High-temperature requirement factor A1 rs11200638 polymorphism and age-related macular degenerative from a comprehensive analysis about 15316 subjects

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Research article

Keywords: high-temperature requirement factor A1, age-related macular degeneration, polymorphism, meta-analysis, risk

Posted Date: February 12th, 2020

DOI: <https://doi.org/10.21203/rs.2.23339/v1>

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Abstract

Background

The high-temperature requirement factor A1 (HTRA1) gene at the 10q26 locus has been associated with age-related macular degenerative (AMD) risk, with the significantly associated polymorphism being (rs11200638, -625G/A), however, above association is not consistent. We investigated an updated meta-analysis to evaluate the association between rs11200638 polymorphism and AMD risk thoroughly addressing this issue.

Methods

An identification was covered with the Pubmed and Chinese Wanfang databases through 27th Jan, 2020. Odds ratios (OR) and 95% confidence intervals (CI) were used to assess the strength of associations. After a thorough and meticulous search, 35 different articles (33 case-control studies with HWE, 22 case-control studies about wet/dry AMD) were retrieved.

Results

Individuals carrying A-allele or AA genotype may have an increased risk to be AMD disease. For example, there has a significantly increased relationship between rs11200638 polymorphism and AMD both for Asians (OR: 2.50, 95%CI: 2.22-2.80 for A-allele vs. G-allele) and Caucasians (OR: 2.11, 95%CI: 1.43-3.13 for A-allele vs. G-allele). Moreover, a similar trend in the source of control subgroup was detected. To classify the type of AMD, increased association was also observed in both wet (OR: 3.40, 95%CI: 2.90-3.99 for dominant model) and dry (OR: 2.08, 95%CI: 1.24-3.48 for dominant model) AMD. Finally, based on the different genotyping methods, increased relationships were identified by sequencing, TaqMan, PCR-RFLP.

Conclusions

Our present meta-analysis suggests that the HTRA1 rs11200638 polymorphism are potentially associated with the risk of AMD development, especially about individuals carrying A-allele or AA genotype, who may be as identified targets to detect and intervene in advance. Further studies using larger sample sizes and including information about gene-environment interactions should be conducted to elucidate.

Introduction

Age-related macular degeneration (AMD) is the leading cause of vision loss in the elderly people in developed countries [1, 2]. The number of individuals affected by AMD may be estimated to reach 17.8 million by 2050 [3]. The visual loss of AMD attributes to dead or non-functional photoreceptors and the underlying retinal pigment epithelium (RPE) [4]. Clinically, AMD is divided into two forms: The early stages, dry (atrophic, non-exudative) that can progress to geographic atrophy (GA) and the late stages, wet (exudative) AMD characterized by choroidal neovascularization (CNV) [5, 6].

Age, ethnicity, family history, smoking and sun exposure are common risk factors [7, 8], another important factor for AMD etiology is the genetic predisposition [9]. A genome-wide association study (GWAS) showed a clearer view about significant links between AMD risk and genetic variations in 2005, suggesting AMD is a polygenic disease [10], which triggered numerous studies involving the genetic associations of AMD in the following 15 years [11–13]. So far, AMRS2 rs10490924 polymorphism, SNPs from complement factor H, C2/CFB, complement component C3, APOE haplotypes have been confirmed as being associated with susceptibility of AMD [14–18].

It is well known that vascular endothelial growth factor (VEGF) is involved in wet AMD development because that the formation of angiogenesis and vascular permeability can lead to fluid leakage across the blood vessels, and visual loss in the final [19]. Anti-VEGF agents such as ranibizumab and bevacizumab have been widely applied in the clinic [20, 21], in addition, have been proved to effectively slow the progress of CNV, however, heterogeneity was observed among patients in terms of the invalid samples and who have shorter duration of treatment [22]. It was hypothesized that genetic factors may participate in this period of this heterogeneous response, such as the variants of CHF, VEGFA, ARMS2 and high-temperature requirement factor A1 (HTRA1) genes [23–26].

HTRA1 encodes a member of the trypsin family of serine proteases and regulates the availability of insulin-like growth factors (IGFs) by cleaving IGF-binding proteins and transforming growth factor- β (TGF- β), which have been suggested to be a regulator of cell growth, angiogenesis and extracellular matrix deposition. In addition, the inhibition of TGF- β may lead to the overexpression of HTRA1 gene in wet AMD [27] (<https://www.ncbi.nlm.nih.gov/gene/5654>).

One of common polymorphisms in HTRA1 gene is rs11200638 (wide allele G to mutation allele A) [28]. Dewan et al. reported that the risk allele (A-allele) of the HTRA1 gene can influence the overexpression of its protein and then possible affect the integrity of Bruch's membrane and stimulate the progression of CNV stage [29].

