Growth disorders in the chromosome 18 syndromes

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Introduction

Short children with poor linear growth and bone maturational delay, in whom serious systemic disease has been excluded, frequently undergo extensive endocrine investigations, particularly focused on growth hormone (GH) and thyroid status. A notable exception is children who have genetic syndromes associated with mental retardation. Historically, the small size and poor growth in these children has been presumed to be multifactorial and related to the 'intrinsic cellular effects of aneusomy' or 'intrauterine growth retardation'. Therefore there are few published studies, other than case reports or small series, on hormonal abnormalities in children with aneusomies associated with mental retardation. In recent years, however, systematic, comprehensive endocrine investigations have begun to be performed on larger cohorts of some of these populations including Turner syndrome [1] and the 18q deletion syndrome [2].

GH deficiency (GHD) in the 18q syndrome

The 18q syndrome, caused by the deletion of a portion of the long arm of chromosome 18 (Fig. 1), was originally described in 1964 [3]. It is characterized by dysmyelination, speech failure, hypotonia, mental retardation and short stature [4]. In a study conducted at the Audie Murphy Veterans Administration Hospital General Clinical Research Center [2, 4–6], the spectrum of growth abnormalities in 50 individuals with a cytogenetically and molecularly confirmed deletion of 18q was assessed by height, growth velocity, insulin-like growth factor (IGF)-I, IGF binding protein-3, bone maturation, and GH response to the GH stimulants, arginine and clonidine.

Some affected children have an unequivocally normal growth axis, as defined by normal height and growth velocity, normal growth factors and normal responses to GH stimulation testing. Others have classical GH deficiency (GHD),

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**Table 1: Summary of growth and growth factors analyses.**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
<th>-1 to -2 SD</th>
<th>&lt;-2 SD*</th>
<th>≈7–10 ng/ml</th>
<th>&lt;7 ng/ml</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTZ</td>
<td>50</td>
<td>-2.2 ± 1.4</td>
<td>-2.4</td>
<td>-5.2–0.8</td>
<td>18</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GVZ</td>
<td>50</td>
<td>-1.0 ± 1.3</td>
<td>-1.2</td>
<td>-3.0–1.7</td>
<td>18</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGFIZ</td>
<td>44</td>
<td>-1.0 ± 1.4</td>
<td>-1.3</td>
<td>-3.4–1.8</td>
<td>27</td>
<td>15</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BP3Z</td>
<td>47</td>
<td>-0.7 ± 0.9</td>
<td>-0.6</td>
<td>-2.7–1.8</td>
<td>26</td>
<td>9</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AMXGH</td>
<td>25</td>
<td>9.0 ± 7.2</td>
<td>5.9</td>
<td>1.2–30.1</td>
<td>16</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMXGH</td>
<td>42</td>
<td>9.5 ± 7.3</td>
<td>8.1</td>
<td>1.1–13.9</td>
<td>36</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HTZ, height z scores (+SD's from mean for age); GVZ, growth velocity z score; IGFIZ, IGF-I z score; BP3Z, IGFBP-3 z score; AMXGH, GH peak in response to arginine stimulation; CMXGH, GH peak in response to clonidine stimulation.

*<-2 SD, more than 2 SD below mean for age.
Fig. 2: Molecular analysis, with PCR-based markers, of DNA from patients with the 18q syndrome who are GHD. Each rectangle represents the estimated size of the chromosome with the deletion. Dark circles represent markers that are present on the deleted chromosome; white circles represent markers that are deleted; dashes represent markers that are uninformative. From this analysis, the breakpoint in individual 1 defines the proximal end of the critical region while the breakpoint in individual 13 defines the distal end.

delineated by height below −2 SD, growth velocity below −1 SD, low growth factor levels, and failure of GH response to two provocative tests. However, most affected children fall somewhere between these two extremes. Table I summarizes the auxological and growth factor evaluations performed on all subjects, showing mean, median and range, and providing the overall distribution of the group.

Children with 18q deletions are short and grow poorly compared with their peers. Of the group, 32 (64%) had heights below −2 SD, and 25 (50%) had growth velocities below −2 SD. Half of the patients had delayed bone age. None of the children had conditions such as cyanotic heart disease or malabsorption that could potentially interfere with normal growth. The children were of appropriate weight for height.

In order to identify the molecular basis of GHD in this population, we performed molecular analysis using polymerase chain reaction and highly polymorphic markers. We have identified a critical region of approximately 2 Mb of the chromosome that is missing from the deleted chromosome in all the subjects with GHD (Fig. 2) [2]. This region is anticipated to contain 5–10 genes and we hypothesize that a single gene, or very closely linked genes, lying within this region is responsible for the neuroendocrine dysfunction. One identified gene within this interval is for the galanin receptor, GALR1 [7, 8]. This gene is of particular interest because galanin is a stimulant of GH, thyroid stimulating hormone and prolactin secretion [9], and GALR1 is found in key hypothalamic and pituitary sites [10].

**GHD in other chromosome 18 syndromes**

There are several reports in the literature of patients with 18p-syndrome (Fig. 1), a deletion of the short arm of chromosome 18, who have GHD [11–15]. We have recently begun to review all of the published cases of 18p-syndrome as the first step in a phenotype/genotype correlation study. To date, 26% of 31 subjects are GHD and have begun GH treatment.

Because individuals with ring 18 have deletions of both the long arm and the short arm (Fig. 1), they are also at risk for being GHD. There are two
reports in the literature of ring 18 individuals with GH deficiency [16, 17].

**Conclusion**

As the understanding of molecular mechanisms increases, it is increasingly evident that growth failure in each aneusomy is unique. Children with chromosome 18 abnormalities have a high frequency of growth failure and GHD and merit a careful, thoughtful evaluation of their growth. The beneficial effect of GH treatment for those children with chromosome 18 abnormalities and GHD is currently an area of active investigation. Preliminary results appear highly positive [18].

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**References**

5. Ghidoni PD, Hale DE, Cody JD et al. Growth hormone defi-