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

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COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests

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Abstract

To identify genetic variants associated with head circumference in infancy, we performed a meta-analysis of seven genome-wide association (GWA) studies (N=10,768 from European ancestry enrolled in pregnancy/birth cohorts) and followed up three lead signals in six replication studies (combined N=19,089). Rs7980687 on chromosome 12q24 ($P=8.1\times 10^{-9}$), and rs1042725 on chromosome 12q15 ($P=2.8\times 10^{-10}$) were robustly associated with head circumference in infancy. Although these loci have previously been associated with adult height¹, their effects on infant head circumference were largely independent of height ($P=3.8\times 10^{-7}$ for rs7980687, $P=1.3\times 10^{-7}$ for rs1042725 after adjustment for infant height). A third signal, rs11655470 on chromosome 17q21, showed suggestive evidence of association with head circumference ($P=3.9\times 10^{-6}$). SNPs correlated to the 17q21 signal show genome-wide association with adult intra cranial volume², Parkinson's disease and other neurodegenerative diseases³⁻⁵, indicating that a common genetic variant in this region might link early brain growth with neurological disease in later life.

MAIN TEXT

Head circumference in infancy is used as a measure for brain size and development⁶⁻⁷. Normal variation in head circumference seems to be associated with cognitive and behavioral development⁸⁻¹⁰. Larger head circumference in infancy is associated with higher IQ scores in childhood¹⁰⁻¹². The underlying mechanisms however, are poorly understood. Head circumference is a complex trait with a high heritability of around 0.7-0.9¹³. Several rare mutations with large effects on head circumference have been identified¹⁴⁻¹⁷, including those resulting in microcephaly and intellectual disability¹⁵⁻¹⁷. Common genetic variants that influence normal variation in head circumference in early life have not yet been identified.

To search for common genetic variants associated with head circumference in infancy, we performed a meta-analysis of GWA studies. We reasoned that finding such common variants

might lead to enhanced understanding of molecular mechanisms important for variation in brain development.

We meta-analyzed association statistics from ~2.5 million directly-genotyped and imputed SNPs in infants of European descent from seven discovery GWA studies (N=10,768; Supplementary Table 1). In all studies head circumference in infancy (age 18 months, range 6 to 30 months) was measured from the occipital protuberance to the forehead, using a flexible, non-stretching measure tape following standardized procedures. If multiple measurements were available for one individual in this time window, only the measurement performed closest to the age of 18 months was used (Supplementary Tables 1 and 2). Since the relationship between head circumference and age during infancy is non-linear and the variance increases with age, we calculated sex- and age-adjusted SD-scores of head circumference in each study separately¹⁸.

In the discovery phase we identified three lead signals (Manhattan plot is shown in Supplementary Fig. 1); two independent loci on chromosome 12 and one on chromosome 17, which showed suggestive evidence for association with head circumference in infancy. These three loci represent the first three independent loci of the discovery analysis and were at 12q24.31, in *SBNO1* (rs7980687, $P_{discovery}=3.3\times 10^{-7}$; Figure 1a), at 12q15, near *HMGA2* (rs1042725, $P_{discovery}=6.6\times 10^{-7}$; Figure 1b) and at 17q21.1, near *CRHR1/MAPT* (rs11655470, $P_{discovery}=1.4\times 10^{-6}$; Figure 1c). Other loci, suggesting an association with infant head circumference ($P<1\times 10^{-5}$) are described in Supplementary Table 3.

Table 1 shows the associations of these three lead SNPs in each cohort. We followed up these three associations in six independent replication samples of European descent (N=8,321; Supplementary Table 2). We genotyped the most strongly associated SNP from each locus (rs7980687 from 12q24.31; rs1042725 from 12q15; rs11655470 from 17q21.1), or a closely-correlated proxy (HapMap R²). Consistent associations were observed for both signals on chromosome 12 in the replication samples ($P=0.003$ and $P=8.1\times 10^{-5}$ for rs7980687 and rs1042725 respectively). Marginal evidence of association for rs11655470 was seen in the replication samples ($P=0.093$). Genomic control correction was applied during the discovery meta-analysis stage to adjust the statistics generated within each cohort (λ -values ranging from 1.007-1.054, Supplementary Table 1). Results from the replication cohorts were combined with the genomic control corrected discovery results to get the overall meta-analysis results. Combining discovery and replication samples (N=19,089; Table 1), each A allele of rs7980687 in *SBNO1* was robustly associated with a 0.074 SD larger head circumference (95% CI: 0.049, 0.099; $P=8.1\times 10^{-9}$, explained variance 0.24%) and each T allele of rs1042725 near *HMGA2* with a 0.065 SD smaller head circumference (95% CI: -0.085, -0.045; $P=2.8\times 10^{-10}$, explained variance 0.33%). This reflects a difference of around 1.2 and 1.0 mm in head circumference respectively. The effect of each T allele of rs11655470 near *CRHR1/MAPT* did not reach genome-wide significance in the combined analysis (effect 0.048 SD larger head circumference; 95% CI: 0.028, 0.068; $P=3.8\times 10^{-6}$, explained variance 0.21%). These three associations showed low heterogeneity ($P>0.1$, $I^2=5-33\%$).

