Heterogeneity of Alzheimer's disease and CSF β Amyloid Profiles
a possible tool for patient stratification?

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The diagnosis of dementia due to Alzheimer's disease: recommendations from the NIA and the Alzheimer's Association workgroup

Progressive cognitive or behavioural impairment involving ≥2 cognitive domains, defined on clinical basis and confirmed by neuropsychological tests

Clinical Heterogeneity

a. Amnestic presentation

b. Non amnestic presentations

- **Language dysfunction**: deficit in word finding
- **Visuospatial dysfunction**: deficit in spatial cognition
- **Executive dysfunction**: impaired reasoning, judgment and problem solving
Asymmetrical cerebral atrophy in Alzheimer's disease

O Bugiani, J Constantinidis, B Ghetti, C. Bouras, F Tagliavini

onset: language disorders

onset: visuospatial disturbances

Morphometry (area 22)

- cortical thickness (μm)
- nerve cell density (n/mm²)
- NFT bearing neurons (n/mm²)
- plaque density (n/mm²)
- plaque size (mm²)

△ between hemispheres

- 825 ± 32 ***
- 219 ± 49 *
- 29 ± 6 **
- 17 ± 8 NS
- 455 ± 53 ***

p < *0.05, ** 0.02, *** 0.01
phenotypic heterogeneity is particularly high in genetic forms of Alzheimer's disease
Phenotypes associated with mutations of the presenilin 1 gene

- **FTD bv-like phenotype**  L113P, P117R, M139V, G184V, E280A, insR352
- **Language presentation**  H163Y, G209V, L262F, R278I, E280A, A413E, A434C
- **Cerebellar Ataxia**  P117A, I143T, L166P, Y256S, L282V
- **Parkinsonism**  E120D, M146L, L250S, C410Y
phenotype of the P117A PS1 mutation

Clinical Features
- early Ataxia
- early Behavioural Disturbances
- Epilepsy
- relatively late Dementia

Neocortex

Cerebellum
Phenotypes associated with mutations of the presenilin 2 gene

- **FTD Bv-like phenotype**
  - M239V  Marcon et al.  J Neuropathol exp Neurol 2004

- **DLB-like phenotype**
  - A85P  Piscopo et al.  Neurology 2008
phenotype of the A85P PS2 mutation

Clinical Features

- early memory and language deficits
- parkinsonism
- visual allucinations and sleep disturbances

\[ \text{ph-tau} \]

\[ \alpha\text{-Syn} \]

\[ A\beta \]
Phenotypes associated with APP mutations

**AD phenotypes**

- KM670/NL671
  - H677R
  - D678N
  - A692G
  - D694N
  - E693G
  - E693Δ (low penetrance)

**CAA phenotypes or AD with severe CAA**

- KM670/NL671
  - A692G
  - D694N
  - E693Q (Dutch)
  - E693K (Italian)
  - E693G
  - L705V
  - A713T

Variants:
- A692G
- D694N
- E693Q
- E693K
- E693G
- L705V
- A713T

Low penetrance variants:
- H677R
- D678N

Severe CAA variants:
- L723P
- K724N
- V717I, V717F, V717G, V717L
- I716V, I716T
- V715M, V715A
- T714I, T714A
A Recessive Mutation in the APP Gene with Dominant-Negative Effect on Amyloidogenesis

Giuseppe Di Fede,1 Marcella Catania,1 Michela Morbin,1 Giacomina Rossi,1 Silvia Suardi,1 Giulia Mazzoleni,1 Marco Merlin,1 Anna Rita Giovagnoli,1 Sara Prioni,1 Alessandra Erbetta,2 Chiara Falcone,3 Marco Gobbi, Laura Colombo,4 Antonio Bastone,4 Marten Beeg,4 Claudia Manzoni,4 Bruna Francescucci,5 Alberto Spagnoli,5 Laura Cantù,6 Elena Del Favero,6 Efrat Levy,7 Mario Salmona,4 Fabrizio Tagliavini1*

Neuropathology of A673V APP mutation
Heterogeneity of Alzheimer’s disease

Neuropathological correlates?

Molecular basis?

