Published in final edited form as:
Hum Genet. 2009 February ; 125(1): 1–9. doi:10.1007/s00439-008-0590-9.

Genome-wide association scan for stature in Chinese: evidence for ethnic specific loci

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Abstract

In Caucasian, several studies have identified some common variants associated with human stature variation. However, no such study was performed in Chinese, which is the largest population in the world and evidently differs from Caucasian in genetic background. To identify common or ethnic specific genes for stature in Chinese, an initial GWAS and follow-up replication study were performed. Our initial GWAS study found that a group of 13 contiguous SNPs, which span a region of ~150 kb containing two neighboring genes, zinc finger protein (ZNP) 510 and ZNP782, achieved strong signals for association with stature, with *P* values ranging from 9.71×10^{-5} to 3.11×10^{-6}. After false discovery rate correction for multiple testing, 9 of the 13 SNPs remain significant (FDR $q = 0.036–0.046$). The follow-up replication study in an independent 2,953 unrelated southern

Chinese confirmed the association of rs10816533 with stature ($P = 0.029$). All the13 SNPs were in consistently strong linkage disequilibrium ($D' > 0.99$) and formed a single perfect haplotype block. The minor allele frequencies for the 13 contiguous SNPs have evidently ethnic difference, which range from 0.21 to 0.33 in Chinese but have as low as ~0.017 reported in dbSNP database in Caucasian. The present results suggest that the genomic region containing the ZNP510 and ZNP782 genes is an ethnic specific locus associated with stature variation in Chinese.

Introduction

Human stature has long been recognized as an index of physical growth and development. Final stature is closely associated with the earlier bone growth and differentiation. In gene mapping for bone disorders, human stature is often used as an important covariate. Genetic analyses for bone diseases may lead to false-positive results if genetic determination of human statue is not appropriately identified and adjusted for (Goring and Terwilliger 2000). Understanding the biological process and genetic determination of stature will provide insights into human development and growth and the genetic architecture of other human complex traits/diseases in general.

Stature is under strong genetic influence, with heritability generally above 0.75 (Carmichael and McGue 1995; Luo et al. 1998; Phillips and Matheny 1990). We identified a high heritability of 0.65 by segregation analyses on a Chinese sample of 1,169 informative individuals from 385 nuclear families (Li et al. 2004). In Caucasian, extensive genetic studies via candidate gene association analyses and whole genome linkage scans were performed to identify genes contributing to the variation of human stature (Deng et al. 2002; Hirschhorn et al. 2001;Liu et al. 2006a; Liu et al. 2004, 2006b; Mukhopadhyay et al. 2003; Perola et al. 2001; Wiltshire et al. 2002; Wu et al. 2003; Xu et al. 2002). Recent developing microarray technology of SNP genotyping provides powerful tool for genome-wide association scan (GWAS) studies to rapidly and systematically identify/confirm functional loci underlying human stature variation. In Caucasian, several GWAS studies have identified some common variants associated with human stature variation (Gudbjartsson et al. 2008; Lettre et al. 2008; Sanna et al. 2008; Weedon et al. 2007, 2008). However, in Chinese, which is the largest population in the world, and apparently differs from Caucasian in ethnic genetic background, no such GWAS study on stature was performed to dissect the genetic basis of stature at the genome-wide scale, or to compare the results for finding ethnic specific genes.

Here, we performed an initial WGAS study in 618 unrelated Chinese subjects, using high density Affymetrix 500 K SNP arrays examining ~500,000 SNPs genome-wide, and the follow-up replication study in an independent 2,953 unrelated southern Chinese. The results suggest a genomic region containing ZNP510 and ZNP782 specifically important to stature in Chinese.

Materials and methods

Samples

The study was approved by the necessary Institutional Review Board or Research Administration of the involved institutions. All study volunteers signed the informed-consent forms before they entered the project.

GWAS sample (Northern Chinese)

A total of 618 Han adult unrelated subjects were recruited from the Xi'an City and its surrounding areas in northern China. The stature for each subject was measured using a stadiometer.

Replication study sample (Sothern Chinese)

Totally, 2,953 healthy unrelated adult subjects including 1,517 females and 1,436 males were recruited from Chinese Han adults living in Changsha, Hunan province, which is more than 1,000 km from Xi'an where the northern Chinese sample was recruited. The basic characteristics of the study samples were given in Table 1.

Genotyping

For GWAS sample

Genomic DNA was extracted from whole human blood using a commercial isolation kit (Gentra systems, Minneapolis, MN, USA) according to the protocols of the kit. For each sample, genotyping with GeneChip® Human Mapping 500 K set containing 250 K Nsp array and 250 K Sty array (Affymetrix, Santa Clara, CA, USA) was performed using the standardized protocols recommended by the manufacturer. Briefly, for each array, 250 ng of DNA was digested with restriction enzyme (NspI or StyI) and ligated to adapters. A single PCR primer that recognizes the adapter sequence was used to amplify the ligated product. The amplified DNA (200–1,100 bp) was fragmentized into approximately 50 bp size, then labeled with biotin and hybridized to the arrays. After 16–18 h of hybridization, the arrays were washed with Wash Buffer A (6 × SSPE, 0.1% Tween 20) and Wash Buffer B (0.6 × SSPE, 0.1% Tween 20), in turn, on an Affymetrix Fluidics Station FS450. Then they were stained subsequently with the Streptavidin Phycoerythrin (SAPE, 10 μg/ml) and Anti-streptavidin antibody. The stained arrays were scanned with an Affymetrix GeneChip® 3000 7G scanner at 0.7 μm solution. SNPs genotypes from the scanned images were extracted using GCOS and GTYPE software (Affymetrix).

