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Review Article

Cytotoxic T Lymphocyte-Associated Antigen 4 Gene Polymorphisms and Autoimmune Thyroid Diseases: An Updated Systematic Review and Cumulative Meta-Analysis

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The association of the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) gene and susceptibility to autoimmune thyroid diseases (AITDs) has been studied extensively. However, the results were not the same in different ethnic groups. We updated the meta-analysis of association of CTLA-4 gene polymorphisms with AITDs and summarized the results in specific ethnicity. The associations of A49G gene polymorphism with GD, A49G gene polymorphism with HT, CT60 gene polymorphism with GD, and CT60 gene polymorphism with HT were summarized based on the literatures published up to October 30, 2014, in English or Chinese languages. The participants involved in the studies of A49G with GD, A49G with HT, CT60 with GD, and CT60HT were 39004 subjects (in 51 studies), 13102 subjects (in 22 studies), 31446 subjects (in 22 studies), and 6948 subjects (in 8 studies), respectively. The pooled ORs of CTLA-4 gene polymorphisms with AITDs were larger than 1.00, and the 95% CIs of ORs were statistically significant among whole population analyses. However, the subgroup analysis demonstrated that pooled ORs of A49G polymorphisms with GD among Africans or Americans are less than 1.00. The accumulated evidence suggests that the G allele mutant of A49G and CT60 increased the risks of HT and GD.

1. Introduction

Autoimmune thyroid diseases (AITDs) are the most popular autoimmune thyroid diseases; hyperthyroid Graves' disease (GD) and Hashimoto's (goitrous) thyroiditis (HT) are two common types of AITDs. It is well known that AITDs are caused partly by specific genetic background [1]. The association of the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) gene and susceptibility to AITDs has been studied extensively [2–4]. The CTLA-4 gene is located on the region of human chromosome 2q33 and encodes the immunoregulatory molecule. It is proved to be a key negative regulator of T-cell activity [5, 6]. Single nucleotide polymorphisms (SNPs) at position 49 in exon 1 (+49 A/G, A49G, rs231775) and +6230 G/A (CT60, rs3087243) showed an association with AITDs. A comprehensive meta-analysis including 43 studies and more than 13,000 subjects was published in 2007 [7]. Subsequently, about 30 studies that investigated the relationship between the CTLA-4 gene SNPs and AITDs have been published. We designed the current systematic review and cumulative meta-analysis to include the most recent data and summarized the results with more genetic models.

2. Methods

2.1. Identification of Eligible Studies. The literature published up to October 30, 2014, in English or Chinese was searched in the MEDLINE, EMBASE, and China Biology Medicine disc (CBMdisc) databases. The search strategy was based on the key terms of "CTLA4," "CTLA-4," "cytotoxic T-cell

Table 1: Characteristics of new studies included in the meta-analysis.

Study	Year	Country	Ethnicity	Gene	Disease	Cases			Controls		
						AA	AG	GG	AA	AG	GG
Wang et al. [24]	2001	China	Asian	A49G	GD	37	47	3	27	26	7
Zhou et al. [25]	2003	China	Asian	A49G	GD	32	14	4	5	5	10
Zhang et al. [8]	2006	China	Asian	A49G	GD	37	18	1	26	25	29
Yao et al. [26]	2006	China	Asian	A49G	GD	58	53	9	55	57	11
Yu et al. [32]	2006	China	Asian	A49G	GD	51	36	13	26	46	28
Wang et al. [9]	2007	China	Asian	A49G	GD	124	69	15	46	60	20
Yu et al. [27]	2008	China	Asian	A49G	GD	67	45	13	13	27	29
Chong et al. [10]	2008	China	Asian	A49G	GD	97	73	7	16	67	103
Cury et al. [11]	2008	Brazil	American	A49G	GD	15	58	43	6	64	47
Bicek et al. [12]	2009	Slovenia	Caucasian	A49G	GD	17	73	33	14	52	24
Kimura et al. [13]	2009	Japan	Asian	A49G	GD	210	143	62	10	42	32
Wang et al. [28]	2010	China	Asian	A49G	GD	38	47	5	16	20	14
Guo et al. [29]	2010	China	Asian	A49G	GD	26	52	24	12	47	41
Zhao et al. [14]	2010	China	Asian	A49G	GD	1030	730	104	295	358	142
Pastuszak-Lewandoska et al. [15]	2012	Poland	Caucasian	A49G	GD	7	6	1	97	77	18
Veeramuthumari et al. [16]	2011	India	Caucasian	A49G	GD	32	37	11	71	56	24
Kimkong et al. [17]	2011	Thailand	Asian	A49G	GD	61	49	22	54	73	26
Farra et al. [18]	2012	Lebanon	Caucasian	A49G	GD	6	18	31	7	32	39
Pastuszak-Lewandoska et al. [19]	2013	Poland	Caucasian	A49G	GD	12	9	3	945	823	156
Pastuszak-Lewandoska et al. [15]	2012	Poland	Caucasian	A49G	HT	6	19	3	5	5	10
Zhou et al. [25]	2003	China	Asian	A49G	HT	24	14	8	46	60	20
Yu et al. [27]	2008	China	Asian	A49G	HT	41	34	5	15	64	22
Dallos et al. [20]	2008	Slovakia	Caucasian	A49G	HT	13	34	16	13	27	29
Kucharska et al. [21]	2009	Poland	Caucasian	A49G	HT	31	40	29	16	67	103
Bicek et al. [12]	2009	Slovenia	Caucasian	A49G	HT	15	46	51	6	64	47
Sahin et al. [22]	2009	Turk	Caucasian	A49G	HT	21	91	85	17	54	49
Farra et al. [18]	2012	Lebanon	Caucasian	A49G	HT	6	31	36	16	20	14
Ying et al. [30]	2012	China	Asian	A49G	HT	46	53	51	31	91	108
Pastuszak-Lewandoska et al. [19]	2013	Poland	Caucasian	A49G	HT	14	8	3	7	48	43
Wang et al. [9]	2007	China	Asian	CT60	GD	138	46	5	30	61	26
Chong et al. [10]	2008	China	Asian	CT60	GD	125	48	4	735	516	84
Tsai et al. [23]	2008	China	Asian	CT60	GD	136	48	5	125	58	9
Bicek et al. [12]	2009	Slovenia	Caucasian	CT60	GD	50	57	16	88	51	12
Kimura et al. [13]	2009	Japan	Asian	CT60	GD	267	127	21	82	59	12
Kimkong et al. [17]	2011	Thailand	Asian	CT60	GD	78	46	8	372	216	32
Qu et al. [31]	2014	China	Asian	CT60	GD	1989	487	114	1550	474	136
Dallos et al. [20]	2008	Slovakia	Caucasian	CT60	HT	31	28	4	20	50	25
Bicek et al. [12]	2009	Slovenia	Caucasian	CT60	HT	37	52	23	30	61	26

