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Research Article

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The Inhibitory Effect of Ginger Extract on Ovarian Cancer Cell Line; Application of Systems Biology

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Abstract

Purpose: Ginger is a natural compound with anti-cancer properties. The effects of ginger and its mechanism on ovarian cancer and its cell line model, SKOV-3, are unclear. In this study, we have evaluated the effect of ginger extract on SKOV-3.

Methods: SKOV-3 cells were incubated with ginger extract for 24, 48 and 72 hours. Cell toxicity assay was performed. Different data mining algorithms were applied to highlight the most important features contributing to ginger inhibition on the SKOV-3 cell proliferation. Moreover, Real-Time PCR was performed to assay p53, p21 and bcl-2 genes expression. For co-expression meta-analysis of p53, mutual ranking (MR) index and transformation to Z-values (Z distribution) were applied on available transcriptome data in NCBI GEO data repository.

Results: The ginger extract significantly inhibited cancer growth in ovarian cancer cell line. The most important attribute was 60 μ g/ml concentration which received weights higher than 0.50, 0.75 and 0.95 by 90%, 80% and 50% of feature selection models, respectively. The expression level of p53 was increased sharply in response to ginger treatment. Systems biology analysis and meta-analysis of deposited expression value in NCBI based on rank of correlation and Z-transformation approach unraveled the key co-expressed genes and co-expressed network of P53, as the key transcription factor induced by ginger extract. High co-expression between P53 and the other apoptosis-inducing proteins such as CASP2 and DEDD was noticeable, suggesting the molecular mechanism underpinning of ginger action. *Conclusion:* We found that the ginger extract has anticancer properties through p53 pathway to induce apoptosis.

Introduction

Ovarian cancer is the main reason of death from gynaecological malignant tumors, worldwide. Although there are advanced improvements in surgical techniques and accurately designed chemotherapy regimens, reversion remains practically unavoidable in patients with progressive disease.^{1,2} Ovarian cancer is the fifth cause of death related to the cancer in women and covers

a histologically and genetically a wide range of malignancies, containing those of epithelial, sex cordstromal and germ cell source.³ In the year 2016, about 22,280 new cases with ovarian cancer were diagnosed and approximately 14,240 women died because of this cancer in the United States.⁴

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There are different kinds of ovarian cancer depend on where the cell type originated. Epithelial cell ovarian cancer (EOC), gonadal-stromal, and germ cell make 90%, 6% and 4% incidence of ovarian cancer in patients, respectively. Epithelial ovarian cancer is derived from the celomic epithelium or mesothelium (epithelial ovarian carcinoma) and others arise from primordial germ cells, ovarian stromal or mesenchyme and sex cord.⁵⁻⁷ Some factors are associated with a high risk of ovarian cancer, such as old age, nuliparity, family history, infertility and endometriosis; on the other hand, factors such as usage of oral contraceptives, salpingo-oopherectomy, tubal ligation, hysterectomy and breast feeding are known to have a more protective effect.^{5,7,8}

Due to the lack of specific symptoms, the most ovarian cancers are diagnosed in the advanced stages. Therefore, the cost of treatment is high and prognosis is poor.⁵ The majority of women whose diseases are at high risk (poorly differentiated or presence of malignant cells in as cites fluid) benefit from postoperative chemotherapy. Combination chemotherapy is recommended for these patients.⁸ Chemotherapy is useful as an adjunct to surgery in some types of ovarian cancers and may be curative. Unfortunately, some factors such as severe disability, old age, malnutrition or direct organ involvement by primary or metastatic cancer influence the incidence of severe side effects of chemotherapy; therefore, using traditional medicine with chemotherapy not only kills cancer cells but also limits the cancer side effects. Ginger is from the rhizome of Zingiber officinale that has been used in traditional medicine for a long time.9

Great progresses in biotechnology and molecular biology have been caused the understanding of the genetics and molecular basis of disease which can help to find strategic therapeutic approaches and novel targeted therapies to manage ovarian cancer. Therefore, it might be possible to choose medications based on the molecular characteristics of tumors and also as basis of personalized medicine. Numerous experimental studies have been conducted in the chemo preventive belongings of ginger and their mechanisms. Their main focus is on antioxidant, neuroprotection, proliferation suppression, cancer prevention, pro-apoptotic and antiinflammatory activities.¹⁰⁻¹⁶ The result of a study on the major extracts of ginger shows that 6-gingerol inhibits angiogenesis in the human endothelial cells, it also down-regulates cyclin D1 and causes cell cycle arrest in the G1 phase.¹⁷ In addition, 6-gingerol plays a rule in oxidative stress, DNA damage, G2/M cell cycle arrest and also it induces autophagy and activates tumor suppressor proteins including P53 and P21.¹⁸ Despite the anticancer activity of ginger, its mechanisms are still poorly understood.

This study focuses on the effects of the ginger extraction on human ovarian cancer cell line (SKOV-3) to find out if the new ginger extraction is effective in treatment of ovarian cancer. In addition, bioinformatics analysis was applied on these datasets to highlight the most important features contribute to ginger inhibition on the SKOV-3 cell proliferation. The expression of p21 (cyclin-dependent kinase inhibitor 1), p53 (tumor suppressor gene), and Bcl-2 (B-cell lymphoma 2) genes following ginger treatment have been investigated. Also, Systems biology analysis and meta-analysis of deposited expression value in NCBI based on rank of correlation and Z-transformation approach were applied for further investigations about effect of ginger extract treatment on ovarian cancer cell line.

Material and Methods

Cell culture

SKOV-3, human epithelial ovarian cancer cell line was purchased from Pasteur Institute Cell Bank of Iran. The cells were grown as monolayer in 25 cm² flask (Orange Scientific) with culture medium (DMEM) (Sigma; Chemical Co., St. Louis, MO, USA) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Gibco-Life technologies), streptomycin (100 µg/mL), penicillin (100 units/mL) (Sigma), and cultured under standard condition at 37°C in a 5% humidified CO₂ incubator. The medium was exchange twice a week.

Cell proliferation assay

The effect of ginger inhibition on the SKOV-3 cell proliferation was determined by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-DiphenyltetrazoliumBromide) assay. The cells were seeded in 96-well tissue culture plates at a density of 3500 cells per well and incubated at 37 °C and 5% CO₂ humidified incubator. After 50% confluency, the cells were treated with the ginger extract (Sigma-Aldrich., W252108) in different concentrations and incubated for 24, 48 and 72 hours in assorted plates. Following the appropriate times, the upper medium was removed and 0.5 mg/ml of MTT (Sigma) solution (PBS and medium) was added to each well and incubated for 4h at 37°C. The medium was removed and the blue formazan crystals were dissolved in 100µl of DMSO. The absorbance was read in a microplate reader (Biotek, model Elx808) at 570 nm. Each experiment was repeated in triplicate format, and results were expressed as means \pm SEM.

Attribute weighting

As described before the inhibitory effects of ginger extracts on the SKOV-3 cell proliferation were determined by MTT assay. MTT assay was performed as described above. The absorbance was read by a microplate reader at 570 nm. Each experiment was repeated in triplicate format. In order to identify the most important attributes and to find the possible patterns in features which determine the effect of ginger inhibition on the SKOV-3 cell proliferation by MTT, 10 different algorithms of weighting models were applied on the datasets. Dataset imported into software (RapidMiner 5.0.001, Rapid-I GmbH, Stochumer Str. 475, 44,227 Dortmund, Germany). The attribute

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weighting models were: weight by information gain, weight by information gain ratio, weight by rule, weight by deviation, weight by chi squared statistic, weight by Gini index, weight by uncertainty, weight by relief, weight by principal component analysis (PCA), and weight by Support Vector Machines (SVM). The algorithms definitions have already been described in our previous paper.¹⁹ Weights were normalized into the interval between 0 and 1 to allow the comparison between different methods.

Decision Tree Models

Decision tree algorithms provide visual explanation of the most important features through depicting an inverted tree with the most important feature as root and other variables as leaves. Various decision trees including Random Forest, Decision Stump Decision, Iterative Dichotomiser 3 (ID3), CHi-Squared Automatic Interaction Detection (CHAID) and Random Tree were applied on dataset. Details of each decision tree model have also been presented before.¹⁹

RNA extraction and c-DNA synthesis

SKO-V cells were seeded 300000 cells per 6 well. After one day, the cells were treated with 30 μ g/ml ginger extract. Forty-eight hours after treatment, the upper medium was removed from monolayer cancer cells and scrapped in 1 ml RNAX-PLUS (Cinagene, Iran). RNA was completely extracted from samples using Cinagene Kit based on the manufacturer's instruction (RNX-Plus Solution, SinaClon, Iran). After purification and quantification, RNA was determined by measuring optical density at 260 and 280 nm by nanodrop (NanoDrop- ND-1000). The cDNA synthesis was performed according to cDNA syntheses kit instruction (Qiagene).

Real-time PCR

Real-time PCR was carried out to detect mRNA expression²⁰ with some modifications. p53, p21 and bcl-2 mRNA expression were investigated using Cycler IQ5 Multicolor Real-time PCR Detection System (Bio-Rad, USA). For various mRNA, first-strand cDNA was amplified using P53, p21 and bcl2 primers as described in the Table 1. β -actin was used as housekeeping gene. Each experiment was repeated in triplicate format, and the results were expressed as means ±SEM.

Statistics

Statistical analysis was performed with SPSS version 16.0 software and ANOVA test was used to compare between groups. Data are represented as Mean \pm SEM. The differences were considered significant when *P<0.05.

Co-expression based meta-analysis and co-expression network construction

For co-expression meta-analysis of p53 (Tp53), mutual ranking (MR) index and transformation to Z-values (Z distribution) were applied on available transcriptome

data in NCBI GEO, as previously described.²¹ MR index is a more reliable index in meta-analysis, compared to Pearson correlation coefficient, as it is based on rank of correlation and geometric average of the Pearson correlation coefficient rank.²² Geometric average is a as correlation coefficient are raked in logarithmic manner.²² Lower amount of MR implies higher correlation and a more strong expression association. To perform coexpression meta-analysis, the deposited transcriptome data in NCBI GEO NCBI were subjected to MR and Ztransformation using COXPRESSdb.²³ to identify the top 100 co-expressed genes with p53 transcription factor with low MR. Calculated MR associations, as metaanalysis co-expression measurement, were used for construction of co-expression network.

