A novel common variant in DCST2 is associated with length in early life and height in adulthood

Ralf J.P. van der Valk1,2,3,†, Eskil Kreiner-Møller5,†, Marjolein N. Kooijman1,2,3,†, Mônica Guxens6,7,8,†, Evangelia Stergiakouli9,†, Annika Sääf12, Jonathan P. Bradfield13, Frank Geller15, M. Geoffrey Hayes16,17, Diana L. Cousminer18, Antje Körner20, Elisabeth Thiering21,22, John A. Curtin25, Ronny Myhre26, Ville Hulka28, Raimo Joro31, Marjan Kerkhof33,34, Nicole M. Warrington37,38, Niina Pirkkänen39, Ioanna Ntalla41,42, Momoko HoriKoshi43,44, Riitta Veijola45, Rachel M. Freathy47, Yik-Ying Teo48,49,50, Sheila J. Barton51, David M. Evans9,38, John P. Kemp9,38, Beate St Pourcain9,10,11, Susan M. Ring9,10, George Davey Smith9,

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Bo Chawes5, Jakob Stokholm5, Johannes Waage5, Patrick Eriksen5, Astrid Sevelsted5,

Mads Melbye15,56, Early Genetics and Lifecourse Epidemiology (EAGLE) Consortium, Cornelia M. van Duijn1, Carolina Medina-Gomez1,3,4, Albert Hofman1,3, Johan C. de Jongste2,3,

H. Rob Taal1, André G. Uitterlinden1,3,4, Genetic Investigation of ANthropometric Traits (GIANT) Consortium, Loren L. Armstrong16,17, Johan Eriksson18, Arno Palotie18,57,59,58,

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Jordi Sunyer6,7,8,62, Nicholas J. Timpson9,1, Fernando Rivadeneira1,3,4,†, Klaus Bønnelykke5,5, and Vincent W.V. Jaddoe1,2,3,4, for the Early Growth Genetics (EGG) Consortium

†To whom correspondence should be addressed at: Generation R Study Group, Department of Epidemiology, Erasmus Medical Center, Sophia’s Children’s Hospital, Postbus 2060, 3000 CB Rotterdam, The Netherlands. Tel: +31 10 707043405; Fax: +31 10 4089382; Email: v.jaddoe@erasmusmc.nl

‡These authors have contributed equally to this work.

*The authors wish it to be known that, in their opinion, J.S., N.J.T., F.R., K.B. and V.W.V.J. should be regarded as joint Lead Senior Authors; these authors jointly directed this work.

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Common genetic variants have been identified for adult height, but not much is known about the genetics of skeletal growth in early life. To identify common genetic variants that influence fetal skeletal growth, we meta-analyzed 22 genome-wide association studies (Stage 1; \( N = 28 \, 459 \)). We identified seven independent top single nucleotide polymorphisms (SNPs) (\( P < 1 \times 10^{-6} \)) for birth length, of which three were novel and four were in or near loci known to be associated with adult height (\( LCORL, PTC\)H1, \( GPR126 \) and \( HMG3A2 \)). The three novel SNPs were followed-up in nine replication studies (Stage 2; \( N = 11 \, 995 \)), with rs905938 in \( DC\)-\( STAMP \) domain containing 2 (\( DC\)-\( STAMP \)) genome-wide significantly associated with birth length in a joint analysis (Stages 1 + 2; \( \beta = 0.046, SE = 0.008, P = 2.46 \times 10^{-8}, \) explained variance = 0.05\%). Rs905938 was also associated with infant length (\( N = 28 \, 228 \); \( P = 5.54 \times 10^{-4} \)) and adult height (\( N = 127 \, 513 \); \( P = 1.45 \times 10^{-7} \)). \( DC\)-\( STAMP \) is a \( DC\)-\( STAMP \)-like protein family member and \( DC\)-\( STAMP \) is an osteoclast cell-fusion regulator. Polygenic scores based on 180 SNPs previously associated with human adult stature explained 0.13\% of variance in birth length. The same SNPs explained 2.95\% of the variance of infant length. Of the 180 known adult height loci, 11 were genome-wide significantly associated with infant length (\( SF3B4, LCORL, SPAG17, C6orf173, PTC\)H1, \( GDF5, ZNFX1, HHIP, ACAN, HLA \) locus and \( HMG3A2 \)). This study highlights that common variation in \( DC\)-\( STAMP \) influences variation in early growth and adult height.

