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SHORT COMMUNICATION

Mapping genetic variants in the *CFH* gene for association with leprosy in Han Chinese

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Complement factor H (CFH) is an essential regulator in the homeostasis of the complement system that plays multiple roles in leprosy. We previously reported a preliminary association of *CFH* with leprosy, but potentially causal variants remain to be identified. In this study, we performed a fine-mapping association analysis in 1110 individuals (527 leprosy patients and 583 controls) followed by bioinformatic analyses. We identified no association of typical missense *CFH* variants with leprosy and factor H-binding protein was not detected in *Mycobacterium leprae*. However, robust associations ($P_{Bonferroni} < 0.003$) of several *CFH* intronic tag single-nucleotide polymorphisms with leprosy were observed. Expression quantitative trait locus analysis showed that these leprosy-protective alleles were associated with higher *CFH* level and lower *CFHR3* (complement factor H-related 3) level. Our results indicated that *CFH* variants may contribute to leprosy pathogenesis through altering *CFH* expression, leading to regulation of complement activity rather than mediating immune evasion by bacteria binding.

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INTRODUCTION

Leprosy, a chronic infectious disease caused by intracellular pathogen *Mycobacterium leprae* (*M. leprae*), is a good model for studying the genetic basis and immune response of chronic infection.[1] Activation of the complement system, which plays multiple roles in host defense against infection, results in opsonization of pathogens, complement-mediated killing and immune recruitment.[2] Involvement of the alternative complement pathway in phagocytosis of leprosy bacilli has been established.[3] Complement factor H (CFH) plays an essential role in the homeostasis of the complement system.[4] CFH is a 155 KD soluble glycoprotein making up of 20 complement control protein (CCP) modules (or short consensus repeats (SCRs), Figure 1) that circulates in human plasma. The modules CCPs 1–4 engage with C3b and mainly effect in complement regulation, the CCPs 16–20 play a role in self-surface recognition, whereas the CCPs 6–20 are enriched of binding sites for pathogens and other substrates.[4] These functional domains with different regulatory activities may be responsible for the molecular basis underlying the different pathologies associated to CFH. It is reported that CFH could be recruited by pathogens mediating immune evasion.[5] However, whether CFH is involved in *M. leprae* evasion of host immunity has not been well studied.

We have previously reported that rs1065489 and rs3753395 of the *CFH* gene were positively associated with leprosy, suggesting an active role of this gene in leprosy.[6] However, it remains unknown whether there are functional variants altering the CFH expression or activity that may contribute to leprosy. Aiming to map the potential causal variants within the *CFH* gene in leprosy, we performed a fine-grained association study followed by bioinformatic analyses in this study.

RESULTS

Association of CFH variants with leprosy

Individual single-nucleotide polymorphism (SNP) association showed that seven SNPs (rs10922096, rs2019727, rs10737680, rs3753395, rs1065489, rs11582939 and rs426736) presented consistently significant or suggestive association with leprosy at both genotypic and allelic levels (Figure 1). Three intronic tag SNPs rs10922096, rs2019727 and rs3753395 remained to be significant after multiple testing correction (Bonferroni corrected $P < 0.0036$). Gene-based association showed that *CFH* was associated with leprosy at the gene level ($P = 0.02$). Moreover, haplotypes covering rs3753395, rs10922096 and rs2019727 showed the highest signal in the sliding window haplotype analysis, with several haplotypes showing significant ($P < 0.001$) associations with leprosy *per se* and multibacillary leprosy (Supplementary Figure S1). Logistic conditional regression (Supplementary Table S1) showed that at least three independent signals were associated with leprosy: positive associations of rs10922096 and rs2019727 were related signals, and positive associations for rs3753395 and rs426736 sustained after conditioning on these positive SNPs. As there are independent associated signals in the *CFH* gene, we evaluated whether there are SNP–SNP interaction by multifactor dimensionality reduction.[7] The top three attributes selected by the ReliefF filtering procedure were rs3753395, rs1065489 and rs426736. Multifactor dimensionality reduction-combined attribute network (Supplementary Figure S1) showed that rs426736 had a synergic effect with rs3753395 and 1065489, whereas rs10922096 and rs2019727 had a redundant effect in leprosy. These signals may reflect independent core regions harboring potential causal variants, consistent with individual SNP association result.

