ORIGINAL RESEARCH

Identification of critically carcinogenesis-related genes in basal cell carcinoma

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Background: Basal cell carcinoma (BCC) is a frequent malignant tumor of skin cancers with high morbidity. The objective of this study was to identify critical genes and pathways related to the carcinogenesis of BCC and gain more insights into the underlying molecular mechanisms of BCC.

Materials and methods: The gene expression profiles of GSE7553 and GSE103439 were downloaded from the Gene Expression Omnibus database with 19 tumors and 6 normal skin tissues. Differentially expressed genes (DEGs) were screened between BCC samples and normal tissues, followed by gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis. Subsequently, protein-protein interaction (PPI) network was constructed for these DEGs, and module analysis was performed.

Results: A total of 313 DEGs were obtained. Among them, 222 genes were upregulated and 91 genes were downregulated. Enrichment analysis indicated that the upregulated genes were significantly enriched in cell cycle and mitosis, while the downregulated genes were mainly associated with unsaturated fatty acid metabolic process and cell differentiation. In addition, TOP2A, CDK1, and CCNB1 were identified as the top three hub genes ranked by degrees in the PPI network. Meanwhile, three subnetworks were derived, which indicated that these DEGs were significantly enriched in pathways, including "cell cycle", "extracellular matrix-receptor interaction", "basal cell carcinoma", and "hedgehog signaling pathway".

Conclusions: The novel critical DEGs and pathways identified in this study may serve pivotal roles in the carcinogenesis of BCC and indicate more molecular targets for the treatment of BCC.

Keywords: basal cell carcinoma, differentially expressed genes, enrichment analysis, bioinformatics analysis

Introduction

Cutaneous basal cell carcinoma (BCC) is recognized as a common subtype of nonmelanoma skin malignancies with high morbidity, which accounts for ~80% of newly diagnosed nonmelanoma skin carcinomas.1 In the last decade, there has been a substantial increase in the incidence of BCC.² Due to the characteristics of slowgrowing and locally aggressive, metastasis rarely occurred in patients with BCC, which resulted in a relatively good prognosis. As we all know, long-term exposure to sunlight, especially ultraviolet light, is considered as the main risk factor of skin cancers.3 However, the underlying molecular mechanisms for the development of BCC has not been completely illuminated. Meanwhile, the treatments of BCC are limited and drug resistance is ubiquitous in advanced or metastatic BCC patients. Therefore, an urgent need exists for further exploring the potential mechanisms of BCC and finding more effective molecular targets for the treatment of BCC.

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OncoTargets and Therapy downloaded from https://www.dovepress.com/ For personal use only To date, several signaling pathways and molecules have been demonstrated to be involved in the tumorigenesis and progression of BCC at the molecular level, such as the hedgehog signaling pathway.⁴ Genes included in this pathway, such as the hedgehog receptors patched (PTCH1) or smoothened (SMO), have been extensively studied.^{5,6} Mutations in these genes may cause constitutive hedgehog pathway activation, which promote the development of BCC. Recently, two new hedgehog pathway inhibitors, Vismodegib and Sonidegib, have been approved by the Food and Drug Administration for the targeted treatment of BCC.^{7,8} However, the response rate of advanced or metastatic BCC is not promising and the secondary drug resistance may also occur.

With the development of high-throughput technology, more and more new potential targets have been uncovered in BCC. In addition to canonical hedgehog pathway components, the transcription factor serum response factor was identified as a noncanonical hedgehog activator by multidimensional genomics analysis, which leads to the amplification of the hedgehog transcription factor glioma-associated oncogene family zinc finger-1 (GLI1).⁹ At the DNA level, Bonilla et al performed a genomic analysis of 293 BCC samples and revealed that mutations in other cancer-related genes also drove the initiation of BCC, including MYCN, PTPN14, and LATS1.¹⁰ Thus, much more molecular targets remain to be elucidated.

Bioinformatics analysis of gene expression profiles or other high-throughput data are now playing a critical role in investigating the mechanisms of human disease, particularly in tumors. Accordingly, in the present study, we first time integratively reanalyzed the gene expression profiles of 19 BCC and 6 normal tissues deposited in two datasets by differentially expressed genes (DEGs) screening and functional and pathway enrichment analysis. By protein–protein interaction (PPI) network analysis, we identified top three hub genes (TOP2A, CDK1, and CCNB1). Finally, module analysis revealed that several critical pathways were mainly associated with the carcinogenesis of BCC, which might be used as molecular targets for the treatment of BCC.

Materials and methods Microarray data

Two datasets (GSE7553 and GSE103439) were respectively retrieved from Gene Expression Omnibus database (<u>http://www.ncbi.nlm.nih.gov/geo/</u>), including 19 BCC and 6 normal tissues (Table 1).¹¹ These gene expression profiles were generated by GPL570 platform (Affymetrix Human Genome U133 Plus 2.0 Array) containing 54,675 probes. The latest

Table I The basal information of two datasets in this study

GEO datasets	Platform	Number of BCC	Number of NS
GSE7553	GPL570	15	4
GSE103439	GPL570	4	2

Abbreviations: BCC, basal cell carcinoma; GEO, Gene Expression Omnibus; NS, normal skin.

annotation file of GPL570 platform was downloaded from Affymetrix official website (<u>http://www.affymetrix.com/</u>), in which 54,675 probes now mapped to 21,297 genes.

