An Ecological Correlation Study of Late Age-Related Macular Degeneration and the Complement Factor H Y402H Polymorphism

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Purpose. To investigate whether variation in the distribution of the risk allele frequency of the Y402H single-nucleotide polymorphism (SNP) across various ethnicities and geographic regions reflects differences in the prevalence of late age-related macular degeneration (AMD) in those ethnicities.

Methods. Published data were obtained via a systematic search. Study samples were grouped into clusters by ethnicity and geographic location and the Spearman correlation coefficient of the prevalence of late AMD and risk allele frequencies was calculated across clusters.

Results. Across all ethnicities, AMD prevalence was seen to increase with age. Populations of European descent had both higher risk allele frequencies and prevalence of late AMD than did Japanese, Chinese, and Hispanic descendants. Results for African descendants were anomalous: although allele frequency was similar to that in European populations, the age-specific prevalence of late AMD was considerably lower. The correlation coefficient for the association between allele frequency and AMD prevalence was 0.40 (95% confidence interval [CI] = −0.36 to 0.84, $P = 0.28$) in all populations combined and 0.71 (95% CI = 0.02–0.94, $P = 0.04$) when people of African descent were excluded.

Conclusions. Evidence was found at the population level to support a positive association between the Y204H risk allele and the prevalence of AMD after exclusion of studies undertaken on persons of African ancestry. Data in African, Middle Eastern, and South American populations are needed to provide a better understanding of the association of late AMD genetic risk across ethnicities. (*Invest Ophthalmol Vis Sci.* 2010;51:2393–2402) DOI:10.1167/iovs.09-4228

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Age-related macular degeneration (AMD) is the leading cause of blindness in older people in Western populations. Several lifestyle and environmental risk factors have been identified for AMD,[1] and more recently, genetic variants with strong effects have also been identified.[2] The genetic variants have mainly been studied in people of European origin. In this study, we focused on the single-nucleotide polymorphism (SNP) Y402H in the complement factor H (*CFH*) gene, which is characterized by a substitution of histidine for tyrosine at codon 402 on the long arm of chromosome 1, region 31 (rs1061170). This SNP is particularly striking because of the strength of its association with late AMD. Odds ratios (ORs) >5 were found for those homozygous for the Y402H risk allele, making this genetic association one of the strongest for a complex disorder yet to be reported.[3]

Although most of the population-based studies reporting the prevalence of late AMD have been undertaken in people of European origin in Western settings, studies are now emerging from other geographic areas. These, along with studies in different ethnic subgroups within Western populations (principally the United States) suggest that there is considerable variation in the distribution of risk alleles of the Y402H SNP[4–8] and that these variations may in part explain the differences in the prevalence of late AMD in the respective population groups. To our knowledge, no studies have been conducted to examine whether differences in the frequency of this variant between populations or ethnic groups can explain differences in the prevalence of late AMD. We therefore conducted an ecological correlation of the prevalence of late AMD with the frequencies of the Y402H risk allele across ethnic groups and geographic regions. We considered only late AMD because of the differences in classification and grading of early AMD across studies.

Methods

We systematically searched the literature for studies of the prevalence of late AMD and studies that included representative data on the frequency of Y402H genotypes or alleles in the general population.

AMD Prevalence

We searched PubMed for relevant articles using the search terms "prevalence" in combination with "age-related macular degeneration" or "AMD," limiting our search to English language papers. The articles that we deemed eligible were those that clearly confirmed the use of robust systems of fundus grading to determine the diagnosis of AMD[9,10] and reported prevalence of late AMD (either neovascular, geographic atrophy, or a combination of both), by age groups and ethnicity of the sample. The search identified 22 eligible

