Genetic and clinicopathological contribution of rare ABCA7 mutations in Belgian early-onset Alzheimer's disease patients.

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Abstract

Recent genetic studies suggested an important role for rare deleterious premature termination codon (PTC) mutations in *ABCA7* in early-onset Alzheimer's disease (EOAD). *ABCA7* was originally associated with late-onset Alzheimer's disease (AD) in genome-wide association studies. These *ABCA7* mutations are predicted to lead to a loss of functional protein, though their exact mode-of-action is still under investigation**.** The pathogenicity and segregation patterns of specific mutations - and possible modifiers thereof - are still poorly understood. We investigated the frequency of *ABCA7* PTC mutations in 734 Belgian EOAD patients (mean onset age 61.2±7.0 years) and the clinicopathological features of the mutation carriers. We identified 13 different *ABCA7* PTC mutations in 32 carriers (32/734, 4.36%). Carriers had a mean onset age of 61.7±5.9 (48-70) years. Clinical presentation was predominantly amnestic, except for one patient. No clear distinguishing features were present in the clinical neurological examination or ancillary investigations. A positive first-degree familial history was present in 73.7% (14/19). Neuropathological examination (n=5) showed hallmark AD lesions in 80% (4/5) combined with a pronounced cerebral amyloid angiopathy (CAA). In summary, PTC mutations in *ABCA7* are relatively frequent in Belgian EOAD patients, particularly in familial EOAD. Most carriers have a predominant amnestic presentation and their neuropathology shows AD hallmarks in combination with CAA. Continued identification and characterization of *ABCA7* mutations is necessary to allow implementation of *ABCA7* screening in clinical practice and genetic counseling. Also, *ABCA7* PTC carriers might represent an important genetic subtype of AD and more knowledge might improve genetic diagnosis, risk prediction and development of targeted therapeutics.

Keywords— *ATP-Binding Cassette Sub-Family A Member 7 (ABCA7), Alzheimer's disease, early-onset, loss-of-function*

Professional Biography

Liene Bossaerts completed her MSc in Biomedical Sciences at the University of Antwerp in 2016 and started a PhD in the Neurodegenerative Brain Disease Group of the Center for Molecular Neurology (VIB-University of Antwerp) led by Prof. Dr. Christine Van Broeckhoven in 2017.



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Any Comments:

N.A.