- Aβ
- Tau
- other
Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: A retrospective study

Melissa E. Murray, PhD¹, Neill R. Graff-Radford, MBBCh, FRCP (London)³, Owen A. Ross, PhD¹, Ronald C. Petersen, MD⁴, Ranjan Duara, MD⁵, and Dennis W. Dickson, MD¹

Study population: 889 AD brains

Subclassification according to an algorithm based on:
(i) hippocampal and cortical NFT density
(ii) ratio of hippocampal to cortical NFT count

Three AD subtypes:
1. typical 75%
2. limbic predominant 14%
3. hippocampal sparing 11%
sporadic and genetic AD variants show different Aβ-related neuropatological profiles

sAD (ApoE ε3)  APP V717F  APP A673V

sAD (ApoE ε4)  APP A713T  PS1 P117A

G. Giaccone
Molecular basis of phenotypic heterogeneity

The model of prion diseases
Human Prion Diseases

• Creutzfeldt-Jakob disease
  - sporadic
  - genetic
  - acquired (iatrogenic, new variant)

• Fatal Insomnia
  - genetic
  - sporadic

• Variable Protease-sensitive Prionopathy
  - sporadic

• Gerstmann-Sträussler-Scheinker Disease
  - genetic

• Kuru
  - acquired (ritualistic cannibalism)
Different prion disease phenotypes are associated with distinct \( \text{PrP}^\text{Sc} \) types which encipher diverse biological properties.

Poggiolini et al. - Int J Cell Biol 2013
variants of sporadic CJD

MM1/MV1
“typical form”

VV2/MV2
“ataxic form”

G. Giaccone
Patterns of PrP deposition in sCJD

- **synaptic**
- **perivacuolar**
- **perineuronal**
- **Kuru plaques**

**MM1/MV1**

**MM2**

**VV2**

**MV2K**
Molecular basis of phenotypic heterogeneity of Alzheimer's disease

Study design

1. Identification of different clinico-pathological AD phenotypes

2. Biochemical profiling of Aβ species in affected brain regions and purified amyloid fractions

3. Propagation of phenotypic diversity in animal models
Biochemical profiling of Aβ species in purified amyloid fractions and brain extracts

Study Population

- **sAD (n=20)**
- **fAD (n=4):** APP A673V, APP A713T, PS1 P117A, PS2 A85V
- **fCAA (n=1):** APP E693K
- **age-matched non-demented controls (n=5)**

Methods

- **Amyloid extraction from leptomeninges** (Vidal et al. Neurology 1992)
- **Amyloid extraction from plaques** (Tagliavini et al. EMBO J. 1991)
- **Simplified amyloid extraction from plaques** (M. Catania, JAD in press)

  Aβ peptide extraction with 80% Formic Acid

  SELDI-TOF MS analysis
AD phenotypic diversity and Aβ profile

APP A673V

APP A713T

PS1 P117A

sAD ApoE ε4/ε4
Aβ profiles as revealed by SELDI-TOF MS

**Profile 1**

sAD (n=14), fAD PS1 P117A, fAD PS2 A85V

(ApoE allele frequency: 69% Apo ε3)

**Predominant species**

Aβ1-42, Aβ4-42, Aβ3pE-42, Aβ11pE-42

**Minor species**

AβX-40

**Profile 2**

sAD (n=5)

(ApoE allele frequency: 60% Apo ε4)

**Predominant species**

Aβ1-40, Aβ1-42

**Minor species**

Aβ2-39, Aβ2-40, Aβ3pE-40
Aβ profiles as revealed by SELDI-TOF MS

**Profile 3**

- **Predominant species**
  - Aβ1-40, Aβ1-38
- **Minor species**
  - Aβ1-37, Aβ1-39

- fAD APP A673V, fAD APP A713T, fCAA APP E693K
  - (ApoE ε3/ε3)

**Profile 4**

- **Predominant species**
  - Aβ1-40, Aβ3pE-40
- **Minor species**
  - Aβ1-36, Aβ2-40, Aβ3pE-42

- sAD-CAA (n=1)
  - (ApoE ε4/ε4)
Different $\mathrm{A}\beta$ profiles show different resistance to proteolytic degradation

profile 1  profile 2

$p<0.0001$
Biochemical data are supported by Aβ immunohistochemistry

Study Population

- **APP mutations**
  - A673V
  - E693Q (Dutch)
  - E693K (Italian)
  - E693G (Arctic)
  - L705V
  - A713T
  - V717F, V717L

