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RESEARCH ARTICLE

The Fc receptor-like 3 gene polymorphisms and susceptibility to autoimmune diseases: An updated meta-analysis

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Abstract

Previous studies have identified several single nucleotide polymorphisms (SNPs) of Fc receptor-like 3 (FCRL3), an excellent susceptibility gene, as predisposing factors for human autoimmune diseases (ADs). However, the results remain inconclusive. To assess the effect of four selected SNPs (rs7528684, rs11264799, rs945635 and rs3761959), we conducted a meta-analysis with 34 case-control studies. Summary odd ratios (ORs) and 95% confidence intervals (95% CIs) for the polymorphisms in FCRL3 and ADs risk were evaluated. Furthermore, this meta-analysis was performed by using allele comparisons, as well as stratified analyses by ethnicity and disease phenotypes under different genetic models. Our data showed that the TC, TT + TC genotypes of rs7528684 contributed to a lower risk of ADs, compared with the CC carriers (OR = 0.91, 95% CI = 0.85–0.97; OR = 0.91, 95% CI = 0.85–0.98). In comparison with rs7528684 TC genotype, the TT + CC carriers were significantly associated with higher ADs risk (OR = 1.03, 95% CI = 1.00–1.07). In terms of stratified analyses by ethnicity and disease phenotypes, there were significant associations of rs7528684 polymorphism both with ADs in Asians and Europeans, and with rheumatoid arthritis, Graves' disease, type-1 diabetes, and other ADs under different genetic models. Moreover, significant associations were also found to be correlated with ADs risk for the SNP rs11264799 in mixed subgroup, for rs945635 in Europeans, North Americans and mixed group, and for rs3761959 in North Americans. These findings indicate that the polymorphisms in FCRL3 may play a role in the pathogenesis of ADs.

Keywords

FCRL3, rs7528684, rs11264799, rs945635, rs3761959, single nucleotide polymorphisms

History

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Introduction

Autoimmune diseases (ADs) are complex disorders and comprise more than 50 distinct diseases and syndromes, leading to about 5% of the population affected with immune-mediated tissue destruction [1]. However, the pathogenesis of ADs still leaves open the potential interaction between the environment and the epigenetic modifications of gene expression.

Studies have clearly identified Fc receptor genes as heritable susceptibility factors for AD [2]. Moreover, a recent review also elaborated in detail the binding of anti-idiotype to both the Fcγ receptor on B lymphocytes and the B cell receptor could lead to the down-regulation of antibody secretion [3]. Fc receptor-like genes (FCRLs), also known as Fc receptor homologys [4], immunoglobulin superfamily receptor translocation associated genes [5] or Src homology-2 domain containing phosphatase anchor protein [6], are located within the classical Fc receptor genes in human chromosome region 1q21-23 [4], which is one of the most important genetic regions implicated in susceptibility to multiple ADs [7,8].

With similarity in structure and sequence to the Fcγ receptor genes (Fc receptor genes superfamily members), FCRLs consist of at least eight genes (FCRL1, FCRL2, FCRL3, FCRL4, FCRL5, FCRL6, FCRLA and FCRLB) [9,10]. Studies subsequently indicated that the FCRL1-5 genes encode proteins, which share similar extracellular Ig-like domains and cytoplasmic regions with consensus immunoreceptor tyrosine-based activation motif (ITAM) and/or immunoreceptor tyrosine-based inhibition motif (ITIM)-like motifs [11], suggesting that the FCRL gene products play important roles in the pathogenesis of ADs.

Being the focus of intense interest, FCRL3 has been confirmed to affect B cell receptor signaling and result in the incomplete induction of anergy to autoreactive B cells [12]. It is also characterized by the simultaneous presence of both inhibitory and activating cytoplasmic sequences, implying further functional complexity. Located at position 169 within the promoter of the FCRL3, the single nucleotide polymorphism (SNP) of rs7528684 has been demonstrated to affect the binding affinity of the nuclear factor-kappa-B, the level of autoantibody production and the expression of FCRL3 gene *in vitro*, as well as *in vivo* [13,14].

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Recently, another three SNPs within the FCLR3 gene (markers rs11264799, rs945635 and rs3761959) have also been described as candidate loci for the susceptibility to ADs. Simmonds et al. [15] found significant associations between rs7528684, rs945635 and rs3761959 polymorphisms and Graves' disease (GD). The association with GD has been replicated in another study [16].

Moreover, the associations of these four SNPs with rheumatoid arthritis (RA) [13,17–24], systemic lupus erythematosus (SLE) [13], autoimmune Addision's disease [25], Hashimoto's disease [13], multiple sclerosis [26,27], Behçet's disease [28], Guillain–Barré syndrome [29], and GD [30] have also been confirmed in different populations. However, results from other studies remain conflicting. Owen et al. [25] failed to find any association of these four SNPs with GD. Negative genetic associations with RA [25,31–36], SLE [14,20,24,35,37–39], type-1 diabetes (T1D) [25,40,41], juvenile idiopathic arthritis [20], Vogt–Koyanagi–Harada disease [42], alopecia areata [43], autoimmune hepatitis [44], autoimmune pancreatitis [45] and primary sclerosing cholangitis [20] were also reported. Therefore, the definite roles of these four polymorphisms of FCRL3 in ADs need to be further clarified.

Considering a single study might be with inadequate statistical power, racial and ethnic differences, and publication bias, we performed this meta-analysis on all published case-control studies to assess whether combined evidence shows associations between the four selected polymorphisms in FCRL3 gene and ADs, and to quantify heterogeneity between the individual studies as well as to investigate the existence of potential publication bias.

Materials and methods

Publication search and inclusion criteria

We conducted a comprehensive search for the studies on the association of the rs7528684, rs11264799, rs945635 and rs3761959 with ADs published before May 2013 in PubMed database. With restriction placed on English language, the following terms were used as searching keywords: ''Fc receptor-like 3'' or ''FCRL3'' and ''polymorphism'' and ''autoimmune disease'' or ''rheumatoid arthritis'' or ''systemic lupus erythematosus'' or ''Addision's disease'' or ''Hashimoto's disease'' or ''Guillain–Barré syndrome'' or ''juvenile idiopathic arthritis'' or ''alopecia areata'' or ''autoimmune hepatitis'' or ''autoimmune pancreatitis'' or ''primary sclerosing cholangitis'' or ''psoriasis'' or ''primary Sjogren's syndrome'' or ''Behcet's disease'' or ''Vogt–Koyanagi–Harada disease'' or ''systemic sclerosis'' or ''multiple sclerosis'' or ''primary antiphospholipid syndrome'' or ''type-1 diabetes'' or ''Grave's disease'' or ''ankylosing spondylitis'' or ''polymyositis'' or ''dermatomyositis'' or ''myasthenia gravis''. In order to identify the relevant publications, the references in the selected studies were scanned. Furthermore, we also carefully noted the authors' names and the different research centers involved to avoid duplication of data.

Studies were included if meeting all the following criteria: (1) case-control studies; (2) full papers in association with ADs, not any meeting or conference abstracts; (3) available genotype frequencies; (4) publications of sufficient information to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). The diagnoses of RA and SLE satisfied the American College of Rheumatology criteria, and other ADs were in accordance with their respective diagnostic criteria. We excluded family-based association studies because of linkage consideration.

Data extraction

Data of this meta-analysis were reviewed and extracted by Yang and Su independently. If the data they obtained were different, the third author (Zhou) would check the data and a consensus would be achieved through discussion. The following information was recorded for each study: first author, year of publication, disease phenotypes, region, genotyping methods, the number of alleles and genotypes, the gender distribution of cases, and Hardy–Weinberg equilibrium in control subjects (Table 1).

