Striatal development and Meis1 Action in ResTless legs syndrome, (SMART)

Project Coordinator: Prof. Dr. Juliane Winkelmann, Institute of Neurogenomics, Helmholtz Zentrum München, BMBF, München, Germany
Project Partners: Prof. Miguel Torres, Centro Nacional de Investigaciones Cardiovasculares (CNIC), MINECO, Madrid, Spain, Dr. Wojciech Krezel, Institut de Génétique et de Biologie Moléculaire et Cellulaire, ANR, France

Restless legs syndrome (RLS) is a common and debilitating neurodevelopmental disorder characterized by persistent discomfort and restlessness in the legs, with symptom severity increasing at night. This causes severe sleep disruption leading to significant secondary effects on physical, mental and social health. The cause of RLS is not well understood, and available treatments such as dopaminergic agents are thus limited in efficacy, particularly for long-term disease management. RLS is a complex disorder with genetic and environmental factors contributing to the phenotype. The strongest known genetic risk factors for RLS are variants in the gene *MEIS1.* Published and preliminary data indicate that the activity of *MEIS1* affects the development of the striatum, an RLSassociated brain region which integrates sensory input and movement-related output. We propose to comprehensively study the role of *MEIS1* in the mechanisms underlying RLS.
We will investigate the effect of *Meis1* deficiency on development of the striatum in mice. In addition, we will investigate genes and proteins targeted by MEIS1 to convey its effects on development. This approach is expected to identify other novel genes and proteins involved in RLS. We will directly test the importance of MEIS1 in the developing striatum for generating RLS by specifically deleting *Meis1* in the developing striatum of mice and evaluating RLS-related behaviors. Finally, we will investigate the effects of *MEIS1* genetic variants on the response to the dopaminergic class of therapeutic agents. This is expected to provide further insight into the effect of *MEIS1* variants on the function of the striatum. In addition, this will enable genotype-based precision medicine for RLS patients. Collectively, these studies are expected to characterize the developmental origin of RLS, provide significant insight into the precise causes of RLS, and define novel targets for more effective therapeutic approaches.