Human Molecular Genetics, 2015, Vol. 24, No. 4 **1155–1168**
doi:10.1093/hmg/ddu510
Advance Access published on October 3, 2014

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

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Received July 3, 2014; Revised and Accepted September 29, 2014

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*, *PTCH1*, *GPR126* and *HMGA2*). The three novel SNPs were followed-up in nine replication studies (Stage 2; $N = 11\,995$), with rs905938 in *DC-STAMP domain containing 2* (*DCST2*) 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 ($N = 127\,513$; $P = 1.45 \times 10^{-5}$). DCST2 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*, *PTCH1*, *GDF5*, *ZNFX1*, *HHIP*, *ACAN*, *HLA* locus and *HMGA2*). This study highlights that common variation in *DCST2* 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

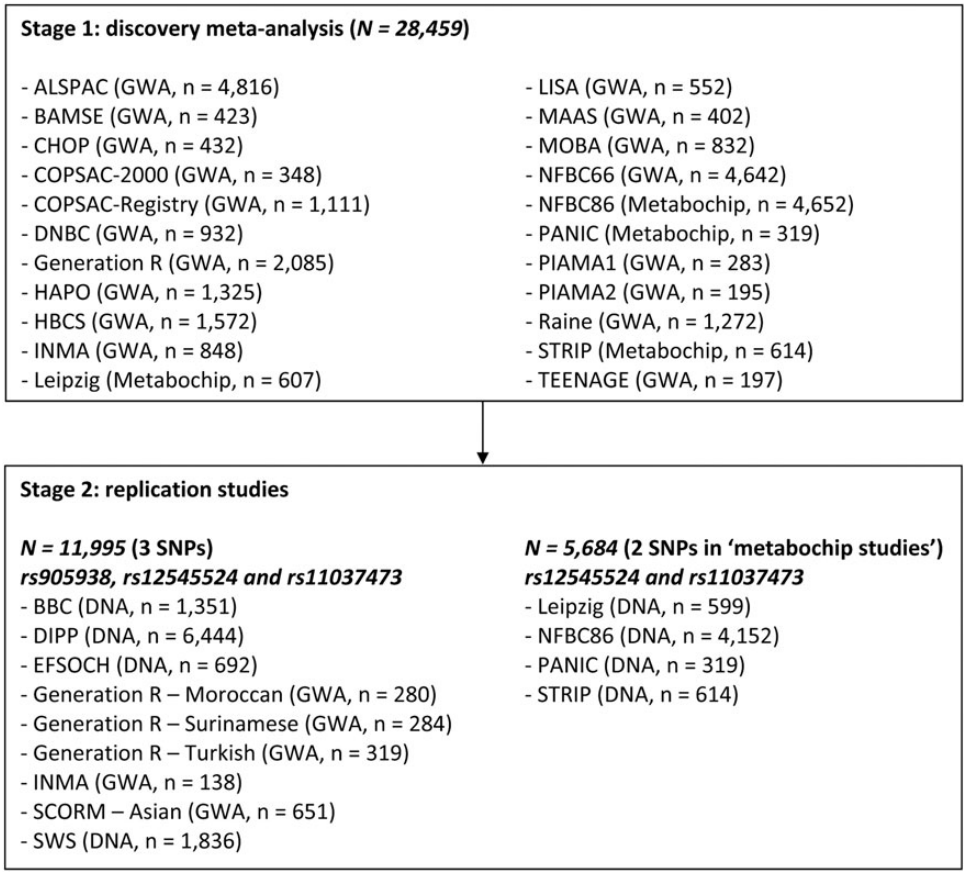

Figure 1 Study design.

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

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

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 *HMGA2*). MAF, minor allele frequency; SE, standard error. β reflects differences in standardized birth length per minor allele. *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.

