Genetic markers of insulin sensitivity and insulin secretion are associated with spontaneous postnatal growth and response to growth hormone treatment in short SGA children: the North European SGA Study (NESGAS)

Rikke Beck Jensen[1,2], Ajay Thankamony[2], Felix Day[3], Robert A Scott[3], Claudia Langenberg[3], Jeremy Kirk[4], Malcolm Donaldson[5], Sten-A. Ivarsson[6], Olle Söder[7], Edna Roche[8], Hilary Hoey[8], Anders Juul[1], Ken K. Ong[3], David B. Dunger[2]

1. Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Denmark
2. Department of Pediatrics, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom
3. MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom
4. Department of Endocrinology, Birmingham Children's Hospital, Birmingham, United Kingdom
5. Department of Endocrinology, Royal Hospital for Sick Children, Glasgow, United Kingdom
6. Department of Clinical Sciences, Endocrine and Diabetes Unit, University of Lund, Malmø, Sweden
7. Pediatric Endocrinology Unit, Department of Women's and Children's Health, Karolinska Institutet & University Hospital, Stockholm, Sweden
8. Department of Pediatrics, The National Children's Hospital, University of Dublin, Trinity College, Dublin, Ireland

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Correspondence to:
Rikke Beck Jensen, MD Ph.D
Department of Growth and Reproduction
Copenhagen University
Rigshospitalet
Blegdamsvej 9
DK-2100 Copenhagen
Denmark
Email: rikke.beck@dadlnet.dk

Abbreviations:

SGA: Small for Gestational Age
GH: Growth Hormone
GS-InSec: Gene Score Insulin Secretion
GS-InSens: Gene Score Insulin Sensitivity

Abstract

Purpose: The wide heterogeneity in the early growth and metabolism of children born small for gestational age (SGA), both before and during growth hormone (GH) therapy, may reflect common genetic variations related to insulin secretion or sensitivity.

Method: Combined multi-allele single nucleotide polymorphism (SNP) scores with known associations with insulin sensitivity or insulin secretion were analysed for their relationships with spontaneous postnatal growth and 1st year responses to GH therapy in 96 short SGA children.

Results: The insulin sensitivity allele score (GS-InSens) was positively associated with spontaneous postnatal weight gain (B:0.12 SD scores per allele, 95% CI:0.01-0.23, p=0.03) and also in response to GH therapy with 1st year height velocity (0.18 cm/year per allele, 0.02-0.35, p=0.03) and change in IGF-I (0.17 SD scores per allele, 0.00-0.32, p=0.03). The association with 1st year height velocity was independent of reported predictors of response to GH therapy (adjusted p=0.04). The insulin secretion allele score (GS-InSec) was positively associated with spontaneous postnatal height gain (0.15, 95% CI:0.01-0.30, p=0.03) and disposition index both before (0.02, 0.00-0.04, p=0.04) and after 1-year of GH therapy (0.03, 0.01-0.05, p=0.002), but not with growth and IGF-I responses to GH therapy. Neither allele scores were associated with size at birth.

Conclusion: Genetic allele scores indicative of insulin sensitivity and insulin secretion were associated with spontaneous postnatal growth and responses to GH therapy. Further pharmacogenetic studies may support the rationale for adjuvant therapies by informing the mechanisms of treatment response.

INTRODUCTION

Small for gestational age (SGA) at birth indicates impaired fetal growth due to a heterogeneous range of intra-uterine conditions or in some infants by innate genetic defects. Around 10% of SGA children do not show spontaneous catch-up growth during the early postnatal years and they are also short as adults if not treated with growth hormone (GH). Most short SGA children have sufficient GH secretion and show generally good responses to GH treatment, although there is considerable variation between patients.

Prediction models of the response to GH therapy in short SGA children have been generated in order to individually tailor treatment, to improve efficacy and safety, and to improve the cost-benefit ratio(1). The prediction model described by Ranke et al.(1) explained 52% of the variance in the first year growth response, with GH dose alone accounting for 35% of the variance.

