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

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

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

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 authors performed a systematic review (to April 2011), including investigator-only data, to quantify the effects of the \( GHR_{fl}^{d} \) and \( GHR_{d}^{d} \) 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 \( GHR_{fl}^{d} \) and of 0.14 (95% CrI: 0.02, 0.26) for \( GHR_{d}^{d} \). 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 \( GHR_{d}^{d} \) polymorphism inheritance is codominant, contrasting with previous reports; 2) \( GHR_{fl} \) genotypes account for modest increases in rhGH effects in children; and 3) considerable unexplained variability in responsiveness remains.

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 (GHRfl fl) or wild type), whereas its absence (GHRd fl and GHRd fl,fl) 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 GHRd3 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 GHRd3 allele compared with homozygous for the full-length allele (GHRfl 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 GHRd3 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, GHRd3 carriers (GHRd3 and GHRd3,fl) versus noncarriers (GHRfl 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 GHRd3 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 GHRd3 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 GHRfl fl, GHRd3, and/or GHRd3 fl, (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 μg/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 GHRfl fl, GHRd3, and GHRd3 or GHRfl fl and GHRd3 (i.e., GHRd3 and GHRd3 fl, 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, ηa, the underlying function for each genotype in study i, and used θij and θk to denote the effect sizes comparing the genotype Ai with AA (the reference group) and comparing AA with AA, respectively, such that θ1i = η2i – η1i, and θ2i = η3i – η1i. The underlying genetic model refers to the relation between the two θs; in the general case, θ1i = λi1 × θ1i, with λ = 1 for a dominant model, λ = 0.5 for an additive or codominant model, and λ = 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 $\lambda$ 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, $\tau$, and the genetic model parameter, $\lambda$. 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/)). If 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 $\theta_2$ and its standard error obtained from the Bayesian modeling.

**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 $\text{GHR}_{3\beta-d3}$ and $\text{GHR}_{3\beta-3\beta}$ genotypes and noncarriers expressed, respectively, as median values of $\theta_1$ and $\theta_2$, with 95% credible intervals, where study-specific $\theta_1$, and $\theta_2$, 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, $\tau$, 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, $\lambda$, 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 $\lambda$ 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 $\lambda$. For the various beta distributions, we evaluated the impacts on the estimates of the medians of $\theta_1$, $\theta_2$, and $\tau$ 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, $\tau$, 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 $\theta_1$, $\theta_2$, and $\tau$ 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 weight 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 $\theta_2$ 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 $\Delta$Ht 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 $\Delta$Ht 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 $\text{GHR}_{3\beta-3\beta}$ genotype in 2 conditions, yet the means and standard deviations were reported; in the Turkish study, there were remarkably large mean $\Delta$Ht standard deviation score values in the $\text{GHR}_{3\beta-3\beta}$ genotype yet inverse growth and zero growth in the $\text{GHR}_{3\beta-3\beta}$ and $\text{GHR}_{3\beta-3\beta}$ genotypes, respectively) (Web Appendix) (Web Table 1). Second, in both, there
was substantial deviation from the observed mean $\lambda$ 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 $GHRd_3$ 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 $\lambda$ 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 $\lambda$, 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 $\lambda$ (Web Table 2).

We then plotted the observed study-specific values for $h_1$ versus $h_2$ 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 $\Delta Ht$ standard deviation score for $GHRd_3$ of $0.09$ (95% CrI: 0.01, 0.17), and that for $GHRd_3$ 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.

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**Figure 1.** Flow diagram of the systematic review search and identified studies. $\Delta Ht$, change in height.
Table 1. Baseline Characteristics of Included Studies (With Recalculated Handy-Weinberg Equilibrium Test)