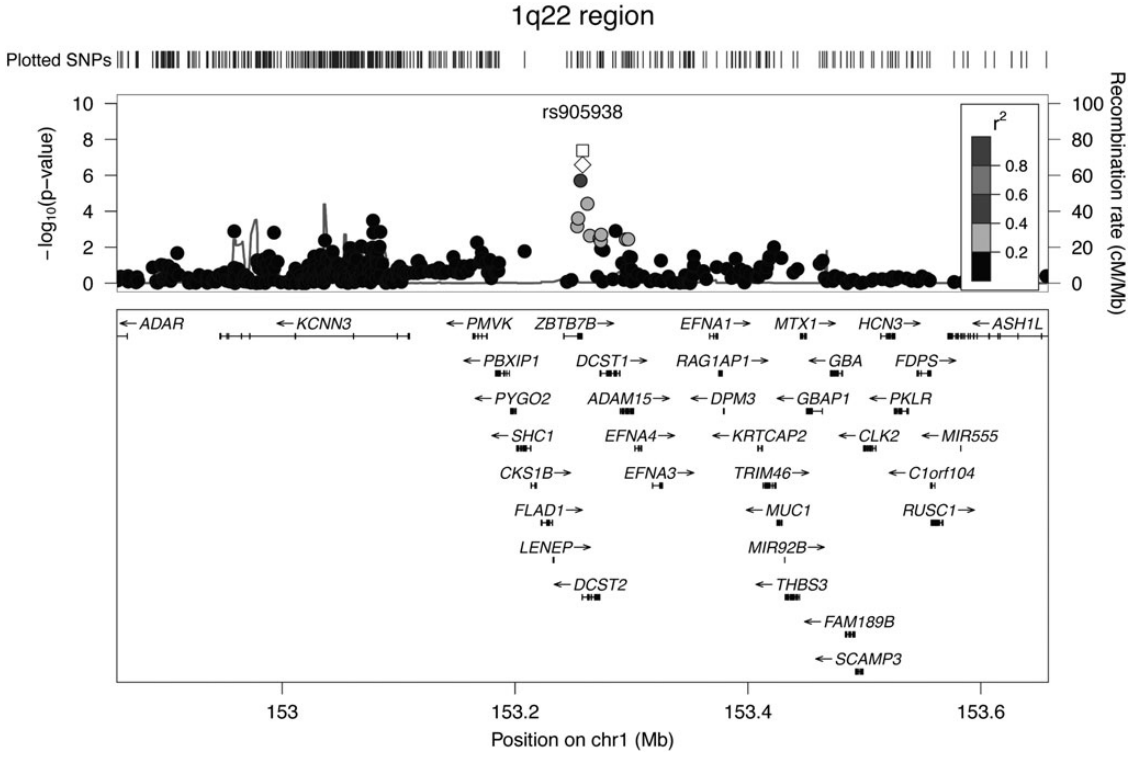

Figure 2 Regional association plot of 1q22 in the 22 birth length discovery studies ($N = 28\,459$). SNPs are plotted with their *P* values (as $-\log_{10}$ values; left *y*-axis) as a function of genomic position (*x*-axis). Estimated recombination rates (right *y*-axis) taken from HapMap are plotted to reflect the local LD-structure around the top associated SNP ('white open diamond') and the correlated proxies ('circles' according to a black-to-gray scale from $r^2 = 0$ to 1). The joint analysis *P* value of discovery and replication studies is reported with the 'white square' ($N = 40\,235$).

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

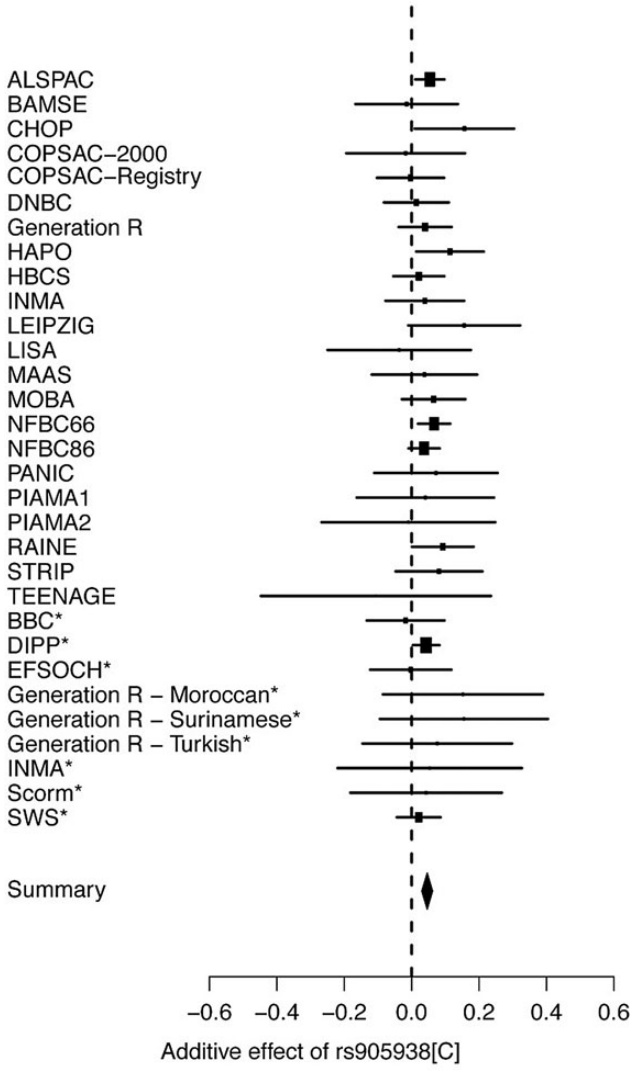

Figure 3 Forest plot of the associations between rs905938[C] and birth length. *Replication studies. The 'black diamond' indicates the overall effect size and the confidence interval of the 31 studies.

