

# New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism

**Birth weight within the normal range is associated with a variety of adult-onset diseases, but the mechanisms behind these associations are poorly understood<sup>1</sup>. Previous genome-wide association studies of birth weight identified a variant in the *ADCY5* gene associated both with birth weight and type 2 diabetes and a second variant, near *CCNLI*, with no obvious link to adult traits<sup>2</sup>. In an expanded genome-wide association meta-analysis and follow-up study of birth weight (of up to 69,308 individuals of European descent from 43 studies), we have now extended the number of loci associated at genome-wide significance to 7, accounting for a similar proportion of variance as maternal smoking. Five of the loci are known to be associated with other phenotypes: *ADCY5* and *CDKAL1* with type 2 diabetes, *ADRB1* with adult blood pressure and *HMGA2* and *LCORL* with adult height. Our findings highlight genetic links between fetal growth and postnatal growth and metabolism.**

To understand further the genetic factors involved in fetal growth and its association with adult diseases, we performed an expanded genome-wide association study (GWAS) of birth weight in up to 26,836 individuals of European ancestry from 18 studies (stage 1; Online Methods, **Supplementary Figs. 1–3** and **Supplementary Table 1**). After follow-up analyses of 21 of the most strongly associated independent SNPs (associated at  $P < 1 \times 10^{-5}$ ) in additional European samples (**Supplementary Tables 2** and **3**), we identified new associations with birth weight at 4 loci ( $P < 5 \times 10^{-8}$ ) and confirmed 3 previously reported associations<sup>2–4</sup> (rs900400 near *CCNLI*,  $P = 3.6 \times 10^{-38}$ ; rs9883204 in *ADCY5*,  $P = 5.5 \times 10^{-20}$ ; rs6931514 in *CDKAL1*,  $P = 1.5 \times 10^{-18}$ ) in a joint meta-analysis of up to 69,308 individuals (**Fig. 1**, **Table 1** and **Supplementary Fig. 4**). The index SNPs at the four newly associated loci were rs1042725 in *HMGA2* ( $P = 1.4 \times 10^{-19}$ ), rs724577 in *LCORL* ( $P = 4.6 \times 10^{-11}$ ), rs1801253 in *ADRB1* ( $P = 3.6 \times 10^{-9}$ ) and rs4432842 on chromosome 5q11.2 ( $P = 4.6 \times 10^{-8}$ ). The effect size estimates for these SNPs ranged from 0.034 s.d. to 0.072 s.d. per allele and were approximately equal to changes in birth weight of 16–35 g (**Table 1**). These estimates did not change materially in sensitivity analyses excluding studies with self- or parentally reported birth weight data and those without a measure of gestational age (**Supplementary Table 4**).

Throughout the cellular processes of gametogenesis and fertilization, fetal genotype is correlated with maternal genotype ( $r \approx 0.5$ ).

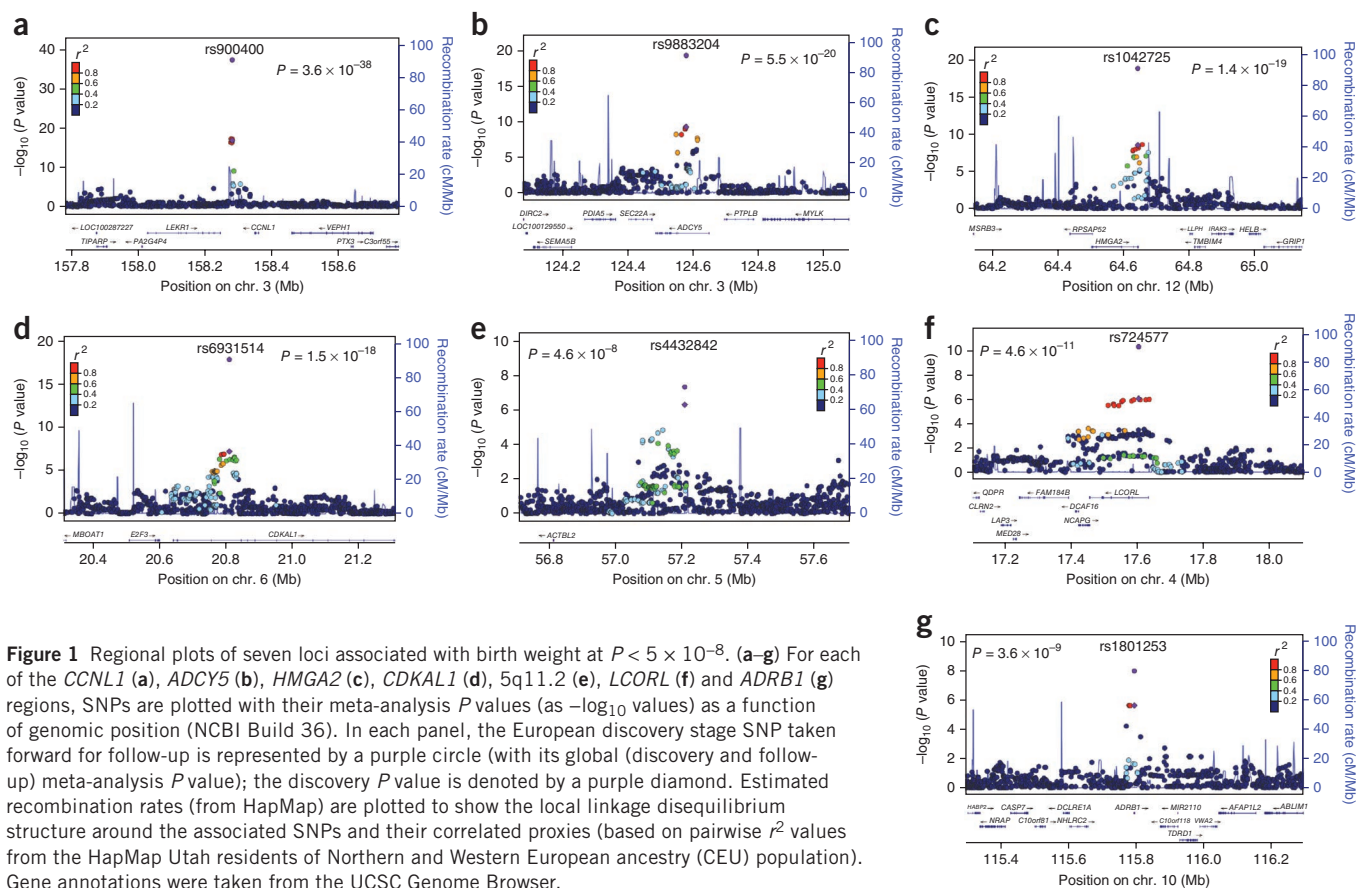
Using up to 11,307 mother-child pairs from a subset of studies, we found no evidence that the 7 associations we observed at  $P < 5 \times 10^{-8}$  were driven by the maternal rather than the fetal genotype (likelihood-ratio test  $P > 0.05$ ; **Table 1**).