Table 1. Primers used for Real time- PCR

| Gens | Genes Primer sequence (5' to 3') |
|----------------|----------------------------------|
| DE 2 | Forward:GTTCCGAGAGCTGAATGAGG |
| F 3 3 | Reverse: ACTTCAGGTGGCTGGAGTGA |
| 021 | Forward: GCTTCATGC CAG CTACTTCC |
| P21 | Reverse: CCCTTCAAAGTG CCATCTGT |
| Rel 2 | Forward: GTCATGTGTGTGGAGAGCGT |
| DU-2 | Reverse: ACAGTTCCACAAAGGCATCC |
| R actin | Forward: CCTTCCTTCCTGGGCATG |
| p-actin | Reverse: TCCTGTCGGCAATGCCAG |

Results

The effect of ginger on cellular proliferation

In order to determine the effect of ginger on the SKOV-3 cell lines proliferation, MTT assay was illustrated at 24, 48 and 72 hours after ginger treatment. As shown in Figure 1 and 2 cell growth was inhibited considerably by ginger; consequently, it can be seen in figures, cell proliferation was decreased to 50% (P<0.05) after 48 and 72 hours of treatment. The results from analysis of the data for cell viability assay via MTT demonstrated that at 24h, 48h and 72h time points, the IC50 of ginger for SKOV-3 was approximately 97 μ g/ml, 60 μ g/ml and 40 μ g/ml. respectively.

Attribute weighting

Following normalization, 10 different attribute weighting models (as described in material and methods) were applied on GAD and RSD datasets. Each attribute was weighted between 0 and 1. These weights determined the importance of attributes in effect of new ginger extract concentration on SKOV3 cancer cell line. Attributes which gained weight equal to 0.5 or higher by at least five weighting models were selected. Table 2 shows the most important attributes was 70µg/ml concentration which received weights higher than 0.50, 0.75 and 0.95 by 90%, 80% and 50% feature selecting models. Concentration of 60µg/ml and 50µg/ml variables were the second and third important features, while 40 µg/ml concentration granted the lowest weights by attribute weighting algorithms.



Figure 1. MTT assay was used to assess the effects of ginger in the Proliferation of SKOV-3 Ovarian Cancer Cell Line after 24h and 48h. There are significant differences between treated cells and controls (P<0.05)*.



Figure 2. MTT assay was used to assess the effects of ginger on the Proliferation of SKOV-3 Ovarian Cancer Cell Line after 72h. There are significant differences between treated cells and controls (P<0.05)*.

Table 2. 10 different algorithms of weighting models applied on the datasets and new generated datasets

| PCA | SVM | Relief | Uncertainty | Gini Index | Chi Squared | Deviation | Rule | Info Gain Ratio | Info Gain | Attribute | Count 0.50 | Count 0.75 | Count0.95 |
|------|------|--------|-------------|---------------|----------------|-----------|------|--------------------|--------------|-----------|---------------|---------------|-----------|
| .79 | 1.00 | .26 | .68 | 1.00 | 1.00 | .80 | 1.00 | 1.00 | 1.00 | 70µg/ml | 9 | 8 | 5 |
| .66 | .84 | .23 | 1.00 | 1.00 | 1.00 | .59 | 1.00 | 1.00 | 1.00 | 50 µg/ml | 9 | 7 | 5 |
| .86 | .65 | .40 | .68 | 1.00 | 1.00 | .82 | 1.00 | 1.00 | 1.00 | 80 µg/ml | 9 | 7 | 4 |
| 1.00 | .61 | .30 | .51 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 60 µg/ml | 9 | 7 | 6 |
| .66 | .68 | .38 | 1.00 | 1.00 | 1.00 | .60 | 1.00 | 1.00 | 1.00 | 90 µg/ml | 9 | 6 | 5 |
| .53 | .72 | .39 | 1.00 | 1.00 | 1.00 | .44 | 1.00 | 1.00 | 1.00 | 100µg/ml | 8 | 6 | 5 |
| .37 | .66 | .34 | .76 | 1.00 | 1.00 | .26 | 1.00 | 1.00 | 1.00 | 110µg/ml | 7 | 6 | 4 |
| .31 | .46 | .22 | .76 | 1.00 | 1.00 | .23 | 1.00 | 1.00 | 1.00 | 120µg/ml | 6 | 6 | 4 |
| .44 | .37 | .00 | .37 | 1.00 | 1.00 | .36 | 1.00 | 1.00 | 1.00 | 40µg/ml | 5 | 5 | 4 |
| .00 | .00 | 1.00 | .00 | .00 | .00 | .00 | 1.00 | .00 | .00 | control | 2 | 2 | 2 |

Tree induction algorithms also underlined the significance of features that weighed most in weighting models. Remarkably, decision tree models appointed the same features selected by attribute weighting as the root features to build the trees, as can be seen in Figure 3. The trees were just single branches showing the selected features were so decisive that can be used as cut off criteria.



Figure 3. Decision Tree algorithm applied on datasets with Gini Index criterion

P53, P21 and Bcl-2 genes expression in SKOV-3 cells were investigated using RT-PCR analysis (Figure 4). The genes Ct values were normalized against mRNA level of β -actin as the housekeeping gene and the relative expression for each group was measured. After 48 hours

of ginger treatment, the level of p53 expression was increased.



Figure 4. Real Time PCR Analysis: All of data were normalized to β -actin gene expression: Increase in P53 genes expression following ginger (30 µg/ml) treatment following 48h treatment.

Co-expression based meta-analysis of p53 (Tp53) and its co-expression network

Among the studied tumor repressor genes, p53 was the top highly upregulated transcription factor in response to

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ginger extract, additional systems biology and metaanalysis were performed to unravel possible involved mechanism of ginger action through p53. Here, rank of correlation value was used rather than correlation value due to its reliability in meta-analysis. The top 100 coexpressed genes with p53 (Tp53) sorted based on low MR are presented in Table 3. The co-expression network, derived based on calculated association coefficients, are presented in Figure 5.

Table 3. The top 100 co-expressed genes with p53 (Tp53) sorted based on low mutual ranking (MR) index are presented. Meta-analysis using transcriptomic data in NCBI GEO was used for co-expression meta-analysis. When a gene list is repeatedly observed in indipendent platforms, the coexpressed gene list can be regarded as reliable with high supportability (value=3).

