Narcolepsy type 1: what have we learned from genetics?

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Abstract

Type-1 narcolepsy is a severe neurological disorder with distinct characteristic of loss of hypocretin neurotransmitter. Genetic analysis in type-1 narcolepsy have revealed a unique signal pointing toward autoimmune, rather than psychiatric origin. While type-1 narcolepsy has been intensively studied, the other subtypes of hypersomnolence, narcolepsy, and hypersomnia are less thoroughly understood. This review summarizes the latest breakthroughs in the field in narcolepsy. The goal of this article is to help the reader to understand better the risk from genetic factors and their interplay with immune, genetic, and epidemiological aspects in narcolepsy.

Key words: narcolepsy; epidemiology; genetics; comorbidity; autoimmune; psychiatric

Introduction

In September 2018, over 100 narcolepsy researchers gathered at the International Symposium on Narcolepsy to synthesize the latest breakthroughs in the field and to understand better the immune, genetic, and epidemiological aspects of the disease. This perspective article draws together the findings in genetics together with epidemiology, how genetic studies have been shaping the field, and what remains to be explored and targeted next.

Genetic studies in narcolepsy have focused mainly on type-1 narcolepsy (NT1). NT1 is a severe neurological disorder with a likely autoimmune mechanism that kills the hypocretin/orexin neurons \cite{1}. This cell loss produces chronic sleepiness cataplexy, episodes of muscle weakness triggered by strong, generally positive emotions. Cataplexy is a key diagnostic marker for NT1 as cataplexy or low hypocretin levels are rarely seen in other diseases \cite{2, 3}. This clinical characteristic of low hypocretin levels, or presence of cataplexy separates NT1 from other neurological causes of other hypersomnia disorders (ICSD3), including those with core complaint of sleepiness such as type-2 narcolepsy (NT2) \cite{4} and idiopathic hypersomnia (IH) \cite{5, 6}. In these other hypersomnia disorders, the characteristics are however otherwise remarkably shared with key component of

Statement of Significance

This review focuses on genetic and epidemiological risk factors for type-1 narcolepsy and discusses these factors in the context of sleepiness and as a spectrum from general population to severe hypersomnia disorders.
severe sleepiness during the day but lack of cataplexy. These hypersomnolence disorders and their symptoms have been detailed earlier here [7].

A curious finding from NT1 is a strong Human Leukocyte Antigen (HLA) association and other genetic associations that affect the immune system. This perspective will synthesize the genetic associations in hypersomnolence disorders focusing on NT1, compare findings with population-level symptoms of sleepiness and long sleep duration, challenge separating normal sleep from sleepiness and long sleep duration, and examine potential functional mechanisms that lead to disease.

**HLA – One Gene to Rule Them All**

One of the reasons behind the success in NT1 genetics is that only individuals with cataplexy or verified low hypocretin levels have been included in these studies. This has resulted in relatively homogenous patient populations, which likely share common genetic disease mechanisms. The most impactful risk factor is the Human Leukocyte Antigen DQB1*06:02 variant in NT1. This genetic variant increases the risk over 20-fold and is sometimes used diagnostically to support other clinical data, estimates of sleepiness, and findings on multiple sleep latency test of polysomnography. Originally, the HLA association was a true surprise as it shifted the focus from the hypothesis of neurological disease into immune mediation of disease onset [8,9]. Within the HLA region, the effect is explained by DRB1*15:01 and DQB1*06:02 alleles. The HLA DRB1*15:01 and DQB1*06:02 alleles are in strong linkage disequilibrium, meaning they nearly always occur together. However, the effect is most likely explained primarily by DQB1*06:02 as the correlation breaks down in Blacks, where haplotypes with DQB1*06:02 alone increase risk the most [10]. In addition, other independent risk alleles at the HLA locus affect NT1 risk. At the DQB1 locus, protective association is seen with DQB1*06:03 [11], whereas DQB1*03:01 allele increases risk for NT1 and also lowers the age of onset for NT1. In addition, DQA1*01:01 and DQA1*01:03 alleles are protective and several other independent alleles from both HLA class I and II regions affect NT1 risk. These include HLA-DPB1*05:01 HLA-DPB1*04:02. HLA-A*11:01, HLA-B*35:01, HLA-B*51:01, and HLA-C*04:01 (Table 1) [12–14]. As HLA class II alleles are recognized by helper CD4+ T cells and class I alleles by cytotoxic CD8+ T cells, these findings suggest the involvement of both helper and cytotoxic CD8+ T cells in the development of NT1.

