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RESEARCH ARTICLE

Ethnic Variation in AMD-Associated Complement Factor H Polymorphism p.Tyr402His

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Age-related macular degeneration (AMD) is the most common cause of irreversible visual loss in the developed world. Previous studies have demonstrated that the c.1204T>C, p.Tyr402His allelic variant in the complement factor H (CFH) gene is associated with an approximately three-fold increased risk for AMD in Caucasians of predominantly European descent. Both the prevalence as well as the phenotypic spectrum of AMD varies widely among persons of different ethnicities. We hypothesized that populations with a lower prevalence of AMD might also have a lower prevalence of the CFH risk allele. In this study we sought to determine the frequency of this sequence variant in control populations of Caucasians, African Americans, Hispanics, Somalis, and Japanese. Normal control populations were assembled for each ethnic group: Caucasian (n = 148), Somali (n = 128), African American (n = 75), Hispanic (n = 81), and Japanese (n = 82). Individuals were genotyped using a restriction digest assay and the frequency of the C allele at nucleotide position 1204 of the CFH gene was determined. A bioinformatic approach was used to identify SNPs in linkage disequilibrium with rs1061170 (c.1204T>C, p.Tyr402His) from the human haplotype map project database (HapMap) in order to validate the findings. We found widely discordant frequencies of the risk allele between some of the different ethnic groups: Japanese 0.07±0.02, Hispanics 0.17±0.03, African-Americans 0.35±0.04, Caucasians 0.34±0.03, and Somalis 0.34±0.03. Allele frequencies generated by analysis of the HapMap database were consistent with these findings. This study suggests that there are other yet unidentified genetic factors important in the pathogenesis of AMD that may mitigate the effects of c.1204T>C, p.Tyr402His variant. Hum Mutat 27(9), 921–925, 2006. **© 2006 Wiley-Liss, Inc.**

KEY WORDS: age-related macular degeneration; AMD; complement factor H; CFH; ethnic variation

INTRODUCTION

Age-related macular degeneration (AMD) is the most common cause of severe visual loss in the developed world, affecting more than 10 million people in the United States alone [Eye Diseases Prevalence Research Group, 2004]. Approximately 1 in 3 people over the age of 75 years are affected to some degree [Klein et al., 1992]. Moreover, the U.S. Census Bureau has predicted that the number of people in this age group will increase by 60 to 80% in the next 25 years, making the prevalence of blindness from AMD greater than that from glaucoma and diabetic retinopathy combined. In the United States, more than 7 million people have macular drusen of sufficient size and number that they are at substantial risk for severe visual loss [Eye Diseases Prevalence Research Group, 2004].

Genetic predisposition plays a significant role in the pathogenesis of this disease [De Jong et al., 1997; Klaver et al., 1998; Seddon et al., 1997]. Recently, a number of studies have

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Dr. Grassi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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demonstrated an association between AMD and the c.1204T>C, p.Tyr402His allelic variant in the Factor H (CFH; MIM# 134370) gene [Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005]. In Caucasian populations of predominantly European-American descent, the histidine allele has a frequency of approximately 35% (29–39%) and confers a three-fold increased risk for AMD (OR 2.45–4.6) [Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005]. It has long been known that the prevalence of AMD varies widely among different ethnicities [Gregor and Joffe, 1978; Munoz et al., 2000; Oshima et al., 2001; Sommer et al., 1991; Eye Diseases Prevalence Research Group, 2004; Varma et al., 2004; Yuzawa et al., 1997]. Moreover, the phenotypic spectrum of AMD among these groups is quite heterogeneous [Andersen, 2004; Lim et al., 1998; Schachat et al., 1995; Sho et al., 2003; Uyama et al., 1992, 2000; Yuzawa et al., 1991].

The purpose of this study was to explore the ethnic variation of the frequency of the p.Tyr402His sequence variant among Caucasians, African Americans, Hispanics, Somalis, and Japanese.

