A Genetic Disposition for Autoimmune Encephalitis: Searching for Human Leukocyte Antigen (HLA) Complex Subtypes

Anti-LGI1 Encephalitis Is Strongly Associated With HLA-DR7 and HLA-DRB4

van Sonderen A, Roelen DL, Stoop JA, Verdijk RM, Haasnoot GW, Thijs RD; Wirtz PW, Schreurs MW, Claas FH, Sillevis Smitt PA, Titulaer MJ. Ann Neurol 2017;81(2):193–198.

Leucine-rich glioma-inactivated1 (LGI1)-encephalitis is an antibody-associated inflammation of the limbic area. An autoimmune etiology is suspected but not proven yet. We performed HLA-analysis in 25 non-tumor anti-LGI1 patients and discovered a remarkably strong HLA-association. HLA-DR7 was present in 88% compared to 19.6% in healthy controls (p=4.1*10-11). HLA-DRB4 was present in all patients and in 46.5% controls (p=1.19*10-7). These findings support the autoimmune hypothesis. An exploratory analysis was performed in a small group of four tumor-LGI1 patients. The strong HLA association seems not applicable in these patients. Therefore, the absence of HLA-DR7 or HLA-DRB4 could raise tumor suspicion in anti-LGI1 patients.

Anti-LGL1 Encephalitis Is Associated With Unique HLA Subtypes

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OBJECTIVE: Autoimmune encephalitis, represented by anti-leucine-rich glioma-inactivated 1 (anti-LGI1) and anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, has increasing clinical significance based on recent discoveries of neuronal autoantibodies. However, its immunopathogenesis is not fully understood. Here, we investigated whether autoimmune encephalitis is associated with the human leukocyte antigen (HLA) subtypes. METHODS:We compared the HLA genotypes of 11 anti-LGI1 and 17 anti-NMDAR encephalitis patients to the control groups, which consisted of 210 epilepsy patients and 485 healthy Koreans. RESULTS: Anti-LGI1 encephalitis was associated with the DRB1*07:01-DQB1*02:02 haplotype (10 patients, 91%) in HLA Class II genes, as well as with B*44:03 (8 patients, 73%) and C*07:06 (7 patients, 64%) in the HLA Class I region. The prevalence of these alleles in anti-LGI1 encephalitis was significantly higher than that in the epilepsy controls or healthy controls. By contrast, anti-NMDAR encephalitis was not associated with HLA genotypes. Additional analysis using HLA-peptide binding prediction algorithms and computational docking underpinned the close relationship. INTERPRETATION: This finding suggests that most anti-LGI1 encephalitis develops in a population with specific HLA subtypes, providing insight into a novel disease mechanism.

Commentary

Leucine-rich glioma inactivated 1 protein (LGI1) encephalitis is a well-described autoimmune syndrome associated with typical faciobrachial dystonic seizures and limbic encephalitis (1). Faciobrachial seizures only last seconds and consist of unilateral, involuntary contractions of the face and arm that may occur dozens of times a day. There has been some discussion about whether faciobrachial seizures are true epileptic events or a movement disorder (2), but patients also have autonomic and tonic-clonic seizures, which confirms an epileptic etiology. Cognitive symptoms occur in 95% of patients, mainly affecting spatial function and memory (3). MRI may show limbic encephalitis, and routine CSF studies are usually normal. LGI1 antibodies are pathognomonic and considered pathogenic for the disease. Pulsed steroids improve seizures but not necessarily memory outcomes (4). LGI1 antibodies are directed at a membrane surface antigen that is part of the voltage-gated potassium channel (VGKC) complex. CASPAR2 antibodies are also directed against a subdomain of the VGKC complex but produce a different clinical syndrome without typical seizures and with a more varied clinical picture of limbic encephalitis,

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cerebellar ataxia, and peripheral nervous system involvement (3, 4). LGI1 encephalitis responds well to steroids and other immunosuppressive agents, although clear treatment strategies have yet to be defined (3). Autoimmune encephalitis and associated antibodies have only recently been described, and the underlying pathophysiology is not completely understood (1).

