

Genome-wide scan on total serum IgE levels identifies no common variants in a healthy Chinese male population

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Abstract Immunoglobulin E (IgE) provides important information on the humoral immune status, and the IgE level is routinely detected in clinical practice. There are many diseases associated with IgE, such as atopic disease, autoimmune diseases, and so on. IgE is a genetically complex trait, but comprehensive genetic assessment of the variability in serum IgE levels is lacking. Previous genome-wide association studies (GWAS) on total serum IgE levels have identified FCER1A as the susceptibility locus; however, the candidate gene association study in southern Chinese patients reported no association. Given the genetic difference in different populations, we firstly conducted this two-stage GWAS in a

Chinese population of 3,495 men, including 1,999 unrelated subjects in the first stage and 1,496 independent individuals replicated in the second stage. In the first stage, we totally identified three single nucleotide polymorphisms (SNPs) which reached a P value of 1.0×10^{-5} . Rs17090302 on chromosome 3 and Rs28708846 on chromosome 13 are intergenic. Rs432085 from chromosome 3p28 is located in the gene CCDC50. When the two-stage data was combined, none of the SNPs reached the genome-wide significant level. Collectively, we did not identify novel loci associated with the serum IgE level in Chinese males, but we hypothesized that CCDC50 was a candidate gene in regulation on IgE level.

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Introduction

Immunoglobulin E (IgE) is frequently realized as the major class of human antibodies which plays a significant role in the immunology of health and disease because of its contribution in type I hypersensitivity (allergic) reaction (Kraft and Kinet 2007). Whereas the role of primary biological IgE as the defense for protection against multicellular parasites has long been suggested (Conrad et al. 2010), more recent studies have highlighted the relationship between elevated level of total IgE and allergic disorders (Gould and Sutton 2008) as well as its importance in antitumoral defense (Gould et al. 1999) and autoimmune diseases (Dimson et al. 2003). Allergic disease is a common disorder in China, such as allergic rhinitis, with high prevalence of 8.7–24.1 % in the center of cities (Chang et al. 2009) and has exhibited a fairly rapid upward trend (Cooper et al. 2008). Not only the pedigree-based and twin-based studies but also the family and case-control studies have suggested that the genetic control in determining total serum IgE levels was stronger than atopic disease (Dizier et al. 1995; Lebowitz et al. 1984; Palmer et al. 2000; Strachan et al. 2001). The heritability of total IgE level is respectively estimated to up to 80 % (Vercelli 2008).

Currently, most studies in search of genetic variations associated with serum IgE level were confined to atopic diseases, but the role and significance of genetic factors influencing IgE regulation is still unclear (Weidinger et al. 2010). While the genome-wide association study (GWAS) is a powerful and unbiased tool for the identification of common genetic variants associated with complex traits, there have been two population-based GWASs published investigating total IgE concentration: the KORA S3/F3 study (Cooperative Health Research in the Region Augsburg) (Weidinger et al. 2008) and the Framingham Heart Study (FHS) (Granada et al. 2012). The GWAS of the Augsburg cohort identified genes encoding the alpha chain of the high-affinity receptor for IgE

(FCER1A) and the signal transducer and activator of transcription 6 (STAT6) as susceptibility loci modulating IgE levels (Weidinger et al. 2008), while the GWAS of the Framingham cohort confirmed susceptibility locus in FCER1A, STAT6, and IL13, but also identified genetic loci in HLA regions that might have a role in the pathogenesis of IgE dysregulation and atopy (Granada et al. 2012). However, in China, there was no GWAS for total IgE level as primary trait, except some candidate gene association studies in allergic rhinitis, atopic dermatitis, or asthma (Leung et al. 2009; Zhang et al. 2010; Zhao et al. 2012; Zhou et al. 2012). Moreover, some studies did not provide the consistent results and fail to confirm the finding from other ethnics (Li et al. 1995; Zhang et al. 2010). Although the latest meta-analysis of GWAS for serum total IgE confirms the findings of earlier GWAS in African American and Latino subjects (Levin et al. 2013), given the diversities in allele and genotype frequencies in different ethnic groups, we conducted the present GWAS in Chinese adult males which may provide a comprehensive understanding of IgE genetic regulation.