PATIENTS AND METHODS

Subjects

The recruitment and research protocols were reviewed and approved by the University of Iowa Institutional Review Board. Informed consent was obtained from all study participants. All collaborator study sites were either approved by local Institutional Review Boards or were part of studies that conformed with the tenets of the Declaration of Helsinki. All subjects (except where noted) were examined by an ophthalmologist and were found to have no signs of macular degeneration. Only those individuals with a normal examination were enrolled as controls. DNA was extracted from peripheral blood according to a previously described protocol (except where noted) [Buffone and Darlington, 1985].

A total of 148 unrelated Caucasian individuals (general-population controls) were enrolled in the study. Subjects were ascertained from the University of Iowa's Department of Ophthalmology. All subjects were over the age of 50 years (average age 75.5 years). Individuals were enrolled during the same period by the same clinic. A total of 128 subjects of Somali ancestry were analyzed for the study. All subjects had self-reported normal vision. Individuals were excluded if they had a significant past ocular history of a vision compromising condition. Subjects were 18 years of age or older. Individuals were first generation emigrants from Somalia residing in Minneapolis, MN. In some of these subjects DNA samples were obtained by cheek swab [Freeman et al., 1997]. A total of 75 African-American individuals were analyzed for the study. All subjects resided in New York City. A total of 81 individuals of Hispanic ancestry were enrolled under the protocol for the Proyecto VER study [Quigley et al., 2001]. This study was a population-based survey of visual impairment and blindness among noninstitutionalized Mexican Americans, age 40 years or older, living in Pima and Santa Cruz counties of southern Arizona. The 82 Japanese individuals analyzed in this study were ascertained at the Gifu University School of Medicine in Gifu, Japan.

Genotyping

A total of 12.5 ng of each patient's DNA were used as template in a 8.35-µl PCR containing: 1.25 µl 10× buffer (100 mM Tris-HCL pH 8.3, 500 mM KCl, 15 mM $MgCl_2$), 300 µm of each dCTP, dATP, dGTP, and dTTP, 1 pmol of each primer, and 0.25 units Biolase (San Clemente, CA; www.biolase.com) polymerase. Samples were denatured for 5 minutes at 94°C and incubated for 35 cycles under the following conditions: 94°C for 30 sec, 55°C for 30 sec, and 72°C for 30 sec in an MJ Research Peltier DNA thermocycler (PTC-225) (Johannesburg, South Africa; www.mjr.com). Primers were generated based on the GenBank sequence of the CFH gene (NM_000186.2): F: 5′ TCATTGT TATGGTCCTTAGGAAA 3′ R: 5′ ACTGTGGTCTGCGCTT TTG 3′, New England Biolabs (Ipswich, MA; www.neb.com/nebecomm/default.asp) restriction endonuclease NlaIII was added to the PCR products in the following reaction per well: 1.2 µl 10× BSA, 1.2 µl NEBuffer 4, 0.2 µl NlaIII (10,000 U/ml), and 1.05 µl nuclease-free water. The samples were incubated at 37°C for 2 hr in a DNA thermocycler (MJR). After digestion, 5 µl of stop solution (95% formamide, 10 mM NaOH, 0.05% Bromophenol Blue, 0.05% Xylene Cyanol) was added to each sample. Digested amplification products were electrophoresed on 2% agarose E-gels from Invitrogen (Carlsbad, CA; www.invitrogen.com). All gels were stained with ethidium bromide for 15 minutes in the Invitrogen E-gel powerbase v4 and the presence of the CFH C allele was determined by inspection of the restriction pattern. Genotype correlation with the restriction pattern was confirmed in a small subset of subjects by automated sequencing.

Bioinformatics

The mutation nomenclature follows the format required by this journal. The cDNA numbering is based on GenBank NM_000186.2 with the A of the ATG initiation codon serving as +1.

Preliminary allele frequencies were identified for ethnic populations based upon the Centre d'Etude du Polymorphisme Humain (CEPH), Nigerian, Japanese, and Han Chinese SNP genotyping from the human haplotype map project database (HapMap; www.hapmap.org). The final frequency of the rs1061170 SNP (c.1204T>C, p.Tyr402His) was inferred in these populations based upon the near-perfect linkage disequilibrium (D′ 0.8–1.0) [Edwards et al., 2005] of rs1061170 (c.1204T>C, p.Tyr402His) to several nearby SNPs (rs1061147, c.921C>A and rs10922094, c.1336+2136G>C).

