

AizSWAN: An Introductory Tutorial

AlzSWAN: Navigating the Home Page

The screenshot shows the SWAN Alzheimer Knowledge Base home page. At the top left, it says "SWAN Alzheimer Knowledge Base beta" and "Semantic Web Applications in Neuromedicine". A horizontal navigation bar contains links for Home, Statements, Genes-Proteins, Evidence Maps, and About. A search box is located below the navigation bar. The main content area features a "Welcome to the SWAN Alzheimer Knowledge Base" message, followed by a "FEATURED CONTRIBUTIONS" section with three articles. Below this are three sections: "HOT TOPICS (browse all hypotheses)", "MECHANISMS", and "KNOWLEDGE BASE". The "HOT TOPICS" section lists various hypotheses related to Alzheimer's Disease pathogenesis. The "MECHANISMS" section lists Energetics, Functional Changes of Proteins, and Structural Changes of Proteins. The "KNOWLEDGE BASE" section provides statistics for Statements, Publications, Research Questions, and Comments. A "HOW TO CONTRIBUTE" section is also present, listing actions like "BUILD A HYPOTHESIS" and "CRITIQUE A HYPOTHESIS".

1 Horizontal navigation bar

2 Search Box: enter keywords and phrases

3 Featured Contributions: newest AlzSWAN content

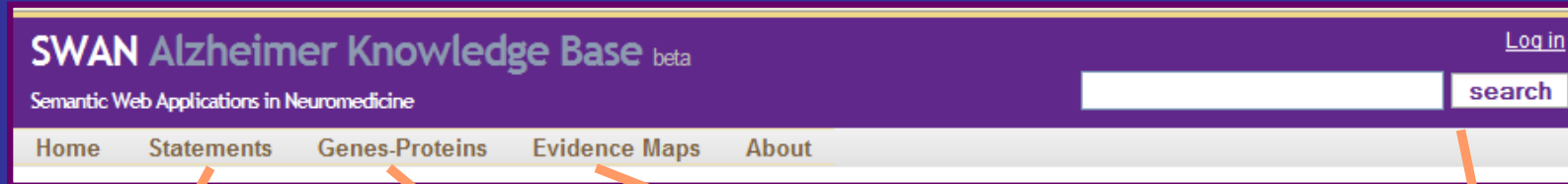
4 Hot Topics: hypotheses are organized under these active areas of research

5 Mechanisms: hypotheses are organized by biological mechanisms

4 Hot Topics: hypotheses are organized under these active areas of research

5 Mechanisms: hypotheses are organized by biological mechanisms

1 The Horizontal Navigation Bar



There are four clickable links in

Statements:

- “Statements” - list of all hypotheses & claims
- “Hypotheses” - full list of hypotheses
- “Research Questions” – lists questions & suggested experiments
- “Comments” – lists comments on hypotheses & claims

Genes-Proteins

- 2 ways to find a gene:
 - Alphabetically
 - Use Search box for synonyms

Evidence Maps:

- Show relationships:
 - between claims and evidence
 - between claims and other AlzSWAN content

Search box:

- available on every page
- search results can be filtered

Note: the Horizontal Navigation bar is active on ALL AlzSWAN pages.

2 Search Strategies: Using the Search Box

Search for key words,
genes/proteins or phrases
e.g. “cell AND death”

SWAN Alzheimer Knowledge Base beta [Log in](#)
Semantic Web Applications in Neuromedicine [SWAN Terms of Use](#)

Home Statements Genes-Proteins Evidence Maps About

Navigation History

[? How to refine the search](#)

Refine your search using AND, OR, NOT - all capital letters - double quotes and parentheses ()

1. aggregation AND inhibit - will retrieve the list of entities that are mentioning both keywords
2. LRP AND apoe AND binding - will retrieve the list of entities that are mentioning all the keywords
3. BACE1 OR "beta secretase" - will retrieve the list of entities that are mentioning at least one of the two keywords
4. APP AND PS1 NOT cholesterol - will retrieve the list of entities that are mentioning the first two keywords but not the last one
5. (PS1 OR Abeta) AND NSAIDS - will retrieve the list of entities that are mentioning the last keyword and at least one of the first two keywords

Results 1-10 of 408 (591 matching fields in milliseconds) - Keywords table

[Hypotheses/Comments](#) [Claims](#) [Publications](#)

C Neurons that show A β accumulations may attempt to reenter the cell cycle. Muresan Z, Muresan V
CAD cells that show the A β accumulations clearly have something in common. One possibility is that the neuritic A β phenotype could result from a failed attempt of neurons to re-enter the cell cycle. Recent work indicates that in AD brains, as well as in mouse models of AD, ectopic initiation of cell-cycle processes in neurons is an early sign of neuronal distress and increased vulnerability to insults. Although A β accumulating cells are only found in cultures maintained under differentiating conditions, they are in fact detectable very early after switching to differentiating conditions, when some cells may still attempt to undergo mitosis. This possibility remains to be tested.
[11 Matches](#) [Show Details](#)

C CAD (Cath.a-differentiated) cells, a mouse neuronal cell line, which originates in the locus coeruleus in the brainstem, have neuronal phenotype when differentiated, with characteristics of catecholaminergic neurons. Muresan Z, Muresan V
CAD cells are normal diploid, chromosomally stable cells. Like PC12 cells, CAD cells can be grown in an undifferentiated state (doubling time 18-22 hours). Differentiation is induced by serum removal, when cells stop dividing, grow processes, and switch to an autocrine survival mode. CAD cells express neuronal markers, maintain active signaling pathways characteristic for catecholaminergic neurons, and possess ion channels, transporters, and synaptic proteins. CAD cells express several dopamine receptor subtypes, and possess the biosynthetic machinery that produces L-DOPA. GFAP, a glia-specific cytoskeletal protein, is not detected in CAD cells by Western blotting, although immunocytochemistry studies suggest that CAD cells may express low levels of GFAP. Initially established by targeted oncogenesis in mice, CAD cells have spontaneously lost the original oncogene, SV40 T antigen. Ultrastructurally, their processes resemble true neurites that contain dense-core and clear vesicles. Electrophysiological experiments indicate that they behave like fully functional neurons. Thus, CAD cells are faithful to brain biology.
[9 Matches](#) [Show Details](#)

C Ectopic stimulation of Fyn activity, which can be mitogenic, potentially could lead to nerve cell >death via mitotic catastrophe to trigger cell >death, an idea supported by findings that the AD brain has ectopically expressed cell cycle proteins.
[8 Matches](#) [Show Details](#)

