Objective

To characterise clinical and biochemical features of two severely growth retarded twins, to identify the genetic cause of their GH insensitivity and to define molecular properties of the affected proteins and pathways.

Background

GH insensitivity (GHI) is caused by disturbances of GH receptor function or inability to transduce the hormone signal. Affected children are severely growth retarded and may also present immune complications when the transducer STAT5B is defective. Only autosomal-recessive STAT5B mutations have been described to date.

Index Patient

- second child of unrelated parents
- 36 gestational week; birth weight, 2500 g (-1.9 SDS); birth length, 45 cm (-1.9 SDS)
- proportionate short stature; no dysmorphic signs (Fig. 1)
- onset of puberty at approximately 15 yrs
- recombinant human rhGH1 treatment commenced at 14.8 yrs (0.12 mg/kg bds); moderate response after 2.6 yrs [height: 1.0 SDS; Table 1, Fig. 1]
- biochemical evaluation indicative for GHI (Table 1)
- clinical and biochemical characteristics of the monogygotic twin very similar to the index patient
- healthy parents; father, 174 cm (-0.9 SDS); mother, 160 cm (-1.2 SDS)
- siblings (brother and half-sister): normal

Table 1. Auxological and biochemical characteristics of the patient

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before rhGH1 tx</th>
<th>During rhGH1 tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>131.5 (-3.3)</td>
<td>149.0 (-4.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>28.0 (-4.5)</td>
<td>42.0 (-3.5)</td>
</tr>
<tr>
<td>Bone age, yrs</td>
<td>9.6</td>
<td>13.5</td>
</tr>
<tr>
<td>GH, basal, µg/l</td>
<td>n.d.</td>
<td>8.1</td>
</tr>
<tr>
<td>GH, stimulated, µg/l</td>
<td>16.2</td>
<td>n.d.</td>
</tr>
<tr>
<td>GHBP, pmol/l</td>
<td>n.d.</td>
<td>404 (369-1876)</td>
</tr>
<tr>
<td>IGF1, µg/l</td>
<td>56 (76-499)</td>
<td>107.2 (-1.5 SDS)</td>
</tr>
<tr>
<td>IGF1BP3, mg/l</td>
<td>n.d.</td>
<td>2.3 (1.7 SDS)</td>
</tr>
<tr>
<td>ALS, pmol/l</td>
<td>n.d.</td>
<td>418 (986-1678)</td>
</tr>
<tr>
<td>Prolactin, µIU</td>
<td>n.d.</td>
<td>290.6 (86-324)</td>
</tr>
</tbody>
</table>

- recurrent eczema, but otherwise healthy
- elevated IgE levels (340 kU/l, normal <114)
- immunological phenotyping otherwise unremarkable
- no chronic pulmonary disease, no lung fibrosis or lymphocytic interstitial pneumonia

Genetic evaluation

- molecular genetic analyses of GHR and STAT5B revealed an heterozygous A to C transversion within exon 5 of STAT5B (CAG to CCG; C.530A>C; Fig. 2)
- twin brother but not parents bear the same mutation (de novo mutation)
- analysis of GHI, IGF1, IGFA1S and IGFI1R genes did not show any further potentially pathogenic aberration
- mutant STAT5B allele expressed on mRNA level (Fig. 2)

Summary

We describe a novel heterozygous p.Gln177Pro STAT5B mutation with potential dominant-negative properties conferring clinical manifestations comparable to reported STAT5B deficient patients but with less severe co-morbidities.

Normal STAT5B activation

- reconstitution studies and immunoblotting in hGHR transfected HEK293 cells (Fig.4)
- p.Gln177Pro expression and phosphorylation comparable to STAT5B wild-type in response to GH

Normal STAT5B dimerisation

- reconstitution experiments in HEK293 cells, co-immunoprecipitation and immunoblotting (Fig.5)
- p.Gln177Pro retains the capability to dimerise with the wild-type STAT5B in response to GH

Abnormal STAT5B trafficking

- reconstitution experiments in HEK293 cells, immunofluorescence and deconvolution microscopy
- p.Gln177Pro does not translocate into the nucleus, neither when transfected alone (data not shown) nor when associated with wild-type STAT5 (Fig. 6)
- wild-type STAT5 is prevented from nuclear translocation when associated with the mutant

Contact:
Jürgen Klammt, MD, Professor for Pediatrics, University of Leipzig, Germany, Department of Pediatrics, University Hospital Leipzig, Germany, and Jürgen.Klammt@medizin.uni-leipzig.de, David Neumann, FNHK, Czech Republic, David.Neumann@fnhk.cz, Vivian Hwa, CCHMC, USA, Vivian.Hwa@cchmc.org; Disclosure: the authors have nothing to declare.