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Genetic modifiers of repeat expansions in *C9ORF72*

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Repeat expansions in chromosome 9 open reading frame 72 (*C9ORF72*) are currently the most frequent genetic cause of frontotemporal dementia (FTD) and motor neuron disease (MND). These devastating neurodegenerative diseases demonstrate considerable clinical heterogeneity, including variability in age at onset and disease duration. To identify genetic modifiers that may account for this heterogeneity, we selected potential modifiers based on literature, and assessed these candidates in more than 300 expansion carriers using Mass Array iPLEX and Taqman genotyping assays, in addition to fragment analysis with fluorescent-labeled primers and multiplex ligation-dependent probe amplification (MLPA) assays. Our studies revealed many interesting variants; for instance, we discovered that variants in transmembrane protein 106 B (*TMEM106B*) protect against developing FTD in *C9ORF72* expansion carriers. On the other hand, intermediate repeat lengths in ataxin-2 (*ATXN2*) may render *C9ORF72* expansion carriers more susceptible to the development of MND. We also identified genetic modifiers associated with age at onset and/or survival after onset, such as prion protein (PRNP), ubiquitin-associated protein 1 (*UBAP1*), progranulin (*GRN*), and elongator acetyltransferase complex subunit 3 (*ELP3*). Although these variants have previously been linked to FTD and/or MND, we are the first to describe their effects on the background of a pathogenic expansion in *C9ORF72*. Importantly, these variants represent promising targets for new therapeutic interventions and prognostic tests aiming at the FTD and MND spectrum.

Biography

Markavan Blitterswijk joined the Mayo Clinic in 2012 to investigate the role of *C9ORF72* in FTD and MND. She graduated at Utrecht University, Utrecht, The Netherlands, where she received her MD degree in 2008. Subsequently, she worked at Harvard Medical School, Boston, USA, and University of Massachusetts Medical School, Worcester, USA. She obtained her PhD degree at Utrecht University in 2012. She has already published more than 30 articles in the field of neuroscience, and she was appointed Assistant Professor of Neuroscience, Mayo Clinic College of Medicine, in 2014.

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