UKE Paper of the Month Mai 2023

Resilience to autosomal dominant Alzheimer's disease in a Reelin-COLBOS heterozygous man

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ABSTRACT:

We characterized the world's second case with ascertained extreme resilience to autosomal dominant Alzheimer's disease (ADAD). Side-by-side comparisons of this male case and the previously reported female case with ADAD homozygote for the APOE3 Christchurch (APOECh) variant allowed us to discern common features. The male remained cognitively intact until 67 years of age despite carrying a PSEN1-E280A mutation. Like the APOECh carrier, he had extremely elevated amyloid plaque burden and limited entorhinal Tau tangle burden. He did not carry the APOECh variant but was heterozygous for a rare variant in RELN (H3447R, termed COLBOS after the Colombia-Boston biomarker research study), a ligand that like apolipoprotein E binds to the VLDLr and APOEr2 receptors. RELN-COLBOS is a gain-of-function variant showing stronger ability to activate its canonical protein target Dab1 and reduce human Tau phosphorylation in a knockin mouse. A genetic variant in a case protected from ADAD suggests a role for RELN signaling in resilience to dementia.

STATEMENT:

This is a full case report from the clinical to the detailed neuropathological study of the second case in history to be protected from hereditary Alzheimer's disease (AD). In collaboration with our colleagues in the US and in Colombia we were able to identify that this man carried a novel mutation in the Reelin gene and was protected from cognitive impairment for more than 25 years. Post-mortem studies, all conducted here at UKE, showed that from a pathological perspective this patient was severely affected from Alzheimer's pathology according to all current criteria. A more thorough and detailed study of this brain showed that neurons in the entorhinal cortex of the patient were more numerous than in the other protected cases previously reported also by us, in other familial AD cases, and in other sporadic AD cases of similar age. We further validated the mutation protective mechanism, modulating tau pathology, in a mutated tau knock in mouse model crossbred with mice carrying the protective Reelin mutation. All together these findings not only suggest possible therapeutic strategies against AD via Reelin downstream pathways, but also questions the current paradigm of Alzheimer's disease etiopathology given that just by protecting a small subset of neurons the dementia was delayed more than two decades in a patient predetermined to suffer from it. This paper currently holds an Altmetric score of 1739 placing it in the top 1% of all Nature Medicine papers ever tracked by Altmetric. It has generated more than 200 news stories worldwide, 800 tweets, and it has been accessed more than 55000 times in Nature Medicine's webpage. .

BACKGROUND:

This work was performed at the Institute of Neuropathology in the group of Dr. med Diego Sepulveda-Falla, an independent group leader at UKE since 2018. It was part of the PhD thesis of M.Sc. Nelson Villalba-Moreno, and funded by the NIH grant RF1 NS110048, the BMBF grant UndoAD, grant funding by the Werner Otto Stiftung, and a generous donation by Open Philantropy / Good Ventures. Dr. Sepulveda-Falla's group is focused on the study of familial Alzheimer's disease using classical neuropathology and high throughput morphological and molecular analyses, to identify the causes underlying disease heterogeneity and protection in familial Alzheimer's. The work was possible by close collaboration to Drs. Susanne Krasemann and Prof. Dr. Markus Glatzel at the Institute of Neuropathology at UKE, Prof. Dr. Francisco Lopera at the University of Antioquia in Medellín, Colombia, and Drs. Yakeel T. Quiroz and Joseph Arboleda-Velzasquez at Harvard University in Boston, USA