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Juvenile rheumatoid arthritis and asthma, but not childhood-onset systemic lupus erythematosus are associated with *FCRL3* polymorphisms in Mexicans☆

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ABSTRACT

A regulatory single nucleotide polymorphism located in the 5′ region (−169T/C) of the *Fc receptor-like 3* (*FCRL3_3*) gene has been associated with both susceptibility and protection in immune diseases. This case–control study aimed to evaluate the association between *FCRL3* polymorphisms and juvenile rheumatoid arthritis (JRA), asthma, and childhood-onset systemic lupus erythematosus (SLE) in a Mexican population. We performed PCR-based genotyping to identify four *FCRL3* single nucleotide polymorphisms (*FCRL3_3 to FCRL3_6)* in patients with JRA ($n = 202$), asthma ($n = 239$), or childhood-onset SLE ($n = 377$), and healthy controls ($n = 400$). The case–control analysis showed a male-gender dependent association between the *FCRL3_3C*, *FCRL3_5C*, and *FCRL3_6A* alleles and either JRA (OR = 0.57, $p = 0.003$; OR = 0.55, $p = 0.002$; OR = 0.53, $p = 0.0007$, respectively) or asthma (OR = 0.72, $p = 0.04$; OR = 0.74, $p = 0.05$; OR = 0.70, $p = 0.02$, respectively). As expected, minor alleles of these SNPs with the CGCA haplotype were also significantly associated with JRA (OR = 0.35, $p = 0.00005$) and asthma (OR = 0.61, $p = 0.007$). We found no association between *FCRL3* SNPs or haplotypes and childhood-onset SLE. These results supported the notion that *FCRL3* is involved in the etiology of several immune diseases. Our results also suggested that SNPs located in the *FCRL3* gene were protective against JRA and asthma in male Mexican patients.

1. Introduction

Immune disorders involve complex etiologies, but many have a strong genetic component in their pathogenesis (Becker et al., 1998; Phelan et al., 2006; Moser et al., 2009; Lee et al., 2011). Genome-wide linkage studies have identified a group of genetic factors that are shared among many autoimmune and other immune-mediated diseases (Becker et al., 1998; Lee et al., 2011). One of the regions implicated in susceptibility to multiple autoimmune diseases is the cytoband 1q21–23. This region harbors the Fcγ receptor (*FcγR*) II/III and Fc receptor-like family genes (*FCRL1* through *FCRL5*) (Davis et al., 2001). The ligands and function of the FCRLs remain unknown; however, some studies have suggested that FCRL proteins may contribute to the pathogenesis of chronic immune diseases, because they affect B-Cell receptor-mediated signaling, growth, and proliferation (Ehrhardt et al., 2003, 2007; Leu et al., 2005; Kochi et al., 2009). Several association studies have supported the hypothesis that *FCRLs* play an important role in immune-mediated pathologies, either as risk or protection factors (Kochi et al., 2005; WTCCC, 2007; Owen et al., 2007; Martínez, 2007; Matesanz et al., 2008; Chen et al., 2011). Furthermore, meta-analysis studies have shown that the *FCRL3_3C* allele was a significant risk factor for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) in Asians, but not in Caucasians (Lee et al., 2010; Mao et al., 2010). On the other hand, *FCRL3* SNPs have been reported to have a protective effect against autoimmune thyroid disease (AITD), Addisonĩs disease (AAD) and multiple sclerosis (MS) (WTCCC, 2007; Owen et al., 2007; Martínez, 2007; Matesanz et al., 2008). These findings have suggested that *FCRLs* have differential effects on different populations.

We investigated whether *FCRL3* SNPs were associated with juvenile rheumatoid arthritis (JRA), asthma, and childhood-onset SLE in Mexican pediatric patients.