Statistical analysis

Hardy–Weinberg equilibrium was examined in controls by using the Chi-square test (significance was set at $p<0.05$). ORs and 95% CIs were calculated to assess the associations between the four SNPs and the risk of ADs. In addition to the comparisons among all subjects, we also performed stratified analyses by ethnicity and disease phenotypes (if one disease type included less than three individual studies, it was combined into the ''other diseases'' group). We evaluated the associations with ADs by allele comparisons, as well as by comparisons of different genetic models.

Heterogeneity across studies was estimated by Cochran's (Q) and Higgins's (I^2) tests [46]. Heterogeneity was considered statistically significant when $p<0.10$. If there was no obvious heterogeneity, the fixed-effects model (the Mantel–Haenszel method) was used to assess the summary OR [47]; otherwise, the random-effects model (the DerSimonian and Laird method) was used [48].

To further explore sources of heterogeneity, we also carried out logistic meta-regression analyses. The following study characteristics were examined: publication year, region, genotyping methods, the number of alleles and genotypes, the number of female and male cases, and the frequencies of T allele of rs7528684 and rs11264799, C allele of rs945635, and A allele of rs3761959 in controls. Publication bias was determined by means of Begg's funnel plot and Egger's test [49]. Sensitivity analysis was investigated to assess the stability of the results in this study. The statistical analyses were performed by STATA 12.0 software (Stata Corp., College Station, TX).

Results

Characteristics of studies

There were 133 papers relevant to the searching words, and additional 1 study was identified by reviewing the references. Through the step of screening the abstracts, 72 articles were removed due to duplicated data, and 18 were excluded for not exploring the associations of these SNPs with ADs, leaving 44 articles to be further assessed for eligibility. By detailed assessment of the 44 full-texts, 10 studies were excluded

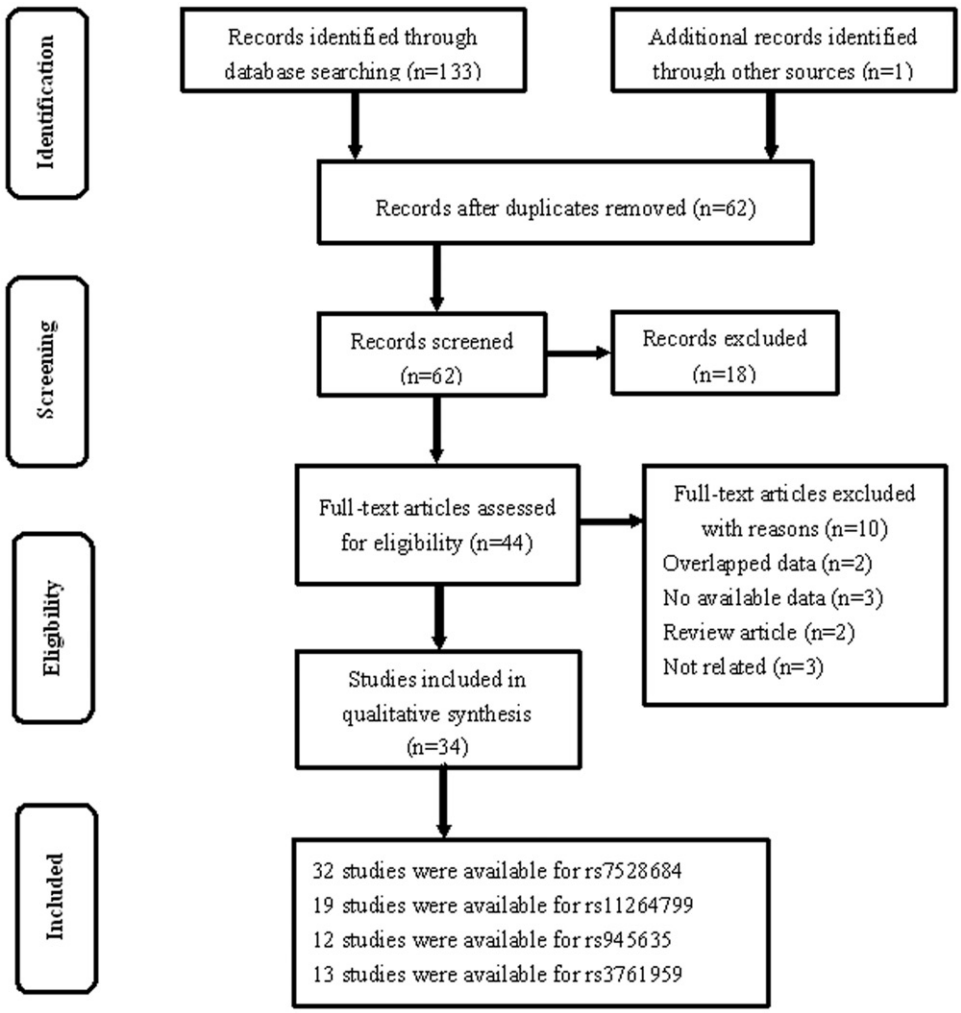

Figure 1. Flowchart for identification of studies.

(2 studies were with duplicated data [50,51]; 3 were due to no available data [52–54]; 2 were reviews [55,56]; and 3 were not related to the selected SNPs [57–59]). Overall, 34 case-control studies met the inclusion criteria for this study (Figure 1). Thirty-two studies with 30 691 cases and 30 271 controls were available for rs7528684; 19 studies with 9053 cases and 7970 controls were available for rs11264799; 12 studies with 6224 cases and 4793 controls were available for rs945635; and 13 studies with 9343 cases and 7498 controls were available for rs3761959. We treated the studies independently which contained data on different disease phenotypes or investigated several of these four SNPs (rs7528684, rs11264799, rs945635, and rs3761959) simultaneously. The ethnicities encompassed in qualified studies were stratified into Asian, European, North American and mixed subgroups.

Four studies were not in Hardy–Weinberg equilibrium for rs7528684 [13,14,28,37], and 2 studies for rs11264799 [28,42]. Characteristics of the studies are summarized in Table 1. Several genotyping methods were used, including Invader assay, MassArray, TaqMan probe, direct sequencing, pyrosequencing, polymerase chain reaction-restriction fragment length polymorphism, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, polymerase chain reaction-oligonucleotide ligation assay, polymerase chain reaction-sequence specific oligonucleotide probes, whole genome amplified, fluorescence resonance energy transfer assays and 500 K/550 K array.

Quantitative synthesis

A summary of meta-analysis findings regarding the associations between the FCRL3 polymorphisms and the ADs are described in Tables 2–4, and the positive associations of allele comparisons in subgroups are shown in Figures 2 and 3. Significantly decreased ADs risk was found to be associated with TC and TT + TC genotypes of rs7528684 compared with CC genotype, and an increased risk of ADs was found to be associated with TT + CC genotype compared with the TC carriers in the overall population (Table 2).

Stratified analysis by ethnicity indicated that there were significant associations between the rs7528684 polymorphism and decreased risk of ADs in Asians (including comparisons of T allele vs. C allele; TT vs. CC; TC vs. CC; and TT + TC vs. CC). Decreased risk of ADs was also observed to be associated with T allele, TT, TC and TT + TC genotypes of rs11264799 in mixed subgroup. Increased ADs risks were associated with the TC + CC genotype of rs7528684 in Asians, TT + CC genotypes of rs7528684 in Europeans and TT + CC genotypes of rs11264799 in mixed subgroup.

