An epigenetic investigation into the role of genomic imprinting in sleep biology

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Rationale: Loss of sleep costs up to 3% of many country's gross domestic product. Most importantly, as humans we spend approximately 1/3 of our time on Earth asleep. This is a burden that evolution has given to virtually all species, but we still do not understand why. In recent years, a better understanding of the heritable epigenetic mechanisms of sleep traits has questioned our understanding of sleep biology. In particular, we provided evidence that imprinted genes are involved in sleep biology in mammals (Tucci 2016). Within this project, we propose a novel investigation of how this specific epigenetic mechanism, genomic imprinting, regulates sleep. Genomic imprinting is well-known in epigenetics as a mark across the genome causing the expression pattern of an allele to depend on its parental origin. At the simplest imprinted loci, alleles are mono-allelically expressed, with either the maternally or paternally inherited allele being transcriptionally silenced (Tucci, Isles et al. 2019).

Hypothesis and aim: The genomic imprinting hypothesis of sleep (Tucci 2016) states that imprinting has set an evolutionary agenda for the physiology of mammalian sleep. Therefore, driven by this hypothesis, we will here address this question: how parent-of-origin inheritance impacts brain responses to sleep loss.

Research Plan: We demonstrated that which parent a gene came from can influence the sleep profile (Tinarelli, Garcia-Garcia et al. 2014). Thus, the candidate within this project will conduct experiments that include new reciprocal F1 mouse hybrids to identify imbalanced allelic expression in specific cell types. In particular, the project will focus on sleep homeostasis in the cortex by identifying cell-type-specific (i.e., by cell-type fluorescence) allelic responses. The experimental strategy will involve isolation of excitatory versus inhibitory neurons, as well as astrocytes, following sleep deprivation in mice. We will use genetically diverse mouse strains and RNA-sequencing to infer imprinted genes, and leverage recently created strain specific long read mouse genomes in combination with pangenome representations to develop approaches for obtaining correct ratios of allele-specific expression in hybrids (Lilue et al., 2018). All new imprinted targets will be validated using independent methods to empirically test the false discovery rate.

Integration of Expertise of Partners: over the last decade, Tucci's lab provided the first direct evidence that specific imprinted genes are important players in sleep regulation and demonstrated that parent-of-origin epigenetic processes can influence mammalian sleep. This epigenetic issue was never considered in sleep and circadian studies before. Imprinted genes are highly expressed in the suprachiasmatic nucleus of the hypothalamus, which serves as the main master clock, and in the hypothalamus and frontal cortex, in which specific circuitries serve as the sleep-wake centres of the brain.

Keane's laboratory has studied laboratory mouse genomes for over a decade, resulting in discoveries of novel genes involved in brain development, genetic variants implicated in cancer and complex traits, and identified and studied the genome structure of the most genetic divergent regions of the mouse genome.

The combination of the expertise across these two laboratories will provide the infrastructure and guidance for the project. In particular in IIT the candidate will conduct the *in vivo* electrophysiological studies, while in EMBL-EBI will carry out the bioinformatics analysis

References:

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Lilue et al. (2018) Sixteen diverse laboratory mouse reference genomes define strain-specific haplotypes and novel functional loci, Nature Genetics, 50, 1574-1583.
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Tinarelli, F., C. Garcia-Garcia, F. Nicassio and V. Tucci (2014). "Parent-of-origin genetic background affects the transcriptional levels of circadian and neuronal plasticity genes following sleep loss." Philos Trans R Soc Lond B Biol Sci **369**(1637): 20120471.
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