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Clock genes, chronotypes and diseases

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Abstract. Many common diseases in humans (such as cancer, heart disease, diabetes mellitus or psychiatric disorders, such as depression) seem to be linked to disruptions of circadian cycles and to clock genes variation. It is unlikely that such diseases to be caused by a genetic variation within a single gene. They must be influenced by complex interactions among multiple genes, as well as environmental and lifestyle factors. Therefore, it is important to understand how the resulting perturbations in our circadian biology could affect our physiological processes and susceptibility to disease. Associations between the polymorphisms of the main components of the circadian molecular clock, circadian type (also known as diurnal preference or chronotype) and diseases are presented.
Key Words: circadian rythms, clock genes, SNPs, chronotype**.**

Rezumat. La oameni, multe dintre boli (precum cancerul, boala cardiacă, diabetul zaharat, tulburări psihiatrice, cum ar fi depresia) par să fie însoţite de modificări ale ciclurilor circadiene şi variaţii ale genelor ceasornic (genele clock). Este puţin probabil ca astfel de boli să fie cauzate de o variaţie a unei singure gene. Trebuie că sunt influenţate de interacţiuni complexe dintre mai multe gene, alături de factori de mediu şi stilul de viaţă. De aceea, este important să înţelegem cum modificările din biologia circadiană ar putea afecta procesele fiziologice şi susceptibilitatea la boală. Asociaţii între polimorfisme ale principalelor componente moleculare ale ceasului circadian, tiparul circadian (cunoscut şi ca preferinţă diurnă sau cronotip) şi boli sunt prezentate.
Cuvinte cheie: ritmuri circadiene, gene clock, SNP-uri, cronotip.

Clocks within Clocks: from Genes to Complex Processes. Behind each rhythm, there is a clock. Circadian clocks control circadian rhythms. These can be divided into two major categories: central and peripheral circadian clocks (Albrecht 2002). The central circadian clock is located within the suprachiasmatic nuclei (SCN), while the peripheral circadian clocks are found elsewhere than suprachiasmatic nuclei, including other regions of the central nervous system (Cermakian & Boivin 2003). Such peripheral circadian clocks have been identified within all mammalians organs investigated, but the testis (Albrecht 2002; Coogan & Wyse 2008; Young & Bray 2007). The differences between central and peripheral clocks consist in their hierarchical position and in the way they are synchronized: while the daily light-dark cycle adjusts the phase of the pacemakers from the suprachiasmatic nuclei, the phase[1] of peripheral oscillators is adjusted by chemical zeitgebers[2], mainly the feeding schedule (Levi & Schibler 2007). The hierarchical structure of the mammalian circadian timing system implies that circadian manifestations in behaviour and physiology result from signals issued directly or indirectly from the

[1] Any cyclical function can be described by three parameters: frequency, phase and amplitude. The frequency is the number of cycles per unit of time. The amplitude is the difference between the maximal and the minimal value. The phase is the relation between endogenous rhythms and astronomical time, or between rhythms themselves.

[2] Zeitgeber (from German for "time giver", synchronizer) or timekeeper is any exogenous (external) cue that entrains the endogenous (internal) time-keeping system of organisms. The strongest zeitgeber is light. Other zeitgebers include temperature, social interactions, pharmacological manipulation and eating/drinking patterns.

suprachiasmatic nuclei, or from rhythms in gene expression or enzymatic activities governed by local circadian clocks in peripheral cells.

The human suprachiasmatic nuclei consist of about 20,000 neurons whose electrical potential frequency fluctuates spontaneously. These nuclei reset and synchronise the circadian rhythms of peripheral tissues. The primary environmental synchronizer of circadian rhythms in mammals is the daily light–dark cycle (Gachon et al 2004; Hastings & Herzog 2004). The suprachiasmatic nuclei entrain peripheral circadian clocks by influencing the levels of various neurohumoral factors. Central and peripheral circadian clocks can be dyssynchronized by manipulating neurohumoral factor oscillations. Various neurohumoral factors have been reported to entrain peripheral circadian clocks. They include glucocorticoids, prostaglandins, epinephrine, norepinephrine, glucose, angiotensin II, and retinoic acid (Cermakian & Boivin 2003; Young & Bray 2007). There is evidence that the master circadian pacemaker is amenable to neuroimmune modulation, and, in turn, influences levels of peripheral and central cytokines (Coogan & Wyse 2008).