In view of the foregoing, we realized that the important role of HTRA1 gene and its common rs11200638 polymorphism, we used the meta-analysis method to perform comprehensive conclusions including 28 different publications (33 case-control studies) [26, 30–57].

Methods

Search Strategy

We searched relative studies from PubMed and Wanfang databases before 27th Jan, 2020. The keywords were “age-related macular degeneration,” “AMD,” “polymorphism or variant,” and “HTRA1 or high-temperature requirement factor A1.” With these terms, a total of 33 different articles were included from above databases based on our inclusion criteria. Stages of AMD were assigned based on the classification of the Age-Related Eye Disease Study (AREDS) [58].

Inclusion and Exclusion Criteria

Included studies were according with (i) the correlation between AMD risk and HTRA1 gene rs11200638 polymorphism; (ii) case-control studies, and (iii) sufficient numbers of each genotypes (AA, AG, and GG) in case and control groups. Studies were excluded if they (i) included no control information; (ii) didn't contain genotype frequency data, and (iii) were duplicated studies with some other papers.

Data Extraction

Two authors (Ying Liu and Dong Wei) independently screened all papers that according with the selection criteria. These data included the first author's last name, publication year, country of origin, ethnicity, Hardy-Weinberg equilibrium (HWE) of control group, genotyping method and AMD disease types (dry and wet AMD). Ethnicity was categorized as Caucasian or Asian. The control subgroups were classified to population-based (PB) and hospital-based (HB).

Statistical Analysis

Based on the genotype frequencies for cases and controls, odds ratios (OR) with 95% confidence intervals (CI) were used to measure the strengths of associations. The statistical significance of the OR was determined with the Z test [59]. The heterogeneity assumption among studies was evaluated using a χ^2 -square-based Q test. If P-value > 0.10 for the Q test was indicated, a lack of heterogeneity among studies, other words, Mantel-Haenszel (fixed-effects model) was chosen, otherwise, the DerSimonian-Laird (random-effects model) was applied [60, 61]. We investigated the correlation between rs11200638 polymorphism and AMD risk by testing whole five genetic models: A versus G, AG versus GG, AA + AG versus GG, AA versus GG and AA versus AG + GG. A sensitivity analysis was performed by omitting studies, one after another, to assess the stability of results. The departure of frequencies of the rs11200638 polymorphism from expectation under HWE was assessed by the Pearson's χ^2 test, P < 0.05 was considered significant [62]. The funnel plot was evaluated by Begg's test, and the publication bias was evaluated by Egger's test, whose P-value < 0.05 was considered significant [63]. All statistical tests for this meta-analysis were performed using version 10.0 Stata software (StataCorp LP, College Station, TX, USA). The power and sample size analysis of our meta-analysis was calculated by a program called PS: Power and Sample Size Calculation (<http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize#Windows>)

Network of gene-interaction of HTRA1 gene

To more complete understanding of the role of HTRA1 in AMD, the network of gene-gene interactions for HTRA1 gene was utilized through String online server (<http://string-db.org/>) [64].

Results

Study searching and their basic information

Using various combinations of key terms, a total of 262 article titles were garnered by a document search using the PubMed (222 titles) and Wanfang (40 titles) databases. As shown in Fig. 1, 178 articles were excluded after screening the Abstract sections of the manuscripts. The full texts were then evaluated, and 51 additional articles were excluded due to duplication (9), meta-analysis or systematic analysis (26), clinical trial (10), randomized controlled trial (6). Finally, 35 different articles [26, 30–57, 65–69] were included in our meta-analysis, including 27 case-control studies about HTRA1 gene rs11200638 polymorphism and wet or dry AMD risk and 38 case-control studies about HTRA1 gene rs11200638 polymorphism and AMD risk. Five case-control studies [65–69] were not consistent with HWE in control groups. To make our analysis to more strict, we deleted above five studies, so there were about 33 case-control studies (8101 cases and 7215 controls) for the whole AMD [26, 30–57](Table 1), and 22 case-control studies for wet or dry (3938 cases and 4427 controls) studies [26, 30, 31, 33, 34, 40, 41, 43, 44, 46–48, 51, 53–56] (Table 2). The frequency of the A allele from case group was found to be higher in control individuals (54.2% vs. 36.5%) (Fig. 2). There were 19 case-control studies of Asian population, and 14 from Caucasian population; source of control in 22 case-control studies were from HB, and 11 were from PB; 17 case-control studies were about wet AMD disease, and 5 were about dry disease. Finally, we checked the Minor Allele Frequency (MAF) reported for the five main worldwide populations in the 1000 Genomes Browser (<https://www.ncbi.nlm.nih.gov/snp/rs11200638>): Global (0.290); East Asian (EAS = 0.411); European (EUR = 0.194); African (AFR = 0.257); American (AMR = 0.250); and South Asian (SAS = 0.340) (Fig. 3). The genotyping methods included polymerase chain reaction-restrictive fragment length polymorphism and matrix-assisted laser desorption/ionization time-of-flight, sequencing, real-time PCR, and TaqMan.