Data preprocessing and DEGs screening

The raw data files (.CEL files) of these 25 samples were processed by the R package "affy".¹² Background adjustment and normalization were performed using the Robust Multichip Average algorithm. Once multiple probes mapped to the same gene, the average value was finally selected to represent the gene expression value. DEGs were screened between BCC and normal tissues by the "limma" package in R.¹³ Then, hierarchical clustering analysis was applied to the DEGs by the "pheatmap" package in R based on the Euclidean distance. The criteria of DEGs was set as $|log_2$ fold change|>1 and false discovery rate (FDR) <0.05.

Functional and pathway enrichment analysis

Gene ontology (GO) analysis defines the functions of gene products covering three domains, including biological process, molecular function, and cellular component.^{14,15} The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database is widely used to map large-scale datasets to pathway maps for higher-order functional information.¹⁶ The Database for Annotation, Visualization and Integrated Discovery (DAVID version 6.8, <u>http://david.abcc.ncifcrf.gov/</u>) consists of an integrated biological knowledgebase and analytic tools, which can systematically extract biological meaning from large gene/protein lists.¹⁷ With the online DAVID tool, we performed functional and pathway enrichment analysis for these DEGs. *P*-value <0.05 was considered as significant.

Construction of PPI network and module analysis

Given the large number of DEGs, the "STRINGdb" package in R was used to investigate the potential interactions that existed in these DEGs.¹⁸ Briefly, 313 DEGs were mapped to their corresponding proteins in the Search Tool for the Retrieval of Interacting Genes/Proteins database. Only interactions with a combined score of >0.4 were imported into Cytoscape software to visualize the PPI network.¹⁹ Each node in the network represents one protein, and the degree of each protein was termed as the number of its interactions. Then, the Molecular Complex Detection (MCODE) plug-in was used to analyze the PPI network to identify significant modules.²⁰ In addition, the functional and pathway enrichment analysis of genes in the subnetworks were performed. *P*-value <0.05 was set as the threshold.

Results Identification of DEGs

We screened DEGs in the two datasets (GSE7553 and GSE103439). Compared with normal skin tissues, 1,871 DEGs and 5,357 DEGs were obtained, respectively (Figure 1A). Finally, a total of 313 aberrantly expressed genes (222 upregulated genes and 91 downregulated genes) were identified by integrated analysis (Figure 1B and C). Strikingly, the number of upregulated genes were largely more than downregulated genes (Table S1). The heatmap of hierarchical clustering analysis showed that these DEGs could clearly distinguish BCC samples from the normal skin samples (Figure 1D and E).

GO and KEGG pathway enrichment analysis

To further investigate the potential functions of these 313 DEGs, GO and KEGG pathways enrichment analysis was performed by the online DAVID tool. The results of GO analysis indicated that upregulated genes enriched in biological process were mainly involved in cell cycle and mitosis, such as the cell division ($P=4.39\times10^{-11}$) and the mitotic nuclear division ($P=5.90\times10^{-8}$) (Table 2). Meanwhile, downregulated genes were significantly enriched in unsaturated fatty acid metabolic process ($P=2.10\times10^{-3}$) and cell differentiation ($P=6.76\times10^{-3}$) (Table 3). With regard to pathway enrichment analysis, the most significant pathway of upregulated genes was cell cycle ($P=4.75\times10^{-9}$) containing 13 genes. Interestingly, another five genes (LEF1, PTCH1, GLI2, FZD7, and GLI1) were enriched in the pathway named "basal cell carcinoma" ($P=2.60\times10^{-3}$) (Table 2), while downregulated genes were most significantly involved in the biosynthesis and metabolism of unsaturated fatty acids $(P=5.26\times10^{-3})$ (Table 3).

PPI network analysis and module analysis

After data of interactions imported into Cytoscape software, the PPI network with 202 nodes and 1,245 edges was constructed. Based on this network, TOP2A (degree =64),



Figure I DEGs in the two datasets.

Notes: (A) Common DEGs between GSE7553 and GSE103439. (B) Common upregulated DEGs between GSE7553 and GSE103439. (C) Common downregulated DEGs between GSE7553 and GSE103439. (D, E) Hierarchical clustering analysis of the DEGs in GSE7553 and GSE103439, respectively. Red and green indicate higher expression and lower expression, respectively.

Abbreviation: DEGs, differentially expressed genes.

