Common variants at 12q15 and 12q24 are associated with infant head circumference

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SUPPLEMENTARY INFORMATION

Nature Genetics: doi:10.1038/ng.2238

Supplementary Table 1. Basic characteristics, exclusions, genotyping, quality control and imputation in discovery studies [see accompanying Excel file].

Supplementary Table 2. Basic characteristics, exclusions, genotyping, quality control and imputation in replication studies [see accompanying Excel file].

Nature Genetics: doi:10.1038/ng.2238

Supplementary table 3. Loci associated with infant head circumference ($P<1x10^{-5}$), which were not taken forward for replication

Index SNP	Locus	Effect on head circumference (SD)	Se	P value	Nearest Gene	Gene function
rs3094072_C	6p21	0.103	0.022	$1.5x10^{-6}$	*HLA-L*	Part of the major histocompatibility complex genes. SNPs in linkage disequilibrium have been associated with Systemic Lupus Erythematosus
rs12438760_T	15q14	0.109	0.023	$2.1x10^{-6}$	*C15orf41*	Unknown
rs17134374_T	15q11	-23.293	5.033	$3.7x10^{-6}$	*POTEB*	Unknown
rs238150_T	20q13	-0.078	0.0171	$4.5x10^{-6}$	*DDX27*	DEAD box proteins, characterized by the conserved motif Asp-Glu-Ala-Asp (DEAD), are putative RNA helicases. They are implicated in a number of cellular processes involving alteration of RNA secondary structure such as translation initiation, nuclear and mitochondrial splicing, and ribosome and spliceosome assembly. Based on their distribution patterns, some members of this family are believed to be involved in embryogenesis, spermatogenesis, and cellular growth and division. This gene encodes a DEAD box protein, the function of which has not been determined. [provided by RefSeq, Jul 2008]
rs9940645_A	16q12	0.066	0.0145	$5.8x10^{-6}$	*ZNF423*	The protein encoded by this gene is a nuclear protein that belongs to the family of Kruppel-like C2H2 zinc finger proteins. It functions as a DNA-binding transcription factor by using distinct zinc fingers in different signaling pathways. It is thought that this gene may have multiple roles in signal transduction during development. [provided by RefSeq, Jul 2008]
rs11683142_A	2q23	0.293	0.065	$6.1x10^{-6}$	*RBM43*	Unknown
rs1385504_A	8q24	0.094	0.021	$7.1x10^{-6}$	*TNFRSF11B*	The protein encoded by this gene is a member of the TNF-receptor superfamily. This protein is an osteoblast-secreted decoy receptor that functions as a negative regulator of bone resorption. This protein specifically binds to its ligand, osteoprotegerin ligand, both of which are key extracellular regulators of osteoclast development. Studies of the mouse counterpart also suggest that this protein and its ligand play a role in lymph-node organogenesis and vascular calcification. Alternatively spliced transcript variants of this gene have been reported, but their full length nature has not been determined. [provided by RefSeq, Jul 2008] SNPs in linkage disequilibrium have been associated with osteoporosis in genome wide association study meta-analysis.
rs2056666_T	8p23	0.067	0.015	$7.3x10^{-6}$	*CSMD1*	Unknown
rs9675157_C	17q23-24	0.185	0.042	$9.6x10^{-6}$	*AXIN2*	The Axin-related protein, Axin2, presumably plays an important role in the regulation of the stability of beta-catenin in the Wnt signaling pathway, like its rodent homologs, mouse conductin/rat axil. In mouse, conductin organizes a multiprotein complex of APC (adenomatous polyposis of the colon), beta-catenin, glycogen synthase kinase 3-beta, and conductin, which leads to the degradation of beta-catenin. Apparently, the deregulation of beta-catenin is an important event in the genesis of a number of malignancies. The AXIN2 gene has been mapped to 17q23-q24, a region that shows frequent loss of heterozygosity in breast cancer, neuroblastoma, and other tumors. Mutations in this gene have been associated with colorectal cancer with defective mismatch repair. [provided by RefSeq, Jul 2008]

Supplementary table 4. Associations of genotype with current height and weight

Index SNP	Association between genotype and height (SD score)			Association between genotype and weight (SD score)		
	N in meta-analysis	effect size (95% CI)	*P* value	N in meta-analysis	effect size (95% CI)	*P* value
rs7980687_A on 12q24	16,664	0.034 (0.009 , 0.059)	$7.3x10^{-3}$	16,532	0.038 (0.013 , 0.064)	$3.3x10^{-3}$
rs1042725_T on 12q15	16,557	-0.042 (-0.063, -0.020)	$1.5x10^{-4}$	16,457	-0.038 (-0.059 , -0.018)	$2.9x10^{-4}$
rs11655470_T on 17q21	16,512	-0.009 (-0.030, 0.012)	0.38	16,392	0.005 (-0.016 , 0.025)	0.67

SD; standard deviation, 95% CI; 95% Confidence interval. Effect estimates reflect the difference in height (SD) or weight (SD) per minor allele. Height and weight were measured at the same age as head circumference. The *P* value is obtained from a linear regression of the SNP on the dependent variable (height or weight SD score) assuming an additive model. All study samples were of European descent. Of the total of 13 study cohorts, 12 study cohorts contributed to these analyses since data on height and weight were not available in the CHOP (Children's Hospital Of Philadelphia) study

Supplementary table 5. Association of genotype with head circumference in infancy, before and after adjustment for current height

Index SNP	[1] Association between genotype and head circumference (SD score)			[2] Association between genotype and head circumference (SD score) adjusted for current height		
	N in meta-analysis	effect size in SD scores (95% CI)	*P* value #	N in meta-analysis	effect size in SD scores (95% CI)	*P* value ##
rs7980687_A on 12q24	16,664	0.065 (0.042 , 0.088)	$3.8x10^{-8}$	16,664	0.057 (0.035 , 0.080)	$3.8x10^{-7}$
rs1042725_T on 12q15	16,557	-0.063 (-0.082 , -0.045)	$3.5x10^{-11}$	16,557	-0.048 (-0.066 , -0.030)	$1.3x10^{-7}$
rs11655470_T on 17q21	16,512	0.045 (0.026 , 0.064)	$3.6x10^{-6}$	16,512	0.048 (0.030 , 0.066)	$1.4x10^{-7}$

SD; standard deviation, 95% CI; 95% Confidence interval. Effect estimates reflect the difference in head circumference SD score per minor allele.