Quality control procedures were as follows. First, only samples with a minimum of 95% call rate were included. The final mean BRLMM call rate of the entire sample reached a high level of 99.02%. Second, out of the initial full-set of 500,568 SNPs, we discarded: (1) SNPs with a call rate <90% in both cases and controls (n = 54,845); (2) those deviating from Hardy–Weinberg equilibrium (HWE) in controls ($P < 0.001$, n = 22,002); and; (3) those having a minor allele frequency (MAF) < 0.05 in the total sample (n = 142,188). Therefore, 281,533 SNPs were available for the subsequent analyses.

For replication study sample

SNP genotyping in this sample was carried out with Mass-ARRAY system (Sequenom, San Diego, CA, USA) using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (Braun et al. 2003) for separation and detection. The entire process has been designed for complete automation including assay design, PCR setup, post-PCR treatment, nanoliter transfer of diagnostic products onto silicon chips, serial reading of chip positions in the mass spectrometer, and final analytical interpretation. The SNP genotyping success rate was 97% and the duplicate concordance rate was 99%.

Statistical analysis

GWAS analysis

Because gender and age are two significant covariates associated with stature, they were used to adjust the raw stature in subsequent analyses. HelixTree 5.3.1 (Golden Helix, Bozeman, MT, USA) performed two types of association analyses (genotypic association analyses and haplotype association analyses). Genotypic association analyses compared the difference of mean stature values among three genotypic groups for each SNP. Haplotype association or block association analyses compared the mean stature values among different haplotype groups formed by a group of SNPs.

Haplotype analysis

Haploview software (Barrett et al. 2005) (available at http:// www.broad.mit.edu/mpg/haploview/) was used to analyze the linkage disequilibrium (LD) [standardized D' (D/D_{max})] patterns of the interesting SNPs and to plot the haplotype block map.

Multiple testing correction

We used the QVALUE software (http://genomine.org/qvalue/) (Storey and Tibshirani 2003) to calculate false discovery rate (FDR)-based *q* values to measure the statistical significance at the genomewide level for the association results. The cutoff for significant association at the genome-wide level was set at FDR *q* value <0.05. We did not use Bonferroni correction for overly conservation for multiple testing adjustment in a GWAS study, since it does not take into account the intrinsic correlations between a large number of tests, which is caused by the extensive LD among SNP markers genomewide.

Population stratification

To detect potential population stratification that may lead to spurious association results, we used STRUCTURE 2.2 program (http://pritch.bsd.uchicago.edu/software.html) to investigate the potential substructure of our sample. The program uses a Markov chain Monte Carlo (MCMC) algorithm to cluster individuals into different cryptic sub-populations on the basis of multi-locus genotype data (Pritchard et al. 2000). We performed the analysis assuming the number of population strata $k = 2$, and using a set of 1,000 un-linked markers randomly selected genomewide. EIGENSTRAT (Price et al. 2006) was employed to perform principal component analysis to correct for stratification in genome-wide association studies. We used ~280,000 SNPs to calculate the principal components and the ten default main eigenvectors were used in the association analysis with the EIGENSTRAT program.

Genotype imputation

Different genotyping platforms were used in our current and previous GWAS studies for stature. To compare the associations at the same SNPs, we impute genotypes for ~2,500,000 HapMap SNPs in our GWAS sample upon a set of known haplotypes and an estimated fine-scale recombination map using a program IMPUTE (Marchini et al. 2007). The imputed genotype for each SNP is expressed as genotype probability. Association analysis was performed between the imputed SNPs (genotype dosage score) and stature using sex and age as covariates using a program called SNPTEST(Marchini et al. 2007).

Functional prediction

In order to analyze and predict the potential functions of the interesting SNPs, we utilized the FASTSNP program (http://fastsnp.ibms.sinica.edu.tw) to analyze SNP functions based on up-to-date information extracted from 11 external bioinformatic databases at query time (Yuan et al. 2006).

Results

Initial GWAS study

From a quantile–quantile (Q–Q) plot for the distribution of *P* values involving ~280,000 eligible SNPs in our sample (Fig. 1), the observed *P* values matched the expected *P* values over the range of $1 < -\log_{10}(P) < 4.0$, but departed at the extreme tail [$-\log_{10}(P) > 4.0$]. This suggests that the associations identified are likely due to true variants rather than potential biases such as genotyping error.

