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Genome-Wide Analysis of the ID Family of bHLH TFs in Glial Tumours

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ABSTRACT

BACKGROUND

The inhibitor of differentiation (ID) family of TFs accumulated the result of development. This subgroup of bHLH TFs is an inverse regulator that acquires to constrain segregation and stimulate proliferation. The ID family of bHLH TFs control the reactions of homodimer and heterodimer by motions of E proteins (Class A) and tissue-specific (Class B) bHLH domain. A recent report suggested ID genes act to enhance the proliferative potential of tumour astrocytes. Those reports sup-ported ID genes are mighty regulators in tumour-angiogenesis and govern the malignant response of glial tumours. So, I performed bioinformatics and computational application to the current knowledge of the ID family in two different genomes.

RESULTS

My analysis data supported the composition of nucleotide, peptides, domain, motif, chromosome location, phylogeny, gene network, and expression of ID genes in the genome. Therefore, I documented the numeral of ID genes and proteins in mammals. Also, the functional mechanisms for-warded the ID1-ID4 genes revealed a dominant role during cellular differentiation, cell-cycle-regulation, and cellular maturation.

CONCLUSION

My documented data proposed the justification of the ID family associated with glial tumours. In contrast, the numerous molecular functional mechanisms demonstrated the feature of glial growth.

KEYWORDS

ID genes; ID proteins; bHLH TFs; Glial tumours and development

INTRODUCTION

The feature of neuroglia originates from the potentiality of genes to segregate the postpartum period. Glial growth characterized encephalon to respond gliosis and malignant fluctuation of neuroglia. The primary tumours in the encephalon represent astrocytic derived tumours.

Astrocytes tend to the malignant transformation that differentiates cells in CNS [1-4]. The astrocytic tumour accord ubiquitous characteristic of effective astrocyte enhances genes and protein's function. Those genes and their encoded proteins oscillation induce at developmental stages of astrocytic differentiation. Known studies exhibit the viability of effective state imparts by astrocytes under the reaction of neoplastic activity. The molecular mechanisms described the salient improvement and stimulating of neuroglia also glial pathology remains unclear. But the neuroglia activation and malignant variation of astrocytes depend on the process of ID genes and proteins [5]. The inhibitor differentiation (ID) genes that act in encephalon are optimum and limited to recover the strength of astrocytes. The likelihood of glial cells differentiates by the robust accumulation of ID genes and their encoded proteins in glial tumours [6]. An earlier study suggested the ID genes expressed at variable levels in cells acquired from glial tumours such as neuroblastoma, glioblastoma and glioma [1]. Recent experimental evidence supported the glial tumours obtained from the CNS also express a high degree of ID1-ID4 genes. The vector of inhibitor differentiation examines depend on the pathological model of the malignancy. Also, the unstable expression of ID genes suggested aggressive growth of glioblastoma multiform and astrocytoma [7]. ID genes explored in malignant cells and blood vessels during the enhancement of astrocytic tumours. The malformed function of ID1-ID3 genes in astrocytic tumours appears in blood vessels correlated by an intensity of endothelial proliferation. Abnormal function of ID1-ID3 suggested glioma, medulloblastoma and neuroblastoma. During angiogenesis, tumours specific ID1/ID3 genes in model organisms fail to develop and metastasize. Under these circumstances, neovascularization cruelly damages substantial regions on haemorrhage and necrosis [7-11]. Since the characteristic of tumour progression in NS is an equilibrium between anti-angiogenic and pro-angiogenic (angiogenic switch) molecules. Those molecules lead to the tumour neovascularization associated with brain tumours [12,13]. The aggressive gliomas generally coordinated with eminent vascular proliferation required oxygen even nutrients to enhance tumour mass. Thus, neo-angiogenesis in tumours drive ID genes and proteins in the tumour endothelium. The degree of ID1-ID4 gene functions supported anti-angiogenic and targets against highly vascularized brain tumours. The maturation of PNS/CNS exhibits the function of E proteins (E2A, E2-2, and HEB) and tissue-specific (TAL, MYOG, MyoD, NeuroD, and MASH) bHLH TF's does enhance a blueprint of cell-fate delimitation [14,15]. During neurogenesis, bHLH residue is a key regulator that develops neuronal differentiation required NeuroD family, OLIG family, NEUROG1-NEUROG3, atonal gene family, and ASCL1 [16-21]. The proneural nuclear genes stimulate lineage-specific differentiation through neurogenesis and determine patterns of cellular differentiation during development [22-25]. The neurogenic factor of HES1 binds and resists the balance of bHLH domains, which inhibit transcriptions and prevent neural segregation and specification [26]. HES1 restrain neurogenic differentiation strategy and exhaust the derivative of neural precursors [27-30]. The ID genes bind and inhabit via the HES1 gene during the improvement of NS (nervous system). Both are inhibitors of neurogenesis and prevent the response of (–)ve regulation to allow transcription of proneural bHLH TF's [31]. Earlier data suggested the elevated ratios of ID1-ID4 genes rapidly induce in cells and survive through the S phase. Those data raised the G1 progression required functions of E2A with ID genes in the cellular process [32]. The signal of ID1-ID4 genes interacts with bHLH, E2A, E2-2, HEB, PAX, E2F, ETS, and other TF's to form segregation for the growth of organisms [33-36]. The ID1-ID4 genes have negative DNA binding control interactions of other factors. But it's unclear that the ID genes have a +ve role in cellular proliferation. A

