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Complement factor H (Y402H) polymorphism and risk of coronary heart disease in US men and women

Jennifer K. Pai[1]*, JoAnn E. Manson[1,2,3], Kathryn M. Rexrode[2,3], Christine M. Albert[2,4], David J. Hunter[1,3], and Eric B. Rimm[1,3]

[1]*Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Kresge 9th Floor, Boston, MA 02115, USA;* [2]*Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [3]*Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; and* [4]*Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*

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Aims Complement factor H (CFH) Y402H polymorphism is located in a region that binds C-reactive protein and may affect inflammatory processes and risk of coronary heart disease (CHD). We assessed the association between Y402H and risk of CHD in nested case–control studies among two large prospective cohorts of US male health professionals and female nurses.
Methods and results Among participants who were disease-free at baseline, we confirmed 266 (men) and 249 (women) incident CHD deaths and non-fatal myocardial infarctions (MIs) over 6 and 8 years of follow-up, respectively. Using risk-set sampling, controls were matched 2:1 on the basis of age, smoking, and date of blood draw. Comparing homozygous HH with YY, the relative risk (RR) of CHD was 0.94 [95% confidence interval (CI) 0.59–1.49] among men and 0.51 (95% CI 0.29–0.89) among women (pooled RR 0.73, 95% CI 0.51–1.04). The HH genotype was inversely associated with CHD among those $<$65 years at onset (men: RR 0.39, 95% CI 0.16–0.95; women: 0.21, 95% CI 0.07–0.65; pooled: 0.30, 95% CI 0.15–0.61), but not among those $\geq$65 years (pooled RR 1.09, 95% CI 0.71–1.68).
Conclusion CFH Y402H was inversely associated with CHD among women, but not men. This inverse association was observed in both populations with earlier age of CHD.

Introduction

Complement activation is a major component of innate immunity and has been considered a key factor in inflammatory processes and host protection against infection. A link between complement activation and atherosclerosis has long been suggested but few studies have prospectively assessed the association between complement regulatory genes and risk of atherosclerotic events.[1] Complement factor H (CFH) is an inhibitor of complement activation and has been found in early human atherosclerotic lesions.[2,3] However, the extent to which CFH is involved in atheroma formation has not yet been determined.

The CFH gene on chromosome 1 encodes a 155 kDa serum protein, which consists of 20 short consensus repeats comprising 60 amino acids each.[4] A tyrosine-to-histidine polymorphism at amino acid 402, Y402H, has been identified in exon 9 of the CFH gene. Carriers of the 402H polymorphism have an increased risk of age-related macular degeneration (AMD), potentially mediated through altered inflammatory response.[2,5,6] Additionally, the Y402H polymorphism occurs in the SCR7 region of the gene which has the overlapping binding sites for C-reactive protein and heparin.[7,8] C-reactive protein, an acute-phase reactant, has been shown to predict risk of coronary events in men and women.[9,10]

Prospective data on CFH Y402H and coronary heart disease (CHD) are scarce and conflicting. One study examined Y402H and risk of thrombo-embolic events among US male physicians and reported no association with risk of events overall or with C-reactive protein levels.[11] The second study, from the Rotterdam group, reported an elevated risk of myocardial infarction (MI) among men and women combined, and no association with C-reactive protein levels.[12] We set out to examine the association of CFH Y402H with C-reactive protein levels and risk of CHD among two independent prospective studies of US men and women.

Methods

Study population

The Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) are prospective cohort investigations among 121 700 female US registered nurses aged 30–55 years at baseline in 1976 (NHS) and 51 529 US male health professionals aged 40–75 years at baseline in 1986 (HPFS). Information about health and disease is assessed biennially and information about diet every 4 years by self-administered questionnaires.[13,14] Between 1989 and 1990, a blood sample was requested from all

