Simposio Internacional / *International Symposium*:

Patología del Sueño: de la Neurobiología a las manifestaciones sistémicas
Sleep disorders: from Neurobiology to Systemic Consequences

Madrid, 18 y 19 de enero de 2018 / *January 18-19, 2018*

ABSTRACT

Genética sistémica de la homeóstasis del sueño

Systems genetics of sleep homeostasis

Paul Franken
Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland

Insufficient or disrupted sleep are widespread in our society and represent a serious public health concern, as they are associated with increased risk for e.g. obesity, diabetes, and high blood pressure, and impaired cognitive performance which increases the likelihood of accidents, medical errors, and loss of productivity. Several hypotheses concerning sleep's still elusive function converge on the notion that staying awake imposes a burden that can only be efficiently alleviated during sleep. The molecular substrates through which sleep delivers these beneficial effects remain, however, largely unknown. Insight into these pathways is therefore considered instrumental in advancing our basic understanding of sleep need under both physiological and pathological conditions.

To this end we implemented a systems genetics approach in the BXD genetic reference population of mice and assembled a uniquely comprehensive experimental knowledge base comprising a deep 'sleep-wake' phenome, central and peripheral transcriptomes, and plasma metabolome data, collected under undisturbed baseline conditions and after sleep deprivation. This integrative, multi-level approach allowed us to follow the flow of information from DNA variants, to molecular intermediate phenotypes, to behavioral and electrophysiological end phenotypes, and to assess how this network of multi-scale effects is perturbed by sleep loss.

We found that a relatively mild sleep disruption (preventing sleep during half of the rest phase) already extensively reshaped the systems genetics landscape by altering up to 80% of the transcriptomes and the metabolome with numerous genetic loci affecting the magnitude and even the direction of change thereby demonstrating that genetic heterogeneity and the effects of insufficient sleep itself on the transcriptome and metabolome are far more widespread than previously reported. Importantly, the pathways we identified were unique to the sleep-deprivation condition and did not explain phenotypic variance of the respective traits under undisturbed baseline conditions. Our results also illustrate the importance of peripheral molecular pathways in regulating brain activity, which is of importance because although many studies have emphasized the deleterious effect of sleep loss on peripheral systems, research on the substrate of sleep need largely remains brain centric.

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I will illustrate several pathways underlying the response to sleep deprivation that emerged from our systems genetics analyses. One such example concerns Acot11 encoding an acyl-CoA thioesterase important in the homeostatic regulation and turn-over of free fatty acids (FFA) and, as we discovered, causally involved in regulating rebound NREM sleep. In humans, it has been observed that sleep deprivation increases circulating FFA and that both elevated FFA levels and sleep restriction predispose to metabolic disease including type-2 diabetes. Our data implicate Acot11 as a mechanistic link between sleep restriction and its adverse effects on fatty acid turnover and its down-stream consequences on metabolism.