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Journal of Sleep Disorders & Therapy

Research Article

Narcolepsy Associated Genetic Variants Associated with Impaired Cognition in A Community Dwelling Older Cohort

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ABSTRACT

Objective: Studies have hypothesised that the combination of pre-existing genetic traits and specific environmental triggers determine the onset of the Narcolepsy. The most impactful genetic risk factor is the presence of Human Leukocyte Antigen (HLA) DQB1*06:02 encoded on the Major Histocompatibility Complex (MHC), however, the presence of HLA-DQB1*06:02 is not ubiquitous in all narcolepsy cases. The most poignant genetic risk factors outside the MHC are predominantly located in genes associated with the immune system. In addition to the traditional symptoms of narcolepsy, the co-morbidities can vary with a cohort of sufferers complaining of cognitive dysfunction, particularly memory and attention. These self-report are not substantiated by consistent scientific evidence whereas there is significant evidence outlining the genetic contribution underpinning variation in cognitive abilities in the general population .

Materials and method: In this study we impute targeted non-MHC narcolepsy associated Single Nucleotide Polymorphisms (SNPs) from 1,558 non-pathological elderly volunteers who have been followed for change in cognitive function for up to a 24-year period. Specifically, we investigate 13 previously documented narcolepsy associated SNPs with an odds ratio greater than or equal to 1.00 combined with a minor allele frequency of greater than 0.05.

Results: We observed an association between rs306336, rs4290173 and rs2834168 and a faster decline in long term memory. Similarly, we observed a protective effect of rs10995245 against the decline of long-term memory loss.

Conclusion: This investigation suggests that the cognitive problems reported by cohorts of narcoleptic patients may be due to genetic predispositions and supports the variation seen in the co-morbidities associated with narcolepsy.

Keywords: Narcolepsy; Cognition; Polymorphism; Immunogenetics; SNP; Neurology

INTRODUCTION

Narcolepsy is a life-long disabling neurological disorder characterised by excessive daytime sleepiness which presents with the onset of Rapid Eye Movements during daytime sleep attacks [1]. Excessive daytime sleepiness consists of periods of irrepressible need to sleep during times of wakefulness which can be promoted by sedentary activities and physical inactivity [2]. Most sufferers also exhibit a sudden loss of muscle tone triggered by strong emotions, termed cataplexy. Narcoleptic patients may also experience disturbed night's sleep, sleep paralysis, hypnagogic and/or hypnopompic hallucinations. Narcolepsy onset is often seen in early adolescence with the rate of concordance in monozygotic twins of 20–30% [3]. The European Narcolepsy Network estimates a prevalence of 0.02% in European populations, which is consistent with prevalence in America [4]. Worldwide, narcolepsy appears to be most common in Japan with a prevalence

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Received: 25-Jul-2023, Manuscript No. JSDT-23-25814; **Editor assigned:** 27-Jul-2023, PreQC No. JSDT-23-25814 (PQ); **Reviewed:** 10-Aug-2023, QC No. JSDT-23-25814; **Revised:** 18-Aug-2023, Manuscript No. JSDT-23-25814 (R); **Published:** 28-Aug-2023, DOI: 10.35248/2167-0277.23.12.452.

Citation: Jervis S, Payton A, Lowe M, Didikoglu A, Verma A, Poluton K (2023) Narcolepsy Associated Genetic Variants Associated with Impaired Cognition in A Community Dwelling Older Cohort. J Sleep Disord Ther.12:452.

of 0.17% [5]. Narcolepsy is suggested to be an autoimmune condition targeting the hypocretin/orexin producing neurons within the hypothalamus, with a genetic predisposition. In addition, disease onset likely requires an environmental trigger such as vaccine administration or streptococcal infection [6,7]. The reported genetic factors that may predispose an individual to an increased risk of narcolepsy are almost exclusively located in genes that encode proteins of the immune system.

