GENETICS OF ALZHEIMER'S DISEASE

Early onset (<10%)
- Ch1 PS2: 20%
- Ch14 PS1: Up to 75%
- Ch21 APP: 5%

Unknown Mutations: > 50%

Late onset (>90%)
- Ch19 APOE: 15 - 50%
- Ch12 ?Locus: Maybe 50%
- Identical Twins: 30% Concordance

GENETIC CASES


**APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy**

Anne Rovelet-Lecrux, et al.

We report duplication of the *APP* locus on chromosome 21 in five families with autosomal dominant early-onset Alzheimer disease (ADEOAD) and cerebral amyloid angiopathy (CAA). Among these families, the duplicated segments had a minimal size ranging from 0.58 to 6.37 Mb. Brains from individuals with *APP* duplication showed abundant parenchymal and vascular deposits of amyloid-β peptides. Duplication of the *APP* locus, resulting in accumulation of amyloid-β peptides, causes ADEOAD with CAA.

APP locus duplication in five kindreds. Detection by QMPSF of APP duplications

*Nature Genetics* 2006; 38, 24 - 26
Top 38 Alzheimer's Disease Genes

| 1. APOE_e2/3/4 | 15. TNF    | 29. IL33   |
| 2. CLU         | 16. CCR2   | 30. IL1B   |
| 3. PICALM      | 17. DAPK1  | 31. PGBD1  |
| 4. SORL1       | 18. GAB2   | 32. THRA   |
| 5. GWA_14q32.13| 19. TF     | 33. ENTPD7 |
| 6. TNK1        | 20. MTHFR  | 34. TFAM   |
| 7. ACE         | 21. LOC651924 | 35. IL1A  |
| 8. IL8         | 22. OTC    | 36. ECE1   |
| 9. LDLR        | 23. ADAM10 | 37. PRNP   |
| 10. CST3       | 24. NEDD9  | 38. GAPDHS |
| 11. CR1        | 25. CH25H  |           |
| 12. hCG2039140 | 26. LOC439999 |      |
| 13. CHRNB2     | 27. CALHM1 |           |
| 14. SORCS1     | 28. GRN    |           |

AlzGene Stats

Studies: 1355
Genes: 660
Polymorphisms: 2825
Meta-analyses: 296
APOLIPOPROTEIN E

ε2, ε3, ε4

Genetic dose of apolipoprotein E Type 4 allele and the risk of Alzheimer’s Disease in late onset families.

E Corder, A Saunders, W Strittmatter, D Schmechel, et al

(Science 261:921-923, 1993)
APOLIPOPROTEIN E

- Is encoded on a gene on chromosome 19
- Is normally involved in cholesterol transport in brain
- Exists in ε2, ε3, ε4 allelic forms

APOLIPOPROTEIN E ε4

- Allelic frequencies in the population are
  ε2 = 8%  ε3 = 77%  ε4 = 15%
- The ε4 allelic frequency in AD is 40 - 50%
- The ε4 allele is therefore a risk factor for AD
THE GENETIC MUTATIONS CAUSAL OF ALZHEIMER’S DISEASE POINT TO THE BIOCHEMICAL PATHWAYS CAUSAL OF SPORADIC ALZHEIMER’S DISEASE

• Increased aggregation of normally synthesized $A\beta_{42}$
• Decreased turnover of $A\beta_{42}$ or $A\beta_{42}(n)$
• Decreased clearance of $A\beta_{42}$ or $A\beta_{42}(n)$
<table>
<thead>
<tr>
<th>Familial AD (30%)</th>
<th>Sporadic AD (70%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP gene-ch21</td>
<td>Toxins</td>
</tr>
<tr>
<td>Presenilin 1 gene-ch14</td>
<td>Infection</td>
</tr>
<tr>
<td>Presenilin 2 gene-ch1</td>
<td>Prions</td>
</tr>
<tr>
<td>Early onset genes</td>
<td>Trauma</td>
</tr>
<tr>
<td>Late onset genes</td>
<td>Environment</td>
</tr>
<tr>
<td>Down Syndrome</td>
<td>Aging</td>
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</tbody>
</table>