In the same issue of the *Annals of Neurology* two independent groups describe an association of LGI1 encephalitis with unique human leukocyte antigen (HLA) subtypes in two separate publications. They both find an association with the HLA-DRB1*07 (HLA-DR7) gene. Van Sonderen et al. finds this association in a Dutch population and Kim et al., in a Korean population.

HLA encodes the major histocompatibility complex (MHC) that is responsible for T-cell mediated immune responses. MHC Class I is responsible for the cytotoxic T-cell response mediated by CD 8+ cells and MHC Class II is responsible for the antibody mediated immune responses involving CD4+ T-cells and resulting in a B-cell activation. As LGI1 encephalitis is considered antibody mediated, an association with HLA genes encoding MHC Class II seems more likely than HLA genes encoding MHC Class I.

The Korean Study by Kim et al., compares LGI1 patients to healthy controls, a control epilepsy cohort, and patients with NMDA receptor encephalitis. Only the epilepsy cohort and the NMDA receptor patients were genotyped by the same method as the LGI1 patients. The healthy controls were genotyped with a lower resolution method. In addition, they confirmed their findings using a computational in silico method to predict connections and affinity between HLA-DR7 and target sequences of the LGI1 protein. The computational docking done to predict HLA-LGI1 binding and identify the target sequence in the LGI1 protein N-terminus is impressive.

They find that HLA-DR7 is neither associated with typical epilepsy control populations nor NMDA receptor encephalitis and concluded that the HLA DR7 association is specific to LGI1. The authors did not find a specific HLA type that correlated with NMDA receptor encephalitis in their cohort. Does that mean NMDA receptor encephalitis is not associated with a specific genetic subtype or have we just been unable to identify it so far? Is NMDA receptor encephalitis a fundamentally different disease compared with LGI-1 encephalitis despite both being associated with limbic encephalitis and a paraneoplastic antibody? Clinically, both seem to be distinct entities.

The Dutch study by van Sonderen et al., compares HLA genes in LGI1 patients to normal controls and compares patients with LGI1 with and without tumor association. In their cohort only patients with nontumoral LGI1 encephalitis had a clear association with HLA DR7. The four patients with tumor-associated LGI1 did not have a definite HLA DR7 association. The authors suggest that HLA-DR7 negativity in patients with LGI1 encephalitis should prompt an extensive search for tumors; however, their tumor-associated population is very small. A similar association has been described in Lambert-Eaton myasthenic syndrome (LEMS). An HLA association with HLA-B8-DR3-DQ2 has only been found in nontumor LEMS, not in tumoral LEMS (5).

In the Korean population, the specific haplotype DRB1*07:01–DQB1*02:02 is more commonly expressed than in other populations as it was present in 9% in the epilepsy controls and 12% in the healthy controls, which could confound results. However, the Dutch study confirms their findings, as they find the same association in a Dutch population.

Discoveries like the association of HLA subtype with certain diseases help us greatly in understanding the underlying pathophysiology. It could inform future treatments that interfere with certain pathophysiological processes in the disease. However, what does the aforementioned HLA association mean for clinical practice?

HLA associations for other neurologic diseases, such as multiple sclerosis or myasthenia gravis, have been described, but the association between HLA types and clinical presentation is not always entirely established (6). It would be of great interest to know whether different clinical subtypes of LGI-1 encephalitis correlate with specific HLA subtypes.

In nonneurologic diseases, such as sacroiliac arthritis, HLA testing can assist with making an early diagnosis before joint destruction occurs. It is unclear whether HLA testing could help in a similar way with diagnosing LGI1 encephalitis, especially as the presence or absence of the antibody is already an established biomarker. But in atypical or early encephalitis testing, the HLA association has the potential to be meaningful. In addition, as van Sonderen suggested, HLA subtyping could help limit the search for tumors in positive cases.

In conclusion, the association of certain HLA subtypes with autoimmune encephalitis is certainly novel and an important finding. The identical association in two separate studies demonstrates validity of the finding and is an important step to understand this disease better.

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