The strongest genetic association with narcolepsy onset is the inheritance of the Human Leukocyte Antigen (HLA) DQB1*06:02 located within the Major Histocompatibility Complex (MHC) and present in more than 95% of confirmed narcolepsy cases [8,9]. Despite the strong association with the presence of a single copy of HLA-DQB1*06:02, only 1/1000 individuals who possess the allele will develop narcolepsy [2]. This association has set a baseline for functional studies that are mostly performed with a cohort of HLA-DQB1*06:02 positive cases and controls [10]. The most promising genetic regions for potential candidate genes outside the MHC are genes that encode subsets of the T cell receptors or genes that regulate immune cell cycling, proliferation and signalling [11,12]. The link between neurodegeneration and impaired/altered immune signalling is well established and as such there are documented connections between the primary symptoms of the disease and other non-traditional symptoms, including altered cognition [13]. Despite the presence of both genetic and environmental factors, the lack of an identified/known auto antigen prevents narcolepsy being officially categorised as an autoimmune condition and the complete pathophysiological mechanisms in narcolepsy are yet to be fully uncovered. Neurological damage in hypocretin axons associated with narcolepsy impacts on other pathways leading to a spectrum of associated symptoms. Hypocretin axons are densely concentrated in the monoaminergic and cholinergic systems [14]. There is documented interaction between the monoaminergic and cholinergic systems and a wide range of disruption to cognitive processes which may accompany the sleep symptoms in Narcolepsy [15]. Cognition is a term which refers to a range of neurological processes relating to the acquisition, storage, manipulation and retrieval of information. Cognition can be measured using several variables, including: Memory, processing speed, fluid intelligence and vocabulary. Studies have explored all four variables in patients suffering with narcolepsy with conflicting results. Several investigations have shown that narcolepsy sufferers report learning and memory difficulties; although these are rarely confirmed by results from neurological evaluations and cognitive problems are often attributed to depressive symptoms as a result of the condition or to medication [5,14,16]. However, poor performance in long tasks that require prolonged attention are frequently reported [17]. Research has suggested that a deficit in the alerting network could be a source which provides the link to an impaired cognitive response [18]. Whereas executive functions that are developed by early adolescence, including adaptable thinking and short term-memory, yield intact performance in narcolepsy patients when compared to healthy controls [19]. In contrast narcolepsy sufferers have shown difficulties in verbal fluency tasks, decision making, and flexible thinking (fluid intelligence) [20].

Narcolepsy is likely to be a complex disorder with multigenic influences. The relative contribution of each associated gene is impossible to evaluate. As such investigating well characterised individuals to find associations of non-HLA narcolepsy associated SNPs with cognitive functions may help segregate the symptoms associated with narcolepsy. In this retrospective study we use longitudinal cognition data from The University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age (UMLCHA) cohort to determine whether any targeted non-MHC derived SNP variants associated with Narcolepsy have an impact on cognitive ability and its decline with age.

MATERIALS AND METHODS

Study cohort

The UMLCHA cohort consisted of 6,063 adult volunteers (4,238 female, 1,825 male, median age 65 years) from Greater Manchester and Newcastle upon Tyne, recruited between 1982 and 1994 [21]. The data was collected using a Personal Details Questionnaire (PDQ) which collected a number of demographics including age, marital status, current health status, alcohol consumption, smoking status and usage of sleep medication completed at up to seven waves over a 24-year period (1985–2010). As the recruitment into the study was distributed throughout the 24 year period, there was a degree of overlap as each participant completed the questionnaire at different dates. Written informed consent was obtained from all respondents at the onset of data collection. All PDQs were collected under the approval of the University of Manchester research ethics committee and this study includes secondary analysis of the anonymised dataset. This research was completed in accordance with Helsinki Declaration.

Genetic variant selection

We selected 13 non-MHC narcolepsy associated SNPs using GWAS studies published before January 2022. All SNPs were selected using the EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/) and were only included if they had an Odds Ratio (OR) greater than or equal to 1.00 and a Minor Allele Frequency (MAF) greater than 0.05. The list of SNPs selected candidate is shown in Table 1.

Table 1: List of SNPs selected or the study.

Chromosome	Gene	SNP	OR	Allele	Minor Allele	MAF
1	*MIR-552*	rs10915020	1.32	A/G	G	0.08
1	*PKN2*	rs306336	1.65	A/G	G	0.09
3	*CCR1/CCR3*	rs3181077	1.63	C/T	C	0.11
6	*H2AC6*	rs198811	1.69	C/G/T	C	0.38

8	*UBXN2B*	rs2859998	1	T/C	T	0.47
10	*A1CF*	rs4290173	1.8	A/G	A	0.12
10	*ZNF365*	rs10995245	1.23	G/A	A	0.31
14	*TRA*	rs1154155	1.64	T/G	T	0.45
19	*DNMT1*	rs1551570	1.32	G/A	G	0.25
19	*DNMT1*	rs16966122	1	C/T	T	0.29
21	*IL10RB-IFNAR1*	rs2834168	1.3	A/C/G/T	A	0.2
21	*IL10RB-IFNAR1*	rs2834118	1	T/G	G	0.16
22	*CPT1B-CHKB*	rs5770917	1.63	C/T	C	0.23

Note: SNP-Single-Nucleotide Polymorphism; OR-Odds Ratio; MAF-Minor Allele Frequency.