For five of the seven confirmed associations with birth weight, correspondence with GWAS findings for adult traits (type 2 diabetes, blood pressure or height) provided clues to the biological pathways involved. Two SNPs represented the same signals as known loci for type 2 diabetes: *ADCY5* (previously reported)<sup>2</sup> and *CDKAL1* (previously examined in smaller candidate gene studies of birth weight)<sup>3–5</sup>. We observed similar *z*-score effect size estimates of the associations between each of these loci and ponderal index (calculated as weight/length<sup>3</sup>, indicating neonatal leanness), length at birth and head circumference (**Table 1**), suggesting a general effect on fetal growth. At both loci, the birth weight-lowering allele was associated with greater type 2 diabetes risk<sup>2–4</sup>. This observation is consistent with the fetal insulin hypothesis<sup>6</sup>, which proposes that common genetic variation influencing insulin secretion or action, both in prenatal development and adult life, could partly explain epidemiological correlations between lower birth weight and type 2 diabetes. The type 2 diabetes risk allele at *ADCY5* is associated with a number of features suggesting impaired insulin secretion, including higher glucose concentration after fasting and 2 h after an oral glucose challenge<sup>7,8</sup>; lower 2-h insulin concentration, adjusted for 2-h glucose concentration<sup>8</sup>; higher fasting proinsulin (relative to mature insulin) concentration<sup>9</sup>; and lower homeostatic model assessment (HOMA)-derived index of  $\beta$ -cell function HOMA-B<sup>7</sup> (**Supplementary Table 5**). The risk allele at *CDKAL1* was strongly associated with reduced insulin secretion in studies of adults<sup>10</sup>. Given the key role of fetal insulin in prenatal growth, we hypothesize that the *ADCY5* and *CDKAL1* risk alleles reduce fetal insulin concentration, which mediates the associations with birth weight.

To investigate whether type 2 diabetes susceptibility loci other than those in *ADCY5* and *CDKAL1* influence fetal growth, we tested the associations between 47 additional published loci for type 2 diabetes and birth weight in our stage 1 meta-analysis. We observed more associations with birth weight than expected by chance (**Fig. 2a**), with seven associations at  $P < 0.05$ , of which four achieved association at  $P < 0.01$  (*MTNR1B*, rs1387153; *KCNQ1*, rs231362; *HHEX-IDE*, rs5015480; *GCK*, rs4607517), including an association in *GCK* at  $P = 1 \times 10^{-4}$ . Meta-analysis of the *HHEX-IDE* result with previously

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**Figure 1** Regional plots of seven loci associated with birth weight at  $P < 5 \times 10^{-8}$ . (**a–g**) For each of the *CCNL1* (**a**), *ADCY5* (**b**), *HMG2* (**c**), *CDK1* (**d**), 5q11.2 (**e**), *LCORL* (**f**) and *ADRB1* (**g**) regions, SNPs are plotted with their meta-analysis  $P$  values (as  $-\log_{10}$  values) as a function of genomic position (NCBI Build 36). In each panel, the European discovery stage SNP taken forward for follow-up is represented by a purple circle (with its global (discovery and follow-up) meta-analysis  $P$  value); the discovery  $P$  value is denoted by a purple diamond. Estimated recombination rates (from HapMap) are plotted to show the local linkage disequilibrium structure around the associated SNPs and their correlated proxies (based on pairwise  $r^2$  values from the HapMap Utah residents of Northern and Western European ancestry (CEU) population). Gene annotations were taken from the UCSC Genome Browser.

published data (total  $n = 51,583$  individuals) strengthened the evidence of association ( $P = 6.9 \times 10^{-7}$ ; **Supplementary Table 6**). The type 2 diabetes risk alleles at *HHEX-IDE* and *KCNQ1* show similar effects to *ADCY5* and *CDK1* in being associated with lower birth weight, providing additional support for the fetal insulin hypothesis, although the associations can only explain a small fraction of the epidemiological association.

In contrast, the type 2 diabetes risk alleles at *GCK* and *MTNR1B* were associated with higher birth weight (**Fig. 2a**). Higher maternal glucose levels are associated with higher offspring birth weight<sup>11</sup>, and both the *GCK* and *MTNR1B* loci influence fasting glucose concentration throughout the normal physiological range<sup>7</sup>. Consistent with these observations and with previous studies of the *GCK* variant<sup>12</sup>, the effect size estimates we observed for the SNPs in *GCK* and *MTNR1B* were lower after adjustment for maternal genotype (**Supplementary Fig. 5**). Well-powered studies of mothers and offspring will be required to formally test the association between maternal genotype and birth weight at these loci. The lack of a fetal association at rs4607517 in *GCK* contrasts with the strong birth weight–lowering effects of rare heterozygous fetal *GCK* mutations<sup>13</sup> and suggests that the common variant in *GCK* does not influence insulin secretion until after birth.

