Genetics of Alzheimer’s Disease

Aina Feliu Cuberes

Introduction

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

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

Amyloid Precursor Protein (APP)

It is located at 21q11.2 and codes for a protein called APP (figure 2). APP undergoes proteolytic processing that results in Aβ formation (figure 3).

Steps:

1. APP (normal condition)
2. Aβ (binding to apoe-ε)
3. Aβ (transport across the blood–brain barrier)
4. Aβ (degradation by γ-secretase)

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

APOE

It is located at 19q13.2 and codes for apoE protein. Its important functions are lipid and Aβ transportation, cellular metabolism regulation and, therefore, there is an APP differential binding. In some cases, it can be caused by insertions or deletions.

Effects:

- Change of the preferred cleavage position at site ε: there is a preference for the Aβ42 production line.
- More efficient folding → faster aggregation. The mutations map in all the sequence of exons 16 and 17.

Additionally, 9 APOE duplicates 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 5). The active site is located between the domains 6 and 7.

Mutations

In PSEN1, 185 pathogenic, 1 of unclear pathogenicity and 4 non-pathogenic point mutations have been described. They cause 15-50% 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.

Presilin 1 (PSEN1)

It comprises 4 subunits: Presilin 1, 2, Nicasin, APH – 1, Pen – 2

Effects:

- 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 Aβ42/Aβ40 processing efficiency is 2–9% compared to the wild type protein and the Aβ42/Aβ43 processing efficiency is 14–40% compared to the wild type.
- Proteolytic inhibition at site ε. The mutations reduce PSEN stability.

The γ-secretase complex

It comprises 4 subunits: Presilin 1, 2, Nicasin, APH – 1, Pen – 2

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:

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Risk of developing Alzheimer depending on age and genotype. From Spinnler, L.14

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