We identified 5 genes that contained SNPs significantly associated with stature at genomewide level (q value < 0.05) (Table 2). In particular, a group of 13 contiguous SNPs, which span a region of ~150 kb containing two neighboring genes (zinc finger protein (ZNP) 510 and ZNP782), achieved strong association signals for stature, with P values ranging from 9.71×10^{-5} to 3.11×10^{-6} (Table 3). Nine of the 13 SNPs (rs10978781, rs10816533, rs35334289, rs10978953, rs10117921, rs10118617, rs10119556, rs7859940, and rs10124033) remain significant at the genomewide significance threshold (FDR $q < 0.05$). The MAFs for the 13 contiguous SNPs have evidently ethnic difference, which range from 0.21 to 0.33 in Chinese but have as low as ~0.017 reported in dbSNP database in Caucasian.

Figure 2 shows the LD pattern and the haplotype block structure for the SNPs in the region of ZNP 510 and ZNP782 genes. These SNPs were in consistently strong LD ($D' > 0.99$) and formed a single perfect haplotype block (i.e., Block 1 in Fig. 2). The haplotype in this block was still significantly associated with stature ($P = 1.01 \times 10^{-3}$). Analyses using FASTSNP program (Yuan et al. 2006) suggest that rs35334289 of the ZNP510 gene and rs7859940 of the ZNP782 gene are located as potential transcription factor binding sites. The rs10978953 in the promoter region of ZNP782 may be a potential regulatory factor for the expression of this gene.

We used the STRUCTURE program (Pritchard et al. 2000) to cluster 618 subjects based on 1,000 or 10,000 SNPs randomly selected genomewide to test the potential population stratification of our sample. According to the results generated by the program, all the subjects were clustered together as a single group by 1,000 or 10,000 SNPs, suggesting no detectable population stratification in our sample. The analyses by EIGENSTRAT confirmed, qualitatively, our main results presented above and consequently, results of the EIGENSTRAT analyses are not detailed here. The “inflation factor” λ calculated by Genomic Control (Devlin and Roeder 1999) is 1.02, indicating that potential population stratification in this homogeneous Chinese population is very minimal.

Replication study

The most significant SNP (rs10816533) in the SNP group is located in intron 1 of ZNP10 gene. In the follow-up replication study, the rs10816533 was significantly ($P = 0.029$) associated with stature in 2,953 unrelated southern Chinese subjects. The subjects with homozygous GG had higher stature (4.26 cm) than those with homozygous CC (Fig. 3). Fisher's combined P analyses (Fisher and Miles 2008), which combined the P values from association tests in the study populations, showed that rs10816533 has more strong association signal ($P = 1.55 \times 10^{-6}$).

Comparison of the current study to the published GWAS studies

Table 4 lists 44 significant or suggestive association SNPs identified in previous GWAS studies in Caucasian and the corresponding association results in present study. Among these SNPs, we impute genotypes for 19 SNPs, which are not included in Affymetrix 500 K SNP Array. If the direction of association effect is the same between the previous GWAS studies and current study, a significant replication threshold can be set at $P = 0.1$. Even in this situation, only six SNPs were replicated their associations, and most of SNP associations identified in previous GWAS studies in Caucasian are unable to be confirmed by the current GWAS results in Chinese. Moreover, the MAFs reported from the dbSNP public database (http://www.ncbi.nlm.nih.gov/SNP/) for most of these SNPs are evidently different; particularly, the alleles with minor frequency for six SNPs (e.g., rs10946808, rs4794665) are different between Caucasian and Chinese. Collectively, these observations seem to suggest there are ethnic specific loci regulating variation of stature.

Discussion

ZNP510 and ZNP782 are two newly identified genes with unclear functions. However, ZNPs are one of the largest families of transcription regulators in humans and play very important roles in a variety of processes associated with skeletal development (Ganss and Jheon 2004). ZNPs are extensively expressed in osteoblasts and chondrocytes. ZNPs by binding to DNA zinc finger motifs regulate transcription processes associated with skeletal development (Ganss and Jheon, 2004). Mutations in ZNPs can cause abnormal stature or skeletal abnormalities (Momeni et al. 2000; Mundlos et al. 1997). For example, mutations of the RUNX2 (Runt-related transcription factor 2) gene, a well-known ZNP, may cause cleidocranial dysplasia characterized by short stature and other anomalies in skeletal growth and development (Mundlos et al. 1997).

In Caucasian, extensive genetic studies using GWLS (Deng et al. 2002; Hirschhorn et al. 2001; Liu et al. 2006a, b, 2004; Mukhopadhyay et al. 2003; Perola et al. 2001; Phillips and Matheny 1990; Wiltshire et al. 2002; Wu et al. 2003; Xu et al. 2002) or GWAS (Gudbjartsson et al. 2008; Lettre et al. 2008; Sanna et al. 2008; Weedon et al. 2007, 2008) studies identified quite a few chromosomal regions potentially harboring genes underlying variation of human stature, or some common variants associated with human stature variation. However, in Chinese, genetics studies on stature still remain a largely uncharted territory. Currently, only a segregation analysis study was performed for stature in Chinese, which suggested a high heritability (Li et al. 2004). The present GWAS for stature in Chinese provided interesting genes for future detailed functional characterization.