| 0TP53Unumo protein p33715701WHAEVariants-in-monoxygenase/(typitophan 5-monoxygenase activation7531142RBM 14RNA binding motif protein 141032211.5.93DNAJCL4DNAJ (ftsp40) nonolog, subfamily C, member 1485406120.44APH1AAPH1A gamma secretase subunit511024.7.15NONOnon-POU domain containing, octamer-binding484134.5.16RBE#retinolosisoma binding protein 4528224.3.47TAPBPTAP binding protein (tapasin)689234.5.19RKR8retinolo X receptor, beta625724.5.111DEDDdeath effector domain containing919134.9.112MAZMCCassociated dinc finger protein [unin-binding transcription factor)15035.9.213FKRP1ARKS06 binding protein 1A, 12K0a228035.114C21073chormosome 21 open reading frame 33228036.1.215WDR1WD repeat domain 1194826.2.77.516IRACIRACL4Icutor entraining 41104826.2.717COIGALT1Ioligalactosyltranferase 1194837.3.118AH40ARH50 Drase activating protein 1194837.519KDEL (Ly-Asp GL-Leu) endoplasmic reciuum protein retention194937.5< | Rank | Gene | Function | Entrez Gene ID | Supportability | MR for TP53 association |
|---|------|----------|---|-------------------|----------------|----------------------------|
| 1 YWHAE Introduct 3-monooxygenias/Ltypipan 5-monooxygeniase activation 7531 1 4 2 RBM14 RMA binding meth protein 14 10432 1 15.9 4 APH1A BMAL(10 DNAL(1000) monology.2000 and incly Chamber 14 10432 1 15.9 5 NOMO non-POU domain containing, octamer-binding 14.1 2 2.4 6 RBBP4 retinoblastoma binding protein (apasin) 682 2 4.3 7 TAPP TAP binding protein (apasin) 682 2 4.3 8 SEN73 SUMO1/sentrin/SMT3 specific petidiase 3 20168 3 4.5 10 MAT2A methionine adenosyltransferse II, alpha 4144 1 4.63 11 DED data frector domain or indig transcription factor) 115.0 40.1 12 MAZ MAC2 sascitated anching frema 3.3 200 6.12 13 FKEP1A KKEP1A 12.12 6.12 14 C21ord3 chromosome 2.1 open rading framera 3.3 | 0 | TP53 | tumor protein p53 | 7157 | | 0 |
| 2RMM 1RMA binding motif protein 14104321115.00DMA(CALDMA (Hzp4) homolog, subfamily C, member 14S6012.0.44APH1A garma servatase subunit5110724.7.57NONOnon-DOU domain containing, octamer-bindingS92824.3.48SFN93SUMO1/Sertir/SMT3 specific perilases 32516834.510MAT2Amethioding protein 14 apha414414.5.311DEDDdeta fector domain containing11414.6.312MAZmethioding protein 14, 12ba1.1.2.12ba34.9.113FKRPAFKSO colding protein 14, 12ba1.2.2.0.335.114C21orf33chromosome 21 open reading frame 23820935.9.215WDR1WC reasociated sing frame 21.1.2.12ba1.0.4.9.926.1.216LIRRC41leucine rich repeat containing 411.0.4.9.926.7.717COLCA11collegen domain 11.0.4.9.926.7.718ARHGAP1RNo GTPase activating protein 11.0.9.9.937.3.119VDELK1collegen domains 41.1.0.1.0.1.0.1.0.1.0.1.0.1.0.1.0.1.0.1 | 1 | YWHAE | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon | 7531 | 1 | 4 |
| 3DNAIC14DNAI (Hspdd) homolog, subfamily C, member 14854061241.75NONOnon-POU domain containing, octame-thinding4841342.56RBBPretinoblastoma binding protein (apasin)6892343.47TAPBPTAP binding protein (apasin)6892345.110MAT2Amethionine adencyltransferase II, alpha6168345.111DEDDdeath effector domain containing9191345.112MAZMC-coscident intic Inger protein (purine-binding transcription factor)1450345.113FKB91ArKS966 binding protein 1A, 12KDa2280351.251.214C21 ordinacoloranin 1948361.261.215WDR1WD regard domain 1948361.264.716IKR61ARelige netaing farme 3392.173.173.117COLGALT1collage beta(1-O)galacton/transferase 173709364.718AHRGAP1HNG of Pase activating protein 139273.174.219KDELKKDEL(1ys Apc Glu-taging farm farge 11396377.820CALRcalerticulan21.375.974.221AHRGAP1HNG of Pase activating protein 123.575.923AHAGIARho GPase activating protein 123.384.524AHRGAP1Rho GPase activating sprotein 123.875.9< | 2 | RBM14 | RNA binding motif protein 14 | 10432 | 1 | 15.9 |
| 4 APH1A APH1A gamma secretase subunit 51107 2 1.17 5 NON non-POU domain containing, cotame-binding 528 2 3.4 6 RBP4 retinoblastoma binding protein (apsain) 528 2 3.4 7 TAPP TAP binding protein (apsain) 528 2 45.5 10 MAT2A methionine adensyltransferase II, ajpha 4144 1 45.3 11 DED death effector domain containing 9191 3 49.1 12 MAZ MYC-associated zinc finger protein (purine-binding transcription factor) 4150 3 49.1 13 FK8P1A Houtone adensyltransferase 1 2080 3 59.2 14 C12.01A1 FK06 binding protein 1A, 12/0a 2080 3 61.2 15 WOR1 WOR repeat domain 1 9488 3 61.2 15 WOR1 Nor Feas activating protein 1 7009 3 73.1 16 LERA Cotal KOEL (Lys App-Cial-Log) adpote | 3 | DNAJC14 | DnaJ (Hsp40) homolog, subfamily C, member 14 | 85406 | 1 | 20.4 |
| 5NONOnon-POU domain containing, otzman-binding444342.57R8Pretinolistoma binding protein (tapasin)6892343.48SLNP3SLMOU/Syntrin/SMT3 specific peptidase 36257245.510MAT2methionine adencytransferase II, ajoha414146.321MAZmethionine adencytransferase II, ajoha9191349.121MAZMC-ascolated zinc Inper protein (purine-binding transcription factor)170.9369.121MAZMC-ascolated zinc Inper protein (purine-binding transcription factor)170.9361.213FKBP1AFKS06 binding protein 1A, 12KDa2280351.214C21ordiadyomosne 21 open reading frame 33948.8361.215WDR1WD repert domain 1948.8362.716LIRKIRGUE (Lyos Asp-Giu-Leu) endoplasmic reticulum protein retention948.8373.117COLGALTIcolatectuloin131.274.274.218ARHGAPRho GP assocation inhibitor (GDI) ajpha336.377.820CALRCaleticuloin27.3275.921GLISGLIS (Lyos Asp-Giu-Leu) endoplasmic reticulum protein regulator of the sactor of the sa | 4 | APH1A | APH1A gamma secretase subunit | 51107 | 2 | 41.7 |
| 6RBBP4retinoblastoma binding protein 14528234448SENP3SUMO1/sentrin/SMT3 specific populates 32616834518Retino 17 streeptor, beta6277245.510MAT2Amethionine adencyltransferase II, alpha4144146.311DEDdeath effector domain containing919349.112MAZMYC-associated inc finger protein functo-binding transcription factor1150349.113FKB1AFK506 binding protein 1A, 12k0a2809351.214C21orf33chromosome 21 open reading frame 338209362.715WDR1WD repect domain 19481262.716LRKC11lecutor fich repeat containing 4110489262.717C0LGALT1collegen beta(1-O)galactosyltransferase 177.93373.120CALRcalreticulingala75.973.121GLE1GLE1 RNA export mediator73.3275.922ARHGDIARb OD Plassociation inhibitor (GDI) alpha75.973.175.923PATC1POLICIS and AT hook containing ratin finger 123.9275.924PR14proline rich 14remediator75.975.925RABIDARb OD Plassociation inhibitor (GDI) alpha76.9384.726RAMC1Stressociation inhibitor (GDI) alpha76.975.975.6 | 5 | NONO | non-POU domain containing, octamer-binding | 4841 | 3 | 42.5 |
| 7TAP Binding protein (tapasin)68923448SLN04SLN040(settin/SMT3 specific pertidase 3625683459RXN8retinoid X receptor, beta6257245.510MAT2methionine adenosyttransferase II, lapha4144146.311DED0dest effector domain containing1911349.112MAZMtC-associated zinc finger protein (purine-binding transcription factor)4150349.113FKBPLAFK306 binding protein 1A, 1240a2280351.214C21orf33chromosome 21 open reading frame 338209364.715WDRWDrepext domain1110489262.716LIRRC41leucine rich repeat containing 4110489262.717KDEL(LY s-As-Gi-L-Le) endoplasmic reticulum protein retention receptor 1709709364.718ARHGAP1Rho GTPase activating protein retention receptor 110945373.119KDEL(LY s-As-Gi-L-Le) endoplasmic reticulum protein retention receptor 110945373.121GLE1GLE1GLE1SUB30.675.823PAT21PO2 (GTB) and AT hook containing zinc finger 123.98276.824PRHE1prober dosciation inhibitor (GDI) alpha3395.2384.525RAB1BRAB1B, member AS oncegene family23.9384.5384.5 | 6 | RBBP4 | retinoblastoma binding protein 4 | 5928 | 2 | 43.4 |
| 8 SKNP3 SUM01/sentirn/SMT3 specific peptidase 3 2616 3 45 10 MAT2A methionine adenosyltranefrase II, alpha 414 1 46.3 11 DED dest fector domain containing 1911 3 49.1 12 MAZ MMC-associated inc finger protein (purine-binding transcription factor) 4150 3 49.1 13 FKBPLA FKS06 binding protein 1A, 12k0a 2280 3 51 14 C21073 chromsome 21 open reading frame 33 2049 3 62.7 15 WDR1 WD repeat domain 1 9484 3 62.7 16 LRRC41 lecience inch repeat containing and protein 1 9484 3 62.7 17 COLGALT1 collagen betai/t0-logialactosyltransferase 1 7970 3 64.7 17 CALR caltericulin 17.8 77.8 77.8 16 LLR MA segont mediator 2359 3 77.8 17 PAC2 RAGDA Af AD containin gaint finge | 7 | ТАРВР | TAP binding protein (tapasin) | 6892 | 3 | 44 |
| 9NKNBretinoid X receptor, beta627245.511DEDdeath effector domain containing9191349.112MAZMC associated din finger protein flpurine-binding transcription factor)1150349.113FKBPLAFK506 binding protein 1A, 12kDa2200351.214C21orf33chromosome 21 open reading frame 338209352.215WDNWD repeat domain 110.489262.716LRRCA1leucine rich repeat containing 4110.489262.717COLGALT1collagen beta[-0.12glactosyltransferase 179709373.118ARHGAP1KDEL(LYS-Ap-Gin-Leudendplasmic reticulum protein retention receptor 110945373.110GLRcaltericuluincaltericuluin273.8275.921ARHGDIARho Def alsociation inhibrior (Gio)1 alpha396377.823PAT21PO2 (ETB) and AT hook containg zinc finger 123508284.524PKB14proline rich 14regular transferase 1, regular or 6384.525RAB118RB118rember AS oncegene family9230384.526SMARCC1chromatin, subfamily c, member 16555285.227NFVCnuclear transcription factor Y, gamma4802185.228FLOT2foldining zince rich 255355.255.229protein | 8 | SENP3 | SUMO1/sentrin/SMT3 specific peptidase 3 | 26168 | 3 | 45 |
| 10MAT2Amethionine adenosyltransferse II, alpha41.4146.311DEDdesh effector domain containing9191349.112MAZMYC-associated zinc finger protein (purine-binding transcription factor)4150349.113FKBP1AFKS06 binding protein 1A, 12kDa2280351.214C10rd33chromosome 2.1 open reading frame 338209362.715WDR1Incline rich repeat containing 4110489262.716LRRC41leucine rich repeat containing fan392172.517COLGALT1collagen betal,-Olgalactosyltransferase 1392373.120CALRcalreticulin811274.221GLR1GETB NA export mediator (GD1) alpha366377.822ARHGDIARho GDP dissociation inhibitor (GD1) alpha366377.823PAT21POZ (RTB) and AT hook containing zinc finger 12308280.624PRR14proline rich 1478.0280.725RAB11BRAB11B, member RAS oncogene family230384.726SMARCC1SWD/SN related, matrix associated, act in dependent regulator of659387.727NFVCnuclear transcription factor Y, gamma4802185.728FLOT2flottilin 29384.729STXscine-threeonine/tyrosine interacting protein52 | 9 | RXRB | retinoid X receptor, beta | 6257 | 2 | 45.5 |
| 11DEDDdeath effector domain containing91349.112MAZMYC-associated inc finger protein (nume-binding transcription factor)115035113FKBP1AFK506 binding protein 1A, 12kDa22809359.214C21orf33chromosome 21 open reading frame 332090361.215WDR1WD repeat domain 19948361.216LRRC41leucine rich repeat containing 411049262.717COLGAT1collage hote(1-Olgalactosyltransferase 179709364.718ARHGAP1Rho GTPase activating protein 1392.172.519KDEL(1)GLE1 RNA export mediator2733273.121GLE1GLE1 RNA export mediator2733277.822ARHGDIARho GDP dissociation inhibitor (GDI) alpha36377.823PAR14proline rich 14798028024PRR14proline rich 147980384.525RMARC1SWI/SMF related, matrix associated, actin dependent regulator of structure, commin, subfamily c, emember 15391384.525SMARC21Rotein phosphatase 5, catalytic subunit5361295.230PPPSCprotein phosphatase 2, regulatory subunit 8', delta397.631TMEM29prosemedromone fo1344397.631TMEM29prosemedromone fo134.43< | 10 | MAT2A | methionine adenosyltransferase II, alpha | 4144 | 1 | 46.3 |
| 12MAZMVC associated ainc finger protein (purine-binding transcription factor)41.0349.114C21orf33chromosome 21 open reading frame 33220035115WDR1WD repeat domain 1948361.216LRRC41leucine rich repeat containing 4110489262.717COLGALT1collagen betal-Olgalactory transferase 1790364.718ARHC61RRho GrPase activating protein 1932172.519KDELR1receptor 110945373.120CALRcalreticulin213275.921GLE1GLE1 RNA export mediator2136373.122ARHCDUARo CDP dissociation inhibitor (GDI) alpha213278.623PATZ1POZ (GTB) and AT hook containing zinc finger 1230384.524RABI1B, member RAS oncogene family230384.525RAB11BRAB11B, member RAS oncogene family2319384.727NFVCnuclear transcription factor Y, gamma802188.629STXserine/threonine/tyrosine interacting protein5536295.231TMEX29protein fopShatase 2, ctalytic subunit B', delta396.132PIPSDprotein phosphatase 2, ctalytic subunit B', delta396.133PPP2K50protein phosphatase 2, ctalytic subunit B', delta396.134< | 11 | DEDD | death effector domain containing | 9191 | 3 | 49.1 |
| 13FKBP1AFKSD6 binding protein 1A, 12kba22035114C21073chronsome 21 open reading frame 338209361.215WDR1WD repeat domain 19448361.216LRRC41leucine rich repeat containing 4110489262.718ARHGAP1Rho GTPase activating protein 1392172.519KDELR1receptor 11092373.120CALRGleitculuin detectuluin protein retention811274.221GLIGLEI RNA seport mediator2733275.922ARHGDIARolo Op dissociation inhibitor (GDI) alpha366377.823PAT21PO2 (BTB) and AT hook containing zinc finger 12359828024PRR14proline rich 14respector78.625SMARCC1SWI/SNF related, matrix associated, actin dependent regulator of summits, subfamily c, member 16599384.727NFVCnuclear transcription factor X, gamma400185.628FLOTfutilin 2catalytic subunit536295.231TMEM259protein phosphatase 2, regulatory subuin B/, deta396.132PPPSC0protein phosphatase 2, regulatory subuin B/, deta396.133PPPSC19protein phosphatase 2, regulatory subuin B/, deta396.134MYBBP1AMYB binding protein 12103.43101.4 | 12 | MAZ | MYC-associated zinc finger protein (purine-binding transcription factor) | 4150 | 3 | 49.1 |