Cognitive tests

Generalised Linear Latent and Mixed Models by maximum likelihood (GLLAMM) was used to generate four cognitive g-factors for vocabulary, processing speed, memory, and fluid intelligence for cross-sectional (initial test score) and longitudinal (trajectory derived from the initial and subsequent test scores) using Stata (StataCorp, College Station, TX: StataCorp LP). All phenotypes were corrected for age, and for longitudinal phenotypes, missing data points were imputed by sampling the posterior distribution of factor scores using Mplus [22]. All cognitive tests were taken at four testing waves (1985-2002) approximately 4 years apart. Vocabulary ability was constructed using the Mill Hill and Wais vocabulary tests which consisted of a series of multiple choice questions and in each question a single word was presented at the top of the screen [23,24]. Below it, 6 other words are presented as the response options. The candidate responded by selecting the option they believe is closest in meaning to the word at the top of the screen. Each correct response was given a score of 1 and any other response is given a score of 0. The total test score was the sum of all the questions with the maximum total score being 33. Factors for memory were generated from immediate and delayed recall, propositions and spatial memory tests. Speed factors were derived from the Alphabet Coding Task and the Random Letters test [25]. In the Alphabet Coding Task two rows of characters are shown, each character in the upper row belongs to a character in the bottom row. The test also contains two rows, one of them containing characters and another row which is empty. The candidate had to complete as many character combinations as possible in one minute by naming the corresponding character. This test is performed in three cycles and the mean score generated is used for analyses. Fluid intelligence was determined using two parts of the Alice Heim test 4 [26] and the four subsets of the Culture Fair test [27]. The Alice Heim test 4 contains 130 questions, with 65 questions each measuring verbal and non-verbal ability. The test is split into four categories, namely General Ability (non-verbal and verbal), Reading Comprehension and Mathematics. The Culture Fair test attempts to measure intelligence devoid of social and environmental influences. The test consists of three scales with non-verbal visual puzzles which includes mazes, copying symbols, completing sequences of drawing and other non-verbal tasks. The volunteer generated a score at the end of the test similar to an IQ score.

Genotyping SNPs

The Dyne Steel DNA Archive for Aging and Cognition was established between 1999–2004. DNA was obtained using a standard phenol/chloroform technique from whole blood on 1,563 volunteers. GWAS data was generated using the Illumina Human610-Quad BeadChip and was available for 1,558 volunteers. The data has been through standard GWAS quality control and was imputed using the 1000 genome reference panel [28].

Statistical analysis

Linear regression analysis was used to determine the association between the chosen SNPs and the four measures of cognition (baseline and longitudinal). Linear regression results are reported in terms of beta and p-values. For longitudinal data the average decline in the general population for each g-factor is expressed as 0. A SNP with a beta value of >0 suggests that the SNP is associated with a slower than average rate of decline in that cognitive function, conversely if the beta value is <0 it indicates that the SNP is associated with a faster rate of decline. Analysis of all SNPs was performed using Plink Software (version 1.9, Shaun Purcell, https://www.cog-genomics.org/plink/) with age and sex included as covariates [29]. P values of ≤ 0.05 were considered significant.

RESULTS

Demographics

The mean age for the cohort at wave one (baseline) was 65.19 years and 82.88 years at the last stage of data collection. The initial study population consisted of 69.9% females and more than 84% participants across all five waves were retired or unemployed (Table 2).

Regression analysis

Three of the thirteen SNPs investigated were associated with a greater than average decline in memory: Namely rs306336 (beta=-0.308, P=0.018), rs4290173 (beta=-0.141, P=0.023) and rs2834168 (beta=-0.087, P=0.036). Conversely, one SNP was significantly associated with a slower than average decline rate, rs10995245 (beta=0.097, P=0.033). There was a single SNP associated with increased longitudinal decline in processing speed–rs1551570

(beta=-0.116, P=0.013). There were no significant associations between the longitudinal decline of fluid intelligence and vocabulary with the SNPs investigated. Likewise, there was no significant association between any of the cross-sectional cognition tests and the thirteen SNPs. Tables 3 and 4 show the association of all SNPs and the four measures of cognition for both cross-sectional and longitudinal scores.