- **PSEN1 mutations** (P117A, I143V, M146L, S169L)
- **PSEN2 mutations** (A85V, M239V)
- **Down’s Syndrome** (n=4)
- **Sporadic AD** (n=12)
Aβ38 is present in amyloid deposits of AD patients with APP mutations within the Aβ region, while is absent in sporadic and other genetic forms of AD and DS

**APP mutations**

- A673V
- E693G
- E693K
- L705V
- A713T
- V717F
- V717L

- PSEN1 and PSEN 2 mutations
- Down’s Syndrome
- Sporadic AD
The differences in Aβ species found in the brain are detectable in CSF as *mirror profiles*.
### Peptides

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Mean Signal Intensity (μA ± SE)</th>
<th>Relative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ1-17</td>
<td>1.0±0.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Aβ1-18</td>
<td>8.2±0.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Aβ1-19</td>
<td>1.7±0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Aβ11-40</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ2-40</td>
<td>21.4±0.4</td>
<td>6.2</td>
</tr>
<tr>
<td>Aβ10-40</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ11-40</td>
<td>19.2±0.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Aβ11-42</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1-33</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1-34</td>
<td>nd</td>
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<tr>
<td>Aβ1-35</td>
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<tr>
<td>Aβ1-36</td>
<td>37.7±0.4</td>
<td>11.0</td>
</tr>
<tr>
<td>Aβ1-37</td>
<td>9.7±0.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Aβ1-38</td>
<td>23.9±0.4</td>
<td>6.9</td>
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<td>Aβ1-39</td>
<td>15.9±0.2</td>
<td>4.6</td>
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<tr>
<td>Aβ1-40</td>
<td>189.0±1.2</td>
<td>55.0</td>
</tr>
<tr>
<td>Aβ1-42</td>
<td>16.0±1.2</td>
<td>4.6</td>
</tr>
<tr>
<td><strong>Total Aβ</strong></td>
<td><strong>343.7</strong></td>
<td><strong>100%</strong></td>
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</table>

### CSF

<table>
<thead>
<tr>
<th>Peptides</th>
<th>CTR</th>
<th>PS1 P117A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ1-17</td>
<td>3.3±0.2</td>
<td>2.2±0.2</td>
</tr>
<tr>
<td>Aβ1-18</td>
<td>6.0±0.6</td>
<td>5.9±0.4</td>
</tr>
<tr>
<td>Aβ1-19</td>
<td>1.8±0.1</td>
<td>1.3±0.1</td>
</tr>
<tr>
<td>Aβ11-40</td>
<td>1.5±0.1</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ2-40</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ10-40</td>
<td>4.3±0.6</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ4-42</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ11-42</td>
<td>1.6±0.1</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1-33</td>
<td>5.5±0.3</td>
<td>1.7±0.1</td>
</tr>
<tr>
<td>Aβ1-34</td>
<td>5.6±0.4</td>
<td>4.3±0.3</td>
</tr>
<tr>
<td>Aβ1-35</td>
<td>1.6±0.1</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1-36</td>
<td>2.7±0.1</td>
<td>nd</td>
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<tr>
<td>Aβ1-37</td>
<td>19.6±1.5</td>
<td>5.2±0.2</td>
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<tr>
<td>Aβ1-38</td>
<td>69.6±6.2</td>
<td>20.1±0.4</td>
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<tr>
<td>Aβ1-39</td>
<td>15.1±1.2</td>
<td>6.9±0.6</td>
</tr>
<tr>
<td>Aβ1-40</td>
<td>180.1±16.5</td>
<td>64.7±1.1</td>
</tr>
<tr>
<td>Aβ1-42</td>
<td>10.9±0.9</td>
<td>4.4±0.3</td>
</tr>
<tr>
<td><strong>Total Aβ</strong></td>
<td><strong>329.1</strong></td>
<td><strong>116.7</strong></td>
</tr>
</tbody>
</table>
Consistency between Aβ species that accumulate in amyloid deposits and those reduced in CSF
Questions

• Is the molecular diversity of Aβ a determinant of phenotypic heterogeneity?

