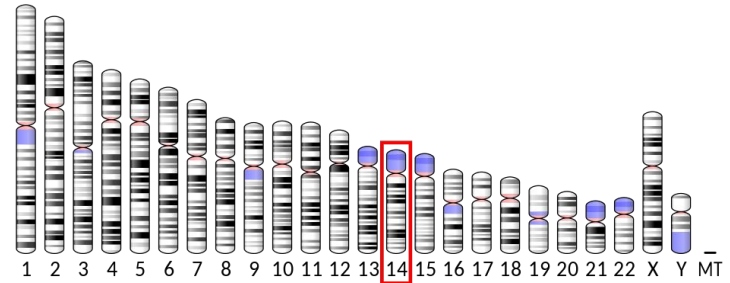


PSEN1 y Alzheimer

Juan Ignacio Cuiule - 158.938-6

Presinilina 1 (PSEN1)

- Es una subunidad de la gamma-secretasa.
- Se encarga de facilitar la proteólisis (separación de otras proteínas en piezas más pequeñas llamados péptidos).
- Tiene un rol en la degradación de la APP (proteína precursora amiloidea) que es precursora del β -amiloide, principal componente de las placas presentes en el tejido cerebral de pacientes que sufren Alzheimer.
- Situada en el cromosoma 14.



Procesamiento de secuencias

sequence-psen1.gb [INPUT]

Secuencia de mARN de la variante “NM_000021.4” (isoform I-467) en formato Genbank extraída de NCBI (https://www.ncbi.nlm.nih.gov/nuccore/NM_000021.4)

sequence-psen1.fasta [OUTPUT]

Traducción directa de formato Genbank a formato FASTA

psen1-orfs.fasta [OUTPUT]

Secuencias de los ORFs encontrados en la secuencia del mARN de esta variante

Homo sapiens presenilin 1 (PSEN1), transcript variant 1, mRNA

NCBI Reference Sequence: NM_000021.4

[FASTA](#) [Graphics](#)

[Go to:](#)

LOCUS NM_000021 6018 bp mRNA linear PRI 12-JUN-2022
DEFINITION Homo sapiens presenilin 1 (PSEN1), transcript variant 1, mRNA.
ACCESSION NM_000021
VERSION NM_000021.4
KEYWORDS RefSeq; MANE Select.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorhini; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 6018)
AUTHORS Jiang L, Qiu Y, Zhao YW, Feng Q, Pan HX, Liu EH, Sun QY, Xu Q, Tan JQ, Yan XX, Li JC, Tang BS and Guo JF.
TITLE PSEN1 G417S mutation in a Chinese pedigree causing early-onset parkinsonism with cognitive impairment
JOURNAL Neurobiol Aging 115, 70-76 (2022)
PUBMED 35485322
REMARK GeneRIF: PSEN1 G417S mutation in a Chinese pedigree causing early-onset parkinsonism with cognitive impairment.
REFERENCE 2 (bases 1 to 6018)
AUTHORS Sidor J, Gillette M, Dezi LA, Univeros G and Strizai L.
TITLE Role of Presenilin-1 in Aggressive Human Melanoma
JOURNAL Int J Mol Sci 23 (9), 4904 (2022)
PUBMED 35563309
REMARK GeneRIF: Role of Presenilin-1 in Aggressive Human Melanoma.
REFERENCE 3 (bases 1 to 6018)
AUTHORS Critte M and DiMaio D.
TITLE Human Papillomavirus L2 Capsid Protein Stabilizes gamma-Secretase during Viral Infection
JOURNAL Viruses 14 (4), 804 (2022)
PUBMED 35451534
REMARK GeneRIF: Human Papillomavirus L2 Capsid Protein Stabilizes gamma-Secretase during Viral Infection.
Publication Status: Online-Only
REFERENCE 4 (bases 1 to 6018)
AUTHORS Garcia-Pretelt FJ, Soares-Relevo JX, Aguillon-Mino DF, Lopez-Restrepo FJ, Ochoa-Gomez JF and Tobon-Quintero CA.
TITLE

Blast (local)

psen1-orfs.fasta [INPUT]

Output del ejercicio anterior que contiene las secuencias de los distintos ORFs de esta variante.

