

Genetics of Delayed Sleep Phase Syndrome

April 13, 2008

Matthew Mitchener

Genetics 301 - Section 001

I have neither given nor received unauthorized aid on this assignment.

Part A

Delayed sleep phase syndrome (DSPS) is a circadian rhythm disorder in which patients have sleep-wake cycles that are abnormally shifted forward. Other types of circadian rhythm disorders are non-24-h sleep-wake syndrome (N-24) and advanced sleep phase syndrome (ASPS). N-24 patients have a sleep cycle that has daily delay usually resulting in cyclic insomnia. DSPS and ASPS patients have a normal sleep cycle but wake and sleep either too early or too late to the desired time schedule (Ebisawa, 2001).

Humans base our bodily functions on a 24-hour cycle. These functions include sleep, plasma melatonin, and core body temperatures. These functions use the light and dark cycle of the sun as well as social time cues to operate rhythmically throughout the day. Patients with DSPS have difficulties synchronizing their sleep cycles with the night and experience side effects such as trouble in their social lives (Ebisawa, 2001).

In general most DSPS patients describe themselves as night owls or night people (Ancoli-Israel, 2001). They sleep from 2:00 am to 6:00 am and sleep till around noon or late afternoon (Ancoli-Israel, 2001). Most people with DSPS report having difficulty making it to classes and jobs if they have conflicts between their sleep cycle and their schedules. In a Wolfson and Carskadon study, high school students who went to bed earlier showed higher GPAs than those that went to bed later (Ancoli-Israel, 2001). In the general population DSPS may also be an important contributor to complaints of sleep onset insomnia (Armstrong, 1993).

There is a lot of evidence to suggest that DSPS is an inherited trait. Dagan and Eisenstein reported that almost half of affected individuals reported biological relatives

with similar symptoms (Ancoli-Israel, 2001). Fukuda found that variances in sleeping patterns associated with DSPS were more similar in monozygotic twins than in dizygotic twins (Ancoli-Israel, 2001).

In a study by Ancoli-Israel and colleagues, a pedigree of a DSPS patient did not give any clear explanation for genetic transmission. However they were able to hypothesize some complex inheritance patterns based on the pedigree of a woman with DSPS. The pattern appeared to be a dominant and bilinear mode of transmission. They believed it was dominant because of it seems to be passed down from generation to generation and believed it was bilinear because both the proband's paternal and maternal branches have individuals with symptoms of DSPS. The prevalence of DSPS in the proband's family is higher than that of the general population. In the general population the prevalence is 0.17% in a Norwegian population of ages 19-67 and 0.13% in a Japan study. The proband's family showed a prevalence of 22%, which is significantly higher than the general population. Based on the data of the pedigree, the trait was believed to be x-linked. This is because there were no observed father-to-son transmissions. The trait was most often passed from mother to daughter (Ancoli-Israel, 2001).

Researchers now believe that genes are associated closely with circadian rhythm. In mammals, researchers have identified genes *Per1/2/3*, *CLOCK*, *Cry1/2*, *BMAL1*, and *Casein Kinase I epsilon (CK I ε)* as being closely related to our internal clocks. These genes are expressed in hypothalamic suprachiasmatic nuclei (SCN). SCN is the site of the principal circadian oscillator. Mutations in the *Per2*, *CLOCK*, *Cry1/2* and *CK I ε* genes are said to cause variations in sleep patterns in hamsters in mice. Therefore it is

believed that similar mutations in humans can cause abnormal sleep patterns in humans (Ebisawa, 2001).

In a case comprised of 48 DSPS patients and 30 N-24 patients of Japan and satisfied the International Classification of Sleep Disorders criteria, Ebisawa and colleagues found that H4 haplotype polymorphisms in the Per3 gene are associated with increased susceptibility to DSPS. The results of the study show that mutations in the clock-related genes may cause various circadian rhythm disorders. Sequence analysis of the cDNA revealed that the human chromosome 1 contained all the coding sequences of the hPer3 gene (Ebisawa, 2001). This contradicts the pedigree study by Ancoli-Israel that hypothesized that DSPS was an x-linked trait.

Evidence supports that light therapy can help DSPS patients. Light therapy involves shining bright light onto patients when they wake up in the morning. While light treatment has been the most widely used for DSPS patients, the treatment will not work with blind patients (Armstrong, 1993). Recent study showed that DSPS patients have an abnormal suppression of melatonin during evening exposure (Ancoli-Israel, 2001). Melatonin is a hormone that the brain releases in the pineal gland, which prepares the body for sleep. This secretion occurs when it gets dark and it is suppressed by light. There has been some interest into whether or not melatonin supplements can help people with DSPS since it has been used to treat the effects of jetlag and work shifts (Swierzewski, 2000).

