**SUPPLEMENTARY MATERIAL**

**Genome-wide association study of offspring birth weight in 86,577 women identifies five novel loci and highlights maternal genetic effects that are independent of fetal genetics**

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**Large Supplementary Tables provided in separate Excel spreadsheets:**

**Table S1:** Basic characteristics, genotyping, imputation and analysis details for participants in the EGG Discovery studies

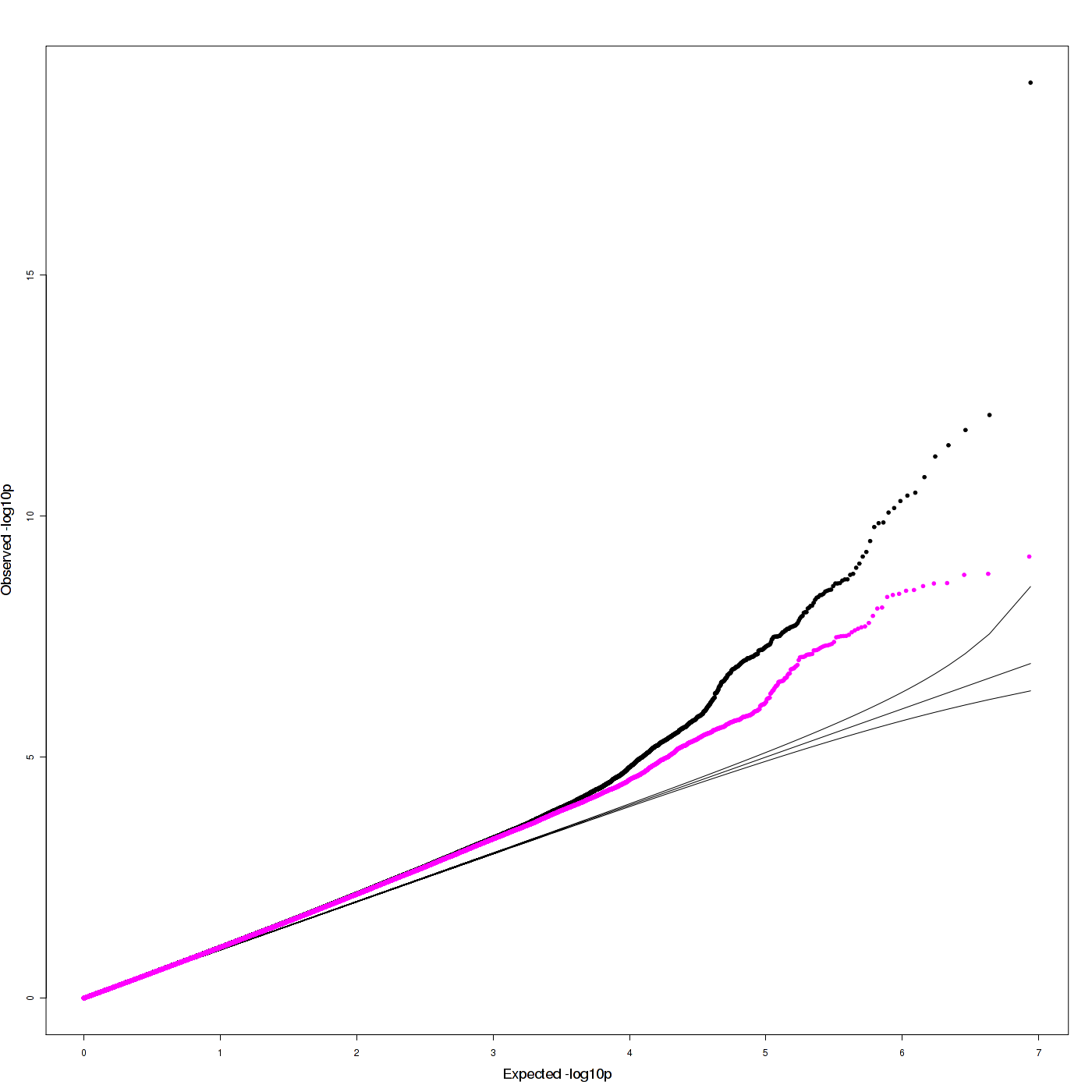
**Table S2:** Basic characteristics, genotyping, imputation and analysis details for participants in the EGG Follow-up studies

**Table S10:** Look-ups of 10 birth weight-associated SNPs in available GWAS data for other growth-related and cardiometabolic traits

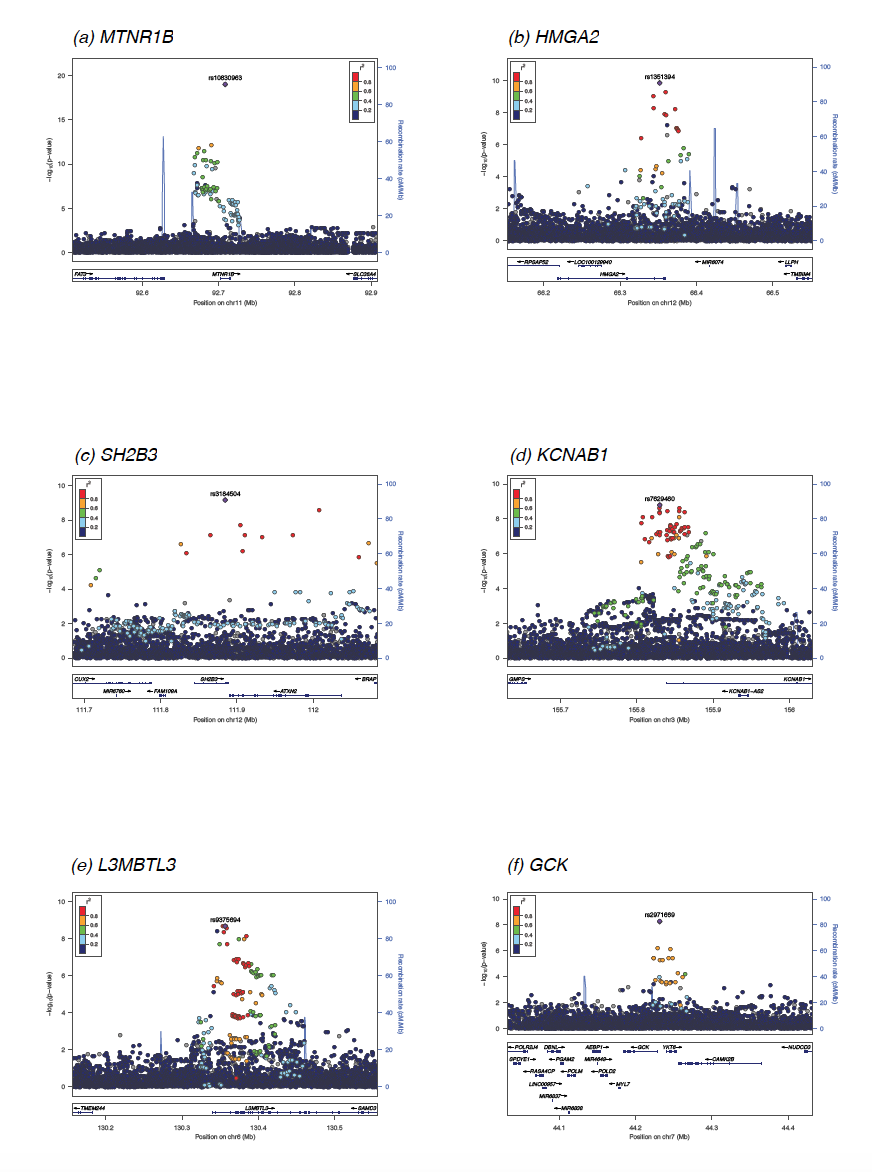
**Figure S1.** Flowchart of study design.

