

Systematic Reviews and Meta- and Pooled Analyses

Growth Hormone Receptor Polymorphism and Growth Hormone Therapy Response in Children: A Bayesian Meta-Analysis

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Initially submitted February 9, 2011; accepted for publication October 12, 2011.

Recombinant human growth hormone (rhGH) therapy is used in the long-term treatment of children with growth disorders, but there is considerable treatment response variability. The exon 3-deleted growth hormone receptor polymorphism ($GHR_{\Delta 3}$) may account for some of this variability. The authors performed a systematic review (to April 2011), including investigator-only data, to quantify the effects of the $GHR_{\Delta 3}$ and $GHR_{\Delta 3-\Delta 3}$ genotypes on rhGH therapy response and used a recently established Bayesian inheritance model-free approach to meta-analyze the data. The primary outcome was the 1-year change-in-height standard-deviation score for the 2 genotypes. Eighteen data sets from 12 studies (1,527 children) were included. After several prior assumptions were tested, the most appropriate inheritance model was codominant (posterior probability = 0.93). Compared with noncarriers, carriers had median differences in 1-year change-in-height standard-deviation score of 0.09 (95% credible interval (CrI): 0.01, 0.17) for $GHR_{\Delta 3}$ and of 0.14 (95% CrI: 0.02, 0.26) for $GHR_{\Delta 3-\Delta 3}$. However, the between-study standard deviation of 0.18 (95% CrI: 0.10, 0.33) was considerable. The authors tested by meta-regression for potential modifiers and found no substantial influence. They conclude that 1) the $GHR_{\Delta 3}$ polymorphism inheritance is codominant, contrasting with previous reports; 2) $GHR_{\Delta 3}$ genotypes account for modest increases in rhGH effects in children; and 3) considerable unexplained variability in responsiveness remains.

Bayesian meta-analysis; genetic model; growth hormone; growth hormone receptor polymorphism

Abbreviations: CrI, credible interval; GHD, growth hormone deficiency; GHR, growth hormone receptor; Δ Ht, change in height; rhGH, recombinant human growth hormone.

Recombinant human growth hormone (rhGH) is used to treat children for a range of growth disturbances, including growth hormone deficiency (GHD), and for being small for gestational age, having idiopathic short stature, and having short stature associated with Turner syndrome (1). With these indications, it is estimated that 400,000 children in the United States qualify for growth hormone therapy (2). rhGH therapy is expensive, with typical costs being \$20,000 per year for a 30-kg child (2) and, as therapy is continued until final adult height, treatment often lasts 5 or more years. However, rhGH use is characterized by considerable variability in growth response (3), and health economic modeling shows that this variability has the greatest

impact on the cost-effectiveness of rhGH therapy (4). Several factors may explain the treatment response variation, including age at start of treatment; cause of short stature; GHD severity and duration; and the dose, frequency, and duration of rhGH therapy (3). More recently, interest has focused on the potential influence of genetic variation within the growth hormone receptor (GHR) as a potential contributor (5).

Growth hormone signals through the homodimeric GHR complex with subsequent insulin-like growth factor I gene (*IGF-I*) transcription (6), necessary for childhood growth. The GHR consists of 3 regions, all encoded by a gene on chromosome 5 (7). The extracellular region is coded by

exons 3–7; the presence of exon 3 (haplotype: *fl/fl*) results in the full-length receptor (GHR_{fl-fl} or wild type), whereas its absence (GHR_{fl-d3} and GHR_{d3-d3}) results in a shorter form (22 amino acid sequence deletion) (7, 8). The absence of exon 3 produces changes in receptor stability, transport, and processing (9).

In 2004, Dos Santos et al. (10) simultaneously demonstrated in vitro that fibroblasts transfected with the GHR_{d3} allele have a higher level of GHR signaling on exposure to exogenous rhGH, and in humans, that first year growth response to rhGH was significantly increased in children with small for gestational age and idiopathic short stature carrying 1 or 2 copies of the GHR_{d3} allele compared with homozygous for the full-length allele (GHR_{fl-fl}). A number of genotype studies followed across a range of short stature diagnoses, but many had small sample sizes, and conclusions were inconsistent. In 2009, Wassenaar et al. (11) performed a meta-analysis based on 15 studies and concluded that the GHR_{d3} genotype is associated with an increased growth velocity (approximately 0.5 cm in the first year of treatment) and that this effect is more pronounced at lower doses of rhGH and higher age.

However, the methodological approach used by Wassenaar et al. (11) was to dichotomize the 3 allelic categories into a dominant inheritance pattern, namely, GHR_{d3} carriers (GHR_{fl-d3} and GHR_{d3-d3}) versus noncarriers (GHR_{fl-fl}) with subsequent estimation of the treatment effect by summation of weighted mean differences (i.e., a pair-wise approach). This modeling is likely to be too simplistic, forcing the assumption that the underlying inheritance is dominant. As an alternative for meta-analyses of genetic associations, inheritance model-free approaches have been suggested and implemented in several frameworks, such as the multivariate method described by Bagos (12), the Mendelian randomization approach (13), and a Bayesian framework incorporating assumptions from the Hardy-Weinberg equilibrium (14). The aims of the present study were 1) to establish the most appropriate genetic model describing the relation between the GHR_{d3} polymorphism and rhGH growth response and 2) to quantify the treatment effect of this polymorphism on rhGH therapy. To these ends, we elected to use the Bayesian framework, as it allowed us to incorporate the uncertainties of the genetic model parameter; the treatment effect; and as a special-purpose algorithm had already been implemented (15), studies that reported results for merged genotypes.

MATERIALS AND METHODS

Search strategy and selection criteria

We performed a systematic search using MEDLINE and EMBASE (from 2004 to April 2011) supplemented by “hand searching” conference proceedings from the American Endocrine Society and European Society for Paediatric Endocrinology (from 2004 to 2010), with no language restrictions, for human studies reporting genotyping of the GHR_{d3} polymorphism and growth-related outcomes to rhGH treatment. We used terms related to growth hormone receptor (“growth hormone receptor,” “growth hormone receptor polymorphism,” “exon 3 deleted,” “d3 GHR,” and “growth hormone receptor exon 3”) and combined these searches with treatment-specific terms (“growth hormone therapy,” “growth hormone dose,”

“growth hormone responsiveness,” and “final height”). Reference lists from reviews (8, 11, 16–18) were scrutinized for additional pertinent studies.

We included studies meeting all 3 of the following criteria: 1) children (at least 50% of cohort aged less than 16 years) treated with rhGH for at least 1 year for the treatment of short stature from any cause; 2) reported mean change in height (ΔHt) and its standard deviation score (or data to calculate same) in the first year for the genotypes GHR_{fl-fl} , GHR_{fl-d3} , and/or GHR_{d3-d3} (the latter 2 either separately or combined); and 3) the number of cases per genotype category. We restricted the analysis to the primary outcome of ΔHt standard deviation score as 1) we judged this to be clinically most relevant and 2) other outcome measures, such as growth velocity, were reported in nonstandardized manners among studies. If a study was reported more than once, we chose the most informative publication relevant to the inclusion criteria. Eligibility was assessed independently by 3 investigators (A. G. R., M. S., and P. E. C.) and concordance was 100%.