Refine a search

Filter search results

Search Strategies: Using the Facet Browser

SWAN Alzheimer Knowledge Base beta

Welcome wonglabow! - Give us your feedback - Log

Semantic Web Applications in Neuromedicine

Home Statements Genes-Proteins Evidence Maps About

Navigation History

Statements » All Hypotheses

LIST • TIMELINE BY YEAR • TABLE

7 Hypothesis filtered from 172 originally (Reset All Filters)

sorted by: status and firstAuthor; then by... grouped as sorted

Extended Annotation (6)

Golde T (1)

The A β hypothesis will lead to rationally-designed therapeutic strategies for the treatment or prevention of Alzheimer disease. Hypothesis

1. Golde T [2005]

Contains 45 statements: 26 with evidence, 19 without evidence, and a total of 44 citations

Relationships with external statements: 16 consistent, 4 inconsistent, 3 alternative to

Genes-Proteins: *Homo sapiens*: APP, Beta-amyloid protein 40, Beta-amyloid protein 42, Beta-secretase 1, APOE, Apolipoprotein E, BACE1, PSEN2, PSEN1, Presenilin-1, Microtubule-associated protein tau;

Hardy John (2)

A critical reappraisal of the Amyloid Hypothesis, in response to inconclusive clinical trial results. Hypothesis

1. Hardy John [2009]

Contains 25 statements: 24 with evidence, 1 without evidence, and a total of 83 citations

Relationships with external statements: 3 consistent, 2 inconsistent, 2 alternative to

Genes-Proteins: *Homo sapiens*: APP, Beta-amyloid protein 42, Microtubule-associated protein tau, MAPT, APOE, Amyloid beta A4 protein, Beta-amyloid protein 40, Presenilin-2, Presenilin-1, PSEN1, PSEN2; *Mus musculus*: Microtubule-associated protein tau;

The Amyloid Hypothesis of Alzheimer Disease. Hypothesis

2. Hardy John - Selkoe Dennis J [2002]

Contains 55 statements: 54 with evidence, 1 without evidence, and a total of 106 citations

Relationships with external statements: 26 consistent, 7 inconsistent, 1 discussed, 16 alternative to

Genes-Proteins: *Homo sapiens*: APP, Amyloid beta A4 protein, Microtubule-associated protein tau, PSEN1, Presenilin-1, APOE, Apolipoprotein E, PSEN2, Presenilin-2, Beta-amyloid protein 42;

Holmes Clive (1)

Plaque removal is not enough to halt progressive neurodegeneration in Alzheimer Disease. Hypothesis

Holmes Clive - Boche Delphine, Wilkinson David, Yadegarfar Ghasem, Hopkins Vivienne, Bayer Anthony, Jones Roy W, Bullock Roger, Love Seth, Neal James W, Zotova Elina, and Nicoll James A [2008]

Contains 33 statements: 32 with evidence, 1 without evidence, and a total of 56 citations

Relationships with external statements: 9 consistent, 1 inconsistent, 5 alternative to

Selectors

Search this page:

Status

6 Extended Annotation

1 Simple Annotation

Hot Topics List

13 ApoE contributes to Alzheimer's pathogenesis through multiple mechanisms

7 A β accumulation in the brain is the primary event in Alzheimer Disease pathogenesis

7 Cell membrane properties play a key role in AD Pathophysiology

5 Changes in calcium homeostasis may provide a common pathway for the neuropathological changes in AD

5 Changes in presenilin 2 mutation lead to dementia and neurodegeneration in Alzheimer disease

7 Defective mechanisms of A β clearance contribute to Alzheimer Disease

6 Failure of axonal transport might be the underlying basis for neurodegeneration in Alzheimer Disease

8 Genetic variants modulate risk of AD

7 Insoluble fibrillar A β leads to AD

3 Misfolded proteins accumulated into protein aggregates characterizes the pathologic lesions of Alzheimer Disease

7 Signaling mechanisms play a critical role in Alzheimer Disease

9 Soluble oligomeric species of A β are toxic

Mechanism Taxonomy

3 Structural Changes of Proteins

4 Generic


The facet browser is displayed on the right hand side of the Search Results page.

- Displays categories (e.g. Hot Topics & Mechanism)
- Displays subcategories
- Displays number of entries under each subcategory
- Can filter search results by checking boxes for desired subcategories


3 Featured Contributions

This panel on the homepage displays the newest content entered into AlzSWAN


» FEATURED CONTRIBUTIONS




H NMDA receptor hypoactivity (NRHypo) may have an important contributory role in Alzheimer disease.
Olney J W et al.



H Aliev comment on Holmes et al hypothesis "Plaque removal is not enough to halt progressive neurodegeneration in Alzheimer Disease."
Aliev Gjumrakch et al.



H Insulin resistance plays a role in brain aging and increases the risk of AD and vascular dementia.
Craft S



H GSK3 is a causal mediator of disease.
Hooper Claudie et al.

click on the title to browse the full content and use the arrows to scroll the list

Click on arrow to scroll and see more entries

4 Hot Topics: Active Areas of Research

» HOT TOPICS (browse all hypotheses)

- o A β accumulation in the brain is the primary event in Alzheimer Disease pathogenesis
- o Soluble oligomeric aggregates of A β are toxic to neurons and cause AD pathology
- o Insoluble fibrillar A β leads to AD
- o Defective mechanisms of A β clearance contribute to AD
- o Tau dysfunction mediates neurodegeneration
- o ApoE contributes to AD through multiple mechanisms
- o Changes in calcium homeostasis may provide a common pathway for the neuropathological changes in AD
- o Changes in presenilin function lead to dementia and neurodegeneration in Alzheimer Disease
- o Misfolded proteins accumulated into protein aggregates characterizes the pathologic lesions of AD
- o The molecular mechanisms of neuronal cell death are involved in the dysfunction and death of neurons in AD
- o Synaptic loss appears to be the most powerful and ubiquitous proximate factor leading to the dementia of AD
- o Failure of axonal transport might be the underlying basis for neurodegeneration in AD
- o Cell membrane properties play a key role in AD Pathophysiology
- o Genetic variants modulate risk of AD
- o Signaling mechanisms play a critical role in Alzheimer Disease

Organizing hypotheses into Hot Topics:

- Readers can browse through many authors' perspectives on the same active area of research at a glance.
- Facet browser allows filtering of search on each page

The screenshot displays the SWAN Alzheimer Knowledge Base interface. The main content area shows a list of hypotheses filtered from 172 originally. The first hypothesis is by Golde T (2005), titled "The A β hypothesis will lead to rationally-designed therapeutic strategies for the treatment or prevention of Alzheimer disease." It contains 45 statements, with 26 with evidence, 19 without evidence, and 44 citations. The second hypothesis is by Hardy John (2009), titled "A critical reappraisal of the Amyloid Hypothesis, in response to inconclusive clinical trial results." It contains 25 statements, with 24 with evidence, 1 without evidence, and 83 citations. The third hypothesis is by Hardy John - Selkoe Dennis J (2002), titled "The Amyloid Hypothesis of Alzheimer Disease." It contains 55 statements, with 54 with evidence, 1 without evidence, and 106 citations. The fourth hypothesis is by Holmes Clive (2008), titled "Plaque removal is not enough to halt progressive neurodegeneration in Alzheimer Disease." It contains 33 statements, with 32 with evidence, 1 without evidence, and 56 citations.