INTRODUCTION

Fetal and infancy length growth are important measures of development in early life. Early length growth seems to be associated with height in adulthood (1). It has been shown that fetal and infant growth are independently associated with higher risks of cardiovascular disease, type 2 diabetes and many other complex diseases. Previous findings suggested genetic links between fetal growth and metabolism (2,3). However, these studies mainly focused on birth weight as early growth measure. Skeletal growth is a different measure of development in early life. Skeletal growth during fetal life and infancy is a complex trait with heritability estimates of 26–72\% (4). Although correlated with each other, fetal, infant and adult skeletal growth may be influenced by different genetic factors. Many common genetic variants have been identified for adult height (5), but not much is known about the genetics of skeletal growth in early life. Although, several rare genetic defects with large effects on length at birth and during infancy have been found (6,7), common genetic variants that influence normal variation in birth and infant length have not yet been identified. Therefore, we aimed to identify common genetic variants influencing early length growth, also in perspective of their effect on adult stature.
RESULTS

To identify common genetic variants associated with birth length, we examined 2,201,971 million directly genotyped and imputed SNPs with birth length in 22 independent discovery studies with genome-wide association (GWA) or Metabochip data (Stage 1; \(N = 28,459\); Fig. 1). Birth length was measured using standardized procedures (Supplementary Material, Tables S1 and S2). Studies with self-reported measurements were excluded a priori. Birth length was standardized using growth analyzer (http://www.growthanalyser.org), transforming birth length into sex- and age-adjusted standard deviation scores (SDS). We used the North-European 1991 reference panel to compare results between studies. We applied linear regression between number of alleles or dosages obtained from imputations and standardized birth length (full details in Materials and Methods).

Gene identification

In the discovery phase (Stage 1), we found seven independent top SNPs with suggestive evidence of association (\(P < 1 \times 10^{-6}\)) with birth length (Supplementary Material, Figs. S1 and S2, QQ- and Manhattan plot). Four SNPs mapped to loci already known to be associated with adult height (Supplementary Material, Table S3, \(LCORL\), \(PTCH1\), \(GPR126\) and \(HMGA2\)) (5). The 3 SNPs reflecting potentially novel associations were taken forward in nine independent replication studies (Stage 2; \(N = 11,995\); Fig. 1). Only one of the three SNPs displayed significant evidence for replication in Stage 2 and reached genome-wide significance in the joint analysis (Stages 1 + 2; \(P < 5 \times 10^{-8}\), Table 1). This novel association arose from SNP rs905938, mapping to chromosome 1q22 in DC-STAMP domain containing 2 (DCST2) (Fig. 2, regional association plot). Each C allele [minor allele frequency (MAF) = 0.24] of rs905938 was associated with an increase (standardized) of 0.046 SDS in birth length (standard error = 0.008, \(P = 2.46 \times 10^{-8}\), explained variance = 0.05%). The genome-wide significantly associated SNP showed low degree of heterogeneity between the discovery studies (\(P = 0.93, I^2 = 0\%\)). Figure 3 shows the forest plot of the associations between rs905938[C] and birth length across all studies. Other suggestive loci in the discovery analysis are shown in Supplementary Material, Table S3 (\(P < 1 \times 10^{-5}\)). Summary statistics of all SNPs are available at http://egg-consortium.org.