Results

The general characteristics of the samples in this study are described in Table 1. There are 1,999 participants in stage one and 1,496 participants in stage two available for our analysis. The age distribution, smoking, and body mass index (BMI) were well-balanced between the two stages.

The quantile–quantile plot of adjusted *P* values with the inflation factor of 1.03 (Fig. 1) show no systematic bias. When the top two Eigens were added to other covariates in the GWAS analysis, similar results were obtained; the inflation factor was 1.03 (Fig. 1), which indicated that there was no population substructure in the GWAS analysis. The Manhattan plot presented the genome-wide association results (Fig. 2).

In the first stage, we chose the single nucleotide polymorphisms (SNPs) that reached a *P* value of 1.0×10^{-5} .

Table 1 General characteristics of the two-stage GWAS study participants

Characteristics	First stage	Second stage	<i>P</i> value ^a
<i>n</i>	1,999	1,496	
IgE, IU/ml (mean ± SD)	128.7 ± 3.6	110.8 ± 3.8	0.73
Age, years (mean ± SD)	37.54 ± 11.10	37.3 ± 110.80	0.54
Smoking, <i>n</i> (%)			0.48
Yes	1,015 (50.8 %)	771 (51.5 %)	
No	984 (49.2 %)	725 (48.5 %)	
Body mass index (kg/m ²)	23.3 ± 3.4	23.5 ± 3.5	0.24

^a *t* test was used to compare means of the continuous variables between the first and the second stages; χ^2 test was used to compare the differences for categorical variables.

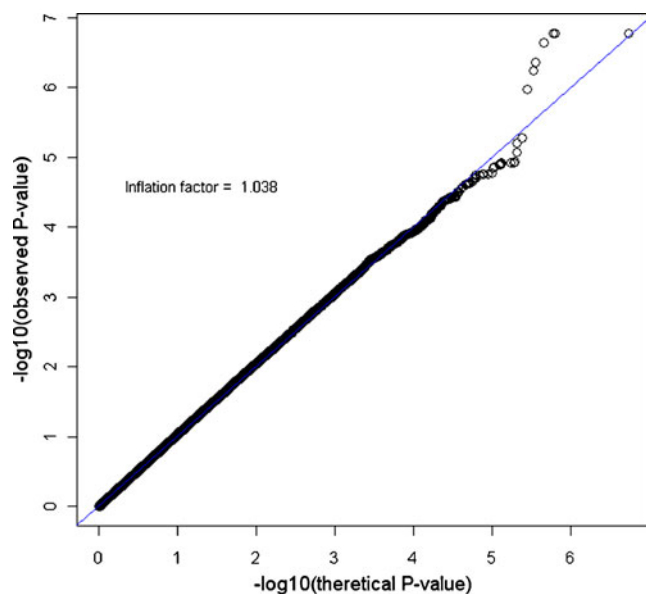


Fig. 1 The quantile–quantile plot of genome-wide QTL mapping for log-transformed IgE level

After testing the independence of each SNP through the multiple regression analysis, one SNP per region remained to be followed in the second stage. According to LD and hap-block of SNPs, three SNPs were finally selected to be further confirmed (Fig. 3). Both rs17090302 on chromosome 13 ($P=1.67\times 10^{-7}$) and rs28708846 on chromosome 3 ($P=1.8\times 10^{-5}$) are intergenic, while rs432085 on 3q28 is located in the intron region of gene CCDC50 ($P=1.40\times 10^{-5}$).

In the second stage, the three candidate SNPs were not confirmed to be statistically significant (all $P>0.05$). The rs17090302, which was the most significantly associated

with IgE level in the first stage, showed a P value of 1.58×10^{-4} when data of two stages were combined. Similarly, neither rs432085 nor rs28708846 reached the potential GWAS significant level of 10^{-5} , but rs432085 was the most closely associated with IgE level with a combined P value of 1.74×10^{-4} (Table 2).

Discussion

We performed this two-stage GWAS in a total of 3,495 Chinese adult males in search of the genetic variations associated with serum IgE levels. Although our results failed to replicate the findings in previous GWAS in other population, such as FCER1A, IL-13, STAT6, and HLA in the significant level (Table S1), we are the first to use the GWAS design to explore the genetic control of serum IgE level in Chinese males. There was one SNP selected in the first stage, locating in the region of gene CCDC50.