*Corresponding author. Tel: +1 617 432 7722; fax: +1 617 432 2435.
E-mail address: jpai@hsph.harvard.edu

participants of the NHS and received from 32 826 women. Similarly, between 1993 and 1995, a blood sample was received from 18 225 men in the HPFS. Participants who provided blood samples were similar to those who did not, although the men who provided were somewhat younger than those who did not. In the NHS, among women without cardiovascular disease or cancer before 1990, we identified 249 women with incident non-fatal MI or fatal CHD between the date of blood drawing and June 1998. In the HPFS, we identified 266 men with incident non-fatal MI or fatal CHD between the date of blood draw and the return of the 2000 questionnaires. Additionally, as a secondary endpoint, we identified 564 men who had coronary artery bypass graft (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) during follow-up. We included all available cases over the respective follow-up period. Using risk-set sampling which selects controls from the base population that gave rise to the cases,[15] controls were randomly selected 2:1 matched on age, smoking, date of blood draw, and fasting status (in women only) from participants free of cardiovascular disease at the time the case was diagnosed. Thus, the controls were at risk of becoming a case over the same time period that the event occurred. Cases and controls were matched on age within 1 year, and month of blood draw within 2 months. Two controls were randomly identified from the base population and all cases had identified controls.

MI was confirmed by study physicians blinded to participant's exposure status if it met the World Health Organization's criteria (symptoms plus either diagnostic electrocardiographic changes or elevated levels of cardiac enzymes). Deaths were identified from state vital records and the National Death Index or reported by the participant's next of kin or the postal system. Fatal CHD was confirmed by hospital records or on autopsy, or if CHD was listed as the cause of death on the death certificate, if it was the underlying and most plausible cause, and if evidence of previous CHD was available. Confirmation of CABG/PCTA was based on self-report; thus, for our analyses, non-fatal MI or fatal CHD was considered the primary endpoint, and CABG/PCTA was considered only in secondary analyses.

The study protocol was approved by the Institutional Review Board of the Brigham and Women's Hospital and the Harvard School of Public Health Human Subjects Committee Review Board, and completion of the self-administered questionnaire was considered to imply informed consent.

Genotyping and measurement of biochemical variables

DNA was extracted from the buffy coat fraction of centrifuged blood, using the QIAmp Blood Kit (Qiagen, Chatsworth, CA, USA). The primary genotyping technique was TaqMan SNP allelic discrimination by means of an ABI 7900HT (Applied Biosystems, Foster City, CA, USA). The dbSNP identifier for CFH Y402H is rs1061170. No alternative genotyping method was used to assess the accuracy of the TaqMan assay. However, 5% replicate quality control (QC) samples were included along with the study samples and the QC samples were genotyped with 100% concordance. Genotype data were available for 751 (94.2%) men and 712 (95.3%) women in the non-fatal MI or fatal CHD sets and 1608 (95.0%) men in the CABG/PTCA sets. Cases were no longer perfectly matched to controls because a percentage of subjects could not be genotyped with this platform.

Plasma biomarkers were measured for non-fatal MI and fatal CHD cases and their controls only. C-reactive protein concentrations were determined using an immunoturbidimetric high-sensitivity assay, using reagents and calibrators from Denka Seiken (Niigata, Japan), with assay day-to-day variability between 1 and 2%. Inflammatory marker levels were largely unaffected by transport conditions and reproducible within persons over time.[16,17] Total and HDL cholesterols were measured using standard methods, with reagents from Roche Diagnostics (Indianapolis, IN, USA).

Study samples were sent to the laboratory for analysis in randomly ordered batches, and the laboratory was blinded to case–control status.

