Genome-Wide Association Study of Height and Body Mass Index in Australian Twin Families

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Human height and body mass index are influenced by a large number of genes, each with small effects, along with environment. To identify common genetic variants associated with these traits, we performed genome-wide association studies in 11,536 individuals composed of Australian twins, family members, and unrelated individuals at ~550,000 genotyped SNPs. We identified a single genome-wide significant variant for height (P value = 1.06×10^{-9}) located in *HHIP*, a well-replicated height-associated gene. Suggestive levels of association were found for other known genes associated with height (P values < 1×10^{-6}): *ADAMTSL3*, *EFEMP1*, *GPR126*, and *HMGA2*; and BMI (P values < 1×10^{-4}): *FTO* and *MC4R*. Together, these variants explain less than 2% of total phenotypic variation for height and 0.5% for BMI.

Keywords: BMI, genetics, height, replication

In recent years, the declining cost of high-throughput genotyping technology in conjunction with the ongoing International HapMap project (Frazer et al., 2007) have led to an explosion in the number of genome-wide association (GWA) studies of complex diseases and quantitative traits. A GWA study is a non-biased and non-hypothesis driven method for identifying correlations between genotype and phenotype. These studies have since successfully identified previously unknown genes affecting many clinically significant traits such as type 2 diabetes (Saxena et al., 2007), bone mineral density (Styrkarsdottir et al., 2009), and age at menarche (Sulem et al., 2009), greatly enhancing our understanding of the genetic mechanisms behind many complex diseases and traits. Their potential clinical implications in the prediction and treatment of common diseases represent an exciting period of human genetics research.

Human stature has been used as a model for quantitative traits for over 120 years. Galton (Galton, 1886) first famously observed the close correlation between height of offspring and those of his/her parents, while Fisher (Fisher, 1912) proposed that the pattern of inheritance in height can be explained by a large number of Mendelian factors, each with a small effect on overall heritability. It has been estimated that genetic factors account for around 80% of the variation in human height (Macgregor et al., 2006; Visscher et al., 2007).

As height is driven by human growth and developmental processes in conjunction with environmental factors such as diet and nutrition, research into the genetics of height may yield insights into many diseases. Children who deviate from normal growth patterns are often admitted to pediatric endocrine programs and treated with growth hormones (Hirschhorn et al., 2001; Lettre et al., 2007). In addition, tall stature has been associated with an increased risk of prostate cancer (Giovannucci et al., 1997; Hebert et al., 1997) and breast cancer (Gunnell et al., 2001; Lahmann et al., 2004), while short stature has been linked to coronary heart conditions (Forsen et al., 2000) and type 2 diabetes (Lawlor et al., 2002). Although the exact natures of these associations are unclear, it has been suggested that common hormonally mediated effects play a role (Weedon & Frayling 2008).

Body mass index is the ratio of an individual's weight (in kilograms) over the square of their height (in metres) and has traditionally been used as an indicator of obesity. A BMI of over 30 kg/m² is often used to define obesity in a clinical setting; however, BMI measurements need to be taken in conjunction with other measurements such as waist circumference and body fat percentage in order to obtain a more accurate judgement of obesity. Estimates of the heritability of BMI have varied from 40-70% (Loos & Bouchard,

2008), and like human height, its phenotype is a combination of both environment and many genetic factors, each with small effects on total variation.

Understanding the genetic contribution to BMI may provide researchers a better understanding of the biological pathways of weight gain. In addition, using associated genes to predict future obesity-related diseases can lead to better methods of early intervention and prevention. The increasing prevalence of obesity in society represents a significant public health issue. Obesity has been described as an 'epidemic' with nearly 1 billion adults overweight and over 300 million obese worldwide (Abelson & Kennedy, 2004). Obesity is a significant risk factor for several diseases, including type 2 diabetes; osteoarthritis; various cardiovascular diseases including coronary heart disease, stroke, and hypertension; and various cancers including breast, colon, and uterine (Haslam & James, 2005).

We performed GWA studies of height and BMI in 11,536 individuals composed of twins and their family members, as well as unrelated individuals, who were genotyped on a combination of Illumina 317K, 370K, and 610K microarray chips. Joint analysis of individuals who were genotyped on the different chips was made possible by imputing ungenotyped SNPs. Previous GWA studies of Caucasian populations have identified over 50 distinct loci associated with height (Gudbjartsson et al., 2008; Johansson et al., 2009; Lettre et al., 2008; Sanna et al., 2008; Soranzo et al., 2009; Weedon et al., 2008) and around a dozen for BMI (Frayling et al., 2007; Loos et al., 2008; Thorleifsson et al., 2009; Willer et al., 2009).

Methods

Phenotype Data Collection and Cleaning

Self-reported and clinical measurements of height and weight were available for 38,418 individuals recruited from the Australian Twin Registry between 1980 and 2004. Subjects included twins and their parents, siblings, spouses, children and other family members, and were part of several studies of investigating the genetics of traits such as asthma and allergy (Duffy et al., 1998), anxiety and depression (Wray et al., 2007), melanoma (Brown et al., 2008), cognition (Wright & Martin, 2004), and cardiovascular diseases (Beekman et al., 2003). As a result, multiple measurements of height and weight, both self reported and clinically measured, were available for individuals who participated in multiple studies. Several rules which were implemented to clean this data are described in detail elsewhere (Cornes et al., 2005; Benyamin et al., 2008). In brief, clinical measurements were used for individuals if available ($N = 7946$), and consistency checks were implemented for multiple self-reported measurements.