Statistics

Standard error (SE) for allele and genotype frequency was calculated using the formula

$$SE = \sqrt{[p(1-p)/n]},$$

where the frequency is p and n is the total number of alleles for allele frequency or the total number of individuals for genotype frequency

RESULTS

Caucasians

The prevalence of the histidine alteration was assessed in 148 unrelated subjects ascertained at the University of Iowa. Both the allele and genotype frequencies were compared to prior published studies (Table 1) [Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005]. The frequency of the risk allele in the University of Iowa control cohort is 34% (Table 2 and 3). The prevalence of histidine ranges from 34 to 39% in the Caucasian population unaffected by AMD.

Ethnicities

Control populations of subjects from four different ethnicities (African-American, Hispanic, Japanese, and Somali) were

TABLE 1. Caucasians of European Descent

	Edwards	Klein	Haines	Hageman
Risk allele frequency (C)[a] (%)	34[b] (39)[c]	35	33	34[b] (34)[c]

[a]c.1204T>C, p.Tyr402His.
[b]First cohort of study that included two independent cohorts.
[c]Second cohort of study that included two independent cohorts.

TABLE 2. Ethnicity Panel*

	Iowa-Caucasian	African-American	Hispanic	Japanese	Somali
C[a]	100 (0.34 ± 0.03)	52 (0.35 ± 0.04)	28 (0.17 ± 0.03)	11 (0.07 ± 0.02)	88 (0.34 ± 0.03)
T	196 (0.66 ± 0.03)	98 (0.65 ± 0.04)	134 (0.83 ± 0.03)	153 (0.93 ± 0.02)	168 (0.66 ± 0.03)
CC	10 (0.07 ± 0.02)	8 (0.11 ± 0.03)	4 (0.05 ± 0.02)	2 (0.02 ± 0.02)	9 (0.07 ± 0.02)
CT	80 (0.54 ± 0.04)	36 (0.48 ± 0.06)	20 (0.25 ± 0.05)	7 (0.09 ± 0.03)	70 (0.55 ± 0.04)
TT	58 (0.39 ± 0.04)	31 (0.41 ± 0.06)	57 (0.70 ± 0.05)	73 (0.89 ± 0.03)	49 (0.38 ± 0.04)
Total patients	148	75	81	82	128

*All allele frequencies are in Hardy-Weinberg equilibrium. Values are number of patients (frequency ± standard error).
[a]c.1204T>C, p.Tyr402His.

TABLE 3. HapMap

	Frequencies (%)			
	CEPH/Utah	Han Chinese	Japanese	Nigerian
rs1061147[a]				
A	39	7.8	6.8	37.5
C				
rs1061170[b]				
C	N/A	N/A	N/A	N/A
T				
rs10922094[c]				
C	39.2	6.7	6.8	31.4
G				

[a]c.921A>C (−5kb).
[b]c.1204T>C, p.Tyr402His.
[c]c.1336+2136G>C (+3kb).

analyzed for the frequency of the risk (C) allele. Widely divergent frequencies were noted between some of these populations (7–35%) (Table 2). The C allele frequency in these populations were: Japanese 0.07 ± 0.02, Hispanics 0.17 ± 0.03, African-Americans 0.35 ± 0.04, Caucasians 0.34 ± 0.03, and Somalis 0.34 ± 0.03. A statistically significant difference in allele frequency was not appreciated between Caucasians, African-Americans, and Somalis. The frequency of alleles in all populations respected Hardy-Weinberg equilibrium.