Table 1
Characteristics of included studies in HTRA1 rs11200638 polymorphism and AMD risk.

Author	Year	Country	Ethnicity	type	Case	Control	SOC	Cases			Controls			HWE	Genotype
								AA	AG	GG	AA	AG	GG		
Tian	2012	China	Asian	AMD	532	468	HB	255	193	84	104	224	140	0.423	Ty
Ruamviboonsuk	2017	Thailand	Asian	wet	377	1073	PB	125	164	88	146	490	437	0.643	Inf 8 v
Chu	2008	China	Asian	wet	144	126	HB	76	52	16	31	69	26	0.276	PC
Losonczy	2011	Hungary	Caucasian	AMD	103	95	HB	23	50	30	3	49	43	0.133	PC
Tuo	2008	USA	Caucasian	AMD	142	132	PB	33	60	49	7	51	74	0.638	PC
Tuo	2008	USA	Caucasian	AMD	330	191	PB	63	164	103	12	73	106	0.904	PC
Tuo	2008	USA	Caucasian	AMD	272	555	PB	15	122	135	20	186	349	0.431	PC
Tuo	2008	USA	Caucasian	AMD	46	22	PB	2	15	29	1	6	15	0.696	PC
Chan	2007	USA	Caucasian	AMD	52	13	HB	14	27	11	0	8	5	0.109	RT
Kanda	2007	USA	Caucasian	AMD	457	280	HB	172	183	102	179	90	11	0.94	RT
Cheng	2013	China	Asian	wet	93	93	HB	52	30	11	21	42	30	0.395	Se
Liang	2012	China	Asian	wet	161	150	HB	61	83	17	30	72	48	0.751	Se
Jiang	2008	China	Asian	wet	159	140	HB	99	47	13	31	67	42	0.662	Se
Lee	2010	Korea	Asian	wet	137	187	HB	57	59	21	35	100	52	0.283	Se
Lin	2008	China-Taiwan	Asian	AMD	95	90	HB	53	33	9	19	47	24	0.651	Se
Kaur	2008	India	Asian	AMD	229	184	HB	90	89	50	21	85	78	0.765	Se
Xu	2007	China	Asian	wet	121	132	HB	56	52	13	24	64	44	0.931	Se
Tam	2008	China-Hong Kong	Asian	wet	163	183	HB	94	51	18	38	90	55	0.916	Se
Mori	2007	Japan	Asian	AMD	123	133	HB	45	52	26	22	57	54	0.298	Se
Askari	2015	Iran	Asian	AMD	120	120	HB	58	42	20	12	66	42	0.057	Se
Lana	2018	Brazil	Caucasian	AMD	204	166	HB	73	89	42	22	77	67	0.987	Se
Kaur	2013	India	Asian	AMD	198	145	PB	84	70	44	17	67	61	0.829	Se
Ng	2016	Hong Kong	Asian	wet	194	183	PB	109	63	22	38	90	55	0.916	Se
Kaur	2013	India	Caucasian	AMD	616	426	PB	130	292	194	17	138	271	0.913	Se
Chen	2013	China	Asian	AMD	158	157	HB	28	74	56	21	77	59	0.599	Ta
Kondo	2007	Japan	Asian	AMD	73	94	HB	29	39	5	16	40	38	0.334	Ta
Leveziel	2007	France	Caucasian	wet	118	116	HB	32	57	29	5	41	70	0.743	Ta
Weger	2007	Austria	Caucasian	wet	242	157	PB	67	108	67	8	50	99	0.609	Ta
Lu	2007	China	Asian	wet	90	106	HB	53	34	3	15	63	28	< 0.05	PC
Cruz-González	2013	Spain	Caucasian	AMD	121	91	HB	29	60	32	61	21	9	< 0.05	PC
Mohamad	2019	Malaysia	Asian	wet	145	145	HB	79	47	19	48	82	15	< 0.05	PC
Yang	2010	China	Asian	wet	109	150	HB	31	45	33	30	50	70	< 0.05	PC
Chen	2008	USA	Caucasian	AMD	776	294	HB	131	400	245	10	128	156	< 0.05	Se
Zeng	2011	China	Caucasian	AMD	1335	509	PB	244	641	450	21	181	307	0.374	SN
HB: hospital-based; PB: population-based; SOC, source of control; PCR-RFLP: polymerase chain reaction followed by restriction fragment length polymorphism; MALDI-TOF: polymerase chain reaction–matrix-assisted laser desorption/ionization time-of-flight; HWE: Hardy–Weinberg equilibrium of control group															