Statistical analyses

Analyses were conducted separately for men and women. For baseline characteristics, we used ANOVA methods to compare least square means adjusted for matching factors, and χ^2 and/or Fisher's exact tests to compare proportions between cases and controls, between genotype and allele frequencies, and to assess Hardy–Weinberg equilibrium. The primary genetic model was co-dominant (where YH and HH were individually compared with YY). Additionally, the additive (genotype as continuous variable), dominant (H carriers compared with YY), and recessive (HH compared with Y carriers) models were also presented. With risk-set sampling, the odds ratio derived from the logistic regression directly estimates the hazard ratio, and thus, the relative risk (RR).[15] Conditional logistic regression was used to estimate the RR in both populations. In our multivariable model, we further adjusted for parental history of CHD before 60 (yes/no), history of diabetes (yes/no) and hypertension (yes/no), total-to-HDL-cholesterol ratio (quintiles), alcohol intake (non-drinker, 0.1–4.9, 5.0–14.9, 15.0–29.9, $\geq$30.0 g/day), body mass index ($<$25, 25–29.9, $\geq$30 kg/m^2), physical activity (quintiles), and non-steroidal anti-inflammatory drug use (yes/no). Multivariable adjustment did not change the results. Subgroup analyses were conducted by age at diagnosis ($<$60 or $\geq$60, and $<$65 or $\geq$65), and *post hoc* analyses used baseline age $<$67.9 and $\geq$67.9 years to compare strata reported in the Rotterdam Study.[12] Tests for interaction were determined by genotype (YY, YH, HH) and age in two categories. To pool the RR estimates for men and women, we used the weighted average of estimates using the DerSimonian and Laird random effects model and test for heterogeneity.[18] Multivariable linear regression analyses were conducted to model the association between CFH Y402H and C-reactive protein levels among control participants. We did not formally account for multiple testing and present uncorrected *P*-values. However, we included a replication study by including two independent populations and presented 95% confidence intervals (CIs) around risk estimates.

All *P*-values presented are two-tailed and *P*-values below 0.05 were considered statistically significant. All analyses were performed using SAS 9 (SAS Institute, Cary, NC, USA).

Results

Expected associations with cardiovascular risk factors were observed between cases and controls (*Table 1*). The observed allele frequencies were within Hardy–Weinberg equilibrium among the controls for both men ($P = 0.19$) and women ($P = 0.61$). For cases with non-fatal MI or fatal CHD, the frequency of YH and HH was 44.4 and 14.7% among men and 50.2 and 8.4% among women. For their matched controls, the frequency was 44.1 and 15.4% among men and 45.9 and 15.2% among women (*Table 2*). For women, the HH genotype was less common among cases than controls (*P*-recessive = 0.01), but there were no differences among men for CHD (*P*-recessive = 0.79) or revascularization (*P*-recessive = 0.57).

Although there was no association between CFH Y402H genotype and risk of CHD or CABG/PTCA among men, there appeared to be a strong inverse association for homozygous HH carriers among women (*Table 3*). For risk of non-fatal MI or fatal CHD, the RR for homozygous HH compared with homozygous YY carriers was 0.94 (95% CI 0.59–1.49) for men and 0.51 (95% CI 0.29–0.89) for women. For risk of CABG/PTCA, the corresponding RR was 0.90 (95% CI

Table 1 Baseline characteristics of participants with incident nonfatal myocardial infarction or fatal coronary heart disease (cases) and matched[a] event-free controls among men (the Health Professionals Follow-up Study, 6 years of follow-up) and women (the Nurses' Health Study, 8 years of follow-up) with complement factor H Y402H genotype

Characteristics[b]	Men			Women		
	Cases	Controls	P^c	Cases	Controls	P^c
n	252	499		239	473	
Age (years)	65.1 ± 0.13	65.1 ± 0.09	–	60.3 ± 0.09	60.3 ± 0.06	–
Current smokers (%)	12.9	12.5	–	32.2	31.9	–
Caucasian[d] (%)	98.4	98.1	>0.99	96.4	96.5	0.83
Postmenopausal (%)	–	–	–	90.3	87.8	0.32
Body mass index (kg/m^2)	26.2 ± 0.22	25.7 ± 0.15	0.09	26.9 ± 0.31	25.4 ± 0.22	<0.001
History of hypertension (%)	42.1	30.1	0.001	57.7	29.4	<0.001
History of diabetes (%)	9.5	4.6	0.009	20.5	6.3	<0.001
Parental history of CHD before age 60 (%)	14.7	10.4	0.09	28.5	12.3	<0.001
C-reactive protein (mg/L)	1.59 (1.38–1.82)	1.17 (1.06–1.29)	<0.001	3.06 (2.64–3.54)	2.14 (1.93–2.38)	<0.001
Total and HDL cholesterol ratio	5.40 ± 0.09	4.77 ± 0.06	<0.001	4.89 ± 0.09	4.05 ± 0.06	<0.001

[a]Matching criteria were age, smoking status, date of blood drawing, and fasting status (women only).
[b]Values are least square mean ± standard error for continuous variables and proportions for categorical variables, except for C-reactive protein, which is shown as log-transformed geometric mean and 95% CI.
[c]*P* for difference between cases and controls by matching factor-adjusted *t*-test for rows with means, and by χ^2 test for rows with proportions.
[d]Race was unknown in 10 cases and 18 controls (HPFS); 17 cases and 16 controls (NHS).