psen1-orfs-1-blast.bls [OUTPUT] (sin hits)
psen1-orfs-2-blast.bls [OUTPUT] (sin hits)
psen1-orfs-3-blast.bls [OUTPUT] (múltiples hits)
psen1-orfs-4-blast.bls [OUTPUT] (1 hit)
psen1-orfs-5-blast.bls [OUTPUT] (sin hits)
psen1-orfs-6-blast.bls [OUTPUT] (sin hits)

Resultado de blast local para cada frame

Descriptions	Graphic Summary	Alignments	Taxonomy					
Sequences producing significant alignments								
Download								
Select columns								
Show 100								
<input checked="" type="checkbox"/> select all 100 sequences selected								
GenPept								
Graphics								
Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
<input checked="" type="checkbox"/> psenlin-1 isoform L467 (Homo sapiens)	Homo.sao...	817	817	23%	0.0	99.79%	467	ANN47477.1
<input checked="" type="checkbox"/> psenlin-1 isoform L467 (Homo sapiens)	Homo.sao...	816	816	23%	0.0	100.00%	467	NP_000012.1
<input checked="" type="checkbox"/> psenlin-1 isoform L467 (Homo sapiens)	Homo.sao...	816	816	23%	0.0	99.79%	467	ANN47471.1
<input checked="" type="checkbox"/> psenlin-1 isoform L467 (Homo sapiens)	Homo.sao...	816	816	23%	0.0	99.79%	467	ANN47470.1
<input checked="" type="checkbox"/> psenlin-1 isoform L467 (Homo sapiens)	Homo.sao...	816	816	23%	0.0	99.79%	467	ANN47474.1
<input checked="" type="checkbox"/> psenlin-1 isoform L467 (Homo sapiens)	Homo.sao...	815	815	23%	0.0	99.79%	467	ANN47476.1
<input checked="" type="checkbox"/> psenlin-1 isoform L467 (Homo sapiens)	Homo.sao...	814	814	23%	0.0	99.79%	467	ANN47472.1
<input checked="" type="checkbox"/> psenlin-1 isoform X1 (Chlorocebus sabaeus)	Chlorocebo...	814	814	23%	0.0	99.79%	467	XP_007985386.1
<input checked="" type="checkbox"/> psenlin-1 isoform X1 (Pongo abelii)	Pongo.abell...	814	814	23%	0.0	99.79%	467	XP_024987005.1
<input checked="" type="checkbox"/> psenlin-1 isoform L467 (Homo sapiens)	Homo.sao...	813	813	23%	0.0	99.79%	467	ANN47473.1
<input checked="" type="checkbox"/> Recognition of the Amyloid Precursor Protein by Human gamma-secr...	Homo.sao...	813	813	23%	0.0	99.79%	467	GIY2_B
<input checked="" type="checkbox"/> Cryo-EM structure of gamma secretase in complex with a drug DAPT...	Homo.sao...	813	813	23%	0.0	99.79%	467	SENG_B
<input checked="" type="checkbox"/> psenlin-1 isoform X1 (Aotus nancymaeae)	Aotus.nanc...	812	812	23%	0.0	99.36%	467	XP_012293628.1
<input checked="" type="checkbox"/> psenlin-1 isoform L467 (Homo sapiens)	Homo.sao...	812	812	23%	0.0	99.79%	467	ANN47475.1
<input checked="" type="checkbox"/> RecName: Full=Psennlin-1; Short=PS-1; Contains: RecName: Full=...	Pongo.abell...	811	811	23%	0.0	99.57%	467	Q68796.1
<input checked="" type="checkbox"/> Cryo-EM structure of gamma secretase in complex with a Notch frag...	Homo.sao...	810	810	23%	0.0	99.57%	467	6DGF_B
<input checked="" type="checkbox"/> RecName: Full=Psennlin-1; Short=PS-1; Contains: RecName: Full=...	Macaca.f...	810	810	23%	0.0	99.36%	467	GH50X05.1
<input checked="" type="checkbox"/> hypothetical protein EGR_18364 (Macaca mulatta)	Macaca...	809	809	23%	0.0	99.79%	466	E1H52620.1
<input checked="" type="checkbox"/> psenlin-1 isoform X1 (Rhinopithecus rosellana)	Rhinopith...	807	807	23%	0.0	99.57%	466	XP_010354140.1
<input checked="" type="checkbox"/> psenlin-1 isoform X1 (Saemini boliviensis boliviensis)	Saemini bo...	807	807	23%	0.0	98.72%	467	XP_003942450.1
<input checked="" type="checkbox"/> psenlin-1 isoform L463 (Homo sapiens)	Homo.sao...	803	803	23%	0.0	99.14%	463	NP_015657.2
<input checked="" type="checkbox"/> Psennlin-1 (Fukomys damarensis)	Fukomya...	802	802	24%	0.0	94.41%	500	KFQ24232.1
<input checked="" type="checkbox"/> psenlin-1 isoform X1 (Callithrix jacchus)	Callitrix j...	802	802	23%	0.0	98.93%	466	XP_002754131.1
<input checked="" type="checkbox"/> psenlin-1 isoform X2 (Pongo abelii)	Pongo.abell...	801	801	23%	0.0	98.93%	463	XP_024987009.1
<input checked="" type="checkbox"/> psenlin-1 isoform X2 (Chlorocebus sabaeus)	Chlorocebo...	801	801	23%	0.0	98.93%	463	XP_007985386.1
<input checked="" type="checkbox"/> psenlin-1 (Homo sapiens)	Homo.sao...	801	801	23%	0.0	98.93%	463	AA046370.1
<input checked="" type="checkbox"/> psenlin-1 isoform X2 (Aotus nancymaeae)	Aotus.nanc...	798	798	23%	0.0	98.50%	463	XP_012293630.1
<input checked="" type="checkbox"/> psenlin-1 isoform L463 variant (Homo sapiens)	Homo.sao...	796	796	23%	0.0	98.72%	463	BAC98893.1
<input checked="" type="checkbox"/> psenlin-1 (Cardito syrichta)	Cardito sy...	794	794	23%	0.0	97.43%	467	XP_008967779.1
<input checked="" type="checkbox"/> psenlin-1 isoform X2 (Rhinopithecus rosellana)	Rhinopith...	793	793	23%	0.0	98.72%	461	XP_010354155.1

