MINI-REVIEW

Circadian Rhythm and Polygenic Risk Scores

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Genome-wide association study (GWAS) have led to paradigm shift in the study of psychiatric illnesses. However, GWAS has certain limitations. Thus, investigators have invented the concept of polygenic risk using GWAS. The current study aimed to review the papers on the association between polygenic risk score (PRS) and circadian rhythm. Circadian preferences are indicative of endogenous circadian rhythms. Some studies have revealed that the PRS for circadian preferences is associated with sleep timing, median sleep time, and the risk of bipolar disorder. Moreover, another study revealed that the PRS for diabetes, Alzheimer's disease, and mood disorders was associated with sleep patterns, wakefulness after sleep onset, and circadian rhythm. In conclusion, the PRS is an anticipated biomarker for predicting diagnosis, treatment response, and clinical outcomes. Thus, PRS will play many roles in personalized medicine soon.

Keywords: Polygenic risk score; Circadian rhythm; Circadian preference

INTRODUCTION

Circadian rhythm is a phenomenon caused by the rotation of Earth and has a cycle of approximately 24 h. In humans, circadian rhythms are activated through suprachiasmatic nuclei following light stimulation and create functioning patterns in the body such as sleep awakening cycles, body temperature regulation, hormone secretion, blood pressure regulation, cognitive function, mood swings, and circadian preference. This circadian rhythm is affected by environmental factors, such as day and night, physical activity, social interaction, and meals [1], and by genetic differences, as indicated by some genome-wide association studies (GWASs) [2-4]. Among the several factors that affect circadian rhythms, this paper focuses on genetic aspects and reviews the association of various genetic factors with circadian rhythms by focusing on genetic studies using polygenic risk scores (PRS).

Recently, determination of PRS using a number of genetic data has been spotlight. PRS is determined using the odds ratios (patients vs. normal controls) from a previous GWAS data and are applied to the GWAS data of a new sample [5].

POLYGENIC RISK SCORES AND CIRCADIAN PREFERENCES

Circadian preferences are indicative of endogenous circadian rhythms. Individuals with the morningness wake up earlier and go to bed earlier and on the contrary, those with eveningness wake up later and go to bed later [6]. An association was found between the chronotype and physical and mental health [7]. For example, individuals with evening preferences has been related to an increased risk of mental and physical illnesses compared to those with morning preferences [8].

First, let us examine the relationship between PRS and the circadian preferences in the general population. Recently, a circadian preference study on the PRS was reported. The PRS for morningness of 100 subjects from a community cohort sample was determined using the GWAS for British subjects who included in the UK Biobank study and 23andMe data [2]. This study used 11 single-nucleotide polymorphisms (SNPs) with $p<5\times10^{-8}$ in GWAS for self-reported chronotypes for PRS production [2]. PRS was derived by performing a logarithmic transformation of the odds ratio of SNPs for morning preference indicated in the previous GWAS and then summing each score across the SNPs within p-value threshold. The PRS for morningness was related to earli-

er median sleep time on weekends. The phase delay of the circadian rhythm in adolescence was significantly weaker among individuals with high PRS for morningness. Additionally, 4 out of the 11 SNPs derived from the GWAS had a significantly different effect on the median sleep time during childhood. The T allele of rs75804782 and the G allele of rs372229746 were also related to an earlier median sleep time at eight years. These SNPs are linked to neurogenesis and the regulation of circadian rhythm [9,10]. This study revealed that the PRS for morningness was significantly related to circadian rhythm in childhood.

Another study examined the PRS and circadian preferences for adults. PRS for morningness of subjects from three cohorts were determined using the previous GWAS of the UK Biobank and 23andMe samples [2]. This study adopted p-value thresholds of 5×10^{-8}, 0.001, 0.01, 0.03, 0.1, and 1. Eveningness was more frequent among women than men. Morningness was more frequent in older individuals than the intermediate type or eveningness (p< 0.0001). Morningness-Eveningness Questionnaire (MEQ) was correlated with PRS for morningness. For all the age groups, a similar finding revealed where the mean MEQ was higher for higher PRS in the group of morningness-best-fit deciles. The mean median sleep time on the weekend for subjects aged 25−69 years was earlier for higher deciles of PRS for morningness-best-fit, suggesting that stronger genetic characteristics for morningness correlated with an earlier sleep-wake rhythm (p<0.0001); however, in this study, the PRS for morningness showed a very low ratio of contribution to the variation in self-reported diurnal preference.

