Title

0153 Extreme Morning Chronotypes Are Often Familial And Not Exceedingly Rare: The Estimated Prevalence Of Familial Advanced Sleep Phase (FASP) In A Sleep Clinic Population

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Extreme morning chronotypes are often familial and not exceedingly rare: The estimated prevalence of Advanced Sleep Phase (ASP), Familial Advanced Sleep Phase (FASP), and Advanced Sleep-Wake Phase Disorder (ASWPD) in a sleep clinic population

Abstract:

Study Objectives: Report the first prevalence estimates of Advanced Sleep Phase (ASP), Familial Advanced Sleep Phase (FASP) and Advanced Sleep-Wake Phase Disorder (ASWPD). This can guide clinicians on the utility of screening for extreme chronotypes both for clinical decision making and to flag prospective participants in the study of the genetics and biology of FASP.

Methods: Data on morning or evening sleep schedule preference (chronotype) were collected from 2,422 new patients presenting to a North American sleep center over 9.8 years. FASP was determined using a severity criterion that has previously identified dominant circadian mutations in humans. All patients were personally seen and evaluated by one of the authors (C.R.J.).

Results: Our results demonstrate an ASP prevalence of 0.33%, an FASP prevalence of 0.21%, and an ASWPD prevalence of at least 0.04%. Most cases of young onset ASP were familial.

Conclusions: Among patients presenting to a sleep clinic, conservatively one out of every 300 patients will have ASP, one out of every 475 will have FASP, and one out of every 2,500 will have ASWPD. This supports obtaining a routine circadian history and, for those with extreme chronotypes, obtaining a circadian family history. This can optimize treatment for evening sleepiness and early morning awakening and lead to additional circadian gene discovery. We hope these findings will lead to improved treatment options for a wide range of sleep and medical disorders in the future.

Introduction:

Advanced Sleep Phase (ASP) is characterized by a stable and unusually phase-advanced circadian sleep-wake rhythm relative to local solar time. We refer to Familial Advanced Sleep Phase (FASP) when ASP is demonstrated in multiple biologically related family members.[1] Advanced Sleep-Wake Phase Disorder (ASWPD) is defined as a marked phase advance of the sleep-wake cycle accompanied by a sleep related complaint. FASP is a subtype of ASP and overlaps with ASWPD (Figure 1). Identifying these individuals in a clinical setting appears challenging as they are presumed to be very rare. As the third edition of the International Classification of Sleep Disorders (ICSD-3)

observes, “The existing literature suggests that clinicians are unlikely to encounter patients with stringently defined ASWPD.”[2] The rarity of encountering patients with stringently defined ASWPD is likely a result of the diagnostic requirement for a chronic or recurrent complaint related to the patient’s advanced sleep-wake schedule.[2] Indeed, in patients with young onset ASP, their early morning awakening may not be perceived as a school or work problem, but rather as an advantage. This may explain why ASP was thought to be exceedingly rare in the general population.[3] Many such individuals do not seek medical attention for their ASP. Prior to 1999, the authors are aware of only two convincing case reports of severe, young onset ASWPD.[4,5] Young onset ASWPD was initially thought to be sporadic, but one of these case reports alluded to a family history.[4] Two other case reports are difficult to interpret due to conventional morning wake time and difficulty maintaining sleep in one report[6] and late age of onset in another.[7]

Another potential obstacle to the clinical identification of patients with ASP, FASP, and ASWPD is a lack of recommended cut-off scores on widely used circadian questionnaires to reliably suggest unusual circadian phase advance. Two questionnaires commonly used for this purpose are the Munich Chronotype Questionnaire (MCTQ)[8] and the Horne-Ostberg Morningness/Eveningness Questionnaire (MEQ).[9] Data from Till Roenneberg and colleagues’ growing MCTQ database[8] suggests that individual sleep schedule on free days, a marker of chronotype, is approximately normally distributed and varies with latitude, geographical region, and urban or rural

lifestyle.[10] Using MSF calculations, chronotype has been shown to delay by four minutes for each degree of longitude one moves from east to west, even within the same time zone.[10] The average midpoint of sleep on work-free days (MSF) corrected for extra catch-up sleep on the weekends (MSFsc) also has a latitudinal dependence. In the northerly latitudes of central Europe, MSFsc is centered on 04:00, whereas MSF distribution in India centers on 03:00. Therefore, “intermediate” chronotypes in central Europe would be “late types” in India.[11] Chronotype also has a strong age dependence, with rapidly increasing phase delay through adolescence that peaks sharply at age 20 and is followed by a gradually slowing but persistent trend back toward typical childhood chronotype by the 8th decade.[12] Therefore, ideal criteria for advanced sleep phase might incorporate age, latitude, and longitude. However, to allow for routine clinical use, our experience identifying and phenotyping FASP kindreds in North America suggests that individuals and families with a MSF ≤ 01:30; MEQ scores ≥ 71; and onset of these sleep schedules occurring prior to the age of 30 likely have a familial form of advanced sleep phase.[1,13–19]