Data extraction

Data were extracted by 2 investigators (M. S., L. P.) and cross-checked independently by 2 others (A. G. R., P. E. C.), including information on study design and growth disorder; baseline patient characteristics (e.g., means for age, height, weight, mean parental height standard deviation score); mean rhGH dose (normalized to $\mu g/kg/day$); and mean ΔHt standard deviation score and its standard deviation per genotype at the end of the first year. Genotype groups were either GHR_{fl-fl} , GHR_{fl-d3} , and GHR_{d3-d3} or GHR_{fl-fl} and GHR_{d3} (i.e., GHR_{fl-d3} and GHR_{d3-d3} merged). Where findings were discussed in a report but without adequate data to calculate the mean ΔHt standard deviation score and its standard deviation, the lead authors of these studies were contacted, and all responded with investigator-only data. For each study, we recalculated the Hardy-Weinberg equilibrium using the “genhwi” command for biallelic loci in Stata, version 11.1, statistical software (StataCorp LP, College Station, Texas) (19).

Inheritance model-free approach

We extended an inheritance model-free approach initially suggested by Minelli et al. (14) for genetic case association studies and subsequently adapted by Salanti and Higgins (15) for data reported as continuous outcomes in genetic studies. Consider a biallelic locus, with A being the “wild type” allele and a the allele associated with altered function, in this example, hypothesized increased growth response to rhGH. We considered a parameter, η_{ji} , the underlying function for each genotype j in study i , and used θ_{1i} and θ_{2i} to denote the effect sizes comparing the genotype Aa with AA (the reference group) and comparing aa with AA , respectively, such that $\theta_{1i} = \eta_{2i} - \eta_{1i}$ and $\theta_{2i} = \eta_{3i} - \eta_{1i}$. The underlying genetic model refers to the relation between the two θ s; in the general case, $\theta_{1i} = \lambda_i \times \theta_{2i}$, with $\lambda = 1$ for a dominant model, $\lambda = 0.5$ for an additive or codominant model, and $\lambda = 0$ for a recessive model.

In the absence of a strong rationale that the genetic model varies across studies, a fixed-effects summary estimate of λ was obtained as the main model. To test whether the model of

inheritance might vary across studies, a hierarchical random-effects model for λ was also fitted in sensitivity analyses. The meta-analysis model was fitted within a Bayesian framework to take advantage of its ability to incorporate uncertainty in all model parameters, including the between-study standard deviation, τ , and the genetic model parameter, λ . Ultimately, the model estimates the probability that each model is the true one (20).

Under a prospective likelihood approach, we modeled the outcome conditional on the genotype for each observation. For studies with data from merged or collapsed genotypes, we exploited assumptions of the Hardy-Weinberg equilibrium, using prior information about genotype prevalence (15) (Web Appendix, which is posted on the *Journal's* Web site (<http://www.aje.oxfordjournals.org/>)).

Prior to fitting the Bayesian genetic model, we examined whether the observed treatment effects across studies were broadly similar. We derived observed study-specific estimates of θ_1 and θ_2 using study-level means and standard deviations for AA, Aa, and aa. From these, we obtained study-specific estimates of λ (i.e., θ_1/θ_2) and bootstrapped 95% confidence intervals assuming normal distributions (13). We then plotted the variation in the observed λ across individual studies, as per Minelli et al. (13), and took study-specific λ estimates outside the range from -3 to 3 as indicative of studies unsuitable to fit into the Bayesian model.

Statistical analysis

We fitted the inheritance-free model in WinBUGS software (21), using 20,000 Markov chain Monte Carlo cycles after 20,000 burn-in iterations (Web Appendix). The primary outcome measures were the differences between the GHR_{fl-d3} and GHR_{d3-d3} genotypes and noncarriers expressed, respectively, as median values of θ_1 and θ_2 , with 95% credible intervals, where study-specific θ_{1i} and θ_{2i} follow normal distributions. Each model was checked for convergence; each parameter was assessed for autocorrelation.

We used minimally informative normal priors centered at zero for genotype-specific mean parameters. For the between-study standard deviation, τ , we placed a half-normal prior derived from a normal distribution with a mean of 0 and a standard deviation of 1.

For the genetic model parameter, λ , we used the beta distribution (i.e., 0.7, 0.7) in the main model (14, 20). For sensitivity analyses, we explored additional distributions: 1) $\lambda \sim \text{beta}(1, 1)$ that is uniform over the interval 0–1; 2) $\lambda \sim \text{beta}(0.5, 0.5)$; and 3) a discrete distribution approach reflecting situations in which λ is allowed to take discrete values 0, 0.5, and 1 only, corresponding to the 3 genetic models (Web Appendix). Therefore, with $\lambda \sim \text{cat}(0, 0.5, 1)$ and corresponding probabilities p_R, p_C, p_D , we set a priori all models to be equally probable and, thus, used $p_R = p_C = p_D = 1/3$ as prior probabilities. We then estimated the posterior distributions for λ . For the various beta distributions, we evaluated the impacts on the estimates of the medians of θ_1 and θ_2 and τ in the primary model. For distribution 3 above, the posterior distribution provides directly the posterior probability for each of 3 inheritance models.

We addressed heterogeneity by examining the between-study standard deviation, τ , and assessing the uncertainty of

the summary estimate by deriving predictive intervals (22). A priori, we tested for differences in treatment effect across growth disorders categorized into 3 groups: 1) GHD; 2) small for gestational age and idiopathic short stature; and 3) Turner syndrome. We additionally performed meta-regression analyses to identify study-level factors that modified the estimates of θ_1 , θ_2 , and τ in the primary model (23). Specifically, we tested a priori for the effects of the categorical variables (population origin, presence or absence of Hardy-Weinberg equilibrium, and publication type) and the continuous variables (mean age at start of therapy, mean growth hormone dose, mean baseline height standard deviation score, and mean parental height standard deviation score).

To assess the relative merits of the Bayesian approach to this clinical question, we repeated the analyses using a frequentist approach, as used by Wassenaar et al. (11), forcing the assumption that the underlying inheritance is dominant. The summary weighted mean difference was derived from a DerSimonian and Laird (24) random-effects analysis. Between-study heterogeneity was evaluated by using the I^2 statistic (25), which describes the proportion of total variation in study estimates that is due to heterogeneity. I^2 values of 25%, 50%, and 75% correspond to cutoff points for low, moderate, and high degrees of heterogeneity. We performed all frequentist analyses in Stata, version 11.1, statistical software.

Finally, we tested for publication biases using the modified Egger's test described by Harbord et al. (26) and constructed funnel plots to assess the effects of published data versus investigator-only data. These were performed by using the updated "metabias" command (27) in Stata software with study-level estimates for mean θ_2 and its standard error obtained from the Bayesian modeling.