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Name, Country</th>
<th>Setting, Period</th>
<th>Condition</th>
<th>Total No.</th>
<th>Males No.</th>
<th>Mean Age, years (SD)</th>
<th>Mean Growth Hormone Dose, μg/kg/day (SD)</th>
<th>Mean Height Standard Deviation Score (SD)</th>
<th>Mean Parental Height Standard Deviation Score (SD)</th>
<th>GHRd, %</th>
<th>HWE Test</th>
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<tbody>
<tr>
<td><strong>Growth hormone deficiency</strong></td>
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<tr>
<td>Blum, 2006 (29)</td>
<td>Short Stature</td>
<td>International Study</td>
<td>IGHD</td>
<td>107</td>
<td>73</td>
<td>68.1 (7.1)</td>
<td>28.6 (2.5)</td>
<td>−3.40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>45</td>
<td>0.101</td>
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<tr>
<td>Jorge, 2006 (34)</td>
<td>Sao Paulo, Brazil</td>
<td>University Hospital</td>
<td>Severe IGHD</td>
<td>58</td>
<td>36</td>
<td>62.8 (3.8)</td>
<td>31.0 (5.0)</td>
<td>−4.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.00 (0.8)</td>
<td>52</td>
<td>0.547</td>
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<td>Wan, 2007 (39)</td>
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<td>University Hospital</td>
<td>GHD</td>
<td>154</td>
<td>108</td>
<td>70.3 (3.1)</td>
<td>25.7 (2.5)</td>
<td>−3.25&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Dutch National Registry</td>
<td>IGHD</td>
<td>40</td>
<td>26</td>
<td>65.7 (7.0)</td>
<td>25.0 (5.0)</td>
<td>−3.30 (1.00)</td>
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<td>MPHD</td>
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<td>29</td>
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<td>University Hospital</td>
<td>Severe IGHD</td>
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<td>98</td>
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<td>−0.50 (1.10)</td>
<td>57</td>
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<tr>
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<tr>
<td>Dos Santos, 2004 (10)</td>
<td>France and Switzerland</td>
<td>SGA</td>
<td>76</td>
<td>46</td>
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<td>SGA</td>
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<td>2001–2006</td>
<td>SGA</td>
<td>68</td>
<td>39</td>
<td>57.1 (7.1)</td>
<td>66.0 (0.5)</td>
<td>−3.32 (0.62)</td>
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<td>56</td>
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<td>138</td>
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<td>SGA/IUGR</td>
<td>13</td>
<td>6</td>
<td>46.8 (2.7)</td>
<td>33.4 (3.1)</td>
<td>−3.31 (0.76)</td>
<td>−0.20 (0.80)</td>
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<tr>
<td>Binder, 2006 (28)</td>
<td>Tuebingen, Germany</td>
<td>Children’s Hospital</td>
<td>TS</td>
<td>53</td>
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<td>−3.21 (1.02)</td>
<td>0.36 (1.27)</td>
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<td>−2.49 (0.89)</td>
<td>0.10 (1.00)</td>
<td>50</td>
<td>0.101</td>
</tr>
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</table>

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; MPH, multiple pituitary hormone deficiency; NESTEGG, Network of European Studies of Genes in Growth; SD, standard deviation; SGA, small for gestational age; TS, Turner syndrome.

<sup>a</sup> Estimated from genotype-specific data.
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 ΔHt standard deviation score for $GHR_{3-3}$ 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 ($τ = 0.23, 95% CrI: 0.15, 0.37$) 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 ($GHR_{3}$) 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 $GHR_{3}$ 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 ΔHt standard deviation score for the differences between $GHR_{3}$ and $GHR_{3}$ 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 $GHR_{3}$. 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 $GHR_{3}$ is relatively common, but differences might be anticipated if the $GHR_{3}$ 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 $GHR_{3}$ carriers. However, there are differences between these reviews. First, in the latter, there may have been duplication between included studies (e.g., Carrascosa...
et al. (32) and Audi et al. (40)). Second, we did not include growth report 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 ∆Ht 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-

Bayesian Meta-Analysis of GHR Polymorphism

Figure 3. Forest plots for all 18 data sets by major growth disorder categories with summary estimates for $\theta_1$ and $\theta_2$. CrI, credible interval; GH, growth hormone; GHD, growth hormone deficiency; GHRfl, GHRfl, GHRfl-d3, and GHRd3, growth hormone receptor polymorphisms with the presence of exon 3 in the full-length (fl) haplotype (GHRfl) and its absence or deletion (d3) in the shorter form (GHRd3) or allele (GHRd3), respectively; ∆Ht, change in height; ISS, idiopathic short stature; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome.
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 \( \text{GHRd}_{3} \) 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, \( \text{GDRfl}_{d_{3}} \), was clinically very modest, such that 2) in populations where the allelic frequency of \( \text{GHRd}_{3}\) 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