The first GWAS investigating total IgE concentration was conducted in a population-based German cohort of 1,530 subjects, with replication analyses performed in four independent population-based study samples that include a total of 9,769 subjects (Weidinger et al. 2008). The susceptibility locus was found to be FCER1A, the gene encoding the chain of the high-affinity receptor for IgE. The associations with this locus were confirmed in subsequent studies (Chen et al. 2009; Moffatt et al. 2010), including the latest GWAS in the FHS cohort (Granada et al. 2012). However, the candidate gene association study in a Han Chinese population failed to find an association between SNPs in the FCER1A gene region and IgE level (Zhang et al. 2010). Similarly, the FHS cohort GWAS identified the genetic loci in HLA genes that might

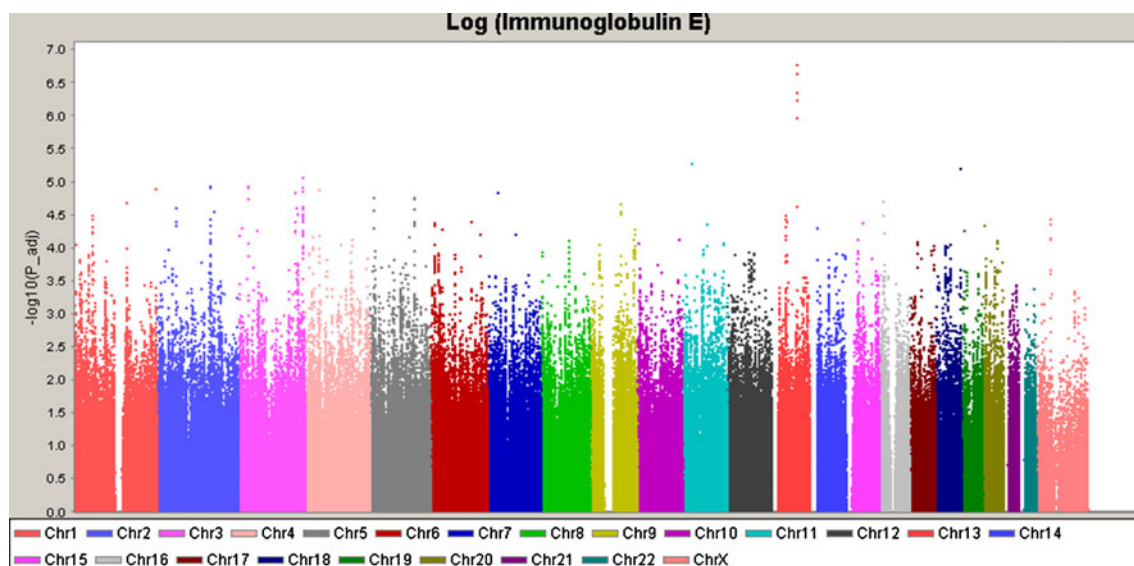


Fig. 2 Manhattan plot of genome-wide association analyses for IgE level. *X* axis shows chromosomal positions. *Y* axis shows $-\log_{10} P$ values from the linear regression