We and others reported that the growth response to GH therapy in short SGA children is associated with baseline insulin sensitivity and IGF-I levels(2, 3). Children with the highest baseline IGF-I levels had lower insulin sensitivity, lower height velocity and IGF-I responses after 1-year after GH therapy(3). Insulin secretion is diminished in SGA children and this has been proposed as a possible factor in the failure to catch-up in some infants(4). Furthermore, growth and IGF-I responses to first year GH treatment were related to insulin secretion in the NESGAS study(3). We hypothesised that genetic variation in insulin sensitivity or insulin secretion would be associated with inter-individual variation in responses to GH in short SGA children.

PATIENTS AND METHODS

Study Population

NESGAS is a multicentre, randomised, parallel group trial (EudraCT 2005-001507-19) of GH treatment in short SGA-born pre-pubertal children, which has been described in detail(3). Data included in the current analyses are related to the first year of high dose GH treatment (67µg/kg/day) in 96 NESGAS participants.

The study was performed according to the Helsinki II declaration and approved by the ethics committees. Written informed consent was obtained from parents.

Study assessments:

Standing height was measured on a wall-mounted stadiometer and weight by electronic scales by staff. All children underwent a fasting blood sample and a short intravenous glucose tolerance test (IVGTT) at baseline and at year 1(3).

Plasma insulin and C-peptide concentrations were measured centrally by a DELFIA-assay (Perkin Elmer Life Sciences, Turku, Finland). Interassay coefficients of variation (CV) were below 4% for both insulin and C-peptide. Serum IGF-I and IGFBP-3 concentrations were determined centrally using an Immulite 2000-assay (Diagnostic Products Corporation, LA, USA) with standards calibrated towards the WHO NIBSC IRR 87/518. Limit of detection (LOD) and CV was 20ng/ml and 5.93% respectively for IGF-I and 500ng/ml and 5.23 % respectively for IGFBP-3. IGF-I and IGFBP-3 SDS were calculated from our reference data (5, 6). Plasma glucose and HbA1c were measured locally.

Genotyping information

The cohort was genotyped using the Metabochip, a custom Illumina iSelect genotyping array that assays nearly 200,000 single nucleotide polymorphisms (SNPs) chosen based on GWAS meta-analyses (7).

In each individual, combined multi-allele scores were generated comprising SNPs for insulin sensitivity (GS-InSens) or insulin secretion (GS-InSec), as recently described(8). The GS-InSens was calculated as a count of the insulin sensitivity-increasing alleles at 10 variants (Supplementary Table 2a). The GS-InSec was calculated as a count of the insulin secretion-increasing alleles at 18 of the 23 variants described by Scott et al. (for the remaining 5 variants, there were no suitable proxies genotyped) (Supplementary Table 2b). Both combined multi-allele scores were recently validated in large population-based studies (8).

Calculations:

Anthropometric measurements are presented as standard deviation scores (SDS) using normal reference materials (9-11). Insulin sensitivity was estimated from the homeostatic model (HOMA) (http://www.dtu.ox.ac.uk/homacalculator/index.php). Acute insulin response (AIR) was calculated as the

IVGTT area under the curve of the insulin response. Disposition index (DI) was calculated as the product of insulin sensitivity and AIR.

Statistics:

Outcome variables were natural-log transformed and standardised. Associations between genetic risk scores and these outcomes were assessed by fitting linear regression models adjusted for age and sex and either BMI or mid-parental height. Statistical analyses were performed using the statistical package IBM SPSS statistics (version 21; SPSS Inc., Chicago, IL).

The genetic allele scores were also added to a reported model for 1st year predicted height velocity (PHV) responses to GH therapy in short SGA children(1), which includes the variables: age (years) and weight SDS at start of treatment, GH dose, and mid-parental height SDS.

RESULTS

Associations with spontaneous growth

Clinical characteristics are presented in supplementary Table 1. Birth weight (mean -3.22 SDS), birth length (mean -3.15 SDS) and gestational age (mean 35.6 weeks) were all unrelated to GS-InSens and GS-InSec (all P>0.24, data not shown).

GS-InSens was unrelated to spontaneous growth (change in height (SDS) from birth to study baseline, p=0.24), but positively associated with spontaneous weight gain (B:0.12 SDS per allele, 95% CI:0.01-0.23, p=0.03). GS-InSec was positively associated with spontaneous growth (B: 0.15, 95% CI 0.01-0.30, p=0.03) and showed a similar trend with spontaneous weight gain (p=0.06) (Table 1).

