The exon3-deleted GH Receptor Gene polymorphism (d3-GHR) is associated with glucose metabolism and spontaneous growth but not fat mass in prepubertal short SGA children (NESGAS)

Mathilde Gersel Wegmann[1,2], Ajay Thankamony[3], Edna Roche[4], Hilary Hoey[4], Jeremy Kirk[5], Guftar Shaikh[6], Sten-A. Ivarsson[7], Olle Söder[8], David B. Dunger[2] Anders Juul[1,2], Rikke Beck Jensen[1,2]

1) Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Denmark, 2) International Research and Research Training Center in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC), Rigshospitalet, University of Copenhagen, Denmark, 3) Department of Pediatrics, University of Cambridge, United Kingdom, 4) Department of Pediatrics, The National Children's Hospital, Trinity College Dublin, The University of Dublin, Ireland, 5) Department of Endocrinology, Birmingham Children's Hospital, Birmingham, United Kingdom, 6) Department of Endocrinology, Royal Hospital for Sick Children, Glasgow, United Kingdom, 7) Department of Clinical Sciences, Endocrine and Diabetes Unit, University of Lund, Malmø, Sweden, 8) Pediatric Endocrinology Unit, Department of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden.

Background

The exon-3 deleted polymorphism in the growth hormone (GH) receptor gene (d3-GHR) has been linked to an increased intra-cellular signaling after GH stimulation in comparison to the full-length GHR (fl/fl-GHR). Previous studies found associations between d3-GHR and growth and responsiveness to GH therapy. The GH/IGF-I axis plays an important role in glucose homeostasis and body composition.

Hypothesis & Aim

We hypothesise that the d3-GHR polymorphism has an impact on response to GH treatment. The aim of the study was to determine the effect of the polymorphism on growth, fat mass and glucose metabolism during the first year of high-dose GH therapy in short, prepubertal children born small for gestational age (SGA).

Methods

The North European Small for Gestational Age Study (NESGAS) is a multicentre study of GH therapy (n=96, 57 males) in prepubertal short SGA children who received high-dose GH therapy (67 µg/kg/day) during the first year of therapy. Insulin sensitivity (IS) was determined using HOMA and insulin secretion from a short IVGTT and their product provided disposition index (DI). Fat mass was determined by dual x-ray absorptiometry (DXA). The d3-GHR locus was determined by simple multiplex PCR on isolated DNA.

Results

Children carrying the d3-allele were grouped together (d3-GHR) and compared to children with the fl-allele homodimer (fl/fl-GHR). At baseline the d3-GHR group had significantly greater levels of glucose (4.5 ± 0.6 vs 4.2 ±0.7 mmol/L, p=0.03) and C-peptide (224.7 ± 1.7 vs. 175.4 ± 1.6 pmol/L, p=0.03) and lower insulin sensitivity (211.3 ± 1.8 vs. 277.3 ±1.7 %, p=0.02) (figure 1). There were no differences in DI or insulin secretion at baseline. Measurements of glucose metabolism did not differ between the different genotypes following one year of GH therapy. Total fat (%) and distribution of fat mass (android and gynoid fat, %) at baseline and after one year of therapy were similar in the d3-GHR and fl/fl-GHR groups.
Spontaneous increase in height from birth to baseline was significantly higher in the d3-GHR group (0.5± 1.3 vs. -0.5 ± 2.0 SDS, p= 0.02). However, following one year of high dose GH therapy there was no significant differences in height between the GHR genotypes (figure 2).