In 1999, three families containing a total of 29 strikingly phase advanced individuals were reported by one of the authors (C.R.J.) under the descriptive term “Familial Advanced Sleep Phase Syndrome (FASPS).”[1] We have modified the term to ‘Familial Advanced Sleep Phase (FASP)’ since ‘syndrome’ may connote a disorder to some while many FASP individuals have no complaint about their sleep schedule. One of these families was

used to genetically map and clone the first reported human circadian clock gene mutation in the hPER2 gene.[1,13] The ASP probands in this study were discovered by C.R.J. because they came to clinical attention with complaints suggestive of obstructive sleep apnea (OSA). Due to the absence of circadian complaints, most ASP probands would not meet ICSD-3 diagnostic criteria for ASWPD.[20] For this reason, we refer to individuals and families with the onset of extreme sleep phase advance by age 30 as Advanced Sleep Phase (ASP) and Familial Advanced Sleep Phase (FASP), respectively.

The ASP participants reported here were living urban lifestyles within the North American state of Utah, comparable with the MCTQ central European database. The initial MCTQ database (N = 500) suggested that no more than 2% of the general population in Germany and Switzerland were self-described “extreme early types,” with only 0.8% having MSF ≤ 02:00.[8] Expansion of the MCTQ database (N ≈ 25,000) found estimates of approximately 2% of the general population with MSF ≤ 02:00 and approximately 0.67% with MSF ≤ 01:30.[12] A more recent expansion of the MCTQ database of central European responders (N = 92,567) found a mean MSF (not corrected for workweek sleep deprivation) of 04:58 (±1.56), 2.89% with MSF ≤ 02:00, and 0.97% with MSF ≤ 01:30 (personal communication, T. Roenneberg in 2012). Correcting for latitude predicts a mean Utah MSF of 04:37. If our clinic population is representative of the local population, this would represent the mean MSF for those presenting to the clinic.

Comparing the MCTQ with another widely used tool to assess chronotype, the Horne-Ostberg Morningness/Eveningness Questionnaire (MEQ),[9] revealed reasonable correlations between MEQ and MSF scores (r = -0.73) in a predominantly young adult Dutch population (N = 2,481).[21] Pooling MEQ data from 741 young adults, 484 adults, and 40 elderly participants in London and the United States yielded a weighted prevalence estimate of extreme morningness (i.e., MEQ scores ≥ 71) of approximately 0.51%.[22–25] Taken together, the MCTQ and MEQ databases would predict a prevalence of individuals with extreme morning chronotypes resembling ASP (i.e., MSF ≤ 01:30 and MEQ ≥ 71) to range between 0.50-1.00% in the North American general population. Whether a similar prevalence range accurately reflects the prevalence of individuals with young onset ASP and FASP is currently unknown.

To address this question, we report here the first estimated prevalence of young onset ASP, FASP, and ASWPD obtained from a sleep clinic population. Data on self-report and objective methods used to characterize chronotype and circadian rhythms in young onset ASP, FASP and ASWPD participants are provided. Next, differences in self-reported markers of circadian rhythms, excessive daytime sleepiness, and depressive affect in young onset ASP participants and their conventional chronotype family members were examined. Finally, we explore whether apnea hypopnea index (AHI) predicts MEQ-determined chronotype to gauge whether using a population presenting with symptoms of OSA has potential for generalizability of the results.

Methods:

Research approval for this study was obtained from the University of Utah Institutional Review Board.

