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Association of the Complement Factor H Y402H Polymorphism With Cardiovascular Disease Is Dependent Upon Hypertension Status: The ARIC Study

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Abstract

BACKGROUND—Complement factor H (CFH) is a plasma protein that is essential in the regulation of the alternative complement pathway and has been implicated as taking part in complement inhibition in atherogenesis. We evaluated the association of the y402H polymorphism with incident coronary heart disease (CHD), incident ischemic stroke, and carotid artery wall thickness (intima-media thickness (IMT)) in the Atherosclerosis Risk in Communities (ARIC) cohort.

METHODS—Incident ischemic stroke and CHD were identified through annual telephone calls and hospital and death certificate surveillance. Carotid IMT was measured by means of high-resolution B-mode ultrasound. Four hundred eighty-three validated ischemic stroke and 1,544 CHD events were identified. Because of allele frequency differences between whites and African Americans, analyses were performed separately according to the racial group.

RESULTS—The 402HH homozygous genotype was a significant predictor of incident ischemic stroke in whites (hazard rate ratio (HRR) 1.47, 95% confidence interval (CI) 1.05–2.05). Significant interaction effects between genotype and hypertension were observed for CHD in whites and for cIMT in whites and African Americans. In further analyses of incident CHD, genotypes carrying the 402H allele were a significant predictor of incident CHD in whites who had hypertension (402yH: HRR 1.19, 95% CI 1.01–1.40; 402HH: HRR 1.28, 95% CI 1.04–1.57). The 402H allele was also associated with higher cIMT measures for whites in the overall cohort, and for whites with hypertension.

CONCLUSION—The CFH 402H allele was associated with an increased risk for incident CHD and ischemic stroke in whites, with the strength and significance of the association dependent upon hypertension status.

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Both human and animal studies have shown complement and complement regulatory proteins to play a role in the pathogenesis of atherosclerosis.[1–3] Complement factor H (CFH) is a plasma protein that is essential in the regulation of the alternative complement pathway and has been implied as taking part in complement inhibition in atherogenesis.[4] Recently, multiple studies have shown an association between the CFH Y402H (rs1061170) polymorphism and age-related macular degeneration, a disease that shares pathological and epidemiological similarities with atherosclerosis and arteriolosclerosis.[5–9] The Y402H polymorphism is located in the SCR7 domain of the CFH protein, a region implicated as a binding site for heparin and C-reactive protein (CRP).[1,4,10,11] The binding of CRP and heparin alters the ability of CFH to downregulate the effect of the complement, and it has been proposed that the amino acid substitution at position 402 may affect these binding properties and result in functional implications.[1,4,10] For example, the Y402H polymorphism may alter the ability of CFH to suppress excess complement activation, leading to complement-related vessel injury and damage to the arterial wall.[4,6]

Recently, studies have evaluated the association of the CFH Y402H polymorphism with CRP levels and risk of coronary heart disease (CHD), ischemic stroke, and venous thromboembolism.[4,10,12] In a prospective cohort of 5,520 men and women from the Netherlands, the CFH Y402H polymorphism was associated with an increased risk for myocardial infarction, but not associated with any established cardiovascular risk factors or CRP levels.[4] However, these results have not been consistent in multiple smaller cross-sectional or case–control studies, and no study has included African Americans.[11,12] Seeing that only a few studies have investigated the association of the CFH Y402H polymorphism with cardiovascular disease outcomes, only one of which was prospective in design, we evaluated this polymorphism in the large (N = 15,792) biethnic Atherosclerosis Risk in Communities (ARIC) cohort with regard to incident CHD, incident ischemic stroke and carotid artery wall thickness.