The *P* value is obtained from a linear regression of the SNP against the head circumference SD score (additive model).

The *P* value is obtained from a linear regression of the SNP + the current height SD score against the head circumference SD score (additive model).

All study samples were of European descent. Of the total of 13 study cohorts, 12 study cohorts contributed to these analyses since data on height and weight were not available in the CHOP (Children's Hospital Of Philadelphia) study

Supplementary table 6. Mediation of effects of genotype on head circumference through an indirect effect on height.

Index SNP	N in meta-analysis	Total effect on head circumference (SD score)		Indirect effect (through height) on head circumference (SD score)		Direct effect on head circumference (SD score)	
		Effect size in SD scores (95% CI)	*P* value	Effect size in SD scores (95% CI)	*P* value	Effect size in SD scores (95% CI)	*P* value
rs7980687_A on 12q24	16,664	0.065 (0.042 , 0.088)	$3.8x10^{-8}$	0.008 (0.002 , 0.014)	0.011	0.057 (0.035 , 0.079)	$3.8x10^{-7}$
rs1042725_T on 12q15	16,557	-0.063 (-0.082 , -0.045)	$3.5x10^{-11}$	-0.015 (-0.021 , -0.009)	$5.6x10^{-7}$	-0.048 (-0.066 , -0.030)	1.3x10-7
rs11655470_T on 17q21	16,512	0.045 (0.026 , 0.064)	$3.6x10^{-6}$	-0.009 (-0.030 , 0.012)	0.38	0.048 (0.030 , 0.066)	$1.4x10^{-7}$

SD; standard deviation, 95% CI; 95% Confidence interval. Effect estimates reflect the difference in head circumference SD score per minor allele.
The *P* value is obtained from a mediation analysis framework (seemingly unrelated regression analysis (STATA) or a simple pathway analysis (MPLUS)) using an additive model.
All study samples were of European descent. Of the total of 13 study cohorts, 12 study cohorts contributed to these analyses since data on height and weight were not available in the CHOP (Children's Hospital Of Philadelphia) study

Supplementary table 7. Association of genotype with head circumference in infancy adjusted for current height, before and after adding principal components

Index SNP	N in meta-analysis	[1] Association of genotype with head circumference (SD score) adjusted for current height		[2] Association of genotype with head circumference (SD score) adjusted for current height and principal components	
		effect size in SD scores (95% CI)	*P* value #	effect size in SD scores (95% CI)	*P* value ##
rs7980687_A on 12q24	12,763	0.067 (0.042 , 0.093)	$2.7x10^{-7}$	0.072 (0.046 , 0.098)	$8.4x10^{-8}$
rs1042725_T on 12q15	12,943	-0.049 (-0.070 , -0.028)	$3.3x10^{-6}$	-0.046 (-0.068 , -0.025)	$1.7x10^{-5}$
rs11655470_T on 17q21	12,712	0.054 (0.033 , 0.074)	$4.2x10^{-7}$	0.056 (0.035 , 0.077)	$2.1x10^{-7}$

SD; standard deviation, 95% CI; 95% Confidence interval. Effect estimates reflect the difference in head circumference SD score per minor allele.
The *P* value is obtained from a linear regression of the SNP + the current height SD score against the head circumference SD score (additive model).
The *P* value is obtained from a linear regression of the SNP + the current height SD score + first two principle components against the head circumference SD score (additive model).
All study samples were of European descent. Of the total 13 study cohorts, 8 study cohorts contributed to these analyses since data on height was not available in CHOP (Children's Hospital Of Philadelphia). Principal components were not available in ALSPAC (Avon Longitudinal Study of Parents And Children) replication sample, EFSOCH (Exeter Family Study Of Childhood Health), LISA (Lifestyle – Immune System – Allergy Study Munich) discovery and replication sample.

Supplementary table 8. Association of genotype with head circumference in infancy, stratified by sex

Index SNP	Association between genotype and head circumference (SD score) in boys			Association between genotype and head circumference (SD score) in girls			
	N in meta-analysis	effect size in SD scores (95% CI)	*P* value	N in meta-analysis	effect size in SD scores (95% CI)	*P* value	P value for heterogeneity (Boys vs Girls)
rs7980687_A on 12q24	9,348	0.074 (0.043 , 0.106)	$4.3x10^{-6}$	9,036	0.048 (0.015 , 0.081)	$3.9x10^{-3}$	0.26
rs1042725_T on 12q15	9,349	-0.056 (-0.082 , -0.031)	$1.2x10^{-5}$	9,013	-0.069 (-0.095, -0.043)	$1.9x10^{-7}$	0.51
rs11655470_T on 17q21	9,305	0.024 (-0.002 , 0.049)	0.067	8,983	0.064 (0.038 , 0.089)	$1.3x10^{-6}$	0.03

SD; standard deviation, 95% CI; 95% Confidence interval. Effect estimates reflect the difference in head circumference SD score per minor allele. The *P* value is obtained from a linear regression of the SNP against the head circumference SD score (additive model), in strata of sex. All study samples were of European descent. All study cohorts contributed to these analyses; *P* value for heterogeneity threshold for significance after Bonferroni correction: 0.05/3 = 0.017.

Supplementary table 9. Association of genotype with head circumference in infancy, stratified by breastfeeding

Index SNP	Association between genotype and head circumference (SD score) in breastfed infants			Association between genotype and head circumference (SD score) in non-breastfed infants			
	N in meta-analysis	effect size in SD scores (95% CI)	*P* value	N in meta-analysis	effect size in SD scores (95% CI)	*P* value	P value for heterogeneity (BF=yes vs BF=no)
rs7980687_A on 12q24	8,779	0.076 (0.044 , 0.108)	$3.0x10^{-6}$	1,558	-0.026 (-0.108 , 0.055)	0.52	0.02
rs1042725_T on 12q15	8,638	-0.074 (-0.099 , -0.048)	$1.1x10^{-8}$	1,529	-0.024 (-0.090 , 0.042)	0.47	0.17
rs11655470_T on 17q21	8,740	0.051 (0.025 , 0.077)	$1.2x10^{-4}$	1,542	0.072 (0.008 , 0.136)	0.03	0.55

SD; standard deviation, 95% CI; 95% Confidence interval. Effect estimates reflect difference in head circumference SD score per minor allele. The *P* value is obtained from a linear regression of the SNP against the head circumference SD score (additive model), in strata of breast feeding. All study samples were of European descent. Of the total 13 study cohorts, 10 study cohorts contributed to these analyses since data on breastfeeding status was not available in Children's Hospital Of Philadelphia (CHOP), Northern Finland Birth Cohort 1986 (NFBC86) and the Northern Finland Birth Cohort 1966 (NFBC66). *P* value for heterogeneity threshold for significance after Bonferroni correction: 0.05/3 = 0.017.

