



PcG蛋白PHF1由结构到生物学功能分析

Structural and functional Analysis of Plant Homeodomain Finger Protein 1 in Human

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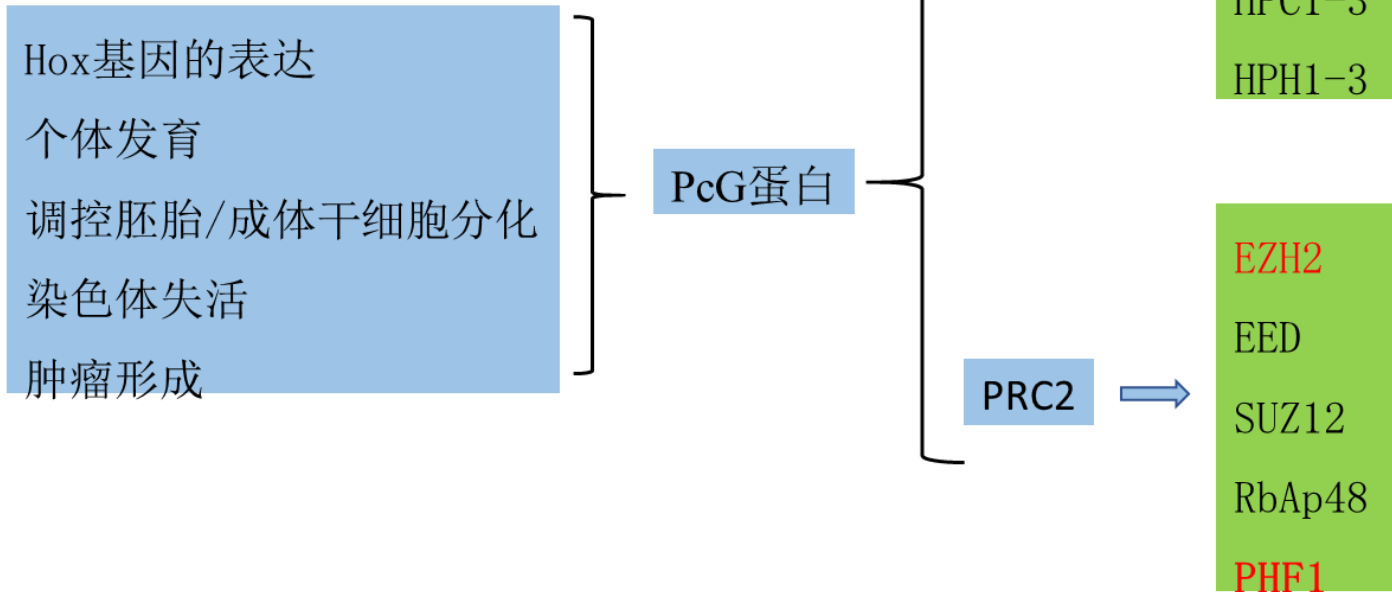
组员：黄露露，丁巍，杨稼琳，王瑞杰

2020-01-04

PHF1蛋白的由来



Polycomb group (PcG)

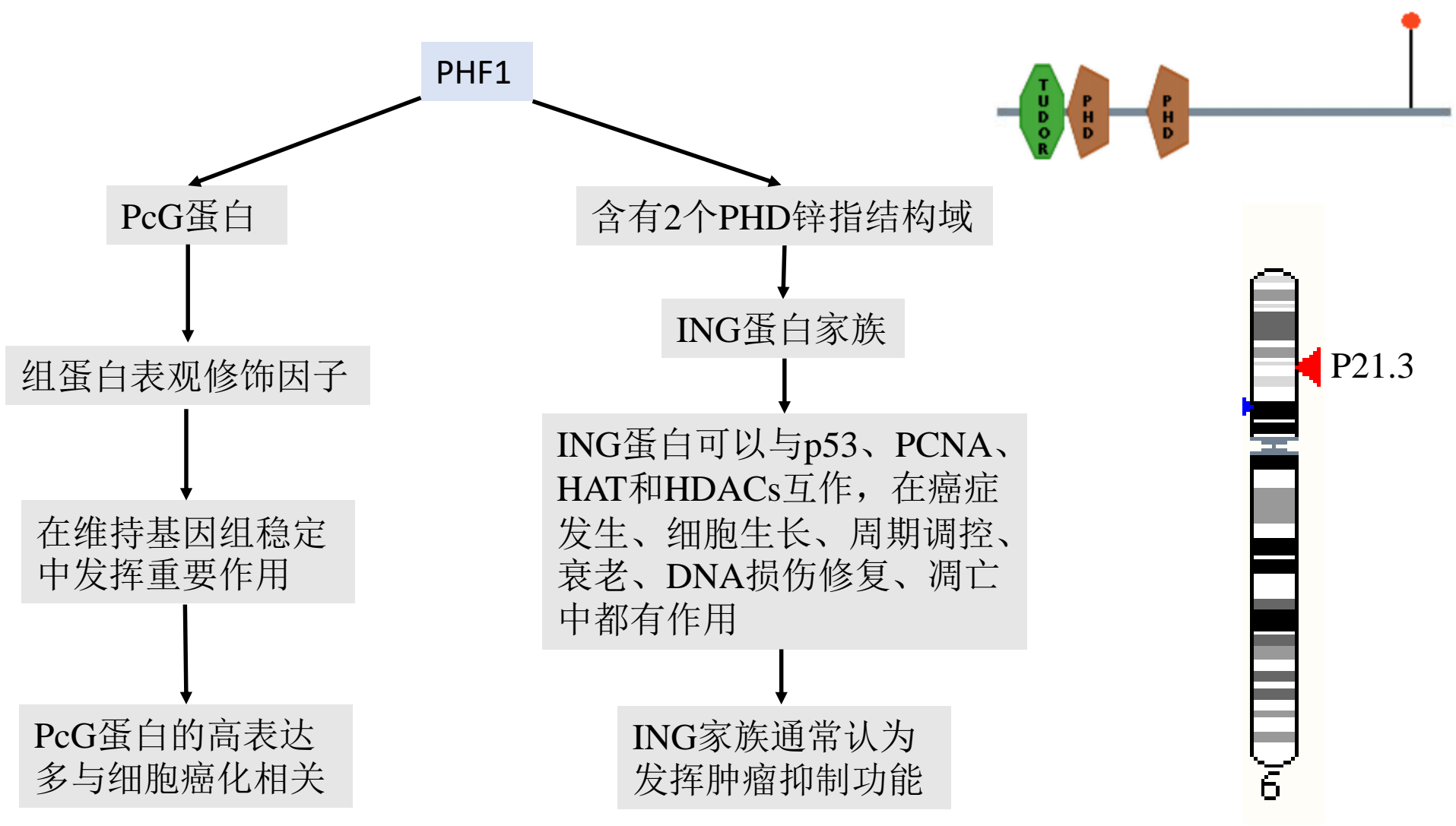


Genomics, 1998, 48(3): 381-383.

Cell Cycle, 2016, 15(3): 305-306.