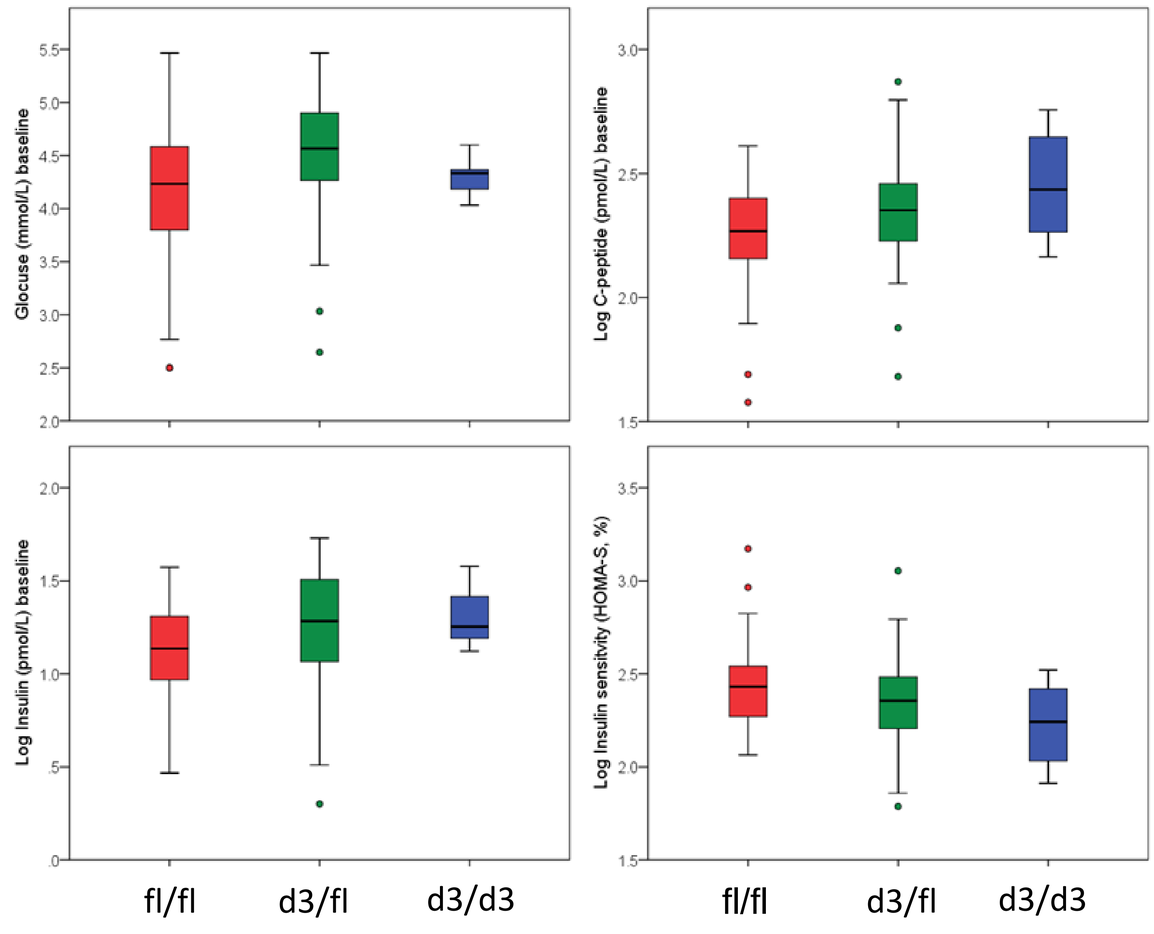

Figure 1
Boxplots of baseline glucose, C-peptide, insulin and IS according to the three genotypes: fl/fl (red), d3/fl (green) and d3/d3 (blue)

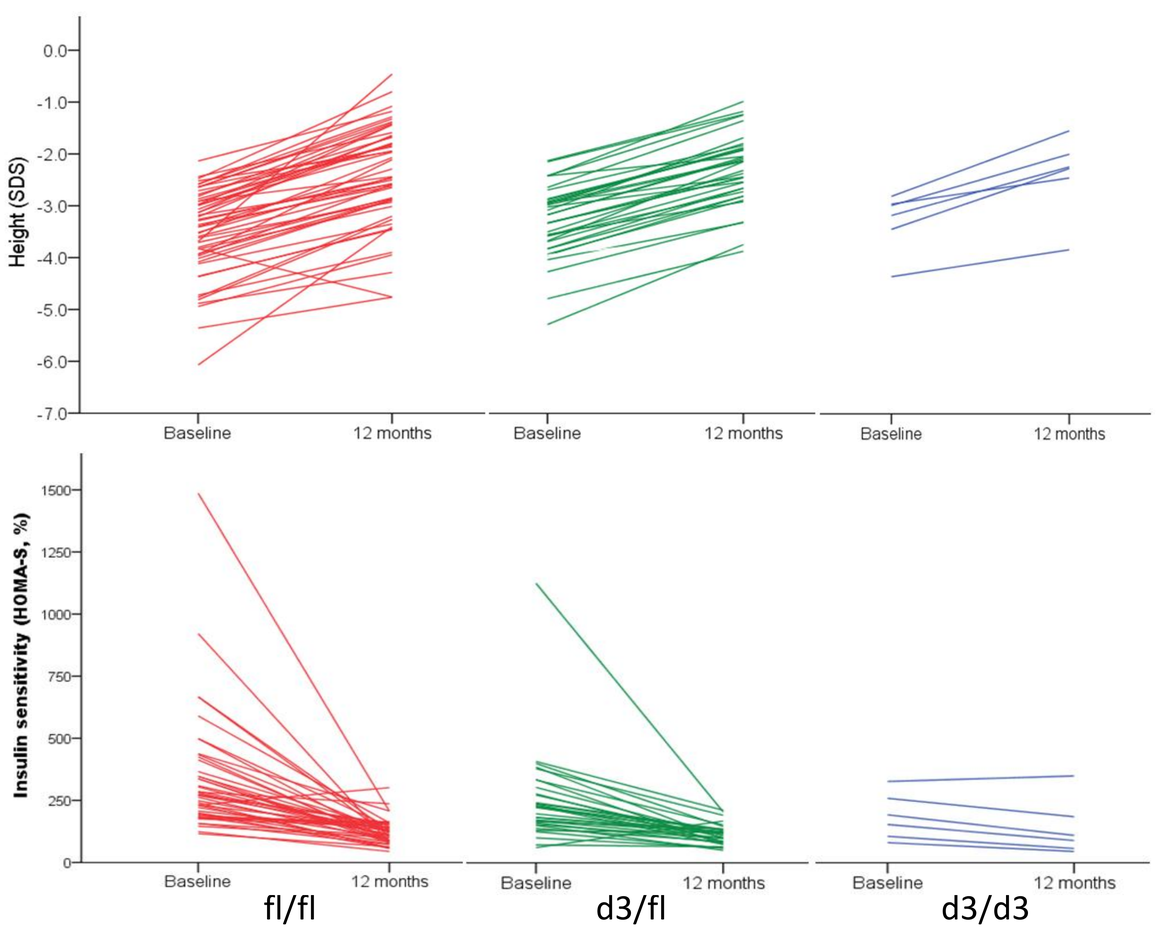

Figure 2
Individual measurements of height (SDS) (top row) and IS (HOMAS-S, %) (bottom row) at baseline and after one year of GH therapy in short SGA children according to the three genotypes: fl/fl (red), d3/fl (green) and d3/d3 (blue)

Conclusion

In this cohort of short, prepubertal children born SGA, we found that the d3-GHR polymorphism was associated with an increased spontaneous growth and lower insulin sensitivity at baseline compared to the fl/fl-GHR group. These associations may reflect a greater response to endogenous GH in the groups with at least one d3-allele leading to effects on both growth and metabolism. However, these differences were not evident following one year of high-dose GH therapy.

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Mathilde Wegmann
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