Molecular Components of the Clock. Circadian oscillators have been genetically and biochemically analysed in several model organisms. In the early 90's, it was discovered that the Drosophila period protein is required for the cyclic accumulation of its own mRNA (Gachon et al 2004). Mammalian clock genes were identified using the data from genetic studies in the fruit fly Drosophila melanogaster, as most essential Drosophila clock genes have orthologs in mammals. Since then, negative feedback loops of clock gene expression have been uncovered in all genetic model systems for circadian oscillators, including humans.

The clock mechanisms in the suprachiasmatic nuclei and the peripheral oscillators are known to be similar at the molecular level, which consist of a network of transcriptional–translational feedback loops that drive rhythmic, 24-hours expression patterns of core clock components. Briefly, ribonucleic acid (RNA) molecules undergo post-transcriptional processing in the nucleus. The messenger RNAs (mARN) are exported to the cytoplasm where ribosomal translation forms proteins. Their stability is affected by kinase-mediated protein phosphorylation that takes place in the cytoplasm. After a time delay, sufficient protein molecules accumulate in the cytoplasm and form heterodimers that are imported into the nucleus, where they regulate gene expression through closure of positive and negative feedback loops. This mechanism is briefly described in the next paragraphs. The positive limb consists of the two groups of transcription factors: BMAL13 (also known as ARNTL or MOP3) or BMAL2 (alias ARNTL2 or MOP9), and CLOCK or NPAS2, a closely related paralogue of CLOCK4 (DeBruyne et al. 2007; von Schantz 2008). A trans-activating factor dimer consisting of a member of each of those two groups (e.g. BMAL1-CLOCK or BMAL1-NPAS2 heterodimers), activate members of negative limb, such as cryptochrome (Cry) and period (Per) genes by binding to the nucleotide sequence CACGTG (termed the E-box). As a consequence, CRY and PER gradually accumulate in the cytoplasm. Three Per (Per1, 2 and 3) and two Cry (Cry1, 2) homologues exist in mammals. Cytoplasmic phosphorylation of PER by several isoforms of casein kinase I (CK1), including CK1 delta and CK1 epsilon, and possibly other kinases, regulates its stability. Eventually, PER attains a critical level, permitting dimerisation with CRY and nuclear translocation. There, CRY suppresses BMAL-CLOCK/NPAS2-induced transcription of Per, Cry, Ror and Rev-Erb. This leads to a decrease of CRY and PER levels below the concentration required for autorepression, and a new cycle of Cry and Per transcription can ensue, thus completing a negative feedback loop (for more details see (Dardente & Cermakian 2007; Duez & Staels 2008; Hastings & Herzog 2004; Hirayama & Sassone-Corsi 2005; Ko & Takahashi 2006; Takahashi et al 2008; Toh 2008)).

Another regulatory loop is induced by CLOCK-BMAL1 heterodimers activating transcription of retinoic acid-related orphan nuclear receptors, Rev-erba and Rora. ROR

[3] Proteins are denoted by capital letters, genes are in italics
[4] NPAS2 is believed to maintain circadian function in the absence of CLOCK

and REV-ERB translocate independently to the nucleus where they compete for binding to the orphan nuclear receptor target sequence, called the RORE sequence (AAAGTAGGTCA), in the Bmal1 promoter. Members of ROR (α, β and γ) and REV-ERB (α and β) are able to regulate Bmal1 through ROREs. Their antagonistic effects (ROR activates Bmal1 transcription, REV-ERB inhibits it) generate a rhythmic level of BMAL1 and thus CLOCK-BMAL1. Additionally, PER2 activates Bmal1 transcription in a positive feedback loop through an unknown mechanism. Although this secondary loop is not essential for rhythm generation, it contributes to the robustness and phase shifting properties of the molecular clock (Takahashi et al 2008).