creative study supported the molecular checkpoint control proliferation through the RB family (i.e. pocket proteins family). Specifically, the ID genes bind with the RB family (Rb, p107, p130 inhibitors) for cell cycle regulations when massive abundance inhibit their anti-proliferative functions [37-40]. This appearance characterized neuroectodermal tumours when ID2 molar redundancy overactive hypophosphorlated RB [41]. Furthermore, the E2F family are vital for RB function, but the functional inhabitation between the cellular RB-ID2 and RB-E2F functions are unclear. However, ID2/E2F participate RB binding, while ID2 revealed by the mobility of the RB family (pocket proteins) family depend on E2F transcription. The enormous RB-ID2 and RBL1 (p107)-ID2 complexes establish S phase quench the signal of ID2 in natural target since the comparison disputed the ID2 activity characterized G1 progression. The negative response of the RB family control ID2 activity is fundamental for the S phase and cell cycle process [42,43]. Since the (-)ve factors in growth-promoting govern by tumour suppressor protein are vital for sustaining tissue-homeostasis [1]. The (-)ve preface of the ID with the RB family is vital to control the inhibitory firing of differentiation and anti-proliferation. Also, recent data proposed the ID1 inhabits the ETS1/ETS2 both are initiate responses of p16 as a tumour suppressor factor that acts uniform to the RB family [42]. Those factors also derive the character of ID genes that dominate the act of the RB family. The anti-apoptotic potentiality of the ID1-ID4 genes assigns a counterforce to support full immortalization. Thus, it is striking the apoptosis promoted by elements of BCL-2/BCL-XL genes (anti-apoptotic) precisely enhance ID-mediated immortalization by accessing dual ability to lead cellular outgrowth and death [44-46]. Inhibitor differentiation (ID1-ID4) genes associated with polypeptides that combine with a genus of bona fide growth-promoting proteins such as MYC and E2F1 gene are robust activators of apoptosis.

The oncogenic action is strongly affected by the survival genes of the BCL-2/BCL-XL in the BCL-2 family [47-49]. In this work, an intense glimmer of hope and evidence justify the inclusion of the inhibitor differentiation family of nuclear oncogenes and their encoded proteins in glial tumours.

MATERIALS AND METHODS

Target Gene and Database

The ID1 gene (UniProtKB ID: P41134) retrieves from the different specific databases (UniProt, KEGG, GenBank, EMBL, DDBJ and NCBI) and performs web-based application SMART for identification of the particular residue in the suspected sequence (query sequence). SWISS-MODEL performs for prediction of the protein structure is bioinformatics webserver for remodelling of the structure of molecules. This method is useful for generating molecular structure and utilizes it in many practical applications. The SWISS-MODEL is an updated database of remodelling of organism proteome for medical research.

Genome

Two organism's genome sequences downloaded from various exclusive databases (Ensemble and NCBI).

a) Homo sapiens: Genome assembly: GRCh38.p13 (GCA_000001405.28)
b) Mus musculus: Genome assembly: GRCm39 (GCA_000001635.9)

Standalone Tools

HMMER software packages executes through MSA of the target domain as a profile search (Parameters: 1.0e-3). HMMER is statistical algorithms that build by MSA of the suspected region for profile search. Is implemented probabilistic model is well-known as the profile Hidden Markov Model (HMM). Standalone BLAST2 executed for homologs gene in both organisms.

Gene Annotation

The BLAST2GO initialized using parameters 1.0e-3 for GO annotation. BLAST2GO is a computational and bioinformatics application for high-throughput GO annotation of particular sequences. The functional property of genes rectify via GO (Gene Ontology) annotation is a popular tool for practical work.

Domain

For observation of the conserved residue in the ID1-ID4 gene, we can perform the MSA method to calculate unique tests of the homologs also streak them up, so we can observe the identity, differences and similarities. MSA of highest hits sequences analysis conducted using web-based application MultAlin for examination of sustain domain.

Motifs

MEME suite application performs for the resolution of sequence motifs in ID1 gene. MEME is a bioinformatics web-based tool for analysis and discovery of the specific motifs.

Phylogeny

For experimentation of the molecular evolutionary relationship of the ID genes in both organisms, we can perform MEGA-X for constructing a phylogenetic tree using Neighbor-Joining Methods.

Gene Expression

The gene expression of ID1-ID4 gene analysis can carry out by GENEVESTIGATOR application. GENEVESTIGATOR is an excessive-performance search engine for gene expression of different organisms. This application performs to determine and validate novel targets.

Chromosome Location

Chromosome location of ID1 gene can retrieve using a web-based application that is well-known as a gene card. The gene card database provides information on all known and predicted genes. This database is currently available for biomedical research such as predictions of genes, encoded proteins and associated diseases.

Gene Networks

The genetic matrix (gene network) is a group of molecules that regulates and interact with one another in the cells to control the expression volume of mRNA or proteins. Many proteins serve to activate genes are the TF's that bind to the pioneer area and initiate the function of other proteins is called regulatory cascades. We can retrieve the STRING database for the prediction of protein-protein interaction. STRING database contains various resources like experimental data and computational prediction of proteins and nucleic acids.

RESULTS

Structural Analysis

The primary structure determines the composition of nucleotides and peptides. The target structure arranges by 468 nucleotides and 155 peptides with 56 peptides tied to DNA (Table 1). A three-dimensional (3D) structure stated that the 56 polypeptides make a bHLH residue is a negative regulator recognized by two alpha-helix linked through a loop. The variability of the loop allows dimerization through folding and filling in the case of other helices. Those amphipathic alpha-helices have separated by a linker region of length (Figure 1A). The Ramachandran diagram (φ, ψ plot) described the polypeptides located in parallel and anti-parallel beta sheets (Figure 1B).

>ID1
atgaaagtcgccagtggcagcaccgccaccgccgccgcgggccccagctgcgcgctgaag
gccggcaagacagcgagcggtgcgggcgaggtggtgcgctgtctgtctgaagcagaagcgtg
gccatctcgcgctgcgccgggggcgccgggggcgcgccctgcctgccctgctggacgagcag
caggtaaacgtgctgctctacgacatgaacggctgttactcacgcctcaaggaagctggtg
cccaccctgccccagaaccgcaaggtgagcaaggtggagattctccagcacgtcatcgac
tacatcagggaccttcagttggagctgaactcggaatccgaagttggaaccccccgggggc
cgaggggctgccggtccgggctccgctcagcaccctcaacggcgagatcagcgccctgacg
gccgaggcggcatgcgttcctgcggacgatcgcatcttgtgtcgctga

(a)

>ID1
mkvasgstataaagpscalkagktasgagevvrclseqsvaisrcaggagarlpalld
eggvnvllydmngcysrlkelvptlpqnrkvskveilghvidyirdlqlelnsesevg
tpggrglpvraplstlngeisaltaeaacvpaddrilcr

(b)

Table 1: Target sequence (Query sequence).

