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Multiple Genetic Variants Associated with Primary Biliary Cirrhosis in a Han Chinese Population

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Abstract

Multiple genome-wide association studies of primary biliary cirrhosis (PBC) in both European and Japanese ancestries have shown significant associations of many genetic loci contributing to the susceptibility to PBC. Major differences in susceptibility loci between these two population groups were observed. In this study, we examined whether the most significant loci observed in either European and/or Japanese cohorts are associated with PBC in a Han Chinese population. In 1070 PBC patients and 1198 controls, we observed highly significant associations at *CD80* (rs2293370, $P=2.67\times 10^{-8}$) and *TNFSF15* (rs4979462, $P=3.86\times 10^{-8}$) and significant associations at *IL12-21* (rs9303277), *PDGFB* (rs715505), *NF-κB1* (rs7665090), *IL12RB2* (rs11209050), and

STAT4 (rs7574865; all corrected *P* values <0.01). However, no association was observed for *POU2AF1* (rs4938534), *IL12A* (rs485499 and rs2366408), *IL7R* (rs6897932), *CXCR5* (rs715412), *SOCS1* (rs725613), and *TNFRSF1A* (rs1800693). *STAT4* (rs7574865) was strongly associated after additional control samples were analyzed. Our study is the first large-scale genetic analysis in a Han Chinese PBC cohort. These results do not only reflect that Han Chinese PBC patients share common genetic susceptibility genes with both their Japanese and European counterparts but also suggest a distinctly different genetic susceptibility profile.

Keywords

Primary biliary cirrhosis; Genetic susceptibility; Han Chinese; Single nucleotide polymorphism; Genotyping

Introduction

Primary biliary cirrhosis (PBC) is an autoimmune disease characterized by chronic inflammation and destruction of intrahepatic bile ducts. It occurs predominantly in females over 40 years of age [1]. There is considerable data available on the immunologic aspects of PBC, including animal models [2–8]. The precise genetic basis of PBC, much like other autoimmune diseases, has been proven elusive. The incidence and prevalence of PBC worldwide are increasing [9]. It is commonly believed that the interplay between genetic and environmental factors leads to the development of PBC. An earlier study of monozygotic and dizygotic twins found a concordance rate of 0.63 for PBC in identical twins, the highest among autoimmune diseases, other than celiac disease [10]. In recent years, genome-wide association studies (GWAS) demonstrated strong associations of PBC with the human leukocyte antigen (HLA) region and other loci in the genome [11–13]. Three GWAS studies in European ancestry PBC cohorts show that in addition to the HLA region, more than 26 non-HLA loci meet genome-wide significance. Among them, loci in the interleukin (IL)-12 signaling pathway (*IL12A*, *IL12RB2*, and *STAT4*) were found to be among those with the strongest association, indicating that deregulation of IL-12 or IL-35 signaling may be involved in the pathogenesis of PBC [11, 13, 14]. A recent GWAS study in a Japanese PBC cohort showed distinct differences in susceptibility loci [15]. The three most significant loci outside the HLA region (*IL12RB2*, *IL12A*, and *IRF5*) were not associated with the Japanese PBC cases, and the strongest associations in the Japanese GWAS cohort were observed for the *TNFSF15* and *POU2AF1* loci that were not associated with PBC in European cohorts. These findings prompted us to investigate whether Han Chinese PBC patients share any genetic susceptibility observed in the two populations. In this study, we report an analysis of 14 most significant single nucleotide polymorphisms (SNPs) identified in either one or both of the European and Japanese cohorts in 1070 Han Chinese PBC cases and 1198 healthy controls.

Materials and Methods

Subjects

Genetically unrelated PBC patients in South China (mainly in Shanghai and Jiangsu Province) were recruited following the research ethics board approval of each of the participating institutions and in accordance with the guidelines of the Declaration of Helsinki (2008). All patients were of Han Chinese origin, according to patient self-report. The diagnosis of PBC was based on the criteria of the American Association for the Study of Liver Diseases [16]. All patients were anti-mitochondrial M2 antibody positive with elevated serum alkaline phosphatase levels (in the initial disease state and/or during the treatment stage), the biochemical evidence of cholestasis. Patients with any of the following conditions were excluded from the study: (1) hepatitis B virus (HBV) surface antigen (HBsAg) positive; (2) serum HBV-DNA 200 copies/ml; (3) hepatitis E antigen positive; (4) serum hepatitis C RNA 500 copies/ml; (5) a history of schistosome infection; and (6) self-reported alcohol consumption higher than 100 ml/day

Genotyping results for healthy controls were based on historical data and consisted of two separate datasets. The first was from 211 healthy Han Chinese samples in the HapMap and 1000 Genome projects [17, 18]. The second dataset came from a previous GWAS study, with 987 control samples collected in the same region as was the PBC cohort [19]. The final control data were composed of 1198 individuals.