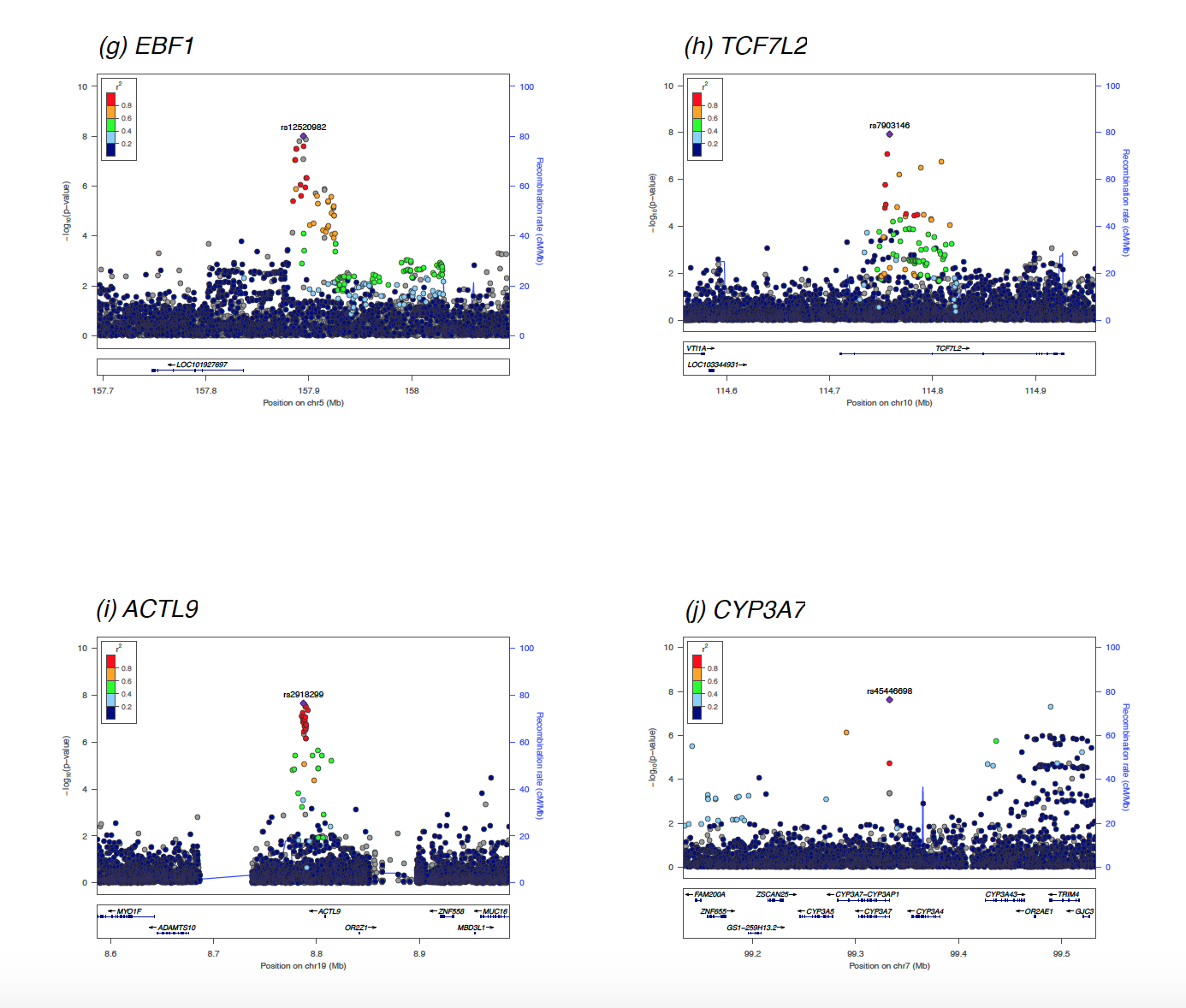
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**Figure S2.** Quantile-quantile plot of 8,723,755 maternal autosomal SNPs and 17,352 maternal X-chromosome SNPs (all MAF >1%) from the meta-analysis of up to 86,577 women. Observed versus expected –log10 *P*-values are plotted in black for all SNPs, and in pink excluding 60 index SNPs (+/-500kb) identified in a previous GWAS of own birth weight (“fetal GWAS”). The fine black lines represent the expected –log10 *P*-values under the null distribution and the 95% concentration bands, which are an approximation to the 95% confidence intervals around the expected line.



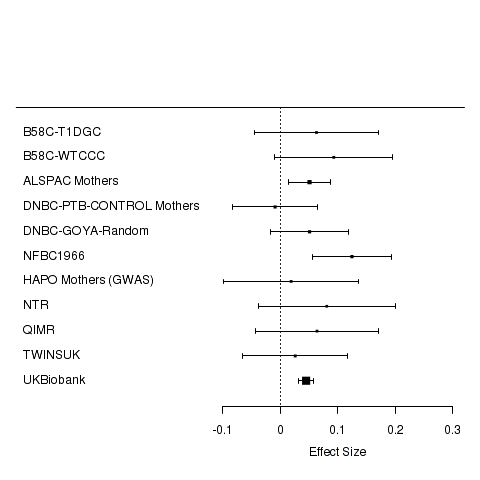
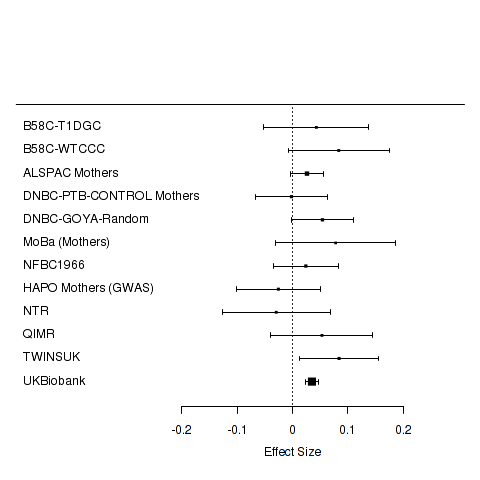
**Figure S3.** Regional plots of association between maternal genotype and offspring birth weight at 10 loci for which associations at index SNPs (purple diamonds) reached *P* < 5x10-8.

