therapeutic targets. We investigated the lncRNA gene expression profiles by utilizing the microarray for the first time in CCHF. LncRNAs were determined by the comparisons between case-control, fatal case-control, and fatal case-nonfatal cases. Quantitative polymerase chain reaction was applied to validate the microarray results of some lncRNAs. In our study, 39 lncRNAs (5 downregulated and 34 upregulated) were found to be significantly regulated in the cases when compared to the controls ($p < 0.05$; $FC \geq 2$). One hundred ten lncRNAs exhibited a statistically significant difference between fatal cases and controls. FER1L4, ECRP, and LOC100133669 are important lncRNAs in both case and fatal case groups compared with controls. These lncRNAs may be considered important therapeutic targets for the CCHF in further studies.

KEYWORDS

CCHF, gene expression, lncRNA, microarray, qPCR

1 | INTRODUCTION

Crimean Congo hemorrhagic fever orthonairovirus (CCHFV) is a member of the *Orthonairovirus* genus and *Nairoviridae* family.[1] This virus has a single-stranded RNA genome containing L, M, and S segments, which encode the RNA-dependent RNA polymerase, viral glycoproteins, and the nucleocapsid protein, respectively.[2] CCHF has wide geographic distribution in Asia, Europe, and Africa.[3] CCHF is a severe form of hemorrhagic fever that can result in death. To date, no effective drug or vaccine that can treat the disease has been developed. CCHF disease is a major health problem in Turkey with seropositivity rates of 26%–57% and a fatality rate of 5%–30%. According to the functional studies related to lncRNAs, they play important roles in different biological processes such as transcriptional and posttranscriptional regulation, chromatin modification, and cell cycle regulation. Viral infections induce strong modifications in the cell transcriptome including lncRNA.[4] Several lncRNAs expressed in the infected cells are used to regulate the expression of viral and host genes. The expression of cellular lncRNAs can also be altered in the antiviral response induced by infection.[5] Our previous study determined the most important miRNAs of the CCHF pathogenesis.[6] Also, in preliminary studies conducted by our study group, some lncRNAs were investigated using quantitative polymerase chain reaction (qPCR) in the pathogenesis of the CCHF.[7,8] According to the literature so far, there is no study on lncRNA gene expression in CCHF. In the present study, we investigate long noncoding RNA (lncRNA) gene expression profiles in patients with CCHF via microarray analysis for the first time. Additionally, we compared lncRNA gene expression levels between fatal case-control and fatal case-nonfatal cases.

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2 | MATERIALS AND METHODS

2.1 | Study population

In this study, we performed microarray analyses on 40 samples, which consisted of 27 cases and 13 controls. Five of the 27 patients died due to the CCHF. Cases were selected from patients hospitalized in Sivas Cumhuriyet University Application and Research Hospital. The study population consisted of patients and controls diagnosed according to the criteria in our previous article.[6] Informed consent was obtained from all participants. The study was approved by the Sivas Cumhuriyet University Ethics Committee (Decision no: 2016-12/61).

2.2 | Experimental protocol

Blood samples were taken into the RNA blood tube (PAXgene) and total RNA was extracted using the PAXgene Blood RNA Kit (QIAGEN). RNA concentration and RNA integrity number (RIN) value of the samples were measured using a Flowmeter (Qubit ver. 3.0) and Agilent 2100 Bioanalyzer, respectively. Microarray was performed on samples with RIN values greater than 7. SurePrint G3 Human Gene Expression v3 8x60K Microarray Kit (G4851C) was used for the microarray analyses of all samples (Agilent Technologies). Microarray steps (sample preparation, labeling, hybridization, and washing) were made according to the standard protocol recommended by Agilent Technologies. The microarray slides were scanned with the Agilent Microarray Scanner G2565A and image analysis was performed using the Agilent Feature Extraction software (version 10.5.1).

2.3 | qPCR validation

We performed the qPCR of randomly selected four lncRNAs to validate microarray gene expression data. These genes are FER1L4, ECRP, HMGB3P1, and PTTG3P. GAPDH was used as an endogenous control in qPCR. First, we synthesized complementary DNA (cDNA) from all RNA samples by using 5 µl hyperscript one-step qPCR premix, 3.5 µl RNase free water (RFW), and 1.5 µl RNA. Then, we used the 10 µl SYBR green, 6 µl RFW, 2 µl optimized lncRNA primer assay (QIAGEN), and 2 µl cDNA to perform qPCR. qPCR protocols were performed using Roche LightCycler® in accordance with the manufacturer's instructions in stages of pre-incubation, two-steps amplification, and melting curve analysis. The fold change (FC) for each lncRNAs was calculated using the ΔΔCq method. Three biological replicates were applied for each group.