Blast (local)

Query= NM_000021 Homo sapiens presenilin 1 (PSEN1), transcript variant 1, mRNA.

Length=2005

Sequences producing significant alignments:			Score (Bits)	E Value	
P49768.1	RecName: Full=Presenilin-1; Short=PS-1; AltName: Full=Pr...	965	0.0	(Homo Sapiens)	
Q5R780.1	RecName: Full=Presenilin-1; Short=PS-1; Contains: RecNam...	960	0.0	(Pongo Abelii)	
Q8HXW5.1	RecName: Full=Presenilin-1; Short=PS-1; Contains: RecNam...	957	0.0	(Macaca fascicularis)	
P79802.1	RecName: Full=Presenilin-1; Short=PS-1; Contains: RecNam...	834	0.0	(Microcebus murinus)	
P97887.1	RecName: Full=Presenilin-1; Short=PS-1; AltName: Full=Pr...	812	0.0	(Rattus norvegicus)	
Q6RH31.2	RecName: Full=Presenilin-1; Short=PS-1; Contains: RecNam...	811	0.0	(Canis lupus)	
P49769.1	RecName: Full=Presenilin-1; Short=PS-1; AltName: Full=Pr...	810	0.0	(Mus musculus)	
Q9XT97.1	RecName: Full=Presenilin-1; Short=PS-1; Contains: RecNam...	793	0.0	(Bos taurus)	
Q4JIM4.1	RecName: Full=Presenilin-1; Short=PS-1; Contains: RecNam...	707	0.0	(Gallus gallus)	
O12976.1	RecName: Full=Presenilin-1; Short=PS-1; AltName: Full=Pr...	641	0.0	(Xenopus laevis)	



Pongo abelii



Macaca
fascicularis



Lemur



Rattus norvegicus (rata)



Perro

MSA

Partiendo de uno de los outputs del ejercicio anterior (psen1-orfs-3-blast.bls) tomamos 5 hits y hacemos un alineamiento usando clustalw

```
P49768.1.fasta > PSN1_HUMAN [INPUT]
Q5R780.1.fasta > sp|Q5R780.1|PSN1_PONAB [INPUT]
Q8HXW5.1.fasta > sp|Q8HXW5.1|PSN1_MACFA [INPUT]
P79802.1.fasta > sp|P79802.1|PSN1_MICMU [INPUT]
P97887.1.fasta > sp|P97887.1|PSN1_RAT [INPUT]
Q6RH31.2.fasta > sp|Q6RH31.2|PSN1_CANLF [INPUT]
```

out-msa [\[OUTPUT\]](#)