Author	Year	Country	Ethnicity	type	Case	Control	SOC	Cases			Controls			HWE	Ge
Li	2015	China	Asian	AMD	146	145	HB	73	54	19	44	74	27	0.674	Mz
Yang	2018	China	Asian	AMD	201	201	HB	103	74	24	42	100	59	0.975	Mz
Matuskova	2020	Czech Republic	Caucasian	wet	307	191	HB	69	148	90	9	66	116	0.921	SN
Fritsche	2008	Germany	Caucasian	AMD	760	549	PB	152	344	264	22	174	353	0.923	Mt
HB: hospital-based; PB: population-based; SOC: source of control; PCR-RFLP: polymerase chain reaction followed by restriction fragment length polymorphism; MALDI-TOF: polymerase chain reaction-matrix-assisted laser desorption/ionization time-of-flight; HWE: Hardy-Weinberg equilibrium of control group															

Table 2
Characteristics of included studies in HTRA1 rs11200638 polymorphism and wet/dry AMD risk, respectively.

Author	Year	Country	Ethnicity	type	Case	Control	SOC	Cases			Controls			HWE	Genotype
								AA	AG	GG	AA	AG	GG		
Lin	2008	China-Taiwan	Asian	dry	52	90	HB	28	19	5	19	47	24	0.651	Sec
Chan	2007	USA	Caucasian	dry	18	13	HB	4	10	4	0	8	5	0.109	RT-H
Mori	2007	Japan	Asian	dry	19	116	HB	4	7	8	5	41	70	0.743	Sec
Askari	2015	Iran	Asian	dry	32	120	HB	11	12	9	12	66	42	0.576	Sec
Ruamviboonsuk	2017	Thailand	Asian	wet	377	1073	PB	125	164	88	146	490	437	0.643	Infl 8 v
Cheng	2013	China	Asian	wet	93	93	HB	52	30	11	21	42	30	0.395	Sec
Ng	2016	Hong Kong	Asian	wet	194	183	PB	109	63	22	38	90	55	0.915	Sec
Liang	2012	China	Asian	wet	161	150	HB	61	83	17	30	72	48	0.75	Sec
Chu	2008	China	Asian	wet	144	126	HB	76	52	16	31	69	26	0.276	PCF
Jiang	2008	China	Asian	wet	159	140	HB	99	47	13	31	67	42	0.662	Sec
Lee	2010	Korea	Asian	wet	137	187	HB	57	59	21	35	100	52	0.283	Sec
Lin	2008	China-Taiwan	Asian	wet	43	90	HB	25	14	4	19	47	24	0.651	Sec
Xu	2007	China	Asian	wet	121	132	HB	56	52	13	24	64	44	0.931	Sec
Tam	2008	China-Hong Kong	Asian	wet	163	183	HB	94	51	18	38	90	55	0.916	Sec
Chan	2007	USA	Caucasian	wet	31	13	HB	8	16	7	0	8	5	0.109	RT-H
Leveziel	2007	France	Caucasian	wet	118	116	HB	32	57	29	5	41	70	0.743	Tac
Mori	2007	Japan	Asian	wet	104	116	HB	41	45	18	5	41	70	0.743	Sec
Askari	2015	Iran	Asian	wet	88	120	HB	47	30	11	12	66	42	0.576	Sec
Weger	2007	Austria	Caucasian	wet	242	157	PB	67	108	67	8	50	99	0.609	Tac
Lu	2007	China	Asian	wet	90	106	HB	53	34	3	15	63	28	< 0.05	PCF
Mohamad	2019	Malaysia	Asian	wet	145	145	HB	79	47	19	48	82	15	< 0.05	PCF
Yang	2010	China	Asian	wet	109	150	HB	31	45	33	30	50	70	< 0.05	PCF
Chen	2008	USA	Caucasian	wet	470	294	HB	76	245	149	10	128	156	< 0.05	Sec
Chen	2008	USA	Caucasian	dry	306	294	HB	55	155	96	10	128	156	< 0.05	Sec
Zeng	2011	China	Caucasian	dry	341	509	PB	60	166	115	21	181	307	0.374	SNr
Zeng	2011	China	Caucasian	wet	994	509	PB	184	475	335	21	181	307	0.374	SNr
Matuskova	2020	Czech Republic	Caucasian	wet	307	191	HB	69	148	90	9	66	116	0.921	SNr

Quantitative Synthesis

Total analysis

Results of the overall meta-analysis were suggestive of increasing associations between this polymorphism and AMD susceptibility in all five genetic models (for example: AA vs. GG: OR = 4.26, 95CI% = 3.19–6.70, P < 0.001) (Table 3). In order to make this study more convincing and reliable, we detected five studies, which were not according with HWE, finally, we tested the 32 case-control studies. Also significantly increasing correlations were observed in whole genetic models (for example: A-allele vs. G-allele: OR = 2.36, 95%CI = 1.98–2.81, P < 0.001; AA + AG vs. GG: OR = 2.53, 95%CI = 2.04–3.14, P < 0.001) (Fig. 4) (Table 3).

