HLA-DRB1

To determine the influence of HLA-DRB1*1501 on long-term disease course in a homogeneous cohort of clinically isolated syndrome (CIS) patients.

Methods: One hundred seven patients underwent clinical and MRI assessment at the time of CIS and after 1, 3, 5 and 15 years. HLA-DRB1*1501 status was determined using Sanger sequencing and tagging of the rs3135388 polymorphism. Linear/Poisson mixed-effects models were used to investigate rates of change in EDSS and MRI measures based on HLA-DRB1*1501 status.

Results: HLA-DRB1*1501 -positive (n = 52) patients showed a faster rate of disability worsening compared with the HLA-DRB1*1501 -negative (n = 55) patients (annualised change in EDSS 0.14/year vs. 0.08/year, $p < 0.025$), and a greater annualised change in T2 lesion volume (adjusted difference 0.45 mL/year, $p < 0.025$), a higher number of gadolinium-enhancing lesions, and a faster rate of brain (adjusted difference -0.12%/year, $p < 0.05$) and spinal cord atrophy (adjusted difference -0.22 mm2/year, $p < 0.05$).

Interpretation: These findings provide evidence that the HLA-DRB1*1501 allele plays a role in MS severity, as measured by long-term disability worsening and a greater extent of inflammatory disease activity and tissue loss. HLA-DRB1*1501 may provide useful information when considering prognosis and treatment decisions in early relapse-onset MS [1)].

Neuroinflammation commences decades before Alzheimer's disease (AD) clinical onset and represents one of the earliest pathomechanistic alterations throughout the AD continuum. Large-scale genome-wide association studies point out several genetic variants-TREM2, CD33, PILRA, CR1, MS4A, CLU, ABCA7, EPHA1, and HLA-DRB5-HLA-DRB1-potentially linked to neuroinflammation. Most of these genes are involved in proinflammatory intracellular signaling, cytokines/interleukins/cell turnover, synaptic activity, lipid metabolism, and vesicle trafficking. Proteomic studies indicate that a plethora of interconnected aberrant molecular pathways, set off and perpetuated by TNF-α, TGF-β, IL-1β, and the receptor protein TREM2, are involved in neuroinflammation. Microglia and astrocytes are key cellular drivers and regulators of neuroinflammation. Under physiological conditions, they are important for neurotransmission and synaptic homeostasis. In AD, there is a turning point throughout its pathophysiological evolution where glial cells sustain an overexpressed inflammatory response that synergizes with amyloid-β and tau accumulation, and drives synaptotoxicity and neurodegeneration in a self-reinforcing manner. Despite a strong therapeutic rationale, previous clinical trials investigating compounds with anti-inflammatory properties, including non-steroidal anti-inflammatory drugs (NSAIDs), did not achieve primary efficacy endpoints. It is conceivable that study design issues, including the lack of diagnostic accuracy and biomarkers for target population identification and proof of mechanism, may partially explain the negative outcomes. However, a recent meta-analysis indicates a potential biological effect of NSAIDs. In this regard, candidate fluid biomarkers of neuroinflammation are under analytical/clinical validation, i.e., TREM2, IL-1β, MCP-1, IL-6, TNF-α receptor complexes, TGF-β, and YKL-40. PET radio-ligands are investigated to accomplish in vivo and longitudinal regional exploration of neuroinflammation. Biomarkers tracking different molecular pathways (body fluid matrixes) along with brain neuroinflammatory endophenotypes (neuroimaging markers), can untangle temporal-spatial dynamics between neuroinflammation and other AD pathophysiological mechanisms. Robust biomarker-drug codevelopment pipelines are expected to enrich large-scale clinical trials testing new-generation compounds active, directly or indirectly, on neuroinflammatory targets and displaying putative disease-modifying effects: novel

NSAIDs, AL002 (anti-TREM2 antibody), anti-Aβ protofibrils (BAN2401), and AL003 (anti-CD33 antibody). As a next step, taking advantage of breakthrough and multimodal techniques coupled with a systems biology approach is the path to pursue for developing individualized therapeutic strategies targeting neuroinflammation under the framework of precision medicine [2].

1)

Brownlee WJ, Tur C, Manole A, Eshaghi A, Prados F, Miszkiel KA, Wheeler-Kingshott CAG, Houlden H, Ciccarelli O. HLA-DRB1*1501 influences long-term disability progression and tissue damage on MRI in relapse-onset multiple sclerosis. Mult Scler. 2022 Nov 18:13524585221130941. doi: 10.1177/13524585221130941. Epub ahead of print. PMID: 36398585.

2)

Hampel H, Caraci F, Cuello AC, et al. A Path Toward Precision Medicine for Neuroinflammatory Mechanisms in Alzheimer's Disease. Front Immunol. 2020;11:456. Published 2020 Mar 31. doi:10.3389/fimmu.2020.00456