Functional analyses

We assessed common variants with deleterious functional implications in linkage disequilibrium (LD, \(r^2 > 0.80\)) with rs905938 using HaploReg (8). There were no non-synonymous variants in LD with rs905938. We found three putative functional intronic variants in high LD with rs905938. Details are depicted in Supplementary Material, Table S4. Subsequently, we assessed whether variants in the identified locus were involved in the

![Figure 1 Study design.](http://egg-consortium.org)
regulation of messenger RNA expression (eQTLs) in genome-wide expression datasets of lymphoblastoid cell lines (LCLs, \(N = 1830\)) (9,10). We found \(cis\) eQTLs [false discovery rate (FDR), 1% account for all SNP-probe pairs that were within 1 Mb of each other] for transcripts of \(PBXIP1\), \(GBA\) and \(ADAM15\). Yet, rs905938 and the \(cis\) eQTL SNPs were not in perfect LD (\(r^2 < 0.80\), Supplementary Material, Table S5).

Therefore, we cannot exclude that multiple independent effects arise from the same region of association.

**DCST2 and growth phenotypes**

We tested the associations of rs905938[C] with ‘fetal growth’ measures in the 1st, 2nd and 3rd trimester of pregnancy in the

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**Table 1** Summary statistics of the three novel SNPs at \(P < 1 \times 10^{-6}\) in the discovery analysis and the replication follow-up results

<table>
<thead>
<tr>
<th>Marker</th>
<th>MAF</th>
<th>(\beta)</th>
<th>SE</th>
<th>(P)</th>
<th>(n)</th>
<th>(I^2)</th>
<th>HetP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery (Stage 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs905938[C] at 1q22 (DCST2)</td>
<td>0.24</td>
<td>0.050</td>
<td>0.010</td>
<td>(2.59 \times 10^{-7})</td>
<td>28 327</td>
<td>0.0</td>
<td>0.930</td>
</tr>
<tr>
<td>rs12545524[G] at 8q22.1 (near GDF6)</td>
<td>0.14</td>
<td>0.078</td>
<td>0.014</td>
<td>(1.54 \times 10^{-8})</td>
<td>22 170</td>
<td>6.6</td>
<td>0.376</td>
</tr>
<tr>
<td>rs11037473[A] at 11p11.2 (nearest genes TTC17-HSD17B12)</td>
<td>0.06</td>
<td>-0.109</td>
<td>0.021</td>
<td>(2.17 \times 10^{-7})</td>
<td>22 259</td>
<td>0.0</td>
<td>0.735</td>
</tr>
<tr>
<td>Replication (Stage 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs905938[C] at 1q22 (DCST2)</td>
<td>0.23</td>
<td>0.035</td>
<td>0.015</td>
<td>(1.99 \times 10^{-2})</td>
<td>11 908</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>rs12545524[G] at 8q22.1 (near GDF6)</td>
<td>0.11</td>
<td>-0.012</td>
<td>0.017</td>
<td>(4.67 \times 10^{-1})</td>
<td>17 614</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>rs11037473[A] at 11p11.2 (nearest genes TTC17-HSD17B12)</td>
<td>0.08</td>
<td>-0.035</td>
<td>0.020</td>
<td>(8.06 \times 10^{-2})</td>
<td>17 606</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Discovery + replication (Stages 1 + 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs905938[C] at 1q22 (DCST2)</td>
<td>0.24</td>
<td>0.046</td>
<td>0.008</td>
<td>(2.46 \times 10^{-8})</td>
<td>40 235</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>rs12545524[G] at 8q22.1 (near GDF6)</td>
<td>0.13</td>
<td>0.042</td>
<td>0.011</td>
<td>(9.08 \times 10^{-5})</td>
<td>39 784</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>rs11037473[A] at 11p11.2 (nearest genes TTC17-HSD17B12)</td>
<td>0.07</td>
<td>-0.069</td>
<td>0.014</td>
<td>(1.49 \times 10^{-6})</td>
<td>39 865</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