Term	Count	P-value	Genes
GO:0051301:cell division	24	4.39E-11	KIF14, CDK1, KIF11, NEK2, NUF2, KIF18B, NDC80, BIRC5, CDC20, CDC25C, MCM5,
			CCNE2, CCNB1, SPC25, MAD2L1, CCNB2, HMCN1, SGO2, SPAG5, NCAPG, NCAPG2,
			ZWINT, CENPW, BUBIB
GO:0007067:mitotic nuclear division	17	5.90E-08	CDK1, KIF11, NEK2, KIF15, NUF2, BIRC5, NDC80, CDC20, PBK, CEP55, CDC25C,
			SPC25, CCNB2, NCAPG2, BUB1B, CENPW, ASPM
GO:0000070:mitotic sister chromatid	7	4.24E-07	MAD2L1, NEK2, SPAG5, ZWINT, NUSAP1, KIF18B, NDC80
segregation			
GO:0007062:sister chromatid cohesion	11	4.75E-07	SPC25, MAD2L1, SGO2, ZWINT, KIF18A, NUF2, BUB1B, NDC80, BIRC5, CDC20,
			CENPK
GO:0007052:mitotic spindle	7	1.35E-06	CCNB1, SPC25, KIF11, PCNT, TTK, NDC80, STMN1
organization			
GO:0007019:microtubule	5	4.11E-06	KIFT4, STMN3, KIFT8A, KIFT8B, STMNT
depolymerization			
GO:0045893:positive regulation of	21	4.56E-06	SOXII, PAX6, TGFB3, ATAD2, LEFI, TBXI, CREB5, SOX9, GLI2, MDK, FZD7, GLII,
transcription, DNA templated			MYCN, SMARCD3, LHX2, ZNF711, TFAP2B, CAND2, RFX3, PTCH1, SOX18
GO:0030574:collagen catabolic process	8	1.18E-05	MMPIO, COL6A3, COL6A2, COL6AI, ADAMTS3, COLIIAI, COL5A2, MMPI2
GO:0007059:chromosome segregation	8	I.77E-05	SPC25, KIFTT, NEK2, SPAG5, NUF2, CENPW, NDC80, TOP2A
GO:0006260:DNA replication	11	1.92E-05	CDK1, GINS2, POLE2, DTL, RRM2, BRIP1, CDC25C, MCM5, FEN1, MCM6, NFIB
hsa04110:cell cycle	13	4.75E-09	CCNE2, CCNB1, CDK1, MAD2L1, CCNB2, GADD45G, TGFB3, TTK, BUB1B, CDC20,
			CDC25C, MCM5, MCM6
hsa04115:p53 signaling pathway	6	6.65E-04	CCNB1, CCNE2, CDK1, CCNB2, RRM2, GADD45G
hsa04974:protein digestion and	6	0.002273	COL6A3, COL6A2, COL6A1, COL11A1, COL5A2, DPP4
absorption			
hsa05217:basal cell carcinoma	5	0.002604	
hsa03030:DNA replication	4	0.006291	POLE2, MCM5, FEN1, MCM6
hsa04512:ECM-receptor interaction	5	0.013198	COL6A3, COL6A2, COL6A1, COL11A1, COL5A2
hsa04914:progesterone-mediated	5	0.013198	CCNBI, CDKI, MAD2LI, CCNB2, CDC25C
oocyte maturation			
hsa05200:pathways in cancer	10	0.021829	CCNE2, TGFB3, RUNXITI, LEFI, BIRC5, PTCHI, GLI2, FZD7, GNG7, GLII
hsa04114:oocyte meiosis	5	0.027764	CCNE2, CDK1, MAD2L1, CDC20, CDC25C
hsa04340:hedgehog signaling pathway	3	0.032592	PTCH1, GL12, GL11

Abbreviations: ECM, extracellular matrix; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

CDK1 (degree =59), and CCNB1 (degree =54) were screened as the top three hub genes due to the higher degrees (Figure 2). Subsequently, we performed module analysis of the whole network by the MCODE plug-in. Three modules were identified and created as subnetworks. In addition, pathway enrichment analysis of genes included in each subnetwork was performed, which revealed that DEGs in modules 1–3 were mainly associated with "cell cycle", "extracellular

Table 3 The top 10 GO terms and KEGG pathways of dow	nregulated genes
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Term	Count	P-value	Genes
GO:0048704:embryonic skeletal system morphogenesis	4	7.52E-04	HOXB2, HOXB7, HOXA5, HOXA6
GO:0036109:alpha-linolenic acid metabolic process	3	0.001566736	ELOVL5, FADS1, FADS2
GO:0006636:unsaturated fatty acid biosynthetic process	3	0.002096572	ELOVL5, FADS1, FADS2
GO:0043651:linoleic acid metabolic process	3	0.002699483	ELOVL5, FADS1, FADS2
GO:0001558:regulation of cell growth	4	0.005913176	MELTF, BCARI, NANOSI, CYR6I
GO:0009952:anterior/posterior pattern specification	4	0.005913176	HOXB2, HOXB7, HOXA5, HOXA6
GO:0007267:cell-cell signaling	6	0.006210487	BMP2, ADRB2, FADS1, AREG, GDF15, CYR6
GO:0055007:cardiac muscle cell differentiation	3	0.006763636	BMP2, SIK1, NRG1
GO:0060325:face morphogenesis	3	0.008308263	DKK I, TIPARP, RRAS
GO:2000726:negative regulation of cardiac muscle cell differentiation	2	0.013694378	BMP2, DKKI
hsa01040:biosynthesis of unsaturated fatty acids	3	0.005255803	ELOVL5, FADS1, FADS2
hsa01212:fatty acid metabolism	3	0.02175659	ELOVL5, FADS1, FADS2
hsa05230:central carbon metabolism in cancer	3	0.037090419	SLCIA5, HKDCI, MYC

Abbreviations: GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.



Figure 2 Histogram of degrees of the top 30 genes in the protein–protein interaction network. Note: The number displayed on each column is the degree of each gene.

matrix (ECM)-receptor interaction", "basal cell carcinoma", and "hedgehog signaling pathway" (Figure 3).

Discussion

BCC, with low malignancy, is the most common skin cancer worldwide. Although rarely metastasize, BCC can cause substantial local tissue damage along with disfigurement and involve other adjacent areas of soft tissue, cartilage, and bone.⁷ Currently, the targeted treatments of BCC implicated in clinical practice mainly focus on the hedgehog signaling pathway.²¹ However, the issue of drug resistance and poor response rate cannot be ignored. In order to explore more potential therapeutic targets, the gene expression profiles of BCC need to be comprehensively studied. In our present study, a bioinformatics approach was conducted to reanalyze the gene expression profiles of 19 BCC and 6 normal skin tissues. A total of 313 DEGs were identified with 222 upregulated genes and 91 downregulated genes. Functional and pathway enrichment analysis indicated that these DEGs were significantly associated with mitosis, cell cycle, and unsaturated fatty acid metabolic process. By PPI network and module analysis, three critical genes and four pathways were finally identified, which may play a key role in the carcinogenesis of BCC.



