Supplementary File

Table S1. List of databases used to reconstruct the Notch signalling pathway and Glioma cancer scenario

Name of the Databases	HTTP Links
Cell Signalling Databases	
KEGG	http://www.genome.jp/kegg/
Signaling Pathway Database (SPAD)	http://www.grt.kyushu-u.ac.jp/spad/
GENEGO: Pathway Maps	http://pathwaymaps.com/maps/
Biocarta	http://www.biocarta.com/
Protein Lounge	http://www.proteinlounge.com/
Millipore	http://www.millipore.com/pathways/pw/pathways
Applied Biosystem	http://www5.appliedbiosystems.com/tools/pathway/
Invitrogen	http://www.invitrogen.com/site/us/en/home/Products-and-Services/Applications/Cell-Analysis/Signaling-Pathways.html
DOQCS	http://doqcs.ncbs.res.in/
Reactome	http://www.reactome.org/ReactomeGWT/entrypoint.html
Pathway Interaction Database (PID)	http://pid.nci.nih.gov/
CPDB	http://cpdb.molgen.mpg.de/
Netpath	http://www.netpath.org/
Pathway Commons	http://www.pathwaycommons.org/about/
Hipathdb	http://hipathdb.kobic.re.kr/browse.php?dbType=1
Signalink	http://signalink.org/
Spike	http://www.cs.tau.ac.il/~spike/
Wikipathways	http://wikipathways.org/index.php/WikiPathways
Innatedb	http://www.innatedb.com/
Inoh	http://www.inoh.org/
BioModels	http://www.ebi.ac.uk/biomodels-main/
GOLD.db	https://gold.tugraz.at/
Cell Signaling Technology	http://www.cellsignal.com/index.jsp
Biocompare	http://www.biocompare.com
Pathway Central	http://www.sabiosciences.com/pathway.php?sn=Hedgehog
Pathway Studio	http://www.ariadnegenomics.com/products/pathway-studio
Protein-Protein Interaction Databases	
HPRD	http://www.hprd.org
APID	http://bioinfow.dep.usal.es/apid/index.htm
STRING 9.05	http://string-db.org/
PIPS	http://www.compbio.dundee.ac.uk/www-pips/textSearch.jsp?searchTerm=notch1&page=1&division=25
HIPPIE	http://cbdm.mdc-berlin.de/tools/hippie/
BioGRID 3.2	http://thebiogrid.org/
Microarray Expression Databases	
EBI-ARRAYEXPRESS	http://www.ebi.ac.uk/arrayexpress/
Gene Expression Omnibus	http://www.ncbi.nlm.nih.gov/geo/
Cancer Related Databases	
NCG 4.0	http://bio.ieo.eu/ncg/
Cancer Resource	http://bioinf-data.charite.de/cancerresource/
Cancer Cell Map	http://cancer.cellmap.org/

Table S2. Comparative statistics of the reconstructed Notch pathway data with other major databases

Database Name	Molecules*	Interactions*
Our Reconstructed Pathway	115	231
KEGG	24	15
Biocarta	7	10
NetPath	85	138
Pathway Central	16	11
Cell Signaling Technology	22	18
Protein Lounge	13	12

*** Based on the data available till 24th September, 2013**

Structural Analysis using Graph Theory:

The structural and topological features of the reconstructed Notch pathway (Figure 1) can be studied using 'Graph theory', which is also useful for visual and /or topological interpretation of a very large complex network [53, 54]. In this work, the entire Notch Signaling Pathway was considered as a Directed network or graph. The molecular entities of the network and their corresponding interactions or reactions are considered as nodes and edges respectively. All these interactions are taken from published experimental data [1-52]. All the proteins and interactions, which are forming the nodes and edges of the network graph has been used to calculate the network parameters [53]. The parameters which we used in our network were able to identify the proteins that played crucial role to operate the Notch pathway normally. In order to identify the central nodes in the network, four types of centrality measurement is usually performed i.e. Degree centrality, Eigen vector Centrality, Closeness Centrality and Betweenness Centrality. All the network parameters are calculated by using Gephi and igraph software applications [55, 56]. A brief definition of these parameters is given bellow.

Degree Centrality: We performed this Connectivity analysis to know the number of connections of each protein with all other proteins in the network. One of the important topological parameter of connectivity analysis is Degree centrality. It refers to the number of connections or neighboring nodes a particular node has in the network. Depending on the directions of the edges formed by the nodes in a directed network, it can be further divided into two categories: In-degree and Out-degree [54]. In-degree of a node refers the total number of incoming connections or edges that are linked to that node, whereas out-degree refers the total numbers of outgoing connections emanating from that node. Figure S1 and S2 show the In-degree and Out-degree distributions of the proteins in the Notch pathway. The sum total of In-degree and Out-degree is called Total-degree of that node, shown in Figure S3. Corresponding average values of In-degree (1.973913), Out-degree (1.973913) and Total-degree (3.947826) are calculated by dividing the summation of the individual parameter values of each nodes of the network to the total number of nodes.

Eigen vector, Closeness and Betweenness Centrality: We also measured the 'Centrality score' of each node or protein in the network after identifying the important "Hub proteins" from the connectivity analysis of the network. We found some important nodes or proteins which were forming important 'Hub' in the whole network structure. In that case we gave the highest importance to a node on the basis of its total number of connections or degree value. Albeit in

biological as well as any real world network the importance of a node or a protein does not depend only on its number of connections or neighbors [57, 58]. Sometimes the importance or significance of a node may increase due to its connections with the other important nodes in the network, though it may have lower number of neighbors or connections or *vice-versa*. "Centrality Values (*Eigenvector, Closeness and Betweenness*)", the most useful parameter, were used to determine the relative importance of a node within a network.

Eigen vector centrality of a node depends on the number of nodes which are also the central nodes of the network. It means this parameter not only signifies the number of neighboring nodes as seen in degree centrality, but also depends on whether the node is connected to another central nodes in the network or not. Therefore, connection to the influential nodes is more desirable for higher values of this parameter in place of total number of connections [53].

Closeness centrality of a node signifies how closely a node is situated from all other nodes in a network. Higher the closeness centrality of a node implies greater connectivity, as well as reachability to all other nodes from that node. On the other hand Betweenness centrality defines the situation of a node in a network where it serves a common point between the shortest connections of all other nodes. Higher Betweenness centrality of a node, refers higher number of shortest paths between all other nodes are intersecting that node [53]. In our Notch signalling pathway the values of Eigen vector centrality, Closeness centrality and Betweeness centrality of each individual molecule are shown in Figures S4, S5 and S6, respectively. The average values of Eigen vector centrality, Closeness centrality and Betweeness centrality are calculated as 0.201943, 0.002324345, and 107.9478, respectively.

