

# Membrane Protein Metabolism in UNG-Activated NCAPH and RFC4 Subnetworks for Viral HCC|blood Cancer Development Via Inside-Out Microtubule Binding

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## Primary research

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# Abstract

**Background:** Our aim is to compute NCAPH and RFC4 subnetworks containing CDKN3 (feedback) for the novel molecular and cellular mechanisms of HCC (HBV or HCV) related cancer development from high UNG-activated upstream network.

**Methods:** Non-SMC condensin I complex subunit H (NCAPH) and replication factor C subunit 4 (RFC4) common molecular and knowledge subnetworks containing cyclin-dependent kinase inhibitor 3-CDKN3 (feedback) related to cancer by references were identified in HCC (HBV or HCV), based on our established significant high expression uracil DNA glycosylase (UNG)-activated upstream Gene (protein) reconstruction network inference (GRNInfer) and Database for Annotation, Visualization and Integrated Discovery (DAVID).

**Results:** Our results show the common molecules MAPT interaction with CDKN3 with RRM2 with HIST1H3H from UNG-activated upstream GRNInfer database; The common biological process and molecular function of MAPT as microtubule binding; HIST1H3H as cellular protein metabolic process from UNG-activated upstream DAVID database; The common cellular component of UNG, NCAPH, CDKN3, RRM2, HIST1H3H at nucleus; NCAPH, HIST1H3H at membrane; The common tissue distributions of NCAPH and RFC4 in Leukemiapromyelocytic(hl60), leukemialymphoblastic(molt4), etc.

**Conclusions:** We propose and mutual positively verify membrane protein metabolism in UNG-activated NCAPH and RFC4 subnetworks for viral HCC|blood cancer development via inside-out microtubule binding.

## Background

Cyclin-dependent kinase inhibitor 3 (CDKN3) is not only the more active molecule in our established high uracil DNA glycosylase (UNG)-activated network, but also CDKN3 (feedback) as the common molecule of non-SMC condensin I complex subunit H (NCAPH) and replication factor C subunit 4 (RFC4) subnetworks in HCC (HBV or HCV). CDKN3, NCAPH and RFC4 or the related family molecules have been previously published associations with cancer in the references. Such as, CDKN3 promotes tumor progression through RAD51 in esophageal cancer [1]. CDKN3 regulates cisplatin resistance to colorectal cancer via TIPE1 [2]. Levels of human replication factor C4 correlate with tumor progression and predict the prognosis for colorectal cancer [3]. DNA replication and sister chromatid cohesion 1 (DSCC1) of the replication factor complex CTF18-RFC is critical for colon cancer cell growth [4]. NCAPH is upregulated in endometrial cancer and associated with poor clinicopathologic characteristics [5]. Overexpression of NCAPH is upregulated and predicts a poor prognosis in prostate cancer [6]. However, NCAPH and RFC4 subnetworks containing CDKN3 (feedback) has not been explored for the novel molecular and cellular mechanisms of HCC (HBV or HCV) related cancer development from high UNG-activated upstream network.

In the paper, NCAPH and RFC4 feedback/up/downstream molecular subnetworks from our established significant high expression UNG-activated upstream Gene (protein) reconstruction network inference (GRNInfer) [7] database will be constructed in HCC (HBV or HCV) successively by significance analysis of microarrays (SAM) (fold change  $\geq 2$ ), Pearson positive correlation coefficient ( $CC \geq 0.25$ ) database with UNG, other mutual positive Pearson correlation ( $CC \geq 0.25$ ), respectively. NCAPH and RFC4 common molecular subnetworks containing CDKN3 (feedback) will be computed from high UNG-activated upstream GRNInfer database. NCAPH and RFC4 common biological process, molecular function, cellular component subnetworks containing CDKN3 (feedback) will be computed from high UNG-activated upstream Database for Annotation, Visualization and Integrated Discovery (DAVID) GOTERM\_BP\_DIRECT, GOTERM\_MF\_DIRECT, GOTERM\_CC\_DIRECT [8, 9]. NCAPH and RFC4 common and different tissue distributions will be calculated from high UNG-activated upstream DAVID GNF\_U133A\_QUARTILE and UNIGENE\_EST\_QUARTILE database.