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 ($N = 127\,513$) (5). Rs905938[C] was not associated with 'fetal growth' measures, but was associated with infant length and adult height ($P < 0.05$; Table 2).

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

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

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

rs905938 C-allele with a genome-wide significant effect on birth length is shown ($P < 5 \times 10^{-8}$) in relation to 'fetal growth' measures, infant length and adult height. SE, standard error. β reflects difference in standard deviation scores per minor allele.

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*, *ZNFX1*, *HHIP*, *ACAN*, *HLA* locus and *HMGA2*) (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 ($P = 3.10 \times 10^{-17}$, 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 ($r^2 < 0.05$) associated at $P < 1 \times 10^{-5}$, 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

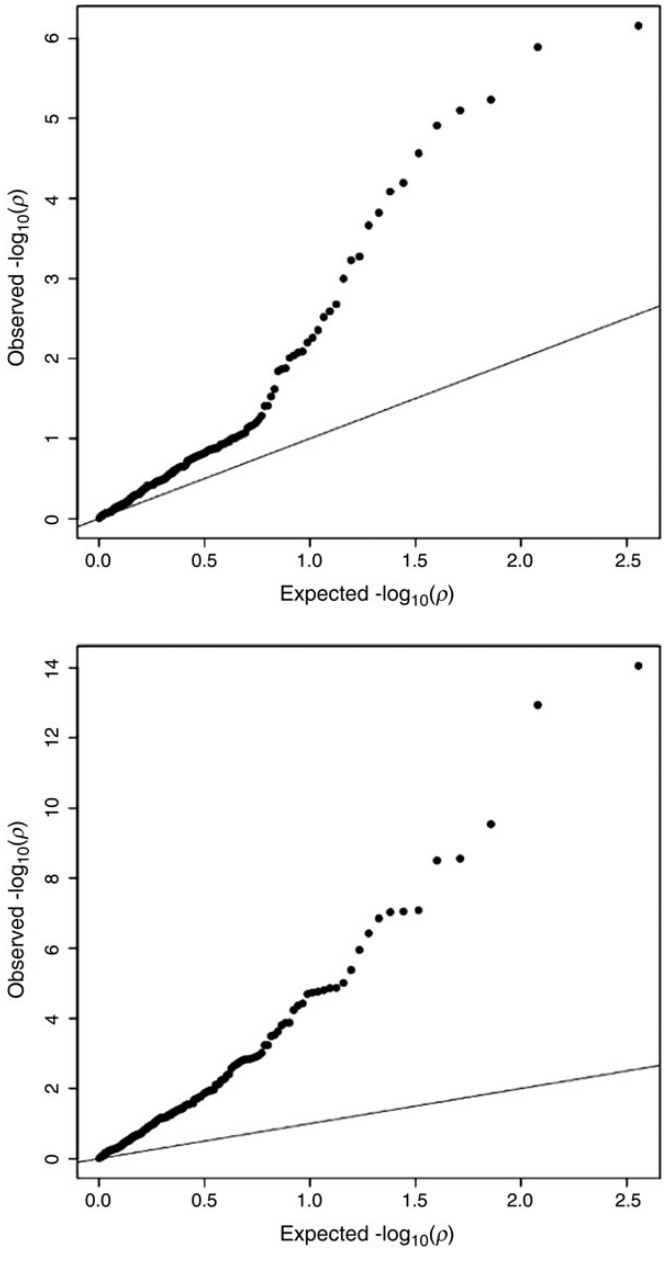

Figure 4 *QQ*-plots of the 180 known adult height SNPs with birth and infant length. *QQ*-plot of the 180 known adult height SNPs in association with birth length (upper panel) in 22 studies ($N = 28\,459$) and with infant length (lower panel) in 19 studies ($N = 28\,238$). The black dots represent observed *P* values and the diagonal lines represent the expected *P* values under the null distribution.

gene sets (e.g. abnormal sternum ossification, regulation of osteoblast proliferation and WNT signaling, Supplementary Material, Table S10). There was no significant enrichment for particular tissue or cell types for any of the two traits.

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 osteoblasts and to a lesser extent in osteoclasts (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 osteoblasts 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, $P = 6.25 \times 10^{-13}$). One hundred sixty-two of the 180 loci were in the same direction for infant length (Supplementary Material, Table S8; probability of success = 0.900, $P = 2.20 \times 10^{-16}$).

Four SNPs associated with birth length ($P < 1 \times 10^{-5}$) 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 ($\beta = 0.035$ SDS, SE = 0.010, $P = 2.35 \times 10^{-4}$, $N = 26\,558$).