The autoregulatory feedback loops described take 24 hours to complete a cycle and constitute a circadian molecular clock. Most clock component messenger RNAs and proteins oscillate with a τ of 24 hours, except for CLOCK, CK1δ and CK1ε. CK1ε and CK1δ are critical factors that regulate the core circadian protein turnover in mammals. There are additional components required for proper clock function (like the protein WDR5, the RNA-and DNA-binding protein NONO). A number of other candidate clock components have been proposed (such as Timeless, Dec1, Dec2, DBP and E4bp4), but their roles have not yet been clearly defined (Takahashi et al 2008).

Circadian Genotypes and Phenotypes. Although study of the association of human body and diseases had been practiced since ancient times, it was only in the 19th century when phenotypes began to be systematically analysed. While studying the way traits were passed on from a generation to the next, Mendel hypothesized that there must be an internal state and an external appearance. At the beginning of the 20th century, these states were labelled "genotype" and "phenotype" respectively, by the botanist Wilhelm Johannsen. He also introduced the distinction between genotype and phenotype, as descriptors of the process of inheritance (genome), and the process of development (phenome), respectively (Groth & Weiss 2006). In short, the genetic constitution of an individual is called genotype, while the physical or biochemical expression of the genotype is called phenotype.

There is a close relationship between genotype and phenotype. Most complex traits, such as hair or skin colour, height, weight or behaviour, are influenced by many genes. Most traits are also influenced by environment. This means that the same genotype can result in different phenotypes, depending on the environment. For example, from two people with a genetic risk for lung cancer, the one that smokes is much more likely to develop the disease. Environmental effects also imply that the same phenotype can result from more than one genotype; smoking again provides an example, because most smokers who are not genetically at risk can also develop lung cancer.

Genetic Markers and Their Importance in Medicine. Genetic variation, in the form of multiple alleles of many genes, exists in most natural populations of organisms. These genetic differences between individuals DNA markers are also called DNA polymorphisms. Among the most widely used DNA polymorphisms are single-nucleotide polymorphisms (SNPs), restriction fragment length polymorphisms (RFLPs), amplified fragment length polymorphisms (AFLPs), simple tandem repeat polymorphisms (STRPs) or variable number of tandem repeats (VNTRs) (Bowen et al 1996).

Single nucleotide polymorphisms (SNPs) are the most prevalent of all DNA sequence variations. SNPs most commonly refer to single-base differences in DNA among individuals. The SNP defines two "alleles" for which there could be three genotypes among individuals in the population: homozygous with either T-A or C-G in both homologous chromosomes, or heterozygous with T-A in one chromosome and C-G in the homologous one. SNPs of various types can change the function or the regulation and expression of a protein (Bowen et al 1996). Although the vast majority of the SNPs are found in noncoding regions of the genome, and most of those found in coding regions do not change the gene products in deleterious ways, SNPs are thought to be the basis for much of the genetic variation found in humans.

SNPs are useful for finding genes that contribute to disease, in two ways. Some SNP alleles are the actual DNA sequence variants that cause differences in gene function

or regulation that directly contribute to disease processes. Most SNP alleles, however, probably contribute little to disease. They are useful as genetic markers that can be used to find the functional SNPs because of associations between the marker SNPs and the functional SNPs. SNPs of various types can change the function or the regulation and expression of a protein (NCBI 2007). The most obvious type is a nonsynonymous SNP, where the alleles differ in the amino acid of the protein product.

Many common diseases in humans (such as cancer, heart disease, diabetes or psychiatric disorders) are not caused by a genetic variation within a single gene, but are influenced by complex interactions among multiple genes as well as environmental and lifestyle factors. Although these factors contribute together to the developing a disease, it is currently difficult to measure and evaluate their overall effect on a disease process. Genetic factors may also confer susceptibility or resistance to a disease (also called genetic predisposition) and determine the severity or progression of disease. Because the factors involved in these intricate pathways are not well known, it is difficult to develop screening tests for most diseases and disorders. Defining and understanding the role of genetic factors in disease may help to better evaluate the role of non-genetic factors (such as behaviour, diet, lifestyle, and physical activity) on disease. It could be only a matter of time before physicians screen patients for susceptibility to a disease by analyzing their DNA for specific SNP profiles. Each person's genetic material contains a unique SNP pattern that is made up of many different genetic variations. Although most SNPs are not responsible for a disease state, they could serve as biological markers for pinpointing a disease on the human genome map, because they are usually located near a gene found to be associated with a certain disease. Sometimes, a SNP causes a disease and, therefore, can be used to search for and isolate the disease-causing gene (NCBI 2007).