Table 3
Results of the meta-analysis on HTRA1 rs11200638 polymorphism and AMD risk in total and types of subgroups.

Variables	N	Case/	A-allele vs. G-allele	AG vs. GG	AA + AG vs. GG	AA vs. GG	AA vs. AG + GG
		Control	OR(95%CI) P _h P	OR(95%CI) P _h P	OR(95%CI) P _h P	OR(95%CI) P _h P	OR(95%CI) P _h P
Total	38	8582/7452	2.18(1.79–2.67)0.000 0.000	1.73(1.45–2.05)0.000 0.000	2.36(1.91–2.91)0.000 0.000	4.26(3.19–6.70)0.000 0.000	3.33(2.39–4.63)0.000 0.000
HWE	33	8101/7215	2.38(2.01–2.82)0.000 0.000	1.78(1.48–2.13)0.000 0.000	2.53(2.04–3.14)0.000 0.000	5.20(3.63–7.46)0.000 0.000	3.67(2.65–5.09)0.000 0.000
Ethnicity							
Asian	19	3424/4004	2.51(2.22–2.83)0.000 0.000	1.65(1.46–1.86)0.186 0.000	2.65(2.24–3.13)0.012 0.000	5.28(4.28–6.51)0.004 0.000	3.69(3.17–4.29)0.013 0.000
Caucasian	14	4677/3211	2.17(1.53–3.10)0.000 0.000	1.82(1.34–2.48)0.000 0.003	2.15(1.46–3.17)0.000 0.000	4.60(1.88–11.24)0.000 0.001	3.61(1.56–8.35)0.000 0.003
SOC							
HB	22	3589/3273	2.29(1.77–2.97)0.000 0.000	1.70(1.33–2.16)0.000 0.000	2.44(1.82–3.27)0.000 0.000	4.86(3.09–7.62)0.000 0.000	3.47(2.37–5.09)0.000 0.000
PB	11	4512/33942	2.50(2.10–2.97)0.000 0.000	2.16(1.84–2.53)0.021 0.000	2.73(2.24–3.32)0.002 0.000	6.07(4.30–8.57)0.002 0.000	4.26(3.22–5.64)0.013 0.000
AMD type							
Wet	17	3476/3579	3.03(2.59–3.55)0.000 0.000	2.11(1.81–2.46)0.138 0.000	3.40(2.90–3.99)0.073 0.000	7.65(5.73–10.21)0.009 0.000	4.65(3.72–5.82)0.008 0.000
Dry	5	462/848	2.36(1.71–3.24)0.750 0.000	1.33(0.76–2.32)0.705 0.316	2.08(1.24–3.48)0.618 0.005	6.01(3.05–11.87)0.889 0.000	4.77(2.79–8.16)0.964 0.000
Genotyping							
Others	5	3004/2599	2.34(2.12–2.58)0.219 0.000	1.83(1.32–2.52)0.018 0.000	2.57(2.22–2.98)0.176 0.000	6.25(4.26–9.15)0.005 0.000	3.56(2.97–4.27)0.144 0.000
Sequencing	14	2613/2332	2.84(2.61–3.09)0.237 0.000	2.08(1.81–2.41)0.252 0.000	3.19(2.79–3.65)0.710 0.000	7.00(5.84–8.39)0.677 0.000	4.51(3.90–5.21)0.169 0.000
TaqMan	4	591/524	2.66(1.43–4.94)0.000 0.002	2.79(1.31–5.91)0.000 0.008	3.61(1.52–8.60)0.000 0.004	7.52(2.05–27.68)0.000 0.002	3.86(1.66–8.98)0.002 0.002
PCR-RFLP	6	1037/1121	2.01(1.77–2.28)0.144 0.000	1.72(1.42–2.07)0.610 0.000	2.08(1.74–2.48)0.539 0.000	4.30(2.51–7.35)0.073 0.000	3.41(2.62–4.43)0.153 0.000
RT-PCR	2	509/293	0.88(0.12–6.27)0.000 0.900	0.53(0.08–3.57)0.010 0.516	0.54(0.03–8.51)0.000 0.663	0.97(0.01–32.38)0.001 0.989	1.37(0.05–38.98)0.019 0.852
MassARRAY MALDI-TOF	2	347/346	2.18(1.39–3.49)0.043 0.001	1.46(0.95–2.24)0.213 0.088	2.22(1.13–4.38)0.099 0.021	3.84(1.53–9.63)0.044 0.004	3.05(1.78–5.23)0.097 0.000
P _h : value of Q-test for heterogeneity test; P: Z-test for the statistical significance of the OR							