| 14C21orB3Chromosone 21 open reading frame 33809359.215WDRWD repext domain 19448361.216LRRC41leucine rich repeat containing 4110489262.717COLGALT1collagen beta[1-O]galatosyltransferase 19709364.718ARHCAP1Rho GTPase activating protein 1972172.573.119KDELR1KDEL (Lys Asp-Glu-Leu) endoplasmic reticulum protein retention10945373.120CALRcalreticulin213275.921GEL1GEL1 RNA export mediator2733275.923PATZ1PO2 (BTB) and AT hook containing zin finger 12598278.624RABD1BRomber RAS oncogene family9230384.525RAB11BRAB11B, member RAS oncogene family9230384.526SMARCC1Simeria transcription factor Y, gamma4802185.627NFYCnuclear transcription factor Y, gamma219388.628FLOT2fotillin 2219388.629STVXserine/threonine/tyrosine interacting protein5136295.231TMEM259transmembrane protein 259104397.634MPBD1AMYB binding protein 10 factor 7519343101.435PTP1polyprimidine tract binding protein 15725103103.636P | 13 | FKBP1A | FK506 binding protein 1A, 12kDa | 2280 | 3 | 51 |
| 15WOR1WD repeat domain 1948361.216LRRC1leucine rich repeat containing 4110489262.717COLGALT1collagen beta[-10]galactos/ttransferase 179709364.718ARHGAP1Rh GTPase activating protein 192173.119KDELR1KDELL1 (Lys-Asp-Gi-Lu-leu) endoplasmic reticulum protein retention receptor 1811274.220CALRcaleticulin8111274.221GLE1GLE1 RNA export mediator2733275.922ARHGDIARho GOP dissociation inhibitor (GDI) alpha356377.823PRR14proline rich 142589286.224PRR14proline rich 14789428025RAB11BRehB12B, member AS oncogene family9230384.526SMARCC1chromatin, subfamily c, member 1219384.727NFVCnuclear transcription factor Y, gamma4802185.228FLOT2flotillin 299384.529STXserine(/threonine/tyrosine interacting protein6815288.730PPP5Cprotein phosphatase 5, catalytic subunit5336295.231TMEM259transmbrane protein 25991.0103.491.032EIFSAeukaryotic transfation initiation factor 5A1984397.633PPP2N5D </td <td>14</td> <td>C21orf33</td> <td>chromosome 21 open reading frame 33</td> <td>8209</td> <td>3</td> <td>59.2</td> | 14 | C21orf33 | chromosome 21 open reading frame 33 | 8209 | 3 | 59.2 |
| 16LRRC41leucine rich repeat containing 4110489262.717COLGN11collagen beta(1-0)galatosyltransferse 1392172.518ARHGAP1Rho GTPase activating protein 1392172.519KDELR1receptor 110945373.120CALRcalreticulin11274.221GLIGLI RNA export mediator73.3275.922ARHGD1ARho GDP dissociation inhibitor (GD) alpha36377.823PATZ1POZ (BTB) and AT hook containing ain finger 123598278.624PRR14proline rich 147899428025RAB118RAB118, member RAS oncogen family2310384.526SMARC1SWI/NF related matrix associated, actin dependent regulator of chromatin, subfamily c, member 178.9428028FLOT2flotillin 22319388.686.729STXXserine//threonine//tyrosine interacting protein65.5295.231TMEM259transmembrane protein 25991.304396.132FPFSCprotein phosphates 5, catalytic subunit55.36293.335PTBP1polypyrimidine tract binding protein 157252103.636FPFSCprotein phosphates 2, regulatory subunit 8', delta3101.435PTBP1polypyrimidine tract binding protein 157252 </td <td>15</td> <td>WDR1</td> <td>WD repeat domain 1</td> <td>9948</td> <td>3</td> <td>61.2</td> | 15 | WDR1 | WD repeat domain 1 | 9948 | 3 | 61.2 |
| 17CDLGALT1collagen beta(1-O)galatosyltransferase 1392364.718ARHGAP1Rho GTPase activating protein 1392172.519KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 110945373.120CALRcalreticulin811274.221GLE1GLE1 RNA export mediator3733275.922ARHGD1Rho GDP dissociation inhibitor (GD) alpha366377.823PAT21POZ (BTB) and AT hook containing cinc finger 123598278.624PRR14proline rich 147899428025SMARCC1SWI/SW related, matrix associated, actin dependent regulator of formatin, subfamily c, member 16599384.726SMARC2ftotilin 2921583.683.727NFYCnuclear transcription factor Y, gamma480218528FLOT2ftotilin 283.783.729STYXserine/threonine/tyrosine interacting protein6515295.231TMEX59transmembrane protein 25991304396.132EIF5Aeukaryotic translation initiation factor SA1984397.633PP22R5Dprotein phosphatae 2, regulatory subunit B', delta105143101.434MPB1AMYB binding protein 110543103.635PTB1polypyrimidine tract binding protein 15725 | 16 | LRRC41 | leucine rich repeat containing 41 | 10489 | 2 | 62.7 |
| 18ARHGAP1Rho GTPase activating protein 1392172.519KDELR1receptor 110945373.120CALRcalreticulin811274.221GLIGLI ENNA export mediator2733275.922ARHGDIARho GDP dissociation inhibitor (GDI) alpha396377.823PAT21POZ (BTB) and AT hook containing inc finger 123598280.24PRR1proline rich 14responter dissociation inhibitor (GDI) alpha396378.625RAB118RAB118, member RAS oncogene family92.30384.526SMARCC1chromatin, subfamily c, member 1chromatin, subfamily c, member 185.084.527NFVCnuclear transcription factor Y, gamma4802185.028STYXserine/threonine/tyrosine interacting protein6615288.730PFPSCprotein phosphatase 5, catalytic subunit55.691.304396.131TMEM259transmembrane protein 2591.304396.132EIF5Aeukaryotic translation initiation factor SA1984391.633PPT2Dpolypyrimidine tract binding protein 157.55210.334MYBBP1AMYB binding protein 18delta105.4100.435PTBP1polypyrimidine tract binding protein 126691105.436PTE12encel transcripti | 17 | COLGALT1 | collagen beta(1-O)galactosyltransferase 1 | 79709 | 3 | 64.7 |
| NDELR1KDEL (lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 110945373.120CALRcalerticulin811274.221GLE1GLE1 RNA export mediator2733275.922ARKD0IARho GDP dissociation inhibitor (GDI) alpha2358278.623PAT21PO2 (BTB) and AT hook containing zinc finger 123598280.624PRR14proline rich 1478994280.725RAB11B, member RAS oncogene family230.384.584.526SMARCC1SW/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 16599384.727NFVCnuclear transcription factor Y, gamma480218528FLOT2flotillin 22319388.629STYXseine/threonine/tyrosine interacting protein6815295.231TMEM259transmerbane protein 25991304396.132PIPSCprotein phosphatase 5, catalytic subunit5143101.433PPP2RSDprotein phosphatase 2, regulatory subunit B', delta105143103.634MYB binding protein (PIGO) 1a105143103.6103.635PIPAolypyrimidine tract binding protein 11723103.636PH73PHO finger protein 672798442107.137EXOSC6exosome component 6 <td< td=""><td>18</td><td>ARHGAP1</td><td>Rho GTPase activating protein 1</td><td>392</td><td>1</td><td>72.5</td></td<> | 18 | ARHGAP1 | Rho GTPase activating protein 1 | 392 | 1 | 72.5 |
| 20CALRcalreticulin811274.221GLE1GLE1 RNA export mediator2733275.923PAT21PC2 (BT8) and AT hook containing zinc finger 1235.98278.624PRR14proline rich 147899428025RAB18RAB118, member RAS oncogene family920384.526SMARCC1SW/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 16599384.727NFYCnuclear transcription factor Y, gamma480218528FLOT2flotillin 22319388.629STXserine/threonine/tyrosine interacting protein6515285.730PPPSCprotein phosphatase 5, catalytic subunit5366295.231TMEM259transmembrane protein 25991304397.633PPP2RSDprotein phosphatase 2, regulatory subunit B, delta5528298.334MYBBP1AMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336FHF23PHD finger protein 5278.942107.337EXOSCexosome component 610723107.338GTF21general transcription factor Hi52642107.339ZMF672zinc finger protein 62278.942107.1 <td< td=""><td>19</td><td>KDELR1</td><td>KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1</td><td>10945</td><td>3</td><td>73.1</td></td<> | 19 | KDELR1 | KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1 | 10945 | 3 | 73.1 |
| 21GLE1GLE1 RNA export mediator2733275.922ARHGDIARho GDP dissociation inhibitor (GDI) alpha396377.823PAT1PO2 (BTB) and AT hook containing zinc finger 17899428024PRR14proline rich 147899428025RAB11BRAB11B, member RAS oncogene family9230384.526SMARCC1SWI/NNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 16599384.727NFYCnuclear transcription factor Y, gamma480218528FLOT2flotillin 288.685384.729STYXserine/threonine/tyrosine interacting protein6815285.730PPPSCprotein phosphatae 5, catalytic subunit5366295.231TMEM259transmembrane protein 25991304396.132PFPSDprotein phosphatae 2, regulatory subunit B', delta528298.334MYBB/IAMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336PFF23PHD finger protein 672798942107.136GTF21general transcription factor Hi29691104.736GTF21general transcription domain-associated protein82953107.337EXOSC6exosome c | 20 | CALR | calreticulin | 811 | 2 | 74.2 |
| 22ARHGDIARho GDP dissociation inhibitor (GDI) alpha396377.823PATZ1POZ (BTB) and AT hook containing zinc finger 123598278.624PRR14proline rich 14789428025RAB11BRAB11B, member AS oncogene family9230384.526SWI/SNF related, matrix associated, actin dependent regulator of formatin, subfamily c, member 16599384.727NFVCnuclear transcription factor Y, gamma480218528FLOT2flotilin 22319388.629STVXserine/threonine/tyrosine interacting protein6815285.730PPPSCprotein phosphatase S, catalytic subunit5536295.231TMK259transmembrane protein 25991304396.132EIFSAeukaryotic translation initiation factor 5A1984397.633PPP2R5Dprotein phosphatase 2, regulatory subunit B', delta5528298.334MYBP1AMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 672788442107.134MYBD14MYB binding protein 12763107.334MPDU1manose-P-dolichol utilization defect 19563107.337EXPGSscoffied attoro B66978 <td>21</td> <td>GLE1</td> <td>GLE1 RNA export mediator</td> <td>2733</td> <td>2</td> <td>75.9</td> | 21 | GLE1 | GLE1 RNA export mediator | 2733 | 2 | 75.9 |
| 23PAT21POZ (BTB) and AT hook containing sinc finger 123598278.624PRR14proline rich 147899428025RAB11BRAB11B, member RAS oncogene family9230384.526SMARCC1SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 16599384.727NFVCnuclear transcription factor Y, gamma480218528FLOT2flotillin 22319388.629STYXserine/threonine/tyrosine interacting protein6515288.730PPPSCprotein phosphatase 5, catalytic subunit5536295.231TMEM259transmembrane protein 25991304396.132EIFSAeukaryotic translation initiation factor 5A1984397.633PPPZbDprotein phosphatase 2, catgulatory subunit B', delta5528298.334MYBBP1AMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 157252103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor IIi29691105.439ZNF672zinc finger protein 672798942107.140TRAPtransformation/transcription domain-associated protein82953107.341CFL1cof | 22 | ARHGDIA | Rho GDP dissociation inhibitor (GDI) alpha | 396 | 3 | 77.8 |
| 24PRR14proline rich 147899428025RAB11BRAB11B, member RAS oncogene family9230384.526SMARCC1SW/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 16599384.727NFVCnuclear transcription factor Y, gamma480218528FLOT2fotillin 22319388.629STYXserine/threonine/tyrosine interacting protein6815285.730PPPSCprotein phosphatase 5, catalytic subunit5536295.231TMEM259transmebrane protein 25991304396.132EIFSAeukaryotic translation initiation factor 5A1984397.633PPP2R5Dprotein phosphatase 2, regulatory subunit B', delta5528298.334MYBB DIAMYB binding protein (P160) 1a105.4101.435PTBP1polypyrimidine tract binding protein 15725210336PHE23PHD finger protein 672798942107.139ZNF672zin finger protein 672798942107.140TRRAPtransfortand membrane 22 homolog (yeast)5593107.341TOMM22transfortand nembrane 22 homolog (yeast)5593108.445MRPU38mitchondrial ribosomal protein 157263108.446MMPU1manoses-0-doltchol utilization defect 15526< | 23 | PATZ1 | POZ (BTB) and AT hook containing zinc finger 1 | 23598 | 2 | 78.6 |
| 25RAB11BRAB11B, member RAS oncogene family9230384.526SMARCC1SWU/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 16599384.727NFYCnuclear transcription factor Y, gamma480218528FLOT2flotillin 22319388.629STXserine/threonine/tyrosine interacting protein6815288.730PPPSCprotein phosphatase 5, catalytic subunit5536295.231TMENZS9transmembrane protein 25991304396.132EIFSAeukaryotic translation initiation factor SA1984397.633PPP2R5Dprotein phosphatase 2, regulatory subunit B', delta5528298.334MYBBP1AMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.543MPDU1manose-P-dolichol utilization defect 195263107.844TOMM22translocase of outer mitochondrial mebrane 22 homolog (yeast)56932108.445 <t< td=""><td>24</td><td>PRR14</td><td>proline rich 14</td><td>78994</td><td>2</td><td>80</td></t<> | 24 | PRR14 | proline rich 14 | 78994 | 2 | 80 |