Participants

As in many general sleep disorder clinics, most participants presented for signs and symptoms concerning for OSA. This is not surprising, given the high prevalence of OSA in men and women and the availability of clinical treatment options.[2] Name, hospital medical record number, date of first visit, new versus return physician evaluation code, and diagnosis code numbers for all patients seen by C.R.J. from January 1994 through October 2003 were imported from our hospital's scheduling and billing computer record system into an Excel spreadsheet. The spreadsheet was then edited to delete patient encounters other than the initial patient visit. Computer data entry from January 1994 to August 1995 did not use sufficiently specific sleep disorder diagnosis codes or discriminate nighttime sleep laboratory procedures performed by technologists from daytime clinic visits with the physician. However, of the 637 encounters from this period, 571 complete paper charts were available for review and the appropriate diagnosis and procedure codes were manually entered into the edited spreadsheet. The total number of patients seen was 2,422, of whom 1,748 (72.2%) had suspected or proven OSA.

Screening for Advanced Sleep Phase (ASP)

Careful screening for ASP began following identification of the first FASP proband seen by C.R.J. in November of 1992. This 72-year-old female was first described in 1999.[1] Habitual workday and free day sleep schedules were routinely discussed with patients during their initial clinic visit, given the relevance of sleep timing to all sleep disorders. Patients describing MSF ≤ 01:30 with onset of this sleep schedule prior to age 30 were informed of our research following their clinic visit. Willing participants signed a consent form approved by the University of Utah Institutional Review Board. Initial contact and enrollment of patient's family members was accomplished by telephone, email, or U.S. Postal Service.

Expanded Phenotyping of Patients Screening Positive for ASP and Their Family Members

Enrolled participants were asked to complete six questionnaires: 1) Participant Information Form detailing demographic information and family medical history; 2) Epworth Sleepiness Scale (ESS)[26]; 3) A "General Sleep Questionnaire" (GSQ) we designed to assess habitual workday and free day sleep schedules, sleep disorders, medical history, and psychosocial influences on sleep (Supplemental Figure 1); 4) A visual-analog "Wake and

Sleep Questionnaire" developed to assess latencies from lights out to initial sleep onset and from final sleep offset to getting out of bed (Supplemental Figure 2); 5) Morningness/Eveningness Questionnaire[9]; and 6) Beck Depression Inventory II (BDI-II).[27] Participants also completed a 45-60 minute structured telephone interview conducted by C.R.J. or a trained research coordinator. Interview questions included habitual workday and free day sleep schedules, alarm use, daytime napping, daily rhythms of mood and alertness, effects of seasonal and time-zone changes on sleep, confounding influences on sleep (e.g., caffeine, alcohol), age-related changes in sleep schedule, and age-related history of chronotype from childhood to the present (Supplemental Figure 3). This detailed screening included evaluation for alternative causes of early morning awakening such as depression, daytime obligations, insomnia, and OSA.

When possible, questionnaires and structured interview results were compared with in-laboratory polysomnography (PSG), home sleep-stage recordings, and 10-day ambulatory wrist actigraphy with coincident sleep logs, and one evening of salivary dim light melatonin onset (DLMO). The phase angle between melatonin onset and the sleep-wake cycle has been correlated with endogenous circadian period[28] and the DLMO itself estimates the magnitude of circadian rhythm advance or delay. PSG was recorded and scored according to standard procedures.[29,30] Home sleep-stage recordings were performed using the Zeo automated wireless system (Zeo, Inc., Newton, MA) that has shown reliability with in-lab PSG[31] and outpatient

actigraphy and sleep logs.[32] Actigraphy was performed using the MicroMini-Motionlogger (Ambulatory Monitoring, Inc., Ardsley, NY) and Actiwatch-L (Respironics, Murrysville, PA) actigraphs. Actigraphy data were downloaded using Action-W 2.4.17 and Actiware-Sleep 3.4 software and scored automatically using the Cole-Kripke sleep algorithm. Saliva samples to determine DLMO were collected every 30 minutes for 5-6 hours before habitual bedtime on non-workdays by participants in their homes using "Salivette" saliva collection tubes (Sarstedt, Inc., Newton, NC). SolidPhase, Inc. (Portland, ME) analyzed saliva melatonin content using the BUHLMANN Direct Saliva Melatonin Radio Immunoassay (ALPCO Diagnostics, Salem, NH). Participants were instructed to remain in ≤ 30 lux of dim lighting throughout their saliva collection protocol. Lux values were obtained using the Sinometer LX1010B Mini Digital Lux Meter (ShenZhen, China) and recorded on a saliva collection log at the time of each saliva sample.