Figure S1. In-Degree values of each molecule of Notch signaling network

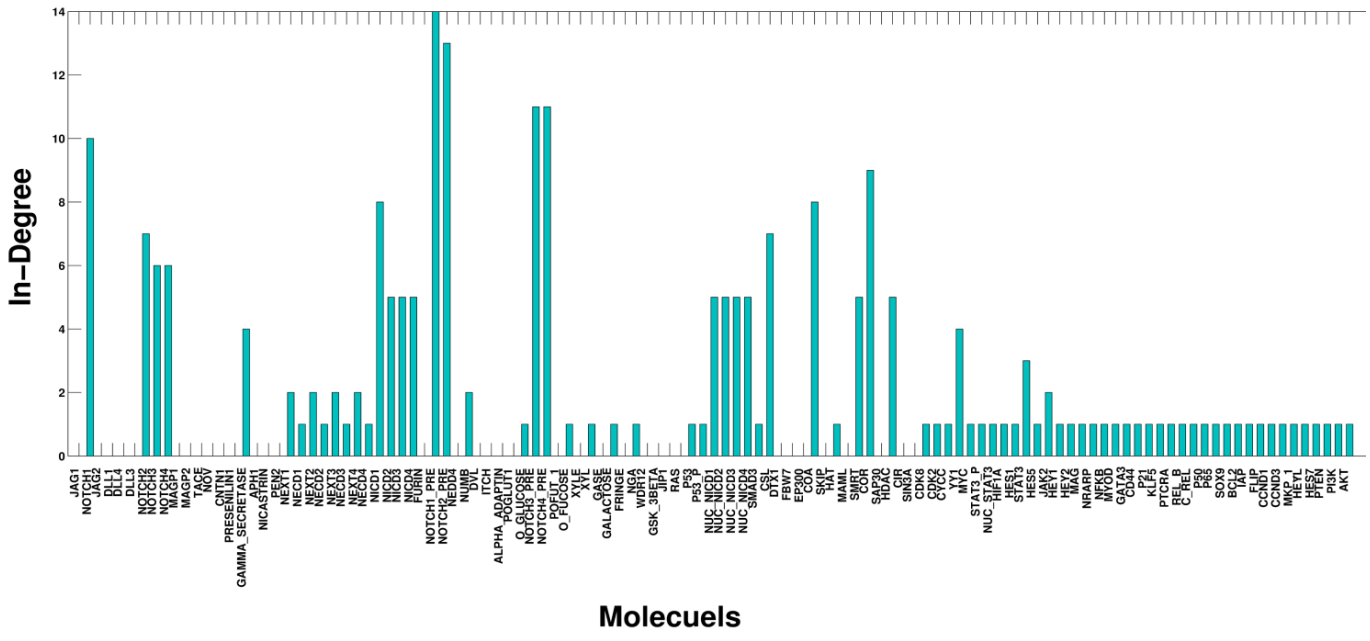


Figure S2. Out-Degree values of each molecule of Notch signaling network

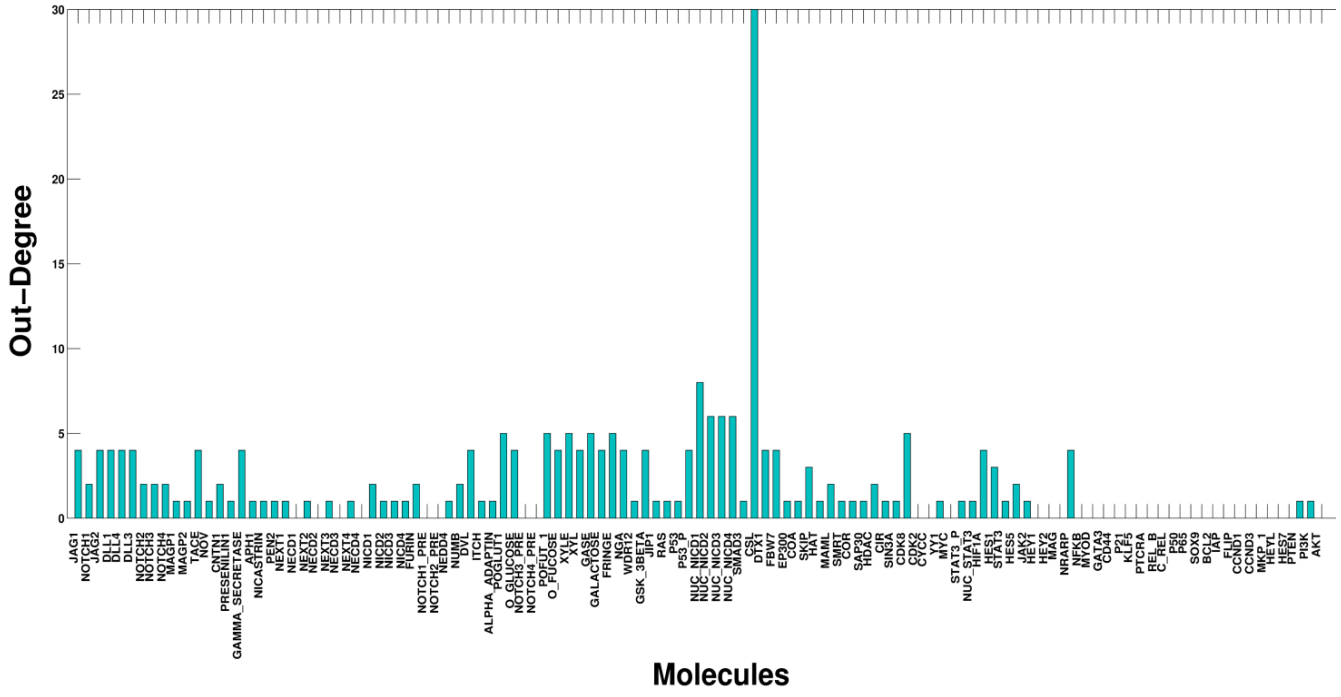


Figure S3. Total-Degree values of each molecule of Notch signaling network

