Commentary

Probing personalized genetic platforms for novel molecular clues for circadian chronotype

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Chronotype (also referred to as morningness-eveningness or diurnal preference) is the tendency to be an early "lark" (alert and preferring to be active early in the day) or a late "owl" (alert and preferring to be active later in the day). Chronotype shows considerable interindividual variation and is the most frequently measured circadian rhythm trait. This trait can be evaluated in an individual via the completion of a self-reported questionnaire, such as the Horne-Östberg Morningness-Eveningness Questionnaire (1) or the Munich Chronotype Questionnaire (2). These are the most commonly utilized measures of circadian phase preference (3,4).

There are well-established and robust individual differences in circadian rhythms, including in chronotype and its extreme clinical variants, namely primary circadian rhythm sleep disorders (3,4). A number of twin studies, which allow the assessment of the relative contributions of genetics and environment, demonstrate chronotype has substantial heritability of about 40–60% (5). The genetic underpinnings of individual differences in the circadian system and chronotype have been investigated in humans mostly using candidate gene approaches, in part due to smaller sample sizes (3,4). These studies—albeit with some inconsistent findings likely due to sample sizes—collectively underscore the involvement of various key core circadian genes involved in chronotype and its extremes (3,4).

Both heritability and candidate gene studies of chronotype successfully laid the groundwork for genome-wide association (GWA) studies. These are genome-wide, systematic, comprehensive and unbiased approaches to identify genes and genomic variants associated with a human trait or disease using population samples. While numerous GWA studies in adults have been conducted for mood disorders and medical conditions (6), and for sleep duration and quality and for sleep disorders (7), the ability to conduct GWA studies of chronotype has remained elusive. However, with the advent of personalized genetic platforms available to the general population, the large sample sizes required for such studies are now possible to obtain, opening the door to such investigations.

The recent article by Hu and colleagues (8) in *Nature Communications* is the first GWAS of self-reported chronotype, yielding new insights for circadian biology. It capitalizes on personalized genetic platforms and gene test technology, allowing the authors access to a remarkable sample size of 89, 283 individuals from the customer database of 23andMe Inc. This study found 15 genetic variants were significantly associated with self-reported morningness, 7 which were near well-defined circadian genes, including *PER2* and *PER3*, which have known associations to chronotype (9-11), and *RGS16*, *VIP*, *HCRTR2*, *RASD1*, and *FBXL3*. There was also a significant genetic correlation between chronotype and self-rated depression, replicating prior findings showing these factors share a significant amount of their underlying genetic variance (12). In addition, chronotype was associated with body mass index (BMI), whereby morning chronotypes were less prevalent in the higher BMI groups, replicating another study in adults (13). While intriguing, Mendelian randomization analysis failed to find causal relationships, highlighting the need for replication of these results.

One month after the publication of Hu *et al.*'s study (8),

another GWA study investigating chronotype was published using the UK Biobank cohort of 100,420 individuals, the largest sample to date (14). Lane and colleagues (14) identified 12 new genetic loci associated with self-reported chronotype, including variants near four genes with known roles in circadian rhythms: *PER2*, *APH1A*, *FBXL13* and *RGS16*. Notably, 8 of the 15 reported gene loci from Hu *et al.*'s study (8) were replicated, with all 15 loci showing a consistent direction of effect. In addition, genetic correlation analysis revealed relationships between chronotype and schizophrenia, educational attainment and BMI, though replication of these findings is needed since two of these relationships did not show causality.

A third GWA study for chronotype by Jones *et al.* (15) was recently posted on a preprint server (and has not yet been peer-reviewed) using 128,666 individuals from the UK Biobank cohort. The authors found 16 variants were associated with self-reported chronotype including variants near two known circadian genes, *RGS16* and *PER2*; both of these were also detected in the Hu *et al.* and Lane *et al.* studies (8,14), thereby underscoring their role in circadian chronotype. The authors replicated their own findings using both the UK Biobank and the same self-reported chronotype dataset from the Hu *et al.* study (8). They found 13 chronotype signals remained significant in this meta-analysis, with 11 remaining significant in the same direction in the 23andMe dataset alone.

The Hu *et al.* study (8) used two questions rather than a standardized questionnaire (1,2) to determine chronotype, which is a phenotypic aspect of circadian rhythmicity in humans. Despite this apparent weakness, the authors' results were consistent with studies using standardized questionnaires in terms of the relationships between age and chronotype and gender and chronotype (16), and their results were remarkably replicated in Lane *et al.*'s (14) and Jones *et al.*'s (15) studies (both which used only one question), suggesting an entire questionnaire may not be necessary for assessing chronotype.

It would be of significant interest to determine whether Hu *et al.*'s findings (as well as those of the other two GWA studies) generalize to African Americans, given robust differences between African Americans and Caucasians in basic properties of the circadian clock that contribute to morningness-eveningness, including endogenous period (tau) and the magnitude of phase advances and delays (17). Similarly, whether the results generalize to other ethnic populations beyond those of European ancestry, such as Asian groups who show noticeable allelic variation differences in circadian genes associated with chronotype and its clinical extremes (18,19), remains to be examined in future studies.

GWA studies such as the one by Hu *et al.* (8) have notable advantages and disadvantages (7,20). GWA studies generate large amounts of genetic data and are well-powered to detect common variants associated with a trait such as chronotype. However, they fail to account for all of the heritability associated with a trait; they rarely detect the causal variant(s) linking heredity genotypes to trait phenotypes; and because of required rigorous corrections for multiple testing, the high statistical cut-off points can produce unduly high rates of false negatives (7). Therefore, GWAS used in conjunction with other next generation techniques such as targeted and exome sequencing, and also with established methods such as candidate gene studies among others (7), will be required to fully elucidate and validate the functional variants underlying human chronotype.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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