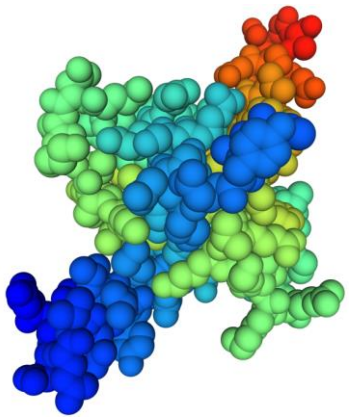


Figure 1A: Tertiary structure of ID1.

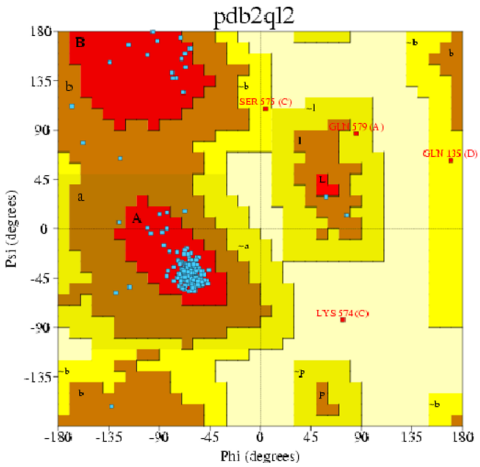


Figure 1B: ID1 polypeptides position in Ramachandran plot.

Genome-Wide Analysis

The genome-wide analysis of both organisms by the HMMER algorithm obtained 72, 62 of bHLH domain in Homo sapiens and Mus musculus, respectively (Table 2). Standalone BLAST2 output represents 12, 13 homologs of inhibitor differentiation genes in Homo sapiens and Mus musculus, respectively (Table 2). The gene ontology annotation confirmed sequence accuracy of ID1-ID4 in the ID Family of bHLH TF's in Homo sapiens and Mus musculus (Table 3 & Table 4).

Organisms	HMMER	BLAST2	BLAST2GO
Homo sapiens	72	11	2
Mus musculus	62	13	2
Total	**134**	**24**	**4**

Table 2: Summary of the bHLH domain and homologs.

Gene	*Homo sapiens*	*Mus musculus*
ID1	2	2
ID2	3	3
ID3	2	1
ID4	1	1
Total	**8**	**7**

Table 3: Summary of the ID family of bHLH TF's.

Gene Id	Gene	Protein
ENSP00000365280.3	ID1	DNA-binding inhibitor ID-1
ENSP00000365273.3	ID1	DNA-binding inhibitor ID-1
ENSP00000379585.1	ID2	DNA-binding inhibitor ID-2
ENSP00000385465.2	ID2	DNA-binding inhibitor ID-2
ENSP00000234091.4	ID2	DNA-binding inhibitor ID-2
ENSP00000489102.1	ID3	DNA-binding inhibitor ID-3
ENSP00000363689.5	ID3	DNA-binding inhibitor ID-3
ENSP00000367972.3	ID4	DNA-binding inhibitor ID-4

(A) *Homo sapiens*.

Gene Id	Gene	Protein
ENSMUSP00000092019.4	ID1	DNA-binding protein inhibitor ID-1
ENSMUSP00000105449.1	ID1	DNA-binding protein inhibitor ID-1
ENSMUSP00000020974.6	ID2	DNA-binding protein inhibitor ID-2
ENSMUSP00000152052.1	ID2	DNA-binding protein inhibitor ID-2
ENSMUSP00000152069.1	ID2	DNA-binding protein inhibitor ID-2
ENSMUSP00000008016.2	ID3	DNA-binding protein inhibitor ID-3
ENSMUSP00000021810.1	ID4	DNA-binding protein inhibitor ID-4

(A) *Mus musculus*.

Table 4: Summary of the gene ontology annotation: **A)** Homo sapiens and **B)** Mus musculus.

Domain, Motifs, and Phylogeny Analysis

The highest hits of ID1 (target gene) listed from both organisms for sequence aligning, MSA re-sults demonstrated conserved bHLH domain. The high consensus (90%) confirmed that the ex-tended bHLH residue (Figure 2A and Figure 2B) and their specific motifs (Figure 3A - Figure 3C). Further observation of the negatively regulated domain concluded that the ID1-ID4 conserved in evolution (Figure 2B). The experiment of the phylogenetic tree suggested the molecular evolutionary relationship of the ID Family of bHLH TF's in-between Homo sapiens and Mus musculus (Figure 4).

Chromosome Location, Gene Network, and Expression Analysis

Chromosome location study confirmed that the ID1 located band 20q11.21. Started 31,605,283 bp and, end 31,606,515 bp in humans (Figure 5). The gene network study determined that the ID1 interacts with other molecules such as TCF3, TCF4, TCF12, RAP1A, ASCL3, THBS1, ETS2, ASCL1 also BMP2. Those molecular interactions govern

the outcome of the ID1 gene in particular cells (Figure 6). The disease state study in humans suggested the ID1-ID4 genes highly expressed in the neoplasm of the eye, brain, CNS, astrocytoma, glioblastoma, oligodendroglioma (Figure 7) (Table 5).

Therefore, the bHLH TF's data analysis concluded the total number of ID genes, peptide structure, conserved domain, motifs, phylogeny, chromosome location, gene network, and gene expression in isolated organisms.