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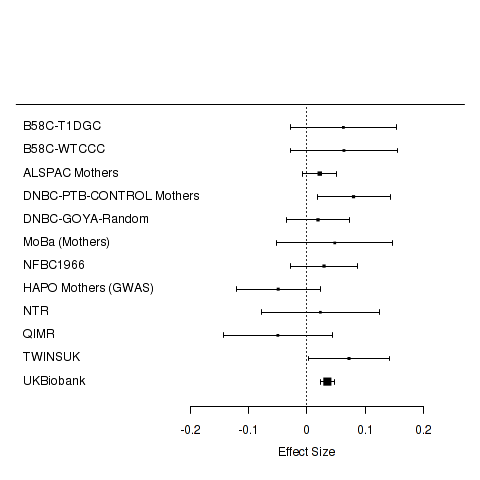
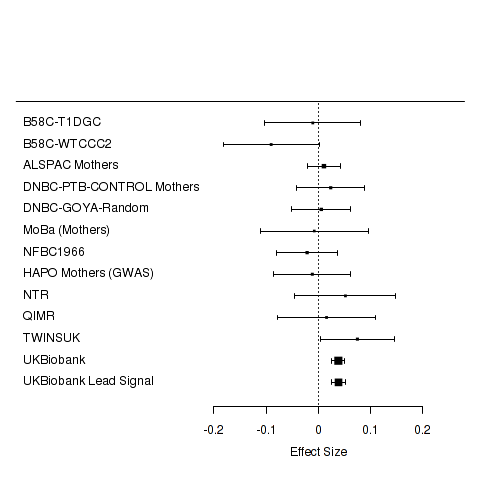
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**Figure S4.** Forest plots showing associations between the index SNP at the identified loci and birth weight in all available studies. At *KCNAB1* and *EBF1* index SNP was only available in UK Biobank, so the plots show results for the most closely correlated proxy (r2 = 1) that was also available in the EGG meta-analysis (the result for the index SNP is also marked as “UKBiobank Lead Signal”. There is no plot for *CYP3A7* because the lead SNP was only available in UK Biobank and there were no proxies at r2 >0.5 available in the EGG meta-analysis.

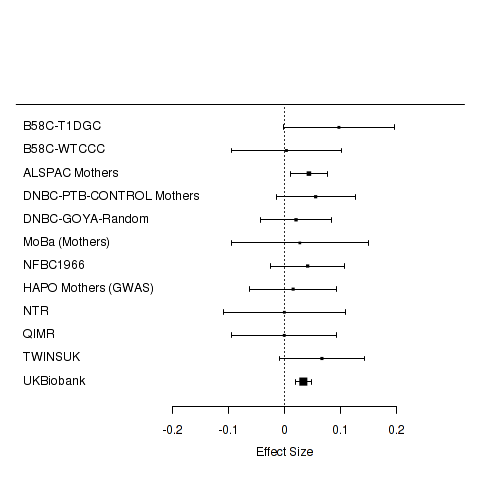
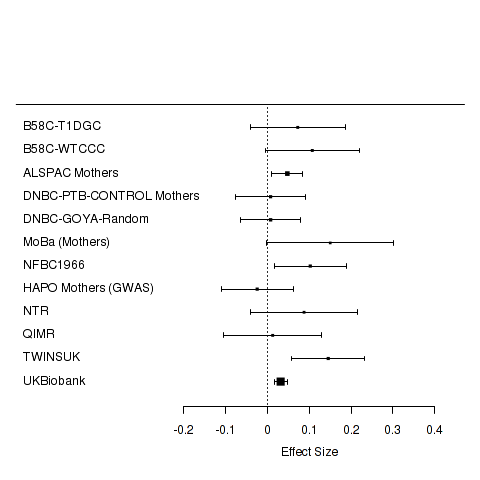
1. *MTNR1B* (b) *HMGA2*

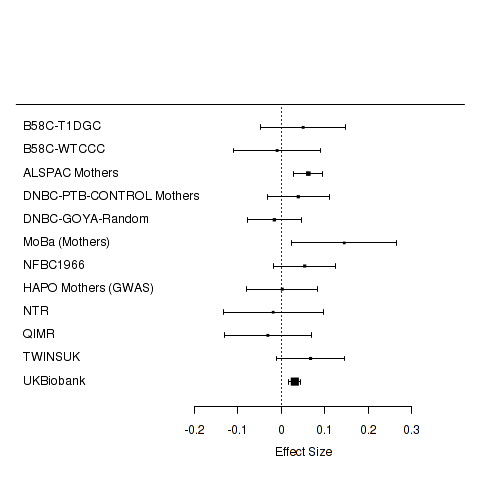
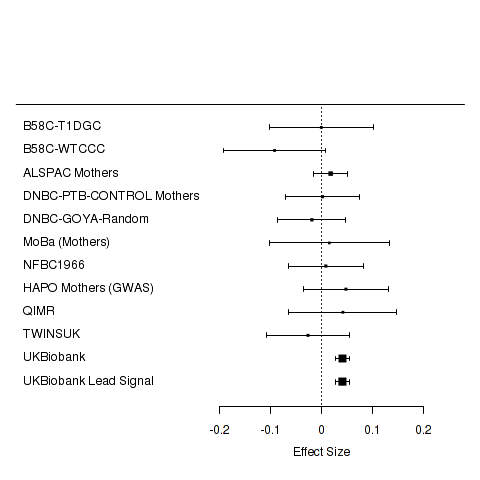
(c) *SH2B3* (d) *KCNAB1*