lymphocyte associated antigen 4," "CD28," "CD152," "Graves' disease," "GD," "Hashimoto's thyroiditis," and "HT." Reference lists of relevant papers were reviewed to find additional studies. H.-F. Hou and X. Jin independently reviewed all studies and assessed the quality of each study according to the following inclusion criteria. (1) The publication was case-control study design, and the associations between A49G or CT60 genetic polymorphisms and AITDs were investigated. (2) Genotype distribution data were offered in both cases and controls. (3) For the overlapping data or the same papers, the largest population or the most recent study was included. (4) We limited the data to studies published in English and Chinese language. We compared our collection information with the data of Kavvoura et al. [7] on The Endocrine Society's Journals Online website (available at http://press.endocrine.org/journal/jcem) and adopted the unpublished studies provided in Kavvoura's meta-analysis.

2.2. Data Extraction. For published studies, two reviewers (H.-F. Hou and T. Sun) independently extracted data and

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI
1.1.1 Caucasian						
Ban 2004	76	176	86	274	2.0%	1.66 [1.12, 2.46]
Bednarczuk 2003	294	602	259	614	2.5%	1.31 [1.04, 1.64]
Bicek et al. 2009	107	246	76	234	2.1%	1.60 [1.10, 2.32]
Chistyakov 2000	122	156	98	186	1.8%	3.22 [2.00, 5.19]
Chistyakov 2006	185	278	138	310	2.2%	2.48 [1.77, 3.47]
Djilali-Saiah 1998	63	146	69	200	1.9%	1.44 [0.93, 2.23]
Donner 1997	287	610	231	650	2.5%	1.61 [1.29, 2.02]
Farra et al. 2012	30	110	99	372	1.8%	1.03 [0.64, 1.67]
Frydecka 2004	83	196	93	210	2.0%	0.92 [0.62, 1.37]
Ghaderi 2006	21	88	62	196	1.5%	0.68 [0.38, 1.20]
Kalantari 2003	89	180	67	180	1.9%	1.65 [1.08, 2.51]
Kouki 2000	45	90	33	86	1.4%	1.61 [0.88, 2.93]
Nakkash-Chmaisse 2004	29	68	14	76	1.1%	3.29 [1.55, 6.99]
Pastuszak-Lewandoska et al. 2012	20	28	15	40	0.7%	4.17 [1.47, 11.79]
Pastuszak-Lewandoska et al. 2013	33	48	53	138	1.2%	3.53 [1.75, 7.11]
Petrone 2005	114	300	186	602	2.3%	1.37 [1.03, 1.83]
Sahin 2005	63	154	62	196	1.9%	1.50 [0.96, 2.32]
Ueda et al. 2003	578	1314	624	1684	2.7%	1.33 [1.15, 1.55]
Vaidya et al. 2002	287	602	248	698	2.6%	1.65 [1.32, 2.07]
Veeramuthumari et al. 2011	101	160	77	160	1.9%	1.85 [1.18, 2.88]
Subtotal (95% CI)	2627	**5552**	2590	**7106**	**38.0%**	**1.60 [1.39, 1.83]**
Total events						
Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 54.40$, df = 19 ($P < 0.0001$); $I^2 = 65\%$						
Test for overall effect: $Z = 6.60$ ($P < 0.00001$)						
1.1.2 Asian						
Akamizu 2006	322	444	310	468	2.4%	1.35 [1.01, 1.79]
Awata 1998	157	222	437	688	2.2%	1.39 [1.00, 1.93]
Ban 2006	306	372	223	358	2.2%	2.81 [2.00, 3.95]
Bednarczuk 2003	396	574	113	190	2.2%	1.52 [1.08, 2.13]
Cho 2006	418	556	687	944	2.5%	1.13 [0.89, 1.44]
Chong et al. 2008	267	354	198	302	2.2%	1.61 [1.15, 2.26]
Guo et al. 2010	138	200	98	200	2.0%	2.32 [1.54, 3.48]
Iwama 2005	59	86	244	400	1.7%	1.40 [0.85, 2.30]
Kimkong et al. 2011	171	264	181	306	2.2%	1.27 [0.90, 1.78]
Kimura et al. 2009	563	830	948	1590	2.7%	1.43 [1.20, 1.70]
Kinjo 2002	162	288	98	220	2.1%	1.60 [1.12, 2.28]
Marron 1997	43	56	137	188	1.2%	1.23 [0.61, 2.48]
Mochizuki 2003	25	32	69	120	0.9%	2.64 [1.06, 6.58]
Nistico 1996	94	194	77	210	2.0%	1.62 [1.09, 2.42]
Park 2000	149	194	271	398	2.0%	1.55 [1.05, 2.30]
Wang et al. 2001	121	174	62	168	1.8%	3.90 [2.49, 6.12]
Wang et al. 2007	317	416	271	384	2.3%	1.34 [0.97, 1.83]
Wang et al. 2010	123	180	80	180	1.9%	2.70 [1.75, 4.15]
Wang 2004	224	296	234	342	2.2%	1.44 [1.01, 2.04]
Weng 2005	183	214	153	202	1.7%	1.89 [1.15, 3.11]
Yanagawa 1997	220	306	244	400	2.3%	1.64 [1.19, 2.25]
Yao et al. 2006	169	240	167	246	2.0%	1.13 [0.77, 1.66]
Yu 2006	138	200	98	200	2.0%	2.32 [1.54, 3.48]
Yu et al. 2008	179	250	152	252	2.1%	1.66 [1.14, 2.41]
Yung 2002	186	246	211	316	2.1%	1.54 [1.06, 2.24]
Zhang et al. 2006	92	112	80	120	1.4%	2.30 [1.24, 4.25]
Zhao et al. 2010	2790	3728	2713	3848	2.8%	1.24 [1.12, 1.38]
Zhou et al. 2003	78	100	52	100	1.4%	3.27 [1.77, 6.05]
Subtotal (95% CI)		**11128**		**13340**	**56.3%**	**1.65 [1.48, 1.84]**
Total events	8090		8608			
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 80.65$, df = 27 ($P < 0.00001$); $I^2 = 67\%$						
Test for overall effect: $Z = 8.85$ ($P < 0.00001$)						
1.1.3 African						
Chen 2000	33	98	29	94	1.4%	1.14 [0.62, 2.09]
Hadj-Kacem 2001	163	288	264	410	2.3%	0.72 [0.53, 0.98]
Subtotal (95% CI)		**386**		**504**	**3.7%**	**0.84 [0.55, 1.28]**
Total events	196		293			
Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 1.73$, df = 1 ($P = 0.19$); $I^2 = 42\%$						
Test for overall effect: $Z = 0.82$ ($P = 0.41$)						
1.1.4 American						
Cury et al. 2008	88	832	46	156	2.0%	0.28 [0.19, 0.43]
Subtotal (95% CI)		**832**		**156**	**2.0%**	**0.28 [0.19, 0.43]**
Total events	88		46			
Heterogeneity: not applicable						
Test for overall effect: $Z = 6.05$ ($P < 0.00001$)						
Total (95% CI)		**17898**		**21106**	**100.0%**	**1.55 [1.40, 1.72]**
Total events	11001		11537			
Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 218.24$, df = 50 ($P < 0.00001$); $I^2 = 77\%$						
Test for overall effect: $Z = 8.59$ ($P < 0.00001$)						
Test for subgroup differences: $\chi^2 = 74.75$; df = 3 ($P < 0.00001$); $I^2 = 96.0\%$						