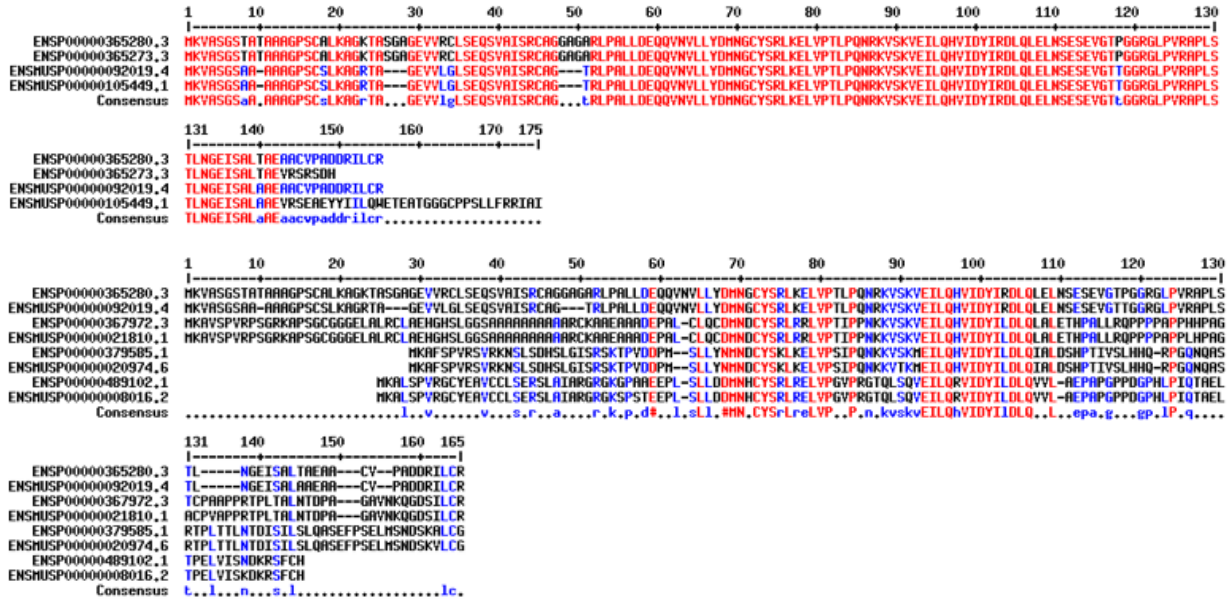


Figure 2: A) ID1 conserved in both organisms. **B)** ID1-ID4 conserved in two organisms.

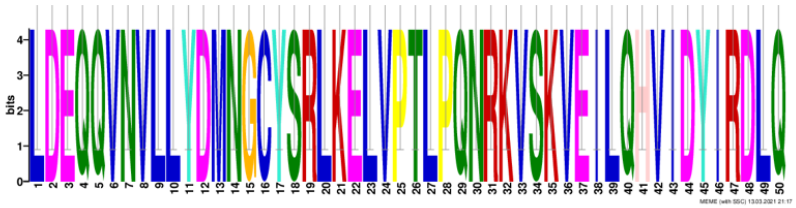


Fig. 3 (a)

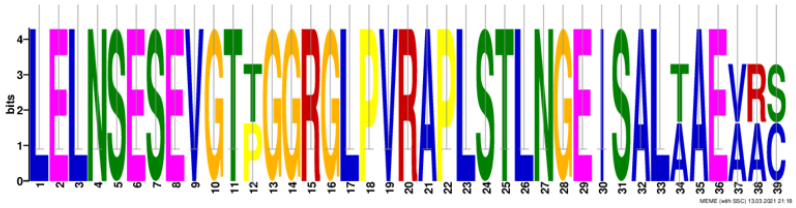
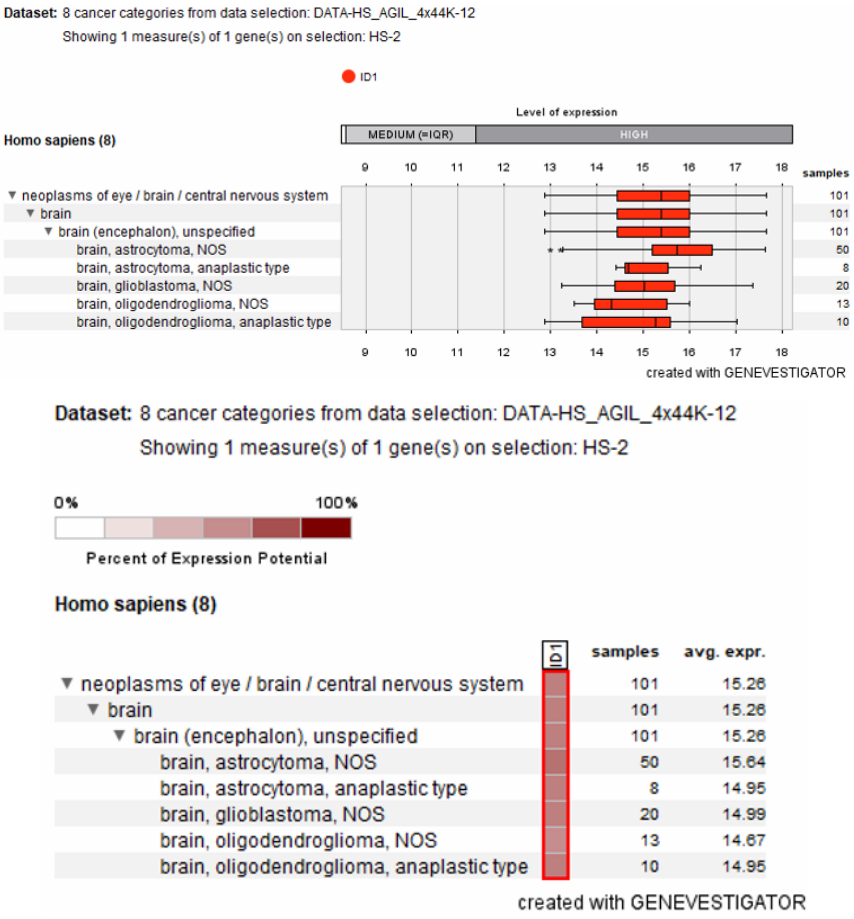


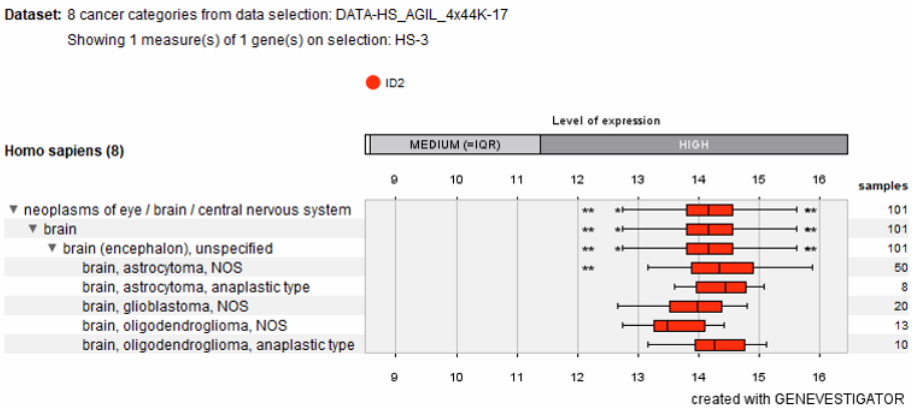
Fig. 3 (b)

Fig. 3 (c)

Figure 3: Sequence motifs of ID1.

