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Analysis of miRNA-Mediated ceRNAs In The Pathogenesis of Renal Cell Carcinoma: An *In Silico* Approach

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ABSTRACT

Renal cell carcinoma (RCC) is the most common form of kidney cancers and derived from kidney epithelium. The prognosis of RCC is still poor despite recent developments in surgical and other novel treatment strategies. Competing endogenous RNAs (ceRNAs) are considered as significant post-transcriptional regulators that modulate gene expression via miRNA-mediated regulatory networks. Furthermore, it has been demonstrated that ceRNAs have remarkable functions in the pathogenesis of cancers by modulating the expression of oncogenes or tumor-suppressive genes. The aim of this study was to define novel molecular biomarkers for RCC via in silico analysis. Seven miRNAs which have clinical significance for renal cell carcinomas were exported through miRTarBase database. 1001 genes which are targeted by these 7 miRNAs simultaneously were determined by ComiR database. The genes with T-UCR in their exonic regions and which have the potential ceRNA activities were extracted. Gene expression differences between RCC and normal kidney tissues according to the renal cell carcinoma-associated ceRNAs involving T-UCR were identified by GEPIA. The statistical analysis of the relationship between NRXN3 and PTBP2 genes with RCC was determined by Spearman correlation test. NRXN3 and PTBP2 were found to be significantly associated with RCC (p=0.0057; R=-0.29). The current study demonstrates for the first time that PTBP2 gene is associated with renal cell carcinoma. The results of *in silico* analysis suppose that PTBP2 gene may have potential tumor suppressor role in RCC and NRXN3 gene may have potential oncogenic activity in RCC. Further *in vitro* and *in vivo* studies are required in order to clarify tumor suppressor role of PTBP2 and oncogenic activity of NRXN3 in RCC.

Keywords:
miRNA; ceRNA; T-UCR; Renal cell carcinoma; PTBP2; NRXN3

INTRODUCTION

Renal cell tumors represent approximately 3% of all cancers in males and lower incidence in females. Several factors such as genetics, obesity, tobacco smoking, hypertension, diuretics, medications such as acetaminophen and non-aspirin non-steroidal anti-inflammatory drugs, viral hepatitis, and chemical carcinogens (asbestos, arsenic, etc.,) are implicated in the pathogenesis of renal cell tumors [1, 2, 3]. Renal cell carcinomas are divided into three subtypes: chromophobe, renal clear cell carcinoma and renal papillary cell carcinoma and this classification is verified by genetic and cytogenetic analysis [4, 5]. The most common form of renal cell tumors (approximately 70% of renal tumors) is renal clear cell carcinoma in adults. Papillary renal cell carcinoma is the second most frequent kidney tumors in adults [6].

MicroRNAs (miRNAs) are small non-coding RNA molecules (composed of 18-22 nucleotides) and conserved among different organisms. miRNAs are also defined as post-transcriptional regulators. miRNAs can bind to the complementary sequence of target mRNAs (target specificity is determined by miRNA sequence that is 6-8 nucleotide in length) and then cause to the degradation of mRNA. Furthermore, miRNAs are able to suppress translation and hence modulate gene and protein expression. miRNA biogenesis and functions are associated with various cancer types and they take significant roles in initiation, progression and metastasis of these cancers. Dysregulated miRNA expression profiles might be used as biomarkers of diagnosis and treatment of cancer [7, 8].

In recent years, competing endogenous RNAs (ceRNAs) are considered as significant post-transcriptional regulators that modulate gene expression via miRNA-mediated regulatory networks. Recent studies have showed that ceRNAs have significant functions in the pathogenesis of cancers by modulating the expression of oncogenes or tumor-suppressive genes. In the human genome, it is supposed that >50% of human mRNA might involve microRNA recognition elements (MREs) and ceRNAs share these sequences. miRNA can modulate several targets which include the typical MRE for miRNA. Similarly, the mRNA which have multiple MREs can be regulated by several miRNAs. Hence, the miRNA-mediated ceRNA network may be a common form of post-transcriptional regulation. ceRNA activity is affected by several factors such as RNA secondary structures, binding affinity of miRNAs, RNA editing, localization of ceRNA components. Disruptions in these factors may cause to the dysregulation of ceRNA network and then some diseases such as cancer [9, 10].

Ultraconserved regions (UCRs) which are 481 DNA elements longer than 200 base pair were discovered in 2004 by bioinformatics analysis. UCRs are completely conserved (no insertions or deletions) among rat, human, and mouse genomes and involved in diverse biological functions. According to the localization, UCRs are divided into five subtypes: intergenic, intronic, exon-containing, partly exonic, and exonic. Most of UCRs are transcribed in human tissues and these transcripts are named as transcribed UCRs (T-UCRs). It has been demonstrated that T-UCRs share tissue-specific expression pattern and have differential expression profiles between tumors. Moreover, it has been suggested that T-UCRs might have a significant role in the pathogenesis of diverse cancers [11, 12].

Studies in recent years have showed that miRNAs are promising for the understanding of the molecular mechanisms of cancer pathogenesis. Novel biomarkers are required to identify in order to elucidate the basis of miRNA-mediated cancer pathogenesis and novel RNA-mediated cancer treatment strategies. In this regard, the aim of the study is to identify novel promising biomarkers for renal cell carcinomas by bioinformatics analysis.

MATERIAL AND METHODS

miRNA Selection for The Pathogenesis of Renal Cell Carcinoma

Seven miRNAs which have clinical significance for renal cell carcinomas and have been proved experimentally were exported through miRTarBase database. The miRTarBase has been developed in order to present experimentally validated and predicted data on miRNA-target interactions due to the biological significance of miRNA. That database enables scientists to verify novel targets of miRNAs. Chou et al. (2018) has described the 'Verified Target Module' [13].

