Abstract:
Neurodegenerative disorders that present in childhood are a group of heterogeneous conditions with a genetic basis that lead to a progressive decline in psychomotor function. The primary target in these disorders may involve any of the structural components of the nervous system (neurons and their projections, and supportive elements; astrocytes and glial cells). These disorders present with developmental regression (loss of developmental milestones) affecting multiple domains (motor, social, cognitive) with or without the presence of seizures. Advances in genomic medicine have begun to unravel the underlying causes for these conditions; several cellular organelles and pathways are involved as targets for pathogenic mutations eventually leading to a degenerating neural network.

In this talk, we will examine the relationship of the mitochondrial oxidative phosphorylation (OXPHOS) system and childhood neurodegenerative disorders such as MELAS (mitochondrial encephalomyopathy, lactic acidosis and strokes), Leigh’s disease, and Alper’s hepatocerebral degeneration and others). The OXPHOS system consists of 5 multiunit complexes comprising 92 different proteins encoded by a unique combination of nuclear (nDNA) and mitochondrial genomic (mtDNA). In addition, the biogenesis of a functioning OXPHOS system requires assembly factors (about 35 known at present) that are nuclear encoded. Pathogenic mutations in the genes underpinning the OXPHOS system (both structural and assembly genes) as well as in genes involved in mtDNA maintenance, replication, transcription, and translation result in primary OPXPHOS disorders. Through illustrative clinical cases with video and neuroimaging, results of molecular genetic testing, the talk will focus on how current advances in genomic medicine have provided us valuable insights into mechanisms of neurodegeneration at a molecular level. The patterns of inheritance, the phenotypic variability and neuropathology of these disorders will be discussed. Finally, the potential availability of gene editing technologies (CRISPR/Cas9) to provide targeted therapeutic interventions and ethical issues surrounding these will be discussed.