Genetics of glucocorticoid receptor-dependent behavioral traits in humans
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The uncontrolled multicrisis related to the ongoing war and pandemic will lead to stress-induced psychiatric problems for which we are not ready with the current pharmacotherapies. The most devasting mental health diseases are major depression and anxiety-related disorders, including post-traumatic stress disorder. Despite decades of research, the exact molecular mechanism by which the effects of stress are translated into psychiatric conditions was not precisely explained.

It is known that the physiological response to negative stimuli is controlled by the HPA axis and regulated by the release of glucocorticoids (GC). The effects of GCs are systemic and glucocorticoid receptor (GR)-mediated molecular regulation occurs in various tissues and cell types. Coordination of the effects of GR activation in multiple organs is carried out through activation or inhibition of specific gene expression patterns. However, up to now, only single links between GR-dependent genes and behavioral phenotypes were indicated, and a large part of the molecular effects of stress remains unknown.

Here, we aim to classify GR-regulated genes and assign them to biological pathways that contribute to the development of stress-related psychiatric disorders. We will use big genomic and population genetics data, the UK Biobank database, offering access to health-related and whole-genome sequences. With this resource, we will search for the associations of variants in genes controlled via GR and human phenotypes (aggregated in four main areas: metabolism, physiology, psychiatry, and pharmacology). Then, we will analyze burden and polygenic risk scores for the aggregated traits to link GR-regulated genes to specific molecular processes and cellular compartments of the brain.

Further, we will investigate the multidimensional profile of the GR-dependent response of the organism. For this purpose, we will develop a database of GR-dependent transcriptomic responses in human neural cells. The latter will be obtained by exposing astrocytes and neurons differentiated from induced pluripotent stem cells (IPSC) lines to GR agonist and merging the resulting data with spatial brain transcriptomic profiles (single-cell sequencing datasets) to determine cell-autonomous pathways. The identified links between gene variants and human phenotypes will be validated by conducting functional experiments in IPSC-derived neural and glial cells.

The end goal is to define GR-dependent metaphenotype based on the genetic associations of the regulated genes and the biological impact of those in the context of specific cell types. We will attempt to dissect roles of GR activation that are specific to the central nervous system. Our results will give novel insight into the biological basis of stress-related, severe psychiatric conditions, such as depression and anxiety disorders. The elucidation of stress-induced molecular patterns would provide a foundation for the development and testing of novel, more effective psychoactive compounds.