RESULTS

From an initial electronic and hand search of potentially relevant articles, we identified 12 studies (18 data sets) for final modeling (10, 28–39) (Figure 1). Of these, one study (37)—the Manchester cohort, comprising 3 data sets—was published in abstract form only (details are shown in the Web Appendix). In 4 studies (10, 29, 34, 38), unreported data on ΔHt standard deviation score per genotype were provided directly from lead investigators. All papers were published in English.

Excluded studies were as follows: 3 duplicate studies (40–42); 3 studies where there was absence of reported data on ΔHt standard deviation score (43–45); 2 studies where the primary outcome of interest was one other than growth response (46, 47); and 1 study with insufficient quantifiable data on growth response (48). Additionally, there were 2 studies published in abstract form only that fulfilled the inclusion criteria but that had other reasons for exclusion. These studies—one from Russia (49) and the other from Turkey (50)—could not be included for 2 reasons. First, they had unusual clinical characteristics (e.g., in the Russian study, there was 1 child with the GHR_{d3-d3} genotype in 2 conditions, yet the means and standard deviations were reported; in the Turkish study, there were remarkably large mean ΔHt standard deviation score values in the GHR_{fl-fl} genotype yet inverse growth and zero growth in the GHR_{fl-d3} and GHR_{d3-d3} genotypes, respectively) (Web Appendix) (Web Table 1). Second, in both, there

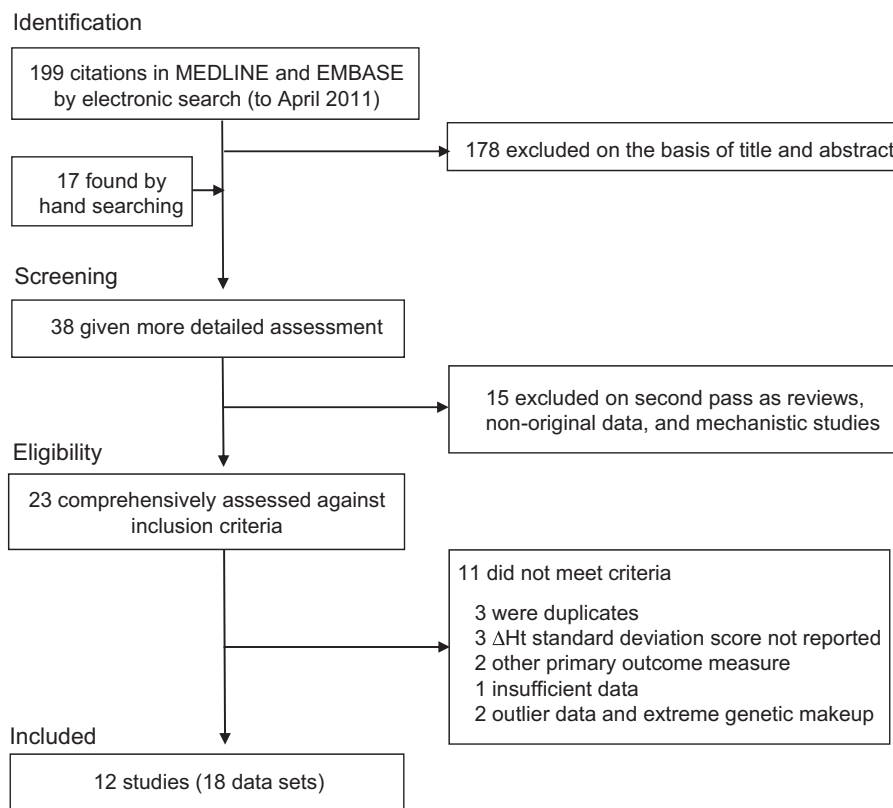


Figure 1. Flow diagram of the systematic review search and identified studies. Δ Ht, change in height.

was substantial deviation from the observed mean λ s in the pre-Bayesian assessments (Web Appendix) (Web Figure 1).

Study characteristics

Among the 18 data sets, the conditions were as follows: 7 GHD; 8 small for gestational age/idiopathic short stature; and 3 Turner syndrome (Table 1). There were 1,527 children (817 boys, 710 girls). All but 4 of the studies (29, 34, 35, 39) were among children of European origin. Notably, several studies did not state the study period in the methods section, and no study mentioned treatment compliance. With the exception of a Korean study (35), all children in other studies were prepubertal. The range of GHR_{d3} carriers was 38%–57% (median: 51%). There were 3 data sets (10, 28, 38) where, upon recalculation, there was evidence of Hardy-Weinberg disequilibrium.

The inheritance model

In the main Bayesian model, the estimate for median λ was 0.64 (95% credible interval (CrI): 0.40, 0.95). Visual inspection of the posterior distribution suggested that the codominant model may be likely, though one could not rule out a dominant model (Figure 2A). By use of the discrete distribution approach for λ , the posterior probability for a recessive model

was 0.00; for the codominant model, 0.93; and for the dominant model, 0.07. Sensitivity analyses applying beta distributions 1 and 2 and the hierarchical random-effects model made no material difference to the estimates of λ (Web Table 2).

We then plotted the observed study-specific values for θ_1 versus θ_2 and superimposed the fitted model line to assess the model's slope against known slopes for dominant, codominant, and recessive inheritance (13); the fitted model best approximated that of the codominant slope (Figure 2B). Having taken these lines of evidence together, we concluded that the most appropriate description of inheritance is codominant.

All study analyses

Figure 3 shows the results of the meta-analyses for the 18 eligible data sets in the main model. Compared with noncarriers, carriers had a median difference in 1-year Δ Ht standard deviation score for GHR_{fl-d3} of 0.09 (95% CrI: 0.01, 0.17), and that for GHR_{d3-d3} was 0.14 (95% CrI: 0.02, 0.26). However, the between-study standard deviation of 0.18 (95% CrI: 0.10, 0.33) was considerable. Incorporating these uncertainties, the respective summary estimates were 0.09 (95% predictive interval: –0.17, 0.37) and 0.14 (95% predictive interval: –0.28, 0.57). From this distribution, we derived that the probability of rhGH therapy's having no benefit in a new trial or in a different setting was 0.22.