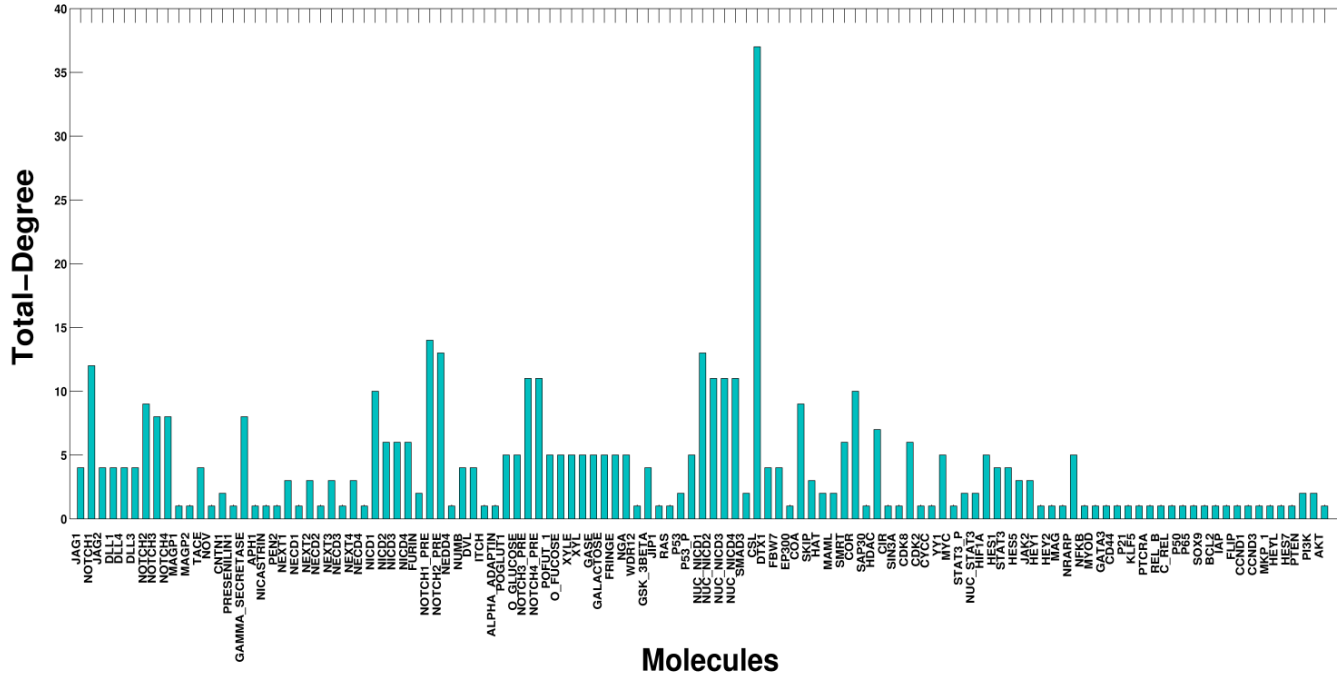


Figure S4. Eigen Vector centrality values of individual molecule of Notch signaling network

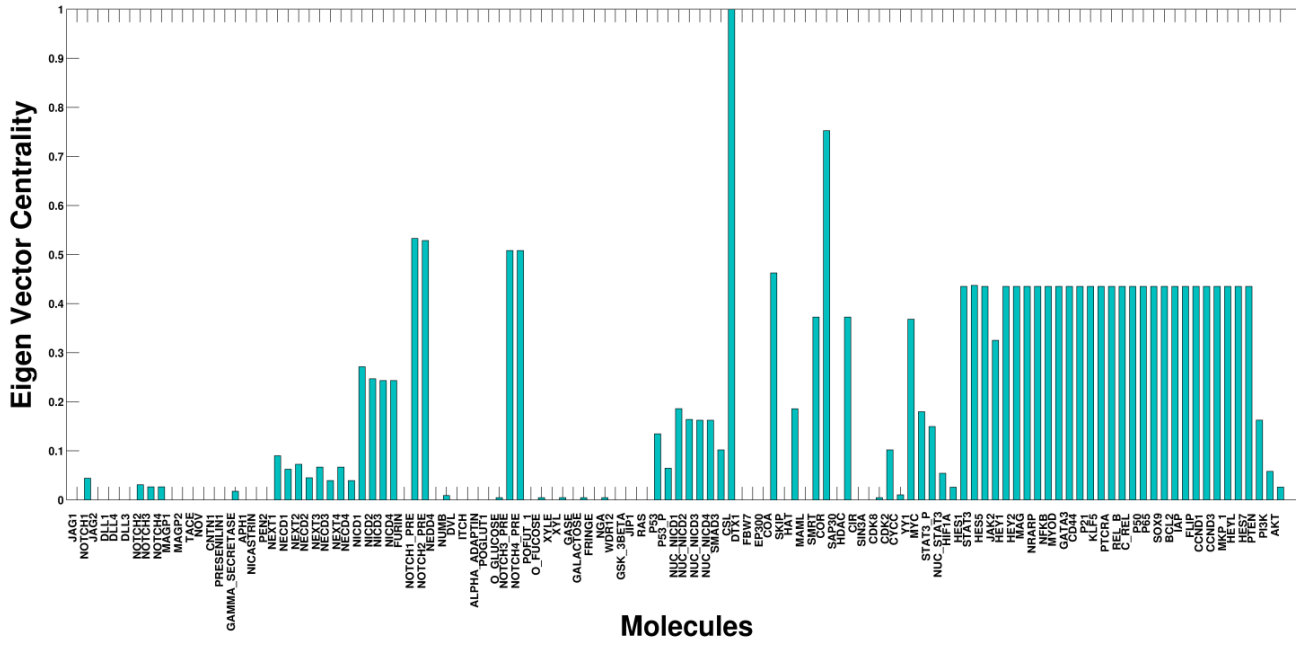


Figure S5. Closeness centrality values of each molecule of Notch signaling network