Figure 4: The evolutionary link between the ID family of bHLH TF's in two different organisms.





Dataset: 8 cancer categories from data selection: DATA-HS_AGIL_4x44K-17

Showing 1 measure(s) of 1 gene(s) on selection: HS-3

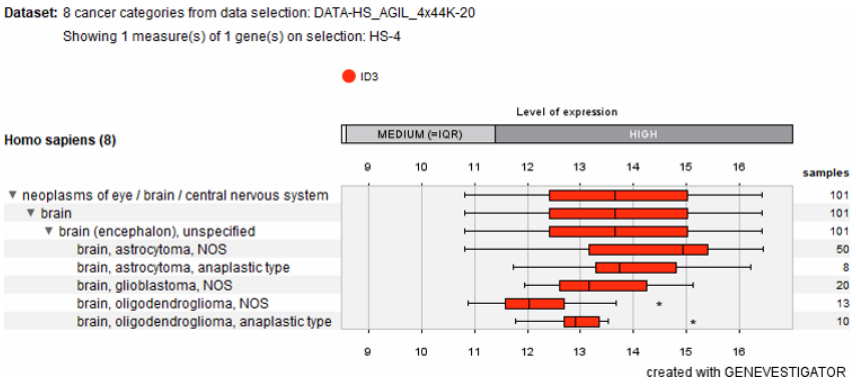
0% 100%

Percent of Expression Potential

Homo sapiens (8)

	ID2	samples	avg. expr.
neoplasms of eye / brain / central nervous system		101	14.18
brain		101	14.18
brain (encephalon), unspecified		101	14.18
brain, astrocytoma, NOS		50	14.39
brain, astrocytoma, anaplastic type		8	14.37
brain, glioblastoma, NOS		20	13.85
brain, oligodendroglioma, NOS		13	13.67
brain, oligodendroglioma, anaplastic type		10	14.31

created with GENEVESTIGATOR



Dataset: 8 cancer categories from data selection: DATA-HS_AGIL_4x44K-20

Showing 1 measure(s) of 1 gene(s) on selection: HS-4

0% 100%

Percent of Expression Potential

Homo sapiens (8)

	ID3	samples	avg. expr.
neoplasms of eye / brain / central nervous system		101	13.70
brain		101	13.70
brain (encephalon), unspecified		101	13.70
brain, astrocytoma, NOS		50	14.31
brain, astrocytoma, anaplastic type		8	13.82
brain, glioblastoma, NOS		20	13.36
brain, oligodendroglioma, NOS		13	12.28
brain, oligodendroglioma, anaplastic type		10	13.06

created with GENEVESTIGATOR

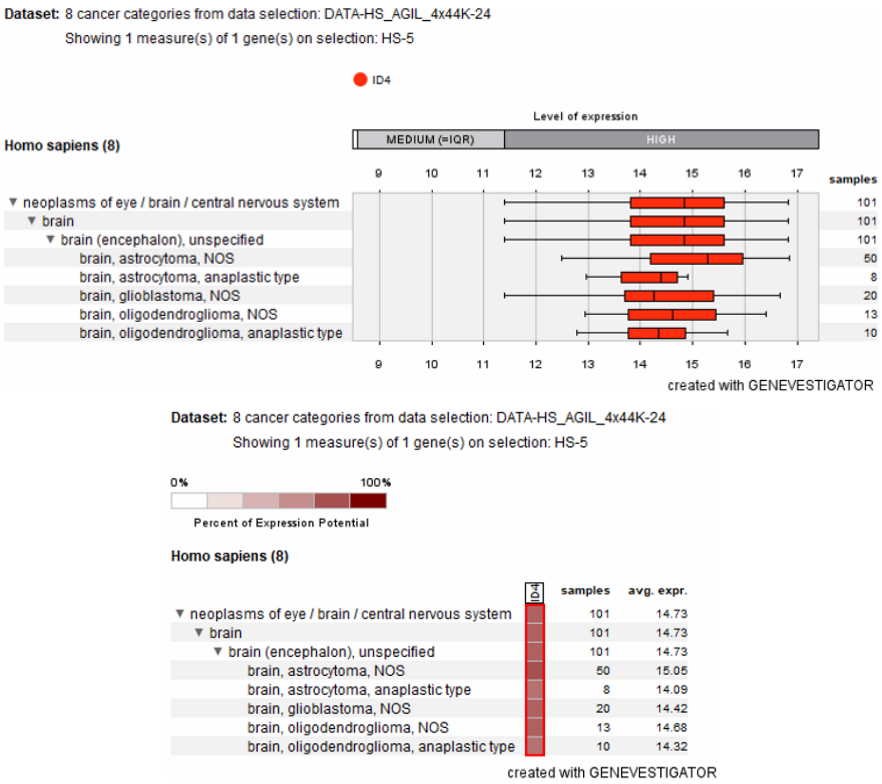


Figure 5: A & B) ID1 expression in Human Brain; **C & D)** ID2 expression in Human Brain; **E & F)** ID3 expression in Human Brain; **G & H)** ID4 expression in Human Brain.

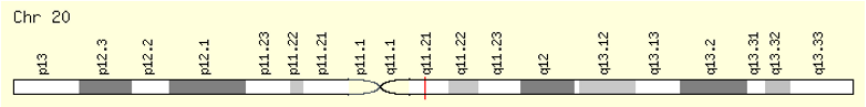


Figure 6: ID1 in humans located at chromosome 20.