Table 1. Characteristics of references included in the meta-analysis.

Reference	Year	Diseases	Region	Genotyping methods	Cases	Controls	Genotype-case			Allele-case		Genotype-control			Allele-control		F[a]	M[b]	HWE
rs7528684							TT	TC	CC	T	C	TT	TC	CC	T	C			
Kochi Y [13]	2005	RA	Japan	Invader/TaqMan	1364	2037	473	655	236	1601	1127	785	995	257	2565	1509			N
Kochi Y [13]	2005	SLE	Japan	Invader/TaqMan	564	2037	205	259	100	669	459	785	995	257	2565	1509			N
Kochi Y [13]	2005	GD	Japan	Invader/TaqMan	351	2037	100	179	72	379	323	785	995	257	2565	1509			N
Kochi Y [13]	2005	HD	Japan	Invader/TaqMan	158	2037	54	74	30	182	134	785	995	257	2565	1509			N
Eyre S [31]	2006	RA	UK	TaqMan/MassArray	1065	2073	324	524	217	1172	958	595	1055	423	2245	1901	690	367	Y
Hu X [32]	2006	RA	America	PCR-OLA/MALDI-TOF	1032	1216	313	517	202	1143	921	366	580	270	1312	1120			Y
Ikari K [17]	2006	RA	Japan	TaqMan	748	934	238	377	133	853	643	333	472	129	1138	730	662	90	Y
Turunen JA [40]	2006	T1D	Finland	TaqMan	725	731	255	358	112	868	582	262	356	113	880	582			Y
Simmonds MJ [15]	2006	GD	UK	PCR-RFLP	983	733	232	508	243	972	994	200	382	151	782	684			Y
Newman WG [18]	2006	RA	Canada	MALDI-TOF	1187	462	359	563	265	1281	1093	163	213	86	539	385	890	297	Y
Schafer N [43]	2006	AA	Belgium/Germany	Direct sequencing	266	281	90	122	54	302	230	79	150	52	308	254	176	90	Y
Martinez A [33]	2006	RA	Spain	TaqMan	669	718	178	351	140	707	631	228	346	144	802	634	559	175	Y
Sanchez E [37]	2006	SLE	Spain		520	540	185	239	96	609	431	177	286	77	640	440			N
Martinez A [26]	2007	MS	Spain	TaqMan	400	508	145	197	58	487	313	157	245	106	559	457	256	144	Y
Thabet MM [19]	2007	RA	Netherlands	MALDI-TOF	931	570	288	428	215	1004	858	177	287	106	641	499	325	650	Y
Owen CJ [25]	2007	AAD	New Zealand/UK	PCR-RFLP	200	1002	82	90	28	254	146	268	512	222	1048	956			Y
Owen CJ [25]	2007	GD	New Zealand/UK	PCR-RFLP	608	1002	172	304	132	648	568	268	512	222	1048	956			Y
Owen CJ [25]	2007	RA	New Zealand/UK	PCR-RFLP	761	1002	207	386	168	800	722	268	512	222	1048	956			Y
Owen CJ [25]	2007	T1D	New Zealand/UK	PCR-RFLP	264	1002	82	117	65	281	247	268	512	222	1048	956			Y
Umemura T [44]	2007	AIH	Japan	TaqMan	87	97	29	45	13	103	71	35	51	11	121	73	73	14	Y
Duchatelet S [60]	2008	T1D	France	TaqMan	830	477	290	375	165	955	705	143	243	91	529	425			Y
Eike MC [20]	2008	RA	Norway	WGA	686	982	199	346	141	744	628	316	503	163	1135	829			Y
Eike MC [20]	2008	JIA	Norway	WGA	512	982	161	246	105	568	456	316	503	163	1135	829			Y
Eike MC [20]	2008	SLE	Norway	WGA	163	982	46	93	24	185	141	316	503	163	1135	829			Y
Eike MC [20]	2008	PSC	Norway/Sweden	WGA	360	982	119	176	65	414	306	316	503	163	1135	829			Y
Matesanz F [27]	2008	MS	Spain	TaqMan	645	776	227	318	100	772	518	226	400	150	852	700	439	206	Y
Li K [28]	2008	BD	China	PCR-RFLP	244	289	54	121	69	229	259	76	127	86	279	299	41	204	N
You Y [38]	2008	SLE	China	PCR-RFLP	240	272	91	110	39	292	188	85	144	43	314	230	235	13	Y
Takata Y [34]	2008	RA	Japan	TaqMan	939	504	170	438	331	778	1100	87	241	176	415	593	751	199	Y
Li K [42]	2009	VKH	China	PCR-RFLP	230	301	67	82	81	216	244	79	135	87	293	309	102	128	Y
Gibson AW [14]	2009	SLE	Japan	Pyrosequencing	1046	1004	175	399	472	749	1343	182	379	443	743	1265			N
Gu LQ [16]	2010	GD	China	MassArray	431	314	132	222	77	486	376	118	142	54	378	250	319	117	Y
Wu H [21]	2010	RA	China	PCR-RFLP	229	252	74	106	49	254	204	98	118	36	314	190	163	66	Y
Chen JY [35]	2011	SLE	Taiwan	MALDI-TOF	573	758	195	293	85	683	463	258	370	130	886	630	529	44	Y
Chen JY [35]	2011	RA	Taiwan	MALDI-TOF	670	758	233	322	115	788	552	258	370	130	886	630	577	93	Y
El-Gabalawy HS [22]	2011	RA	Canada	PCR-SSOP	333	490	154	123	56	431	235	204	222	64	630	350	273	60	Y
Plagnol V [41]	2011	T1D	Britain	500 K/550 K array	8596	10596	2669	4213	1714	9551	7641	3151	5246	2199	11548	9644			Y
Han SW [23]	2012	RA	Korea	FRET assays	377	298	132	180	65	444	310	114	133	51	361	235	295	82	Y
Inoue N [30]	2012	GD	Japan	PCR-RFLP	96	86	22	51	23	95	97	29	47	10	105	67	86	17	Y
Inoue N [30]	2012	HD	Japan	PCR-RFLP	87	86	31	42	14	104	70	29	47	10	105	67	79	15	Y
Sang D [29]	2012	GBS	China	MALDI-TOF	106	242	36	48	22	120	92	102	116	24	320	164			Y
Ramirez-Bello J [24]	2013	RA	Mexico	TaqMan	87	200	38	35	14	111	63	50	101	49	201	199	115	87	Y
Ramirez-Bello J [24]	2013	SLE	Mexico	TaqMan	65	200	15	43	7	73	57	50	101	49	201	199	312	65	Y
Piotrowski P [39]	2013	SLE	Poland	PCR-RFLP	263	528	65	137	61	267	259	121	269	138	511	545	263	0	Y
rs11264799							TT	TC	CC	T	C	TT	TC	CC	T	C			
Eyre S [31]	2006	RA	UK	TaqMan/MassArray	761	484	61	296	404	418	1104	36	190	258	262	706	690	367	Y
Simmonds MJ [15]	2006	GD	UK	PCR-RFLP	898	611	70	393	435	533	1263	41	242	328	324	898			Y