Sample Preparation and SNP Genotyping

Genomic DNA was prepared mainly from the blood clot collected from yellow blood tubes after serum was removed. Serum was used for clinical biochemical tests and autoantibody analysis. The blood clot was frozen and minced in phosphate-buffered saline (PBS) buffer. The pulp was washed twice in PBS with 0.1 % Tween-20. After removal of most red blood cells, the remaining part was digested with proteinase K overnight, followed with salt precipitation. DNA was precipitated with 2 vol. of pure ethanol. The DNA pellet was redissolved in distilled water and then digested repeatedly with proteinase K. Purified DNA was dissolved in double distilled water. Fifteen SNPs previously identified to be associated with PBC in Caucasian and/or Japanese cohorts were selected for genotyping. SNP genotyping was performed using the MALDI-TOF MassARRAY system (Sequenom, San Diego, USA). The fifteen SNPs were used to develop a multiplex reaction using the iPLEX genotyping method [20]. Assay design was performed with the Sequenom AssayDesignSuite1.0 software. Genotyping results were read and processed with the MassARRAY Analyzer 4.

Statistical Analysis

Hardy–Weinberg equilibrium in controls and significance of allelic and genotypic frequency between PBC and control groups was evaluated and calculated using Haploview program [21]. The odds ratio and 95 % confidence interval was calculated using the Chi-square test. To control for multiple testing, the P values were corrected (P_c) by the number of SNPs analyzed in this study, according to Bonferroni's correction.

Results

Based on the European and Japanese PBC cohort GWAS, we tested the most significant 15 SNPs from 14 loci outside the HLA region in 1070 Han Chinese PBC patients and 1198 healthy controls. Of the 1070 PBC patients, 920 (86 %) were female and 150 (14 %) were male. Patients' ages ranged from 17 to 87, with a median age of 54.

Of the 15 SNPs genotyped, no variant was found for rs10488631 (*IRF5*) in either of our PBC and control cohorts. The strongest allelic associations were observed for rs2293370, a SNP located 13.2 kb downstream of *CD80*, and rs4938534, a SNP in the intron of *TNFSF15* (both with $P < 5 \times 10^{-8}$) (Table 1). Five other SNPs (rs9303277 in *17q12-21*, rs715505 in *PDGFB*, rs7665090 in *NF-κB1*, rs11209050 in *IL12RB2*, and rs7574865 in *STAT4*) showed evidence of association ($5 \times 10^{-8} < p < 1 \times 10^{-3}$) and were significant after Bonferroni correction based on the number of SNPs tested (Table 1). The SNP rs7574865, located in intron 3 of *STAT4*, showed association in our PBC cohort ($P = 9.0 \times 10^{-4}$). The SNP rs7574865 has been reported to be strongly associated with primary Sjögren's syndrome and systemic lupus erythematosus in the Han Chinese population [22, 23]. Since rs7574865 has been genotyped in multiple studies in Han Chinese control cohorts, we performed a combined analysis with healthy controls from other autoimmune genetic studies [23]. The combined dataset for rs7574865 included 1070 PBC patients and 8333 healthy controls. The result showed a combined P value of 3.77×10^{-7} and an odds ratio of 1.272 (1.159–1.397) (Table 2), providing further evidence that rs7574865 is associated with PBC in the Han Chinese population. Also in our study, no association was observed for *IL12A* (rs485499 and rs2366408), *IL7R* (rs6897932), *POU2AF1* (rs4938534), *CXCR5* (rs715412), *TNFRSF1A* (rs1800393), and *SOCS1* (rs725613) loci.

Discussion

Our study is the first large-scale genetic analysis in Han Chinese PBC cohort. Our study suggests that the genetics of PBC susceptibility in Han Chinese partially overlaps with that found in studies of Japanese and European populations (Table 3). Using a panel of 14 loci selected for association in European and/or Japanese PBC GWAS, our results showed significant association of seven loci in Han Chinese. These included 6 of 12 genes that were significant in previous European studies and 5 of 7 genes that were either associated or strongly suggested ($P < 2 \times 10^{-6}$) in the Japanese study. These included three of the four loci that were the same in both the European and Japanese GWAS (*CD80*, *STAT4*, *NF-εB1*, and *17q12-21*). The notable exception was *IL7R* that showed no association signal in our study of Han Chinese.

