HLA DQB1*06:02 negative narcolepsy with hypocretin/orexin deficiency.

Abstract:
To identify rare allelic variants and HLA alleles in narcolepsy patients with hypocretin (orexin, HCRT) deficiency but lacking DQB1*06:02. China (Peking University People’s Hospital), Czech Republic (Charles University), Denmark (Golstrup Hospital), Italy (University of Bologna), Korea (Catholic University), and USA (Stanford University). CSF hypocretin-1, DQB1*06:02, clinical and polysomnographic data were collected in narcolepsy patients (552 with and 144 without cataplexy) from 6 sites. Numbers of cases with and without DQB1*06:02 and low CSF hypocretin-1 were compiled. HLA class I (A, B, C), class II (DRBs, DQA1, DQB1, DPA1, and DPB1), and whole exome sequencing were conducted in 9 DQB1*06:02 negative cases with low CSF hypocretin-1. Sanger sequencing of selected exons in DNMT1, HCRT, and MOG was performed to exclude mutations in known narcolepsy-associated genes. Classic narcolepsy markers DQB1*06:02 and low CSF hypocretin-1 were found in 87.4% of cases with cataplexy, and in 20.0% without cataplexy. Nine cases (all with cataplexy) were DQB1*06:02 negative with low CSF hypocretin-1, constituting 1.7% [0.8%-3.4%] of all cases with cataplexy and 1.8%
[0.8%-3.4%] of cases with low CSF hypocretin independent of cataplexy across sites. Five HLA negative subjects had severe cataplexy, often occurring without clear triggers. Subjects had diverse ethnic backgrounds and HLA alleles at all loci, suggesting no single secondary HLA association. The rare subtype DPB1*0901, and homologous DPB1*10:01 subtype, were present in 5 subjects, suggesting a secondary association with HLA-DP. Preprohypocretin sequencing revealed no mutations beyond one previously reported in a very early onset case. No new MOG or DNMT1 mutations were found, nor were suspicious or private variants in novel genes identified through exome sequencing. Hypocretin, MOG, or DNMT1 mutations are exceptional findings in DQB1*06:02 negative cases with hypocretin deficiency. A secondary HLA-DP association may be present in these cases. These represent particularly difficult diagnostic challenges.