Table 1. Baseline Characteristics of Included Studies (With Recalculated Handy-Weinberg Equilibrium Test)

| First Author, Year (Reference No.) | Study Name, Country | Setting, Period | Condition | Total No. | Males | | Mean Age, years (SD) | Mean Growth Hormone Dose, μg/kg/day (SD) | Mean Height Standard Deviation Score (SD) | Mean Parental Height Standard Deviation Score (SD) | GHR _{d3} , % | HWE Test |
|--|-----------------------------------|---------------------|-------------|--------------|-------|----|-------------------------|--|--|---|-----------------------|-------------|
| | | | | | No. | % | | | | | | |
| Growth hormone deficiency | | | | | | | | | | | | |
| Blum, 2006 (29) | Short Stature International Study | | IGHD | 107 | 73 | 68 | 7.1 | 28.6 | −3.40 ^a | | 45 | 0.101 |
| Jorge, 2006 (34) | Sao Paulo, Brazil | University Hospital | Severe IGHD | 58 | 36 | 62 | 8.9 (3.8) | 31.0 (5.0) | −4.25 ^a | 0.00 (0.82) | 52 | 0.547 |
| Wan, 2007 (39) | China | University Hospital | GHD | 154 | 108 | 70 | 7.8 (3.1) | 25.7 | −3.25 ^a | −0.78 (1.08) | 49 | 0.058 |
| de Graaff, 2008 (33) | Dutch National Registry | | IGHD | 40 | 26 | 65 | 7.0 | 25.0 (5.0) | −3.30 (1.00) | | 53 | 0.279 |
| de Graaff, 2008 (33) | Dutch National Registry | | MPHD | 45 | 29 | 64 | 4.8 | 25.0 (5.0) | −2.90 (1.30) | | 53 | 0.347 |
| Raz, 2008 (36) | Bern, Switzerland | University Hospital | Severe IGHD | 181 | 98 | 54 | 6.6 | 26.8 (2.1) | −3.97 ^a | −0.03 (0.08) | 50 | 0.201 |
| Solomon, 2008 (37) | Manchester, United Kingdom | University Hospital | GHD | 44 | 25 | 57 | 6.1 (4.3) | 25.3 (5.3) | −2.85 (1.55) | −0.50 (1.10) | 57 | |
| Small for gestational age/idiopathic short stature | | | | | | | | | | | | |
| Dos Santos, 2004 (10) | France and Switzerland | | | 76 | 46 | 61 | 6.6 | 51.0 | −2.51 ^a | | 53 | 0.005 |
| Dos Santos, 2004 (10) | France and Switzerland | | | 96 | 61 | 64 | 7.7 | 33.7 | −2.72 ^a | | 48 | 0.838 |
| Binder, 2006 (28) | Tuebingen, Germany | Children’s Hospital | SGA | 60 | 38 | 63 | 7.1 (2.3) | 56.0 (11.0) | −3.41 (0.94) | 0.08 (1.03) | 52 | 0.328 |
| Carrascosa, 2006 (32) | 30 hospitals, Spain | 2001–2006 | SGA | 68 | 39 | 57 | 7.1 | 66.0 | −3.32 (0.62) | −1.23 (0.97) | 56 | 0.781 |
| Tauber, 2007 (38) | NESTEGG project | | SGA | 240 | 138 | 58 | 6.6 (2.3) | 57.1 (24.3) | −3.00 (0.70) | −0.90 (1.20) | 40 | 0.000 |
| Carrascosa, 2008 (30) | Barcelona, Spain | 2000–2005 | SGA | 49 | 36 | 73 | 6.9 (2.2) | 32.1 (3.8) | −3.29 (0.74) | −1.06 (0.98) | 53 | 1.000 |
| Carrascosa, 2008 (31) | Barcelona, Spain | 1999–2005 | ISS | 106 | 58 | 55 | 7.8 (2.3) | 31.7 (3.5) | −3.42 (0.81) | −1.06 (0.98) | 57 | 0.127 |
| Solomon, 2008 (37) | Manchester, United Kingdom | University Hospital | SGA/IUGR | 13 | 6 | 46 | 7.8 (2.7) | 33.4 (3.1) | −3.31 (0.76) | −0.20 (0.80) | 38 | |
| Turner syndrome | | | | | | | | | | | | |
| Binder, 2006 (28) | Tuebingen, Germany | Children’s Hospital | TS | 53 | 0 | | 8.9 (3.1) | 38.0 (8.0) | −3.21 (1.02) | 0.36 (1.27) | 49 | 0.006 |
| Ko, 2010 (35) | Seoul, Korea | University Hospital | TS | 115 | 0 | | 15.8 (6.0) | 42.9 (8.6) | −2.50 (0.80) | −0.50 (0.08) | 36 | 0.424 |
| Solomon, 2008 (37) | Manchester, United Kingdom | University Hospital | TS | 22 | 0 | | 8.2 (3.4) | 35.3 (7.8) | −2.49 (0.89) | 0.10 (1.00) | 50 | 0.101 |

Abbreviations: GHD, growth hormone deficiency; GHR, growth hormone receptor; HWE, Handy-Weinberg equilibrium; IGHD, idiopathic growth hormone deficiency; ISS, idiopathic short stature; IUGR, intrauterine growth retardation; MPHD, multiple pituitary hormone deficiency; NESTEGG, Network of European Studies of Genes in Growth; SD, standard deviation; SGA, small for gestational age; TS, Turner syndrome.

^a Estimated from genotype-specific data.

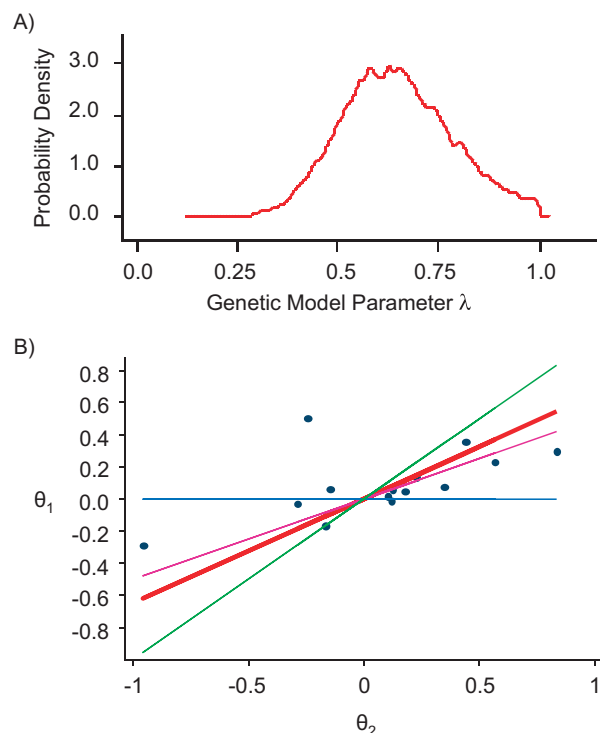


Figure 2. A, the posterior distribution for λ for the main genetic model. By visual inspection, the codominant model ($\lambda = 0.5$) is most probable, with the recessive ($\lambda = 0$) but not dominant ($\lambda = 1$) model being ruled out. B, plot of observed study-specific values for θ_1 versus θ_2 and superimposed the fitted model line (heavy red) to assess the model's slope against known slopes for dominant (green), codominant (pink), and recessive (blue) inheritance to investigate the genetic effect explained by the mean differences between the genotypes. The figure allows visual illustration that the observed data are likely to fit best to that of a codominant model.

For the same 18 data sets, the summary mean difference estimated by using the DerSimonian and Laird random-effects analysis was 0.14 (95% confidence interval: 0.07, 0.20), with a moderate level of between-study heterogeneity ($I^2 = 46\%$; $P = 0.018$) (Web Figure 2).