Due to the nature of human growth, where height continues to increase until an individual's late teens followed by a slight decrease in later adult years, the sample was separated into two cohorts composed of adolescents (under 18 years of age, $N = 4352$) and adults (over 18 years of age, $N = 34066$) (Figure 1). Height was approximately normally distributed for both groups, while a Box-Cox transformation (power parameter $\lambda = -1.152$) was applied to normalise BMI. For each group, separate polynomial regression models were fitted for height and BMI with age, age^2, and sex along with their interaction terms as covariates. A further 2007 individuals had height and weight clinically measured at combinations of ages 12, 14, and 16. These multiple measurements were treated as separate individuals in the initial modeling, before averaging the residuals for each individual in the final analysis. Consistent with other studies (Benyamin et al., 2008; Willer et al., 2009), outliers were indicated by individuals whose residuals deviated by more than 4 standard deviations from the mean and removed (6 adolescents and 110 adults).
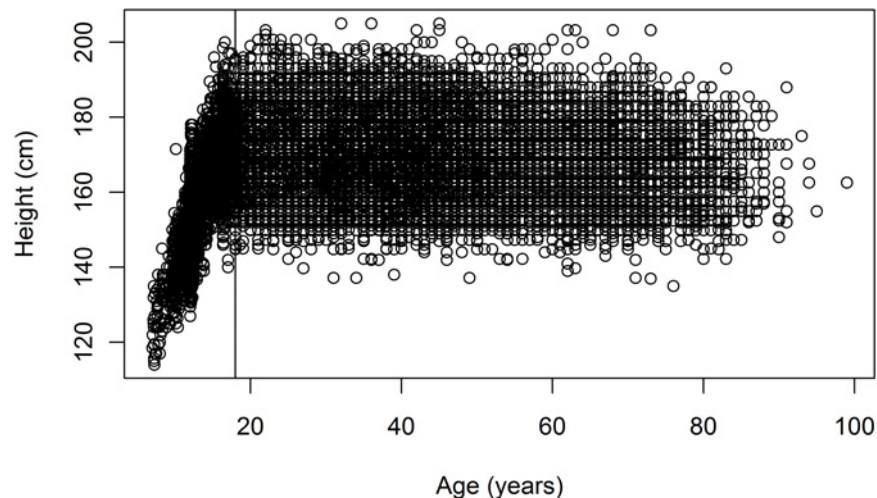
Genotyping

Genotyping and data cleaning are described in detail elsewhere (Medland et al., 2009). Briefly, genotyping was performed on 11,766 of the 38,418 individuals through five separate genotyping projects on a combination of Illumina 317K, Illumina 370K, and Illumina 610K microarray chips. Quality control measures used to clean genotype data included removing SNPs based on low genotype quality (GenCall < 0.7), high missingness (> 5% missing), deviations from Hardy-Weinberg equilibrium ($p < 10^{-6}$), and low allele frequencies (minor allele frequency < 0.01 or monomorphic). Individuals in families with a large number of Mendelian errors, cryptic relationships, or incompatible genotype with reported sex were also removed. In addition, population stratification checks were performed using EIGENSTRAT (Price et al., 2006) with HapMap CEU (release 22, build 36) and GenomEUTwin populations as references, and individuals of non-European origin were excluded ($N = 230$ across all genotyping projects). A summary of the five genotyping projects are given in Table 1. Ungenotyped SNPs were imputed using the software MACH in order to facilitate joint analysis of individuals.

Statistical Analysis

Height and BMI (normalized) were each fitted to separate polynomial regression models with age, age^2, and sex along with their interaction terms as covariates. The residuals from these models were standardized to z scores and used as the trait for association analysis. A family-based test for association was performed using the rapid-score test implemented in MERLIN (Abecasis et al., 2002). Altogether, four separate GWA analyses were performed: height in adolescents, height in adults, BMI in adolescents and BMI in adults. Adolescent and adult results for each of the traits were combined using the meta-analysis software METAL (http://www.sph.umich.edu/csg/abecasis/metal).

For comparison purposes, the power to detect the 26 height-associated SNPs identified in Gudbjartsson

Figure 1

Scatter plot of height against age in 38,418 individuals. Separate GWA analyses were performed for those under and over 18 years of age (indicated by the vertical line).

et al. (2008) and 11 BMI-associated SNPs identified in Thorleifsson et al. (2009) at genome-wide significance of $p < 10^{-7}$ and nominal significance of $p < 10^{-3}$ in our sample was estimated. Gudbjartsson and Thorliefsson both performed GWA studies for height and BMI with the same ~35,000 individuals. Power estimates were calculated in QUANTO (Gauderman & Morrison, 2006), where power was initially estimated assuming a sample of 11,536 independent individuals, before approximately correcting for the relatedness between individuals (Visscher et al., 2008).

Results

Genome-Wide Association

To identify SNPs that contribute to natural variation in height and BMI, GWA analyses on 11,536 individuals of European descent were performed. Quantile-quantile plots of the distribution of test statistics for height in adolescents showed little deviation from the expected distribution under no association, while there was a slight excess of low p values in the adult sample (Figure 2). However, much greater deviations from the expected distribution were found from the combined set of results, consistent with the power increase afforded by the increase in sample size. For BMI, there were no significant deviations from expectation in the adolescents and only slight deviations in both the adults and combined sets of results (Figure 3). There was only modest evidence of any overall systematic bias due to possible population stratification in the results (all λs < 1.063).

For the combined height results, only one SNP reached the stringent Bonferroni corrected genome-wide significance of $p < 10^{-7}$ ($\approx 0.05/550,000$) although there was strong suggestive evidence of additional associations at other loci (Figure 4a). The variant rs1812175 ($p = 1.06 \times 10^{-9}$) has been robustly

implicated in previous GWA studies for height (Gudbjartsson, et al., 2008; Lettre, et al., 2008; Weedon, et al., 2008) and maps to the *HHIP* gene (hedgehog interacting protein). In our sample, the C allele of rs1812175 increases height by ~0.118 standard deviations and explains ~0.25% of total genetic variance. A further 7 SNPs reached significance levels of $p < 10^{-6}$, all of which mapped to previously identified genes associated with height (*ADAMTSL3*, *EFEMP1*, *GPR126*, *HMGA2*) (Table 2). In addition, most of the SNPs identified in previous studies showed suggestive levels of significance in our results (Table 4). These include all SNPs replicated in two or more studies: *ZBTB* (rs6763931, $p = 2.88 \times 10^{-5}$), *LCORL* (rs6817306, $p = 7.63 \times 10^{-6}$), Histone class I (rs10946808, $p = 2.48 \times 10^{-5}$), *CDK6* (rs2282978, $p = 1.16 \times 10^{-4}$), *JAZF1* (rs849141, $p = 2.05 \times 10^{-3}$) and the *UQCC-GDF* region (rs4911494, $p = 1.4 \times 10^{-4}$). Their effect sizes range from 0.007 to 0.11 standard deviations and on average explains ~0.1% of total genetic variance each.