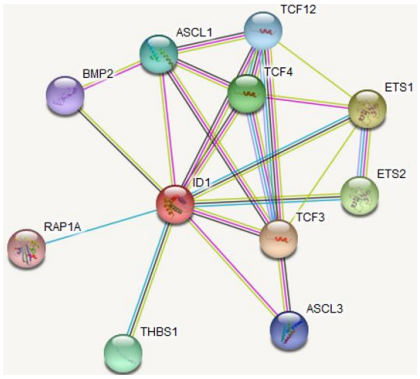


Figure 7: ID1 interact with various TF's.

Gene	Tumor Type	References
ID1, ID3	Glioblastoma	Lyden et al., 1999
ID1, ID3	Medulloblastoma	Lyden et al., 1999
ID1, ID3	Neuroblastoma	Lyden et al., 1999
ID1, ID2, ID3	Astrocytic tumor	Vandeputte, D.A. et al., 2002
ID1, ID2, ID3	Pancreatic cancer	Maruyama et al., 1999
ID1, ID2, ID3	Head and Neck cancer	Langlands, K. et al., 2000
ID1, ID2, ID3	Colorectal adenocarcinoma	Wilson, J.W. et al., 2001
ID1, ID2, ID3, ID4	Seminoma	Sablitzky et al., 1998
ID1, ID2	Pancreatic cancer	Maruyama, H. et al., 1999

ID1, ID2	Pancreatic cancer	Lee, K.T. et al., 2004
ID1, ID2	T-cell lymphoma	Kim, D. et al., 1999
ID1, ID2	T-cell lymphoma	Morrow, M.A. et al., 1999
ID1	Medullary thyroid cancer	Kebebew et al., 2000
ID1, ID2, ID3	Squamous cell cancer	Langlands et al., 2000
ID1	Breast cancer	Lin et al., 2000
ID1	Breast cancer	Fong, S. et al., 2003
ID1	Breast cancer	Schoppmann, S.F. et al., 2003
ID2	Breast cancer	Itahana, Y. et al., 2003
ID3	Breast cancer	de Candia, P. et al., 2003
ID4	Breast cancer	Beger et al., 2001
ID1	Endometrial cancer	Takai et al., 2001
ID1	Cervical cancer	Schindl et al., 2001
ID1	Melanoma	Polsky et al., 2001
ID2	Neuroblastoma	Lasorella et al., 2002
ID2	Ewing's sarcoma	Fukuma, M. et al., 2003
ID2	Ewing's sarcoma	Nishimori, H. et al., 2002
ID1	Ovarian tumors	Schindl, M. et al., 2003
ID3	Ovarian tumors	Arnold, J.M. et al., 2001
ID1	Prostate cancer	Ouyang, X.S. et al., 2002
ID1	Prostate cancer	Coppe, J.P. et al., 2004
ID1	Esophageal cancer	Maruyama, H. et al., 1999
ID1	Oral cancer	Nishimine, M. et al., 2003
ID1	Melanoma	Polsky, D. et al., 2001
ID1	Hepatocellular cancer	Lee, T.K. et al., 2003
ID4	Acute lymphoblastic leukemia	Bellido, M. et al., 2003

Table 5: ID family of bHLH TF's in primary human tumors.

DISCUSSION

The genomics study suggested the dominant outcome of the ID family of bHLH TF's revealed numerous hallmarks of development such as stem cell defence, cellular growth, differentiation, lineage determination, cell-cycle regulation, angiogenesis, vasculogenesis, migration, proliferation, tumorigenesis, immune response, and energy metabolism [1,42,50-57]. The ID1-ID4 of bHLH TF's shares negative DNA binding residue and their motif-initiated dimerization by the interactions of other bHLH TF's like E2A, HEB, and E2-2 are primarily the groups of E protein. The ID proteins have a negative DNA binding domain (amino acids residues). But ID proteins serve natural occurring dominant negative inhibiter of E proteins by the reaction of non-functional heterodimers. The ID1-ID4 TF's has similar functions to suppress the DNA-binding response of E proteins. The sequestering of E proteins suggested inhibiter differentiation proteins decrease reactions of heterodimers via tissue-specific bHLH polypeptides [58]. The stability of inhibiter differentiation (ID) proteins for the E proteins governs discharge functions during sequestering by the motion of their structure. Hence, we can consider that the E proteins activity in the cells determines by the total concentration of E proteins subtracted by inhibiter differentiation proteins. The functional study supported inhibiter differentiation proteins engaged as an effective approach to delineate the collective activity of E proteins [59-61]. Precisely, the combination of inhibiter differentiation proteins, artificial molecule (recombination), and ET2 is supported and exploited. ET2 contains N-terminal polypeptides of E47 with two transcriptional residues and C-terminal polypeptides of SCL/TAL1 composed of the basic helix-loop-helix domain. Since the residues of SCL & TAL1 do not have to dimerize via ID proteins but has good stability for E protein [62]. But ET2 interact with E proteins greedily and bind to DNA sequences (E box) since ET2 contains transcriptional arouse domains of E47, which is heterodimers between ET2 and E proteins that raise transcription of target associated genes. Consequently, the ET2 compete with the ID family to coordinate the other proteins and neutralize the inhibitory impact of inhibiter differentiation proteins. Also, ID proteins resist the functions of E proteins through the interaction of various

