Five subtypes found under Alzheimer’s umbrella

Alzheimer’s disease has five distinct subtypes, say researchers, and these subtypes need different treatments.

A recent study has identified five molecular subtypes of Alzheimer’s disease (AD), and reveals that these subtypes are linked to different genetic risk factors and disease pathologies. Published in the journal ‘Nature Aging’, the research findings highlight the need for personalised medicine that will take this heterogeneity into account during diagnosis and treatment of the condition.

AD is a growing public health concern in Europe’s rapidly ageing population and already affects around 7 million people on the continent. It is the leading cause of dementia, characterised by a decline in memory, thinking, behaviour and the ability to perform everyday activities. Since there is currently no cure for AD, treatments focus on slowing disease progression and managing symptoms.

The answers in the proteins

Supported by the EU-funded EPAD, EPND, MIRIADE, and 3TR projects, researchers set out to explore the heterogeneity of AD, aided by proteomics. Proteomics is the study of the structure and composition of different proteins, how they interact with each other and the roles they play inside the body.
Using mass spectrometry proteomics, the team analysed the cerebrospinal fluid of 419 individuals with AD and 187 healthy controls. Of the AD cases, 107 showed normal cognition, 103 had mild cognitive impairment and 209 had dementia. A series of analyses led to the identification of 1 058 AD-related proteins, which – in conjunction with patients’ clinical characteristics – revealed five distinct subtypes of AD.

The alterations in the protein levels of the different AD subtypes pointed to distinct molecular processes. Subtype 1 was characterised by proteins related to neuronal hyperplasticity, subtype 2 by innate immune activation, subtype 3 by RNA dysregulation, subtype 4 by choroid plexus dysfunction and subtype 5 by blood–brain barrier impairment. Subtype 3 showed significantly more aggressive disease progression than the other four subtypes.

The team noted that each AD subtype was associated with distinct genetic risk factors, as well as different survival times and rates of disease progression. “Given the distinct patterns of molecular processes and AD genetic risk profiles, it is likely that AD subtypes will require specific treatments,” the researchers conclude. “For example, subtype 1 individuals may benefit from TREM2-activating treatments, subtype 2 from innate immune inhibitors, subtype 3 from antisense oligonucleotides that restore RNA processing, subtype 4 from inhibition of monocyte infiltration and subtype 5 from cerebrovascular treatments. At the same time, side effects arising from certain treatments may also depend on subtype. For example, while antibodies may more easily cross the blood–brain barrier in subtype 5, these individuals may be at increased risk for cerebral bleeding that can occur with antibody treatment. Future studies should aim to (re)analyze proteomics in clinical trial samples to test whether particular treatments have subtype-specific effects.”

The EPAD, EPND and 3TR projects are supported by the Innovative Medicines Initiative, a partnership between the European Union and the European pharmaceutical industry. EPAD (European Prevention of Alzheimer’s Dementia Consortium) ended in 2019. MIRIADE (Multi-omics Interdisciplinary Research Integration to Address DEmentia diagnosis) ends in 2024, and EPND (European platform for neurodegenerative disorders) and 3TR (Identification of the Molecular Mechanisms of non-response to Treatments, Relapses and Remission in Autoimmune, Inflammatory, and Allergic Conditions) in 2026.

For more information, please see:
EPAD project [↩]
EPND project website [↩]
MIRIADE project website [↩]
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Keywords

EPAD, EPND, MIRIADE, 3TR, Alzheimer’s disease, subtype, proteomics, dementia, protein

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