## Methods

225 significant high expression molecules in 25 HCC (HBV or HCV) were identified based on 6144 genes compared with the corresponding low expression of 25 no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) in GSE10140-10141 [10, 11] (public free from NCBI) by SAM [12] (<http://www-stat.stanford.edu/~tibs/SAM/>). Data were processed using a log base of two and two unpaired classes with minimum fold change ( $\geq 2$ ). A false-discovery rate of 0% was chosen.

Low and high expression Pearson positive correlation coefficient ( $CC \geq 0.25$ ) molecules with UNG were calculated in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) and HCC (HBV or HCV) from our established Pearson correlation coefficient database of total 225 significant expression molecules by SPSS. Low and high UNG-activated upstream molecular lists in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) and HCC (HBV or HCV) were calculated from our established significant low and high expression UNG activation GRNInfer database. GRNInfer is a tool used to construct the activation and inhibition feedback/up/downstream molecular network based on linear programming and decomposition procedure defined by the following equation:

$$J = (\hat{X} - B)UE^{-1}V^T + YV^T = \hat{J} + YV^T$$

The other mutual positive Pearson correlation ( $CC \geq 0.25$ ) molecules except UNG were computed in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) based on low UNG-activated upstream molecular list. Low UNG-activated upstream molecular network based on the corresponding mutual positive Pearson correlation database was constructed in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) from our established significant low expression UNG activation GRNInfer database.

Low UNG-activated upstream knowledge network was identified in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) from our established significant low expression UNG activation DAVID database

(<https://david.ncifcrf.gov/>). Low UNG-activated upstream common biological process, molecular function, cellular component network was set up in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) from low UNG activation DAVID GOTERM\_BP\_DIRECT, GOTERM\_MF\_DIRECT, GOTERM\_CC\_DIRECT database. Low UNG-activated upstream common tissue distribution network was set up in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) from low UNG activation DAVID GNF\_U133A\_QUARTILE and UNIGENE\_EST\_QUARTILE database.

The other mutual positive Pearson correlation ( $CC \geq 0.25$ ) molecules except UNG were computed in HCC (HBV or HCV) based on high UNG-activated upstream molecular list. High UNG-activated upstream molecular network based on the corresponding mutual positive Pearson correlation database was set up in HCC (HBV or HCV) from our established significant high expression UNG activation GRNInfer database. NCAPH and RFC4 feedback/up/downstream direct and indirect molecular subnetwork containing CDKN3 (feedback) in HCC (HBV or HCV) was constructed from our established significant high expression UNG-activated upstream GRNInfer database, respectively. NCAPH and RFC4 common molecular subnetworks containing CDKN3 (feedback) in HCC (HBV or HCV) were computed from our established NCAPH and RFC4 feedback/up/downstream direct and indirect molecular database.

High UNG-activated upstream knowledge network in HCC (HBV or HCV) was identified from our established significant high expression UNG activation DAVID database. NCAPH and RFC4 common biological process, molecular function, cellular component subnetwork containing CDKN3 (feedback) was set up in HCC (HBV or HCV) from our established significant high expression UNG-activated upstream DAVID GOTERM\_BP\_DIRECT, GOTERM\_MF\_DIRECT, GOTERM\_CC\_DIRECT database, respectively. NCAPH and RFC4 common and different tissue distributions were set up in HCC (HBV or HCV) from high UNG-activated upstream DAVID GNF\_U133A\_QUARTILE and UNIGENE\_EST\_QUARTILE database.

## Results

NCAPH and RFC4 common molecular subnetworks containing CDKN3 (feedback) from our established significant high expression UNG-activated upstream GRNInfer database were identified as BUB1B (upstream), MAPT (upstream), CDKN3 (feedback), RRM2 (downstream), HIST1H3H (downstream) in HCC (HBV or HCV) successively by SAM and Pearson using GSE10140-10141. CDKN3 activates to CDKN3, CDKN3 to RRM2, CDKN3 to HIST1H3H, CDKN3 to MAPT, MAPT to CDKN3, MAPT to HIST1H3H, MAPT to MAPT, BUB1B to HIST1H3H, HIST1H3H to CDKN3, HIST1H3H to RRM2, RRM2 to CDKN3, RRM2 to RRM2, RRM2 to HIST1H3H, RRM2 to MAPT, RRM2 to BUB1B, as shown in Fig. 1–2.