Additionally, the signals in *SBNO1* and near *HMGA2*, but not the one near *CRHR1/MAPT*, were associated with height measured at the same visit as head circumference (Supplementary Table 4). When we adjusted the model for current height, the associations of rs7980687 and rs1042725 with head circumference were slightly attenuated (effect size 0.057 SD; 95% CI: 0.035, 0.080; $P=3.8\times 10^{-7}$ and -0.048 SD; 95% CI: -0.066, -0.030; $P=1.3\times 10^{-7}$ for rs7980687 and rs1042725 respectively, Supplementary Table 5). The association of the third signal near *CRHR1/MAPT* was unaffected. In depth mediation analysis showed that the effects of rs7980687 and rs1042725 on head circumference were

only partly (12% and 24% respectively) explained by height (Supplementary Fig. 2, Supplementary Table 6). The effect of rs11655470 was a completely direct effect of the SNP on head circumference (Supplementary Table 6). To further adjust for possible population stratification we added principal components to the model, in cohorts where these measures were available (total N = 12,763). This did not materially change the effect on head circumference, indicating that the utilized association tests are robust to population stratification (Supplementary Table 7). The three variants were not associated with other covariates such as breast feeding, socioeconomic status or educational level (data not shown). We did not find evidence for an interaction of these variants with infant sex or breastfeeding after Bonferroni correction ($P > 0.017$, Supplementary Table 8 and 9).

In order to further investigate an effect of the three lead signals on fetal head growth, we assessed the associations of the variants with head circumference using third trimester fetal ultrasound data ($n=3,781$) and head circumference measured at birth ($n=13,775$), in discovery and replication cohorts that had these data available (Supplementary Table 2). All three signals showed evidence of association with head circumference in third trimester of pregnancy and at birth (Table 2). The directions of the effects were consistent with those in infancy.

Next, we assessed the associations of the three lead signals with intra-cranial volume (ICV) in adulthood, measured by magnetic resonance imaging (MRI), in 8,175 individuals in the CHARGE-consortium². There was evidence of association between the signals near *HMGA2* and *CRHR1/MAPT* and ICV (Table 2). For the signal near *CRHR1/MAPT*, a variant further downstream (rs9915547; r^2 0.22 HapMap CEU) showed a genome-wide significant association ($P < 5 \times 10^{-8}$). All directions of the effects were consistent with the observed associations for head circumference in infancy (Table 2).

We also assessed if there were possibly functional common variants in LD ($r^2 > 0.50$) with our three lead SNPs, being either non-synonymous SNPs or eQTLs. One variant, rs1060105, in high LD with our lead signal (rs7980687 with HapMap r^2 0.89), was a non-synonymous SNP located in exon 5 of *SBNO1* (missense; AGT(Ser) => AAT(Asn)). The minor allele (A) of rs1060105 was associated with an increased head circumference in infancy (effect size 0.081 SD; 95% CI: 0.048, 0.115; $P = 2.4 \times 10^{-6}$ ($N=10,768$)). The underlying mechanism is unknown. Considering that transcription regulation is highly cell-type specific, we next evaluated whether we could find eQTLs established in brain tissue¹⁹. We did not find eQTLs in publicly available brain expression data¹⁹. Subsequently, we also explored eQTL databases from other tissues and identified three SNPs in LD with rs7980687 ($r^2 > 0.7$ HapMap CEU) associated with gene transcript expression of *CDK2AP1* and *MPHOSPH9* in liver tissue, monocytes and lymphoblastoid cell lines²⁰⁻²². Little is known on these genes except that both *CDK2AP1* and *MPHOSPH9* are involved in cell-cycle regulation (Supplementary Table 10)²³⁻²⁴.