The association with birth weight at rs1801253 in *ADRB1* (encoding a p.Arg389Gly alteration) links prenatal growth with blood pressure in adulthood because the same SNP is strongly associated with both systolic and diastolic blood pressure ( $P < 5 \times 10^{-8}$ )<sup>14</sup>. Epidemiological associations between birth weight and systolic blood pressure (SBP) constitute some of the strongest evidence supporting the fetal origins of adult disease<sup>15</sup>. Most studies report a linear inverse association throughout the birth weight distribution, whereby lower birth weight

is associated with higher adult SBP. There is also evidence that birth weights at the high end of the distribution are associated with higher SBP<sup>16</sup>. On the basis of results from the majority of studies, we might therefore expect a fetal SBP-raising allele to be associated with lower birth weight; however, the birth weight–lowering allele at rs1801253 (encoding Gly389) was associated with lower blood pressure in later life. We observed similar effect size estimates for associations between *ADRB1* and various birth measures (**Table 1**), suggesting a general effect on fetal growth. We tested for associations between birth weight and 29 additional blood pressure–associated loci<sup>17</sup> in our stage 1 meta-analysis. Although we did not observe strong evidence of deviation from the null distribution of no association with birth weight (**Fig. 2b**), associations between the SBP-raising allele and lower birth weight achieved  $P < 0.01$  at rs13139571 in *GUCY1A3-GUCY1B3* ( $P = 0.0008$ ) and rs11191548 in *CYP17A1-NT5C2* ( $P = 0.009$ ). These associations were little altered by adjustment for maternal genotype (**Fig. 2b** and **Supplementary Table 7**).

The associations with birth weight at the *HMG2* and *LCORL* loci link prenatal growth with postnatal stature. At both loci, the birth weight–lowering allele was also associated with lower adult height, and associations were consistent with a primary effect on length at birth (**Table 1**). The SNP in *HMG2* was also strongly associated with head circumference at birth and is known to associate with head circumference in infancy and intracranial volume in adulthood<sup>18,19</sup>, suggesting a general effect on growth. Variation at *LCORL* has also been associated with peak height velocity in infancy<sup>20</sup>, indicating an effect on growth in childhood. When testing 178 additional published loci associated with height<sup>21</sup>, we observed more associations with birth weight than expected by chance (**Fig. 2c**), indicating that

many adult height-associated loci influence prenatal growth. Of all 180 loci, 132 showed the same direction of effect for birth weight as for height (binomial sign test  $P = 3 \times 10^{-10}$ ), although there was not

a strong correlation between effect sizes for adult height and birth weight (Fig. 2c). We did not observe any evidence that these associations were driven by maternal genotype (Supplementary Table 8).

**Table 1 Associations between seven loci for birth weight and various anthropometric measures taken at birth from a joint meta-analysis of up to 69,308 individuals**