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

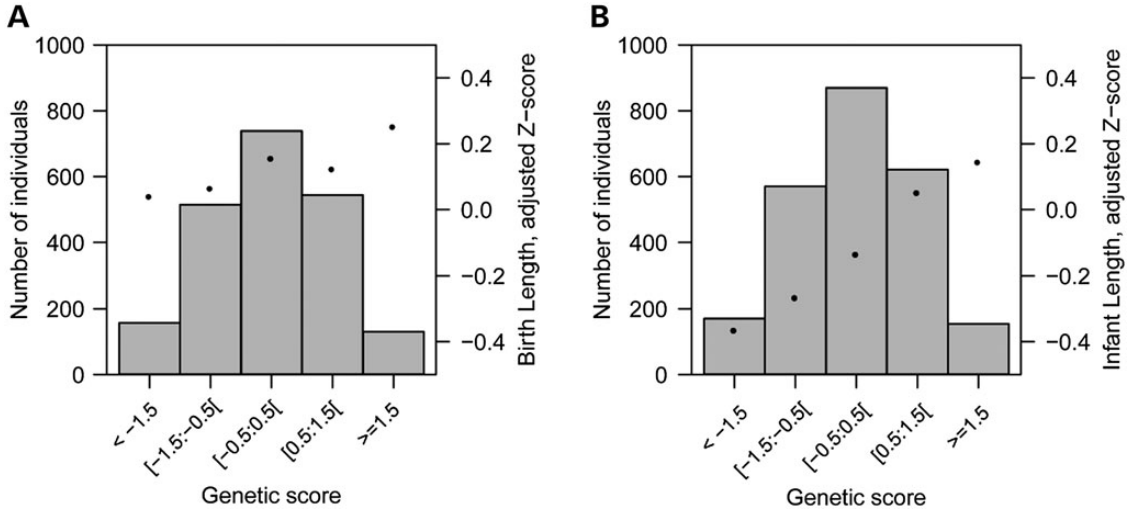

Figure 5 Height-increasing-alleles score of known adult height SNPs predicting birth and infant length. Genetic risk-allele scores (sum of height-increasing alleles weighted by known effect on adult height (5) transformed to standard deviation *Z*-scores) in the Generation R study plotted against length adjusted for sex and age. The distribution of the genetic risk-allele score is depicted as bars. (**A**) Mean birth length plotted against the genetic score ($N = 2085$). (**B**) Mean infant length plotted against the genetic score ($N = 2385$).

Table 3 Summary statistics of the eleven known adult height SNPs in association with infant length at $P < 5 \times 10^{-8}$

Marker	MAF	β	SE	P	n	I^2	*HetP*
rs7536458[G] at 1p12 (*SPAG17*)	0.25	−0.064	0.010	9.61×10^{-11}	28234	0.0	0.403
rs11205303[C] at 1q21.2 (*SF3B4*)	0.34	0.087	0.011	1.79×10^{-16}	26559	0.0	0.864
rs1380294[T] at 4p15.31 (*LCORL*)	0.15	−0.108	0.014	2.54×10^{-14}	23079	13.7	0.184
rs1812175[A] at 4q28-q32(*HHIP*)	0.18	−0.068	0.011	2.33×10^{-9}	28227	0.0	0.398
rs592229[G] at (*HLA* locus)	0.43	0.048	0.009	2.22×10^{-8}	28223	0.6	0.326
rs9385399[T] at 6q22.32 (*C6orf173*)	0.46	0.055	0.009	1.68×10^{-10}	28224	0.0	0.943
rs1984119[C] at 9q22.3 (*PTCH1*)	0.26	−0.063	0.010	1.77×10^{-10}	28197	0.0	0.490
rs7970350[T] at 12q15 (*HMGA2*)	0.49	−0.047	0.009	2.90×10^{-8}	28226	0.0	0.426
rs2280470[A] at 15q26.1 (*ACAN*)	0.36	0.053	0.009	6.43×10^{-9}	27443	0.0	0.436
rs143384[G] at 20q11.2 (*GDF5*)	0.44	0.058	0.009	2.87×10^{-10}	28232	0.0	0.996
rs1567865[T] at 20q13.13 (*ZNFX1*)	0.21	0.063	0.010	1.10×10^{-9}	28229	22.5	0.104

SNPs markers are identified according to their standard rs numbers (NCBI build 36). The total sample includes data of 19 independent datasets ($N = 28\,238$). MAF, minor allele frequency; SE, standard error. β reflects differences in standardized infant length per minor allele. *P* values are obtained from linear regression of each SNP against standardized infant length adjusted for sex and age. We included both GWA and metabochip cohorts in our discovery analysis, 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.

