Genomics-To-Therapy: a concept illustrated by CMT-SORD

Abstract

The discovery of the CMT-SORD subtype of inherited peripheral neuropathies and its translation towards a therapy has been teaching us many lessons. Bi-allelic changes in the sorbitol hydrogenase gene SORD cause a motor dominant axonal form of CMT and dHMN, that accounts for up to 10% of undiagnosed patients. The discovery was only made in 2020, as the immediatly upstream non-functional pseudogene SORD2P is highly homologous to SORD and has misled bioinformatic approaches based on short-read sequencing data. Aggregation of over 2,000 CMT exomes and genomes in the GENESIS database, mostly from index cases and sib-pairs, alternative software approaches, and talented young scientists have led to the correct gene identification. Rapid follow up with animal models, the development of a new rat model, and studies in patient derived iPSC further confirmed the principle pathomechanism and validated a therapeutic approach. Within two years of the publication, a multi-center trial was underway and a recent read-out suggested promising trends. This presentation will give a comprehensive overview of the many activities around SORD, its importance to the field, and the rapid development of a therapy.