Table 2 Genotype and allele frequency of complement factor H Y402H among coronary heart disease[a] cases and matched controls in the Health Professionals Follow-up Study and the Nurses' Health Study

CFH	Men						Women	
	Non-fatal MI or fatal CHD		CABG/PTCA		Any CHD		Non-fatal MI or fatal CHD	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Genotype (%)								
YY	103 (40.9)	202 (40.5)	216 (40.3)	409 (38.2)	319 (40.5)	611 (38.9)	99 (41.4)	184 (38.9)
YH	112 (44.4)	220 (44.1)	247 (46.1)	503 (46.9)	359 (45.5)	723 (46.0)	120 (50.2)	217 (45.9)
HH	37 (14.7)	77 (15.4)	73 (13.6)	160 (14.9)	110 (14.0)	237 (15.1)	20 (8.4)	72 (15.2)
Total	252	499	536	1072	788	1571	239	473
P-value[b]	0.96		0.64		0.67		0.04	
P-dominant	0.92		0.41		0.46		0.52	
P-recessive	0.79		0.48		0.47		0.01	
Allele, %								
Y	0.63	0.63	0.63	0.62	0.63	0.62	0.67	0.62
H	0.37	0.37	0.37	0.38	0.37	0.38	0.33	0.38

[a]Any CHD in men includes non-fatal MI or fatal CHD or CABG/PTCA. CHD in women includes non-fatal MI or fatal CHD.
[b]*P*-values from χ^2.

0.65–1.25) among men. For comparability between the sexes, we pooled the RR estimates for non-fatal MI or fatal CHD and excluded the CABG/PTCA set from further pooled analyses. The pooled risk estimates for men and women compared with YY was 0.73 (95% CI 0.51–1.04) for HH homozygotes (*P* heterogeneity = 0.26).

Stratification by age of CHD onset further suggested a difference between earlier age (<65 years) and later age (≥65 years) at diagnosis for the association of the CFH H allele and risk of non-fatal MI or fatal CHD, but not CABG/PTCA (*Table 4*). Among participants <65 years at diagnosis, the RR of non-fatal MI or fatal CHD for CFH homozygous HH compared with YY was 0.39 (95% CI 0.16–0.95) for men, 0.21 (95% CI 0.07–0.65) for women, and 0.30 (95% CI 0.15–0.61) when pooled. Among participants ≥65 years at diagnosis, the RR of non-fatal MI or fatal CHD for homozygous HH compared with YY was 1.40 (95% CI 0.80–2.43) for men, 0.76 (95% CI 0.39–1.50) for women, and 1.09 (95% CI 0.71–1.68) when pooled. These findings represent statistically significant interactions between CFH Y402H genotype and age of CHD onset among men and women combined (*P* for interaction = 0.002) (*Table 5*). Additional multivariable adjustment for cardiovascular risk factors did not substantially affect the RR estimates, nor did restricting to Caucasians only (data not shown). Furthermore, among men and women with earlier age of onset, there was suggestion that HH homozygous controls had lower age- and gender-adjusted C-reactive protein levels than homozygous YY controls; this association was stronger and statistically significant when examined among cases (*Figure 1*).

Table 3 Relative risk[a] and 95% confidence interval for complement factor H Y402H genotype and risk of coronary heart disease among men (Health Professionals Follow-up Study) and women (Nurses' Health Study)

