RiMod-FTD
Risk and Modifying factors in Fronto Temporal Dementia

Fronto Temporal Dementia (FTD) is a devastating pre-senile dementia characterized by the progressive deterioration of the frontal and anterior temporal lobes. The most common symptoms include severe changes in social and personal behaviour as well as a general blunting of emotions. Clinically, genetically and pathologically there is considerable overlap with a wide spectrum of neurodegenerative diseases. FTD has a very strong genetic influence. Up to 40% of cases have a positive family history and this has been the key to the remarkable progress in our understanding of the molecular basis of FTD. Mutations in MAPT, GRN and C9Orf72 explain >50% of familial cases, but how these different genes lead to a very similar clinical phenotype despite very distinct pathologies, is still an unanswered question. For sporadic FTD the role of genetic factors and their interplay with environmental risk factors is largely unknown.

Currently, there is no cure for FTD and the strategies for the development of successful therapies will depend on whether a single therapy can be applied to all patients or if specific approaches are needed for the distinct genetic, clinical and pathological subgroups. Therefore, it is essential to identify allmajor genetic risk factors and find both common environmental and genetic modifiers important in the pathogenesis of the disease as well as factors that are specific for subgroups of patients.

To reach these goals we have used the extensive genetic and pathological knowledge that already exists for FTD, including newly identified from our whole exome/genome sequencing and GWAS efforts, as a starting point to decode common and distinctly affected processes and pathways in different groups of Mendelian and sporadic FTD patients using a multi level approach based on a range of “omics” data sets from selected patient groups as well as corresponding animal and cellular model systems. The data generated in this project allows us to work in a model guided and hypothesis driven fashion. Based on the generated data, testable hypotheses on affected common and distinct gene networks are being generated and the biological significance of identified networks can be validated in our cellular and animal models in a targeted fashion and these experiments will pinpoint potential pathomechanisms that are specific to a single FTD-subtype or common to all forms. The results will be utilized to refine theoretical disease models and improve the quality of our approaches towards targeted intervention.