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Martinez A [33]	2006	RA	Spain	TaqMan	626	704	49	278	299	376	876	69	285	350	423	985	559	175	Y
Sanchez E [37]	2006	SLE	Spain		495	459	43	188	264	274	716	45	178	236	268	650			Y
Umemura T [45]	2006	AIP	Japan	TaqMan	59	97	8	18	33	34	84	2	35	60	39	155			Y
Martinez A [26]	2007	MS	Spain	TaqMan	399	507	34	151	214	219	579	49	215	243	313	701			Y
Thabet MM [19]	2007	RA	Netherlands	MALDI-TOF	941	581	72	373	496	517	1365	39	217	325	295	867	325	650	Y
Owen CJ [25]	2007	AAD	New Zealand/UK	PCR-RFLP	200	1030	10	66	124	86	314	92	417	521	601	1459			Y
Owen CJ [25]	2007	GD	New Zealand/UK	PCR-RFLP	614	1030	54	252	308	360	868	92	417	521	601	1459			Y
Owen CJ [25]	2007	RA	New Zealand/UK	PCR-RFLP	769	1030	51	277	441	379	1159	92	417	521	601	1459			Y
Owen CJ [25]	2007	T1D	New Zealand/UK	PCR-RFLP	269	1030	21	100	148	142	396	92	417	521	601	1459			Y
Umemura T [44]	2007	AIH	Japan	TaqMan	87	97	4	34	49	42	132	2	35	60	39	155	73	14	Y
Matesanz F [27]	2008	MS	Spain	TaqMan	642	770	50	251	341	351	933	74	294	402	442	1098	439	206	Y
Li K [28]	2008	BD	China	PCR-RFLP	241	288	17	85	139	119	363	46	95	147	187	389	41	204	N
You Y [38]	2008	SLE	China	PCR-RFLP	202	247	13	66	123	92	312	20	91	136	131	363	235	13	Y
Li K [42]	2009	VKH	China	PCR-RFLP	228	299	16	81	131	113	343	46	98	155	190	408	102	128	N
Gu LQ [16]	2010	GD	China	MassArray	431	314				216	646				149	481	319	117	
Wu H [21]	2010	RA	China	PCR-RFLP	229	252	16	95	118	127	331	9	85	158	103	401	163	66	Y
El-Gabalawy HS [22]	2011	RA	Canada	PCR-SSOP	332	490	28	101	203	157	507	23	182	285	228	752	273	60	Y
Han SW [23]	2012	RA	Korea	FRET assays	377	298	22	130	225	174	580	15	105	178	135	461	295	82	Y
Sang D [29]	2012	GBS	China	MALDI-TOF	102	242	10	36	56	56	148	12	100	130	124	360			Y
Ramirez-Bello J [24]	2013	RA	Mexico	TaqMan	87	200	3	35	49	41	133	8	73	119	89	311	115	87	Y
Ramirez-Bello J [24]	2013	SLE	Mexico	TaqMan	64	200	3	21	40	27	101	8	73	119	89	311	312	65	Y
rs945635							CC	CG	GG	C	G	CC	CG	GG	C	G			
Eyre S [31]	2006	RA	UK	TaqMan/MassArray	735	441	164	362	209	690	780	118	200	123	436	446	690	367	Y
Simmonds MJ [15]	2006	GD	UK	PCR-RFLP	1011	808	244	524	243	1012	1010	225	427	156	877	739			Y
Thabet MM [19]	2007	RA	Netherlands	MALDI-TOF	939	568	290	425	224	1005	873	173	286	109	632	504	325	650	Y
Owen CJ [25]	2007	AAD	New Zealand/UK	PCR-RFLP	200	1030	29	91	80	149	251	223	532	275	978	1082			Y
Owen CJ [25]	2007	GD	New Zealand/UK	PCR-RFLP	616	1030	149	300	167	598	634	223	532	275	978	1082			Y
Owen CJ [25]	2007	RA	New Zealand/UK	PCR-RFLP	764	1030	161	383	220	705	823	223	532	275	978	1082			Y
Owen CJ [25]	2007	T1D	New Zealand/UK	PCR-RFLP	269	1030	55	130	84	240	298	223	532	275	978	1082			Y
Umemura T [44]	2007	AIH	Japan	TaqMan	87	97	13	45	29	71	103	11	51	35	73	121	73	14	Y
Li K [28]	2008	BD	China	PCR-RFLP	244	289	81	122	41	284	204	97	134	58	328	250	41	204	Y
You Y [38]	2008	SLE	China	PCR-RFLP	211	253	48	109	54	205	217	48	128	77	224	282	235	13	Y
Li K [42]	2009	VKH	China	PCR-RFLP	230	299	75	104	51	254	206	100	141	58	341	257	102	128	Y
Gu LQ [16]	2010	GD	China	MassArray	431	314				475	363				372	258	319	117	
Wu H [21]	2010	RA	China	PCR-RFLP	229	252	48	109	72	205	253	36	121	95	193	311	163	66	Y
Sang D [29]	2012	GBS	China	MALDI-TOF	106	242	18	53	35	89	123	40	129	73	209	275			Y
Ramirez-Bello J [24]	2013	RA	Mexico	TaqMan	87	200	12	36	39	60	114	48	99	53	195	205	115	87	Y
Ramirez-Bello J [24]	2013	SLE	Mexico	TaqMan	65	200	9	42	14	60	70	48	99	53	195	205	312	65	Y
rs3761959							AA	AG	GG	A	G	AA	AG	GG	A	G			
Eyre S [31]	2006	RA	UK	TaqMan/MassArray	751	471	172	370	209	714	788	127	220	124	474	468	690	367	Y
Simmonds MJ [15]	2006	GD	UK	PCR-RFLP	1003	788	242	519	242	1003	1003	155	408	225	718	858			Y
Owen CJ [25]	2007	AAD	New Zealand/UK	PCR-RFLP	200	1014	29	91	80	149	251	236	513	265	985	1043			Y
Owen CJ [25]	2007	GD	New Zealand/UK	PCR-RFLP	608	1014	150	294	164	594	622	236	513	265	985	1043			Y
Owen CJ [25]	2007	RA	New Zealand/UK	PCR-RFLP	762	1014	155	386	221	696	828	236	513	265	985	1043			Y
Owen CJ [25]	2007	T1D	New Zealand/UK	PCR-RFLP	270	1014	58	135	77	251	289	236	513	265	985	1043			Y
Umemura T [44]	2007	AIH	Japan	TaqMan	87	97	13	45	29	71	103	11	51	35	73	121	73	14	Y
Li K [28]	2008	BD	China	PCR-RFLP	244	288	40	122	82	202	286	54	140	94	248	328	41	204	Y
You Y [38]	2008	SLE	China	PCR-RFLP	216	224	42	110	64	194	238	56	108	60	220	228	235	13	Y
Li K [42]	2009	VKH	China	PCR-RFLP	209	256	135	72	2	342	76	150	91	15	391	121	102	128	Y
Plant D [36]	2009	RA	UK	Iplex chemistry	3700	3056	786	1879	1035	3451	3949	633	1538	885	2804	3308			Y
Gu LQ [16]	2010	GD	China	MassArray	431	314				361	469				258	374	319	117	

(*continued*)

Table 1. Continued

Reference	Year	Diseases	Region	Genotyping methods	Cases	Controls	Genotype-case			Allele-case		Genotype-control			Allele-control		F[a]	M[b]	HWE
Wu H [21]	2010	RA	China	PCR-RFLP	229	252	48	114	67	210	248	38	120	94	196	308	163	66	Y
Han SW [23]	2012	RA	Korea	FRET assays	377	298	66	179	132	311	443	51	133	114	235	361	295	82	Y
Sang D [29]	2012	GBS	China	MALDI-TOF	104	240	19	53	32	91	117	21	114	105	156	324			Y
Ramirez-Bello J [24]	2013	RA	Mexico	TaqMan	87	200	11	37	39	59	115	47	103	50	197	203	115	87	Y
Ramirez-Bello J [24]	2013	SLE	Mexico	TaqMan	65	200	7	42	16	56	74	47	103	50	197	203	312	65	Y

[a]The number of female cases; [b]The number of male cases.