Supplementary table 10. Significant associations of lead SNP rs7980687 and cis-eQTLs in publicly available datasets

Lead SNP	eQTL	Chromosome	Position	Correlation of eQTL with lead SNP (HapMap r2)	Tissue	eQTL dataset	Gene	P value	Gene function
rs7980687 on 12q24	rs1569068	12	122198229	0.898	Liver	Schadt et al. Plos Biology 2008 [1]	CDK2AP1	$3.6x10^{-15}$	The protein encoded by this gene is a specific CDK2-associated protein, which is thought to negatively regulate CDK2 activity by sequestering monomeric CDK2, and targeting CDK2 for proteolysis. This protein was found to also interact with DNA polymerase alpha/primase and mediate the phosphorylation of the large p180 subunit, which suggested the regulatory role in DNA replication during S phase of the cell cycle. A similar gene in hamster was isolated from, and functions as a growth suppressor of normal keratinocytes. [provided by RefSeq, Jul 2008]
	rs2695478	12	122255474	0.8	Monocytes	Zeller et al. Plos One 2010 [2]	MPHOSPH9	$5.9x10^{-14}$	Unknown
	rs655293	12	122094358	0.738	Lymphoblastoid cell lines	Veyrierias et al. Plos Genetics 2008 [3]	CDK2AP1	$5.3x10^{-6}$	See above

Supplementary table 11. Association of 180 known adult height variants with head circumference in infancy

Chromosome	Position	SNP	Effect height (SD)	Effect head circumference (SD)	Standard error	P-value †	Gene	EFFECT_OTHER
1	118657110	rs9428104	-0.041	0.006	0.017	0.72	SPAG17	A/G
1	148159496	rs11205277	-0.046	0.022	0.015	0.13	SF3B4	A/G
1	170319910	rs17346452	-0.04	-0.024	0.016	0.14	DNM3	T/C
1	17179262	rs2284746	-0.04	0.032	0.014	0.03	MFAP2	C/G
1	175058872	rs1325598	-0.022	-0.019	0.014	0.18	PAPPA2	A/G
1	182290152	rs1046934	-0.044	-0.008	0.016	0.62	TSEN15	A/C
1	2059032	rs425277	0.022	0.003	0.016	0.84	PRKCZ	T/C
1	210304421	rs10863936	-0.021	-0.007	0.014	0.60	DTL	A/G
1	216676325	rs6684205	-0.028	0.024	0.016	0.13	TGFB2	A/G
1	217810342	rs11118346	-0.025	0.006	0.014	0.67	LYPLAL1	T/C
1	225978506	rs10799445	0.032	-0.026	0.017	0.13	JMJD4	A/C
1	23409478	rs1738475	0.025	0.017	0.015	0.26	HTR1D	C/G
1	24916698	rs4601530	-0.028	-0.010	0.016	0.55	CLIC4	T/C
1	26614131	rs7532866	0.021	-0.003	0.015	0.84	LIN28	A/G
1	41518357	rs2154319	-0.03	-0.011	0.017	0.53	SCMH1	T/C
1	78396214	rs17391694	0.042	0.026	0.024	0.28	GIPC2	T/C
1	88896031	rs6699417	0.021	0.019	0.015	0.19	PKN2	T/C
1	93096559	rs10874746	-0.024	-0.002	0.015	0.91	RPL5	T/C
2	134151294	rs7567288	-0.032	0.018	0.018	0.32	NCKAP5	T/C
2	178392966	rs7567851	0.037	0.023	0.026	0.38	PDE11A	C/G
2	217980143	rs1351164	0.034	0.012	0.017	0.48	TNS1	T/C
2	219616613	rs12470505	0.041	-0.018	0.024	0.44	CCDC108/IHH	T/G
2	224755988	rs2629046	0.024	0.048	0.014	$8.0x10^{-4}$	SERPINE2	T/C
2	232506210	rs2580816	-0.045	-0.026	0.019	0.17	NPPC	T/C
2	241911659	rs12694997	-0.024	0.023	0.017	0.18	SEPT2	A/G
2	25041103	rs4665736	0.029	0.001	0.014	0.93	DNAJC27	T/C
2	33214929	rs6714546	-0.026	-0.002	0.017	0.89	LTBP1	A/G
2	37814117	rs17511102	-0.06	0.004	0.027	0.88	CDC42EP3	A/T
2	44621706	rs2341459	0.025	-0.016	0.016	0.33	C2orf34	T/C
2	46774789	rs12474201	0.028	-0.007	0.015	0.64	SOCS5	A/G
2	55964813	rs3791675	-0.053	-0.008	0.017	0.66	EFEMP1	T/C