To our knowledge, this is the first genome-wide association study on head circumference in infancy. The top two signals (rs7980687 in *SBNO1* and rs1042725 near *HMGA2*) associated with infant head circumference have previously been associated with adult height¹. Therefore, we also assessed the association between the 180 known height variants and head circumference during infancy¹. A strong deviation from the null-line was observed on the QQ-plot (Supplementary Fig. 3). Besides *SBNO1* and *HMGA2*, 23 other height variants were nominally associated with head circumference in infancy (Supplementary Table 11). After applying Bonferroni correction for multiple testing in this candidate gene analysis ($P < 2.8 \times 10^{-4}$), markers in/near *ZNFX1* ($P = 6.1 \times 10^{-6}$), *OR2J3* ($P = 1.8 \times 10^{-5}$) and *ZBTB38* ($P = 1.8 \times 10^{-4}$) remained statistically significant associated with head circumference in infancy.

The relative effect size of rs1042725 near *HMGA2* was similar for infant head circumference (0.065 SD) and adult height (0.060 SD). However, the effect size of rs7980687 in *SBNO1* on infant head circumference (0.074 SD) was considerably larger than for adult height (0.035 SD). As head size is correlated with total body size²⁵, it might be that the top two loci have a more general regulating role in skeletal growth and bone development. It also could be that variants in *SBNO1* affect brain growth and concurrent head circumference, or that they affect skull growth rather than skeletal growth. The *SBNO1*-gene is involved in the Notch signaling pathway²⁶. In *Drosophila*, a similar gene (*sno*) is required for early embryogenesis, and absence of this gene leads to maldevelopment of the central nervous system²⁶. In humans *SBNO1* has been implicated in oncogenic processes²⁷⁻²⁸.

The variant near *HMGA2* was one of the first to be associated with adult height. Deletions and truncations in the *HMGA2*-gene in mice and humans have been associated with small and large stature²⁹⁻³⁰. The effect of *HMGA2* is similar for head circumference and adult height, thus it seems likely that it has a more general role in skeletal growth.

A third variant (rs11655470), in the promoter region of *CRHR1/MAPT*, was also related to head circumference, though this signal did not reach genome-wide significance. Rs11655470 lies within the 17q21 inversion, but is not strongly correlated with the inversion (r^2 0.22 HapMap CEU). This 900kb region, corresponding to the conversion, contains several genes. The SNP is closely related to the *CRHR1*-gene (r^2 0.59 HapMap CEU with rs171440). Variants in/near *CRHR1* have been associated with brain development and bone mineral density³¹⁻³², although the underlying mechanisms are largely unknown. Another gene included in the 17q21 inversion is *MAPT* (r^2 0.22 HapMap CEU). Both common variants and mutations in *MAPT* are known to be associated with Parkinson's disease and other neurodegenerative diseases^{3-5,33-34}. Other genes in this region are saithohin (*STH*) and granulin (*GRN*). *STH* has been associated with progressive supranuclear palsy and increased risk of late-onset Alzheimer's disease³⁵⁻³⁶. Mutations in *GRN* have been shown to cause fronto-temporal degeneration³⁷. It might be that common genetic variants in/near *CRHR1/MAPT* affect early brain development, by altering the stability and assembly of microtubules. Ikram et al. showed that a correlated SNP in the same region (rs9303525, HapMap r^2 0.22 with rs11655470) is associated with adult intra cranial volume, reaching genome-wide significance². Since the LD between the variants is low, it could be that they represent separate independent effects on different phenotypes. When we adjusted the effect of rs11655470 on infant head circumference for the CHARGE ICV signal (rs9915547), the effect was attenuated but remained significant (0.059 SD ($P=1.0 \times 10^{-5}$) and 0.037 SD ($P=7.3 \times 10^{-3}$) before and after adjustment for rs9915547 respectively), suggesting that these signals both tag a third marker influencing both phenotypes (Supplementary Table 12). However, although the association attenuates after conditioning on the CHARGE ICV signal, the two signals might still independently tag different causal markers in the region and the attenuation might be due to the weak LD, because of proximity, between the two signals. The marker associated with head circumference is in low LD with the chromosome 17q21 inversion, while the CHARGE ICV signal is in high LD with the inversion. Therefore, it does not seem likely that the 17q21 inversion is causally related to infant head circumference. The biological mechanisms underlying these associations are largely unknown.