| 26SMARCC1SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 16599384.727NFYCnuclear transcription factor Y, gamma480218528FLOT2flotilin 22319388.629STXxserine/threonine/tyrosine interacting protein6815288.730PPPSCprotein phosphatase 5, catalytic subunit5536295.231TMEM259transmembrane protein 25991304396.132EIF5Aeukaryotic translation initiation factor SA1984397.633PPP2R5Dprotein phosphatase 2, regulatory subunit B', delta5528298.334MYBBP1AMYB binding protein (16160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription domain-associated protein82953107.343MPDU1manose-P-dolichol utilization defect 195263108.344TOMM22transformation/transcription domain-associated protein82953107.542SAFBscaffold attachment factor B62943107.543MPDU1manose-P-dolichol utilization defect 195263108.344 <td>25</td> <td>RAB11B</td> <td>RAB11B, member RAS oncogene family</td> <td>9230</td> <td>3</td> <td>84.5</td> | 25 | RAB11B | RAB11B, member RAS oncogene family | 9230 | 3 | 84.5 |
| PFYCnuclear transcription factor Y, gamma480218528FLOT2fotillin 22319388.629STYXserine/threonine/tyrosine interacting protein6815288.730PPPSCprotein phosphatase 5, catalytic subunit5536295.231TMEM259transmembrane protein 25991304396.132EIF5Aeukaryotic translation initiation factor 5A1984397.633PPP2R5Dprotein phosphatase 2, regulatory subunit B', delta105143101.435PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor IIi29691105.439ZNF672zinc finger protein 672798942107.140TRRAPtransfordin/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.843MPDU1manose-P-dolichol utilization defect 1952.63108.344TOMM22transfordind a membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein 138649783109.646MTMR1myotubularin related protein 18776112.2112.6 <td>26</td> <td>SMARCC1</td> <td>SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily c member 1</td> <td>6599</td> <td>3</td> <td>84.7</td> | 26 | SMARCC1 | SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily c member 1 | 6599 | 3 | 84.7 |
| 28FLOT2flotilin 2fortilin 22319388.629STYXserine/threonine/tyrosine interacting protein6815288.730PPPSCprotein phosphatase 5, catalytic subunit5536295.231TMEM259transmembrane protein 25991304396.132EIF5Aeukaryotic translation initiation factor 5A1984397.633PPP2R5Dprotein phosphatase 2, regulatory subunit B', delta5528298.334MYBBP1AMYB binding protein (P160) 1a105143101.455PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor IIi29691105.439ZNF672zinc finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1coflin 1 (non-muscle)10723108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTNR1myotubularin related protein 152163114.548PFN1proflin 152163 | 27 | NFYC | nuclear transcription factor Y. gamma | 4802 | 1 | 85 |
| 29STYXserine/threonine/tyrosine interacting protein6815288.730PPPSCprotein phosphatase 5, catalytic subunit5536295.231TMEM259transmembrane protein 25991304396.132EIF5Aeukaryotic translation initiation factor 5A1984397.633PPP2R5Dprotein phosphatase 2, regulatory subunit B', delta5528298.334MYBBP1AMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor Ili29691105.439ZNF672zin finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.542SAFBscaffold attachment factor B62943107.843MPDU1manose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)56932108.445MRPL38mitochondrial ribosomal protein L3864783109.646MTMR1myotubularin related protein 1 | 28 | FLOT2 | flotillin 2 | 2319 | 3 | 88.6 |
| 30PPP5Cprotein phosphatase 5, catalytic subunit5536295.231TMEM259transmembrane protein 25991304396.132EIF5Aeukaryotic translation initiation factor 5A1984397.633PPP2R5Dprotein phosphatase 2, regulatory subunit B', delta5528298.334MYBBP1AMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor IIi29691105.439ZNF672zinc finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 15163 </td <td>29</td> <td>STYX</td> <td>serine/threonine/tyrosine interacting protein</td> <td>6815</td> <td>2</td> <td>88.7</td> | 29 | STYX | serine/threonine/tyrosine interacting protein | 6815 | 2 | 88.7 |
| 1TMEM259transmembrane protein 25991304396.132EIF5Aeukaryotic translation initiation factor 5A1984397.633PP22B5Dprotein phosphatase 2, regulatory subunit B', delta5528298.334MYBBP1AMYB binding protein (P160) 1a105143101.455PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor IIi29691105.439ZNF672zinc finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein 1387761112.246MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933 | 30 | PPP5C | protein phosphatase 5, catalytic subunit | 5536 | 2 | 95.2 |
| 32EIF5Aeukaryotic translation initiation factor 5A1984397.633PPP2R5Dprotein phosphatase 2, regulatory subunit B', delta5528298.334MYBBP1AMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor Ili29691105.439ZNF672zinc finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 152163112.247SRSF1serine/arginine-rich splicing factor 164263112.649EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa19683115.550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAM | 31 | TMEM259 | transmembrane protein 259 | 91304 | 3 | 96.1 |
| 33PPP2RSDprotein phosphatase 2, regulatory subunit B', delta5728298.334MYBBP1AMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor Ili29691105.439ZNF672zinc finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotibularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa19683115.550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 131873123.353STIP1< | 32 | EIF5A | eukarvotic translation initiation factor 5A | 1984 | 3 | 97.6 |
| 34MYBBP1AMYB binding protein (P160) 1a105143101.435PTBP1polypyrimidine tract binding protein 15725210336PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor Ili29691105.439ZNF672zinc finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.542SAFBscaffold attachment factor B62943107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein 138649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 2, subunit 3 gamma, 52kDa19683114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa19683115.550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 13163118.452HNRNPH1< | 33 | PPP2R5D | protein phosphatase 2, regulatory subunit B', delta | 5528 | 2 | 98.3 |
| 35 PTBP1 polypyrimidine tract binding protein 1 5725 2 103 36 PHF23 PHD finger protein 23 79142 3 103.6 37 EXOSC6 exosome component 6 118460 1 104.7 38 GTF21 general transcription factor IIi 2969 1 105.4 39 ZNF672 zinc finger protein 672 79894 2 107.1 40 TRRAP transformation/transcription domain-associated protein 8295 3 107.3 40 TRRAP transformation/transcription domain-associated protein 8295 3 107.5 41 CFL1 cofilin 1 (non-muscle) 1072 3 107.8 43 MPDU1 manose-P-dolichol utilization defect 1 9526 3 108.3 44 TOMM22 translocase of outer mitochondrial membrane 22 homolog (yeast) 56933 2 108.4 45 MRPL38 mitochondrial ribosomal protein 138 64978 3 109.6 46 MTMR1 myotubularin related protein 1 8776 1 112.2 | 34 | MYBBP1A | MYB binding protein (P160) 1a | 10514 | 3 | 101.4 |
| 36PHF23PHD finger protein 23791423103.637EXOSC6exosome component 61184601104.738GTF21general transcription factor IIi29691105.439ZNF672zinc finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.542SAFBscaffold attachment factor B62943107.843MPDU1manose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa19683115.650FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 131873123.353STIP1stress-induced phosphonoratein 1109632130.9 | 35 | PTBP1 | polypyrimidine tract binding protein 1 | 5725 | 2 | 103 |
| 37EXOSC6exosome component 61184601104.738GTF21general transcription factor IIi29691105.439ZNF672zinc finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.542SAFBscaffold attachment factor B62943107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa19683115.650FARSAphenylalanyl-tRNA synthetase, alpha subunit21933118.451LAMP1lysosomal-associated membrane protein 131873123.353STIP1stress-induced phosphorartein 1109632130.9 | 36 | PHF23 | PHD finger protein 23 | 79142 | 3 | 103.6 |
| 38GTF21general transcription factor IIi29691105.439ZNF672zinc finger protein 672788942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.542SAFBscaffold attachment factor B62943107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa19683115.650FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 1139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced nbosphorprotein 1109632130.9 | 37 | EXOSC6 | exosome component 6 | 118460 | 1 | 104.7 |
| 39ZNF672zinc finger protein 672798942107.140TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.542SAFBscaffold attachment factor B62943107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263114.548PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa19683115.550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-indured hosphonrotein 1109632130.9 | 38 | GTF2I | general transcription factor IIi | 2969 | - | 105.4 |
| 40TRRAPtransformation/transcription domain-associated protein82953107.341CFL1cofilin 1 (non-muscle)10723107.542SAFBscaffold attachment factor B62943107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263114.548PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa19683115.650FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced nbosphornzein 1109632130.9 | 39 | ZNF672 | zinc finger protein 672 | 79894 | 2 | 107.1 |
| 41CFL1cofilin 1 (non-muscle)10723107.542SAFBscaffold attachment factor B62943107.843MPDU1mannose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa1968311550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphorncrien 1109632130.9 | 40 | TRRAP | transformation/transcription domain-associated protein | 8295 | 3 | 107.3 |
| 42SAFBscaffold attachment factor B62943107.843MPDU1manose-P-dolichol utilization defect 195263108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa1968311550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphorncrein 1109632130.9 | 41 | CFI 1 | cofilin 1 (non-muscle) | 1072 | 3 | 107.5 |
| 43MPDU1manose-P-dolichol utilization defect 1952.63108.344TOMM22translocase of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa1968311550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphorncrein 1109632130.9 | 42 | SAFB | scaffold attachment factor B | 6294 | 3 | 107.8 |
| 44TOMM22translocate of outer mitochondrial membrane 22 homolog (yeast)569932108.445MRPL38mitochondrial ribosomal protein L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa1968311550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced nbosphornratein 1109632130.9 | 43 | MPDU1 | mannose-P-dolichol utilization defect 1 | 9526 | 3 | 108.3 |
| 45MRPL38mitochood of order initiation initiation initiation initiation in L38649783109.646MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa1968311550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphoprotein 1109632130.9 | 44 | TOMM22 | translocase of outer mitochondrial membrane 22 homolog (yeast) | 56993 | 2 | 108.4 |
| 46MTMR1myotubularin related protein 187761112.247SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa1968311550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphorprotein 1109632130.9 | 45 | MRPI 38 | mitochondrial ribosomal protein 138 | 64978 | 3 | 109.6 |
| 47SRSF1serine/arginine-rich splicing factor 164263112.648PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa1968311550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphorprotein 1109632130.9 | 46 | MTMR1 | myotubularin related protein 1 | 8776 | 1 | 112.2 |
| 48PFN1profilin 152163114.549EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa1968311550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphoprotein 1109632130.9 | 47 | SRSF1 | serine/arginine-rich solicing factor 1 | 6426 | 3 | 112.6 |
| 49EIF2S3eukaryotic translation initiation factor 2, subunit 3 gamma, 52kDa1968311550FARSAphenylalanyl-tRNA synthetase, alpha subunit21933116.651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphoprotein 1109632130.9 | 48 | PFN1 | nrofilin 1 | 5216 | 3 | 114 5 |
| 50FARSAphenylalanyl-tRNA synthetase, alpha subunit2193311651LAMP1lysosomal-associated membrane protein 139163118.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphoprotein 1109632130.9 | 49 | FIF2S3 | eukarvotic translation initiation factor 2 subunit 3 gamma 52kDa | 1968 | 3 | 115 |
| 51LAMP1lysosomal-associated membrane protein 139163110.052HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphonrotein 1109632130.9 | 50 | FARSA | nhenvlalanvl-tRNA synthetase alnha subunit | 2193 | 3 | 116.6 |
| 51515151116.452HNRNPH1heterogeneous nuclear ribonucleoprotein H1 (H)31873123.353STIP1stress-induced phosphonrotein 1109632130.9 | 51 | LAMP1 | lysosomal-associated membrane protein 1 | 3916 | 3 | 118.4 |
| 52 STIP1 stress-induced nboshonrotein 1 100 100 100 100 100 100 100 100 100 | 52 | HNRNPH1 | heterogeneous nuclear ribonucleoprotein H1 (H) | 3187 | 3 | 123.3 |
| | 53 | STIP1 | stress-induced nosnhonrotein 1 | 10963 | 2 | 130.9 |

