PMG-AD

Personalized medicine approach for novel microglia-associated genetic variants in Alzheimer's disease

The role of inflammation and innate immune system in Alzheimer's disease (AD) has been recently emphasized as GWAS and WES studies as well as functional studies have identified several AD-associated genes, including TREM2, ABI3, and PLCG2 that are expressed selectively or preferentially in microglia in the brain. These genetic and functional findings highlight an essential role for the innate immune system in the onset and progression of AD and thus provide also novel biomarker and therapeutic prospects for precision medicine applications.

The goal in the PMG-AD project is to establish a personalized medicine-based approach for identification of early biomarkers and therapeutic targets in AD by focusing on novel AD-associated genetic variants in ABI3 (S209F; risk variant) and PLCG2 (P522R; protective variant) genes. ABI3 and PLCG2 are preferentially expressed in microglia, reinforcing the idea that microglia-mediated innate immune response directly contributes to the development of AD. Thus, the rationale in PMG-AD is that the protein-altering changes in ABI3 and PLCG2 represent the extreme ends in the genotype-phenotype spectrum with respect to microglia functions in AD.

The two main missions are:

1) To characterize the microglia-specific mechanism(s) of ABI3 and PLCG2 variants in molecular, cellular, and behavioral processes relevant for AD in already generated Abi3-S209F and Plcg2-P522R knock-in mouse models crossed with transgenic AD mouse model as well as in human induced pluripotent stem cell -derived microglia cells from genetically defined ABI3 and PLCG2 individuals.

2) To discover novel biomarker targets by using omics-based (global RNA-Seq and proteomics) approaches in combination with bioinformatics to analyze human monocyte-derived microglia from cognitively normal, aged individuals carrying ABI3 and PLCG2 variants. In addition, the same genetically defined individuals will undergo PET brain imaging, in which the focus is set on changes in microglial activity. It is expected that identified biomarker and therapeutic targets in PMG-AD will provide a frame for the development of novel diagnostic and treatment modalities, which will lay the foundation for monitoring therapy-related outcome measures and disease progression of AD in a personalized manner.

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