NCAPH and RFC4 common biological process and molecular function subnetworks containing CDKN3 (feedback) were identified MAPT as microtubule binding; HIST1H3H as cellular protein metabolic process from high UNG-activated upstream DAVID GOTERM\_BP\_DIRECT and GOTERM\_MF\_DIRECT database. NCAPH and RFC4 common cellular component subnetwork containing CDKN3 (feedback) was selected

UNG, NCAPH, CDKN3, RRM2, HIST1H3H at nucleus; NCAPH, HIST1H3H at membrane in HCC (HBV or HCV) from high UNG-activated upstream DAVID GOTERM\_CC\_DIRECT database, as shown in Table 1.

Table 1

NCAPH and RFC4 common biological process, molecular function, cellular component subnetworks containing CDKN3 (feedback) in HCC (HBV or HCV) from our established significant high expression UNG-activated upstream DAVID GOTERM\_BP\_DIRECT, GOTERM\_MF\_DIRECT, GOTERM\_CC\_DIRECT database.

<b>NCAPH and RFC4 common biological process, molecular function, cellular component subnetworks in HCC (HBV or HCV)</b>		
<b>NCAPH subnetwork</b>	<b>RFC4 subnetwork</b>	<b>Terms</b>
UNG (first-core), NCAPH (second-core), CCNA2 (upstream), ECT2 (upstream), CDKN3 (feedback), KIAA0101 (feedback), NUSAP1 (downstream), RRM2 (downstream), HIST1H3H (downstream), TOP2A (downstream)	UNG (first-core), FOXM1 (upstream), KIAA0101 (upstream), TOP2A (upstream), NUSAP1 (feedback), CDKN3 (feedback), ECT2 (feedback), RRM2 (downstream), HIST1H3H (downstream), NCAPH (downstream)	nucleus
BUB1B (upstream), CCNA2 (upstream), ECT2 (upstream), CDKN3 (feedback), TROAP (feedback), GPSM2 (feedback), UBE2C (feedback), KIAA0101 (feedback), NUSAP1 (downstream), RRM2 (downstream)	BUB1B (upstream), FOXM1 (upstream), GPSM2 (upstream), KIAA0101 (upstream), UBE2C (upstream), NUSAP1 (feedback), CDKN3 (feedback), ECT2 (feedback), RRM2 (downstream)	cytoplasm
UNG (first-core), CCNA2 (upstream), RFC4 (upstream), UBE2C (feedback), KIAA0101 (feedback), RRM2 (downstream), HIST1H3H (downstream), TOP2A (downstream)	UNG (first-core), RFC4 (second-core), FOXM1 (upstream), KIAA0101 (upstream), TOP2A (upstream), UBE2C (upstream), RRM2 (downstream), HIST1H3H (downstream)	nucleoplasm
NCAPH (second-core), BUB1B (upstream), ECT2 (upstream), MAPT (upstream), UBE2C (feedback), RRM2 (downstream)	BUB1B (upstream), MAPT (upstream), UBE2C (upstream), ECT2 (feedback), RRM2 (downstream), NCAPH (downstream)	cytosol
BUB1B (upstream), CDKN3 (feedback), KIAA0101 (feedback)	BUB1B (upstream), KIAA0101 (upstream), CDKN3 (feedback)	perinuclear region of cytoplasm
NCAPH (second-core), HIST1H3H (downstream)	HIST1H3H (downstream), NCAPH (downstream)	membrane
BUB1B (upstream), UBE2C (feedback)	BUB1B (upstream), UBE2C (upstream)	anaphase promoting complex
HIST1H3H (downstream), TOP2A (downstream)	TOP2A (upstream), HIST1H3H (downstream)	nuclear chromosome
HIST1H3H (downstream), TOP2A (downstream)	TOP2A (upstream), HIST1H3H (downstream)	protein complex