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type-1 diabetes; GD, Grave's disease; JIA, juvenile idiopathic arthritis; BD, Behçet's disease; VKH, Vogt–Koyanagi–Harada disease; HD, Hashimoto's disease; AA, alopecia areata; AAD: autoimmune Addison's disease; AIH, autoimmune hepatitis; AIP, autoimmune pancreatitis; GBS, Guillain–Barré syndrome; MS, multiple sclerosis; PSC, primary sclerosing cholangitis.

PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; PCR-OLA, polymerase chain reaction-oligonucleotide ligation assay; PCR-SSOP, polymerase chain reaction-sequence specific oligonucleotide probes; WGA, whole genome amplified; FRET assays, fluorescence resonance energy transfer.

Table 2. Total and stratified analyses of the rs7528684 and rs11264799 polymorphisms in autoimmune diseases.

	T/C		TT/CC		TC/CC		TT + TC/CC		TC + CC/TT		TT + CC/TC	
	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a
rs7528684												
Total	0.97 (0.93–1.01)	<0.001	0.92 (0.84–1.01)	<0.001	***0.91 (0.85–0.97)***	<0.001	***0.91 (0.85–0.98)***	<0.001	1.01 (0.95–1.07)	<0.001	***1.03 (1.00–1.07)***	0.078
Ethnicities												
Asian	***0.88 (0.82–0.94)***	0.009	***0.75 (0.65–0.87)***	0.002	***0.81 (0.72–0.92)***	0.023	***0.79 (0.69–0.89)***	0.003	***1.13 (1.04–1.23)***	0.110	1.02 (0.96–1.08)	0.491
European	1.00 (0.95–1.05)	0.003	0.98 (0.88–1.10)	0.002	0.94 (0.86–1.03)	0.020	0.95 (0.87–1.05)	0.005	0.97 (0.90–1.04)	0.027	***1.04 (1.00–1.08)***	0.181
North American	1.09 (0.90–1.31)	0.003	1.14 (0.78–1.67)	0.004	1.05 (0.75–1.49)	0.006	1.10 (0.79–1.53)	0.005	0.91 (0.69–1.19)	0.004	0.99 (0.88–1.11)	0.006
Mixed	1.08 (0.94–1.25)	0.003	1.15 (0.88–1.49)	0.007	0.99 (0.88–1.11)	0.398	1.03 (0.88–1.21)	0.110	0.86 (0.69–1.07)	0.004	1.07 (0.97–1.18)	0.323
Diseases												
RA	0.95 (0.89–1.01)	0.001	***0.88 (0.770–0.998)***	0.001	***0.89 (0.81–0.98)***	0.049	***0.89 (0.80–0.98)***	0.007	1.05 (0.96–1.14)	0.007	1.02 (0.97–1.08)	0.291
SLE	0.99 (0.92–1.06)	0.259	0.96 (0.80–1.16)	0.089	0.99 (0.79–1.24)	0.002	0.99 (0.81–1.20)	0.006	1.01 (0.92–1.11)	0.493	1.03 (0.94–1.12)	0.022
GD	***0.83 (0.70–0.98)***	0.003	***0.67 (0.47–0.96)***	0.001	0.83 (0.67–1.04)	0.086	0.77 (0.59–1.00)	0.010	***1.27 (1.02–1.58)***	0.023	0.97 (0.87–1.08)	0.508
T1D	***1.04 (1.00–1.08)***	0.845	***1.08 (1.00–1.16)***	0.929	0.98 (0.88–1.09)	0.298	1.03 (0.97–1.10)	0.632	0.93 (0.86–1.00)	0.340	1.04 (0.99–1.09)	0.093
Others	1.02 (0.90–1.15)	<0.001	0.99 (0.76–1.29)	<0.001	0.89 (0.74–1.09)	0.005	0.93 (0.75–1.15)	<0.001	0.91 (0.78–1.06)	0.006	***1.11 (1.02–1.22)***	0.556
rs11264799												
Total	0.96 (0.89–1.04)	<0.001	0.93 (0.77–1.12)	0.001	0.97 (0.91–1.03)	0.081	0.95 (0.87–1.04)	0.008	1.07 (0.89–1.27)	0.002	1.02 (0.96–1.08)	0.171
Ethnicities												
Asian	1.01 (0.83–1.22)	0.001	1.13 (0.61–2.09)	<0.001	1.01 (0.87–1.17)	0.481	0.99 (0.81–1.20)	0.082	0.89 (0.49–1.61)	<0.001	0.97 (0.84–1.12)	0.501
European	1.01 (0.93–1.09)	0.182	0.96 (0.82–1.13)	0.451	1.05 (0.96–1.14)	0.270	1.03 (0.93–1.14)	0.184	1.06 (0.91–1.24)	0.614	0.95 (0.87–1.04)	0.396
North American	1.02 (0.84–1.23)	0.909	1.49 (0.90–2.45)	0.643	0.86 (0.68–1.09)	0.427	0.93 (0.74–1.17)	0.681	0.63 (0.39–1.03)	0.522	1.20 (0.95–1.52)	0.319
Mixed	***0.84 (0.71–0.99)***	0.030	***0.74 (0.56–0.99)***	0.178	***0.85 (0.75–0.95)***	0.124	***0.81 (0.67–0.98)***	0.048	1.23 (1.00–1.53)	0.382	***1.14 (1.01–1.28)***	0.268
Diseases												
RA	1.03 (0.91–1.16)	0.012	1.08 (0.82–1.42)	0.045	0.99 (0.91–1.09)	0.030	1.02 (0.89–1.19)	0.016	0.94 (0.73–1.20)	0.073	1.01 (0.92–1.10)	0.051
SLE	0.90 (0.77–1.05)	0.781	0.83 (0.57–1.21)	0.844	0.89 (0.72–1.10)	0.794	0.88 (0.72–1.07)	0.782	1.15 (0.80–1.65)	0.869	1.09 (0.89–1.34)	0.796
Others	0.93 (0.82–1.05)	0.001	0.85 (0.62–1.16)	0.001	0.96 (0.88–1.05)	0.190	0.92 (0.80–1.04)	0.028	1.16 (0.86–1.55)	0.001	1.02 (0.93–1.11)	0.287

Boldfaced values indicate a significant difference at the 5% level.

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type-1 diabetes; GD, Grave's disease.

OR, odds ratio; CI, confidence interval.

[a]p Value of Q-test for heterogeneity test. When the p value was less than 0.10, the random-effects model was used to assess the summary OR.

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Table 3. Total and stratified analyses of the rs945635 polymorphism in autoimmune diseases.