A rapidly emerging field of medicine is the so called "predictive medicine" (Tailliez 2008). Its aim is to prevent the disease or significantly decrease its impact upon the patient (such as by preventing mortality or limiting morbidity). While different prediction methodologies exist, such as genomics, proteomics, and cytomics, the most common way to predict future disease is based on genetics5. Although proteomics and cytomics may detect disease earlier, most of the time they detect biological markers that exist because a disease process has already started (Bernas et al 2006).

Using SNPs to study the genetics of drug response will help in the creation of "personalized" medicine. Currently, pharmaceutical companies are limited to developing agents to which the "average" patient will respond. A treatment proven effective in one patient may be ineffective in others, or even worse, cause adverse reactions. Because genetic factors also affect a person's response to drug therapy, DNA polymorphisms such as SNPs might be useful in understanding why individuals differ in their abilities to absorb or clear certain drugs, as well as why they experience an adverse side effect to a particular drug. The discovery of SNPs could revolutionize the process of disease detection and the practice of preventative and curative medicine.

Clock Genes Polymorphisms Associated to Diseases. The first clock gene polymorphism that was reported to be associated with phenotype in humans was a single-nucleotide polymorphism (SNP) in the 3-untranslated region of Clock (T3111C), where the minor allele (C) was reported to be associated with an increased evening preference, in a mostly North American population (Katzenberg et al 1998). These findings were confirmed by two other studies in North-American (Friedman et al 2009) and Japanese populations (Mishima et al 2005). By contrast, five other studies in British (Robilliard et al 2002), mixed European (Johansson et al. 2003), Japanese (Iwase et al 2002), Korean (Lee et al 2007) and Brazilian (Pedrazzoli et al 2007) populations did not find associations with diurnal preference. Further research showed that this SNP is associated with insomnia (Benedetti et al 2007; Serretti et al 2003), impaired cognitive

[5] Genetics uses the information from one or two genes to explain a disease state, while genomics examines all the genetic information to determine biological markers predisposing an individual to disease

performance (Benedetti et al 2008b) and altered response to antidepressant therapy (Serretti et al 2005) in Italian subjects affected by mood disorders. These findings were not confirmed in Austrian (Bailer et al 2005), North-American (Desan et al 2000; Shi et al 2008), mixed European (Johansson et al 2003) and Korean (Paik et al 2007) populations.

Two trials focused on an association with schizophrenia in Japanese population, with divergent results (Kishi et al 2009; Takao et al 2007). Adult ADHD was also found to be associated with this Clock polymorphism in a German group (Kissling et al 2008). No association was found with cluster headache, obesity and eating disorders in Italian subjects (Cevoli et al 2008; Monteleone et al 2008; Tortorella et al 2007).

Following the interest stirred by T3111C polymorphism, other Clock SNPs were investigated. The most consistent results were regarding rs4864548 polymorphism that was found to be associated with metabolic syndrome in British (Scott et al 2008) and obesity in Argentinians (Sookoian et al 2008).

Bmal1 SNPs were cited to be associated with seasonal affective disorder (Partonen et al 2007) and bipolar disorder (Nievergelt et al 2006), but also with type 2 diabetes and arterial hypertension (Woon et al 2007). A number of novel polymorphisms in both Bmal genes were reported, although association with phenotype was not investigated (Ciarleglio et al 2008).

Npas2 is a relatively new member of the circadian genes family. No association between variability in the human Npas2 gene and circadian rhythm or sleep parameters have been published, although two reports describes a link between a coding-region polymorphism, seasonal affective disorder (Johansson et al 2003) and winter depression (Partonen et al 2007). Autistic disorder (Nicholas et al 2007) and non-Hodgkin lymphoma (Zhu et al 2007) were reported to be associated with Npas2 polymorphisms.