proteins without the bHLH domain. Such as ID2 interacts with RB proteins that differentially repress G1/S and G2/M associated genes after P53 activations. That leads to an antagonistic relationship between ID2-RB [47,40]. Indifference, the ID1 bind to membrane-associated molecule regulates integrin signals (CAV1) [41,63]. ID3 implicates coimmunoprecipitate with PAX5 to control its transcriptional mobility [35]. Even the ID1/ID3 regulates cellular processes and transcribed the G1 cycle by a reaction of serum stimulation. ID1 functions promote the outgrowth of NIH3T3 fibroblast during the variation of the G1 to S cycle. Besides, elevated levels of E47 arrest cell cycles through a transformation in the NIH3T3 cell line. These mechanisms are constant for E proteins implicated during transcriptional catalysts of the p16/p21 are enzymes of the cycling-dependent kinase. The link between inhibitor differentiation proteins and E proteins in cell cycle-regulated fashion suggested the E2A (E12 or E47) as homodimer initiate transcription of CDKIs. So, antagonize ID proteins to E protein-initiated transcriptional catalysts of p16/p21 recognized as cell-cycle controllers. Other mechanisms suggested the resistance of ETS1 by inhibitor differentiation proteins controls the reaction of p16, a leading switch of the cycling-D-dependent kinase [64-68]. Also, ID1/ID3 stimulates the response of genes complex in proliferation, invasion, and survival outside the E proteins [51]. In some circumstances, the ID1 attach to the p65 subunit of NF-kB and enhance the NF-kB targets genes. The formation of NF-kB activity and the anti-apoptotic effecter's genes is BCL-XL and ICAM-1 (CD54). Therefore, ID proteins can either function as pro-apoptotic or as anti-apoptotic molecules. ID1-transfected cells resistance by tumour necrosis factor (TNF) through the inactivation of BAX and CASPASE 3 [60,69-71]. The ID1/ID3 in angiogenesis suggested function in the blood vessels of integrins (α6, β4, and αvβ3 integrins), FGFR1, and MMP2 by the response TSP-1. The above initiations are important for regulating bone-marrow-derived endothelial-cell attack and relocation. The recovery of angiogenesis impaired ID-initiated HSP90 inhibitor, 17-allylamino-17 demethoxygeldanamycin or Tanespimycin suppresses HER2-neu-dependent manner [7,73-75]. In fibroblasts, ID proteins promote the tendency of blood vessels through the response of TSP-1, a robust inhibitor during angiogenesis [73]. Additionally, ID proteins boost the mobility of VEGF. Also, ID proteins prefer endothelial cells proficient for mobilization and maturation of VEGF [10,76,77]. Furthermore, a shed light of BMP-dependent repression of ID1 through TGFβ-specific SMAD2/SMAD3 requires synthesis via ATF (ATF3)/CREB family. The variation of CREB/ATF site for TGFβ-mediated suppression of promoter elements is necessary for BMP signalling. Synthesis of ATF3 induces by the function of TGFβ assist naturally through SMAD3 but no BMP-specific SMAD1, enabling cells to characterize between BMP and TGFβ [78]. TGFβ act as an inhibitor or activator of endothelial cells based on two TGF-β receptors: (A) ALK5 signalling through TGFβ-initiated SMAD2 and (B) ALK1 activate SMAD5 through BMP response. The aggregation of TGFβ suggested ALK1 signalling via SMAD5 that accumulate migration and proliferation of endothelial cells by the function of ID1. Also, ALK5 suggested a high quantity of TGFβ that inhibit endothelial cell proliferation and regeneration through induction of PAI [79]. Besides, TGFβ and ID2 induce diverse cell lineages in the immune system. The trafficking of dendritic cells occupied by the TGFβ directly initiates transcription of ID2. Precisely, early B-cell progenitors revealed TGFβ1 initiated by the process of ID2/ID3. Also, ID3 adoption is prominent at the pro-and pre-B-cell stages, whereas ID2 initiation is powerful during the development of B cells. Therefore, TGFβ-mediated activity of ID2 function leads to IgE associated gene and CSR (class switch recombination) [80-82]. In estimation, the ID2 function regulated by GFI-1 is zinc-fingering proteins that act as a repressor. GFI-1 plays a dominant role in

hematopoietic stem cells that maintenance even binds to the ID2 promoter and inhibits transcription. Also, ID2 accord a preface in erythroid differentiation and promote the growth of erythroid linage cells [83-85]. In a variation, the lipopolysaccharides (LPS) stimulate ID1 function in HSC. The response of LPS potentially attributed to transient functions of IL-10 (inflammatory cytokines) and TNFα increase turnover of HSC. These mechanisms reveal the ID1 function that initiates the HSC by the response of LPS that promote TLR signalling [86]. Furthermore, the ID1 to an immunoglobulin enhancer component found at the 3′-end of gene negotiates transcriptional catalyst by responses of STAT5 and C/EBPβ. ID1 function in myeloid tissue revealed CCAAT enhancer-binding proteins that play vital roles by cytokines such as IL-3 and GM-CSF activated by STAT5. Additional inflammatory cytokine of IL-6 also stimulates ID1 functions. Also, the ID2 function conveys to be initiated by C/EBPβ. Invariance, ID3 inflicts RAS/MAPK initiation by responses of the EGR TF's [87-92,62]. ID3 function in humoral immunity correlated with a low degree of IgG1 and IgG2 challenged the T-cell-dependent or T-cell-independent antigens that block thymocytes during the transition from single to double-positive cells. This functional mechanism suggested TCR (T-cell receptor) signalling enables ID3 to captivate several immune checkpoints during T cell maturation [7,54,93,94]. In cancer biology, the ID family of bHLH TF's well characterized in diverse cancers such as glioblastoma, medulloblastoma, neuroblastoma, seminoma, prostate cancer, epithelial ovarian cancer, cervical cancer, endometrial cancer, breast carcinoma, melanoma, pancreatic carcinoma, head & neck cancer, medullary thyroid carcinoma, gastric cancer, T-cell lymphoma, B-cell leukaemia, colon carcinoma, and Ewing sarcoma [50-57]. ID genes function proposed as a prognostic signature in various cancers. In some conditions, it is adequate to render cells immortal or induce oncogenic mutation. Genomic stability of the ID family of bHLH TF's in molecular cancer therapy originates from the hypothesis that accumulates blocking of cellular differentiation and ability to drive proliferation. The ID family of bHLH TF's has negative functions to govern cellular differentiation and cell cycle regulation. Overwhelming evidence supported the resolution of ID genes act to enhance proliferative factors in different neural cell types. Also, the ID genes are a supreme regulator of proliferation in the NS. The functions of ID genes in neural growth suggested the encoded ID proteins control impulsive segregation and ultimately cell cycle block. These mobilities recognize by ID proteins to irritate bHLH TF's and tumour suppressor proteins (RB family). It is supported the ID1-ID4 proteins in post-natal tissues abnormally expressed in tumour endothelial cells attained from CNS and PNS [1]. During development, ID genes set the timing of differentiation in various neural cells includes neurons and oligodendrocytes. Deregulation and malformed expressions of ID genes are associated with neo-angiogenesis, relentless proliferation, and lack of differentiation, a landmark of neural tumour progression [1]. ID2 play a key role in cell fate judgment and oncogenesis. The process of ID2 initiated the mutation of a neural crest [95]. ID2 function increases by the response of N-MYC, a key regulator of differentiation and growth in the neural crest [41,96]. ID2 activate by the function of N-MYC and EWS-ETS (chimeric proteins). The top degree of ID2 function control by the response of EWS-ETS (fusion oncoproteins) and C-MYC. The targets of EWS-ETS are co-express with ID2/N-MYC that restrains the ID2 in the cellular process. Interestingly, ID2 functions expand by the mobility of insulin growth factor (IGF) in pediatric neuroectodermal tumours [97-99]. Indifference, the NSCs revealed the self-renewal ability to originate all the major cells type in the NS. ID proteins maintain NSCs by regulating lineage commitment and preventing NSCs from premature differentiation. Precisely, ID2/ID4 blocks oligodendrocytes by inhibiting OLIG1/OLIG2 are bHLH