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| Develo | Come | Function | Entrez | Compared a billion | MR for TP53 |
|-----------|-----------|--|--------------|--------------------|----------------|
| капк | Gene | Function | Gene ID | Supportability | association |
| 54 | HSF1 | heat shock transcription factor 1 | 3297 | 3 | 135.6 |
| 55 | GANAB | glucosidase, alpha; neutral AB | 23193 | 3 | 135.7 |
| 56 | ASB16-AS1 | ASB16 antisense RNA 1 | 339201 | 2 | 136 |
| 57 | LIX1L | Lix1 homolog (chicken) like | 128077 | 3 | 136.8 |
| 58 | KLHDC3 | kelch domain containing 3 | 116138 | 3 | 137.2 |
| 59 | DRG2 | developmentally regulated GTP binding protein 2 | 1819 | 3 | 139 |
| 60 | BANF1 | barrier to autointegration factor 1 | 8815 | 3 | 139.8 |
| 61 | AKIRIN2 | akirin 2 | 55122 | 1 | 140.8 |
| 62 | RELA | v-rel avian reticuloendotheliosis viral oncogene homolog A | 5970 | 3 | 141.5 |
| 63 | CASP2 | caspase 2, apoptosis-related cysteine peptidase | 835 | 2 | 145.9 |
| 64 | MAP2K2 | mitogen-activated protein kinase kinase 2 | 5605 | 3 | 146.8 |
| 65 | RANGAP1 | Ran GTPase activating protein 1 | 5905 | 3 | 150.6 |
| 66 | NAP1L4 | nucleosome assembly protein 1-like 4 | 4676 | 2 | 151.7 |
| 67 | MTA1 | metastasis associated 1 | 9112 | 3 | 154.1 |
| 68 | REPIN1 | replication initiator 1 | 29803 | 2 | 154.3 |
| 69 | ZBTB45 | zinc finger and BTB domain containing 45 | 84878 | 3 | 155.4 |
| 70 | PPP2R1A | protein phosphatase 2, regulatory subunit A, alpha | 5518 | 3 | 156.1 |
| 71 | CYB5R3 | cytochrome b5 reductase 3 | 1727 | 2 | 157.6 |
| 72 | UBE4B | ubiquitination factor E4B | 10277 | 1 | 159.4 |
| 73 | ACLY | ATP citrate lyase | 47 | 3 | 160.4 |
| 74 | UBE2G2 | ubiquitin-conjugating enzyme E2G 2 | 7327 | 0 | 163.2 |
| 75 | DNAAF5 | dynein, axonemal, assembly factor 5 | 54919 | 3 | 170 |
| 76 | GDI2 | GDP dissociation inhibitor 2 | 2665 | 3 | 170.1 |
| 77 | BSG | basigin (Ok blood group) | 682 | 3 | 171.8 |
| 78 | SLC25A11 | solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11 | 8402 | 3 | 173.4 |
| 79 | BTBD2 | BTB (POZ) domain containing 2 | 55643 | 3 | 173.7 |
| 80 | C1orf174 | chromosome 1 open reading frame 174 | 339448 | 2 | 176.2 |
| 81 | ABCC1 | ATP-binding cassette, sub-family C (CFTR/MRP), member 1 | 4363 | 3 | 178.4 |
| 82 | DCAF15 | DDB1 and CUL4 associated factor 15 | 90379 | 2 | 180.4 |
| 83 | SLC29A1 | solute carrier family 29 (equilibrative nucleoside transporter), member 1 | 2030 | 2 | 181 |
| 84 | KCTD5 | potassium channel tetramerization domain containing 5 | 54442 | 1 | 191.8 |
| 85 | TBC1D5 | TBC1 domain family, member 5 | 9779 | 2 | 192.7 |
| 86 | SHC1 | SHC (Src homology 2 domain containing) transforming protein 1 | 6464 | 3 | 192.9 |
| 87 | CRTAP | cartilage associated protein | 10491 | 2 | 194.3 |
| 88 | NUCKS1 | nuclear casein kinase and cyclin-dependent kinase substrate 1 | 64710 | 3 | 197.2 |
| 89 | STAT2 | signal transducer and activator of transcription 2, 113kDa | 6773 | 3 | 198.6 |
| 90 | NFRKB | nuclear factor related to kappaB binding protein | 4798 | 2 | 200.8 |
| 91 | ANKFY1 | ankyrin repeat and FYVE domain containing 1 | 51479 | 3 | 207.5 |
| 92 | TRAPPC1 | trafficking protein particle complex 1 | 58485 | 3 | 208 |
| 93 | CBFB | core-binding factor, beta subunit | 865 | 2 | 210 |
| 94 | NCOA5 | nuclear receptor coactivator 5 | 57727 | 3 | 211.2 |
| 95 | GLYR1 | glyoxylate reductase 1 homolog (Arabidopsis) | 84656 | 2 | 213.7 |
| 96 | HNRNPU | heterogeneous nuclear ribonucleoprotein U (scaffold attachment factor | 3192 | 3 | 213.9 |
| 97 | NUICB1 | יס nucleobindin 1 | 1071 | 3 | 21/1 7 |
| 97 00 | | nucleoprimulii 1 | 4924 | ა ი | 214.7 216.2 |
| 90 | | nuclear millolic apparatus protein 1 catonin (cadhorin associated protein), dolta 1 | 4920 1500 | э э | 210.3 216.6 |
| 33 100 | | catenin (caunerin-associated protein), delid 1 | 1405 | ა ი | 210.0 |
| 100 | CHNNAL | caterini (cauterin-associateu protein), alpha 1, 102kDa | 1495 | ۷ | 211.2 |

