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PHYSIOLOGY AND GENETICS OF CIRCADIAN RHTHYMS AND SLEEP IN HUMAN HEALTH AND DISEASE

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Circadian rhythms and sleep are fundamental biological processes that regulate daily patterns in physiology and behavior. The circadian system follows an approximately 24-hour cycle and is controlled by a central pacemaker in the hypothalamic superchiasmatic nucleus (SCN) and peripheral oscillators present in virtually all organs and tissues, ranging from the heart to the liver and even skin cells. Sleep is regulated by the interaction between circadian timing and homeostatic sleep pressure.

Disruption of these systems is associated with major health consequences, including cognitive impairment, metabolic dysfunction, cardiovascular disease, immune disturbances, and mental health disorders. This highlights the importance of understanding the biological mechanisms underlying sleep and circadian regulation.

Genetics contributes significantly to individual differences in sleep traits such as chronotype, sleep duration, and sleep quality. These traits moderately heritable. Research methods such as genome-wide association studies (GWAS) and family based studies have identified both rare mutations with strong effects and many common variants with small effects.

Recent large-scale GWAS using self-reported diurnal preference in the UK Biobank and 23andMe cohorts have found over 350 genetic loci surpassing genome-wide signifance, comprising genes enriched in circadian rhythm, cyclic adenosine monophosphate (cAMP), glutamate and insulin signaling pathways, and those expressed in the retina, hindbrain, hypothalamus and pituitary gland.

Circadian rhythms are strongly influenced by core clock genes (such as PER and CRY), which regulate biological timing. In contrast, sleep is a complex and multidimensional trait influenced by many genes, particularly those involved in brain activity and neuronal signaling, making sleep highly polygenic.

Genetic factors also contribute to sleep disorders. Insomnia is highly polygenic and often linked with psychiatric conditions. Sleep apnea involves genetic and environmental factors such as obesity. Restless legs syndrome is associated with iron metabolism and dopamine pathways. Narcolepsy is an autoimmune disorder involving loss of orexin neurons. Circadian rhythm disorders often result from mutations in clock genes.

Sleep and circadian traits are measured using subjective methods (questionnaires, diaries) and objective methods (wearables and polysomnography). A major challenge is balancing large-scale data collection with precise and accurate measurements.

Genetic studies show strong links between sleep and other diseases. There is shared genetic architecture with psychiatric disorders, especially depression. Evidence also suggests that poor sleep can casually contribute to conditions such as heart disease and mental illness.

Genetics has important clinical implications, including identifying potential drug targets and enabling personalized treatments. For example, therapies for narcolepsy increasingly target the orexin system, although many treatments still focus on symptoms rather than underlying causes.

Challenges remain, including complex and heterogeneous phenotypes, limitations in measurement, and lack of diversity in genetic studies. Future research will require better phenotyping, larger and more diverse datasets, and integration of genetic data with wearable technology.

In conclusion, sleep and circadian rhythms are critical for health and are influenced by complex genetic factors. Continued research will improve understanding, diagnosis and treatment through more precise and personalized approaches.