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## BASIC SCIENCE AND PATHOGENESIS



POSTER PRESENTATION

# MOLECULAR AND CELL BIOLOGY

# ABCA7-dependent Neuropeptide-Y signalling is a resilience mechanism required for synaptic integrity in Alzheimer's disease

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### Abstract

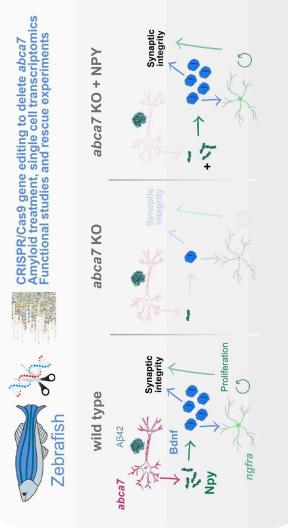
Background: Genetic variations have emerged as crucial players in the etiology of Alzheimer's disease (AD), and they serve for a better understanding of the disease mechanisms; yet the specific roles of these genetic variants remain uncertain. Animal models with reminiscent disease pathology could uncover previously uncharacterized roles of these genes. Therefore, we generated zebrafish models for AD variants to analyze the in depth molecular and biological functions of these variants.

Method: Using CRISPR/Cas9, we generated a knockout model for abca7, orthologous to human ABCA7. We performed single cell transcriptomics and analyzed the altered genes and molecular pathways in zebrafish. We leveraged data from multiethnic AD cohorts at Mayo Clinic and Columbia University, to perform genetic association studies, co-expression analyses, in silico interaction mapping, family based variant segregation analyses and epigenetic association studies, and the functional and histological studies in zebrafish.

Result: The abca7<sup>±</sup> zebrafish reduced astroglial proliferation, synaptic integrity, and microglial response after Aβ42 toxicity. We found that the abca7 loss-of-function (LOF) reduced neuropeptide Y (npy) expression as well as Brain-derived neurotrophic factor (bdnf) and Nerve growth factor receptor (ngfr). Human brain analysis showed reduced NPY in AD, regulatory interaction between NPY and BDNF, genetic variants in NPY associated with AD, and segregation of variants in ABCA7, BDNF and NGFR in families. ABCA7 variants altered the epigenetic codes in NPY, BDNF, and NGFR promoter regions. Human results paralleled with zebrafish findings to indicate an evolutionarily conserved disease mechanism through ABCA7-NPY signalling axis. NPY administration to zebrafish rescued the phenotypes in abca7 knockout, suggesting a true biological relevance.

Conclusion: Our results demonstrate a previously unknown link between ABCA7 and NPY in regulation of synaptic integrity and neurogenesis in AD. We propose that ABCA7-dependent NPY is a resilience factor in vertebrate brains, and this reserve mechanism is impaired in AD.

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Genetic association, co-expression, segregation, epigenetic regulation, in silico interaction and disease association studies in different large multiethnic cohorts (EFIGA, NIA-LOAD, New York Brain Bank, ADNI, Mayo Clinic, MSBB, ROSMAP)

# Immunohistochemistry and transcriptomics

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Segregation in families

Gene co-expression network analyses















NPY and BDNF variants segregate in families with AD with high CADD score





neurons

Reduced ABCA7 and NPY associates with higher Braak stage and NGFR expression Association with Braak stage

ABCA7-dependent NPY signaling maintains synaptic integrity and is impaired in Alzheimer's disease