Investigating the role of ancestral metabolism and circadian clock on transgenerational inheritance

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Rationale: While the link between animal physiology and the environment is well-established, in recent years it has become increasingly appreciated that environments experienced by one generation can influence health and fitness of the subsequent ones, in the absence of changes in the DNA sequence. Putatively, informing one's offspring about the availability of nutrients, predators or other environmental variables could provide it with an adaptive advantage; however, how specific non-genic information is passed on from one generation to the next is still unclear. Furthermore, whether and when such adaptive traits become 'fixed' in the population through changes in the genetic code remains under-investigated. Interestingly, subtle changes in ancestral genetic variants may have played a pivotal role through evolution, including the recent evolution of humans. In particular, *H. sapiens* genomes carry evidence of approximately 2% *H. neanderthal* DNA. Importantly, Neanderthal alleles that increased in frequency across modern humans showed association with variations within two of the most fundamental mechanisms of life on Earth, namely metabolism and circadian clock.

As Neanderthals lived during harsh cold climate conditions in Europe, the environmental influence on their metabolism and circadian clock played a crucial role in their physiology and/or evolution. Several theories were proposed, affirming that nutrient deprivation, during prolonged famines, and sunlight at different latitudes, challenged survival, therefore generating selective pressure for traits that increase fat storage. Whilst these traits represented an advantage for ancient humans, they might result today in a maladaptation that predispose modern societies to obesity and other metabolic diseases.

Aim: This project aims to uncover how epigenetic mechanisms affect both metabolism and circadian clock between generations in mammals. The goals of the project are to: (*i*) understand how ancestral and modern specific haplotypes impact on developmental growth, metabolism and circadian behavior; (*ii*) uncover the mechanistic details through which environmental challenges influence (epi)genetic variation within populations.

Research Plan: the candidate will divide her/his time between IIT in Genoa and EMBL in Rome, and she/he will have access to an exclusive catalogue of genetically modified mice, advanced technologies in studying epigenetic inheritance (including DNA methylation and small RNA measurements in sperm and the early embryo) home-cage behaviour, as well as computational analyses that allow to extract meaningful behavioural measures from mice.

Integration of Expertise of Partners: The combination of the expertise and previous works across our laboratories will provide the infrastructure and guidance for the project. In particular in IIT the candidate will find support to develop the evolutionary, behavioural and delivery part of the study, while in EMBL in Rome the candidate will gain expertise in molecular embryology and cutting-edge genomics. Moreover, across both IIT and EMBL network she/he will have access to a unique and complementary set of facilities, including (but not limited to) mouse genetics, NGS bioinformatics and microscopy.

References:

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