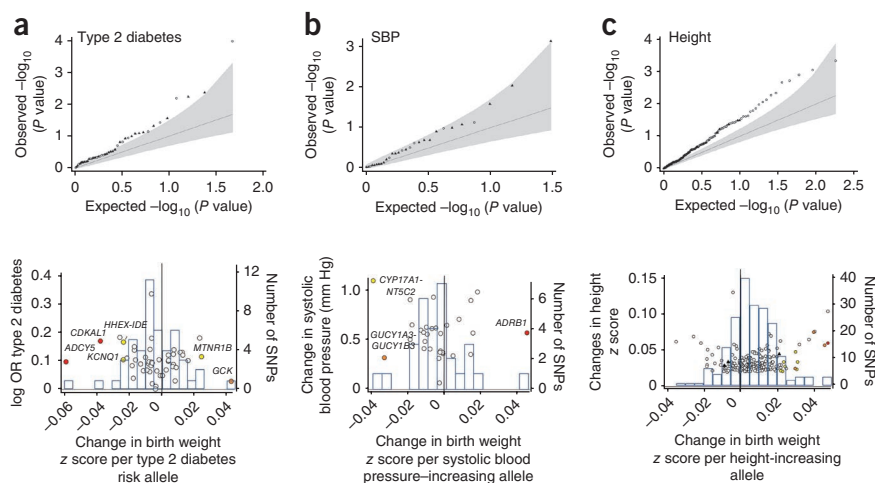
| Locus (index SNP, effect allele/other allele) |  | Birth weight (from combined meta-analysis of European discovery and follow-up studies) | Birth weight, adjusted for maternal genotype | Birth weight, adjusted for birth length | Birth length          | Birth head circumference | Ponderal index (weight/length <sup>3</sup> ) |
|---|--|--|--|---|-----------------------|--------------------------|--|
| <i>CCNL1</i> (rs900400, C/T)                  | <i>n</i>                               | 61,142   | 11,130                                       | 36,209                                  | 35,953                | 23,000                   | 35,708                                       |
|   | $\beta$ (s.e.)                         | -0.072 (0.006)<br>(-35 g)  | -0.108 (0.014)                               | -0.067 (0.005)                          | -0.025 (0.007)        | -0.033 (0.009)           | -0.090 (0.008)                               |
|   | <i>P</i> value                         | $3.6 \times 10^{-38}$  | $7.5 \times 10^{-14}$                        | $1.2 \times 10^{-35}$                   | $6.7 \times 10^{-4}$  | $2.3 \times 10^{-4}$     | $9.5 \times 10^{-28}$                        |
|   | Unadjusted $\beta$ (s.e.) <sup>a</sup> | -  | -0.109 (0.013)                               | -0.085 (0.008)                          | -                     | -                        | -  |
|   | Unadjusted <i>P</i> value <sup>a</sup> | -  | $7.5 \times 10^{-18}$                        | $8.81 \times 10^{-29}$                  | -                     | -                        | -  |
| <i>ADCY5</i> (rs9883204, C/T)                 | <i>n</i>                               | 61,509   | 11,307                                       | 36,015                                  | 36,084                | 23,184                   | 35,836                                       |
|   | $\beta$ (s.e.)                         | -0.059 (0.006)<br>(-29 g)  | -0.077 (0.016)                               | -0.032 (0.006)                          | -0.035 (0.009)        | -0.031 (0.010)           | -0.034 (0.010)                               |
|   | <i>P</i> value                         | $5.5 \times 10^{-20}$  | $1.5 \times 10^{-6}$                         | $5.8 \times 10^{-7}$                    | $5.0 \times 10^{-5}$  | 0.0027                   | $2.9 \times 10^{-4}$                         |
|   | Unadjusted $\beta$ (s.e.) <sup>a</sup> | -  | -0.064 (0.014)                               | -0.058 (0.009)                          | -                     | -                        | -  |
|   | Unadjusted <i>P</i> value <sup>a</sup> | -  | $5.7 \times 10^{-6}$                         | $7.4 \times 10^{-11}$                   | -                     | -                        | -  |
| <i>HMGA2</i> (rs1042725, T/C)                 | <i>n</i>                               | 68,655   | 9,649  | 35,961                                  | 36,030                | 23,277                   | 35,781                                       |
|   | $\beta$ (s.e.)                         | -0.047 (0.005)<br>(-23 g)  | -0.025 (0.015)                               | -0.018 (0.005)                          | -0.046 (0.007)        | -0.039 (0.009)           | -0.016 (0.008)                               |
|   | <i>P</i> value                         | $1.4 \times 10^{-19}$  | 0.096  | $5.5 \times 10^{-4}$                    | $1.7 \times 10^{-10}$ | $5.4 \times 10^{-6}$     | 0.049  |
|   | Unadjusted $\beta$ (s.e.) <sup>a</sup> | -  | -0.029 (0.013)                               | -0.053 (0.007)                          | -                     | -                        | -  |
|   | Unadjusted <i>P</i> value <sup>a</sup> | -  | 0.027  | $1.2 \times 10^{-12}$                   | -                     | -                        | -  |
| <i>CDKAL1</i> (rs6931514, G/A)                | <i>n</i>                               | 68,822   | 9,415  | 35,789                                  | 35,861                | 22,894                   | 35,614                                       |
|   | $\beta$ (s.e.)                         | -0.050 (0.006)<br>(-24 g)  | -0.056 (0.017)                               | -0.026 (0.006)                          | -0.035 (0.008)        | -0.019 (0.010)           | -0.034 (0.009)                               |
|   | <i>P</i> value                         | $1.5 \times 10^{-18}$  | 0.001  | $9.4 \times 10^{-6}$                    | $1.7 \times 10^{-5}$  | 0.042                    | $8.6 \times 10^{-5}$                         |
|   | Unadjusted $\beta$ (s.e.) <sup>a</sup> | -  | -0.045 (0.015)                               | -0.051 (0.008)                          | -                     | -                        | -  |
|   | Unadjusted <i>P</i> value <sup>a</sup> | -  | 0.003  | $6.7 \times 10^{-10}$                   | -                     | -                        | -  |
| 5q11.2 (rs4432842, C/T)                       | <i>n</i>                               | 53,619   | 6,136  | 28,465                                  | 28,532                | 20,222                   | 28,290                                       |
|   | $\beta$ (s.e.)                         | -0.034 (0.006)<br>(-16 g)  | -0.040 (0.021)                               | -0.018 (0.006)                          | -0.023 (0.008)        | -0.030 (0.010)           | -0.023 (0.009)                               |
|   | <i>P</i> value                         | $4.6 \times 10^{-8}$   | 0.056  | 0.003                                   | 0.006                 | 0.003                    | 0.010  |
|   | Unadjusted $\beta$ (s.e.) <sup>a</sup> | -  | -0.043 (0.018)                               | -0.034 (0.008)                          | -                     | -                        | -  |
|   | Unadjusted <i>P</i> value <sup>a</sup> | -  | 0.018  | $4.6 \times 10^{-5}$                    | -                     | -                        | -  |
| <i>LCORL</i> (rs724577, C/A)                  | <i>n</i>                               | 55,877   | 8,733  | 29,956                                  | 30,027                | 21,065                   | 29,781                                       |
|   | $\beta$ (s.e.)                         | -0.042 (0.006)<br>(-20 g)  | -0.078 (0.018)                               | -0.010 (0.006)                          | -0.047 (0.009)        | -0.027 (0.010)           | -0.011 (0.010)                               |
|   | <i>P</i> value                         | $4.6 \times 10^{-11}$  | $2.0 \times 10^{-5}$                         | 0.13                                    | $8.3 \times 10^{-8}$  | 0.008                    | 0.258  |
|   | Unadjusted $\beta$ (s.e.) <sup>a</sup> | -  | -0.071 (0.016)                               | -0.042 (0.009)                          | -                     | -                        | -  |
|   | Unadjusted <i>P</i> value <sup>a</sup> | -  | $8.4 \times 10^{-6}$                         | $3.8 \times 10^{-6}$                    | -                     | -                        | -  |
| <i>ADRB1</i> (rs1801253, G/C)                 | <i>n</i>                               | 49,660   | 6,231  | 29,695                                  | 29,762                | 17,833                   | 29,519                                       |
|   | $\beta$ (s.e.)                         | -0.041 (0.007)<br>(-20 g)  | -0.029 (0.023)                               | -0.021 (0.006)                          | -0.027 (0.009)        | -0.033 (0.011)           | -0.035 (0.009)                               |
|   | <i>P</i> value                         | $3.6 \times 10^{-9}$   | 0.18   | 0.001                                   | 0.002                 | 0.004                    | $2.3 \times 10^{-4}$                         |
|   | Unadjusted $\beta$ (s.e.) <sup>a</sup> | -  | -0.036 (0.019)                               | -0.045 (0.009)                          | -                     | -                        | -  |
|   | Unadjusted <i>P</i> value <sup>a</sup> | -  | 0.058  | $4.3 \times 10^{-7}$                    | -                     | -                        | -  |