• Does phenotypic diversity of AD propagate to susceptible mice challenged with different molecular AD subtypes?
Exogenous induction of cerebral \( \beta \)-amyloidogenesis

*Meyer-Luehmann et al. Science 2006*

AD brain

![AD brain image](image1)

Normal brain

![Normal brain image](image2)
Challenge of APP-Tg mice with brain extracts from AD with different Aβ profiles

- **Aβ profile 1**
  - PS1 P117A (n=1)
  - sAD (n=3)

- **Aβ profile 3**
  - APP A673V (n=1)
  - APP A713T (n=1)

- **Aβ profile 4**
  - sAD-CAA (n=1)

6-month-old Tg mice expressing human APP with the Swedish mutation on endogenous APP knock-out background (n= 9/group)

Stereotactic inoculation of 10% homogenates in the hippocampus

Culling 5 months after challenge
Phenotypic diversity is maintained upon transmission to mice

fAD PS1 P117A (Aβ profile 1)

fAD APP A713T (Aβ profile 3)

sAD-CAA ApoE ε4/ε4 (Aβ profile 4)
Amyloid burden in different brain regions of APP-Tg mice after i.c. inoculation with brain extracts from AD patients and controls.
Amyloid angiopathy

- mock
- APP A713T
- PS1 P117A
- APP A673V
- sAD ApoE ε3/ε3
- sAD ApoE ε4/ε4

Graph showing the distribution of Amyloid angiopathy across different brain regions (Motor Cx, Somatosensory Cx, Piriform Cx, Hippocampus, Fimbria, Thalamus, Meninges).
Serial propagation of distinct strains of Aβ prions from Alzheimer’s disease patients

Joel C. Watts, Carlo Condello, Jan Stöhr, Abby Oehler, Joanne Lee, Stephen J. DeArmond, Lars Lannfelt, Martin Ingelsson, Kurt Giles, and Stanley B. Prusiner

A

Swedish AD
Wild-type Aβ
Arctic AD
Arctic Aβ (E22G)
Sporadic AD
Wild-type Aβ
Tg(APP23:Gfap-luc)

B

Inoculum (days)

Inoculum: Spor AD i  Spor AD ii  Swe AD  Arc AD
Sex: Female  Male

C

Aβ42 : Aβ42 ratio

Inoculum: Spor AD i  Spor AD ii  Swe AD  Arc AD

D

Inoculum: Arctic AD  Sporadic AD i

Aβ (42kDa)

Inoculum: Swedish AD  None

AD

PK: +  +  +  +
kDa
3.5−

Aβ38

Inoculum: Arctic AD  Sporadic AD ii

Aβ38 (BA1-13)

D

Aβ38-positive vessels per section

Inoculum: Spor AD i  Spor AD ii  Swe AD  Arc AD

*** ***
Different $\beta$ strains can be propagated in vitro by RT-QuIC and can be distinguished by different aggregation kinetics.
Conclusions

• Different AD phenotypes show differences in biochemical composition, assembly state, protease resistance and targeting of Aβ species, and different propagation patterns in animal models and in cell-free systems.

• These data suggest that a different composition, aggregation state and pathogenic properties of Aβ species could be the basis of phenotypic diversity of AD.

• The differences in Aβ species found in the brain are detectable in CSF as mirror profiles. Accordingly, CSF analysis with advanced techniques could allow early diagnosis and stratification of AD patients with atypical presentation.
Clinical Unit
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V. Redaelli
S. Prioni
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I. Campagnani
A. Indaco
S. Spinello
E. Maderna

Genetics & Mol. Biology
G. Di Fede
G. Rossi
M. Catania
E. Piccoli
I. D’Amato

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F. Moda
S. Suardi
L. Palamara

Ultrastructure
M. Morbin
S. Saccucci
V. Fugnanesi

Key collaborators to these studies
- Roberta Ghidoni
  IRCCS FBF Brescia
- Bernardino Ghetti
  Indiana University, IN

Support
- Italian Ministry of Health
- MIUR
- Cariplo Foundation
- Telethon
- European Union
- Alzheimer Association
- AIEnP
Detection of Misfolded Aβ oligomers for Sensitive Biochemical Diagnosis of Alzheimer’s Disease

CSF + seed-free Aβ 1-42 + thioflavin T

repeated cycles of incubation/agitation

Salvatores et al. Cell Reports 2014

![Graph showing aggregation percentage over time for Alzheimer's patients and controls](graph.png)
$A\beta$ Seeding Activity in CSF is higher in AD patients than in controls
# Sensitivity, specificity and predictive value for AD-PMCA using CSF samples