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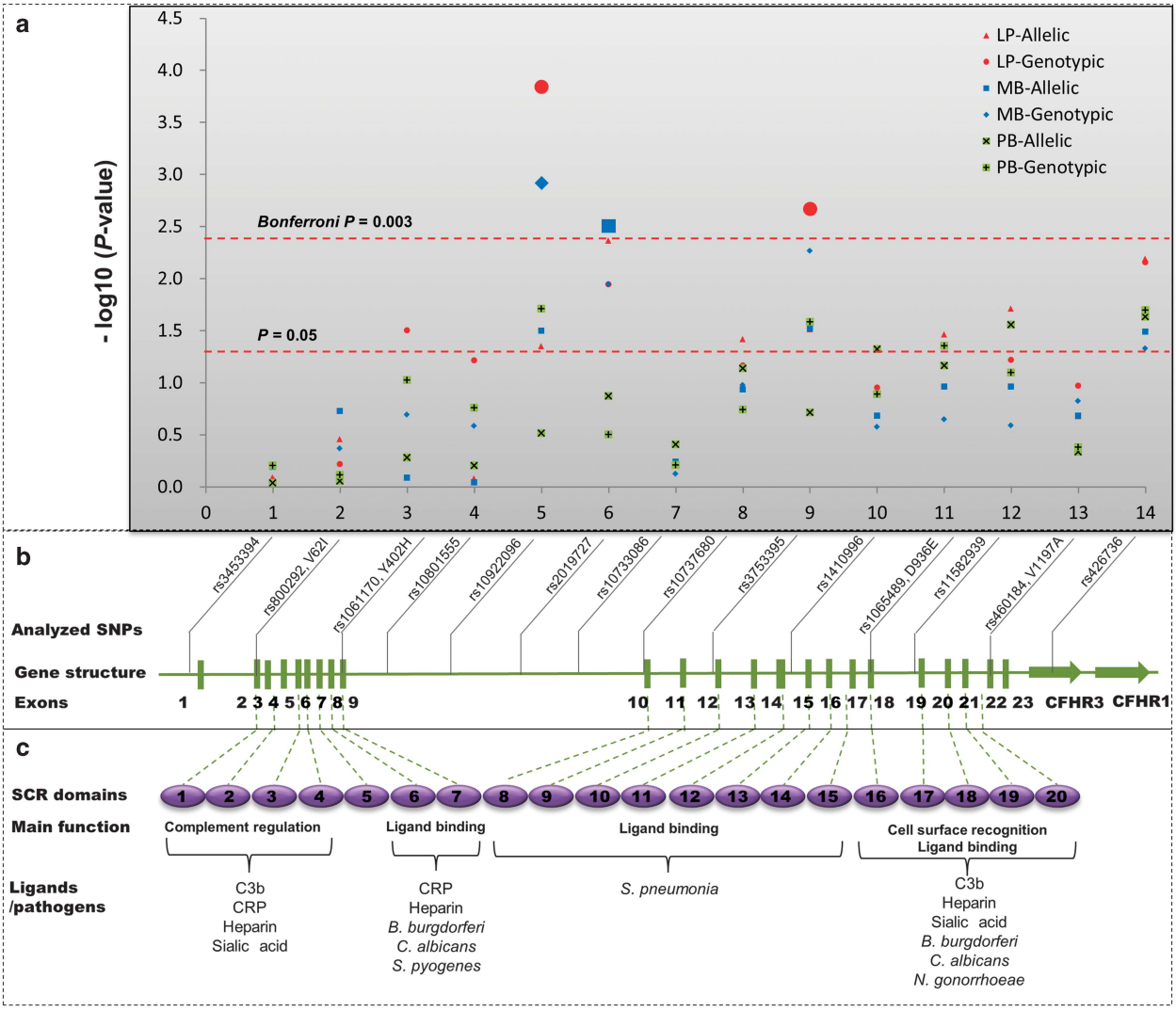


Figure 1. Gene and protein structure of *CFH* and its association with leprosy. Associations of *CFH* variants with leprosy *per se* (LP) and subtypes (multibacillary (MB) and paucibacillary leprosy (PB)) are shown at the genotypic and allelic levels (**a**). Schematic map of the 14 SNPs in the *CFH* gene (**b**) and functional annotation of the CFH domains (**c**) were not drawn to scale. A *P*-value of <0.0036 (Bonferroni corrected *P*-value for 0.05) is marked with larger icons.

Although these intronic variants rs10922096, rs2019727, rs3753395 and rs426736 showed robust associations with leprosy, the typical nonsynonymous variants in different important domains of the CFH protein (rs800292, p.V62I, SCR1; rs1061170, p.Y402H, SCR7; rs1065489, p.D936E, SCR16; rs460184, p.V1197A, SCR20) showed weak associations with leprosy. We also performed the association analyses in patients with different leprosy subtypes (multibacillary leprosy and paucibacillary leprosy). Similar association pattern, as we observed between *CFH* and leprosy *per se*, was observed in multibacillary leprosy (Figure 1 and Supplementary Figure S1). The *CFH* variants showed weak associations with paucibacillary leprosy (Figure 1 and Supplementary Figure S1).