No SNPs reached genome-wide significance in the combined GWA results for BMI, nor were any suggestively associated regions as well defined as those for height (Figure 4b, Table 3). The most significantly associated SNP, rs2275215 ($p = 3.76 \times 10^{-7}$), is closest to *LAMA2* (lamin alpha 2). The variant rs10458787 was the only other SNP to reach $p < 10^{-6}$, and is located in an intergenic region on the short arm of chromosome 10. Suggestive associations were found for the previously well replicated BMI-associated genes *FTO* (rs3751812, $p = 5.86 \times 10^{-5}$), *MC4R* (rs12970134, $p = 5.10 \times 10^{-5}$) and *TMEM18* (rs7561317, $p = 7 \times 10^{-4}$) (Table 5). As expected, these associations all show modest effect sizes of between 0.01 and 0.07 standard deviations and explain less than 1% of total genetic variance.

Table 1

Summary of Genotyping Projects

Genotype chip	No. of SNPs passing QC	No. of individuals passing QC	Average age (years) (SD)	Average height (cm) (SD)		Average BMI (kg/m²) (SD)	
				Males	Females	Males	Females
Illumina 370K	323,093	4305	42.23 (14.19)	178.18 (7.17)	164.29 (6.93)	26.13 (3.92)	25.21 (5.41)
Illumina 610K	529,379	2833	14.27 (1.63)	163.71 (11.36)	159.48 (7.94)	20.63 (3.67)	20.67 (3.51)
Illumina 370K	321,267	2626	43.39 (13.71)	178.21 (7.12)	164.05 (6.63)	26.18 (4.38)	25.29 (5.11)
Illumina 610K	530,922	922	38.03 (12.66)	178.77 (6.46)	163.62 (6.60)	25.32 (4.19)	24.14 (4.44)
Illumina 317K	312,937	850	47.01 (12.73)	–	161.42 (6.66)	–	25.15 (4.66)
Total:	559,712	11,536					

Table 2

SNPs That Reached Combined $p < 10^{-6}$ for Combined GWA Results for Height

SNP	Chr	Position	Gene(s)	Allele	Freq	Adolescents			Adults			Combined			R² (%)
						Effect	SE	P-value	Effect	SE	P-value	Effect	SE	P-value	
rs3791679	2	55950395	EFEMP1	T	0.77	0.115	0.034	$7.37×10^{-4}$	0.076	0.020	$1.13×10^{-4}$	0.086	0.023	$5.06×10^{-7}$	0.26
rs6845999	4	145785276	HHIP	C	0.58	−0.057	0.029	0.050	−0.076	0.017	$4.59×10^{-6}$	−0.071	0.020	$7.28×10^{-7}$	0.25
rs1812175	4	145794293	HHIP	C	0.83	0.148	0.041	$3.14×10^{-4}$	0.108	0.022	$6.73×10^{-7}$	0.118	0.027	$1.06×10^{-9}$	0.39
rs6570507	6	142721264	GPR126	G	0.71	0.083	0.033	0.012	0.081	0.018	$5.93×10^{-6}$	0.081	0.022	$2.16×10^{-7}$	0.27
rs3748069	6	142809325	GPR126	A	0.71	0.084	0.033	0.011	0.077	0.018	$1.87×10^{-5}$	0.079	0.022	$6.20×10^{-7}$	0.26
rs8756	12	64646018	HMGA2	A	0.51	−0.051	0.029	0.079	−0.079	0.016	$1.46×10^{-6}$	−0.072	0.019	$4.26×10^{-7}$	0.26
rs7183263	15	82364045	ADAMTSL3	G	0.52	0.123	0.029	$1.70×10^{-5}$	0.056	0.016	$6.93×10^{-4}$	0.072	0.019	$3.89×10^{-7}$	0.26
rs4842838	15	82373127	ADAMTSL3	T	0.52	0.123	0.029	$1.70×10^{-5}$	0.055	0.016	$7.47×10^{-4}$	0.072	0.019	$4.27×10^{-7}$	0.26

Note: SNPs are ordered by chromosome and position. Positions are based on NCBI build 126. Allele and frequency refers to the major allele. Effect sizes and corresponding standard errors are in units of standard deviations of height. R² represents the percentage of phenotypic variance explained by the SNP.

Table 3

SNPs That Reached Combined $p < 10^{-6}$ for Combined GWA Results for (Normalized) BMI

SNP	Chr	Position	Gene	Allele	Freq	Adolescents			Adults			Combined			R² (%)
						Effect	SE	P-value	Effect	SE	P-value	Effect	SE	P-value	
rs2275215	6	129903085	LAMA2	T	0.73	−0.046	0.033	0.170	−0.097	0.019	$4.10×10^{-7}$	−0.085	0.022	$3.76×10^{-7}$	0.28
rs1058787	10	4645565	Intergenic	G	0.76	0.118	0.035	$8.10×10^{-4}$	0.076	0.02	$1.90×10^{-4}$	0.086	0.024	$9.61×10^{-7}$	0.27

Note: SNPs are ordered by chromosome and position. Positions are based on NCBI build 126. Allele and frequency refers to the major allele. Effect sizes and corresponding standard errors are in units of standard deviations of normalized BMI. R² represents the percentage of phenotypic variance explained by the SNP.