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2. Patients and methods

2.1. Study subjects for genetic analysis

This study included 818 patients with JRA ($n = 202$), asthma ($n = 239$), or SLE ($n = 377$). All cases were under 16 years of age and were recruited from five tertiary level Institutions in Mexico City. The diagnosis of asthma was based on criteria published by the American Thoracic Society and the Global Initiative for Asthma. The diagnosis of JRA and SLE were based on criteria published by the American College of Rheumatology. We also included 400 unrelated, healthy control subjects, ethnically matched to the patients, with no history of autoimmune or inflammatory diseases. No previous studies have shown a correlation between the *FCRL3* alleles and age; therefore, the controls were older than 18 years of age. Additionally, allelic frequencies of *FCRL3* polymorphisms were not different between genders; therefore, we used the same control group for all analyses. Patients and controls were descended from parents and grandparents born in Mexico. Ethics and Research Committee approvals were obtained from all participating Institutions, and informed consent was obtained from each individual. Parents provided consent for child participation, and all children assented.

2.2. Analysis of genetic polymorphisms

We obtained genomic DNA from peripheral blood leukocytes with a standard salt precipitation technique (QIAgen Systems, Inc., Valencia, CA, USA). Ethnic matching between cases and controls was previously evaluated with a panel of 10 ancestry informative markers (AIMs: rs4884, rs2695, rs17203, rs2862, rs3340, rs722098, rs203096, rs223830, rs1800498, and rs281478) (Jiménez-Morales et al., 2009). These AIMs mainly identify Amerindian and European ancestry in Mexican population. We performed genotyping to reveal *FCRL3_3* (−169T/C or rs7528684), *FCRL3_4* (−110G/A or rs11264799), *FCRL3_5* (+358G/C or rs945635), and *FCRL3_6* (+1381G/A or rs3761959) polymorphisms. The PCR assay used to identify these four SNPs was performed with TaqMan MGB chemistry (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Each PCR reaction contained 10 ng of DNA, 2.5 μl of TaqMan Master Mix, 0.065 μl of 40× assay mixture, and 2.435 μl of distilled, DNase free water in a final volume of 5 μl. The amplification protocol included denaturing at 95 °C for 10 min, followed by 40 cycles of denaturing at 95 °C for 15 s and annealing and extension at 60 °C for 1 min. Genotypes were assigned by detecting allele-specific fluorescence with SDS 2.2.3 software for allelic discrimination (Applied Biosystems, Foster City, CA). The overall genotype call rate was 99.9%, and 30% of randomized samples showed 100% reproducibility in duplicate assays for the four polymorphisms. Genotyping accuracy was confirmed by direct sequencing of PCR products in 50 randomly chosen samples. The PCR products were sequenced directly with a DNA Sequencing Kit and the Big Dye Terminator on an automated ABI PRISM 3100 DNA sequencer (Applied Biosystems, Foster City, CA, USA). The primer sequences used to recognize the *FCRL3* were 5′-GAAGACACGAAAGCAATCAAGGAA-3′ and 5′-CATATGGGAAACCCCTTCACTACC-3′. PCR was performed in a 50 μl reaction mixture that contained 60 ng of genomic DNA, 2.5 mM MgCl2, 1.25 units of Amplitaq Gold (Applied Biosystems), 2.5 mM of each primer, 250 mM dNTPs mixed (Takara), and 1X PCR buffer (Applied Biosystems). The amplification protocol included denaturing at 95 °C for 10 min, followed by 35 cycles of denaturing at 94 °C for 30 s, annealing at 58 °C for 30 s, and extending at 72 °C for 35 s; with a final extension at 72 °C for 5 min.

3. Statistical analysis

The FINETTI program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) was used to test for Hardy–Weinberg equilibrium (HWE) in genotype distributions for the cases and controls. Association between *FCRL3* SNPs and the three diseases were analyzed with X^2 tests on 2×2 and 2×3 contingency tables for allele and genotype frequencies, respectively. Statistical analysis was performed with a standard statistical package (Epic Info 2005 V.3.2; Centers of Disease Control and Prevention, Atlanta, GA). Odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated with the same software. Haplotype frequencies and linkage disequilibrium (LD; r^2) were calculated with the Haploview software (Barrett et al., 2005). The p-value was corrected by applying a permutation test based on 100,000 permutations. The ADMIXMAP program (McKeigue et al., 2000; Hoggart et al., 2003) was used to test the possible effect of population stratification, as described previously (Bonilla et al., 2004; Choudhry et al., 2006), in the two primary parental populations of the Mexican–Mestizo (Amerindian and European).