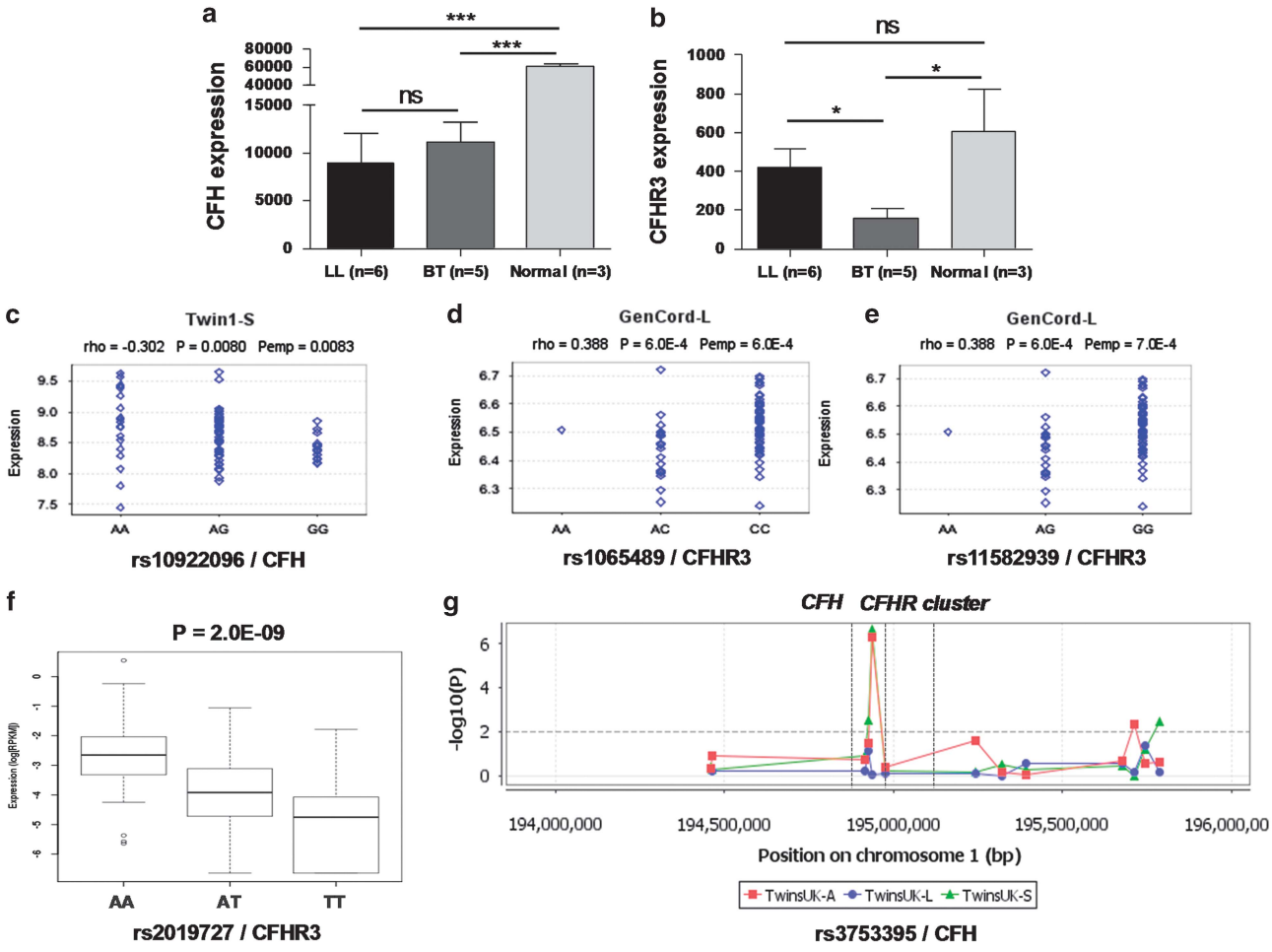
Searching for factor H-binding protein (fHbp) ortholog in *M. leprae*

To determine whether the association of *CFH* with leprosy reflects the interaction between *M. leprae* and CFH protein in the progress of bacterium invasion, we performed a search for fHbp ortholog in *M. leprae*. No fHbp ortholog was identified in *M. leprae*, suggesting negative role of CFH in the *M. leprae* invasion by bacterium-factor H binding. However, considering the limited coverage of the current BLAST and the high diversity of fHbp,[8] we cannot completely rule out the possibility that there may be putative proteins having the ability of factor H binding.

