INTRODUCTION and OBJECTIVES

We previously described two siblings with a frameshift mutation (c.1927_1928insAT, p.D643fs25*) resulting in loss of function in the gene for pregnancy-associated plasma protein A2 (PAPP-A2) [1,2]. The female was 10.5-years of age (1.7 SDS below target height at diagnosis). Her brother was 6-years of age and 1.3 SDS below target height, with both children experiencing a decelerating growth velocity. These patients presented elevated serum GH, total IGF-1, IGFBP-3 and ALS levels, but extremely low free/bioactive IGF-1 levels. Hence, they were treated with rhIGF1. The growth response and improvement in bone mineral density have been previously reported [3].

Aim: Investigate the changes in metabolism associated with the response to rhIGF1 treatment

METHODS

TREATMENT

Siblings were treated with progressive doses (40, 80, 100, and 120 μg/kg) of recombinant human IGF1 twice daily for 1 year.

• Samples were collected at 0, 60, 120, 240, 360 minutes after administration of the treatment.
• Serum samples were collected before the treatment and every 6 months after the first day of treatment.

RESULTS

PRINCIPAL COMPONENT ANALYSIS (PCA)

Naive sample clustering is shown according to the acute & long-term effect of the rhIGF1-1 treatment

DISCUSSION & CONCLUSION

This study depicts a metabolic snapshot of the changes induced by rhIGF1 that, together with the improved linear growth [2], help to provide a more comprehensive overview of the effects of this treatment, as well as new insights into this IGF1 deficiency syndrome.

➢ Decreased free fatty acid and glycerol levels have been detected, pointing to enhanced FFA use and promotion of lipogenesis during both acute and long-term treatment. This has been described to enhance insulin signalling and sensitivity, which is in accordance with the observation that rhIGF1 treatment improved the mild basal hyperinsulinaemia observed in the two patients before the treatment.

➢ Increased serum 4-hydroxyproline levels in response to the treatment were observed. As 4-hydroxyproline is a marker of collagen catabolism and bone resorption, this observation could represent an increase in bone turnover. Indeed, the greatest increase in 4-hydroxyproline corresponded to the period of highest growth velocity.

The dramatic change in hydroxyproline and increases in FFAs and specific amino acids following therapy might be used as informative patterns for the assessment of the metabolic effects of IGF1 treatment, suggesting an insightful role for metabolomics in therapy monitoring.

REFERENCES