Table 2: Volunteer demographics.

Variables	Categories	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5
Total attendance		6,063	3,176	624	751	575
Age	Mean	65.19	67.87	76.23	80.56	82.88
Marital status	Married, living with someone	58.45	57.42	56.48	49.53	47.72
	Single, widowed, divorced, separated	41.55	42.58	43.52	50.47	52.28
Current health	Very good	24.86	16.87	19.2	14.85	18.15
	Good	46.69	47.6	53.98	47.14	42.88
	Fair	25.06	32.77	24.22	32.02	33.27
	Bad	2.92	2.41	2.6	5.45	4.98
	Very bad	0.48	0.34	0	0.54	0.71
Smoking (%)	No	82.22	85.37	94.6	96.64	96.1
	Yes	17.78	14.63	5.4	3.36	3.9
Alcohol drinking (%)	No	18.83	34.52	22.4	29.25	31.48
	Less than once in a day	71.8	56.08	68.46	51.97	51.88
	Once in a day or more	9.37	9.4	9.14	18.78	16.64
Usage of sleep medication (%)		n=5,635	n=2,978	n=575	n=716	n=558
	Yes	12.09	11.28	7.3	6.15	5.91
	No	87.91	88.72	92.7	93.85	94.09

Table 3: Cross-sectional scores were those taken at the initial point of testing.

SNP	Memory		Fluid intelligence		Speed		Vocabulary	
	BETA	P	BETA	P	BETA	P	BETA	P
rs10915020	0.087	0.154	0.082	0.154	0.111	0.062	0.078	0.175
rs306336	-0.012	0.923	0.083	0.455	0.064	0.579	0.094	0.403
rs3181077	0.005	0.896	-0.034	0.351	0.006	0.864	-0.018	0.617
rs198811	0.044	0.203	0.038	0.249	0.047	0.169	0.025	0.442
rs2859998	-0.002	0.968	0.056	0.115	0.06	0.106	0.009	0.803
rs4290173	0.022	0.701	-0.032	0.552	-0.04	0.473	-0.005	0.927
rs10995245	-0.039	0.294	-0.046	0.188	-0.01	0.77	-0.043	0.219
rs1154155	0.037	0.457	-0.013	0.774	0.01	0.831	-0.048	0.311
rs1551570	-0.029	0.421	-0.006	0.863	-0.033	0.348	0.001	0.965
rs16966122	0.004	0.933	0.002	0.955	-0.059	0.191	0.013	0.774
rs2834168	-0.025	0.518	-0.031	0.382	-0.028	0.453	-0.016	0.654
rs2834188	0.043	0.266	0.013	0.724	0.015	0.681	0.066	0.071
rs5770917	-0.042	0.606	-0.04	0.603	-0.002	0.976	-0.019	0.807

Table 4: Longitudinal scores are the measure of the trajectory of decline over 12–18 year period.

SNP	Memory		Fluid intelligence		Speed		Vocabulary	
	BETA	P	BETA	P	BETA	P	BETA	P
rs10915020	-0.004	0.956	-0.035	0.612	0.081	0.309	0.035	0.595
rs306336	-0.308	0.018	-0.1	0.452	-0.017	0.91	-0.104	0.416
rs3181077	0.007	0.867	0.019	0.665	-0.025	0.614	-0.004	0.932
rs198811	-0.002	0.968	0.031	0.436	-0.014	0.761	0.032	0.401
rs2859998	-0.033	0.419	0.024	0.582	0.029	0.56	0.026	0.518
rs4290173	-0.141	0.023	-0.041	0.519	-0.015	0.839	0.008	0.89
rs10995245	0.085	0.033	0.013	0.744	0.088	0.065	0.026	0.508
rs1154155	-0.034	0.533	0.056	0.317	0.072	0.266	-0.05	0.35
rs1551570	0.006	0.882	-0.013	0.747	-0.116	0.013	0.03	0.438
rs16966122	-0.003	0.955	-0.028	0.589	0.021	0.723	0.032	0.52
rs2834168	-0.087	0.036	-0.016	0.701	-0.089	0.072	-0.044	0.278
rs2834188	0.028	0.498	0.054	0.216	-0.01	0.843	0.032	0.443
rs5770917	0.009	0.916	0.066	0.473	0.2	0.063	0.029	0.745

