The mammalian organism fully depends on the oxidative phosphorylation system (OXPHOS) as the major energy (ATP) producer of the cell. Disturbances of OXPHOS may be caused by mutations in either mitochondrial DNA (mtDNA) or nuclear DNA. One part of the thesis is focused on the role of early and late assembled nuclearencoded structural subunits of cytochrome c oxidase (CcO) as well as Oxa1l, the human homologue of the yeast mitochondrial Oxa1 translocase, in the biogenesis and function of the human CcO complex using stable RNA interference of COX4, COX5A, COX6A1 and OXA1L, as well as expression of epitope-tagged Cox6a, Cox7a and Cox7b, in HEK (human embryonic kidney)-293 cells. Our results indicate that, whereas nuclear- encoded CcO subunits Cox4 and Cox5a are required for the assembly of the functional CcO complex, the Cox6a subunit is required for the overall stability of the holoenzyme. In OXA1L knockdown HEK-293 cells, intriguingly, CcO activity and holoenzyme content were unaffected, although the inactivation of OXA1 in yeast was shown to cause complete absence of CcO activity.
In addition, we compared OXPHOS protein deficiency patterns in mitochondria from skeletal muscle, heart, liver and frontal cortex of patients with Leigh (mtDNA mutation 8363G>A), MERRF (mtDNA mutation 8344A>G), and MELAS (mtDNA mutation 3243A>G) syndromes. Our data show new effects of mt-tRNA mutations on the brain which differ substantially from those described for other tissues. Furthermore, we found that mtDNA 9205TA microdeletion in the ATP6 gene prevents the synthesis of ATPase subunit a and also affects the biogenesis of CcO.