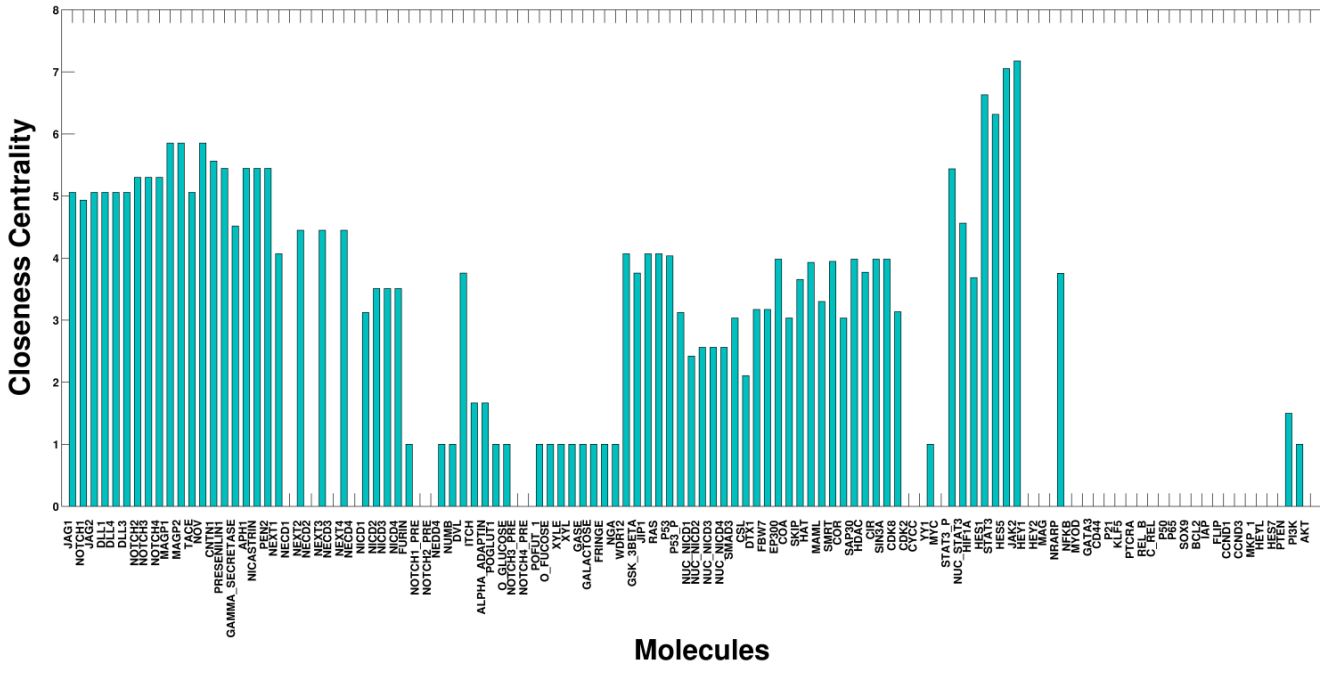
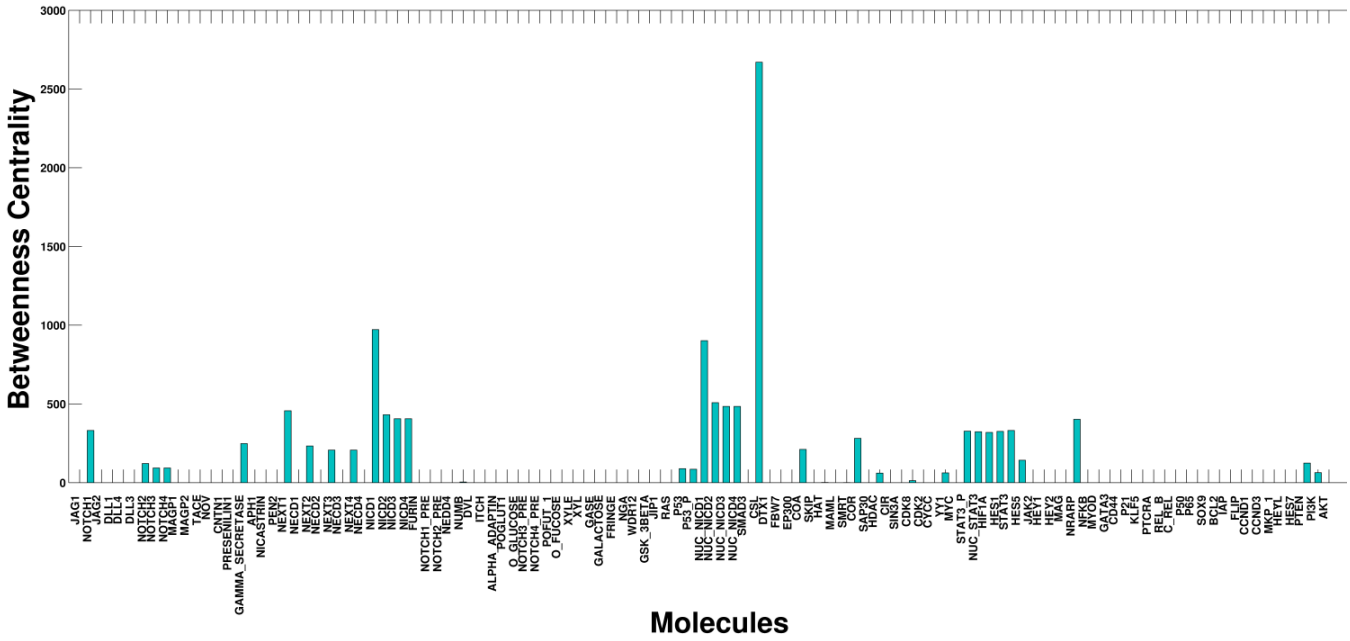


Figure S6. Betweenness centrality values of each molecule of Notch signaling network



Pathway simulation using Logical Model:

The entire Notch signaling network was organized into a three layered system of input, intermediate reactions and output molecules, with input signals orchestrating cellular responses to output via intermediate molecules. To visualize and analyze the Notch signal transduction network, we constructed the Logical or Boolean Interaction Hyper-graph with large number of nodes and interactions or hyper-arc [53, 59]. In our Boolean network each node represented a protein (Ligands, Receptors, kinase or Transcription factor), Protein complex (transcription co-activators or co-repressor) and metabolites. Depending on the cellular function and/or location, the proteins may be active (ON) or inactive (OFF). The entire simulation of Boolean modeling was performed in CellNetAnalyzer [60-62].

We know that the molecular species of a biological signaling network is highly interconnected and interdependent with each other. Using this phenomena one can easily construct Boolean or Logical equations that could show their inter relationship with each other within the network. We manually formed the Boolean equations among all the nodes of the Notch signaling network using our biological understanding of the interactions from various literature sources and databases. In Table S3, we have shown all the logical or Boolean equations which were used to simulate the pathway in CellNetAnalyzer. In the second column, documentation of the equations with references has been given. This entire set of Boolean equations was our "Master Boolean Model", which we used to simulate different scenarios by varying the logical states of the input proteins (see Table S4).