TABLE 1. General Characteristics of AMD Prevalence Studies Selected

Study	Year	Study Name	Country	Ethnicity	% Male	Mean Age (SD)	Sample Size (*n*)	Grading System
Andersen et al.[20]	2008	Inuit	Greenland	Inuit			660	ICSARM
Augood et al.[21]	2006	Eureye	7 European countries*	European			4753	ICSARM
Chen et al.[22]	2008	Shihpai	Taiwan	Chinese	62.3	71.8 (4.8)	1058	WARMGS
Friedman et al.[23]	1999	BES	Unites States	African			1836	
			Unites States	European			2475	ICSARM
Gupta et al.[24]	2007	INDEYE	India	Indian			1101	WARMGS
Jonasson et al.[25]	2006	Reykjavik	Iceland	Icelandic	48		922	ICSARM
Kawasaki et al.[5]	2008	Funagata	Japan	Japanese	43.8	70.6 (6.8)	1625	WARMGS
Kawasaki et al.[7]	2008	Sing Malay	Singapore	Malay	48.1	58.67	3265	WARMGS
Klein et al.[26]	1992	Beaver Dam	Unites States	European	44.5		4771	WARMGS
Klein et al.[27]	2003	CHD	Unites States	African			363	WARMGS
				European			1998	
Klein et al.[28]	2006	MESA	Unites States	African	45.1	62.4 (9.9)	1590	
				Chinese	49.4	62.4 (10)	699	
				Hispanic	48.1	61.6 (10)	1280	WARMGS
				European	48.8	63 (10)	2315	
Klein et al.[29]	1999	NHANES	Unites States	African			2129	
				Hispanic			1925	WARMGS
				European			4267	
Krishnaiah et al.[4]	2005	APES	India	Indian	47	54 (10.6)	3723	
Li et al.[30]	2006	Beijing	China	Chinese		56.1 (10.5)	4376	WARMGS
Mitchell et al.[31]	1995	Bluemountain	Australia	European	43.3		3654	WARMGS
Munoz et al.[32]	2005	Proyecto VER	Unites States	Hispanic		68	2807	WARMGS
Oguido et al.[33]	2008		Brazil	Japanese		71	483	ICSARM
Oshima et al.[34]	2001	Hisayama	Japan	Japanese	40.1		1486	ICSARM
Schachat et al.[6]	1995	Barbados	Barbados	African			3344	WARMGS
vanNewkirk et al.[35]	2000	MVIP	Australia	European	45	60.2 (12.9)	3271	ICSARM
Varma et al.[36]	2004	LALES	Unites States	Hispanic	42	54.9 (10.7)	5875	WARMGS
Vingerling et al.[37]	1995	Rotterdam	Netherlands	European	40.3		6251	WARMGS

BES, Baltimore Eye Study; INDEYE, India Eye Feasibility Study; CHD, cardiovascular Health Study; MESA, Multi-ethnic Study of Atherosclerosis; NHANES, National Health and Nutrition Examination Survey; Proyecto VER, Vision and Eye Research Project; MVIP, Melbourne Visual Impairment Project; LALES, Los Angeles Latino Eye Study; ICS ARM, International Classification System for ARM[9]; WARMGS, Wisconsin Age-Related Maculopathy Grading System.[10]

* Multicountry study of Norway, Estonia, United Kingdom, France, Italy, Greece, and Spain.

articles, some of which reported prevalence in samples from two or more ethnic groups, resulting in a total of 29 unique samples. The studies reported AMD prevalence using different age ranges starting from as low as 35 to above 90.

CFH Y402H Polymorphism

We searched PubMed for relevant articles by using the search terms "age-related macular degeneration" and "gene" or "complement factor H" as well as "complement factor H" on its own. We searched for articles on association studies of AMD as well as non-AMD diseases with the Y402H polymorphism. Among these, we included those that reported SNP allele or genotype frequencies of non-AMD cases. Studies were included irrespective of whether Hardy-Weinberg equilibrium (HWE) was observed for the Y402H genotypes in non-AMD cases, since this is not necessarily reflective of poor study design, but may instead be reflective of copy number variation within the complement factor genetic region.[11] Furthermore, in studies in which HWE was observed, the association between the Y402H risk allele and AMD has been shown to be the same as in studies in which HWE was not observed (see, for example, Thakkinstian et al.[12]). Our search resulted in 50 eligible articles, some of which included two or more samples or samples from more than one ethnic group, hence 67 unique samples. Tables 1 and 2 give general characteristics of the prevalence and Y402H studies that were selected in our search.

Analysis

Our hypothesis was that the observed differences in the Y402H risk allele frequencies between ethnicities reflects various prevalence rates of late AMD in these ethnicities. We assumed that the estimates given by the samples in the studies are measures of true allele frequencies and prevalence of late AMD in their respective populations and geographic regions. We thus defined clusters of samples within studies based on both ethnicity and geographic region. For example, people of non-Hispanic European origin living in the United States were categorized in the European-American cluster. For each cluster, mean log-transformed prevalence and mean risk allele frequencies were calculated across all samples, weighted by the sample sizes. Spearman's rank correlation coefficient was calculated.

RESULTS

The prevalence of late AMD and allele frequency data in our analysis came from independent samples within ethnicities and regions, except for four studies that sampled from the same populations: MVIP (Melbourne Visual Impairment Project), LALES (Los Angeles Latino Eye Study), ProyectoVER (Vision and Eye Research Project), and the Rotterdam Eye Study (Tables 1 and 2). Our selected publications produced 11 clusters on prevalence of AMD and 12 on Y402H studies. Of these, nine clusters had data on both the prevalence and Y402H frequencies. The age groups used in the prevalence studies varied slightly from study to study, and we therefore merged some of these to create three common groups: below 60, between 60 and 69, and above 70 years.

