

Impact of the GH-IGF-I axis in adults - pharmacogenetic and genetic association studies



UNIVERSITY OF GOTHENBURG

Akademisk avhandling

som för avläggande av medicine doktorsavhandling kommer att offentligens försvaras i Sahlgrenska Aula, Sahlgrenska Universitetssjukhuset, Blå Stråket 5, Göteborg, fredagen den 5 april kl 09:00

av

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Avhandlingen baseras på följande delarbeten:

- Paper I. **Influence of the exon 3-deleted/full-length growth hormone (GH) receptor polymorphism on the response to GH replacement therapy in adults with severe GH deficiency.**
Barbosa EJ, Palming J, Glad CA, Filipsson H, Koranyi J, Bengtsson BA, Carlsson LM, Boguszewski CL, Johannsson G.
J Clin Endocrinol Metab. 2009 Feb;94(2):639-44.
- Paper II. **Rapid and high throughput genotyping of the growth hormone receptor exon 3 deleted/full-length polymorphism using a tagSNP.**
Glad CA, Johannsson G, Carlsson LM, Svensson PA.
Growth Horm IGF Res. 2010 Jun;20(3):270-3.
- Paper III. **SNPs within the GH signaling pathway are associated with the early, but not the long-term, IGF-I response to GH replacement therapy in GHD adults.**
Glad CA, Barbosa EJJ, Filipsson Nyström H, Carlsson LMS, Nilsson S, Nilsson AG, Svensson PA, Johannsson G.
Manuscript.
- Paper IV. **The growth hormone receptor exon 3 deleted/full-length polymorphism is associated with body weight and body composition in the general population.**
Glad CA, Carlsson LMS, Sjöström L, Nilsson S, Larsson I, Svensson PA, Johannsson G.
Manuscript.

ABSTRACT

Growth hormone (GH) is a polypeptide hormone which is secreted from the anterior pituitary in a pulsatile pattern. GH is best known by its strong effects on longitudinal growth in children, but the importance of GH is maintained also in adulthood due to the powerful effects on cellular differentiation and fuel homeostasis. GH deficient (GHD) adults often present with abdominal obesity, insulin resistance and an almost doubled risk for cardiovascular mortality. These problems are to a varying extent reversed during GH replacement therapy (GHRT). Variability in treatment response is large and probably at least partly mediated by genetic variation. The effects of GH are mediated by the GH receptor (GHR), a transmembrane glycoprotein expressed on most human cell types. In humans, there are two isoforms of the GHR which differ in regards to retention (fl-GHR) or exclusion (d3-GHR) of exon 3. The two isoforms are simply two different alleles of a common *GHR* polymorphism (the *GHR* d3/fl polymorphism), which has been suggested to influence GH sensitivity.

This thesis is based on four studies, with the common, overall, aim to test the hypothesis that polymorphisms in genes within the GH-IGF-I axis influence body composition, metabolism and serum IGF-I concentrations.

In an initial study we found that the *GHR* d3/fl polymorphism was not associated with the 1 year changes in IGF-I concentrations and body composition in response to GHRT. During this study, which was fairly small, we realized the need for a different genotyping method for analyses of the *GHR* d3/fl polymorphism in larger cohorts. Therefore, in the subsequent study, we evaluated the use of tagSNP rs6873545 as a marker for the *GHR* d3/fl polymorphism, and showed that it does indeed perfectly tag the different *GHR* d3/fl alleles. In the next study, we investigated the impact of the *GHR* SNP rs6873545 and five other polymorphisms in genes within the GH-IGF-I axis on the early and the long-term IGF-I responses to GHRT in a large cohort of GHD adults. In this study we found that the *GHR* SNP rs6873545 and the *PIK3CB* SNP rs361072 were associated with the early, but not the long-term, IGF-I response. In the last study, we analysed the tagSNP rs6873545 in a study representative of the general Swedish population and found that homozygosity for the d3-GHR was associated with an adverse anthropometric and metabolic profile.

In conclusion, the results of this thesis suggests that 1) the *GHR* d3/fl polymorphism is indeed of functional importance, and influences both the response to GHRT in GHD adults as well as body composition and metabolism in the general Swedish population, and 2) other SNPs in genes within the GH-IGF-I axis may be of an equal importance in terms of the response to GHRT in GHD adults.

Key words: growth hormone, growth hormone receptor, genetic association study, pharmacogenetic, growth hormone deficiency, polymorphism, candidate gene approach, metabolism, anthropometry.

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