The vast number of significant and independent high-risk loci from HLA region show that while DQB1*06:02 is essentially required for developing NT1, other genetic variants from the HLA locus likely shape immune system responses toward infection, autoimmunity, or both. Similarly, HLA alleles influence our thinking in basic and clinical experiments. In addition, HLA alleles have been earlier shown to shape the immune system, so that depending on expressed HLA allele, the immune system works slightly differently compared with individuals with other HLA alleles [15–17]. Indeed, the first point in this perspective is that the effect of HLA on immunity is so strong that it needs to be matched even for functional, biological immune assays.

Recent immunology research on narcolepsy matches cases and controls to be DQB1*06:02 positive, or at a minimum explores how the effects differ between DQB1*06:02-positive versus -negative controls. This approach was pursued by studies presented at the International Symposium on Narcolepsy, some now published [18–21]. One of these studies found that individuals with NT1 have autoreactive CD4+ T cells that recognized hypocretin [21]. Interestingly, the modulating HLA allele was HLA-DRB1, and not DQB1 specific. In addition, this article suggested that NT1 is not an attack on one single sequence that is recognized by T cells, but autoimmunity by CD4+ T cells can develop toward several distinct epitopes of the hypocretin neuropeptides [21]. Similar findings of hypocretin-reactive T cells were found in other independent studies, in which patients and controls were also matched for DQB1*06:02. In contrast to the study by Latorre Kallweit et al., the main effect was self-reactivity toward amidated hypocretin and not the nascent form of the hypocretin peptide. It is therefore possible that a specific

| Trait | NT1 | NT2 [10,14] | IH | Long sleep duration [73] | Sleepiness [76] | Napping [77] |
|-------|-----|-------------|----|-------------------------|---------------|-------------|
| Associated loci | HLA-alleles: | Higher frequency of DQB1*06:02 carriers | None | CAMTA1, PAX8, S100PBP, PATJ, ZNF326, BARHL2, LMOD1, SUSD4, SNX17, TIMM247, LOC644456, LOC730134, LOC728815, LOC644426, PLCL1, ERBB4, AGAP1, GBE1, CYP51P1, CYP51P1, LOC100131101, LOC440970, CADM2, ECE2, GABRA2, SLC39A8, CTT2P2, LOC391811, SIL1, POM121L2, FKSGB3, BTBD9, HCRTR2, LOC100129963, LOC644403, LOC100126313, ASAP1, KRT16P24, CHCHD9, GAPVD1, MAPKAP1, LOC119358, HTR7, CAGNA1C KSR2, EEF1A1P2, RPLP9E, CPEB1, PRKCB, RA11, LOC6444191, MGC57346, FUSSE1L8, TAPREF1, NAKIN, DOCK1, LOC100132285, RPF1-356K22.1, CYP1A1, CYP1A2, HDGFPR3, BNC1 | SHISA4, LMOD1, SHISA4, LMOD1, IPO9, RNPEP, FAM38B, ARL17B, SPATA32, CRHR1, SPPL2C, ARHGAP27, KANSL1, HOXB2, HOXB2, HOXB2, MAPT, LRRCS7A2, NSF, ARL17A, WNT3, FMN1, ACBD4, GOSR2, PLEXHM1, LRRCS7A, IER3IP1, KATNAL2, HDHD2, PIA52 |
form of hypocretin peptide is needed to trigger autoimmunity. In addition, in this study, the amidated hypocretin peptide was recognized also by influenza-A specific T cells, suggesting that immune cells may confuse hypocretin with influenza-A. This finding supports mimicry with influenza-A as one of the mechanisms in NT1 predisposition [20]. The findings of these two studies are complementary and overall show how different HLA alleles (primarily DRB1*15:01 or DQB1*06:02) modulate the risk for NT1 through environmental triggers, such as influenza-A and through direct mechanisms on autoreactivity toward hypocretin. Although these findings reflect an important breakthrough, it seems clear that the precise mechanisms and the sequence by which T-cell subtypes lead to hypocretin cell death remains somewhat speculative [22]. In addition, T cells in the bloodstream may have different HLA preference than those in the brain, an important consideration since hypothalamic neurons do not typically express class II MHC molecules (e.g. HLA-DR and DQ) to which CD4 T cells bind. However, they express the class I MHC molecules that CD8 T cells recognize [4, 23–25]. Finally, central nervous system (CNS) microglia that are class II MHC-positive function as antigen presenting cells in the brain can modulate local immune responses and the role of these cells in NT1 pathology is likely.