Results are from inverse-variance fixed-effects meta-analysis of all available study samples of European ancestry. The effect allele for each SNP is labeled on the positive strand according to HapMap. The  $\beta$  value is the change in z score per birth weight-lowering allele from linear regression, adjusted for sex and gestational age (where available), assuming an additive genetic model. To obtain the equivalent birth weight effect in grams, we multiplied by 484 g, the median birth weight standard deviation of European studies<sup>2</sup>. There was little detectable heterogeneity between studies (all  $P > 0.01$ ).

<sup>a</sup>Results are unadjusted for maternal genotype or birth length, only in samples where data for maternal genotype or birth length were available (for direct comparison with the model that was adjusted for maternal genotype or birth length, respectively).

**Figure 2** Associations between birth weight and loci previously associated with adult traits.

(a–c) Associations between birth weight and known type 2 diabetes (a), SBP (b) and height (c) loci from the discovery meta-analysis of 26,836 individuals. Top, quantile-quantile plots. Black triangles (associated with lower birth weight) and circles (associated with higher birth weight) represent observed  $P$  values after removing the loci that achieved association at  $P < 5 \times 10^{-8}$  in the overall meta-analysis; the black line represents expected  $P$  values under the null. The gray area defines the approximate 95% confidence interval around the expected line. Bottom, the type 2 diabetes, SBP or height effect size (left y axes in a–c, respectively) taken from published meta-analyses<sup>14,17,21,22</sup> against the birth weight effect size (x axis), with a superimposed frequency histogram showing the number of SNPs in each category of birth weight effect size (right y axis). The odds ratios for type 2 diabetes were all obtained from the published DIAGRAM+ Consortium meta-analysis<sup>22</sup>, the largest available reference sample of European descent, and, although they did not necessarily reach genome-wide significance in that sample, all loci have shown associations with type 2 diabetes at  $P < 5 \times 10^{-8}$  (see Online Methods for details of published studies). Effect sizes are aligned to the type 2 diabetes risk allele or the SBP- or height-increasing allele. Colors indicate birth weight association  $P$  values: red,  $P < 5 \times 10^{-8}$ ; yellow,  $5 \times 10^{-8} \leq P < 0.001$ ; white,  $0.001 \leq P < 0.01$ ; orange,  $P > 0.01$ . The triangles in c represent SNPs known to be associated with age at menarche. There were more associations between height loci and higher birth weight than expected under the null and a slight excess of associations between loci for type 2 diabetes or SBP and lower birth weight (binomial sign test  $P = 0.02, 0.09$  and  $3 \times 10^{-10}$  in a–c, respectively).



The remaining two loci (near *CCN1* and on chromosome 5q11.2) are not known to be associated with any trait besides birth weight. The previously reported association near *CCN1* represents the strongest association with birth weight and showed a strong association with ponderal index but relatively weak associations with birth length and head circumference (Table 1), strengthening the evidence that this locus primarily acts by influencing non-skeletal growth. In a subset of seven studies with available postnatal data, the association had disappeared by 3 months of age (0.001 s.d. (95% confidence interval (CI)  $-0.030$  to  $0.032$ ) for the C allele at rs900400, relative to birth weight with  $-0.084$  s.d. (95% CI  $-0.106$  to  $-0.062$ ); Supplementary Fig. 6 and Supplementary Table 9), suggesting that the growth effects of the locus at *CCN1* are specifically intrauterine. Little is known about the birth weight-associated locus on chromosome 5q11.2: the nearest gene, *ACTBL2*, is approximately 400 kb away and has no obvious link with fetal growth. Associations at this locus are similar across the different anthropometric birth measures (Table 1), and there are no associations with adult metabolic or anthropometric traits in published studies (Supplementary Table 5).

We were interested to explore whether the same variants have any impact on birth weight in other ancestry groups. Using data from a range of non-European studies, including those of individuals of Middle Eastern, East and Southeast Asian and African origin (total  $n = 11,848$ ; Supplementary Table 10), we observed that the 7 SNPs together explained between 0.32% and 1.52% of the variance in birth weight, which was similar to that of the percentage explained in Europeans (0.76%; Supplementary Figs. 7 and 8 and Supplementary Table 11).

To conclude, we have identified four loci and confirmed three associated with birth weight, which explain a similar proportion of variance to that explained by maternal smoking exposure in pregnancy (Supplementary Fig. 9). The associations between five of the loci and adult traits (i) highlight biological pathways of relevance to the fetal origins of type 2 diabetes; (ii) reveal complexity, in that type 2 diabetes risk alleles can be associated with either higher or lower birth weight; (iii) illuminate a new genetic link between fetal growth and adult blood pressure and (iv) show substantial overlap between the genetics of prenatal growth and adult height.

**URLs.** HapMap, <http://hapmap.ncbi.nlm.nih.gov/>; PLINK, <http://pnuu.mgh.harvard.edu/~purcell/plink/>; SIMBioMS platform, <http://www.simbio.ms.org/>; SNAP, <http://www.broadinstitute.org/mpg/snap/>; LocusZoom, <http://csg.sph.umich.edu/locuszoom/>; binomial probability (sign) test, <http://vassarstats.net/binomialX.html>; Growth Analyser 3.0, <http://www.growthanalyser.org/>. The full association results of the stage 1 meta-analysis of discovery studies are available at <http://egg-consortium.org/>.