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 subsample 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, Metbochip, $n = 607$); Lifestyle Immune System Allergy study (LISA, GWA, $n = 552$);

Manchester Asthma and Allergy Study (MAAS, GWA, $n = 402$); Norwegian Mother and Child Cohort study (MOBA, GWA, $n = 832$); Northern Finland Birth Cohorts 1966 (NFBC66, GWA, $n = 4642$); Northern Finland Birth Cohorts 1986 (NFBC86, Metabochip, $n = 4652$); Physical Activity and Nutrition in Children study (PANIC, Metabochip, $n = 319$); two subsamples from the Prevention and Incidence of Asthma and Mite Allergy birth cohort study (PIAMA1, GWA, $n = 283$; PIAMA2, GWA, $n = 195$); The Western Australian Pregnancy Cohort Study (RAINE, GWA, $n = 1272$); Special Turku Coronary Risk Factor Intervention Project (STRIP, Metabochip, $n = 614$); and TEENs of Attica: Genes and Environment (TEENAGE, GWA, $n = 197$). While no systematic phenotypic differences were observed between the sub-samples of the PIAMA birth cohort study, they were analyzed separately due to genotyping on different platforms and at different time periods. Genotypes within each study were obtained using high-density SNP arrays and then imputed for ~2.5 M HapMap SNPs (Phase II, release 22; http://hapmap.ncbi.nlm.nih.gov/). The basic characteristics, exclusions applied (for example, individuals of non-European ancestry, family related individuals), genotyping, quality control and imputation methods for each discovery study are presented in Supplementary Material, Table S1.

Statistical analysis within discovery studies

In all studies, birth length was measured using standardized procedures. 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 SDS. We used the North-European 1991 reference panel to compare results between studies. Multiple births and twins were excluded from all analyses. We applied linear regression between number of alleles or dosages obtained from imputations and standardized birth length. The GWA analysis per study was performed using MaCH2qtl (28), SNPTEST (29), PLINK (30) or PropABEL (31). The secured data exchange and storage were facilitated by the Erasmus Medical Center, Department of Internal Medicine (32).

Meta-analysis of discovery studies

Prior to meta-analysis, SNPs with a MAF <0.01 and poorly imputed SNPs [r2hat <0.3 (MaCH); proper_info <0.4 (IMPUTE2); R2_BEALE <0.4 (BEAGLE)] were filtered. Genomic control (GC) (33) was applied to adjust the statistics generated within each cohort (see Supplementary Material, Table S1 for individual study λ values). Four out of the twenty-two sub-samples were genotyped on Metabochips. These SNP-arrays were enriched with 'adult height SNPs'. Normal variation in early length growth seems to be associated with height in adulthood (1). Therefore, we assumed more true-positive hits in these studies and did not apply GC in these studies (GIANT *et al.*, unpublished data). Details of any additional corrections for study specific population structure are given in the Supplementary Material, Table S1. Inverse variance fixed-effects meta-analyses were analyzed using METAL (released 2010-08-01) (34) by two meta-analysts in parallel and blinded to obtain identical results. After the METAL meta-analysis, we filtered SNPs with a MAF <0.05 and SNPs that were not available in at least 12 sub-samples to avoid false-positive findings. We used Cochran's Q test and the derived inconsistency statistic I^2 to assess evidence 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 ≤ 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 Heading 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.

ACKNOWLEDGEMENTS

Avon Longitudinal Study of Parents And Children (ALSPAC): We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. GWAS data were generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) supported by 23andMe. The Wellcome Trust and Swiss National Science Foundation funded the expression data. Ethical approval was obtained from the ALSPAC Law and Ethics Committee and the Local Ethics Committees. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

BAMSE: Supported by the Swedish Research Council, the Swedish Heart Lung Foundation, the Centre for Allergy Research (CfA), Stockholm County Council (ALF) and SFO Program in Epidemiology, KI.

Children's Hospital Of Philadelphia (CHOP): The authors thank the network of primary care clinicians and the patients and families for their contribution to this project and to clinical research facilitated by the Pediatric Research Consortium (PeRC) at The Children's Hospital of Philadelphia. R. Chiavacci, E. Dabaghyan, A. (Hope) Thomas, K. Harden, A. Hill, C. Johnson-Honesty, C. Drummond, S. Harrison, F. Salley, C. Gibbons, K. Lilliston, C. Kim, E. Frackelton, F. Mentch, G. Otieno, K. Thomas, C. Hou, K. Thomas and M.L. Garris provided expert assistance with genotyping and/or data collection and management. The authors would also like to thank S. Kristinsson, L.A. Hermannsson and A. Krisbjörnsson of Raförninn ehf for extensive software design and contributions. This research was financially supported by an Institute Development Award from the Children's Hospital of Philadelphia, a Research Development Award from the Cotswold Foundation and NIH grant R01 HD056465.

COPSAC-2000/Registry: We gratefully express our gratitude to the children and families of the COPSAC2000 cohort study for all their support and commitment. We acknowledge and appreciate the unique efforts of the COPSAC research team.

Danish National Birth Cohort (DNBC): Support for the Danish National Birth Cohort was obtained from the Danish National Research Foundation, the Danish Pharmacists' Fund, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation and the Health Fund of the Danish Health Insurance Societies. The generation of GWAS genotype data for the DNBC samples was carried out within the GENEVA consortium with funding provided through the NIH Genes, Environment and Health Initiative (GEI) (U01HG004423). Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (U01HG004446). Genotyping was performed at Johns Hopkins University Center for Inherited Disease Research, with support from the NIH GEI (U01HG004438).