In summary, these findings along with the number of different HLA associations highlight the need for a deeper understanding of genetic risk factors and their impact on physiology and infection that are important in directing our understanding of cellular mechanisms that lead to autoimmunity. The second point that I want to make is that the findings highlight the importance of HLA fine mapping, identification of high-risk variants, and functional characterization of effects across hypersomnolence disorders.

Genetic Factors in NT1 Provide Evidence for Immunity

Since the early discovery of the HLA association, a number of novel genetic factors have surfaced for NT1. In contrast, only one genetic variant, HLA-DQB1*06:02, is systematically associated with NT2 [10, 14] and no variants are known for IH.

For NT1, the genetic risk factors include both T-cell receptor alpha [26] and T-cell receptor beta [27] as well as at least 10 other genes involved in the immune system, primarily in the antigen presenting pathway [4, 28–32]. One gene does not fit this pattern; CPT1B is involved in mitochondrial transport and energy metabolism, suggesting additional, yet uncharacterized disease mechanisms in NT1 [33, 34]. However, the vast majority of genetic associations affect immune function and include common genetic variants from HLA, TRA, TRB, CTSH, TNFSF4, IFNAR1, ZNF365, F2RY11, SIRPG, PRF1, CD207, CCR1, and ZFAND2A [27, 33, 35–38]. These variants have been systematically discovered across ethnic groups, by different research groups and global consortia.

In addition, while Influenza immunization was a unique trigger for NT1 the major genetic risk factors seem to be similar. In both instances, all cases are DQB1*06:02 positive and share the other major HLA risk factors. In addition, the only consistently associating non-HLA association in vaccination-related NT1 is TRA [36, 39]. This association is most likely also the only one with large enough effect size to be detectable in the relatively small studies.

These genetic risk variants are shared with deeply studied autoimmune traits such as type-1 diabetes, systemic lupus erythematosus, Crohn’s disease, or celiac disease, further supporting that NT1 shares also individual genetic risk factors that overall increase the risk for autoimmune traits [38]. These genetic findings are interesting in the light of epidemiological studies, where shared etiology with autoimmunity and higher prevalence of autoimmune diseases has been reported for NT1 [40, 41] or even for NT2 and IH [42]. However, we are yet to prove causality for hypocretin cell destruction through autoimmune mechanisms.

In contrast to the genetics of NT1, little is known about the genetics of NT2, IH, and other CNS hypersomnolence disorders. As part of the disease risk may be shared across some hypersomnolence disorders, we need to systematically be able to characterize both the shared environmental and comorbid risk factors as well as the genetic risk factors for these disorders. To do this the field needs well phenotyped large cohorts, which include both NT2 and IH in addition to NT1 patients. In addition, we need to start to collect sleep questionnaires and face-to-face interview data as well as objective sleep measures from polysomnography, activity tracking, and blood biomarkers systematically in all these patient groups. In addition, we should expand on the current sleep symptom questionnaires as efficiently as possible in novel patient and population cohorts that are being collected.