Figure 3 Three subnetworks obtained from the whole protein–protein interaction network.

Notes: (A, B) Module I and the pathway enrichment analysis of genes in module I. (C, D) Module 2 and the pathway enrichment analysis of genes in module 2. (E, F) Module 3 and the pathway enrichment analysis of genes in module 3. Vertical axis represents GO or pathway terms. *P*-values are displayed by gradient colors. Abbreviations: ECM, extracellular matrix; KEGG, Kyoto Encyclopedia of Genes and Genomes.

With regard to functional and pathway enrichment analysis, upregulated DEGs were mainly involved in the process of mitosis and cell cycle. Deregulation of cell cycle is a common feature in the initiation and progression of various cancers, which is often mediated by alterations in cyclin and cyclin-dependent kinase (CDK) activity.²² CDK1, as a mitotic CDK, is sufficient to drive the mammalian cell cycle without other interphase CDKs.²³ Accumulating evidences indicated that dysregulation of CDK1 activity was participated in a variety of tumors, including lung cancer,²⁴ prostate cancer,²⁵ and colorectal cancer.²⁶ Schmit et al also discovered that increased level of CDK1 and CCNB1 presented in nonmelanoma skin cancer cells (BCC and squamous cell carcinoma) compared with normal human epidermal keratinocytes growth.²⁷ Moreover, patched1, the BCC-related protein, was found to be interacted with cyclin B1 to regulate cellcycle progression in BCC.^{28,29} Recently, targeting cyclindependent kinases has become a promising approach in cancer therapy. AZD5438, as a highly specific inhibitor of CDK1, 2, and 9, was discovered to enhance the radiosensitivity of non-small-cell lung cancer.³⁰ In the present study, our results revealed that CDK1 was significantly upregulated in BCC samples and enriched in many cell cycle-related GO terms, which indicated the potential to be a therapeutic target in BCC.

Topoisomerases have been considered as important therapeutic targets for human malignancies. TOP2A, the major isoform of topoisomerase II, is capable of resolving catenanes and supercoils during DNA metabolic processes and plays a critical role in condensation and segregation of chromosomes at mitosis. Accumulating studies highlighted that higher TOP2A expression level was correlated to advanced tumor stage and poor patients' survival in human cancers. At the protein level, increased expression of topoisomerase II α was demonstrated to be associated with elevated cell replication in BCC compared with squamous cell carcinoma.³¹ In our study, TOP2A was screened as the most significant gene with the highest degree and was up-regulated in BCC. Elevated expression of TOP2A was implicated in cell cycle, and targeting TOP2A was also considered as an important therapy for human cancers.³² Thus, TOP2A could be a critical target in BCC.

COL6A1, COL6A2, COL6A3, COL5A2, and COL11A1 are members of the collagen family, and these five genes are enriched in the pathway of "ECM–receptor interaction", which leads to a direct or indirect control of cellular activities such as adhesion, migration, differentiation, proliferation, and apoptosis. Accumulating evidence indicated that the "ECM–receptor interaction" pathway served as a critical role in the carcinogenesis and metastasis of human cancers, such as prostate cancer,³³ breast cancer,³⁴ and colorectal cancer.³⁵ In this study, we also screened "ECM–receptor interaction" as an important pathway by module analysis, which indicated the potential role in the pathogenesis of BCC.

Hedgehog signaling pathway, a highly conserved evolutionary pathway of signal transmission from the cell membrane to the nucleus, has been revealed to be associated with the development of cancers, especially in BCC.⁵ The main downstream genes of hedgehog signaling pathway include PTCH1, GL11, and GL12. In the module 3 analysis, these three genes were significantly enriched in "basal cell carcinoma", "hedgehog signaling pathway", and "pathways in cancer". Currently, targeting the hedgehog signaling pathway has been an important strategy for cancer therapy, which has achieved a promising success in BCC.²¹ However, the targeted genes were restricted to two genes (PTCH1 and SMO). Therefore, the other critical genes in this pathway are expected to be studied.

Of note, several limitations also existed in our work. First, the inclusive criteria for BCC patients and normal controls was not available due to lack of data from the public database. Second, the same as most previous studies, two relatively small patient cohorts were performed in this study. Third, there was a lack of validation in biological experiments or another dataset, which might increase the FDR in our results.

In conclusion, we performed a comprehensive bioinformatics analysis of DEGs obtained from 19 BCC and 6 normal skin tissues. Three hub genes and four pathways were finally identified, which might play a critical role in BCC. Our results further revealed the potential molecular mechanisms during the initiation of BCC and laid the foundation of exploring effective molecular targets for the treatment of BCC. However, future biology experiments are required to confirm these findings.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table SI Differentially expressed genes between basal cell carcinoma and normal skin tissues

	LOC101929122
Upregulated genes	F2RL2
ADAMTS3	DTL
LHX2	TSPYL5
CHGA	CASC15
LGR5	PELI2
SOXII	NRTN
SIODA9	GLII
PTCHI	SETBPI
	FNDCI
FBN3	MEGF6
FAT3	RAD5 I AP I
TMSB15A	PAPPA
KCNEI	SOBP
MYCN	HUNK
CRNN	NINL
COLITAT	UCP2
MMPIO	HIST1H4C
BNC2	ADGRL3
GAS2	CHRDL2
TOX2	NAPIL3
SPON2	NTRK3
TFAP2B	TOP2A
GLI2	SOX9
НЕРН	TSPAN I 8
LMO3	H2BFXP
ADAMTS17	DLGAP5
VASH2	MAD2LI
LINGO I	SI00A8
DIO2	PLEKHG4B
CHST2	NUF2
PCDHB2	GMPR
PCDH8	NDC80
NPNT	LRIG3
SOX18	SLC7A2
PITX2	CENPK
UHRFI	KRT85
TBXI	ALDH I A3
CREB5	MMP12
ABI3BP	
LINC00865	BIRC5 PCNT
EDIL3	
GPC4	KALRN
SHCBPI	KCNS3
SLC6A1	SDC2
	CYFIP2
SERPINB4	KIFI I
GJB6	COL5A2
APCDDIL	CNTN4
SOSTDCI	GBP6
LRRNI	BACH2
VCAN	HS3ST3AI
BGN	LEFI
FZD7	SGO2
SFRP5	GINS I
	CDHII
TNRC6C	TM4SF1