<table>
<thead>
<tr>
<th>Groups</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD versus non-AD degenerative neurological diseases</td>
<td>100.0 %</td>
<td>94.6 %</td>
<td>96.2 %</td>
<td>100.0 %</td>
</tr>
<tr>
<td>AD versus non-degenerative neurological disorders</td>
<td>90.0 %</td>
<td>84.2 %</td>
<td>88.2 %</td>
<td>86.5 %</td>
</tr>
<tr>
<td>AD versus Controls</td>
<td>90.0 %</td>
<td>92.0 %</td>
<td>88.2%</td>
<td>93.2 %</td>
</tr>
</tbody>
</table>
Heterogeneity of Alzheimer’s Disease

- Clinical phenotypes
- Neuropathology
- Molecular correlates: Aβ strains
- CSF: Aβ amyloid profiles
Brain lesion profile of APP-Tg mice after i.c. inoculation with brain extracts from AD patients and controls

Control

Aβ Profile 1
PS1 P117A

Aβ Profile 1
sAD

Aβ Profile 3
APP A673V

Aβ Profile 3
APP A713T

Aβ Profile 4
sAD-CAA

Brain lesion profile of APP-Tg mice after i.c. inoculation with brain extracts from AD patients and controls.
Frontal cortices from sporadic AD

15% brain homogenates in 10mM Tris HCl
pH=7.5
Ultracentrifugated 100,000xg, 4°C, 1h
Supernatant = Soluble Fraction

ThT assay on soluble fractions:
Incubation Temperature=25°C
Shake=1 minute/hour

Homogenates aggregation assay

Nonlinear fit

T50 of aggregation kinetics
p=0.02

Slope of aggregation kinetics
p=0.032
Soluble fraction of brain homogenates from profile 1 (n=16), profile 2 (n=5), profile 3 (n=3), profile 4 (n=1) incubated for 48h at 37°C (seed) + Fresh sAD brain homogenate (substrate)

↓

**RT-QuIC**
IncubationTemperature = 37°C
Shake = 1 minute/hour

Aggregated soluble extracts act as a seed when diluted into a fresh brain homogenate, modifying its aggregation kinetics.
Alzheimer's disease

- **Italy**: 0.7 millions
- **EU**: 7.3 millions
- **World**: 35 millions

- **sporadic**: ~99%
- **familial**: ~1%

caused by mutation in
- Aβ precursor protein (APP)
- presenilin 1 / presenilin 2

All mutations alter APP processing and/or Aβ properties

\[\text{increased Aβ production and/or Aβ aggregation}\]
Revising the definition of AD: a new lexicon
Dubois et al. – Lancet Neurology 2010

Diagnosis of Alzheimer’s disease
Defined by a clinical-biological algorithm which takes into account characteristic pattern of episodic memory deficit + presence of disease-related pathophysiological or topographical biomarkers
It comprises the whole spectrum of the clinical phase, including the prodromic (or “pre-dementia”) stage

<table>
<thead>
<tr>
<th></th>
<th>Pathophysiological marker</th>
<th>Topographical marker</th>
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<tbody>
<tr>
<td>CSF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Amyloid β_{42}</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>• Total tau, ph-tau</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Amyloid tracer uptake</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>• FDG</td>
<td></td>
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<tr>
<td>Structural MRI</td>
<td>Medial temporal atrophy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
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</table>
Research criteria for the diagnosis of AD: revising the NINCDS-ADRDA criteria

Dubois et al. - Lancet Neurology 2007

➢ Probable

1. Episodic memory deficits: early symptom, progressive, > 6 months, documented by tests, isolated or associated with other cognitive deficits

2. At least one of
   
   A. Mesial temporal atrophy on MRI
   B. Specific neuroimaging pattern
      - FDG-PET: bilateral temporo-parietal hypometabolism
      - positive PET with amyloid tracers
   C. Changes of CSF biomarkers: < Aβ42, > total and phospho-Tau
   D. APP, PS1 or PS2 autosomal dominant mutations in the family

➢ Definite

• Clinical + neuropathological evidence of AD (NIA- Regan criteria)
• Clinical + genetic evidence of AD
### Peptides in amyloid-enriched fraction from leptomeninges of the A673V mutation

