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The Intersection of Cultural Characteristics and Genetics on the Prevalence of Delayed Sleep Phase Syndrome in Brazilian and Japanese Adults

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Abstract

Delayed sleep phase syndrome (DSPS) is a circadian rhythm disorder where individuals experience difficulty modifying the time they go to sleep and wake up in response to environmental changes. The circadian rhythm itself is regulated by a variety of clock genes, and various other genes (e.g., AA-NAT gene, CKIε gene) code for proteins that regulate clock genes. Various polymorphisms of the clock gene influencers have been shown to increase susceptibility to DSPS. This paper seeks to examine how certain cultural characteristics (e.g., napping, timing of meals, exposure to artificial light) and the presence of the AA-NAT gene (G619A polymorphism) and the CKIε gene (S408N polymorphism) influence the prevalence of DSPS amongst Japanese and Brazilian populations.

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Introduction

The circadian rhythm is an intrinsic oscillator of physiological function that results in 24-hour day and night cycles[1]. These cycles allow organisms to adapt to changes in the environment, such as changes in light duration[2]. Zeitgebers are stimuli that act as time-cues for the circadian rhythm[3] and help adjust the duration of sleep to 24 hours[3,4]. Examples of zeitgebers include the amount of light present during the day[2], feeding pattern (breakfast, lunch, and dinner), social/academic commitments, and exercise, with the amount of daylight being the dominant zeitgeber. The center of the circadian rhythm is the suprachiasmatic nucleus (SCN) of the hypothalamus[1]. SCN neurons receive light from the retina, and this photic information is converted into chemical information that alters gene expression of SCN neurons[2]. The SCN transmits the rhythmic information it receives, such as the amount of daylight, to cells found elsewhere in the body (e.g., pineal gland) that results in a variety of outputs (e.g., endocrine signals, body temperature changes)[2]. The SCN induces the pineal gland to secrete melatonin. The expression of melatonin is an important regulator of sleep as it correlates with an increase in sleep propensity[5] and decreased sleep onset latency[6].

Sleep itself is influenced by a variety of cultural and genetic factors, which affect sleep by influencing the circadian rhythm. An example of a cultural factor found in Brazil is the presence of a late evening dinner[7]. Studies have shown that mammals alter their circadian rhythm based on food availability. For example, if mammals are presented with food during the second half of the day, they become more active and experience an increase in body temperature a few hours before the food is given[8]. Thus, the presence of a late evening dinner may decrease sleep onset in Brazilians by increasing physiologic functions such as body temperature. Genes may also influence circadian rhythm. A cluster of genes known as clock genes regulate the circadian rhythm, including cortisol secretion, body temperature, and the actual sleep/wake cycle[9]. These genes have been demonstrated to be present at different frequencies among different ethnic groups. For example, one study demonstrated that the clock gene polymorphisms PER3 and T3111C were found to be present at a higher frequency among Asian descendants in Brazil, as compared to Caucasian descendants[9]. The presence of various polymorphisms has been shown to increase susceptibility to sleep disorders. For example, one study demonstrated that a polymorphism of the PER2 gene showed a significant association with delayed sleep phase syndrome (DSPS) in Japanese adults[10]. This review selected Brazil and Japan as the countries of interest due to the amount of existing literature that focuses on the prevalence of the same types of genes that influence sleep as well as on the different cultural characteristics that may potentially influence sleep trends in both countries.

DSPS is a circadian rhythm disorder where individuals have a sleep schedule that has a considerably later time of sleep onset than is preferred by the individual or is the societal and cultural convention[11]. As a result, individuals with DSPS experience difficulty falling asleep and difficulty waking up, especially when they have to modify the time they go to sleep to meet environmental changes, such as a new work schedule[11]. While the cause of DSPS is unknown[11], the factors that contribute to DSPS likely include behavioral and biological factors[6]. One factor that potentially contributes to DSPS is the use of artificial light before falling asleep[6]. Exposure to artificial light may inhibit the production of melatonin, a hormone that decreases sleep onset latency[12]. Another potential influence on DSPS may be some genes that have been found to have effects on clock proteins, such as the casein kinase I epsilon (CKIϵ) protein which phosphorylates clock proteins[13]. These genes that regulate clock proteins have polymorphisms that have been associated with different disorders of the circadian rhythm, such as DSPS.

While there has been an examination of the genetic influences on the prevalence of DSPS, to the writers' knowledge, there have been no studies to examine how the sleep trends – a cultural factor – of Brazil and Japan may modify how clock genes influence the prevalence of DSPS. The purpose of this review is to examine how the presence of certain genes that influence clock genes and certain cultural characteristics of Brazil and Japan may play a role in the prevalence of DSPS.