Table SI (Continued)

MUMILI ZNF711

SHOX2

LOCI01929122

(Continued)

MARCISLICDC4EPFIACM5XMNTLOC40173XMNTLOC40173XMNTDOHB10XMAGROBECAZM567AROBECACB755AROBECAMCC1MARCD3MCC1MARCD3MCC1MARCD3MCC1SC646ABPC41MDK1ZM5666CMP22AMACD3SC646ABPC41MDK1ZM5666CMP22AMACD3MDK1ZM5666CMP22AMACD3SC646ABPC41MDK2ZM5666CMP23CMAD2APELAADELMDK3CC1CMP24ZM5766CMP25CMAD2SCMACD3CM21CMP24ALM51CMM25CC1TTMALM51CMM24ALM51CMM25CC1TTMCM62CMM24PM71CMM34CM262CM24CM242CMM34CM223CMM34CM224CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CM34CM242CM34CM344CM34CM344CM34CM344CM34CM344 <tr< th=""><th>Table SI (Continued)</th><th>Table SI (Continued)</th></tr<>	Table SI (Continued)	Table SI (Continued)
MARCISLICDC4EPFIACM5XMNTLOC40173XMNTLOC40173XMNTDOHB10XMAGROBECAZM567AROBECACB755AROBECAMCC1MARCD3MCC1MARCD3MCC1MARCD3MCC1SC646ABPC41MDK1ZM5666CMP22AMACD3SC646ABPC41MDK1ZM5666CMP22AMACD3MDK1ZM5666CMP22AMACD3SC646ABPC41MDK2ZM5666CMP23CMAD2APELAADELMDK3CC1CMP24ZM5766CMP25CMAD2SCMACD3CM21CMP24ALM51CMM25CC1TTMALM51CMM24ALM51CMM25CC1TTMCM62CMM24PM71CMM34CM262CM24CM242CMM34CM223CMM34CM224CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CMM34CM242CM34CM242CM34CM344CM34CM344CM34CM344CM34CM344 <tr< td=""><td>KIF14</td><td>STONI</td></tr<>	KIF14	STONI
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NEIC2ZP187APGBEC3ACEP55SMARCD3HMCN1IPI27TMTC1SMACD3BUB IBSIGL3BUB IBSIGL3BUB IBSIGL4PARC4.NUDT10FANC1MKXCAN2APELACAN2APELACAN2APELACAN2APELASTG1APELASTG1APELASTG1CAN55GCICICONS1STG1TTKAPELACONS1CICITTKSTG1TTKCONS1CONS1CICITTKCONS1CONS1CICITTKCONS1CONS1CICITTKCONS1CONS1CICITTKCONS1CONS1CICICONS1CICICONS2CICICONS1CICICONS2CICICONS1CICICONS2CICICON		
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SMARCD3HKNIIHZ7HMICIIHZ7HMICISH3CJ3BUB IBSICGA6BUB IANUDTIOPAPC/LMDKZN556CMPC2CAND2APELADLE2SIGMA7STCIGADD35GCLGADD45GSSTCITTKALMSICONEPAPCITTKALMSICONEPAPCITTKALMSICONEPAPCITTKCONECONEPAPCITTTNIBTTTNIBCONECONEPARCPAPRICONECONEPARCPARCIRUNXITINIAPRICOLDNCAPGPARCPARCIPARCPARCIRUNAPRIPARCIPARCIPARCIRUNAPRIPARCIPARCIPARCIRUNAPRIPARCIPARCIPARCISIMMAPARCI <td< td=""><td>APOBEC3A</td><td></td></td<>	APOBEC3A	
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Shrank2CDKIGDDA5GSTCIRUNX1TISTCIRUNX1TIMNSICCNBIPLCEICCNBIPLCEISTTMSSSPEKCOL6AICOL0NCAPGCOL0NCAPGDCND2ACOLE2BEND5PAK1SNSPMIR3682NUSSPIRRT2RRM2GINS2COLMAICOL6AIDDDCAPGDSND5APAK5SSPNMIR3682SSPNSSPNSSPNSSPNDSSPICOL6AIDSSPISSPNDSSPISSPNDSSPISSPNDSSPISSPNDSSPISSPNDSSPISSPNDSSPISSPNDSSPISSPNDSSPISSPNDSSPISSPNDSSPISSPNDSSPISSPNDCSSSSPNDCSSSSPNDCSSSSPNDCSSSSPNDCSSSSPNDCSSSSPNDCSSSSPNDSSPNSSPNDCSSSSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPNTGDISSPN </td <td></td> <td></td>		
GADDAGSSTC /RUNXITIALMS IRUNXITIAALMS ITTKALMS ICORBIMEBCORDINEBLTBP IPCSK SBENDSPARIACCI 2BHIHE41DENND2ACOKE2BENDSPARI2SAPMMIR3682NUSAPI IPRRI2GENPWGINS2CENPWGINS2CENPWGINS2SANNIFENISINPOTNSFI0SINPOTNSFI0SINPOTNS51GADZTMEX173GADZCOLGAISINNOTNS3SINNOTNS3GADZCOLGAICOLS2GINS2COLS2COLGAISINNOTNS510GARS2TAD2GARS3TAD2SINNOTONS510MCM6COLGAICOLS2GINS2COLS2GI		