APOE ε4 - ch19
Polymorphisms
ALZHEIMER - TYPE NEUROPATHOLOGY IN TRANSGENIC MICE OVEREXPRESSING V717F β AMYLOID PRECURSOR PROTEIN

D Games, D Adams, R Alessandrini, et al

(Nature 373:523-527, 1995 )
IMMUNIZATION WITH AMYLOID-β ATTENUATES ALZHEIMER-DISEASE-LIKE PATHOLOGY IN THE PDAPP MOUSE

D Sckenk, R Barbour, W Dunn, et al and P Seubert

(Nature 400:173-177, 1999)
CONTROL MOUSE - 13 MONTHS

Aβ42 Plaques
Dystrophic Neurites
Reactive Gliosis

Aβ42 MOUSE - 13 MONTHS

No Plaques
Minimal Dystrophic Neurites
Minimal Reactive Gliosis
From plaque inception to maturity, Meyer-Luehmann et al.1 studied a mouse model of Alzheimer’s disease, monitoring 5–6-month-old animals — the age at which they begin to form the plaques characteristic of the disorder. The day on which the authors first detected a small extracellular amyloid deposit, or microplaque, was designated day 1. At that time, there was minimal alteration in the neurites surrounding the microplaque. But by day 2, the amyloid deposit had grown rapidly, and alterations in neighbouring axons and dendrites had become apparent. Migration of support cells, such as astroglia and microglia, to the vicinity of the growing plaque had also begun. By day 3, frank damage to the neighbouring axons was apparent. By day 7, the plaque had reached maturity, and its structure had stabilized.

**NATURE** 2008; 451:638-639
Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer’s disease

Melanie Meyer-Luehmann…, Bradley T. Hyman

Appearance of a novel plaque is a rapid process. a–c, Lowmagnification images provide an overview of the areas of potential plaque formation. The angiogram (red, Texas red), amyloid deposition (blue, methoxy-XO4) and neurons (green, YFP) are easily identified on the initial day of surgery (a) as well as one week (b) and two weeks later (c), allowing reimaging of the same sites over different imaging sessions. A new parenchymal amyloid deposition was identified one week (b) and two weeks (c) after the first imaging at this site. The new plaque appearing is indicated by an arrow (b and c). d–i,
Memory function often declines with age, and is believed to deteriorate initially because of changes in synaptic function rather than loss of neurons. Some individuals then go on to develop Alzheimer’s disease with neurodegeneration. Here we use Tg2576 mice, which express a human amyloid-β precursor protein (APP) variant linked to Alzheimer’s disease, to investigate the cause of memory decline in the absence of neurodegeneration or amyloid-β protein amyloidosis. Young Tg2576 mice (<6 months old) have normal memory and lack neuropathology, middle-aged mice (6–14 months old) develop memory deficits without neuronal loss, and old mice (>14 months old) form abundant neuritic plaques containing amyloid-β. We found that memory deficits in middle-aged Tg2576 mice are caused by the extracellular accumulation of a 56-kDa soluble amyloid-β assembly, which we term Aβ*56 (Aβ star 56). Aβ*56 purified from the brains of impaired Tg2576 mice disrupts memory when administered to young rats. We propose that Aβ*56 impairs memory independently of plaques or neuronal loss, and may contribute to cognitive deficits associated with Alzheimer’s disease.

A Specific Amyloid-β Protein Assembly in the Brain Impairs Memory

Sylvain Lesné, Ming Teng Koh, Linda Kotilinek, Rakez Kayed, Charles G. Glabe, Austin Yang, Michela Gallagher & Karen H. Ashe

Memory function often declines with age, and is believed to deteriorate initially because of changes in synaptic function rather than loss of neurons. Some individuals then go on to develop Alzheimer’s disease with neurodegeneration. Here we use Tg2576 mice, which express a human amyloid-β precursor protein (APP) variant linked to Alzheimer’s disease, to investigate the cause of memory decline in the absence of neurodegeneration or amyloid-β protein amyloidosis. Young Tg2576 mice (<6 months old) have normal memory and lack neuropathology, middle-aged mice (6–14 months old) develop memory deficits without neuronal loss, and old mice (>14 months old) form abundant neuritic plaques containing amyloid-β. We found that memory deficits in middle-aged Tg2576 mice are caused by the extracellular accumulation of a 56-kDa soluble amyloid-β assembly, which we term Aβ*56 (Aβ star 56). Aβ*56 purified from the brains of impaired Tg2576 mice disrupts memory when administered to young rats. We propose that Aβ*56 impairs memory independently of plaques or neuronal loss, and may contribute to cognitive deficits associated with Alzheimer’s disease.

