Rare variants in \(\beta\)-Amyloid precursor protein (APP) and Parkinson's disease.

Many individuals with Parkinson's disease (PD) develop cognitive deficits, and a phenotypic and molecular overlap between neurodegenerative diseases exists. We investigated the contribution of rare variants in seven genes of known relevance to dementias (\(\beta\)-amyloid precursor protein (APP), PSEN1/2, MAPT (microtubule-associated protein tau), fused in sarcoma (FUS), granulin (GRN) and TAR DNA-binding protein 43 (TDP-43)) to PD and PD plus dementia (PD+D) in a discovery sample of 376 individuals with PD and followed by the genotyping of 25 out of the 27 identified variants with a minor allele frequency (p.(E599K))) was significantly associated with the PD phenotype but was not found in either the PD cases or controls of an independent replication sample. One of the identified rare variants (c.2125G>A (p.(G709S))) shifted the A\(\beta\) spectrum from A\(\beta\)40 to A\(\beta\)39 and A\(\beta\)37. Although the precise mechanism remains to be elucidated, our data suggest a possible role for
APP in modifying the PD phenotype as well as a general contribution of genetic factors to the development of dementia in individuals with PD.