2	88705737	rs11684404	-0.028	-0.010	0.015	0.51	EIF2AK3	T/C
3	130533446	rs6439167	-0.034	-0.026	0.018	0.15	C3orf47	T/C
3	13530836	rs2597513	-0.036	-0.036	0.024	0.13	HDAC11	T/C
3	137456906	rs9844666	-0.024	-0.026	0.017	0.12	PCCB	A/G
3	**142588260**	**rs724016 #**	**-0.07**	**-0.054**	**0.015**	**$1.8x10^{-4}$**	**ZBTB38**	**A/G**
3	173648421	rs572169	0.033	0.013	0.015	0.38	GHSR	T/C
3	187031377	rs720390	0.029	-0.010	0.015	0.50	IGF2BP2	A/G
3	51046753	rs13088462	-0.052	-0.055	0.032	0.09	DOCK3	T/C
3	53093779	rs2336725	-0.027	0.002	0.015	0.92	RTF1	T/C
3	56642722	rs9835332	-0.026	-0.012	0.014	0.42	C3orf63	C/G
3	67499012	rs17806888	0.036	0.008	0.024	0.75	SUCLG2	T/C
3	72520103	rs9863706	-0.031	0.007	0.017	0.68	RYBP	T/C
4	106325802	rs10010325	0.024	-0.004	0.014	0.76	TET2	A/C
4	145787802	rs7689420	-0.073	-0.015	0.019	0.43	HHIP	T/C
4	1671115	rs2247341	0.025	0.027	0.015	0.07	SLBP	A/G
4	17642586	rs6449353	0.075	0.031	0.021	0.15	LCORL	T/C
4	184452669	rs955748	-0.023	-0.001	0.017	0.97	WWC2	A/G
4	57518233	rs17081935	0.03	0.006	0.018	0.73	POLR2B	T/C
4	73734177	rs7697556	0.028	0.035	0.014	0.02	ADAMTS3	T/C
4	82369030	rs788867	-0.043	0.011	0.015	0.48	PRKG2	T/G
5	108141243	rs13177718	-0.04	-0.001	0.029	0.98	FER	T/C
5	122685098	rs1582931	-0.023	-0.027	0.015	0.07	CEP120	A/G
5	131727766	rs274546	-0.029	0.008	0.015	0.57	SLC22A5	A/G
5	134384604	rs526896	0.03	0.003	0.016	0.84	PITX1	T/G
5	168188818	rs4282339	-0.036	-0.017	0.017	0.34	SLIT3	A/G
5	171136043	rs12153391	-0.03	-0.010	0.017	0.56	FBXW11	A/C
5	172916720	rs889014	-0.03	-0.008	0.015	0.60	BOD1	T/C
5	176449932	rs422421	-0.031	-0.003	0.018	0.88	FGFR4/NSD1	T/C
5	179663620	rs6879260	-0.022	-0.018	0.015	0.23	GFPT2	T/C
5	32866278	rs1173727	0.034	0.001	0.015	0.94	NPR3	T/C
5	55037656	rs11958779	-0.027	-0.010	0.015	0.51	SLC38A9	A/G
5	88390431	rs10037512	0.032	0.019	0.014	0.18	MEF2C	T/C
6	105485647	rs7759938	-0.045	-0.012	0.015	0.42	LIN28B	T/C
6	109890634	rs1046943	0.02	0.017	0.014	0.25	ZBTB24	A/G
6	117628849	rs961764	-0.024	0.005	0.014	0.75	VGLL2	C/G

6	126892853	rs1490384	0.034	0.024	0.014	0.01	C6orf173	T/C
6	130390812	rs6569648	-0.04	-0.036	0.017	0.04	L3MBTL3	T/C
6	142838982	rs7763064	-0.048	0.022	0.016	0.16	GPR126	A/G
6	152152636	rs543650	-0.034	-0.015	0.015	0.32	ESR1	T/G
6	158849430	rs9456307	-0.048	-0.047	0.034	0.17	TULP4	A/T
6	19949472	rs1047014	-0.032	-0.026	0.017	0.11	ID4	T/C
6	26308656	rs806794	0.052	0.033	0.016	0.04	Histone cluster	A/G
6	**29192211**	**rs3129109 #**	**-0.032**	**-0.112**	**0.026**	**$1.8x10^{-5}$**	**OR2J3**	**T/C**
6	31488508	rs2256183	0.04	0.032	0.014	0.03	MICA	A/G
6	32771977	rs6457620	-0.029	-0.024	0.014	0.09	HLA locus	C/G
6	34307070	rs2780226	-0.076	0.006	0.027	0.84	HMGA1	T/C
6	35510783	rs6457821	-0.104	0.030	0.055	0.58	PPARD/FANCE	A/C
6	45054484	rs9472414	-0.026	0.004	0.017	0.81	SUPT3H/RUNX2	A/T
6	76322362	rs9360921	-0.042	-0.011	0.023	0.64	SENP6	T/G
6	7670759	rs3812163	-0.036	0.019	0.014	0.18	BMP6	A/T
6	81857081	rs310405	0.026	0.001	0.015	0.95	FAM46A	A/G
7	148281567	rs822552	-0.025	0.012	0.019	0.52	PDIA4	C/G
7	150147955	rs2110001	-0.031	0.008	0.016	0.65	TMEM176A	C/G
7	19583047	rs4470914	0.029	0.001	0.019	0.95	TWISTNB	T/C
7	23469499	rs12534093	-0.034	-0.060	0.018	$6.4x10^{-4}$	IGF2BP3	A/T
7	2768329	rs798489	-0.048	0.001	0.016	0.97	GNA12	T/C
7	28156471	rs1708299	0.04	0.005	0.016	0.77	JAZF1	A/G
7	38094851	rs6959212	-0.024	-0.003	0.016	0.84	STARD3NL	T/C
7	92086012	rs42235	0.057	-0.041	0.016	0.01	CDK6	T/C
8	130794847	rs6470764	-0.05	-0.023	0.018	0.22	GSDMC	T/C
8	135706519	rs12680655	0.028	-0.009	0.015	0.52	ZFAT	C/G
8	24172249	rs1013209	-0.025	-0.027	0.017	0.11	ADAM28	T/C
8	57356717	rs7460090	0.058	0.012	0.022	0.59	SDR16C5	T/C
8	78341040	rs6473015	-0.029	-0.031	0.016	0.05	PEX2	A/C
9	108638867	rs7027110	0.031	0.009	0.017	0.59	ZNF462	A/G
9	112846903	rs1468758	-0.026	0.001	0.017	0.96	LPAR1	T/C
9	118162163	rs751543	0.026	-0.011	0.018	0.55	PAPPA	T/C
9	132453905	rs7466269	0.032	0.008	0.015	0.58	FUBP3	A/G
9	138251691	rs7849585	0.029	-0.012	0.016	0.44	QSOX2	T/G
9	16358732	rs7864648	0.022	0.042	0.016	$6.7x10^{-3}$	BNC2	T/G