Height velocity and IGF-I responses to GH therapy

GS-InSens was positively associated with height velocity (B:0.18 cm/year per allele, 0.02-0.35, p=0.03), weight (SDS) (B:-0.10 SDS per allele, -0.20 to -0.003, p=0.04) and change in IGF-I levels (0.17 SDS/year per allele, 0.00-0.32, p=0.03) in response to GH therapy.

The variance in 1st year height velocity in response to GH therapy predicted by the Ranke model (R^2 0.17) was lower than that in the original report, but the SE (1.72 cm) was similar, likely reflecting the uniform GH dose used in our study. Addition of GS-InSens to this prediction model explained an additional 5% of the variance in the 1st year height velocity response (R^2 0.22, SE 1.71 cm; p-value for R^2 change =0.04). Alternatively, addition of baseline IGF-I SDS to the model also increased the explained variance in the 1st year height velocity response (R^2 0.26; SE 1.65 cm, p-value for R^2 change=0.009) and addition of both baseline IGF-I and GS-Insens increased the explained variance, but this change in R^2 was not significant (R^2 0.29; SE 1.63 cm, p-value for R^2 change=0.09).

Associations with insulin traits

Consistent with its expected functional role, GS-InSec was positively associated with disposition index, both before (B:0.02 per allele, 95% CI:0.00-0.04, p=0.04) and 1-year after GH therapy (0.03, 0.01-0.05, p=0.002). However, the GS-InSens was unrelated to HOMA-S or the disposition index at baseline and after 1 year of therapy (Table 2).

DISCUSSION

In this study of short SGA-born children, validated genetic determinants of insulin sensitivity were associated with both height velocity and circulating IGF-I level responses to GH therapy. The findings provide insights into the mechanisms that contribute to GH responses and also insights into the pathophysiology of poor spontaneous postnatal growth in SGA infants.

Pharmacogenetics considers the possible contribution of genetic factors to the prediction of individual treatment efficacy and/or risks of treatment-related adverse events and forms the basis for many putative strategies for stratified medicine(12). Prediction of individual growth responses to GH therapy has been suggested to optimise treatment in a range of childhood disorders. However, the reported prediction model for short SGA children was largely reliant on historical heterogeneity in the GH dose(1) , which in current clinical practice is standardised. In our fixed GH dose study, inclusion of the insulin sensitivity allele score

186 improved the explained variance by only 5%, from 17 to 22%, which is insufficient for such scores to have
187 clinical utility in individual treatment prediction.
188
189 An alternative application of pharmacogenetics is to inform the mechanisms of treatment response, by
190 considering informative genotypes or allele scores as indicators of the likely causal effects of their target
191 traits. Such inference forms the basis of the so-called 'Mendelian randomisation' approach(13). The
192 independent association between the insulin sensitivity allele score and 1st year height velocity responses
193 supports observations in non-genetic studies of SGA infants, where insulin resistance has been associated
194 with poor response to GH therapy. IGF-I resistance has also been implicated because of the close functional
195 relationship between the insulin receptor and the type 1 IGF-I receptor (IGF-IR). We previously reported
196 that children with relatively high baseline IGF-I levels had lower insulin sensitivity and impaired IGF-I
197 generation in response to GH therapy(3). Our genetic associations support the possible causality of such
198 associations and may allow a quantitative estimation of the relationship between insulin sensitivity and
199 growth response. Such causal inference relies on various assumptions and therefore requires experimental
200 validation, but it would support the rationale for the clinical testing of adjuvant insulin sensitisation in
201 combination with GH therapy(14).
202
203 The insulin secretion allele scores were associated with spontaneous postnatal growth in height and weight,
204 whereas the insulin sensitivity allele scores were associated with weight gain. In the population-based
205 ALSPAC cohort, insulin secretion was positively related to size at birth, and to childhood height and IGF-I
206 levels(4). Similarly, in an earlier study of short SGA children, insulin secretion was positively related to
207 height velocity(15). Thus, beta-cell function appears to have a key role in spontaneous height growth, and
208 this mechanism may underlie observed associations between shorter adult stature or lower IGF-I levels and
209 higher risk for type 2 diabetes (T2D)(16, 17). Common genetic mechanisms between early growth patterns
210 and later risk of metabolic disease have been proposed, however, there is inconsistent evidence linking SNPs
211 related to T2D or obesity to risk of SGA at birth(18-20). Our findings support common genetic mechanisms
212 linking spontaneous postnatal height growth to disposition index, a marker of insulin secretory capacity,

before and during GH treatment. The positive association between insulin sensitivity alleles and spontaneous postnatal weight gain is discordant with observed associations between rapid postnatal weight gain and insulin resistance(4), but is consistent with recent findings in adults(8) and likely indicates the positive anabolic effects of insulin signalling. Future studies should test the combination of the insulin sensitivity and insulin secretion allele scores for prediction of T2D in SGA-born or other high-risk groups.