YWHAE (tyrosine 3-monooxygenase) was the top coexpressed genes with P53 according to meta-analysis (Table 3, Figure 5). Interestingly, two apoptosis inducing genes, including DEDD (death effector domain containing) and CASP2 (caspase 2, apoptosis-related cysteine peptidase) are highly co-expressed with P53 which can be induced after ginger application. Based on normalized meta-data derived from expression data of different tissues and cell lines in NCBI GEO (Supplementary 1 and Supplementary 2), we calculated the Pearson correlation, in addition to MR. Highly positive and significant correlation was observed between P53 and CASP2 (Pearson correlation = 94.1%,

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P-Value = 0.000) and also P53 and DEDD (Pearson correlation = 90%, P-Value = 0.000).

Discussion

In this study, we investigated the effects of the ginger extract on ovarian cancer cell line and used bioinformatics analysis to find out the most accurate and reliable results. Ginger (Zingiber officinale), a natural poly-phenol constituent from rhizomes and ginger root, is extensively used as a spice or a traditional medicine. Researchers have been consistently revealed anti-cancer activities of phenolic substance in vegetables and fruits both in vitro and in vivo.^{17,24-27} Recently, different

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publications reveled the anticancer effect of ginger on various human cancer cell lines such as breast cancer (BC), prostate adeno-carcinoma (PC-3), Hela (Human cervical cancer), lung non-small cancer (A549), and colon cancer.²⁸⁻³² Weng and the colleagues reported that 6-Shogaol and 6-gingerol efficiently block invasion and metastasis of hepatocellular carcinoma by different molecular mechanisms.²⁶



Figure 5. Co-expression network of Tp53, ginger associated transcription factor, derived from co-expression meta-analysis of Tp53 in transcriptomic data of NCBI GEO.

Our studies by MTT assay illustrated that the ginger extract displayed strong cytotoxicity effects on ovarian cancer cell line, SKOV-3. Attribute weighting algorithms weighs the importance of each attribute in distinguishing between different concentrations of ginger; the results showed a few ranges of concentrations, from 50µg/ml to 80µg/ml, gained the highest possible weights and this range can be used to find the best concentration in lab works. Decision tree models also confirmed the above findings and clearly showed that these concentrations are playing crucial roles in suppressing SKOV-3 cancer cell line toxicity. In order to normal cells are transformed into a fully malignant cancer cells, a set of genetic and epigenetic alterations must be occurred.33 Genes associated with cell death program is considered crucial for the appropriate function and development of most mammalian organisms. BCL-2 (B-Cell Lymphoma 2), a member of the human Bcl-2 family is one of the main anti-apoptotic genes and seems to be a good target for cancer therapy in the future. They control the status of unreturnable for clonogenic cell survival and thereby

affect tumorigenesis and host-pathogen interactions

and also regulate animal development.³⁴⁻³⁶ Today's

clinical trials which target Bcl-2 family proteins or

mRNA are giving hopes for discovering a new group of anticancer drugs.³⁷ Our studies demonstrated that Bcl-2 has more than 0.4-fold reduction in expression after 48 hours ginger treatment compared to control group. Previously, Wang and colleagues in 2002 demonstrated 6-gingerol effects on apoptosis induction and inhibition of Bcl-2 expression in promyelocytic leukemia HL-60 cell.³⁸

Furthermore, we investigated tumor suppressor p53 and cyclin-dependent kinase inhibitor 1 p21 genes in this study to find out their role in SKOV-3 cell death after ginger therapy. In many cell types, inactivation of the p53 gene is the most common alternation explained in ovarian cancer.^{39,40} P53 is involved in some cell pathways such as cell cycle arrest, apoptosis, metastasis, invasion, stem cell maintenance, metabolism, cell cycle and DNA repair.⁴¹⁻⁴³ Moreover, P53-target genes play important roles in cell cycle arrest (e.g., p21) and apoptotic (e.g.; Bax) pathway.44 p21 is expressed by both p53-dependent and independent mechanisms after stress.⁴⁵ In cell cycle arrest pathway, p53 affects p21 expression, thus p21 stimulation inhibits tumor development and causes cell arrest;45,46 however, it can be activated independently and can have cancer-promoting properties.⁴⁷ Therefore, the control of p53's transcriptional activity is critical for novel therapeutic approaches to design drugs for ovarian cancer treatment.^{47,48}

Our result showed that the level of p53 expression in the ginger extract treated ovarian cancer cell line was increased about 7-fold compared to the control group (Figure 4). On the other hand, the level of p21 expression was decreased after drug treatment., Therefore, it could be understood that p53 might regulate the cell death in other pathway. Besides, p53 regulates transcription of apoptotic target genes such as Bcl-2 and Bax.⁴⁹ Our results revealed bcl-2 gene expression decreased in ginger treated cells, so p53 might stimulate apoptosis through bcl-2 elimination.

Additional, Systems biology analysis and meta-analysis of deposited expression value in NCBI based on rank of correlation and Z-transformation approach unraveled the key co-expressed genes and co-expressed network of P53, as the key transcription factor induced by ginger extract. High co-expression between P53 and the other apoptosis-inducing proteins such as CASP2 and DEDD was noticeable, suggesting the molecular mechanism underpinning of ginger action.

Conclusion

Our study revealed that p53 expression is the main reason for the cytotoxicity effects of ginger in ovarian cancer cells and the cause of cell death in SKOV-3 cells. Bioinformatics analysis help to confirm and get more accurate and reliable results driven from ginger effect on the cell line and p53 expression. The data outlined the key co-expressed genes and co-expressed network of P53, as the key transcription factor induced by ginger extract.

It could be suggested that p53 in new ginger extract treated ovarian cancer cell line stimulates tumor suppression through apoptosis, rather than cell cycle arrest.

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Ethical Issues

Not applicable.

Conflict of Interest

The authors declare no conflict of interests.

References

- 1. Yap TA, Carden CP, Kaye SB. Beyond chemotherapy: Targeted therapies in ovarian cancer. *Nat Rev Cancer* 2009;9(3):167-81. doi: 10.1038/nrc2583
- Dong A, Lu Y, Lu B. Genomic/epigenomic alterations in ovarian carcinoma: Translational insight into clinical practice. *J Cancer* 2016;7(11):1441-51. doi: 10.7150/ica.15556
- Karnezis AN, Cho KR, Gilks CB, Pearce CL, Huntsman DG. The disparate origins of ovarian cancers: Pathogenesis and prevention strategies. *Nat Rev* Cancer 2017;17(1):65-74. doi: 10.1038/nrc.2016.113
- 4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7-30. doi: 10.3322/caac.21332
- 5. Jones HW, Rock JA. Te linde's operative gynecology. 11th ed. US: Lippincott Williams & Wilkins; 2015.
- Gubbels JA, Claussen N, Kapur AK, Connor JP, Patankar MS. The detection, treatment, and biology of epithelial ovarian cancer. *J Ovarian Res* 2010;3:8. doi: 10.1186/1757-2215-3-8
- Rice MS, Hankinson SE, Tworoger SS. Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the nurses' health studies. *Fertil Steril* 2014;102(1):192-8 e3. doi: 10.1016/j.fertnstert.2014.03.041
- Di Saia PJ, Creasman WT. Clinical gynecologic oncology. 8th Edition. Philadelphia, PA: Elsevier/Saunders; 2012.
- Park EJ, Pezzuto JM. Botanicals in cancer chemoprevention. *Cancer Metastasis Rev* 2002;21(3-4):231-55. doi: 10.1023/a:1021254725842
- Chrubasik S, Pittler MH, Roufogalis BD. Zingiberis rhizoma: A comprehensive review on the ginger effect and efficacy profiles. *Phytomedicine* 2005;12(9):684-701. doi: 10.1016/j.phymed.2004.07.009
- 11. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (zingiber officinale roscoe): A

review of recent research. *Food Chem Toxicol* 2008;46(2):409-20. doi: 10.1016/j.fct.2007.09.085