9	77732106	rs11144688	-0.049	0.002	0.035	0.96	PCSK5	A/G
9	85742025	rs7853377	-0.024	-0.003	0.017	0.87	C9orf64	A/G
9	88306448	rs8181166	0.026	0.036	0.015	0.01	ZCCHC6	C/G
9	90025546	rs2778031	0.031	-0.008	0.017	0.66	SPIN1	T/C
9	94468941	rs9969804	0.03	0.039	0.014	$6.5x10^{-3}$	IPPK	A/C
9	95933766	rs1257763	0.069	0.014	0.044	0.75	PTPDC1	A/G
9	97296056	rs473902	0.065	0.048	0.036	0.18	PTCH1	T/G
10	101795432	rs11599750	-0.028	0.014	0.015	0.33	CPN1	T/C
10	12958770	rs7909670	-0.021	-0.015	0.015	0.32	CCDC3	T/C
10	80791702	rs2145998	-0.026	0.001	0.014	0.95	PPIF	A/T
11	118079885	rs494459	0.02	0.028	0.014	0.05	TREH	T/C
11	12654616	rs7926971	-0.023	-0.009	0.014	0.55	TEAD1	A/G
11	128091365	rs654723	0.025	-0.032	0.015	0.04	FLI1	A/C
11	17272605	rs1330	0.022	-0.001	0.015	0.93	NUCB2	T/C
11	2767307	rs2237886	0.046	-0.017	0.024	0.45	KCNQ1	T/C
11	48054856	rs10838801	-0.027	-0.033	0.016	0.03	PTPRJ/SLC39A13	A/G
11	49515748	rs1814175	0.022	0.022	0.016	0.15	FOLH1	T/C
11	51270794	rs5017948	0.027	0.036	0.018	0.05	OR4A5	A/T
11	65093395	rs3782089	-0.058	0.054	0.030	0.07	SSSCA1	T/C
11	66582736	rs7112925	-0.023	0.009	0.015	0.57	RHOD	T/C
11	74959700	rs634552	0.039	-0.021	0.021	0.32	SERPINH1	T/G
12	100897919	rs7971536	-0.028	-0.004	0.015	0.80	CCDC53/GNPTAB	A/T
12	11747040	rs2856321	-0.029	0.010	0.015	0.51	ETV6	A/G
12	**122389499**	**rs11830103**	**-0.035**	**-0.080**	**0.018**	**$5.9x10^{-6}$**	**SBNO1**	**A/G**
12	20748734	rs10770705	0.033	0.019	0.015	0.22	SLCO1C1	A/C
12	28425682	rs2638953	0.032	0.003	0.015	0.85	CCDC91	C/G
12	55026949	rs2066807	-0.054	-0.020	0.029	0.50	STAT2	C/G
12	**64638093**	**rs1351394**	**0.06**	**0.064**	**0.014**	**$9.0x10^{-6}$**	**HMGA2**	**T/C**
12	68113925	rs10748128	0.038	-0.012	0.016	0.45	FRS2	T/G
12	92502635	rs11107116	0.052	0.013	0.017	0.46	SOCS2	T/G
13	32045548	rs7332115	-0.023	0.004	0.015	0.80	PDS5B	T/G
13	50003335	rs3118905	-0.056	0.004	0.016	0.81	DLEU7	A/G
13	90822575	rs7319045	0.025	0.025	0.015	0.09	GPC5	A/G
14	23900690	rs1950500	0.034	-0.005	0.016	0.75	NFATC4	T/C
14	60027032	rs2093210	-0.032	-0.025	0.015	0.10	SIX6	T/C

14	67882868	rs1570106	-0.026	-0.010	0.018	0.59	RAD51L1	T/C
14	74060499	rs862034	-0.028	-0.013	0.015	0.40	LTBP2	A/G
14	91555634	rs7155279	-0.024	-0.042	0.015	$5.3x10^{-3}$	TRIP11	T/G
15	49317787	rs16964211	-0.05	0.039	0.031	0.21	CYP19A1	A/G
15	60167551	rs7178424	-0.021	0.003	0.015	0.86	C2CD4A	T/C
15	67835211	rs10152591	0.041	0.008	0.025	0.75	TLE3	A/C
15	69948457	rs12902421	-0.062	-0.100	0.046	0.03	MYO9A	T/C
15	72123686	rs5742915	-0.031	-0.024	0.015	0.10	PML	T/C
15	82371586	rs11259936	-0.044	0.006	0.014	0.69	ADAMTSL3	A/C
15	87189909	rs16942341	-0.13	-0.078	0.048	0.11	ACAN	T/C
15	97012419	rs2871865	0.057	0.029	0.024	0.23	IGF1R	C/G
15	98577137	rs4965598	-0.028	-0.006	0.016	0.70	ADAMTS17	T/C
16	14295806	rs1659127	0.027	-0.028	0.016	0.08	MKL2	A/G
16	2189377	rs26868	0.034	0.027	0.015	0.07	CASKIN1	A/T
16	732191	rs11648796	-0.034	-0.022	0.017	0.21	NARFL	A/G
16	87304743	rs8052560	0.029	0.007	0.021	0.76	CTU2	A/C
17	21224816	rs4640244	0.024	-0.005	0.016	0.78	KCNJ12	A/G
17	24941897	rs3110496	-0.022	0.036	0.015	0.02	ANKRD13B	A/G
17	26188149	rs3764419	-0.035	-0.027	0.015	0.06	ATAD5/RNF135	A/C
17	27367395	rs17780086	0.028	0.018	0.021	0.40	LRRC37B	A/G
17	34175722	rs1043515	-0.023	-0.006	0.014	0.67	PIP4K2B	A/G
17	40571807	rs4986172	-0.032	-0.022	0.015	0.14	ACBD4	T/C
17	44745013	rs2072153	0.021	0.041	0.016	$8.5x10^{-3}$	ZNF652	C/G
17	46599746	rs4605213	0.021	-0.000	0.016	0.99	NME2	C/G
17	52133816	rs227724	-0.03	-0.002	0.015	0.88	NOG	A/T
17	56851431	rs2079795	0.04	0.003	0.015	0.82	TBX2	T/C
17	59320197	rs2665838	-0.042	-0.020	0.016	0.23	CSH1/GH1	C/G
17	65601802	rs11867479	0.025	0.010	0.015	0.51	KCNJ16	T/C
18	18981609	rs4800452	0.051	0.010	0.018	0.57	CABLES1	T/C
18	45213498	rs9967417	-0.038	0.002	0.015	0.91	DYM	C/G
18	56002077	rs17782313	-0.028	-0.005	0.017	0.75	MC4R	T/C
19	17144303	rs2279008	0.025	-0.021	0.017	0.21	MYO9B	T/C
19	2128193	rs12982744	-0.03	0.018	0.015	0.23	DOT1L	C/G
19	3379834	rs7507204	0.036	0.025	0.017	0.15	NFIC	C/G
19	46628935	rs17318596	0.032	0.021	0.015	0.18	ATP5SL	A/G