On the right side, there is a "Hot Topics List" with several items, each with a checkbox. The first item is "A β accumulation in the brain is the primary event in Alzheimer Disease pathogenesis" which is checked. Other items include "Cell membrane properties play a key role in AD Pathophysiology", "Changes in calcium homeostasis may provide a common pathway for the neuropathological changes in AD", "Changes in presenilin function lead to dementia and neurodegeneration in Alzheimer Disease", "Defective mechanisms of A β clearance contribute to Alzheimer Disease", "Failure of axonal transport might be the underlying basis for neurodegeneration in Alzheimer Disease", "Genetic variants modulate risk of AD", "Insoluble fibrillar A β leads to AD", "Misfolded proteins accumulated into protein aggregates characterizes the pathologic lesions of Alzheimer Disease", "Signaling mechanisms play a critical role in Alzheimer Disease", and "Soluble oligomeric aggregates of A β are toxic".

At the bottom of the interface, there is a "Mechanism Taxonomy" section with two items: "Structural Changes of Proteins" and "Generic".

5 Mechanisms: Another Way to Provide Context

» MECHANISMS

- Energetics
- Functional Changes of Proteins
- Structural Changes of Proteins

» HOW TO CONTRIBUTE

- BUILD A HYPOTHESIS
- CRITIQUE A HYPOTHESIS
- NOMINATE A KEY PAPER
- HELP FIND CONNECTIONS
- PROPOSE NEW FEATURES
- ADD SUPPORTING EVIDENCE

Contact us!

» KNOWLEDGE BASE

Statements

2105 Research Statements

- » 172 Hypotheses
 - » 47 with Extended annotation
 - » 125 with Simple annotation
 - » 1933 Claims
- 57 Research Questions
44 Comments

Publications

2024 Journal Articles
8 Journal Comments
6 Journal News
33 Web Comments

Organizing hypotheses by biological mechanisms provides readers with a taxonomy from Mesulam & Khachaturian

The screenshot displays the WAN Alzheimer Knowledge Base interface. At the top, it says "Welcome wonglab@wan - Give us your feedback - Login". The main navigation bar includes "home", "Statements", "Genes-Proteins", "Evidence Maps", and "About". The current view is "Statements" with a sub-menu for "All Hypotheses". A filter bar shows "52 Hypothesis filtered from 172 originally (Reset All Filters)" and sorting options: "sorted by: status and firstAuthor; then by...".

The main content area shows a list of hypotheses. The first hypothesis is titled "The $\alpha 4$ (CHRNA4) and $\beta 2$ (CHRN2) neuronal nicotinic acetylcholine receptor subunit genes may be involved in impaired neuronal survival and the cholinergic system deficits that are evident in AD." It includes a citation: "Cook Lynnette J - Ho Luk W, Taylor Alison E, Brayne Carol, Evans John Grimley, Xuereb John, Cairns Nigel J, Pritchard Antonia, Lemmon Helen, Mann David, St Clair David, Turic Dragana, Hollingworth Paul, Moore Pamela J, Jehu Luke, Archer Nicola, Walter Sarah, Foy Catherine, Edmondson Amanda, Powell John, Lovestone Simon, Owen Michael J, Williams Julie, Lendon Corinne, and Rubinstztein David C [2004]". It indicates it contains 13 statements, with 12 with evidence and 1 without evidence, and has 21 citations.

The second hypothesis is "Oligomeric amyloid beta ligands (ADDLs) are a molecular basis for reversible memory loss." by "Gong Yuesong - Chang Lei, Lambert Mary P, Klein W L, Lacor Pascale N, Finch Caleb E, Krafft Grant A, and Viola Kirsten L [2003]". It contains 46 statements, with 46 with evidence, 0 without evidence, and 106 citations.

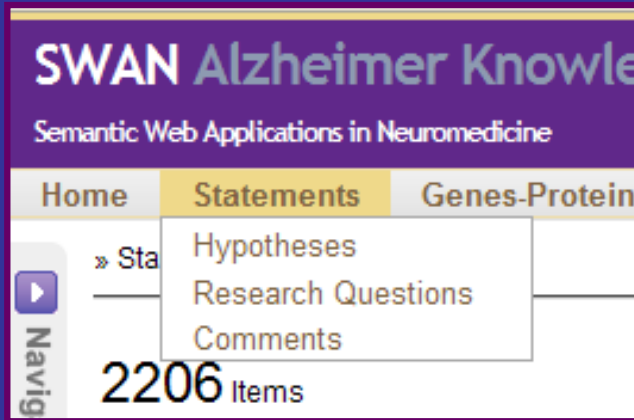
The third hypothesis is "The Amyloid Hypothesis of Alzheimer Disease." by "Hardy John - Selkoe Dennis J [2002]". It contains 55 statements, with 54 with evidence, 1 without evidence, and 106 citations.

The fourth hypothesis is "A β Plaques Lead to Aberrant Regulation of Calcium Homeostasis In Vivo Resulting in Structural and Functional Disruption of Neuronal Networks." by "Kuchibhotla Kishore V - Goldman Samuel T, Lattarulo Carl R, Wu Hai-Yan, Hyman Bradley T, and Backal Brian J [2008]". It contains 10 statements, with 10 with evidence, 0 without evidence, and 26 citations.

The fifth hypothesis is "Diffusible, nonfibrillar ligands derived from A β 42 are potent central nervous system neurotoxins." by "Lambert M P - Barlow A K, Chromy B A, Edwards C, Freed R, Liosatos M, Morgan T E, Rozovsky I, Trommer B, Viola K L, Wals P, Zhang C, Finch C E, Krafft G A, and Klein W L [1998]".

On the right side, there is a "Selectors" section with a search box. Below it is a "Status" section showing "13 Extended Annotation" and "39 Simple Annotation". A "Hot Topics List" is also visible, listing topics like "A β accumulation in the brain is the primary event in Alzheimer Disease pathogenesis" and "Changes in calcium homeostasis may provide a common pathway for the neuropathological changes in AD". At the bottom right, a "Mechanism Taxonomy" sidebar shows a tree structure: "21 Energetics", "32 Functional Changes of Proteins", "52 Structural Changes of Proteins", and "67 Generic".