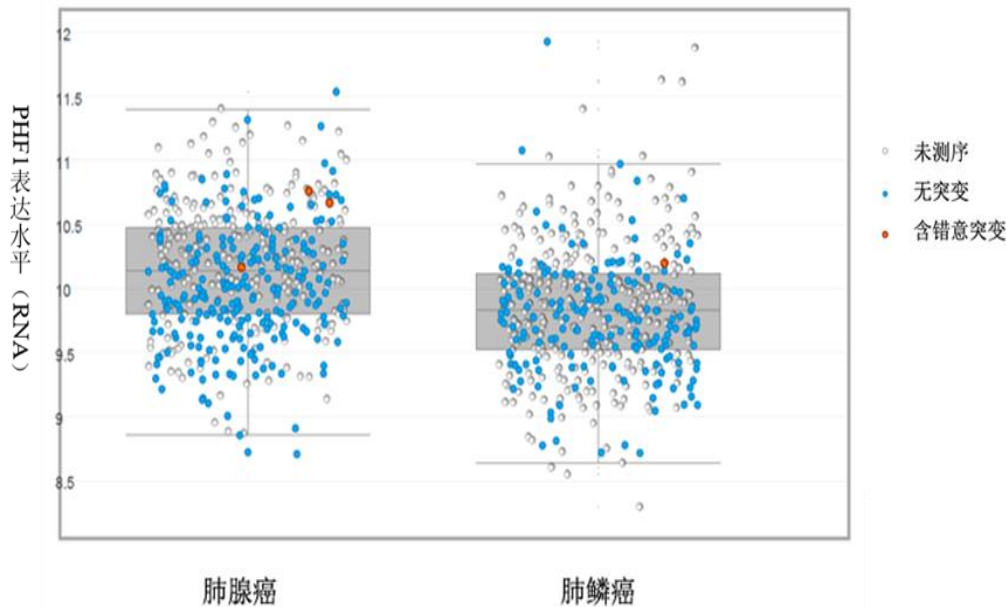
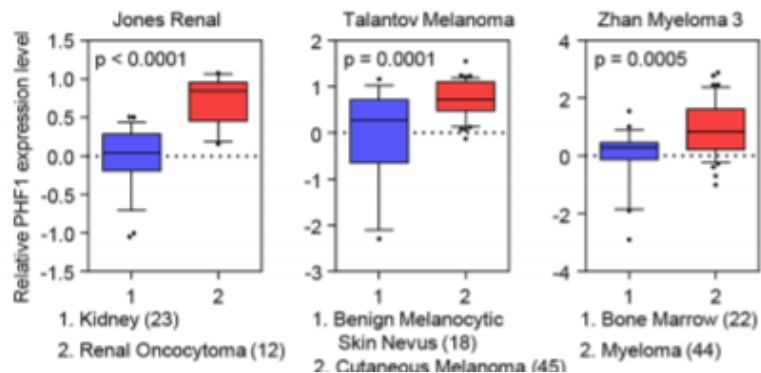
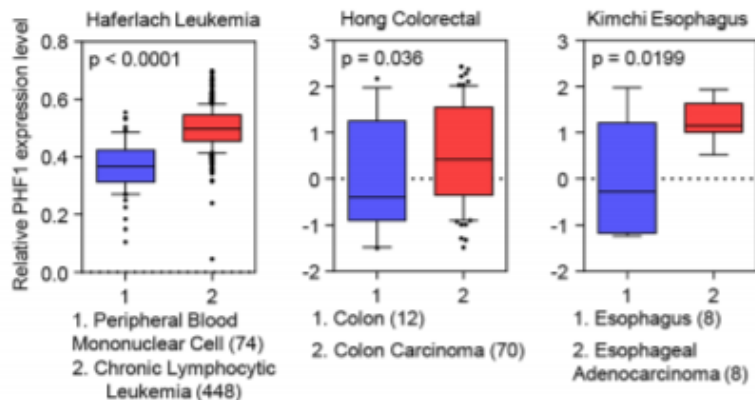
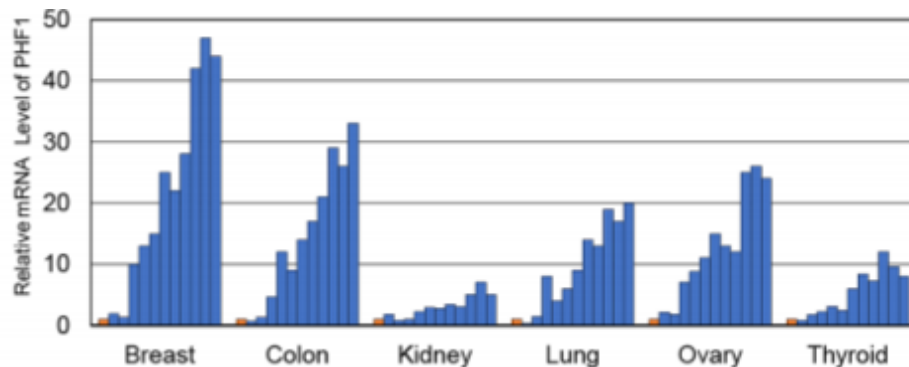
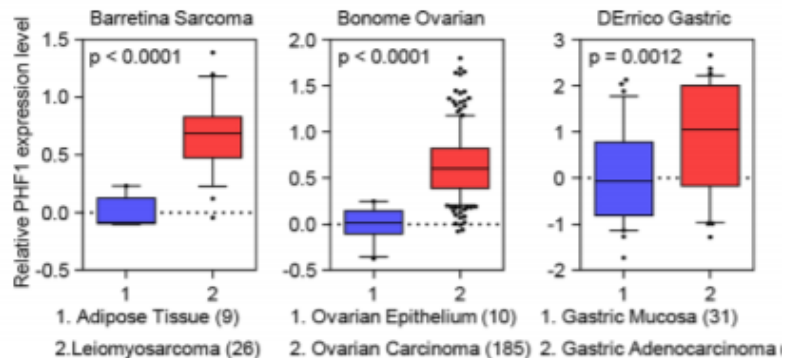
P53

PHF1的主要特征



推测：同时具备PcG和PHD特征的PHF1可能在癌症发生发展中具有重要作用

PHF1蛋白在多种癌症中上调表达



PHF1蛋白所参与的生物学过程

PHF1 是 PcG 蛋白家族中的重要组分，参与众多复杂的生物学过程

1. DNA 损伤修复 —— 涉及到：同源修复和非同源末端连接两种修复方式

Nucleic Acids Res, 2008, 36(9): 2939-2947.

2. 细胞休眠或凋亡 —— PHF1通过与p53互作阻止 Mdm2 对 p53 的泛素化，促进p53的稳定从而介导细胞的休眠或凋亡

The Journal of biological chemistry, 2013, 288(1): 529-539.

Genes & development, 2015, 29(21): 2231-2243.

3. 组蛋白 H3K27me3\H3K36me3 的翻译后修饰

—— 通过调节PRC2的酶活性来选择性激活两种翻译后修饰途径从而抑制或促进下游基因的表达

Journal of molecular biology, 2014, 426(8): 1651-1660.

4. 染色体重排

—— 在子宫内膜间质细胞瘤中存在JAZF1 /PHF1 、 EPC1 /PHF1和MEAF6 /PHF1融合基因；在骨化性纤维黏液样瘤中，同样发现 PHF1 与 EPC1、MEAF6 基因发生上述染色体重排

Cancer research, 2006, 66(1): 107-112.

Cancer genetics and cytogenetics, 2008, 185(2): 74-77.

Cancer letters, 2014, 347(1): 75-78.

Genes, chromosomes & cancer, 2014, 53(2): 183-193.

但仍无具体研究报道具体的分子作用机制。

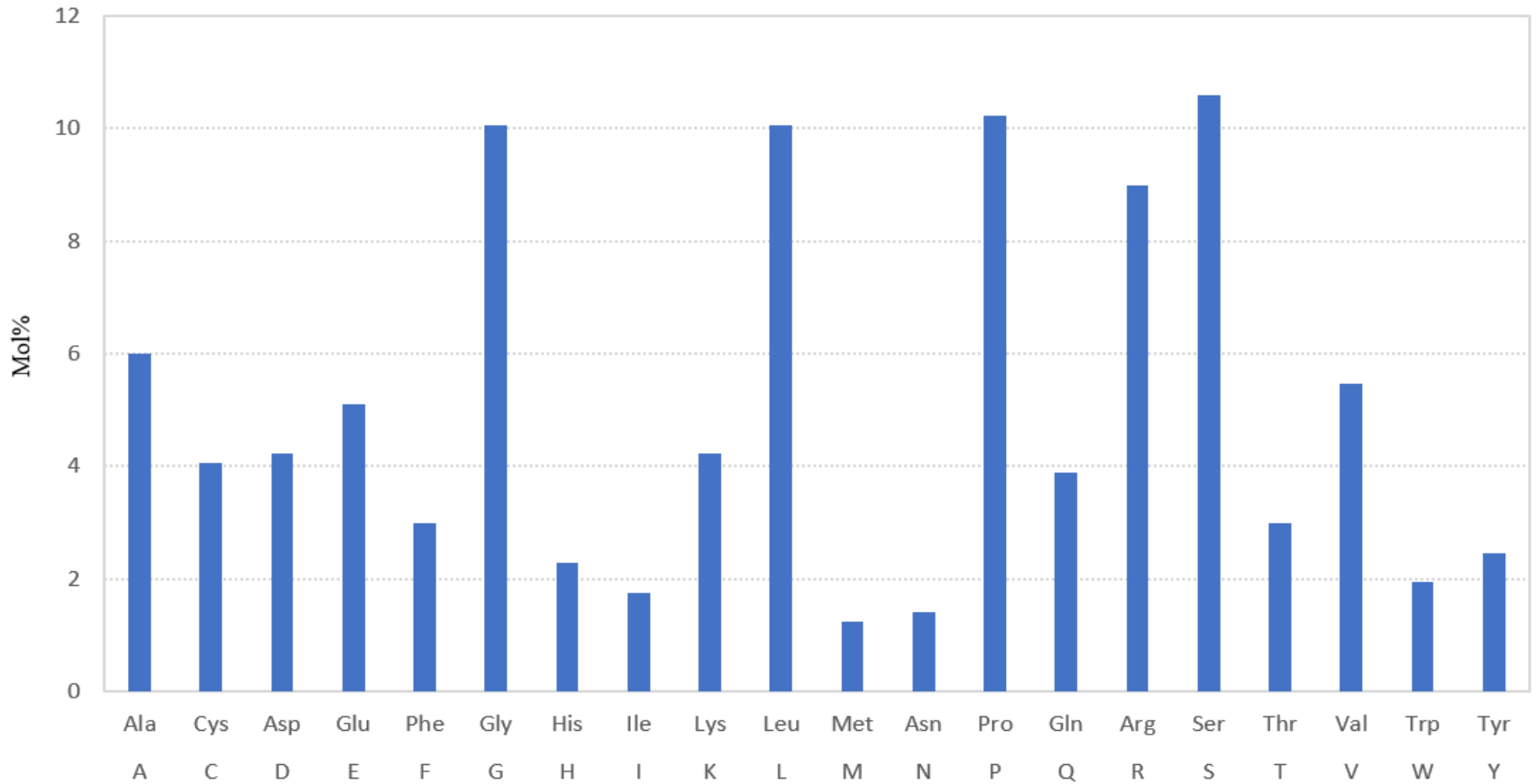


由于其一级结构决定高级结构，PHF1与MTF2、PHF19相似的一级结构促使其必然具有相似的生物学功能，在后续的功能研究中三个蛋白可以相互印证、相互辅助，为后续更为全面的生物学功能研究提供理论基础。

1. 氨基酸组成分析
2. 理化性质分析
3. 亲疏水性分析
4. 信号肽和跨膜结构域分析
5. 亚细胞定位分析
6. 磷酸化位点分析
7. 蛋白二级结构分析
8. 蛋白质互作分析汇总
9. 高级结构分析
10. 亲缘关系及保守性分析

