Determining the genetic cause of short stature as a way to understand the pathophysiological mechanisms affecting human growth

Abstract

Short stature is one of the most common disorders followed-up by a paediatric endocrinologist. Pathophysiologic mechanisms leading to growth disorders are complex, however, the exact cause is mostly unknown. Our study is the first to evaluate the aetiopathogenesis of familial short stature (FSS). Using next-generation sequencing (NGS) techniques, we aimed to describe the monogenic aetiology of growth impairment in a group of FSS families, and therefore to elucidate mechanisms leading to this specific growth disorder. In selected genetic diagnoses, we additionally aimed to describe the phenotype including GH treatment response. Within Motol University Hospital centre for GH therapy, we formed a group of 98 FSS families with clear height definition in ≤-2 SD in both the child height before GH therapy and in his shorter parent. Using NGS, the FSS aetiology was elucidated in 40/98 (41%) families; 32/40 had a genetic growth plate disorder. Within the cohort, three genetically homogeneous subgroups of families were described (collagenopathies – 10/98 [10.2%] families, SHOX deficiency – 6/98 [6.1%] families, and C type natriuretic peptide receptor disorder – 4/98 [4.1%] families). Dominant phenotype in all the subgroups was the growth disorder without apparent associated pathologies. As mutations in growth plate collagen genes have previously been known only to cause syndromic short stature, a new phenotype has been revealed. Moreover, the clinical predictors for monogenic FSS have been proposed. All the subgroups responded well to GH treatment.

Key words

Familial short stature, growth disorders, growth hormone treatment, growth plate, growth plate disorders, next-generation sequencing, short stature