CFH Y402H	Co-dominant			Other mode of inheritance		
	YY	YH	HH	Additive	Dominant	Recessive
Men						
Non-fatal MI or fatal CHD (252/499)[b]	1.0	1.06 (0.76–1.47)	0.94 (0.59–1.49)	0.99 (0.80–1.23)	1.03 (0.76–1.39)	0.91 (0.59–1.41)
P-value		0.74	0.79	0.93	0.88	0.69
CABG/PTCA (536/1072)	1.0	0.95 (0.76–1.19)	0.90 (0.65–1.25)	0.95 (0.81–1.11)	0.94 (0.76–1.17)	0.93 (0.68–1.26)
P-value		0.66	0.54	0.51	0.57	0.63
Any CHD (788/1571)	1.0	0.98 (0.82–1.19)	0.92 (0.70–1.20)	0.96 (0.85–1.09)	0.97 (0.81–1.15)	0.92 (0.72–1.19)
P-value		0.87	0.52	0.56	0.71	0.53
Women						
Non-fatal MI or fatal CHD (239/473)	1.0	1.06 (0.77–1.47)	0.51 (0.29–0.89)	0.83 (0.65–1.04)	0.93 (0.68–1.27)	0.49 (0.29–0.84)
P-value		0.71	0.02	0.10	0.63	0.009
Men and women pooled						
Non-fatal MI or fatal CHD (491/972)	1.0	1.06 (0.84–1.34)	0.73 (0.51–1.04)	0.91 (0.78–1.07)	0.98 (0.78–1.21)	0.71 (0.51–1.00)
P-value		0.59	0.07	0.24	0.82	0.04

[a]Results obtained from conditional logistic regression.
[b]Number of (cases/controls).

However, among participants with later age of onset, there was no clear association between CFH genotype and C-reactive protein levels.

Stratification by age of CHD onset <60 and ≥ 60 years resulted in similar findings, but with wider CIs. Among participants <60 years, the risk of non-fatal MI or fatal CHD comparing homozygous HH with YY was 0.37 (95% CI 0.09–1.48) for men, 0.24 (95% CI 0.07–0.91) for women, and 0.30 (95% CI 0.12–0.78) when pooled. We further replicated analyses on the basis of the cut-point of 67.9 years used in the Rotterdam Study,[12] and our findings remained similar in direction.

Discussion

In two nested case–control studies among US men and women, we found no overall association of the Y402H polymorphism with risk of CHD among men, but an inverse association among women. This inverse association became consistently stronger among both men and women after stratifying by earlier age of CHD onset. Additionally, among the younger subsets, the 402H allele was also associated with lower C-reactive protein levels. These findings indicate that CFH Y402H may be inversely associated with the risk of earlier onset CHD, and this risk may be mediated through altered inflammatory processes.

The complement system is complex and comprised 30 compensatory components that defend against infection, generate inflammatory responses, and repair tissues. Three separate pathways activate the complement cascade: the classic pathway activated by C-reactive protein, the lectin pathway activated by mannose-binding lectin, and the alternative pathway activated by foreign pathogen surfaces and extracellular cholesterols.[19,20] Upon complement activation, the unstable protease complexes, C3-convertases, are formed and subsequently cleaved to produce C3a and C3b complexes. The C3a and C3b complexes form C5 convertases which cleave C5 into C5a and C5b, and ultimately produce the terminal C5b-9 complexes which have been found in human atheromas.[4,21] C3a and C5a are pro-inflammatory mediators which activate the endothelium and recruit leucocytes to inflammatory sites.[22] CFH regulates complement activation and decreases inflammatory products by inhibiting the cleavage of C3 and inactivating C3b.[6]

In addition to activating the classic pathway, C-reactive protein binding to CFH also inhibits complement amplification at the C3 level[3,8] and affects the metabolism of LDL in atherosclerotic plaques.[20] *In vitro* studies of early atherosclerotic lesions suggest that complement activation is limited to C3 levels in the superficial arterial intima where C-reactive protein and CFH are found, whereas C5b-9 and extracellular lipids are found in the deep arterial intima where there is a relative absence of CFH.[3] C5b-9 may be required for the atherosclerotic progression of foam cells,[23] and C-reactive protein may exert a balancing act of pro-atherogenic and anti-atherogenic effects on the arterial wall. Thus, variation in the CFH gene may also influence the C-reactive protein-dependent complement pathway. It has been suggested that replacing the neutral tyrosine with a positively charged histidine (Y402H) would alter binding ability and interfere with protein secretion or protein function.[4]