In the studies on prevalence of late AMD, a clear increase was observed with advancing age but there was a marked variation between studies in the prevalence rates.

TABLE 2. General Characteristics of the Y402H Studies Selected

Study	Year	Country	Ethnicity	Sample Size*	Mean Age	Disease† and Study
Baird et al.[38]	2006	Australia	European	144	70	AMD-MVIP
Brantley et al.[39]	2007	Unites States	European	189	69.5	AMD-AREDS
Chen et al.[40]	2006	China	Chinese	244	73.5	AMD
Chowers et al.[41]	2008	Israel	Israeli	1180	70.8	AMD
Conley et al.[42]	2005	Unites States	European	210		AMD
DeJong et al.[43]	2007	Netherlands	European	5066		AMD-Rotterdam
Despriet et al.[44]	2006	Netherlands	European	3619		AMD
				2392		
Droz et al.[45]	2008	Switzerland	European	52	74.9	AMD
Edwards et al.[46]	2005	Unites States	European	134		AMD
			European	68		AMD
Fisher et al.[47]	2007	Russia	European	151	71	AMD
Fuse et al.[48]	2006	Japan	Japanese	192	68.6	AMD
Gotoh et al.[49]	2006	Japan	Japanese	105	60.2	AMD
Gotting et al.[50]	2008	German	European	189	0	AMD
Grassi et al.[8]	2006	Unites States	African	75		AMD
			European	148		
			Hispanic	81		
			Japanese	82		
			Somali-African	128		
Hageman et al.[18]	2005	Unites States	European	131	78.4	AMD
			European	275	68.84	
Haines et al.[51]	2005	Unites States	European	24	69.8	AMD
Jakobsdottir et al.[52]	2005	Unites States	European	117		AMD
Kaur et al.[19]	2006	India	Indian	120	63.9	AMD
Kim et al.[53]	2008	Korea	Koreans	187		AMD
Lau et al.[54]	2006	China	Chinese	232		AMD
Lee et al.[55]	2008	Singapore	Chinese	93		AMD
LeFur et al.[56]	2008	France	European	6348		Dementia
			European	642		Alzheimer's
Lin et al.[57]	2008	Taiwan	Chinese	180		AMD
Magnusson et al.[58]	2006	Iceland	Icelandic	171		AMD
			Icelandic	891		AMD
		Unites States	European	203		AMD
Maller et al.[59]	2006	Unites States	European	934	74	AMD-AREDS
Mooijaart et al.[60]	2007	Netherlands	European	640		Inflammation,
			European	552		Cardiovascular-PAMD
Mori et al.[61]	2007	Japan	Japanese	139		AMD
Narayanan et al.[62]	2006	Unites States	European	58	72.5	AMD
Ng et al.[63]	2008	China	Chinese	155	73.1	AMD
Okamoto et al.[64]	2006	Japan	Japanese	89		AMD
Pai et al.[65]	2007	Unites States	European	499	65.1	Coronary
			European	473	60.3	Heart Disease
Pulido et al.[66]	2007	Unites States	European	120		Coronary Heart Disease
Rivera et al.[67]	2005	Germany	European	611		AMD
			European	335		
Schaumberg et al.[68]	2007	Unites States	European	1071	60.2	AMD-NHS
Seddon et al.[16]	2006	Unites States	European	280		AMD
Seitsonen et al.[69]	2006	Finland	European	105	76.9	AMD
Sepp et al.[70]	2006	England	European	262	75.8	AMD
Simonelli et al.[71]	2001	Italy	European	47	0	AMD
Souied et al.[72]	2005	France	European	91	74.6	AMD
Stark et al.[73]	2007	Germany	European		56.9	Myocardial Infarction-GMI
				973		
Tanimoto et al.[74]	2007	Japan	Japanese	99	73.5	AMD
Tedeschi-Blok et al.[75]	2007	Unites States	Hispanic	570		AMD-LALES
Uka et al.[76]	2006	Japan	Japanese	107		AMD
Volcick et al.[77]	2008	Unites States	African	3010		Atherosclerosis-ARIC
			European	8217		
Wegscheider et al.[78]	2007	Austria	European	163	77.5	AMD
Xing et al.[79]	2008	Australia	European	2381		AMD-Blue Mountains
Xu et al.[80]	2008	China	Chinese	132	66.1	AMD
Zareparsi et al.[81]	2005	Unites States	European	275		AMD
Zee et al.[82]	2006	Unites States	European	335		Cardiovascular diseases-PHS
			European	235		
			European	34		
Zetterberg et al.[83]	2008	Sweden	European	1265	78.6	Alzheimer's
Ziskind et al.[13]	2008	South Africa	African	98	76	AMD

LALES, Los Angeles Latino Eye Study; MVIP, Melbourne Visual Impairment Project; NHS, Nurses' Health study; BMI, German Myocardial Infarction Study; PHS, Physician Health Study; ARIC, Atherosclerosis Risk in Communities.