Two reports describe the effect of a Per1 polymorphism on circadian parameters in humans. A silent polymorphism in exon 18, T2434C, conferred a tendency towards morning preference on carriers of the C allele (Carpen et al 2006), while 2548G had no effect on chronotype (Katzenberg et al 1999). A Per1 polymorphism was associated with autistic disorder (Nicholas et al 2007).

In contrast, reports that evaluate Per2 polymorphism effects on circadian parameters in humans are available. A SNP in the 5'-UTR of Per2 was associated with morning preferences (Carpen et al 2005). The same polymorphism was reported in patients in a small group of Japanese subjects with advanced sleep phase syndrome (Satoh et al 2003), and so was the S662G polymorphism (Toh et al 2001). An additional, silent polymorphism (G2114A), has recently been described, where the A allele associated with eveningness in a Japanese population (Matsuo et al 2007). Polymorphisms of potential functional importance were reported in relation to regulation of alcohol intake (Spanagel et al 2005). Seasonal affective disorder was also associated with Per2 SNPs in a Finnish population (Partonen et al 2007).

One of the most interesting sequence variants is a variable-number tandem-repeat (VNTR) polymorphism in the Per3 gene, which encodes 18 amino acids repeating either four times (Per3-4 allele) or five times (Per3-5 allele). In a UK-based population sample, it was found that the shorter allele (Per34) was associated with evening preference and delayed phase sleep syndrome, whereas the longer one (Per35) with morning preference (Archer et al 2003; Jones et al 2007). In contrast to this finding, a study in a Brazilian population found that the frequency of the longer allele was higher in patients with delayed phase sleep syndrome (Pereira et al 2005). The Per3 VNTR polymorphism might also contribute to sleep homeostasis: differences in sleep–wake structure, sleep propensity and cognitive performance during sleep loss were noted between individuals who are homozygous for the shorter or longer allele in the general population (Viola et al 2007; Viola et al 2008). It might also influence the age of onset of bipolar disorder (Benedetti et al 2008a) and it was associated to breast cancer (Zhu et al 2005) and heroin dependence (Zou et al 2008). A study of the Japanese population described a haplotype, defined by two missense SNPs, which significantly associated with delayed phase sleep syndrome (Ebisawa et al 2001). One of these SNPs was reported to be linked with morning preference in a mixed European population (Johansson et al

2003). Other Per3 polymorphisms are described in relation to depressive and bipolar disorders (Artioli et al 2007; Nievergelt et al 2006).

There are no reports of any genetic variability in either one of the human Cry genes associated with circadian or sleep parameters, or with any factors other than an increased cancer risk found to be connected with a Cry2 polymorphism (Chu et al 2008). Although Casein kinase 1 epsilon and Casein kinase 1 delta (CK1ε and CK1δ) are just factors that regulate the core circadian protein turnover, a mutation in Csnk1d, the gene encoding CK1δ, was found in a pedigree in which advanced sleep phase syndrome was inherited in an autosomal dominant way (Xu et al 2005). A polymorphism in Csnk1e gene, encoding casein kinase 1ε, was found to be linked to bipolar disorder (Shi et al 2008).

A summary of the findings regarding circadian genes and their implications in disease development are presented in Table 1.

Table 1.