A limitation of this study is the relatively small population, even though the cohort is well-characterised phenotypically. To increase statistical power, we examined combined allele scores rather than individual SNP genotypes. We are therefore unable to pinpoint individual variants or genes that regulate response to GH therapy, however, this approach allows broader support for a causal role of insulin sensitivity in general.

In conclusion, these novel data indicate causal influences of insulin secretion and insulin sensitivity on spontaneous postnatal height growth and growth responses to GH therapy, respectively in short SGA-born children. The findings also support the relationship between insulin resistance and putative IGF-I resistance, which may impair responses to GH therapy and potentially increase the risk of T2D. It will be interesting to examine whether similar mechanisms contribute to growth responses in patients with other conditions that warrant GH therapy, such as GH deficiency.

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Table 1

Clinical characteristics in 96 children (60 boys) at baseline and after 1 year of GH treatment

	Baseline	**After 1 yr of treatment**
Age (year)	6.25 (1.67)	7.31 (1.64)
Height (cm)	102.21 (9.38)	113.09 (8.96)
Height (SDS)	-3.41 (0.77)	-2.35 (0.84)
Weight (cm)	15.55 (5.00)	18.95 (4.25)
Weight (SDS)	-3.13 (1.05)	-2.13 (1.04)
BMI (SDS)	-1.21 (1.33)	-1.01 (1.27)
IGF-I (SDS)	-1.14 (1.20)	2.73 (1.50)
Glucose Metabolism		
Glucose (nmol/l)	4.36 (0.68)	4.74 (0.54)
Insulin (pmol/l)	15.63 (7.99-30.20)	39.8 (23.82-66.53)
C-peptide (pmol/l)	194.98 (110.15-334.97)	416.87 (249.46-696.63)
HOMA %	239.88 (134.90-424.62)	109.64 (74.47-169.04)
Acute Insulin Response (10^2*pmol*min)	13.49 (7.76-23.44)	23.98 (13.18-43.65)
Disposition Index (10^4*pmol*min)	32.21 (18.11-57.28)	26.92 (15.14-47.86)

Data are presented as means (SD) or back transformed geometric means (1SD ranges)

Table 2

Associations to measures of growth and metabolism for Insulin secretion multi-allele score (GS-InSec)

Measure of growth and metabolism	Effect size per allele (B)	95%CI	P value
Insulin Secretion multi-allele score (GS-InSec)			
Height (SDS) baseline**	0.02	-0.04-0.08	0.49
Height (SDS) 1yr**	0.03	-0.04-0.09	0.41
Δ Height (SDS) (baseline to 1yr)**	0.004	-0.03-0.04	0.80
Δ Height (cm) (baseline to 1yr)**	-0.008	-0.14-0.13	0.91
Weight (SDS) baseline**	0.06	-0.02-0.14	0.17
Weight (SDS) 1 yr**	0.04	-0.04-0.13	0.30
Δ Weight (SDS) (baseline to 1yr)**	-0.02	-0.05-0.02	0.30
Δ Weight (kg) (baseline to 1yr)**	-0.17	-0.49-0.15	0.30
IGF-I (SDS) baseline**	-0.03	-0.13-0.07	0.54
IGF-I (SDS) 1 yr**	0.005	-0.11-0.12	0.94
Δ IGF-I (SDS) (baseline to 1yr)**	0.04	-0.09-0.15	0.57
AUC insulin baseline*	0.02	-0.003-0.04	0.09
AUC insulin 1yr*	0.03	0.005-0.05	**0.02**
Δ AUC insulin (baseline to 1yr)*	62.36	-51.3-176.0	0.28
HOMA-S baseline*	0.01	-0.01-0.03	0.33
HOMA-S 1 yr*	0.006	-0.01-0.02	0.47
Δ HOMA-S (baseline to 1yr)*	-9.19	-27.9 to 8.9	0.32
Disposition index baseline*	0.02	0.001-0.04	**0.04**
Disposition index 1 yr*	0.03	0.01-0.05	**0.002**
Δ Disposition index (baseline to 1yr)*	2141.9	-20976-25260	0.85
Δ Height from birth to baseline**	0.15	0.01-0.30	**0.03**
Δ Weight from birth to baseline**	0.09	-0.003-0.17	0.06