Subgroup analysis

Coming up, we all know that the frequency of A-allele in different races was not the same, so we tried to analysis the relationships by ethnicity subgroups in further, which indicated an incremental statistically association between this polymorphism and both in Asians (A-allele vs. G-allele: OR = 2.51, 95% CI = 2.22–2.83, P_{heterogeneity} < 0.001, P < 0.001, AA vs. AG + GG: OR = 3.69, 95% CI = 3.17–4.29, P_{heterogeneity} = 0.013, P < 0.001) and Caucasian populations (dominant model, OR = 2.15, 95% CI = 1.46–3.17, P_{heterogeneity} < 0.001; heterozygote comparison, OR = 1.82, 95% CI = 1.34–2.48, P_{heterogeneity} < 0.001; allelic comparison, OR = 2.11, 95% CI = 1.43–3.13, P_{heterogeneity} < 0.001, P < 0.001) (Table 2) (Fig. 4). In addition, regular analysis by source of control, also significantly increased

risks were detected for this SNP both in PB and HB studies (AG vs. GG: OR = 1.70, 95% CI = 1.33–2.16, $P_{\text{heterogeneity}} < 0.001$, $P < 0.001$ for HB; AG vs. GG: OR = 2.09, 95% CI = 1.75–2.49, $P_{\text{heterogeneity}} = 0.028$, $P < 0.001$ for HB) (Table 2) (Fig. 5). AMD have different types and stages, the different of clinical presentation for dry and wet AMD is completely different, so we firmly believed that the correlations existed should be evaluated separately, significant positive associations were found both for dry (such as AA + AG vs. GG: OR = 2.08, 95% CI = 1.24–3.48, $P_{\text{heterogeneity}} = 0.618$, $P = 0.005$) and wet AMD (for example in AA + AG vs. GG: OR = 3.40, 95% CI = 2.90–3.99, $P_{\text{heterogeneity}} = 0.073$, $P < 0.001$) (Fig. 6A,B). Finally, different genotype methods were applied in included studies, we tried in each method, whether associations may exist in our analysis, we found some positive results in some methods (such as in AA vs. GG model: OR = 7.00, 95% CI = 5.84–8.39, $P_{\text{heterogeneity}} = 0.677$ about sequencing; OR = 7.52, 95% CI = 2.05–27.68, $P_{\text{heterogeneity}} < 0.001$, $P = 0.002$ about TaqMan; OR = 4.30, 95% CI = 2.51–7.35, $P_{\text{heterogeneity}} = 0.073$) (Fig. 7A,B) (Table 3).

Bias Diagnosis for publication and sensitivity Analysis

The publication bias was evaluated by both Begg’s funnel plot and Egger’s test. At beginning, the shape of the funnel plots seemed asymmetrical in allele comparison for rs11200638 by Begg’s test, suggesting no publication bias was existed. Then, Egger’s test was applied to provide statistical evidence of funnel plot symmetry. As a result, no obvious evidence of publication bias was observed (A-allele vs. G-allele, $t = 0.89$, $P = 0.38$ for Egger’s test; $z = 0.85$, $P = 0.396$ for Begg’s test, Fig. 8A,B)(Table 4).

Table 4
Publication bias tests (Begg’s funnel plot and Egger’s test for publication bias test) for HTRA1 rs11200638 polymorphism.

Egger's test						Begg's test	
Genetic type	Coefficient	Standard error	t	P value	95%CI of intercept	z	P value
A-allele vs. G-allele	1.181	2.034	0.89	0.38	(-2.367- 5.996)	0.85	0.396
AG vs. GG	0.104	0.835	0.12	0.902	(-1.612- 1.820)	0.18	0.859
AA + AG vs. GG	0.058	0.879	0.07	0.948	(-1.748- 1.865)	0.14	0.89
AA vs. GG	0.302	0.712	0.42	0.675	(-1.162-1.766)	0.26	0.797
AA vs. AG + GG	1.92	1.148	1.67	0.106	(-0.440-4.280)	0.45	0.65

To delete studies which may influence the power and stability of whole study, we applied the sensitive analysis, finally, no sensitive case-control studies were found (Fig. 9).

Gene-gene network diagram and interaction of online website

String online server indicated that HTRA1 gene interacts with numerous genes. The network of gene-gene interaction has been illustrated in Fig. 10.