* *

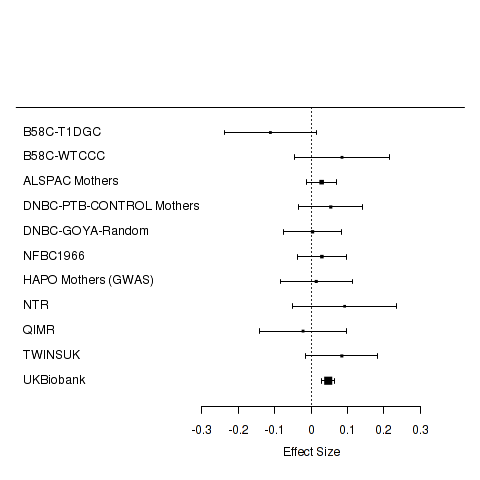
(e) *L3MBTL3* (f) *GCK*

* *

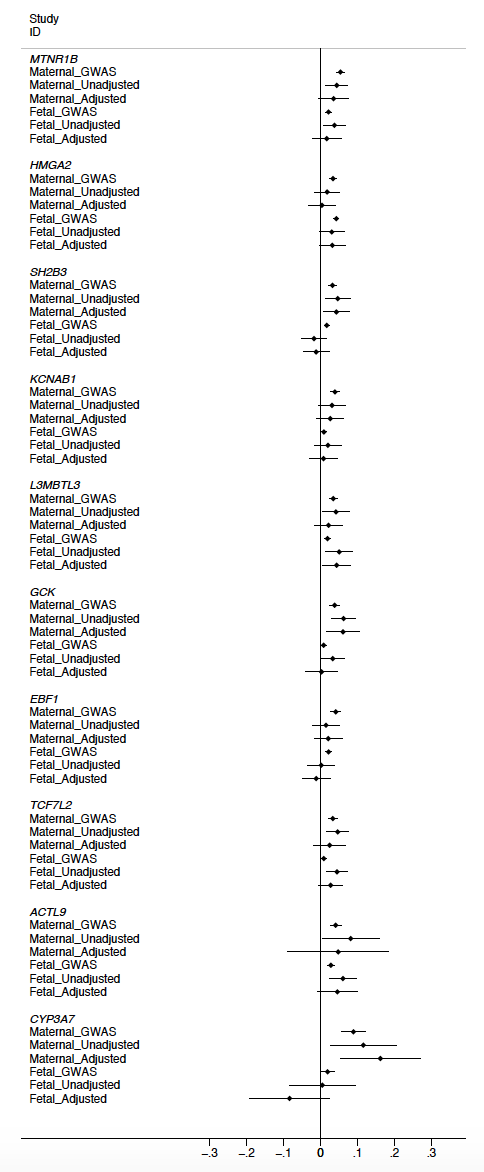
(g) *EBF1* (h) *TCF7L2*

**

(h) *ACTL9*

**

**Figure S5.** Comparison of maternal effect sizes with fetal effect sizes at 10 loci identified in the current study. For each locus, the following effect sizes (with 95% CI) are shown, all aligned to the same allele: Maternal\_GWAS, maternal allelic effect on offspring BW (from meta-analysis of n = up to 86,577 European mothers); Maternal\_unadjusted, maternal allelic effect on offspring birth weight (unconditioned, n = up to 8705 mother–child pairs); Maternal\_adjusted, maternal effect (conditioned on fetal genotype, n = up to 8705); Fetal\_GWAS, fetal allelic effect on BW (from European ancestry meta-analysis of n =up to 143,677 individuals (2)); Fetal\_unadjusted, fetal allelic effect on BW (unconditioned in n = up to 8705); Fetal\_adjusted, fetal effect (conditioned on maternal genotype, n = up to 8705).

****

**Table S3.** Basic characteristics of UK Biobank participants, with observational associations between reported birth weight of first child and other variables

|  |  |  |
| --- | --- | --- |
| Ethnicity | | British descent |
| Country (Sample source) | | UK |
| Year(s) of birth of offspring | | 1934 to 2008 |
| Number of mothers included in the analyais | | 48632 |
| Birth weight data | | Reported by mothers at baseline or follow-up study visit |
| Birth weight of first child [Mean (sd)], grams (converted from pounds) | | 3255 (396) |
| Gestational age available? | | No |
| Offspring sex available? | | No |
| Maternal age at baseline [Mean (sd)], years | | 57.2 (7.7) |
| Maternal age at first birth [Mean (sd)], years | | 25.9 (5.1) |
| Maternal BMI at baseline [Mean (sd)], kg/m2 | | 27.43 (4.80) |
| Mean (SD) birth weight of first child by smoking information collected at baseline (n=214,367) | Never (59.6 %) | 3198 (569) |
| Former (32.3 %) | 3194 (568) |
| Current (8.1 %) | 3101 (587) |
| P value for association | 4.9 x 10-57 |
| Mean (SD) birth weight of first child by maternal BMI tertile (in kg/m2) measured at baseline (n=215,657) | 1 (12.12 to 25.03) | 3170 (559) |
| 2 (25.04 to 28.68) | 3195 (567) |
| 3 (28.68 to 74.68) | 3206 (590) |
| P value for association | 5.0 x 10-46 |
| Mean (SD) birth weight of first child by maternal height tertile (in cm) measured at baseline (n=216,096) | 1 (75 to 164) | 3131 (563) |
| 2 (164 to 173) | 3280 (569) |
| 3 (173 to 209) | 3402 (585) |
| P value for association | <1 x 10-100 |
| Mean (SD) birth weight of first child by tertiles of Townsend deprivation index at baseline (n=216,547) | 1 (-6.26 to 3.15) | 3214 (559) |
| 2 (-3.14 to -0.59) | 3201 (563) |
| 3 (-0.58 to 11) | 3145 (592) |
| P value for association | <1 x 10-100 |