Analysis of Renal Cell Carcinoma-Specific miRNA-Mediated ceRNAs

1001 genes which are targeted by these 7 miRNAs simultaneously were determined by the use of online ComiR database. ComiR, combinatorial miRNA targeting, is an online tool and estimates if a specific mRNA is targeted by a cluster of miRNAs. ComiR defines the potency for being targeted by a cluster of miRNAs. The ComiR database computes the potency of the regulation of each individual mRNA by a group of miRNAs according to the expression levels of miRNA in a combinational way. It is estimated that RNA transcripts of the genes might have the potential of ceRNA activity of the defined miRNAs [14].

Matching of Renal Cell Carcinoma-Associated ceRNA with Genes Consisting T-UCR

Ultraconserved regions (UCRs) with evolutionary conservation among organisms were determined in the human genome. Genes which contain these ultraconserved regions are divided into two as upstream (in the exonic region) and downstream [15]. In this study, the genes with T-UCR in their exonic regions and also genes which have the potential ceRNA activities among them were described.

Analysis of Renal Cell Carcinoma-associated ceRNAs Involving T-UCR for the Gene Expression Comparison Between Renal Cell Carcinoma and Normal Kidney Tissues

Gene expression differences between renal cell carcinomas and normal kidney tissues according to the renal cell carcinoma-associated ceRNAs involving T-UCR were determined by using Gene Expression Profiling Interactive Analysis (GEPIA) database. GEPIA which is a web-based and interactive bioinformatics tool is used for the analysis of gene expression [16].

Correlation Analysis of NRXN3 and PTBP2 Genes in Renal Cell Carcinoma

The statistical analysis of the relationship between NRXN3 and PTBP2 genes with renal cell carcinoma was determined by the use of Spearman correlation test in the GEPIA database.

RESULTS AND DISCUSSION

The list of seven miRNAs which are experimentally associated with RCC by the use of miRTarBase database is given in Table 1.

Table 1. List of miRNAs which are involved in the pathogenesis of renal cell carcinomas.

hsa-miR-141
hsa-miR-15a
hsa-miR-192
hsa-miR-200c
hsa-miR-21
hsa-miR-215
hsa-miR-23b

The list of 1001 genes which are targeted by the 7 miRNAs simultaneously is seen in Table A.1. According to the study that was conducted by Bejerano et al. [15] the genes which contain T-UCR in their exonic regions were given in Table A.2. The genes which have potential ceRNA activities were extracted and shown in Table 2. The genes which have expression profile differences between RCC and normal kidney tissue among renal cell carcinoma-associated ceRNAs with T-UCR have been designated. This analysis enabled to show that PTBP2 gene expression was significantly higher in normal kidney tissue than in kidney chromophobe. On the other hand, NRXN3 gene expression was significantly higher in kidney chromophobe and in renal clear cell carcinoma than in normal kidney tissue (Table 3, Table 4, Table 5).

Table 2. The list of renal cell carcinoma-associated ceRNAs cross-matching with genes involving T-UCR in the exonic regions.

UCR number	Length (bp)	Gene Name
uc.33	312	PTBP2
uc.378	251	NRXN3
uc.393	275	CLK3
uc.406	211	NFAT5

The association between NRXN3 and PTBP2 genes and renal cell carcinomas were carried out by the use of GEPIA database. Spearman correlation analysis has determined that NRXN3 and PTBP2 gene pair are significantly associated with renal cell carcinoma (figure 1) (p=0.0057; R=-0.29).

Table 3. Expression values of renal cell carcinoma-associated ceRNAs involving T-UCR between kidney chromophobe and normal kidney tissue.

Gene ID	Kidney chromophobe	Normal kidney
PTBP2*	**2.94**	**8.36**
NRXN3*	**19.24**	**0.88**
CLK3	30.35	35
NFAT5	7.54	6.82

*significant differential expression pattern between kidney chromophobe and normal kidney tissues

Table 4. Expression values of renal cell carcinoma-associated ceRNAs involving T-UCR between renal clear cell carcinoma and normal kidney tissue.

Gene ID	Renal clear cell carcinoma	Normal kidney
PTBP2	8.33	7.15
NRXN3*	**2.25**	**1.09**
CLK3	37.42	27.7
NFAT5	5.91	8.74

*significant differential expression pattern between renal clear cell carcinoma and normal kidney tissues

Table 5. Expression values of renal cell carcinoma-associated ceRNAs involving T-UCR between renal papillary cell carcinoma and normal kidney tissue.

Gene ID	Renal clear cell carcinoma	Normal kidney
PTBP2	8.33	7.15
NRXN3*	**2.25**	**1.09**
CLK3	37.42	27.7
NFAT5	5.91	8.74

Renal cell carcinoma is the most common form of kidney cancers and derived from kidney epithelium. Renal cell carcinoma is the third frequent urogenital malignancy and the twelfth most frequent cancer type in the world [17, 18]. The prognosis of RCC is still poor despite recent developments in surgical and other novel treatment strategies. Molecular characterization of renal cell carcinomas has led to the definition of particular molecular pathways, genes and miRNAs. Moreover, the increasing knowledge about the functions of miRNAs in the pathogenesis of cancers may give remarkable clue for the determination of potential diagnostic biomarkers and therapeutic targets for RCC. It appears that identification of disease-specific miRNAs may help to better clarify prognostic and therapeutic aspects of renal cell carcinomas [19, 20]. For these reasons, identification of molecular biomarkers for early diagnosis, the surveillance of RCC treatments and classification becomes more of an issue. The aim of this study was to define novel molecular biomarkers for RCC via *in silico* analysis. In this regard, RCC-specific miRNAs, their combinatorial target genes (potential ceRNAs) were determined and those with T-UCR were selected. Subsequently, the relationship between miRNA-mediated ceRNAs and RCC was analyzed by the use of statistical correlation methods.