Our study highlights early effect of variants in/near *SBNO1* and *HMGA2* on head circumference in fetal life and infancy, and shows that a variant near *CRHR1/MAPT* is marginally associated with head circumference in infancy. Our findings suggest that the genetic variants in the *CRHR1/MAPT* region might link early brain growth with

neurological disease in later life. Further research is needed to elucidate whether these variants influence brain growth and neurodevelopment in early life.

ONLINE METHODS

Stage 1: GWA meta-analysis of head circumference

Discovery samples, genotyping and imputation—We selected seven population-based studies with head circumference measured in infancy (study cohort specific median age range 11-18 months) and GWA data available by the beginning of March 2010 (combined N=10,768): the Avon Longitudinal Study of Parents And Children (ALSPAC; N=1,748); The Children’s Hospital of Philadelphia (CHOP; N=1,008); the Copenhagen Study on Asthma in Childhood (COPSAC; N=369); The Generation R Study (Generation R; N=2,240); the Lifestyle – Immune System – Allergy Study (LISA; N=357); the Northern Finland 1966 Birth Cohort (NFBC1966; N=4,287) and the Western Australian Pregnancy study (RAINE; N=759). Genotypes were obtained using high-density SNP arrays, and then imputed for ~2.4 million HapMap SNPs (Phase II, release 21/22, <http://hapmap.ncbi.nlm.nih.gov/>). The basic characteristics, exclusions (e.g. samples of non-European ancestry), genotyping, quality control and imputation methods for each discovery sample are presented in Supplementary Table 1.

Statistical analysis within discovery samples—Head circumference was measured in infancy (age window: 6-30 months). If multiple measurements were available for one individual within this age window, the measurement closest to 18 months was used. Sex- and age-adjusted standard deviation scores (SD score) were constructed using Growth Analyser 3.0 (<http://www.growthanalyser.org>; Dutch Growth Research Foundation, Rotterdam, the Netherlands) in each study separately¹⁸. The association between each SNP and head circumference was assessed in each study sample using linear regression of head circumference SD score against genotype, assuming an additive model. Imputed genotypes were only used where directly-assayed genotypes were unavailable.

Meta-analysis of discovery samples—Data exchange was facilitated by the SIMBioMS platform (simbioms.org)³⁸. Prior to meta-analysis, SNPs with a minor allele frequency <1% and poorly-imputed SNPs ($\text{proper_info} < 0.4$ [SNPTEST]; $r^2 < 0.3$ [MACH2QTL]) were filtered. Fixed effects meta-analyses were independently conducted by two investigators (H.R.T., D.O.M-K.). Meta-analysis was performed using the software package: METAL (<http://www.sph.umich.edu/csg/abecasis/metal/index.html>); Genomic control³⁹ was applied during the meta-analysis stage to adjust the statistics generated within each cohort (see Supplementary Table 1 for individual study χ^2 -values, discovery meta-analysis χ^2 -value: 1.043). Meta-analysis was done using the inverse-variance method; a fixed effects model was assumed. SNPs available in less than four discovery cohorts were excluded. Final meta-analysis results were obtained for 2,449,806 SNPs. We considered the top three lead signals (representing 3 distinct genomic regions on chromosomes 12 and 17) in the discovery analysis for further follow-up in additional samples. The two loci at chromosome 12 reached the threshold of $P < 1 \times 10^{-6}$ and were therefore selected for replication and the third locus at chromosome 17 was just above that threshold ($P = 1.4 \times 10^{-6}$) and was selected because of prior knowledge of the nearby genome wide significant hit on intra cranial volume as described by Ikram et al.²

Stage 2: Follow-up of three lead signals in additional samples

Follow-up samples, genotyping and analysis—We used 6 independent study samples (combined N=8,321) to follow up the three lead signals from the GWA meta-analysis (represented by index SNPs rs7980687, rs1042725 and rs11655470). Details of

these study samples are presented in Supplementary Table 2. If the index SNP was unavailable, a closely correlated proxy was substituted (rs12322888 or rs12316131 for rs7980687 [HapMap $r^2=0.95$]; rs7970350 or rs1351394 for rs1042725 [HapMap $r^2=1$ and 0.91 respectively]; rs12938031 for rs11655470 [HapMap $r^2=0.58$]). In 3 of the replication studies, the index SNPs were imputed from genome-wide genotype data (see Supplementary Table 2). The head circumference analysis (as described above) was performed within each study sample.

Statistical analysis

Meta-analyses of discovery and replication samples—We performed fixed effects inverse variance meta-analyses of the head circumference association results for the three lead signals in the seven discovery samples and six replication samples combined. Fixed effects meta-analyses were conducted independently by two investigators (H.R.T., D.O.M.-K.), using RMeta in R [v.2.7.0]). We used the Cochran Q test and the I^2 statistic⁴⁰ to assess evidence of between-study heterogeneity of effect sizes.