4. Results

The mean (±SD) age at onset of JRA, asthma, and SLE were 8.7 ± 2.46, 8.4 ± 2.8, and 11.62 ± 2.46 years, respectively. The female/male gender distribution was 115/87 (57/43%) for JRA, 92/147 (38/62%) for asthma, and 312/65 (83/17%) for SLE. The control population comprised 200 (50%) females and 200 (50%) males. We used the same control group for all analyses, because no differences between genders were found in the allele frequencies of *FCRL3_3*, *FCRL3_4*, *FCRL3_5*, and *FCRL3_6* SNPs. Genotype distributions of polymorphisms were in HWE for both cases and controls. The AIM distributions were not significantly different between cases and controls.

When the JRA, asthma, and childhood-onset SLE cohorts were compared to controls, only the JRA population exhibited significant differences, and only in the *FCRL3_3* and *FCRL3_6* minor allele frequencies (MAF) ($p = 0.03$ and $p = 0.01$, respectively). After gender stratification, the *FCRL3_5C* allele exhibited a male gender-dependent association with JRA. The *FCRL3_3C*, *FCRL3_5C*, and *FCRL3_6A* allele frequencies were higher in the control group than in the JRA group (OR = 0.57, 95% CI 0.40–0.83, $p = 0.003$; OR = 0.55, 95% CI 0.38–0.80, $p = 0.002$; and OR = 0.53, 95% CI 0.36–0.76, $p = 0.0007$, respectively). Similarly, the same alleles were higher in the control group than in the asthma group (OR = 0.72, 95% CI 0.54–0.98, $p = 0.04$; OR = 0.74, 95% CI 0.55–1.00, $p = 0.05$; and OR = 0.70, 95% CI 0.52–0.95, $p = 0.02$, respectively). Homozygosity for the *FCRL3_3C* minor allele conferred higher protection from JRA (OR = 0.38, 95% CI 0.18–0.78, $p = 0.007$) and asthma (OR = 0.54, 95% CI 0.29–0.99, $p = 0.05$) compared to the other genotypes. However, after applying the Bonferroni correction test, statistical significance persisted only for homozygous *FCRL3_3C* protection against JRA (Table 1).

On the other hand, the haplotype analysis showed that *FcRL3_3*, *FcRL3_5*, and *FcRL3_6* were in high LD, but not *FcRL3_4* (pair-wise r^2 values > 0.9) (Fig. 1). We identified a total of four haplotypes with frequencies >0.01 (Table 2). The haplotype CGCA, which carried the three minor alleles, *FcRL3_3C*,*_5C*, and *_6A*, and the major allele, *FcRL3_4G*, showed male gender-dependent protection to JRA and asthma (OR = 0.35, 95% CI 0.20–0.60, $p = 0.00005$; OR = 0.61, 95% CI 0.41–0.89, $p = 0.007$, respectively). This significant association between the CGCA haplotype and protection from both diseases remained after 100,000 permutations.

A comparative analysis between healthy individuals from different populations showed that the frequency of the *FCRL3_3C* allele was higher in Mexicans (49.7%) than in Japanese (37%) and

Table 1
Allele and genotype distributions of the four *FCRL3* SNPs in males with JRA, asthma and childhood-onset SLE.

