Abstract

Collagen VI-related myopathies are a group of rare inherited genetic disorders with varying degree of clinical severity, caused by mutations in the Collagen type VI genes: COL6A1, COL6A2, and COL6A3.

As a national reference center for diagnosis of neuromuscular disorders, 245 patients were analyzed in the Medical Genetics Unit over a 12-year period (2006-2018). The aim of this thesis is to provide a nationwide study of patients with COLVI phenotype and an overview of COL6 genes variants. The detection of mutations in collagen VI genes remains the gold standard for diagnosis, but traditional diagnostic tools do not completely achieve this goal. Next generation sequencing panel offers the ability to efficiently and cost-effectively screening all exons of the three COL6A genes. However, it is known the importance of studying transcriptome to enhance the diagnostic rate and to study the mutation functional consequence, therefore confirming their pathogenicity. In our results, the RNA-seq was shown to be the innovative strategy to explore RNA profile of COL6 genes in patients.

To date, a disease cellular model for COL6-RD with the capacity to completely recapitulate the pathological phenotype in humans is yet to be established. Having this in mind, the use of Urine Stem cells (USCs) as a collagen VI cellular model was in this study developed and validated at the RNA level. Despite being a preliminary study defining whether USCs could be a good collagen VI cellular model, the data presented herein hold good promise. In contrast to skin and muscle biopsies, USCs can easily and non invasively be retrieved from urine samples. Hence, the collagen VI cellular model employing USCs with the ability to function equally well to the existing using fibroblasts could have many advantages. We propose these cells as COLVI disease in vitro model for functional studies, drug screening and validation.