Sources of heterogeneity

We searched for sources of heterogeneity using meta-regression within the Bayesian model. First, we tested categorical study variables (Table 2). Some heterogeneity was explained by differences across diagnostic groups: The median differences in 1-year Δ Ht standard deviation score for GHR_{d3-d3} compared with noncarriers were as follows: 0.18 (95% CrI: -0.22, 0.51) for GHD; 0.17 (95% CrI: -0.02, 0.34) for small for gestational age/idiopathic short stature; and 0.01 (95% confidence interval: -0.72, 0.92) for Turner syndrome with low probability of between-group difference. We additionally tested the effects of population origin, presence or absence of Hardy-Weinberg equilibrium, and publication type but found none that materially influenced the regression model. However, the probability that investigator-only data were associated with a greater treatment effect was 0.88.

Second, we tested continuous study variables, including the mean age at start of therapy, the mean growth hormone dose, the mean height standard deviation score at study baseline, and the mean parental height standard deviation score (Table 3). We found none that materially influenced the regression model.

We tested the influence of adding back in the Russian and Turkish abstract-only studies of the genetic model. This produced a model with a very large between-study standard deviation ($\tau = 0.23$, 95% CrI: 0.15, 0.37) and a λ suggestive of a recessive inheritance, which seemed biologically implausible (10). By excluding these studies, the precision of the model improved by 32%.

Publication biases

For the data sets from published studies, including the investigator-only data, the Egger bias test P value was 0.549. Excluding 4 studies (10, 29, 34, 38) with investigator-only data, the Egger bias test P value was only 0.103. The funnel plot suggested that, without the investigator-only data, there was a risk of outcome reporting bias (Figure 4).

DISCUSSION

Summary of principal findings

This systematic review evaluated the impact of the exon-3 deleted growth hormone receptor polymorphism (GHR_{d3}) on 1-year growth response to rhGH in childhood short stature disorders and, prior to data synthesis, addressed the genetic model of inheritance underlying this potential treatment effect. Using an inheritance model-free approach, we showed that the most probable model for this polymorphism's influence is codominant and that GHR_{d3} genotypes account for modest increases in rhGH effects. There was considerable between-study heterogeneity, such that in some future settings, some children may not benefit. We searched for potential sources of this heterogeneity based on the available data, but unexplained variability in responsiveness remained.

Findings in context with other studies

Our summary estimate for 1-year Δ Ht standard deviation score for the differences between GHR_{d3-d3} and GHR_{fl-fl} estimated by the Bayesian model was similar to that estimated by conventional meta-analysis in our study, the latter being forced to be a dominant and, thus, failed to derive an estimate for GHR_{fl-d3} . The confidence intervals were narrower for the conventional approach, with the risk that one may be lured into an inflated level of confidence above the pharmaco-genetic association. A similar finding for the Bayesian and conventional models is perhaps not unexpected given that the majority of the included studies were from populations where GHR_{d3-d3} is relatively common, but differences might be anticipated if the GHR_{d3-d3} allele frequency were rare.

Like our conventional meta-analysis, the analysis reported by Wassenaar et al. (11) found a significant treatment effect of rhGH in GHR_{d3} carriers. However, there are differences between these reviews. First, in the latter, there may have been duplication between included studies (e.g., Carrascosa

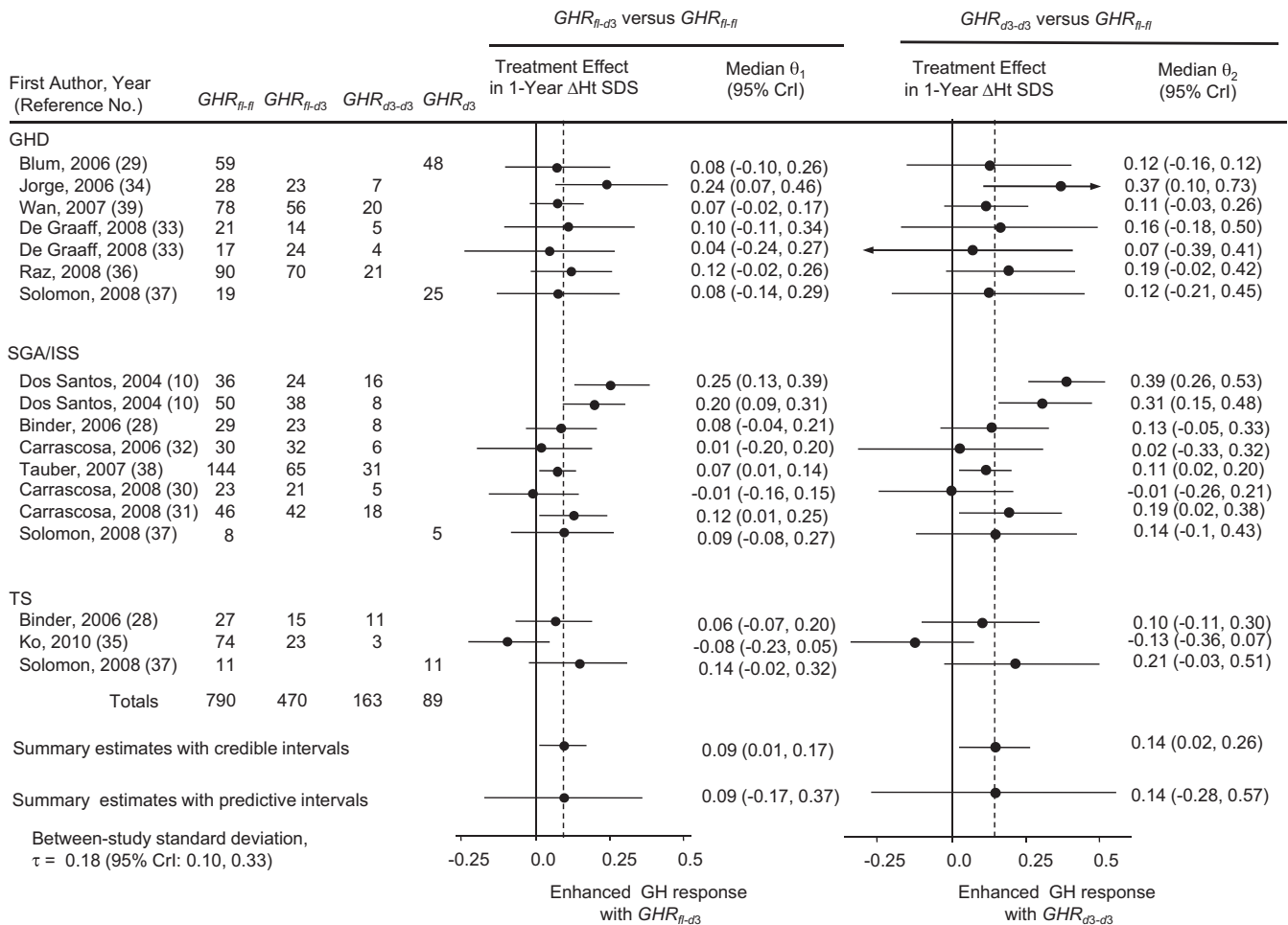


Figure 3. Forest plots for all 18 data sets by major growth disorder categories with summary estimates for θ_1 and θ_2 . CrI, credible interval; GH, growth hormone; GHD, growth hormone deficiency; *GHR_{fl-fl}*, *GHR_{fl-d3}*, *GHR_{d3-d3}*, and *GHR_{d3}*, growth hormone receptor polymorphisms with the presence of exon 3 in the full-length (fl) haplotype (*GHR_{fl-fl}*) and its absence or deletion (d3) in the shorter form (*GHR_{fl-d3}*, *GHR_{d3-d3}*) or allele (*GHR_{d3}*), respectively; ΔHt, change in height; ISS, idiopathic short stature; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome.