SNP ID	Population	Allele 1 2	Genotype			Genotypes			Allele		Alleles		
			n (%)			OR	95% CI	*p*	*n* (%)		OR	95% CI	*p*
			1 1	1 2	2 2	11 *vs.* (12+2 2)			1	2	1 *vs.* 2		
FCRL3_3	Controls	T C	50 (25.0)	101 (50.5)	49 (24.5)				201 (50.3)	199 (49.7)			
(rs7528684)	JRA		38 (43.7)	35 (40.2)	14 (16.1)	0.43	(0.25–0.73)	0.002[a]	111 (63.8)	63 (36.2)	0.57	(0.40–0.88)	0.003[a]
	Asthma		51 (34.9)	68 (46.6)	27 (18.5)	0.62	(0.39–0.99)	0.04	170 (58.2)	122 (42.8)	0.72	(0.54–0.98)	0.04
	SLE		15 (23.1)	43 (66.2)	7 (10.7)	1.11	(0.57–2.15)	0.75	73 (56.2)	57 (43.8)	0.79	(0.53–1.17)	0.24
FCRL3_4	Controls	G A	119 (59.5)	73 (36.5)	8 (4.0)				311 (77.8)	89 (22.2)			
(rs11264799)	JRA		49 (56.3)	35 (40.2)	3 (3.5)	1.14	(0.69–1.90)	0.61	133 (76.4)	41 (23.6)	1.08	(0.71–1.64)	0.73
	Asthma		92 (62.6)	47 (32.0)	8 (5.4)	0.88	(0.57–1.36)	0.56	231 (74.6)	63 (21.4)	0.95	(0.66–1.37)	0.80
	SLE		40 (62.5)	21 (32.8)	3 (4.7)	0.88	(0.49–1.57)	0.67	101 (78.9)	27 (21.1)	0.93	(0.58–1.52)	0.78
FCRL3_5	Controls	G C	53 (26.5)	99 (49.5)	48 (24.0)				205 (51.3)	195 (48.7)			
(rs945635)	JRA		39 (44.8)	36 (41.4)	12 (13.8)	0.44	(0.26–0.76)	0.002[a]	114 (65.5)	60 (34.5)	0.55	(0.38–0.80)	0.002[a]
	Asthma		51 (35.4)	67 (46.5)	26 (18.1)	0.66	(0.41–1.05)	0.08	169 (58.7)	119 (41.3)	0.74	(0.55–1.00)	0.05
	SLE		14 (21.5)	42 (64.6)	9 (13.9)	1.31	(0.67–2.57)	0.42	70 (53.8)	60 (46.2)	0.90	(0.61–1.34)	0.61
FCRL3_6	Controls	G A	50 (25.0)	103 (51.5)	47 (23.5)	0.41	(0.24–0.70)	0.0008[a]	203 (50.8)	197 (49.2)			
(rs3761959)	JRA		39 (44.8)	37 (42.5)	11 (12.7)	0.59	(0.37–0.93)	0.02	115 (66.1)	59 (33.9)	0.53	(0.36–0.76)	0.0007[a]
	Asthma		53 (36.3)	68 (46.6)	25 (17.1)	1.02	(0.53–1.95)	0.95	174 (59.6)	118 (40.4)	0.70	(0.52–0.95)	0.02
	SLE		16 (24.6)	42 (64.6)	7 (10.8)				74 (56.9)	56 (43.1)	0.78	(0.52–1.16)	0.22

OR: odds ratio; CI: confidence interval; *p*: p value.
[a] Statistical significants after Bonferroni correction test.

Brazilian (36.8%) populations ($p < 1 \times 10^{-4}$) (Kochi et al., 2005; Teles et al., 2011), but similar to those reported for Caucasian populations (Martínez, 2007; Hu et al., 2006) (44.8–48%). The *FCRL3_5C* and *FCRL3_6C* frequencies reported here were also different than those reported for other populations, including Chinese and Dutch (Thabet et al., 2007; Li et al., 2008).

5. Discussion

The complete etiology of immune-mediated diseases has not been clarified. One of the most important loci for susceptibility to immune diseases is at the 1q21–q23 chromosome, which harbors the *FCRL3* gene. Several studies have suggested that the *FCRL3* exhibited a complex pattern of association with immune diseases, because it appeared to be either a risk (RA and SLE), protective (AITD, AAD, and MS) or modifier factor. In particular, in a Taiwanese population the *FCRL3_3C* allele, was associated with a protective effect against the development of specific phenotypes, like SLE leucopenia, but it was also related with RA disease severity (Chen et al., 2011).