Informed consent (or parental consent, as appropriate) was obtained from all discovery and follow-up study participants and study protocols were approved by the local ethics committees.

Analyses of potential confounders

To verify that the investigated lead SNPs were not associated with other covariates which could theoretically confound the observed associations with head circumference (including height, weight and age at measurement; breastfeeding; maternal educational level; and sex), we used linear or logistic regression models to assess the associations between each covariate and genotype, in all discovery and replication samples. For height and weight, we constructed sex- and age-adjusted SD scores using Growth Analyser 3.0 (<http://www.growthanalyser.org>; Dutch Growth Research Foundation, Rotterdam, the Netherlands) in each study separately, similar to the head circumference SD score. To investigate possible effects of the three lead signals on head circumference through height, we first conducted linear regression analysis with and without adjustment for height SD score. Second, we conducted a mediation analysis and assessed the direct SNP effects and indirect SNP effects (mediated through height) on head circumference for each of the signals using a seemingly unrelated regression model (STATA, StataCorp LP, College Station, TX, USA) or a simple path analysis model (MPLUS, Muthen & Muthen, Los Angeles, CA, USA), which provide identical effect estimates. To investigate whether the associations between genotypes and infant head circumference were similar in the sexes, we repeated the analyses in males and females separately. Furthermore, we evaluated possible effect modification by breastfeeding status for each of the SNPs. Where possible, we meta-analyzed results to assess overall evidence of association.

Analysis of fetal head circumference and intra cranial volume

We explored associations of rs7980687, rs1042725 and rs11655470 with third trimester fetal head circumference and head circumference at birth, assuming an additive model using linear regression. Fetal head circumference was measured by ultrasound in three studies (combined N=3,781 singleton pregnancies) in third trimester of pregnancy (gestational age window 27-36 weeks). Only one measurement per subject was included in the time window. If multiple measurements were available within the time-window, the one closest to the median of 32 weeks of the gestation was used. We calculated gestational age specific SD scores using previously published growth charts⁴¹. This analysis was adjusted for sex. Head circumference was measured at birth, or within the 31st day of life, in 12 studies (N=13,775; Supplementary table 2). We created SD scores for head circumference within each of the

cohorts and assessed the association with each SNP, adjusted for sex and gestational age. If head circumference was measured in the first month, we used gestational age at birth + age (weeks) at measurement in the first month. Combined effect estimates were calculated using fixed effects meta-analyses.

We used the meta-analysis on intracranial volume in adults, measured by MRI, in the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) consortium⁴² as a third additional phenotype. Data collection methods, phenotype definition, baseline characteristics, and results of the meta-analysis are described elsewhere in this issue^{2,43}.

Analysis of known adult height variants with infant head circumference

We used the discovery meta-analyses to assess the associations of the previously identified 180 known adult height loci¹ with head circumference in infancy, using the same model as described above. We also checked whether very closely related SNPs (HapMap $r^2 > 0.95$) showed higher significance levels than the originally reported SNPs. SNPs with a P-value lower than 2.8×10^{-4} ($0.05/180$) were considered significant.

Variance explained

To estimate the percentage of variation in birth weight explained by each of the associated loci, we obtained the adjusted- R^2 from univariate linear regression models of head circumference against genotype. We then calculated a mean value from all discovery and replication studies, weighted by sample size.

Non-synonymous SNPs and eQTLs

We assessed SNPs in LD with the three lead signals and checked for non-synonymous SNPs or eQTLs to identify possible functional variants explaining the associations with head circumference. First, we used the SNP Annotation and Proxy search developed by the Broad institute (<http://www.broadinstitute.org/mpg/snap/>) to select all SNPs in LD ($r^2 > 0.50$) with our three lead signals. We used the 1000 Genomes Pilot 1 set as SNP dataset for rs7980687 and rs1042725 and the HapMap r22 as SNP dataset for rs11655470 ($r^2 > 0.50$) since this SNP was not available on the 1000 Genomes dataset. Next, we evaluated whether these SNPs were non-synonymous using dbSNP search engine from NCBI. To evaluate whether there were cis-eQTLs in LD with our lead signals we searched publicly available eQTL databases through the NCBI GTEx (Genotype-Tissue Expression) eQTL Browser (<http://www.ncbi.nlm.nih.gov/gtex/test/GTEX2/gtex.cgi>) and the Generic Genome Browser (<http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl/>). In total, these browsers search nine databases for eQTLs. Only cis-associations (defined as genes within 1Mb) that reached the P-value threshold for significance, as used in the original papers describing the gene expression datasets, were included in Supplementary Table 10. The statistics behind the eQTL analysis and calculation of the threshold for declaring significance of the associations are described in the published and validated eQTL datasets²⁰⁻²².