To date, studies on PRS and chronotype have shown significant results; although there were differences in results according to methodology or age, the correlation between the PRS and chronotype was low. This cannot be ruled out because the GWAS of the discovery sample was limited to 40−69 years of age, and the discovery sample and target sample were obtained from different countries. Despite these limitations, the two studies reported the relationship between circadian preference and PRS in healthy people, and I think they will serve as a touchstone for future research.

There have been reports related to PRS and chronotype in patients with bipolar disorder (BD) risk. In one study, the relationship between chronotype and PRS in the normal group was investigated [6]. This study performed a GWAS to evaluate diurnal preferences in Mexican Americans and American Indians. Genetic data from the two cohorts were analyzed to determine the association of BD risk with the evening type. PRS detected a common genetic relationship between evening preference and related disorders. PRS analysis provided evidence that a BD-PRS p-value threshold of 0.03 and PRS for depressive symptoms (DS) at a p-value threshold of 0.49 predicted the risk of being an evening type (BD: p=0.012 and DS: p=0.032). The PRS for schizoprenia did not significantly predict the evening type. Additionally, four variants of the KIAA1549L gene previously associated with suicide attempt in individuals with BD [11] were associated with the eveningness. This study used the term 'genetic risk scores (GRS)' instead of PRS. PRS and GRS are sometimes used interchangeably

but they have slightly different meanings. GRS is also calculated by summing the disease risk for several alleles, similar to PRS. However, unlike PRS, it can also add up a much smaller number of SNPs. In conclusion, PRS is a component included in GRS [5]. However, when adding a large number of SNPs, the term PRS is generally used, and GRS can be used when adding a relatively small number of SNPs.

POLYGENIC RISK SCORES AND CIRCADIAN RHYTHM RELATED TO THE RISK OF VARIOUS DISEASE

Some investigators examined [12] the association between diabetes and genetic risk, sleep components, and their interactions. Participants of European ancestry consisted of 360,460 population-based cohorts from the UK Biobank study [13]. Sleep behaviors were analyzed using self-report questionnaires at baseline. The PRS for type 2 diabetes was calculated based on a previous GWAS that analyzed European ancestors with type 2 diabetes [14]. Additionally, genetic risk was divided into three categories: low, intermediate, and high, based on the PRS for diabetes. This study revealed that genetic risk and sleep patterns are independently related to the risk of type 2 diabetes. In spite of the genetic risk of type 2 diabetes, a favorable sleep pattern was related to the lower risk of type 2 diabetes compared with intermediate and unfavorable sleep patterns.

Another study examined the association of sleep abnormalities in patients with Alzheimer's disease (AD) with eight genes on circadian rhythms [15]. Movement data and sleep variables were obtained using accelerometers and sleep logs. The PRSs for various circadian rhythms were calculated using previous GWASs [16]. Only 2 of the 30 PRSs for circadian rhythms were significantly associated with wakefulness after sleep onset. Thus, it is unclear whether PRSs for circadian rhythms are related to circadian abnormalities in individuals with AD.

A recent study examined the association between the rhythm of rest and activity using accelerometer data with PRS [17]. A total of 91,448 participants with accelerometer data from the UK Biobank cohort [13] were enrolled. The relationship between the PRS for relative amplitude and psychiatric disorders was also evaluated. Additionally, the relationship between the PRS for relative amplitude and mood instability/neuroticism was evaluated. PRS, including SNPs at six different significance thresholds, were divided into three or four different PRS. The PRS for low relative amplitude of rest was significantly related to mood instability, major depressive disorder, and neuroticism. These findings suggest a genetic link between abnormal circadian rhythms and mood disorders.

A study on the role of PRS in circadian rhythms and stress responses has also been reported [18]. A total of 186 children were enrolled in this study. PRS was based on six genome-wide significant SNPs calculated from CORtisol NETwork (CORNET) meta-analyses [19]. Salivary cortisol levels were evaluated at the base-

line following a stress test. In group with higher PRS, the diurnal salivary cortisol levels reduced less from wake-up to sleep at night than in group with lower PRS. After a stress test, cortisol levels escalated in group with higher PRS but remained unchanged in group with lower PRS. These findings were primarily derived by rs7161521 (SERPINA6) and rs4900229 (SERPINA1) and genetic variation in SERPINA6/ 2/1loci might support higher hypothalamic-pituitary-adrenocortical axis activity.

CONCLUSION

In conclusion, the PRS is a promising marker for predicting diagnosis, treatment response, and clinical outcomes. Thus, in the future, PRS will play an important role in personalized medicine.

Conflicts of Interest
The author has no potential conflicts of interest to disclose.

Availability of Data and Material
Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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