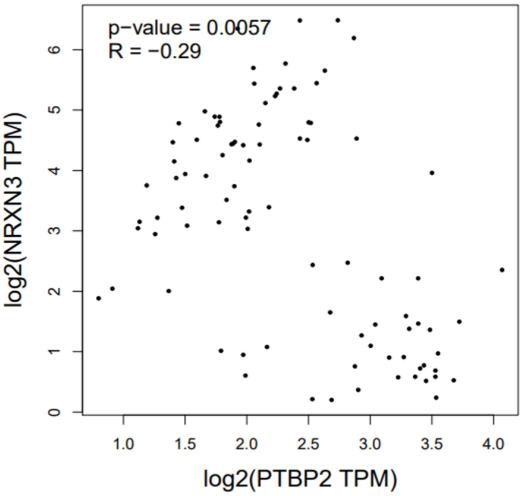

Figure 1. Spearman correlation analysis of NRXN3 and PTBP2 genes with renal cell carcinomas.

In this study, seven miRNAs experimentally associated with RCC were designated through miRTarbase database (Table 1). The genes with ComiR equal abundance score were listed among 1001 genes targeted by these seven miRNAs simultaneously. Then, the genes with T-UCR in exonic regions were determined according to the genes that contain T-UCR [15]. Furthermore, the ones with potential ceRNA activities were identified (Table 2). Afterwards, the genes with remarkable expression differences between RCC and normal kidney tissues from RCC-associated ceRNAs that contain T-UCR were selected. According to this study, PTBP2 gene expression was significantly lower in kidney chromophobe than in normal kidney tissue and NRXN3 gene expression was significantly higher in kidney chromophobe and in renal clear cell carcinoma than in normal kidney tissue. On the other hand, the other genes did not demonstrate any remarkable differential expression patterns. According to the Spearman correlation analysis, NRXN3 and PTBP2 gene pair were shown to be remarkably associated with RCC. PTBP2 gene has not been experimentally associated with renal cell carcinoma in the literature. This study is the first one to associate these two genes (NRXN3 and PTBP2) with RCC.

Neurexins are a class of protein family and encoded by the three mammalian neurexin genes NRXN1, NRXN2, NRXN3. Neurexin-3 protein which is encoded by NRXN3 gene takes a role in cell adhesion and cell recognition and modulates intracellular signaling. It has been reported that polymorphism of NRXN3 gene (rs10146997) and mutations of NRXN3 gene are related with higher breast cancer risk [21, 22]. Forkhead box protein Q1 (FOXQ1) is a transcription factor and takes a role in cancer, aging and development. It has been demonstrated that overexpression of FOXQ1 is associated with various cancer types such as lung cancer and breast cancer and the upregulation of this gene promotes tumor proliferation, invasion and metastasis. It is supposed that FOXQ1 may stimulate tumor growth and invasion via targeting NRXN3 gene in a direct way [23].

Polypyrimidine tract-binding protein 2 (RNA-binding protein) which is encoded by PTBP2 gene binds to clusters of polypyrimidine in pre-mRNAs and involved in the regulation of assembly of the other splicing-regulatory proteins. PTBP2 is implicated in neural differentiation, brain development and function and essential for postnatal survival. Moreover, in neuroblastoma and HeLa cells, PTBP2 modulates alternative splicing of several RNA molecules. Expression of PTBP2 is affected by tissue-specific miRNAs [24]. It has been reported that PTBP2 as a splicing factor induces proliferation and migration in glioma cell lines [25]. It has been known that PTBP2 is highly expressed in cancer cells and acts as a proto-oncogene and promotes the growth of tumor cells [26]. On the other hand, it has been reported that PTBP2 as a target of the oncomir miR-132 acts as a tumor suppressor in glioblastoma cells [27]. Similarly, in a study conducted with *in vitro* experiments, it was shown that PTBP1 (paralog of PTBP2) stimulated proliferation, migration, and invasion in clear-cell renal cell carcinoma [28].

The current study demonstrates for the first time that PTBP2 gene is associated with renal cell carcinoma. The results of in silico analysis suppose that PTBP2 gene may have potential tumor suppressor role in RCC and NRXN3 gene may have potential oncogenic activity in RCC.

CONCLUSION

Studies in recent years have showed that miRNAs are promising for the understanding of the molecular mechanisms of cancer pathogenesis. On the other hand, results of various studies for miRNAs in RCC have been contradictory. It has been supposed that variable roles of miRNAs at different stages of RCC or their potencies to interact with numerous targets may affect these discrepancies [29, 30]. Novel biomarkers and studies are required to identify in order to elucidate the basis of miRNA-mediated RCC pathogenesis and novel RNA-mediated cancer treatment strategies. NRXN3 and PTBP2 genes are significantly correlated with RCC for the first time. Further in vitro and *in vivo* studies are required in order to illuminate tumor suppressor role of PTBP2 and oncogenic activity of NRXN3 in RCC.

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APPENDIX

Table A.1. List of genes that are targeted by seven renal cell carcinoma-associated miRNAs simultaneously.