DISCUSSION

Narcolepsy is a neurodegenerative disease with an autoimmune pathogenesis. Genetic evidence suggests that immune pathway dysregulation including changes in cytokine signalling, immune cell proliferation and alterations in the process of phagocytosis are common features of neurodegeneration [13]. Initially, alterations in the immune system were thought to be because of neurodegenerative progression but recent evidence implies that genetic variants in the genes encoding areas of the immune system may be central to disease onset and progression [13]. Cognitive functions studied in narcolepsy patients have shown that this patient group displays a pattern of cognitive impairment that does not solely result from the traditional symptoms exhibited. Combined with the knowledge that some narcolepsy patients suffer a range of cognitive impairments may suggest an underlying genetic predisposition. This study was a targeted approach with SNPs selected for biological purpose as they are significantly associated with narcolepsy onset, and therefore we feel that significant SNPs may of interest for future replication studies. We observed three SNPs were associated with an increased rate of memory decline-rs306336, rs2834168 and rs4290173. Both rs306336 and rs2834168 are in the intronic region of the corresponding gene. rs306336 is located on chromosome 1 upstream of genes encoding proteinase K2 (*PKN2*) which is highly expressed in neutrophils and key in the regulation of the cell cycle. rs2834168 is located on chromosome 21 upstream of the region encoding *IL10RB-IFNAR1*. The protein encoded by this gene belongs to the cytokine receptor family and acts as an accessory chain for the IL-10 receptor complex. The additional SNP shown to be associated with an increased decline in long term memory loss prior to correction is the intergenic variant (rs4290173). rs10995245 was significantly associated with a protective impact on long term memory decline. rs10995245 is an exonic SNP located in the genes encoding *ZNF365* on chromosome 10. It has been suggested that *ZNF365* aka zinc finger protein 365 may play a role in the repair of DNA damage and help maintains the stability of the genome.

Narcolepsy has mainly been attributed to the dysfunction of the hypocretin system due to a loss of self-tolerance leading to damage of the monoaminergic and cholinergic nuclei of the brainstem resulting in the symptoms seen [14]. It is well established that monoaminergic and cholinergic systems contribute to a range of cognitive processes implying that impairment of cognition may accompany the traditional narcolepsy symptoms. Previous studies investigating the link between narcolepsy impaired memory have yielded largely contrasting results. Naumann et al., and Rogers et al., reported non-significant results, suggesting that memory is unaffected by the condition, whereas a small number of case reports have suggested there is a significant link between narcolepsy and accelerated memory decline [14,16]. This current work supports the latter, demonstrating that certain narcolepsy associated variants are associated memory decline.

In this study we show that single nucleotide polymorphisms discovered as a result of genome wide association studies associated with the onset of narcolepsy are also significantly associated with memory decline. Conversely, we have also shown that another narcolepsy associated SNP (rs10995245) is protective against natural rate of long-term memory decline. This study further establishes a link between Narcolepsy and Cognition. A recent systematic review which included 35 studies that focused on narcolepsy examined the current literature investigating cognitive dysfunction and hypersomnolence, concluding that there appears to be no or little memory impairment in these patients [17]. However, the supporting evidence is both scarce and conflicting and the number of studies is too limited to draw any meaningful conclusion. Also, all of the recent studies only investigated working and short term memory with no studies focusing on long-term memory. Previous studies have shown significant differences between narcolepsy patients and controls for short term procedural memory, referring to the memory

system responsible for procedures and cognitive skills without conscious awareness of the previous experiences [17]. Additional investigations could be performed to determine the association of genetic polymorphisms to specific cognitive tasks as described recently by Filardi et al., in a narcolepsy cohort to further determine the genetic link between narcolepsy and cognition [17].

CONCLUSION

This is the first study to show the link between narcolepsy associated SNPs and the accelerated decline in long-term memory. Genetic studies provide a largely unbiased way to examine disease pathways in autoimmune conditions and highlight the multifactorial and heterogenous nature of autoimmune conditions. The polymorphisms associated with narcolepsy are pre-dominantly immune based which ultimately impacts on phenotypic cell signalling driving the impaired neuronal effects seen in any neurodegenerative disease. This work further highlights the variation seen in the co-morbidities associated with narcolepsy and suggests that the variation in symptoms is predisposed by the genetics of the individual. It also contradicts the current narrative that any memory loss seen in narcolepsy patients is due to the symptoms of the condition but may be because of the pre-existing genetic markers present.

ACKNOWLEDGEMENTS

There are no competing interests for all authors

Funding was provided by VH Bio (Grant Number N/A)

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