The present study along with other genetic studies on stature suggests that there are ethnic specific loci regulating variation of stature. Direct evidences may come from: First, the MAFs for a cluster of SNPs significantly associated with stature in the present study have evidently ethnic difference between in Chinese and in Caucasian; Second, most of loci identified in previous GWAS studies in Caucasian (Gudbjartsson et al. 2008; Lettre et al. 2008; Sanna et al. 2008; Weedon et al. 2007, 2008) do not overlap their associations in Chinese. Moreover, the MAFs reported from the dbSNP public database (http://www.ncbi.nlm.nih.gov/SNP/) for most of these SNPs are evidently different; particularly, the alleles with minor frequency for six SNPs (e.g., rs10946808, rs4794665) are different between Caucasian and Chinese; Third, most of the linkage regions identified in previous GWLS studies can not be confirmed by the present association results. On the other hand, indirect evidences may also support this. It is well-known that the stature in Caucasian is apparently higher than in Chinese, probably suggesting a different genetic background to determinate stature. Some phenotypes (such as bone) closely related to stature are clearly under ethnic-specific genetic determination (Dvornyk et al. 2005; Dvornyk et al. 2003; Lei et al. 2006, 2003). For example, five candidate genes (Dvornyk et al. 2005) were tested for their contribution of ethnicity to bone mineral density variation in Caucasian and Chinese. The frequencies and distribution patterns of SNPs of some prominent bone candidate genes were different between Caucasian and Chinese (Lei et al. 2003), The above observed inconsistencies between the two ethnic populations may be partially attributed to ethnic difference in genetic background that may play an important role in genetic determination of stature.

It is well recognized that population stratification may yield spurious association results. Therefore, potential population stratification should be rigorously tested and excluded in the sample for association analyses. Using the STRUCTURE program (Pritchard et al. 2000) to analyze our sample, all the subjects were clustered into a single group, suggesting no significant population stratification in our sample. Therefore, our association results are unlikely to be plagued by spurious associations due to population stratification and thus robust.

Using a threshold $P = 0.05$, the statistical power in a sample size of 618, estimated by the software Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/qtlassoc.html), is less than 50% for detecting a gene that accounts for 0.3% of stature variation. (Most of the previously published loci explained <0.3% of stature variation.). Therefore, the limited power in our GWAS study may another possible reason for the failure of replicating most of previously identified height loci. Another potential explanation, as discussed in the "Results", for such failure is that some of the previously identified loci may be population specific.

In conclusion, the present study reported the first GWAS for adult stature in Chinese population which was often neglected by genetics community. The results of the present study suggest that a region is significantly associated with stature and interethnic differentiation at some loci may contribute to the interethnic difference in stature.

Acknowledgments

The study was partially supported by grants from Natural Science Foundation of China (30600364, 30470534, and 30230210). HWD was partially supported by grants from NIH (R01 AR050496-01, R21 AG027110, R01 AG026564, and P50 AR055081) and the Dickson/Missouri endowment.

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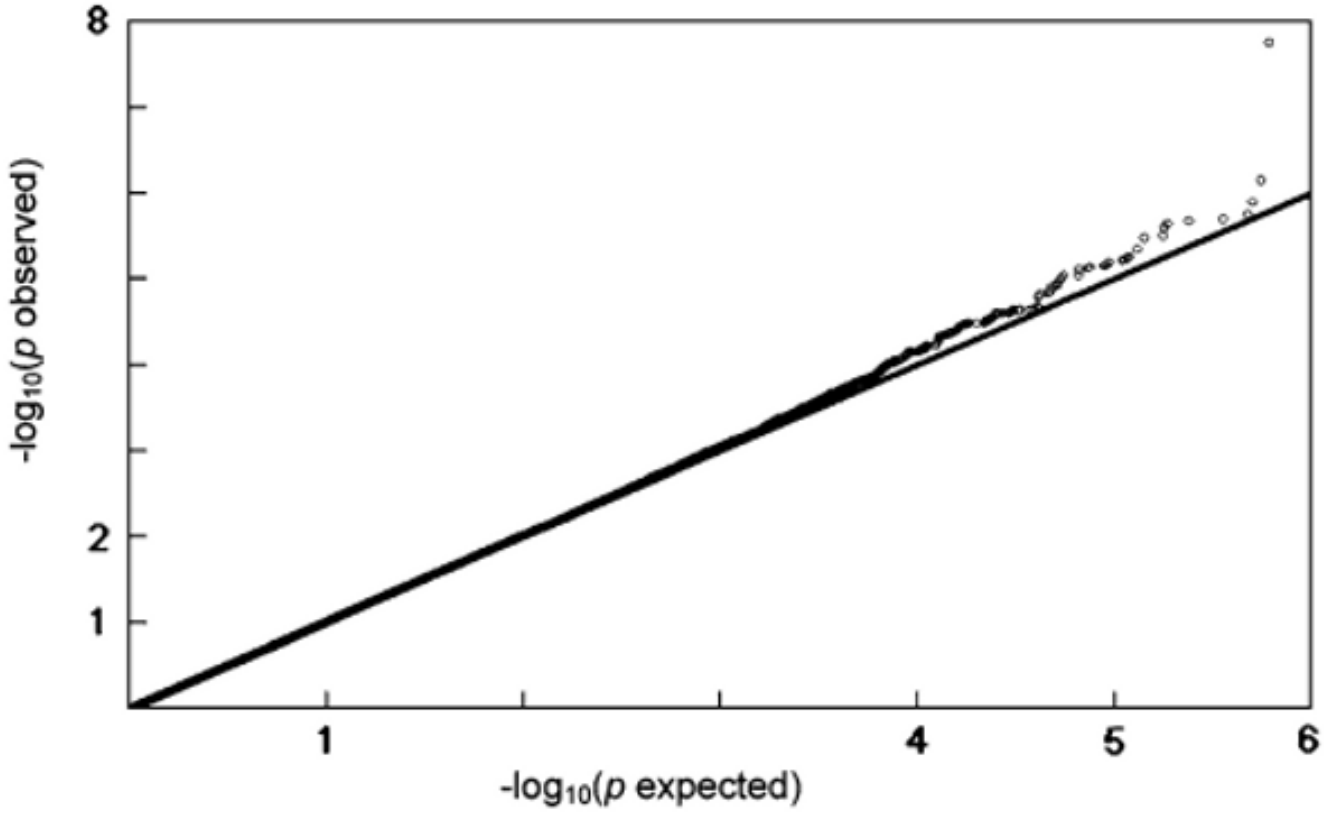