Gene ID	ComiR equal Abundance score
HS3ST1	0.9066
HECW1	0.9112
CFLAR	0.9157
SLC7A2	0.915
SARM1	0.9153
THSD7A	0.9116
LIG3	0.9065
KDM7A	0.907
CDKL5	0.9181
REV3L	0.9229
IYD	0.912
VTA1	0.9154

ZNF207	0.9232
IDS	0.9118
BTBD7	0.907
MBTD1	0.9138
DCN	0.9195
NRXN3	0.9196
NDUFS1	0.9121
SEC63	0.9112
SNX1	0.912
SLC39A9	0.9143
IKZF2	0.9208
UBA6	0.912
VCL	0.9108
CUL3	0.9204
TLL1	0.9147
INPP4A	0.9223
RAB27B	0.9196
ADAM28	0.9067
DCUN1D1	0.9155
PREX2	0.9068
HDAC9	0.9196
RSF1	0.9217
CELF2	0.9072
ADAMTS6	0.9069
SLC4A8	0.918
PTGER3	0.9068
HEBP2	0.9232
SIKE1	0.9112
FNIP2	0.9108
AP5M1	0.9232
KIF1B	0.9151
EIF2AK2	0.9155
KMT2C	0.9238
SOAT1	0.9175
BCAT1	0.918
PRDM6	0.912
NCKAP1	0.924
MON2	0.9217
EPN1	0.9219
CDON	0.9067
HIPK2	0.9225
GNAI3	0.924
WDR3	0.9206
MYLK	0.9202
SNAP91	0.915
CYB5R4	0.9071
ASB1	0.9118
SLC9A7	0.9198
CD84	0.9071
ATXN3	0.9237
RRP15	0.9154
POLR1A	0.9117
NUCKS1	0.9117
HS3ST1	0.9066
HECW1	0.9112
CFLAR	0.9157
SLC7A2	0.915
SARM1	0.9153
THSD7A	0.9116
LIG3	0.9065
KDM7A	0.907
CDKL5	0.9181
REV3L	0.9229
IYD	0.912
VTA1	0.9154
ZNF207	0.9232
IDS	0.9118
BTBD7	0.907
MBTD1	0.9138
DCN	0.9195
NRXN3	0.9196
NDUFS1	0.9121
SEC63	0.9112
SNX1	0.912
SLC39A9	0.9143
IKZF2	0.9208
UBA6	0.912
VCL	0.9108
CUL3	0.9204
TLL1	0.9147
INPP4A	0.9223
RAB27B	0.9196
ADAM28	0.9067
DCUN1D1	0.9155
PREX2	0.9068
HDAC9	0.9196
RSF1	0.9217
CELF2	0.9072
ADAMTS6	0.9069
SLC4A8	0.918
PTGER3	0.9068
HEBP2	0.9232
SIKE1	0.9112
FNIP2	0.9108
AP5M1	0.9232
KIF1B	0.9151
EIF2AK2	0.9155
KMT2C	0.9238
SOAT1	0.9175
BCAT1	0.918

PRDM6	0.912
NCKAP1	0.924
MON2	0.9217
EPN1	0.9219
CDON	0.9067
HIPK2	0.9225
GNAI3	0.924
WDR3	0.9206
MYLK	0.9202
SNAP91	0.915
CYB5R4	0.9071
ASB1	0.9118
SLC9A7	0.9198
CD84	0.9071
ATXN3	0.9237
RRP15	0.9154
POLR1A	0.9117
NUCKS1	0.9117
SH3BP2	0.9118
C14orf166	0.9153
KLHL42	0.9149
PTPN4	0.9228
MAVS	0.9198
ZBTB25	0.9224
GPATCH2L	0.9238
IRAK3	0.9119
ZNF268	0.9181
TNRC6A	0.9198
OSBPL8	0.9115
WDR7	0.9218
TXNL1	0.9154
NA	0.9154
RGS17	0.9176
AGO1	0.918
RFFL	0.915
NUP50	0.9107
SEC22C	0.9149
CBX5	0.9199
FKBP5	0.9154
MTAP	0.912
CECR2	0.9067
MAPK1	0.9217
ADRBK2	0.9179
MIEF1	0.9146
TNRC6B	0.9236
KIAA0930	0.9066
DESI1	0.9141
KCNK10	0.9153
NIN	0.9171
DDHD1	0.9181
TMED8	0.907
PPM1A	0.9197
SIX4	0.9147
DICER1	0.9219
ZC3H14	0.9238
PCNX	0.9116
RPS6KA5	0.9241
YY1	0.9196
RNF24	0.9207
NDUFAF5	0.9108
CDS2	0.9198
VAPA	0.9177
ST8SIA5	0.9155
CEP192	0.9121
MIB1	0.9208
XIAP	0.9206
ZC3H12B	0.911
FGF14	0.9225
NDFIP2	0.9111
FGF9	0.9105
DGKH	0.9234
KATNAL1	0.9119
INTS6	0.9234
NFAT5	0.9181
SLC7A6	0.9151
CMC2	0.9155
MLYCD	0.9198
KNOP1	0.9205
ATP8B4	0.9068
DTWD1	0.9234
SLC30A4	0.9118
MYEF2	0.9121
ZDHHC2	0.9174
FZD3	0.92
UBE2W	0.9154
ERI1	0.911
MTMR9	0.9175
FCGRT	0.9077
DMPK	0.9216
ELL	0.9103
AVL9	0.917
GTPBP10	0.9207
CDK6	0.9122
ITGB8	0.9148
MPP6	0.9154
TFEC	0.9196
LMBR1	0.9118
PLEKHA8	0.9207
RBM28	0.9229
TMEM106B	0.9074