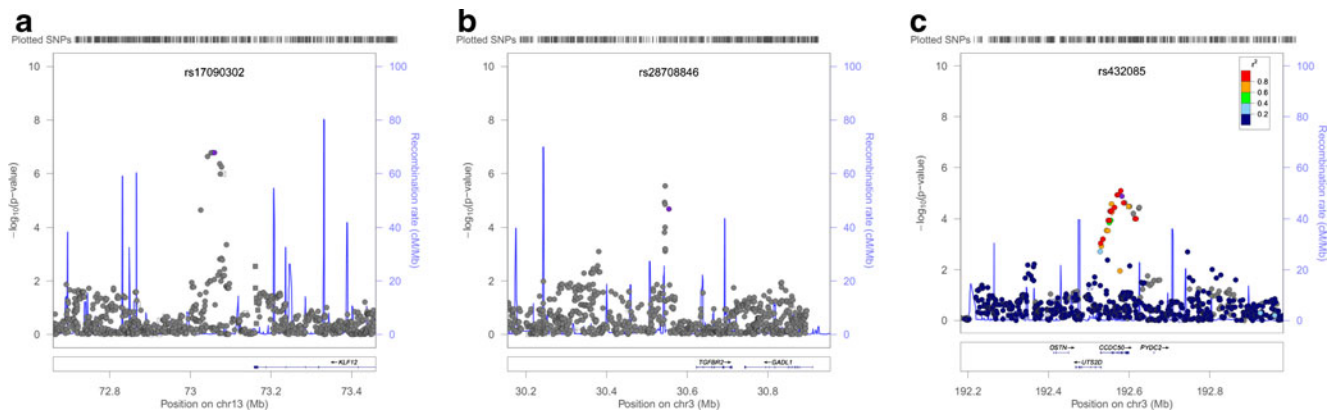


Fig. 3 Regional plots of three candidate SNPs in this study. Results are shown for the rs17090302 (a), rs28708846 (b), rs432085 (c) SNPs. SNPs are plotted by their position on the chromosome against their association ($-\log_{10} P$) with IgE. Symbol colors represent the LD of the candidate SNP at each locus (purple circle). The right Y axis shows the

recombination rate estimated from 1,000 Genomes Project CHB and JPT data. The positions of genes and exons, as well as the direction of transcription, are shown below the plots (using data from the UCSC Genome Browser). Plots were generated using LocusZoom

have a role in the pathogenesis of IgE dysregulation and atopy (Granada et al. 2012). So did the meta-analysis in different race-ethnic groups including African American, Latino, and European American (Levin et al. 2013). However, the candidate gene association study in southern Chinese patients reported no association between HLA-DQ and -DR genotypes and IgE levels (Li et al. 1995). Additionally, in the present GWAS, the previous confirmed IgE level-associated SNPs in the regions such as FCER1A, STATA6, IL13, and HLA did not reach the genome-wide significant level. Although ethnic differences in total serum IgE were previously reported (Lester et al. 2001; Litonjua et al. 2005), no studies were conducted to compare the serum IgE levels in Chinese with other ethnic groups. The lack of significant association in our GWAS was probably due to the genetic difference in different population, thus a comparative analysis of different ethnic groups, even within the Chinese population would be very valuable. Additionally, the role of environmental backgrounds or gene-environment interactions cannot be ignored either (Custovic et al. 2012).

Although the FCER1A, STAT6, RAD50, and HLA region have been identified as susceptibility loci influencing IgE levels by the GWASs, the role of these genes in atopic diseases is unclear. For example, the STAT6 identified in the GWAS on IgE in the FHS was associated with airway hyper-responsiveness and atopic asthma (Daley et al. 2009; Granada et al. 2012). Similarly, the RAD50 identified in the GWAS on IgE would increase the risk for atopic eczema and asthma (Weidinger et al. 2008). However, analysis of the FCER1A variants, identified in GWAS on IgE in both cohorts of Augsburg and Framingham, revealed epistatic effects on eczema risk (Mahachie John et al. 2010), while analysis of the FCER1A gene region in the Han Chinese population showed association with atopic dermatitis (Zhou et al. 2012) but not allergic rhinitis (Zhang et al. 2010). Similarly, the HLA-

DR/DQ region identified in the GWAS on IgE in the FHS has been previously identified as susceptibility locus in the GWAS of patients with severe or difficult-to-treat asthma (Granada et al. 2012; Li et al. 2010), but it was failed to be confirmed in the GWAS of southern Chinese patients with asthma (Li et al. 1995). Although total IgE levels are considered a useful endophenotype for studying the genetics of atopic diseases, the role and significance of genetic factors influencing IgE regulation for atopic diseases as endpoints needs further exploration (Weidinger et al. 2010).