Fig. 1.

Quantile–quantile (Q–Q) plot for stature. From the Q–Q plot, the observed *P* values of stature match the expected *P* values under the null distributions over the range of [$1 < -\log_{10}(P) < 4.0$] and an excess of low *P* values is observed above 4.0 of $-\log_{10}(P)$ for stature

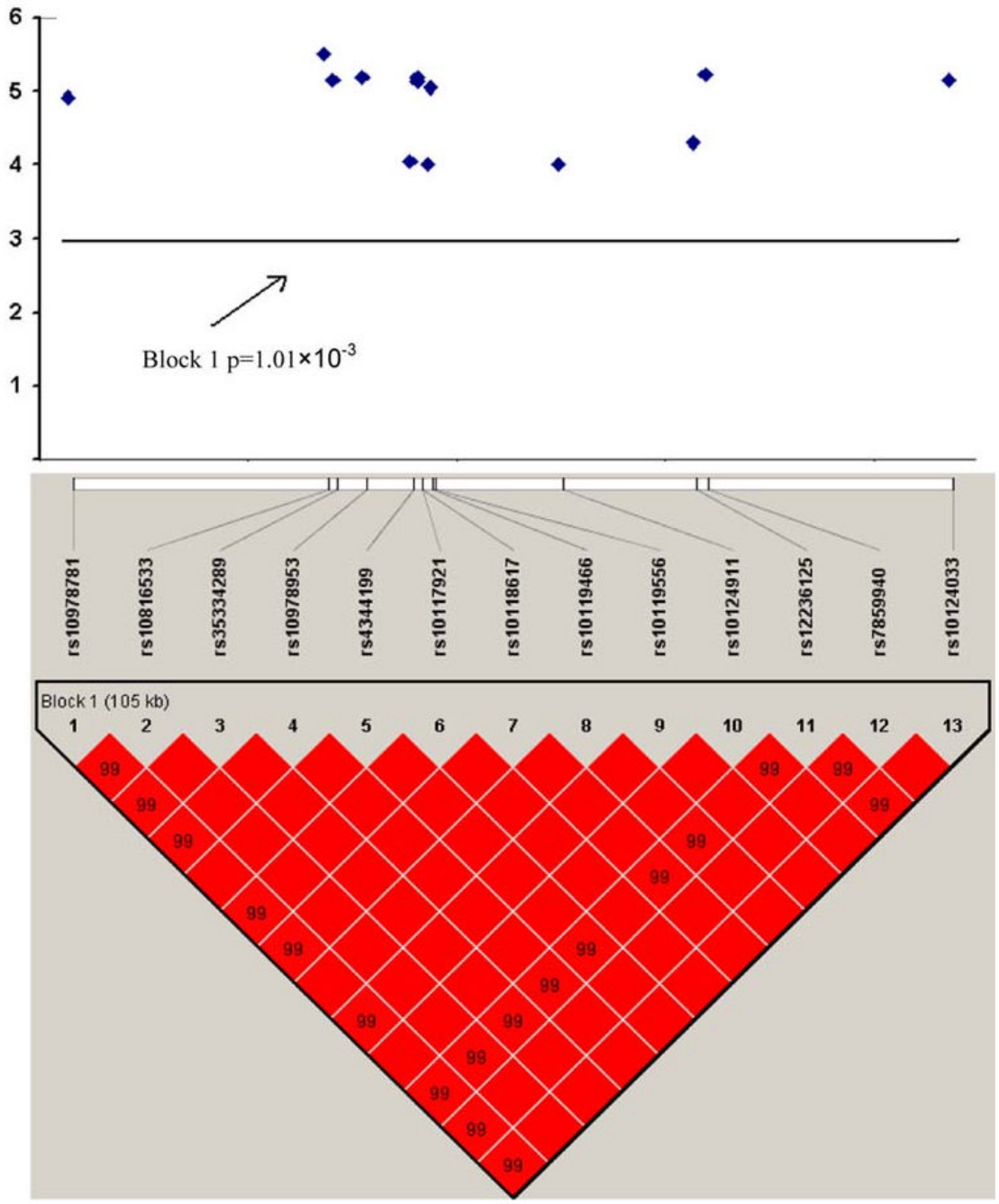

Fig. 2.