ASP criteria included the following: 1) the ability to fall asleep before 20:30 and to wake before 05:30 throughout the year in the absence of professional or psychosocial demands or environmental influences (e.g., early morning work start-time, self-imposed morning bright light); 2) the presence of only one major sleep period each day; 3) onset of this stable sleep-wake schedule before the age of 30; 4) the sleep pattern is not maintained by morning stimulants or evening sedative use; 5) the sleep pattern did not develop within 3 months of a traumatic brain injury; and 6) the sleep pattern is not

due to another medical, neurological, or mental disorder (e.g., chronic insomnia disorder, major depressive disorder).

Apnea Hypopnea Index Predicting MEQ-Determined Chronotype

To gauge whether an OSA population is skewed toward morningness or eveningness, we assessed whether AHI selects for MEQ using the Wisconsin Sleep Cohort. Repeated measures linear regression analysis (Proc Mixed, SAS) was performed on MEQ and the log of the apnea hypopnea index (AHI) scores from 3,188 studies on 1,324 participants from the Wisconsin Sleep Cohort. The Wisconsin Sleep Cohort's methods for collection and interpretation of PSG recordings and AHI scores have been described.[33]

Results:

Estimated North American Prevalence of Early Onset ASP and FASP

Eight patients with ASP (three females) were identified and enrolled from January 1994 through October 2003 (9.8 consecutive years). Seven ASP subjects presented with excessive daytime sleepiness (EDS) as their primary complaint. The eighth ASP subject presented with a previous diagnosis of OSA, complaining of nasal continuous positive airway pressure (CPAP) mask discomfort. Diagnostic PSG demonstrated OSA in all five male ASP subjects. The first female ASP proband had suspected upper airway resistance syndrome and declined PSG and multiple sleep latency testing (MSLT),

anticipating a change in her condition after completion of her pregnancy. Subsequently, she had upper airway surgery with self-reported resolution of her hypersomnia. The second female ASP proband presented with worsening EDS secondary to a previous diagnosis of narcolepsy without cataplexy. Diagnostic PSG demonstrated obstructive hypopneas of mild degree (AHI = 11) plus respiratory effort related arousals of approximately five per hour in supine and lateral positions. The third female proband was diagnosed with insufficient sleep associated with advanced sleep phase syndrome and possible idiopathic hypersomnia without long sleep time following PSG and MSLT recordings.

No ASP probands presented with chief complaint of their advanced schedule, and it was thought to contribute to the ultimate diagnosis in one of eight patients. Two probands had ASP onset before the age of 12 and the remaining six probands had ASP onset before the age of 22. All eight ASP probands reported at least one first-degree relative with a similarly advanced sleep-wake schedule, suggesting FASP. At least one relative with ASP from each proband was willing to be interviewed for research purposes. Family member enrollment and circadian phenotyping revealed 15 ASP participants in five families, confirming FASP in five kindreds consistent with an autosomal dominant mode of transmission (Figure 2). Two ASP relatives had age of onset by age 40, with the remaining ASP relatives having onset prior to the age of 22.

Of the 2,422 patients that were seen from January 1994 through October 2003, eight ASP probands and five FASP kindreds were identified who met our ASP criteria. One ASP proband had a sleep complaint related to her advanced sleep schedule. Therefore, the estimated prevalence of early onset ASP, FASP and ASWPD among patients pursuing evaluation at a North American academic medical center is 0.33% (8/2,422), 0.21% (5/2,422), and 0.04% (1/2422) respectively (Figure 3). We consider these estimates to be conservative, as four subjects describing FASP declined research participation and were not included in the above results. If these 4 individuals do, in fact, have ASP, the ASP prevalence estimate is 0.50% (12/2,422). Assuming the 4 to have FASP, an upper estimate of FASP from the dataset would be 0.37% (9/2,422). Further, more mild sleep patterns that did not meet our strict criteria were seen in family members of the three ASP individuals who were not categorized as FASP. Four additional individuals and eight of their relatives were also initially enrolled in our study but ultimately were not included in this data due to not meeting the strict criteria.

We also considered the prevalence estimate for ASP and FASP among the population pursuing evaluation for OSA whose ASP was not thought to directly contribute to the diagnosis. Of the 1,748 patients with suspected or proven OSA that were seen from January 1994 through October 2003, seven patients met criteria for ASP and four for FASP. Therefore, the estimated prevalence of early onset ASP and FASP among patients pursuing evaluation

at a North American academic medical center for symptoms of OSA is 0.40% (7/1,748) and 0.23% (4/1,748), respectively.