**Table S4.** Associations between SNPs at 10 loci and birth weight in different stages of the study.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Locus*** | **Lead SNP** | **Chr** | **Position (bp, b37)** | **Alleles** | **EAF** | **EGG discovery meta-analysis** | | | | **EGG replication** | | | | **UK Biobank only (*N*=48632)** | | **EGG + UK Biobank meta-analysis** | | | |
| **Effect / Other** | **Effect (SE)** | ***P*-value** | ***N* [*N* studies]** | **Het *P-*value** | **Effect** | ***P*-value** | ***N* [*N* studies]** | **Het *P-*value** | **Effect (SE)** | ***P*-value** | **Effect (SE)** | ***P*-value** | ***N*** | **Het *P-*value** |
|
| *MTNR1B\** | rs10830963 | 11 | 92708710 | G/C | 0.29 | 0.055 (0.012) | 3.8 x 10-6 | 18971 [10] | 0.36 | 0.071 (0.011) | 1.6 x 10-10 | 16851 [11] | 0.30 | 0.045 (0.007) | 1.9 x 10-10 | 0.052 (0.006) | 1.0 x 10-19 | 71341 | 0.27 |
| *HMGA2* | rs1351394 | 12 | 66351826 | T/C | 0.49 | 0.031 (0.010) | 1.2 x 10-3 | 19615 [11] | 0.45 | - | - | - | - | 0.035 (0.006) | 3.1 x 10-8 | 0.034 (0.005) | 1.4 x 10-10 | 68247 | 0.70 |
| *SH2B3* | rs3184504 | 12 | 111884608 | C/T | 0.52 | 0.028 (0.009) | 3.2 x 10-3 | 19617 [11] | 0.24 | - | - | - | - | 0.035 (0.006) | 5.1 x 10-8 | 0.033 (0.005) | 6.9 x 10-10 | 68249 | 0.54 |
| *KCNAB1* | rs7629460 | 3 | 155829938 | C/A | 0.59 | - | - | - | - | - | - | - | - | 0.039 (0.007) | 1.6 x 10-9 | - | - | - | - |
| *KCNAB1†* | rs9872556 | 3 | 155829855 | T/C | 0.57 | 0.007 (0.010) | 0.45 | 19620 [11] | 0.40 | - | - | - | - | 0.039 (0.007) | 2.9 x 10-9 | 0.029 (0.005) | 8.1 x 10-8 | 68253 | 0.008 |
| *L3MBTL3* | rs9375694 | 6 | 130356608 | G/A | 0.31 | 0.038 (0.011) | 3.6 x 10-4 | 19591 [11] | 0.92 | - | - | - | - | 0.033 (0.007) | 1.4 x 10-6 | 0.035 (0.006) | 2.1 x 10-9 | 68223 | 0.74 |
| *GCK* | rs2971669 | 7 | 44231778 | T/C | 0.23 | 0.053 (0.012) | 1.5 x 10-5 | 19530 [11] | 0.14 | - | - | - | - | 0.032 (0.008) | 3.2 x 10-5 | 0.038 (0.007) | 5.5 x 10-9 | 68162 | 0.16 |
| *GCK‡* | rs4607517 | 7 | 44235668 | A/G | 0.21 | 0.035 (0.013) | 5.9 x 10-3 | 19619 [11] | 0.01 | 0.046 (0.012) | 2.7 x 10-4 | 18128 [13] | 0.10 | 0.030 (0.008) | 2.7 x 10-4 | 0.035 (0.006) | 7.2 x 10-9 | 86379 | 0.14 |
| *EBF1* | rs12520982 | 5 | 157894747 | T/C | 0.74 | - | - | - | - | - | - | - | - | 0.041 (0.007) | 9.9 x 10-9 | - | - | - | - |
| *EBF1†* | rs2964484 | 5 | 157897437 | A/G | 0.71 | 0.006 (0.011) | 0.62 | 18914 [10] | 0.66 | - | - | - | - | 0.041 (0007) | 1.2 x 10-8 | 0.031 (0.006) | 4.6 x 10-7 | 67547 | 0.007 |
| *TCF7L2* | rs7903146 | 10 | 114758349 | T/C | 0.30 | 0.039 (0.011) | 2.7 x 10-4 | 19621 [11] | 0.23 | - | - | - | - | 0.031 (0.007) | 9.5 x 10-6 | 0.034 (0.006) | 1.2 x 10-8 | 68253 | 0.54 |
| *ACTL9* | rs2918299 | 19 | 8787273 | C/T | 0.83 | 0.028 (0.013) | 3.6 x 10-2 | 18971 [10] | 0.46 | - | - | - | - | 0.047 (0.009) | 9.4 x 10-8 | 0.041 (0.007) | 2.2 x 10-8 | 67603 | 0.21 |
| *CYP3A7* | rs45446698 | 7 | 99332948 | G/T | 0.04 | - | - | - | - | - | - | - | - | 0.089 (0.016) | 2.4 x 10-8 | - | - | - | - |

Effects were aligned to the birth weight-raising allele and are presented in SD units (1 SD of birth weight = 484g (3)). Chr, chromosome; bp, base pair; b37, build 37; EAF, effect allele frequency; Het, heterogeneity; SE, standard error.

\* The total number of individuals in the overall meta-analysis for this SNP is lower than the sum of EGG discovery + EGG replication + UK Biobank studies because we excluded discovery studies in which the SNP was imputed with r2\_hat or proper\_info <0.8.

†Index SNPs available in UK Biobank only, so these are the results for proxy SNPs (r2 = 1), available in both UK Biobank and EGG (imputed to HapMap Phase 2) were as follows. No proxy with r2 > 0.5 available at *CYP3A7* in HapMap Phase 2.

‡For the *GCK* locus,SNP rs4607517 (r2=0.73 with rs2971669) was initially followed for replication in EGG due to published fasting glucose association (4) but rs2971669 remained most strongly associated with offspring birth weight in the full meta-analysis (including UK Biobank) and is thus reported here as the index SNP.

**Table S5.** Associations between SNPs at *KCNAB1* and *EBF1* and gestational duration or preterm birth in publicly available data from a GWAS of 43,568 women (1).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus** | **SNP** | **Alleles (Effect/Other)** | **Maternal SNP association with offspring gestational duration** | | | **Maternal SNP association with preterm birth** | | |
|
| **Effect** | **SE** | ***P-*value** | **Effect** | **SE** | ***P-*value** |
| *KCNAB1* | rs7629460 | C/A | 0.48 | 0.12 | 1.1 x 10-4 | 0.91 | 0.026 | 4.0 x 10-4 |
| *KCNAB1* | rs9872556 | T/C | 0.46 | 0.12 | 1.3 x 10-4 | 0.91 | 0.026 | 5.8 x 10-4 |
| *EBF1* | rs12520982 | T/C | 1.29 | 0.13 | 2.5 x 10-21 | 0.81 | 0.028 | 5.5 x 10-13 |
| *EBF1* | rs2964484 | A/G | 1.27 | 0.13 | 5.1 x 10-21 | 0.81 | 0.028 | 4.2 x 10-13 |

Effects (beta values) were aligned to the birth weight-raising allele from the main meta-analysis and are presented as days (gestational duration) or odds ratio (preterm birth). SE, standard error. *P* values were adjusted for inflation (gestational duration lambda =1.038; preterm birth lambda=1.025).

