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MONOZYGOTIC TWINS DISCORDANT FOR NARCOLEPSY TYPE 1 AND MULTIPLE SCLEROSIS

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Narcolepsy type 1 (NC1) is a neurologic sleep disorder caused by the loss of hypothalamic neurons that produce the sleep–wake regulating neuropeptides, the hypocretins (orexins). The pathogenesis is believed to be mainly autoimmune, based on the observation of a 95% to 100% association with the HLA-DQB1*06:02 allele, and on the recent strong indication of antigen presentation to T cells as central factors.¹ In Caucasians and Asians, the DQB1*06:02 allele is tightly linked to the HLA-DRB1*15:01 allele, which itself is associated with multiple sclerosis (MS), a CNS autoimmune disorder. Herein, we describe a DRB1*15:01/DQB1*06:02-positive monozygotic twin pair discordant for NC1 and MS.

Case report. In 2004, a 34-year-old, otherwise healthy Caucasian man (twin A) was diagnosed with narcolepsy NC1, 19 years after the onset of sleepiness. At the time of diagnosis, he presented severe daytime sleepiness (Epworth Sleepiness Scale score of 22/24), hypnagogic hallucinations, and dream enactment during sleep (REM sleep behavior disorder), but no cataplexy or sleep paralyzes. Sleep investigations confirmed narcolepsy: the polysomnography was normal except for REM sleep without atonia, which was consistent with the reported dream enactment; the Multiple Sleep Latency Test showed a mean sleep latency of 6 minutes, with sleep-onset REM periods in 4 of 4 naps. He was hypocretin-deficient (CSF hypocretin-1: 58 pg/mL, compared with normal levels of ≥ 200 pg/mL) and his HLA type was DRB1*15:01/13:01; DQB1*06:02/06:03. In 2008, cataplexy triggered by laughter and surprise evolved. In 2011, serologic tests confirmed Epstein-Barr/cytomegaloviral infection and he experienced temporary leg paraesthesia, from which he quickly and fully recovered. Neurologic examinations, MRI of the brain and spinal cord, and measurement of the immunoglobulin G (IgG) index gave normal results. Oligoclonal bands were absent. The low CSF hypocretin-1 level was unchanged.

In 2006, his brother (twin B) was healthy, with a normal Epworth Sleepiness Scale score (8/24) and

no narcoleptic symptoms. He declined to participate in sleep investigations, but was confirmed to be DRB1*15:01/13:01; DQB1*06:02/06:03-positive. In 2010, he developed bilateral hand/forearm paraesthesia. MRI of the brain and neck revealed >9 demyelinating periventricular lesions and a hyperintense lesion at the C2 level. Definite MS was diagnosed according to the 2010 revised McDonald criteria² after an additional clinical attack, an elevated IgG index (1.22), and the presence of oligoclonal bands in the CSF. The CSF hypocretin-1 level was normal (283 pg/mL). He confirmed that he experienced “tiredness” (fatigue), but reported no sleep attacks or other core narcoleptic symptoms. As narcolepsy was not suspected and because he had a severe crisis reaction after his MS diagnosis, we refrained from undertaking a sleep investigation.

The DNA was typed for monozygosity using 16 polymorphic microsatellite (short tandem repeat) markers: D1S1656, D2S441, D2S1338, D3S1358, D8S1179, D10S1248, D12S391, D16S539, D18S51, D19S433, D21S11, D22S1045, FGA, SE33, TH01, vWA, and the sex marker Amelogenin (AmpFLSTR NGM Select PCR Amplification kit; ThermoFisher Scientific, Waltham, MA). The likelihood ratio in favor of monozygosity was greater than 10,000:1.

Discussion. The present case is notable for several reasons. Monozygotic twin pairs discordant for NC1 and MS are rare. The presence of MS—an autoimmune CNS disorder—in the genetically identical twin of a hypocretin-deficient patient with narcoleptic supports the pathophysiologic importance of the recently found association between NC1 and genes involved in antigen processing, presentation, and T cell response.¹

Comorbid autoimmune disease³ and cases of comorbid MS have been observed in single cases of sporadic NC1 and, notably, in an H1N1-vaccinated NC1 patient.⁴ We have previously reported that sleepiness and hypocretin levels are generally normal in MS,⁵ but secondary hypocretin deficiency and hypersomnia/NC1 have been reported in a few cases of neuromyelitis optica.⁶ The NC1- and MS-predisposing HLA-DRB1*15:01/DQB1*06:02 haplotype is also found in approximately 25% of the general population. Several other predisposing genes,

none of which overlap, have been reported and account for some of the missing heritability in both diseases. However, the present monozygotic twin A, who, when last examined, still had isolated NC1 without signs of comorbid MS, and twin B, who still had isolated MS without signs of secondary NC1, had an asymptomatic DRB1*15:01/DQB1*06:02 homozygote father and an asymptomatic DRB1*15:01/DQB1*06:02-negative mother. This strongly suggests that a shared genetic background of DRB1*15:01/DQB1*06:02 is not sufficient to account for a predisposition to either of these autoimmune CNS disorders. Additional predisposing genes are most likely uncommon since comorbidity is rare, but environmental factors, for example, bacterial or viral infections, are believed to be equally important in the pathogenesis of autoimmune disorders. Pandemrix is a vaccine whose effect is reduced in patients with MS treated with immunomodulatory drugs such as glatiramer acetate or natalizumab but not in patients on interferon β .⁷ Given the dramatic increase of NC1 cases following H1N1 vaccinations with Pandemrix (GlaxoSmithKline), our present twin case and cases of comorbid MS and NC1 after H1N1 vaccination⁴ could be valuable for further studies of the genetic background and specific triggers (or drivers) of autoimmunity in these CNS disorders.

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Author contributions: S.K., P.J.J., B.R.K., and S.G. designed the study. S.K. and N.M.I. handled patients and CSF/blood samples. P.J.J. analyzed the sleep investigation data. S.G. and S.K. measured the hypocretin levels. N.T., N.M., and Z.T. handled the genetic samples and designed and performed the genetic tests. S.K., P.J.J.,

and B.R.K. wrote the manuscript. Z.T., N.M.I., and N.M. revised the manuscript.

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