	C/G		CC/GG		CG/GG		CC+CG/GG		CG + GG/CC		CC + GG/CG	
	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a
rs945635												
Total	0.93 (0.86–1.01)	0.003	0.87 (0.74–1.04)	0.003	0.89 (0.79–1.00)	0.035	0.88 (0.77–1.01)	0.004	1.06 (0.98–1.16)	0.056	1.06 (0.99–1.14)	0.351
Ethnicities												
Asian	1.05 (0.94–1.17)	0.325	1.21 (0.96–1.52)	0.420	1.08 (0.89–1.30)	0.698	1.11 (0.93–1.34)	0.552	0.89 (0.74–1.07)	0.580	1.00 (0.85–1.17)	0.936
European	***0.88 (0.81–0.96)***	0.671	***0.77 (0.65–0.91)***	0.668	0.84 (0.68–1.05)	0.125	***0.82 (0.70–0.96)***	0.289	1.14 (0.99–1.30)	0.263	1.04 (0.93–1.18)	0.081
North American	0.70 (0.44–1.13)	0.078	***0.47 (0.23–0.96)***	0.226	0.88 (0.28–2.78)	0.009	0.75 (0.26–2.17)	0.012	***1.97 (1.18–3.30)***	0.993	0.91 (0.63–1.33)	0.016
Mixed	0.89 (0.75–1.05)	0.006	0.80 (0.58–1.11)	0.012	***0.81 (0.68–0.98)***	0.138	0.81 (0.64–1.01)	0.024	1.04 (0.90–1.19)	0.082	***1.12 (1.00–1.26)***	0.787
Diseases												
RA	0.92 (0.78–1.09)	0.006	0.86 (0.63–1.18)	0.011	0.87 (0.70–1.09)	0.041	0.86 (0.68–1.10)	0.012	1.05 (0.92–1.20)	0.041	1.06 (0.95–1.19)	0.187
Others	0.93 (0.85–1.02)	0.030	0.88 (0.71–1.10)	0.021	0.90 (0.77–1.05)	0.092	0.90 (0.76–1.06)	0.023	1.07 (0.96–1.20)	0.150	1.06 (0.96–1.16)	0.416

Boldfaced values indicate a significant difference at the 5% level.
RA, rheumatoid arthritis.
OR, odds ratio; CI, confidence interval.
[a]p Value of Q-test for heterogeneity test. When the p value was less than 0.10, the random-effects model was used to assess the summary OR.

Table 4. Total and stratified analyses of the rs3761959 polymorphism in autoimmune diseases.

	A/G		AA/GG		AG/GG		AA + AG/GG		AG + GG/AA		AA + GG/AG	
	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a
rs3761959												
Total	0.99 (0.90–1.09)	<0.001	0.96 (0.78–1.18)	<0.001	0.99 (0.88–1.12)	0.005	0.98 (0.85–1.13)	<0.001	1.04 (0.90–1.20)	<0.001	0.99 (0.93–1.05)	0.804
Ethnicities												
Asian	1.14 (0.99–1.31)	0.040	1.39 (0.91–2.14)	0.004	1.18 (0.97–1.44)	0.280	1.22 (0.95–1.56)	0.062	0.87 (0.67–1.13)	0.062	0.93 (0.81–1.08)	0.994
European	1.04 (0.91–1.19)	0.023	1.08 (0.82–1.42)	0.019	1.06 (0.97–1.17)	0.557	1.07 (0.93–1.24)	0.172	0.97 (0.78–1.20)	0.026	0.98 (0.90–1.06)	0.768
North American	***0.64 (0.44–0.93)***	0.161	***0.36 (0.19–0.65)***	0.490	0.75 (0.28–2.04)	0.022	0.63 (0.26–1.55)	0.033	***2.29 (1.33–3.95)***	0.748	0.96 (0.66–1.40)	0.021
Mixed	0.86 (0.73–1.02)	0.005	0.75 (0.54–1.05)	0.010	0.84 (0.69–1.01)	0.134	0.80 (0.64–1.01)	0.417	1.17 (0.93–1.47)	0.056	1.06 (0.95–1.19)	0.696
Diseases												
RA	0.96 (0.83–1.10)	0.001	0.92 (0.70–1.21)	0.002	0.99 (0.84–1.17)	0.046	0.96 (0.79–1.17)	0.003	1.07 (0.89–1.28)	0.038	0.98 (0.90–1.05)	0.673
Others	1.01 (0.88–1.16)	<0.001	1.02 (0.72–1.44)	<0.001	1.01 (0.83–1.23)	0.012	1.01 (0.81–1.27)	<0.001	1.02 (0.81–1.28)	0.001	1.01 (0.92–1.12)	0.675

Boldfaced values indicate a significant difference at the 5% level.
RA, rheumatoid arthritis.
OR, odds ratio; CI, confidence interval.
[a]p Value of Q-test for heterogeneity test. When the p value was less than 0.10, the random-effects model was used to assess the summary OR.

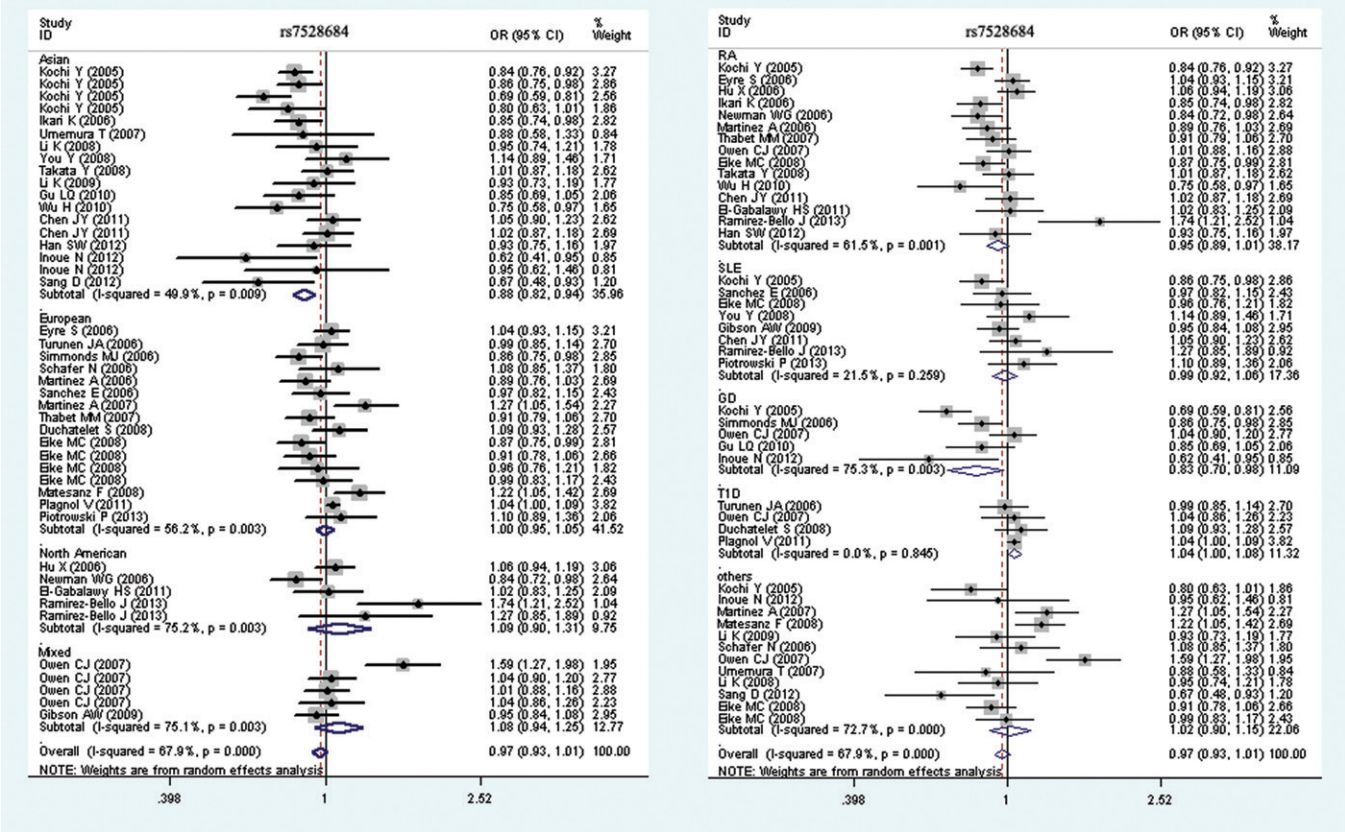

Figure 2. Forest plot for the meta-analysis of associations between FCRL3 rs7528684 polymorphism and autoimmune diseases stratified by the ethnicity, as well as by the different disease subgroups. ORs for the outcomes compared the T allele vs. the C allele of rs7528684.