Similar to the Japanese study, no association was found for *IL12A* (one of the strongest loci in Europeans) and a strong association was found for *TNFSF15* (not associated in Europeans). Also in line with the Japanese cohort but contrary to the European ancestry cohorts, no association was observed for the *IL12A*, *SOCS1*, and *TNFRSF1A* loci, and there was no variation in rs10488631 (*IRF5*). However, in contrast to the Japanese study, there was no signal observed for the *POU2AF1* SNP. In addition, we found a significant signal after Bonferroni correction for two loci (*IL12RB2* and *PDGFB*) that were not observed in

the Japanese GWAS. In total of 14 loci considered, 10 showed concordant results with the Japanese study and 7 showed concordance with the European studies. Considering only those nine loci discordant between the Japanese and European, our Han Chinese results were concordant with six of the Japanese and only three of the European results.

Differences in susceptibility genes and/or susceptibility SNP alleles in different population groups are not surprising. Previous studies of both rheumatoid arthritis and systemic lupus erythematosus have shown substantial differences in association results when European and East Asian populations are compared [23–26]. There are also some differences that have been noted between Japanese and Chinese susceptibility genes for rheumatoid arthritis (RA). Notably, the common variants of PADI4 that are associated with RA in Japanese are not associated in Chinese cohorts [26]. The stronger similarity of our Han Chinese results with Japanese rather than European populations is consistent with the closer relationship of the two East Asian groups.

There are several potential limitations in our study. First, the study included genotyping performed on different platforms. Although it is possible that some of our results could be due to differences in genotyping accuracy, the methods utilized are highly accurate and we observed very similar allele frequencies in the different control sets and no deviations from HW expectations (Supplemental Table 1). Second, only a single SNP, or for IL12A two SNPs, were tested for each locus. It is possible and even probable that for some of the loci, the chosen SNP was not in linkage disequilibrium with the causal variant and hence would miss an association if present. Third, the study did not measure or account for possible substructure differences between cases and controls. However, this is unlikely to be a problem since there is very little substructure that has been observed in Han Chinese [27].

In summary, our results indicate that the Han Chinese PBC cohort not only shares some of the major loci in genetic susceptibility with both the Caucasian and Japanese cohorts but also differs from either of them in some of the loci tested, indicating genetic differences among the three different PBC cohorts. Based on these results, a large scale of GWAS with a Han Chinese PBC cohort is required to systematically unearth the genetic susceptibility of this population and uncover risk variants that may either be unique or at higher odds ratios or frequency in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association of 14 SNPs analyzed in the Han Chinese 1070 PBC and 1198 healthy control cohort

SNP	Locus	Chr	Position ^a	Alleles	AA	HWP (controls)	MAF (PBC)	MAF (controls)	P value	P _c	OR	95 % CI
rs11209050	IL12RB2	1p31.3	67791986	C/A	A	0.819	0.299	0.252	4.00×10 ⁻⁴	0.0056	1.27	1.11–1.44
rs7574865	STAT4	2q32.3	191964883	G/T	T	0.458	0.381	0.334	9.00×10 ⁻⁴	0.0126	1.23	1.09–1.39
rs2293370	CD80	3q13.33	119220184	G/A	G	0.685	0.263	0.339	2.67×10 ⁻⁸	3.74×10 ⁻⁷	1.44	1.27–1.63
rs2366408	IL12A second signal	3q25.33	159696349	G/T	G	0.030	0.140	0.147	0.49	n/a	1.06	0.90–1.25
rs485499	IL12A	3q25.33	159746113	T/C	T	0.737	0.111	0.131	0.042	n/a	1.2	1.01–1.44
rs7665090	NF-kB1	4q24	103551853	G/A	G	0.109	0.442	0.499	8.52×10 ⁻⁵	1.19×10 ⁻³	1.26	1.13–1.42
rs6897932	IL7R	5p13.2	35874825	C/T	C	0.487	0.131	0.141	0.35	n/a	1.08	0.92–1.29
rs4979462	TNFSF15	9q32	117567263	C/T	T	0.064	0.349	0.274	3.86×10 ⁻⁸	5.39×10 ⁻⁷	1.42	1.26–1.62
rs4938534	POU2AF1	11q23.1	111275383	A/G	A	0.651	0.448	0.486	0.011	n/a	1.17	1.04–1.31
rs715412	CXCR5	11q23.3	118684860	G/A	G	0.939	0.103	0.126	0.013	n/a	1.26	1.05–1.52
rs1800693	TNFRSF1A	12p13.31	6440259	T/C	C	0.952	0.137	0.121	0.094	n/a	1.16	0.98–1.38
rs725613	SOCs1	16p13.13	11169933	T/G	T	0.789	0.215	0.232	0.18	n/a	1.10	0.96–1.27
rs9303277	17q12	17q12	37976719	C/T	T	0.291	0.349	0.28	5.58×10 ⁻⁷	7.81×10 ⁻⁶	1.38	1.22–1.56
rs715505	PDGFB	22q13.1	39751501	C/G	C	0.254	0.176	0.226	4.50×10 ⁻⁵	6.30×10 ⁻⁴	1.36	1.17–1.58