Expression and eQTL analyses

Expression levels of both *CFH* ($P<0.0001$) and *CFHR3* (*CFH-related protein 3*, $P<0.05$) mRNA were significantly decreased in leprosy patients compared with normal tissues, suggesting that complement system is highly altered in leprosy pathogenesis and progress. When compared with the mild leprosy tuberculoid (borderline tuberculoid) form, *CFH* expression was slightly decreased whereas *CFHR3* expression was significantly increased in the severe lepromatous (lepromatous leprosy) form (Figure 2). This indicates an opposite and significant effect of CFHR3 in leprosy progress, as reported that CFHR3 functions as a competitive antagonist of CFH to modulate complement activation.[9] However, these preliminary observations should be interpreted with caution and need further validation in larger samples.

SNP rs3753395 showed a strong association ($P<1.0\times10^{-6}$) with *CFH* mRNA expression. Leprosy-protective allele of



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SNP ID	Minor allele	OR	Leprosy effect	eQTL gene	eQTL effect	eQTL gene – leprosy effect
rs10922096	A	0.785	Protective	CFH	↑	Protective
rs2019727	T	0.625	Protective	CFHR3	↓	Risk
rs3753395	T	0.823	Protective	CFH	-	-
rs1065489	A	0.833	Protective	CFHR3	↓	Risk
rs11582939	A	0.819	Protective	CFHR3	↓	Risk
rs426736	C	0.793	Protective	-	-	-

Figure 2. The eQTL analysis and *CFH* and *CFHR3* mRNA expression in leprosy skin lesions. The expression data of *CFH* (**a**) and *CFHR3* (**b**) in skin biopsy specimens were obtained from the Gene Expression Omnibus. The analyzed skin tissues were collected from leprosy skin lesions of six tuberculoid form (borderline tuberculoid (BT)) and five lepromatous leprosy (LL) patients[14] (DataSet Record: GDS358; Reference Series: GSE443) and three normal individuals[15] (DataSet Record: GDS3113; Reference Series: GSE7905). Data are shown as mean with s.e.m. Expression difference was measured by Student's *t*-test using GraphPad Prism 5. The eQTL data of rs10922096 (**c**), rs1065489 (**d**) and rs11582939 (**e**) were obtained from the Genevar platform (http://www.sanger.ac.uk/resources/software/genevar/). Twin1-S, skin tissue in Genevar (MuTHER Pilot). GenCord-L, lymphoblastoid cell line from GenCord project. (**f**) The eQTL of rs2019727 was obtained from the Genotype-Tissue Expression Portal (GTEx, http://www.gtexportal.org/home/searchEqtls), and only one representative plot (in lung tissue) is shown. (**g**) rs3753395 showed a significant association ($P<1.0\times10^{-6}$) with *CFH* mRNA expression in both adipose (TwinsUK-A) and skin (TwinsUK-S) tissues, although its SNP association plot was not available in Genevar (MuTHER Resoure). (**h**) Summarized effect of these positively associated SNPs according to the association analysis, expression and eQTL analysis. Higher mRNA expression of the eQTL gene is marked as '↑' and lower expression is marked as '↓'. *$P<0.05$, ***$P<0.0001$; ns, not significant; -, not available.

rs10922096 was associated with higher CFH mRNA level, whereas the leprosy-protective alleles of rs2019727, rs1065489 and rs11582939 were associated with lower *CFHR3* mRNA level. The effect of these positively associated SNPs was summarized according to the association analysis and expression quantitative trait locus (eQTL) analyses (Figure 2). These observations indicated that upregulation of *CFH* mRNA expression may be protective in leprosy pathogenesis, whereas CFHR3 acts as an antagonist of *CFH* and plays a risk role.

DISCUSSION

Recruitment of CFH in immune evasion by numerous pathogens has been reported.[2,5] A recent genome-wide association study

reported that SNPs (rs1065489 and rs426736) within the *CFH* gene were strongly associated with host susceptibility to meningococcal disease.[10] Meningococcal meningitis is an infection caused by *Neisseria meningitidis* that is known to evade complement-mediated killing by binding host CFH to the meningococcal fHbp.[10] However, the role of CFH in leprosy pathogenesis remains unknown.

We previously showed that *CFH* variants were associated with leprosy.[6] Identification of causal variants within *CFH* contributing to leprosy susceptibility is needed. In this study, we analyzed 14 *CFH* SNPs (including three previously reported SNPs[6]) that cover >80% of the entire gene region. We found that the intronic tag SNPs rs10922096, rs2019727 and rs3753395 showed robust associations with leprosy (Figure 1). The meningitis-related SNPs (rs1065489 and rs426736) also showed associations with leprosy.

Does *M. leprae* share similar mechanism with these factor H-binding bacteria? Although the meningitis-related SNPs rs1065489 and rs426736 showed associations with leprosy here, no fHbp ortholog, as in *N. meningitidis*, was identified in *M. leprae*. Moreover, the four analyzed missense variants located in different CFH protein domains (Figure 1) showed weak associations with leprosy. These observations suggest that altered CFH protein structure or activity may not account for the association of *CFH* with leprosy.