NOWITHALMS1TKPLCE1CCNB1PLCE1CCNB1PLCE1TTF1PLCE1TTF1PCSK5PBKPLPPR1CDC20COL6A1CDC20CCH22BEND5APAK6SSPMMIR3682NUSAP1PRT2CDC20CCH22BEND5PRT2SSPMCCH22SIN103CGN23CDC20CCH22BEND5PRT2SSPMCCH22NUSAP1CCH23NUSAP1CCH24STMN3CGN24STMN3STMS10STMN3NUSAP1STMN3SSP10STMN3SSP10STMN3SSP10STMN3SSP33STMN3SSP33STMN3SSP33CDC20COCA1CDC32COCA2STMN3SSP33STMN3SSP33STMN3SSP33STMN3SSP33STMN3SSP33CDC32COCA2CDC32COCA2CDC32COCA2SDRC52DSP27SDRC52SSP25TTGD1SGP33STMS3STGP33STMS3SCS1STMS3SCS1STMS3SCS2STMS3SCG24STMS3SCG24STMS3SCG24STMS4SCS1STMS5SCG25STMS5SCG24STMS5SCG25STMS5SCG24 <t< td=""><td></td><td></td></t<>		
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NFIB TETI NFIB TETI PCSK5 ITBPI PCSK5 PBK PLPRI KRT13 COL6AI DCO20 NCAPG BCC12 BLHE4I DENND2A CCNE2 BEND5 PAX6 SAFM MRI3682 NUSAPI PRT2 RM2 GINS2 CENPW COL6A3 DMD CAP44 BRP1 COL6A3 SAININ FENI SYNPO TNSF10 PTPRN2 PEKHO1 MXRAS TAS3 STMN3 KTBB MXRAS STMR3 MCM6 CO2A1 CDL52 GIN57 CDL622 BCD1 CDL622 SURPI DCHSI SURPI CDL622 SURPI DCHSI SURPI CDL624 SURPI CDL625 SURPI CDL624 SURPI <td></td> <td></td>		
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KT13C0L6A ICDC20NCAPGABCC12BHLHE41DENND2ACCNE2BEND5PAX6ASPMMIR6802NUSAPIPRRT2RM2GINS2CENPWNCAPG2DMDCGA33SIAINIFENISYNPOPIEKHOIPTRN2PIEKHOINRXA3TNS3STMN3TNS3MXRA5ATAD2ASPATMEN13COL52COL631SIAINIFENISTMN3SIAINISTMN3TNS3MXRA5GINS2COL51TMEN13COL52SIAINICOL52SIAINISTMN3TISS3MXRA5GINS2COL52SIAINICOL52SIAINICHS1GNG7COL52SPC1SPR4SPC2SPR4SPC3SPR53SIAINISPR53SIAINISPR53SIAINISPR53SIAINISPR53SPC1SPR4SPC1SPR4SPC2SPR4SPC3SPR53SIGINSPR4SIGINSPR4SIGINSPR4SIGINSPR4SIGINSPR4SIGINSPR4SIGINSPR4SIGINSPR5SIGINSPR4SIGINSPR4SIGINSPR4SIGINSPR4SIGINSPR4SIGINSPR4 </td <td></td> <td></td>		
CDC20NCAPGABCC12BHLHE41DENND2ACCNE2BEND5PAX6ASPMMISA62NUSAPIPRRT2RM2GINS2CENPWCOL6A3SINICOL6A3SINITNSFFI0SINN3NISSFI0RMX3STMN3STMN3SISSTMN3SISCOL5CCOL6A3SINN3SISSTMN3SISSTMN3SISCOL5CCOL6A3STMN3SISSTMN3SISSTMN3SISSTMN3SISSTMN3SISSTMN3SISSTMN3SISCOL5CSICO2AICOL5SCSICO3AISORCS2DEPCISORCS2SPCSISPAGSTAGINSIFL3SISSIGS <td></td> <td></td>		
ABCC12BHLHE41DENDD2ACCNE2BEND5PAX6SPMMIR562NUSAPIPRR72RM2GINS2CENPWCGP44BRP1COL6A3SIANIVAFENISYNPOTNFSF10PTRN2PLEKH01STMN3TNS3STMN3TNS3STMN3STAD2CCL52TAD2CM66SLC2AICOL6A2TNEM173COL6A3TATD2STMN3TNS3STMN3SURS3COL6A2SLC2AICOL6A2SLC2AICOL6A2SLC2AICOL6A2SSBP17COL6A2SSBP17STGSTAGLNSTGSTAGLNSPAGSTAG		
DENND2ACCNE2BENDSPAX6ASPMPRRT2RMQGINS2CENPWNCAPG2DMDCOL6A3SIANIFENISYNPOTNFSFI0PTRN2DEKHO1NRXN3TNS3STM3KIF18BMCM6ZNP653COL52SICO2AICOL632SICO2AIDCSSSICO2AITRSSTNS3STM3SICO2AIDCL52SICO2AIDCL52SICO2AICOL632SICO2AICOL632SICO2AITGTN3TNS3MCM6SICO2AICDC2SCSICO2AICDL32DEPCISTMS3SICO2AICDL42SICO2AICDL42SICO2AICDL42SICO2AICDL53SICO2AICDL42SICO2AICDL42SICO2AICDL42SICO2AICDL42SICO2AICDL42SICO2AICDL43SICO2AICDL44SICO2AICDL44SICO2AICDL44SICO2AICDL44SICO2AICDL44SICO2AICD144SICO2AICD145SICO2AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AISICO3AIS		
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CENPWNCAPG2DMDCFAP44BRIP1COLGA3SLAIN1FEN1STMPOFEN1PTPRN2NESF10NTSN3TNS3STMN3KIF18BAXRA5ATAD2FANCD2TMEM173COLGA2SLO2A1COLGA2GNG7COLGA2GNG7SORSS2JENES1DF4OSBPL7TIGD1SOSPL7STF15TGEN3KIF18ASICOLAMTRF2TGF33KIF18ABICC1KIF18AGICGKIF18AMINIKIF18AMIG7CINASMIG7CINASMIG7CINASMIG7CINASMIG7CINASMINICINASM		
DMDCFAP44BRPICOL6A3SLAINIFENISTMPOFENIPTPRN2PLEKHOINRXN3TNS3STM3KIFI8BMXRA5TMENI73DCLSSZCO2AICD2SCSLCO2AICD422BCDICD423SDEPCISORS2DEPCIDF4SSPI77TIGDISSPI77TIGDISSPI77KIFI8ARICINKIFI8ABCCIKIFI8ABCCIRIFACSRS3KIFI8ABCCIRIFACSRS3KIFI8ABCCIRIFACSRS3KIFI8ABCCIRIFAFERARIFASCO2AIKIFI8ABCCIRIFASCO3RIFABCCIRIFASCO3KIFI8ABCCIRIFASCO3RIFASCO3<		