* Sample sizes of the control group.

† Disease studied.

TABLE 3. Weighted AMD Prevalence by Age-Group and Cluster and Number of Samples Contributing to Each Estimate

Cluster	Age <60		Age 60–70		Age 70+		Prevalence Total % (SE)
	Samples (*n*)	% (SE)	Samples (*n*)	% (SE)	Samples (*n*)	% (SE)	
African (American and Caribbean)	4	0.28 (0.09)	4	0.29 (0.18)	5	0.47 (0.26)	0.34 (0.12)
Chinese	2	0.14 (0.07)	3	0.32 (0.21)	3	1.67 (0.54)	0.55 (0.16)
European Australia	0	—	2	0.24 (0.15)	2	3.4 (0.47)	1.13 (0.18)
European Europe*	0	—	1	0.96 (0.24)	1	4.58 (0.0.37)	2.39 (0.21)
European American	4	0.12 (0.08)	4	0.46 (0.1)	5	2.03 (0.35)	1.18 (0.19)
Hispanic American	4	0.07 (0.04)	4	0.38 (0.22)	4	1.15 (0.36)	0.37 (0.10)
Icelandic	1	0.30 (0.29)	1	1.20 (0.59)	1	10.55 (1.9)	3.47 (0.60)
Indian	2	0.97 (0.22)	2	2.63 (0.45)	2	4.06 (1.14)	1.78 (2.53)
Inuit Greenland	0	—	1	3.84 (0.94)	1	18.52 (2.4)	9.24 (1.13)
Japanese	2	0.19 (0.14)	2	0.87 (0.39)	2	0.94 (0.39)	0.67 (0.21)
Japanese-Brazilian	0	—	0	—	1	1.24 (0.50)	1.24 (0.15)
Malay	1	0.11 (0.08)	1	0.38 (0.22)	1	2.49 (0.58)	0.70 (0.15)

* The European Europe cluster estimates by age group exclude one study (Vingerling et al.[37], Rotterdam study) that did not give sample sizes by age group.

Most notably, lower rates were observed in Chinese, Japanese, and African Americans. At the other extreme were very high prevalence rates in the Icelandic population, whereas the Greenland Inuit had an overall prevalence that was even 2.5 times higher than that of the Icelandics (Table 3, Fig. 1).

In studies on CFH Y402H allele distribution, low-risk allele frequencies (<1%) were observed in the Japanese, Chinese, and Koreans. In most other populations studied, the allele frequencies were between 36% and 42% (Table 4, Figs. 2, 3). Figure 4 shows a plot of the log-transformed, weighted AMD prevalence by age group against the weighted risk allele frequencies. This relationship, across all age groups, is plotted in Figure 5. Only nine clusters are depicted on the graphs because other clusters (Inuit Greenland, South African, Malay, Korean, Israeli, and Japanese-Brazilians) either had prevalence or allele frequency data, but not both, as shown in Tables 3 and 4.

Spearman's rank correlation between weighted AMD prevalence and *CFH* risk allele frequency was 0.40 ($P = 0.28$) and after the studies undertaken on persons of African ancestry were excluded, it was 0.71 ($P = 0.04$).