SNPs markers are identified according to their standard rs numbers (NCBI build 36). Independent novel SNPs with a strong suggestive effect in the discovery analysis on birth length are shown \((P < 1 \times 10^{-6})\). SNPs in loci that are known to be associated with adult height were excluded for replication efforts (adult height loci: \(LCORL\), \(PTCH1\), \(GPR126\) and \(HMG2\)). MAF, minor allele frequency; SE, standard error. \(P\) values are obtained from linear regression of each SNP against standardized birth length adjusted for sex and gestational age. We included both GWA and metabochip cohorts in our discovery analysis, rs905938 is on the metabochip, and rs12545524 and rs11037473 are not, this explains the differences in numbers \((n)\). Derived inconsistency statistic \(I^2\) and HetP values reflect heterogeneity across discovery studies with the use of Cochran’s \(Q\) tests.
Generation R Study (N = 5756) (11), infant length at 1 year of age (range 6–18 months; N = 28 228) in the Early Growth Genetics (EGG) consortium (12), and adult height in the Genetic Investigation of Anthropometric Traits (GIANT) consortium (127 513) (5). Rs905938[C] was not associated with birth length variation. For both traits, we used independent SNPs (Supplementary Material, Table S7). We identified genome-wide significant associations at 11 genetic loci (Supplementary Material, Figs S3 and S4, QQ- and Manhattan plot), which all are known to be associated with adult height (Table 3, SNPs in or near SF3B4, LCORL, SPAG17, C6orf173, PTCH1, GDF5, ZNF51, HHIP, ACAN, HLA locus and HMGAL2) (5,13). In addition, we found that variants in 58 of the adult height loci were associated with infant length at an FDR of 5% (Supplementary Material, Table S8; Fig. 4, QQ-plot of 180 SNPs and infant length). Next, we tested in the Generation R Study (N = 2385) how much of the phenotypic variance in infant length was explained by the score composed of height-increasing-alleles. Variants from the 180 known adult height loci together explained 2.95% of the variance in infant length (P = 3.10 × 10⁻¹⁷, Fig. 5).

**DEPICT analysis of birth and infant length**

Finally, we used a pathway analysis tool called DEPICT (Pers et al., unpublished data) to prioritize genes at associated regions, search for reconstituted gene sets that were enriched in genes near associated variants, and identify tissue and cell types in which genes from loci associated with birth and infant length were highly expressed (full details in Materials and Methods). For both traits, we used independent SNPs (r² < 0.05) associated at P < 1 × 10⁻⁵, from 21 birth length and 44 infant length loci. There were no pathways significantly overrepresented in the birth length results. In contrast, for infant length DEPICT significantly prioritized nine genes which were overrepresented (FDR < 5%, Supplementary Material, Table S9), including three known Mendelian human stature genes (ACAN, GDF5 and PTCH1) as well as several relevant reconstituted genes.

Table 2  Associations of rs905938[C] in DCST2 related to birth length with ‘fetal growth’ measures, infant length and adult height

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generation R: fetal growth (N = 5756)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crown-rump length (n = 1126)</td>
<td>0.003</td>
<td>0.045</td>
<td>0.952</td>
</tr>
<tr>
<td>Second trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur length (n = 5361)</td>
<td>−0.035</td>
<td>0.023</td>
<td>0.129</td>
</tr>
<tr>
<td>Third trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur length (n = 5532)</td>
<td>−0.015</td>
<td>0.022</td>
<td>0.490</td>
</tr>
<tr>
<td>EGG: infant length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant length at 1 year of age (N = 28 228)</td>
<td>0.035</td>
<td>0.010</td>
<td>5.54 × 10⁻⁴</td>
</tr>
<tr>
<td>GIANT: adult height</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult height (N = 127 513)</td>
<td>0.024</td>
<td>0.006</td>
<td>1.45 × 10⁻⁵</td>
</tr>
</tbody>
</table>

rs905938 C-allele with a genome-wide significant effect on birth length is shown (P < 5 × 10⁻⁵) in relation to ‘fetal growth’ measures, infant length and adult height. SE, standard error. β reflects difference in standard deviation scores per minor allele.

**Known adult height loci in relation to birth and infant length**

We also explored whether common genetic variants known to be associated with adult height (5) influenced birth length variation. We found that 17 out of 180 known adult height loci were associated with birth length (FDR < 5%, Supplementary Material, Table S6; Fig. 4, QQ-plot of 180 SNPs and birth length). We then calculated a height-increasing-alleles score of the 180 known height loci (5) to predict birth length in the Generation R Study (N = 2085; Fig. 5). The score composed of variants associated with adult height explained 0.13% of the variance in birth length (P = 0.1), in contrast to the ~10% of the phenotypic variation in adult height reported in the original manuscript (5).