Clock genes polymorphisms and their association with phenotype

Gene	*Position*	*Population*	*Phenotype*	*Association*	*Publication*
Clock	T3111C-5'-UTR	European	Eveningness	Yes	(Katzenberg et al 1998)
		Japanese	Eveningness	Yes	(Mishima et al 2005)
		Italian	Sleep in bipolar disorder	Yes	(Benedetti et al 2007)
		Italian	Cognitive performance in depressed	Yes	(Benedetti et al 2008b)
		North American	Eveningness	Yes	(Friedman et al 2009)
		German	Adult ADHD	Yes	(Kissling et al 2008)
		Italian	Insomnia, response to antidepressant therapy	Yes	(Serretti et al 2003; Serretti et al 2005)
		Japanese	Schizophrenia	Yes	(Takao et al 2007)
		Austrian	Depressive disorder	No	(Bailer et al 2005)
		Italian	Cluster headache	No	(Cevoli et al 2008)
		British	Diurnal preference or DSPS	No	(Robilliard et al 2002)
		North American	Depressive disorder	No	(Desan et al 2000)
		Japanese	DSPS and N24	No	(Iwase et al 2002)
		Swedish/Finish/Austrian/German	Diurnal preference or SAD	No	(Johansson et al 2003)
		Japanese	Schizophrenia, depressive disorder and bipolar disorder	No	(Kishi et al 2009)
		Korean	Diurnal preference	No	(Lee et al 2007)
		Italian	Obesity or binge eating	No	(Monteleone et al 2008)
	T3111C or T257G				
	3092 T/C	Korean	SAD	No	(Paik et al 2007)
	rs11932595,	North American	Bipolar Disorder	No	(Shi et al 2008)
	rs6843722	Italian	Anorexia and bulimia nervosa	No	(Tortorella et al 2007)
		Brazilian	DSPS	No	(Pedrazzoli et al 2007)
		Italian	Cluster headache	No	(Rainero et al 2005)
		Argentinean	Non-alcoholic fatty liver disease	Yes	(Sookoian et al 2007)
	rs4864548	British	Protection against metabolic syndrome	Yes	(Scott et al 2008)
	rs534654	North American	Bipolar disorder	Yes	(Shi et al 2008)

	rs1554483G, rs4864548A	Argentinean	Obesity	Yes	(Sookoian et al 2008)
	?	?	Cocaine dependence	No	(Malison et al 2006)
Npas 2	471Leu/Ser	Swedish/Finish/Austrian/German	SAD	Yes	(Johansson et al 2003)
	?	Finnish	SAD	Yes	(Partonen et al 2007)
	?	?	Autistic Disorder	Yes	(Nicholas et al 2007)
	394A/T	?	Non-Hodgkin lymphoma	Yes	(Chu et al 2008)
Bmal 2	-	-	-	-	-
Bmal 1	11p15	North American	Bipolar disorder	Yes	(Nievergelt et al 2006)
	rs2290035	Finnish	SAD	Yes	(Partonen et al 2007)
	haplotypes	British	Type 2 diabetes, arterial hypertension	Yes	(Woon et al 2007)
Per1	T2434C	British	Morningness	Yes	(Carpen et al 2006)
	2548G	European	Diurnal preference	No	(Katzenberg et al 1999)
	?	?	Autistic disorder	Yes	(Nicholas et al 2007)
	?	?	Cocaine dependence	No	(Malison et al 2006)
Per2	C111G - 5'-UTR	British	Morningness	Yes	(Carpen et al 2005)
		Japanese	ASPS	Yes	(Satoh et al 2003)
	S662G	Pedigree	ASPS	Yes	(Toh et al 2001)
	?	Finnish	SAD	Yes	(Partonen et al 2007)
	?	German	Alcoholism	Yes	(Spanagel et al 2005)
	G2114A	Japanese	Eveningness	Yes	(Matsuo et al 2007)
	?	?	Cocaine dependence	No	(Malison et al 2006)
Per3	H4 haplotypes	Japanese	DSPS	Yes	(Ebisawa et al 2001)
	G647	Swedish/Finish/Austrian/German	Morningness	Yes	(Johansson et al 2003)
	4 or 5 repeats (VNTR)	British	Short allele – DSPS Long allele -morningness	Yes	(Archer et al 2003)
		British	Short allele – DSPS Long allele - morningness	Yes	(Jones et al 2007)
		Brazilian	Long allele – DSPS	Yes	(Pereira et al 2005)
		British	Long allele –sleep loss	Yes	(Viola et al 2007)
		North American	Long allele – breast cancer	Yes	(Zhu et al 2005)

		Italian	Age onset in bipolar disorder	Yes	(Benedetti et al 2008a)
		Chinese	Heroin dependence	Yes	(Zou et al 2008)
	Per3 ex18 44	Italian	Depressive disorder	Yes	(Artioli et al 2007)
	1p36.23	North American	Bipolar disorder	Yes	(Nievergelt et al 2006)
Cry1	?	North American	Bipolar disorder	No	(Nievergelt et al 2005)
Cry2	?	Chinese	Prostate cancer	Yes	(Chu et al 2008)
CK1δ	T44A	Pedigree	ASPS	Yes	(Xu et al 2005)
CK1ε	S408N	Japanese	Protection against DSPS	Yes	(Takano et al 2004)
		Brazilian	Rare	No	(Castro et al 2008)
	rs1534891	North American	Bipolar Disorder	Yes	(Shi et al 2008)

