THE UNIVERSITY OF ARIZONA
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Department of Family and Community Medicine
Healthy Families in Healthy Communities

SLEEP IN-EQUALITY: Functional gene variant in the pseudo-autosomal ASMT gene, delayed circadian rhythms, and depression in African Individuals.

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Introduction

Melatonin is a neurohormone secreted by the pineal gland that regulates the function of the suprachiasmatic nucleus. Acetylserotonin O-methyltransferase (ASMT) catalyzes the final reaction in the synthesis of melatonin. **Single nucleotide polymorphisms (SNPs) of ASMT gene and promoter region in humans have been associated with dramatic decreases in melatonin synthesis in patients with neuropsychiatric disorders.** Moreover, people with depression tend to display circadian rhythm phase delays, most notably in the melatonin offset, and eveningness has been associated with more severe depressive symptoms [2]. Interestingly, sex-linked ASMT SNP (rs4446909) has been associated with depression and bipolar disorder [3-6].

Data from the 1000 genomes project suggests there are **racial/ethnic differences in the population distribution of rs4446909 alleles**. The frequency of the G at risk allele is around 85% for Hispanics/Latin Americans, compared to 99% for African Americans, and 70% for Caucasians. The inte-racial/ethnic differences in the frequency of allele G may represent a genetic basis for differences in circadian phase and depression.

Methods

DATABASE: **H3 Africa** Cohort (Nigeria & Ghana) n~6,000

- Inclusion: only individuals with complete data on sleep measures, age, sex, medications, genotype, & ethnic background
- Exclusions: shift-workers, sleep duration <3, >14 hrs

Genotyping: rs4446909.

Main Outcome Variables:
- Sleep Onset Time *(MCTQ)*

Secondary Outcome Variables:
- Depression defined by CES-D

Preliminary Data

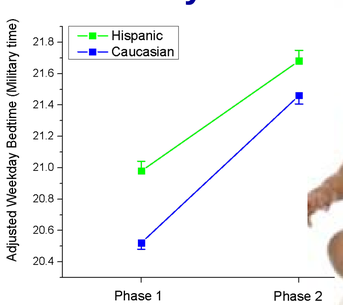
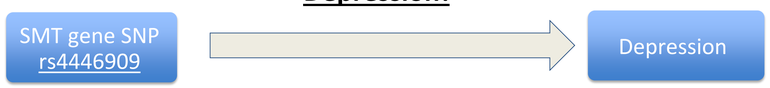


Figure 1.
Hispanic children slept less than Caucasian children at phase 1 (9.5 hours vs. 10 hours, p<0.0001), and went to bed at a later time (9 pm vs. 8:30 pm, p<0.0001) [8]. ***African Americans had a delayed bedtime when compared to Caucasians and Hispanics and greater depression scores***.

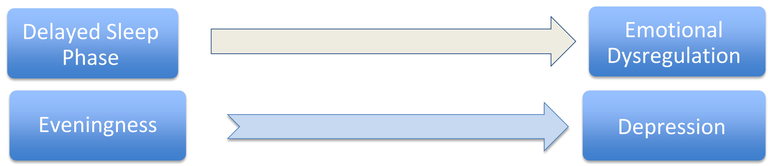
Study Question

We know that ASMT gene SNP is association with Depression!



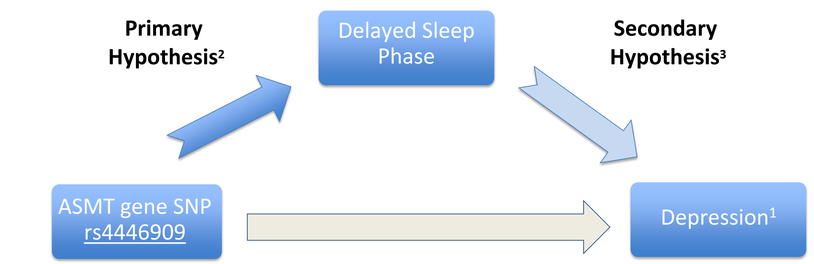
Etain et al, Hum Mol Genet. 2012 Sep 15;21(18):4030-7.