2.4 | Statistical analysis

Microarray raw gene expression data were normalized by the Quantile method using the GeneSpring GX 10.0 Software which was used to find differentially expressed lncRNAs. lncRNAs were detected by using Bonferroni correction and Student's *t*-test in case versus control, fatal case versus control, fatal case versus nonfatal case. The qPCR results were uploaded onto the MedCalc software (https://www.medcalc.com.tr/features.php). The *p* value was calculated based on the Student's *t*-test for each gene and *p* values lower than 0.05 were considered statistically significant.

3 | RESULTS

We used 40 samples at lncRNA gene expression microarray analysis. Our samples were composed of 13 controls and 27 cases, five patients of which died due to CCHF. The case group was composed of 15 male (55.56%) and 12 female (44.44%) individuals. The Control group was composed of seven males (53.85%) and six female individuals (46.15%). The mean age of the case group and control group was 45.07 and 43.31, respectively. There were not any statistically significant differences in age and sex distribution between the CCHF patients and the control group. Also, in our previous study, we were determined in viral load of CCHF patients.[6]

In this study, 39 lncRNAs were statistically significant, 5 of these lncRNAs were downregulated while 34 lncRNAs were upregulated ($p < 0.05$; FC ≥ 2). The scatter plot showed differentially expressed lncRNAs according to fold change in patients compared with controls (Figure 1). Five upregulated lncRNAs that have the highest FC, are FER1L4, HMGB3P1, ECRP, lnc-PIK3CG-4, and PTTG3P; five

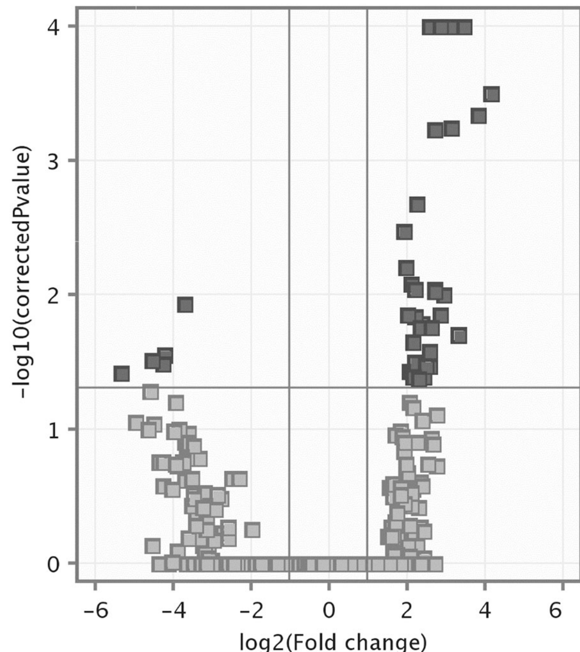

FIGURE 1 Scatter plot of differentially expressed lncRNAs between cases and controls. Spots above the horizontal midline represent statistically significant lncRNAs. FC < 1 and FC > 1 represent the downregulated and upregulated significant lncRNAs, respectively. FC, fold change.

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TABLE 1 LncRNAs in cases compared with controls.

LncRNA	Fold change	Regulation	LncRNA	Fold change	Regulation
lnc-SAMD11-2	40.37	Down	LOC100507195	6.00	Up
lnc-CMTM4-1	22.85	Down	USP30-AS1	5.95	Up
lnc-PRMT6-2	19.02	Down	FAM27C	5.64	Up
LINC00094	18.47	Down	SNAR-H	5.48	Up
FER1L4	13.95	Up	SNORD43	5.29	Up
HMGB3P1	7.90	Up	LOC101927027	5.09	Up
lnc-AL079342.1-1	12.83	Down	ATP2A1-AS1	4.94	Up
ECRP	7.50	Up	LINC00659	4.74	Up
lnc-PIK3CG-4	9.90	Up	LINC01358	4.68	Up
PTTG3P	4.75	Up	NRIR	4.63	Up
LOC100133669	8.77	Up	MIR503HG	4.62	Up
SNAR-G2	7.79	Up	LOC100419583	4.47	Up
SNAR-D	7.35	Up	SCARNA22	4.44	Up
TPRG1-AS1	7.27	Up	TRERNA1	4.43	Up
SNRNP25	6.68	Up	LOC100130298	4.33	Up
PIK3CD-AS2	6.58	Up	IDH1-AS1	4.20	Up
lnc-SNRPD3-2	6.55	Up	NR1H3	4.08	Up
MT1L	6.54	Up	MIR4435-1HG	3.87	Up
FAM225A	6.13	Up	LINC00152	3.81	Up
SNAR-B2	6.03	Up			

