Mitochondria are the major source of ATP, which is synthesized by the mitochondrial respiratory chain through the process of oxidative phosphorylation (OXPHOS). OXPHOS is a complex biochemical process, carried out under the control of two different genomes, nuclear and mitochondrial and involves hundreds of genes. ATP deficiency leads to cellular dysfunction and ultimately cell death, especially in tissues with high energy demand. This explains the vast heterogeneity of mitochondrial disorders, a challenge to both diagnosis and clinical management. The prevalence of mitochondrial disorders estimated in Europe is about 1-2 in 10,000 live births. In an attempt to address the challenges of diagnosing and treating the heterogeneous group of patients with OXPHOS disorders, local and national networks are currently being established with the aim to provide specialized care centres for patients with mitochondrial disorders.

Furthermore research in an European concerted action is necessary to concentrate expertise and to collect patients and patient samples from several competence centers in order to increase the number in each subgroup of the heterogenous mitochondrial diseases. Therefore a network of specialized centres in Germany, Italy, France, Israel, Austria and Belgium (GENOMIT) was created to apply for an e-rare grant with the aim to improve diagnosis, molecular understanding and treatment of patients with mitochondrial disorders in Europe. This goal will be accomplished with four workpackages: First, establishment of a European catalogue of databases and a collection of biomaterials from patients with mitochondrial diseases. Second, development of new diagnostic protocols based on next generation sequencing techniques that will be applied to shared sample collections. Third, extention of functional studies of genes and pathways involved in the pathophysiology of mitochondrial disorders. Fourth, testing of new therapeutic options by improving the range of and the access to animal disease models. GENOMIT partners are active as national centers for the diagnosis and care of patients with mitochondrial diseases. In addition, each of them has developed unique expertise that will be shared synergistically within the network.

Our Department of Pediatrics at the Paracelsus Medical University is a national center for the diagnosis of patients with mitochondrial disorders in a close cooperation with the Department of Pediatrics (Munich-Schwabing) and the Institute of Human Genetics, Technical University Munich (www.mito-center.org) and furthermore already a part of the German network for mitochondrial disorders (MITONET) (www.mitonet.org). Our focus is laid on the functional investigation of unfrozen samples which led to the detection of novel disorders in the mitochondrial pyruvate oxidation and ATP synthesis. Furthermore the patient samples are investigated with various other biochemical, histological and genetic techniques to unravel the underlying molecular defects. Several of these methods have been optimized for the use of small tissue samples from pediatric patients.

Our part in the e-rare project is mainly focused on the third working package of GENOMIT, using especially the expertise of the functional and biochemical characterization of OXPHOS for the understanding of key molecular and biochemical mechanisms responsible for mitochondrial diseases. This is also a prerequisite for the identification of new drug targets and the development of novel treatments. Defined respiratory chain complex defects will be evaluated using existing cellular models. Our part in the project covers an optimal use of the wide spectrum of established assays and makes them available to consortium members and has the objectives i) to validate newly identified disease gene candidates, ii) to delineate pathways involved in the pathogenesis of mitochondrial disorders and iii) to validate therapeutic approaches in in-vitro models.