**Table S6.** Candidate genes at newly identified loci

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus** | **Lead SNP** | **Chr** | **Position (b37)** | **Candidate gene(s) at the locus\*** | **Reports on eQTL\*\*** | **Genes +-300kb** | **Literature search for nearby genes of relevance (300kb)** |
| *SH2B3* | rs3184504 | 12 | 111884608 | *SH2B3[C,N,E],*  *ATXN2[E],*  *ALDH2[E]* | *ALDH2:* Skin - Sun Exposed (Lower leg) eQTL, *ATXN2:* Whole Blood eQTL, *SH2B3:* Whole Blood eQTL | *CUX2, FAM109A, SH2B3, ATXN2, BRAP, ACAD10* | - |
| *KCNAB1* | rs7629460 | 3 | 155829938 | *KCNAB1[E,N]* | *KCNAB1:* Artery - Aorta eQTL | *SLC33A1, KCNAB1, GMPS, AK130481* | - |
| *TCF7L2* | rs7903146 | 10 | 114758349 | *TCF7L2[N]* | - | *VTI1A, TP11-57H14, TCF7L2* | Hyperglycemia and adverse pregnancy outcome study: common genetic variants in *GCK* and *TCF7L2* are associated with fasting and postchallenge glucose levels in pregnancy and with the new consensus definition of gestational diabetes mellitus from the International Association of Diabetes and Pregnancy Study Groups; PMID 20682688. Bayesian refinement of association signals for 14 loci in 3 common diseases; PMID 23104008. |
| *CYP3A7* | rs45446698 | 7 | 99332948 | *CYP3A7[E,B],*  *ZSCAN25[N,E],* | *CYP3A7:* Adrenal Gland eQTL, *ZKSCAN5:* Skin - Not Sun Exposed (Suprapubic) eQTL | *PTCD1, CPSF4, ATP5J2, AC073063, ZNF789, ZKSCAN5, GS1-259H13, FAM200A, ZSCAN25, CYP3A5, CYP3A7, CYP3A4, CYP3A43, OR2AE1, TRIM4, SNORA40, AZGP1, ZKSCAN1* | Cytochrome P450 allele CYP3A7\*1C associated with adverse outcomes in chronic lymphocytic leukemia, breast, and lung cancer; PMID 26964624. Molecular mechanisms of polymorphic *CYP3A7* expression in adult human liver and intestine; PMID 11940601. |

\*B=biological candidate, C=coding variant, E=eQTL (from GTEx), N=nearest

\*\* eQTL reported from GTEx v4, GEUVADIS, and 11 other studies for the lead variant using Haploreg v4.1 (http://archive.broadinstitute.org/mammals/haploreg/haploreg.php). When there was no eQTL report for the lead variant, eQTL reports are for the proxy SNPs (r2 >0.8)

**Table S7.** Analysis of index SNPs from maternal GWAS of birth weight conditional on index SNPs from fetal GWAS of birth weight (2) at the at *L3MBTL3*and *GCK* loci.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus** | **Lead SNP** | **Chr** | **Position (bp, b37)** | **Alleles** | **EAF** | **UK Biobank unconditional** | | | **Conditioned on** | **UK Biobank conditional** | | |
| **Effect/Other** | **Effect (SE)** | ***P-*value** | **N** | **Effect (SE)** | ***P-*value** | **N** |
| *L3MBTL3* | rs9375694 | 6 | 130356608 | G/A | 0.31 | 0.033 (0.007) | 1.4 x 10-6 | 48632 | rs1415701 | 0.024 (0.008) | 1.2 x 10-3 | 48632 |
| *GCK* | rs2971669 | 7 | 44231778 | T/C | 0.23 | 0.032 (0.008) | 3.2 x 10-5 | 48632 | rs138715366 | 0.031 (0.008) | 6.8 x 10-5 | 48632 |

Effects were aligned to the birth weight-raising allele and are presented in SD units (1 SD of birth weight = 484g (3)). Chr, chromosome; bp, base pair; b37, build 37; EAF, effect allele frequency; SE, standard error.

NB Approximate conditional analysis of the full meta-analysis summary statistics using GCTA (5) produced similar results: *L3MBTL3*: unconditional *P*=2.1 x 10-9, conditional P=3.3 x 10-5 (N=68,223); *GCK*: unconditional P=5.5 x 10-9 conditional P=1.0 x 10-8 (N=68,162).