Note: p values of lncRNAs are lower than 0.05; FC, fold change (abs).

downregulated lncRNAs were lnc-SAMD11-2, lnc-CMTM4-1, lnc-PRMT6-2, LINC00094, and lnc-AL079342.1-1 (Table 1). NRIR and MIR503HG were also upregulated 4.63- and 4.62-fold in cases compared with controls (Table 1). A total of 110 lncRNAs were statistically significant between fatal cases and control individuals ($p < 0.05$; FC ≥ 2). Nine lncRNAs were upregulated whereas 101 of them were downregulated. The lncRNA genes (up and down) according to FC were shown in Table 2. ECRP, LOC100133669, TRERNA1, and LINC00659 were upregulated while lnc-PRMT6-2 and lnc-AL079342.1-1 were downregulated statistically significant both in the case and fatal case groups compared with controls (Tables 1 and 2).

We found only two statistically significant lncRNAs (lnc-KLF7-1, TTN-AS1/upregulated) in fatal cases compared with nonfatal cases.

qPCR was applied to validate the microarray results of some lncRNAs. FER1L4, ECRP, HMGB3P1, PTTG3P were upregulated. qPCR results were consistent with microarray results (Figure 2).

4 | DISCUSSION

CCHF is a viral disease that appears in many areas of the world and causes deaths. Transcriptome responses given by the host immune system after virus infection are important in terms of developing drug strategies against the virus. We previously performed microarray to detect miRNA expression in transition from acute to convalescence period.[9] In this study, we detected lncRNA expression changes occurring in the host cell after CCHF infection. We think that these lncRNAs markers will contribute to understanding the immune response of the virus-infected mammalian host cells and the pathogenesis of the disease.

In this study, we found 39 lncRNAs showing a statistically significant difference between the case and control groups. Fer-1-like protein 4 (FER1L4) is the highest upregulated lncRNA in the cases when compared to the control group patients ($p \leq 0.05$; FC: 13.95). Some studies suggest that FER1L4 may play important roles in different cancer types.[10] In our previous study, it was found that miR-18a-5p was significantly downregulated in CCHF.[6] As a result, FER1L4 was upregulated and miR-18a-5p was expressed at lower levels in CCHF. MiR-18a-5p targets the transforming growth factor-beta (TGF-β) receptor, suppressor of cytokine signaling 5 (SOCS5), Notch2 pathway, E2F transcription factor, and interferon regulatory factor (IRF) signal pathway.[11] The IRF signal pathway is one of the main actors in inflammation and antiviral response. Our studies suggest that FER1L4/miR-18a-5p may play an important role in the pathogenesis of CCHF.[6] Detailed functional studies are required to assess whether these genes are targets for the treatment of CCHF

TABLE 2 LncRNAs in fatal cases compared with controls.