## METHODS

Methods and any associated references are available in the online version of the paper.

Note: Supplementary information is available in the online version of the paper.

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## ONLINE METHODS

**Stage 1 genome-wide association meta-analysis discovery studies, genotyping and imputation.** We combined 18 population-based European studies with birth weight and genome-wide association data available (total  $n = 26,836$  individuals), including 2 subsamples from the 1958 British Birth Cohort (B58C-WTCCC,  $n = 2,195$ ; B58C-T1DGC,  $n = 2,037$ ); the Avon Longitudinal Study of Parents And Children (ALSPAC (Discovery);  $n = 1,418$ ); the Children's Hospital of Philadelphia (CHOP,  $n = 7,380$ ); the Copenhagen Prospective Study on Asthma in Childhood (COPSAC-2000,  $n = 353$ ); the European Prospective Investigation of Cancer (EPIC,  $n = 1,478$ ); the Erasmus Rucphen Family (ERF) study ( $n = 325$ ); 2 subsamples from the Generation R study (Generation R (Discovery 1),  $n = 1,194$ ; Generation R (Discovery 2),  $n = 1,410$ ); the Helsinki Birth Cohort Study (HBCS,  $n = 1,566$ ); the Lifestyle-Immune System-Allergy (LISA) study ( $n = 387$ ); the Northern Finland 1966 Birth Cohort (NFBC1966,  $n = 4,333$ ); 2 subsamples of singleton births from the Netherlands Twin Register (NTR1,  $n = 414$ ; NTR2,  $n = 247$ ); the Orkney Complex Disease Study (ORCADES,  $n = 328$ ); the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study ( $n = 368$ ); the Raine study (RAINE,  $n = 1,105$ ); and the Sorbs study (SORBS,  $n = 298$ ).

Although no systematic phenotypic difference was seen between the subsamples of the 1958 British Birth Cohort, Generation R and the Netherlands Twin Register, these samples were analyzed separately because they were genotyped on different platforms and/or at different times.

Genotypes within each study were obtained using high-density SNP arrays and then imputed for up to  $\sim 2.7$  million HapMap SNPs (Phase 2, release 21/22). The basic characteristics, exclusions applied (for example, for individuals of non-European ancestry and related individuals), genotyping, quality control and imputation methods for each discovery sample are presented in **Supplementary Table 1**. The study protocol was approved by the local research ethics committee at each study. Written informed consent was obtained from all participants and/or their parent(s) or legal guardians.

**Statistical analysis within the discovery studies.** Birth weight (BW) was transformed to a  $z$  score ((BW value – mean BW)/s.d. BW) to facilitate comparison of the data across studies. Multiple births and, where information was available (**Supplementary Table 1**), preterm births (gestational age of  $< 37$  weeks) were excluded from all analyses. The association between each SNP and birth weight was assessed in each study sample using linear regression of the birth weight  $z$  score against genotype using an additive genetic model, with sex and, where available, gestational age as covariables. Because gestational age was not available in all studies, we later performed a sensitivity analysis, excluding the studies that did not have this covariable. The genome-wide association analysis was performed using SNPTEST<sup>23</sup>, mach2qt<sup>24</sup>, PLINK<sup>25</sup>, GenABEL<sup>26</sup> or ProbABEL<sup>27</sup>. Details of any additional corrections for study-specific population structure are given in **Supplementary Table 1**. Data annotation, exchange and storage were facilitated by the SIMBioMS platform<sup>28</sup>.

**Meta-analysis of discovery studies.** Before meta-analysis, SNPs with a minor allele frequency (MAF) of  $< 0.01$  and poorly imputed SNPs (proper\_info of  $\leq 0.4$  (SNPTEST) or  $r^2$  of  $\leq 0.3$  (mach2qt)) were filtered out. Genomic control<sup>29</sup> was applied to adjust the statistics generated within each cohort ( $\lambda$  values for individual studies are given in **Supplementary Table 1**). Inverse-variance fixed-effects meta-analyses were undertaken using the different software packages METAL (2009-10-10 release)<sup>30</sup> and GWAMA (version 2.0.6)<sup>31</sup> by two meta-analysts in parallel, and findings were compared to obtain identical results. Meta-analysis results were obtained for a total of 2,684,393 SNPs. We applied a second genomic control correction to adjust the overall meta-analysis statistics ( $\lambda = 1.051$ ) before selecting 21 SNPs for follow-up that surpassed a  $P$ -value threshold of  $P < 1 \times 10^{-5}$ . This additional genomic control correction was, however, only applied for the purpose of choosing the arbitrary significance threshold; we report here stage 1  $P$  values after only the first genomic control correction (**Supplementary Table 2**), as a second genomic control correction is generally considered to be overconservative<sup>32</sup>. We additionally selected rs6537307 ( $P = 4.3 \times 10^{-5}$ ), which is in linkage disequilibrium with a known height-associated variant in *HHIP* (HapMap  $r^2 = 0.58$  with rs6854783)<sup>33</sup>. Of the 22 selected SNPs, rs1004059 at *SYNP02L* ( $P = 2.3 \times 10^{-6}$ ) had data available in only 8 studies because its MAF was close to 0.01.

After obtaining data for this SNP from all available stage 1 studies, we observed a meta-analysis  $P$  value of  $6 \times 10^{-5}$  and therefore did not consider it further.