Genetic Variants Shape the Immune System and Regulate the Response to Infections

Earlier studies discovered that DRB1*15:01 and DQB1*06:02, the same HLA haplotypes that predispose people to NT1, also affect the response to influenza-A infections [43, 44]. In addition, we examined genetic predisposition within NT1 patients comparing those who had onset before Pandemic 2009–2010 influenza-A season in China vs. those who developed NT1 during or closely after the Influenza-A flu season. We identified genetic variants at the HLA-DRB1 and HLA-DQB1 region that modulated NT1 disease risk before vs. after the 2009–2010 Pandemic H1N1 influenza [27]. These findings suggested that the risk to develop NT1 with influenza as a trigger was modulated by genetic risk factors at the HLA. Potentially, both the genetic risk and the critical infectious trigger were needed to develop NT1 [27]. These findings are in line with earlier findings that elucidate that genetic variation acts in the context of environmental triggers modulating infection and immunity [45, 46]. Similarly in NT1, we can identify genetic variants that regulate expression in immune cells [47] or responses to flu infection; for example, variants from interferon-alpha/beta receptor alpha chain (IFNAR1) affect IFNAR1 expression after flu infection specifically [38]. Together these findings demonstrate that genetic variations shed light on the disease mechanisms of NT1 and suggest that these mechanisms are triggered by environmental factors such as influenza-A infection.

Environmental Risk Factors Connect Hypersomnolence With Psychiatric and Immune Mechanisms

Similar to genetic findings highlighting the role of immunity, NT1 is probably triggered by upper airflow infections, including influenza-A and streptococcus (reviewed in [30, 31, 48]). In
addition, multiple studies have shown that one specific brand of influenza-A vaccine, Pandemrix, was associated with an increase in narcolepsy incidence in the Northern European and Scandinavian countries where it was administered in 2009–2010 [49–52]. While association with Pandemrix immunization has been systematically seen in each country where this vaccine was used, the role of natural influenza infection increasing or modifying the risk for NT1 has remained elusive. Increase in NT1 incidence has been reported in China and in Taiwan following seasonal influenza [53, 54]. Similarly, findings from a recent meta-analysis suggest that at least some NT1 cases are attributable to natural influenza infection or modifying effects with immunization [55]. In contrast, assessing natural infection in cases with vaccination onset narcolepsy did not reveal any serological evidence that natural infection would play a role in NT1 [56]. Upper airway infections have been suggested but not proven as risk factors for other hypersomnolence disorders, including Kleine–Levin syndrome [57, 58] and in other neurological disorders including Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS/PANDAS). However, showing causality between a neuropsychiatric disorder such as NT1, NT2, KLS, or PANDAS and upper airway infections has been challenging due to (1) differences in estimating the timing of infection (claims vs. questionnaire), (2) inconsistency in reporting infections, and (3) the frequency of upper respiratory tract infections (URI) in general; children can have 6–10 URI per year. Finally, diagnostic criteria for neuropsychiatric disorders vary between physicians and institutes all which contribute to findings being inconsistent (as shown for example in PANDAS and reviewed in [59]).

Similarly, the association with natural infection does not currently implicate causation but merely a correlation. Indeed, other factors and stressors overall affect our immune system. For example, stress, depression, and insomnia have all been consistently associated with URI [60–63].