In this case–control study, which included patients with SLE, JRA, and asthma, we found that *FCRL3_3*C, *FCRL3_5C*, and *FCRL3_6A*, but not *FCRL3_4G* alleles, were significantly associated with protection to JRA and asthma in males, although this last did not remain after Bonferroni correction. It is known that *FCRL3_3*C is a functional variant that promotes the *FCRL3* mRNA transcription (Kochi et al., 2005). This functional variant was in LD with the *FCRL3_5C* and *FCRL3_6A* alleles; thus, as expected, the haplotype that carried these three alleles (CCA) was also significantly associated with protection to JRA and asthma in males.

These data suggested that *FCRL3* SNPs conferred protection against both diseases in a gender-dependent manner (Table 1). Gender-dependent associations are frequently found in immune pathologies. In a previous study, we documented an association between *TNFα* SNPs and JRA and asthma in females (Jiménez-Morales et al., 2009). This phenomenon was also reported for several other immune entities, including MS, RA, asthma (*IL4*, *IL13*, and *COX-2* SNPs), and inflammatory bowel disease (HLA SNPs) (Yamada et al., 2001; Fisher et al., 2002; Szczeklik et al., 2004; Akkad et al., 2007).

Some studies have suggested that a common pathogenic mechanism may exist between immune diseases; for example, the presence of autoantibodies is characteristic of autoimmune diseases, but these have also been identified in patients with non-allergic asthma (Hahm et al., 2002; Yim et al., 2006; Kwon et al., 2009).

In this study, we found no association between *FCRL3* and childhood-onset SLE, as has been reported to European-derived populations and some Asian-descendent groups. (Matesanz et al., 2008; Mao et al., 2010; Choi et al., 2006; You et al., 2008)

Controversial findings in association studies involving the same allele in different populations might be explained by the following: (1) a dual function of the protein since FCRL3 contains both immunoreceptor tyrosine-based activation and inhibition motifs; (2) the susceptibility allele may lie within a LD block that could be different among populations; (3) interactions between this allele and other genetic or environmental factors, as in Canadian and Spanish populations, where it was shown that interactions between *FCRL3_3* and (*PTPN22*), -94ATTG/- (*NFKappa1*), or *HLA-DRB1*0103* increased the risk for Graveïs disease, RA, or inflammatory bowel disease, respectively (Newman et al., 2006; Martínez et al., 2006, 2007); and (4) variations with an ethnic-specific effect (Kochi et al., 2010), in fact, our population exhibited the highest frequency of *FCRL3_3C*.

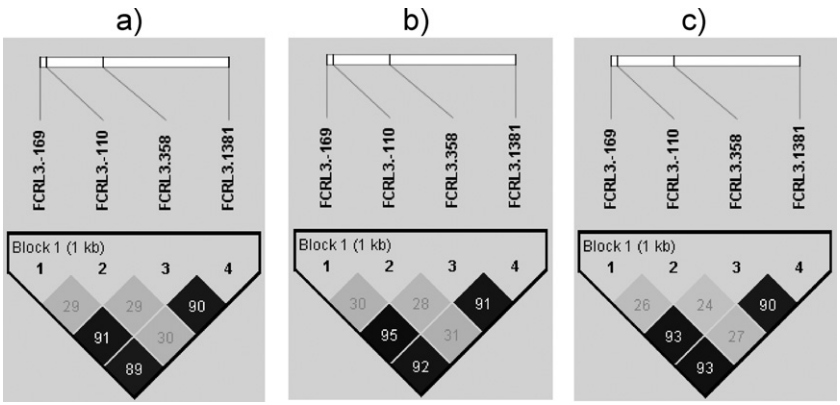

Fig. 1. Location and pair-wise linkage disequilibrium values of four *FCRL3* SNPs in Mexican pediatric patients. Values of the pair-wise (r^2) are shown to JRA (a), asthma (b) and SLE (c).

Table 2
FCRL3 haplotypes structure and frequencies in male groups of patients and controls.