Research Statements

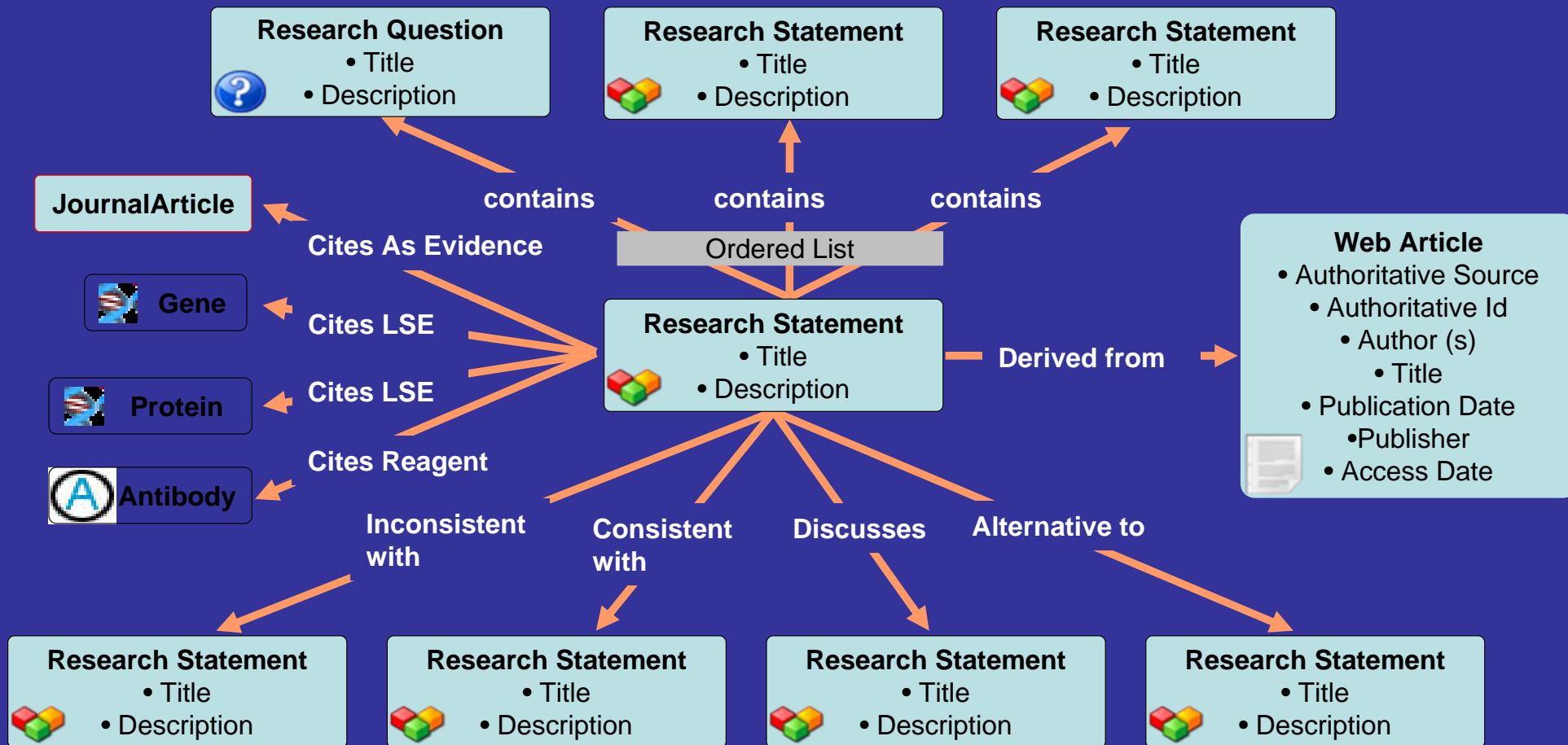


There are 4 different types of research statements.

1. **Hypothesis** – a scientific story
2. **Claim** – an individual finding or thought
3. **Research Question** – a forward looking statement
4. **Comment** – a response to another statement

	Definition	AlzSWAN use of term
Hypothesis	A testable proposal suggesting an explanation for a set of observations or a correlation between multiple observations	Over 170 significant hypotheses describing Alzheimer Disease cause and pathology; a growing subset has been extensively annotated.
Claim	A statement of something as a reproducible observation; an assertion of research finding or conclusion	The building blocks of hypotheses: scientific assertions, most are backed by published evidence.
Research Question	Research Questions are future-focused statements on relevant, useful, and important issues that require further study.	Scientifically testable questions arising from hypotheses, claims and comments
Comment	a written explanation or criticism or reaction by a reader; a statement that expresses a personal opinion or belief or adds information;	AlzSWAN version of commentaries published on Alzforum; comments submitted directly to AlzSWAN; updates of hypotheses submitted by authors

Research Statement: Hypothesis or Claim



AlzSWAN: Navigating the Hypothesis Page

SWAN Alzheimer Knowledge Base beta

Semantic Web Applications in Neuromedicine

Home Statements Genes-Proteins Evidence Maps About

Statements > Hypotheses

The Amyloid Hypothesis of Alzheimer Disease. 2 Comment(s)

Submit a comment Show graph (Experimental!)

Description:
This hypothesis proposes that A β accumulation in the brain is the primary event in Alzheimer Disease pathogenesis.

Authors: Hardy J Selkoe D

Derived from:

Hardy J, Selkoe D
The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics
Science (New York, N.Y.). 2002 Jul 19;297(5580):353-6

Hardy, John Selkoe, Dennis J

Contains 55 Statements:
54 with evidence 1 without evidence and a total of 106 citations ; Related to external statements: 26 consistent 7 inconsistent 1 discussed 16 with alternatives

Expand All Details Collapse All Details

- The amino acid sequence of amyloid β -peptide (A β) was first identified from Alzheimer Disease patient blood vessels and Downs syndrome.
Supporting(2) Genes/Proteins: (2)
- The A β peptide was recognized as the primary component of AD plaques.
Supporting(1) Consistent(2) Genes/Proteins: (2)
- Cloning of the APP gene and identification of its Chromosome 21 location, in the context of the invariant development of typical AD neuropathology in patients with trisomy 21 (Down syndrome) is the primary event in AD pathogenesis.
Supporting(5) Consistent(2) Inconsistent(1) Genes/Proteins: (2)
- Mutations of APP cause A β deposition.
Supporting(2) Genes/Proteins: (2)
- The first genetic mutation that caused AD was discovered in APP.
Supporting(4)

- 1 Horizontal navigation bar
- 6 Hypothesis title: with Comments & Graph view
- 7 Derived from article citation
- 8 Summary of hypothesis content: lists annotations; expands to show details
- 9 Claim: with annotations, including cited "supporting" articles, discourse relationships, discussed genes/proteins

6 Comments Provide Updates and Perspective

SWAN Alzheimer Knowledge Base beta
Semantic Web Applications in Neuromedicine

Home Statements Genes-Proteins Evidence Maps About

» Statements » Hypotheses


The Amyloid Hypothesis of Alzheimer Disease. 2 Comment(s)

[Submit a comment](#) [Show graph \(Experimental!\)](#)

Description:
This hypothesis proposes that A β accumulation in the brain is the primary event in Alzheimer Disease pathogenesis.