Table 4

Genome-wide association results for 61 known height-associated SNPs

SNP	Chr	Position	Gene(s)	Allele	Freq	Adolescents			Adults			Combined			R² (%)	P-value hetero
						Effect	SE	P-value	Effect	SE	P-value	Effect	SE	P-value		
rs11809207	1	26393727	CATSPER4	A	0.23	0.049	0.038	0.195	0.060	0.029	0.039	0.057	0.031	0.014	0.11	0.87
rs668842	1	41303458	SCMH1	C	0.56	−0.046	0.030	0.126	−0.005	0.017	0.770	−0.015	0.020	0.315	0.01	0.23
rs12735613	1	11868496	SPAG17	G	0.76	0.008	0.033	0.820	0.056	0.019	3.60×10^{-3}	0.044	0.022	9.73×10^{-3}	0.07	0.21
rs11205277	1	148159496	Histone class 2A, MTMR11, SV2A, SF3B4	G	0.44	0.067	0.029	0.021	0.022	0.017	0.174	0.033	0.020	0.018	0.05	0.14
rs678962	1	170456512	DNM3	G	0.22	0.053	0.035	0.130	0.034	0.020	0.088	0.039	0.024	0.018	0.05	0.46
rs2274432	1	182287568	C1orf19, GLT25D2	T	0.37	0.007	0.030	0.804	0.061	0.018	6.86×10^{-4}	0.048	0.021	2.23×10^{-3}	0.11	0.12
rs1390401	1	225864573	ZNF678	G	0.18	0.093	0.037	0.012	0.011	0.021	0.620	0.031	0.025	0.096	0.03	0.05
rs3791675	2	55964813	EFEMP1	C	0.77	0.115	0.034	7.80×10^{-4}	0.081	0.020	4.80×10^{-5}	0.089	0.023	3.16×10^{-7}	0.28	0.39
rs6724465	2	219652090	IHH	G	0.90	0.114	0.049	0.020	0.033	0.029	0.250	0.053	0.034	0.033	0.05	0.15
rs10935120	3	135715782	ANAPC13, CEP63	G	0.67	0.047	0.031	0.132	0.000	0.018	0.999	0.011	0.021	0.457	0.01	0.19
rs6440003	3	142576899	ZBTB38	G	0.55	−0.037	0.029	0.210	−0.057	0.017	6.90×10^{-4}	−0.052	0.020	4.62×10^{-4}	0.13	0.55
rs6763931	3	142585523	ZBTB38	A	0.35	0.048	0.029	0.091	0.062	0.016	1.51×10^{-4}	0.059	0.019	3.13×10^{-5}	0.16	0.76
rs724016	3	142588260	ZBTB38	A	0.56	−0.053	0.029	0.067	−0.063	0.017	1.60×10^{-4}	−0.061	0.020	3.93×10^{-5}	0.18	0.77
rs16896068	4	17553938	LCORL	G	0.84	0.052	0.040	0.190	0.094	0.023	2.90×10^{-5}	0.084	0.027	2.68×10^{-5}	0.19	0.36
rs6830062	4	17626828	LCORL	T	0.84	0.051	0.040	0.203	0.098	0.022	9.70×10^{-6}	0.087	0.026	7.64×10^{-6}	0.20	0.30
rs2011962	4	82439348	PRKG2	T	0.16	−0.060	0.033	0.070	−0.031	0.019	0.102	−0.038	0.022	0.018	0.04	0.39
rs6854783	4	145862529	HHIP	A	0.59	0.106	0.030	3.86×10^{-4}	0.051	0.016	2.05×10^{-3}	0.064	0.019	9.22×10^{-6}	0.20	0.11
rs1492820	4	145869471	HHIP	A	0.54	0.090	0.029	2.20×10^{-3}	0.044	0.017	7.90×10^{-3}	0.055	0.020	1.64×10^{-4}	0.15	0.17
rs12198986	6	7665058	BMP6	A	0.50	0.020	0.028	0.479	0.044	0.017	7.46×10^{-3}	0.038	0.020	8.98×10^{-3}	0.07	0.41
rs10946808	6	26341366	HIST1H1D	G	0.28	−0.078	0.032	0.016	−0.063	0.019	6.90×10^{-4}	−0.067	0.022	2.73×10^{-5}	0.18	0.60
rs9358913	6	26347383	HIST1H4F	A	0.15	0.074	0.033	0.023	0.053	0.019	4.94×10^{-3}	0.058	0.022	2.90×10^{-4}	0.09	0.48
rs4711269	6	31462798	HLA-B	T	0.16	0.022	0.035	0.523	−0.017	0.020	0.383	−0.007	0.024	0.556	0.00	0.47
rs2844479	6	31680935	HLA class III	T	0.68	−0.006	0.032	0.862	0.024	0.017	0.171	0.017	0.021	0.270	0.01	0.41
rs3130050	6	31726740	HLA class III	A	0.84	0.052	0.040	0.199	−0.062	0.023	6.83×10^{-3}	−0.034	0.027	0.086	0.03	0.01
rs185819	6	32158045	HLA class III	T	0.52	0.022	0.029	0.439	0.041	0.016	0.013	0.036	0.019	0.013	0.07	0.53
rs1776897	6	34302989	HMGA1	T	0.49	−0.088	0.054	0.203	−0.125	0.029	1.31×10^{-5}	−0.111	0.035	7.37×10^{-6}	0.62	0.44
rs2814993	6	34728871	C6orf106	A	0.15	0.054	0.040	0.182	0.084	0.023	3.36×10^{-4}	0.077	0.027	1.69×10^{-4}	0.15	0.52
rs4713858	6	35510763	ANKS1, TCP11, ZNF76, DEF6, SCUBE3	G	0.86	0.054	0.040	0.177	0.018	0.022	0.432	0.027	0.026	0.238	0.02	0.61
rs314277	6	105514355	LIN28B	A	0.13	−0.029	0.041	0.479	0.068	0.023	3.75×10^{-3}	0.044	0.027	0.032	0.04	0.04

(continued over)

Table 4 (continued)