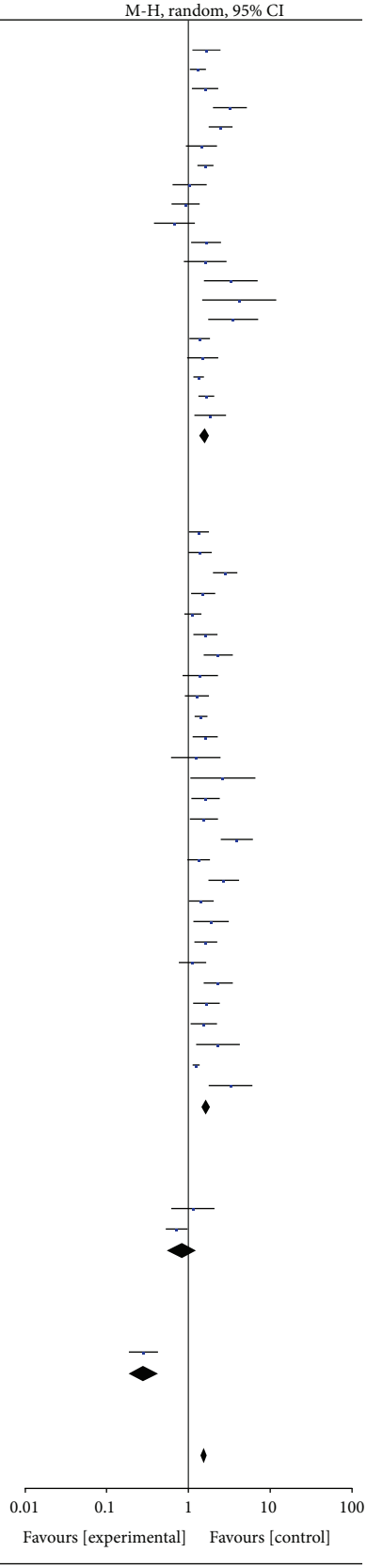

Figure 1: Forest plot of the association between an allele model of A49G polymorphism and GD.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI
1.1.1 Caucasian						
Ban 2004	0	0	0	0		Not estimable
Bednarczuk 2003	80	167	60	168	3.4%	1.66 [1.07, 2.56]
Bicek et al. 2009	17	50	6	53	1.8%	4.04 [1.44, 11.32]
Chistyakov 2000	50	56	30	55	1.9%	6.94 [2.56, 18.87]
Chistyakov 2006	68	90	39	95	2.8%	4.44 [2.36, 8.34]
Djilali-Saiah 1998	13	36	16	63	2.1%	1.66 [0.68, 4.03]
Donner 1997	63	144	41	176	3.3%	2.56 [1.58, 4.14]
Farra et al. 2012	6	37	16	119	1.8%	1.25 [0.45, 3.46]
Frydecka 2004	17	49	20	52	2.3%	0.85 [0.38, 1.91]
Ghaderi 2006	3	29	8	52	1.2%	0.63 [0.15, 2.61]
Kalantari 2003	20	41	7	37	1.8%	4.08 [1.46, 11.38]
Kouki 2000	8	16	5	20	1.2%	3.00 [0.73, 12.27]
Nakkash-Chmaisse 2004	3	11	0	24	0.3%	20.18 [0.94, 432.12]
Pastuszak-Lewandoska et al. 2012	7	8	5	15	0.5%	14.00 [1.33, 147.43]
Pastuszak-Lewandoska et al. 2013	12	15	13	42	1.2%	8.92 [2.15, 37.07]
Petrone 2005	23	82	24	163	2.8%	2.26 [1.18, 4.32]
Sahin 2005	15	44	7	50	1.8%	3.18 [1.15, 8.75]
Ueda et al. 2003	123	325	111	440	3.8%	1.80 [1.32, 2.46]
Vaidya et al. 2002	74	162	45	191	3.4%	2.73 [1.73, 4.30]
Veeramuthumari et al. 2011	32	43	26	55	2.2%	3.24 [1.37, 7.71]
Subtotal (95% CI)		**1405**		**1870**	**39.4%**	**2.51 [1.94, 3.24]**
Total events	634		479			
Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 36.16$, df = 18 ($P = 0.007$); $I^2 = 50\%$						
Test for overall effect: $Z = 7.00$ ($P < 0.00001$)						
1.1.2 Asian						
Akamizu 2006	112	124	103	130	2.5%	2.45 [1.18, 5.08]
Awata 1998	57	68	137	181	2.5%	1.66 [0.80, 3.45]
Ban 2006	147	174	69	94	2.9%	1.97 [1.07, 3.65]
Bednarczuk 2003	134	159	31	44	2.4%	2.25 [1.03, 4.88]
Cho 2006	155	170	245	275	2.7%	1.27 [0.66, 2.43]
Chong et al. 2008	97	104	71	95	2.1%	4.68 [1.91, 11.47]
Guo et al. 2010	26	50	12	53	2.2%	3.70 [1.58, 8.66]
Iwama 2005	17	18	78	112	0.7%	7.41 [0.95, 57.94]
Kimkong et al. 2011	61	83	54	80	2.7%	1.34 [0.68, 2.62]
Kimura et al. 2009	210	272	295	437	3.7%	1.63 [1.15, 2.31]
