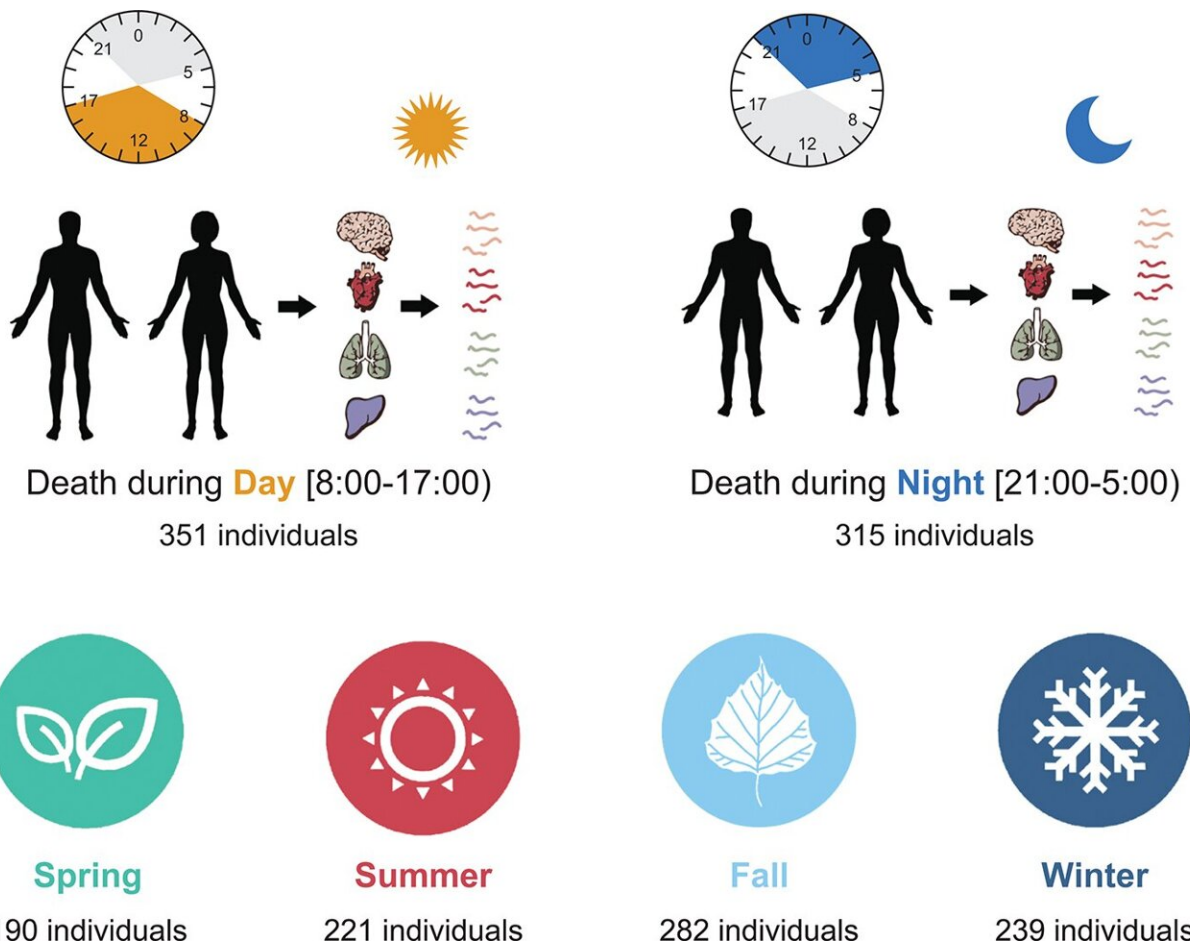


Seasonal and circadian genetic variation charted across the human body

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Overview of donors from the GTEx project, with time of death and season of death recorded when measurements are taken. Credit: Wucher V et al., 2023, PLOS Biology, CC BY 4.0

The daily rotation of Earth and its yearly voyage around the sun marks the natural rhythm of life on the planet. Human health indicators such as body temperature, blood pressure and sleep, as well as animal behavior including foraging, molting, mating or hibernating, is influenced by innate biological clocks that work over circadian (day-night and twenty-four hour) and/or circannual (seasons and twelve-month) cycles.

A research team led by Dr. Manuel Irimia and Dr. Roderic Guigó at the Centre for Genomic Regulation (CRG) in Barcelona have published research in *PLOS Biology* which details how the circadian and circannual cycles influence humans at the [molecular level](#) by measuring changes to the activity of [genes](#) inside cells across different types of tissues.

The researchers studied gene expression, a vital process by which the information encoded in genes is used to create useful products like proteins, which cells, tissues and organs require to stay alive and function properly. Alterations to gene expression can benefit or have adverse effects for [human health](#), which is why researchers study which factors regulate the process to develop effective diagnostic and therapeutic strategies.

The study analyzed [gene expression data](#) from 46 different human tissues provided by 932 donors for the Genotype-Tissue Expression (GTEx) project, a database and tissue bank used by the scientific community to explore the effects of gene expression and variation on human health and disease.

