

Practical guidelines for molecular testing in Alzheimer Dementia

Disease definition : Alzheimer disease is the most common form of dementia. Other genetic disorders characterised by dementia include Frontotemporal dementia, diffuse Lewy body disease, Huntington disease, Parkinson disease, and CADASIL.

Frequency : Dementia is the most common neurodegenerative disorder affecting more than 5 % of individuals over age 70 years and 25-45 % of those over 85.

Main clinical symptoms : Alzheimer disease typically starts with subtle memory loss, slowly progresses to severe dementia. Other findings include language disturbance, behavioral and psychiatric disturbances, seizures, and Parkinsonism.

Clinical diagnosis : Alzheimer disease is a clinical diagnosis based on the combination of progressive dementia and gross cerebral cortical atrophy on neuroimaging. Postmortem pathologic examination shows β -amyloid plaques, intraneuronal neurofibrillary tangles, and amyloid angiopathy.

Differential diagnosis : Other genetic disorders characterised by dementia include Frontotemporal dementia, Picks disease, diffuse Lewy body disease, Huntington disease, Parkinson disease, and CADASIL.

- **Frontotemporal dementia (including Picks disease)** : this disease generally affects the frontal and temporal cortex leading to behavioral changes, executive dysfunction, and language disturbances. The parietal cortex and basal ganglia may be affected as well, resulting in parkinsonism, cortical basal syndrome, and memory impairment. The disease progresses over a few years into profound dementia. Computed tomography (CT) or magnetic resonance imaging (MRI) may

show focal, often asymmetrical, atrophy in the frontal and/or temporal regions. Most monogenic forms are caused by autosomal dominant mutations in the MAPT or GRN genes, but in rare families mutations in additional genes, including VCP, CHMP2B or IFT74, have been described.

- **Frontotemporal dementia associated with MAPT mutations (FTD-17)** : Tau-positive neuronal intranuclear inclusions are found in the neocortex and striatum. About 5% of patients with Frontotemporal dementia have a MAPT mutation.
- **Frontotemporal dementia associated with GRN mutations (FTD-GRN)** : ubiquitin-positive (Tau-negative, alpha-synuclein-negative) "cat-eye" or lentiform-shaped neuronal intranuclear inclusions are found in the neocortex and striatum. About 5% of patients with Frontotemporal dementia have a GRN mutation.
- **Diffuse Lewy body dementia** : this is a neurodegenerative disorder characterized by dementia and parkinsonism, visual hallucinations, syncopal episodes, and sensitivity to neuroleptic medication. Lewy bodies are present. The disease can be caused by mutation in the alpha-synuclein (SNCA), the beta-synuclein (SNCB) gene, the prion protein gene (PRNP) or the LRRK2 gene.

Clinical classification :

- Late-onset: Alzheimer disease (95 %) : onset after age 65 years.
- Early-onset: Alzheimer disease (5 %) : onset before age 65 years.

Inheritance :

- Late-onset Alzheimer disease is a complex disorder that may involve multiple susceptibility genes, including APOE (association with e4 allele).
- Early-onset Alzheimer disease is inherited in an autosomal dominant manner in only a minority of cases (< 5 %).

Molecular testing :

- Late-onset Alzheimer disease : no diagnostic tests are advised as the predictive value of susceptibility genes, including APOE is too low to be useful in a clinical setting.
- Early-onset Alzheimer disease : Autosomal dominant Alzheimer disease represents less than 5 % of Alzheimer disease overall. Three nuclear genes PSEN1 (Presenilin-1), PSEN2 (Presenilin-2), APP (Amyloid) have been shown to be implicated. Whereas PSEN2 mutations are rare, PSEN1 occur in 20-70 % of autosomal dominant forms (< 5 % of all Alzheimer patients), and APP mutations in 10-15 % of autosomal dominant forms (< 1 % of all Alzheimer patients).

References

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Raux G. et al. Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update. *J Med Genet*. 2005; 10: 793-795.

Table 1. Different types of Alzheimer disease with the proportion of the respective gene, its size, price indication, and test advise

Type	Gene	Protein	Relative gene contribution	Number of Exons (AA)	Price indication (Euro)	Test Advise
Late-onset Alzheimer	No disease genes known, only risk factors					No test advised
Early-onset Alzheimer	PSEN1	Presenilin-1	20-70 %	12 exons (467 AA)	400	Test 1
	PSEN2	Presenilin-2	Rare	13 exons (448 AA)	400	No test advised
	APP	Amyloid beta A4 protein	10-15 %	18 exons (770 AA)	700	Test 2
Frontotemporal dementia	GRN	Granulin	5 %	18 exons (637 AA)	1300	Test 1
	MAPT	Microtubule-associated protein TAU	5 %	15 exons (776 AA)	1500	Test 2
Lewy body dementia	SNCA	Alpha-synuclein	?	6 exons (140 AA)	900	Test 1
	SNCB	Beta-synuclein	?	7 exons (134 AA)		No test advised
	PRNP	Prion	?	2 exons (253 AA)	450	No test advised
	LRRK2	Leucine-rich repeat kinase 2	?	51 exons (2527 AA)	3000	No test advised