Genome-wide association results for 61 known height-associated SNPs

SNP	Chr	Position	Gene(s)	Allele	Freq	Adolescents			Adults			Combined			R² (%)	P-value hetero
						Effect	SE	P-value	Effect	SE	P-value	Effect	SE	P-value		
rs4549631	6	127008001	LOC387103	C	0.51	0.046	0.030	0.120	0.010	0.017	0.560	0.019	0.020	0.206	0.02	0.30
rs4896582	6	142745570	GPR126	G	0.70	0.084	0.033	9.70×10^{-3}	0.079	0.018	1.40×10^{-5}	0.080	0.022	6.77×10^{-7}	0.27	0.89
rs798544	7	2729628	GNA12	G	0.72	0.052	0.032	0.106	0.054	0.018	2.85×10^{-3}	0.054	0.021	8.49×10^{-4}	0.12	0.92
rs849141	7	28151616	JAZF1	A	0.23	0.065	0.032	0.044	0.044	0.018	0.016	0.049	0.021	2.05×10^{-3}	0.09	0.57
rs2040494	7	92094841	CDK6	T	0.53	0.095	0.029	8.60×10^{-4}	0.037	0.017	0.028	0.051	0.020	4.43×10^{-4}	0.13	0.08
rs2282978	7	92102346	CDK6	C	0.33	0.116	0.030	1.43×10^{-4}	0.042	0.018	0.017	0.060	0.021	1.12×10^{-4}	0.16	0.05
rs10958476	8	57258362	PLAG1, MOS, CHCHD7, RDHE2, RPS20, LYN, TGS1, PENK	C	0.23	0.037	0.035	0.291	0.048	0.020	0.016	0.045	0.024	7.18×10^{-3}	0.07	0.90
rs9650315	8	57318152	CHCHD7, RDHE2	G	0.87	0.066	0.044	0.136	0.074	0.025	3.00×10^{-3}	0.072	0.030	1.12×10^{-3}	0.12	0.87
rs7846385	8	78322734	PXMP3, ZFHX4	C	0.27	0.002	0.032	0.945	0.008	0.018	0.677	0.007	0.021	0.648	0.00	0.96
rs10512248	9	97299524	PTCH1	T	0.69	−0.105	0.031	7.70×10^{-4}	−0.053	0.018	3.20×10^{-3}	−0.066	0.021	3.10×10^{-5}	0.18	0.15
rs4743034	9	108672174	ZNF462	A	0.23	0.071	0.035	0.040	0.011	0.020	0.568	0.026	0.024	0.165	0.02	0.20
rs7466269	9	132453905	FUBP3	A	0.65	0.037	0.030	0.228	0.045	0.017	9.11×10^{-3}	0.043	0.020	4.20×10^{-3}	0.08	0.82
rs1042725	12	64644614	HMGA2	C	0.51	0.039	0.029	0.190	0.076	0.017	5.80×10^{-6}	0.067	0.020	6.84×10^{-6}	0.22	0.27
rs11107116	12	92502635	SOCS2	T	0.23	0.045	0.035	0.198	0.121	0.052	0.020	0.102	0.048	8.74×10^{-3}	0.37	0.22
rs3116602	13	50009356	DLEU7	T	0.79	−0.034	0.036	0.350	0.054	0.020	7.10×10^{-3}	0.033	0.024	0.068	0.04	0.03
rs3118914	13	50014902	DLEU7	A	0.39	−0.043	0.036	0.231	0.060	0.020	2.46×10^{-3}	0.035	0.024	0.032	0.06	0.02
rs7153027	14	91496975	TRIP11, FBLN5, ATXN3, CPSF2	A	0.52	0.015	0.030	0.610	0.052	0.017	1.82×10^{-3}	0.043	0.020	3.11×10^{-3}	0.09	0.30
rs8007661	14	91529711	FBLN, TRIP11, ATXN3	C	0.54	0.019	0.029	0.514	0.001	0.046	0.976	0.005	0.042	0.728	0.00	0.74
rs2562784	15	82077496	SH3GL3, ADAMTSL3	T	0.79	−0.091	0.035	9.98×10^{-3}	−0.034	0.054	0.538	−0.048	0.049	0.071	0.08	0.38
rs10906982	15	82359162	SH3GL3, ADAMTSL3	A	0.52	0.123	0.029	1.60×10^{-5}	0.057	0.017	6.90×10^{-4}	0.073	0.020	5.31×10^{-7}	0.27	0.05
rs8041863	15	87160693	ACAN	T	0.53	−0.038	0.029	0.190	−0.038	0.017	0.022	−0.038	0.020	9.51×10^{-3}	0.07	1.00
rs4533267	15	98603794	ADAMTS17	A	0.28	0.061	0.033	0.061	0.045	0.018	0.015	0.049	0.022	1.88×10^{-3}	0.10	0.56
rs3760318	17	26271841	CRLF3, ATAD5, CENTA2, RNF135	C	0.63	0.090	0.030	2.44×10^{-3}	0.048	0.017	4.09×10^{-3}	0.058	0.020	5.54×10^{-5}	0.16	0.18
rs4794665	17	52205328	NOG, DGKE, TRIM25, COIL, RISK	A	0.48	0.055	0.029	0.059	0.064	0.016	8.79×10^{-5}	0.062	0.019	1.80×10^{-5}	0.19	0.74

(continued over)

Table 4 (continued)
Genome-wide association results for 61 known height-associated SNPs

SNP	Chr	Position	Gene(s)	Allele	Freq	Adolescents			Adults			Combined			R²(%)	P-value hetero
						Effect	SE	P-value	Effect	SE	P-value	Effect	SE	P-value		
rs757608	17	56852059	*BCAS3, NACA2, TBX2, TBX4*	T	0.35	0.036	0.030	0.234	0.062	0.018	5.13×10^{-4}	0.056	0.021	2.97×10^{-4}	0.14	0.49
rs4800148	18	18978326	*CABLES1, RBBP8, C18orf45*	A	0.79	0.105	0.035	2.45×10^{-3}	0.023	0.020	0.242	0.043	0.024	0.014	0.06	0.05
rs8099594	18	45245158	*DYM*	A	0.66	-0.013	0.031	0.680	0.043	0.018	0.015	0.029	0.021	0.061	0.04	0.12
rs12986413	19	2121954	*DOT1L*	A	0.55	-0.030	0.029	0.310	-0.043	0.017	0.010	-0.040	0.020	7.40×10^{-3}	0.08	0.70
rs967417	20	6568893	*BMP2*	C	0.53	0.012	0.029	0.676	0.032	0.017	0.056	0.027	0.020	0.063	0.04	0.55
rs6060369	20	33370575	*BFZB*	T	0.56	-0.069	0.030	0.020	-0.047	0.017	6.40×10^{-3}	-0.052	0.020	5.29×10^{-4}	0.14	0.52
rs6060373	20	33377622	*GDF5*	A	0.38	-0.069	0.030	0.020	-0.047	0.017	6.40×10^{-3}	-0.052	0.020	5.29×10^{-4}	0.13	0.52
rs4911494	20	33435328	*UQCC*	A	0.05	-0.061	0.030	0.039	-0.052	0.017	1.91×10^{-3}	-0.054	0.020	1.50×10^{-4}	0.03	0.66

Note: SNPs are based on those that reached $p < 10^{-7}$ in Gudbjartsson et al. (2008); Lettre et al. (2008); Sanna et al. (2008); Soranzo et al. (2009); or Weedon et al. (2008). Positions are based on NCBI build 126. Genes, allele and frequency are those given in the original studies. SNPs in *italics* indicate those that were not directly genotyped as part of this study, and were imputed instead.

Power Estimates

The statistical power to detect significant associations is primarily a function of an allele's frequency and effect size, and the number of individuals in the study. The use of familial rather than unrelated individuals also slightly reduces power (Visscher, et al., 2008). Our study sample size of 11,536 is modest compared with previous GWA studies of height and BMI.