Pathology	Haplotype FCRL3_3, 4, 5, 6	Frequency		OR	95% CI	*p*
		Cases	Control ($n = 200$)			
JRA	TGGG	0.62	0.48	1.78	(1.21–2.60)	0.005[a]
($n = 87$)	CACA	0.21	0.20	1.06	(0.66–1.68)	1.00
	CGCA	0.12	0.28	0.35	(0.20–0.60)	0.00005[a]
	TAGG	0.02	0.02	0.99	(0.20–4.32)	1.00
Asthma	TGGG	0.58	0.48	1.48	(1.08–2.03)	0.01[a]
($n = 147$)	CACA	0.21	0.20	1.07	(0.73–1.58)	1.00
	CGCA	0.19	0.28	0.61	(0.41–0.89)	0.007[a]
SLEp	TGGG	0.53	0.48	1.21	(0.80–1.84)	0.81
($n = 65$)	CACA	0.19	0.20	0.95	(0.56–1.61)	1.00
	CGCA	0.23	0.28	0.78	(0.48–1.27)	0.86
	TAGG	0.01	0.02	0.77	(0.11–3.95)	1.00

OR: odds ratio; CI: confidence interval.
[a] Statistical significance after 100,000 permutation.

Other genes and cohorts should be genotyped in the future to investigate differences in the effects of *FCRL3* variants on immune diseases among different populations.

Conflict of interest

The authors declare no conflict of interest.

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References

Akkad, D.A., Arning, L., Ibrahim, S.M., Epplen, J.T., 2007. Sex specifically associated promoter polymorphism in multiple sclerosis affects interleukin 4 expression levels. Genes Immunology 8, 703–706.

Barrett, J.C., Fry, B., Maller, J., Daly, M.J., 2005. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21, 263–265.

Becker, K.G., Simon, R.M., Bailey-Wilson, J.E., Freidlin, B., Biddinson, W.E., McFarland, H.F., et al., 1998. Clustering of non-major histocompatibility complex susceptibility candidate loci in human autoimmune diseases. Proceedings of the National Academy of Sciences of the United States of America 95, 9979–9984.

Bonilla, C., Parra, E.J., Pfaff, C.L., Dios, S., Marshall, J.A., Hamman, R.F., et al., 2004. Admixture in the Hispanics of the San Luis Valley, Colorado, and its implications for complex trait gene mapping. Annals of Human Genetics 68, 139–153.

Chen, J.Y., Wang, C.M., Wu, Y.J., Kuo, S.N., Shiu, C.F., Chang, S.W., et al., 2011. Disease phenotype and gender association of FCRL3 single-nucleotide polymorphism −169T/C in Taiwanese patients with systemic lupus erythematosus and rheumatoid arthritis. Journal of Rheumatology 38, 264–270.

Choi, C.B., Kang, C.P., Seong, S.S., Bae, S.C., The, Kang C., 2006. −169C/T polymorphism in FCRL3 is not associated with susceptibility to rheumatoid arthritis or systemic lupus erythematosus in a case–control study of Koreans. Arthritis and Rheumatism 54, 3838–3841.

Choudhry, S., Coyle, N.E., Tang, H., Salari, K., Lind, D., Clark, S.L., et al., 2006. Population stratification confounds genetic association studies among Latinos. Human Genetics 118, 652–664.

Davis, R.S., Wang, Y.H., Kubagawa, H., Cooper, M.D., 2001. Identification of a family of Fc receptor homologs with preferential B cell expression. Proceedings of the National Academy of Sciences of the United States of America 98, 9772–9777.

Ehrhardt, G.R., Leu, C.M., Zhang, S., Aksu, G., Jackson, T., Haga, C., et al., 2007. Fc receptor-like proteins (FCRL): immunomodulators of B cell function. Advances in Experimental Medicine and Biology 596, 155–162.

Ehrhardt, G.R., Davis, R.S., Hsu, J.T., Leu, C.M., Ehrhardt, A., Cooper, M.D., 2003. The inhibitory potential of Fc receptor homolog 4 on memory B cells. Proceedings of the National Academy of Sciences of the United States of America 100, 13489–13494.

Fisher, S.A., Hampe, J., Macpherson, A.J., Forbes, A., Lennard-Jones, J.E., Schreiber, S., et al., 2002. Sex stratification of an inflammatory bowel disease genome search shows male-specific linkage to the HLA region of chromosome 6. European Journal of Human Genetics 10, 259–265.