METHODS

The ARIC study

Participants were selected from the ARIC study, a prospective investigation of atherosclerosis and its clinical sequelae involving 15,792 individuals aged 45–64 years at recruitment (1987–1989). Institutional review boards approved the ARIC study, and all participants provided their written informed consent. A detailed description of the ARIC study design and methods, as well as details on quality assurance for ascertainment and classification of CHD and stroke events, have been published elsewhere[13–15] and are available on the ARIC study website (http://www.cscc.unc.edu/aric/index.htm). Briefly, subjects were selected by probability sampling from four communities: Forsyth County, North Carolina; Jackson, Mississippi; northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. The incidence of CHD and ischemic stroke were determined by contacting participants annually to identify hospitalizations during the previous year and by surveying discharge lists from local hospitals and death certificates from state vital statistics offices for potential cardiovascular and cerebrovascular events.[13–15] Participants were excluded from analyses (n = 2,915) if they (i) had a positive or unknown history of prevalent stroke or CHD or a history of transient ischemic attack/stroke symptoms at the initial clinic visit, (ii) prohibited use of their DNA for research purposes, (iii) had an ethnic background other than white or African American, (iv) had missing genotype information for the CFH Y402H polymorphism, or (v) had missing information for any of the endpoints or covariates included in the analyses. Incident CHD cases were defined as any one of these: definite or probable myocardial infarction, silent myocardial infarction (if it took place between examinations by ECG), definite CHD death, or coronary revascularization. Incident ischemic stroke cases were defined as validated definite or probable hospitalized embolic or

thrombotic brain infarctions. Following exclusions, a total of 1,544 CHD cases and 483 ischemic stroke cases were identified.

Baseline examination and laboratory measures

Seated blood pressure was measured three times with a random-zero sphygmomanometer and the last two measurements were averaged. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medications. Questionnaires and in-person interviews were used to assess the use of antihypertensive medications. Diabetes was defined by a fasting glucose level ≥126 mg/dl, a nonfasting glucose level ≥200 mg/dl, and/or history of or treatment for diabetes. Cigarette-smoking status was analyzed by comparing current smokers to individuals who had formerly or never smoked. Body mass index (kg/m^2) was calculated from height and weight measurements. Plasma total cholesterol was measured by an enzymatic method16 and low-density lipoprotein cholesterol was calculated (for participants with triglyceride levels >400 mg/dl, low-density lipoprotein cholesterol measurements were set to missing).17 High-density lipoprotein cholesterol was measured after dextran-magnesium precipitation of non-high-density lipoprotein lipoproteins.18 White blood cell counts were measured by Coulter cell counters. Carotid artery intima-media thickness (IMT) was determined by high-resolution B-mode ultrasound, as described previously.19–20

Genotype determination

Genotyping of the CFH Y402H polymorphism (rs1061170) was performed using the TaqMan Assay-by-Design system (Applied Biosystems, Foster City, CA). PCR product was amplified utilizing 0.9 mmol/l each of the forward primer 5′-GTTATGGTCCTT-AGGAAAATG TTATTTTCCTTATTT-3′ and the reverse primer 5′-GCAG GCAACGTCTA-TAGATTTACCC-3′, 0.2 mmol/l of each of the sequence-specific probes 5′-6FAM-TGGAT-ATAATCA AAATTATGGAAG-3′ and 5′-VIC-TGG-ATATAATCAAAA TCATGGAAG-3′, 3 ng DNA and 1× TaqMan Universal PCR Master Mix containing AmpliTaq Gold DNA Polymerase in a 5.5-μl reaction volume. After an initial step of 10 min at 95 °C to activate the AmpliTaq Gold, the products were amplified using 50 cycles of 15 s at 92 °C and 1 min at 60 °C. Allele detection and genotype calling were performed using the ABI 7900HT and the Sequence Detection System software (Applied Biosystems, Foster City, CA).

Statistical analysis

All statistical analyses were conducted utilizing STATA version 9.2 (College Station, TX). Allele frequencies were estimated by gene counting. Hardy–Weinberg equilibrium expectations were tested using a χ^2 goodness-of-fit test. Because allele frequencies for the CFH Y402H polymorphism were different for whites and African Americans, all analyses were done separately according to race. Proportions, means, and s.e.m. of established cardiovascular risk factors were calculated. A multiple linear regression model was used to assess the relationship between CFH genotype and baseline carotid IMT; covariates included age and gender, with additional analyses including field center, body mass index, low-density lipoprotein and total cholesterol, smoking, diabetes, and hypertension status.