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Signal Intensity (µA) ± SE</th>
<th>Relative Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ1-17</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1-18</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1-19</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ11-40</td>
<td>3.8 ±0.1</td>
<td>0.4±0</td>
</tr>
<tr>
<td>Aβ10-40</td>
<td>nd</td>
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<td>Aβ11-42</td>
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<td>Aβ1-35</td>
<td>nd</td>
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<tr>
<td>Aβ1-36</td>
<td>10.6± 0.1</td>
<td>1±0</td>
</tr>
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<td>Aβ1-37</td>
<td>30.9 ±1.2</td>
<td>2.9±0.1</td>
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<tr>
<td>Aβ1-38</td>
<td>73.7± 2.5</td>
<td>7±0.1</td>
</tr>
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<td>Aβ1-39</td>
<td>47.5± 1.6</td>
<td>4.5±0.1</td>
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<tr>
<td>Aβ1-40</td>
<td>792 ± 4.4</td>
<td>75.4±0.1</td>
</tr>
<tr>
<td>Aβ1-42</td>
<td>22.6 ± 0.4</td>
<td>2.2±0.1</td>
</tr>
<tr>
<td><strong>Total Aβ</strong></td>
<td><strong>1050.8</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

**SELDI-TOF MS**

Graph showing Aβ peptides with Aβ1-40, Aβ1-37, Aβ1-39, Aβ1-42, and Aβ1-38 peaks.
Consistency between Aβ species that accumulate in amyloid deposits and those reduced in CSF

PS1 P117A

Amyloid from leptomeninges

![Graph showing signal intensity for Amyloid from leptomeninges and CSF with PS1 P117A in different conditions.]

CSF

![Graph showing signal intensity for CSF with Control, typical sAD, and PS1 P117A in different conditions.]
Consistency between Aβ species that accumulate in amyloid deposits and those reduced in CSF

APP A673V
Amyloid from leptomeninges

CSF

Signal intensity

Signal intensity
# Analysis of Aβ peptides in CSF from the A673V patient and controls using SELDI TOF MS

<table>
<thead>
<tr>
<th>Peptides</th>
<th>CTR</th>
<th>sAD</th>
<th>APP A673V T1</th>
<th>APP A673V T2</th>
<th>APP A673V T3</th>
<th>APP A673V T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ1-17</td>
<td>3,3 ± 0,2</td>
<td>3,8 ± 0,3</td>
<td>1,7 ± 0,1</td>
<td>1,4 ± 0,1</td>
<td>1,3 ± 0,2</td>
<td>1,8 ± 0,1</td>
</tr>
<tr>
<td>Aβ1-18</td>
<td>6 ± 0,6</td>
<td>6,3 ± 0,8</td>
<td>1,7 ± 0,1</td>
<td>0,6 ± 0,3</td>
<td>0,3 ± 0,3</td>
<td>1,5 ± 0,1</td>
</tr>
<tr>
<td>Aβ1-19</td>
<td>1,8 ± 0,1</td>
<td>1,9 ± 0,1</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ11-40</td>
<td>1,5 ± 0,1</td>
<td>1,8 ± 0,1</td>
<td>5,0 ± 0,3</td>
<td>2,2 ± 0,4</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ10-40</td>
<td>4,3 ± 0,6</td>
<td>5,0 ± 0,8</td>
<td>4,0 ± 0,5</td>
<td>4,9 ± 1,2</td>
<td>11,7 ± 2,6</td>
<td>6,8 ± 0,5</td>
</tr>
<tr>
<td>Aβ11-42</td>
<td>1,6 ± 0,1</td>
<td>1,7 ± 0,1</td>
<td>nd</td>
<td>0,6 ± 0,3</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1-33</td>
<td>5,5 ± 0,3</td>
<td>5,1 ± 0,5</td>
<td>2,6 ± 0,3</td>
<td>2,3 ± 0,5</td>
<td>0,6 ± 0,2</td>
<td>0,6 ± 0,1</td>
</tr>
<tr>
<td>Aβ1-34</td>
<td>5,6 ± 0,4</td>
<td>5,3 ± 0,5</td>
<td>2,7 ± 0,3</td>
<td>2,4 ± 0,5</td>
<td>0,8 ± 0,1</td>
<td>0,7 ± 0,0</td>
</tr>
<tr>
<td>Aβ1-35</td>
<td>1,6 ± 0,1</td>
<td>2,1 ± 0,2</td>
<td>nd</td>
<td>1,8 ± 1,1</td>
<td>1,0 ± 0,5</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1-36</td>
<td>2,7 ± 0,1</td>
<td>2,8 ± 0,2</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aβ1-37</td>
<td>19,6 ± 1,5</td>
<td>20,0 ± 2,2</td>
<td>4,1 ± 0,3</td>
<td>2,1 ± 0,1</td>
<td>2,9 ± 0,3</td>
<td>2,7 ± 0,2</td>
</tr>
<tr>
<td>Aβ1-38</td>
<td>69,6 ± 6,2</td>
<td>71,5 ± 8,5</td>
<td>4,5 ± 0,4</td>
<td>3,5 ± 0,6</td>
<td>5,7 ± 0,5</td>
<td>3,6 ± 0,3</td>
</tr>
<tr>
<td>Aβ1-39</td>
<td>15,1 ± 1,2</td>
<td>15,6 ± 1,3</td>
<td>4,7 ± 0,4</td>
<td>1,9 ± 0,2</td>
<td>0,6 ± 0,6</td>
<td>0,7 ± 0,4</td>
</tr>
<tr>
<td>Aβ1-40</td>
<td>180,1 ± 16,5</td>
<td>183,1 ± 20,5</td>
<td>3,6 ± 0,6</td>
<td>4,6 ± 1,1</td>
<td>7,1 ± 0,9</td>
<td>4,3 ± 0,6</td>
</tr>
<tr>
<td>Aβ1-42</td>
<td>10,9 ± 0,9</td>
<td>5,8 ± 0,6</td>
<td>1,1 ± 0,2</td>
<td>1,0 0,1±</td>
<td>1,6 ± 0,2</td>
<td>1,4 ± 0,3</td>
</tr>
<tr>
<td><strong>Total Aβ</strong></td>
<td>329,1</td>
<td>331,7</td>
<td>32,4</td>
<td>29,1</td>
<td>33,7</td>
<td>24,0</td>
</tr>
</tbody>
</table>
Molecular basis of phenotypic variability in sporadic CJD