NCAPH and RFC4 common biological process, molecular function, cellular component subnetworks in HCC (HBV or HCV)		
UNG (first-core), NCAPH (second-core), BUB1B (upstream), CCNA2 (upstream), ECT2 (upstream), MAPT (upstream), RFC4 (upstream), CDKN3 (feedback), TROAP (feedback), GPSM2 (feedback), UBE2C (feedback), KIAA0101 (feedback), NUSAP1 (downstream), RRM2 (downstream), HIST1H3H (downstream), TOP2A (downstream)	UNG (first-core), RFC4 (second-core), BUB1B (upstream), FOXM1 (upstream), GPSM2 (upstream), KIAA0101 (upstream), MAPT (upstream), TOP2A (upstream), UBE2C (upstream), NUSAP1 (feedback), CDKN3 (feedback), ECT2 (feedback), RRM2 (downstream), HIST1H3H (downstream), NCAPH (downstream)	protein binding
NCAPH (second-core), BUB1B (upstream), CCNA2 (upstream), RFC4 (upstream), UBE2C (feedback), RRM2 (downstream), TOP2A (downstream)	RFC4 (second-core), BUB1B (upstream), FOXM1 (upstream), TOP2A (upstream), UBE2C (upstream), RRM2 (downstream), NCAPH (downstream)	mitotic cell cycle
NCAPH (second-core), BUB1B (upstream), CCNA2 (upstream), UBE2C (feedback)	BUB1B (upstream), UBE2C (upstream), NCAPH (downstream)	cell division
BUB1B (upstream), RFC4 (upstream), UBE2C (feedback), TOP2A (downstream)	RFC4 (second-core), BUB1B (upstream), TOP2A (upstream), UBE2C (upstream)	ATP binding
BUB1B (upstream), ECT2 (upstream), HIST1H3H (downstream)	BUB1B (upstream), ECT2 (feedback), HIST1H3H (downstream)	small GTPase mediated signal transduction
RFC4 (upstream), KIAA0101 (feedback), RRM2 (downstream)	RFC4 (second-core), KIAA0101 (upstream), RRM2 (downstream)	DNA replication
NUSAP1 (downstream), HIST1H3H (downstream), TOP2A (downstream)	FOXM1 (upstream), TOP2A (upstream), NUSAP1 (feedback), HIST1H3H (downstream)	DNA binding
BUB1B (upstream), MAPT (upstream)	BUB1B (upstream), MAPT (upstream)	apoptotic process
BUB1B (upstream), UBE2C (feedback)	BUB1B (upstream), UBE2C (upstream)	mitotic spindle assembly checkpoint
BUB1B (upstream), UBE2C (feedback)	BUB1B (upstream), UBE2C (upstream)	anaphase promoting complex dependent proteasomal ubiquitin dependent protein catabolic process
BUB1B (upstream), UBE2C (feedback)	BUB1B (upstream), UBE2C (upstream)	negative regulation of ubiquitin protein ligase activity involved in mitotic cell cycle

NCAPH and RFC4 common biological process, molecular function, cellular component subnetworks in HCC (HBV or HCV)		
BUB1B (upstream), UBE2C (feedback)	BUB1B (upstream), UBE2C (upstream)	regulation of ubiquitin protein ligase activity involved in mitotic cell cycle
CCNA2 (upstream), MAPT (upstream)	FOXM1 (upstream), MAPT (upstream)	protein kinase binding
MAPT (upstream), NUSAP1 (downstream)	MAPT (upstream), NUSAP1 (feedback)	microtubule binding
MAPT (upstream), TOP2A (downstream)	MAPT (upstream), TOP2A (upstream)	enzyme binding
CDKN3 (feedback), RRM2 (downstream)	CDKN3 (feedback), RRM2 (downstream)	G1/S transition of mitotic cell cycle
RRM2 (downstream), HIST1H3H (downstream)	RRM2 (downstream), HIST1H3H (downstream)	protein heterotetramerization
HIST1H3H (downstream), TOP2A (downstream)	TOP2A (upstream), HIST1H3H (downstream)	protein heterodimerization activity
HIST1H3H (downstream), TOP2A (downstream)	TOP2A (upstream), HIST1H3H (downstream)	cellular protein metabolic process
BUB1B (upstream)	BUB1B (upstream)	BUB1 mitotic checkpoint serine/threonine kinase B (BUB1B)
MAPT (upstream)	MAPT (upstream)	microtubule associated protein tau (MAPT)
CDKN3 (feedback)	CDKN3 (feedback)	cyclin-dependent kinase inhibitor 3 (CDKN3)
RRM2 (downstream)	RRM2 (downstream)	ribonucleotide reductase regulatory subunit M2 (RRM2)
HIST1H3H (downstream)	HIST1H3H (downstream)	histone cluster 1 H3h (HIST1H3H)