Cox proportional hazards models were used to estimate the hazard rate ratios (HRRs) of incident CHD and ischemic stroke. For analyses of incident CHD and stroke, follow-up time intervals were defined as the time between the initial clinical visit and the date of the first event. For noncases, follow-up continued until 31 December 2003, the date of death, or the date of last contact if lost to follow-up, whichever came first. For analyses of incident CHD, the covariates included age and gender, with additional analyses including field center, body mass index, high-density lipoprotein and total cholesterol, smoking, diabetes, and

hypertension status. For incident stroke analyses, the covariates included age and gender, with additional analyses including field center, smoking, diabetes, and hypertension status (identified by the National Institute of Neurological Disorders and Stroke, http://www.ninds.nih.gov). Covariates were assessed for statistical significance in the models by the Wald χ^2 statistic. Evidence for hypertension effect modification was assessed by including a genotype-by-hypertension interaction term, with statistical significance assessed by means of the Wald χ^2 statistic. Considering the frequencies of the heterozygotes in whites observed here, the power of the Cox proportional hazards models were 33, 99, <99, and <99% for hazards ratios of 1.1, 1.3, 1.5, and 2.0, respectively.

RESULTS

Baseline characteristics of the overall ARIC cohort are presented in Table 1 by race. African Americans had significantly higher mean high-density lipoprotein cholesterol and body mass index measures, as well as a significantly higher percentage of diabetics, hypertensives, and smokers. Whites had significantly higher mean white blood cell counts and had a significantly higher frequency of the CFH 402HH homozygous genotype. CFH genotype distributions were in accordance with Hardy–Weinberg equilibrium expectations for each race (data not shown). Because of the allele frequency differences between whites and African Americans, analyses were performed separately according to racial group. For all analyses, 402YH heterozygotes and 402HH homozygotes were individually compared to the referent genotype (402YY homozygotes) within the same model.

Analyses evaluating whether the characteristics presented in Table 1 differed according to CFH genotype (while adjusting for age and gender) showed no significant mean or frequency differences among CFH genotypes for any of the variables considered (data not shown). Results from the Cox proportional hazards models used to estimate the HRRs of both incident CHD and ischemic stroke, for the CFH Y402H polymorphism, are presented in Table 2 by racial group. The 402HH homozygous genotype was a significant predictor of incident ischemic stroke in whites (HRR 1.47, 95% confidence interval (CI) 1.05–2.05). No significant findings were observed for incident ischemic stroke in African Americans, or for incident CHD in whites or African Americans. We observed that the HRR trends were heterogeneous between whites and African Americans for both incident CHD and ischemic stroke.

Due to the involvement of CFH in the inflammatory process, and the association of inflammation with hypertension, we evaluated the interaction effects between genotype and hypertension in CHD, stroke and carotid IMT. Significant interaction effects between genotype and hypertension were observed in the case of CHD in whites with the 402YH genotype (interaction $P = 0.05$), for carotid IMT in whites with the 402YH and 402HH genotypes (interaction $P = 0.009$ and 0.04, respectively), and for carotid IMT in African Americans with the 402HH genotype (interaction $P = 0.04$). Therefore, we performed additional analyses investigating those participants who were normotensive at baseline and those participants who were classified as being hypertensive at any of the four clinic examinations (or period prevalent hypertensives) (Table 2). Although no significant interaction effects between genotype and hypertension were observed in the case of ischemic stroke, we performed stratified analyses in this subgroup for consistency. In the baseline normotensives, the 402HH homozygous genotype remained a significant predictor of incident ischemic stroke in whites (HRR 1.62, 95% CI 1.03–2.56). Again, no significant findings were observed for African Americans, but the HRR trend was similar to that observed in whites. Although not significant, a similar trend for an increased risk for ischemic stroke associated with the 402H allele was also observed in whites for the period prevalent hypertensives. As shown in Table 3, the frequency of white incident ischemic

stroke cases with the 402HH genotype is higher than the frequency of white noncases with the 402HH genotype, and this is observed in the overall cohort as well as in each subgroup evaluated.

Further analyses of incident CHD in baseline normotensives showed a similar nonsignificant trend for an increased risk for incident CHD associated with the 402HH genotype in both whites and African Americans (Table 2). However, genotypes carrying the 402H allele were a significant predictor of incident CHD only in whites who were period prevalent hypertensives (402YH: HRR 1.19, 95% CI 1.01–1.40; 402HH: HRR 1.28, 95% CI 1.04–1.57). Table 3 provides Y402H genotype frequencies in white and African-American incident CHD cases and noncases, both for the overall ARIC cohort and according to hypertension status. The frequency of white incident CHD cases with the 402HH genotype is higher than the frequency of white noncases with the 402HH genotype, and this is observed in the overall cohort as well as in each subgroup evaluated.