19	7135762	rs891088	-0.029	0.021	0.016	0.21	INSR	A/G
19	8550031	rs4072910	-0.031	0.007	0.017	0.68	ADAMTS10	C/G
20	31796842	rs7274811	-0.041	-0.001	0.017	0.93	ZNF341	T/G
20	33489170	rs143384	-0.063	0.010	0.016	0.51	GDF5	A/G
20	4049800	rs1741344	-0.023	0.008	0.015	0.63	SMOX	T/C
20	**47336426**	**rs237743**	**0.041**	**0.078**	**0.017**	**$6.1x10^{-6}$**	**ZNFX1**	**A/G**
20	6574218	rs2145272	-0.039	-0.015	0.015	0.31	BMP2	A/G
21	34612656	rs2834442	0.026	0.010	0.015	0.49	KCNE2	A/T
22	31386341	rs4821083	0.031	-0.016	0.020	0.42	SYN3	T/C

[#] Results reported for very closely related SNP (rs3117141 for rs3129109, HapMap R^2=1.000; rs6440006 for rs724016, HapMap R^2=0.967).

† The *P* value is obtained from a linear regression model of the SNP against the head circumference SD score (additive model).

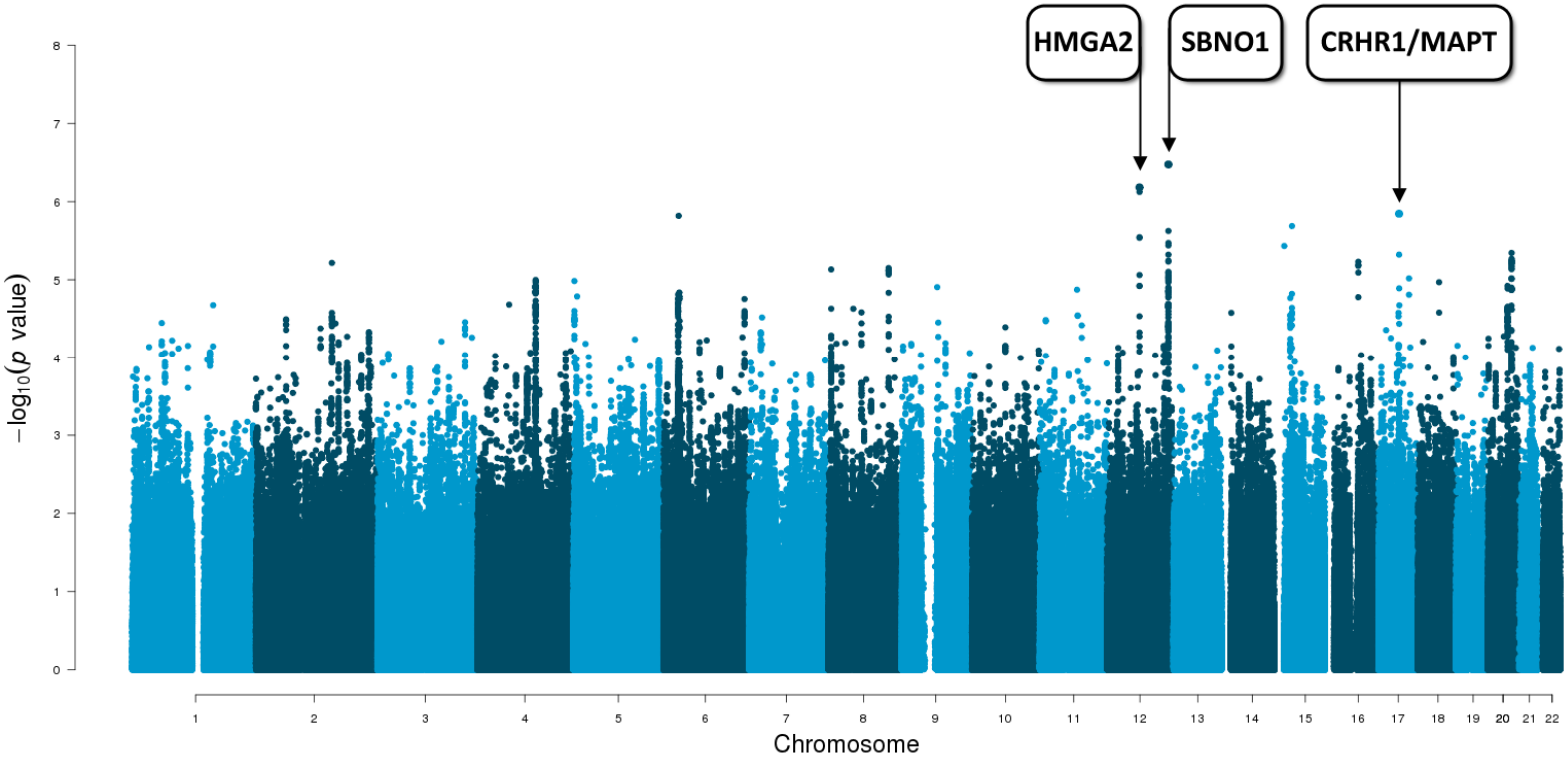
Bold results are statistically significant after applying Bonferroni correction. *P*-value threshold for significance : 0.05/180 = $2.8x10^{-4}$.