PHF1蛋白氨基酸组成分析

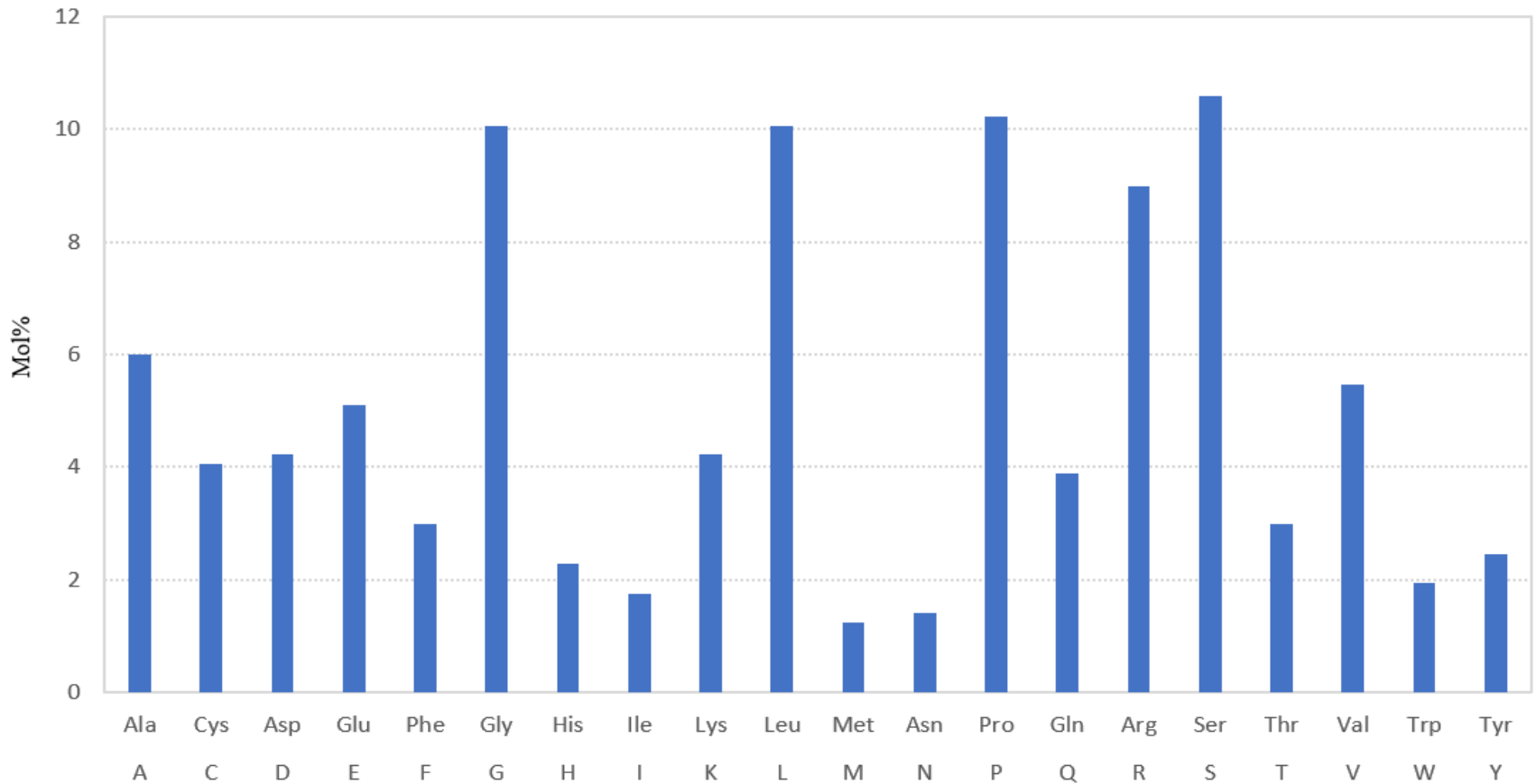
Amino Acid composition
sp|O43189|PHF1_HUMAN PHD finger protein 1 OS=Homo sapiens OX=9606 GN=PHF1 PE=1 SV=3



MTF2蛋白氨基酸组成分析

Amino Acid composition

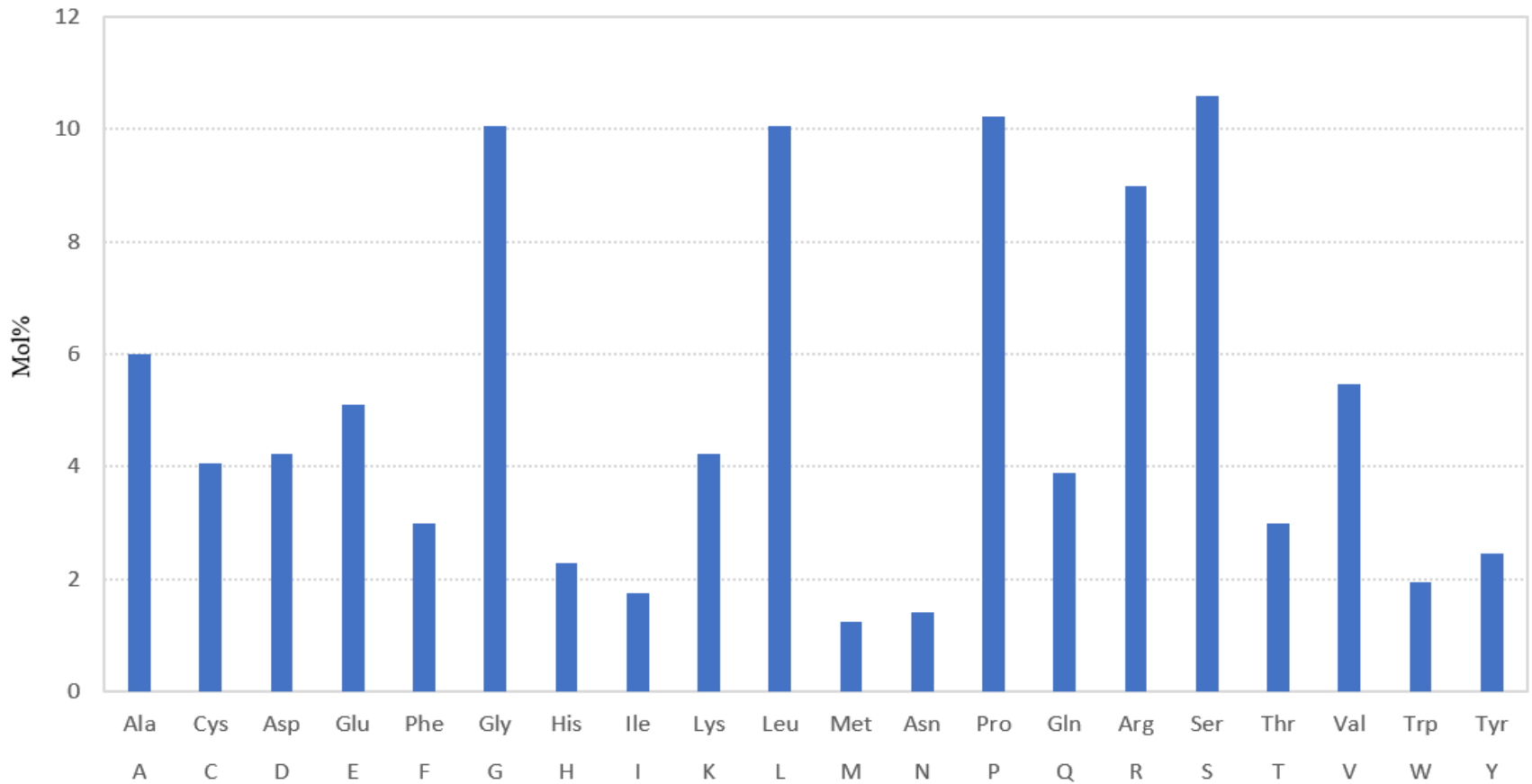
sp|O43189|PHF1_HUMAN PHD finger protein 1 OS=Homo sapiens OX=9606 GN=PHF1 PE=1 SV=3



PHF19蛋白氨基酸组成分析

Amino Acid composition

sp|O43189|PHF1_HUMAN PHD finger protein 1 OS=Homo sapiens OX=9606 GN=PHF1 PE=1 SV=3



PHF1、MTF2和PHF19理化性质分析

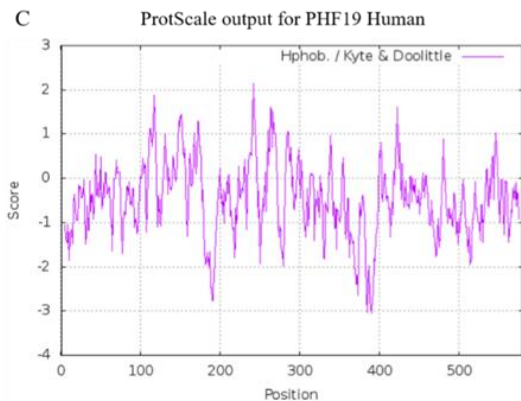
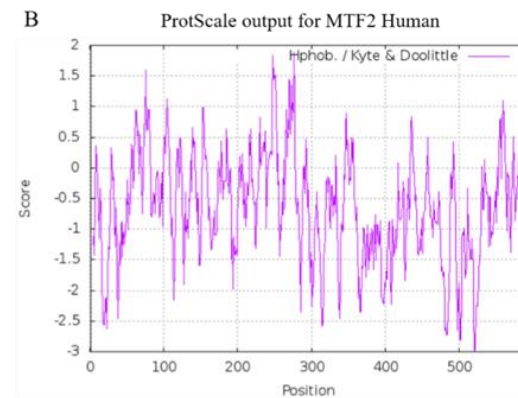
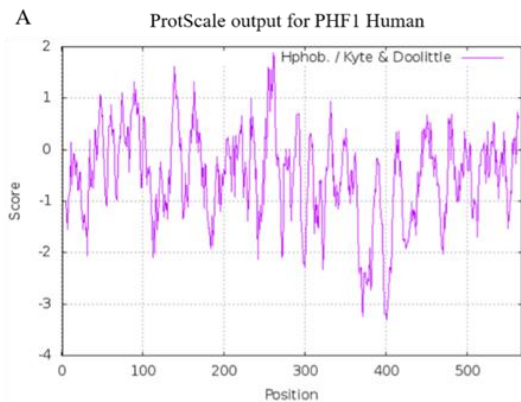
理化性质	PHF1	MTF2	PHF19
蛋白质编号	O43189	Q9Y483	Q5T6S3
染色体	6	1	9
氨基酸长度	567	593	580
分子量	62105.80	67105.62	65590.92
等电点	9.27	8.98	9.08
带负电荷氨基酸残基数	(Asp+Glu) 53	(Asp+Glu) 71	(Asp+Glu) 60
带正电荷氨基酸残基数	(Arg+Lys) 75	(Arg+Lys) 90	(Arg+Lys) 80
主要氨基酸残基	S P L G R A V E	K L S G E T R A D	L S K G R A E P
分子式	$C_{2726}H_{4289}N_{811}O_{795}S_3$	$C_{2950}H_{4671}N_{841}O_{883}S_3$	$C_{2919}H_{4544}N_{820}O_{846}S_2$
	0	3	9
不稳定系数	71.53	46.90	49.05
消光系数	1.310	1.346	1.613
脂肪系数	67.94	70.24	73.34
半衰期预测	30 hours	30 hours	30 hours