et al. (32) and Audi et al. (40)). Second, we did not include growth velocity at 1 year, as there were concerns regarding lack of standardization of reporting across studies (e.g., most studies report growth velocity as cm/year, but Raz et al. (36) reported the height velocity standard deviation score). Third, whereas Wassenaar et al. (11) found a significant effect modification from the mean rhGH dose on growth velocity (increased difference at lower rhGH doses) and a near-significant effect on 1-year ΔHt standard deviation score (increased differences at higher ages), we failed to observe similar effects in our Bayesian model. In turn, our analyses had a larger number of data sets in these regressions and were less likely to be influenced by extreme mean rhGH dose value duplicates.

Limitations and strengths

There are potential study limitations. First, meta-analyses of observational studies are vulnerable to the biases and confound-

ing inherent in the original studies. This is partly overcome by using a gene association approach but, additionally, to minimize biases further, the Bayesian model allowed us to simultaneously incorporate the uncertainties of both the treatment effect and the genetic model parameter. Second, unreported confounding, for example, lack of treatment compliance, could not be tested.

The strengths of this study are as follows. First, before synthesizing the data to estimate the treatment effect, we addressed the question of the genetic inheritance. The genetic model-free approach was not constrained to the classical modes of inheritance in recognition of the fact that the gene's mode of action in complex diseases might differ from that found in Mendelian traits, where the association between genotype and disease tends to be deterministic. Second, in our meta-analysis, we used data from all 3 genotypes to fit our model, as an a priori combination of genotypes (as in a pair-wise analysis) fails to "borrow strength" from across the 3 correlated genotypes and is potentially misleading. Third, we used investigator-only data

Table 2. Subgroup Analyses by Categorical Study Characteristics

| Variable | No. of Data Sets | Median θ_1 | 95% Credible Interval | Median θ_2 | 95% Credible Interval | Posterior Probability of Between-Group Difference | Between-Study Standard Deviation | τ |
|--|------------------|-------------------|-----------------------|-------------------|-----------------------|---|----------------------------------|------------|
| Condition | | | | | | | | |
| Growth hormone deficiency | 7 | 0.07 | −0.06, 0.25 | 0.18 | −0.22, 0.51 | 0.51 | 0.24 | 0.02, 0.88 |
| Small for gestational age/idiopathic short stature | 8 | 0.12 | −0.02, 0.24 | 0.17 | −0.02, 0.34 | 0.43 | 0.18 | 0.07, 0.43 |
| Turner syndrome | 3 | 0.00 | −0.27, 0.32 | 0.01 | −0.72, 0.92 | 0.60 | 0.42 | 0.05, 1.56 |
| Population | | | | | | | | |
| European | 14 | 0.11 | 0.03, 0.20 | 0.17 | 0.04, 0.28 | | 0.14 | 0.05, 0.29 |
| Other countries/international | 4 | 0.04 | −0.20, 0.35 | 0.14 | −0.52, 0.87 | 0.46 | 0.49 | 0.16, 1.43 |
| Hardy-Weinberg equilibrium | | | | | | | | |
| Yes | 11 ^a | 0.07 | −0.06, 0.19 | 0.11 | −0.11, 0.31 | | 0.24 | 0.09, 0.55 |
| No | 3 | 0.14 | −0.28, 0.59 | 0.21 | −0.41, 0.81 | 0.13 | 0.30 | 0.09, 1.30 |
| Reporting | | | | | | | | |
| Data reported in original paper | 10 | 0.01 | −0.06, 0.10 | 0.03 | −0.17, 0.18 | | 0.16 | 0.01, 0.42 |
| Investigator-only data | 8 | 0.18 | 0.06, 0.30 | 0.27 | 0.09, 0.48 | 0.88 | 0.17 | 0.07, 0.45 |
| Publication type ^b | | | | | | | | |
| Published data set | 15 | 0.09 | 0.00, 0.18 | 0.14 | −0.01, 0.27 | NA | 0.20 | 0.10, 0.38 |

Abbreviation: NA, not applicable.

^a Excluded studies with merged genotypes.^b The 3 unpublished data sets were from Manchester, United Kingdom; these were collapsed data and not possible to model.

in 4 published studies. Without these, we demonstrated that there was a risk of outcome reporting bias (in this example, the published studies may paradoxically have underestimated the effect). Fourth, we explored for study-level factors that may impact on the main finding, but none of these were significant modifiers. Finally, we undertook a variety of sensitivity analyses to test the assumptions in our model and showed these to have little material impact.

Plausible mechanisms

In the original description of the association between the *GHR_{d3}* polymorphism and the 1-year growth response to rhGH, Dos Santos et al. (10) described the mode of inheritance as dominant. In a subsequent commentary, Bougnères (51)

termed the inheritance as “nearly dominant.” The collective testing in our modeling points to a codominant inheritance. The clinical implications are 2-fold: 1) the treatment effect due to the presence of the heterozygous allele, *GDR_{fl-d3}*, was clinically very modest, such that 2) in populations where the allelic frequency of *GHR_{d3-d3}* is low (e.g., <5% in Chinese and Korean populations but 9%–15% in European populations (45)), the routine use of genetic determination may be cost ineffective.

The GHR exists as a dimer receptor, such that there is a need to understand whether long and short isoforms hybridize, what the effect of this hybridization is, and whether the effect of the short form polymorphism is quantitative (i.e., in a heterozygous patient, what proportion of GHRs are long and short?). Additionally, there may be a mixture of codominant and dominant

Table 3. Meta-Regression Analyses by Study Characteristics and Continuous Variables

| Variable | No. of Data Sets | Beta Coefficient | | Posterior Probability of Between-Group Difference |
|--|------------------|------------------|-----------------------|---|
| | | Median | 95% Credible Interval | |
| Mean child's age, years | 18 | 0.0141 | −0.0233, 0.0530 | 0.77 |
| Mean growth hormone dose, $\mu\text{g/kg/day}$ | 18 | −0.0028 | −0.0070, 0.0013 | 0.09 |
| Mean baseline height standard deviation score | 18 | 0.0630 | −0.0740, 0.1977 | 0.82 |
| Mean parental height standard deviation score | 13 | −0.0024 | −0.1131, 0.1091 | 0.48 |