Authors: Hardy J Selkoe D

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Hardy J, Selkoe D
The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics.
Science (New York, N. Y.). 2002 Jul 19;297(5580):353-6

Hardy, John Selkoe, Dennis J

A

Comments on this hypothesis

B

Submit a Comment: let your opinion and knowledge count

Experts weigh in on hypotheses & claims

Comments: [Submit a comment](#)

Amyloid is the consequence, not the cause, of AD.
Smith M, Perry G, Castellani R, Lee H Fri, Nov 14 2008 14:49:32 EST
Rather than amyloid being responsible for causing disease, we suspect that Alzheimer Disease is responsible for causing amyloid. In fact, amyloid may even be a protective response. As such, removing amyloid would be predicted to either have no effect or a detrimental effect on AD progression.

- Joseph et al., 2001
- Smith et al., 2002
- Lee et al., 2004
- Smith et al., 2002
- Perry et al., 2000
- Atwood et al., 2002
- Lee et al., 2006

April 2008 Update of the Amyloid Hypothesis contributed by John Hardy and Dennis Selkoe
Hardy J, Selkoe D Mon, Apr 14 2008 13:43:09 EDT
This comment includes updates of research statements and additional supportive evidence to supplement those found in the Amyloid Hypothesis, authored by John Hardy and Dennis Selkoe, published in 2002 in Science.

• Updates of a hypothesis by original authors
- Read what they think and know now, years after publication

⑥ How to Submit a Comment

Click on Submit a Comment link to open up this comments form

The screenshot shows the SWAN Alzheimer Knowledge base interface. The page title is "The Amyloid Hypothesis of Alzheimer Disease." with 2 Comment(s). A "Submit a comment" link is highlighted with a dashed orange box and an arrow pointing to it. Below the link, there is a login prompt: "Please log in if you have an account in SWAN" with a checkbox "I do not have an account or I am not sure what is my user name and password". The form fields include "First Name:", "Last Name:", "Email:", "Comment Title:" (with a pre-filled value: "A comment on hypothesis 'The Amyloid Hypothesis of Alzheimer Disease.'"), and "Comment:". At the bottom, there is a "Citations: Add Citation" link highlighted with a dashed orange box and an arrow pointing to it, and "Save" and "Reset" buttons.

To submit a comment:
Enter first and last name
Provide email address

The screenshot shows the "Citations: Done adding citations" form. It includes a field "Enter a Pubmed ID:" with a "Look Up" button and a "PubMedOpen" link. Below this, there is a "PubMed Window" section with instructions: "To include citations with your comment, look them up by entering a publication Pubmed ID. To search for publications, the link above will open Pubmed in a new window." There is a large empty text area below the instructions.

To add a citation to support a comment, enter a PubMed ID number.

⑥ Graphing of AlzSWAN Content

SWAN Alzheimer Knowledge Base beta
Semantic Web Applications in Neuromedicine

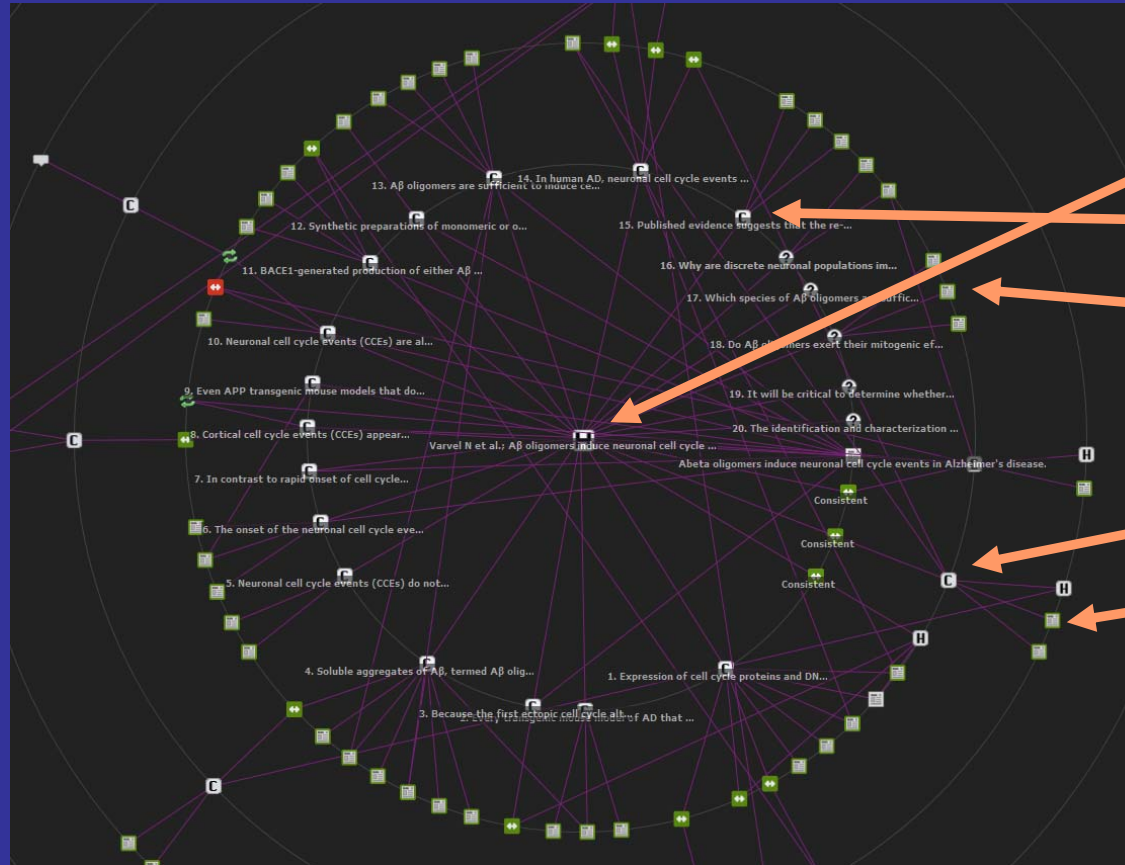
Home Statements Genes-Proteins Evidence Maps About

» Statements » Hypotheses

The Amyloid Hypothesis of Alzheimer Disease 0 Comment(s)

Submit a comment Show graph (Experimental!)