Hahm, D.H., Lee, Y.E., Yim, E.J., Park, H.S., Yim, H., Kang, Y., et al., 2002. Identification of cytokeratin 18 as a bronchial epithelial autoantigen associated with nonallergic asthma. American Journal of Respiratory and Critical Care Medicine 165, 1536–1539.

Hoggart, C.J., Parra, E.J., Shriver, M.D., Bonilla, C., Kittles, R.A., Clayton, D.G., et al., 2003. Control of confounding of genetic association in stratified populations. American Journal of Human Genetics 72, 1492–1504.

Hu, X., Chang, M., Saiki, R.K., Cargill, M.A., Begovich, A.B., Ardlie, K.G., et al., 2006. The functional −169TC single-nucleotide polymorphism in FCRL3 is not associated with rheumatoid arthritis in white North Americans. Arthritis and Rheumatism 54, 1022–1025.

Jiménez-Morales, S., Velázquez-Cruz, R., Ramírez-Bello, J., Bonilla-Gonzáles, E., Romero-Hidalgo, S., Escamilla-Guerrero, G., et al., 2009. Tumor necrosis factor-alpha is a common genetic risk factor for asthma, juvenile rheumatoid arthritis, and systemic lupus erythematosus in a Mexican pediatric population. Human Immunology 70, 251–256.

Kochi, Y., Yamada, R., Suzuki, A., Harley, J.B., Shirasawa, S., Sawada, T., et al., 2005. A functional variant in FCRL3, encoding Fc receptor-like 3, is associated with rheumatoid arthritis and several autoimmunities. Nature Genetics 37, 478–485.

Kochi, Y., Myouzen, K., Yamada, R., Suzuki, A., Kurosaki, T., Nakamura, Y., et al., 2009. FCRL3, an autoimmune susceptibility gene, has inhibitory potential on B-cell receptor-mediated signaling. Journal of Immunology 183, 5502–5510.

Kochi, Y., Suzuki, A., Yamada, R., Yamamoto, K., 2010. Ethnogenetic heterogeneity of rheumatoid arthritis-implications for pathogenesis. Nature Reviews Rheumatology 6, 290–295.

Kwon, B., Lee, H.A., Choi, G.S., Ye, Y.M., Nahm, D.H., Increased, Park H.S., 2009. IgG antibody-induced cytotoxicity against airway epithelial cells in patients with nonallergic asthma. Journal of Clinical Immunology 29, 517–523.

Lee, Y.H., Woo, J.H., Choi, S.J., Ji, J.D., Song, G.G., 2010. Fc receptor-like 3–169C/T polymorphism and RA susceptibility: a meta-analysis. Rheumatology International 30, 947–953.

Lee, S.H., Park, J.S., Park, C.S., 2011. The search for genetic variants and epigenetics related to asthma. Allergy, Asthma and Immunology Research 3, 236–244.

Leu, C.M., Davis, R.S., Gartland, L.A., Fine, W.D., Cooper, M.D., 2005. FcRH1: an activation coreceptor on human B cells. Blood 105, 1121–1126.

Li, K., Zhao, M., Hou, S., Du, L., Kijlstra, A., Yang, P., 2008. Association between polymorphisms of FCRL3, a non-HLA gene, and Behçet's disease in a Chinese population with ophthalmic manifestations. Molecular Vision 14, 2136–2142.

Mao, C., Pan, H., Chen, Q., Wang, X., Ye, D., Qiu, L., 2010. Association between Fc receptor-like 3 C169T polymorphism and risk of systemic lupus erythematosus: a meta-analysis. Molecular Biology Reports 37, 191–196.

Martínez, A., Mas, A., de las Heras, V., Bartolomé, M., Arroyo, R., Fernández-Arquero, M., et al., 2007. FCRL3 and multiple sclerosis pathogenesis: role in autoimmunity? Journal of Neuroimmunology 189, 132–136.

Martínez, A., Sánchez, E., Valvidia, A., Orozco, G., López-Nevot, M.A., Pascual-Salcedo, D., et al., 2006. Epistatic interaction between FCRL3 and NFκB1 genes in Spanish patients with rheumatoid arthritis. Annals of the Rheumatic Diseases 65, 1188–1191.