We know that people with Delayed Sleep Phase experience Emotional Dysregulation!



We know that Eveningness is associated with Major Depression!

Does delayed sleep phase mediate the functional gene variant's association with depression?



1) Etain, B. *et al Hum Mol Genet* **21,** 4030–4037 (2012)

2) Kripke, D. F. *et al. J Circadian Rhythms* **9,** 8 (2011).

3) Shirayama, M. *et al. Sleep Med.* **4,** 427–433 (2003)

Research Hypothesis

Primary Hypothesis:

rs446909 is associated with delayed sleep phase as measured by self-reported bedtime. We hypothesize that subjects carrying the common allele G will have later sleep onset time than those carrying the less common allele A.

Secondary Hypotheses:

rs446909 is associated with depression. Delayed sleep phase mediates the
relationshi between the Sex-linked functional gene variant in ASMT promoter
gene (**rs4446909**) and depression.

References

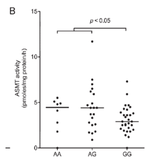
1.Etain et al, Hum Mol Genet. 2012 Sep 15;21(18):4030-7.
2.Kripke, D. F. *et al. J Circadian Rhythms* **9,** 8 (2011).
3.Shirayama, M. *et al. Sleep Med.* **4,** 427–433 (2003)

Rs4446909 is associated with Bipolar Disorder

	French sample BD ($n = 345$)	Controls ($n = 272$)	German sample BD ($n = 480$)	Controls ($n = 672$)	Meta-analysis
SNPs					
rs4446909					
f(G)	0.74	0.67	0.76	0.72	
P-value (P_G)	**0.01 (0.04)**		**0.05** (0.20)		**0.002**
OR [95% CI]	1.38 [1.07–1.76]		1.22 [1.00–1.48]		1.28 [1.09–1.49], $Q = 0.45$

"Eveningness" (Owl-like sleep-wakefulness behavior) was associated with non-remission of Depression

Variables	Adjusted model 2 [b] OR (95% CI)	P
ISI	1.12 (1.05–1.19)	< 0.001
Eveningness	3.36 (1.35–8.34)	< 0.01



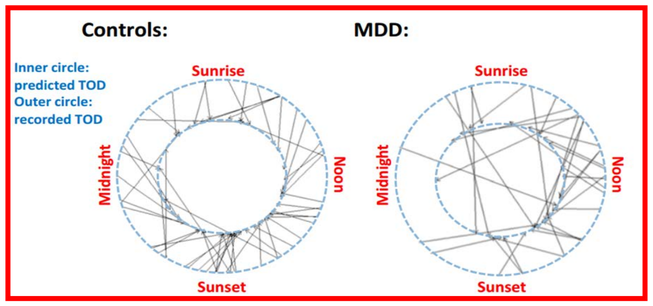


Figure 2 . In 2013, Li et al have shown that cyclic patterns of clock gene expression transcripts were shifted (delayed) in donated brains of those with major depression when compared to those without depression[7]

Etain et al, Hum Mol Genet. 2012 Sep 15;21(18):4030-7.

Data Analysis

Linear regressions models will be fitted to assess whether the association between 'depression' (D) and 'genotype' (G) time is mediated by 'sleep onset time' (S). The first equation will regress the outcome (D) on the independent variable (G) and the mediator (S) [1]. The second equation will regress mediator (S) on the independent variable (G). In both regressions, the covariates (C) will be included.

$$E[D|g,s,c] = \theta_0 + \theta_1 g + \theta_2 s + \theta_4{}'c \quad [1]$$
$$E[S|g,c] = \beta_0 + \beta_1 g + \beta_2{}'c \quad [2]$$

Future Plans

Our next steps are to complete data collection of sleep onset data and actigraphy on our African cohort. These results will be compared with sleep and depression data on Africans in America with the G- genotype. Our potential findings may have a direct impact on identifying the genetic basis for susceptibility to misaligned circadian timing (delayed sleep phase) and relevant patients outcomes (depression) in under-served populations.

Acknowledgments

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