SNPs within the GH signalling pathway are associated with the fast, but not the long term, IGF-I response to GH replacement therapy in GH deficient adults

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BACKGROUND

Growth hormone (GH) deficiency (GHD) in adults is associated with low serum levels of insulin-like growth factor I (IGF-I) and a deteriorated cardio-metabolic profile. GH replacement therapy (GHRT) increases serum IGF-I, an important mediator of the treatment response and safety marker of dose titration. The interindividual variation in treatment response is large and most likely influenced by genetic factors.

AIM

To test the hypothesis that single-nucleotide polymorphisms (SNPs) in genes within the GH signalling pathway impact on the fast (early) and/or long term IGF-I response to GHRT.

SUBJECTS AND METHODS

The GH2 study

This is an ongoing, longitudinal, prospective study of adult patients with hypopituitarism and severe GHD (n=313; see Table 1A for baseline patient characteristics.) Diagnosis of GHD was performed using standard consensus criteria (Ho KK, 2007). GH dose was individually titrated to attain sex- and age adjusted normal serum IGF-I levels. The study was approved by the Ethics Committee at the University of Gothenburg, Sweden, and performed according to the Declaration of Helsinki.

Response definition

Response to GHRT was defined as the percentage of change in serum IGF-I concentrations.

- Early response at 1 week (change from baseline).
- Long-term response at 6 and 12 months (change from 1 week).

Genotyping

Using a candidate gene approach, six SNPs (Table 1B) were chosen and subsequently analyzed using either TaqMan or Sequenom SNP genotyping. The *GHR* exon 3 deleted/full-length polymorphism was analyzed using tagSNP rs6873545, as previously validated (Glad CA *et al*, 2010).

Statistics

Genotype data was analyzed in an additive model. Multiple regression analyses adjusting for sex, age and GH dose were performed.

CONCLUSIONS

- *GHR* and *PIK3CB* SNPs rs6873545 and rs361072 were associated with the early response to GHRT.
- When dissecting the long-term response into one that depends on the early response, no SNPs were associated with the 6 months and 1 year response to GHRT.
- The effect of genetics on response to GHRT is most likely best captured in the early response.

RESULTS

- Average genotyping success rate was 98.8%. Minor allele frequencies (MAFs) and Hardy-Weinberg Equilibrium (HWE) χ^2 test *p*-values are presented in Table 1B.
- One year of GH replacement therapy increased serum concentrations of IGF-I (Table 1C; $p<0.001$).
- *GHR* and *PIK3CB* SNPs rs6873545 and rs361072 were significantly associated with the early IGF-I response to GHRT (Table 1D; $p=0.016$ and $p=0.025$, respectively).
- No SNPs were associated with the long-term response to GHRT, when the 1 week serum IGF-I levels were used as reference (Table 1D).

TABLE 1. Clinical and genetic background information and results.

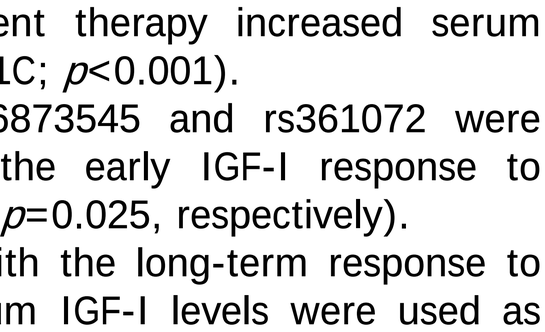
A

Aetiology	n (%)	Clinical characteristics	n (%)
NFPA[1]	128 (40.9)	n	313
Idiopathic GHD	29 (9.3)	Male sex	182 (58.1)
Prolactinoma	27 (8.6)	Age, yrs (range)	49.7 (17-77)
Craniopharyngeoma	24 (7.7)	Current smoker	25.2
Hypophysitis	22 (7.0)	Adult onset GHD	89.8
Previous Cushing	20 (6.4)	Isolated GHD	11.3
Previous Acromegaly	10 (3.2)	Duration of GHD, yrs (range)	4.48 (0-47)
Other aetiologies	53 (16.9)	**Sex steroids**	
Pre-study treatment		- Men	134 (73.6)
- Surgery	163 (54.7)	- Women	50 (38.2)
- Radiotherapy (RT)	16 (5.4)	Diabetes insipidus	52 (16.6)
- Surgery + RT	48 (16.1)		

B

dbSNP ID	Gene	MAF	HWE X^2 *p*
rs6873545	*GHR*	23.8 % (C)	0.430
rs361072	*PIK3CB*	40.2 % (G)	0.412
rs7849191	*JAK2*	36.9 % (T)	0.755
rs3780378	*JAK2*	48.2 % (C)	0.042*
rs6503691	*STAT5b*	12.5 % (T)	0.267
rs11107116	*SOCS2*	26.6 % (T)	0.761

C



D

dbSNP ID	1 week (n=253)	6 months (n=251)	1 year (n=256)
rs6873545	-45.3[2]	NS	NS
rs361072	37.5[3]	NS	NS
rs7849191	NS	NS	NS
rs6503691	NS	NS	NS
rs11107116	NS	NS	NS

Panel A shows general patient characteristics of the 313 adult GHD subjects. [1]NFPA=non-functioning pituitary adenoma. **Panel B** shows dbSNP ID, associated gene name, MAFs and HWE X^2 *p*-values for the six candidate SNPs. *deviation from the HWE. **Panel C** shows mean±SD serum IGF-I levels during 12 months of GHRT. **Panel D** shows the results from the linear regression analyses. Effect sizes refer to the adjusted difference between the heterozygotes and homozygotes of the major allele for each SNP, negative values correspond to a lower increase in serum IGF-I levels for the heterozygotes as compared to the homozygotes of the major allele. [2]$p=0.016$. [3]$p=0.025$. NS=non-significant.

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