Finally, ascertainment bias may explain some of these associations as those who have either got influenza and even vaccination and are DQB1*06:02 positive will be more readily recognized as NT1 cases. In contrast to immunity, we and others have previously shown the overlap between NT1 and other hypersomnolence disorders with psychiatric traits as these previous studies evidence the co-occurrence of depression with hypersomnolence disorders [64, 65]. Whether this is a cause or consequence of poor sleep is however still unknown. However, data are emerging of a bidirectional association: poor sleep leads to depression, and depression can include hypersomnolence or poor sleep. Furthermore, we and others have identified that individuals that develop NT1 also may develop severe psychiatric symptoms that reflect those seen in schizophrenia [64, 66–68]. It is possible that some of these symptoms are explained by severe hypnagogic hallucinations. However, schizophrenia is partially mediated by immune factors [69] and overlaps with autoimmune traits [70]. Consequently, it is possible that neuronal loss in some NT1 patients is more severe and affects a larger area of neurons in the hypothalamus so that additional cell populations in addition to hypocretin neurons are destroyed. Indeed, symptoms of hallucinations and sleepiness take place also in other neuroimmune disorders such as paraneoplastic disorders, especially NMDA encephalitis, where the causal role is destruction of glutaminergic neurons in the CNS. Importantly, cataplexy and hypnagogic hallucinations have also been detected with anti-MA encephalitis [71]. It is possible that in some patients with NT1 direct destruction of neurons results in hallucinations. Such a mechanism or larger neuronal loss in NT1 could lead to larger disease burden or atypical symptoms. Alternatively, individuals with risk for psychiatric disease may manifest the disease more readily when a strong additional burden such as NT1 or other hypersomnolence disorders are present. Together, these findings suggest that some environmental factors may be shared across hypersomnolence disorders, but whether specific environmental risk factors cause hypersomnolence disorders other than NT1 stills need to be systematically examined.

Genetic Findings Support Psychiatric and Immune Mediation of Sleepiness, Sleep Duration, and Hypersomnolence Disorders

With the availability of large clinical cohorts for NT1 through a consortium as well as large population samples such as the UK Biobank, we can now estimate genetic and environmental risks for sleep disorders, as well as common traits such as sleep duration, sleepiness, and naps in the general population. These studies discovered genetic variants in neurotransmitter genes that have been shown in previous animal and in human studies to be critical for sleep regulation. Indeed, the genetic association studies of population-level sleep traits have identified variants in potassium channels (NKAIN2, KCN5H, and KCNQ5) [72] and dopaminergic (DRD2, SLC6A3) and gabaergic pathways (GABRA2, GABBR1) [73], essentially validating the relevance of these neurotransmitter systems in human sleep regulation and highlighting that common variants in genes in these essential neurotransmitter pathways have a large impact on sleep. This is evidenced both at the individual level and at the population level. However, the most famous of these variants are regulatory and missense variants in the hypocretin receptor 2 (HCRTR2), which affect a variety of sleep traits including sleepiness, chronotype, and insomnia [73–76]. In addition, these studies provided novel insight how deviating sleep leads to diseases and what are causal factors behind sleep disorders. For the hypersomnia field, the most exciting associations are those found for sleepiness, naps, and sleep duration [72, 73, 76–78]. As clinical cohorts tend to capture the most severely ill patients with smaller disease burden at the population cohorts, these traits are likely capturing mild associations, ranging from similar patterns to clinical sleep disorders, including hypersomnia or sleep apnea. Interestingly, studies in sleep duration discovered a genetic correlation with long sleep and depression and with schizophrenia [73]. In addition, sleepiness and naps are associated with psychiatric traits, most notably depression and bipolar disorder.

However, clinically patients can have several causes for hypersomnolence and can have underlying sleep disorder such as obstructive sleep apnea that increase sleepiness complaints. These underlying conditions will also affect how individuals answer to sleep questions in population cohorts. Indeed, for any genetic study identifying biomarkers it would be essential to validate the underlying clinical complaints. Therefore, difference between natural long sleepers that are refreshed after 12 hours of sleep needs to be distinguished from those individuals that sleep long but still report sleepiness during the day or those
that are chronically sleep deprived and report sleepiness during the day and finally those with underlying, often untreated, sleep disorder. Therefore, the novel population collections as well as clinical collections should consider the measures closely in order to capture differences between normal sleep and clinical complaints.