Click on “Show graph” to view a graphical representation like the one shown at below left



②

Graph view: visualize relationships among statements and citations

- Hypothesis title is center of wheel
- Claims in a hypothesis radiate out from the hypothesis title
- Supportive evidence, and relationships are shown in 2nd concentric circle
- Related statements are in 3rd circle, linked to supportive evidence in 4th circle

Click on any object and it moves to the center as the focus of a new cluster.

7 Annotation of Journal Articles

SWAN Alzheimer Knowledge Base beta
Semantic Web Applications in Neuromedicine

Home Statements Genes-Proteins Evidence Maps About

» Digital Resource » Journal Articles

The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics.

Citation:
Hardy J, Selkoe D
The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics.
Science (New York, N.Y.). 2002 Jul 19;297(5580):353-6
[PubMed] [Alzforum]

Source For Statements:

- A frequent criticism of the amyloid hypothesis is that number of amyloid plaques does not correlate well with degree of cognitive impairment.
[SHOW Details](#) [Consistent\(4\)](#)
- Therapeutics to prevent A β oligomerization are in development.

Journal article page lists:

- Full publication citation
- Link to PubMed abstract
- Link to Alzforum POW entry, Alzforum comments
- Claims from this article source

Supporting:

- Therapeutics to prevent A β oligomerization are in development.
[SHOW Details](#) [Supporting\(1\)](#) [Consistent\(4\)](#)
- Because EOAD and late-onset AD (LOAD) phenocopy each other clinically and histologically, the amyloid hypothesis—although based on molecular defects isolated in EOAD—was plausibly proposed to underlie all forms of the disease.
[HIDE Details](#) [Supporting\(2\)](#) [Consistent\(2\)](#) [Alternative to: \(2\)](#) [Genes/Proteins: \(3\)](#)
Experimental Approach: Biomarkers, Genetics
Pathogenic Narrative Tags: Initial condition
Supporting Evidence
Hardy J, Selkoe D
The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics.
Science (New York, N.Y.). 2002 Jul 19;297(5580):353-6
Tanzi R, Bertram L
Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective.
Cell. 2005 Feb 25;120(4):545-55

Consistent statements

- PS1 mutations cause an aggressive form of FAD with a particularly early age of onset, while PS2 mutations result in a form of FAD that is more akin to sporadic AD, bearing a later age of onset. Smth I Green K LaFerla F
- No alternative hypothesis with as much experimental support as the amyloid hypothesis can explain the cause and pathogenesis of AD, despite discussion on the deficiencies of the amyloid hypothesis. Hardy J Selkoe D

Alternative statements

- Because aging is the most important risk factor for late onset AD, it is likely that specific biochemical pathways are activated or inhibited in an age-dependent fashion and these changes are linked to AD neuropathology.
- Late onset AD (LOAD) is associated with both environmental and genetic risk factors, including hypercholesterolemia, atherosclerosis, history of head trauma, stroke.

Genes/Proteins

- Protein: Microtubule-associated protein tau [Homo sapiens]
- Protein: Beta-amyloid protein 42 [Homo sapiens]
- Protein: Beta-amyloid protein 40 [Homo sapiens]


- Diffuse A β deposits are analogous to early fatty streaks of cholesterol that appear prior to mature atherosclerotic plaques.
[SHOW Details](#) [Supporting\(1\)](#)
- A pathological hallmark of Alzheimer's disease is an accumulation of insoluble plaque containing the A β peptide of 40–42 amino acid residues.

Journal article page also lists:

- Claims by other authors who cited this article
- Relationships of these claims with other claims or hypotheses.

8 Hypothesis Content and Annotation

Derived from:



Hardy J. Selkoe D
The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics.
Science (New York, N.Y.). 2002 Jul 19;297(5580):353-6

Hardy, John Selkoe, Dennis J

Contains 55 Statements:
54 with evidence 1 without evidence and a total of 106 citations ; Related to external statements: 26 consistent 7 inconsistent 1 discussed 16 with alternatives

Expand All Details Collapse All Details

A

Contains 55 Statements:
54 with evidence 1 without evidence

Claims will be highlighted with a box if there is cited published evidence.

B

Expand All Details Collapse All Details

Expand details to see citations, discourse relationships and genes/proteins.

C


Related to external statements: 26 consistent 7 inconsistent 1 discussed 16 with alternatives

Discourse relationships are highlighted with a box when selected.


Contains 55 Statements:
54 with evidence 1 without evidence and a total of 106 citations ; Related to external statements: 26 consistent 7 inconsistent 1 discussed 16 with alternatives

Expand All Details Collapse All Details

Navigation History

- The amino acid sequence of amyloid β -peptide (A β) was first identified from Alzheimer Disease patient blood vessels and Downs syndrome.
[HIDE Details](#) [Supporting\(2\)](#) [Genes/Proteins: \(2\)](#)
Experimental Approach: Mechanism - molecular and cell, Biomarkers, Pathophysiology
Pathogenic Narrative Tags: Pathologic change
Supporting Evidence
 Glenner G, Wong C
 Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein.
Biochemical and biophysical research communications. 1984 May 16;120(3):885-90
 Glenner G, Wong C
 Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein.
Biochemical and biophysical research communications. 1984 Aug 16;122(3):1131-5
Genes/Proteins
 Gene: APP amyloid beta (A4) precursor protein [Homo sapiens]
 Protein: Amyloid beta A4 protein [Homo sapiens]
- The A β peptide was recognized as the primary component of AD plaques.

Navigation History

- Neurofibrillary tangles of tau are likely to occur after changes in A β generation, A β oligomerization and initial plaque formation, not before these changes occur.
[HIDE Details](#) [Supporting\(1\)](#) [Consistent\(1\)](#) [Inconsistent\(1\)](#)
Description: Even the most severe consequences of tau alteration — profound neurofibrillary tangle formation leading to fatal neurodegeneration seen in FTDP patients — are not sufficient to induce the amyloid plaques characteristic of AD.
Experimental Approach: Mechanism - biochemistry and structural biology, Pathophysiology
Pathogenic Narrative Tags: Pathogenic event
Supporting Evidence
 Hardy J, Duff K, Hardy K, Perez-Tur J, Hutton M
 Genetic dissection of Alzheimer's disease and related dementias: amyloid and its relationship to tau.
Nature neuroscience. 1998 Sep;1(5):355-8
Consistent statements
 Data overwhelmingly support the 'A β aggregate/amyloid cascade' hypothesis, which posits that A β aggregation and accumulation precedes, and therefore drives, tau accumulation. Golde T Miller V
Inconsistent statements
 The serial model of causality, even with a trigger caveat, is strained by the evidence suggesting that tau hyperphosphorylation spread throughout the brain, reaching as far as primary cortex. Small S Duff K
- In transgenic mouse studies, both mutant human APP and mutant human tau undergo increased formation of tau-positive tangles (as compared with mice overexpressing tau alone), whereas the structure and number of their amyloid

