Clinical and preliminary molecular description of a cohort of patients with growth retardation due to severe primary IGF1 deficiency (GROWPATI study)

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Background

Severe primary insulin-growth factor-1 (IGF1) deficiency (SPIGF1D) is a rare cause of growth retardation. Diagnostic criteria include age- and sex-dependent low basal IGF1 levels (<2.5th percentile), height ≤−3SDS, absence of growth hormone (GH) deficiency and of any secondary causes of growth failure.

Objectives

Phenotypic description, follow-up and molecular studies in a cohort of patients diagnosed with growth failure due to SPIGF1D

Results

45 patients with SPIGF1D (M/F : 24/21)

27 SGA patients
18 ISS patients

Follow-up:
- Ongoing puberty for most patients, normal onset
- Final height: 157cm (−2.8SDS) and 159cm (−2.5SDS) for 2 male patients, 152cm (−1.2SDS) for one female patient
- Constitutional bone disease diagnosed for 4 patients (2 SGA, 2 ISS)
- Treatment: Growth hormone for 27 patients, rhIGF1 for 2 patients (patient#1 and #3, below) without any adverse effects

Clinical and biochemical features in patients with identified mutations in known genes so far

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>Birth Wt. SDS</th>
<th>Birth Height SDS</th>
<th>Target height SDS</th>
<th>Actual height SDS</th>
<th>GH basal (mIU/L)</th>
<th>GH max (mIU/L)</th>
<th>IGF1 (ng/mL)</th>
<th>IGF1 SDS</th>
<th>Clinical features</th>
<th>Consanguinity and ethnicity</th>
<th>Gene and mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>F</td>
<td>+0.2</td>
<td>−0.5</td>
<td>−1</td>
<td>−6</td>
<td>ND</td>
<td>&lt;5</td>
<td>−24</td>
<td></td>
<td>Dwarfism, protruding forehead, acromegalia, trunci obesity</td>
<td>+ Algerian</td>
<td>Hom GHR c.703C&gt;T, p.R217X, Laron syndrome</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>F</td>
<td>+0.4</td>
<td>−1.2</td>
<td>−0.8</td>
<td>−1.7</td>
<td>10.6</td>
<td>28.1</td>
<td>33</td>
<td>−2.5</td>
<td></td>
<td>- Caucasian</td>
<td>Het GHR c.535C&gt;T, p.Arg179Cys</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>M</td>
<td>−0.7</td>
<td>−1.2</td>
<td>−2.3</td>
<td>−4.1</td>
<td>12.6</td>
<td>43</td>
<td>65</td>
<td>−3.2</td>
<td></td>
<td>- Caucasian</td>
<td>Het GHR c.876G&gt;T, p.Arg292Ser*7</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>F</td>
<td>−0.6</td>
<td>−1.5</td>
<td>−1.8</td>
<td>−1.4</td>
<td>5</td>
<td>34</td>
<td>19</td>
<td>−2</td>
<td>Skeletal dysplasia</td>
<td>- Caucasian</td>
<td>Het PFGF3 c.1657G&gt;A, p.Val553Met, Hypochondroplasia</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>F</td>
<td>−0.1</td>
<td>−0.2</td>
<td>−2.8</td>
<td>−3.2</td>
<td>2.1</td>
<td>32.3</td>
<td>61</td>
<td>−5.2</td>
<td>Deafness, cardiac malformations, dropping eyelids</td>
<td>- Caucasian / Moroccan</td>
<td>Het PTPN11 c.1472C&gt;T, p.Pro491Leu, Noonan syndrome</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>M</td>
<td>−2</td>
<td>−2</td>
<td>+0.8</td>
<td>−4</td>
<td>2.2</td>
<td>22.4</td>
<td>38.6</td>
<td>−3.7</td>
<td>Hypophosphaemic, relative macrocephaly, triangular face</td>
<td>- Caucasian</td>
<td>Maternal unparental disomy chr7, Silver Russell syndrome</td>
</tr>
</tbody>
</table>


Conclusions

- The clinical description of this well-characterised cohort of patients confirms the heterogeneous spectrum of the disease
- Long-term follow-up is necessary especially for adult height
- Genetic studies (candidate gene-approach or targeted next generation sequencing) can expand the current knowledge and provide more insights in the understanding of SPIGF1D

References
1 Teissier et al, Characterization and prevalence of severe primary IGF1 deficiency in a large cohort of French children with short stature; EJE 2014