Kinjo 2002	50	82	26	64	2.7%	2.28 [1.17, 4.45]
Marron 1997	16	17	49	55	0.6%	1.96 [0.22, 17.52]
Mochizuki 2003	10	11	21	33	0.6%	5.71 [0.65, 50.28]
Nistico 1996	0	0	0	0		Not estimable
Park 2000	57	62	98	124	1.8%	3.02 [1.10, 8.31]
Wang et al. 2001	37	40	10	42	1.2%	39.47 [9.99, 155.97]
Wang et al. 2007	124	139	97	115	2.5%	1.53 [0.74, 3.20]
Wang et al. 2010	38	43	14	38	1.6%	13.03 [4.16, 40.81]
Wang 2004	87	98	81	99	2.3%	1.76 [0.78, 3.95]
Weng 2005	78	80	54	56	0.7%	1.44 [0.20, 10.57]
Yanagawa 1997	78	89	78	112	2.5%	3.09 [1.46, 6.54]
Yao et al. 2006	58	67	55	66	1.9%	1.29 [0.50, 3.35]
Yu 2006	51	64	26	54	2.3%	4.22 [1.88, 9.50]
Yu et al. 2008	67	80	46	66	2.3%	2.24 [1.01, 4.95]
Yung 2002	66	69	76	99	1.4%	6.66 [1.91, 23.18]
Zhang et al. 2006	37	38	27	34	0.6%	9.59 [1.11, 82.62]
Zhao et al. 2010	1030	1134	945	1101	3.9%	1.63 [1.26, 2.13]
Zhou et al. 2003	32	36	16	30	1.4%	7.00 [1.98, 24.75]
Subtotal (95% CI)		**3371**		**3689**	**54.7%**	**2.57 [2.03, 3.27]**
Total events	2932		2814			
Heterogeneity: $\tau^2 = 0.18$; $\chi^2 = 60.09$, df = 26 ($P = 0.0002$); $I^2 = 57\%$						
Test for overall effect: $Z = 7.75$ ($P < 0.00001$)						
1.1.3 African						
Chen 2000	4	24	5	28	1.1%	0.92 [0.22, 3.90]
Hadj-Kacem 2001	50	81	85	111	2.8%	0.49 [0.26, 0.92]
Subtotal (95% CI)		**105**		**139**	**4.0%**	**0.54 [0.31, 0.97]**
Total events	54		90			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.60$, df = 1 ($P = 0.44$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.07$ ($P = 0.04$)						
1.1.4 American						
Cury et al. 2008	15	58	7	46	1.9%	1.94 [0.72, 5.26]
Subtotal (95% CI)		**58**		**46**	**1.9%**	**1.94 [0.72, 5.26]**
Total events	15		7			
Heterogeneity: not applicable						
Test for overall effect: $Z = 1.31$ ($P = 0.19$)						
Total (95% CI)		**4939**		**5744**	**100.0%**	**2.41 [2.01, 2.89]**
Total events	3635		3390			
Heterogeneity: $\tau^2 = 0.20$; $\chi^2 = 119.04$, df = 48 ($P < 0.00001$); $I^2 = 60\%$						
Test for overall effect: $Z = 9.56$ ($P < 0.00001$)						
Test for subgroup differences: $\chi^2 = 25.30$; df = 3 ($P < 0.0001$); $I^2 = 88.1\%$						