NCAPH and RFC4 common tissue distributions were identified Leukemiapromyelocytic(hl60), leukemialymphoblastic(molt4), lymphomaburkittsRaji, Heart, lymphnode, Thyroid, Testis Germ Cell, TestisLeydig Cell from high UNG-activated upstream DAVID GNF\_U133A and UNIGENE\_EST database. NCAPH and RFC4 different tissue distributions demonstrate Cerebellum, Trachea, BM CD34+, fetallung, salivarygland, PB CD14 + Monocytes, germ cell tumor\_disease, PLACENTA, non glioma\_disease, CD8 + T

cells, bronchialepithelialcells, Cardiac Myocytes, infant (< 3 years old)\_development, PB CD56 + NKCells, Testis Interstitial, embryonic tissue\_normal, Thalamus, adrenal tumor\_disease, etc. as shown in Table 2.

Table 2

NCAPH and RFC4 common and different tissue distributions in HCC (HBV or HCV) from our established significant high expression UNG-activated upstream DAVID GNF\_U133A\_QUARTILE and UNIGENE\_EST\_QUARTILE database.

NCAPH and RFC4 common and different tissue distributions in HCC (HBV or HCV)		
Common NCAPH and RFC4	Different NCAPH	Different RFC4
ADIPOCYTE_3rd	Cerebellum_3rd	Trachea_3rd
BM CD33 + Myeloid_3rd	BM CD34+_3rd	fetallung_3rd
BM CD71 + EarlyErythroid_3rd	salivarygland_3rd	PB CD14 + Monocytes_3rd
lymphomaburkittsRaji_3rd	germ cell tumor_disease_3rd	PLACENTA_3rd
Heart_3rd	non glioma_disease_3rd	CD8 + T cells_3rd
leukemiapromyelocytic(hl60)_3rd	bronchialepithelialcells_3rd	Cardiac Myocytes_3rd
lymphnode_3rd	infant (< 3 years old)_development_3rd	PB CD56 + NKCells_3rd
CD4 + T cells_3rd	Testis Interstitial_3rd	
leukemialymphoblastic(molt4)_3rd	embryonic tissue_normal_3rd	
Thyroid_3rd	Thalamus_3rd	
Testis Germ Cell_3rd	adrenal tumor_disease_3rd	
TestisLeydig Cell_3rd	juvenile (< 17 years old)_development_3rd	
	Testis Seminiferous Tubule_3rd	
	lymph node_normal_3rd	
	testis_normal_3rd	
	thymus_normal_3rd	
	esophageal tumor_disease_3rd	
	esophagus_normal_3rd	
	neonate (< 4 weeks old)_development_3rd	
	bone_normal_3rd	
	oral tumor_disease_3rd	
	small intestine_normal_3rd	
	laryngeal cancer_disease_3rd	

<b>NCAPH and RFC4 common and different tissue distributions in HCC (HBV or HCV)</b>
<b>pancreatic tumor_disease_3rd</b>
<b>pancreas_normal_3rd</b>

## Discussion

NCAPH and RFC4 common molecular subnetworks and the related family members have been reported relationship with cancer including BUB1B (upstream), MAPT (upstream), CDKN3 (feedback), RRM2 (downstream), HIST1H3H (downstream) in the references. For instance, prevalence of germline mutations in BUB1B in individuals with early-onset colorectal cancer [13]. MAPT is a promising independent prognostic marker and tumor suppressive protein of clear cell renal cell carcinoma [14]. LncRNA TTN-AS1 regulates RRM2 to promote breast cancer progression [15]. KMT2A histone methyltransferase contributes to colorectal cancer development via promoting cathepsin Z transcriptional activation [16].