Carotid IMT measures are presented in Table 4 according to race and Y402H genotype for the overall cohort and each subgroup (baseline normotensives and period prevalent hypertensives). The 402H allele was associated with higher IMT measures for whites in the overall cohort and each subgroup. Similar to our analyses of incident disease, the trend for higher IMT measures observed in whites with the 402H allele was only observed in baseline normotensive African Americans.

For all analyses presented, further adjustment for additional covariates did not alter the results (data not shown). Additional covariates included in the analyses are provided in the Methods.

DISCUSSION

Multiple studies have shown an association between the CFH Y402H polymorphism and age-related macular degeneration, with subsequent studies that evaluated the association of this polymorphism with the risk for cardiovascular disease lending inconsistent results.[4–10,12] The present study investigated the CFH Y402H polymorphism in the large biethnic ARIC cohort and showed an increased risk for incident CHD and ischemic stroke in whites carrying the 402H allele, with the strength and significance of the association dependent upon hypertension status. The 402H allele was also associated with higher carotid IMT measures in whites only.

It is clear from pathological studies[21,22] and from animal models[23,24] that complement activation contributes to end-organ damage in both CHD and stroke; thus it is attractive to postulate that the Y402H polymorphism alters the ability of CFH to suppress excess complement activation, leading to increased complement-dependent damage to the arterial wall and vessel injury. However, the functional impact of the polymorphism on alternative pathway activation has not been fully defined and it has recently been shown that the Y402H polymorphism alters the ability of CFH to bind CRP,[25] and thus may limit the ability of complement activation to clear cells damaged in “nonimmunological” injury. It is possible therefore that the Y402H polymorphism in fact reduces the functional ability of the complement to participate in vascular repair via its interactions with CRP. At present it is difficult to reconcile these two possible mechanisms. Nevertheless, both mechanisms could serve to accelerate injury to the vessel wall, increasing end-organ damage.

The finding of a significantly increased risk for incident CHD and significantly higher carotid IMT measures in white hypertensives, but not normotensives, supports the hypothesis that the risk for CHD associated with the 402H allele is only evident in those persons who have a pre-existing condition resulting in vascular injury. On the other hand, a

significantly increased risk for ischemic stroke in whites was observed for the overall cohort and for baseline normotensives, with a nonsignificant increased risk observed in white hypertensives. However, we may not have had suffi cient power to detect a significant association in the smaller group of hypertensives. Alternatively, the different disease etiology of ischemic stroke, as compared to CHD, may not require a pre-existing condition (i.e., hypertension) in persons carrying the 402H allele to result in an ischemic event, or that the relative contribution for complement in these disease processes is fundamentally different. It would be of interest to investigate the association between the CFH Y402H polymorphism and CRP levels and to explore how this association influences the findings observed in the current study. Unfortunately, CRP levels are only available on a subsample of the ARIC cohort, and the small sample size would preclude any conclusions regarding a CFH–CRP association.

The lack of association detected in African Americans from the ARIC cohort is intriguing, and to our knowledge this is the first study to investigate the CFH polymorphism in a population of African Americans. There are, however, a number of potential explanations. Owing to the fact that linkage disequilibrium patterns are different between whites and African Americans, the CFH Y402H polymorphism, although determined to have a functional consequence, may be in linkage disequilibrium with the true functional variant. Therefore, we may have detected an association with a “marker” polymorphism in whites and not in African Americans. We must also acknowledge that our results may be due to chance findings when one considers that significant findings were not consistent between racial groups. Previous studies of cardiovascular disease have focused only on Caucasian populations; therefore, additional studies in African Americans are warranted to investigate the differences in cardiovascular disease risk between racial groups with regard to CFH genotype.

