SUPPLEMENTARY ONLINE MATERIAL

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

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Supplementary Figure 1. Summary of study design.

Stage 1: Discovery

- 18 European GWA studies
- N=26,836 European descent individuals
- Imputed for HapMap2 (2,684,393 SNPs)

Stage 2: Follow-up

- 25 European studies
  - 12 custom genotyping
  - 1 custom + Metabochip
  - 1 custom + in silico GWA
  - 8 in silico GWA
  - 3 Metabochip

- max N=42,519 European descent individuals

Meta-analysis

- 20 SNPs with association P<10^{-5} + HHIP rs6537307 (P=4x10^{-5})

Joint meta-analysis

P<5x10^{-8} represent robust evidence of association
Supplementary Figure 2. Quantile-quantile plot of 2,684,393 single nucleotide polymorphisms (SNPs) from the meta-analysis of up to N=26,836 discovery samples. The black dots represent observed $P$ values and the black line represents the expected $P$ values under the null distribution. The red dots represent observed $P$ values after excluding the previously identified ADCY5 and CCNL1 signals.
Supplementary Figure 3. Manhattan plot of the association $P$ values for birth weight from the discovery meta-analysis ($n$ = up to 26,836). The $-\log_{10}$ of the $P$ value for each of 2,684,393 SNPs (y-axis) is plotted against the genomic position (NCBI Build 36; x-axis). Association signals that reached genome-wide significance ($P < 5 \times 10^{-8}$) in the global meta-analysis of discovery and follow-up studies are shown in red.
**Supplementary Figure 4.** Forest plots of the associations between birth weight and (a) **CCNL1**, (b) **ADCY5**, (c) **HMGA2**, (d) **CDKAL1**, (e) **5q11.2**, (f) **LCORL** and (g) **ADRB1** in Europeans. In each plot, the dashed red line indicates the effect size from the overall meta-analysis of discovery and follow-up samples.

(a) **CCNL1** (overall $n = 61,142$; $P = 3.6 \times 10^{-38}$; heterogeneity $P = 0.49$)
(b) ADCYS (overall $n = 61,509$; $P = 5.5 \times 10^{-20}$; heterogeneity $P = 0.69$)
(c) HMGA2 (overall $n = 68,655$; $P = 1.4 \times 10^{-19}$; heterogeneity $P = 0.82$)
(d) CDKAL1 (overall $n = 68,822$; $P = 1.5 \times 10^{-18}$; heterogeneity $P = 0.57$)
(e) 5q11.2 (overall n = 53,619; P = 4.6x10^{-8}; heterogeneity P = 0.40)
(f) \( LCORL \) (overall \( n = 55,877; P = 4.6 \times 10^{-11} \); heterogeneity \( P = 0.16 \))
(g) *ADRB1* (overall \( n = 49,660; P = 3.6 \times 10^{-9}; \) heterogeneity \( P = 0.97 \))
Supplementary Figure 5. Plot of type 2 diabetes effect size against birth weight effect size (n=5,327 ALSPAC mother-child pairs) for loci achieving $P < 0.01$ in the discovery meta-analysis. Circles are unadjusted for maternal genotype; triangles are adjusted for maternal genotype.
**Supplementary Figure 6.** Associations between SNP rs900400 near *CCNL1* and weight from birth to 6 months in seven studies with available postnatal data. The vertical lines show 95% confidence intervals around the effect size estimates. Total sample sizes: $n = 15,090$ (0 months); $n = 6,952$ (1 month); $n = 5,720$ (2 months); $n = 7,857$ (3 months); $n = 7,535$ (6 months).
**Supplementary Figure 7.** Forest plots of the associations between birth weight and (a) CCNL1, (b) ADCYS, (c) HMGA2, (d) CDKAL1, (e) 5q11.2, (f) LCORL and (g) ADRB1 in non-Europeans. The overall European result is shown for comparison. The non-European studies are from East/Southeast Asia (Chinese [SCORM] and Filipino [CLHNS]), Africa (African-American [CHOP-AfAm], Mandinka [MRC Keneba] and Moroccan [Generation R]), Middle East (Arab [SAUDI], Turkish [Generation R]), and South America (Surinamese [Generation R]).