Our results show the common molecules MAPT interaction with CDKN3 with RRM2 with HIST1H3H; The common biological process and molecular function of MAPT as microtubule binding; HIST1H3H as cellular protein metabolic process in HCC (HBV or HCV) from our established high UNG-activated upstream GRNInfer, DAVID GOTERM\_BP\_DIRECT and GOTERM\_MF\_DIRECT database (Fig. 1–2, Table 1, Supp 4–6). Therefore, we put forward and mutual positively verify protein metabolism in UNG-activated NCAPH and RFC4 subnetworks for viral HCC development via microtubule binding.

Low UNG-activated upstream molecular network in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) was identified as NKX2\_5 activation to UNG from our established significant low expression UNG activation GRNInfer database (Supp 1–2). Low UNG-activated upstream common biological process and molecular function network shows UNG, CIAO1, NKX2\_5, REG3A as protein binding; UNG, NKX2\_5 as negative regulation of apoptotic process from our established low UNG activation DAVID GOTERM\_BP\_DIRECT and GOTERM\_MF\_DIRECT database (Supp 3). We put forward negative regulation of apoptotic process in low UNG-activated upstream network for no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) development via protein binding.

Our results show the common cellular component of UNG, NCAPH, CDKN3, RRM2, HIST1H3H at nucleus; NCAPH, HIST1H3H at membrane in HCC (HBV or HCV); The common tissue distributions of NCAPH and RFC4 in Leukemiapromyelocytic(hl60), leukemialymphoblastic(molt4), etc. from our established high UNG-activated upstream DAVID GOTERM\_CC\_DIRECT, GNF\_U133A and UNIGENE\_EST database. NCAPH and RFC4 different tissue distributions demonstrate Cerebellum, Trachea, BM CD34+, fetallung, salivarygland, PB CD14 + Monocytes, germ cell tumor\_disease, etc. (Fig. 1–2, Table 1–2, Supp 4–6). Therefore, we propose and mutual positively verify membrane protein metabolism in UNG-activated NCAPH and RFC4 subnetworks for viral HCC|blood cancer development via nucleus microtubule binding. The different tissue distributions of NCAPH and RFC4 negatively verify our hypothesis.

Low UNG-activated upstream common cellular component network demonstrates UNG, NKX2\_5 at nucleus from our established low UNG activation DAVID GOTERM\_CC\_DIRECT database. Low UNG-activated upstream most common tissue distribution network was identified Tonsil from our established low UNG activation DAVID GNF\_U133A and UNIGENE\_EST database (Supp 3). We put forward negative regulation of apoptotic process in low UNG-activated upstream network for no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) and tonsil development via nucleus protein binding, and negatively verify our hypothesis.

## **Conclusion**

We put forward and mutual positively verify membrane protein metabolism in UNG-activated NCAPH and RFC4 subnetworks for viral HCC|blood cancer development via inside-out microtubule binding, and also negatively verify our hypothesis in low UNG-activated upstream network of no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection). Other UNG-activated upstream molecular and knowledge subnetworks containing CDKN3 (feedback) will be computed and the hypotheses proposed for the whole systemic molecular and cellular mechanisms of HCC (HBV or HCV) related cancer development in the future.

## **Declarations**

### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

All authors have approved the manuscript for submission.

### **Availability of data and materials**

We declare the study data GSE10140-10141 public free from NCBI.

### **Competing interests**

The authors report no conflicts of financial and non-financial interests.

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### **Authors' contributions**

LW designed the whole experiment and wrote the paper. LW & MJ & QC analyzed the data and look up in references. JH & MJ & ZJ computed CC and GRNInfer. JH & QC & HF prepared figures and tables.