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

See also Supplementary Note for detailed acknowledgments by study.

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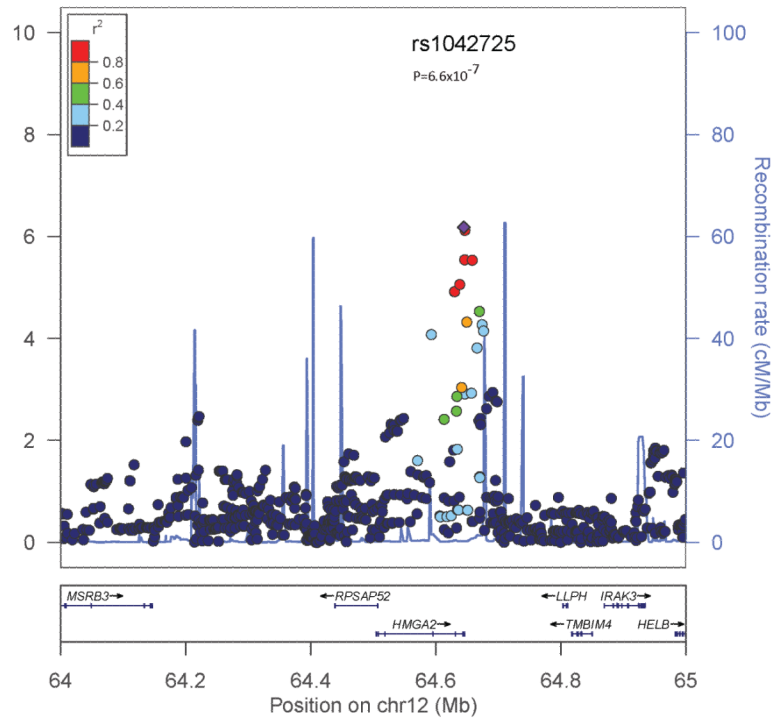
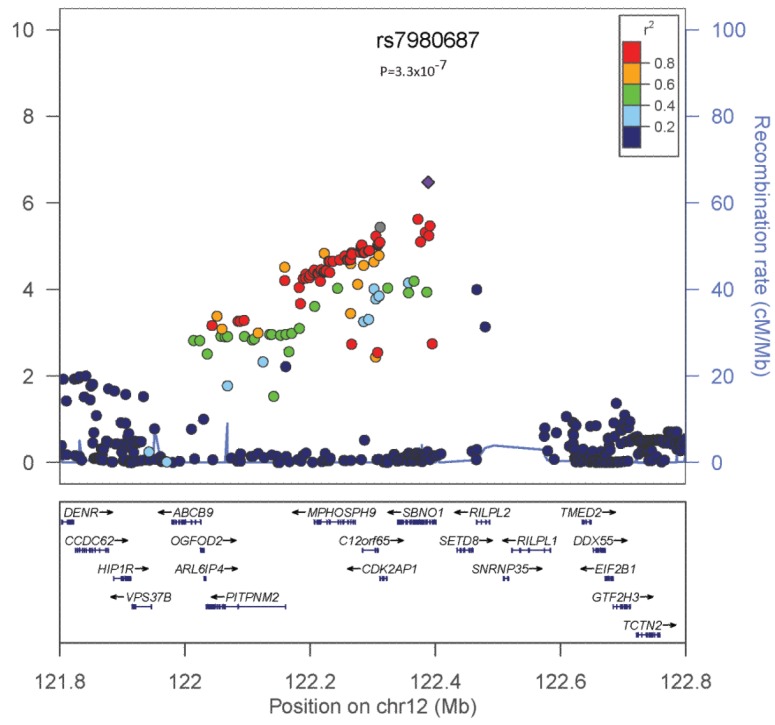
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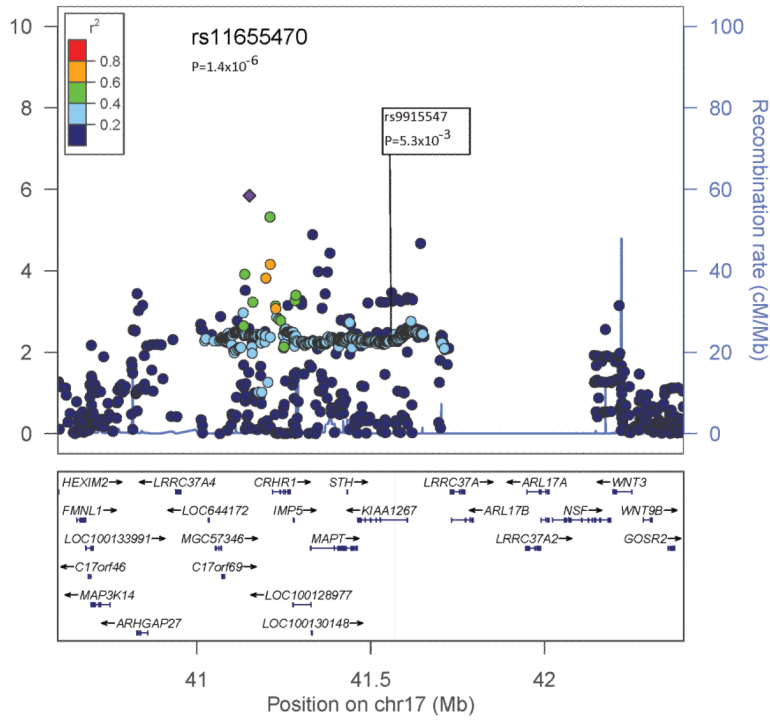