Supplementary table 12 Effect of rs11655470 conditional on the ICV signal (rs9915547)[4]

Index SNP	N in meta-analysis	[1] Effect on head circumference (SD score)		[2] Effect on head circumference (SD score) conditional on CHARGE ICV signal (rs9915547)	
		Effect size in SD scores (95% CI)	*P* value[#]	Effect size in SD scores (95% CI)	*P* value[##]
rs11655470_T on 17q21	11,188	0.059 (0.033, 0.085)	$1.0x10^{-5}$	0.037 (0.010 , 0.065)	$7.3x10^{-3}$

SD; standard deviation, 95% CI; 95% Confidence interval. ICV; Intracranial volume. Betas reflect the difference in head circumference (SD) per minor allele of rs11655470.
The *P* value is obtained from a linear regression of rs11655470 against the head circumference SD score (additive model).
The *P* value is obtained from a linear regression of rs11655470 and rs9915547 against the head circumference SD score (additive model).
All study samples were of European descent. NFBC66 used rs10221243 as proxy for rs9915547 (HapMap r2: 1.000). In total, nine study cohorts contributed to these analyses; data on rs9915547 was not available in ALSPAC (Avon Longitudinal Study of Parents And Children) replication sample, EFSOCH (Exeter Family Study Of Childhood Health) and NFBC86 (Northern Finland Birth Cohort 1986).

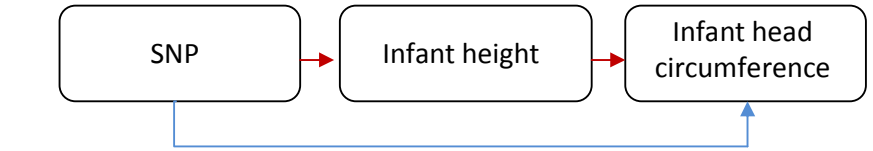
Supplementary figure 1. Manhattan plot of discovery genome-wide association meta-analysis



Manhattan Plot of the meta-analysis of infant head circumference GWAS in the discovery stage (N=10,768), with the three loci selected for replication indicated.

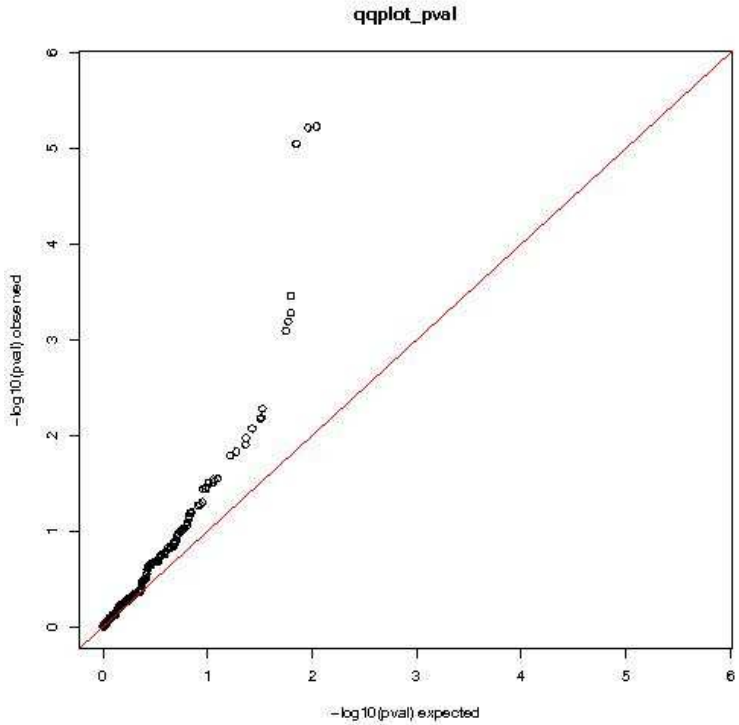
Nature Genetics: doi:10.1038/ng.2238

Supplementary figure 2. Mediation of effects of genotype on head circumference through an indirect effect on height.



Nature Genetics: doi:10.1038/ng.2238

Supplementary figure 3. QQ-plot of association of 180 height SNPs with head circumference in infancy



Quantile-quantile plot of 180 adult height SNPs from the meta-analysis of seven discovery studies (N=10,768). The black dots represent the observed P-values and the red line represents the expected P-values under the null hypothesis.

Supplemental References

1. Schadt, E.E. et al. Mapping the genetic architecture of gene expression in human liver. *PLoS Biol* **6**, e107 (2008).
2. Zeller, T. et al. Genetics and beyond--the transcriptome of human monocytes and disease susceptibility. *PLoS One* **5**, e10693 (2010).
3. Veyrieras, J.B. et al. High-resolution mapping of expression-QTLs yields insight into human gene regulation. *PLoS Genet* **4**, e1000214 (2008).
4. Ikram, M.A. et al. Genome-wide association studies implicate loci on 6q22 and 17q21 in intracranial volume and early life brain growth. *Nature Genetics* **advance online publication**(2012).

SUPPLEMENTARY NOTE

Acknowledgements by study

Avon Longitudinal Study of Parents And Children (ALSPAC): We are grateful to all the families who took part in ALSPAC, 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. The UK Medical Research Council, the Wellcome Trust (Joint MRC/Wellcome Trust grant ref 092731), and the University of Bristol provided core support for ALSPAC and this work.

Children's Hospital Of Philadelphia (CHOP): We would like to thank all participating subjects and families. 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 1R01HD056465-01A1.