Martínez, A., Nuñez, C., Martín, M.C., Mendoza, J.L., Taxonera, C., Díaz-Rubio, M., et al., 2007. Epistatic interaction between FCRL3 and MHC in Spanish patients with IDB. Tissue Antigens 69, 313–317.

Matesanz, F., Fernández, O., Milne, R.L., Fedetz, M., Leyva, L., Guerrero, M., et al., 2008. The high producer variant of the Fc-receptor like-3 (FCRL3) gene is involved in protection against multiple sclerosis. Journal of Neuroimmunology 195, 146–150.

McKeigue, P.M., Carpenter, J.R., Parra, E.J., Shriver, M.D., 2000. Estimation of admixture and detection of linkage in admixture populations by a Bayesian approach: application to African-American populations. Annals of Human Genetics 64, 171–186.

Moser, K.L., Kelly, J.A., Lessard, C.J., Harley, J.B., 2009. Recent insights into the genetic basis of systemic lupus erythematosus. Genes and Immunity 10, 373–379.

Newman, W.G., Zhang, Q., Liu, X., Walker, E., Ternan, H., Owen, J., et al., 2006. Rheumatoid arthritis association with the FCRL3 −169C polymorphism is restricted to PTPN22 1858T-homozygous individuals in a Canadian population. Arthritis and Rheumatism 54, 3820–3827.

Owen, C.J., Kelly, H., Eden, J.A., Merriman, M.E., Pearce, S.H., Merriman, T.R., 2007. Analysis of the Fc receptor-like-3 (FCRL3) locus in Caucasians with autoimmune disorders suggests a complex pattern of disease association. Journal of Clinical Endocrinology and Metabolism 92, 1106–1111.

Phelan, J.D., Thompson, S.D., Glass, D.N., 2006. Susceptibility to JRA/JIA: complementing general autoimmune and arthritis traits. Genes and Immunity 7, 1–10.

Szczeklik, W., Sanak, M., Szczeklik, A., 2004. Functional effects and gender association of COX-2 gene polymorphism G-765C in bronchial asthma. Journal of Allergy and Clinical Immunology 114, 248–253.

Teles, J.S., Bianco, B., Vilarino, F.L., André, G.M., Christofilini, D.M., Barbosa, C.P., 2011. Association of FCRL3 C-169 T promoter single-nucleotide polymorphism with idiopathic infertility and infertility-related endometriosis. Journal of Reproductive Immunology 89, 212–215.

Thabet, M.M., Wesoly, J., Slagboom, P.E., Toes, R.E., Huizinga, T.W., 2007. FCRL3 promoter 169CC homozygosity is associated with susceptibility to rheumatoid arthritis in Dutch Caucasians. Annals of the Rheumatic Diseases 66, 803–806.

Welcome Trust Case Control Consortium, Australo-Anglo_American Spondylitis Consortium (TASC), Burton, P.R., Clayton, D.G., Cardon, L.R., Craddock, N., Deloukas, P., Duncanson, A., et al., 2007. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nature Genetics 39, 1329–1337.

Yamada, R., Tanaka, T., Unoki, M., Nagai, T., Sawada, T., Ohnishi, Y., et al., 2001. Association between a single-nucleotide polymorphism in the promoter of human interleukin-3 gene and rheumatoid arthritis in Japanese patients, and maximum-likelihood estimation of combinatorial effect that two genetic loci have on susceptibility to the disease. The American Journal of Human Genetics 68, 674–685.

Yim, H., Kim, J.E., Shin, J.Y., Ye, Y.M., Park, H.S., Nahm, D.H., 2006. Antigen-binding characteristics of circulating IgG autoantibodies to cytokeratin 18 protein in patients with nonallergic asthma. Journal of Korean Medical Science 21, 652–655.

You, Y., Wang, Z., Deng, G., Hao, F., 2008. Lack of association between Fc receptor-like 3 gene polymorphisms and systemic lupus erythematosus in Chinese population. Journal of Dermatological Science 52, 118–122.