

Abstract

Rare diseases represent a clinically and genetically heterogeneous group of diseases affecting various organs and presenting at different ages. Identification and functional characterization of genetic defects causing individual rare diseases represent unique opportunity to understand biological functions of human genes and gene products as well as to basic pathogenetic mechanisms of individual diseases. This knowledge is prerequisite for their effective diagnosis, specific treatment and prevention and it also opens up an avenue for better understanding of complex diseases.

My thesis documents basic conceptual and methodological developments of biochemical genetics, functional cloning, genetic mapping, positional cloning, DNA microarrays and genomic sequencing, which have provided a universal framework for effective characterization of the genetic architecture of almost all human diseases. This conceptual and technological developments are demonstrated on several cases of rare genetic diseases - adenylosuccinate lyase deficiency, mucopolysaccharidosis type IIIC, Rotor syndrome, deficiency of ATP synthase, neuronal ceroid lipofuscinosis, GAPO syndrome and X -linked restrictive cardiomyopathy, which genetic and molecular basis I have helped to elucidate.