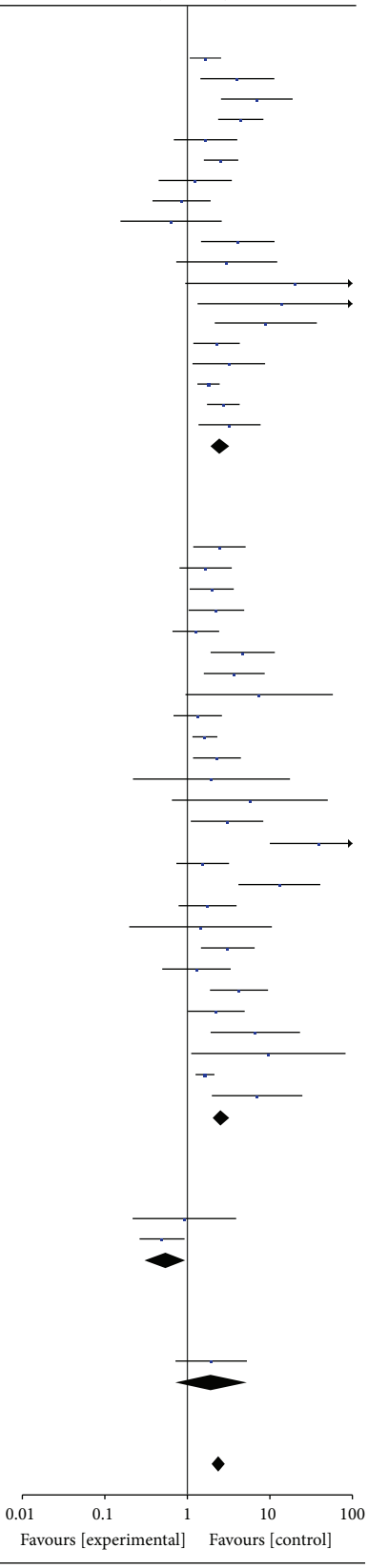

Figure 2: Forest plot of the association between an additive model of A49G polymorphism and GD.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI
1.1.1 Caucasian						
Bicek et al. 2009	76	224	76	234	4.8%	1.07 [0.72, 1.58]
Dallos et al. 2008	60	126	153	460	4.6%	1.82 [1.22, 2.72]
Donner 1997	71	146	351	932	5.3%	1.57 [1.10, 2.22]
Farra et al. 2012	43	146	99	372	4.4%	1.15 [0.75, 1.76]
Ghaderi 2006	24	74	62	196	3.0%	1.04 [0.59, 1.84]
Kouki 2000	14	36	33	86	1.8%	1.02 [0.46, 2.27]
Kucharska et al. 2009	102	200	94	202	4.7%	1.20 [0.81, 1.77]
Pastuszak-Lewandoska et al. 2012	31	56	15	40	1.7%	2.07 [0.90, 4.74]
Pastuszak-Lewandoska et al. 2013	36	50	53	138	2.2%	4.12 [2.04, 8.36]
Petrone 2001	84	252	188	602	5.8%	1.10 [0.80, 1.51]
Sahin et al. 2009	133	394	62	196	5.1%	1.10 [0.76, 1.59]
Ueda et al. 2003	185	420	624	1684	7.3%	1.34 [1.08, 1.66]
Subtotal (95% CI)		**2124**		**5142**	**50.8%**	**1.33 [1.13, 1.56]**
Total events	859		1810			
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 19.64$, df = 11 ($P = 0.05$); $I^2 = 44\%$						
Test for overall effect: $Z = 3.49$ ($P = 0.0005$)						
1.1.2 Asian						
Akamizu 2006	199	278	310	468	5.7%	1.28 [0.93, 1.77]
Awata 1998	127	176	537	850	5.2%	1.51 [1.06, 2.16]
Ban 2005	203	266	260	358	5.1%	1.21 [0.84, 1.75]
Ban 2006	240	366	223	358	5.9%	1.15 [0.85, 1.56]
Park 2000	142	220	231	318	5.0%	0.69 [0.47, 0.99]
Terauchi 2003	97	140	120	210	4.1%	1.69 [1.08, 2.66]
Tomoyose 2002	193	286	211	398	5.8%	1.84 [1.34, 2.52]
Ying et al. 2012	145	300	88	240	5.3%	1.62 [1.14, 2.29]
Yu et al. 2008	116	160	152	252	4.3%	1.73 [1.13, 2.66]
Zhou et al. 2003	62	92	52	100	2.9%	1.91 [1.06, 3.43]
Subtotal (95% CI)		**2284**		**3552**	**49.2%**	**1.39 [1.15, 1.67]**
Total events	1524		2184			
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 22.95$, df = 9 ($P = 0.006$); $I^2 = 61\%$						
Test for overall effect: $Z = 3.40$ ($P = 0.0007$)						
Total (95% CI)		**4408**		**8694**	**100.0%**	**1.36 [1.20, 1.53]**
Total events	2383		3994			
Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 42.86$, df = 21 ($P = 0.003$); $I^2 = 51\%$						
Test for overall effect: $Z = 4.99$ ($P < 0.00001$)						
Test for subgroup differences: $\chi^2 = 0.10$; df = 1 ($P = 0.75$); $I^2 = 0\%$						

