Gene Expression Profiling of Children with Growth Hormone Deficiency Prior to Treatment with Recombinant Human Growth Hormone is Associated with Growth Response Over 5 Years of Therapy

Adam Stevens1, Philip Murray2, Ekaterina Koledova2, Pierre Chatelain2, Peter Clayton3
1University of Manchester and Royal Manchester Children’s Hospital, Manchester, UK; 2Merck KGaA, Darmstadt, Germany; 3Université Claude Bernard, Lyon, France

INTRODUCTION

• The relationship between pre-treatment gene expression and long-term growth response in growth hormone deficiency (GHD) is unknown.
• Prediction of long-term responses to recombinant human growth hormone (r-hGH) therapy would enable better decision-making about the start and maintenance doses and, hence, improve the cost-benefit ratio of r-hGH therapy.

OBJECTIVES

• To investigate the relationship between baseline gene expression and response to r-hGH over 5 years of therapy in children with GHD.

METHODS

• Patient population
  – Pre-pubertal children with GHD (N=50) were enrolled from the PREDICT (NCT00255612) and PREDICT long-term follow-up (NCT00699855) studies.
  – Treatment
    – Children started with a 35 μg/kg/day r-hGH dose (all same brand, Saizen®) for the first month.
    – During the long-term follow-up period, patients could use any available r-hGH at a dose recommended by the physician.
• Genomic analysis
  – Baseline whole-blood gene expression was determined from peripheral blood mononuclear cells using Affymetrix U133 v2.0 microarray and Gene Expression Barcode 3.0.
  – Gene expression data were normalised for Tanner stage.
• Analysis of network modules was performed using Moduland algorithm.
• A Random Forest algorithm was tested for prediction of growth response.
• Statistical analyses
  – Height velocity (cm/year) on r-hGH over 5 years was used as the marker for growth response.
  – Two groups of patients were defined according to growth response over 5 years of treatment:
    – Always above the median (G1, n=9).
    – Always below the median (G2, n=10).
  – The effect of age, gender and distance to target height were also assessed.
  – The robustness of the gene expression markers was assessed using a one-way permutation test (1000 permutations) in R 3.3.1.

RESULTS

Patient Characteristics and Height Velocity

• The patient characteristics and the height velocity for the complete PREDICT LTFU cohort (N=125) are shown in Tables 1 and 2.

• There was no difference in age, gender and distance to target height between the G1 and G2 height velocity groups (data not shown).

CONCLUSIONS

• We have identified genes uniquely expressed before treatment in 50 pre-pubertal patients with GHD that are associated with quality of growth response (responsiveness) over 5 years of therapy.
• Responsiveness to r-hGH therapy seems to be genetically controlled in GHD, which may have implications for personalised therapy.
• These gene expression markers may be used prior to r-hGH treatment to identify which patients will be good or poor long-term responders.
• Further assessment is required to validate the predictive value and determine the functional significance of the gene subsets we have identified.

ACKNOWLEDGMENTS

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DISCLOSURES

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REFERENCES


Table 1. Patient Characteristics of Whole PREDICT LTFU Cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GHD (N=125)</th>
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<tbody>
<tr>
<td>Gender (male/female)</td>
<td>78 (62.4%):47 (37.6%)</td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td>9.6 (6.3, 11.2)</td>
</tr>
<tr>
<td>Baseline height SDS</td>
<td>–2.2 (–2.7, –1.7)</td>
</tr>
<tr>
<td>Baseline BMI SDS</td>
<td>–1.4 (–2.1, –0.8)</td>
</tr>
<tr>
<td>Bone age (years)</td>
<td>7.0 (5.5, 9.5)</td>
</tr>
<tr>
<td>Basal height velocity (cm/year)</td>
<td>4.0 (3.0, 6.0)</td>
</tr>
<tr>
<td>Mid-parental height SDS</td>
<td>–0.8 (–1.7, –0.1)</td>
</tr>
<tr>
<td>GH peak response (μg/L)</td>
<td>4.1 (2.4, 5.6)</td>
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</tbody>
</table>

Table 2. Height Velocity (cm/year) Throughout Treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>GHD (N=125)</th>
</tr>
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<tbody>
<tr>
<td>Mean (±SD)</td>
<td>Median (min, max)</td>
</tr>
<tr>
<td>Year 1</td>
<td>8.9 (±2.1)</td>
</tr>
<tr>
<td>Year 2</td>
<td>7.4 (±1.6)</td>
</tr>
<tr>
<td>Year 3</td>
<td>6.7 (±2.0)</td>
</tr>
<tr>
<td>Year 4</td>
<td>6.1 (±2.3)</td>
</tr>
<tr>
<td>Year 5</td>
<td>5.1 (±2.3)</td>
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Data are mean (±SD) or median (min, max).