Intriguingly, the most significantly associated SNPs rs10922096 and rs3753395 are eQTLs for *CFH*, whereas rs2019727, rs1065489 and rs11582939 are eQTLs for *CFHR3*. The leprosy-protective alleles were associated with higher *CFH* mRNA level and lower *CFHR3* mRNA level (Figure 2). These observations indicated that it is the altered CFH and CFH-related protein expression that would account for the association of *CFH* with leprosy. Upregulation of *CFH* expression may be protective in leprosy pathogenesis, and CFHR3 may play a risk role in leprosy as CFHR3 functions as a competitive antagonist of CFH to modulate complement activation.[9] Note that the meningitis-related SNP rs426736 showed no signal as eQTL for any gene. But it has a synergic effect with rs3753395 and 1065489 according to the multifactor dimensionality reduction analysis. Involvement of the *CFHR3* gene in leprosy and the overlapping underpinning between leprosy and meningitis needs further study.

Taken together, *CFH* genetic variants would alter expression level of *CFH* and *CFHR3*, resulting in regulation of the complement activity in phagocytosis and immune evasion of leprosy bacilli that finally contribute to leprosy pathogenesis. Further validation and functional studies are essential to confirm our results.

MATERIALS AND METHODS

Subjects

Subjects recruited in this study were described in our previous studies.[6,11] In brief, a total of 527 Han Chinese with leprosy (mean onset age 24.7 ± 12.3 years, containing 279 multibacillary leprosy and 248 paucibacillary leprosy patients) were collected from Yunnan, Southwest China. These patients were diagnosed based on clinical and histopathological features and/or bacteriological index (if available). As the control group, 583 healthy individuals (mean age 36.0 (± 15.5) years) without any history of leprosy infection, HIV and tuberculosis from the same geographic area were enrolled. Informed consents conforming to the tenets of the Declaration of Helsinki were obtained before this study. The institutional review board approved this study.

SNP selection and genotyping

In our previous study for association of *CFH* genetic variants with leprosy,[6] we only analyzed three SNPs. To achieve a higher (>80%) coverage of the *CFH* gene (Figure 1), 11 additional SNPs that met the following criteria were selected in this study: (1) SNPs with a high capability of tagging according to the linkage disequilibrium pattern of the *CFH* gene in HapMap CHB data set (http://hapmap.ncbi.nlm.nih.gov, Supplementary Figure S2); (2) SNPs with a minor allele frequency >5% in HapMap CHB data set and dbSNP (http://www.ncbi.nlm.nih.gov/SNP); (3) SNPs annotated with an important function and located in different domains of CFH. Among them, nine (rs800292, rs10801555, rs10922096, rs10733086, rs10737680, rs11582939, rs2019727, rs1410996 and rs426736) were tag SNPs and three (rs800292, p.V62I, SCR1; rs1061170, p.Y402H, SCR7; rs460184, p.V1197A, SCR20) were nonsynonymous variants located in three important domains of the CFH protein. These 11 SNPs were detected by the SNaPshot assay following the procedure described in our previous study.[11] Approximately 5% of the samples were sequenced to validate the genotyping results and we obtained 100% consistency. None of the analyzed SNPs (except for rs460184) showed a deviation from the Hardy–Weinberg equilibrium.

Association analysis

Individual SNP association, gene-based association, sliding window haplotype analysis and SNP–SNP interaction were performed for the 11 SNPs genotyped in this study, together with the previously reported 3 SNPs (rs3753394, rs3753395 and rs1065489). Conditional logistic regression analysis conditioning on the positively associated SNPs were also conducted. Statistical analyses for individual SNPs and sliding window haplotype associations were carried out using the software PLINK.[12] Sliding window sizes from two to six SNPs per window sliding by one SNP was performed and shown in Supplementary Figure S1. SNP rs460184 was excluded because of a deviation from the Hardy–Weinberg equilibrium. The SNP–SNP interaction was determined by multifactor dimensionality reduction.[7] Gene-based association was calculated by program Versatile Gene-based Association Study (VEGAS)[13] using the default settings.

Searching for fHbp ortholog in *M. leprae*

To determine whether the association of *CFH* with leprosy reflects the interaction between *M. leprae* and CFH protein in the progress of bacterium invasion, we performed a search for fHbp ortholog in *M. leprae*. Both fHbp gene and protein sequences, from seven known factor H-binding bacteria[8] (*Borrelia hermsii* isolate WAD, *Borrelia turicatae* isolate 91E135, *Neisseria gonorrhoeae* JP 2012502073-A/25, *N. meningitidis* strain M98 253393, *Streptococcus pneumoniae* strain HU160/07, *Streptococcus pyogenes* JP 2012502073-A/40 and *Treponema denticola* strain ASLM), were obtained from GenBank (http://www.ncbi.nlm.nih.gov). Nucleotide BLAST, protein BLAST and translated BLAST (tblastn) searches (http://blast.ncbi.nlm.nih.gov/Blast.cgi) were performed.