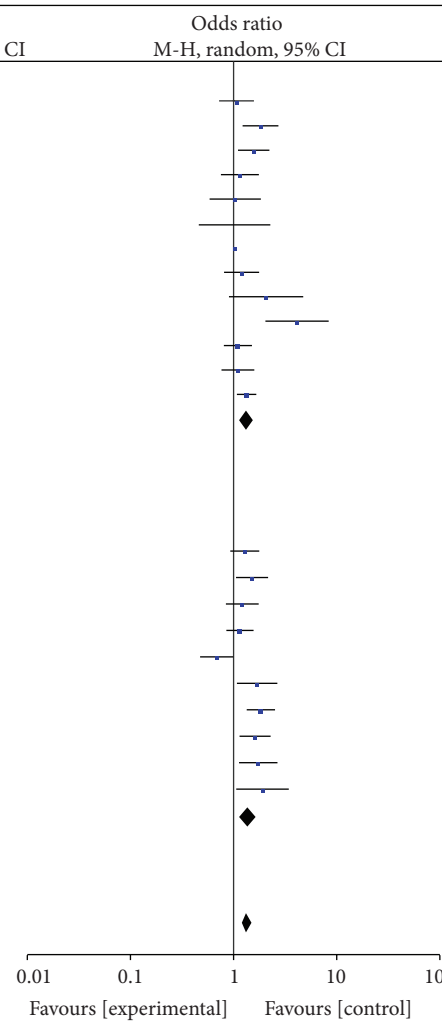

Figure 3: Forest plot of the association between an allele model of A49G polymorphism and HT.

resolved disagreements by discussion or with a third party (Li QW) when necessary. We collected the following information carefully: author name, journal source, publication year, ethnicity of study population (Asian, Caucasian, African, and American), the number of individuals in case and control groups, and genotype distribution of cases and controls.

2.3. Meta-Analysis Methods. The analysis of data was performed with Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK). Allele frequencies at the A49G or CT60 gene polymorphisms from the literatures were calculated by the allele counting method. Four genetic models, (1) allele contrast (G versus A), (2) additive genetic model (GG versus AA), (3) dominant model (GG + AG versus AA), and (4) recessive model (GG versus AG + AA), were measured in this meta-analysis, and association values of the CTLA-4 genetic polymorphisms with risk of AITDs were estimated by odds ratios (ORs) and 95% confidence intervals (CIs). We also assessed Hardy-Weinberg Equilibrium (HWE) of genotype frequencies in the control group with a chi-square test, and P value < 0.05 was considered to be significant. The heterogeneity across all studies was tested by the I^2 statistics and chi-square-based Q-test. The heterogeneity was considered to be significantly large when $P < 0.10$ and $I^2 > 50\%$. Then random effects model was used to combine eligible data. The statistical significance of pooled ORs was measured by the Z-test. Subgroup meta-analyses were conducted according to different ethnicities. In addition, sensitivity analysis was implemented to assess stability of the summary result by sequential removal of individual studies. Furthermore, publication bias was measured by funnel plots.

3. Results

3.1. Identification of Eligible Studies. Besides the 43 studies mentioned in Kavvoura et al.'s meta-analysis [7], 25 additional studies were included in this review (Table 1). Sixteen studies were English language publications [8–23] and 9 studies were published in Chinese [24–32]. Thus, the present updated meta-analysis consisted of 68 studies.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI
1.1.1 Caucasian						
Ban 2004	113	180	164	300	3.7%	1.40 [0.96, 2.04]
Bednarczuk 2006	397	568	366	596	5.7%	1.46 [1.14, 1.86]
Bicek et al. 2009	157	246	121	234	3.9%	1.65 [1.14, 2.37]
Chistiakov 2006	174	278	125	310	4.3%	2.48 [1.78, 3.45]
Frydecka 2006	125	196	121	196	3.4%	1.09 [0.72, 1.64]
Ghaderi 2006	35	86	90	198	2.5%	0.82 [0.49, 1.38]
Petrone 2005	169	300	287	602	5.1%	1.42 [1.07, 1.87]
Ueda et al. 2003	835	1316	875	1646	7.6%	1.53 [1.32, 1.77]
Subtotal (95% CI)		**3170**		**4082**	**36.3%**	**1.47 [1.24, 1.74]**
Total events	2005		2149			
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 16.96$, df = 7 ($P = 0.02$); $I^2 = 59\%$						
Test for overall effect: $Z = 4.53$ ($P < 0.00001$)						
1.1.2 Asian						
Akamizu 2006	350	430	305	414	4.4%	1.56 [1.13, 2.17]
Ban 2006	492	604	260	358	4.6%	1.66 [1.21, 2.26]
Ban 2005	220	262	260	358	3.5%	1.97 [1.32, 2.96]
Cho 2006	465	556	793	944	5.1%	0.97 [0.73, 1.29]
Chong et al. 2008	298	354	227	302	3.6%	1.76 [1.19, 2.59]
Hiromatsu 2006	456	574	130	190	3.9%	1.78 [1.24, 2.57]
Ikegami 2006	331	426	1073	1430	5.5%	1.16 [0.90, 1.50]
Kimkong et al. 2011	202	264	223	306	3.7%	1.21 [0.83, 1.77]
Kimura et al. 2009	661	830	1986	2670	6.7%	1.35 [1.11, 1.63]
Qu et al. 2014	4465	5180	3574	4320	8.2%	1.30 [1.17, 1.46]
Tai 2008	320	378	960	1240	4.7%	1.61 [1.18, 2.19]
Wang 2006	242	284	234	342	3.5%	2.66 [1.78, 3.96]
Wang et al. 2007	322	378	308	384	3.7%	1.42 [0.97, 2.07]
Weng 2005	183	214	153	202	2.6%	1.89 [1.15, 3.11]
Subtotal (95% CI)		**10734**		**13460**	**63.7%**	**1.48 [1.32, 1.67]**
Total events	9007		10486			
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 30.10$, df = 13 ($P = 0.005$); $I^2 = 57\%$						
Test for overall effect: $Z = 6.47$ ($P < 0.00001$)						
Total (95% CI)		**13904**		**17542**	**100.0%**	**1.48 [1.35, 1.63]**
Total events	11012		12635			
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 48.49$, df = 21 ($P = 0.0006$); $I^2 = 57\%$						
Test for overall effect: $Z = 8.12$ ($P < 0.00001$)						
Test for subgroup differences: $\chi^2 = 0.01$; df = 1 ($P = 0.93$); $I^2 = 0\%$						