LncRNA	Fold change	Regulation	LncRNA	Fold change	Regulation
lnc-CDC25A-1	2228	Down	LINGO1-AS1	50.85	Down
lnc-AP001496.1-10	606.71	Down	lnc-COX19-2	50.71	Down
lnc-LSR-1	446.30	Down	lnc-STT3B-1	50.49	Down
LINC00644	397.09	Down	lnc-DYM-1	49.82	Down
PRKAR2A-AS1	289.47	Down	LOC100128714	49.12	Down
lnc-LCP1-1	191.83	Down	LINC01397	48.93	Down
lnc-C1orf177-1	185.21	Down	LINC01389	48.50	Down
LOC100133286	177.47	Down	CALML3-AS1	48.20	Down
ZNF337-AS1	171.54	Down	LOC101929439	47.94	Down
lnc-SH2D7-5	163.12	Down	lnc-APOA4-1	47.57	Down
USP2-AS1	160.70	Down	lnc-C10orf11-1	46.33	Down
WASH5P	134.87	Down	lnc-WDR60-7	45.76	Down
lnc-IRF2BP2-3:1	129.25	Down	lnc-ANKRD6-1	45.56	Down
lnc-PRMT6-2	125.92	Down	linc RNA 385	44.54	Down
lnc-TAF12-3	120.57	Down	KRT16P3	43.84	Down
linc RNA 393	107.64	Down	LOC101926960	42.99	Down
lnc-GNB2-1	102.60	Down	lnc-MYC-2	42.42	Down
LOC100505736	100.17	Down	lnc-CNNM1-2	42.28	Down
LOC100129931	99.92	Down	lnc-MFSD2A-1	41.88	Down
lnc-ADD3-2	97.81	Down	lnc-TIMP3-1	41.76	Down
lnc-CEBPB-3	93.24	Down	LINC00400	40.94	Down
lnc-AC003101.1.1-1	90.37	Down	lnc-SUN3-1	40.11	Down
lnc-CDK2AP1-1	88.20	Down	lincRNA 639	39.44	Down
lnc-SYT13-2	86.67	Down	lnc-KCNA5-3	37.68	Down
Rt-13I SNURF-SNRPN	85.62	Down	lnc-AIPL1-2	36.55	Down
TEX26-AS1	80.78	Down	lnc-EPB41-1	36.43	Down
Rt-7 SNURF-SNRPN	79.92	Down	lnc-NEO1-1	35.80	Down
LINC00494	78.71	Down	lnc-FANCI-3	33.29	Down
linc RNA 299	78.56	Down	LOC90768	32.90	Down
lnc-CLEC18B-3	76.83	Down	lnc-CSN2-1	32.42	Down
lnc-RP11-362K2.2.1-1	75.75	Down	lnc-EZH2-1	31.56	Down
lnc-ADCY6-1	75.47	Down	LOC100507388	30.48	Down
lnc-ZKSCAN1-1	74.82	Down	lnc-PHYHIP-2	29.34	Down
lnc-MKL1-1	72.26	Down	lnc-AMELY-4	28.15	Down
LINC00659	69.65	Down	DNAJC27-AS1	28.04	Down
lnc-CLVS2-2	69.47	Down	lnc-SLA2-3	26.96	Down
linc RNA 350	67.74	Down	lnc-CD83-2	26.69	Down
lnc-ZKSCAN1-1	66.26	Down	lnc-SUCLA2-4	26.20	Down
lnc-MARVELD3-2	62.77	Down	lnc-PIPOX-1	25.55	Down
lnc-DUSP1-1	62.16	Down	LOC100133669	24.71	Up

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TABLE 2 (Continued)

LncRNA	Fold change	Regulation	LncRNA	Fold change	Regulation
lnc-TCN2-1	62.10	Down	PKNOX2-AS1	22.87	Down
lnc-RP11-778D12.2.1-4	61.28	Down	lnc-EIF5AL1-1	21.66	Down
lnc-USP14-5	60.37	Down	LINC00969	20.97	Down
Rt-12 SNURF-SNRPN	60.04	Down	KIR2DL4	20.38	Down
lnc-BTRC-2	59.16	Down	lnc-TUBGCP3-6	20.18	Down
LOC102724484	58.82	Down	lnc-TRIM16-1	20.01	Up
lnc-SLC4A1AP-1	58.18	Down	lnc-ASCL4-1	19.72	Down
lnc-KCNJ12-1	58.15	Down	ATE1-AS1	10.96	Up
lnc-GUSB-2	57.88	Down	GBP1P1	10.93	Up
lnc-PBX1-2	54.07	Down	lnc-STOX2-1	8.76	Up
linc RNA 384	53.86	Down	lnc-HDAC2-1	8.51	Up
SSTR5-AS1	53.68	Down	TRERNA1	7.83	Up
TTTY16	52.96	Down	lnc-SLC4A10-4	6.20	Up
lnc-ALDH3A2-2	52.21	Down			
ECRP	51.42	Up			
lnc-DPP6-2	51.21	Down			
lnc-AL079342.1-1	50.97	Down			

Note: *p* values of lncRNAs are lower than 0.05; FC, fold change (abs).