**Table S8.** Associations between maternal genotype and birth weight, adjusted for fetal genoype, and vice versa, in two different study samples: (1) unrelated individuals from the UK Biobank (n=45,436 women with birth weight of first child; n=57,711 participants with own birth weight, using either a linear model (unadjusted for maternal or fetal effects) or a structural equation model (adjusted for both fetal and maternal effects); (2) up to 8705 mother-child pairs from 4 studies: ALSPAC, EFSOCH, DNBC-PTBCTRLS and HAPO (non-GWAS) using linear regression.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus (lead SNP)** | **Alleles (Effect / Other)** | **Study sample** | **Unadjusted maternal effect** | | **Adjusted maternal effect** | | **Unadjusted fetal effect** | | **Adjusted fetal effect** | |
| **Beta (SE)** | **P value** | **Beta (SE)** | **P value** | **Beta (SE)** | **P value** | **Beta (SE)** | **P value** |
| *MTNR1B* (rs10830963) | G/C | UKB unrelated | 0.045 (0.007) | 1.2 x 10-9 | 0.046 (0.010) | 7.0 x 10-6 | 0.022 (0.007) | 0.001 | -0.002 (0.010) | 0.86 |
| m/ch pairs (n=8705) | 0.044 (0.015) | 0.004 | 0.036 (0.020) | 0.08 | 0.038 (0.015) | 0.01 | 0.017 (0.020) | 0.4 |
| **M/A** | **0.045 (0.006)** | **1.6 x10-12** | **0.044 (0.009)** | **8.7 x 10-7** | **0.025 (0.006)** | **8.9 x 10-5** | **0.002 (0.009)** | **0.84** |
| *HMGA2* (rs1351394) | T/C | UKB unrelated | 0.036 (0.007) | 6.9 x 10-8 | 0.021 (0.009) | 0.03 | 0.042 (0.006) | 6.8 x 10-13 | 0.032 (0.009) | 2.0 x 10-4 |
| m/ch pairs (n=6316) | 0.018 (0.018) | 0.31 | 0.004 (0.018) | 0.82 | 0.031 (0.018) | 0.08 | 0.032 (0.018) | 0.08 |
| **M/A** | **0.034 (0.007)** | **2.5 x 10-7** | **0.018 (0.008)** | **0.03** | **0.041 (0.006)** | **6.7 x 10-13** | **0.032 (0.008)** | **7.0 x 10-5** |
| *SH2B3* (rs3184504) | C/T | UKB unrelated | 0.032 (0.007) | 1.8 x 10-6 | 0.024 (0.009) | 0.01 | 0.025 (0.006) | 1.8 x 10-5 | 0.013 (0.009) | 0.12 |
| m/ch pairs (n=6316) | 0.047 (0.018) | 0.008 | 0.043 (0.018) | 0.02 | -0.017 (0.017) | 0.32 | -0.012 (0.018) | 0.52 |
| **M/A** | **0.034 (0.007)** | **1.9 x 10-7** | **0.028 (0.008)** | **5.5 x 10-4** | **0.020 (0.006)** | **3.2 x 10-4** | **0.008 (0.008)** | **0.32** |
| *KCNAB1* (rs7629460) | C/A | UKB unrelated | 0.042 (0.007) | 5.4 x 10-10 | 0.055 (0.009) | 4.3 x 10-9 | -0.0003 (0.006) | 0.96 | -0.028 (0.009) | 0.001 |
| m/ch pairs (n=6159) | 0.031 (0.018) | 0.09 | 0.026 (0.019) | 0.16 | 0.02 (0.019) | 0.27 | 0.008 (0.019) | 0.66 |
| **M/A** | **0.041 (0.007)** | **5.1 x10-10** | **0.05 (0.008)** | **1.0 x 10-9** | **0.002 (0.006)** | **0.79** | **-0.021 (0.008)** | **0.009** |
| *L3MBTL3* (rs9375694) | G/A | UKB unrelated | 0.032 (0.007) | 7.1 x 10-6 | 0.026 (0.010) | 0.009 | 0.024 (0.006) | 2.0 x 10-4 | 0.01 (0.009) | 0.27 |
| m/ch pairs (n=6159) | 0.042 (0.019) | 0.02 | 0.022 (0.019) | 0.25 | 0.051 (0.019) | 0.007 | 0.044 (0.019) | 0.02 |
| **M/A** | **0.033 (0.007)** | **4.3 x 10-7** | **0.025 (0.009)** | **0.005** | **0.026 (0.006)** | **3.8 x 10-6** | **0.016 (0.008)** | **0.05** |
| *GCK* (rs2971669) | T/C | UKB unrelated | 0.032 (0.008) | 6.4 x 10-5 | 0.036 (0.011) | 0.001 | 0.009 (0.007) | 0.21 | -0.009 (0.010) | 0.36 |
| m/ch pairs (n=8551) | 0.063 (0.016) | 1.0 x 10-4 | 0.061 (0.022) | 0.006 | 0.033 (0.017) | 0.05 | 0.003 (0.023) | 0.9 |
| **M/A** | **0.038 (0.007)** | **9.4 x 10-8** | **0.041 (0.01)** | **3.1 x 10-5** | **0.012 (0.006)** | **0.05** | **-0.007 (0.009)** | **0.44** |
| *EBF1* (rs12520982) | T/C | UKB unrelated | 0.039 (0.008) | 1.9 x 10-7 | 0.033 (0.010) | 0.001 | 0.028 (0.007) | 3.7 x 10-5 | 0.011 (0.010) | 0.24 |
| m/ch pairs (n=6159) | 0.015(0.019) | 0.42 | 0.021 (0.019) | 0.27 | 0.002 (0.019) | 0.91 | -0.012 (0.019) | 0.54 |
| **M/A** | **0.035 (0.007)** | **1.6 x 10-6** | **0.03 (0.009)** | **5.9 x 10-4** | **0.025 (0.007)** | **1.5 x 10-4** | **0.006 (0.009)** | **0.5** |
| *TCF7L2* (rs7903146) | T/C | UKB unrelated | 0.034 (0.007) | 3.9 x 10-6 | 0.031 (0.010) | 0.003 | 0.02 (0.006) | 0.002 | 0.005 (0.009) | 0.57 |
| m/ch pairs (n=8696) | 0.047 (0.015) | 0.002 | 0.025 (0.022) | 0.26 | 0.045 (0.015) | 0.003 | 0.027 (0.016) | 0.09 |
| **M/A** | **0.036 (0.006)** | **1.03x10-8** | **0.03 (0.009)** | **9.9 x 10-4** | **0.023 (0.006)** | **2.6 x 10-5** | **0.01 (0.008)** | **0.19** |
| *ACTL9* (rs2918299) | C/T | UKB unrelated | 0.047 (0.009) | 4.9 x 10-7 | 0.046 (0.013) | 5.0 x 10-4 | 0.027 (0.008) | 0.001 | 0.003 (0.012) | 0.78 |
| m/ch pairs (n=6159) | 0.082 (0.039) | 0.04 | 0.048 (0.070) | 0.49 | 0.061 (0.019) | 0.001 | 0.046 (0.028) | 0.1 |
| **M/A** | **0.049 (0.009)** | **2.68x10-8** | **0.046 (0.013)** | **3.1 x 10-4** | **0.032 (0.007)** | **1.3 x 10-5** | **0.010 (0.011)** | **0.38** |
| *CYP3A7* (rs45446698) | G/T | UKB unrelated | 0.088 (0.017) | 1.2 x 10-7 | 0.103 (0.023) | 8.1 x 10-6 | 0.018 (0.015) | 0.22 | -0.033 (0.021) | 0.13 |
| m/ch pairs (n=6159) | 0.116 (0.046) | 0.01 | 0.162 (0.055) | 0.003 | 0.005 (0.046) | 0.91 | -0.084 (0.055) | 0.13 |
| **M/A** | **0.091 (0.016)** | **1.01x10-8** | **0.112 (0.021)** | **1.4 x 10-7** | **0.017 (0.014)** | **0.24** | **-0.039 (0.020)** | **0.04** |

Effects (beta values) were aligned to the birth weight-raising allele and are presented in SD units (1 SD of birth weight = 484g (3)). SE, standard error; SEM, structural equation model; M/A, meta-analysis (fixed effects, inverse variance). There was little detectable heterogeneity in the meta-analysis (all *P >* 0.05, Bonferroni corrected for 40 tests; median *I2 =* 0.0% [inter-quartile range 0.0% to 39.8%]).