Figure 1. Directly genotyped and imputed SNPs are plotted using filled circles with their meta-analysis P values (as $-\log_{10}$ values) as a function of genomic position (NCBI Build 36). In each plot, the discovery-stage SNP taken forward to replication stage is represented by a purple diamond (defining a global meta-analysis P value). Local LD structure is reflected by the plotted estimated recombination rates (taken from HapMap) in the region around the associated SNPs and their correlated proxies. The correlations of the lead SNP to other SNPs at the locus are shown on a color scale from $r^2 < 0.2$ dark blue; $0.2 \leq r^2 < 0.4$ light-blue; $0.4 \leq r^2 < 0.6$ green; $0.6 \leq r^2 < 0.8$ orange; $r^2 \geq 0.8$ red. Superimposed on the plot are the recombination rates (light blue line, second y axis). Gene annotations are shown as the dark blue arrows. The regional plots were drawn using the LocusZoom software³⁶.
 1a Regional plot of locus 12q24.31
 1b Regional plot of locus 12q15
 1c Regional association plot of locus 17q21.1; downstream of the lead signal, rs9915547 is indicated (r^2 0.22 HapMap CEU with rs11655470), which showed a genome wide significant association with adult intra cranial volume ($P=1.5 \times 10^{-12}$) as described in Ikram et al.²