根据表中数据预测如下：

- ① PHF1、MTF2和PHF19三个蛋白的等电点均大于7且带正电荷氨基酸残基数均多于带负电荷氨基酸残基数，因此推测三个蛋白均为碱性氨基酸。
- ② 三个蛋白共有的主要氨基酸残基为S，L，G，R，A，E。可预测其共有的特征为：胶原蛋白及一些RNA结合模体。
- ③ 三个蛋白的不稳定系数均分别为71.53、46.90和49.05，均高于阈值40，推测三个蛋白均为不稳定蛋白且PHF1更不稳定。

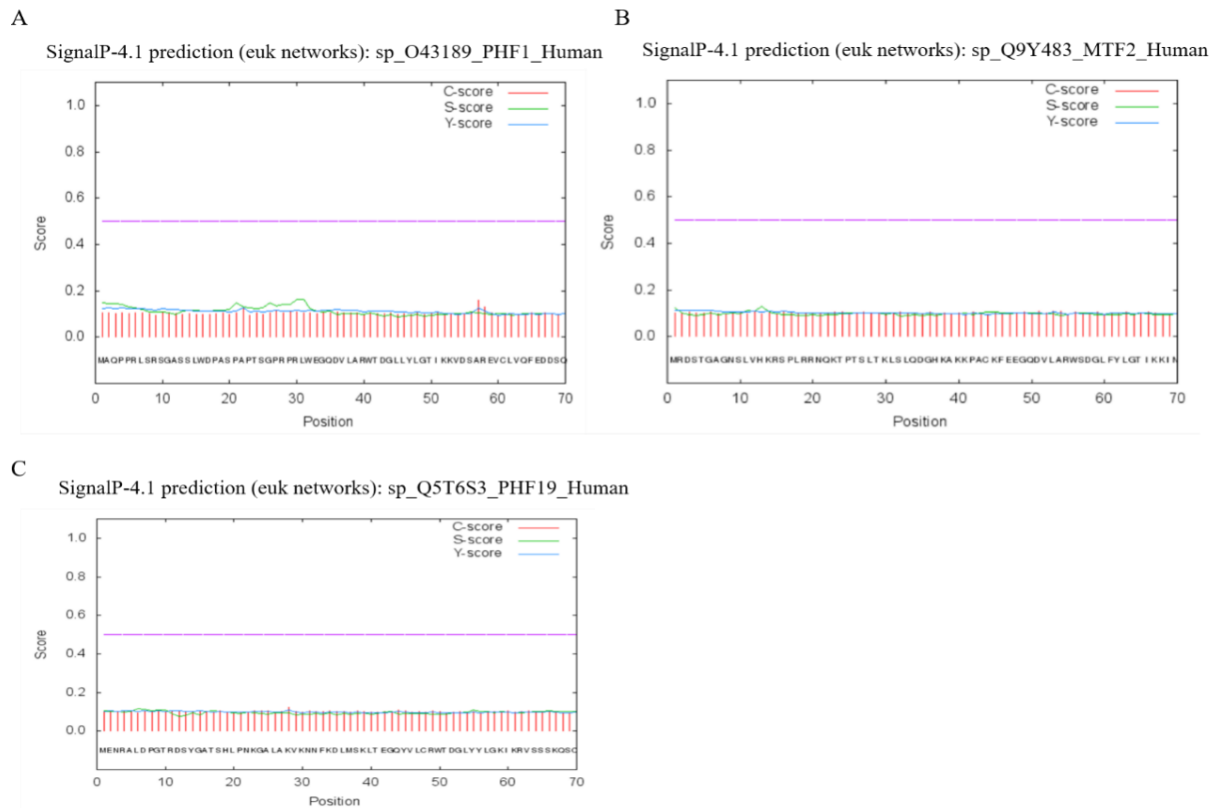
PHF1、MTF2和PHF19蛋白疏水性分析

通过ProtScale对PHF1、MTF2和PHF19进行疏水性分析，位于0刻度线以上为疏水性蛋白，0刻度线以下为亲水性蛋白。如图所示，三个蛋白多数曲线均位于0刻度线下方，总平均疏水性值分别为-0.507、-0.638和-0.491，即：三个蛋白均为亲水性蛋白。

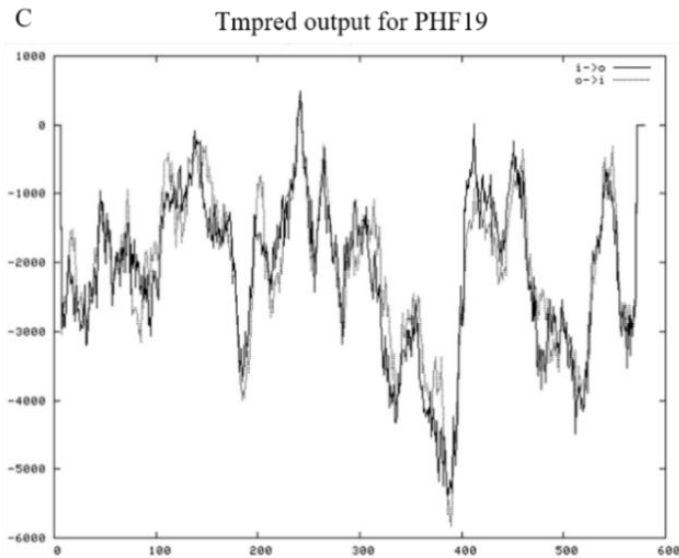
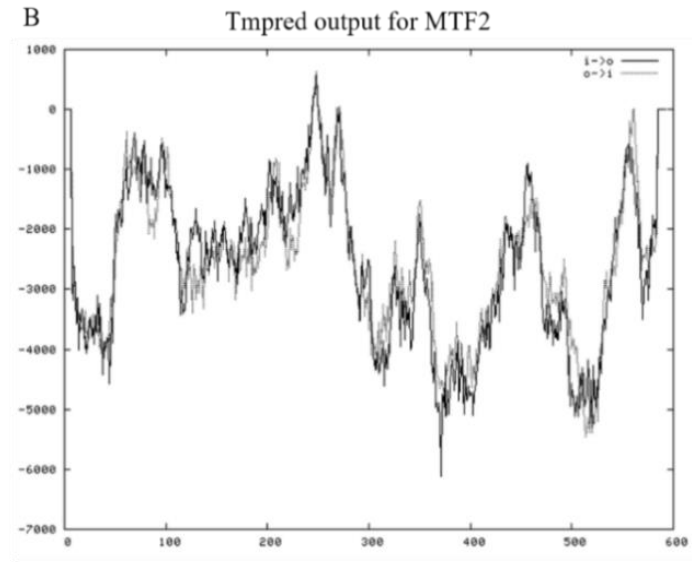
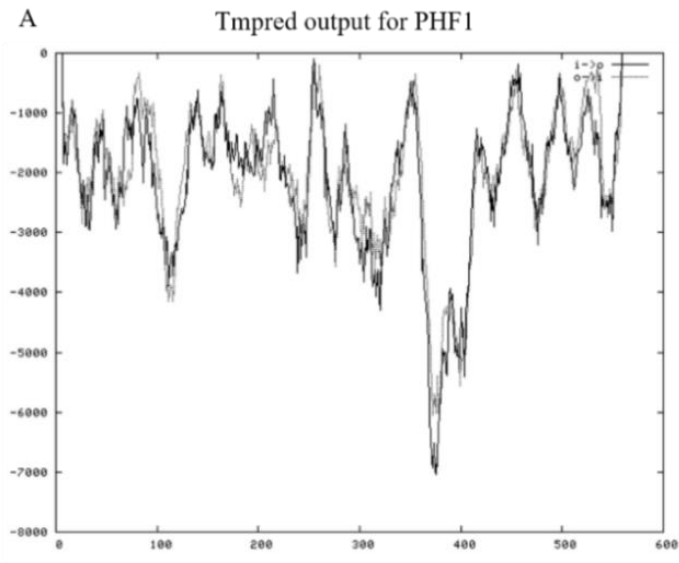


PHF1、MTF2和PHF19蛋白进行信号肽和跨膜结构区

利用SignalP和Tmmpred在线网站对PHF1及其同源蛋白进行信号肽和跨膜结构区及跨膜方向进行预测。PHF1、MTF2及PHF19不存在跨膜域，且无信号肽，因此推测为膜内参与细胞内信号传递的蛋白，其中PHF1定位于细胞核。



