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Association of the HTRA1 -625G>A promoter gene polymorphism with exudative age-related macular degeneration in a Central European population

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Purpose: Exudative age-related macular degeneration (AMD) is one of the most common causes of severe visual loss. Both environmental and genetic factors, such as the complement factor H (CFH) 402H allele, have been associated with AMD. Recently, the HTRA1 -625A allele was identified as a novel risk marker in both a North American and a Chinese population. The present study was performed to evaluate the association of the HTRA1 -625A allele with exudative AMD in a Central European population.

Methods: The present case-control study included 242 patients with exudative AMD and 157 control subjects. Genotypes of the HTRA1 -625G>A polymorphism were determined by a 5'-exonuclease assay (TaqMan). Determination of CFH Y402H genotypes was done by allele specific digestion of polymerase chain products.

Results: Carriers of the HTRA1 -625AA genotype were found significantly more often in AMD patients than among control subjects (27.7% versus 5.1%; p<0.001). Binary logistic regression analysis binary logistic regression analysis revealed an odds ratio (OR) of 2.7 (95% confidence interval (CI): 1.1-6.8) for AMD among subjects heterozygous for the HTRA1 -625A allele compared to those with the wildtype genotype, when adjusted for CFH Y402H genotypes (p=0.034). The OR increased to 10.2 (95% CI: 3.0-34.5) among subjects homozygous for the HTRA1 -625A allele (p<0.001). The OR for AMD among heterozygous carriers of the CFH 402H variant was 3.6 (95% CI: 1.6-7.8) compared to those with the wildtype genotype, when adjusted for HTRA1 -625G>A genotypes (p=0.001). The OR increased to 9.8 (95% CI: 3.7-25.9) among subjects homozygous for the CFH 402HH genotype (p<0.001). Interaction terms between CFH and HTRA1 genotypes were not significantly associated with AMD.

Conclusions: Our data suggest that both the HTRA1 -625A allele and the CFH 402H allele are independently associated with exudative AMD in a Central European population.

Exudative age-related macular degeneration (AMD) is a common vision-threatening disease primarily occurring in patients older than 60 years [1,2]. Both environmental and genetic factors have been shown to affect susceptibility to AMD [3-7]. In 2005, a common polymorphism in the complement factor H gene (CFH Y402H, rs1061170) was found to be associated with increased risk for AMD in a North American population [8-10]. This connection has subsequently been confirmed, and extended to several other populations of different ethnic origin [11-33].

HTRA1, a heat shock serine protease, is encoded at chromosome 10q26, which has also previously been identified as a major AMD gene locus [34-41]. Only recently, a polymorphism in the promoter of the HTRA1 gene (HTRA1 -625G>A, rs11200638) was found to be associated with AMD risk [42,43]. Both in vitro and in vivo HTRA1 has been shown to affect the signaling pathway of the transforming growth factor-beta (TGF-β) family of proteins, which play an important role in angiogenesis, cell proliferation, and deposition of extracellular matrix proteins [44-46]. Further evidence for the role of HTRA1 in AMD comes from an immunohistochemical study demonstrating positive HTRA1 staining in drusen from eyes with exudative AMD [43]. Additionally, enhanced expression of the HTRA1 protein has been found in the retinal pigment epithelium (RPE) of AMD eyes carrying the HTRA1 -625AA genotype compared to those from normal controls homozygous for the HTRA1 -625G allele [43].

Both the HTRA1 -625A and the CFH 402H alleles have been suggested to contribute independently to exudative AMD risk with similar magnitude. In a North American population an odds ratio of 31.5 for AMD has been conferred by the combined presence of the HTRA1 -625AA and CFH 402HH genotypes [43].

Importantly, homozygosity for the CFH 402H allele has been found to be more prevalent in Caucasians than in an Asian population [25,47-51]. Replication of association studies in different populations is imperative to draw firm conclusions about the role of genetic factors. To the best of our knowledge, no data on the role of the HTRA1 -625G>A polymorphism has yet been reported for European AMD patients. The purpose of the present study was therefore to investigate the

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role of the HTRA1 -625G>A gene polymorphism in Central European patients with exudative AMD.