**Stage 2 follow-up of lead signals in European studies.** Twenty-one SNPs selected from the discovery meta-analysis were taken forward for either custom genotyping or analysis in studies with newly available genome-wide or CardioMetachip array genotyping (the latter included 6 of the 21 SNPs). If data for the index SNP were not available, this SNP was substituted by a closely correlated proxy from HapMap (**Supplementary Table 12**). Of a total of 25 available studies (maximum combined  $n = 42,519$  individuals), there were 14 studies with custom genotyping ( $n = 22,569$  individuals), of which 2 studies later acquired additional *in silico* data (ALSPAC (Replication),  $n = 6,315$  with genome-wide association data; NFBC1986,  $n = 4,897$  with CardioMetachip data). Eight further studies had *in silico* genome-wide association data ( $n = 13,992$  individuals), and 3 further studies had *in silico* CardioMetachip array data ( $n = 5,958$  individuals). Details of these studies are presented in **Supplementary Table 3**. Because resources for custom genotyping were limited, the total number of analyzed individuals varied by SNP, with three SNPs analyzed in available *in silico* studies only (**Supplementary Table 2**). Within each study, we analyzed the association between each available SNP and birth weight  $z$  score in the same way as described for the stage 1 studies.

**Combined discovery and follow-up meta-analyses.** We performed fixed-effects inverse-variance meta-analyses of the association between each SNP and birth weight, including up to 43 discovery and follow-up samples of European descent (maximum total  $n = 69,308$ ). Individual study results for any SNP showing strong evidence of deviation from Hardy-Weinberg equilibrium ( $P < 1 \times 10^{-4}$ ) were excluded. Meta-analyses were performed in parallel at two different study centers using two software packages in parallel (METAL 2009-10-10 release<sup>30</sup> and GWAMA version 2.0.6 (ref. 31)). We used Cochran's  $Q$  test and the derived inconsistency statistic ( $I^2$ )<sup>34</sup> to assess evidence of between-study heterogeneity of effect size. Results that crossed the widely accepted genome-wide significance threshold of  $P < 5 \times 10^{-8}$  were considered to represent robust evidence of association.

**Sensitivity analyses and phenotypic data quality checks.** The ascertainment and availability of phenotype data varied widely among the 43 studies (**Supplementary Tables 1 and 3**). For example, birth weight was measured by trained personnel in some studies but in others was self-reported in adulthood. Gestational age was not available as a covariable in all studies. We therefore performed further analyses to verify data quality and check that the effect size estimates in our meta-analyses were not greatly influenced by poor-quality data or lack of adjustment for gestational age.

To identify any studies that showed unusual relationships between birth weight and other phenotypes, we obtained from each study the percentage of variance in birth weight explained individually by sex, parity, maternal smoking, gestational age and maternal pre-pregnancy body mass index (BMI) as 100 times the adjusted  $R^2$  value from linear regression of birth weight against each individual trait. The observed relationships between birth weight and each related trait were reasonably consistent across all of the 43 studies (**Supplementary Fig. 9 and Supplementary Table 13**).

To assess whether adjustment for gestational age or measurement versus recall bias of birth weight influenced the associations between each of the 21 SNPs and birth weight, we repeated the fixed-effects inverse-variance meta-analyses of the European results in three different subsets of studies: (i) studies with birth weight collected by any method that adjusted for gestational age ( $n = 35$ ); (ii) studies with measured or medical records of birth weight that adjusted for gestational age only where available ( $n = 26$ ); and (iii) studies with measured or medical records of birth weight that also adjusted for gestational age ( $n = 24$ ). We compared the effect size estimates between each of these three meta-analyses and the overall meta-analysis result (**Supplementary Table 4**).

**Associations between birth weight and seven confirmed loci in non-European samples of varying ancestry.** Using eight study samples of varying ancestry, we investigated the seven loci that showed associations at genome-wide significance with birth weight in the combined meta-analysis of European discovery and follow-up studies. The eight non-European studies were from



East and/or Southeast Asia (Chinese and Filipino), Africa (African-American, Mandinka and Moroccan), the Middle East (Arab and Turkish) and South America (Surinamese) (total  $n = 11,848$  individuals; **Supplementary Table 10**). Samples were genotyped either by custom SNP assay (two studies), CardioMetaboChip (one study) or genome-wide chip (five studies). The index SNP from the European meta-analysis was taken forward as the index SNP for the non-European analyses, and associations with birth weight were analyzed as described. If the index SNP was not available, it was substituted by a closely correlated ancestry-specific proxy from the 1000 Genomes Project Pilot 1 Yoruba from Ibadan, Nigeria (YRI) and combined Japanese in Tokyo, Japan (JPT) and Han Chinese in Beijing, China (CHB) samples (released June 2010), which was found using SNAP (**Supplementary Table 12**). In the five studies with genome-wide association data, we considered all SNPs within 250 kb on either side of the index SNP in individuals of European ancestry.

We then performed 3 analyses: (i) for meta-analysis of single-SNP associations with birth weight, we performed fixed-effects inverse-variance meta-analyses of available studies, as described, for each of the 7 loci; (ii) for ancestry-specific regional analysis, we performed fixed-effects inverse-variance meta-analyses for SNPs within the 500 kb surrounding the 7 index SNPs in an ancestry-specific manner for  $n = 2,135$  East and/or Southeast Asian and  $n = 6,315$  African-American samples and plotted the association results against chromosomal position using LocusZoom; and (iii) for combined genotype risk score analysis to assess the associations between birth weight and the 7 confirmed loci in combination, we created a risk allele count (RAC) by summing the birth weight–lowering alleles at each SNP. We performed this latter analysis in 7 non-European studies in which 6 to 7 SNPs were available (combined  $n = 11,014$  individuals) and 1 representative European stage 2 study (NFBC1986,  $n = 4,647$ ). If a SNP was missing, all individuals were assigned a value of two times the frequency (HapMap, ancestry specific) of the birth weight–lowering allele. We performed linear regression of birth weight  $z$  score against RAC (additive model), with sex and gestational age (where available) as covariables. A genetic risk score, weighted by effect size in Europeans, gave similar results in all non-European studies (data not shown).

**Variance explained.** To estimate the percentage of variation in birth weight explained jointly by the seven confirmed birth weight–associated loci, we obtained the adjusted  $R^2$  value from the univariate linear regression of birth weight against risk allele count in six non-European studies and one European study (NFBC1986).