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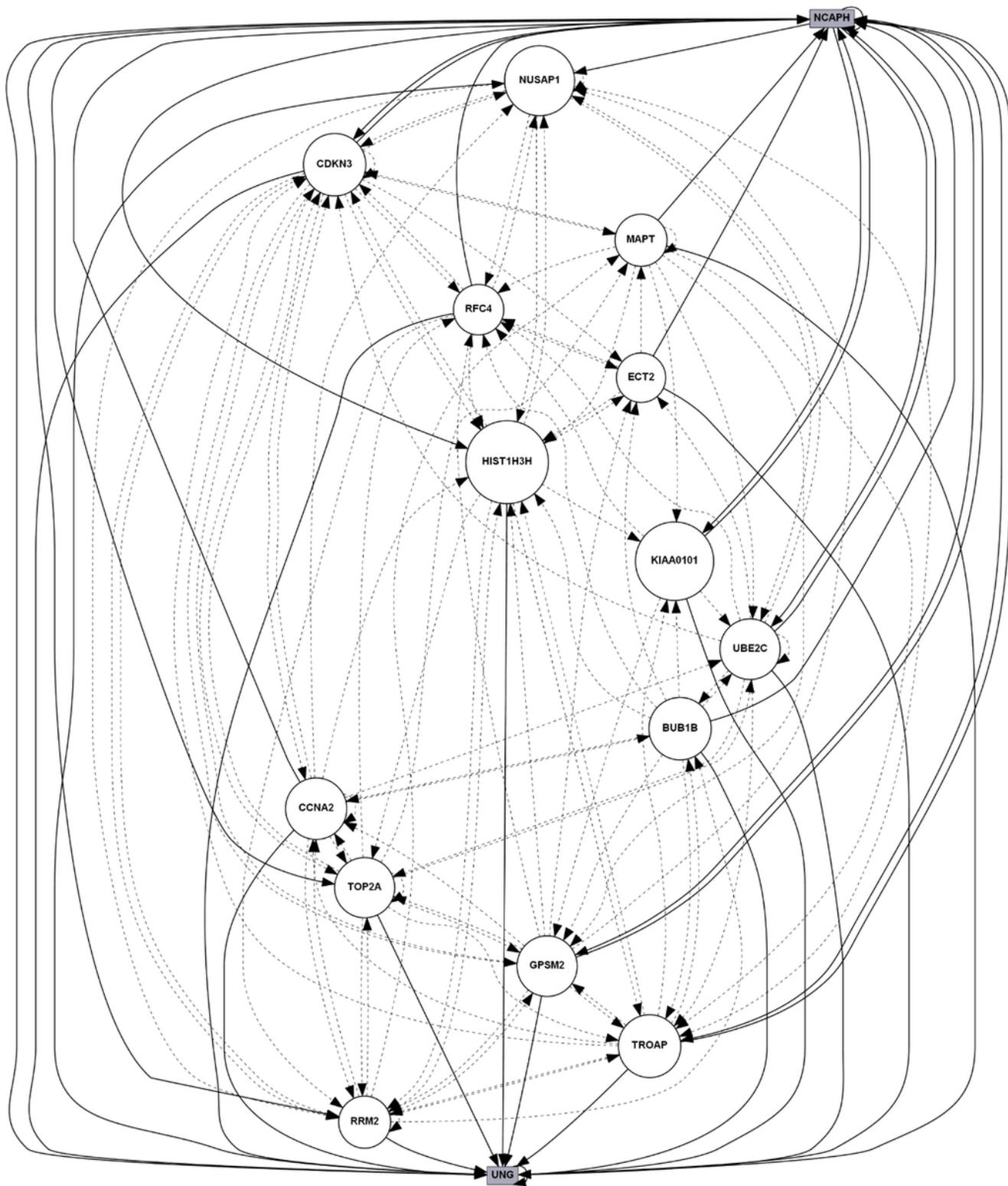
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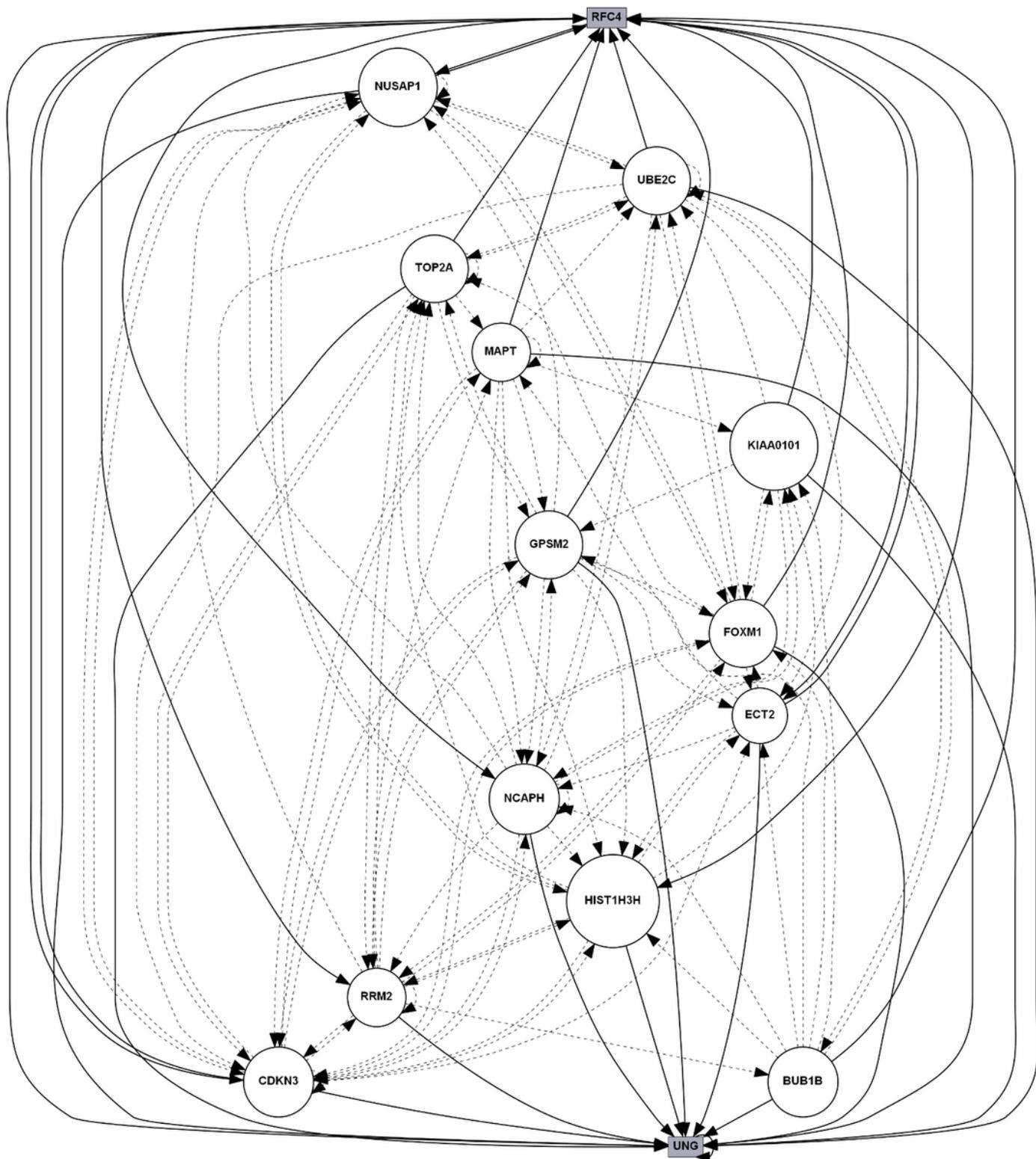
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## Figures



**Figure 1**

NCAPH direct and indirect molecular subnetwork construction containing CDKN3 (feedback) in HCC (HBV or HCV) from our established significant high expression UNG-activated upstream GRNInfer database. Solid line with black arrow represents direct activation relationships with NCAPH and UNG, respectively. Dashed line with black arrow represents indirect activation relationships with UNG. NCAPH direct and indirect molecular subnetwork construction containing CDKN3 (feedback) in HCC (HBV or HCV)



**Figure 2**

RFC4 direct and indirect molecular subnetwork construction containing CDKN3 (feedback) in HCC (HBV or HCV) from our established significant high expression UNG-activated upstream GRNInfer database. Solid line with black arrow represents direct activation relationships with RFC4 and UNG, respectively. Dashed line with black arrow represents indirect activation relationships with UNG. RFC4 direct and indirect molecular subnetwork construction containing CDKN3 (feedback) in HCC (HBV or HCV)

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarymaterial.docx](#)