Genetics of Alzheimer's Disease

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Introduction

- Neurodegenerative disease.
- Most frequent cause of dementia: it represents 66% of all dementias[1]
- High prevalence: 13% of the population over 65 and 45% of population over 85 years old.
- 2 types and different genes related (figure 1)

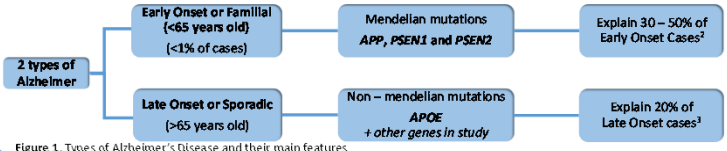

Figure 1. Types of Alzheimer's Disease and their main features

- **Diagnosis**: family history + psychic and cognitive tests + magnetic resonance (to rule out other dementia causes)
- **Risk factors**. Genetic factors and age.
- **Molecular features**. Presence of:
  - Senile plaques: extracellular β – amyloid deposits (Aβ)
  - *Neurofibrillary tangles*: intraneuronal tau protein aggregates
- **Treatment**. Without treatment, but several strategies have been tested:
  - Facilitate Aβ clearance + prevent Aβ aggregation[4]
  - Inhibit or modulate γ – secretasa complex activity[5]
  - Modulate apoE function[6]

Genes related to Early Onset Alzheimer's Disease (EOAD)

Amyloid Precursor Protein (APP)

It is located at 21q21.2 and codes for a protein called APP (figure 2). APP undergoes a proteolytic processing that results in Aβ formation (figure 3).

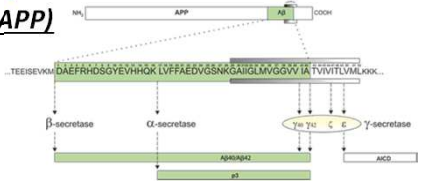

Figure 2. APP structure. From Van Broeck, *et al*[7].

Steps:

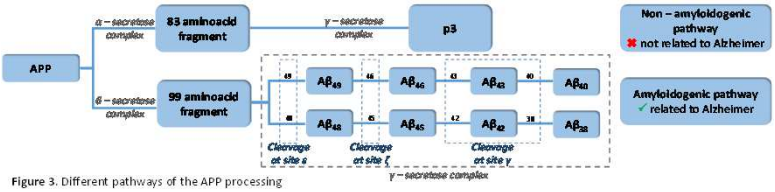

Figure 3. Different pathways of the APP processing

The two major Aβ forms are $Aβ_{40}$ (under normal conditions it represents 90% of Aβ[8]) and $Aβ_{42}$. The different forms have different aggregation properties: $Aβ_{40}$ aggregates less than $Aβ_{42}$, $Aβ_{43}$ and $Aβ_{38}$ forms[5].
During the processing the C terminus, which is hydrophobic, is shortened, such that the shorter the fragments the easier they are to release.

Mutations and its effect on Alzheimer's Disease

In *APP*, 24 pathogenic, 1 of unclear pathogenicity, 1 protective and 5 non-pathogenic point mutations have been described. They cause 15% of all Early Onset Alzheimer's Disease cases. They affect through different pathways[3]:

- Aβ production modulation: the mutations map in the β – secretase and γ – secretase cleavage area.
- Change of the preferred cleavage position at site ε: there is a preference for the $Aβ_{48}$ production line.
- More efficient folding → faster aggregation. The mutations map in all the sequence of exons 16 and 17.

Additionally, 9 *APP* duplications have been described. They affect the APP dosage.

Presenilins (*PSEN1* and *PSEN2*)

PSEN1 is located at 14q24.3 and *PSEN2* at 1q42.13. They code for the catalytic subunit of the γ – secretase complex. *PSEN1* has 9 transmembranal domains (figure 4). The active site is located between the domains 6 and 7[9].

Mutations

In *PSEN1*, 185 pathogenic, 1 of unclear pathogenicity and 4 non-pathogenic point mutations have been described. They cause 18-50% of all Early Onset Alzheimer's Disease cases.
In *PSEN2*, 13 pathogenic, 7 of unclear pathogenicity and 5 non-pathogenic point mutations have been described.