Resultado del alineamiento múltiple con esas secuencias

```
PileUp

MSF: 469 Type: P Check: 7246 ..

Name: sp|P79802.1|PSN1_MICMU oo Len: 469 Check: 3354 Weight: 23.0
Name: sp|Q6RH31.2|PSN1_CANLF oo Len: 469 Check: 2707 Weight: 30.7
Name: PSN1_HUMAN oo Len: 469 Check: 2043 Weight: 0.1
Name: sp|Q8HXW5.1|PSN1_MACFA oo Len: 469 Check: 2592 Weight: 7.6
Name: sp|Q5R780.1|PSN1_PONAB oo Len: 469 Check: 2102 Weight: 7.6
Name: sp|P97887.1|PSN1_RAT oo Len: 469 Check: 4448 Weight: 30.7

sp|P79802.1|PSN1_MICMU MTLPAPLSY FQNAQMSEDN HLSNTVRSQN DNREQQDHGD RRRLGNPEPL
sp|Q6RH31.2|PSN1_CANLF MTLPAPLSY FQNAQMSEDN HLSNTVRSQN DSREQHSS.E RRRRGNPEPL
PSN1_HUMAN MTLPAPLSY FQNAQMSEDN HLSNTVRSQN DNREQQDHGD RRRSLGHPEPL
sp|Q8HXW5.1|PSN1_MACFA MTLPAPLSY FQNAQMSEDN HLSNTVRSQN DNREQQDHGD RRRSLGHPEPL
sp|Q5R780.1|PSN1_PONAB MTLPAPLSY FQNAQMSEDN HLSNTVRSQN DNREQQDHGD RRRSLGHPEPL
sp|P97887.1|PSN1_RAT MTEIPAPLSY FQNAQMSEDS HSS.SVRSQN DNREQQDHGD RRLDNPESI

sp|P79802.1|PSN1_MICMU SNGRPQGN.S GPVVERDEE DEELTLKYGA KHVINFVPV TLMVVVVAT
sp|Q6RH31.2|PSN1_CANLF SNGRPQGS.S HQVVEQDEE DEELTLKYGA KHVINFVPV TLMVVVVAT
PSN1_HUMAN SNGRPQGN.S RQVVEQDEE DEELTLKYGA KHVINFVPV TLMVVVVAT
sp|Q8HXW5.1|PSN1_MACFA SNGRPQGN.S RQVVEQDEE DEELTLKYGA KHVINFVPV TLMVVVVAT
sp|Q5R780.1|PSN1_PONAB SNGRPQGS.S RQVVEQDEE DEELTLKYGA KHVINFVPV TLMVVVVAT
sp|P97887.1|PSN1_RAT SNGRPQSNFT RQVVEQDEE DEELTLKYGA KHVINFVPV TLMVVVVAT
```

Blast output

Partiendo del resultado blast del orfs 3 (psen1-orfs-3-blast.bls) y de un patrón de búsqueda guarda secuencias fasta de los hits que cumplan con el patrón

```
psen1-orfs-3-blast.bls [INPUT]  
<patrón de búsqueda> [INPUT]  
  
ej: perl ex4.pm ./out-blast/psen1-orfs-3-blast.bls "Macaca"
```

```
out-4/<patron de búsqueda>/... [OUTPUT]
```

En caso de encontrar hits que cumplan con el patrón crea una carpeta con ese nombre donde deja archivos fasta que representan la secuencia de cada uno de los hits

```
▼ out-4  
  ▼ macaca  
    ≡ Q8HXW5.1.fasta  
  ▼ mus musculus  
    ≡ P49769.1.fasta  
    ≡ Q61144.3.fasta  
  ▼ sapiens  
    ≡ P49768.1.fasta  
    ≡ P49810.1.fasta  
    ≡ Q5JPI9.2.fasta  
    ≡ Q8N976.1.fasta
```

EMBOSS

Usa los programas “getorf” y “patmatmotifs” de EMBOSS para encontrar los orfs y hacer un análisis de dominio.

sequence-psen1.fasta [INPUT]

Recibe la secuencia en formato fasta

out-5/orgs.fasta [OUTPUT]
out-5/ex5.patmatmotifs [OUTPUT]

Un archivo con los distintos orfs encontrados y otro con el análisis de dominios de las secuencias obtenidas.

Genes Homólogos

Ensembl: 203 secuencias en primates, roedores, laurasiterios y placentarios.