**Analysis of additional anthropometric phenotypes measured at birth.** Where available, in both stage 1 and 2 European studies, we created within-study  $z$  scores for birth length (available for 27 studies,  $n = 36,084$ ), birth head circumference (20 studies,  $n = 23,277$ ) and ponderal index (calculated as birth weight/length<sup>3</sup>; 27 studies,  $n = 35,836$ ). The  $z$  scores were calculated by the same method as was used for birth weight. We used linear regression to assess the association between each outcome and each of the seven confirmed birth weight–associated SNPs, with sex and gestational age (where available) as covariables. We combined the results across studies using fixed-effects inverse-variance meta-analysis.

**Analysis of birth weight adjusted for birth length.** Where data for both birth weight and birth length were available, we used linear regression to assess the association between birth weight  $z$  score and the seven confirmed birth weight–associated SNPs, with sex, gestational age (where available) and birth length as covariables. In the same set of samples, we again performed linear regression to assess the association between birth weight  $z$  score and SNP, with only sex and gestational age (where available) as covariables, to allow direct comparison of analyses with and without adjustment for birth length. Meta-analysis was performed as described.

**Analysis of birth weight adjusted for maternal genotype.** To assess whether the birth weight associations at the seven confirmed loci for birth weight were independent of maternal genotype, we used mother–offspring pairs from up to 10 European studies with both maternal and fetal genotype available (discovery  $n = 7,879$ ; follow-up  $n = 3,428$ ; total  $n = 11,307$ ). Within each study, we performed linear regression of birth weight  $z$  score against each of the SNPs, with sex, gestational age (where available) and maternal genotype as

covariables. For direct comparison, we repeated this analysis without maternal genotype, using only subjects for whom maternal genotype was available. Fixed-effects inverse-variance meta-analysis was performed to combine results across studies for (i) fetal genotype and (ii) fetal genotype adjusted for maternal genotype. We performed a likelihood-ratio test to compare the model fit before and after adjustment for maternal genotype.

**Analysis of associations between known loci for type 2 diabetes, blood pressure, height and BMI and birth weight.** Of the seven confirmed birth weight–associated loci, five had previously been associated with type 2 diabetes (*CDKAL1* and *ADCY5*), blood pressure (*ADRB1*) or adult height (*LCORL* and *HMG2*). To assess whether association with birth weight was a common feature of loci associated with these adult traits, we extracted results from our stage 1 discovery meta-analysis for 49 published SNPs associated with type 2 diabetes<sup>7,22,35–48</sup>, 180 SNPs associated with height<sup>21</sup> and 30 SNPs associated with blood pressure<sup>14,17</sup>. To complement these analyses, we studied the associations between the same sets of SNPs and birth weight  $z$  score in 5,327 mother–child pairs from the ALSPAC study. We adjusted for sex and gestational age, recorded the results before and after adjustment for maternal genotype and compared the fit of the two models using a likelihood-ratio test to assess evidence of confounding by maternal genotype. This was particularly important for the analyses of SNPs associated with type 2 diabetes, as there is evidence that at least two of the known loci influence birth weight via maternal genotype<sup>49,50</sup>. For each set of loci, we used the binomial probability (sign) test (see URLs) to assess whether there was more evidence of negative or positive association with birth weight than the 50% expected under the null.

For the *HHEX-IDE* locus (type 2 diabetes), there are previously published studies reporting associations with birth weight, not all of which overlap those identified in our stage 1 discovery samples<sup>4,5</sup>. To obtain an approximate overall result for this locus, we therefore performed meta-analysis (inverse variance, fixed effects) of our stage 1 result with additional published data from the ALSPAC, Inter99 and EFSOCH studies and *in silico* data available from stage 2 (total  $n = 51,583$ ). Two SNPs at the locus were represented in the meta-analysis: rs1111875 and rs5015480 ( $r^2 = 0.97$ ). Because the effect sizes for the published studies were in grams, we first converted them to equivalent  $z$ -score values by dividing effect size estimates and 95% confidence limits by 484 (the median standard deviation of birth weight in grams, determined in our previous GWAS of birth weight)<sup>2</sup>.

**Analysis of the associations between seven confirmed loci for birth weight and adult metabolic and anthropometric traits in publicly available results of genome-wide association meta-analyses.** We looked up the seven confirmed index SNPs for birth weight in publicly available published meta-analysis data sets to assess their associations with adult metabolic and anthropometric traits, including (i) fasting glucose and fasting insulin concentrations<sup>7</sup>, (ii) fasting proinsulin concentration<sup>9</sup>, (iii) triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol concentrations<sup>51</sup>, (iv) height<sup>21</sup> and (v) BMI<sup>52</sup>.

**Analysis of the association between *CCNLI* and weight up to 6 months in seven studies.** We used available postnatal weight data from EFSOCH, Generation R (Discovery 1), Generation R (Discovery 2), LISA, HBCS, NFBC1966 and NFBC1986 (maximum total  $n = 15,090$ ). Each study analyzed weight data at the following time points, where available: birth; 1 ( $\pm 0.2$ ) month; 2 ( $\pm 0.2$ ) months; 3 ( $\pm 0.3$ ) months; and 6 ( $\pm 0.4$ ) months. Within each study, we created weight-for-age  $z$  scores for each of the postnatal time points using Growth Analyser 3.0 (Dutch Growth Research Foundation). The reference was a cohort of 475,588 children born between 1977 and 1981 in Sweden<sup>53</sup>. Birth weight was analyzed as described. For each time point, we performed linear regression of weight-for-age  $z$  score against rs900400 genotype (or genotype at the designated proxy SNP; **Supplementary Table 12**), with gestational age at birth as a covariable. We combined the results across studies using fixed-effects inverse-variance meta-analysis.

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