The Generation R Study (Generation R): The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from all participants. The generation and management of GWAS genotype data for the Generation R Study were done at the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Netherlands. We would like to thank Karol Estrada, Dr Tobias A. Knoch, Anis Abuseiris, Luc V. de Zeeuw and Rob de Graaf, for their help in creating GRIMP, BigGRID, MediGRID and Services@MediGRID/D-Grid, (funded by the German Bundesministerium fuer Forschung und Technology; grants 01 AK 803 A-H, 01 IG 07015 G) for access to their grid computing resources. We thank Mila Jhamai, Manoushka Ganesh, Pascal Arp, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters for their help in creating, managing and QC of the GWAS database. Also, we thank Karol Estrada for their support in creation and analysis of imputed data. The Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development.

Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: We are indebted to the participants, investigators and

research staff of the HAPO study at each of the following centers: Newcastle and Brisbane, Australia; Bridgetown, Barbados; Toronto, Canada; Hong Kong, Hong Kong; Bangkok, Thailand; Belfast and Manchester, UK; Bellflower, CA, Chicago, IL, Cleveland, OH and Providence, RI, USA. This work was supported by US National Institutes of Health (NIH) grants (HD34242, HD34243, HG004415 and CA141688) and by the American Diabetes Association. Genotype cleaning and general study coordination were provided by the GENEVA Coordinating Center (U01HG004446). Genotyping was performed at the Broad Institute of MIT and Harvard, with funding support from the NIH GEI (U01HG04424), and Johns Hopkins University Center for Inherited Disease Research, with support from the NIH GEI (U01HG004438) and the NIH contract 'High throughput genotyping for studying the genetic contributions to human disease' (HHSN268200782096C).

Helsinki Birth Cohort Study (HBCS): The Helsinki Birth Cohort Study (HBCS/HBCS 1934-44) thanks Professor David Barker and Tom Forsen. Major financial support was received from the Academy of Finland (project grants 209072, 129255 grant) and British Heart Foundation. The DNA extraction, sample quality control, biobank up-keep and aliquoting were performed at the National Institute for Health and Welfare, Helsinki, Finland.

The INMA Project: This study was funded by grants from Instituto de Salud Carlos III (Red INMA G03/176 and CB06/02/0041), FIS-FEDER 03/1615, 04/1509, 04/1112, 04/1931, 05/1079, 05/1052, 06/1213, 07/0314, 09/02647, 11/01007, 11/02591, 13/02032, 13/1944, PI041436, PI081151, CP11/00178, 97/0588, 00/0021-2, PI061756 and PS0901958, Spanish Ministry of Science and Innovation (SAF2008-00357), European Commission (ENGAGE project and grant agreement HEALTH-F4-2007-201413), Fundació La Marató de TV3, Generalitat de Catalunya-CIRIT 1999SGR 00241 and Conselleria de Sanitat Generalitat Valenciana. Part of the DNA extractions and genotyping was performed at the Spanish National Genotyping Centre (CEGEN-Barcelona). The authors are grateful to Silvia Fochs, Anna Sànchez, Maribel López, Nuria Pey, Muriel Ferrer, Amparo Quiles, Sandra Pérez, Gemma León, Elena Romero, Maria Andreu, Nati Galiana, Maria Dolores Climent and Amparo Cases for their assistance in contacting the families and administering the questionnaires. The authors would particularly like to thank all the participants for their generous collaboration. A full roster of the INMA Project Investigators can be found at http://www.proyectoinma.org/presentacion-inma/listado-investigadores/en_listado-investigadores.html.

Leipzig Obesity Childhood Cohort: The Leipzig Childhood Obesity cohort is supported by grants from Integrated Research and Treatment Centre (IFB) Adiposity Diseases FKZ: 01EO1001, from the German Research Foundation for the Clinical Research Center 'Obesity Mechanisms' CRC1052/1 C05. We are grateful to all the patients and families for contributing to the study. We highly appreciate the support of the Obesity Team and Auxo Team of the Leipzig University Children's Hospital for management of the patients and to the Pediatric Research Center Lab Team for support with DNA banking.

Lifestyle—Immune System—Allergy (LISA) Study Munich: Generation of GWA data in the LISAplus study in Munich were covered by Helmholtz Zentrum Munich, Helmholtz Centre for Environmental Research. In addition, this work was supported by the Kompetenznetz Adipositas (Competence Network Obesity) funded by the Federal Ministry of Education and Research (FKZ: 01GI1121A).The authors thank all families for participation in the study; the obstetric units for allowing recruitment and the LISA study teams for excellent work.