Expression and eQTL analyses

CFH expression and eQTL were analyzed using publicly available databases. The mRNA expression data of *CFH* and *CFHR3* in skin biopsy specimens (Figure 2) were obtained from the Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/sites/GDSbrowser). The analyzed skin tissues were collected from leprosy skin lesions of six tuberculoid form (borderline tuberculoid) and five lepromatous leprosy patients[14] (DataSet Record: GDS358; Reference Series: GSE443) and three normal individuals[15] (DataSet Record: GDS3113; Reference Series: GSE7905). Statistical analysis was performed by GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA).

The eQTL analysis was performed for all genotyped *CFH* SNPs using several eQTL databases. Data of rs3753395, rs10922096, rs1065489 and rs11582939 were obtained from the Genevar platform (http://www.sanger.ac.uk/resources/software/genevar/). The eQTL of rs2019727 was obtained from the Genotype-Tissue Expression Portal (GTEx, http://www.gtexportal.org/home/searchEqtls).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on Genes and Immunity website (http://www.nature.com/gene)

Table S1. Association of *CFH* variants with leprosy conditioning on the positively associated SNPs

#	SNP	Original[a]	Condition on																	
			rs10922096			rs2019727			rs3753395			rs1065489			rs11582939			rs426736		
			LP	MB	PB	LP	MB	PB	LP	MB	PB	LP	MB	PB	LP	MB	PB	LP	MB	PB
1	rs3753394	0.854	0.587	0.733	0.362	0.515	0.641	0.328	0.338	0.284	0.346	0.931	0.980	0.719	0.748	0.957	0.419	0.459	0.656	0.272
2	rs800292	0.601	0.602	0.607	0.761	0.270	0.295	0.486	0.227	0.129	0.572	0.992	0.999	0.974	0.803	0.862	0.769	0.534	0.668	0.508
3	rs1061170	0.031	0.517	0.560	0.550	1.000	0.968	0.996	1.000	1.000	0.988	1.000	0.981	0.998	0.984	0.997	0.988	0.935	0.993	0.939
4	rs10801555	0.061	0.457	0.445	0.587	0.999	0.934	1.000	1.000	0.992	0.997	0.997	0.947	1.000	0.992	0.977	0.975	0.952	1.000	0.911
5	rs10922096	0.0001	NA	NA	NA	0.097	0.120	0.551	0.132	0.265	0.499	**0.015**	0.094	0.122	**0.008**	0.081	0.063	**0.005**	0.062	0.049
6	rs2019727	0.011	0.250	0.439	0.684	NA	NA	NA	0.266	0.644	0.577	0.052	0.298	0.201	0.028	0.252	0.107	0.030	0.313	0.143
7	rs10733086	0.575	0.159	0.058	0.763	0.866	0.508	0.904	0.978	0.886	0.797	0.901	0.721	0.741	0.909	0.794	0.608	0.858	0.885	0.484
8	rs10737680	0.068	0.067	0.193	0.061	0.016	0.088	0.017	**0.001**	**0.004**	**0.005**	0.186	0.544	0.135	0.273	0.436	0.333	0.591	0.455	0.859
9	rs3753395	**0.002**	0.038	0.014	0.207	0.065	0.025	0.266	NA	NA	NA	**0.006**	**0.001**	0.109	**0.004**	**0.001**	0.068	**0.001**	**0.000**	**0.040**
10	rs1410996	0.111	0.115	0.377	0.049	0.031	0.196	0.014	**0.003**	**0.012**	**0.004**	0.303	0.799	0.101	0.435	0.601	0.256	0.667	0.340	0.794
11	rs1065489	**0.044**	0.226	0.293	0.240	0.246	0.254	0.300	0.064	0.015	0.266	NA	NA	NA	0.841	0.964	0.654	0.410	0.707	0.284
12	rs11582939	0.060	0.050	0.167	0.042	0.062	0.149	0.066	0.013	0.016	0.039	0.481	0.830	0.352	NA	NA	NA	0.112	0.069	0.265
13	rs460184	0.106	0.253	0.374	0.393	0.095	0.189	0.220	0.031	0.031	0.148	0.441	0.647	0.617	0.647	0.712	0.876	0.928	0.973	0.997
14	rs426736	**0.007**	**0.006**	**0.025**	**0.007**	**0.012**	**0.035**	**0.017**	**0.000**	**0.001**	**0.003**	**0.020**	0.068	**0.020**	**0.014**	**0.012**	**0.047**	NA	NA	NA

[a] General genotypic *P* value for leprosy *per se*.