NATURE 2006;440:352-357
Levels of the 56-kDa Aβ assembly show the strongest inverse correlation with spatial memory. a–f, Lack of significant correlations between retention of spatial memory and monomeric (4.5 kDa), trimeric (14 kDa) or hexameric (27 kDa) soluble Aβ species detected in extracellular-enriched fractions of 5-month-old (open circles) and 6-month-old (filled circles) Tg2576+/+ mice. g, h, Levels of Aβ assemblies corresponding to nonameric (40 kDa) and dodecameric (56 kDa) species correlate inversely with memory at 6 months of age (ANOVA).

*NATURE* 2006;440:352-357

**A Specific Amyloid-β Protein Assembly in the Brain Impairs Memory**
Purification of Aβ*56 from Tg2576 brain and effects of purified Aβ*56 on memory in young rats. 

a, Purification of total (RIPA-buffersoluble) Aβ species using immunoaffinity purification columns (IPC) packed with 200 mg of 6E10 or 4G8 antibodies (left panel). Right panel shows absorbance at 595nm (A595) of proteins isolated by affinity chromatography with 4G8 (AC4G8) that were separated by size-exclusion chromatography (SEC) to yield fractions containing Aβ*56. 
b, There is no difference between rats that received Aβ*56 and vehicle (50mM ammonium acetate, pH8.5) in terms of latency to locate a hidden platform during training. Data show blocks of two training trials each (mean ± s.e.m.). 
c, There is no difference between rats (Aβ*56 and vehicle treatment groups) in terms of latency to locate a visible platform. 
d, e, Aβ*56 impairs spatial memory. Rats that received vehicle, but not Aβ*56, injections showed a significant spatial bias for the escape location 24 h after training. Target annulus measures are shown in d, and number of annulus crossings in e (mean ± s.e.m.). Two-way ANOVA (P < 0.05) followed by t-test (*, P < 0.05), n = 10 animals per group.

*NATURE* 2006;440:352-357
Neuropathology of human Alzheimer disease after immunization with amyloid-β peptide: a case report

James A.R. Nicoll, David Wilkinson, Clive Holmes, Phil Steart, Hannah Markham & Roy O. Weller

Distribution and quantitation of Aβ pathology. 

Distribution and quantitation of Aβ pathology. 

MRI scan at the time of acute illness, showing widespread signal alteration in cerebral white matter. 

Corresponding granular change in cerebral white matter seen in a coronal slice of the cerebral hemispheres at post-mortem examination. 

Patches of Aβ plaques largely restricted to deep cortical laminae in the cingulate gyrus and medial frontal gyrus (immunized case). 

Absence of Aβ plaques from parietal neocortex of the immunized case, with persistent vascular amyloid (CAA). 

Relatively uniform distribution of Aβ plaques in corresponding regions of cerebral cortex in unimmunized AD. 

Quantitative image analysis showing plaque density (plaques/mm²; g) and Aβ load (h). For the immunized case in the medial frontal gyrus (c), values were within the range of unimmunized Alzheimer's disease. In contrast, the plaque density and Aβ load of the immunized case was lower than in unimmunized AD in the cingulate gyrus, and the inferior, middle and superior temporal gyri. 

Nature Medicine 2003; 9, 448 - 452
Model of response to Aβ vaccine.
Areas of cerebral cortex in a treated AD patient suggest clearance of neuritic plaques and inflammation surrounding some amyloid-containing vessel segments. The data suggested that there was no effect on non-Aβ lesions such as neurofibrillary tangles and dystrophic neurites. The foci of microglia in these regions may represent cells involved in the phagocytotic removal of Aβ.