BRIPICOL6A3SLAINIFEN ISTNPOTNFSF I.0PTRRN2PLEKH OINRXN3TNS3STMN3KIF I BBMXRA5ATAD2FANCD2TMEM I 73DCHS1SLC02AICD25CSLC02AICD422BLD1COL6A2DEPDCISORS2DEPDCISPAGSTAGLNSPAGSTAGLNMTFR2NTNIKIF18ABECIKIF18ABECIKIF18ABICCIKIF18A<		
SLAINIFEN ISYNPOTNFSF IOPTPRN2PLEKHOINRXN3TNSSSTMN3KIF IBBMXRA5ATAD2FANCD2TMEM I 73CQL5SUCO2AICDC35CSUCO2AICDL6A2GNG7COL6A2SPDC ISORS2DEPDC ISPAG5TAGLNMTFR2NTNIKIF13GGF3KIF13GFB3KIF13ABLCO2IKIF13AGIC3KIF13AGIC3KIF13AGIC3KIF13AGIC3KIF13AGIC3KIF13AGIC3KIF13AGIC4RXF33HI44PRMAIMKI67CONB2LUM		
SYNPO TNFSF IO PTPRN2 PLEKHO I NRXN3 TNS3 STMN3 KIF IAB MXRAS TMEM I73 FANCD2 TMEM I73 DCHS1 XMR6 CD25C SICO2AI CD422 GNG7 CD423 SPC1 CD444 SPC25 TIGD I SSBPI7 SFAG5 NGN MTF2 NTNI KIF18 SICO2AI PKF10 SPC1 SFAG5 GNG7 SFAG5 SECDI	SLAIN I	
PTPRN2 PLEKH01 NRXN3 TNS3 STMN3 KIF18B MXRA5 ATAD2 FANCD2 TMEM173 DCHS1 ZNR853 CDC25C SLC02A1 CDL422 BKD7 COL6A2 GNG7 SORCS2 DEPDC1 DFP4 SSBP17 TIGD1 SSBP17 MTFR2 NTNI KIF18A BICC1 RFX3 IF44 PRIMA1 MK167	SYNPO	
NRXN3 TNS3 STMN3 KIF18B MXRA5 ATAD2 FANCD2 TMEM173 DCHS1 ZNF853 MCM6 ZNF853 CD25C SLC02A1 CD422 BCID1 COL6A2 GNG7 SORCS2 DEPDC1 DP4 SSPLG5 TIGD1 SSPLG5 SPAG5 TAGLN MTFR2 TAGLN KIF18A BICC1 RFX3 IFI44 PRIMA1 MKI67	PTPRN2	
STMN3 KIF 18 B MXRA5 ATAD2 FANCD2 TMEM 173 DCHS1 ZNF853 MCM6 SLC02AI CD25C TBCI DI CD422 GNG7 C06A2 DEPDC I SORCS2 DEPDC I SPAG5 TAGLN MTFR2 NTNI KIF 18A BICC I KIF 18A BICC I RFX3 IFI44 PRIMAI LUM		
MXRAS ATAD2 FANCD2 TMEM173 DCHS1 ZNF853 MCM6 SLC02A1 CDC25C TBC1D1 CDH22 GNG7 C0L6A2 SPC25 SORCS2 DEPDC1 DPP4 SPC25 TIGD1 OSBP17 SPAG5 TAGLN MTFR2 TGFB3 KIF18A BICC1 RFX3 IFI44 PRIMA1 MKI67		
FANC D2 TMEM 173 DCHS1 ZNF853 MCM6 SLC02A1 CDC25C TBC1D1 CDH22 GNG7 COL6A2 DEPDC1 SORCS2 DEPDC1 TIGD1 SSBP17 TIGD5 TGCIN YFR2 TGFB3 KIF18A BICC1 RFX3 IH44 PRIMA1 UM	MXRA5	
DCHSI ZNF853 MCM6 SLC02AI CDC25C TBC1D1 CDH22 GNG7 C0L6A2 DEPDC1 SORCS2 DEPDC1 TIGD1 OSBPL7 SPAG5 TAGLN MTFR2 NTN1 KIF15 GFB3 KIF18A BICC1 RFX3 HI44 PRIMA1 LUM CCNB2 LUM	FANCD2	
MCM6 SLC02AI CDC25C TBCIDI CDH22 GNG7 C0L6A2 DEPDCI SORCS2 DEPDCI DP4 SSBPL7 TIGD I OSBPL7 SPAG5 TAGLN MTFR2 NTNI KIF15 TGFB3 KIF18A BICCI RFX3 FI44 PRIMAI MKI67 CCNB2 LUM		
CDC3C TBC1D1 CDH22 GNG7 C0L6A2 DEPDC1 SORCS2 DEPDC1 DPP4 SPC25 TIGD1 OSBPL7 SPAG5 TAGLN MTFR2 NTN1 KIF15A TGFB3 KIF18A BICC1 RFX3 FI44 PRIMA1 MKI67 CCNB2 LUM		
COLA22 GNG7 COL6A2 DEPDC1 SORCS2 DEPDC1 DPP4 SPC25 TIGD1 OSBPL7 SPAG5 TAGLN MTFR2 NTN1 KIF15 TGFB3 KIF18A BICC1 RFX3 FI44 PRIMA1 MKI67 CCNB2 LUM		
COLOR DEPDC1 SORCS2 SPC25 DPP4 OSBPL7 TIGD1 SPAGS SPAG5 TAGLN MTFR2 NTN1 KIF15 TGFB3 KIF18A BICC1 RFX3 IF144 PRIMA1 MK167 CCNB2 LUM		
Solicities Spc25 DPP4 OSBPL7 TIGD I OSBPL7 SPAG5 TAGLN MTFR2 NTN I KIF15 TGFB3 KIF18A BICC I RFX3 IFI44 PRIMA I MKI67 CCNB2 LUM		
TIGD I OSBPL7 SPAG5 TAGLN MTFR2 NTN I KIF15 TGFB3 KIF18A BICC I RFX3 IFI44 PRIMA I MKI67 CCNB2 LUM		
TAGLN SPAGS TAGLN MTFR2 NTN I KIF15 TGFB3 KIF18A BICC I RFX3 IFI44 PRIMA I MKI67 CCNB2 LUM		
MTFR2 NTN I KIF15 TGFB3 KIF18A BICC I RFX3 IFI44 PRIMA I MKI67 CCNB2 LUM		
KIF15 TGFB3 KIF18A BICC1 RFX3 IFI44 PRIMA1 MKI67 CCNB2 LUM		
KIF18A BICC I RFX3 IFI44 PRIMA I MKI67 CCNB2 LUM		
RFX3 IFI44 PRIMA I MKI67 CCNB2 LUM		
PRIMA I MKI67 CCNB2 LUM		
CCNB2 LUM		
		(Continued)