FSD1L	0.9227
NCS1	0.9107
ATRNL1	0.9149
RAB11FIP2	0.921
PLEKHA1	0.9236
BMPR1A	0.9156
CPEB3	0.9153
MTPAP	0.911
CCNY	0.9106
TSPAN14	0.921
NUFIP2	0.9199
FBXL20	0.9073
CPD	0.9152
LUC7L3	0.9152
SMURF2	0.9154
TMEM33	0.912
DCUN1D4	0.9066
GAB1	0.9153
TRIM2	0.9173
CLNK	0.9065
WHSC1	0.9154
CTSC	0.9068
CBL	0.9155
PVRL1	0.9107
HIPK3	0.917
FBXO3	0.9197
SLC1A2	0.9156
SOX6	0.9069
LIN7A	0.922
PPM1H	0.9116
KCNA1	0.9194
C12orf49	0.9119
CAND1	0.912
CPSF6	0.9116
KRR1	0.9229
NT5DC3	0.9177
ST8SIA1	0.9179
FRK	0.9229
RWDD1	0.9065
CEP85L	0.9212
SASH1	0.9167
SOD2	0.9181
MDGA1	0.9119
GPR63	0.917
FBXL4	0.9152
E2F3	0.9138
SIM1	0.9069
KIAA1244	0.918
SLC16A10	0.9228
PHACTR2	0.9217
QKI	0.9218
CLIC5	0.915
TBX18	0.9191
SEMA5A	0.918
RNF130	0.9072
CDH6	0.9178
NPR3	0.9113
PRLR	0.9155
SKP1	0.9209
PPP2CA	0.9108
LIFR	0.9071
RARS	0.912
WWC1	0.9163
SMAD5	0.9152
ARMC8	0.9099
XRN1	0.9068
FXR1	0.9217
HEMK1	0.9074
ACVR2B	0.9236
INO80D	0.9218
PIKFYVE	0.9145
LANCL1	0.9099
GGCX	0.9115
KDM3A	0.9153
STRN	0.9117
PRKD3	0.9101
KYNU	0.9239
ORC4	0.9176
AAK1	0.923
PLEKHA3	0.92
PARD3B	0.9067
RALGPS2	0.9215
KCNC4	0.9219
RAP1A	0.9066
C1orf21	0.9181
SLC35D1	0.915
TROVE2	0.9153
TTF2	0.9154
TMED5	0.9149
DR1	0.9209
PTBP2	0.921
DIEXF	0.9203
RCAN3	0.9068
PROX1	0.9069
RCN2	0.9066
STAG1	0.9174
CAMSAP2	0.9138
ATF6	0.9115
CREB1	0.9069
FILIP1	0.9146

FBXO30	0.9179
MED28	0.9218
SLC16A7	0.9199
KLF12	0.9229
PCDH17	0.9173
CCND2	0.9068
ELL2	0.917
FKBP15	0.9114
ONECUT2	0.921
YLPM1	0.9111
AREL1	0.9104
RBM25	0.9111
NRDE2	0.9155
YIPF4	0.9218
OGFRL1	0.9198
PRLHR	0.9145
WDR11	0.9109
PANK3	0.9156
TEK	0.9108
TARDBP	0.911
PAPD5	0.9179
NAA50	0.9152
CD80	0.9139
ZMYM2	0.9177
GTDC1	0.9155
ACVR2A	0.9201
SERAC1	0.9069
ODF2L	0.9173
FAM126A	0.9181
MED13L	0.9073
RASSF8	0.9202
NLN	0.907
USP45	0.9117
FAM199X	0.907
METTL8	0.9155
ACVR1C	0.9208
LPGAT1	0.9154
TTPAL	0.9067
NCOA3	0.9109
VAPB	0.912
ZNF831	0.9173
RAB22A	0.9071
BCAS4	0.9068
ATP8A1	0.9222
SSR1	0.9199
ATXN1	0.9155
EFNB2	0.9108
ATP5S	0.9154
GTF3C4	0.912
CEP250	0.9222
AGO3	0.9237
PCNXL4	0.9237
TRMT5	0.9142
BCL11B	0.9114
MASP1	0.9102
HELB	0.9218
RAP1B	0.9225
RAB3IP	0.9121
PTPRB	0.9067
DYRK2	0.9198
FOXP2	0.9069
MKLN1	0.9199
NDUFA5	0.9195
MYO5C	0.9146
TTBK2	0.9197
ICE2	0.912
FAM63B	0.9179
SPCS3	0.9167
KIF1C	0.9139
CCNT1	0.9215
TULP4	0.9065
PRRG1	0.9144
GFAP	0.9177
RLIM	0.9118
GRSF1	0.9068
XPO4	0.9208
CHRM3	0.9118
SCO1	0.9121
MPRIP	0.9155
DCLK1	0.9071
FAM83F	0.9219
TRPM1	0.9109
SYT6	0.9147
WNT2B	0.9121
KIDINS220	0.9208
RSAD2	0.9158
IL6ST	0.9071
NAV1	0.9153
CRB1	0.9068
EMP1	0.9151
SOX5	0.9174
KLRD1	0.9234
DSC2	0.9228
ELP2	0.9153
CLOCK	0.9217
DZIP1	0.9171
ARHGAP32	0.9117
KLB	0.9101
APC	0.9228
HRK	0.9114