Nature Medicine 2003; 9, 389 - 397
Antibodies against β-Amyloid Slow Cognitive Decline in Alzheimer's Disease

Christoph Hock, Uwe Konietzko, Johannes R. Streffer, Jay Tracy, Andri Signorell, Britta Müller-Tillmanns, Ulrike Lemke, Katharina Henke, Eva Moritz, Esmeralda Garcia, M. Axel Wollmer, Daniel Umbricht, Dominique J. F. de Quervain, Marc Hofmann, Alessia Maddalena, Andreas Papassotiropoulos and Roger M. Nitsch

The Generation of Antibodies against β-Amyloid Was Associated with Slowed Declines in Cognitive Functions and Activities of Daily Living AD patients who generated antibodies against β-amyloid (filled symbols, solid lines) were compared to patients without this immune response (controls, open symbols, dashed lines).

Neuron 2003, 38:, 547-554
The human disease network

Kwang-Il Goh, Michael E. Cusick, David Valle, Barton Childs, Marc Vidal, and Albert-László Barabási

The HDN and the DGN. (a) In the HDN, each node corresponds to a distinct disorder, colored based on the disorder class to which it belongs, the name of the 22 disorder classes being shown on the right. A link between disorders in the same disorder class is colored with the corresponding dimmer color and links connecting different disorder classes are gray. The size of each node is proportional to the number of genes participating in the corresponding disorder (see key), and the link thickness is proportional to the number of genes shared by the disorders it connects. We indicate the name of disorders with 10 associated genes, as well as those mentioned in the text. For a complete set of names..
VACCINATION THERAPY FOR ALZHEIMER’S DISEASE:

The Promise and the Problem

Amyloid: (Aβ42)n is the Prime Target for Immunotherapy
Gene Vaccination to Bias the Immune Response to Amyloid-β Peptide as Therapy for Alzheimer’s Disease

Baoxi Qu, MD; Roger N. Rosenberg, MD; Liping Li, MD; Philip J. Boyer, PhD; Stephen A. Johnston, PhD

Genetic immunization vector contains a synthetic SP72 promoter, a Aβ42 gene sequence fused between a human alpha antitrypsin secretory signal and a MHCII targeting peptide sequence, and the ampicillin resistance gene, Aβ42 monomer or dimer, followed by a MHC II targeting sequence.

Mouse Aβ42:DAEFGHDGFEVR HQKLVFFAEDVGSNKGAIIGLMVGVVIA
Human Aβ42: DAEF RHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGVVIA

Archives of Neurology, 2004;61:1859-1864
The gene gun ballistically accelerates the passage of gold beads (1-3 micron) coated with DNA plasmids through the epidermis, where DNAs are taken up by dendritic (Langerhans’) cells (Fig A). The dendritic cells further migrate to the draining lymph node and the foreign DNA is expressed. The expressed polypeptide antigens bind to the major-histocompatibility complex and activate T cells. These activated T cells interact with activated B cells to induce a humoral response (Fig. B).
Aβ42 gene vaccination reduces brain amyloid plaque burden in transgenic mice

Baoxi Qu, Philip J. Boyer, Stephen Albert Johnston, Linda S. Hynan and Roger N. Rosenberg

ELISA shows all six mice treated with Aβ_{42} (1-3) and Aβ1-16 (4-6) gene vaccine have high antibody against GST- Aβ 1-16. (Serum dilution 1:200)
ELISPO for blood T cells using mixture of Aβ₄₂ and Aβ 9-18 peptide as Antigen to show no significant cell-mediated Immunity In gene-gun mediated Aβ₄₂ gene vaccine in mixture of 6 Treated mice and 3 control.
Aβ_{42} Levels in Treated and Control AD Tg Mouse Brain and Serum

Levels of Aβ_{42} in forebrain (A) and in plasma (B) of 15 months old APPswe/PS1ΔE9 transgenic mice treated with the Aβ_{42} gene vaccine (T) and control (C). Bars represent Mean±SEM of four mice in both groups. (A) The forebrain was extracted with 5 M quanidine and Aβ_{42} was quantified by sandwich ELISA. There is about 70% reduction of total Aβ_{42} in the forebrain of vaccinated mice compare to the control. (B) Plasma samples were diluted in 1:100 in blocking buffer and Aβ_{42} levels were measured by sandwich ELISA.
Aβ\textsubscript{42} plaque density in cortex stained with anti-Aβ\textsubscript{42} antibody. 10x