PHF1、MTF2和PHF19蛋白跨膜区分析



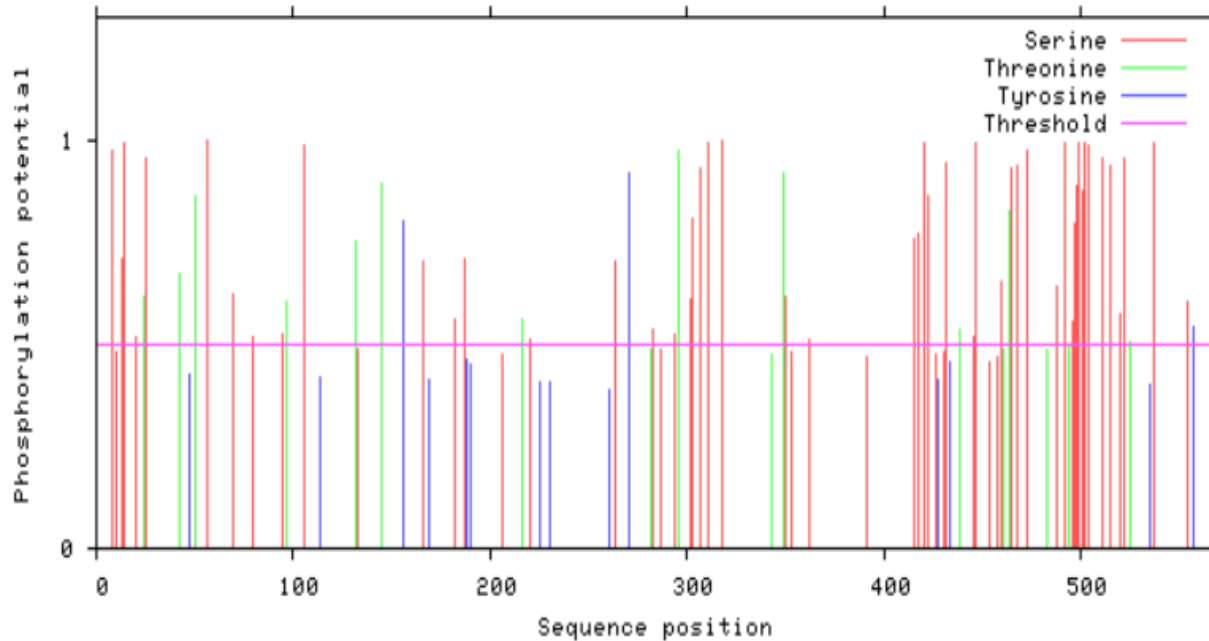
PHF1、MTF2和PHF19蛋白亚细胞定位分析

上一步分析可知，3个蛋白均为膜内蛋白，进一步进行亚细胞定位分析可知，PHF1与PHF19主要定位于细胞核，而MTF2则主要定位于细胞核和线粒体中。

基因名称	肯定度						
	细胞核	细胞骨架	细胞质	囊泡分泌系统	质膜	线粒体	内质网
PHF1	69.6%	13%	4.3%	4.3%	4.3%	4.3%	—
MTF2	39.1%	4.3%	8.7%	—	4.3%	39.1%	4.3%
PHF19	78.3%	—	8.7%	4.3%	—	8.7%	—

PHF1、MTF2和PHF19蛋白磷酸化均以丝氨酸为主

NetPhos 3.1a: predicted phosphorylation sites in sp 043189 PHF1 HUMAN



PHF1共567个氨基酸，

Ser——50处

Thr——12处

Tyr——3处

NetPhos

由于PHF1含丝氨酸（Ser, S）和精氨酸（Arg, R）较多，因此可作为RNA结合模体。

PHF1、MTF2和PHF19蛋白磷酸化均以丝氨酸为主

MTF2共593个氨基酸，其中丝氨酸（Ser）有42处、苏氨酸（Thr）有22处、酪氨酸（Tyr）有7处可能被磷酸化，可见MTF2以丝氨酸磷酸化为主，苏氨酸磷酸化也占有一定的比例。

PHF19共580个氨基酸，其中丝氨酸（Ser）有39处、苏氨酸（Thr）有17处、酪氨酸（Tyr）有9处可能被磷酸化，可见PHF19以丝氨酸磷酸化为主。

PHF1、MTF2和PHF19蛋白磷酸化位点分析

预测PHF1、MTF2和PHF19可能含有PKA、PKC、PKG、p38MAPK、cdc2、cdk5、CKI、CKII、RSK、INSR等磷酸化位点，以及GSK3磷酸化识别位点。

激酶	PHF1		MTF2		PHF19	
	位点	得分	位点	得分	位点	得分
PKA	42 T	0.674	4 S	0.638	13 S	0.596
	95 S	0.525	27 S	0.524	51 T	0.663
	166 S	0.701	57 S	0.763	64 S	0.714
	187 S	0.672	181 T	0.574	107 S	0.534
	220 S	0.511	288 S	0.578	374 S	0.814
	303 S	0.701	380 S	0.813	396 S	0.868
	307 S	0.549	401 S	0.612	500 S	0.609
	511 S	0.668	483 T	0.525	538 S	0.689
	520 S	0.573	488 S	0.525	—	—
	554 S	0.606	551 S	0.644	—	—
	—	—	576 T	0.683	—	—

PKC	24 T	0.542	26 T	0.535	18 S	0.537
	50 T	0.860	29 T	0.602	64 S	0.780
	145 T	0.558	65 T	0.916	65 S	0.803
	182 S	0.561	141 S	0.529	66 S	0.635
	216 T	0.563	158 T	0.746	275 S	0.868
	263 S	0.701	159 T	0.875	307 T	0.736
	311 S	0.810	160 T	0.539	319 S	0.883
	350 S	0.616	181 T	0.593	366 S	0.508
	445 S	0.518	250 S	0.615	410 T	0.519
	459 S	0.560	278 S	0.800	421 S	0.699
	463 T	0.800	314 S	0.514	432 S	0.733
	492 S	0.636	333 S	0.719	441 T	0.682
	496 S	0.556	401 S	0.849	454 T	0.739
	497 S	0.585	460 S	0.648	463 S	0.723
498 S	0.654	461 S	0.677	469 T	0.833	
499 S	0.561	465 T	0.569	472 S	0.919	
501 S	0.533	468 S	0.781	533 S	0.712	
—	—	477 S	0.830	—	—	
—	—	485 T	0.867	—	—	
—	—	488 S	0.531	—	—	
—	—	510 T	0.679	—	—	
PKG	511 S	0.663	57 S	0.533	51 T	0.567
	—	—	380 S	0.609	302 T	0.526

PHF1主要含有PKA、PKC、PKG、p38MAPK、cdc2、cdk5、CKI、 CKII、RSK、INSR、GSK3等磷酸化识别位点

激酶	PHF1 位点	得分	PKG	511-S	0.663	CKII	282-S	0.535
PKA	42-T	0.674	p38MAPK	20-S	0.518	GSK3	294-S	0.527
	95-S	0.525		79-S	0.518		20-S	0.507
	166-S	0.701		420-S	0.579		79-S	0.503
	187-S	0.672		504-S	0.617		420-S	0.512
	220-S	0.511	cdc2	13-S	0.545		422-S	0.517
	303-S	0.701		296-T	0.576	446-S	0.528	
	307-S	0.549		415-S	0.548	473-S	0.508	
	511-S	0.668		417-S	0.542	504-S	0.502	
	520-S	0.573		438-T	0.537	515-S	0.520	
	554-S	0.606		446-S	0.522	RSK	187-S	0.554
	—	—		497-S	0.546		307-S	0.614
PKC	24-T	0.542	499-S	0.578	318-S		0.578	
	50-T	0.860	504-S	0.519	INSR	557-Y	0.540	
	145-T	0.558	—	—		—	—	
	182-S	0.561	cdk5	417-S	0.562	ATM	69-S	0.625
	216-T	0.563		420-S	0.503		DNAPK	69-S
	263-S	0.701		422-S	0.674			
	311-S	0.810		446-S	0.592			
	350-S	0.616		473-S	0.516			
	445-S	0.518		502-S	0.601			
	459-S	0.560		504-S	0.608			
	463-T	0.800		515-S	0.723			
	492-S	0.636	522-S	0.560				
	496-S	0.556	CKI	463-T	0.552			
	497-S	0.585		522-S	0.540			
498-S	0.654	525-T		0.503				
499-S	0.561							
501-S	0.533							

PHF1、MTF2和PHF19蛋白二级结构分析

使用<http://bioinf.cs.ucl.ac.uk/psipred/>网站对PHF1、MTF2和PHF19蛋白进行二级结构分析可知，3个蛋白的二级结构主要由 α -螺旋、扩展链结构和 β -转角3种形式构成，其中， α -螺旋>扩展链结构> β -转角。

基因名称	二级结构		
	α -螺旋	扩展链结构	β -转角
PHF1	47.8%	45.0%	16.4%
MTF2	63.6%	50.6%	15.2%
PHF19	61.2%	35.5%	15.0%

PHF1及其同源蛋白MTF2、PHF19保守性高

Entry	Entry name	Protein names	Gene names	Organism	Length
☑ O43189	PHF1_HUMAN	PHD finger protein 1	PHF1 PCL1	Homo sapiens (Human)	567

Enter Query Sequence

Enter accession number(s), gi(s), or FASTA sequence(s) Clear

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Or, upload file 选择文件 未选择任何文件

Job Title
 Enter a descriptive title for your BLAST search

Align two or more sequences

Choose Search Set

Database

Organism
 Enter organism common name, binomial, or tax id. Only 20 top taxa will be shown

Exclude Optional Models (XM/XP) Non-redundant RefSeq proteins (WP) Uncurated

Program Selection

Algorithm

blastp (protein-protein BLAST)

PSI-BLAST (Position-Specific Iterated BLAST)

PHI-BLAST (Pattern Hit Initiated BLAST)

DELTA-BLAST (Domain Enhanced Lookup Time Accelerated BLAST)

