Deleterious ABCA7 mutations and transcript rescue mechanisms in early onset Alzheimer's disease.

Abstract:
Premature termination codon (PTC) mutations in the ATP-Binding Cassette, Sub-Family A, Member 7 gene (ABCA7) have recently been identified as intermediate-to-high penetrant risk factor for late-onset Alzheimer's disease (LOAD). High variability, however, is observed in downstream ABCA7 mRNA and
protein expression, disease penetrance, and onset age, indicative of unknown modifying factors. Here, we investigated the prevalence and disease penetrance of ABCA7 PTC mutations in a large early onset AD (EOAD)-control cohort, and examined the effect on transcript level with comprehensive third-generation long-read sequencing. We characterized the ABCA7 coding sequence with next-generation sequencing in 928 EOAD patients and 980 matched control individuals. With MetaSKAT rare variant association analysis, we observed a fivefold enrichment (p = 0.0004) of PTC mutations in EOAD patients (3%) versus controls (0.6%). Ten novel PTC mutations were only observed in patients, and PTC mutation carriers in general had an increased familial AD load. In addition, we observed nominal risk reducing trends for three common coding variants. Seven PTC mutations were further analyzed using targeted long-read cDNA sequencing on an Oxford Nanopore MinION platform. PTC-containing transcripts for each investigated PTC mutation were observed at varying proportion (5-41% of the total read count), implying incomplete nonsense-mediated mRNA decay (NMD). Furthermore, we distinguished and phased several previously unknown alternative splicing events (up to 30% of transcripts). In conjunction with PTC mutations, several of these novel ABCA7 isoforms have the potential to rescue deleterious PTC effects. In conclusion, ABCA7 PTC mutations play a substantial role in EOAD, warranting genetic screening of ABCA7 in genetically unexplained patients. Long-read cDNA sequencing revealed both varying degrees of NMD and transcript-modifying events, which may influence ABCA7 dosage, disease severity, and may create opportunities for therapeutic interventions in AD.