Genetic Influencers on the Prevalence of Delayed Sleep Phase Syndrome

The arylalkylamine N-acetyltransferase (AA-NAT) gene, which is involved in melatonin synthesis, and specifically its G619A polymorphism, has been examined in DSPS and non-DSPS patients[14,15]. Hohjoh et al. (2002) examined a Japanese DSPS population in Tokyo. The population was diagnosed based on the diagnostic criteria of the International Classification of Sleep Disorders. The study demonstrated that the G619A polymorphism had a higher prevalence (16.0%) among patients with DSPS, compared to their healthy cohorts who had a prevalence of 3.1%. In contrast, Pereira et al. (2007) found a 0% prevalence of the same G619A polymorphism amongst Brazilian DSPS patients, while a 0.2% prevalence was found amongst the non-DSPS group. The study did not specify which diagnostic criteria was used to select the DSPS patients.

The prevalence of the S408N polymorphism of the casein kinase I epsilon (CKIε) gene, which is expressed in the SCN and encodes a protein that phosphorylate clock proteins, has also been examined in DSPS and non-DSPS patients. Takano et al. (2004) examined DSPS patients in Japan who were diagnosed based on the International Classification of Sleep Disorders and found that the prevalence of the S408 polymorphism of the CKIε gene in their DSPS patients was 6.1%, as compared to 12.3% in non-DSPS patients. Castro et al. (2008) examined the same polymorphism of the CKIε gene in a Brazilian DSPS population, which was diagnosed based on the diagnostic criteria of the International Classification of Sleep Disorders. They found a prevalence of 0% among their DSPS patients and 1.5% among their non-DSPS patients[13].

A comparison of these studies is presented in Table 1.

Intersection of Genetics and the Cultural Characteristics of Brazil and Japan that Influence Sleep on DSPS

The sleep trends found in Brazil and Japan may influence the effect genes have on the prevalence of DSPS in those countries. This may explain why the patients of Pereira et al. (2007) who had DSPS did not have significant prevalence of the AA-NAT gene but still had DSPS. This may also explain why the patients of Takano et al. (2004) and Castro et al. (2008) still had DSPS, despite the fact that they did not have a significant prevalence of the CKIε gene. For example, according to Brazilian custom, dinner is served in the

Table 1. Prevalence of genes associated with DSPS in DSPS and non-DSPS patients

Study	Location	Sample size	Gene	Prevalence
Hohjoh et al. (2002)	Japan	50 DSPS patients; 161 non-DSPS patients	AA-NAT gene (G619A polymorphism)	DSPS patients 16.0%; Non-DSPS patients 3.1%
Pereira et al. (2007)	Brazil	17 DSPS patients; 372 non-DSPS patients	AA-NAT gene (G619A polymorphism)	DSPS patients 0%; Non-DSPS patients 0.2%
Takano et al. (2004)	Japan	196 DSPS patients; 276 non-DSPS patients	CKIε gene (S408N polymorphism)	DSPS patients 6.1%; Non-DSPS patients 12.3%
Castro et al. (2008)	Brazil	16 DSPS patients; 195 non-DSPS patients	CKIε gene (S408N polymorphism)	DSPS patients 0%; Non-DSPS patients 1.5%

DSPS = delayed sleep phase syndrome

late evening, which necessitates a later sleep time[7]. This may be a risk factor for individuals in Brazil who practice this custom to have a delay in their sleep onset. Another study by Santos-Silva et al. (2009) examined sleep trends in the city of Sao Paulo, Brazil. The study examined a variety of sleep habits and complaints over three decades – in 1987, 1995, and 2007. The study showed that over the last few decades, adults have gone to bed at later times. While the population has also woke up at later times, the total time of sleep duration has decreased. The study also demonstrated that complaints of insomnia have increased over the last three decades[17]. The study proposed that the reason for this increase in sleep complaints may be due to the frequent exposure to artificial light that comes with living in an industrialized society. This may also explain why the Brazilian population of Pereira et al. (2007) had DSPS even though there was no significant association of the AA-NAT gene with DSPS. A study by Gooley et al. (2011) demonstrated that exposure to room light before bedtime suppresses melatonin production. Because melatonin decreases sleep onset latency, the use of room light in an industrialized society like Sao Paulo, Brazil may predispose the population to DSPS, even though they do not have the G619A polymorphism of the AA-NAT gene.