METHODS

Recruited were 242 unrelated patients with exudative AMD and 157 control subjects to participate in the present retrospective case-control study. The exudative AMD group was comprised of 156 (64.5%) females and 86 (35.5%) males, and the mean age was 78.0±7.2 years (range: 56-94 years). The control group consisted of 86 (54.8%) females and 71 (45.2%) males, and the mean age was 77.4±6.5 years (range: 53-91 years). All participants were of Caucasian origin. They lived in the same geographical area in the southern part of Austria and were seen at the local Department of Ophthalmology. Written informed consent was obtained prior to enrollment. The study was performed in accordance with the Austrian Gene Technology Act, the tenets of the Declaration of Helsinki, and the guidelines of the local ethics committee.

According to the Age-Related Eye Disease Study system for classification of AMD, all exudative AMD patients enrolled in the present study were classified as AMD level 4 (advanced disease) [52]. Exudative AMD was diagnosed by ophthalmoscopic fundus examination and fluorescein/indocyanine angiography, revealing choroidal neovascularization (CNV). Excluded from the study were patients with polypoidal choroidal vasculopathy or secondary CNV due to pathologic myopia (>-6 diopters, spherical equivalent), angioid streaks, inflammatory or infectious chorioretinal disease, trauma, or hereditary diseases.

The control participants were given a detailed eye examination with fundus examination. Exclusion criteria for controls comprised evidence of age-related maculopathy (drusen as well as pigmentary changes), macular hemorrhages of any cause, or media opacities resulting in impaired visualization of the macula. Only participants of Caucasian origin were considered eligible. Controls were from the same population as AMD patients and lived in the same geographical region.

A fraction (84.2%) of the study participants were enrolled in a previous case-control study investigating the role of the CFH Y402H polymorphism in different subtypes of exudative AMD [33].

Genotype determination: Genomic DNA was isolated from whole blood using a commercial kit (QIA-AMP DNA blood mini kit, Qiagen, Vienna, Austria). HTRA1 -625G>A genotypes were determined by 5'-exonuclease assay (TaqMan™). Primer and probe sets were designed and manufactured using Applied Biosystems 'Assay-by-Design' custom service (Applera, Vienna, Austria) and assays were performed according to the manufacturer's instructions. Fluorescence was measured in a lambda Fluoro 320 plus plate reader (MWG Biotech AG, Ebersdorf, Germany) using excitation/emission filters of 485/530 nm and 530/572 nm, respectively. The data were exported into Excel format and depicted and analyzed as a scatter plot.

Genotyping of the CFH Y402H polymorphism, was done by polymerase chain reaction amplification of a 338-basepair segment containing the polymorphic site followed by digestion with restriction enzyme NIaIII [33]. The 402Y allele was cut into two fragments of 283 and 55 base pairs, whereas the 402H allele yielded fragments of 198, 85, and 55 base pairs. Fragments were separated on 2% agarose gels and were visualized by use of ethidium bromide.

Table 2. HTRA serine peptidase 1

			HTRA1 -625 GG	HTRA1 -625 GA	HTRA1 -625 AA
Control subjects	CFH 402	YY	51 (32.5%)	22 (14.0%)	5 (3.2%)
		YH	38 (24.2%)	24 (15.3%)	3 (1.9%)
		HH	10 (6.4%)	4 (2.5%)	0
AMD patients	CFH 402	YY	12 (5.0%)	14 (5.8%)	12 (5.0%)
		YH	32 (13.2%)	52 (21.5%)	37 (15.3%)
		HH	23 (9.5%)	42 (17.4%)	18 (7.4%)
Odds ratio (95% CI)	CFH 402	YY	1; reference	2.7 (1.1-6.7)	10.2 (3.1-33.3)
		YH	3.6 (1.7-7.8)	9.2 (4.2-20.2)	52.4 (14.4-186.4)
		HH	9.8 (3.7-25.6)	44.6 (13.8-142.5)	infinite

This table shows HTRA serine peptidase 1 (HTRA1) -625G>A and complement factor H (CFH) Y402H genotype combination frequencies in patients with exudative age-related macular degeneration (AMD) and control subjects. 95% CI represents 95% confidence interval.