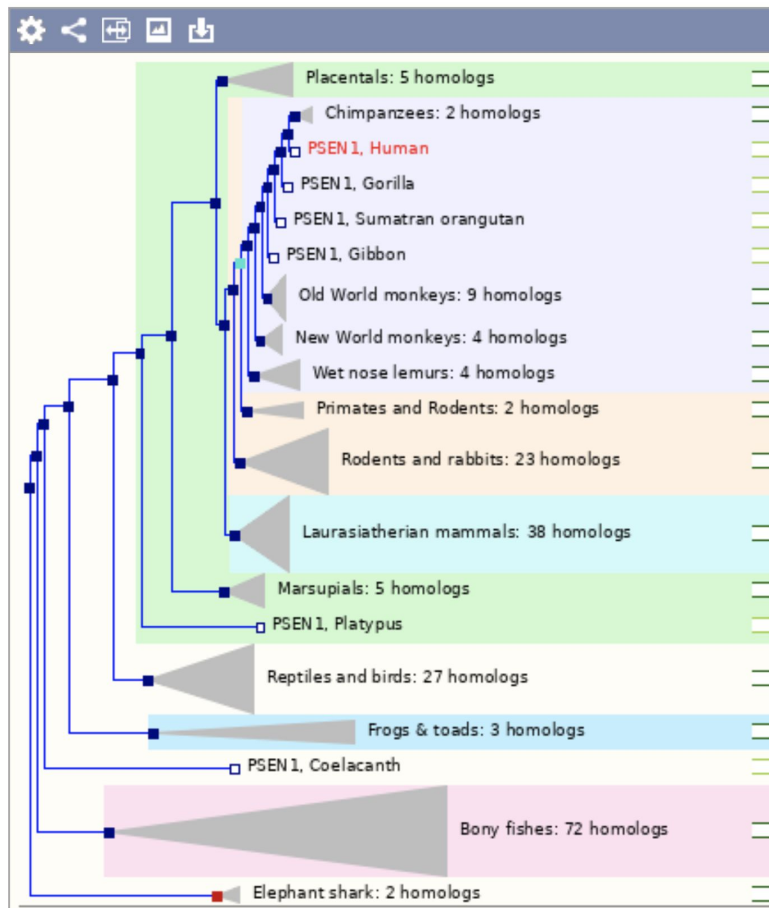
HomoloGene: 14 ocurrencias en distintas especies.

HomoloGene:7186. Gene conserved in Eukaryota

Genes

Genes identified as putative homologs of one another during the construction of HomoloGene.

PSEN1, *H.sapiens*
presenilin 1
PSEN1, *P.troglodytes*
presenilin 1
PSEN1, *M.mulatta*
presenilin 1
PSEN1, *C.lupus*
presenilin 1
PSEN1, *B.taurus*
presenilin 1
Psen1, *M.musculus*
presenilin 1
Psen1, *R.norvegicus*
presenilin 1
PSEN1, *G.gallus*
presenilin 1
psen1, *X.tropicalis*
presenilin 1
psen1, *D.rerio*
presenilin 1
sei-12, *C.elegans*
sei-12
PS2, *A.thaliana*
PS2
PS1, *A.thaliana*
PS1
Osa03g0603700, *O.sativa*
Osa03g0603700



Variantes

missense:


- rs63750592
- rs17125721

intronic:

- rs3025786
- rs165932

rs17125721

Current Build 155
Released April 9, 2021

Organism	Homo sapiens	Clinical Significance	Reported in ClinVar
Position	chr14:73206470 (GRCh38.p13) ?	Gene : Consequence	PSEN1 : Missense Variant
Alleles	A>G	Publications	13 citations 
Variation Type	SNV Single Nucleotide Variation	Genomic View	See rs on genome
Frequency	G=0.012226 (3236/264690, TOPMED) G=0.014607 (3664/250846, GnomAD_exome) G=0.018355 (4080/222280, ALFA) (+ 18 more)		

Population	Group	Sample Size	Ref Allele	Alt Allele
Total	Global	222280	A=0.981645	G=0.018355
European	Sub	192276	A=0.980252	G=0.019748
African	Sub	4996	A=0.9950	G=0.0050
African Others	Sub	176	A=0.994	G=0.006
African American	Sub	4820	A=0.9950	G=0.0050
Asian	Sub	6400	A=1.0000	G=0.0000
East Asian	Sub	4550	A=1.0000	G=0.0000
Other Asian	Sub	1850	A=1.0000	G=0.0000
Latin American 1	Sub	804	A=0.993	G=0.007
Latin American 2	Sub	974	A=0.997	G=0.003
South Asian	Sub	282	A=1.000	G=0.000

Interacción con otras proteínas

Buscando en uniprot vemos la interacción proteína a proteína en distintas bases de datos.