Chronotype and Circadian Rhythm Markers of Young Onset ASP and FASP Participants

MEQ scores, MSF times, and saliva DLMO for the ASP probands and their ASP relatives are included in Table 1.

Fourteen non-advanced and non-delayed (i.e., “conventional”) chronotype family members were also identified and characterized in our ASP and FASP kindreds. Comparison between self-reported markers of circadian rhythms, excessive daytime sleepiness, and depressive affect in ASP participants and their conventional chronotype family members are included in Table 2. Comparison of MSF and MEQ in the ASP cohort versus the conventional sleeping family members is demonstrated in supplemental Figure 4.

Apnea Hypopnea Index Severity Does Not Predict MEQ-Determined Chronotype

The majority of the ASP and FASP probands in this investigation pursued evaluation at an academic medical center for symptoms of potential OSA. To assess if OSA selects for chronotype, data was obtained on MEQ and apnea hypopnea index (AHI) scores from 3,188 studies on 1,324 participants from

the Wisconsin Sleep Cohort.[33] Repeated Measures Linear regression analysis revealed no significant predictive relationship between MEQ-determined early morning or late night sleep schedule preference and AHI severity (Figure 4).

Discussion:

In this study, we provide the first prevalence estimates of ASP, FASP, and ASWPD based on a sleep clinic population. All patients were personally seen and evaluated by one of our authors (C.R.J.). Of the eight young onset ASP probands, five FASP families were identified who met our strict ASP criteria. Estimates show an ASP prevalence of 0.33% (8/2,422), FASP prevalence of 0.21% (5/2,422), and ASWPD prevalence of 0.04% (1/2422) (Figure 3). Of the 2,422 total patients, 1,748 presented for OSA. Therefore, the estimated prevalence in an OSA population is 0.40% (7/1,748) for ASP and 0.23% (4/1,748) for FASP. As the eighth proband did not have OSA and instead had a complaint related to FASP, she meets criteria for ASWPD and is not included in the estimate from an OSA population.

Data characterizing chronotype and circadian rhythms using subjective and objective methods for the 8 young onset ASP probands and their ASP family members in this study are given in Table 1. Clock times are reported in participants' local time zone and not solar time. MCTQ data from 21,600 German participants strongly suggests that the human circadian clock is

predominantly entrained by solar time rather than local legal (“social”) time.[10] Therefore, we consider our phenotyping to be conservative, as four ASP probands and one ASP relative performed recordings during Daylight Saving Time, effectively delaying these clock times by one hour in reference to solar time. Three ASP probands (32966, 101344, and 51146) reported routinely delaying their evening sleep onset to avoid early morning awakening, making their advanced MSF times all the more impressive. Proband 101263 denied delaying evening sleep onset, and we were unable to collect this information from probands 25823, 28414, 100381, and 101311. Salivary DLMOs collected on 170 North American adult participants (85 females, average MEQ = 52.11 ± 9.10) revealed a mean DLMO of 20:50 (±1:12).[37] Using the same method of DLMO calculation, ASP proband 101311 is within the earliest 0.21% of this normative database. Similarly, ASP proband 28414 and ASP family member 101382 are within the earliest 0.50% and 20.5% of this normative database, respectively. As 101382 performed her DLMO during Daylight Saving Time, she would be predicted to be within the earliest 4.7% of this normative database using solar (i.e., non-social) time. Due to financial constraints, sleep logs, actigraphy, Zeo, DLMO, and PSG data were collected on fewer conventional chronotypes than ASP participants, limiting statistical comparisons on these measures.

Significant differences in MSF clock times and MEQ scores and between ASP participants and their conventional chronotype family members were expected given our ASP classification criteria (Table 2, Supplemental Figure

4). The tendency towards rigid sleep schedules on workdays (MSW) and non-workdays (MSF) in “extreme early types” have been reported in a large North American FASP kindred[1] and a European study using the MCTQ.[8] Our data confirm this tendency. Young onset ASP participants sleep an average of 5-10 minutes later on weekends compared to an average of 30-38 minutes for their conventional chronotype family members (Table 2). Latency of final sleep offset (Speed WU) was determined using a visual-analog scale we developed that ranges from 0-100: “On awakening most mornings, how long does it take you to become fully alert and active?” (0 = several hours; 100 = seconds; Supplemental Figure 2). Our findings suggest that ASP individuals feel alert more quickly in the morning, i.e. have less sleep inertia, compared to their conventional chronotype family members (Table 2). The tendency for morning types to be more subjectively alert upon awakening may be explained, in part, by core body temperature rhythms. Previous research suggests that morning types sleep at a later portion of their temperature rhythm compared to conventional and evening chronotypes.[24]