(Continued)

(Continued)

Downregulated genes CRTAP ID3 CNTNI NRGI SLC22AI5 TIPARP MMP28 IDHI-ASI KLHDC8B	DLK2 CTH GNAII HOXA6 CORO2A CIorf2I MSTIR EVPLL PYROXD2 CYR6I SYBU
CRTAP ID3 CNTNI NRGI SLC22A I 5 TIPARP MMP28 IDH I-ASI	GNAII HOXA6 CORO2A CI orf2 I MST I R EVPLL PYROXD2 CYR6 I
ID3 CNTN I NRG I SLC22A I 5 TIPARP MMP28 IDH I-AS I	HOXA6 CORO2A C I orf2 I MST I R EVPLL PYROXD2 CYR6 I
CNTN I NRG I SLC22A I 5 TIPARP MMP28 IDH I-AS I	CORO2A C I orf2 I MST I R EVPLL PYROXD2 CYR6 I
NRGI SLC22A I 5 TIPARP MMP28 IDH I-AS I	Clorf2l MSTIR EVPLL PYROXD2 CYR6l
SLC22A I 5 TIPARP MMP28 IDH I-AS I	MSTIR EVPLL PYROXD2 CYR61
TIPARP MMP28 IDH I-AS I	EVPLL PYROXD2 CYR61
MMP28 IDH I-AS I	PYROXD2 CYR61
IDH I -AS I	PYROXD2 CYR61
	CYR61
XG	
SMIM2 I	ELOVL5
HOXB2	HOOK2
NEFL	SERPINB2
CRELDI	FAS
HKDCI	AREG
CI lorf70	FAM89A
MYADM	HIST I H2BD
LPAR3	ILI 3RA2
ILI7RC	QPRT
FAMIIOA	APISI
BMP2	BTBD16
CBS	ACP5
NUDT16P1	MFSD2A
PHLDB2	ANTXR2
IMPACT	RAB5C
HOXB7	NANOSI
RTN4RLI	CCPGI
SLCIA5	CI I orf63
RRAS	FADSI
SNORA4	HIST I H2AC
GDF15	EML2
C8orf88	TSC22D3
COMPOS CDKN2AIPNL	DKKI
ESPN	FKBP5
ADGRF4	МҮС
ADGRF4 KLF6	ATF3
NLF0 PTPN20	HOXA5
BCARI	ENI
PRSS21	SIKI
MOCOS	ECM2
PLPP2	CHMP4C
LURAPIL	RNF128
LUKAPTL MINDY2	FADS2
MINDY2 MAFF	MELTF
	ADRB2
ERRFII (Continued	

(Continued)

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