Association signals of SNPs in the region of ZNP510 and ZNP782 genes. The *Y* axis is the negative Log_{10} *P* value. The LD between two SNPs is standardized *D*′ ($D/D_{\max}$). Within the block, the LD signal is very strong

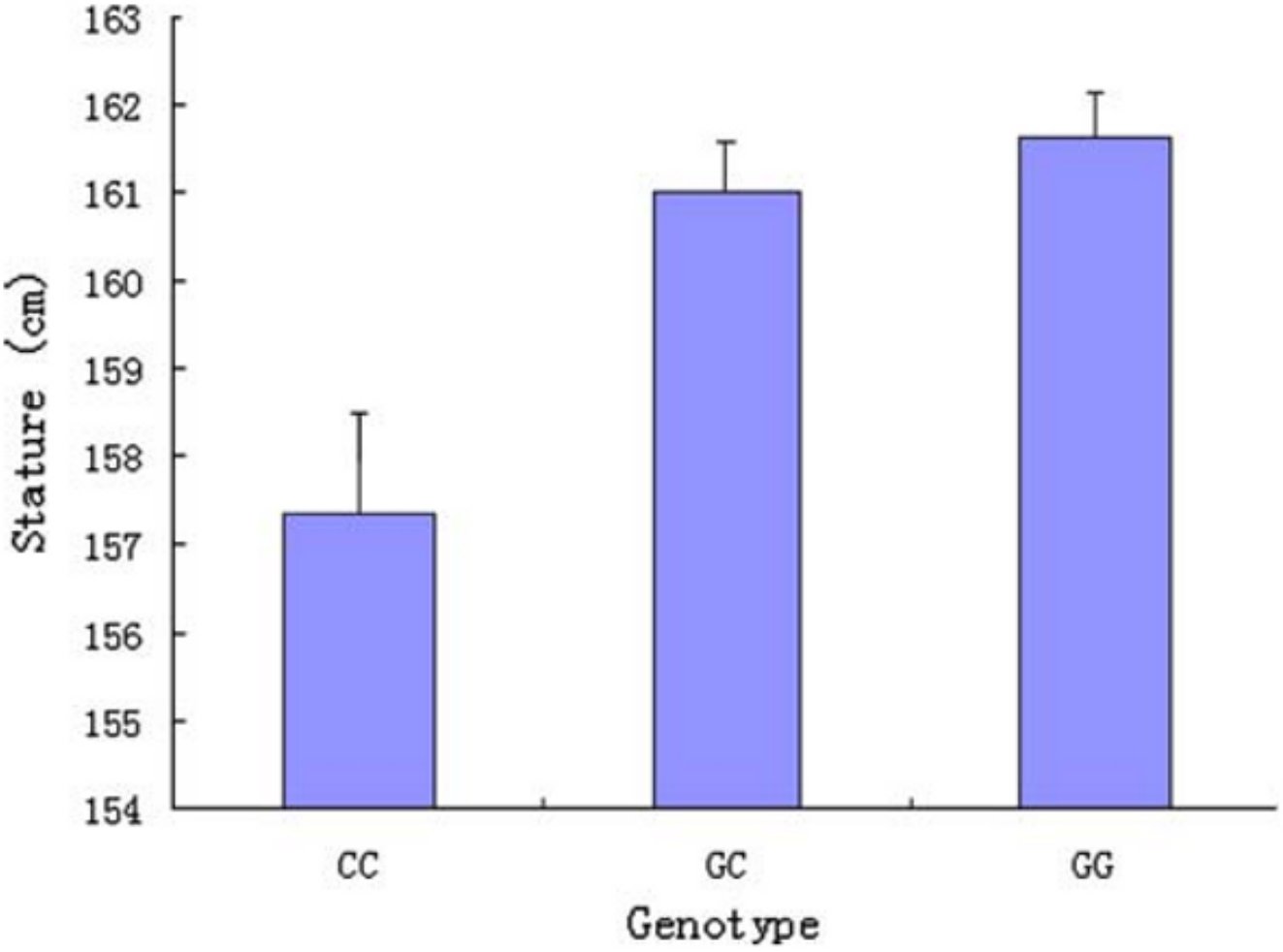

Fig. 3.
The distribution of stature in different genotype groups of rs10816533 in Chinese in GWAS study [mean (SE)]

Table 1

Basic characteristics of the study subjects

	Region		Total	Female	Male
GWAS	Northern Chinese	Sample size	618	351	267
		Age (years)	70.6 (7.8)	70.2 (8.2)	71.1 (7.1)
		Stature (cm)	160.9 (9.0)	155.5 (6.2)	168.0 (6.9)
Replication study	Southern Chinese	Sample size	2953	1517	1436
		Age (years)	33.0 (14.5)	35.4 (15.7)	30.5 (12.5)
		Stature (cm)	163.7 (7.9)	158.1 (5.3)	169.6 (5.6)