Table 1. Genotype distribution of the HTRA serine peptidase 1

Genotype		AMD patients	Control subjects	Odds ratio (95% confidence interval)	p
HTRA1 -625	GG	67 (27.7%)	99 (63.1%)	1 (reference)	-
	GA	108 (44.6%)	50 (31.8%)	2.7 (1.1-6.8)	0.034
	AA	67 (27.7%)	8 (5.1%)	10.2 (3.0-34.5)	<0.001
CFH 402	YY	38 (15.7%)	78 (49.7%)	1 (reference)	-
	YH	121 (50.0%)	65 (41.4%)	3.6 (1.6-7.9)	0.001
	HH	83 (34.3%)	14 (8.9%)	9.8 (3.7-25.9)	<0.001

A stepwise binary logistic regression analysis was performed to assess the influence of HTRA1 and complement factor H (CFH) genotypes on age-related macular degeneration (AMD) risk. To test for independence, interaction terms of HTRA1 and CFH genotypes were entered in the regression analysis and interaction terms between CFH and HTRA1 genotypes were not significantly associated with AMD, when adjusted for CFH and HTRA1 genotypes.

Statistics: SPSS for windows (release 14.0; SPSS, Inc) was used for statistical analyses. Continuous variables were analyzed by t-test and presented as means +/-standard deviation (SD). Categorial variables are presented as percentages and were compared by chi-square test. A stepwise binary logistic regression analysis was performed to assess the influence of HTRA1 and CFH genotypes on AMD risk. Odds ratios (OR) estimated from logistic regression were reported with corresponding 95% confidence intervals (95% CI). A $p<0.05$ was considered statistically significant.

RESULTS

Prevalences of HTRA1 -625G>A and CFH Y402H genotypes are summarized in Table 1. There was no deviation in either patients or controls from the HTRA1 as well as CFH genotype distributions predicted by the Hardy-Weinberg equilibrium.

Homozygosity for the HTRA1 -625A allele was significantly more prevalent in patients with exudative AMD than among control subjects (27.7% vs. 5.1%, $p<0.001$). Binary logistic regression analysis revealed significant increased risks for exudative AMD among subjects heterozygous for the HTRA1 -625A allele compared to those with the wildtype genotype, when adjusted for CFH Y402H genotypes. The OR increased among subjects homozygous for the HTRA1 -625A allele compared to those with the wildtype genotype. Similarly, heterozygous carriers of a CFH 402H allele were at increased risk for AMD compared to those with the CFH wildtype genotype, when adjusted for HTRA1 -625G>A genotypes. Again, the OR increased among subjects carrying the homozygous CFH 402HH genotype. Interaction terms between CFH and HTRA1 genotypes were not significantly associated with AMD.

Frequencies and ORs of HTRA1 and CFH genotype combinations are shown in Table 2 and Figure 1. Interestingly, the combined presence of the HTRA1 -625AA and CFH 402HH genotypes was found in 18 (7.4%) patients with exudative AMD, but not in any of the control subjects ($p<0.001$).

Adjustment for smoking habits did not substantially alter any of the aforedescribed ORs (data not shown).

DISCUSSION

The HTRA1 -625A allele was found to be strongly associated with exudative AMD, and the observed effect was comparable to that of the CFH 402H allele. Both polymorphisms were independently associated with increased risk for AMD and showed clear allele-dose effects. An allele-dose effect of the HTRA1 -625G>A polymorphism has also previously been observed among North American AMD patients, but not in a Chinese population [42,43]. In the present study, the combined effects of CFH and HTRA1 genotypes were more pronounced than those reported previously in a Caucasian cohort from Utah [43]. Interestingly, we observed the combined presence of the CFH 402HH and the HTRA1 -625AA genotypes only in patients with AMD, but not in any of the control subjects, suggesting a remarkable high risk for AMD associated with this genotype combination.

