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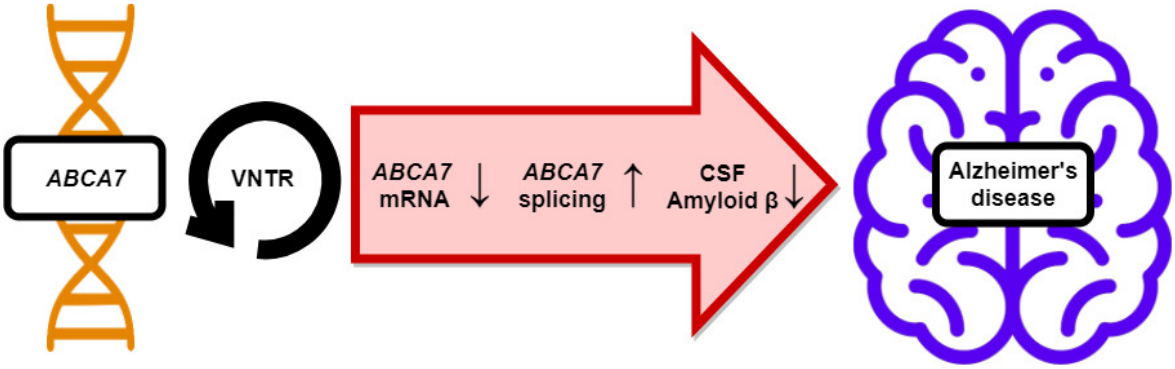
Repetitive DNA in the ABCA7 gene influences Alzheimer's disease

Dementia, which is characterized by decline of memory or other cognitive traits to the extent that a person's daily functioning is affected, is one of the most important global health challenges of our time. Approximately 50 million people suffer from this disorder and this number will multiply in the following decades due to a worldwide increasing life expectancy. Alzheimer's disease (AD) is the most common form of dementia and no cure is available. To find a therapy, we need a better understanding of the underlying disease-causing mechanisms.



We aim to identify the origins of Alzheimer's disease by studying our DNA and the genes embedded in it, which form the blueprint of life. Humans contain approximately 20,000 genes and in one of them, a gene termed "*ABCA7*", we identified repetitive elements. More precisely, we observed that highly similar DNA sequences in the middle of *ABCA7* varied from as few as twelve copies to more than 400 copies. This phenomenon is termed a variable number tandem repeat (VNTR). While this type of repetitive DNA variation is difficult to study with conventional methods, we were able to design an experimental assay to study length differences of the *ABCA7* VNTR in people with Alzheimer's and healthy elderly control individuals. This revealed that very long ("expanded") VNTR lengths were more prominent in patients than controls, and carrying such an expansion corresponded to a fourfold increase in risk to develop Alzheimer's disease.

We then further analyzed the biological consequences of varying *ABCA7* VNTR lengths. For this purpose we used immortalized blood cells extracted from people with Alzheimer's and healthy elderly control individuals for which we previously determined the VNTR length. Genes exert their function by transcription of the gene-DNA into messenger RNA (mRNA), which in turn can be translated into proteins. We observed that with increasing VNTR length, the amount of *ABCA7* mRNA went down. Furthermore, we saw that long VNTR lengths also led to more alternatively spliced *ABCA7* mRNA, hence a different protein is more preferentially formed. Overall both mechanisms lead to a reduction of canonical *ABCA7* gene product, which has previously been linked to Alzheimer's disease. Finally, by measuring amyloid β (a protein which plays a key role in AD) levels in cerebrospinal fluid (CSF, fluid found in the brain and spinal cord), we saw that long VNTR lengths lowered the concentration, hence further corroborating a role of the *ABCA7* VNTR in Alzheimer's disease.

In this study, we identified a new mutational mechanism for AD, and we demonstrate the importance of assessment of difficult repetitive DNA regions. We hope that these findings will eventually pave the way

towards a better Alzheimer's disease management, and that it will inspire researchers in other biological fields in their search for novel causes of disease.

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