In order to simulate the Glioblastoma scenario using our logical model, we acquired the mRNA expression profile of human Glioblastoma cell line [63]. We also considered both the 'gain-of-function' ("ON" or "1") states of transcription initiation proteins like MAML, SKIP, EP300, HAT, PRESENILIN1 etc. and the "loss of functions" ("OFF" or "0") of few transcription suppressor

proteins like CIR, DVL etc. while creating different cancer scenarios in the logical simulation. Also, in order to simulate the scenarios in temporal space, we accounted the time scales into the Boolean equations of our master model. We simulated our model using both the synchronous and asynchronous updating approaches in Odefy (software package used in CellNetAnalyzer [60-62], but after attaining at the logical steady state we found that both the simulation results were showing same dynamics (results not shown), since no further changes in the states of the nodes can be observed once it reaches at the logical steady state [60].

Table S3. Master Logical model used for Notch pathway simulation

LOGICAL EQUATIONS	DOCUMENTATION
INPUTS	
JAG1 JAG2 DLL1 DLL3 DLL4 MAGP1 MAGP2 NOV CNTN1 PRESENILIN1 NICASTRIN APH1 PEN2 FURIN NEDD4 ITCH NUMB ALPHA_ADAPTIN O_GLUCOSE POGLUT_1 XYL XYLE NGA O_FUCOSE FRINGE GALACTOSE GASE POFUT_1 JIP1 RAS DVL JAK2 STAT3 GSK_3BETA WDR12 P53	Input proteins of our logical model.

FBW7 CDK8 CYCC DTX1 MAML EP300 SKIP HAT SMAD3 CSL SMRT SAP30 HDAC CIR SIN3A YY1 TACE NICD_ACTIVE	
INTERMEDIATE REACTIONS	
JAG1+NOTCH1+TACE=NECD1 JAG1+NOTCH1+TACE=NEXT1 JAG1+NOTCH2+TACE=NECD2 JAG1+NOTCH2+TACE=NEXT2 JAG1+NOTCH3+TACE=NECD3 JAG1+NOTCH3+TACE=NEXT3 JAG1+NOTCH4+TACE=NECD4 JAG1+NOTCH4+TACE=NEXT4	NOTCH receptors (NOTCH1, NOTCH2, NOTCH3, NOTCH4) bind with membrane bound ligand JAG1. Followed by this interaction, a metallo-protease enzyme TACE (TNFalpha-converting enzyme) cleaves the NOTCH receptors and produces NECD (Notch extracellular domain 1) and NEXT (Notch Extra cellular Truncated Protein) [1, 2].
JAG2+NOTCH1+TACE=NECD1 JAG2+NOTCH1+TACE=NEXT1 JAG2+NOTCH2+TACE=NECD2 JAG2+NOTCH2+TACE=NEXT2 JAG2+NOTCH3+TACE=NECD3 JAG2+NOTCH3+TACE=NEXT3 JAG2+NOTCH4+TACE=NECD4 JAG2+NOTCH4+TACE=NEXT4	NOTCH receptors (NOTCH1, NOTCH2, NOTCH3, NOTCH4) bind with membrane bound ligand JAG2. Followed by this interaction, a metallo-protease enzyme TACE (TNFalpha-converting enzyme) cleaves the NOTCH receptors and produces NECD (Notch extracellular domain 1) and NEXT (Notch Extra cellular Truncated Protein) [1, 2].
DLL1+NOTCH1+TACE=NECD1 DLL1+NOTCH1+TACE=NEXT1 DLL1+NOTCH2+TACE=NECD2 DLL1+NOTCH2+TACE=NEXT2 DLL1+NOTCH3+TACE=NECD3 DLL1+NOTCH3+TACE=NEXT3 DLL1+NOTCH4+TACE=NECD4 DLL1+NOTCH4+TACE=NEXT4	NOTCH receptors (NOTCH1, NOTCH2, NOTCH3, NOTCH4) bind with membrane bound ligand DLL1. Followed by this interaction, a metallo-protease enzyme TACE (TNFalpha-converting enzyme) cleaves the NOTCH receptors and produces NECD (Notch extracellular domain 1) and NEXT (Notch Extra cellular Truncated Protein) [1, 2].
DLL3+NOTCH1+TACE=NECD1	NOTCH receptors (NOTCH1, NOTCH2,

DLL3+NOTCH1+TACE=NEXT1 DLL3+NOTCH2+TACE=NECD2 DLL3+NOTCH2+TACE=NEXT2 DLL3+NOTCH3+TACE=NECD3 DLL3+NOTCH3+TACE=NEXT3 DLL3+NOTCH4+TACE=NECD4 DLL3+NOTCH4+TACE=NEXT4	NOTCH3, NOTCH4) bind with membrane bound ligand DLL3. Followed by this interaction, a metallo-protease enzyme TACE (TNFalpha-converting enzyme) cleaves the NOTCH receptors and produces NECD (Notch extracellular domain 1) and NEXT (Notch Extra cellular Truncated Protein) [1, 2].
DLL4+NOTCH1+TACE=NECD1 DLL4+NOTCH1+TACE=NEXT1 DLL4+NOTCH2+TACE=NECD2 DLL4+NOTCH2+TACE=NEXT2 DLL4+NOTCH3+TACE=NECD3 DLL4+NOTCH3+TACE=NEXT3 DLL4+NOTCH4+TACE=NECD4 DLL4+NOTCH4+TACE=NEXT4	NOTCH receptors (NOTCH1, NOTCH2, NOTCH3, NOTCH4) bind with membrane bound ligand DLL4. Followed by this interaction, a metallo-protease enzyme TACE (TNFalpha-converting enzyme) cleaves the NOTCH receptors and produces NECD (Notch extracellular domain 1) and NEXT (Notch Extra cellular Truncated Protein) [1, 2].
NEXT1+GAMMA_SECRETASE=NICD1 NEXT2+GAMMA_SECRETASE=NICD2 NEXT3+GAMMA_SECRETASE=NICD3 NEXT4+GAMMA_SECRETASE=NICD4	Notch extracellular truncated domains (NEXT1, NEXT2, NEXT3 and NEXT4) are cleaved by intracellular proteolytic enzyme called Gamma_Secretase and produces Notch intracellular domains NICD1, NICD2, NICD3 and NICD4 [1].
PRESENILIN1+NICASTRIN+APH1+PEN2 =GAMMA_SECRETASE	The component proteins of GAMMA_SECRETASE are PRESENILIN1, NICASTRIN, APH1 and PEN2. A charged aspartate in 19 residues long trans-membrane domain of PRESENILIN1 helps to stabilize the GAMMA_SECRETASE enzyme complex [3].
MAGP1+NOTCH1=NEXT1 MAGP1+NOTCH1=NECD1 MAGP2+NOTCH1=NEXT1 MAGP2+NOTCH1=NECD1	MAGP1 and MAGP2 proteins, present on microfibrils can interact with NOTCH1 and form NEXT1 and NECD1 by a furin-like cleavage without the help of TACE metallo protease enzyme [4].
NOV+NOTCH1=NEXT1 NOV+NOTCH1=NECD1	Nephroblastoma overexpressed protein (NOV) associates with NOTCH1 and induces the subsequent release of Notch extracellular proteins (NEXT1 and NECD1) [5].
CNTN1+NOTCH1=NECD1 CNTN1+NOTCH1=NEXT1 CNTN1+NOTCH2=NEXT2 CNTN1+NOTCH2=NECD2	Trans-extracellular interaction between F3/Contactin (CNTN1) and NOTCH1 or NOTCH2 can trigger the notch signaling pathway [6, 7].