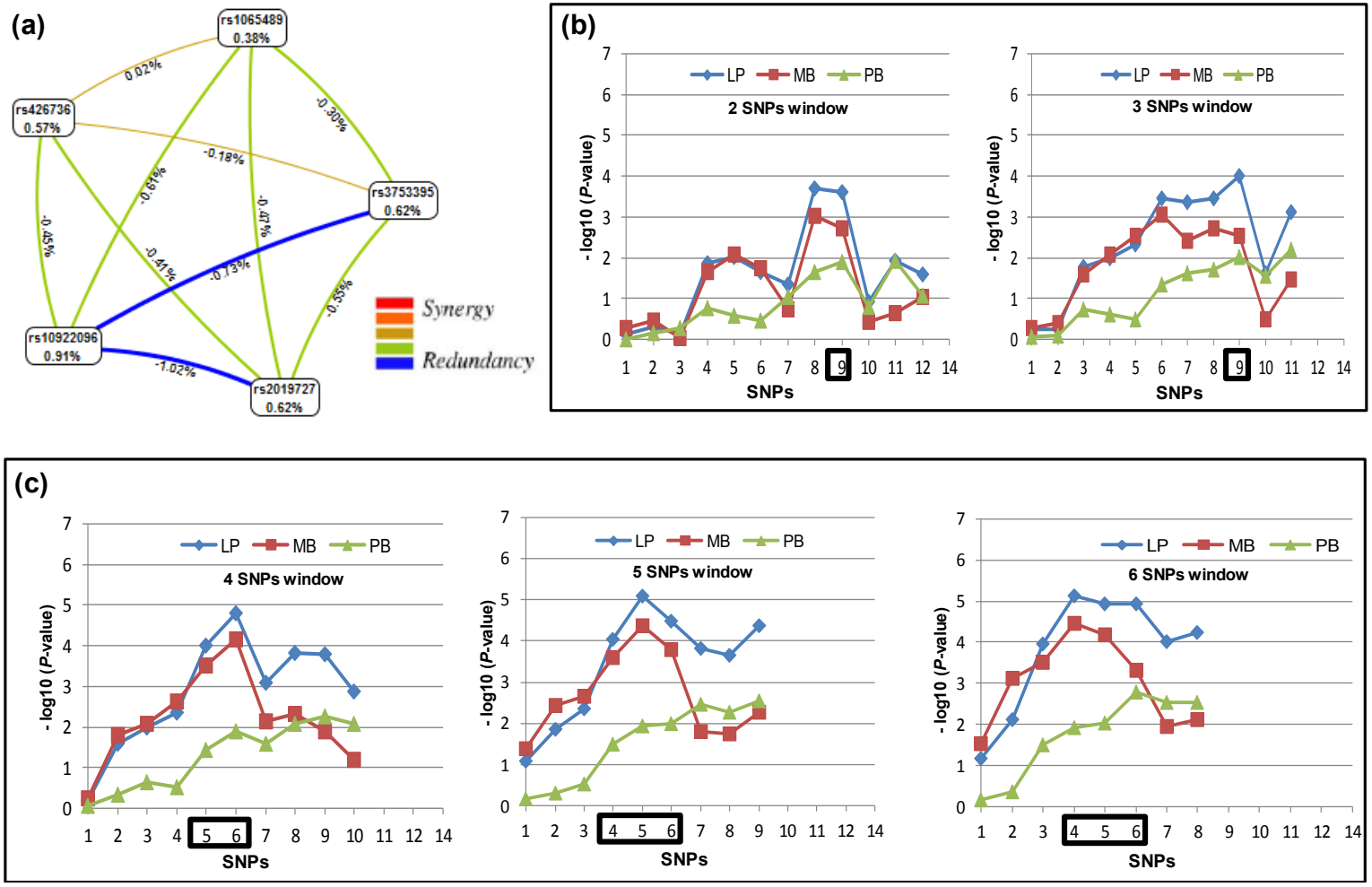
(a)
rs1065489
0.38%
rs426736
0.57%
rs3753395
0.62%
rs10922096
0.91%
rs2019727
0.62%
0.02%
-0.30%
-0.18%
-0.61%
-0.47%
-0.45%
-0.41%
-0.73%
-0.55%
-1.02%
Synergy
Redundancy
(b)
LP MB PB
2 SNPs window
3 SNPs window
- log10 (P-value)
SNPs
(c)
4 SNPs window
5 SNPs window
6 SNPs window

Figure S1. Sliding window haplotype analysis and MDR analysis of SNP-SNP interactions of the 14 *CFH* variants.