Note: Presented are mean (SD)

Table 2

Five genes that contained SNPs significantly associated with stature at genomewide level (q value < 0.05)

Associated gene	dbSNP ID	Physical position	Chromosomal position	*P* value[a]	*q* value
KRT33A	rs16966703	36755924	17q21	1.74×10^{-8}	0.002
ZNF510	rs10816533	98578959	9q22	3.11×10^{-6}	0.036
ZNF782	rs7859940	98624701	9q22	5.77×10^{-6}	0.039
RAP2A	rs2793701	97198607	13q32	7.85×10^{-6}	0.038
SLC8A1	rs7606245	41871622	2p21	9.59×10^{-6}	0.041

[a]If there are multiple SNPs with significant association with stature in a gene, we only list the most significant SNP

Table 3

SNPs with strong association signals ($q < 0.1$) in the region of ZNP510 and ZNP782 genes

Associated gene	dbSNP	Physical position	Role	Allele[a]	MAF[b]	MAF[c]	MAF[d]	*P* value[e]	FDR *q* value
ZNP510 (9q22)	rs10978781	98548301	3′ downstream	C/T	0.30	0.33	0.017	1.19×10^{-5}	0.046
	rs10816533	98578959	Intron 1	C/G	0.29	0.32	0.017	3.11×10^{-6}	0.036
	rs35334289	98580112	Intron 1	C/T	0.29	0.33	0.017	7.00×10^{-6}	0.038
	rs10978953	98583622	5′ upstream	T/G	0.30	0.33	0.017	6.41×10^{-6}	0.038
	rs4344199	98589270	5′ upstream	G/A	0.21	0.22	0.017	8.83×10^{-5}	0.079
	rs10117921	98590255	5′ upstream	G/A	0.30	0.33	0.017	6.35×10^{-6}	0.038
	rs10118617	98590290	5′ upstream	C/T	0.30	0.33	0.017	7.19×10^{-6}	0.038
	rs10119466	98591446	5′ upstream	G/A	0.21	0.22	0.017	9.71×10^{-5}	0.080
ZNP782 (9q22)	rs10119556	98591807	3′ downstream	G/A	0.30	0.33	0.017	8.97×10^{-6}	0.040
	rs10124911	98607205	3′ downstream	A/C	0.21	0.22	0.017	9.71×10^{-5}	0.080
	rs12236125	98623289	Intron 5	C/G	0.23	0.21	0.017	4.96×10^{-5}	0.064
	rs7859940	98624701	Intron 5	A/G	0.31	0.33	0.017	5.77×10^{-6}	0.038
	rs10124033	98653925	Intron 3	A/G	0.31	0.32	0.017	6.90×10^{-6}	0.038

[a] The former allele represents the minor one of each locus

[b] MAF (minor allele frequency) calculated in the present Chinese sample

[c] MAF reported in Chinese or Asian in dbSNP public database (http://www.ncbi.nlm.nih.gov/SNP/)

[d] MAF reported in Caucasian in dbSNP public database

[e] *P* value for genotypic association using single-SNP marker test

Table 4

Comparison of the current study to the published GWAS studies for stature

Present GWAS						Published GWAS		
SNP	**Associated gene**	**Chromosome**	**Position**	***P* value**	**MAF[a]**	***P* value**	**MAF[b]**	**Reference**
rs757608	BCAS3	17	56852059	0.011	0.26/T	3.00×10^{-7}	0.30/T	Gudbjartsson et al. (2008)
rs12198986	BMP6	6	7665058	0.056	0.24/A	6.40×10^{-11}	0.50/A	Gudbjartsson et al. (2008)
rs4800148	CABLES1	18	18978326	0.061	0.23/G	9.40×10^{-8}	0.26/G	Gudbjartsson et al. (2008)
rs11107116	SOCS2	12	92502635	0.086	0.30/T	2.50×10^{-5}	0.20/T	Weedon et al. (2008)
rs10946808	HIST1H1D	6	26341366	0.093	0.24/A	3.30×10^{-8}	0.28/G	Lettre et al. (2008)
rs4713858	ANKS1	6	35510763	0.097	0.18/A	4.90×10^{-8}	0.16/A	Gudbjartsson et al. (2008)
rs798544	GNA12	7	2729628	0.11	0.30/A	4.50×10^{-12}	0.28/A	Gudbjartsson et al. (2008)
rs1812175	HHIP	4	145794294	0.11	0.40/T	2.80×10^{-10}	0.17/T	Gudbjartsson et al. (2008)
rs4794665	NOG	17	52205328	0.25	0.31/G	9.20×10^{-6}	0.39/A	Gudbjartsson et al. (2008)
rs3760318	CRLF3	17	26271841	0.25	0.22/T	1.80×10^{-9}	0.36/T	Gudbjartsson et al. (2008)
rs10906982	ADAMTSL3	15	82359162	0.26	0.29/T	5.40×10^{-7}	0.48/A	Weedon et al. (2008)
rs185819	HLA class III	6	32158045	0.26	0.33/T	1.90×10^{-6}	0.44/T	Gudbjartsson et al. (2008)
rs6060369	GDF5	20	33370575	0.27	0.24/C	1.00×10^{-11}	0.36/C	Sanna et al. (2008)
rs12986413	DOT1L	19	2121954	0.29	0.47/T	2.00×10^{-5}	0.45/T	Lettre et al. (2008)
rs967417	BMP2	20	6568893	0.35	0.25/G	4.60×10^{-6}	0.41/A	Gudbjartsson et al. (2008)
rs4743034	ZNF462	9	108672174	0.35	0.17/A	5.20×10^{-7}	0.24/A	Gudbjartsson et al. (2008)
rs9650315	CHCHD7	8	57318152	0.37	0.04/T	9.60×10^{-6}	0.13/T	Lettre et al. (2008)
rs8041863	ACAN	15	87160693	0.38	0.13/T	2.20×10^{-5}	0.49/A	Weedon et al. (2008)
rs3116602	DLEU7	13	50009356	0.39	0.01/G	5.60×10^{-6}	0.18/G	Weedon et al. (2008)
rs1042725	HMGA2	12	64644614	0.39	0.23/C	4.00×10^{-8}	0.49/T	Weedon et al. (2007)
rs10935120	ANAPC13	3	135715782	0.41	0.19/A	2.20×10^{-6}	0.36/A	Weedon et al. (2008)