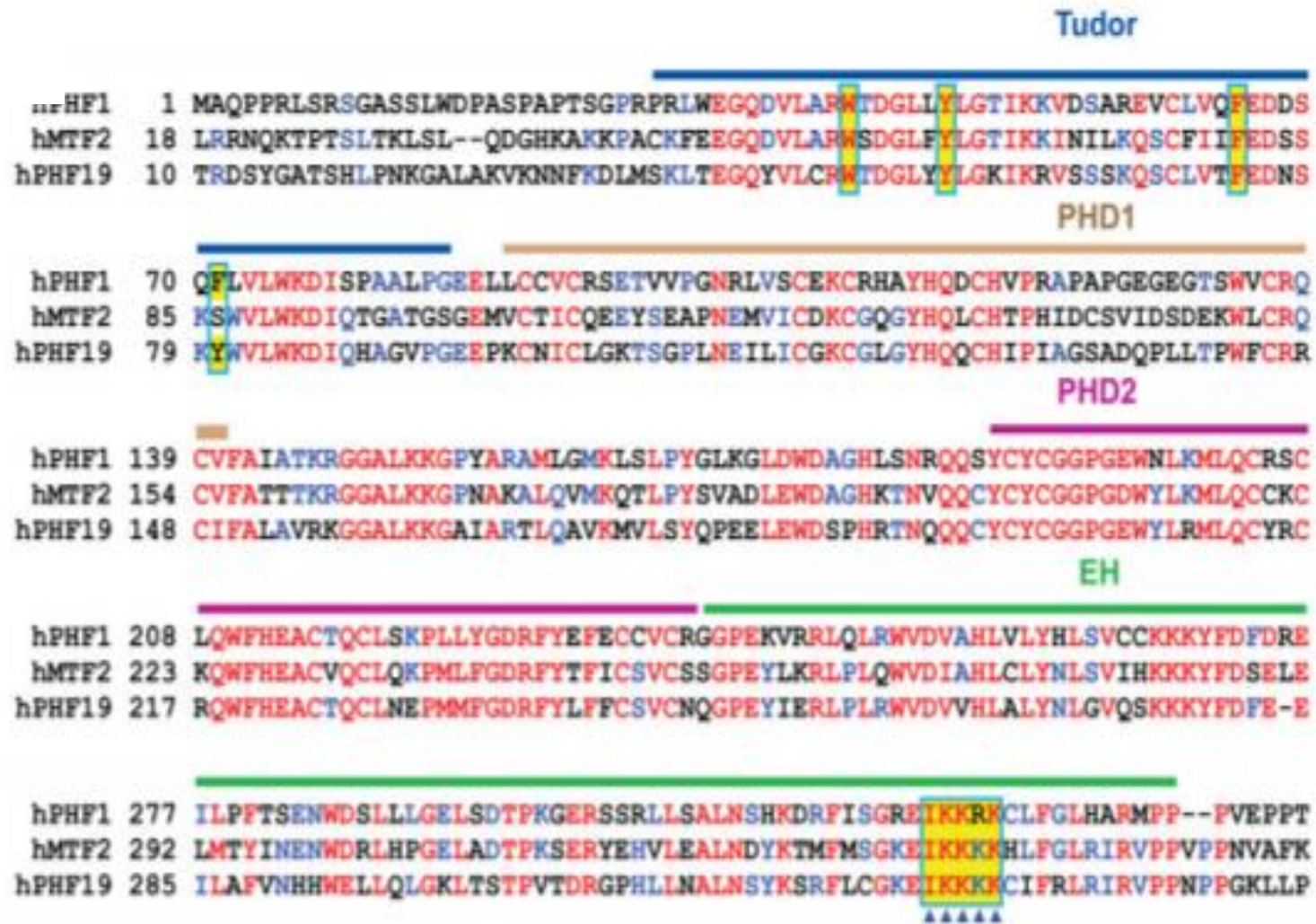
Choose a BLAST algorithm

BLAST Search database swissprot using Blastp (protein-protein BLAST)
 Show results in a new window

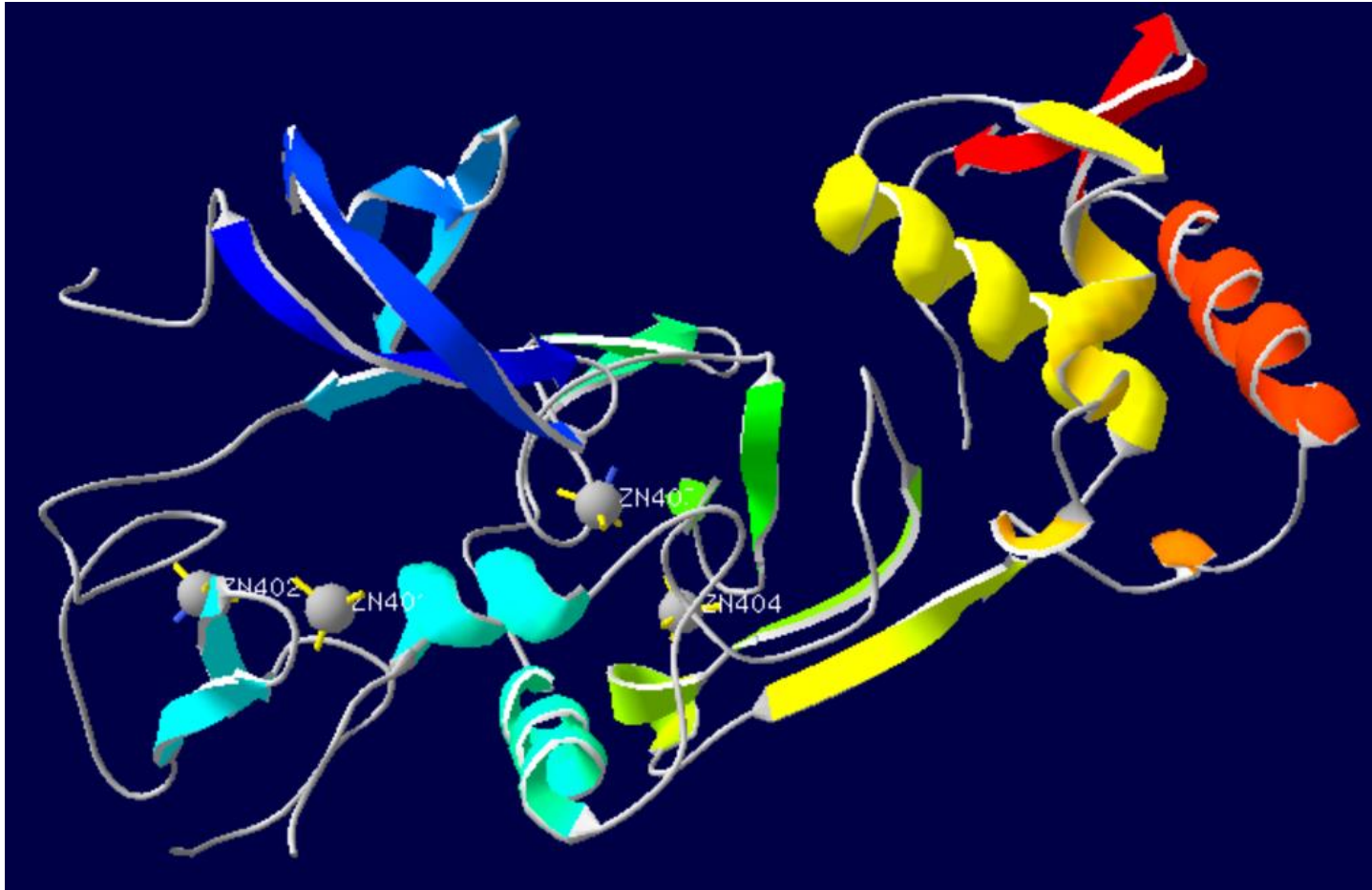
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<input checked="" type="checkbox"/> PHD finger protein 2 [Homo sapiens]	1144	1144	100%	0.0	99.82%	AAC13273.1
<input checked="" type="checkbox"/> PHD finger protein 1 isoform X2 [Homo sapiens]	1140	1140	100%	0.0	99.82%	XP_011512965.1
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<input checked="" type="checkbox"/> PHF1 [Homo sapiens]	724	724	62%	0.0	98.32%	AAC52062.1
<input type="checkbox"/> unnamed protein product [Homo sapiens]	724	724	62%	0.0	98.32%	BAG58363.1
<input checked="" type="checkbox"/> PHD finger protein 1 isoform X6 [Homo sapiens]	723	723	61%	0.0	100.00%	XP_011512971.1
<input checked="" type="checkbox"/> Chain A, Phd Finger Protein 1 [Homo sapiens]	697	697	59%	0.0	100.00%	5XFP_A
<input checked="" type="checkbox"/> Chain A, Phd Finger Protein 1 [Homo sapiens]	659	659	55%	0.0	100.00%	5XFN_A
<input checked="" type="checkbox"/> PHD finger protein 1 isoform X8 [Homo sapiens]	418	418	37%	1e-142	100.00%	XP_016866428.1
<input type="checkbox"/> metal-response element-binding transcription factor 2 isoform a [Homo sapiens]	411	411	94%	3e-136	40.79%	NP_031384.1
<input checked="" type="checkbox"/> Chain A, Metal-response Element-binding Transcription Factor 2 [Homo sapiens]	382	382	53%	5e-129	58.03%	5XFR_A
<input checked="" type="checkbox"/> PHD finger protein 19 isoform CRA_a [Homo sapiens]	387	387	94%	5e-127	42.60%	EAW87475.1
<input checked="" type="checkbox"/> PHD finger protein 19 isoform a [Homo sapiens]	385	385	94%	3e-126	41.82%	NP_056466.1
<input checked="" type="checkbox"/> PHD finger protein 19 isoform c [Homo sapiens]	382	382	94%	4e-125	41.64%	NP_001273769.1
<input type="checkbox"/> hypothetical protein [Homo sapiens]	381	381	94%	2e-124	41.64%	CAE45832.1
<input checked="" type="checkbox"/> PHD finger protein 19 isoform CRA_d [Homo sapiens]	381	381	94%	3e-124	41.64%	EAW87478.1
<input checked="" type="checkbox"/> PHD finger protein 19 isoform X5 [Homo sapiens]	371	371	54%	4e-123	56.17%	XP_011516817.1
<input checked="" type="checkbox"/> PHD finger protein 19 isoform X7 [Homo sapiens]	370	370	54%	5e-123	56.17%	XP_011516818.1
<input checked="" type="checkbox"/> PHD finger protein 19 isoform X3 [Homo sapiens]	370	370	54%	2e-122	56.17%	XP_016870102.1
<input checked="" type="checkbox"/> PHD finger protein 19 isoform CRA_c [Homo sapiens]	370	370	54%	2e-122	56.17%	EAW87477.1
<input type="checkbox"/> unnamed protein product [Homo sapiens]	374	374	54%	4e-122	56.17%	BAG59700.1
<input checked="" type="checkbox"/> PHD finger protein 19 isoform X2 [Homo sapiens]	370	370	54%	9e-122	56.17%	XP_011516819.1
<input checked="" type="checkbox"/> metal-response element-binding transcription factor 2 isoform b [Homo sapiens]	363	407	58%	3e-118	55.81%	NP_001157864.1
<input checked="" type="checkbox"/> metal-response element-binding transcription factor 2 isoform c [Homo sapiens]	343	343	84%	5e-111	39.16%	NP_001157863.1

