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Abstract

Background: Initially, ABCA7 was associated with Alzheimer’s disease (AD) in large genome-wide association studies. Targeted resequencing of ABCA7 suggested a role for rare premature termination codon (PTC) mutations. We observed loss of ABCA7 in PTC carriers, although with high variability due to differences in transcript rescue. Additionally, rare missense mutations are present in ABCA7 with unknown effect on the protein. We aimed to investigate the contribution of rare (MAF ≤ 1%) mutations or compound heterozygous mutations in ABCA7 in Belgian AD patient and control cohorts, as well as the effect of rare missense mutations on the subcellular localization of the protein.

Method: Targeted resequencing or whole exome sequencing of ABCA7 exons and splice sites in 1375 Belgian AD patients and 976 controls. We validated all rare, non-synonymous coding and splice mutations. Allele-specific PCR, haplotype sharing analysis and long-read sequencing to determine cis/trans configuration of compound heterozygous mutations. In vitro mutagenesis to introduce missense mutations of interest in an entry vector. Gateway cloning to generate wild type and mutant ABCA7 pCR3 expression vectors with a C-terminal EmGFP-tag. Transfection of HeLa and HEK293 cells for immunofluorescence microscopy to localize wild type versus mutant ABCA7.

Result: We identified rare mutations in 12.7% (175/1375) of the patients and in 7.8% (76/976) of the controls. We validated all rare, non-synonymous coding and splice mutations. Allele-specific PCR, haplotype sharing analysis and long-read sequencing to determine cis/trans configuration of compound heterozygous mutations. In vitro mutagenesis to introduce missense mutations of interest in an entry vector. Gateway cloning to generate wild type and mutant ABCA7 pCR3 expression vectors with a C-terminal EmGFP-tag. Transfection of HeLa and HEK293 cells for immunofluorescence microscopy to localize wild type versus mutant ABCA7.
**Conclusion:** We observed an enrichment in patients of rare single mutations and compound heterozygous mutations. In addition, *trans* compound heterozygous mutations might modify penetrance and pathogenicity. Functional studies of missense mutations are necessary to determine their potential pathogenic effect.