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## Protective Association of HLA-DRB1\*04 Subtypes in Neurodegenerative Diseases Implicates Acetylated Tau PHF6 Sequences

Guo Luo, Yann Le Guen, Adityasai Ambati, Selina Yogeshwar, Vicente Peris-Sempere, Jean-Charles Lambert, Michael Greicius, Emmanuel Mignot, AD/PD Collaborators

### Objective

To explore genetic association between human leukocyte antigen (HLA) and neurodegenerative diseases and investigate mechanisms behind the association.

### Background

Pathophysiology of Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) involves accumulation of tau (neurofibrillary tangles) and amyloid- $\beta$ -rich (amyloid plaques) aggregates in AD,  $\alpha$ -synuclein-rich aggregates (Lewy bodies) in PD and TDP-43 aggregates in ALS, although these aggregates may also co-occur. Likewise, consensus is growing that tau may play a key role in PD and ALS as well.

### Design/Methods

We analyzed HLA associations in ~176,000 individuals with PD or AD versus controls across ancestry groups. Pursuing this, we also compared postmortem brain density of neurofibrillary tangles and amyloid plaques in brain, tau and A $\beta$ 42 levels in cerebrospinal fluid (CSF) of ~8,000 individuals (controls and AD), and examined association of HLA in ~2,500 patient with pathologically demonstrated Lewy Body Dementia. This was followed by HLA binding and tetramer T cell studies.

### Results

A shared genetic association was observed across AD and PD at rs601945 (PD: odds ratio (OR) = 0.84; 95% confidence interval, [0.80; 0.88];  $p = 2.2 \times 10^{-13}$ ; AD: OR = 0.91[0.89; 0.93];  $p = 1.8 \times 10^{-22}$ ) and with a protective HLA association recently reported in ALS. Hierarchical protective effects of HLA-DRB1\*04 subtypes best accounted for the association, strongest with HLA-DRB1\*04:04 and HLA-DRB1\*04:07, intermediary with HLA-DRB1\*04:01 and HLA-DRB1\*04:03 and absent for HLA-DRB1\*04:05. The same signal was associated with decreased neurofibrillary tangle (but not neuritic plaque) density postmortem and was more associated with lower tau levels than A $\beta$ 42 level changes in CSF. Furthermore, protective HLA-DRB1\*04 subtypes strongly bound the aggregation-prone tau PHF6 sequence, but only when acetylated at K311, a modification central to aggregation. T cells recognizing this epitope were identified, showing relevance of this immune response in patients with neurodegenerative disorders.

### Conclusions

An HLA-DRB1\*04-mediated adaptive immune response, potentially against tau, decreases PD, AD and ALS risk, offering the possibility of new therapeutic avenues.

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## Real-World Resource Utilization and Productivity Loss Among Patients With Myasthenia Gravis in Sweden: A Nationwide Population-Based Study

Qiaoyi Zhang, Qian Cai, Nurgul Batyrbekova, Lilla Di Scala, Shane Kavanagh

### Objective

To assess annual healthcare resource utilization including inpatient admission and outpatient visits, employment status, and sickness absence associated with myasthenia gravis (MG).

### Background

MG is a rare, chronic and debilitating autoimmune neuromuscular disease characterized by muscle weakness and fatigue that leads to hallmark symptoms including ptosis, dysphagia, dyspnea and limb weakness. Nearly 10% of patients are estimated to have treatment-refractory MG.

### Design/Methods

Data were linked from four longitudinal nationwide population-based registries in Sweden. Patients with = 1 diagnosis of MG (ICD-10 G70.0) from 01/01/2001 to 12/30/2017 were selected. Date of 1st MG diagnosis in the national patient register was designated as index date. The healthcare resource use, employment status, and sickness absence for all cause and associated with MG within 1-year post-index period were evaluated.

### Results

A total of 4,339 patients with newly diagnosed MG were identified from 2001 and 2017. Mean ( $\pm$ SD) age at index date was 59.8 ( $\pm$ 19.5) years; 54% were female. During the first year post-MG diagnosis, 50.6% of patients had = 1 MG-related inpatient admission and 23.6% spent >1 month as an inpatient. Most patients (89.3%,  $n = 3,875$ ) had = 1 specialist visits for MG and 16.1% had >5 visits during 1-year post-index period. 58.9% of patients had = 1 all-cause inpatient admission and 97.5% of patients used = 1 outpatient specialist services in the same period. Among patients of working age with =1-year follow-up ( $n = 2,006$ ), 37.3% of them were not employed; among those in employment ( $n = 1,250$ ), 44.6% reported = 1 sickness absences within 1-year post-index period.

### Conclusions

Patients with MG require considerable care both for MG and comorbidities over a period of years. An important sub-population of patients (e.g., those with MG crisis) may be the intensive users of both inpatient and outpatient care. Future research needs to detail treatment pattern and outcomes in this population.

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## Anti-myelin Oligodendrocyte Glycoprotein Antibody-Associated Disorder (MOGAD) in a Pediatric Patient with Rare Presentation of a Cerebellar Tumefactive Lesion

Avni Sanghi, Grace Gombolay, Tuba Khan

### Objective

NA.

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