在Homo sapien (taxid:9606)中共找到5条与PHF1相似性为100%的蛋白质序列，8条相似性大于90%的蛋白质序列，其余序列相似性稍低，但分析不难发现这些序列均为PHF1的同源序列MTF2、PHF19及其各个亚型。

PHF1及其同源蛋白MTF2、PHF19保守性高



PHF1蛋白N端三维结构解析



ZN 401-404位

人PHF1蛋白与大鼠、小鼠亲缘关系近

Needle

Aligned_sequences: 2

1: PHF1_HUMAN

2: PHF1_MOUSE

Matrix: EBLOSUM62

Gap_penalty: 10.0

Extend_penalty: 0.5

#

Length: 567

Identity: 524/567 (92.4%)

Similarity: 534/567 (94.2%)

Gaps: 8/567 (1.4%)

Score: 2820.0

EBI EMBOSS tools

<https://www.ebi.ac.uk/Tools/emboss/>

```
PHF1_HUMAN      551 PDGSVQYLVEWGGGGIF      567
      |||
PHF1_MOUSE      543 PDGSVQYLVEWGGGGIF      559
```

```
PHF1_HUMAN      1 MAQPPRLSRSGASSLWDPASPAPTSGPRPRLWEGQDVLARWTDGLLYLGT      50
      |||
PHF1_MOUSE      1 MAQLPRLSRLGAPSLWDPASPAPTSGPRPRLWEGQDVLARWTDGLLYLGT      50

PHF1_HUMAN      51 IKKVSAREVCLVQFEDDSQFLVLWKDISPAALPGEELLCCVCRSETVVP      100
      |||
PHF1_MOUSE      51 IKKVSAREVCLVQFEDDSQFLVLWKDISPAALPGEELLCCVCRSETVVP      100

PHF1_HUMAN      101 GNRLVSCEKCRHAYHQDCHVPRAPAPGEGEGTSWVCRQCVFAIATKRGGGA      150
      |||
PHF1_MOUSE      101 GNRLVSCEKCRHAYHQDCHVPRAPAPGEGEGASWVCRQCVFAIATKRGGGA      150

PHF1_HUMAN      151 LKKGPYARAMLGMKLSLPYGLKGLDWDAGHLSNRQSSYCYCGGPGEWNLK      200
      |||
PHF1_MOUSE      151 LKKGPYARAMLGMKLSLPYGLKGLDWDAGHLSNRQSSYCYCGGPGEWNLK      200

PHF1_HUMAN      201 MLQCRSCLQWFHEACTQCLSKPLLYGDRFYEFECVCRGGPEKVRRLQLR      250
      |||
PHF1_MOUSE      201 MLQCRSCLQWFHEACTQCLSKPLLYGDRFYEFECVCRGGPEKVRRLQLR      250

PHF1_HUMAN      251 WVDVAHLVLYHLSVCCKKKYFDFDREILPFTSENWDSLGLGELSDTPKGE      300
      |||
PHF1_MOUSE      251 WVDVAHLVLYHLSVCCKKKYFDFDREILPFTSENWDSLGLGELSDTPKGE      300

PHF1_HUMAN      301 RSSRLLSALNSHKDRFISGREIKKRKCLFGLHARMPPPVEPTGDGALTS      350
      |||
PHF1_MOUSE      301 RSSQLLSALNSHKDRFISGREIKKRKCLFGLHARTPPPVELLTDGAPTS      350

PHF1_HUMAN      351 FPSGQGPGGVSRPLGKRRRPEPEPLRRRQKKGVEELGPSSAVRNQPEPQ      400
      |||
PHF1_MOUSE      351 FPSGQGPGGVSRPLGKRWRSEPEPLRRRQKKGVEELGPPTAAHSRHGSR      400

PHF1_HUMAN      401 EQRERAHLQALQASVSPSPSPNQSYQGSSGYNFRPTDARCLPSSPIRM      450
      |
PHF1_MOUSE      401 E-----QALQASVSPPPSPNQSYEGSSGYNFRPTDARCLPSSPIRM      443

PHF1_HUMAN      451 FASFHPSASTAGTSGDSEPPDRSPLGLHIGFPTDIPKSAPHSMTASSSSV      500
      |||
PHF1_MOUSE      444 FASFHPSASTAGTSGDSEPPDRSPLGLHIGFPTDIPKSSPHSVTASSSSV      493

PHF1_HUMAN      501 SSPSPGLPRRSAPPSPLCRSLSPGTGGGVRGGVYLSRGDPVRLARRVR      550
      |
PHF1_MOUSE      494 PALTPGFSRHS-PPSPLCRSLSPGTGGGVRGGVYLSRGDPVRLARRVR      542
```


人PHF1蛋白与大鼠、小鼠亲缘关系近

```
# Aligned_sequences: 2
# 1: PHF1_HUMAN
# 2: Q6MGC9_RAT
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 567
# Identity: 527/567 (92.9%)
# Similarity: 538/567 (94.9%)
# Gaps: 7/567 ( 1.2%)
# Score: 2850.0
```

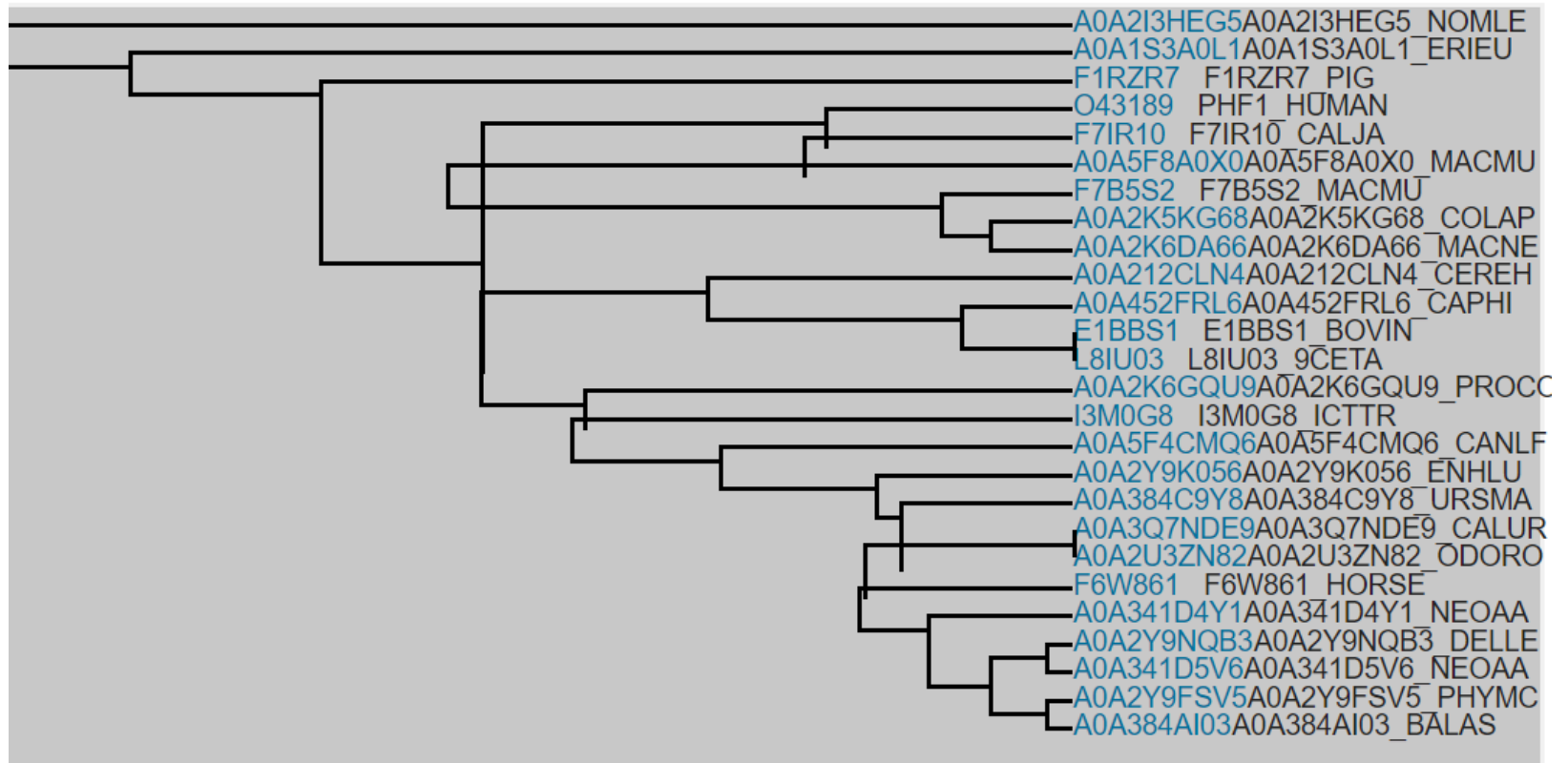
```
# Aligned_sequences: 2
# 1: PHF1_MOUSE
# 2: Q6MGC9_RAT
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 560
# Identity: 548/560 (97.9%)
# Similarity: 554/560 (98.9%)
# Gaps: 1/560 ( 0.2%)
# Score: 2984.0
```