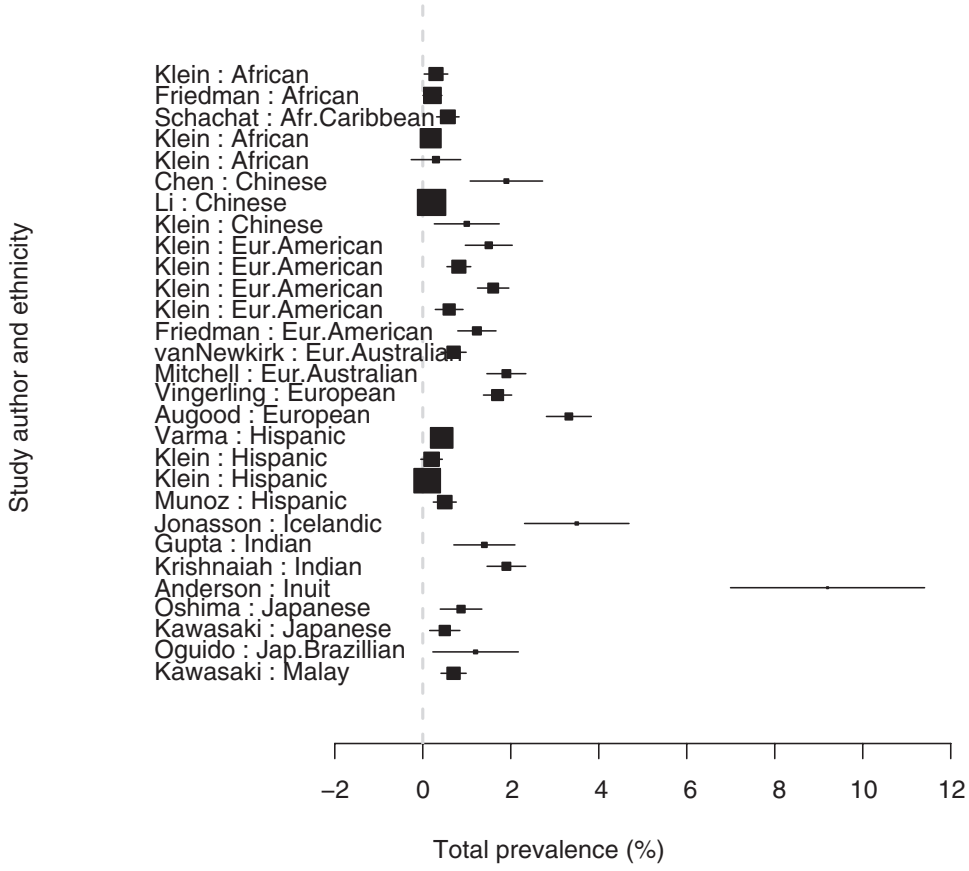

FIGURE 1. Forest plot of total prevalence across all age groups.

TABLE 4. Weighted Risk Allele Frequencies by Cluster

Cluster	Samples (*n*)	Weighted Risk Allele Frequency (SE)
African American	3	0.371 (0.008)
African South America	1	0.420 (0.035)
Chinese	6	0.041 (0.011)
European Australia	2	0.361 (0.008)
European Europe	19	0.359 (0.078)
European American	22	0.378 (0.009)
Hispanic American	2	0.170 (0.005)
Icelandic	2	0.383 (0.014)
Indian	1	0.260 (0.028)
Israeli	1	0.356 (0.009)
Japanese	7	0.069 (0.016)
Korean	1	0.065 (0.013)

DISCUSSION

Overall, our results suggest evidence of a positive association between the prevalence of late AMD and Y402H risk-allele frequency across ethnicities, except in those of African descent. We observed marked differences in both AMD prevalence and allele frequency in different ethnicities and geographic regions. We therefore used an ecological study design to combine evidence of gene–disease association based on published data. To our knowledge, until now, this approach has not been applied to the study of AMD. It provides a useful way of comparing gene–disease associations between ethnicities and geographic regions when large interpopulation-based studies do not exist. The criteria we used to select studies ensured that we included prevalence estimates that were measured using standard diagnostic techniques in different ethnicities. We did not analyze the results by type of late AMD, because not all studies reported prevalence in that way, and therefore we used estimates of any late AMD.

There are several limitations in our analysis. Only four of the prevalence studies listed in Table 1 had the risk allele frequency derived from the same populations. Most of the studies on the Y402H variant were designed as case–control studies and therefore AMD prevalence was not established within them. Risk allele frequencies were strongly homogeneous within each of the clusters, and therefore it was sensible to cluster study samples in that way. This homogeneity within clusters suggests that, at least for the studies in our analysis, within a given homogenous residential population, a representative sample of genetic information is meaningful for others in the same population. With increased ethnic mixing, populations may be more genetically heterogeneous, and self-reported ethnicity may not reflect this. Ethnic mixing and migration may apply to populations of African origin, but the results of the three African American studies and one South African study show similar allele frequencies.

It is interesting that the prevalence of late AMD among African descendants does not match their allele frequencies. This mismatch is unlikely to be due to bias in the corresponding prevalence studies, as they have been carefully designed and rigorously implemented. It may be that an association of the Y402H risk allele with late AMD does not exist or is less pronounced in these populations. At present, there are not sufficient data from association studies on those of African ancestry. There is only one study in Africa in which the association between Y204H and AMD (early form) was investigated.[13] The investigators found a nonsignificant odds ratio of 1.56 (95% confidence interval [CI] = 0.75–3.33) for

