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World Congress on

Dementia, Alzheimer's, Parkinson's & Neurodegenerative Disorders

July 09-10, 2026 | Frankfurt, Germany

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Chr17q21.31 locus risk haplotype H1 susceptibility to Ferroptosis is mediated by the endolysosomal system

GWAS consistently identifies chr:17q21.31 locus H1 haplotype as a major risk factor for a wide spectrum of neurodegenerative diseases (NDs), including AD, PD, PSP & ALS. Despite the strong genetic association, functional experimental evidence linking the H1 haplotype with NDs related molecular signatures was missing. Chr:17q21.31 is a complex genomic locus harboring several genes, including MAPT, thousands of SNPs, an inversion polymorphism, and structural variants under strong linkage disequilibrium (LD), giving rise to two major haplotypes, the H1 and H2. In a Genome - Environment Interaction study with iPSC-derived neurons, we observed an increased susceptibility of the H1 haplotype to Mild Chronic Oxidative Stress. The sensitivity was manifested as extensive signs of axonal degeneration in the form of blebs/swellings due to microtubbule (MT)-unbundling, followed by neuronal death that progressed and spread in a wave-like manner, mimicking the pathophysiology of NDs. Drug screening and Cell Painting assay showed that the neuronal death observed earlier in the H1 versus the H2 haplotype was via the iron-dependent lipid oxidation-mediated ferroptosis, while RNA-Seq and longitudinal assays revealed the differential reactive oxygen species and lysosomal biogenesis between the two haplotypes. We conclude that the increased susceptibility of the H1 haplotype to ferroptosis is attributable to SNPs and variants in LD on functionally related genes clustered within the locus. It is anticipated that an altered endolysosomal clearance pathway in the H1 genetic background, in conjunction with other risk variants causing protein misfolding and aggregates, will exaggerate the causality of risk genes, explaining the increased association of the locus in genomic studies.

Keywords: Drugs-screening, chronic oxidative-stress, cell-painting, lysosomes, MT-unbundling

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Biography

Dr. Eldem Sadikoglou is a senior research technician in Genome Biology of Neurodegenerative Diseases (NDs) at DZNE-Tübingen. Her research focuses on the genome-environment intersection of NDs. Dr. Sadikoglou employs among others, high-throughput screening and longitudinal imaging assays to monitor neuronal resillience in real-time. Previously, she received her PhD from DUTH in Greece, where she investigated the DNA-binding properties of a neurodevelopmental transcription factor. Her current work is focused on identifying specific genetic alleles that confer resillience to NDs.

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