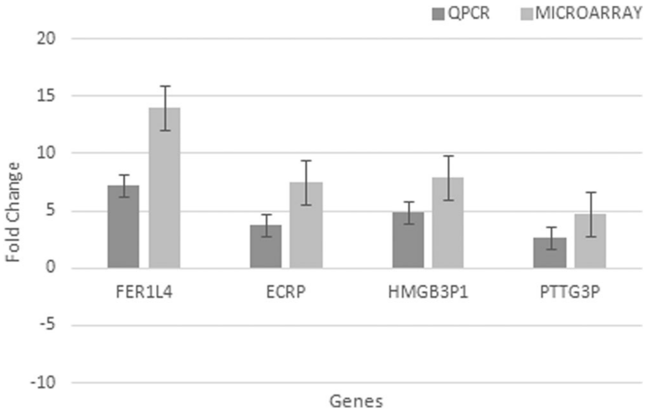

FIGURE 2 Validation of microarray data by qPCR. qPCR results and microarray data of selected lncRNAs in cases compared with controls. The vertical axis represents the FC (log2 transformed) of four lncRNAs. FC, fold change; qPCR, quantitative real-time polymerase chain reaction.

disease. Metallothionein 1L (MT1L) was upregulated in the case group compared with controls. MTs were one of the important IFN response genes.[12] The lncRNA-CMPK2/NRIR is a negative regulator of the interferon response. NRIR expression was upregulated significantly in our microarray study ($p \le 0.05$; FC: 4.63). Furthermore, in our previous qPCR study, NRIR expression was found statistically significant in CCHF cases and fatal cases compared with controls.[8] Silencing the NRIR gene led to a marked decrease in HCV replication in hepatocytes which is induced by IFN, suggesting that NRIR can modulate the antiviral effect of IFN.[13] Due to the NRIR role in regulating the interferon response, we think that NRIR can play an important role in the pathogenesis of CCHF. In our study, lncRNA MiR503HG was found to be 4.62-fold upregulated statistically significant in the CCHF diseases.[14] MIR503HG is associated with some types of cancer by inhibiting the NF-κB signaling pathway which is important in the host's immune response.[15] Viral proteins are known to be methylated by host protein arginine methyltransferases (PRMTs) necessary for the viral life cycle. We found that lnc-PRMT6-2 was downregulated 19.02-fold in CCHF patients. PRMT6 diminishes HIV-1 Rev binding to and export of viral RNA.[16]

We detected many statistically significant lncRNAs between CCHF patients and control group participants. Although these lncRNAs have been known to be bound to the cis or trans positions of some genes, their functions are not known. There is a need for new studies to learn the regulation of these lncRNAs in viral infections.

In this study, we detected statistically significant regulations of lncRNAs specific to fatal individuals with CCHF. We detected some lncRNAs such as ECRP, TRERNA1, PRKAR2A-AS1, and LOC100133669 which may be related to CCHF fatality. Human eosinophil granule ribonuclease (ECRP) was found to be significantly upregulated in fatal individuals with CCHF ($p \le 0.001$). Some studies suggest that ECRP has ribonuclease activity which causes antiviral activity against some viral infections including respiratory syncytial

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virus-B and Hepatitis B virus.[17] LncRNA TRERNA1 was found to be statistically significantly upregulated between CCHF patients (FC: 4.43) and fatal cases (FC: 7.83) compared with controls ($p \leq 0.05$). It has been demonstrated that the miR-190a mediated TRERNA inhibition was associated in hepatoma progression and lncRNA-based cancer therapies for hepatoma patients at high risk of metastasis.[18] LOC100133669 is LY6E divergent transcript. LOC100133669 was 24.71-fold upregulated in the fatal cases in comparison with the control group participants. LY6E has been shown to associate with HIV infection.[19] It has been suggested that LY6E relates to host IFN-inducible factors that affect viral infectivity.[20] In addition, Zhao et al.[21] reported that LY6E restricts entry of SARS-CoV-2 and it is an important antiviral effector.

In this study, we investigated the lncRNA gene expression in the CCHF for the first time in the world. As a result of the study, we detected statistically significant regulation for lncRNAs in CCHF disease. Also, these lncRNAs may be considered as an important molecular marker and therapeutic target related to fatality in CCHF infection. In further studies, it is necessary to research whether lncRNAs can be targeted for treatment using different molecular methods.

AUTHOR CONTRIBUTIONS

Serdal Arslan: Microarray, molecular evaluation of all experimental studies, and bioinformatic analyses. Mehmet Bakir: Sample collection and clinical evaluation. Burcu Bayyurt: RNA isolation and qPCR. Eylem I. Aydemir: Bioinformatic analyses. Kenan Kinaci: Bioinformatic analyses. Aynur Engin: Sample collection.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared. Participants of this study did not agree for their data to be shared publicly due to ethical restrictions, so supporting data are not available.

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