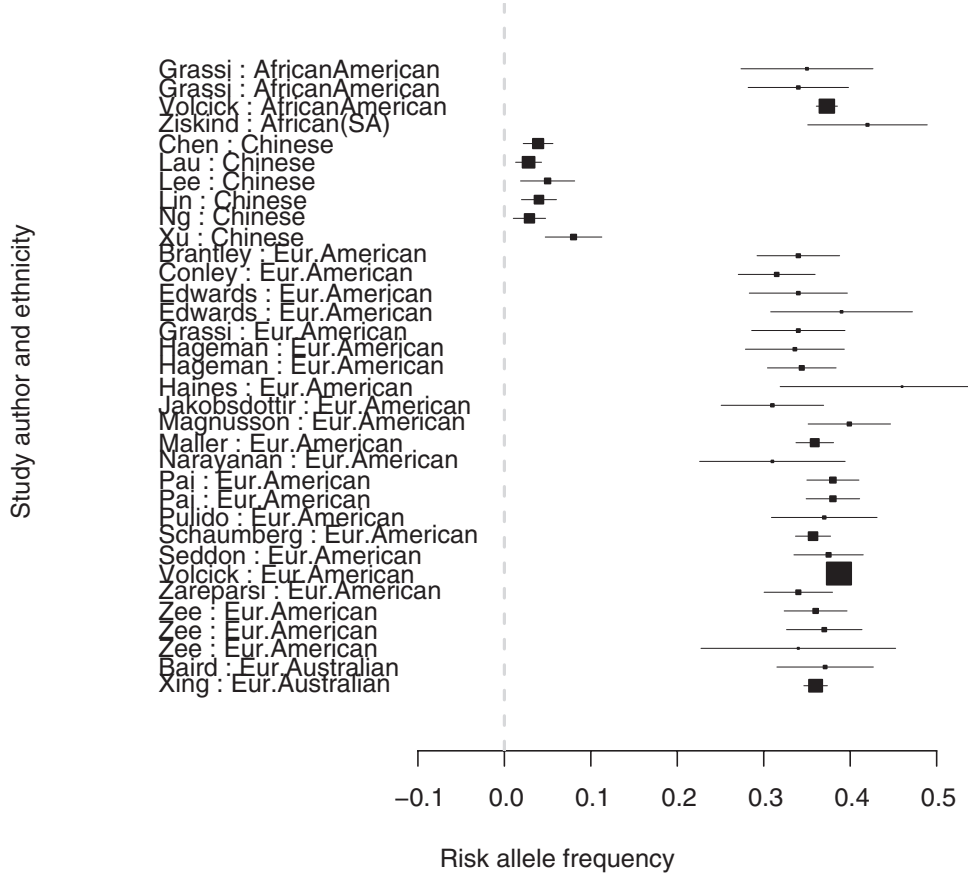

FIGURE 2. Forest plot of risk allele frequency for the first 34 studies.

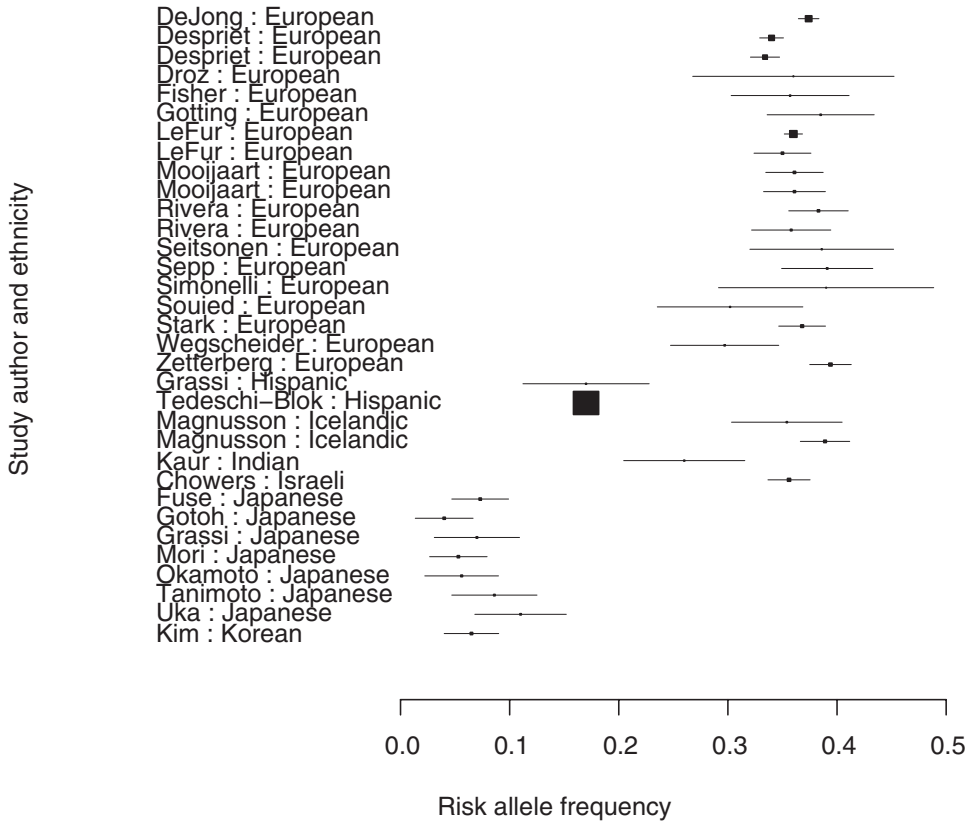

FIGURE 3. Forest plot of the risk allele frequency for the last 33 studies.