In the first stage of our GWAS, one of the three candidate SNPs was located in the region of gene CCDC50. Given some genes may be genuinely associated with the complex traits but may not reach the stringent genome-wide significance threshold in any GWAS, we cannot rule out the possibility that this gene may involve in the regulation of IgE level. CCDC50 and its encoded protein Ymer has been reported to regulate the nuclear factor- κ B signaling (Farfaring et al. 2009). Moreover, Ymer is the effector of epidermal growth factor (EGF)-mediated cell signaling that is ubiquitously expressed in different organs (Modamio-Hoybjør et al. 2007). A Mutation in CCDC50 cause progressive hearing loss (Modamio-Hoybjør et al. 2007), but its role in IgE-induced type I hypersensitivity reactions is poorly studied. Nevertheless, Ymer has been suggested to inhibit down-regulation of the EGF receptor (EGFR) (Tashiro et al. 2006), and EGFR interacting with integrin is necessary for FcRI signaling (Kim et al. 2011). EGFR signaling has been identified to mediate the airway hyper-reactivity and the remodeling in the mouse model of chronic asthma (Le Cras et al. 2011) but the role of Ymer in asthma remains unclear.

Our knowledge on the genetic architecture of basal IgE regulation is limited. The results need to be interpreted with caution, and some limitations in our study should be

Table 2 SNPs associated with levels of total IgE levels

First stage (N=1,999)										Second stage (N=1,496)									
Mean										Mean									
SNP	Chr	Position	Function	Allele	Allelem	Freq-m	mm	mM	MM	P value ^a	hwe	Freq-m	mm	mM	MM	P value ^a	hwe	combined P value ^a	
rs17090302	13	73059877	Intergenic	A/G	G	0.04386	570.2	199.9	123	1.67E-07	0.5887	0.03531	32.49	110.5	111.39	0.6182	0.4264	0.0001578	
rs28708846	3	30554539	Intergenic	C/A	A	0.09429	135.2	175.4	121	1.81E-05	0.1908	0.09276	196.96	105.11	111.83	0.9382	0.7565	0.00124	
rs432085	3	192582162	CCDC50	C/T	T	0.07139	204.6	175	122	1.40E-05	0.866	0.06709	152.02	116.16	109.95	0.492	0.2072	0.0001744	

IgE levels were log-transformed and the values presented were back-transformed. A genomic position is based on NCBI build 36.

m minor allele, M major allele

^a The P values are based on linear regression analysis on the log-transformed TGs and adjusted for population stratification; the combined P values are calculated based on the linear regression model, adjusting for covariates and stage information.

evaluated objectively. Firstly, the sample size is probably not sufficient enough to make some genuine SNPs to reach the GWAS significant level as expected. Further study of the Chinese population with a larger sample size or meta-analysis of GWASs in different populations is recommended. Secondly, all the samples in our study were healthy males, which would lead to some selection bias. So, it is probably a major source of heterogeneity resulting from non-systemic samples. Thirdly, GWAS is mainly used to identify common genetic loci because chips are designed for good coverage of the whole genome but not for complete coverage of specific regions that may be genuinely associated with complex traits, thus alternative or complementary approaches for GWAS analysis are needed.

In conclusion, our study is the first to explore the genetic influence on serum IgE level by performing the two-stage GWAS in the healthy Chinese male population. Currently, there is no reliable genetic evidence to identify common variants associated with serum IgE level in Chinese. More well-designed studies are encouraged to precisely demonstrate the genetic control of IgE.

Material and methods

Study participants

Unrelated healthy Chinese men aged 20–69 years were enrolled from the Fangchenggang Area Male Health and Examination Survey (FAMHES) in the stage 1 of the GWAS. The FAMHES is described elsewhere (Yang et al. 2012). In this study, we mainly observe the effects of genetic factors on the IgE level in healthy men. From September 2009 to December 2009, the men invited to participate in our study, who participated in physical examinations, were recruited by the Medical Centre of Fangchenggang First People's Hospital ($n=4,364$). A total of 4,303 participants (98.6 %) provided informed consent and blood samples. The 1,999 people in stage 1 were all from southern Chinese Han ethnicity and they were randomly selected by age criteria. When the heritability of serum IgE was considered as 30 % (Jacobsen et al. 2001), the statistical power is closed to 100 %, calculated by PowerGWAS/QT which is a statistical program developed for medical investigators to estimate statistical power of detecting SNPs association with quantitative trait in GWAS (Feng et al. 2011).

