Dr. Garg has received intellectual property interests from a discovery or technology relating to health care. Dr. Garg has received intellectual property interests from a discovery or technology relating to health care.

## Rank Wise Effect of HLA-DQ5 Explains Risk for the Development of Anti-IgLON5 Disease

Selina Yogeshwar, Vicente Peris-Sempere, Sergio Muñiz-Castrillo, Guo Luo, Carsten Finke, Jerome Honnorat, Emmanuel Mignot, Anti-IgLON5 Disease Collaborators

### Objective

To better characterize the genetic association between human leukocyte antigen (HLA) and anti-IgLON5 disease and to explore auto-antigen binding to associated HLA molecules and their functional involvement in pathophysiology.

### Background

Anti-IgLON5 disease is a rare, but likely underdiagnosed type of autoantibody encephalitis with a heterogeneous clinical phenotype, including sleep, movement and brainstem dysfunction. Its pathophysiology remains elusive, although dominant association with HLA-DRB1*10:01-DQB1*05:01 strongly supports an autoimmune basis.

### Design/Methods

A multicentric cohort of 62 patients and 433 controls matched by principal component analysis was included. Genome-wide association analysis was performed with 4-digit resolution HLA imputation and selected 8-digit resolution validation typing. A generalized logistic model was used to determine the association with individual alleles and haplotype counts to establish haplotype associations. Furthermore, we computationally predicted binding of IgLON5-derived peptides to risk-associated HLA-molecules.

### Results

Our results indicate a rank wise effect of HLA-DQA1*01:05~DQB1*05:01 (heterozygotes: OR 46.6), HLA-DQA1*01:01~DQB1*05:01 (homozygotes: OR 26.9; heterozygotes: OR 2.5) and HLA-DQA1*01:04~DQB1*05:03 (homozygotes: OR 30.9; heterozygotes: OR 5.6), in order of descending relative risk predisposition. Differences between encoded heterodimers are minimal (a few amino acids outside the main HLA sequence binding region), suggesting a common function. Computational binding predictions support similar, high binding affinity for IgLON5275-283 in a post-translationally modified (N-deglycosylated) form by all three of these HLA-DQ molecules and other common binders. In contrast, association analysis suggests that effects of HLA-DR are likely explained by linkage disequilibrium.

### Conclusions

This study is the, so far, largest genetic study on anti-IgLON5 disease. Our results strongly suggest HLA-DQ over HLA-DR association, with higher reactivity against post-translationally modified versus physiological peptides, in line with reduced T cell priming against these epitopes. Further studies should address the functional implications of these HLA associations.

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## Cohort Study of Autoimmune Encephalitis (AIE) in Pediatric and Adult Population from India-A Single Tertiary Centre Experience

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### Objective

Study and compare clinico-epidemiological data and long-term outcomes in pediatric (<18 yrs) and adult AIE patients based on serostatus.

### Background

India is a burgeoning hub for autoimmune diseases. Studies on AIE comparing seropositive and seronegative outcomes in pediatric and adult population are lacking. We highlight age and serostatus specific approach in low resource country settings.

### Design/Methods

Retro-prospective study from Narayana Institute of Neurosciences, Bangalore (2016-2021) included AIE patients as per Autoimmune Encephalitis International Working Group and Autoimmune Encephalitis Alliance Clinicians Network. Serum and CSF autoimmune encephalitis panels, CSF meningitis panel was incorporated to exclude infections and other demyelinating disorders. With phone calls and outpatient follow ups (1-4 yrs), results were statistically analyzed and compared based on age and serostatus.

### Results

Adult AIE was commoner than pediatric (75% vs 25%,n = 60) and seronegative than seropositive (56.7% vs43.3%) with overall male preponderance. NMDAR (11.7%), MOG (8.3%), LGI1 and GAD65 (5% each) were common antibodies (MOG commoner than NMDAR in children; NMDAR, LGI1 and GAD 65 equally predominant in adults). Common presentations included seizures (75%) and memory disturbances (66.7%) independent of serostatus. There were no differences in MRI and EEG parameters based on age or serostatus. Methylprednisolone mono-therapy (46.6%) was multitude than add on rescue immunosuppressants [IVIG (28.3%),rituximab (10%), PLEX & cyclophosphamide (3.3% each)]. Pediatric age, specific antibodies, status epilepticus and dysautonomia were markers requiring aggressive immunotherapy. Oral steroids (61.7%),mycophenolate (8.3%)and azathioprine (6.7%) were maintenance immunosuppressants. 10% patients (mostly seropositive) had poor outcome with Modified Rankin Scale (MRS) >3. Deaths (all adults) though rare was slightly preponderant in seronegative type owing to lack of consent for aggressive immunosuppression. Clinical relapse was noted in 10% (mostly seropositive). 86% patients were weaned off maintenance immunosuppression (earlier in seronegative).

### Conclusions

Seronegative and pediatric AIE had better long term outcomes. Methylprednisolone mono-therapy is efficacious in majority of the cases when started early. Early recognition and aggressive management in high risk groups has pivotal role. Further multi-centric studies are needed to confirm these findings.

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