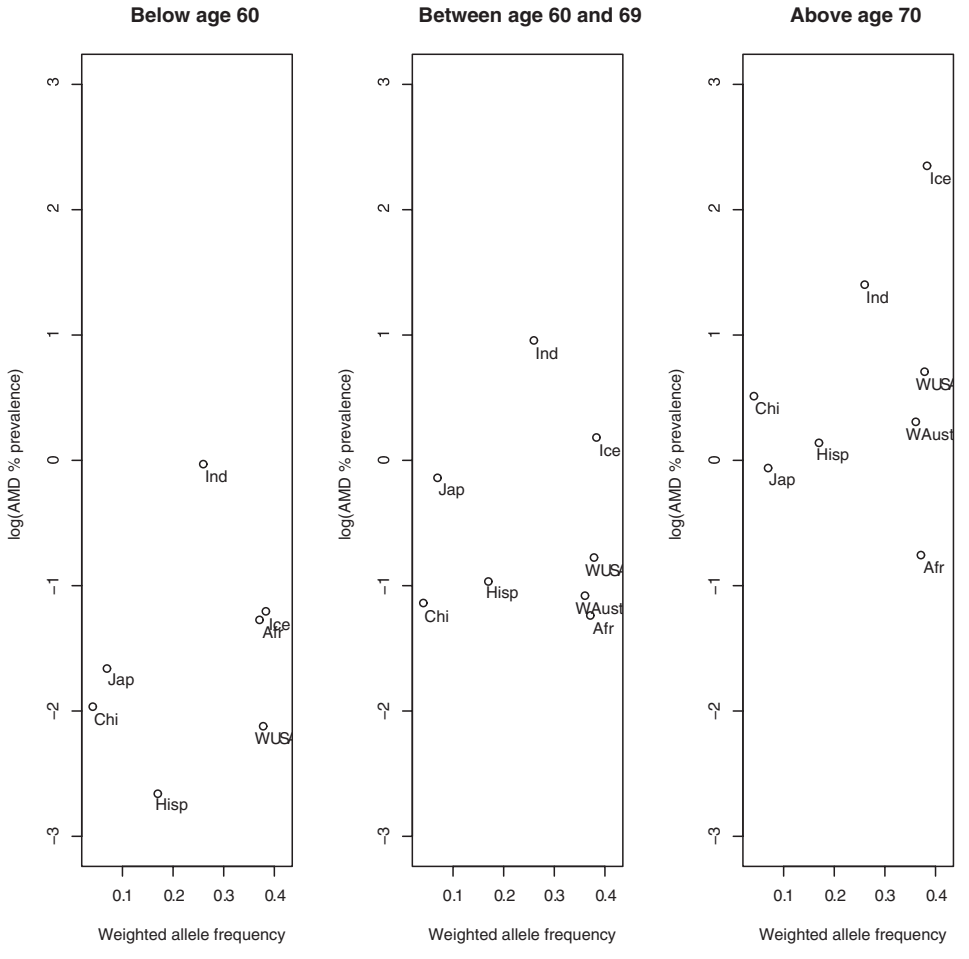

FIGURE 4. Log-transformed AMD prevalence versus risk allele frequencies by age weighted by sample size.