FURIN+!NUMB+!ITCH+ALPHA_ADAPTIN +NOTCH1_PRE =NOTCH1 FURIN+!NUMB+!ITCH+ALPHA_ADAPTIN +NOTCH2_PRE=NOTCH2	During maturation procedures, pre-processed NOTCH1 and NOTCH2 molecules (NOTCH1_PRE and NOTCH2_PRE) are cleaved by FURIN like protease and form the processed NOTCH molecules (NOTCH1 and NOTCH2) for further ligand binding and signal transduction [8, 9]. Onco suppressor protein NUMB, with the help of ITCH or ALPHA_ADAPTIN, promotes the degradation of NOTCH1_PRE and NOTCH2_PRE (but not NOTCH3_PRE or NOTCH4_PRE) by recruiting the E3 ubiquitin ligase [10, 11].
!NEDD4+NOTCH1_PRE=NOTCH1	Pre-processed NOTCH1 (NOTCH1_PRE) is the direct target of ubiquitin-protein ligase NEED4. Overexpression of NEDD4 in atrophy muscle cell cause down-regulation of NOTCH1 as ubiquitination causes rapid degradation of pre-processed NOTCH1 [12, 13].
GSK_3BETA+!DVL+!JIP1 +NICD1 =NUC_NICD1 GSK_3BETA+!DVL+!JIP1 +NICD2 =NUC_NICD2 GSK_3BETA+!DVL+!JIP1 +NICD3 =NUC_NICD3 GSK_3BETA+!DVL+!JIP1 +NICD4 =NUC_NICD4	GSK_3BETA phosphorylates NICD and then phosphorylated NICD goes into the nucleus for further transcription process. For simplicity the phosphorylated NICD are not considered in this model [14]. On the other hand it has also been found that DVL, JIP1 and P53 proteins can also exert inhibitory effect on Notch intracellular domains in cytoplasm (NICD1, NICD2, NICD3 and NICD4) [15, 16, 17].
RAS+NICD1=NUC_NICD1	Experimental findings have proven the cross talk between RAS/MAPK pathways with NOTCH1 intracellular domains. This cross talk results the activation of Notch pathway in various cancer cell line including Glioma, Breast cancer etc. [18].
!P53_P+NUC_NICD1+CSL=NOTCH1_PRE !P53_P+NUC_NICD2+CSL=NOTCH2_PRE !P53_P+NUC_NICD3+CSL=NOTCH3_PRE !P53_P+NUC_NICD4+CSL=NOTCH4_PRE	P53 the tumor suppressor protein has found to be the suppressor of NOTCH proteins in Glioblastoma cell line. P53 have been considered as the transcription repressor of NUC_NICD and CSL and thus reducing the concentration of NOTCH precursor proteins [19-22].
P53+!NICD1=P53_P	Activated NOTCH1 (or NICD1) interacts with P53 and inhibits its phosphorylation [23].
WDR12+NICD1=NUC_NICD1	WD-repeat protein contains NLS sequence has been found to interact with Notch1 intracellular domain (NICD1). Although the end result of this interaction is still not known, but it is quite intuitive that WDR12 may help to the nuclear translocation of NICD1 from cytoplasm and thereby modulate NOTCH signaling pathway [24].