Manchester Asthma and Allergy Study (MAAS): We would like to thank the children and their parents for their continued support and enthusiasm. We greatly appreciate the commitment they have given to the project. We would also like to acknowledge the hard work and dedication of the study team (post-doctoral scientists, research fellows, nurses, physiologists, technicians and clerical staff). MAAS was supported by the Asthma UK Grants No 301 (1995–1998), No 362 (1998–2001), No 01/012 (2001–2004), No 04/014 (2004–2007) and The Moulton Charitable Foundation (2004-current); age 11 years clinical follow-up is funded by the Medical Research Council (MRC) Grant G0601361.

Norwegian Mother Child Cohort (MoBa): his work was supported by grants from the Norwegian Research Council (FUGE 183220/S10, FRIMEDKLI-05 ES236011), Swedish Medical Society (SLS 2008-21198), Jane and Dan Olsson Foundations and Swedish government grants to researchers in the public health service (ALFGBG-2863, ALFGBG-11522), and the European Community's Seventh Framework Programme (FP7/2007–2013), ENGAGE Consortium, grant agreement HEALTH-F4-2007–201413. The Norwegian Mother and Child Cohort Study was also supported by the Norwegian Ministry of Health and the Ministry of Education and Research, NIH/NIEHS (contract no. N01-ES-75558), NIH/NINDS (grant no.1 UO1 NS 047537-01 and grant no.2 UO1 NS 047537-06A1), and the Norwegian Research Council/FUGE (grant no. 151918/S10). We are grateful to all the participating families in Norway who take part in this ongoing cohort study. Researchers interested in using MoBa data must obtain approval from the Scientific Management Committee of MoBa and from the Regional Committee for Medical and Health Research Ethics for access to data and biological material.

Northern Finland Birth Cohort 1966 (NFBC1966) and 1985–1986 (NFBC1986): We acknowledge late Professor Paula Rantakallio (launch of NFBC1966 and initial data collection), Ms Sarianna Vaara (data collection), Ms Tuula Ylitalo (administration), Mr Markku Koiranen (data management), Ms Outi Tornwall and Ms Minttu Jussila (DNA biobanking).

The PANIC Study: We thank the voluntary children and their families who participated in The PANIC Study. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo. All children and their parents gave their informed written consent. The PANIC Study has been financially supported by grants from the Ministry of Social Affairs and Health of Finland, the Ministry of Education and Culture of Finland, the University of Eastern Finland, the Finnish Innovation Fund Sitra, the Social Insurance Institution of Finland, the Finnish Cultural Foundation, the Juho Vainio Foundation, the Foundation for Paediatric Research, the Paulo Foundation, the Paavo Nurmi Foundation, the Diabetes Research Foundation, Kuopio University Hospital (EVO-funding number 5031343) and the Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding.

The prevention and incidence of asthma and mite allergy birth cohort study (PIAMA1 and PIAMA2): The PIAMA birth cohort

study is a collaboration of the Institute for Risk Assessment Sciences, University Utrecht (B. Brunekreef), Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (H.A. Smit), Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven (A.H. Wijga), Department of Pediatrics, Division of Respiratory Medicine, Erasmus MC-Sophia, Rotterdam (J.C.d.J.), the Departments of Epidemiology (M.K.), Pulmonology (D.S.P.) and Pediatric Pulmonology and Pediatric Allergology (G.H.K.) of the University Medical Center Groningen and the Department of Immunopathology, Sanquin Research, Amsterdam (R.C. Aalberse), the Netherlands. The study team gratefully acknowledges the participants in the PIAMA birth cohort study, and all coworkers who helped conducting the medical examinations, field work and data management. The PIAMA study was funded by grants from the Dutch Asthma Foundation (grant 3.4.01.26, 3.2.06.022, 3.4.09.081 and 3.2.10.085CO), the ZON-MW Netherlands Organization for Health Research and Development (grant 912-03-031), the Stichting Astmabestrijding and the Ministry of the Environment. Genome-wide genotyping was funded by the European Commission as part of GABRIEL (a multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community) contract number 018996 under the Integrated Program LSH-2004-1.2.5-1 Post genomic approaches to understand the molecular basis of asthma aiming at a preventive or therapeutic control.

The Western Australian Pregnancy (RAINE) Cohort: The authors are grateful to the Raine Study participants and their families, and to the Raine Study research staff for cohort coordination and data collection. The authors gratefully acknowledge the NH&MRC for their long-term contribution to funding the study over the last 20 years and also the following Institutions for providing funding for Core Management of the Raine Study: The University of Western Australia (UWA), Raine Medical Research Foundation, UWA Faculty of Medicine, Dentistry and Health Sciences, The Telethon Institute for Child Health Research, Curtin University and Women and Infants Research Foundation. The authors gratefully acknowledge the assistance of the Western Australian DNA Bank (National Health and Medical Research Council of Australia National Enabling Facility). The authors also acknowledge the support of the National Health and Medical Research Council of Australia (Grant ID 403981 and ID 003209) and the Canadian Institutes of Health Research (Grant ID MOP-82893). The study was conducted with appropriate institutional ethics approval, and written informed consent was obtained from mothers at all follow-ups and participants at the year 17 follow-up.