En BioGRID hay **196 interacciones** registradas mientras que en NCBI aparecen más (265) porque incluye otras bases además de BioGrid

Predicted Functional Partners:

NOTCH1	Neurogenic locus notch homolog protein 1; Functions as a receptor for membrane-bound ligands Jagged1, Jagged2 and Delt...
APP	Amyloid-beta A4 protein; N-APP binds TNFRSF21 triggering caspase activation and degeneration of both neuronal cell bodies ...
NCSTN	Nicastrin; Essential subunit of the gamma-secretase complex, an endoprotease complex that catalyzes the intramembrane cl...
CTNNB1	Catenin beta-1; Key downstream component of the canonical Wnt signaling pathway. In the absence of Wnt, forms a complex ...
APH1A	Gamma-secretase subunit APH-1A; Non-catalytic subunit of the gamma-secretase complex, an endoprotease complex that ca...
PSENEN	Gamma-secretase subunit PEN-2; Essential subunit of the gamma-secretase complex, an endoprotease complex that catalyz...
APH1B	Aph-1 homolog B, gamma-secretase subunit; Gamma-secretase subunit APH-1B; Probable subunit of the gamma-secretase c...
TRAF6	TNF receptor-associated factor 6; E3 ubiquitin ligase that, together with UBE2N and UBE2V1, mediates the synthesis of 'Lys-6...
CDH1	Cadherin-1; Cadherins are calcium-dependent cell adhesion proteins. They preferentially interact with themselves in a homoph...
CTNND2	Catenin delta-2; Has a critical role in neuronal development, particularly in the formation and/or maintenance of dendritic spin...

En STRING vemos una predicción de interacciones basadas en las funciones que cumplen las distintas proteínas.

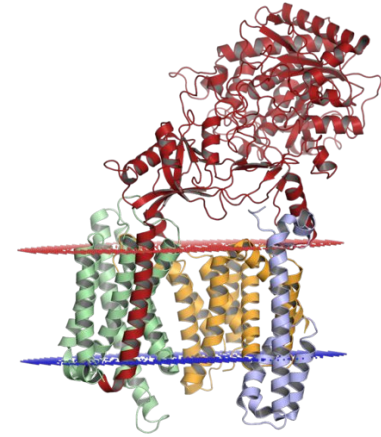
APP - NCSTN - APH1A - PSENEN - APH1B
Son proteínas principalmente relacionadas con la gamma-secretasa

Componente celular

Gamma-secretase complex

[The \$\gamma\$ -secretase complex: from structure to function - PMC](#)

Membrana de Golgi



Procesos biológicos

- Smooth endoplasmic reticulum calcium ion homeostasis: incrementa la concentración de iones de calcio en el retículo endoplasmático
- Notch receptor processing, ligand-dependent
- Amyloid-beta formation: generación de beta-amiloide por escisión de la APP
- Positive regulation of amyloid fibril formation
- Astrocyte activation involved in immune response (célula encontrada en el sistema nervioso que participa en el almacenamiento de energía, la modulación de sinapsis y reparación de tejidos, entre otras cosas)

Función molecular

Adhesión y comunicación celular

- Beta-catenin binding (β -catenin está involucrada en la adhesión celular y en transcripción genética)
- Growth factor receptor binding (intercellular signaling)
- Cadherin binding
- Endopeptidase activity
- Cell adhesion molecule binding
- Signaling receptor binding
 - binding de uno o más puntos específicos en una molécula receptora que se combina con alguna hormona, neurotransmisor, droga o mensajero intracelular para iniciar un cambio en el funcionamiento de una célula.

Pathways

- Notch signaling pathway: sistema de señalización celular altamente conservado que controla el destino celular. Mayormente estudiado en la producción de células nerviosas en un proceso de inhibición lateral que permite que células individuales expresen un grupo de genes que indiquen a las células adyacentes que expresen un grupo distinto.
- Wnt signaling: vía conservada evolutivamente que regula aspectos cruciales de la diferenciación celular, la organogénesis durante el desarrollo embrionario.

Gracias