MDR combined attribute network showed that rs426736 has a synergic effect with rs3753395 and 1065489 while rs10922096 and rs2019727 have a redundant effect in leprosy (a). Haplotypes covering SNP rs3753395 (#9) showed the highest signal in 2-SNPs and 3-SNPs windows (b). Haplotypes covering SNPs rs10922096 and rs2019727 (#5 and #6) showed the highest signal in 4-SNPs, 5-SNPs, and 6-SNPs windows (c).

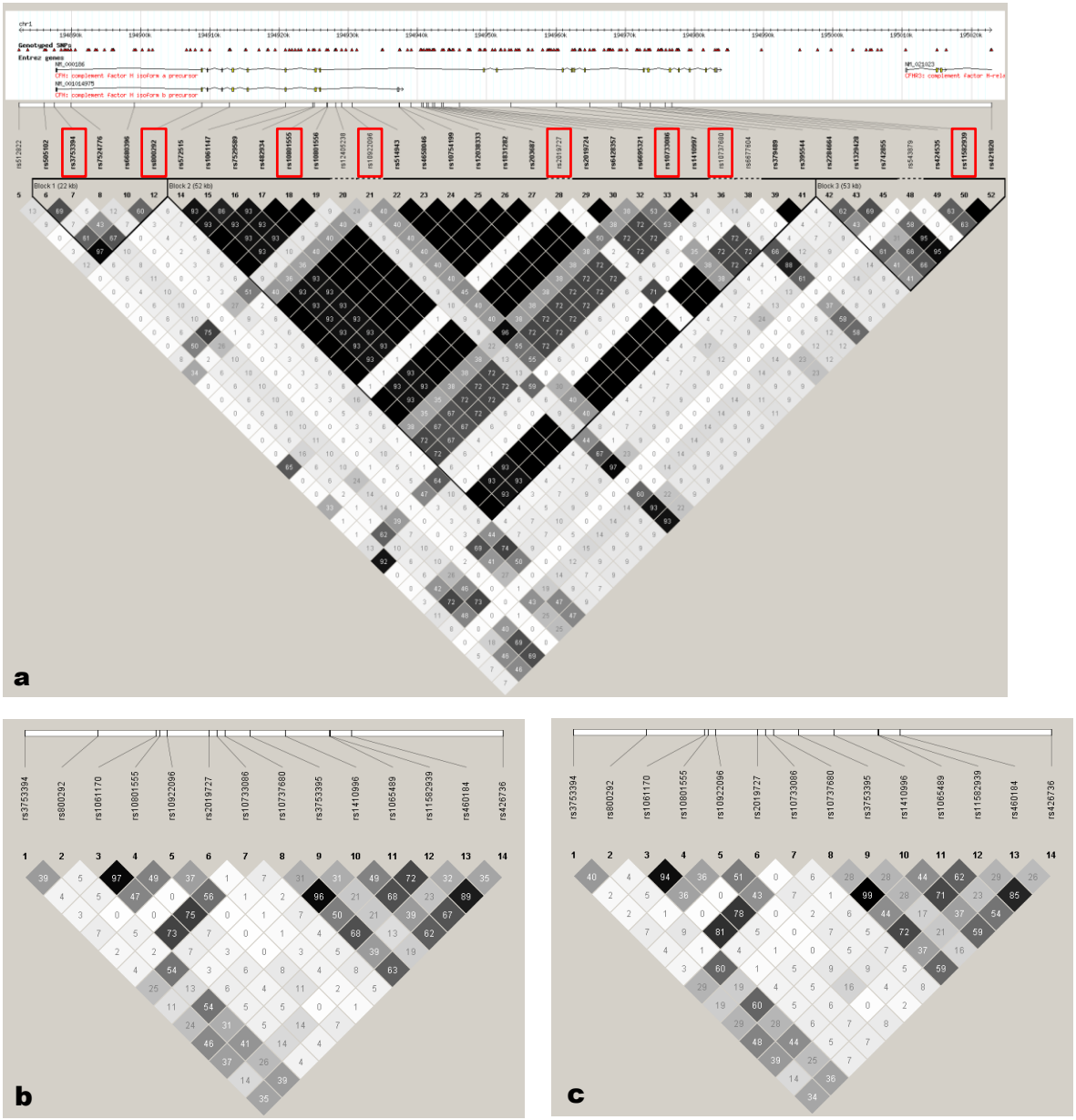

Figure S2. Linkage disequilibrium (LD) pattern of the *CFH* gene in CHB (a), leprosy patient (b), and control (c) populations.

Results were performed by Haploview 4.2 based on the HapMap and our case-control data. r^2 was used for the LD color scheme. Black squares represent high LD as measured by r^2, gradually coloring down to white squares of low LD. The individual square shows the 100 × r^2 value for each SNP pair. For the CHB population, three blocks are observed. SNPs marked by red frames are chosen as tag SNPs in the analyses.