To evaluate whether different common genetic variants influenced both birth and infant length, we tested 2 193 675 million SNPs for association with infant length in almost the same set of samples used for the analysis of birth length (19 studies, N = 28 238; Supplementary Material, Table S7). We identified genome-wide significant associations at 11 genetic loci (Supplementary Material, Figs S3 and S4, QQ- and Manhattan plot), which all are known to be associated with adult height (Table 3, SNPs in or near SF3B4, LCORL, SPAG17, C6orf173, PTCH1, GDF5, ZNF51, HHIP, ACAN, HLA locus and HMGAL2) (5,13). In addition, we found that variants in 58 of the adult height loci were associated with infant length at an FDR of 5% (Supplementary Material, Table S8; Fig. 4, QQ-plot of 180 SNPs and infant length). Next, we tested in the Generation R Study (N = 2385) how much of the phenotypic variance in infant length was explained by the score composed of height-increasing-alleles. Variants from the 180 known adult height loci together explained 2.95% of the variance in infant length (P = 3.10 × 10⁻¹⁷, Fig. 5).

**Figure 3** Forest plot of the associations between rs905938[C] and birth length. The ‘black diamond’ indicates the overall effect size and the confidence interval of the 31 studies.

- ALSPAC
- BAMSE
- CHOP
- COPSAC–2000
- COPSAC–Registry
- DNBC
- Generation R
- HAPO
- HBCS
- INMA
- LEIPZIG
- LISA
- MAAS
- MOBA
- NFBC66
- NFBC86
- PANIC
- PIAMA1
- PIAMA2
- RAINE
- STRIP
- TEENAGE
- BBc
- DIPP
- EPSOCh
- Generation R – Moroccan
- Generation R – Surinamese
- Generation R – Turkish
- INMA
- ScorM
- SWS

| Additive effect of rs905938[C] | −0.40 | −0.30 | −0.20 | −0.10 | −0.01 | 0.00 | 0.01 | 0.02 | 0.03 | 0.04 | 0.05 | 0.06 | 0.07 | 0.08 | 0.09 | 0.10 | 0.11 | 0.12 | 0.13 | 0.14 | 0.15 | 0.16 | 0.17 | 0.18 | 0.19 | 0.20 | 0.21 | 0.22 | 0.23 | 0.24 | 0.25 |
|------------------------------|-------|-------|-------|-------|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|

Table 2  Associations of rs905938[C] in DCST2 related to birth length with ‘fetal growth’ measures, infant length and adult height
DISCUSSION

In the present study we identified one previously unknown locus (rs905938 in DCST2 at 1q22) to be associated with birth length at a genome-wide significant level. This common genetic variant was also associated with infant length and adult height.

It was not possible to identify eQTLs for transcripts of DCST2 in the MRCA and MRCE databases, as there were no probes available (9). Also, there was no significant eQTL of DCST2 in immortalized LCLs (10). However, DCST2 is a DC-STAMP-like protein family member and DC-STAMP is an important regulator of osteoclast cell-fusion in bone homeostasis (14–16). The transcripts of PBXIP1, GBA and ADAM15 were in weak LD with our lead SNP rs905938. The PBXIP1 protein is known to regulate estrogen receptor functions (17). Mutations in the GBA gene cause Gaucher disease, and strong associations with Parkinson’s disease and dementia with Lewy bodies have been described (18–21). ADAM15 is prominently expressed in osteoclasts and to a lesser extent in osteoblasts (22). A study in mice showed that ADAM15 is required for normal skeletal homeostasis and that its absence causes increased nuclear translocation of β-catenin in osteoclasts leading to increased osteoblast proliferation and function, which results in higher trabecular and cortical bone mass (23). The 1q22 locus is a complex region harboring multiple interesting genes that could affect birth length. We emphasize that we could not specifically pinpoint the causal gene(s) as our lead SNP (rs905938) was not in perfect LD with our cis eQTL SNPs.