Estimates of the power to detect associated SNPs identified in Gudbjartsson et al. (Gudbjartsson et al., 2008; Thorleifsson et al., 2009) and Thorleifsson et al. (2009) at genome-wide significance of $p < 10^{-7}$ and nominal significance of $p < 10^{-3}$ in our sample are shown in Figure 5. There was less than 10% power to detect the majority of the height-associated SNPs in Gudbjartsson at genome-wide significance. There was only ~14% power to detect rs1812175, the only variant that reached genome-wide significance in our study. For BMI, there was less than 1% power to detect 8 of the 11 variants identified in Thorleifsson at genome-wide significance. There was ~55% power to detect rs8050136, a variant which maps to *FTO* and reached a significance level of $p = 7.61 \times 10^{-5}$ in this study. These results show that the lack of significant associations after correcting for multiple testing in the GWA analyses is primarily a reflection of the modest sample size of our study combined with the small genetic effect sizes of associated variants. The fact that the majority of known associations showed suggestive levels of significance demonstrates the difficulty of separating these signals from random noise.

Discussion

Height and weight are both well defined, remain relatively consistent throughout life, and are easy to measure. As a result, measurements are readily available to form large studies that are not complicated by difficulties in phenotype definition, such as the time of onset and inconsistencies in clinical reporting that can plague studies of disease. However, results from previous GWAS on height and weight have demonstrated that these traits are associated with a large number of genes each having a relative small effect. Thus very large cohorts are required to achieve statistical significance in GWAS for these traits.
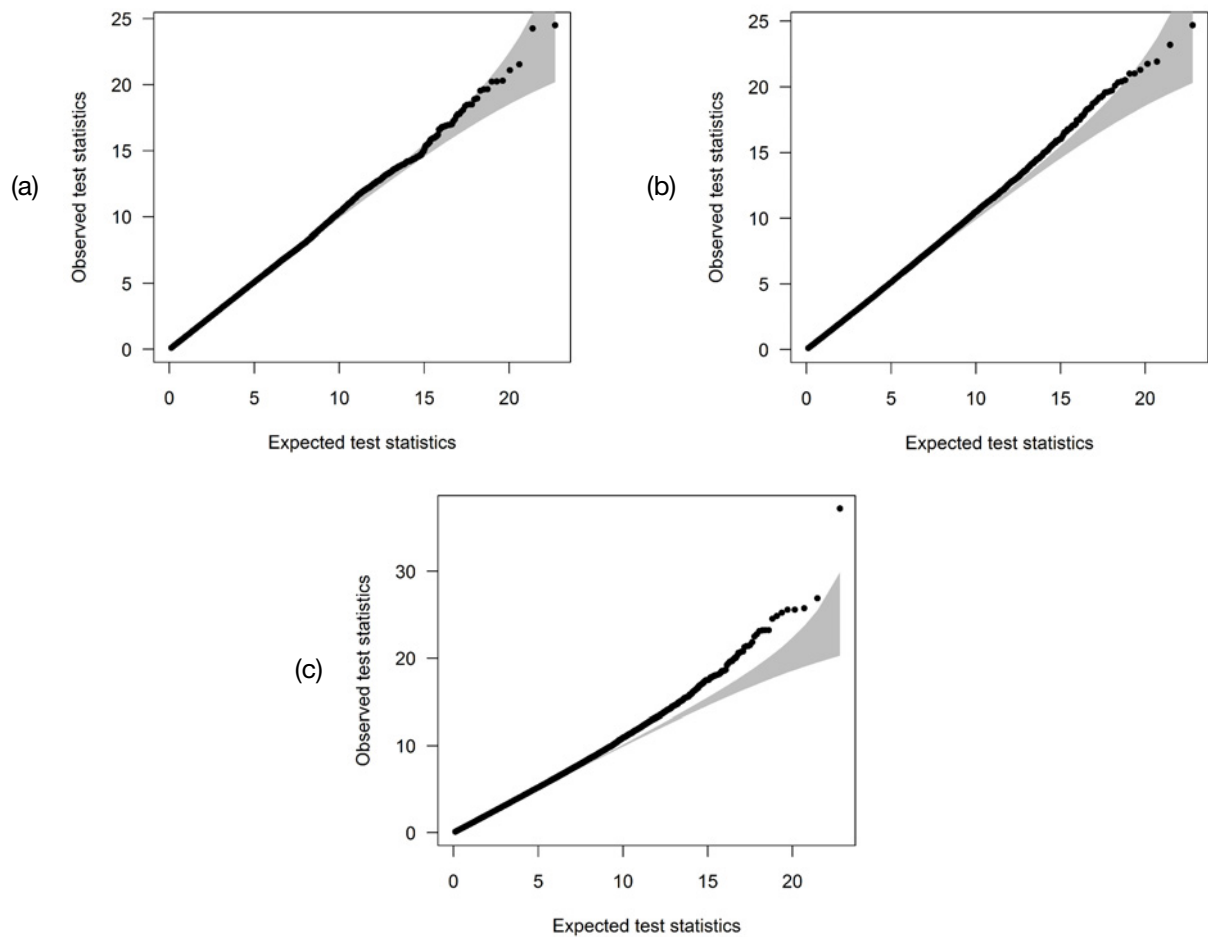
In this study, one genome-wide significant association was identified for height and none for BMI. This is a reflection of a samples size that although would have been considered large only a year or two ago, is now recognized as being modest for the investigation of the genetics of height and BMI. The power to detect significant genetic associations in this cohort was further reduced by the order of 1–15% through the use of family data (Visscher, et al., 2008), although the use of family data also confers advantages in GWA studies, namely more robust methods of genotype quality control and the ability to perform transmission-disequilibrium association tests which are robust to stratification. Indeed, there was less than 10% power