Armstrong and colleagues studied the effects of melatonin's effects in lab rats that had altered sleeping patterns. After 8.7 days of exogenous melatonin injection the lab rats had returned to a new steady state. There were no differences between amount of

melatonin that was injected into the rats and the time it took to reach a new steady state. After the state was reached, the rats slowly delayed back towards their original positions. However, fifteen of the eighteen rats had a sleeping pattern stabilize at a time earlier than their original time. In some cases the difference was as large as 4.5 hours. The exact timing of optimizing the melatonin's effect is critical and can be deduced by a phase-response curve of its outcome (Armstrong, 1993).

According to the study if melatonin advanced the phase shift in rats it could have similar results in humans and could be a great utility for the treatment for circadian rhythm disorders in both blind and sighted humans. In humans, but not rats, differences between phase delays or advances depend on the time of day that melatonin is administered. One downside to using melatonin is that it can induce hypnotic states if taken when endogenous levels of the hormone are high (Armstrong, 1993). At the current time, melatonin supplements are not widely used, but could perhaps be implemented in the future as a possible cure for patients suffering from DSPS.

Part A References

- Ancoli-Israel, S., Schnierow, B., Kelsoe, J., Fink, R. (2001). A pedigree of one family with delayed sleep phase syndrome. *Chronobiology International*, 18(5), 831-840.
- Armstrong, S.M., McNulty, O.M., Guardiola-Lemaitre, B., Redman, J.R. (1993). Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome (DSPS). *Pharmacology Biochemistry and Behavior*, 46, 45-49.
- Ebisawa, T., Uchiyama, M., Kajimura, N., Mishima, K., Kamei, Y., Katoh, M., et al. (2001). Association of structural polymorphisms in human period3 gene with delayed sleep phase syndrome. *EMBO*, 2(4), 342-346.
- Swierzewski, S.J. (2000). Delayed Sleep Phase Syndrome. Retrieved April 9, 2008 from <http://www.sleepdisorderchannel.com/dsps>

Part B

The topic of DSPS is a subject that has a particular personal interest and significance to me. Although I've never been diagnosed as having DSPS I have recently suspected that I have had it my whole life. When I was a baby I would stay up till midnight every night with my dad. My mom said I defied every sleep pattern a newborn was supposed to have. During my school years I would frequently go to bed late at night and have a very hard time waking up in the mornings. I made up for my loss of sleep by taking naps, usually in my classes. Not surprisingly, I was classified as being lazy and apathetic by most of my teachers. For some reason it never got under my skin. Somehow I knew it wasn't my fault, I can't control my sleep.

When I got to college, my sleep cycle got even worse. Instead of falling asleep around 2-3am every night, my schedule jumped to falling asleep around 5-7am. I'm not sure why it did, although there is evidence that stress can affect DSPS. Since it's impossible for me to go to bed at 5-7am every night and still make most of my classes, I've resulted to continually pushing my sleep cycle forward until I can manage a decent schedule. However I've still failed numerous classes because of my excessive absences. Usually once I get on a good schedule it lasts 1-2 weeks before gravitating back to 5-7am every night. Searching for a better solution, I went to the student medical center. They diagnosed me with depression and insomnia. According to the student medical center psychiatrist, the depression was either a result of insomnia, or the other way around. So she planned to cure it all by prescribing Remenon, a sleeping pill and depression prescription. The medication only aggravated my current problem and made me feel even more hopeless. The first night of taking the medication I fell asleep easily, but I

slept 17 hours and missed all my classes that day. Eventually I quit taking the medication. It made me tired all the time and didn't solve my dilemma. An example of how DSPS can be misdiagnosed as sleep onset insomnia (Armstrong, 1993).

When looking at my pedigree, I think there is a fairly strong indication of where I have inherited this trait. My dad and his sister both struggle falling asleep at night. My grandfather also struggled with evening oriented sleep schedule and my grandmother shows no signs of struggling to fall asleep. So this trait appears to have been passed on from my granddad to my dad to me. Which would completely contradict Ancoli-Israel's findings that DSPS is an x-linked trait (Ancoli-Israel, 2001). However in the Ebisawa study, results found that DSPS was connected with the gene Per3, which is in Chromosome 1 (Ebisawa, 2001). Based on the my own personal information and the fact that Ancoli-Israel based her study on one pedigree, I think it is a safe bet that DSPS is probably not an x-linked characteristic. Although my grandparents on my dad's side had four children, only my dad bore children. I also have 2 siblings, however neither of them show signs of sleep struggle.