!FBW7+NICD4=NUC_NICD4	FBW7 expressed in mouse embryo is found to negatively regulate the NOTCH4-HEY1 dependent pathway. The FBW7 degrades intracellular domain of NOTCH4 through its ubiquitin ligase mediated activity [25].
POGLUT_1+O_GLUCOSE+NOTCH1_PRE =NOTCH1 POGLUT_1+O_GLUCOSE+NOTCH2_PRE =NOTCH2 POGLUT_1+O_GLUCOSE+NOTCH3_PRE =NOTCH3 POGLUT_1+O_GLUCOSE+NOTCH4_PRE =NOTCH4	Post-translational modification of NOTCH precursor proteins with O-linked glucose (O_GLUCOSE) molecule by Protein O-glucosyltransferase -1 is a conserved process. This modification is found to be required for NOTCH pathway activation and ligand binding [26].
XYL+O_GLUCOSE+!XYLE+NOTCH1_PRE =NOTCH1 XYL+O_GLUCOSE+!XYLE+NOTCH2_PRE =NOTCH2 XYL+O_GLUCOSE+!XYLE+NOTCH3_PRE =NOTCH3 XYL+O_GLUCOSE+!XYLE+NOTCH4_PRE =NOTCH4	Addition of Xylose (XYL) molecule to the O-GLUCOSE linked NOTCH precursor proteins is mediated by an enzyme Xylosyltransferase (XYLE). Loss or gain of function of XYLE has strongly suggested that Xylose modification is negatively correlated with the notch pathway activation [26].
O_FUCOSE+NGA+FRINGE+POFUT_1 +NOTCH1_PRE=NOTCH1 O_FUCOSE+NGA+FRINGE+POFUT_1 +NOTCH2_PRE=NOTCH2 O_FUCOSE+NGA+FRINGE+POFUT_1 +NOTCH3_PRE=NOTCH3 O_FUCOSE+NGA+FRINGE+POFUT_1 +NOTCH4_PRE=NOTCH4	FRINGE catalyses the addition of N-acetylglucosamine (NGA) to O-fucose in NOTCH precursor proteins. NGA modification plays positive role for ligand receptor binding in Notch signaling pathway [27]. Fucosylation of Notch molecules is mediated by the enzyme POFUT_1 (GDP-fucose protein O-fucosyltransferase 1) [28].
GALACTOSE+GASE+ O_FUCOSE+ NOTCH1_PRE=NOTCH1 GALACTOSE+GASE+ O_FUCOSE +NOTCH2_PRE=NOTCH2 GALACTOSE+GASE+ O_FUCOSE +NOTCH3_PRE=NOTCH3 GALACTOSE+GASE+ O_FUCOSE +NOTCH4_PRE=NOTCH4	GALACTOSE addition to O_FUCOSE linked Notch precursors molecules are mediated by the enzyme GASE (Galactosyltransferase) [29].
NUC_NICD1+YY1=MYC	NUC_NICD1 interacts directly with YY1 transcription factor and regulates the expression of MYC protein [30].
NUC_NICD1+SMAD3+CSL=HES1	NUC_NICD1 and SMAD3 are seen to interact directly and thereafter regulate the expression of HES1 through CSL [31].
HDAC+SAP30+CIR+SIN3A+SMRT=COR	On the other hand, the proteins HDAC, SMRT, CIR, SAP30, SIN3A forms a co-repressor complex (COR) of CSL which in turn regulates the expression of Notch target genes [32-35].

EP300+MAML+ HAT +SKIP=COA	In order to reduce the complexity of the model, a dummy node NICD_ACTIVE has been considered in place of all NUC_NICD1, 2, 3 and 4. This dummy species is not shown in the main figure. Transcription co-activator complex (COA), consisting of CSL, NICD, Mastermind (MAML), EP300 and histone acetyltransferase (HAT) induces the transcriptional activation of several Notch target genes, such as HES1, HES5, HES7, HEY1, HEY2, HEYL, GATA3, CCND1, CCND3, CD44, KLF5, SOX9, NFKB, [36-42].
NUC_NICD1=NICD_ACTIVE NUC_NICD2=NICD_ACTIVE NUC_NICD3=NICD_ACTIVE NUC_NICD4=NICD_ACTIVE NICD_ACTIVE+CSL+!COR+COA= HES1/HES5/HES7/HEY1/HEY2/HEYL /GATA3/CCND3/CCND1/CD44/KLF5/SOX9 /PTCRA/MKP_1/NFKB/	
NUC_NICD1+COA+CSL+!COR= BCL2 /FLIP/IAP/ P21/P65/P50/C_REL/REL_B	Nuclear NICD1 (NUC_NICD1) has found to activate the anti-apoptosis proteins BCL2, FLIP, IAP as well as other NFkB pathway proteins P65, P50, C_REL, REL_B [43, 44]. It also induces the expression of growth arrest factor P21 in primary differentiating keratinocytes cell lines [45].
NUC_NICD1/2+DTX1+CSL+!COR+COA =MAG	F3/contactin trans-extracellular ligand dependent NOTCH pathway promotes oligodendrocyte precursor cell differentiation and upregulates the myelin-related protein MAG. NOTCH1/2 and DTX1 mediated signaling cascade with the help of transcription factor CSL induces the transcription of MAG in OLN-93 cell line [6].
!HES1=MYOD	Ligand-induced Notch signaling in myeloma cell up-regulates HES1 mRNA expression and subsequently reduced expression of MYOD [46].
MAML+!CDK8+!CYCC+!FBW7 =NUC_NICD1/2/3/4	MAML directly interacts with CDK8 and recruits it to hyper-phosphorylate the NICD in nucleus. Followed by the hyper-phosphorylation, NICD undergoes FBW7 dependent ubiquitin degradation [47].
NICD_ACTIVE+CSL+!COR+COA =NRARP	NRARP is the notch target gene which is transcribed by the CSL dependent NOTCH pathway activation [48].
!NRARP+NICD1/2/3/4=NUC_NICD1/2/3/4	NRARP is found to form a ternary complex with NICD in cytoplasm which in turn inhibits the further NICD dependent transcription. This is one of the identified negative feedback loop in NOTCH signaling pathway [48].
NUC_NICD1=CDK2	NUC_NICD1 induces the activation of CDK2 [38].
HES1/5+JAK2+STAT3=STAT3_P STAT3_P=NUC_STAT3	HES1 and HES5 are found to interact with JAK2 and STAT3, and facilitate the complex formation between JAK2/STA3. This complex formation promotes the phosphorylation of STAT3 [49]. Phosphorylated STAT3_P then translocate into the nucleus.

NUC_STAT3=HIF1A	NUC_STAT3 is found to activate HIF1A [50].
HIF1A=NICD1/2/3/4	HIF1A can interact with NICD1/2/3/4 to enhance the NOTCH pathway activity by up regulating the NOTCH pathway target genes [51].
!HES1=PTEN !PTEN=PI3K PI3K=AKT	NOTCH pathway is found to activate the PTEN/AKT pathway by upregulating HES1 production. HES1 is found to inhibit the PTEN dependent suppression of AKT activation [52].
OUTPUT MOLECULES	
NECD1 NECD2 NECD3 NECD4 AKT CDK2 HEY1 HEY2 MAG NFKB MYOD GATA3 CD44 P21 KLF5 PTCRA MYC HES7 HEYL MKP_1 CCND3 CCND1 FLIP IAP BCL2 SOX9 P65 P50 C_REL REL_B	Output molecules of the model.

Here ‘+’ sign in the logical equations signifies the ‘AND’ operation instead of conventional ‘OR’ logical operator. In CellNetAnalyzer the input equations should contain ‘+’ sign to signify the AND relation among the nodes. Nodes related with OR operations are given by individual logical equations.