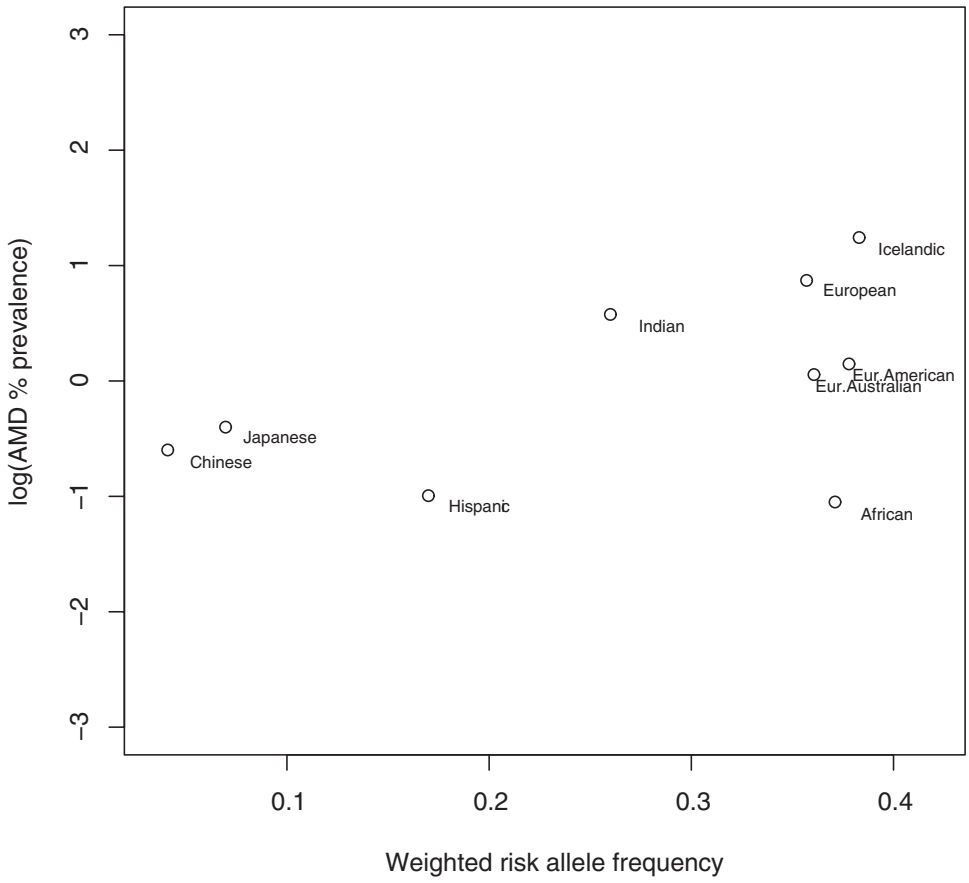

FIGURE 5. Log-transformed AMD prevalence across all age groups versus risk allele frequencies weighted by sample size.

the risk allele, but it was based on a very small sample size. A neighboring deletion allele delCFHR1 confers a protective effect in Europeans.[14] Based on high frequencies of Y402H and delCHFR1 alleles in African Americans, the hypothesis in one study[15] of the complement factor H and related genes was that the effect of these explains the low prevalence of late AMD in African Americans. This notion is in line with what our ecological analysis showed. Further studies are needed in African populations to substantiate this conclusion. It is also plausible that differences between Africans and Europeans in risk factors such as smoking and sunlight may partly explain the lower prevalence of AMD in people of African descent, but at present, there is insufficient evidence to address this point.

There is a notably high prevalence of late AMD among the Icelandics and the Greenland Inuit. Only one prevalence study was available from each of these two fairly environmentally similar but racially different regions, with sample sizes of 922 and 660 for Iceland and Greenland, respectively. The prevalence estimates in these studies may be imprecise due to small sample sizes, but the response rates for both studies were high (76% and 75%), and so the estimates are unlikely to be biased. The allele frequency for the Icelandic study was 0.38, which is comparable to those of European populations. There may be environmental and lifestyle factors that contribute to such a high prevalence of late AMD in these two populations.

Differences in observed prevalences within a given cluster may reflect the paucity of people in the very elderly age group in some studies, perhaps due to response bias. (Older people may be less likely to participate for reasons associated with AMD.) Differences between clusters may also have arisen because, in some ethnicities, the proportion of the older age group is lower in the population. A low number of people in the oldest age groups, where AMD rates are the highest, can lead to imprecision in the estimation of the prevalence (i.e., sampling error). More detailed data, such as the mean ages within the age categories, would have enabled us to investigate potential age bias between ethnicities.

We could not include environmental risk factors that are known to be associated with AMD, such as tobacco smoking,[16,17] because most papers reporting the association of these factors with AMD do not mention the prevalence of the risk factors for the population controls. It is unlikely, however, that even a strong risk factor such as smoking can explain much of the variation in prevalence of AMD. For example, most studies document a lower prevalence of smoking in women, but there is little, if any, variation in prevalence between men and women. In addition, there is no reason to suspect that allele frequency would be related to such environmental factors. We note that the Y402H SNP has been found to be in linkage disequilibrium with other loci on the *CFH* gene,[18,19] suggesting that there is a haplotype effect. We limited our study to this particular SNP because it is the most widely reported genetic variant in relation to AMD and appears to have very strong effects. We note that there are other genes that increase the risk of development of AMD and that such genes may differ across ethnic groups.

In conclusion, we found evidence at the population level to support a positive association with the Y204H risk allele and the prevalence of AMD. We highlight the anomalous result of the high-risk allele frequency and the low prevalence of late AMD in African Americans. There are none or very few articles on populations from the African continent or indeed from other regions, such as the Middle East, parts of Asia, and South America. In some of these areas, only the

proportion of blindness due to AMD in a population has been reported, rather than prevalence of late AMD among the elderly. This deficiency highlights the need for better reporting of findings from these populations obtained with standard diagnostic techniques to quantify the effects of the Y402H SNP (and other risk genetic variants) on AMD prevalence across ethnicities and regions.

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