The 1,496 healthy Chinese men aged 20–69 years comprised the participants in stage 2 of the GWAS. They were randomly selected from the men who participated in physical examinations from September 2009 to September 2010 in the Medical Center of Fangchenggang First People's Hospital, Guigang People's Hospital and Yulin First People's Hospital. The people in stage 2 from Fangchenggang

First People's Hospital were independently recruited from stage 1. In stage 2, 996 were of Han ethnicity and 500 were of Zhuang ethnicity. The same recruitment strategy was used in stages 1 and 2.

Comprehensive health information was collected through clinical examination, and additional demographic information was obtained via a standardized questionnaire. All participants self-reported to be free of diabetes mellitus, coronary heart disease, stroke, atopic dermatitis, bronchial asthma, hyperthyroidism, rheumatoid arthritis, tumors, and impaired hepatic or renal function. We obtained written documentation of informed consent from all study participants, and the research protocol was approved by the local Ethics Committee. Drinking behavior was assessed on the basis of a self-administered lifestyle questionnaire.

Measurement of IgE

The description of the laboratory test has been previously reported in detail (Yang et al. 2012). Briefly, overnight fasting venous blood specimens were collected between 8:00 and 11:00 a.m., and were transported frozen to the testing center of the Department of Clinical Laboratory at the First Affiliated Hospital of Guangxi Medical University in Nanning in 2 h, which were centrifuged within 15 to 25 min and stored at -80°C until analysis. IgE were measured with electrochemiluminescence immunoassay on COBAS 6000 system E601 (Elecsys module), immunoassay analyzers (Roche Diagnostics, IN, Germany) with the same batch of reagents. And inter-assay coefficient of variation was 3.3 % for IgE respectively.

SNP genotyping

Two different platforms were used for SNP genotyping. Stage 1 used the Illumina Omni 1 platform for a genome-wide assay of samples. Stage 2 chose the Sequenom iPLEX system (Sequenom, Inc., San Diego, CA, USA). Polymerase chain reaction and extension primers were designed using Mass ARRAY Assay Design 3.1 software (Sequenom, Inc.). Genotyping procedures were performed according to the manufacturer's iPLEX Application Guide (Sequenom Inc.). All of the genotyping reactions were performed in 384-well plates. Each plate included a duplicate for three or four participants selected at random, as well as six to nine negative controls in which water was substituted for DNA. The average concordance rate was 99.8 %.

Statistical analysis

Quality control (QC) procedures were first applied to 2,012 individuals that were genotyped using the Illumina Omni-

Express platform. A total of 1,999 individuals passed the call rate of 95 % and were used in the final statistical analysis. We then applied the following QC criteria to filter SNPs: $P < 0.001$ for the Hardy–Weinberg equilibrium test, minor allele frequency < 0.01 and genotype call rate $< 95\%$. Based on these criteria, 709,211 SNPs were retained. The IMPUTE computer program (Marchini et al. 2007) was then used to infer the genotypes of SNPs (e.g., SNPs catalogued in Hapmap Phase II CHB population release #24) in the genome that was not directly genotyped. A posterior probability of > 0.90 was applied to call genotypes that were imputed using IMPUTE software. After applying the same QC criteria, as used above, a total of 1,940,243 SNPs remained in the final analysis.

Analysis for IgE was performed on log-transformed values. SNP association tests were performed using linear regression implemented in PLINK (Purcell et al. 2007) under the assumption of an additive relationship between the number of copies of the minor allele. Population stratification was estimated by a principal component approach, as implemented by EIGENSTRAT software (Price et al. 2006). The top two Eigens were adjusted as covariates in the linear regression analysis. Clinical covariates utilized the linear regression modeling included age at the time of IgE measurement, BMI (weight in kg divided by the height in m^2), and cigarette smoking (yes, no).

For regions with multiple SNPs that were significant at $P < 10^{-5}$, multivariate linear regression analysis was applied to test the independence of the respective SNPs. Only the SNPs that remained significant at 10^{-5} in the multivariate analysis were selected. The combined analysis of two-stage data was performed using a linear regression, adjusting for the covariates and stage information.

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Conflict of interest The authors have declared that no competing interests exist.

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