Gene expression profiles in growth hormone deficient (GHD) children relate peak GH levels to circadian clock, chromatin remodelling and WNT signalling pathways

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Background

• Growth Hormone (GH) deficiency is classically defined on the basis of a cut-off applied to the peak GH level during stimulation tests; a process with recognised limitations. Identifying the functional role of genes whose expression is associated with peak GH levels may help with our understanding and classification of GHD.

Objectives

• Identify patterns of gene expression (GE) related to peak GH levels and to describe the function, and regulation of these genes.

Methods

• Pre-pubertal children with GHD (n=89) were recruited from the PREDICT study (NCT00505632) and childhood controls were obtained from available online datasets. GHD was defined at peak GH levels < 10µg/L to two stimulation tests.

• Gene expression analysis was conducted in a library of gene expression datasets from normal children with age matching obtained from the NCBI Gene Expression Omnibus (GEO) and ENA ArrayExpress database (ESE2484, ESE26440 and TABM00066). As the children in PREDICT were all prepuberal, GE profiles from normal children were removed if they were aged > 11 which left 33 normal children.

• Whole blood GE was determined prior to GH treatment using Affymetrix U133v2 microarrays. GE was correlated with peak GH using rank regression (gender, ethnicity, age and body mass index (BMI) as co-variates).

• Network models were generated and the hierarchy of gene modules determined; upstream activity in the network model was assessed using causal network analysis.

Results

• Rank expression identified 247 probesets where expression correlated with peak GH concentrations: 188 positively and 159 negatively correlated (Rs +/- 0.28, p<0.01). A heatmap of the genes identified by the rank regression plotted against peak GH (µg/L) as a continuous variable was generated (Figure 1).

• A point of inflection between the wound- or correlations is seen at around a peak GH of 4.83 µg/L (arrow on Figure 1). From the dendrogram 6 clusters of gene expression were identified – 2 related to genes where there is a positive correlation with peak GH and 3 related to genes where there was a negative correlation with peak GH.

Conclusions

• This study has demonstrated the potential for gene expression profiling to aid in both the diagnosis and classification of GHD and in addition has identified the functions of the networks of genes related to peak GH concentrations along with their master regulators.

• Normal children appear to have a different pattern of GE to GHD children.

• GE profiling identified a genomic signature of GH functionally linked to circadian clock and growth factor signalling and regulated by PKI3, SIRT2 and APC2.

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Disclosures

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