GDF11	0.912
ESPL1	0.9149
REPS1	0.9067
USP15	0.9229
CPM	0.9065
MDM2	0.9181
NTPCR	0.9116
FAM129A	0.9105
REV1	0.9112
GCC2	0.9154
ITM2B	0.9198
TMOD1	0.9095
TFAP2A	0.9124
KIAA0319	0.9133
RAB30	0.9198
PPP2R1B	0.9147
ITGA11	0.9116
ADAM10	0.9072
SEMA6D	0.9142
TTLL7	0.9066
DBT	0.9199
EPT1	0.912
PREPL	0.9109
ENTPD1	0.9218
HECW2	0.9071
SSFA2	0.9067
ABI2	0.924
ITGAV	0.911
USP8	0.9219
SECISBP2L	0.9107
TMOD3	0.9223
PCDH10	0.9149
FGF2	0.9227
BMP2K	0.9171
CNOT6L	0.9227
METTL20	0.9113
ETNK1	0.9151
NDUFA9	0.9154
LLPH	0.9179
GLIPR1	0.9116
PHLDA1	0.9107
TMTC3	0.9065
GAS2L3	0.9139
NUPL1	0.9114
WDFY2	0.9121
SRRM4	0.9149
NOVA1	0.907
C14orf37	0.92
SYT16	0.9219
ESR2	0.9115
KCNH5	0.9209
SLC24A4	0.9178
FGF7	0.9203
BNIP2	0.9175
TSPAN3	0.9065
NCOA2	0.9147
IGF1R	0.907
ABHD2	0.9177
NTRK3	0.9234
FTO	0.918
NKD1	0.9178
CDH11	0.9167
KSR1	0.9115
VPS53	0.9157
ASXL3	0.9068
GAREM	0.9111
RNF165	0.9066
ZFP14	0.9116
IFNAR1	0.9109
SIK1	0.9192
WTIP	0.9121
PRKACB	0.914
ZNF697	0.9108
POU2F1	0.9226
ILDR2	0.9219
SDHC	0.9157
ABL2	0.918
TOR1AIP1	0.9197
SNX27	0.9069
GABPB2	0.9207
SYT14	0.9157
VASH2	0.914
GATAD2B	0.9116
LYST	0.918
ASXL2	0.912
SPOPL	0.9111
GULP1	0.9072
UNC80	0.9146
RBMS3	0.9117
OSBPL10	0.9117
PTPRG	0.9149
LIMD1	0.9224
ZNF660	0.9065
NXPE3	0.9118
LPP	0.9234
TIFA	0.9112
GLRA3	0.9072
RPL37	0.9179
SSBP2	0.9071
PPIP5K2	0.921

BDP1	0.9141
TNFAIP8	0.9117
GFOD1	0.9154
IRAK1BP1	0.9174
MMS22L	0.9112
FAXC	0.9209
TBC1D32	0.9151
CLVS2	0.9236
RNF217	0.9234
SHPRH	0.9156
CREB5	0.9217
EGFR	0.9178
ATXN7L1	0.91
TMEM168	0.9117
NLGN4X	0.9101
LANCL3	0.9122
CASK	0.9237
FBXO25	0.9073
ERLIN2	0.9144
TACC1	0.9194
WHSC1L1	0.9176
PMP2	0.9141
VLDLR	0.9222
NFIB	0.912
CEP78	0.9071
NTRK2	0.9152
SNX30	0.9197
NR6A1	0.9115
WDR31	0.9102
USP6NL	0.921
ZEB1	0.9236
EIF4EBP2	0.9155
CNNM2	0.9225
ADAM12	0.9194
SLC5A12	0.9065
CELF1	0.9152
SESN3	0.9179
TENM4	0.9066
ZC3H12C	0.9154
HMGA2	0.9209
CDH8	0.9224
LPHN3	0.9207
CD226	0.9073
FREM2	0.9155
THRB	0.9151
GXYLT1	0.9177
AKAP6	0.9071
ADAMTS12	0.9171
FER	0.918
FAM160B1	0.9166
AKR1C2	0.9098
KIN	0.915
WWC2	0.915
BICD1	0.9151
GABRA2	0.9153
CACUL1	0.9218
RABGAP1L	0.9114
FAM168B	0.9067
PTPN14	0.9229
MGAT5	0.9144
PDK1	0.9225
UHMK1	0.912
GUCY1A2	0.9157
CCDC50	0.9217
CAMK4	0.9219
GPR180	0.9155
WDR78	0.9198
FARP1	0.9069
ZNF117	0.9232
RAB3C	0.918
SREK1IP1	0.9217
SCOC	0.9204
HNRNPU	0.9107
ASAP1	0.9069
PLEKHG4B	0.9067
CNKSR3	0.9238
DGKE	0.9155
HS2ST1	0.9206
CACNA2D1	0.9109
PPP2R5E	0.9175
CHST9	0.9181
OTULIN	0.907
UBASH3B	0.9068
TBRG1	0.9107
PITPNC1	0.9149
PRKCA	0.9153
ABCA5	0.9107
ENAH	0.92
CCSAP	0.9066
PDE1C	0.912
ADAMTS5	0.912
TTC39B	0.9199
C16orf87	0.9119
MIER3	0.9116
FAM126B	0.9228
SLC26A2	0.9119
AFF2	0.9218
GNAQ	0.9152
MMP16	0.9237
KCNMA1	0.9155

N6AMT1	0.9147
PPP2R2B	0.918
SAMD8	0.9178
MYO1E	0.9174
KCNJ6	0.9237
KCNJ15	0.9153
TAB3	0.9178
DGKI	0.9073
UBN2	0.9236
AGAP1	0.9118
CLSTN2	0.9181
SHROOM4	0.9177
ELK4	0.9198
RUNX1	0.9203
ZNF230	0.9149
ZNF233	0.9163
ZNF761	0.92
TAOK1	0.921
IL6R	0.9144
ACOX1	0.9118
ZYG11B	0.9213
PRKAA2	0.9121
GMEB1	0.911
AK4	0.9117
NFIA	0.9217
ZNF326	0.9072
ARPC5	0.9154
DDR2	0.9178
ARL5A	0.9116
PDLIM5	0.9065
CCNYL1	0.9101
GABRG1	0.9195
NIPAL1	0.9196
EIF4E3	0.9199
LRRC58	0.9196
AZI2	0.9103
NFASC	0.9178
PPM1L	0.9238
RYBP	0.9216
PPM1K	0.9115
GMPS	0.9231
SMIM14	0.9153
RPP14	0.907
GRIK3	0.9152
INTU	0.9199
HSPA4L	0.9223
OTUD4	0.9111
LMBRD2	0.9196
C5orf63	0.9151
CFAP97	0.9101