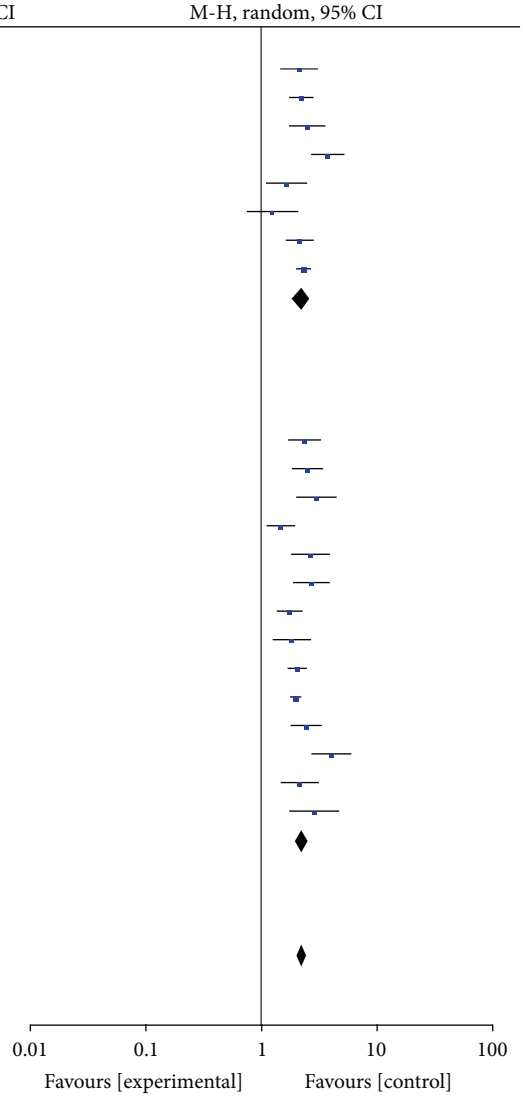

Figure 4: Forest plot of the association between an allele model of CT60 polymorphism and GD.

3.2. Quantitative Analysis

3.2.1. A49G Gene Polymorphism and GD. The summary OR of included studies was increased 1.55-fold in susceptibility to GD in subjects with the G allele, and the associations of GD and A49G polymorphisms were statistically significant in an additive genetic model (GG versus AA: OR = 2.41, 95% CI: 2.01–2.89), a dominant genetic model (GG + AG versus AA: OR = 1.76, 95% CI: 1.52–2.03), and a recessive genetic model (GG versus AG + AA: OR = 1.79, 95% CI: 1.58–2.02). The detailed results were shown in Figures 1 and 2 and Supplemental Figures 1 and 2 in Supplementary Material available online at http://dx.doi.org/10.1155/2015/747816.

The subgroup analysis was performed by ethnicity to decrease the heterogeneity. As shown in Figures 1 and 2, significant associations between A49G SNP and GD risk were identified in Asians and Caucasians.

3.2.2. A49G Gene Polymorphism and HT. The meta-analysis suggested (see Figure 3 and Supplemental Figures 3–5) that A49G polymorphisms increased the risk of HT significantly in the allele frequencies (G versus A: OR = 1.36, 95% CI: 1.20–1.53), the additive genotype (GG versus AA: OR = 2.10, 95% CI: 1.75–2.51), the dominant genotype (GG + AG versus AA: OR = 1.57, 95% CI: 1.26–1.96), and the recessive genotype (GG versus AG + AA: OR = 1.46, 95% CI: 1.19–1.81). The subgroup analyses showed that A49G polymorphism was one of the risk factors for GD in Asians and Caucasians.

3.2.3. CT60 Gene Polymorphism and GD. The summary analyses of CT60 gene polymorphism and GD are shown in Figure 4 and Supplemental Figures 6–8. The pooled ORs of CT60 polymorphisms with GD in allele frequencies, the additive genetic model, the dominant genetic model, and the recessive genetic model were 1.48 (95% CI: 1.35–1.63), 1.98