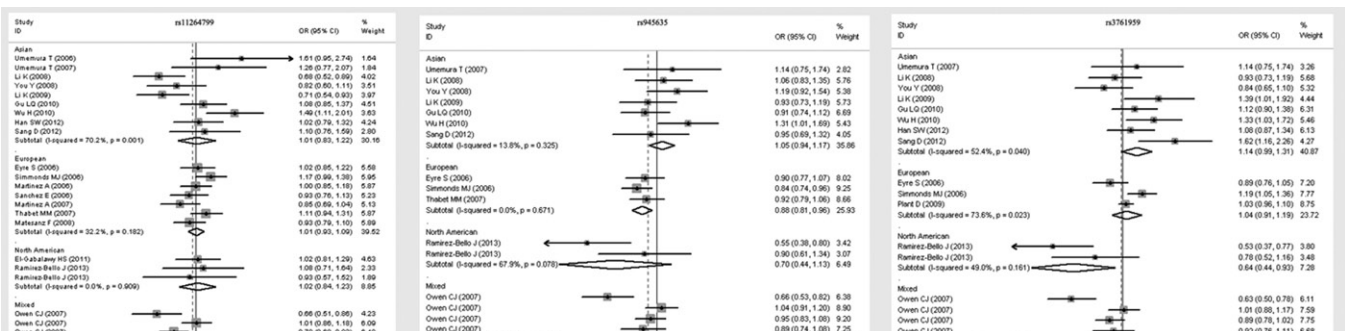

Figure 3. Forest plot for the meta-analysis of associations between FCRL3 rs11264799, rs945635 and rs3761959 polymorphisms and autoimmune diseases stratified by the ethnicity. ORs for the outcomes of the allelic comparisons, respectively (T allele vs. C allele of rs11264799; C allele vs. G allele of rs945635; and A allele vs. G allele of rs3761959).

In terms of stratified analysis by disease type for rs7528684, TT, TC, TT + TC genotypes were significantly correlated with lower risk of RA compared with the CC carriers. Moreover, in comparison with the C allele and CC carriers of rs7528684, T allele and TT genotype were associated with higher risk of T1D, but reduced GD risk. And TC + CC genotype was associated with increased risk of GD. Elevated other ADs risk was also found to be associated with TT + CC genotype compared with TC carriers (Table 2).

For SNP rs945635, in comparison with G allele and GG genotype carriers, significantly reduced ADs risk was observed to be correlated with the C allele in Europeans, CC genotype both in Europeans and in North Americans, CG genotype carriers of mixed subgroup and CC + CG genotype in Europeans; compared with the CC genotype in North Americans, and CG in mixed group, CG + GG and CC + GG genotype carriers were significantly associated with increased risk of ADs (Table 3). For SNP rs3761959, significantly decreased ADs risk was found to be correlated with A allele and AA genotype, compared with the G allele and GG carriers in North Americans; however, the AG + GG genotype carriers showed highly increased risk of ADs in North Americans in comparison with AA genotype (Table 4).

Evaluation of heterogeneity

Obvious heterogeneity among studies was found in the overall comparisons ($I^2 = 67.9\%$, $Tau^2 = 0.012$, $p < 0.001$ for SNP rs7528684; $I^2 = 59.1\%$, $Tau^2 = 0.019$, $p < 0.001$ for SNP rs11264799; $I^2 = 56.5\%$, $Tau^2 = 0.014$, $p = 0.003$ for SNP rs945635; $I^2 = 74.9\%$, $Tau^2 = 0.025$, $p < 0.001$ for SNP rs3761959). We tried to explore the heterogeneity through subgroup analyses by ethnicity and disease type. To further explore the sources of the heterogeneity, we also conducted the meta-regression analysis. We assessed allele comparisons by potential sources of publication year, region, genotyping methods, the number of genotypes and alleles, the number of female and male cases, and the frequencies of T allele for rs7528684 and rs11264799, C allele for rs945635 and A allele for rs3761959 in controls.

For SNP rs7528684, meta-regression analysis indicated that the number of T allele in cases as well as controls simultaneously contributed to the heterogeneity. The number of C allele of rs11264799 in cases, coupled with the frequency of T allele in controls could explain 100% of I^2. For SNP rs3761959, the number of G allele in cases and controls, the number of A allele and AG genotype in controls, and the frequency of A allele in controls combined to influence to a large degree the heterogeneity. However, none of the potential sources could explain the heterogeneity among the studies associated with SNP rs945635 by meta-regression analysis.

Sensitivity analysis and publication bias

The influence of each study on the overall pooled estimate of effect was investigated through sequential removal of individual studies at one time, and the omission of any study made no significant differences, indicating that our results were statistically reliable. Begg's funnel plot and Egger's test were performed to assess publication bias. According to the results shown in Figure 4, no obvious asymmetry in the overall comparisons for every SNP was found, and Egger's test also didn't provide statistical evidence for publication bias in the current meta-analysis ($p = 0.30$ for SNP rs7528684; $p = 0.68$ for SNP rs11264799, $p = 0.93$ for SNP rs945635; $p = 0.65$ for SNP rs3761959).

Discussion

FCRL genes, sharing conserved genomic structures, extracellular domain compositions, and signaling motifs with Fc receptor gene relatives, are named according to the chromosomal order [4]. The FCRL3 gene is expressed primarily by mature B cells in secondary lymphoid organs, indicating a functional role in modulating the later stages of B cell maturation [4]. FCRL3 is a type I transmembrane protein in which the extracellular domain contains six Ig-like domains [4]. In the receptor cytoplasmic domain, however, FCRL3 comprises four tyrosine residues at 650, 662, 692, and 722, which could generate both an ITAM and an ITIM. The