ADHD- Attention Deficit Hyperactivity Disorder; ASPS - Advanced Sleep Phase Syndrome; DSPS - Delayed Sleep Phase Syndrome; N24- Non-24-Hour Sleep-Wake Syndrome; SAD - Seasonal Affective Disorder;

Diurnal Preference (Chronotype). One of the most important aspects of individual differences in circadian rhythms is the chronotype, also referred to as circadian type, diurnal preference or diurnal variation. Chronotype is an attribute of human beings reflecting whether they are alert and prefer to be active early or late in the day. Three major circadian types are described: morning, intermediate and evening. Morning type (also called "lark") wakes up spontaneously early in the morning, is more active in the first part of the day and tends to go to bed early in the evening. Evening type (also called "owl") finds it difficult to wake up in the morning and tends to be more active in the second part of the day. Those eliciting patterns of behaviour falling in an intermediate area between the two extremes of this continuum are intermediate or neither type individuals (Horne & Ostberg 1976).

Most people are neither evening nor morning types, but lie somewhere in between. Estimates vary, but up to half are either morning or evening people (Paine et al 2006). A recent meta-analysis showed a significant overall effect of gender on morningness with girls and women scoring higher on these scales (Randler 2007). A trend for increasing morningness with age is often found, but the mechanism is unknown yet (Paine et al 2006).

As with most other diurnal beings, human activity-rest patterns are endogenously controlled by circadian rhythms. Investigations in chronobiology and chronopsychology have provided important differential results, especially between the extreme groups (morning- and evening-types). Body temperature and subjective alertness have been the most extensively studied parameters. Evening types started their waking day at a lower body temperature than morning-type subjects, their temperature increased throughout the day reaching its peak in the late afternoon. Morning types showed a steeper rise in body temperature and reached their peak approximately 1 to 3 h earlier than evening types (Baehr et al 2000; Bailey & Heitkemper 2001; Mongrain et al 2004). Evening chronotypes showed a delay in their early-morning peak of salivary cortisol and higher cortisol levels in the first hour after awakening (Bailey & Heitkemper 1991; Kudielka et al 2006). Circadian type was strongly related to the melatonin acrophase, with morning types having a more rapid decline in melatonin levels after the peak than evening types (Gibertini et al 1999).

There also appear to be some personality differences between chronotypes. Larks appeared conscientious, trustworthy and emotionally stable, while owls were creative, emotionally unstable and had difficult social and familial relations (Mecacci & Rocchetti 1998). Cognitive performance might also be under the influence of chronotypes. Evening types were reported to be more intelligent, but despite this, morning types coped better with early school start times and performed better (Roberts & Kyllonen 1999). Differences in the thinking styles were described, too: morning types scored higher in the left-thinking scale and evening types in the right-thinking scale (Fabbri et al 2007).

Researchers pointed out that evening types are prone to addiction (alcohol and coffee) and are more often habitual smokers (Adan 1994; Mecacci & Rocchetti 1998; Taillard et al 2001) and display higher levels of anxiety (Díaz-Morales & Pilar Sánchez-López 2008). Clinically depressed patients were found to be more eveningness than age- and sex-matched controls. The authors concluded that eveningness could be rather a premorbid trait than a characteristic of the depressive state (Drennan et al 1991). This correlation was found also in another study, among so-called "depressive" students (Chelminski et al 1999). In a study on younger patients with bipolar disorder, schizophrenia or schizoaffective disorder, bipolar disorder patients were more likely to score in the "evening" range. These relationships were not observed among the other patients (Mansour et al 2005). In contrast, a recent study revealed that patients having the co-morbid alcohol use and bipolar disorders have more often the circadian phenotype of the morning type as compared with those with bipolar disorder only (Hatonen et al 2008).