Table 1

Individual association results by study and meta-analysis

Study type	Study	Year(s) of birth	Median age (months)	Total N	% male	rs7980687_A on 12q24 -SBNJ1				rs1042725_T on 12q15 nearest gene HMG2				rs11655470_T on 17q21 nearest genes CRR1/MAAT			
						MAF	Beta	Se	P-value	MAF	Beta	Se	P-value	MAF	Beta	Se	P-value
Discovery	ALSPAC (D)	1991-2	18.9	1,748	53	0.19	0.105	0.038	6×10^{-3}	0.47	-0.071	0.031	0.02	0.41	0.114	0.031	3×10^{-4}
	CHOP	2006-10	18.5	1,008	59	0.20	0.041	0.058	0.48	0.48	-0.017	0.046	0.72	0.39	0.036	0.048	0.45
	COPSAC	1998-2001	18.1	369	49	0.19	0.083	0.086	0.33	0.47	-0.026	0.065	0.69	0.45	0.159	0.063	0.01
	Generation R	2002-6	13.1	2,240	52	0.21	0.064	0.031	0.04	0.49	-0.059	0.026	0.02	0.42	0.060	0.026	0.02
	LISA (D)	1998-9	11.8	357	56	0.21	-0.045	0.077	0.56	0.48	-0.059	0.060	0.33	0.39	0.068	0.061	0.26
	NFBC1966	1966	12.3	4,287	49	0.20	0.181	0.041	1×10^{-5}	0.49	-0.074	0.033	0.02	0.49	0.068	0.033	0.04
	RAINE	1989-91	13.1	759	53	0.19	0.108	0.058	0.06	0.50	-0.179	0.043	4×10^{-5}	0.41	-0.001	0.044	0.09
	Discovery meta-analysis			10,768			0.091	0.018	3.3×10^{-7}		-0.072	0.014	6.6×10^{-7}		0.070	0.015	1.4×10^{-6}
Replication	ALSPAC (R)	1991-2	18.9	3,163	51	0.20	0.042	0.030	0.16	0.49	-0.088	0.024	3×10^{-4}	0.40	0.044	0.024	6×10^{-4}
	DNBC	1996-2002	12.1	531	54	0.20	0.120	0.070	0.09	0.45	-0.049	0.058	0.40	0.45	0.060	0.058	0.30
	EFSOCH	2000-4	12.1	703	52	0.20	0.054	0.061	0.37	0.50	-0.019	0.046	0.67	0.41	0.027	0.046	0.56
	INMA	2004-7	13.9	693	53	0.16	0.020	0.062	0.75	0.44	-0.029	0.045	0.52	0.36	0.022	0.046	0.64
	GINI+LISA (R)	1995-9	11.8	698	51	0.21	0.020	0.060	0.74	0.50	-0.092	0.049	0.06	0.40	-0.070	0.050	0.16
	NFBC1986	1985-6	12.0	2,533	48	0.22	0.082	0.035	0.02	0.49	-0.034	0.029	0.25	0.50	0.019	0.287	0.51
	Replication meta-analysis			8,321			0.055	0.018	2.5×10^{-3}		-0.058	0.015	8.3×10^{-5}		0.025	0.015	0.093
	Overall meta-analysis			19,089			0.074	0.013	8.1×10^{-9}		-0.065	0.010	2.8×10^{-10}		0.048	0.010	3.6×10^{-6}

MAF; Minor allele frequency, Se; standard error. Beta's reflect difference in head circumference SD score per minor allele (additive model).

P value is obtained from linear regression of the SNP against head circumference SD score (additive model). All study samples were of European descent.

Key to study names: ALSPAC (D), Avon Longitudinal Study of Parents and Children Discovery subset; CHOP, Children's Hospital Of Philadelphia; COPSAC, Copenhagen Prospective Study on Asthma in Childhood; Generation R, the Generation R Study; LISA (D), Lifestyle – Immune System – Allergy Discovery subset; NFBC1966, Northern Finland Birth Cohort 1966; RAINE, The Western Australian Pregnancy Study; ALSPAC (R), Avon Longitudinal Study of Parents and Children Replication subset; DNBC, Danish National Birth Cohort; EFSOCH, Exeter Family Study Of Childhood Health; INMA, Infancia y Medio Ambiente [Environment and Childhood] Project; GINI+LISA (R), German Infant Study on the influence of Nutrition Intervention Munich + Lifestyle – Immune System – Allergy Replication subset; NFBC1986, Northern Finland Birth Cohort 1986.

Table 2
Association of the three lead signals related to head circumference with additional phenotypes

Marker	Head circumference in third trimester of pregnancy (SD score)				Head circumference at birth (SD score)				Intra cranial volume (ml)				
	Total N	Beta	Se	P-value	Total N	Beta	Se	P-value	Total N	Mean age at measurement (years)	Beta	Se	P-value
rs7980687_A on 12q24	3,781	0.089	0.029	1.9×10^{-3}	17,330	0.050	0.012	5.2×10^{-5}	8,175	67.5	0.72	2.03	0.72
rs1042725_T on 12q15	3,781	-0.075	0.023	9.9×10^{-4}	17,074	-0.031	0.010	1.9×10^{-3}	8,175	67.5	-7.18	1.61	8.8×10^{-6}
rs11655470_T on 17q21	3,781	0.049	0.024	0.037	17,695	0.030	0.010	2.0×10^{-3}	8,175	67.5	3.54	1.69	0.036 [#]

SD; standard deviation, Se; standard error. Beta's reflect difference in head circumference SD score per minor allele, or difference in intra cranial volume (ml) per minor allele (additive model). P-value is obtained from linear regression the SNP and sex against of head circumference SD score in fetal life (additive model), SNP, sex and gestational age at against birth head circumference SD score at birth (additive model); SNP, age and sex against Intra cranial volume (ml) (additive model)². All study samples were of European descent.

[#] A variant further downstream (rs9915547; $r^2 = 0.22$ HapMap CEU) showed a genome-wide significant association ($P = 1.5 \times 10^{-12}$) with adult intra cranial volume.²