No significant differences were observed in Beck Depression Inventory scores between ASP participants and their family members with conventional chronotypes (Table 2). This supports that early morning awakenings observed in ASP and FASP probands are not the result of comorbid depression. No significant differences were observed between ASP participants and their conventional chronotype family members in self-reported daytime sleepiness (Table 2). Elevated ESS scores may be expected

for the eight ASP probands who each presented with clinical symptoms of EDS related to OSA (n = 7) or idiopathic hypersomnia (n = 1). However, ESS scores from these eight ASP probands were combined with ESS scores from 7 FASP family members (total n = 15), which may account for these non-significant results. Sleep quality and quantity are typically reported as normal for age when ASWPD patients without comorbidities allow themselves to fall asleep and awaken without regard to social constraints.[2]

Our method of screening for FASP began with habitual sleep time and thus does not account for individuals who may be advanced but can easily overcome their circadian clock and sleep at a more conventional time. Additionally, our criteria rely on mid-sleep time on free days and responses to the MEQ, which may have excluded some individuals who appear advanced by other measures. While this may lead to an underestimate of ASP, our rigorous screening method has proven effective in identifying FASP. These strict criteria avoid false positives and increases the yield for genetic screening in families with a dominant pattern of inheritance. This method has led to successful identification of multiple clock genes that co-segregate in the family and are then recapitulated in mouse models.[1,13,15,17,18] Therefore, this screening method can translate simple questions about sleep timing on an entry sleep clinic questionnaire into identification of families with an autosomal dominant sleep trait and lead to identification of genes controlling our circadian clock.

Our ASWPD prevalence estimate of 0.04% includes only those individuals presenting with ASP prior to age 30. This estimate does not account for individuals with ASP of aging, whose schedule advance with aging prompts complaint. Therefore, the present estimate likely underestimates the true prevalence of ASWPD, even within a sleep clinic population. Figure 1 illustrates the relationship between ASP, FASP, ASWPD, and ASP of aging. FASP represents the majority of young onset ASP, and a small portion of this group will complain of their advanced phase, thus falling into ASWPD. However, some with ASWPD may have ASP only due to aging or other unidentified causes. While it is known that chronotype advances with age, the formal definition and prevalence of ASP of aging is not defined.[12] Therefore the relative size of the circles in figure 1 does not reflect the relative prevalence of ASP vs. ASP of aging, as the prevalence of ASP of aging is not known.

The young onset ASP and FASP prevalence estimates reported here were based on a clinical population presenting to an academic medical center. We have also calculated the prevalence from the population presenting only for OSA, resulting in an ASP prevalence of 0.40% (7/1,748) and FASP prevalence of 0.23% (4/1,748). This limited sample was used because we can assess whether this sample selects for chronotype and thus can consider whether the estimate may have a potential for generalizability. We conducted a linear regression analysis of MEQ and AHI scores from 1,324 participants using the Wisconsin Sleep Cohort database (Figure 4). Results of this analysis found no

significant predictive relationship between these variables, indicating that using a sleep clinic population presenting for symptoms of OSA does not appear to bias the chronotype of the sample. Whether our ASP and FASP prevalence estimates can be further generalized to the population merits additional investigation. Additionally, as our team published research on FASP beginning in 1999; it is possible this altered the patient group seeking care in the clinic, making this clinic estimate less representative of other sleep clinics. This is not a population-based sample.

We aim to raise awareness about ASP and FASP with the hope this prompts routine screening, enhancing clinical care for those affected. It is notable that many with ASP and FASP are not troubled by this sleep pattern. Increased awareness will improve screening for these phenotypes and enrollment in related research. Taken together, our findings suggest that ASP and FASP subjects routinely present to sleep centers with primary complaints that do not appear directly related to sleep-wake schedule advance. Our ASP and FASP prevalence estimates are higher than one would predict based on the prevailing understanding of ASP from ASWPD. Our data supports that ASWPD is very rare at one out of every 2,500. Milder versions or those who develop ASP of aging are not accounted for in the dataset.