Special Turku Coronary Risk Factor Intervention Project (Strip): The study was approved by the Joint Commission on Ethics of the Turku University and the Turku University Central Hospital. Informed consent was obtained from all parents at the beginning of the trial and from the children at 15 years of age. The STRIP study was financially supported by Academy of Finland (grants 206374 and 251360); Juho Vainio Foundation; Finnish Cardiac Research Foundation; Finnish Cultural Foundation; Finnish Ministry of Education and Culture; Sigrid Juselius Foundation; Yrjö Jahnsson Foundation; C.G. Sundell Foundation; Special Governmental Grants for Health Sciences Research, Turku University Hospital; Foundation for Pediatric Research; and Turku University Foundation.

TEENAGE: TEENAGE study has been co-financed by the European Union (European Social Fund—ESF) and Greek national funds through the Operational Program 'Education and Lifelong Learning' of the National Strategic Reference Framework (NSRF)—Research Funding Program: Heracleitus II Investing in knowledge society through the European Social Fund. This work was funded by the Wellcome Trust (098051). We would like to thank all study participants and their families as well as all volunteers for their contribution in this study. We thank the following staff from the Sample Management and Genotyping Facilities at the Wellcome Trust Sanger Institute for sample preparation, quality control and genotyping: Dave Jones, Doug Simpkin, Emma Gray, Hannah Blackburn, Sarah Edkins.

Berlin Birth Cohort (BBC): The Berlin Birth Cohort study was funded by the Deutsche Forschungsgemeinschaft (DFG), Else Kröner-Fresenius Foundation, Jackstädt-Foundation and a research grant of the University of Potsdam, Germany. Details of the study are provided in refs (43–45). We deeply acknowledge the contribution of the participating families. Replication genotyping was supported by ENGAGE Framework VII HEALTH-F4-2007-201413 and Wellcome Trust 098381.

Diabetes Prediction and Prevention (DIPP): The DIPP study was supported by the following grants: International: Juvenile Diabetes Research Foundation International (grants 4-1998-274, 4-1999-731, 4-2001-435); European Union (grant BMH4-CT98-3314); Novo Nordisk Foundation; the Academy of Finland (Decision No. 250124 and Centre of Excellence in Molecular Systems Immunology and Physiology Research 2012–2017, Decision No. 250114), the Sigrid Jusélius Foundation, and the Special Research Funds for University Hospitals in Finland. We thank the participating DIPP families and the DIPP staff.

Exeter Family Study Of Childhood Health (EFSOCH): The EFSOCH study was supported by South West NHS Research and Development, Exeter NHS Research and Development, the Darlington Trust, and the Peninsula NIHR Clinical Research Facility at the University of Exeter. We are extremely grateful to the EFSOCH study participants and the EFSOCH study team. The opinions given in this paper do not necessarily represent those of NIHR, the NHS or the Department of Health. Genotyping of EFSOCH DNA samples was supported by Diabetes UK grant RD08/0003692. The local research ethics committees approved the study, and all adult participants gave informed written consent.

Singapore Cohort study Of the Risk factors for Myopia study (SCORM): This study is supported by the National Medical Research Council Grant NMRC/0695/2002, Singapore.

Southampton Women''s Survey (SWS): The SWS was funded by the Medical Research Council Of Great Britain, the British Heart Foundation, the European Union Framework 7 Programme, the NIHR Nutrition Biomedical Research Centre, University of Southampton, and Arthritis Research UK. We thank the mothers of the Southampton Women's Survey who gave us their time and the team of dedicated research nurses and ancillary staff for their assistance.

Netherlands Twin Register (NTR): This project was supported by ARRA RC2 2MH08995; the European Research Council (Genetics of Mental Illness, ERC-230374); Spinozapremie (NWO/SPI 56-464-14192) and Twin-family database for behavior genetics and genomics studies (NWO 480-04-004).

Conflict of Interest statement. None declared.

FUNDING

R.M.F. is supported by a Sir Henry Wellcome Postdoctoral Fellowship (Wellcome Trust grant 085541/Z/08/Z). T.H.P. is supported by The Danish Council for Independent Research Medical Sciences (FSS) The Alfred Benzon Foundation. B.F. is supported by an Oak Foundation fellowship. M.M. is a Wellcome Trust Senior Investigator (Wellcome Trust grant 090532) and a NIHR Senior Investigator. T.M.F. is supported by the European Research Council grant: SZ-245 50371-GLUCOSEGENES-FP7-IDEAS-ERC. F.R. (VIDI 016.136.367) and V.W.V.J. (VIDI 016.136.361) received grants from the Netherlands Organization for Health Research and Development. The other authors did not receive funding for this manuscript.

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