Lack of public awareness about DSPS has resulted in considerable difficulties by DSPS patients. In fact, after doing an extensive search for popular media articles I came up empty handed. Consequently most cases of DSPS have been stereotyped that they are lazy and undisciplined. Patients with DSPS have difficulty keeping jobs and doing well in school especially if their schedules require them to work early in the morning (Swierzewski, 2000). For many patients simply learning about the disorder can be a life changing experience but by the time most patients get diagnosed they have already are mislabeled as incompetent workers or students for many years. Yaron Dagan of the

Institute for Fatigue and Sleep Medicine has realized that a lot of people suffering from DSPS are incurable even after light therapy and melatonin supplements. In a 1998 study he found that out of 61 DSPS patients, 90% had relapsed to their original sleep schedule a year after their six-week treatment and 28.8% after only one week (Dagan, 1998). He proposed a new medical terminology for such cases called the sleep-wake schedule disorder (SWSD). Although some cases of DSPS cannot be treated, they can rehabilitate patients and help them accept their disability even if most civil and military authorities will not (Dagan, 2001).

In some cases, DSPS patients have become dependent on alcohol and sedatives to help them sleep. However, these solutions only aggravate the problem by complicating the disorder and the body's attempt to reconcile sleeping patterns. If a person's lifestyle is accommodated by DSPS, the symptoms of the disorder do not occur (Swierzeweski, 2000).

Most people with DSPS are often more alert, creative, and responsive late at night. Since most jobs and one's education usually take place in morning, people struggling with DSPS find it hard to be productive. Companies and educators need to learn that they can use people with circadian rhythm disorders more efficiently if they place them on schedules that better suite their sleep cycle.

On the bright side, many DSPS people are finding ways they can cope with their disability with the emergence of the Internet and other work-at-home jobs. One woman going by the alias of Nightweaver, wrote on an internet forum that she had suffered from DSPS for 53 years. It wasn't until the Internet came out that she finally found a way to make some income for her family by becoming a web designer. This also helps explain

her alias (Unknown, 2008). Other DSPS-friendly jobs could include security work, work in theater, the entertainment industry, media, freelance writing, call center work, nursing, taxi or truck driving and work in hospitality.

The Internet has also provided support groups for people struggling with sleep disorders as well as a source of information on ways they can improve their current situation. Sites such as sleepdisorderchannel.com and NiteOwl have given patients comfort in their own situation, knowing that others struggle with their problem.

The social difficulties of DSPS patients are challenging as well. Considering most of the time people with DSPS are awake during the night hours, they don't have frequent social interaction. The psychological effect of lack of social interaction during the night hours needs to be researched further. Many of this disorder report that DSPS causes problems within their marriage, since their spouses sleep at conflicting hours and don't get to see them often.

Depression is a strongly linked characteristic in DSPS cases as well. Depression might cause or result from the disorder. Improving sleep quality and duration is been shown to help with depression. In one study 90% of patients who suffer from depression have some type of sleep disorder. The basic premise is that lack of REM sleep in circadian rhythm disorders is similar to those in cases of depression. REM sleep is also said to produce effects similar to those caused by antidepressant medications (Swierzewki, 2000). So it is understandable that DSPS patients, who have a conflicting work or school schedule, might be susceptible to depression because of their REM sleep duration.

DSPS is a disorder that will take time to fully be accepted by society. At the present it is a disorder that causes people to face adversity for a behavior that they cannot control. It is a disease that receives no sympathy. It is simply looked down upon as an internal attribute caused by a person's laziness and incompetence. Our world needs to start looking for ways to accommodate people struggling with their sleep cycle, not frown upon them. In the future, public awareness is the only way that any improvements can be done to improve the current condition of people living with DSPS and other sleep disorders.

Part B References

- Ancoli-Israel, S., Schnierow, B., Kelsoe, J., Fink, R. (2001). A pedigree of one family with delayed sleep phase syndrome. *Chronobiology International*, 18(5), 831-840.
- Dagan, Y., Yovel, I., Hallis, D., Eisenstein, M., Raichik, I. (1998). Evaluating the role of melatonin in the long-term treatment of delayed sleep phase syndrome. *Chronobiology International*, 18(6), 1019-1027.
- Dagan, Y., Ayalon, L. (2001). Sleep-wake schedule disorder disability: a lifelong untreatable pathology of circadian time structure. *Chronobiology International*, 18(6), 1019-1027.
- Ebisawa, T., Uchiyama, M., Kajimura, N., Mishima, K., Kamei, Y., Katoh, M., et al. (2001). Association of structural polymorphisms in human period3 gene with delayed sleep phase syndrome. *EMBO*, 2(4), 342-346.
- Swierzewski, S.J. (2000). Delayed Sleep Phase Syndrome. Retrieved April 9, 2008 from <http://www.sleepdisorderchannel.com/dsps>.
- Unknown. (2008). DSPS for 53 years... just didn't know the name! Retrieved April 9, 2008 from http://livingwith.sleepdisorderchannel.com/delayed-sleep-phase-syndrome/20080117_3737.