- 12. Tao QF, Xu Y, Lam RY, Schneider B, Dou H, Leung PS, et al. Diarylheptanoids and a monoterpenoid from the rhizomes of zingiber officinale: Antioxidant and cytoprotective properties. *J Nat Prod* 2008;71(1):12-7. doi: 10.1021/np070114p
- Shukla Y, Singh M. Cancer preventive properties of ginger: A brief review. *Food Chem Toxicol* 2007;45(5):683-90. doi: 10.1016/j.fct.2006.11.002
- Rhode J, Fogoros S, Zick S, Wahl H, Griffith KA, Huang J, et al. Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells. *BMC Complement Altern Med* 2007;7:44. doi: 10.1186/1472-6882-7-44
- Peng F, Tao Q, Wu X, Dou H, Spencer S, Mang C, et al. Cytotoxic, cytoprotective and antioxidant effects of isolated phenolic compounds from fresh ginger. *Fitoterapia* 2012;83(3):568-85. doi: 10.1016/j.fitote.2011.12.028
- Prasad S, Tyagi AK. Ginger and its constituents: Role in prevention and treatment of gastrointestinal cancer. *Gastroenterol Res Pract* 2015;2015:142979. doi: 10.1155/2015/142979
- 17. Kim EC, Min JK, Kim TY, Lee SJ, Yang HO, Han S, et al. [6]-gingerol, a pungent ingredient of ginger, inhibits angiogenesis in vitro and in vivo. *Biochem Biophys Res Commun* 2005;335(2):300-8. doi: 10.1016/j.bbrc.2005.07.076
- Rastogi N, Duggal S, Singh SK, Porwal K, Srivastava VK, Maurya R, et al. Proteasome inhibition mediates p53 reactivation and anti-cancer activity of 6-gingerol in cervical cancer cells. *Oncotarget* 2015;6(41):43310-25. doi: 10.18632/oncotarget.6383
- 19. Pashaiasl M, Khodadadi K, Kayvanjoo AH, Pashaeiasl R, Ebrahimie E, Ebrahimi M. Unravelling evolution of nanog, the key transcription factor involved in self-renewal of undifferentiated embryonic stem cells, by pattern recognition in nucleotide and tandem repeats characteristics. *Gene* 2016;578(2):194-204. doi: 10.1016/j.gene.2015.12.023
- Gholizadeh-Ghaleh Aziz S, Pashaei-Asl F, Fardyazar Z, Pashaiasl M. Isolation, characterization, cryopreservation of human amniotic stem cells and differentiation to osteogenic and adipogenic cells. *PloS One* 2016;11(7):e0158281. doi: 10.1371/journal.pone.0158281
- Ebrahimie M, Esmaeili F, Cheraghi S, Houshmand F, Shabani L, Ebrahimie E. Efficient and simple production of insulin-producing cells from embryonal carcinoma stem cells using mouse neonate pancreas extract, as a natural inducer. *PloS One* 2014;9(3):e90885. doi: 10.1371/journal.pone.0090885
- Obayashi T, Kinoshita K. Rank of correlation coefficient as a comparable measure for biological significance of gene coexpression. *DNA Res* 2009;16(5):249-60. doi: 10.1093/dnares/dsp016
- 23. Okamura Y, Aoki Y, Obayashi T, Tadaka S, Ito S, Narise T, et al. Coxpresdb in 2015: Coexpression

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database for animal species by DNA-microarray and rnaseq-based expression data with multiple quality assessment systems. *Nucleic Acids Res* 2015;43(Database issue):D82-6. doi: 10.1093/nar/gku1163

- 24. Mahmoud NN, Carothers AM, Grunberger D, Bilinski RT, Churchill MR, Martucci C, et al. Plant phenolics decrease intestinal tumors in an animal model of familial adenomatous polyposis. *Carcinogenesis* 2000;21(5):921-7.
- 25. Murakami A, Tanaka T, Lee JY, Surh YJ, Kim HW, Kawabata K, et al. Zerumbone, a sesquiterpene in subtropical ginger, suppresses skin tumor initiation and promotion stages in ICR mice. Int J Cancer 2004;110(4):481-90. doi: 10.1002/ijc.20175
- 26. Weng CJ, Chou CP, Ho CT, Yen GC. Molecular mechanism inhibiting human hepatocarcinoma cell invasion by 6-shogaol and 6-gingerol. *Mol Nutr Food Res* 2012;56(8):1304-14. doi: 10.1002/mnfr.201200173
- Kim SO, Chun KS, Kundu JK, Surh YJ. Inhibitory effects of [6]-gingerol on PMA-induced COX-2 expression and activation of NF-kb and p38 MAPK in mouse skin. *Biofactors* 2004;21(1-4):27-31. doi: 10.1002/biof.552210107
- Karna P, Chagani S, Gundala SR, Rida PC, Asif G, Sharma V, et al. Benefits of whole ginger extract in prostate cancer. *Br J Nutr* 2012;107(4):473-84. doi: 10.1017/S0007114511003308
- 29. Liu Q, Peng YB, Qi LW, Cheng XL, Xu XJ, Liu LL, et al. The cytotoxicity mechanism of 6-shogaol-treated hela human cervical cancer cells revealed by label-free shotgun proteomics and bioinformatics analysis. *Evid Based Complement Alternat Med* 2012;2012:278652. doi: 10.1155/2012/278652
- Eren D, Betul YM. Revealing the effect of 6-gingerol, 6-shogaol and curcumin on mPGES-1, GSK-3β and βcatenin pathway in A549 cell line. *Chem Biol Interact* 2016;258:257-65. doi: 10.1016/j.cbi.2016.09.012
- Sanaati F, Najafi S, Kashaninia Z, Sadeghi M. Effect of ginger and chamomile on nausea and vomiting caused by chemotherapy in iranian women with breast cancer. *Asian Pac J Cancer Prev* 2016;17(8):4125-9.
- 32. Zhang M, Xiao B, Wang H, Han MK, Zhang Z, Viennois E, et al. Edible ginger-derived nano-lipids loaded with doxorubicin as a novel drug-delivery approach for colon cancer therapy. *Mol Ther* 2016;24(10):1783-96. doi: 10.1038/mt.2016.159
- Delbridge AR, Grabow S, Strasser A, Vaux DL. Thirty years of BCL-2: Translating cell death discoveries into novel cancer therapies. *Nat Rev Cancer* 2016;16(2):99-109. doi: 10.1038/nrc.2015.17
- Youle RJ, Strasser A. The BCL-2 protein family: Opposing activities that mediate cell death. *Nat Rev Mol Cell Biol* 2008;9(1):47-59. doi: 10.1038/nrm2308

- 35. Reed JC. Apoptosis-targeted therapies for cancer. *Cancer Cell* 2003;3(1):17-22. doi: 10.1016/S1535-6108(02)00241-6
- Cory S, Huang DC, Adams JM. The BCL-2 family: Roles in cell survival and oncogenesis. *Oncogene* 2003;22(53):8590-607. doi: 10.1038/sj.onc.1207102
- 37. Yip KW, Reed JC. BCL-2 family proteins and cancer. Oncogene 2008;27(50):6398-406. doi: 10.1038/onc.2008.307
- Wang CC, Chen LG, Lee LT, Yang LL. Effects of 6gingerol, an antioxidant from ginger, on inducing apoptosis in human leukemic HL-60 cells. *In Vivo* 2003;17(6):641-5.
- Kohler MF, Marks JR, Wiseman RW, Jacobs IJ, Davidoff AM, Clarke-Pearson DL, et al. Spectrum of mutation and frequency of allelic deletion of the p53 gene in ovarian cancer. *J Natl Cancer Inst* 1993;85(18):1513-9. doi: 10.1093/jnci/85.18.1513
- 40. Elbendary AA, Cirisano FD, Evans AC Jr, Davis PL, Iglehart JD, Marks JR, et al. Relationship between p21 expression and mutation of the p53 tumor suppressor gene in normal and malignant ovarian epithelial cells. *Clin Cancer Res* 1996;2(9):1571-5.
- Bates S, Vousden KH. Mechanisms of p53-mediated apoptosis. *Cell Mol Life Sci* 1999;55(1):28-37. doi: 10.1007/s000180050267
- Bieging KT, Mello SS, Attardi LD. Unravelling mechanisms of p53-mediated tumour suppression. *Nat Rev Cancer* 2014;14(5):359-70. doi: 10.1038/nrc3711
- 43. Kato H, Yoshikawa M, Fukai Y, Tajima K, Masuda N, Tsukada K, et al. An immunohistochemical study of p16, prb, p21 and p53 proteins in human esophageal cancers. *Anticancer Res* 2000;20(1A):345-9.
- 44. Pant V, Quintás-Cardama A, Lozano G. The p53 pathway in hematopoiesis: Lessons from mouse models, implications for humans. *Blood* 2012;120(26):5118-27. doi: 10.1182/blood-2012-05-356014
- 45. Gartel AL, Tyner AL. The role of the cyclin-dependent kinase inhibitor p21 in apoptosis. *Mol Cancer Ther* 2002;1(8):639-49.
- 46. Ahmadian N, Pashaei-Asl R, Samadi N, Rahmati-Yamchi M, Rashidi MR, Ahmadian M, et al. Hesa-a effects on cell cycle signaling in esophageal carcinoma cell line. *Middle East J Dig Dis* 2016;8(4):297-302. doi: 10.15171/mejdd.2016.39
- Zlotorynski E. Cancer biology: The dark side of p21. Nat Rev Mol Cell Biol 2016;17(8):461. doi: 10.1038/nrm.2016.90
- Vousden KH, Prives C. Blinded by the light: The growing complexity of p53. *Cell* 2009;137(3):413-31. doi: 10.1016/j.cell.2009.04.037
- 49. Wiman KG. Strategies for therapeutic targeting of the p53 pathway in cancer. *Cell Death Differ* 2006;13(6):921-6. doi: 10.1038/sj.cdd.4401921