Humans show large inter-individual differences in organizing their behavior within the 24-hour day, and multiple studies showed that this diurnal preference, or chronotype, is highly heritable. Until now, only a few reports about the genetic basis of human natural diurnal variation have been published. Taking advantage of genomic approaches and the conservation of circadian clocks in peripheral tissues, we employed a lentiviral circadian reporter system and real-time bioluminometry to determine different clock properties in a fully genotyped cohort of 200 human primary umbilical cord fibroblast lines, with the aim of deciphering functional genetic variants that determine natural human individual differences in circadian chronotype at a cellular level. Using this methodology, we have uncovered hundreds of polymorphisms reaching suggestive significance, including a novel SNP in a putative Per1 enhancer region, as well as two SNPs reaching stringent genome-wide significance criteria and affecting the expression of Per2. Currently, we are validating candidates by genome-wide RNAi-based screen technologies and by looking for global enrichment of relevant alleles in extreme chronotypes cohorts.

The same technology can be applied as well to examine links between the circadian clock and disease. Beyond the core circadian clockwork, many other conserved signaling pathways influencing both circadian clock function and its effects upon human physiology and behavior can also be examined. For example, although we saw no changes in core circadian function in fibroblasts from a cohort of patients with Bipolar Disorder, we made the further observation that the amplitude of drug-activated CREB signalling in cells from human skin biopsies correlated with bipolar disorder in affected individuals. cAMP/CREB signalling is known to be important to circadian hormonal variation and to synaptic plasticity.

Knowing that inter-individual differences in cAMP/CREB signaling affect both the human endocrine response to light and susceptibility to bipolar disorder would make it a common neurological signaling pathway that could help explain the observed relationship between this disorder, circadian behavior, and light exposure. Consistent with this hypothesis, we also found that subjects with elevated CREB signaling in fibroblasts showed reduced suppression of melatonin levels by light in vivo, reflecting the dependence of melatonin synthesis upon adrenergic mechanisms. Given the role of the cAMP/CREB-signaling pathway in synaptic plasticity, as a part of the circadian clockwork, and in the regulation of melatonin synthesis, the relationships that we uncover could help furnish therapeutically useful endophenotypes of bipolar disorder and its treatment.