In Japan, some individuals practice a daytime nap known as *inemuri*, which often occurs in public areas[18]. The presence of *inemuri* creates a situation where individuals consolidate some of their sleep during the day and the rest of their sleep at night. In the chapter *Negotiating sleep patterns in Japan*[18], Steger describes *inemuri* as an individual sleeping in a situation where they should not be asleep, such as at work[18]. The lack of consistent sleep timing with *inemuri* may create difficulty with sleep onset at night, where the majority of sleep is consolidated in Japan[18], which may be a predisposing factor for DSPS. In addition, a study by Liu et al. (2000) examined 4000 adult individuals over age 20 from mostly suburban and urban regions around Japan. The study found that the overall presence of symptoms of insomnia was 21.4%. While the study did not assess the use of artificial light before bedtime, it can be reasonably presumed that many in their surveyed population used artificial room light before bedtime as is common in many industrialized cities. As discussed previously, exposure to artificial light may suppress melatonin production, which may contribute to a predisposition to DSPS.

Discussion

The results of the four studies examined indicate relationships between the examined genes and the prevalence of DSPS. Based on the four studies examined, the presence of the AA-NAT gene (G619A polymorphism) increased the susceptibility to DSPS among Japanese individuals but not Brazilian individuals. The presence of the CKIε gene (S408N polymorphism) did not increase susceptibility to DSPS among Japanese or Brazilian individuals.

Several theories have been proposed as to why there are genetic differences between ethnicities when it comes to genes that potentially predispose to DSPS. One theory relates the impact of human migration out of the continent of Africa and to various geographic latitudes[20]. These various latitudes present differences in light intensity, temperature, and seasonal changes in the length of a day[20]. The function of the circadian rhythm biological clock is to provide extrinsic information, such as changes in light intensity or day length, so that an organism can modify their intrinsic physiological and/or extrinsic behavioral response to optimize adaptiveness to a changing environment[20]. Thus, the different gene polymorphisms found across various ethnicities may be the result of natural selection to optimize adaptiveness based on differing latitudinal environments[20]. This theory is consistent with the findings of Hohjoh et al. (2002), in which Japanese DSPS patients had a higher prevalence of the AA-NAT gene as compared to the Brazilian DSPS patients studied by Pereira et al. (2007).

One limitation of this review is that other polymorphisms may exist in the samples studied that may contribute to DSPS. The studies that this review examined only looked at two polymorphisms – the G619A polymorphism of the AA-NAT gene and the S408N polymorphism of the CKIε gene. Another limitation to this review is the lack of standardized criteria to determine DSPS in patients across all studies examined. Both Hojhoh et al. (2002) and Pereira et al. (2007) examined the prevalence of the AA-NAT gene (G619A polymorphism) in DSPS patients. Hohjoh et al. (2002) mentioned that the criteria used to diagnose

DSPS was the International Classification of Sleep Disorders. Pereira et al. (2007) did not mention which diagnostic criteria they used. Thus, this may potentially be a confounding factor, as the two sets of DSPS patients from the studies may not have been diagnosed according to the same criteria. Another limitation is the focus on the countries of Brazil and Japan only. Brazil and Japan were selected due to the amount of existing literature examining the genes of interest – the AA-NAT gene and CKIε gene – as well as how specific cultural characteristics potentially affect sleep trends found in both countries. Future studies should examine the same phenomenon in other countries with both similar and different latitudes as well as other genetic polymorphisms that may lead to susceptibility to DSPS.

Conclusion

We reviewed two studies that examined the prevalence of the AA-NAT gene (G619A polymorphism) among DSPS patients in a Brazilian and Japanese population and two studies that examined the prevalence of the CKIε gene (S408N polymorphism) in a Brazilian and Japanese population. While the presence of certain polymorphisms contributes to the presence of DSPS as concluded by the individual studies, this review also examined how the sleep trends found in Japan and Brazil – such as exposure to artificial light before bedtime, the presence of the midday nap in Japan (*inemuri*), and the presence of later dinners in Brazil – may affect the prevalence of DSPS. This review serves to fill a gap in the existing literature by assessing how sleep trends may affect the prevalence of DSPS. Continuing to research in this area would aid clinicians in better understanding the role that sleep habits play in sleep disorders, specifically DSPS, which may in turn facilitate more effective treatment of these conditions.