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**Table 2. Subgroup Analyses by Categorical Study Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Data Sets</th>
<th>Median ( \theta_1 )</th>
<th>95% Credible Interval</th>
<th>Median ( \theta_2 )</th>
<th>95% Credible Interval</th>
<th>Posterior Probability of Between-Group Difference</th>
<th>Between-Study Standard Deviation</th>
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<tbody>
<tr>
<td>Condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Growth hormone deficiency</td>
<td>7</td>
<td>0.07</td>
<td>-0.06, 0.25</td>
<td>0.18</td>
<td>-0.22, 0.51</td>
<td>0.51</td>
<td>0.24</td>
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<tr>
<td>Small for gestational age/idiopathic short stature</td>
<td>8</td>
<td>0.12</td>
<td>-0.02, 0.24</td>
<td>0.17</td>
<td>-0.02, 0.34</td>
<td>0.43</td>
<td>0.18</td>
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<tr>
<td>Turner syndrome</td>
<td>3</td>
<td>0.00</td>
<td>-0.27, 0.32</td>
<td>0.01</td>
<td>-0.72, 0.92</td>
<td>0.60</td>
<td>0.42</td>
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<td>Population</td>
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<td></td>
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<td></td>
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<tr>
<td>European</td>
<td>14</td>
<td>0.11</td>
<td>0.03, 0.20</td>
<td>0.17</td>
<td>0.04, 0.28</td>
<td>0.14</td>
<td>0.05</td>
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<tr>
<td>Other countries/international</td>
<td>4</td>
<td>0.04</td>
<td>-0.20, 0.35</td>
<td>0.14</td>
<td>-0.52, 0.87</td>
<td>0.46</td>
<td>0.16</td>
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<td>Hardy-Weinberg equilibrium</td>
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<tr>
<td>Yes</td>
<td>11*</td>
<td>0.07</td>
<td>-0.06, 0.19</td>
<td>0.11</td>
<td>-0.11, 0.31</td>
<td>0.24</td>
<td>0.09</td>
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<tr>
<td>No</td>
<td>3</td>
<td>0.14</td>
<td>-0.28, 0.59</td>
<td>0.21</td>
<td>-0.41, 0.81</td>
<td>0.13</td>
<td>0.30</td>
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<td>Reporting</td>
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</tr>
<tr>
<td>Data reported in original paper</td>
<td>10</td>
<td>0.01</td>
<td>-0.06, 0.10</td>
<td>0.03</td>
<td>-0.17, 0.18</td>
<td>0.16</td>
<td>0.01</td>
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<tr>
<td>Investigator-only data</td>
<td>8</td>
<td>0.18</td>
<td>0.06, 0.30</td>
<td>0.27</td>
<td>0.09, 0.48</td>
<td>0.88</td>
<td>0.17</td>
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<tr>
<td>Publication typeb</td>
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<td></td>
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<tr>
<td>Published data set</td>
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<td>0.00, 0.18</td>
<td>0.14</td>
<td>-0.01, 0.27</td>
<td>NA</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

* 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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Data Sets</th>
<th>Beta Coefficient</th>
<th>95% Credible Interval</th>
<th>Posterior Probability of Between-Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean child’s age, years</td>
<td>18</td>
<td>0.0141</td>
<td>-0.0233, 0.0530</td>
<td>0.77</td>
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<tr>
<td>Mean growth hormone dose, ( \mu \text{g/kg/day} )</td>
<td>18</td>
<td>-0.0028</td>
<td>-0.0070, 0.0013</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean baseline height standard deviation score</td>
<td>18</td>
<td>0.0630</td>
<td>-0.0740, 0.1977</td>
<td>0.82</td>
</tr>
<tr>
<td>Mean parental height standard deviation score</td>
<td>13</td>
<td>-0.0024</td>
<td>-0.1131, 0.1091</td>
<td>0.48</td>
</tr>
</tbody>
</table>
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, 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.

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REFERENCES


