**Supplemental Material**

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**Table e-1 Demographic data, CSF and flow cytometry data of all patients included in the analyses**

|  |  |
| --- | --- |
| Number of patients | 1279 |
| **Demographic data** | |
| Gender, female (%) | 868 (67.9) |
| Age at lumbar puncture in years, median (MAD) | 34 (8) |
| **CSF data** | |
| Number of patients with CSF IgG data (%) | 1269 (99.2) |
| CSF IgG concentration in mg/dl, median (MAD) | 44.7 (15.9) |
| Number of patients with CSF IgM data (%) | 1198 (93.7) |
| CSF IgM concentration in mg/dl, median (MAD) | 0.6 (0.4) |
| Number of patients with CSF IgA data (%) | 1191 (93.1) |
| CSF IgA concentration in mg/dl, median (MAD) | 3.1 (1.2) |
| Number of patients with Serum IgG data (%) | 1266 (99.0) |
| Serum IgG concentration in g/dl, median (MAD) | 10.6 (1.4) |
| Number of patients with Serum IgM data (%) | 1198 (93.7) |
| Serum IgM concentration in g/dl, median (MAD) | 1.2 (0.4) |
| Number of patients with Serum IgA data (%) | 1190 (93) |
| Serum IgA concentration in g/dl, median (MAD) | 2 (0.5) |
| Number of patients with IgG index data (%) | 1279 (100.0) |
| IgG index, median (MAD) | 0.7 (0.2) |
| Number of patients with IgM index data (%) | 1200 (93.8) |
| IgM index, median (MAD) | 0.1 (0.0) |
| Number of patients with IgA index data (%) | 1192 (93.2) |
| IgA index, median (MAD) | 0.3 (0.0) |
| **Flow cytometry data** | |
| Number of patients with CSF flow cytometry data (%) | 348 (40.5) |
| CSF B cell proportion in %, median (MAD) | 3.33 (1.5) |
| CSF plasmablast proportion in %, median (MAD) | 0.53 (0.4) |
| Number of patients with blood flow cytometry data (%) | 301 (35.0) |
| Blood B cell proportion in %, median (MAD) | 11.13 (3.01) |
| Blood plasmablast proportion in %, median (MAD) | 0.03 (0.02) |

Abbreviations: IgA = immunoglobulin A, IgG = immunoglobulin G, IgM = immunoglobulin M, MAD = median absolute deviation with constant=1.

**Figure e-1 Causal mediation analysis results and epistasis between HLA alleles and IGHC variants**

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(A, B) Causal mediation analyses showed that the associations of some HLA alleles with CSF plasmablasts explain their associations with Ig indices. (A) Mediation effect: HLA-DQB1\*06:02 🡪 CSF plasmablast proportion 🡪 IgG index. Direct effect: HLA-DQB1\*06:02🡪 IgG index. (B) Mediation effect: HLA-C\*02:02 🡪 CSF plasmablast proportion 🡪 IgM index. Direct effect: HLA-C\*02:02🡪 IgM index. (C, D) Evidence of epistatic effects between HLA alleles and IGH variants. (C) Only in the absence of HLA-B\*44:02, SNP rs12897751 had a dominant positive effect on IgG indices. In carriers of HLA-B\*44:02, this effect was not present; instead, a tendency for a negative association was observed. (D) HLA from the HLA-DQA1\*01:03-DQB1\*06:03-DRB1\*13:01 haplotype (DQ6-DR13 haplotype) alleles only affected IgA indices in the absence of SNP rs12884389. The point size in (C) and (D) represents sample size.

**Figure e-2 The HLA region and the IGHC locus and their association with intrathecal Igs**



HLA alleles from the HLA-B\*07:02-DRB1\*15:01-DQA1\*01:02-DQB1\*06:02 haplotype appear to influence the proportion of intrathecal B cells and plasmablasts and thereby increase the intrathecal synthesis of immunoglobulins, especially of IgG. Variants at the IGHC locus that correlate with the Gm21*\** haplotypes appear to influence intrathecal immunoglobulin levels via other mechanisms.