Navigation History

- The amyloid hypothesis relies on a genetic framework.
[SHOW Details](#) [Supporting\(2\)](#)
- Cloning and characterization of PS1 and PS2 AD-causing mutations revealed that these enhance APP processing to generate amyloidogenic A β .
[SHOW Details](#) [Supporting\(3\)](#) [Consistent\(1\)](#) [Inconsistent\(1\)](#) [Alternative to: \(1\)](#) [Genes/Proteins: \(7\)](#)
- PS1 and PS2 alter APP metabolism through a direct effect on the γ -secretase protease.
[SHOW Details](#) [Supporting\(5\)](#) [Genes/Proteins: \(4\)](#)
- Mutations in tau cause frontotemporal dementia with parkinsonism (FTDP) and are not sufficient to induce amyloid plaque formation.
[SHOW Details](#) [Supporting\(3\)](#) [Consistent\(1\)](#) [Genes/Proteins: \(1\)](#)
- Neurofibrillary tangles of tau are likely to occur after changes in A β generation, A β oligomerization and initial plaque formation, not before these changes occur.
[SHOW Details](#) [Supporting\(1\)](#) [Consistent\(1\)](#) [Inconsistent\(1\)](#)
- In transgenic mouse studies, both mutant human APP and mutant human tau undergo increased formation of tau-positive tangles (as compared with mice overexpressing tau alone), whereas the structure and number of their amyloid plaques are essentially unaltered.
[SHOW Details](#) [Supporting\(1\)](#)
- A β toxicity is tau dependent.
[SHOW Details](#) [Supporting\(1\)](#) [Genes/Proteins: \(3\)](#)
- ApoE pathogenesis in AD involves A β metabolism.
[SHOW Details](#) [Supporting\(2\)](#) [Consistent\(4\)](#) [Genes/Proteins: \(2\)](#)
- A β catabolism and clearance contributes to risk of late onset AD.
[SHOW Details](#) [Supporting\(1\)](#) [Consistent\(1\)](#) [Genes/Proteins: \(2\)](#)

Claims Are Annotated With Additional Content and Context

10. Cloning and characterization of PS1 and PS2 AD-causing mutations revealed that these enhance APP processing to generate amyloidogenic Aβ.

Supporting(3) Consistent(1) Inconsistent(1) Alternative to: (1) Genes/Proteins: (7)

Experimental Approach: Pathophysiology, Genetics, Mechanism - biochemistry and structural biology

Pathogenic Narrative Tags: [initial condition](#)

Supporting Evidence

Sherrington R, Rogaev E, Liang Y, Rogaeva E, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K
Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease.
Nature. 1995 Jun 29;375(6534):754-60

Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, Bird T, Hardy J, Hutton M, Kukull W, Larson E, Levy-Lahad E, Vitanen M, Peskind E, Poorkaj P, Schellenberg G, Tanzi R, Wasco W, Lannfelt L, Selkoe D, Younkin S
Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease.
Nature medicine. 1996 Aug;2(8):864-70

Levy-Lahad E, Wasco W, Poorkaj P, Romano D, Oshima J, Pettingell W, Yu C, Jondro P, Schmidt S, Wang K
Candidate gene for the chromosome 1 familial Alzheimer's disease locus.
Science (New York, N.Y.). 1995 Aug 18;269(5226):973-7

Consistent statements

PS2 is a less efficient generator of Aβ peptide than PS1. Bentahir M Nyabi O Verhamme J Tolia A Horré K Wilfang J Esselmann H De Strooper B

Inconsistent statements

It is difficult to explain how all 150 known mutations in PS1, scattered throughout the molecule, have the same gain of function effect of increasing Aβ42. Marchesi V

Alternative statements

The molecular mechanism(s) of Aβ production remains unclear, and alternative pathways for the processing of APP to Aβ have been proposed. Suzuki T Oishi M Marshak D Czernik A Nairn A Greengard P

Genes/Proteins

Protein: Presenilin-2 [Homo sapiens]

Protein: Beta-amyloid protein 42 [Homo sapiens]

Gene: PSEN1 presenilin 1 [Homo sapiens]

Gene: PSEN2 presenilin 2 (Alzheimer disease 4) [Homo sapiens]

Protein: Presenilin-1 [Homo sapiens]

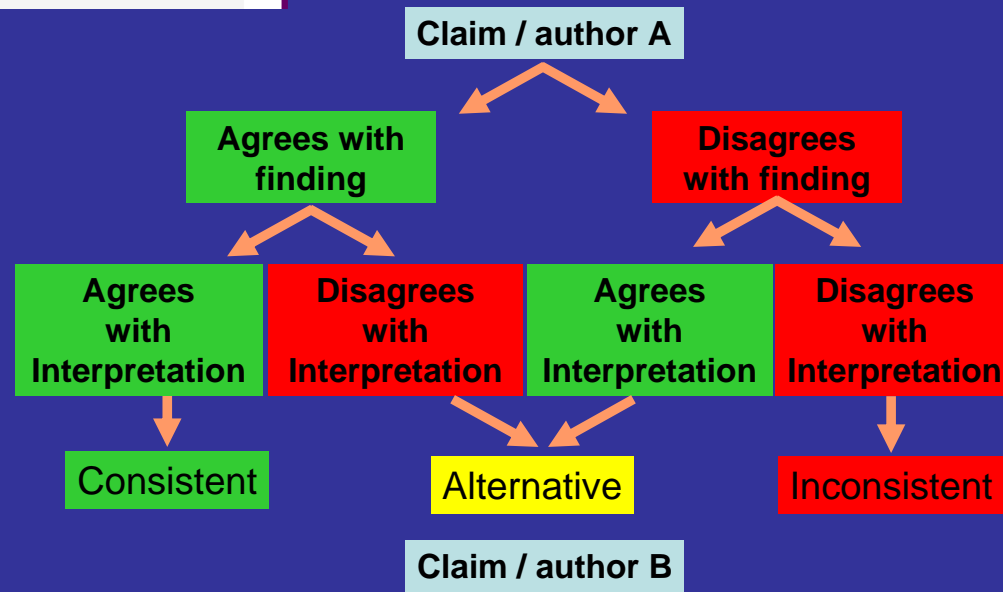
Protein: Amyloid beta A4 protein [Homo sapiens]

Gene: APP amyloid beta (A4) precursor protein [Homo sapiens]

- 1 Claim statement
- 2 Cited supportive evidence
- Click on each citation to see article annotations
- 3 Consistent statement
- 4 Inconsistent statement
- 5 Alternative statement

6 Genes and proteins

Definitions of relationships



Gene and Protein Annotations

Genes have EntrezGene and possibly AlzGene source links.
Proteins have UniProt source links.
Each gene and protein is linked to hypotheses and claims that discuss it.