Although there is some overlap between adult height loci and birth length, which is illustrated by 17 shared loci, the genetic architecture of adult height seems more similar to the genetic architecture of infant length than birth length [58 shared loci for infant length, based on conservative statistical method (FDR)]. One point of consideration for the interpretation of our findings is the potential of measurement error for birth length (24). This may lead to less power to detect novel genetic variants as standard errors of SNPs could be increased. The estimate of the risk-allele score slope of Figure 5 is not influenced by measurement error and the differences in the slopes suggest that birth and infant length are influenced by distinct genetic variants. We found that the SNP effects for birth length of 137 of the 180 established height loci were in the same direction as reported in the GIANT paper (5) (Supplementary Material, Table S6; probability of success = 0.761, P = 6.25 × 10^{-13}). One hundred sixty-two of the 180 loci were in the same direction (Supplementary Material, Table S8; probability of success = 0.990, P = 2.20 × 10^{-16}).

Four SNPs associated with birth length (P < 1 × 10^{-5}) are in or near loci known to be associated with birth weight (LCORL, HMGA2, ADCY5 and ADRB1). LCORL is associated with birth weight, birth length, infant length and adult height, but we could not find an obvious link between the gene and adult-onset diseases. HMGA2 is associated with aortic root size (25), type 2 diabetes (26), and many other traits like tooth development, head circumference and brain structure (12,27). ADCY5 is also associated with type 2 diabetes and ADRB1 with adult blood pressure (2,3). These findings highlight genetic links between fetal growth and metabolism (2,3,26). As we found overlap between genetic variants of birth weight and birth length, we looked-up the effect of rs905938 in DCST2 on birth weight in a previous EGG study (3). Rs905938 was associated with birth weight, but weaker as compared with birth length (β = 0.035 SDS, SE = 0.010, P = 2.35 × 10^{-4}, N = 26 558).

In conclusion, in the present study we identified one novel locus (rs905938 in DCST2 at 1q22) associated with birth length at a genome-wide significant level. This common
genetic variant was also associated with infant length and adult height, with decreasing magnitude of the associations in later life (0.046 SDS for birth length, 0.035 SDS for infant length and 0.024 SDS for adult height). To our knowledge, no phenotype has been previously associated with the DCST2 gene and while the gene is expressed in osteoclasts, its function should be further studied.

MATERIALS AND METHODS

Stage 1: discovery genome-wide association analyses of birth length

We combined 21 population-based studies with GWA or Metabochip data and birth length available (total \( N = 28,459 \) individuals). One of our discovery cohorts had two independent sub-samples within their study leading to a total of 22 independent GWA/Metabochip sub-samples for our analysis: one sub-sample from the Avon Longitudinal Study of Parents and Children (ALSPAC, GWA, \( n = 4816 \)); Children, Allergy, Milieu, Stockholm, Epidemiology [Swedish] (BAMSE, GWA, \( n = 423 \)); Children’s Hospital Of Philadelphia (CHOP, GWA, \( n = 432 \)); Copenhagen Study on Asthma in Childhood 2000 (COPSAC-2000, GWA, \( n = 348 \)); Copenhagen Study on Asthma in Childhood Registry (COPSAC-Registry, GWA, \( n = 1111 \)); Danish National Birth Cohort (DNBC, GWA, \( n = 932 \)); Generation R Study (Generation R, GWA, \( n = 2085 \)); Hyperglycemia and Adverse Pregnancy Outcomes study (HAPO, GWA, \( n = 1325 \)); Helsinki Birth Cohort Study (HBCS, GWA, \( n = 1572 \)); Infancia y Medio Ambiente (INMA, GWA, \( n = 848 \)); Leipzig Childhood Obesity cohort (LEIPZIG, Metabochip, \( n = 607 \)); Lifestyle Immune System Allergy study (LISA, GWA, \( n = 552 \));
of between-study heterogeneity of the effect sizes. The meta-analysis results were obtained for a total of 2,201,971 SNPs. SNPs that crossed the threshold of $P \leq 1 \times 10^{-6}$ were considered to represent strong suggestive evidence of association with birth length. SNPs that were already known to be associated with adult height were excluded for the replication analysis (5). The explained variance of the top SNPs were calculated in one of the largest cohorts, the Generation R Study ($n = 2085$).