*corrected for age, sex and BMI, **corrected for age, sex and mid-parental height

Table 3

Associations to measures of growth and metabolism for Insulin Sensitivity multi-allele score (GS-InSens)

Measure of growth and metabolism	Effect size per allele (B)	95%CI	P value
Insulin Sensitivity multi-allele score (GS-InSens)			
Height (SDS) baseline**	-0.05	-0.13-0.02	0.17
Height (SDS) 1yr**	-0.08	-0.15 to -0.001	**0.048**
Δ Height (SDS) (baseline to 1yr)**	-0.02	-0.06-0.02	0.24
Δ Height (cm) (baseline to 1yr)**	-0.18	-0.35 to -0.02	**0.03**
Weight (SDS) baseline**	-0.10	-0.20 to -0.005	**0.04**
Weight (SDS) 1 yr**	-0.10	-0.20 to -0.003	**0.04**
ΔWeight (SDS) (baseline to 1 yr)**	-0.01	-0.05-0.03	0.63
Δ Weight (kg) (baseline to 1yr)**	-0.16	-0.56 to 0.23	0.41
IGF-I (SDS) baseline**	0.04	-0.080-0.170	0.47
IGF-I (SDS) 1 yr**	-0.15	-0.30 to -0.002	**0.047**
Δ IGF-I (SDS) (baseline to 1yr)**	-0.17	-0.32 to -0.002	**0.03**
AUC insulin baseline*	-0.006	-0.03 to 0.02	0.63
AUC insulin 1yr*	-0.01	-0.04 to 0.01	0.47
Δ AUC insulin (baseline to 1yr)**	-60.2	-208 to 88	0.42
HOMA-S baseline*	-0.007	-0.03 to 0.02	0.59
HOMA-S 1 yr*	-0.004	-0.02 to 0.01	0.64
Δ HOMA-S (baseline to 1yr)*	2.16	-20.1 to 24.4	0.85
Disposition index baseline*	-0.01	-0.04 to 0.01	0.30
Disposition index 1 yr*	-0.01	-0.04 to 0.01	0.27
Δ Disposition index (baseline to 1yr)*	-4858	-34565 to 24939	0.75
Δ Height from birth to baseline**	-0.003	-0.19-0.18	0.95
Δ Weight from birth to baseline**	-0.12	-0.23 to -0.01	**0.03**

*corrected for age, sex and BMI, **corrected for age, sex and mid-parental height

The regression coefficient (B) are the inverse of the Insulin resistance score (IR score) described by Scott et al. An increase in multi-allele score reflects a decrease in insulin sensitivity.

Table 4a Regression equation variables for predicting the first-year growth response (cm/yr) to GH therapy in the NESGAS cohort

	Parameter estimate (B)	95% CI	P value
Intercept (constant)	13.9		
Age at start (yr)	-0.37	-0.59 to -0.15	0.001
Weight (SDS) at start	0.17	-0.27-0.45	0.35
GH dose (µg/kg/day)	4.23	-101.7-96.8	0.93
MPH (SDS)	0.46	0.05-0.75	0.01
R^2	0.17		
Error SD (cm)	1.72		

Table 4b Regression equation variables for predicting the first-year growth response (cm/yr) to GH therapy in the NESGAS cohort including GS-InSens

	Parameter estimate (B)	95% CI	P value
Intercept (constant)	16.1		
Age at start (yr)	-0.37	-0.59 to -0.15	0.001
Weight (SDS) at start	0.09	-0.27-0.45	0.61
GH dose (µg/kg/day)	2.44	-101.7-96.8	0.96
MPH (SDS)	0.40	0.05-0.75	0.03
GS-IR	-0.17	-0.34 to -0.01	0.04
R^2	0.22*		
Error SD (cm)	1.71		

*The change in R^2 between the two models was significant ($p<0.05$)