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» Genes-Proteins

LIST • TABLE

2 Gene-Protein groups filtered from 212 originally (Reset All Filters)

sorted by: labels; then by... ○ grouped as sorted

Psen2 presenilin 2 [Mus musculus] Gene-Protein groups
Psen2 - ALG-3, Ad4h, PS2, PS-2, Psen2, and AI266870 [Entrez Gene]

» Protein(s): Presenilin-2 NTF subunit (Mus musculus) [UniProt], Presenilin-2 CTF subunit (Mus musculus) [UniProt], Presenilin-2 (Mus musculus) [UniProt]

PSEN2 presenilin 2 (Alzheimer disease 4) [Homo sapiens] Gene-Protein groups
PSEN2 - STM2, AD4, PSEN2, AD3L, and PS2 [Entrez Gene] [AlzGene]

» Protein(s): Presenilin-2 NTF subunit (Homo sapiens) [UniProt], Presenilin-2 (Homo sapiens) [UniProt], Presenilin-2 CTF subunit (Homo sapiens) [UniProt]

Selectors

Search this page:
PSEN2

Organism

- 1 Homo sapiens
- 1 Mus musculus

Select gene (top line of each group) for claims about the gene.

Select protein (bottom lines of each group) for claims about the protein.

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» Genes-Proteins

PSEN2 presenilin 2 (Alzheimer disease 4) [Homo sapiens]
[Entrez Gene] [AlzGene]

Full Name:
presenilin 2 (Alzheimer disease 4)

Preferred Symbol:
PSEN2

Symbol(s):
STM2, AD4, PSEN2, AD3L, PS2

Other id(s):
[HGNC:9509, Ensembl:ENSG00000143801, HPRD:02860, MIM:600759]

Gene Encodes Protein(s):
Protein: Presenilin-2 NTF subunit [Homo sapiens]
Protein: Presenilin-2 [Homo sapiens]
Protein: Presenilin-2 CTF subunit [Homo sapiens]

Cited by (relationships chart):

- H The A β hypothesis will lead to rationally-designed therapeutic strategies for the...
- C Presenilin mutations increase A β 42, accelerating aggregation.
- C Mutations in APP, PS1 and PS2, or variant ApoE4 alter A β production that promotes...
- H The Amyloid Hypothesis of Alzheimer Disease.
- C Cloning and characterization of PS1 and PS2 AD-causing mutations revealed that these...
- C PS1 and PS2 alter APP metabolism through a direct effect on the γ -secretase protease.
- H GAB2 alleles modify Alzheimer's risk in APOE ϵ 4 carriers.
- C Whereas more than 150 mutations of the presenilin 1 (PS1), presenilin 2 (PS2), and...
- H The α 4 (CHRNA4) and β 2 (CHRN2) neuronal nicotinic acetylcholine receptor subunit...
- C Autosomal dominant mutations have been identified in three separate genes which...
- H Aph1B complex contributes to total γ -secretase activity in the human brain.
- C Two presenilin (PS1 and PS2) genes and two APH1 (APH1A and APH1B) genes, which are...
- H A "dual pathway" model of AD causality, whereby A β and tau can be linked by separate...
- C Disease-causing mutations of EOAD in presenilin1 and 2 have a primary effect on...
- H Loss of essential functions of presenilin can explain dementia and neurodegeneration...
- C Although initial investigations of FAD-linked PS mutations in mammalian systems...
- C The ability of mutant presenilins to suppress the Egl phenotype is dose-dependent...
- C Impairment of the γ -secretase-dependent S3 cleavage of Notch and consequent reduction...
- C Transgenic expression of wild-type human PS1 and PS2 rescued the Egl phenotype caused...
- C FAD-linked PS mutations impair γ -secretase-dependent proteolysis of N-cadherin...
- C Numerous mutations in PS1 and PS2 can cause significant reductions in the production...
- C PS mutations can cause neurodegenerative dementia in the absence of A β accumulation...
- C Six different FAD-linked human presenilin mutations reduced the ability of PS1 to...
- H A critical reappraisal of the Amyloid Hypothesis, in response to inconclusive clinical...
- C The explicit prediction that causes of Alzheimer Disease would relate to amyloid...
- H Diffusible, non-fibrillar ligands derived from A β 42 are potent central nervous system...
- C Mutant presenilin genes, which elevate production of A β 42 and are associated with...

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Proteins list statements that cite the protein

Proteins have UniProt source links.
All have listed hypotheses and claims that discuss it.

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» Genes-Proteins

Presenilin-2 [Homo sapiens]

[UniProt]

Preferred Name:
Presenilin-2

Name(s):
Presenilin-2, AD3LP, STM-2, AD5, E5-1, PS-2

Encoded By:
Gene: PSEN2 presenilin 2 (Alzheimer disease 4) [Homo sapiens]

Derived Protein(s):
Protein: Presenilin-2 CTF subunit [Homo sapiens]
Protein: Presenilin-2 NTF subunit [Homo sapiens]

Organism:
[Homo sapiens]

Cited by:

- 1 Different γ -secretase complexes containing different Presenilin or Aph1 protein subunits are present in various tissues. (Sermeels et al., 2009)
- 2 PS1 and PS2 alter APP metabolism through a direct effect on the γ -secretase protease. (Hardy et al., 2002)
- 3 γ -secretase activity is responsible for the final cleavage of the amyloid precursor protein (APP), causing release of the A β peptide, cleaves Notch, N-Cadherin, and other important signaling molecules and is mediated by a multiprotein complex consisting of Presenilin (PS), Aph1, Pen2, and Nicastrin (NCT). (Sermeels et al., 2009)
- 4 The deleterious functional impact of pathogenic presenilin mutations may reflect a general destabilization of PS structure. (Shen et al., 2007)
- 5 The first direct evidence that FAD-linked mutations impair the biological activity of PS came from genetic complementation studies in *Caenorhabditis elegans* in which loss-of-function mutations in SEL12, which exhibits ~50% sequence identity to PS1 and PS2, reduce LIN12 activity and confer an egg-laying defective phenotype (Egl). (Shen et al., 2007)
- 6 Cloning and characterization of PS1 and PS2 AD-causing mutations revealed that these enhance APP processing to generate amyloidogenic A β . (Hardy et al., 2002)
- 7 PS2 is a less efficient generator of A β peptide than PS1. (Bentahir et al., 2006)
- 8 PS1-L166P and PS2-N141I fail to produce any detectable level of Notch NICD. (Bentahir et al., 2006)

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