CCDC127	0.9121
CREBRF	0.9152
KIF6	0.9153
USP49	0.9154
ZNF704	0.9219
FOXK1	0.9207
DIRAS2	0.9112
KIAA1958	0.912
PTCHD1	0.921
PCDH19	0.9175
BRWD3	0.9066
SLITRK5	0.9233
FAT3	0.9221
CFL2	0.9216
SUGT1	0.9219
AMER2	0.9072
PDZD8	0.9177
TSC1	0.9194
RET	0.9102
KIAA1462	0.9145
TTC7B	0.9226
TC2N	0.9107
CPSF2	0.9073
HIF1AN	0.92
AVPR1A	0.9066
FRS2	0.9117
ARIH1	0.924
STXBP4	0.923
TRIM44	0.9199
TRIM66	0.9176
PRTG	0.9231
PRKCB	0.9115
NA	0.9209
TMED3	0.9234
GALR1	0.9122
SLFN5	0.9071
TMEM170A	0.911
ZBTB39	0.911
GREM1	0.9209
FBXO22	0.918
TBC1D16	0.9197
MYO5B	0.917
ZNF226	0.9195
ZNF641	0.9117
TRANK1	0.9112
HOOK3	0.9225
MAPK1IP1L	0.9153
RFWD3	0.909
FNTA	0.9194
LDLRAD4	0.9228

SNTB2	0.9228
SPRY3	0.9155
IRS1	0.9177
MECP2	0.9121
RAB3B	0.9122
B3GALNT1	0.9096
SHE	0.9118
SLC33A1	0.9119
PTK2	0.9111
PLEKHA2	0.9065
C15orf40	0.9072
LUZP1	0.915
REPS2	0.9215
OTUD3	0.9152
MAP3K2	0.9217
TMEM154	0.9209
SIK2	0.9071
RNF150	0.9069
USP38	0.9066
LONRF2	0.92
NUDCD2	0.9197
SGCD	0.9231
ATF7	0.9148
SOCS6	0.9191
TTLL6	0.9136
FOXN2	0.9109
PYGO1	0.9217
INSR	0.9171
KCNK3	0.9148
CLCN5	0.9119
APLN	0.9076
KSR2	0.9122
MCC	0.9114
ZNF562	0.9157
ATF7IP	0.9175
PCDHB1	0.9146
PTEN	0.9198
MALT1	0.9094
NEGR1	0.9199
CERS6	0.907
ARNT2	0.9203
FUT9	0.9239
ZNF24	0.912
ZMAT3	0.9198
CORO1B	0.9098
DCP2	0.9218
BNC2	0.9232
VANGL1	0.9071
STOX2	0.9071
SFT2D3	0.9103
PEAK1	0.9233
NABP1	0.9199
CHD2	0.9188
CEP83	0.916
SULT1B1	0.9069
NUDT4	0.9122
SCAI	0.9199
AGFG1	0.9178
PHC3	0.9218
UBXN2A	0.9115
CD34	0.9071
CYB561D1	0.9149
ATP2A2	0.9116
TMEM167A	0.9174
C4orf32	0.9121
FZD4	0.9193
PDE12	0.912
GK5	0.911
VCPIP1	0.9069
ZNF654	0.9143
CADM2	0.9156
PPM1E	0.9173
SMAD2	0.9241
ARL10	0.9181
PPP2R2D	0.9072
DPP10	0.9144
ALG10B	0.918
SLC35E3	0.921
CREG2	0.9195
ZDHHC21	0.9231
UNC119B	0.9111
JAKMIP2	0.9177
IP6K1	0.9121
SPRYD4	0.9209
SYNE3	0.9224
KIAA2018	0.9069
RNF152	0.9155
POLE	0.9067
ZBTB34	0.9232
RIMKLA	0.918
RPS6KA3	0.9151
CHD9	0.9113
MIEF2	0.9153
NR2C2	0.9179
ZBTB33	0.9104
ST8SIA3	0.9121
TBL1XR1	0.915
IL17RA	0.9112
FAM26E	0.9121
C2orf69	0.9092

PDE4DIP	0.9152
LCORL	0.9112
GEN1	0.9179
CD28	0.9109
EPM2AIP1	0.9175
ERBB4	0.9155
CSRNP3	0.9121
KCTD12	0.9067
CLK3	0.9179
CIITA	0.9069
AKAP5	0.9067
FAM73A	0.9112
SSTR2	0.9194
PCGF5	0.9178
YOD1	0.9213
CHRM2	0.911
ZNF678	0.9223
PLAG1	0.9222
RFX7	0.9178
RNF41	0.9115
MGAT4C	0.9241
ZNF716	0.9106
ZNF708	0.9213
EXT1	0.9195
FIGN	0.9179
CLN8	0.9068
PAPPA	0.9178
C16orf72	0.9181
GJC1	0.9153
CADM1	0.9208
SLC8A1	0.9226
CALN1	0.907
CHST6	0.9151
CTNNA3	0.9224
GRIN2A	0.9156
FAM46C	0.9102
LHFP	0.9077
MACC1	0.9229
KCTD16	0.9234
B3GALT5	0.9181
ST6GALNAC3	0.9196
PCDH9	0.924
AMER1	0.9171
SDR42E1	0.9156
RBM33	0.9069
FLRT2	0.9241
PURA	0.9232
ZBTB37	0.9237
HS6ST3	0.9227
RAD51D	0.9176
GPRIN3	0.921
SV2B	0.9179
LSAMP	0.9121
BRWD1	0.9177
C16orf52	0.9147
KCNQ5	0.9143
PIGP	0.912
PTCH1	0.9228
LRCH3	0.9206
MARC1	0.9069
MKL2	0.907
KPNA4	0.9216
PCLO	0.9146
LYRM7	0.9068
PPARA	0.9198
NAP1L1	0.9218
AKR1C1	0.9117
TSPYL4	0.9107
SESTD1	0.9199
FAM9C	0.9116
DCC	0.9117
TET3	0.9119
LIN28B	0.9193
ZNF626	0.9149
ZC3H6	0.9198
NCR3LG1	0.9115
DCUN1D3	0.9116
ZNF793	0.9066
CENPP	0.9155
ZNF559	0.9096
PDCD1	0.9106
CHM	0.9108
PTAR1	0.9217
VWC2	0.9122
RPL14	0.9106
BEND4	0.912
LRRK2	0.9177
PTPLAD2	0.9072
SF3B3	0.
TMEM194B	0.9113
IL1RAP	0.9144
PTPRT	0.9121
ACADSB	0.9198
LCOR	0.9178
XPNPEP3	0.9207
ZNF471	0.9068
ZNF493	0.9166
FUT4	0.9114
ZNF774	0.9067
ZNF765	0.9153