The present study is the first to confirm the previously reported role of the HTRA1 -625G>A polymorphism in AMD patients of Caucasian descent and extends our knowledge to a

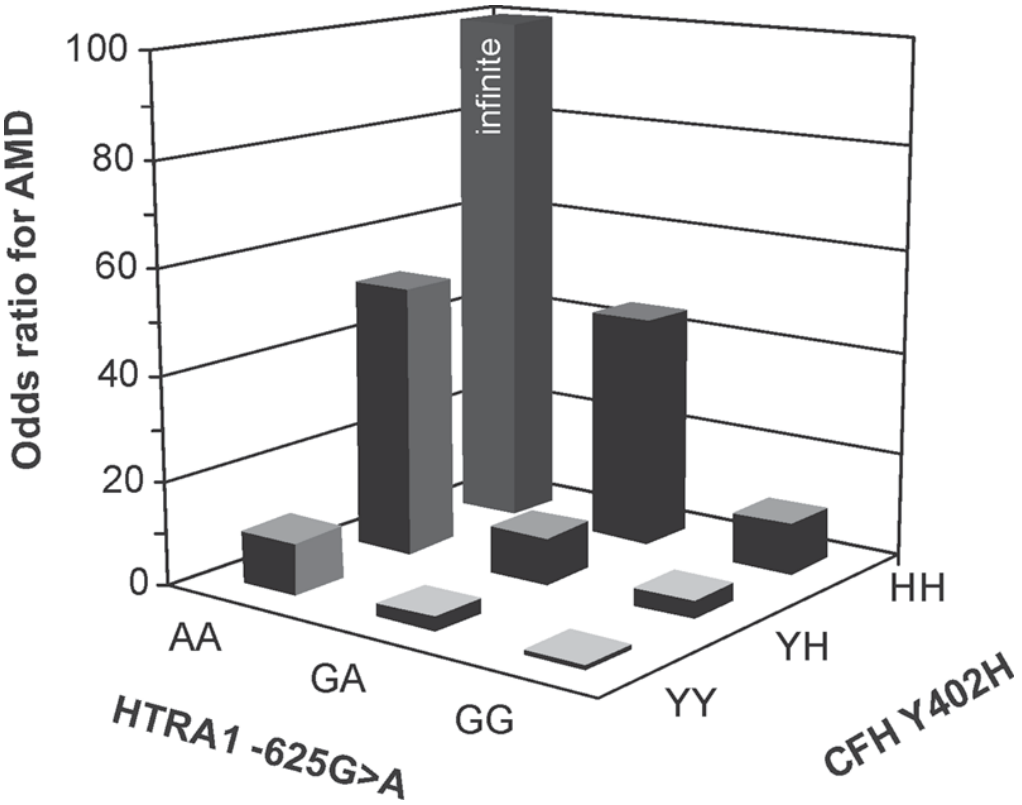

Figure 1. HTRA1 -625G>A and complement factor H Y402H genotype combinations and odds ratios for age-related macular degeneration. Odds ratios were calculated using carriers of both complement factor H (CFH) and HTRA1 wildtype genotypes as reference group. The HTRA1 -625AA and CFH 402HH genotype combination was not found among controls and the odds ratio for this age-related macular degeneration (AMD) combination was infinite.

European population. In the present study the HTRA1 -625A allele frequency was 0.21 among control subjects, similar to that reported for North American control subjects of Caucasian descent [43]. Independent contribution of similar magnitude to the risk of exudative AMD may be explained by the fact that CFH and HTRA1 are encoded by separate genes on different chromosomes and act through different pathways previously shown to play a role in the pathogenesis of AMD [11,42,43,53].

The precise pathomechanism by which the HTRA1 -625A allele affects susceptibility to AMD, however, is still elusive. In vitro, higher luciferase expressions have been reported in both ARPE19 and HeLaS3 cells transfected with the HTRA1 -625AA genotype compared to those homozygous for the -625G allele [42]. It has been suggested that the presence of the HTRA1 -625A allele may alter the affinity of transcription factors including adaptor-related protein complex 2 alpha and serum response factor to the HTRA1 promoter [42].

A potential mechanism by which the HTRA1 -625A allele may contribute to AMD risk is its ability to bind to TGF-β family members and to inhibit signaling of TGF-β family proteins such as Bmp2 and Bmp4, which have previously been reported to act as negative growth regulators in the RPE [44,54]. In addition, HTRA1 is thought to contribute to the destruction of extracellular matrix by affecting the expression of metalloproteases [55].