TF's robust during oligodendrocyte growth [100]. Surprisingly, ID4 as a BRCA1-regulating gene expression decreases BRCA1 and enhances tumorigenicity via HSP90 inhibitor in cancer. In addition, ID1-ID3 blocks early differentiation by a function of HES1 that inhibits the function of proneural genes. Also, ID proteins restrain neuronal differentiation by binding with NeuroD and E47 elements to E-boxes. ID proteins emerge to sustain self-renewal ability in NSC for differentiation and stimulate proliferation. Notably, the p53 activity as a repressor of ID1/ID2 and p53 of NSCs raised ID functions and proliferation. This phenomenon is vital for cancer therapy since p53 is necessary for restraining glioblastoma [51,75,101-105]. Furthermore, ID1-ID4 proteins are illiberal with a short-life (<30 minutes) even the substrates of ubiquitin 26S proteasome system is a proteolytic molecule of eukaryotic cells [106,107]. UB is an 8-kDa protein driven to ubiquitin-initiative enzyme E1 in ATP-dependent fashion and then to the ubiquitin-implicate enzyme E2. Generally, the ubiquitin covalently linked to the target protein by E3 ubiquitin ligase deploys to derive a polyubiquitin chain. The polyubiquitinated protein is rewarded by 26S proteasome and dehydrated in ATP dependent manner [52]. The E3 ubiquitin ligases categorize into four superior classes: (1) RING-finger-type, (2) U-box-type, (3) HECT-type, and (4) PHD-finger-type. The RING-finger-type subdivides into (A) Cullin E3 ligase and (bB) Aanaphasepromoting complex/cyclosome (APC/C). The E3 ubiquitin ligase of APC/C indeed for CDC20 or CDH1 co-activators that bind the substrate via specific destruction box domains [52]. The ubiquitin/proteasome machinery includes two variable steps: (A) ubiquitination and (B) degradation. Ubiquitination mediated protein is described by abundant ubiquitin molecules recognized by proteasome complex from other proteins. Degradation of multi-ubiquitinated proteins prevails on a massive 26S proteasome aggregation. Those mechanisms exposed the cyclin-B synthesis is a regulated factor for the cells to drive mitosis. Even cyclin-B degradation is the central component that governs exit from mitosis and drives into the G1 phase of the next cell cycle. The cell cycle-dominated control of cyclin B-initiated catalyzes by ubiquitin/proteasome-dependent fashion. Similarly, cycling E synthesis controls the late G1 progression and breakdown of cycling by the ubiquitin/proteasome for cells to move in the S phase. Invariance, p21/p27 (CDK inhibitors) is a repressor of p53, E2F-1, and pRB degraded through ubiquitin/proteasome machinery. Furthermore, the precision mediated by ubiquitin ligase maintains the elevated ratio of specificity for the substrate [108-110]. The ubiquitin ligase is a dominance of ID proteins for proteasomal-mediated degradation via APC/C (cell-cycle regulator). The APC/C and co-activator of CDH1 (CD324) recognize by ID1/ID2 and ID4 through the conserved D-box motif situated in C-terminus to the helix-loop-helix domain. Indeed, variations of the D-box of ID2 suggested a remarkable equilibrium of substances. During the cellular process, APC6/CDC16, APC8/CDC23, and APC3/CDC27 are core components of APC/C are fundamental for the ubiquitination substrates. The ID1-ID4 proteins are essentially for targets of APC/C for control of axonal growth in post-mitotic neurons via the signal of NOTCH1, NOGO receptor, SEMA3F, UNC5A, and JAG2 [3,52,111]. The degradation-resistant variation of ID2 acquired through mutations of a recognition site of APC/C (D-box) is sufficient to enhance axonal maturation and control inhibitory effects on axonal elongation imposed by myelin components. Besides, myelin of CNS inhibits neurite growth and stimulate the collapse of outgrowth cones through NOGO receptor, NOGO66, MAG, and OMPG molecules initiate axon-repulsive signals by UNC5A and SEMA3F both participate in the regulation of myelination through the signal of NOTCH and JAGGED. Therefore, ID1-ID4 proteins in post-mitotic neurons establish a novel loop among cancer and axonal regeneration. Also, dominant-negative antagonists prefer

to induce cytoplasmic relocation of ID proteins are the interferon-inducible protein p204. Interestingly, p204 promote the ubiquitin-initiated degradation of ID3 and probably remaining ID proteins activation required for ubiquitin ligase(s) [52,112]. Therefore, the ubiquitin/proteasome executes a core function in the degradation of these regulatory proteins. Future work will require to achieve the targets in clinical cohorts. So, the functional mechanisms epitomize the ID family of bHLH TF's is a novel regulator in tumour biology.

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ETHICAL STATEMENT

The study contains an *in-silico* analysis of the mammalian genome examination and validation of the particular gene in different organisms.

AVAILABILITY OF DATA AND MATERIALS

The data and materials are available on reasonable request. The corresponding author is ready to submit the data and materials by reasonable request or demand.

CONFLICT OF INTEREST

The author declared that the work has no conflict of interest.

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