Table 5

Genome-Wide Association Results for 18 Known BMI-Associated SNPs

SNP	Chr	Position	Gene(s)	Allele	Freq	Adolescents			Adults			Combined			R² (%)	P-value hetero
						Effect	SE	P-value	Effect	SE	P-value	Effect	SE	P-value		
rs2568958	1	72537704	*NEGR1*	A	0.60	-0.029	0.030	0.337	-0.037	0.017	0.033	-0.035	0.020	0.023	0.06	0.82
rs2815752	1	72585028	*NEGR1*	T	0.60	-0.029	0.030	0.332	-0.034	0.018	0.064	-0.033	0.021	0.037	0.05	0.89
rs10913469	1	176180142	*SEC16B, RASAL2*	T	0.80	0.007	0.037	0.839	0.061	0.021	3.44×10^{-3}	0.048	0.025	0.010	0.07	0.20
rs2867125	2	612827	*TMEM18*	G	0.83	-0.137	0.039	4.98×10^{-4}	-0.046	0.023	0.040	-0.068	0.027	5.91×10^{-4}	0.13	0.04
rs6548238	2	624905	*TMEM18*	C	0.84	-0.136	0.041	8.40×10^{-4}	-0.042	0.024	0.075	-0.065	0.028	1.38×10^{-3}	0.11	0.05
rs7561317	2	634953	*TMEM18*	A	0.84	-0.132	0.040	8.60×10^{-4}	-0.048	0.023	0.033	-0.069	0.027	3.83×10^{-4}	0.13	0.07
rs7647305	3	187316984	*SFRS10, ETV5, DGKG*	C	0.78	-0.009	0.036	0.802	-0.045	0.021	0.030	-0.036	0.025	0.051	0.04	0.39
rs10938397	4	44877284	*GNPDA2*	A	0.55	0.094	0.030	1.70×10^{-3}	0.050	0.017	4.30×10^{-3}	0.061	0.020	8.13×10^{-5}	0.18	0.99
rs925946	11	27623778	*LGR4, LIN7C, BDNF*	G	0.68	0.060	0.031	0.053	0.022	0.018	0.231	0.031	0.021	0.050	0.04	0.29
rs10838738	11	47619625	*MTCH2*	A	0.64	-0.007	0.031	0.812	0.020	0.018	0.263	0.013	0.021	0.408	0.01	0.45
rs7138803	12	48533735	*BCDIN3D, FAIM2*	G	0.62	0.077	0.030	0.012	0.015	0.018	0.412	0.030	0.021	0.054	0.04	0.08
rs4788102	16	28780899	*SH2B1, ATP2A1*	G	0.63	0.071	0.031	0.023	0.016	0.017	0.343	0.029	0.020	0.056	0.04	0.12
rs7498665	16	28790742	*SH2B1*	A	0.56	0.069	0.031	0.027	0.017	0.022	0.437	0.030	0.024	0.145	0.04	0.17
rs9939609	16	52378028	*FTO*	T	0.59	0.087	0.031	4.60×10^{-3}	0.052	0.017	2.60×10^{-3}	0.061	0.020	8.63×10^{-5}	0.18	0.99
rs17782313	18	56002077	*MC4R*	T	0.76	0.108	0.036	2.50×10^{-3}	0.049	0.020	0.014	0.063	0.024	2.83×10^{-4}	0.15	0.15
rs12970134	18	56035730	*MC4R*	G	0.74	0.097	0.034	4.11×10^{-3}	0.063	0.019	8.21×10^{-4}	0.071	0.023	2.36×10^{-5}	0.20	0.38
rs11084753	19	39013977	*KCTD15*	G	0.67	-0.012	0.031	0.710	-0.015	0.018	0.400	-0.014	0.021	0.371	0.01	0.54
rs29941	19	39001372	*CHST8, KCTD15*	C	0.68	-0.017	0.032	0.599	-0.011	0.018	0.525	-0.012	0.021	0.427	0.01	0.87

Note: SNPs are based on those that reached $p < 10^{-7}$ in Frayling et al. (2007); Loos et al. (2008); Thorleifsson et al. (2009) or Willer et al. (2009). Positions are based on NCBI build 126. Genes, allele and frequency are those given in the original studies. SNPs in *italics* indicate those that were not directly genotyped as part of this study, and were imputed instead.
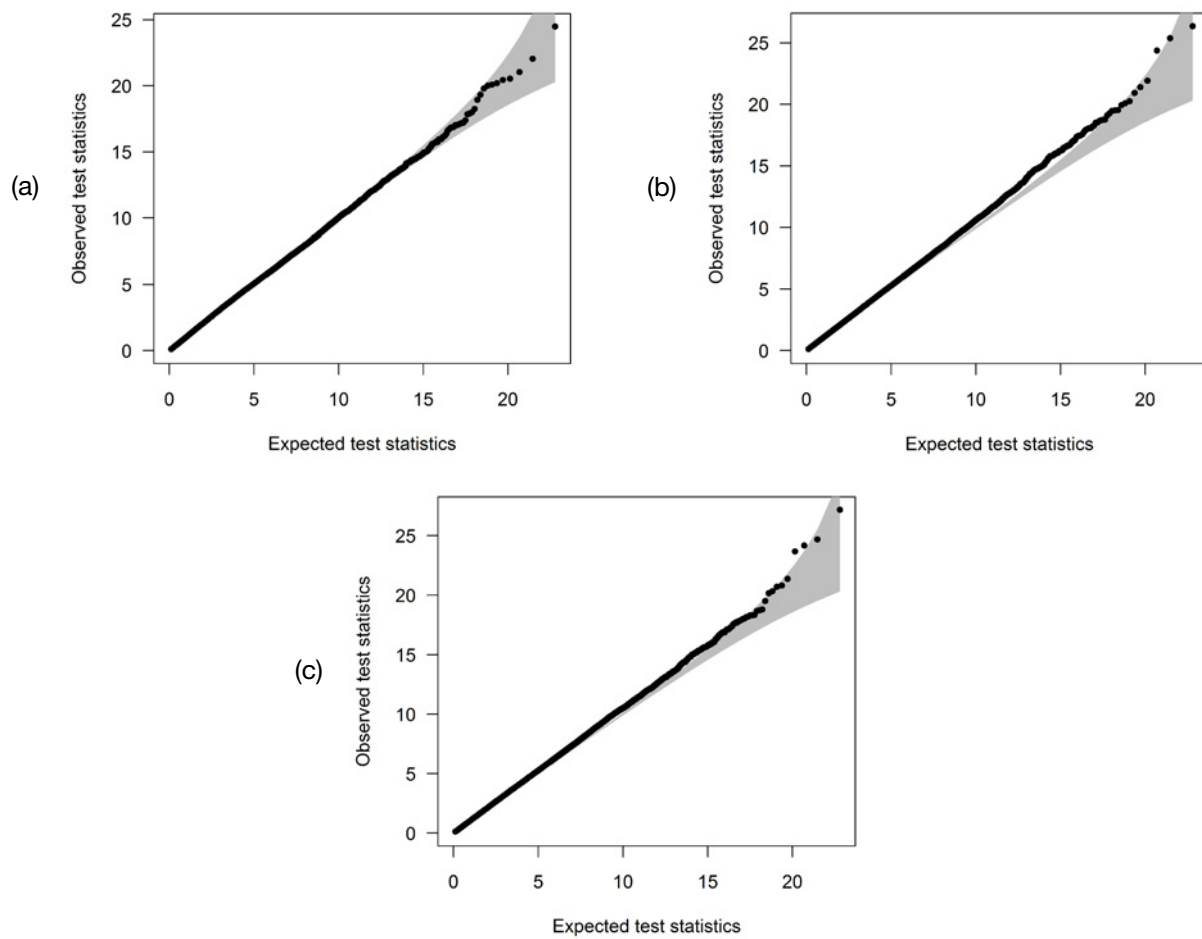
Figure 2