HapMap

Data from the HapMap project database were analyzed to confirm the variation that was noted in the Tyr402His sequence variant between the sampled ethnic groups in this study (Table 3). The specific SNP (rs1061170, c.1204T>C, p.Tyr402His) is not included in the HapMap as of the preparation of this manuscript. Published SNPs (rs1061147, rs10922094) in linkage disequilibrium with rs1061170 were used as surrogates. We confirmed similar haplotype frequencies in all comparable populations. At this locus the haplotype frequency for Japanese subjects in the HapMap is 6.8% vs. 7% determined by our study. Interestingly, the Nigerian and the Somali haplotype frequencies were also very similar (37.5 vs. 35%).

DISCUSSION

To date only Caucasian populations of predominantly European descent have been assessed for the p.Tyr402His polymorphism association with AMD. The attributable fraction of AMD due to this polymorphism is approximately 50% [Edwards et al., 2005; Haines et al., 2005; Klein et al., 2005]. The frequency of this allele may even vary between Caucasian subpopulations. For instance, a statistically significant 33% difference in the prevalence of AMD was noted when comparing two Caucasian populations of different European ancestry [Cruickshanks et al., 1997]. There was no difference between these groups in other known acquired risk factors for AMD thereby implicating variations in underlying genetic susceptibility. Interestingly, when individuals of English ancestry were removed from the analysis this difference disappeared.

Early AMD in Japanese is much less frequent than in Caucasians of European descent (12.7% vs. 28%) [Oshima et al., 2001]. Late AMD is also about half as common (0.87% vs. 1.7%). However, the proportionate frequency of the histidine (His/C) allele in Japanese subjects is much lower than this (7% compared to 34% in Caucasians). While the recent increased incidence of AMD in Japan [Bird, 2003; Ishiko et al., 2002; Kubo et al., 1989, 1990; Maruo et al., 1991; Miyazaki et al., 2005; Yuzawa et al., 1991, 1997] may be secondary to changing dietary and lifestyle habits, it is more difficult to reconcile the gender and phenotypic differences [Uyama et al., 1992] from Caucasians without invoking other genetic factors. Thus, not only does the AMD phenotype of the Japanese differ from that of Caucasians, but also the frequencies of their CFH genotypes are quite dissimilar as well.

In contrast, African-Americans have similar genotype frequencies at this locus to Caucasians, but their prevalence of AMD is much lower [Friedman et al., 1999; Munoz et al., 2000; Eye

Diseases Prevalence Research Group, 2004]. The observed frequency of the risk allele is similar in African-Americans and Caucasians (35% vs. 34%, respectively). However, the rate of late AMD in African-Americans is five times lower than that in Caucasians despite the same risk allele frequency in these groups [Klein et al., 1999; Pieramici et al., 1994]. Varying rates of known environmental risk factors like smoking and hypertension between Latinos, African-Americans, and Caucasians have not been found to explain the differences in the prevalence of AMD between these groups [Cruickshanks et al., 1997; Friedman et al., 1999; Klein et al., 1999]. It has been postulated that the increased melanin in the choroid of African-Americans may serve a protective, antioxidant function [Pieramici et al., 1994]. Therefore, the relative paucity of late AMD in African Americans [Pieramici et al., 1994; Schachat et al., 1995; Sommer et al., 1991] despite this high allele frequency suggests a role for additional genetic factors that may be protective or mitigate the affects of the Tyr402His sequence variant in this population.

There are a number of limitations to this study. Control individuals were only ascertained for analysis. In future studies it would be desirable to assess individuals affected with AMD from each ethnicity in order to determine if the histidine alteration confers the same degree of risk for the development of AMD in these populations. Another limitation of this study is related to the sample size of the subject populations. This is especially evident in the Japanese cohort in which only two individuals homozygous for the risk allele (CC) were identified.

In conclusion, this study suggests that there are other yet unidentified genetic factors important in the pathogenesis of AMD. These factors may operate independently or mitigate the affects of the p.Tyr402His sequence variant. Specifically, the findings suggest the presence of additional genetic risk factors for AMD in Japanese individuals thereby explaining differences in prevalence, phenotype, and natural history from AMD in Caucasians. Moreover, individuals of African and Hispanic descent may have a genetic factor that mitigates the affects of the p.Tyr402His polymorphism and is protective for the risk of late AMD.

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