AA affected allele, HWP Hardy–Weinberg P value in the controls, MAF minor allele frequency, P_c Bonferroni corrected P value, OR odds ratio, CI confidence interval, n/a not applied^aBased on GRCh37/hg19

Table 2

Analysis of rs7574865 (*STAT4*) with combined control data

	PBC patients	Control (panel A) ^a	Control (panel B) ^b	Control (panel C) ^b	Control (combined)	P value	OR	95 % CI
Sample size	1070	1198	1205	5930	8333	3.77×10 ⁻⁷	1.272	1.159–1.397
MAF	0.381	0.332	0.3249	0.3248	0.326			

MAF, minor allele frequency, OR odds ratio, CI confidence interval

^aControl panel in this study

^bControl samples from Ref. [23]

Table 3

Comparison of association of 14 SNPs with PBC among Caucasian, Japanese, and Han Chinese PBC cohorts

Locus	Candidate gene(s)	Caucasian PBC ^a		Japanese PBC ^b		Han Chinese PBC	
		2861 cases and 8514 controls		1274 cases and 1091 controls		1,070 cases and 1,198 controls	
		OR	P value	OR	P value	OR	P value
1p31.3	<i>IL12RB2</i>	1.61	2.47×10 ⁻³⁸	1.12	5.40×10 ⁻²	1.266	4.0×10 ⁻⁴
3q25.33	<i>IL12A</i>	1.35	3.92×10 ⁻²²	1.02	3.40×10 ⁻¹	1.205	4.23×10 ⁻²
7q32	<i>IRF5</i>	1.52	6.53×10 ⁻²²	n/a	n/a	n/a	n/a
2q32.2	<i>STAT4</i>	1.62	2.59×10 ⁻¹⁸	1.35	1.11×10 ⁻⁶	1.229	9.0×10 ⁻⁴
3q13.3	<i>CD80</i>	1.39	6.84×10 ⁻¹⁶	1.48	3.04×10 ⁻⁹	1.438	2.67×10 ⁻⁸
11q23.3	<i>CXCR5, DDX6</i>	1.39	7.20×10 ⁻¹⁶	1.42	4.11×10 ⁻⁴	1.264	1.34×10 ⁻²
12p13.2	<i>TNFRSF1A</i>	1.27	1.18×10 ⁻¹⁴	1.12	6.10×10 ⁻²	1.16	9.39×10 ⁻²
9p32	<i>TNFSF15</i>	n/a	n/a	1.57	2.84×10 ⁻¹⁴	1.424	3.86×10 ⁻⁸
17q12	<i>ORMDL3, GSDMB, IKZF3</i>	1.26	6.05×10 ⁻¹⁴	1.44	3.66×10 ⁻⁹	1.379	5.58×10 ⁻⁷
4q24	<i>NFKB1</i>	1.26	8.48×10 ⁻¹⁴	1.35	1.42×10 ⁻⁷	1.264	8.52×10 ⁻⁵
22q13.1	<i>PDGFB</i>	1.29	1.29×10 ⁻¹³	n/a	n/a	1.361	4.51×10 ⁻⁵
16p13.13	<i>SOC31, CLEC16A</i>	1.29	2.19×10 ⁻¹³	1.1	1.20×10 ⁻¹	1.099	1.84×10 ⁻¹
5p13	<i>IL7R</i>	1.3	2.26×10 ⁻¹³	1.47	3.66×10 ⁻⁸	1.085	3.49×10 ⁻¹
11q23	<i>POU2AF1</i>	n/a	n/a	1.38	3.27×10 ⁻⁸	1.165	1.12×10 ⁻²

OR odds ratio, n/a data not available due to non-significance

^aBased on Ref. [28]^bBased on Ref. [15]