**Stage 2: replication analysis of top birth length SNPs**

In the discovery phase, we found seven independent SNPs with strong suggestive evidence of association ($P < 1 \times 10^{-6}$) with birth length. Four SNPs were already known to be associated with adult height (5). These SNPs were excluded for follow-up analyses. The three remaining novel SNPs were followed-up in replication studies. We included both GWA and Metabochip studies in our discovery analysis. Rs905938 was on our Metabochips, and rs12545524 and rs11037473 were not. This results in differences in numbers for our top SNPs in the discovery and replication analyses. Rs905938 was taken forward in 9 independent replication studies ($N = 11,995$), rs12545524 and rs11037473 in 13 independent replication studies including the four discovery Metabochip studies ($N = 17,679$). Details of the replication studies are presented in Supplementary Material, Table S2. Within the replication studies, we analyzed the association between number of alleles and standardized birth length. Combined effect estimates and heterogeneity between cohorts was calculated using fixed effects meta-analyses in R Version 2.8.1 (The R foundation for Statistical Computing, library rmeta). Top SNPs that crossed the significant threshold of $P$-replication $\leq 0.05$ and the widely accepted genome-wide significance threshold of $P \leq 5 \times 10^{-8}$ for all studies combined were considered to represent robust evidence of association with birth length. The institutional review boards for human studies approved the protocols and written consent was obtained from the participating subjects or their caregivers if required by the institutional review board.

**DEPICT analysis**

We used the novel Data-driven Expression-Prioritized Integration for Complex Traits (DEPICT) method (Pers et al., unpublished data). DEPICT is designed to systematically identify the most likely causal gene at a given locus, gene sets that are enriched in genetic associations, and tissues and cell types in which genes from associated loci are highly expressed. First, DEPICT assigns genes to associated SNPs using LD $r^2 > 0.5$ distance to define locus boundaries, merges overlapping loci and discards loci mapping within the extended major histocompatibility complex region (chromosome 6, base pairs 25 000–35 000). Next, the DEPICT method prioritizes genes within a given associated locus based on the genes’ functional similarity to genes from other associated loci. Genes that are highly similar to genes from other loci obtain low prioritization $P$ values, and simulated GWAS results are used to adjust for gene length bias as well as other potential confounders. There can be several prioritized genes in a given locus. Next, DEPICT conducts gene set enrichment analysis by testing whether genes in associated loci enrich for reconstituted versions of known pathways, gene
sets as well as protein complexes. Leveraging the guilt by association hypothesis that genes co-expressing with genes from a given gene set are likely to be part of that gene set (see Cvejic et al. (35), for details), the gene set reconstitution is accomplished by identifying genes that were co-expressed with genes in a given gene set based on a panel of 77,840 gene expression microarrays. Gene sets from the following repositories were reconstituted: 5984 protein complexes that were derived from 169,810 high-confidence experimentally derived protein–protein interactions (36); 2473 phenotypic gene sets derived from 211,882 gene–phenotype pairs from the Mouse Genetics Initiative (37); 737 Reactome database pathways (38); 184 KEGG database pathways (39); and 5083 Gene Ontology database terms (40). Finally, DEPICT conducts tissue and cell type enrichment analysis, by testing whether genes in associated loci are highly expressed in any of 209 Medical Subject Headings annotations of 37,427 microarrays from the Affymetrix U133 Plus 2.0 Array platform (see Wood et al. (41) and Geller et al. (42) for previous applications of DEPICT). In this work, 21 autosomal SNPs for birth length and 44 autosomal SNPs for infant length were used as input to DEPICT resulting in 21 and 41 non-overlapping loci, respectively, that covered a total of 34 genes and 83 genes, respectively. The gene prioritization, gene set enrichment and tissue/cell type enrichment analyses were run using the default settings in DEPICT.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG online.

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