Discussion

Because of the critical consequences about the visual loss caused by AMD, especially advanced AMD (atrophic/dry or neovascular/wet), it is necessary to study its etiology and mechanism, then to development early diagnostic methods and effective treatment. Nowadays, VEGF inhibitors are widely recognized as effective drugs in clinical application for CNV (wet AMD) [3, 70, 71], instead of dry AMD. Therefore, to identify some novel detection markers and target drugs for different types of AMD is the current and future research focus on the direction. In the introduction section, we have enunciated the genetic factors may help us to search potential high-risk group about AMD, which can be prevented and treated in advance. In our analysis, we chose the HTRA1 gene, which can regulate some kinds of growth factors. Rs11200638 polymorphism in HTRA1 is the most common SNP, which is getting noticed. Mori et al. first investigated the association between HTRA1 gene rs11200638 polymorphism and risk of AMD [47]. Other more following researchers duplicated their work in different populations and different types of AMD. However, results were confounding, even within same populations, though two published meta-analysis. It is well known that meta-analysis provides a means for effectively increasing the size of the sample by pooling data from individual correlation studies, thus enhancing the statistical power of the analysis to estimate genetic effects [72], which used this method to demonstrate statistically significant genetic associations.

Two previous meta-analysis [73, 74] about rs11200638 polymorphism and AMD have been reported, however, each study has its limitations. For example, Tang et al. just included fourteen case-control studies, two studies [65, 67] were not consistent with HWE, and Tuo et al. actually reported four-source case-control studies, which shouldn’t be combined together [74]. Chen et al. also performed a meta-analysis in the same year including 14 case-control studies, similar limitations were existed [73]. After year of 2008, newly added studies have been published, and to perfect the above deficiencies, we performed an updated meta-analysis to come to a more convincing conclusion about HTRA1 gene rs11200638 polymorphism and AMD susceptibility.

To the best of our knowledge, this is the comprehensive and systematic meta-analysis exploring the associations between HTRA1 gene rs11200638 polymorphism and AMD risk; it involved about 8101 AMD individuals and 7215 controls. Increased associations were found in the whole group, in Asian and Caucasian subgroups, source of control subgroup, and dry/wet sub-types of AMD, different genotyping methods (Sequencing, TaqMan, PCR-RFLP and MassARRAY MALDI-TOF), which means that A-allele or AA genotype is the risk factor for AMD, in other words, if individuals carry on this SNP from peripheral blood test, which may indicate that it is possible to increase the occurrence of AMD for them in present time or at some point in the future. Therefore, it can

offer us some preventions to intervene, or carry out treatments as soon as possible. To sum up, we wish to use this method to reduce the incidence of AMD and improve the cure rate of early treatment. In addition, the power of present study was 1.00, which suggested our conclusions were stable and convincing.

In addition, the online analysis system-String was applied to predict potential and functional partners related to HTRA1, which can help us to better understand the value for detection and concern. Finally, ten genes were predicted. Among them, the highest score of association was ACAN (0.943), however, so far, no research has been reported between this gene and AMD and interaction between this gene and HTRA1. Future research should be paid attention to above information, which may be in favor of AMD early detection/prevention and intervention. In other partners, ARMS2 and CFH have been shown to associate with AMD. The ARMS2 and HTRA1 genes are located nearby on the 10q26 chromosome in a strong linkage disequilibrium. Significant association was observed that ARMS2 rs10490924 was related response to ranibizumab treatment among wet AMD subjects [68]. CFH gene T1277C polymorphism is strong associated with both wet and dry AMD and may be contribute to the inflammation in the pathogenesis of AMD [75]. As for the rest interaction genes (CLPP, CTRC, YME1L1, HSPD1, RPL34, CLPX and PLEKHG4) both had moderate score and no literature to support. In a word, we should deep explore these partners of HTRA1 gene, and gene-gene interactions in the development of AMD in the next step.

There are some inherent limitations of our study should be declared. First, further studies should focus on Mixed and African populations, which was vacant in present analysis. Second, gene-gene and gene-environment interactions were not well analyzed. It is possible that specific environmental and lifestyle factors alter the associations between HTRA1 rs11200638 polymorphism and AMD, including age, diabetes, smoking, familial history, and hypertension. Third, vision is the most concerned-clinical indicator of AMD, future studies should include the value of the vision and analyze the relationships between rs11200638 polymorphism and the degree of visual impairment, which may help us to better detect disease progression.

In conclusion, our present meta-analysis suggests that HTRA1 rs11200638 polymorphism may be powerful associated with AMD risk, which may be as a clinical biomarker for detection.

Declarations

Acknowledgements

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author contributions

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Investigation: Wenxiu Li.

Methodology: Wenxiu Li.

Project administration: Dong Wei.

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Funding

This study was supported by Heilongjiang Health and Family Planning Commission Research Project (No. 2016-379).