1. Polymorphism at codon 129 of PrP

2. PrP\textsuperscript{Sc} characteristics

PrP\textsuperscript{res} type 1 2A

21 kd -
19 kd -
### Relationship between codon 129 polymorphism and PrP<sup>Sc</sup> type

<table>
<thead>
<tr>
<th></th>
<th>MM</th>
<th>MV</th>
<th>VV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>type 1 PrP&lt;sup&gt;Sc&lt;/sup&gt;</strong></td>
<td>94.4</td>
<td>3.7</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>type 2 PrP&lt;sup&gt;Sc&lt;/sup&gt;</strong></td>
<td>14.0</td>
<td>31.4</td>
<td>54.6</td>
</tr>
</tbody>
</table>

- **typical**
- **ataxic**
### Heterogeneity of Creutzfeldt-Jakob disease in relation to codon 129 PRNP genotype and PrPSc type

<table>
<thead>
<tr>
<th>previous terminology</th>
<th>%</th>
<th>onset yrs</th>
<th>duration mo</th>
<th>distinctive features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MM1</strong>&lt;br&gt;<strong>MV1</strong>&lt;br&gt;typical or Heidenhain's form</td>
<td>73</td>
<td>66 (42-91)</td>
<td>4 (1-24)</td>
<td>Typical picture early myoclonus (97%)</td>
</tr>
<tr>
<td><strong>VV1</strong></td>
<td>1</td>
<td>43 (19-71)</td>
<td>19 (4-72)</td>
<td>Atypical dementia late myoclonus (41%)</td>
</tr>
<tr>
<td><strong>MM2 cortical</strong></td>
<td>1</td>
<td>66 (49-82)</td>
<td>14 (3-24)</td>
<td>Atypical dementia late myoclonus (83%)</td>
</tr>
<tr>
<td><strong>MM2 thalamic or sFI</strong>&lt;br&gt;thalamic</td>
<td>1</td>
<td>46 (24-74)</td>
<td>24 (10-73)</td>
<td>Cognitive decline, ataxia, psychiatric, insomnia late myoclonus (32%)</td>
</tr>
<tr>
<td><strong>MV2</strong>&lt;br&gt;cerebellar</td>
<td>9</td>
<td>62 (40-81)</td>
<td>17 (4-43)</td>
<td>Ataxia, cognitive decline late myoclonus (74%)</td>
</tr>
<tr>
<td><strong>VV2</strong>&lt;br&gt;cerebellar</td>
<td>15</td>
<td>64 (41-83)</td>
<td>6 (3-18)</td>
<td>Ataxia late myoclonus (66%)</td>
</tr>
</tbody>
</table>

**Mixed cases & Atypical forms**