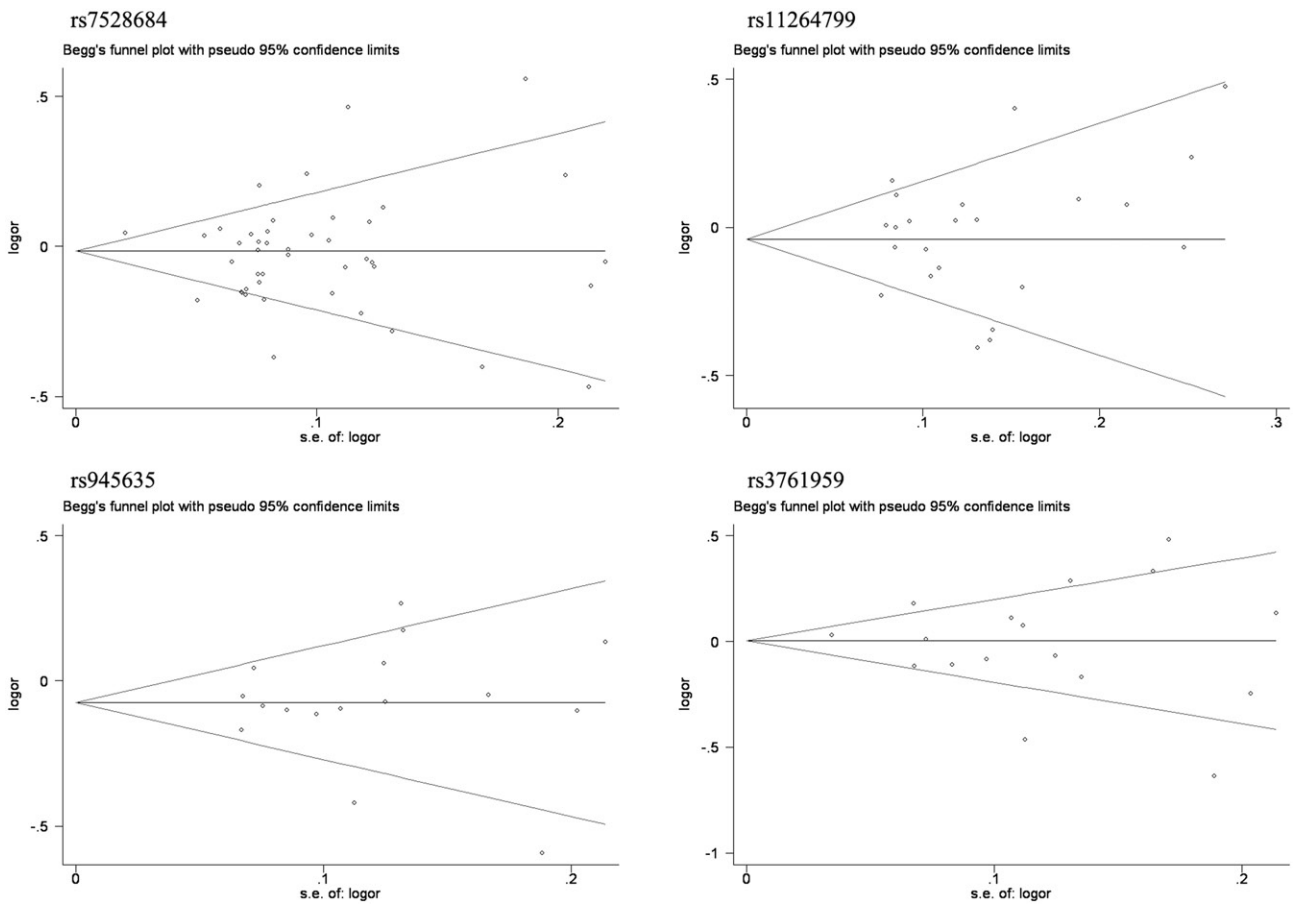

Figure 4. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. s.e., standardised effect.

sequence motif around tyrosines at 620 and 650 closely resembles the canonical ITAM, and the tyrosine motif at 692 is perceived to function as an ITIM [60,61], through which FCRL3 transduces signals into cells [10]. Moreover, the unique property of having both kinase and phosphatase implys that, as a coreceptor on B cells, FCRL3 regulates B cells either positively or negatively [12]). Taken together, FCRL3 is probably a functional molecule in immunity and potentially pathogenic in autoimmune disorders.

The associations between the functional FCRL3 promoter SNP rs7528684 and multiple ADs have been confirmed in many genetic studies. Moreover, studies have also shown that patients carrying the disease-susceptibility genotype of rs7528684 were significantly associated with increased level of the production of disease-associated autoantibodies [13]. Concerning the other three SNP rs11264799, rs945635, and rs3761959, positive correlations were also observed to be related to ADs [15,21,24,25]. However, the results were inconsistent [28,38,44]. Therefore, we conducted the current meta-analysis to identify the definite roles of these four SNPs in the pathogenesis of ADs.

In the present study, there were 34 independent case-control studies available. Among the four SNPs, rs7528684 and rs11264799 are in the promoter region. Our results revealed that C allele and CC genotype carriers were related to higher ADs risk both in the Asian subgroup of rs7528684 and in mixed group of rs11264799. Furthermore, the increased ADs risk was also associated with TC + CC genotype of rs7528684 in Asians, and TT + CC genotype of rs7528684 in Europeans, as well as rs11264799 in mixed group. In addition, in terms of analysis by disease phenotype for SNP rs7528684, significantly reduced risk of RA was found to be related with TT, TC, TT + TC genotypes, supporting the theory that rs7528684 may play a potential role in the pathogenesis of RA, which was consistent with a recent meta-analysis partly [62]. However, we didn't find the association of rs7528684 with RA under the allele comparison and dominant model (CC + TC/TT). The discrepancies in Nong et al's results [62] may be that we excluded two studies due to duplicated data, which may substantially affect the meta-analysis results. Compared with the C allele and CC genotype of rs7528684, decreased risk of GD, as well as increased risk of T1D, was more likely to be present in T and TT carriers. The TC + CC and TT + CC genotypes were found to be related with higher GD risk and other ADs risk, respectively. Another meta-analysis demonstrated that the polymorphism of rs7528684 didn't contribute to SLE neither in Europeans nor in Asians under different genetic models [63], which was in agreement with our present results.

The SNPs of rs945635 and rs3761959 are located in 5′ untranslated region and intron 2, respectively. As we all know, the 5′ untranslated region influences posttranscriptional various stages and is involved in the translation adjustment. Moreover, introns may function as network control molecules in the higher organisms and influence the activity of other genes [64].

Just as talked above, the rs945635 and rs3761959 polymorphisms have been indicated as susceptibility loci for several ADs such as GD [15], and autoimmune Addision's disease [25] in European populations. The associations between these two SNPs and ADs risk were also confirmed by replication studies using RA cohorts in Chinese and Mexicans [21,24], and Guillain–Barré syndrome cohorts in the Chinese population [29]. However, the results of previous studies were inconsistent. Although positive associations of rs945635 and rs3761959 polymorphisms with ADs in Europeans, North Americans, and mixed subgroup were found in this meta-analysis, there was no evidence for association of FCRL3 polymorphisms with RA and other ADs under different genetic models.

The present study has some limitations. First, at present, the number was not sufficiently large for a fully comprehensive analysis. It was also difficult to perform stratified analyses by ethnicity and disease phenotypes (especially for rs945635 and rs3761959). The reason for why there was an association between a certain SNP and ADs in mixed subgroup, but not in other subgroups, may be partly attributed to the relatively small sample size.

Second, obvious between-study heterogeneity in some comparisons, together with confounding factors, may be distorting the meta-analysis, although different ADs themselves are heterogeneous and the meta-regression analysis could explain most of the observed heterogeneity. Third, most of the enrolled studies only investigated the associations between these four SNPs and ADs, without evaluating the gene–gene and gene–environment interactions. Despite these limitations, our meta-analysis has several advantages: the substantial number of cases and controls pooled from different studies could increase the statistical power of the analysis; we investigated the associations of four FCRL3 SNPs with different ADs using stratification by ethnicity as well as disease phenotypes simultaneously; the qualities of the case-control studies included in this analysis satisfied our selection criteria strictly.

In summary, our meta-analysis demonstrates that the FCRL3 polymorphisms are associated with not only ADs including RA, GD, T1D, and other disease under different genetic models, but also different ethnic subgroups. However, further prospective, multicentre and larger-scale studies are required to elucidate the definite roles of FCRL3 polymorphisms in the pathogenesis of ADs.

Declaration of interest

The authors declare no competing financial interests. The authors are responsible for the content and the writing of this paper.

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