物种	序列名	登录号	得分	相同位点 (比例)	相同加相似位点 (比例)
人/小鼠	PHF1_HUMAN/ PHF1_MOUSE	O43189/Q9Z1B8	2820.0	524/567 (92.4%)	534/567 (94.2%)
人/大鼠	PHF1_HUMAN/ Q6MGC9_RAT	O43189/Q6MGC9	2850.0	527/567 (92.9%)	538/567 (94.9%)
小鼠/大鼠	PHF1_MOUSE/ Q6MGC9_RAT	Q9Z1B8/Q6MGC9	2984.0	548/560 (97.9%)	554/560 (98.9%)

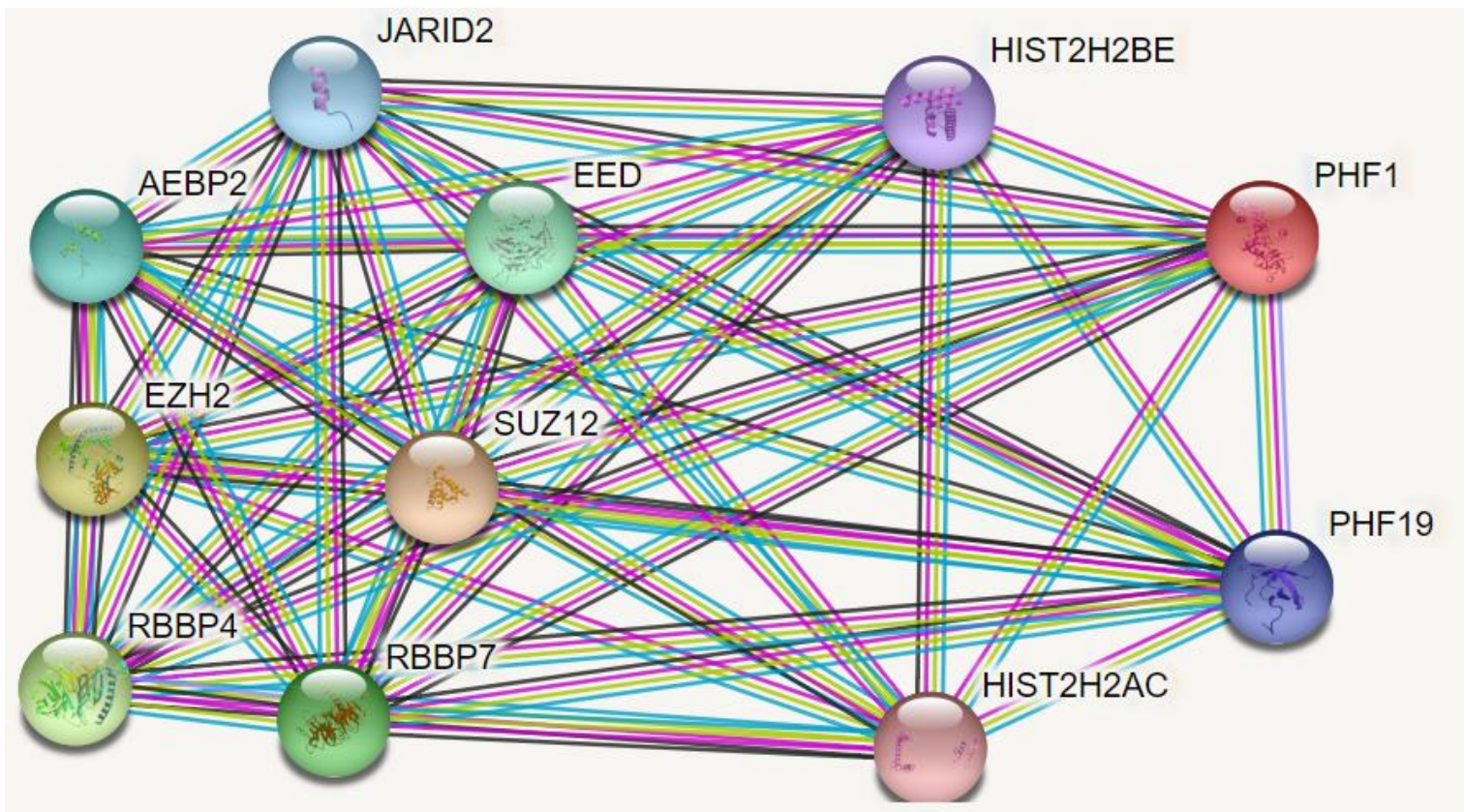
PHF1蛋白在不同物种中具有保守性

Identical positions: 371

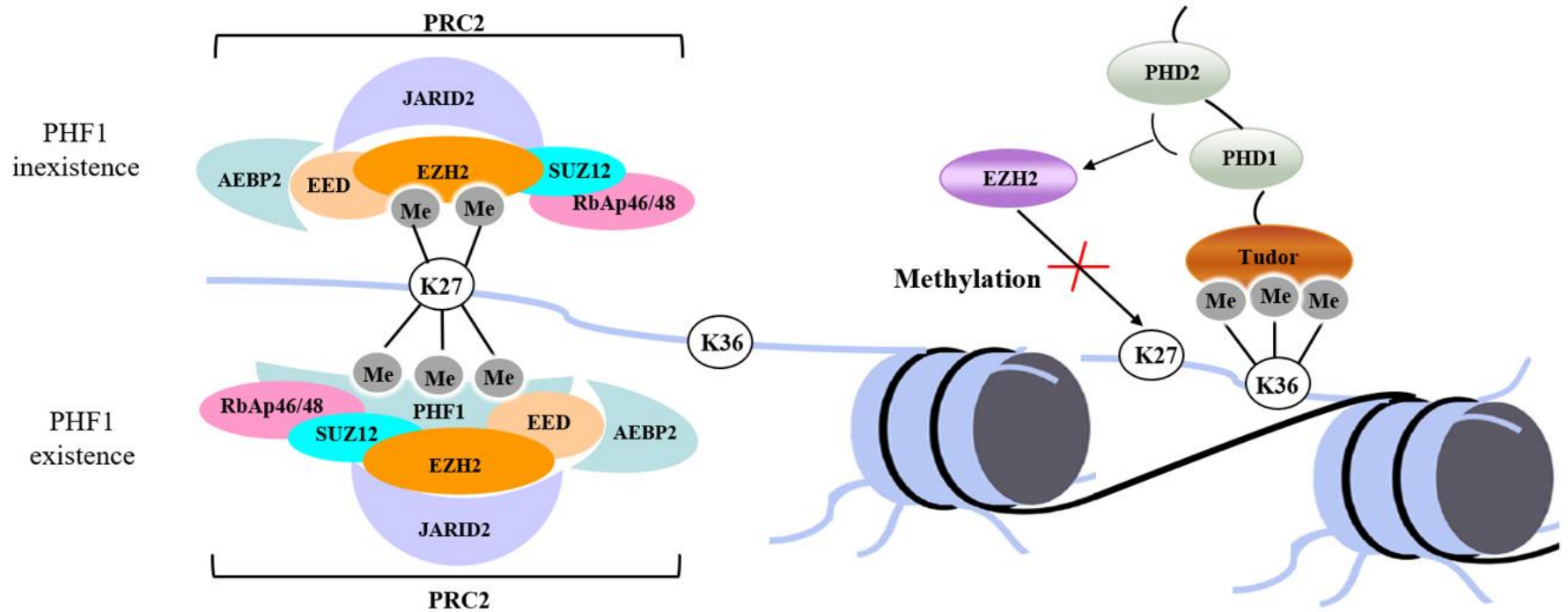
Identity : 64.298%



PHF1蛋白互作情况分析



PHF1介导的组蛋白H3K27me3和H3K36me3示意图



Nat Commun, 2013, 4(2):969-989.

Biochemical and biophysical research communications, 2013, 430(2): 547-553.

Journal of molecular biology, 2014, 426(8): 1651-1660.

Epigenetics, 2015, 10(6): 467-473.

Proceedings of the National Academy of Sciences of the United States of America, 2011, 108(2): 540-545.

Molecular and cellular biology, 2008, 28(5): 1862-1872.

四、参考

蛋白特性分析	expasy	https://www.expasy.org/
跨膜结构分析	TMHMM	http://www.cbs.dtu.dk/services/TMHMM/
信号肽分析	SignalP	http://www.cbs.dtu.dk/services/SignalP/
亚细胞定位	psort	https://psort.hgc.jp/form.html
蛋白结构预测	pfam	http://pfam.xfam.org/
二级结构预测	psipred	http://bioinf.cs.ucl.ac.uk/psipred/
三级结构预测	swissmodel	https://swissmodel.expasy.org/
使用软件	MEGA; SWISS-PDB;	

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致谢

感谢罗老师一学期的悉心讲解

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请大家批评指正