Quantile-quantile plot of χ^2 (1df) test statistics for 559,655 SNPs from the GWA analysis of (a) height in adolescents, genomic inflation $\lambda = 1.016$; (b) adults, $\lambda = 1.004$; and (c) combined, $\lambda = 1.019$. The 95% confidence interval of the expected χ^2 statistics under the null hypothesis of no association are indicated by the shaded regions.

to detect the majority of the height-associated SNPs identified in Gudbjartsson (2008) and less than 1% for all but two of the BMI-associated SNPs identified in Thorleifsson (2009) at genome-wide significance threshold of $p < 10^{-7}$. It is also likely that these power estimates were inflated given that they were based on the effect sizes reported in their respective original studies, which themselves may have been overestimated due to the 'winner's curse' effect (Garner, 2007; Xiao & Boehnke, 2009).

While only one SNP passed the Bonferroni threshold of $p < 10^{-7}$, a large number of other SNPs identified in previous studies were nominally replicated. This demonstrates one of the major issues facing GWA studies; the separation of true positive results from the random noise obtained from the large amounts of multiple testing. Given the small fraction of total genetic variation explained by the known genes, the obvious solution of increasing sample size will likely hit an upper limit before the genetic architecture of these traits is completely elucidated. However, some insights are already starting to emerge about the biological

processes involved in human stature growth. As expected, several of the genes implicated for height are involved in skeletal development, especially the Hedgehog signalling pathway and bone and cartilage formation growth factors and the formation of the extracellular matrix. Other less obvious biological functions include genes involved with chromatin structure and cell cycle regulation (Weedon & Frayling, 2008). For BMI, the majority of associated genes appear to be involved in neuronal functions and development, especially hypothalamic signalling, while others, such as *FTO*, appear to affect BMI through energy intake rather than energy expenditure (Cecil et al., 2008; Haupt et al., 2009), suggesting that to some extent, obesity is a result of neuronal functions related to control of hunger and appetite.

Genome-wide association studies represent a major step in understanding the genetics of complex diseases and traits. Despite recent successes in identifying previously unknown genes responsible for a wide variety of traits, current approaches can only explain a fraction of total genetic variation and are of limited use
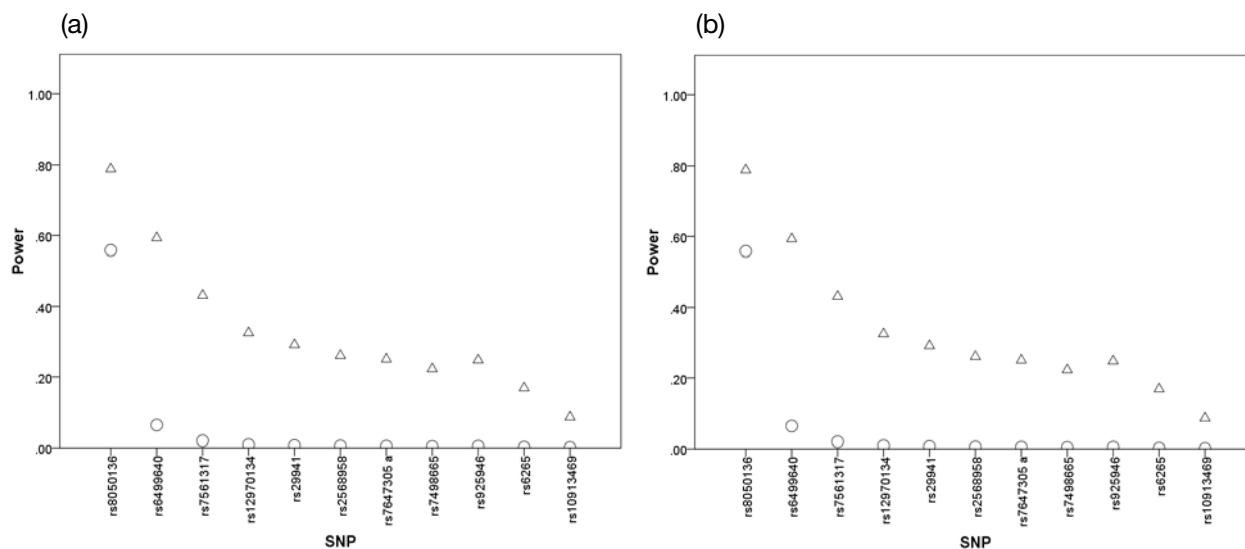
Figure 3

Quantile-quantile plot of χ^2 (1df) test statistics for 559,655 SNPs from the GWA analysis of (a) BMI in adolescents, genomic inflation $\lambda = 1.021$; (b) adults, $\lambda = 1.063$; and (c) combined, $\lambda = 1.061$. The 95% confidence interval of the expected χ^2 statistics under the null hypothesis of no association are indicated by the shaded regions.

Figure 4

Manhattan plot of 559,655 SNPs from the combined GWA analyses of (a) height and (b) BMI. Horizontal lines represent p values of $p = 10^{-10}$, 10^{-8} and 10^{-6}.

(a)

(b)

Figure 5

Statistical Power of this study to detect to detect the (a) 26 height-associated SNPs identified in Gudbjartsson et al. (2008) and (b) 11 BMI-associated SNPs indentified in Thorleifsson et al. (2009) at genome wide significance ($p < 10^{-7}$, circles) and nominal significance ($p < 10^{-3}$, triangles).

for practical clinical applications in disease prediction, treatment and prevention. It remains to be seen how much of the 'missing heritability' we can ultimately explain using this approach.

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