Measurements for the GTEx project are taken when a donor dies, and the authors of the study used time and season of death in the metadata of the project to assess the impact of circadian and circannual variation on gene expression across the human body. Unlike other studies that could only infer time of death, GTEx data provides the exact time—a measurement that is important for the validity of the findings.

The analysis revealed that tissues in the thoracic cavity had the largest number of day-night genes, including the lung (17.2% of all genes expressed in the tissue) and the left ventricle of the heart (19.2%), which can be explained by differences in heart rate and breathing patterns between day and night. In contrast, only 85 genes in the salivary glands showed circadian variation (0.63%), followed by 92 in the transverse colon (0.67%) and 105 in the testis (0.66%).

The researchers next examined the ratio of day vs. night genes within each tissue. This revealed that the stomach has a strong diurnal preference for gene expression, whereas skin that hasn't been exposed to sun showed strongest nocturnal preferences. As expected, sun-exposed skin showed the opposite effect and had a diurnal preference, which may be because ultraviolet light alters gene expression inside cells.

The authors of the study also created a list of 445 genes with a consistent day or night pattern across multiple tissues. The list includes "clock genes" already known to play an essential role in the circadian rhythm and which control when humans are awake and active. The authors found that expression variation of clock genes is also conserved in baboons and mice, although in the case of mice the clock is inverted, as expected from a nocturnal animal.

The list also revealed many genes not previously known to vary during the day-night cycle. One example is THRA, a thyroid hormone receptor that was found to peak at night in 15 different types of human tissues. Another example is TRIM22, which peaks during the day and which is known to be expressed in response to viral infections, restricting their ability to replicate, for example by inhibiting the transcription of HIV-1.

The effect of seasonality on gene expression revealed that twelve-month variation has a similar size of effect to 24-hour variation. The highest proportion of seasonal genes were found in the testes (25.6%)—one of

the tissues with lowest proportion of day-night genes—followed by multiple subregions of the brain. In contrast, the left ventricle of the heart showed the lowest level of seasonality (2.8%).

"We found that day-night and seasonal variation are largely uncoupled. Brain and gonadal tissues exhibited the highest seasonality, whereas those in the thoracic cavity showed stronger day-night regulation. This shows that not only genes, but also tissues, are differently affected by day-night and [seasonal variation](#)," explains ICREA Research Professor Manuel Irimia, co-author of the study and researcher at the Centre for Genomic Regulation.

Most tissues did not show any bias for season-specific changes in gene expression except for the testes, which showed massive increases in gene expression during autumn and decreases in spring. The finding could reflect seasonal changes in gonadal function.

The authors created a list of 1,748 unique genes with a consistent seasonal pattern across multiple tissues—308 in spring, 361 in summer, 1,072 in autumn and 322 in winter. Many of these genes are linked to immune function and their expression is boosted in autumn and winter, consistent with the seasonality of [viral infections](#). Some genes were also linked to the activity of hormones in the hypothalamus and pituitary glands. For example, pituitary hormone genes peaked during the summer months.

The list revealed seasonal fluctuations of genes previously linked to various disorders. For example, the expression of Glioma tumor suppressor candidate region gene 1 (GLTSCR1) increases in autumn across 16 different types of tissues, including in the brain's cerebral hemisphere. GLTSCR1 has previously been linked to intellectual disability disorders.

Researchers also found that the expression of Keratin 1 (KRT1) decreases in winter across 24 different types of tissues. KRT1 mutations in mice have previously been linked to the production of abnormal levels of proteins that regulate the immune system, as well as aberrant pigmentation in skin.

Previous studies have shown that seasonal changes can alter the structural arrangement of neurons and other cell types within the central nervous system. The researchers used the study to explore this at the gene expression level, and found patterns that suggest that the volume and relative arrangement of brain cells including neurons, astrocytes and oligodendrocytes change in particular subregions of the brain.

For example, the expression of astrocytes, cells which support neurons, increased in autumn and winter and generally fell in summer. Further research could assess the functional impact of this finding and whether it is linked to seasonal patterns of psychiatric and brain diseases.

Finally, the researchers compared their list of 445 day-night genes and the list of 1,748 seasonal genes with a database that includes known gene targets for drugs treating various types of diseases. They found that 91 day-night genes (20%) are currently being targeted by 1,071 different drugs, each of which could stand to benefit from being administered at the right time of day.

They also found that 307 seasonal genes (18%) are targeted by 2,632 different drugs, each of which could stand to benefit from being administered at the right season—summer, autumn, winter or spring. This included 11 anticancer drugs including bortezomib, which targets 16 genes and cisplatin, which targets 15. It also included an anticancer drug still in clinical trial phase.

"These findings have implications for administering drugs that target

specific genes in specific body parts. For example, the higher the expression of a gene during a particular time of day, the larger dose is required to block their action. Administering a drug could be timed to best match the circadian pattern of [gene expression](#). Our findings could also have an impact on clinical trials, as the effect of the same drug dose may change depending on the season of the year," says Dr. Roderic Guigó, co-author of the study and researcher at the Centre for Genomic Regulation.

More information: Valentin Wucher et al, Day-night and seasonal variation of human gene expression across tissues, *PLOS Biology* (2023). [DOI: 10.1371/journal.pbio.3001986](https://doi.org/10.1371/journal.pbio.3001986)

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