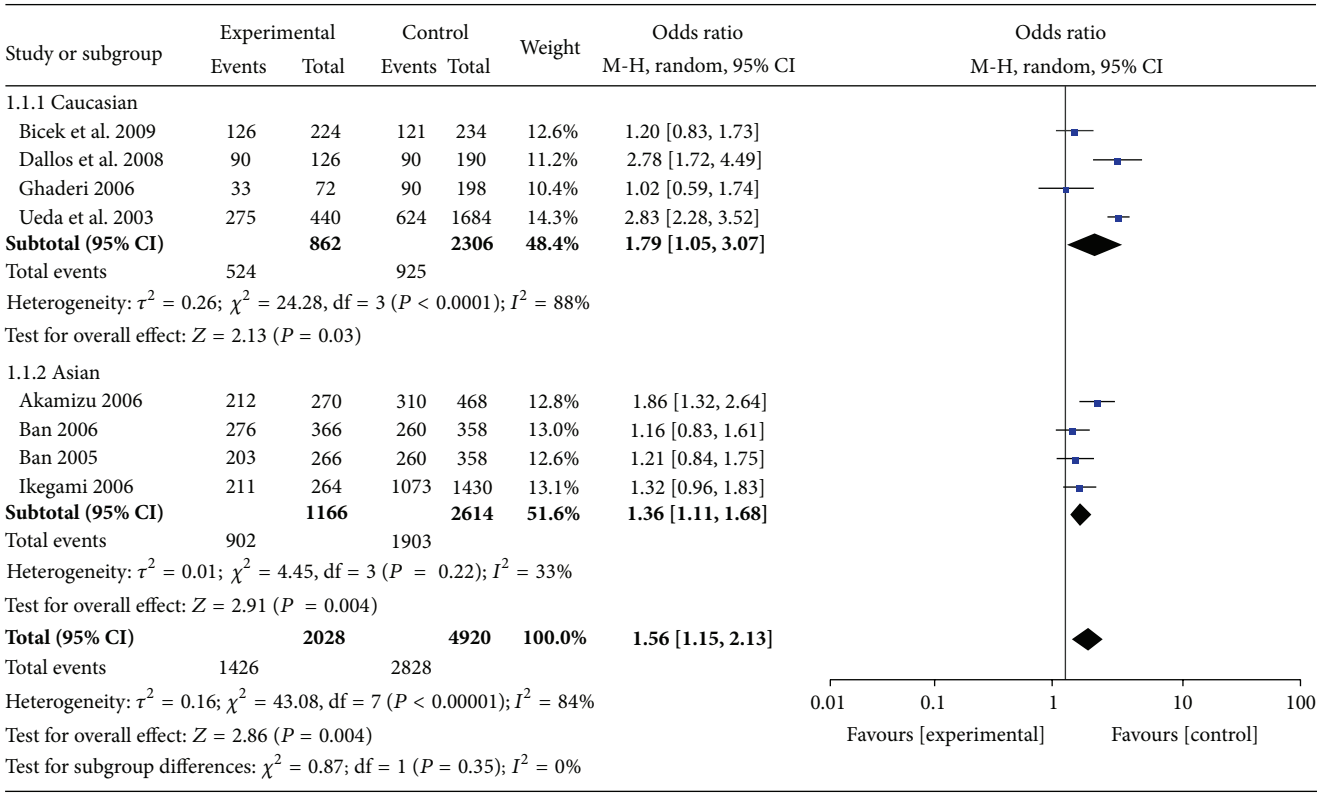

Figure 5: Forest plot of the association between an allele model of CT60 polymorphism and HT.

(95% CI: 1.73–2.27), 1.72 (95% CI: 1.52–1.96), and 1.56 (95% CI: 1.39–1.76), respectively. The subgroup analyses suggested that CT60 polymorphism was a risk factor for GD in Asians and Caucasians.

3.2.4. CT60 Gene Polymorphism and HT. As shown in Figure 5 and Supplemental Figures 9–11, CT60 genetic polymorphisms increased HT risk significantly in the allele frequencies contrast (G versus A: OR = 1.56, 95% CI: 1.15–2.13), the additive genetic contrast (GG versus AA: OR = 2.58, 95% CI: 1.33–5.01), the dominant genetic contrast (GG + AG versus AA: OR = 1.95, 95% CI: 1.20–3.15), and the recessive genetic contrast (GG versus AG + AA: OR = 1.79, 95% CI: 1.20–2.67). The subgroup analyses showed that CT60 genetic polymorphism was one of the risk factors for GD in Asians and Caucasians.

3.3. Publication Bias. In order to evaluate publication bias in this updated systematic review, Begg's Funnel plots were performed, and the results showed that no obvious asymmetry existed for the meta-analyses of A49G and CT60 genetic polymorphisms.

3.4. Sensitivity Analysis. In order to conduct sensitivity analyses, we calculated the pooled ORs through removing each study sequentially and leaving out certain studies, such as studies conducted among special population. The analyses showed that the results were not changed significantly. However, the summary results of the association between CT60 and HT among Caucasians were shifted in the sensitivity analyses.

4. Discussion

GD and HT are the most prevalent autoimmune thyroid diseases (AITDs), which represent two opposite pathogenic paths: hyperthyroidism in GD and thyroid destruction in HT [15, 19]. Although the etiological mechanisms of GD and HT are not distinctly clarified, CTLA-4 gene polymorphisms (A49G and CT60) have been identified as the most important genetic factors in many genetic researches and genome-wide association study (GWAS) [2, 12]. A large-scale meta-analysis including 43 studies and more than 13,000 subjects was published in the present journal in 2007 [7]. The results identified the roles of A49G and CT60 gene polymorphism in AITDs. Subsequently, more than 30 studies repeatedly confirmed the associations of the CTLA-4 gene with GD and HT. The current updated meta-analysis included the most recent eligible studied and summarized the data in specific ethnicity.

A49G gene polymorphism was widely investigated for the susceptibility to AITDs; the G allelic gene variation was considered as a risk factor of GD and HT. Our current meta-analysis showed that A49G polymorphisms significantly increased the risk of GD in total population. Nevertheless, the

genetic variation had a protective effect in Africans according to the additive model analysis. Furthermore, a total of 22 studies were summarized for the A49G gene polymorphism with HT. The results suggested that the polymorphism distinctly increases the risk of HT among Caucasians and Asians.

The G allele of CT60 gene is another focused genetic pathogenesis associated with HT and GD. A total of 22 studies were included in our meta-analysis for CT60 polymorphism and GD, and the pooled OR values indicated that G allele carriers might increase GD risk. Moreover, the summarized result involving 8 original studies suggested that CT60 polymorphisms were associated with susceptibility to HT among Caucasian and Asian population, except that no significant pooled OR was found in dominant genetic model of Caucasians.

In this updated meta-analysis, we guaranteed the stability of results with sensitivity analysis.No obvious publication bias existed according to funnel plot test. We performed heterogeneity test to assess the reliability of the results and conducted subgroup analysis.

There are some limitations in our study. The sample size in Africans or Americans was not large enough. More well-designed studies need to be conducted in Africans or Americans to clarify the associations of the CTLA-4 gene with AITDs.

Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contribution

Hai-Feng Hou and Xu Jin contributed equally to this work.

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