Present GWAS						Published GWAS		
SNP	**Associated gene**	**Chromosome**	**Position**	***P* value**	**MAF[a]**	***P* value**	**MAF[b]**	**Reference**
rs7846385	PXMP3	8	78322734	0.46	0.26/C	5.30×10^{-7}	0.34/C	Gudbjartsson et al. (2008)
rs2562784	SH3GL3-	15	82077496	0.49	0.17/C	2.90×10^{-5}	0.37/C	Lettre et al. (2008)
rs4533267	ADAMTS17	15	98603794	0.49	0.19/A	3.80×10^{-7}	0.29/A	Gudbjartsson et al. (2008)
rs6724465	IHH	2	219652090	0.49	0.12/A	3.10×10^{-5}	0.16/A	Weedon et al. (2008)
rs2844479	HLA class III	6	31680935	0.51	0.40/G	8.40×10^{-9}	0.32/G	Gudbjartsson et al. (2008)
rs3791675	EFEMP1	2	55964813	0.60	0.22/G	7.10×10^{-8}	0.28/A	Weedon et al. (2008)
rs6440003	ZBTB38	3	142576899	0.60	0.35/A	1.30×10^{-14}	0.48/A	Weedon et al. (2008)
rs4549631	LOC387103	6	127008001	0.62	0.01/T	1.20×10^{-8}	0.43/C	Weedon et al. (2008)
rs10512248	PTCH1	9	97299524	0.65	0.32/C	1.50×10^{-6}	0.32/C	Weedon et al. (2008)
rs6686842	SCMH1	1	41303458	0.70	0.41/T	8.60×10^{-6}	0.39/T	Weedon et al. (2008)
rs3748069	GPR126	6	142809326	0.73	0.40/G	4.90×10^{-11}	0.27/G	Gudbjartsson et al. (2008)
rs7153027	TRIP11	14	91496975	0.75	0.28/C	1.10×10^{-10}	0.39/C	Gudbjartsson et al. (2008)
rs10958476	PLAG1	8	57258362	0.82	0.17/C	1.40×10^{-6}	0.13/C	Gudbjartsson et al. (2008)
rs12735613	SPAG17	1	118685496	0.83	0.17/A	3.40×10^{-8}	0.31/A	Weedon et al. (2008)
rs1390401	ZNF678	1	225864573	0.86	0.09/G	4.30×10^{-6}	0.23/G	Weedon et al. (2008)
rs12449568	ANKFN1	17	51785154	0.88	0.49/C	4.70×10^{-6}	0.47/C	Lettre et al. (2008)
rs6830062	LCORL	4	17626828	0.89	0.11/C	7.60×10^{-8}	0.16/C	Gudbjartsson et al. (2008)
rs314277	LIN28B	6	105514355	0.90	0.02/A	5.90×10^{-9}	0.13/A	Lettre et al. (2008)
rs4896582	GPR126	6	142745570	0.91	0.17/G	3.20×10^{-8}	0.27/A	Lettre et al. (2008)
rs3130050	HLA class III	6	31726740	0.92	0.02/G	5.10×10^{-7}	0.23/G	Gudbjartsson et al. (2008)
rs8756	HMGA2	12	64646019	0.93	0.11/C	2.20×10^{-13}	0.47/C	Gudbjartsson et al. (2008)
rs16896068	LCORL	4	17553938	0.99	0.11/A	1.00×10^{-4}	0.16/A	Weedon et al. (2008)
rs2814993	C6orf106	6	34726871	0.99	0/A	8.90×10^{-9}	0.10/A	Weedon et al. (2008)

[a] MAF: minor allele frequency (Frequency/Allele) in Chinese reported from dbSNP public database (http://www.ncbi.nlm.nih.gov/SNP/)

[b] MAF: minor allele frequency (Frequency/Allele) in Caucasian reported from dbSNP public database (http://www.ncbi.nlm.nih.gov/SNP/)