(a) CCNL1
(b) \textit{ADCY5}
(c) HMGA2
(d) **CDKAL1**

Study ID

- EUROPEAN
- CHOP-AfAm
- CLHNS
- Generation R (Moroccan)
- Generation R (Surinamese)
- Generation R (Turkish)
- MRC Keneba
- SAUDI
- SCORM

![Graph showing study IDs and results for CDKAL1]
(e) 5q11.2
(f) LCORL

Study ID

EUROPEAN
CHOP-AfAm
CLHNS
Generation R (Moroccan)
Generation R (Surinamese)
Generation R (Turkish)
MRC Keneba
SAUDI
SCORM
(g) ADRB1

Study ID

EUROPEAN
CHOP-AfAm
CLHNS
Generation R (Moroccan)
Generation R (Surinamese)
Generation R (Turkish)
SAUDI
SCORM
Supplementary Figure 8. Ethnicity-specific regional plots for (a) CCNL1 and (b) ADCYS in European (n=26,813), East/Southeast Asian (n=2,135) and African American (n=6,315). Directly genotyped or imputed SNPs are plotted as a function of genomic position (NCBI Build 36). In each panel, the European discovery stage SNP taken forward for follow-up, i.e. rs900400 in CCNL1 and rs9883204 in ADCYS, is represented by a purple diamond. Estimated recombination rates are plotted to reflect the local LD structure around these SNPs (according to a blue to red scale from $r^2 = 0$ to $1$, based on pairwise $r^2$ values from HapMap CEU, JPT+CHB, and YRI, respectively).
(a) CCNL1

European

East/Southeast Asian

African American
(b) ADCY5

European

East/Southeast Asian

African American
**Supplementary Figure 9.** Box plot showing the percentage variance in birth weight explained by five related characteristics (x-axis) in all 43 European studies. Diamond = median; box = interquartile range; whiskers = median +/- 2*interquartile range; circle = outlier.
SUPPLEMENTARY NOTE

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written informed consent was obtained from mothers at all follow-ups and participants at the year 17 follow-up.

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SUPPLEMENTARY NOTE

The Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) investigators:


AFFILIATIONS
1Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden; the 2Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts; the 3National Heart, Lung, and Blood Institute’s Framingham Heart Study, Framingham, Massachusetts; the 4Oxford Centre for Diabetes Endocrinology and Metabolism, University of Oxford, Oxford, U.K.; the 5Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, U.K.; the 6MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke’s Hospital, Cambridge, U.K.; the 7Department of Clinical Sciences, Diabetes and Endocrinology, University Hospital and Malmö, Lund University, Malmö, Sweden; the 8Boston University Data Coordinating Center, Boston, Massachusetts; the 9BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, U.K.; the 10Université Lille-Nord de France, Lille, France; the 11CNRS UMR 8199, Institut Pasteur de Lille, Lille, France; the 12Department of Genetic Medicine and Development, University of Geneva Medical School, Geneva, Switzerland; the 13Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, U.K.; the 14Metabolic Disease Group, Wellcome Trust Sanger Institute, Hinxton, Cambridge, U.K.; the 15Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts; the 16Center for Human Genetic Research and Diabetes Research Center (Diabetes Unit), Massachusetts General Hospital, Boston, Massachusetts; the 17Department of Dietetics-Nutrition, Harokopio University, Athens,
Health, Bethesda, Maryland; the 59Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford, U.K.; the 60General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts; the 61Department of Medicine, Harvard Medical School, Boston, Massachusetts; the 62University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke’s Hospital, Cambridge, U.K.; the 63Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; and the 64Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California.
SUPPLEMENTARY NOTE

Early Growth Genetics Consortium (EGG) Membership and Affiliations


1. Department of Nutrition, University of North Carolina, Chapel Hill, NC.
2. School of Women’s and Infants’ Health, The University of Western Australia, Perth, Australia.
3. Department of Physiology, Institute of Biomedicine, University of Eastern Finland, Kuopio, Finland.
4. Department of Biological Psychology, VU University, Amsterdam, The Netherlands.
5. The Generation R Study Group, Erasmus Medical Center, Rotterdam, the Netherlands.
6. Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands.
7. Centre For Paediatric Epidemiology and Biostatistics/MRC Centre of Epidemiology for Child Health, University College of London Institute of Child Health, London, UK.
9. Hospital del Mar Research Institute (IMIM), Barcelona, Catalonia, Spain.
10. Centro de Investigacion Biomedica en Red en Epidemiologia y Salud Publica (CIBERESP), Barcelona, Catalonia, Spain.
11. Center for Research in Environmental Epidemiology (CREAL), Barcelona, Catalonia, Spain.
12. Genes and Disease Program, Centre for Genomic Regulation (CRG), UPF, Barcelona, Catalonia, Spain.
40

13. Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, UK.
14. Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
15. Medical Research Council (MRC) Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King’s College London, UK.
16. MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom.
17. Institute of Molecular Medicine Finland, University of Helsinki, Helsinki, Finland.
18. Department of Dietetics - Nutrition, Harokopio University of Athens, Athens, Greece.
19. MRC Health Protection Agency (HPA) Centre, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK.
20. Pompeu Fabra University (UPF), Barcelona, Catalonia, Spain.
21. MRC Centre for Causal Analyses in Translational Epidemiology, School of Social and Community Medicine, University of Bristol, Bristol, UK.
22. Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark.
23. Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland.
24. Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, University of Exeter, Magdalen Road, Exeter, EX1 2LU, UK.
25. Obesity Prevention Program, Department of Population Medicine, Harvard Medical School/Harvard Pilgrim Health Care Institute, Boston, MA 02215 USA.
27. Saw Swee Hock School of Public Health, National University of Singapore.
29. Department of Pediatrics, University of Pennsylvania, Philadelphia PA 19104, USA.
30. Peninsula National Institute for Health Research (NIHR) Clinical Research Facility, Peninsula College of Medicine and Dentistry, University of Exeter, Barrack Road, Exeter, EX2 5DW, UK.
31. Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA.
32. Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Essen, Germany.
33. Division of Genetics, Children’s Hospital, Boston, Massachusetts 02115, USA.
34. Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA.
35. Metabolism Initiative, Broad Institute, Cambridge, Massachusetts 02142, USA.
36. Division of Endocrinology, Children’s Hospital, Boston, Massachusetts 02115, USA.
37. Program in Genomics, Children’s Hospital, Boston, Massachusetts 02115, USA.
38. Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts 02142, USA.
39. Institute of Nutritional Science, University of Potsdam, D-14558 Nuthetal Potsdam, Germany.
40. Center for Cardiovascular Research/Institute of Pharmacology, Charité, Berlin, Germany.
41. Human Genetics and Medical Genomics, Human Development & Health, Faculty of Medicine, University of Southampton.
42. Clinical & Experimental Sciences, Faculty of Medicine, University of Southampton.
43. Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark.
44. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LJ, UK.
45. Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK.
46. Institute of Health Sciences, University of Oulu, Finland.
47. Department of Genomics of Common Disease, School of Public Health, Imperial College London.
48. Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany.
49. Hannover Unified Biobank, Hannover Medical School, Hannover, Germany.
50. Division of Environment and Health, Center for Public Health Research-CSISP, Valencia, Spain.
51. Department of Paediatrics, Erasmus Medical Center, Rotterdam, the Netherlands.
52. Biocenter Oulu, University of Oulu, Finland.
54. Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.
55. Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland.
56. Department of Public Health, Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio Campus, Finland.
57. Department of Genetics, University of North Carolina, Chapel Hill, NC.
58. Department of Clinical Chemistry, Tampere University Hospital, Tampere, Finland.
59. Department of Clinical Chemistry, University of Tampere School of Medicine, Tampere, Finland
60. Genetic and Genomic Epidemiology Unit, The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
61. Estonian Genome Center, University of Tartu, Tartu, Estonia.
62. Oxford NIHR Biomedical Research Centre, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LJ, UK.
63. Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford, UK.
64. Department of Physiology and Biophysics, Weill Cornell Medical College - Qatar, Doha, Qatar.
65. Department of Pediatrics, University of Iowa, Iowa City, Iowa, USA.
66. MRC Epidemiology Unit, Institute of Metabolic Science, Cambridge, CB2 0QQ, United Kingdom.
67. Samuel Lunenfeld Research Institute, University of Toronto, Toronto, Canada
68. Genetic Epidemiology and Biostatistics Platform, Ontario Institute for Cancer Research, Toronto, Ontario, Canada
69. Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK.
70. Biomedical Research Institute, University of Dundee, Dundee, UK.
71. Department of Clinical Physiology, University of Turku and Turku University Hospital, Turku, Finland.
72. Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland.
73. Department of Psychology, Mid Sweden University, Sweden.
74. Singapore Eye Research Institute, Singapore.
75. Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany.
76. Department of Pediatrics, University of Turku and Turku University Hospital, Turku, Finland.
77. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom.
78. Department of Psychological Medicine and Neurology, Cardiff University School of Medicine, Cardiff, UK
79. MRC Centre in Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK.
80. Division of Population Health Sciences and Education, St George's, University of London
81. Division of Metabolic Diseases and Nutritional Medicine, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University of Munich, Munich, Germany.
82. Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands.
83. Chair of Epidemiology, Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany.
84. Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians-Universität, Munich, Germany.
85. MRC Institute of Genetics and Molecular Medicine at the University of Edinburgh, Western General Hospital, Edinburgh, EH4 2XU, Scotland