References

1. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. Nature 2002; 418: 935-941.
2. Dibner D, Schibler U, and Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annu Rev Physiolg 2010; 72: 517-549.
3. Mistlberger R, Skene D. Social influences on mammalian circadian rhythms: animal and human studies. Biol Rhythm 2004, 79:533-556.
4. Edwards B, Reilly T, Waterhouse J: Zeitgeber effects of exercise on human circadian rhythms: what are alternative approaches to investigating the existence of a phase-response curve to exercise? Biol Rhythm Res 2009; 40: 53-69.
5. Zisapel, N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br J Pharmacol 2018; 175 (16): 3190-3199.
6. Nesbit, AD. Delayed sleep-wake phase disorder. Journal of Thoracic Disease 2018; 10 (1): 103-111.
7. Krahn LE, Silber MH, Morgenthaler TI. (2010). Atlas of Sleep medicine. Boca Raton, Fl: CRC Press.
8. Stephan FK. The "other" circadian system: food as a Zeitgeber. J Biol Rhythms 2002; 17 (4): 284-292.
9. Barbosa AA, Pedrazzoli M, Koike BDV, Tufik S. Do Caucasian and Asian clocks tick differently? Braz J Med Biol Res 2010; 43 (1): 96-99
10. Miyagawa T, Hida A, Shimada M, Uehara C, Nishino Y, Kadotani H, Uchiyama M, Ebisawa T, Inoue Y, Kamei Y, Tokunaga K, Mishima K, Honda M. A missense variant in PER2 is associated with delayed sleep-wake phase disorder in a Japanese population. Journal of Human Geneitcs 2019; 64: 1219-1225.
11. Sack RL, Auckley D, Auger RR, Carskadon MA, Wright Jr., KP, Vitiello MV, Zhdanova IV. Circadian Rhythm Sleep Disorders: Part II, Advanced Sleep Phase Disorder, Delayed Sleep Phase Disorder, Free-Running Disorder, and Irregular Sleep-Wake Rhythm. American Academy of Sleep Medicine 2007; 30 (11): 1484-1501.
12. Gooley, JJ, Chamberlain K, Smith KA, Khalsa SBS, Rajaratnam SMW, Reen EZ, Zeitzer JM, Czeisler CA, Lockley SW. Exposure to Room Light before Bedtime Suppresses Melatonin Onset and Shortens Melatonin Duration in Humans. J Clin Endocrinol Metab 2011; 96 (3): 463-472.
13. Takano A, Uchiyama M, Kajimura N, Mishima K, Inoue Y, Kamei Y, Kitajima T, Shibui K, Katoh M, Watanabe T, Hashimotodani Y, Nakajima T, Ozeki Y, Hori T, Yamada N, Toyoshima R, Ozaki N, Okawa M, Nagai K, Takahashi K, Isojima Y, Yamauchi T,

Ebisawa T. A Missense Variation in Human *Casein Kinase I Epsilon* gene that Induces Functional Alteration and Shows an Inverse Association with Circadian Rhythm Sleep Disorders. Neuropsychopharmacology 2004; 29(10): 1901-1909.

14. Pereira DS, Pedrazzoli M, Koike Bdel V, Louzada FM, Benedito-Silva AA, Lopez AR. Tufik S. The G619A Aa-nat gene polymorphism does not contribute to sleep time variation in the Brazilian population. Behav Genet 2007; 37: 637-638.
15. Hohjoh H, Takasu M, Shishikura K, Takahashi Y, Honda Y, Tokunaga K. Significant association of the arylalkylamine Nacetyltransferase (AA-NAT) gene with delayed sleep phase syndrome. Neurogenetics 2003; 4: 151-153.
16. Castro RMRPS, Barbosa AA, Pedrazzoli M, Tufik S. Casein kinase I epsilon (CKIϵ) N408 allele is very rare in the Brazilian population and is not involved in susceptibility to circadian rhythm sleep disorders. Behav Brain Res. 2008; 193(1): 157-157.
17. Santos-Silva R, Bittencourt LR, Pires ML, de Mello MT, Taddei JA, Benedito-Silva AA, Pompeia C, Tufik S. Increasing trends of sleep complaints in the city of Sao Paulo, Brazil. Sleep Medicine 2010; 11 (6): 520-524.
18. Steger B, Brunt L. (2003). Night-time and Sleep in Asia and the West. New York, NY. Routledge-Curzon.
19. Lui X, Uchiyama M, Kim K, Okawa M, Shibui K, Kudo Y, Doi Y, Minowa M, Ogihara R. Sleep loss and daytime sleepiness in the general adult population of Japan. Psychiatry Research 2000; 14 (93) 1-11.
20. Ciarleglio CM, Ryckman KK, Servick SV, Hida A, Robbins S, Wells N. Genetic differences in human circadian clock genes among worldwide populations. J Biol Rhythms 2008; 23: 330-340.