CFH is involved in the regulation of the alternative complement pathway. Complement components have previously been found in drusen, suggesting dysregulation of complement activation may be involved in the development of AMD [53]. Recently, Laine and coworkers reported that the binding of the CFH 402H variant to C-reactive protein was strongly reduced compared to the wildtype 402Y variant [56]. This indicates that the association of the CFH 402H allele with AMD could be due to reduced clearance of cellular debris and increased local inflammation.

In addition to the investigated gene variants, other polymorphisms encoded by several genes such as CFH, CFHR1, CFHR3, complement factor B, complement component 2, LOC387715, and vascular endothelial growth factor have recently been associated with AMD [13,17,19,28,31,57-62]. As AMD is a multifactorial disease, the interaction between these genetic variants and environmental factors may affect the development of different AMD phenotypes as well as AMD progression. Subsequent studies focusing on the identification of these interactions are therefore of utmost importance.

Recent progress in the knowledge of the association of genetic factors with increased risk for AMD has substantially improved insight into the pathogenesis of this disease. In the future, determination of risk alleles may contribute to the identification of patients at risk and lead to the development of new therapeutic approaches.

In conclusion, our study suggests that both the HTRA1 -625A and the CFH 402H alleles are independently associated with exudative AMD in a Central European population.

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Purpose: Exudative age-related macular degeneration (AMD) is one of the most common causes of severe visual loss. Both environmental and genetic factors, such as the complement factor H (CFH) 402H allele, have been associated with AMD. Recently, the HTRA1 -625A allele was identified as a novel risk marker in both a North American and a Chinese population. The present study was performed to evaluate the association of the HTRA1 -625A allele with exudative AMD in a Central European population. Methods: The present case-control study included 242 patients with exudative AMD and 157 control subjec Association of the HTRA1 -625G>A promoter gene polymorphism with exudative age-related macular degeneration in a Central European population. M. Weger, W. Renner, +6 authors A. Haas. Medicine. Molecular vision.Â Polymorphisms in Complement Factor H and Hemicentin-1 genes in a Japanese population with dry-type age-related macular degeneration. Age-related macular degeneration (AMD) is the leading cause of irreversible severe vision loss in Caucasians over the age of 50.[1] Evidence from familial aggregation studies, twin studies, and segregation analysis all point to a significant role for genetic factors in the etiology of AMD.[2], [3] Among common genetic polymorphisms, the ApoE 2 allele appears to be associated with. increased susceptibility to AMD.[4] Recent genetic research has focused primarily on the nuclear genome and resulted in significant new associations, such as those in the Complement Factor H gene (CFH) on Chromosome Age-related Macular Degeneration detection using deep convolutional neural network. Fulltext Access 9 Pages 2018. Therapeutic potential of omega-3 fatty acid-derived epoxyeicosanoids in cardiovascular and inflammatory diseases.Â Language processing in age-related macular degeneration associated with unique functional connectivity signatures in the right hemisphere. Fulltext Access 47 Pages 2018. A comprehensive review on contact lens for ophthalmic drug delivery. Fulltext Access 68 Pages 2018.Â R102G polymorphism of the complement component 3 gene in Malaysian subjects with neovascular age-related macular degeneration. Fulltext Access 5 Pages 2018. Leaves of Acer palmatum thumb. Ageâ€related macular degeneration is a complex disease caused by environmental and genetic factors. Two major genetic loci were identified at chromosomes 1q31 and 10q26 which account for more than 50% of cases (Weger et al. 2007). They involve a variant in the complement factor H (CFH) gene, encoding the main regulator of the alternative complement pathway (Hageman et al. 2005), and a polymorphism on chromosome 10q26 encompassing the ageâ€related maculopathy susceptibility 2 (ARMS2) gene (Rivera et al.Â (2007): Association of the HTRA1 â€625G>A promoter gene polymorphism with exudative ageâ€related macular degeneration in a Central European population . Mol Vis 13 : 1274 â€“ 1279 . CAS PubMed Web of ScienceÂ® Google Scholar.