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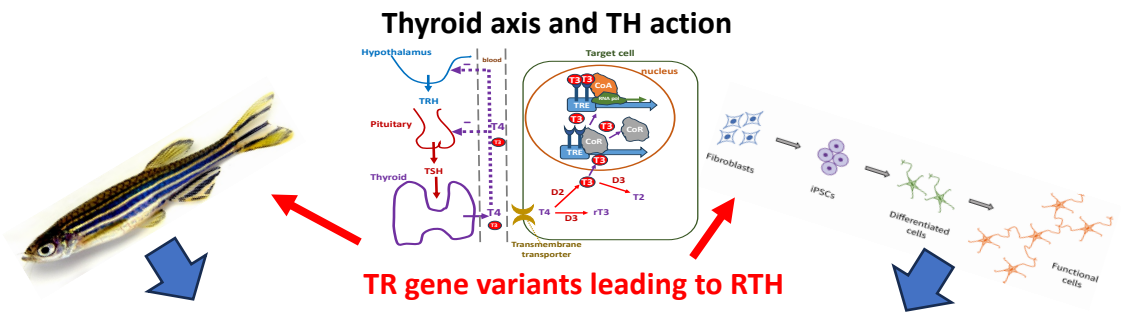
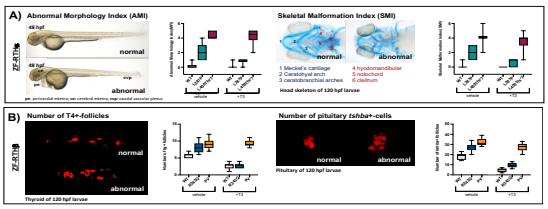
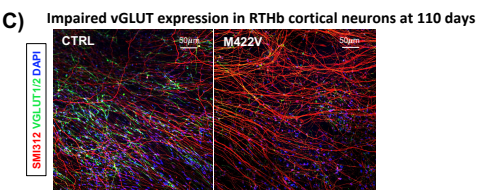
Advanced understanding of Thyroid Hormone action in brain and heart using zebrafish model and induced pluripotent stem cells (iPSC).

Thyroid hormones (TH) are indispensable for proper embryonic development and homeostasis of almost all tissues and organs. TH action defects (THAD) are a group of rare syndromes characterized by abnormal TH cell signaling due to defective transport, metabolism or action of TH via binding with nuclear receptors (TRs). Among them, mutations of THRA or THRB genes cause two distinct syndromes with Resistance to Thyroid Hormone (RTH) action.. RTHα is due to dominant negative (DN) heterozygous mutations in THRA and characterized by dramatic manifestations in TRα-expressing tissues resembling untreated congenital hypothyroidism (CH) and including growth retardation, intellectual disability, autism spectrum disorder, anemia and metabolic disorders. Unlike CH, RTHα lacks a clear-cut thyroid biochemical signature and cases cannot be disclosed by neonatal TSH screening. RTHß is due to DN heterozygous THRB mutations, which cause variable TH resistance in TRß-expressing tissues (hypothalamus, pituitary, liver), resulting in distinctive biochemical signature (high free TH and unsuppressed TSH) together with additional features like deafness, impaired color vision and thyrotoxic-related symptoms (goiter, tachyarrhythmias, osteoporosis, anxiety and Attention-Deficit/Hyperactivity Disorder, ADHD). Depending on the type of genetic mutations, the phenotypic manifestations RTHα and RTHß can largely vary, but they generally impact significantly the development and quality of life of affected patients. Importantly, neurocognitive impairment of RTHα can be severe, whereas behavior disorders and foggy brain of RTHß can also impact on working ability and social life. Moreover, cardiovascular features of RTHß can be very similar to those of unrecognized hyperthyroidism as a consequence of the chronic exposure to a TH excess of an organ prevalently expressing TRα. The underlying mechanisms of all these manifestations remain unclear. Outstandingly, early treatment with TH or its analogues is expected to reduce most of the adverse consequences of RTHs but early/neonatal diagnosis is presently not feasible due to the lack of accurate biomarkers. Indeed, uniform characterization is essential for a rare disease, and establishment of clear-cut endocrine fingerprints for RTHα and RTHß are essential for a timely diagnosis. In addition, the wide application of next generation sequencing (NGS) has yielded an unprecedented wealth of genetic information, calling for proper instruments to distinguish benign from pathogenic variants. Finally, biomarkers for monitoring treatment of these conditions have not been established or validated. Here, we aim to: a) understand the pathogenicity of newly discovered THRB or THRA variants in in vivo model or identify new mechanisms b) generate induced pluripotent stem cells from RTH patients to understand the molecular mechanisms underlying neurological and cardiovascular consequences and correlate in vitro and clinical data, with the final goal to identify potential biomarkers for monitoring treatment of these rare diseases.





A-B) Zebrafish models of RTHα and RTHβ (example of mild and severe hTR mutations)



C) Preliminary characterization of iPSCs-derived cortical neurons of RTHβ patient and healthy control.