Table S4. Logical expressions of the input molecules used for simulation of Notch pathway under different scenarios

MOLECULES	EXPERIMENT (GBE)	SIMULATION (GBS)	GAMMA_SECRETASE INHIBITION (GSI)	NORMAL NOTCH SCENARIO (NNS)	TS2	TS1
JAG1	1	1	1	1	1	1
JAG2	0	0	0	1	0	0
DLL1	0	0	0	1	0	0
DLL3	0	0	0	1	0	0
DLL4	2	1	2	1	1	1
MAGP1	1	1	1	0	1	1
MAGP2	2	0	2	0	0	0
NOV	2	1	2	0	1	1
CNTN1	0	0	0	0	0	0
TACE	1	1	1	1	1	1
PRESENILIN1	0*	1*	0	1	1	1
NICASTRIN	1	1	1	1	1	1
APH1	1	1	1	1	1	1
PEN2	1	1	1	1	1	1
FURIN	2	1	2	0	1	1
NEDD4	1	1	1	0	1	1
ITCH	1	1	1	0	1	1
NUMB	2	0	2	0	0	0
ALPHA_ADAPTIN	2	0	2	1	0	0
O_GLUCOSE	2	1	2	1	1	1
POGLUT_1	1	1	1	1	1	1
XYL	2	0	2	0	0	0
XYLE	0	0	0	1	0	0
NGA	2	1	2	1	1	1
O_FUCOSE	2	1	2	1	1	1
FRINGE	1	1	1	1	1	1
GALACTOSE	2	1	2	1	1	1
GASE	1	1	1	1	1	1
POFUT_1	1	1	1	1	1	1
JIP1	0	0	0	1	0	0
RAS	0	0	0	1	0	0
DVL	0	0	0	0	0	0
JAK2	2	1	2	0	1	1
STAT3	1	1	1	0	1	1
GSK_3BETA	0	0	0	0	0	0
WDR12	1	1	1	1	1	1
P53	1	1	1	1	1	1
FBW7	0	0	0	0	0	0
CDK8	0	0	0	0	0	0
CYCC	2	0	2	0	0	0
DTX1	0	0	0	0	0	0
MAML	1	1	1	1	0	1
EP300	2	1	2	1	1	1
SKIP	2	1	2	1	1	1
HAT	1	1	1	1	1	1
SMAD3	2	1	2	1	1	1
CSL	2	1	2	1	1	1
SMRT	1	1	1	0	1	1
SAP30	1	1	1	0	1	1
HDAC	2	0	2	0	0	0
CIR	0	0	0	0	0	0
SIN3A	2	0	2	0	0	0
YY1	0	0	0	1	0	0

* The expression of PRESENILIN1 was found “down regulated” in Glioblastoma cell line but at the time of Glioblastoma Simulation (GBS), logical expression of PRESENILIN1 was considered as ‘1 to show up regulation of GAMMA SECREATASE.

Table S5. The simulation result of the intermediate and output proteins of Notch pathway under different scenarios

MOLECULES	EXPERIMENT (GBE)	SIMULATION (GBS)	GAMMA_SECRETASE INHIBITION (GSI)	NORMAL NOTCH SCENARIO (NNS)	TS2	TS1
NOTCH1	1	1	1	1	0	1
NOTCH2	1	1	1	1	0	1
NOTCH3	1	1	1	1	0	1
NOTCH4	2	1	1	1	0	1
NEXT1	2	1	1	1	0	1
NEXT2	2	1	1	1	0	1
NEXT3	2	1	1	1	0	1
NEXT4	2	1	1	1	0	1
GAMMA_SECRETASE	1	1	0	1	1	1
NOTCH1_PRE	2	1	1	1	0	1
NOTCH2_PRE	2	1	1	1	0	1
NOTCH3_PRE	2	1	1	1	0	1
NOTCH4_PRE	2	1	1	1	0	1
PTEN	0	0	0	0	0	1
STAT3_P	2	1	1	0	0	1
PI3K	2	1	1	1	0	1
AKT	1	1	1	1	0	1
NICD1	2	1	1	1	0	0
NICD2	2	1	1	1	0	0
NICD3	2	1	1	1	0	0
NICD4	2	1	1	1	0	0
P53_P	2	0	0	0	0	1
NUC_NICD1	2	1	1	1	0	1
NUC_NICD2	2	1	1	1	0	1
NUC_NICD3	2	1	1	1	0	1
NUC_NICD4	2	1	1	1	0	1
NUC_STAT3	2	1	1	0	0	1
CDK2	1	1	1	1	0	1
COR	2	0	0	0	0	0
COA	2	1	1	1	0	0
NECD1	2	1	1	1	0	0
NECD2	2	1	1	1	0	0
NECD3	2	1	1	1	0	0
NECD4	2	1	1	1	0	1
HES1	2	1	1	1	0	1
HES5	0	1	1	1	0	1
HES7	1	1	1	1	0	1
HEY1	2	1	1	1	0	1
HEY2	0	1	1	1	0	1
HEYL	1	1	1	1	0	1
MAG	0	0	0	0	0	0
NRARP	2	1	1	1	0	1
NFKB	1	1	1	1	0	1
MYOD	0	0	0	0	1	0
GATA3	1	1	1	1	0	1
CD44	1	1	1	1	0	1
P21	1	1	1	1	0	1
KLF5	2	1	1	1	0	1
PTCRA	2	1	1	1	0	1
MYC	1	0	0	1	0	1
HIF1A	1	1	1	1	0	0
MKP_1	1	1	1	1	0	1
CCND3	2	1	1	1	0	1
CCND1	2	1	1	1	0	1
FLIP	1	1	1	1	0	1
IAP	2	1	1	1	0	1
BCL2	2	1	1	1	0	1
SOX9	1	1	1	1	0	1
P65	1	1	1	1	0	1
P50	0	1	1	1	0	1
C_REL	2	1	1	1	0	1
REL_B	1	1	1	1	0	1
NICD_ACTIVE	2	1	1	1	0	1

Table S4 and **S5** show the Logical states used in CellNetAnalyzer for simulating the Notch Pathway model of Normal Notch Scenario (NNS); Glioblastoma Scenario (GBS); Gamma Secretase Inhibition (GSI), *In-silico* Treatment Scenario by inhibiting NICD1 and MAML (TS2); and the inhibition by NICD1 and HIF1A (TS1). The logical states of the input proteins for each scenario and the respective simulated results of the output proteins are given in Table S4 and S5 respectively. The logical state '1' or '0" represent the ON or OFF state of a protein in the simulation respectively. The Logical states of the input proteins (Table S4) have considered from the previous experiment of mRNA expression profile of human Glioblastoma cell line [63].

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