In our clinical experience, a six-bed sleep clinic running five nights per week may see 1,500 patients and perform 450 new diagnostic PSGs annually. Our FASP prevalence estimate of 0.21% would predict approximately one incidental FASP PSG recording per six-bed sleep center per year. The 2016-

2017 American Academy of Sleep Medicine (AASM) Membership Directory (www.aasmnet.org) lists 1,512 AASM-accredited sleep centers currently operating within the United States. Therefore, approximately 1,000 diagnostic PSG recordings may be performed on potential OSA patients who also have FASP in the United States annually. This number is likely conservative, as 1,615,135 PSG recordings were estimated to have been performed in the United States in the year 2001.[34] Assuming only 50% of these recordings were performed for new patient OSA evaluations, our FASP prevalence in an OSA population estimate of 0.23% predicts 1,857 PSG recordings were performed on potential OSA patients with FASP in 2001 alone. To our knowledge, only 11 FASP families have been reported to date,[1,15–18,35,36] suggesting that there is potential to identify far more FASP individuals during routine clinic evaluation.

Individuals with ASP often complain of a longstanding pattern of evening sleepiness and early morning awakening with trouble returning to sleep. They may have shorter sleep hours if attempting to stay up for social, work, or family obligations without the ability to awaken later. There is a growing body of literature linking fewer hours of sleep to multiple negative health outcomes including increased mortality, diabetes mellitus, hypertension, cardiovascular disease, and obesity.[38] It is essential for clinicians to appreciate the circadian explanation for shorter sleep hours for this patient population to provide appropriate counseling and treatment options.

Therefore, we recommend routine screening for circadian phenotypes in all sleep clinics with two questions:

1) On a long weekend or vacation with few or no responsibilities or obligations, when would you go to bed?

2) On a long weekend or vacation with few or no responsibilities or obligations, when is your final awakening for the night?

These simple questions included in new patient packets can allow the clinician to screen for both ASP and DSP, with follow up questions if atypical timing is noted. Asking about long weekend and vacation rhythms is important to remove the extrinsic demands of school, work, and family and rebound sleep during weekends.

Recognizing that extreme sleep-wake schedule advance is not exceedingly rare may assist clinicians in separating the early morning awakenings of ASP from the early morning awakenings of insomnia, nocturia, environmental sleep disruptions, and major depressive disorder. Identifying FASP subjects will require clinicians to routinely ask about habitual workday and free day sleep-wake schedules and explore familial patterns of ASP if extreme sleep-wake schedule advances are described. Our findings further suggest that ASP individuals with onset prior to age 30 should be considered likely FASP probands.

Importantly, the clinical identification of young onset FASP individuals and their family members has facilitated the discovery of autosomal dominant circadian clock gene mutations in hPer2,[13,14] CKIδ,[15,16] PERIOD3,[17] CRY2,[18]

TIM,[39] and DEC2.[19] FASP clock gene mutations have been found to co-segregate with familial migraine (casein kinase 1δ)[15] and depressive affect (PER3),[17] and regulatory roles for core clock genes in tumor suppression,[40] sugar metabolism,[41] behavioral activation,[19] and the age of onset of bipolar disorder[42] have been reported. Therefore, functional characterization of newly discovered clock gene mutations may lead to improved treatment options for a wide range of sleep and medical disorders in the future. Our findings provide an indication and mechanism for clinicians to routinely screen for ASP and FASP subjects.

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Figures

Figure 1: Venn diagram of relationship between advanced sleep phase (ASP), familial advanced sleep phase (FASP), advanced sleep-wake phase disorder (ASWPD) and ASP of aging

Figure 2: FASP Pedigrees. Circles: females. Squares: males. Diagonal line through symbols: deceased. Numbers underneath symbols: DNA identifier. Arrows: probands.

Figure 3: Flow chart of patient enrollment and prevalence estimates.

Figure 4: Apnea Hypopnea Index (AHI) Severity Does Not Predict Morningness-Eveningness Questionnaire (MEQ)-Determined Chronotype. Note: N = 3,188. Females: 1491 (mean age = 57.7). Males: 1697 (mean age: 59.4). Mean MEQ scores = 62.08 ± 9.71. Mean AHI scores = 14.08 ± 17.78. Trend line reveals no significant relationship between AHI and MEQ ($\beta = 0.08$, SE $\beta = 0.13$, $p = 0.52$, $R^2 = 1.0\ e^{-5}$).