TSC22D2	0.9218
ESRRG	0.9112
GDAP2	0.9227
AJAP1	0.9209
MYO6	0.9149
HDAC2	0.9218
WNK3	0.9206
SLC30A10	0.9133
ZNF431	0.9225
NF1	0.912
VKORC1L1	0.9067
CD47	0.9065
NHLRC2	0.9156
SCN8A	0.9173
FLNA	0.9222
TMEM26	0.9108
SRGAP1	0.924
ZNF138	0.9217
GMFB	0.9198
ZNF257	0.9227
DDI2	0.9156
TRIM33	0.9176
ZNF655	0.9174
DCHS2	0.9104
ZNF81	0.9152
ZNF780A	0.9118
PLCG2	0.9108
MBP	0.9072
DLGAP2	0.9154
MRPL42	0.92
ZNF273	0.9202
ZNF667	0.9145
SVIP	0.9114
CACNA1E	0.918
HELZ	0.9209
ASPH	0.9176
GFPT1	0.9178
ZNF26	0.9238
ITSN2	0.9107
NUDT16	0.9118
TLK1	0.9165
IPO9	0.9217
SLC5A3	0.9234
LRIG2	0.918
MFAP3L	0.9067
RORB	0.9155
ZNF525	0.9199
INF2	0.9234
CHIC1	0.9117
BMPR2	0.918
MBD5	0.9117
FAM155A	0.9198
C9orf170	0.9103
ZNF468	0.9195
PCDHA4	0.9218
SLC35B4	0.9214
TMEM170B	0.9209
CCDC85C	0.9181
ITPRIPL2	0.9116
DOK6	0.9198
TMEM200C	0.9197
VGLL3	0.9181
TRIM71	0.9117
XKR4	0.9234
STK38L	0.911
C17orf51	0.9224
ZNF611	0.9203
DENND1B	0.9195
FGFR1OP	0.9181
ARHGAP19	0.9172
PPP1CB	0.9191
DNASE1	0.9176
GANC	0.911
ZNF891	0.9226
LYRM4	0.915
HAUS3	0.9108
EML6	0.9092
PEX26	0.9123
SIAH3	0.9152
APOL6	0.9121
ANKRD34C	0.9111
SHISA9	0.9068
N4BP2L2	0.918
NA	0.9212
FMN1	0.918
PCDHA10	0.9238
ATXN7L3B	0.9231
PCDHGA6	0.9105
SOGA3	0.9156
NOX5	0.9153
CLLU1	0.9101
CUX1	0.9209
FRRS1L	0.912
TMEM178B	0.9199
GAN	0.9181
DYNLL2	0.907
RNF115	0.9179
RASSF5	0.9174
GTF2H5	0.9217
NUDT3	0.9181

GRIN2B	0.9241
ZBTB8B	0.9229
NA	154
SOCS7	0.9118
TRPM1	0.9109
NA	0.9191
PIP4K2B	0.9147
ZNF8	0.9152

Table A.2. The list of genes including T-UCR in their exonic regions according to the study [2].

UCR number	Length (bp)	Gene Name
uc.13	237	EIF2C1
uc.28	355	SFRS11
uc.33	312	**PTBP2**
uc.45	203	HNRPU
uc.46	217	HNRPU
uc.48	298	PUM2
uc.49	207	BC060860
uc.50	222	SFRS7
uc.61	326	BCL11A
uc.77	296	ZFHX1B
uc.97	442	HAT1
uc.102	338	PTD004
uc.129	212	MBNL1
uc.135	201	AK096400
uc.138	419	SFRS10
uc.143	218	AB014560
uc.144	205	HNRPDL
uc.151	214	ZFR
uc.174	260	MATR3
uc.183	236	FBXW1B
uc.184	230	CPEB4
uc.185	411	CLK4
uc.186	305	HNRPH1
uc.189	573	SFRS3
uc.193	319	SYNCRIP
uc.194	201	EPHA7
uc.203	203	AB067798
uc.208	218	TRA2A
uc.209	250	TRA2A
uc.233	266	CENTG3
uc.263	207	HNRPK
uc.264	267	HNRPK
uc.280	220	PBX3
uc.282	207	GRIN1
uc.285	232	CARP-1
uc.292	217	MLR2
uc.313	231	TIAL1
uc.324	225	C11orf8
uc.330	207	RBM14
uc.331	218	DLG2
uc.333	270	FLJ25530
uc.338	223	PCBP2
uc.339	252	ATP5G2
uc.356	251	MBNL2
uc.375	300	MIPOL1
uc.376	290	PRPF39
uc.377	217	PRPF39
uc.378	251	NRXN3
uc.393	275	CLK3
uc.395	249	RBBP6
uc.406	211	NFAT5
uc.409	244	L32833
uc.413	272	BC060758
uc.414	246	THRA
uc.419	289	SFRS1
uc.436	210	TCF4
uc.443	239	HNRPM
uc.454	208	SLC23A1
uc.455	245	RNPC2
uc.456	320	SFRS6
uc.471	239	DDX3X
uc.473	222	NLGN3
uc.474	210	ZNF261
uc.475	397	OGT
uc.477	209	RAB9B
uc.478	252	GRIA3
uc.479	302	GRIA3