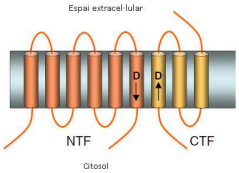

Figure 4. Presenilin strucure. Adapted from Wolfe, M. S.[9]

Effects[5,10]

- Change of the preferred cleavage position at site ε. There is a preference for the position 48. It can be due to a missense mutation that changes PSEN1 conformation and, therefore, there is an APP differential binding. In some cases, it can be caused by insertions or deletions.
- Changes in processing efficiency. There is a reduction: the $Aβ_{49}$ → $Aβ_{40}$ processing efficiency is 2-9% compared to the wild type protein and the $Aβ_{48}$ → $Aβ_{42}$ processing efficiency is 17-40% compared to the wild type.
- Proteolysis inhibition at site ε. The mutations reduce PSEN stability.
- 4th cleavage efficiency reduction. The mutations cause conformational changes in the active site and a premature release of $Aβ_{42}$ and $Aβ_{43}$ peptides.

The γ – secretasa complex

It comprises 4 subunits.

- Presenilin
- Nicastrin
- APH – 1
- Pen – 2

Genes related to Late Onset Alzheimer's Disease (LOAD)

APOE

It is located at 19q13.2 and codes for apoE protein. Its more important functions are lipid and Aβ transportation, cellular metabolism regulation and participation in the reparation of neuronal injuries caused by oxidative stress. It has 3 common variants (apoE2, apoE3 and apoE4) that differ in the amino acids of the positions 112 and 158 (figure 5). These variations affect apoE structure and its capacity to bind Aβ, among other effects[12].

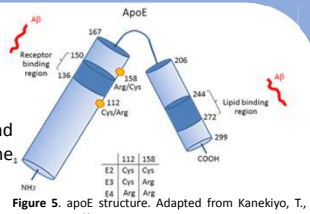

Figure 5. apoE structure. Adapted from Kanekiyo, T., Xu, H., Bu, G.[11].

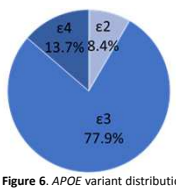

Figure 6. *APOE* variant distribution in general population

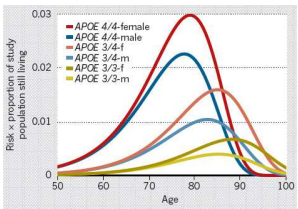

Figure 7. Risk of developing Alzheimer depending on age and genotype. From Spinney, L.[13]

The ε4 allele is a risk factor: its frequency among affected individuals is 40 – 50%, whilst in the general population it is 13.7% (figure 6).
Aβ levels and senile plaques charge depend on the allele. The risk depends on the genotype: 91% of ε4/ε4 individuals and 47% of ε4/ε- individuals, but only 20% of ε4 non-carrier individuals are affected (figure 7)[13].

Effects[6,11]

- Clearance of Aβ. Different ways: absorption and cellular degradation, transport across the blood – brain barrier or enzymatic degradation. The apoE4 – Aβ union is less efficient than apoE2/3 – Aβ union.
- Aggregation promotion. apoE and Aβ coaggregate. apoE4 might stabilize Aβ oligomers more than apoE3/2.
- Differential regulation of cholesterol levels → the cholesterol regulates the γ – secretase complex.
- Other mechanisms. Tau phosphorylation, synaptic function regulation, neuroinflammation and neurogenesis.

Conclusions

- **Study of the known genes and risk factors**. More investigation about these genes' influence mechanisms should be carried out in order to improve prevention, diagnosis and design new treatments.
- **Study of the unknown genes and risk factors**. Only 30-50% of EOAD cases are caused by identified mutations, and only 20% of the LOAD risk is explained by known factors. More investigation should be carried out to identify more genes and risk factors related to Alzheimer's Disease. That would also allow improvement in prevention, diagnosis and would open the door to new treatment strategies.

References

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