Special interest was paid to the impact of chronotype on sleep, particularly on sleep quality. Earlier studies on sleep architecture provided conflicting results, a possible explanation being that the subjects had been studied according to forced sleep schedules and not their preferred ones. With this corrected, morning and evening types did not

differ in sleep architecture, despite having differences in the preferred timing of the sleep period (Mongrain et al 2005). Instead, differences between chronotypes were found in the variability of the sleep schedule: evening types showed more irregular sleep/wake habits, a greater need for sleep, less time in bed during the week (and consequently more time in bed at the weekend) and a later bedtime and waking-up time (especially at the weekend) (Taillard et al 1999). A study on shift nurses revealed that evening types had a negative effect on subjective sleep quality and sleep duration. The authors concluded that the strongest predictor of sleep quality was morningness–eveningness and not the shift schedule or shift pattern (Chung et al 2008). Evening types also complained of higher levels of daytime sleepiness (Carrier et al 1997) and had more maladaptive beliefs about sleep, chronotype being possible a risk factor for worse sleep hygiene (Adan et al 2006).

A single nucleotide polymorphism located in the human CLOCK gene was proposed to be a predictor of diurnal preference in normal adults: subjects with one of the two Clock alleles, 3111C were shifted toward Eveningness tendency (Katzenberg et al 1998). This polymorphism was further investigated in other populations. Associations were found in North-Americans (Friedman et al 2009) and Japanese (Mishima et al 2005); negative results were reported in British (Robilliard et al. 2002) and Korean samples (Lee et al 2007). Further researched focused on Per1-3 homologues and some polymorphisms were reported to be associated to diurnal preference. A silent polymorphism (in exon 18, T2434C) in Per1 confers a tendency towards morning preference on carriers of the C allele (Carpen et al 2006), while 2548G has no effect on chronotype (Katzenberg et al 1999). A SNP in the 5'-UTR of Per2 was also reported to be linked with morning preferences (Carpen et al 2005). An additional, silent polymorphism (G2114A) in Per2, has recently been described, where the A allele associated with eveningness in a Japanese population (Matsuo et al 2007). A variable-number tandem-repeat (VNTR) polymorphism in the Per3 gene, which encodes 18 amino acids repeating either four times (Per3-4 allele) or five times (Per3-5 allele). In a UK-based population sample, it was found that the shorter allele (Per34) was associated significantly with evening preference, whereas the longer one (Per35) was linked with morning preference (Archer et al 2003; Jones et al 2007). G647 polymorphism in Per3 was reported to be connected with morning preference in a mixed European population (Johansson et al 2003).

An original study showed that there was significant correlation between human chronotype and dermal fibroblast period length and that daytime preferences could be studied in primary dermal cells. Biopsies from subjects of early and late chronotypes were cultivated, and the clock properties of fibroblast pools measured. Subjects of early chronotype in general displayed a shorter fibroblast than those of late chronotype (Brown et al 2008).

Conclusions. Each cell contains a set of core clock genes – Clock, Bmal1, Cry 1-2, Per 1-3 and nuclear receptors (Rev-erbα, ROR). Through complex positive and negative transcriptional and translational feedback loops, they generate an endogenous rhythm of intracellular protein expression, leading to rhythmic cell and tissue function that oscillates over approximately 24 hours. The molecular clock has been demonstrated to regulate the daily sleep and wake cycle and other physiological processes such as the metabolism and energy homeostasis.

Our understanding of the complex genetics that underlie chronotype is still at the beginning. Nevertheless, if diurnal preference is a stable characteristic that is better explained by endogenous factors, then an accurate chronotype assessment might help the everyday medical practice by tailoring individual examination and treatment to optimise both diagnostics and therapy. Other fields that might particularly benefit are education, sports, work scheduling (Smith et al 2002).

Biological rhythms are disrupted in a many disorders, i.e. depression, addiction, diabetes mellitus or even cancers. Establishing the contribution of clock genes to cause and effect in these disorders is still difficult. The systematic characterisation of behavioural phenotypes, the identification of new genetic factors that contribute to circadian and

behavioural function, and the investigations of clock gene polymorphisms should lead to new insights into the causes and progression of certain disorders.

Given the influence of the circadian clock on several other physiological systems and behaviours, such interactions could be more widespread. Like an iceberg, the observed interactions could be providing only a glimpse of the importance of circadian temporal organization for health and disease.

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