To date, only two studies have assessed the association with CHD and findings have been conflicting. Zee *et al.*[11] reported no association of CFH Y402H with risk of MI, ischaemic stroke, or venous thrombo-embolism among men in the Physicians Health Study (PHS). The genotype frequency for homozygous HH was 18.8% in cases and 14.9% in controls, and the RR of MI (comparing 335 cases and 335 controls) was 1.09 (95% CI 0.88–1.36) under the additive model. The authors reported no association by subgroup of age (<60 or ≥ 60 years), or with C-reactive protein levels; however, the trend was suggestive of lower C-reactive protein levels

Table 4 Genotype and allele frequency of complement factor H Y402H among coronary artery bypass graft/percutaneous transluminal coronary angioplasty (men), and non-fatal myocardial infarction or fatal coronary heart disease cases and matched controls in the Health Professionals Follow-up Study and the Nurses' Health Study by age at diagnosis

CFH	Men (CABG/PTCA)				Men (non-fatal MI or fatal CHD)				Women (non-fatal MI or fatal CHD)			
	Age < 65		Age ≥ 65		Age < 65		Age ≥ 65		Age < 65		Age ≥ 65	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Genotype (%)												
YY	78 (41.5)	141 (36.4)	138 (39.7)	268 (39.1)	40 (45.5)	65 (37.6)	63 (38.4)	137 (42.0)	44 (40.4)	88 (41.5)	55 (42.3)	96 (36.8)
YH	86 (45.7)	179 (46.3)	161 (46.3)	324 (47.3)	41 (46.6)	78 (45.1)	71 (43.3)	142 (43.6)	61 (56.0)	90 (42.5)	59 (45.4)	127 (48.7)
HH	24 (12.8)	67 (17.3)	49 (14.1)	93 (13.6)	7 (7.9)	30 (17.3)	30 (18.3)	47 (14.4)	4 (3.6)	34 (16.0)	16 (12.3)	38 (14.5)
Total	188	387	348	685	88	173	164	326	109	212	130	261
P-value[a]	0.29		0.95		0.10[b]		0.50		0.001[b]		0.56	
P-dominant	0.24		0.87		0.22		0.44		0.84		0.29	
P-recessive	0.16		0.82		0.04[b]		0.27		<0.001[b]		0.64	

[a]*P*-values from χ^2 unless otherwise noted.
[b]*P*-values from Fisher's exact test.

for each increasing copy of the H allele. Kardys *et al.*[12] reported an increased risk of MI (with 226 incident cases) associated with CFH Y402H among older men and women in the Rotterdam Study. The overall genotype frequency for homozygous HH was 14% in the Rotterdam cohort, and the hazard ratio comparing homozygous HH with YY carriers was 1.95 (95% CI 1.21–3.13) in men, but not statistically significant among women [1.54 (95% CI 0.87–2.73)]. The authors reported no association between CFH Y402H and C-reactive protein levels, and no interaction by age (<67.9 or ≥67.9 years). Although the overall allele frequencies for PHS and Rotterdam studies were very similar to our studies, the homozygous HH frequency was higher among controls compared with cases in the NHS.

Although the Y402H polymorphism has been positively associated with AMD, studies with CHD have been conflicting. It was hypothesized that a similar inflammatory pathway would be observed in the development of atherosclerosis; however, the innate immune response is multifactorial and the biological mechanism for AMD is not identical to atherosclerosis. It is reasonable to expect that a true genetic effect would be observed among earlier onset CHD rather than later. Additionally, a recent study reported that early AMD was not associated with the risk of CHD, whereas late AMD was associated with an increased risk of CHD.[24] This study supports the observed increased risk of CHD in older adults in the Rotterdam Study and the possible age effect observed in younger or middle-aged adults in the HPFS and NHS.

Several potential limitations should be discussed regarding the current two studies. In genetic association studies of this design, population stratification is a concern. However, population stratification should be minimized in the NHS and HPFS because both cohorts are predominantly of Caucasian descent, and similar results were observed when the analyses were restricted to Caucasian participants only. Additionally, we recognize that the relative socioeconomic homogeneity of the cohorts does not represent random samples of US men and women and may not be generalizeable to other populations. Though the homogeneity is unlikely to influence genetic predisposition, it may also be a strength in reducing residual confounding from unmeasured factors related to socioeconomic status. Also, the distribution of cardiovascular risk factors such as smoking status and history of diabetes were different between the men and women and may have mediated influences through C-reactive protein.