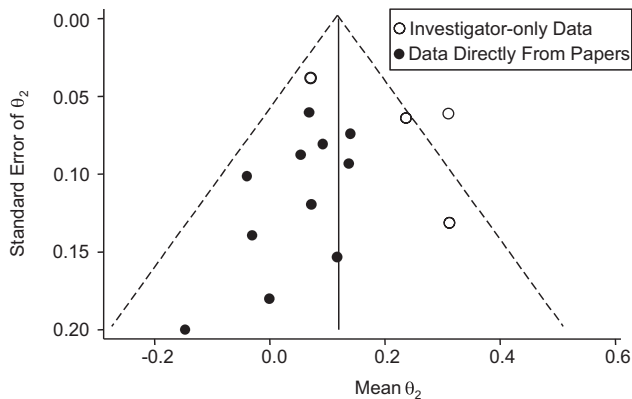


Figure 4. Reported and investigator-only data shown in a funnel plot for 15 data sets (the unpublished Manchester cohort was excluded).

inheritance (i.e., codominance in some studies and dominance in others). Alternatively, in complex diseases, the genotype may be only one of many factors acting in a complex causal cascade leading to the disease. Although, at the molecular level, the polymorphism of interest might act in a Mendelian manner on some intermediate phenotype, that Mendelian “signal” may be “diluted” or “distorted” when measured at the level of the final step in the cascade. By corollary, λ may be a more flexible and appropriate way to discuss genetic models in complex disease.

Unanswered questions

In contrast to the hypotheses of other investigators (52, 53) and the findings in the meta-analysis by Wassenaar et al. (11), our study results failed to show a modifying effect of age. It is conceivable that the range of mean ages (7–9 years, with the exception of Ko et al. (35)) in the studies included in our meta-analysis was too narrow. Similarly, Keni and Cohen (18) have argued that the *GHR_{d3}* genotype has a larger impact at higher rhGH doses, which contrasts with the findings from our analysis and those of the analyses of Wassenaar et al. (11). These issues would best be resolved by using an individual data meta-analysis. In future studies, there is a need for standardization of reporting outcome measures, exploration of the interaction of genetic inheritance with treatment, and consideration of individual children’s age-specific growth trajectories.

ACKNOWLEDGMENTS

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This work was supported by the National Institute for Health Research Manchester Biomedical Research Centre, United Kingdom. A. G. R. holds a senior lectureship award supported by the United Kingdom Clinical Research Collaboration. M. Z.’s position is currently funded by the Swiss School of Public Health (<http://www.ssphplus.ch>).

A. G. R. has received payment for advisory board consultation, lecture honoraria, and research support from Novo Nordisk. W. B. is employed by and holds stock in Eli Lilly and Company. P. E. C. has received payment for advisory board consultation, lecture honoraria, and research support from Merck Serono, Ipsen, Novo Nordisk, and Pfizer. The remaining authors declare no conflict of interest.

REFERENCES

1. Bryant J, Baxter L, Cave CB, et al. Recombinant growth hormone for idiopathic short stature in children and adolescents. *Cochrane Database Syst Rev*. 2007;(3):CD004440. (doi:10.1002/14651858.CD004440.pub2).
2. Cuttler L, Silvers JB. Growth hormone treatment for idiopathic short stature: implications for practice and policy. *Arch Pediatr Adolesc Med*. 2004;158(2):108–110.
3. Ranke MB, Lindberg A. Predicting growth in response to growth hormone treatment. *Growth Horm IGF Res*. 2009;19(1):1–11.
4. Lee JM, Davis MM, Clark SJ, et al. Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. *Arch Pediatr Adolesc Med*. 2006;160(3):263–269.
5. Bougnères P, Goffin V. The growth hormone receptor in growth. *Endocrinol Metab Clin North Am*. 2007;36(1):1–16.
6. Rosenfeld RG, Belgorosky A, Camacho-Hubner C, et al. Defects in growth hormone receptor signaling. *Trends Endocrinol Metab*. 2007;18(4):134–141.
7. Kelly PA, Goujon L, Sotiropoulos A, et al. The GH receptor and signal transduction. *Horm Res*. 1994;42(4-5):133–139.
8. Buzi F, Mella P, Pilotta A, et al. Growth hormone receptor polymorphisms. *Endocr Dev*. 2007;11:28–35. (doi:10.1159/000111055).