**Table S9.** Look-up of fetal genotype associations with birth weight (unadjusted for maternal genotype) in up to 143,675 individuals, for the 10 loci identified in the maternal GWAS of birth weight (unadjusted for fetal genotype).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus** | **Lead SNP** | **Chr** | **Position (bp, b37)** | **Alleles** | **Maternal GWAS (current study)** | | | | **Fetal GWAS\*** | | | | **Difference (Maternal beta - Fetal beta)** |
| **Effect/Other** | **Beta** | **SE** | ***P*-value** | **N** | **Beta** | **SE** | **P-value** | **N** |
|
| *MTNR1B* | rs10830963 | 11 | 92708710 | G/C | 0.052 | 0.005 | 1.0 x 10-19 | 71341 | 0.023 | 0.004 | 2.9 x 10-8 | 143663 | 0.029 |
| *HMGA2* | rs1351394 | 12 | 66351826 | T/C | 0.034 | 0.005 | 1.4 x 10-10 | 68247 | 0.044 | 0.004 | 1.9 x 10-32 | 143671 | -0.01 |
| *SH2B3* | rs3184504 | 12 | 111884608 | C/T | 0.033 | 0.005 | 6.9 x 10-10 | 68249 | 0.017 | 0.004 | 2.9 x 10-6 | 142404 | 0.016 |
| *KCNAB1* | rs7629460 | 3 | 155829938 | C/A | 0.039 | 0.007 | 1.6 x 10-9 | 48632 | 0.009 | 0.004 | 1.7 x 10-2 | 139423 | 0.03 |
| *L3MBTL3* | rs9375694 | 6 | 130356608 | G/A | 0.035 | 0.006 | 2.1 x 10-9 | 68223 | 0.019 | 0.004 | 1.7 x 10-6 | 139427 | 0.016 |
| *GCK* | rs2971669 | 7 | 44231778 | T/C | 0.038 | 0.007 | 5.5 x 10-9 | 68162 | 0.010 | 0.005 | 2.8 x 10-2 | 143671 | 0.028 |
| *EBF1* | rs12520982 | 5 | 157894747 | T/C | 0.041 | 0.007 | 9.9 x 10-9 | 48632 | 0.021 | 0.004 | 3.1 x 10-7 | 143669 | 0.02 |
| *TCF7L2* | rs7903146 | 10 | 114758349 | T/C | 0.034 | 0.006 | 1.2 x 10-8 | 68253 | 0.007 | 0.004 | 7.7 x 10-2 | 143675 | 0.027 |
| *ACTL9* | rs2918299 | 19 | 8787273 | C/T | 0.041 | 0.007 | 2.2 x 10-8 | 67603 | 0.028 | 0.005 | 1.4 x 10-7 | 131197 | 0.013 |
| *CYP3A7* | rs45446698 | 7 | 99332948 | G/T | 0.089 | 0.016 | 2.4 x 10-8 | 48632 | 0.021 | 0.010 | 3.7 x 10-2 | 131089 | 0.068 |

Effects (beta values) were aligned to the birth weight-raising allele and are presented in SD units (1 SD of birth weight = 484g (3)). Chr, chromosome; bp, base pair; b37, build 37; SE, standard error.

\*These results are look-ups in published summary data from the most recent fetal GWAS of birth weight (European-only meta-analysis (2)).

**Table S11.** Results of gene set enrichment analysis

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Database** | **Gene set** | **Number of genes (mapped to MAGENTA)** | **95th percentile enrichment cutoff** | | | **75th percentile enrichment cutoff** | | |
| **P** | **FDR** | **Expected (observed) number of genes** | **P** | **FDR** | **Expected (observed) number of genes** |
| REACTOME | Xenobiotics | 15(11) | 0.000002 | 0.0003 | 1(6) | 0.03 | 1.0 | 3(6) |
| GOTERM | Drug metabolic process | 15(14) | 0.00003 | 0.01 | 1(6) | 0.002 | 1.0 | 4(9) |
| KEGG | Linoleic acid metabolism | 29(21) | 0.0004 | 0.02 | 1(6) | 0.02 | 0.25 | 5(10) |
| Ingenuity | PXR/RXR activation | 49(45) | 0.0002 | 0.03 | 2(9) | 0.008 | 0.25 | 11(19) |
| Ingenuity | GM-CSF signaling | 23(20) | 0.002 | 0.04 | 1(5) | 0.22 | 0.55 | 5(7) |
| Ingenuity | Neurotrophin. TRK signalling | 16(15) | 0.004 | 0.04 | 1(4) | 0.31 | 0.64 | 4(5) |
| PANTHER Molecular function | Other actin family cytoskeletal protein | 31(22) | 0.0003 | 0.04 | 1(6) | 0.003 | 0.11 | 6(12) |

Analysis of the overall GWAS summary data to identify enrichment in biological pathways. Top results (FDR < 0.05 at the 95th percentile enrichment threshold) from a total of 3230 pathways tested for enrichment of multiple modest associations between maternal genotype and offspring birth weight.

**Table S12.** Details of proxy SNPs analysed in EGG follow-up studies if the index SNP was unavailable

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **LEAD SNP** | **NEAREST GENE** | **BEST PROXY SNP** | **R2 (1000G PILOT1 CEU)** | **2ND-BEST PROXY SNP** | **R2 (1000G PILOT1 CEU)** |
| rs1920773 | *KERA* | rs1861129 | 1 | rs4842749 | 1 |
| rs17065363 | *LOC285501* | rs62342764 | 1 | rs17065376 | 1 |
| rs11811998 | *MYCL1* | rs72939665 | 1 | rs34387655 | 1 |
| rs10830963 | *MTNR1B* | rs11020124 | NA | NA |  |
| rs4849902 | *INHBB* | NA |  | NA |  |
| rs6692555 | *PLEKHM2* | rs72878883 | 1 | rs6674904 | 1 |
| rs7721459 | *GRAMD3* | rs6879479 | 1 | rs28580210 | 0.908 |
| rs311565 | *POLR1A* | rs311566 | 1 | rs311567 | 1 |
| rs989264 | *NEDD1* | rs989265 | 1 | rs76003827 | 1 |
| rs838324 | *TBX3* | NA |  | NA |  |
| rs12056975 | *ANKS6* | rs10987747 | 1 | rs33998698 | 1 |
| rs9549119 | *FOXO1* | NA |  | NA |  |
| rs3887673 | *CMTM7* | rs77036319 | 1 | rs2304594 | 1 |
| rs17384756 | *EPB41L3* | rs4798380 | 1 | rs4798381 | 1 |
| rs2748343 | *GRAMD4* | rs2748341 | 0.905 | rs2748338 | 0.87 |
| rs4607517 | *GCK* | rs1799884 | 1 | rs2908286 | 1 |
| rs204928 | *LMO1* | rs204926 | 0.967 | rs110420 | 0.935 |
| rs7972086 | *RAD51AP1* | rs7314915 | 1 | rs2907492 | 1 |

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