Since we did not conduct haplotype-based analyses, we cannot fully describe the variation in the CFH gene by this single SNP, and the Y402H polymorphism may simply be in linkage disequilibrium with another unidentified variant. According to the International Hap Map Project,[25,26] three tagging SNPs (rs1329421, rs1329423, rs10922096) capture the common variation in the CFH gene. Hageman *et al.*[27] reported that Y402H was in virtual linkage disequilibrium with rs1061147, which is captured by tagging SNP rs1329421. Additionally, several independent research groups have conducted extensive haplotype analyses of the CFH gene and identified the Y402H variant as the most important in complement activation and AMD.[2,5,6] However, atherosclerosis is a complex disease and it is difficult to demonstrate the impact of a single polymorphism. Additional CFH variants may influence risk of CHD in particular and should be examined.

Table 5 Relative risk[a] (95% confidence intervals) for complement factor H Y402H genotype and risk of non-fatal myocardial infarction or fatal coronary heart disease, stratified by age at diagnosis

Subgroup	Men			Women			Men and women pooled		
	YY	YH	HH	YY	YH	HH	YY	YH	HH
Age									
<65 years	1.0	0.94 (0.54–1.67)	0.39 (0.16–0.95)	1.0	1.39 (0.85–2.25)	0.21 (0.07–0.65)	1.0	1.18 (0.81–1.70)	0.30 (0.15–0.61)
P-value		0.84	0.04		0.19	0.006		0.36	<0.001
≥65 years	1.0	1.14 (0.76–1.71)	1.40 (0.80–2.43)	1.0	0.85 (0.54–1.33)	0.76 (0.39–1.50)	1.0	1.00 (0.74–1.35)	1.09 (0.71–1.68)
P-value		0.54	0.24		0.48	0.43		0.99	0.70
P-interaction		0.06			0.02			0.002	

[a]Results obtained from conditional logistic regression.

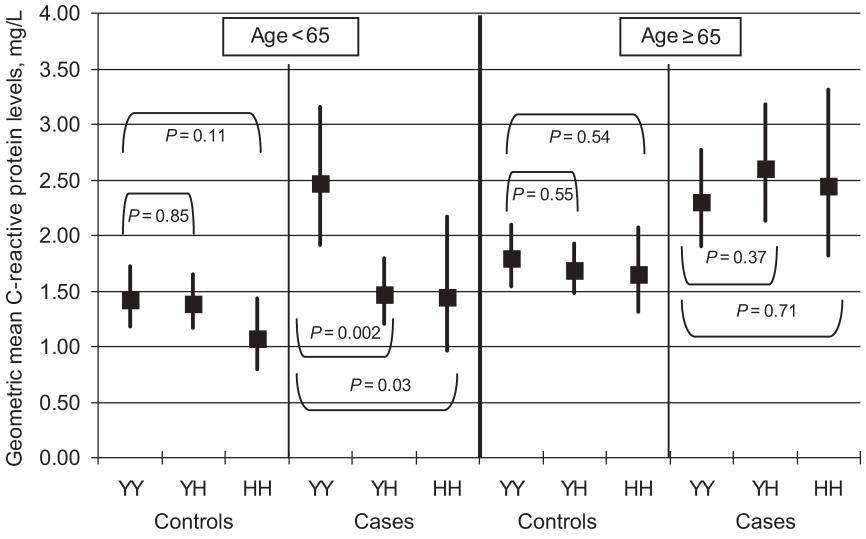

Figure 1 Age- and gender-adjusted, log-transformed geometric means of C-reactive protein by age at diagnosis <65 and ≥65 years and complement factor H Y402H genotype.

Finally, chance may be a potential explanation for our significant findings. It should be noted that there were very few events in the younger age groups and we had limited power to detect stratum-specific effects. However, we included a replication study. In particular, our findings for early age of CHD onset were observed and confirmed in two independent populations of men and women.

In summary, the CFH Y402H polymorphism was inversely associated with the risk of CHD among women, but not men. Further analyses by age at onset showed the Y402H polymorphism was inversely associated with risk of early CHD in both men and women. This study including men and women is the largest to date and suggests a potentially important modification of CHD risk by age at onset.

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