COPSAC: We thank all the families participating in the COPSAC cohort for their effort and commitment; Kirsten Hinsby Mathiesen, Lotte Klansø, Lena Vind and the rest of the COPSAC study team. COPSAC is funded by: the Lundbeck Foundation, the Danish Council for Strategic Research, the Augustinus Foundation, the Pharmacy Foundation, the Danish Agency for Science, Technology and Innovation, the EU Seventh Framework Programme, Ronald McDonald House Charities, the Global Excellence in Health award Programme, the Danish Medical Research Council, the Director K. GAD and family Foundation, the A. P. Møller og Hustru Chastine Mc-Kinney Møller General Purpose Foundation, the Aage Bang Foundation, the Health Insurance Foundation, the East Danish Medical Research Council, the Copenhagen City Council Research Foundation, the Kai and Gunhild Lange Foundation, the Dagmar Marshall Foundation, the Ville Heise legacy, the Region of Copenhagen, the Ib Henriksen foundation, the Birgit and Svend Pock-Steen foundation, the Danish Ministry of the Interior and Health's Research Centre for Environmental Health, the Gerda and Aage Hensch foundation, the Rosalie Petersens Foundation, the Hans and Nora Buchard Foundation, the Gangsted Foundation, the Danish Medical Association, Asthma-Allergy Denmark, the Danish Otolaryngology Association, the Oda Pedersen legacy, the Højmosegaard Legacy, the A. P. Møller og Hustru Chastine Mc-Kinney Møller Foundation for the advancement of Medical Knowledge, the Jacob and Olga Madsen Foundation, the Aase and Einar Danielsen Foundation, and Queen Louise's Children's' Hospital Research Foundation. The funding agencies did not have any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Danish National Birth Cohort (DNBC): Funding support for the Danish National Birth Cohort (DNBC) was provided by 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 genotype data were derived from a GWAS of preterm birth in the Gene Environment Association Studies (GENEVA) consortium funded by the NIH Genes, Environment and Health Initiative (GEI, U01HG004423). Genotyping was performed at Johns Hopkins University Center for Inherited Disease Research, with support from the NIH GEI (U01HG004438). The study protocol was approved by the Danish Scientific Ethical Committee and the Danish Data Protection Agency for all Danish subjects. The analysis was supported in part by grants from the Lundbeck Foundation (R19-A2059) and the Danish Medical Research Council (09-065592).

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 (UK). 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.

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 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 and Carolina Medina-Gomez 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 (ZonMw 21000074). Vincent Jaddoe received an additional grant from the Netherlands Organization for Health Research and Development (ZonMw 90700303, 916.10159). Additional support was provided by a grant from the Dutch Kidney Foundation (C08.2251).

German Infant Study on the influence of Nutrition Intervention (GINI) Munich : The study team wishes to acknowledge the following : Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Munich (Heinrich J, Wichmann HE, Sausenthaler S, Chen C-M, Thiering E, Tiesler C, Standl M, Schnappinger M, Rzehak P); Department of Pediatrics, Marien-Hospital, Wesel (Berdel D, von Berg A, Beckmann C, Groß I); Department of Pediatrics, Ludwig Maximilians University, Munich (Koletzko S, Reinhard D, Krauss-Etschmann S); Department of Pediatrics, Technical University, Munich (Bauer CP, Brockow I, Grübl A, Hoffmann U); IUF - Institut für Umweltmedizinische Forschung at the Heinrich-Heine-University, Düsseldorf (Krämer U, Link E, Cramer C); Centre for Allergy and Environment, Technical University, Munich (Behrendt H)

Helsinki Birth Cohort Study (HBCS): We thank Professor David Barker, Professor Clive Osmond, Associate professors Eero Kajantie and Tom Forsen. Major financial support was received from the Academy of Finland (project grants 209072, 129255 grant) and British Heart Foundation and the Academy of Finland (grants 134839 and 129287). The DNA extraction, sample quality control, biobank up-keep and aliquotting was performed at the National Public Health Institute, Helsinki, Finland.

The INMA Project: This study was funded by grants from Instituto de Salud Carlos III (CB06/02/0041, FIS PI041436, PI081151, PI041705, and PS09/00432, FIS-FEDER 03/1615, 04/1509, 04/1112, 04/1931, 05/1079, 05/1052, 06/1213, 07/0314, and 09/02647), 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, Conselleria de Sanitat Generalitat Valenciana, and Fundación Roger Torné. Part of the DNA extraction and genotyping was performed at the Spanish National Genotyping Center (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, 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.

Lifestyle – Immune System – Allergy (LISA) Study Munich: The study team wishes to acknowledge the following: Helmholtz Zentrum Muenchen - German Research Center for Environment and Health, Institute of Epidemiology, Neuherberg (Wichmann HE, Heinrich J, Illig T, Klopp N, Bolte G, Belcredi P, Jacob B, Schoetzau A, Franke K, Laubereau B, Sausenthaler S, Zutavern A, CM Chen); Department of Pediatrics, University of Leipzig (Borte M); Department of Pediatrics, Marien-Hospital, Wesel (von Berg A); Bad Honnef (Schaaf B); Department of Human Exposure Research and Epidemiology, UFZ-Centre for Environmental Research Leipzig-Halle (Herbarth O); Department of Environmental Immunology, UFZ- Centre for Environmental Research Leipzig-Halle (Lehmann I);IUF-Institut für Umweltmedizinische Forschung, Düsseldorf (Krämer); Department of Pediatrics, Technical University, Munich (Bauer CP).

Northern Finland Birth Cohort 1966 (NFBC1966) and 1985-86 (NFBC1986): We thank Professor Paula Rantakallio (launch of NFBC1966 and 1986), Ms Outi Tornwall and Ms Minttu Jussila (DNA biobanking). Financial support was received from the Academy of Finland (project grants 104781, 120315, 129269, 1114194, Center of Excellence in Complex Disease Genetics and SALVE), University Hospital Oulu, Biocenter, University of Oulu, Finland (75617), the European Commission (EURO-BLCS, Framework 5 award QLG1-CT-2000-01643), NHLBI grant 5R01HL087679-02 through the STAMPEED program (1RL1MH083268-01), NIH/NIMH

(5R01MH63706:02), the Medical Research Council, UK (G0500539, G0600705, PrevMetSyn/SALVE) and the Wellcome Trust (project grant GR069224), UK., ENGAGE project and grant agreement HEALTH-F4-2007-201413. The DNA extractions, sample quality controls, biobank up-keeping and aliquotting was performed in the National Public Health Institute, Biomedicum Helsinki, Finland and supported financially by the Academy of Finland and Biocentrum Helsinki.

The prevention and incidence of asthma and mite allergy birth cohort study (PIAMA): The PIAMA birth cohort study is a collaboration of the Institute for Risk Assessment Sciences, University Utrecht (B. Brunekreef), Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven (A.H. Wijga, H.A. Smit), Department of Pediatrics, Division of Respiratory Medicine, Erasmus MC - Sophia, Rotterdam (J.C. de Jongste), the Departments of Epidemiology (M. Kerkhof), Pulmonology (D.S. Postma) and Pediatric Pulmonology and Pediatric Allergology (G.H. Koppelman) 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, the Ministry of the Environment and ZON-MW BBMRI-NL

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, Women and Infants Research Foundation and Curtin University. 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).