With genetic instruments, such as Mendelian randomization techniques, it is also possible to examine the direction of these associations. In sleepiness, no effect was seen from sleepiness toward psychiatric traits or vice versa. In contrast, long sleep duration was an independent risk factor for both schizophrenia and depressive symptoms. Interestingly, the effect of schizophrenia was bidirectional, so that schizophrenia also increases the risk for long sleep duration [76]. Together, these findings suggest that clear causal pathways connect long sleep duration with psychiatric traits, whereas those with immune traits need to be validated at the population level.

In contrast to sleep duration, daytime sleepiness and napping was primarily explained by a large heterogenous group of metabolic and neuronal genes with a very small immune signal, which was not shared with narcolepsy and did not include significant association at the HLA locus [76, 77]. One of the most interesting results provided from these studies show high effect coding variant in the hypocretin receptor 2 (HCRTR2). As individuals with NT1 are deficient of hypocretin neuropeptide, it is remarkable that the receptor for hypocretin associates with sleepiness at the population level.

Overall, these findings suggest that in addition to NT1, the hypocretin system regulates hypersomnia, sleepiness, and naps at the population level. In addition, sleepiness can be caused by direct destruction of the cells that produce the neurotransmitter as seen in NT1. Furthermore, based on large-scale population studies, genetic variants in genes such as HCRTR2 influence sleepiness in nonclinical, normal population. In addition, potassium channels, dopaminergic neurotransmitter, and gabaergic neurotransmitter have a clear effect on sleepiness and sleep duration in population studies. As we do not understand the genetic mechanisms and fundamental disease mechanisms yet in any of the other hypersomnolence disorders, besides NT1, it is critical that these diseases be investigated by genetic studies that are implemented with clear phenotypic characterization, to identify shared and unique disease risk factors.

Conclusions and Next Steps: Fundamental Characterization of Hypersomnolence Disorders Is Needed

Discovery of these genetic variants strongly supports an autoimmune mechanism as the primary disease mechanism in NT1. The first genetic loci in NT1 were discovered in just 80 patients for HLA, and 1,830 patients for the second strongest signal in T-cell receptor alpha in NT1. In addition, the remarkable HLA association has set a baseline where current functional studies are done always in context of correct HLA allele and usually fixed for DQB1*06:02-positive cases and controls, with additional control group of DQB1*06:02-negative individuals. In addition, findings from genetics have inspired researchers to examine T-cell receptor chain usage, largely verifying those findings from NT1 genetic associations and identifying additional regulatory regions. As genetic studies provide a unique way to examine unbiased disease pathways in traits, genetic studies are now needed to explore causal effects across different hypersomnolence disorders and validate the role of previously suggested environmental triggers and differences in these diseases.

In contrast to NT1, over 100,000 individuals were needed to discover the associations in one of the key complaints of hypersomnolence: sleepiness [79]. The larger number of individuals needed does not mean that genetics is less important for the common sleepiness traits or other hypersomnolence disorders. On the contrary, it highlights the multifactorial and heterogeneous nature of sleep traits and how they relate to multiple other traits including both metabolic and psychiatric outcomes. Furthermore, we now understand how a multitude of genetic risk factors can affect even clinically relatively homogenous and severe patient populations, and how disease mechanisms are partially shared with common sleeping traits at the population level.

It is tempting to conclude that with genetics we will be able to examine the overlapping mechanisms between NT1 and NT2, IH, and even related, largely neglected disorders such as chronic fatigue syndrome. However, to do that correctly, we will need to implement clear phenotypic characterization and to examine carefully shared and unique disease risk factors. It is time that we as a field collect a sufficient sample size to study all hypersomnia disorders, perform deeper phenotyping whenever possible, and include atypical cases in genetic studies to reveal the underlying disease mechanisms in these disorders. These mechanisms will serve as starting point for validating disease mechanisms in hypersomnolence disorders, and for understanding novel, yet unexplored disease mechanisms across hypersomnolence disorders.

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