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Abbreviations

Age-related macular degeneration = AMD, genome-wide association studies = GWAS, high-temperature requirement factor A1 = HTRA1, choroidal neovascularization = CNV, vascular endothelial growth factor = VEGF, retinal pigment epithelium = RPE, Age-Related Eye Disease Study = AREDS, single nucleotide polymorphism = SNP, hospital-based = HB, population-based = PB, source of control = SOC, polymerase chain reaction followed by restriction fragment length polymorphism =PCR-RFLP, a chip-based matrix-assisted laser-desorption/ionization time-of-flight = MALDI-TOF.

Figures

Figure 1

Flowchart illustrating the search strategy used to identify association studies for HTRA1 gene rs11200638 polymorphism and AMD risk.

Figure 2

The MAF of minor-allele (mutant-allele) for HTRA1 gene rs11200638 polymorphism from the 1000 Genomes online database and present analysis. EAS: East Asian; EUR: European; AFR: African; AMR: American; SAS: South Asian.

rs11200638

Figure 3

A-allele frequencies for the HTRA1 gene rs11200638 polymorphism among cases/controls stratified by ethnicity. Vertical line, allele frequency; Horizontal line, case/control groups.

Figure 4

Forest plot of AMD risk associated with HTRA1 gene rs11200638 polymorphism (A-allele vs. G-allele) by ethnicity subgroup. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Figure 5

Forest plot of AMD risk associated with HTRA1 gene rs11200638 polymorphism (AG vs. GG) by source of control subgroup.

Figure 6

Forest plot of AMD risk associated with HTRA1 gene rs11200638 polymorphism (AA+AG vs. GG) by AMD type subgroup. A: wet AMD; B: dry AMD.

Figure 7

Forest plot of AMD risk associated with HTRA1 gene rs11200638 polymorphism (AA vs. GG) by genotyping methods subgroup. A: random model; B: fixed model.

Figure 8

A: Begg's funnel plot for publication bias test (A-allele vs. G-allele). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line, mean effect size. B: Egger's publication bias plot (A-allele vs. G-allele).

Figure 9

Sensitivity analysis between HTRA1 gene rs11200638 polymorphism and AMD risk (A-allele vs. G-allele).

Serine protease HTRA1; Serine protease with a variety of targets, including extracellular matrix proteins such as fibronectin. HTRA1-generated fibronectin fragments further induce synovial cells to up-regulate MMP1 and MMP3 production. May also degrade proteoglycans, such as aggrecan, decorin and fibromodulin. Through cleavage of proteoglycans, may release soluble FGF-glycosaminoglycan complexes that promote the range and intensity of FGF signals in the extracellular space. Regulates the availability of insulin-like growth factors (IGFs) by cleaving IGF-binding proteins. Inhibits signa [...] (480 aa)

Predicted Functional Partners:

		Neighborhood	Gene Fusion	Cooccurrence	Coexpression	Experiments	Databases	Textmining	[Homology]	Score
ACAN	Aggrecan core protein; This proteoglycan is a major component of extracellular matrix of cartilagenous tissues. A major func...									0.943
ARMS2	Age-related maculopathy susceptibility 2 (107 aa)									0.787
CLPP	ATP-dependent Clp protease proteolytic subunit, mitochondrial; Protease component of the Clp complex that cleaves peptide...									0.776
CTRC	Chymotrypsin-C; Regulates activation and degradation of trypsinogens and procarboxypeptidases by targeting specific cleav...									0.716
YME1L1	ATP-dependent zinc metalloprotease YME1L1; ATP-dependent metalloprotease that catalyzes the degradation of folded and ...									0.706
CFH	Complement factor H; Factor H functions as a cofactor in the inactivation of C3b by factor I and also increases the rate of dis...									0.692
HSPD1	60 kDa heat shock protein, mitochondrial; Chaperonin implicated in mitochondrial protein import and macromolecular assem...									0.691
RPL34	60S ribosomal protein L34; Component of the large ribosomal subunit (117 aa)									0.676
CLPX	ATP-dependent Clp protease ATP-binding subunit clpX-like, mitochondrial; ATP-dependent specificity component of the Clp p...									0.674
PLEKHG4	Puratrophin-1; Possible role in intracellular signaling and cytoskeleton dynamics at the Golgi; Pleckstrin homology domain co...									0.672

Figure 10

Human HTRA1 interactions network with other genes obtained from String server. At least 10 genes have been indicated to correlate with HTRA1 gene. ACAN: aggrecan core protein; ARMS2: age-related maculopathy susceptibility; CLPP: ATP-dependent Clp protease proteolytic subunit; CTRC: chymotrypsin-C; YME1L1: ATP-dependent zine metalloprotease YME1L1; CFH: complement factor H; HSPD1: 60 kDa heat shock protein; RPL34: 60S ribosomal protein L34; CLPX: ATP-dependent Clp protease ATP-binding subunit clpX-like; PLEKHG4: Puratrophin-1.