9. Sobrier ML, Duquesnoy P, Duriez B, et al. Expression and binding properties of two isoforms of the human growth hormone receptor. *FEBS Lett.* 1993;319(1-2):16–20.
10. Dos Santos C, Essioux L, Teinturier C, et al. A common polymorphism of the growth hormone receptor is associated with increased responsiveness to growth hormone. *Nat Genet.* 2004;36(7):720–724.
11. Wassenaar MJ, Dekkers OM, Pereira AM, et al. Impact of the exon 3-deleted growth hormone (GH) receptor polymorphism on baseline height and the growth response to recombinant human GH therapy in GH-deficient (GHD) and non-GHD children with short stature: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2009;94(10):3721–3730.
12. Bago PG. A unification of multivariate methods for meta-analysis of genetic association studies. *Stat Appl Genet Mol Biol.* 2008;7(1). Article31. (doi:10.2202/1544-6115.1408).
13. Minelli C, Thompson JR, Abrams KR, et al. The choice of a genetic model in the meta-analysis of molecular association studies. *Int J Epidemiol.* 2005;34(6):1319–1328.
14. Minelli C, Thompson JR, Abrams KR, et al. Bayesian implementation of a genetic model-free approach to the meta-analysis of genetic association studies. *Stat Med.* 2005;24(24):3845–3861.
15. Salanti G, Higgins JP. Meta-analysis of genetic association studies under different inheritance models using data reported as merged genotypes. *Stat Med.* 2008;27(5):764–777.
16. Ihara K, Hara T. Genetic polymorphisms in the growth hormone receptor: impact on growth response and disease susceptibility. *Curr Pharmacogenomics Person Med.* 2008;6(3):295–301.
17. Jorge AA, Arnhold JJ. Growth hormone receptor exon 3 isoforms and their implication in growth disorders and treatment. *Horm Res.* 2009;71(suppl 2):55–63.
18. Keni J, Cohen P. Optimizing growth hormone dosing in children with idiopathic short stature. *Horm Res.* 2009;71(suppl 1):70–74.
19. Cleves M. Hardy-Weinberg equilibrium test and allele frequency estimation. *STB-48. Stata Tech Bull.* 1999;8(48):280–284.
20. Salanti G, Southam L, Altshuler D, et al. Underlying genetic models of inheritance in established type 2 diabetes associations. *Am J Epidemiol.* 2009;170(5):537–545.
21. Spiegelhalter D, Thomas A, Best N. *WinBUGS User Manual Version 1.4.5 August 2009.* Cambridge, United Kingdom: MRC Biostatistics Unit; 2009.
22. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc.* 2009;172(1):137–159.
23. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med.* 2002;21(11):1559–1573.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177–188.
25. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557–560.
26. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med.* 2006;25(20):3443–3457.
27. Harbord RM, Harris RJ, Sterne JAC. Updated tests for bias in meta-analysis sbe19_6. *Stata J.* 2009SJ9–2.
28. Binder G, Baur F, Schweizer R, et al. The d3-growth hormone (GH) receptor polymorphism is associated with increased responsiveness to GH in Turner syndrome and short small-for-gestational-age children. *J Clin Endocrinol Metab.* 2006;91(2):659–664.
29. Blum WF, Machinis K, Shavrikova EP, et al. The growth response to growth hormone (GH) treatment in children with isolated GH deficiency is independent of the presence of the exon 3-minus isoform of the GH receptor. *J Clin Endocrinol Metab.* 2006;91(10):4171–4174.
30. Carrascosa A, Audí L, Esteban C, et al. Growth hormone (GH) dose, but not exon 3-deleted/full-length GH receptor polymorphism genotypes, influences growth response to two-year GH therapy in short small-for-gestational-age children. *J Clin Endocrinol Metab.* 2008;93(1):147–153.
31. Carrascosa A, Audí L, Fernández-Cancio M, et al. The exon 3-deleted/full-length growth hormone receptor polymorphism did not influence growth response to growth hormone therapy over two years in prepubertal short children born at term with adequate weight and length for gestational age. *J Clin Endocrinol Metab.* 2008;93(3):764–770.
32. Carrascosa A, Esteban C, Espadero R, et al. The d3/fl-growth hormone (GH) receptor polymorphism does not influence the effect of GH treatment (66 microg/kg per day) or the spontaneous growth in short non-GH-deficient small-for-gestational-age children: results from a two-year controlled prospective study in 170 Spanish patients. *J Clin Endocrinol Metab.* 2006;91(9):3281–3286.
33. de Graaff LC, Meyer S, Els C, et al. GH receptor d3 polymorphism in Dutch patients with MPPH and IGHD born small or appropriate for gestational age. *Clin Endocrinol (Oxf).* 2008;68(6):930–934.
34. Jorge AA, Marchisotti FG, Montenegro LR, et al. Growth hormone (GH) pharmacogenetics: influence of GH receptor exon 3 retention or deletion on first-year growth response and final height in patients with severe GH deficiency. *J Clin Endocrinol Metab.* 2006;91(3):1076–1080.
35. Ko JM, Kim JM, Cheon CK, et al. The common exon 3 polymorphism of the growth hormone receptor gene and the effect of growth hormone therapy on growth in Korean patients with Turner syndrome. *Clin Endocrinol (Oxf).* 2010;72(2):196–202.
36. Ráz B, Janner M, Petkovic V, et al. Influence of growth hormone (GH) receptor deletion of exon 3 and full-length isoforms on GH response and final height in patients with severe GH deficiency. *J Clin Endocrinol Metab.* 2008;93(3):974–980.
37. Solomon M, Morjaria R, Patel L, et al. Exon 3 deletion polymorphism of the growth hormone receptor (GHR) and GH response: a report of 97 cases (Manchester) and literature meta-analysis [abstract]. *Growth Horm IGF Res.* 2008;18(suppl):S5–S6.
38. Tauber M, Ester W, Auriol F, et al. GH responsiveness in a large multinational cohort of SGA children with short stature (NESTEGG) is related to the exon 3 GHR polymorphism. *Clin Endocrinol (Oxf).* 2007;67(3):457–461.
39. Wan L, Chen WC, Tsai Y, et al. Growth hormone (GH) receptor C.1319 G>T polymorphism, but not exon 3 retention or deletion is associated with better first-year growth response to GH therapy in patients with GH deficiency. *Pediatr Res.* 2007;62(6):735–740.
40. Audí L, Carrascosa A, Esteban C, et al. The exon 3-deleted/full-length growth hormone receptor polymorphism does not influence the effect of puberty or growth hormone therapy on glucose homeostasis in short non-growth hormone-deficient small-for-gestational-age children: results from a two-year controlled prospective study. Spanish SGA Study Group. *J Clin Endocrinol Metab.* 2008;93(7):2709–2715.
41. Binder G, Trebar B, Baur F, et al. Homozygosity of the d3-growth hormone receptor polymorphism is associated with a high total effect of GH on growth and a low BMI in girls with Turner syndrome. *Clin Endocrinol (Oxf).* 2008;68(4):567–572.
42. Marchisotti FG, Jorge AA, Montenegro LR, et al. Comparison between weight-based and IGF-I-based growth hormone (GH) dosing in the treatment of children with GH deficiency and influence of exon 3 deleted GH receptor variant. *Growth Horm IGF Res.* 2009;19(2):179–186.

43. Drori-Herishanu L, Lodish M, Verma S, et al. The growth hormone receptor (GHR) polymorphism in growth-retarded children with Cushing disease: lack of association with growth and measures of the somatotrophic axis. *Horm Metab Res.* 2010;42(3):194–197.
44. Ito Y, Makita Y, Matsuo K, et al. Influence of the exon 3 deleted isoform of GH receptor gene on growth response to GH in Japanese children [abstract]. *Horm Res.* 2005; 64(suppl 1):45.
45. Ko JM, Park JY, Yoo HW. Common exon 3 polymorphism of the GH receptor (*GHR*) gene and effect of GH therapy on growth in Korean children with idiopathic short stature (ISS). *Clin Endocrinol (Oxf).* 2009;70(1):82–87.
46. Jensen R, O'Connell S, Salgin B, et al. Insulin-like growth factor-I, *d3-GHR* polymorphism, prematurity and height at start as determinants of one year growth response during high dose GH; preliminary results from the NESGA Study (NESGAS) [abstract]. *Horm Res.* 2009;72(suppl 3):440.
47. Toyoshima MT, Castroneves LA, Costalonga EF, et al. Exon 3-deleted genotype of growth hormone receptor (*GHR*_{d3}) positively influences IGF-1 increase at generation test in children with idiopathic short stature. *Clin Endocrinol (Oxf).* 2007;67(4):500–504.
48. Pilotta A, Mella P, Filisetti M, et al. Common polymorphisms of the growth hormone (GH) receptor do not correlate with the growth response to exogenous recombinant human GH in GH-deficient children. *J Clin Endocrinol Metab.* 2006; 91(3):1178–1180.
49. Pyathushkina G, Peterkova V. *d3-GHR* gene polymorphism and GH recombinant treatment efficacy in children with GH deficiency, Turner syndrome, and SGA [abstract]. *Horm Res.* 2007;68(suppl 1):166.
50. Darendeliler FF, Bas F, Bozkurt N, et al. The exon 3 deleted/full length growth hormone receptor polymorphism and response to GH therapy in GH deficiency and Turner syndrome: a multicenter study [abstract]. *Horm Res.* 2009;72(suppl 3):109.
51. Bougnères P. The exon-3 deletion of the growth hormone receptor (GHR) gene still has a limited impact in clinical endocrinology. *J Clin Endocrinol Metab.* 2010;95(1):56–59.
52. Bakker B, Frane J, Anhalt H, et al. Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. *J Clin Endocrinol Metab.* 2008;93(2):352–357.
53. Ranke MB, Lindberg A, Cowell CT, et al. Prediction of response to growth hormone treatment in short children born small for gestational age: analysis of data from KIGS (Pharmacia International Growth Database). *J Clin Endocrinol Metab.* 2003;88(1):125–131.