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Table 1

Baseline characteristics of the overall Atherosclerosis Risk in communities (ARIC) cohort, by race

	White (*N* = 9,424)	African American (*N* = 3,347)	
Characteristic	**Mean (s.e.m.)**	**Mean (s.e.m.)**	***P****
Age (years)	54.2 (0.06)	53.3 (0.1)	<0.0001
Body mass index (kg/m^2)	26.9 (0.05)	29.5 (0.1)	<0.0001
HDL cholesterol (mg/dl)	51.4 (0.2)	55.5 (0.3)	<0.0001
LDL cholesterol (mg/dl)	136.8 (0.4)	137.0 (0.7)	0.9
Total cholesterol (mmol/l)	5.53 (0.01)	5.53 (0.02)	0.9
WBC count (10^3 cells/mm^3)	6.24 (0.02)	5.63 (0.03)	<0.0001
	%	%	*P**
Diabetic	8	18	<0.001
Hypertensive	25	54	<0.001
Smoker	24	29	<0.001
	N (%)	*N* (%)	*P**
CFH genotype			
YY	3,576 (38)	1,302 (39)	
YH	4,371 (46)	1,593 (48)	0.01
HH	1,477 (16)	452 (13)	

CFH, complement factor H; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC, white blood cell.

**P* value comparing means or proportions between whites and African Americans.

Table 2

Hazard rate ratios (HRRs) relating CFH variant genotypes to incident CHD and ischemic stroke (ISC), in the overall ARIC cohort and by hypertension statue

Incident CHD	**Overall cohort**	**Baseline normotensives**	**Period prevalent hypertensives**
Genotype[a]	**HRR (95% CI), *P***	**HRR (95% CI), *P***	**HRR (95% CI), *P***
YH (white)	1.06 (0.94–1.20), 0.3	0.97 (0.83–1.13), 0.7	1.19 (1.01–1.40), 0.03
HH (white)	1.12 (0.95–1.32), 0.2	1.08 (0.88–1.34), 0.5	1.28 (1.04–1.57), 0.02
YH (African Am)	1.14 (0.90–1.43), 0.3	1.20 (0.76–1.89), 0.4	1.13 (0.88–1.44), 0.3
HH (African Am)	0.89 (0.62–1.27), 0.5	1.31 (0.69–2.46), 0.4	0.81 (0.54–1.20), 0.3
Incident ISC	**Overall ARIC cohort**	**Baseline normotensives**	**Period prevalent hypertensives**
Genotype[a]	**HRR (95% CI), *P***	**HRR (95% CI), *P***	**HRR (95% CI), *P***
YH (white)	1.13 (0.86–1.49), 0.4	1.15 (0.79–1.67), 0.5	1.17 (0.84–1.63),0.3
HH (white)	1.47 (1.05–2.05), 0.02	1.62 (1.03–2.55), 0.04	1.46 (0.98–2.18), 0.06
YH (African Am)	1.15 (0.86–1.53), 0.3	1.03 (0.58–1.83), 0.9	1.17 (0.87–1.59), 0.3
HH (African Am)	0.84 (0.53–1.33), 0.5	1.10 (0.48–2.50), 0.8	0.75 (0.45–1.24), 0.3

All analyses adjusted for age and gender.

ARIC, Atherosclerosis Risk in Communities; CFH, complement factor H; CHD, coronary heart disease; CI, confidence interval.

[a]Referent group for analysis: YY; adjustments for additional covariates did not alter the HRRs and *P* values presented here (data not shown).

Table 3

CFH genotype frequencies for incident CHD cases, incident ischemic stroke (ISC) cases, and noncases, in the overall ARIC cohort and by hypertension status

	Overall cohort			Baseline normotensives			Period prevalent hypertensives		
CFH genotype	**CHD cases (*n*, %)**	**Noncases (*n*, %)**	***P****	**CHD cases (*n*, %)**	**Noncases (*n*, %)**	***P****	**CHD cases (*n*, %)**	**Noncases (*n*, %)**	***P****
White									
YY	441 (36.5)	3,135 (38.1)	Ref	288 (38.6)	2,398 (38.1)	Ref	256 (33.9)	1,340 (38.2)	Ref
YH	562 (46.6)	3,809 (46.4)	0.5	335 (44.8)	2,942 (46.7)	0.5	361 (47.7)	1,611 (46.0)	0.07
HH	204 (16.9)	1,273 (15.5)	0.1	124 (16.6)	955 (15.2)	0.5	139 (18.4)	553 (15.8)	0.02
African American									
YY	123 (36.5)	1,179 (39.2)	Ref	31 (33.3)	577 (39.8)	Ref	109 (37.1)	817 (38.6)	Ref
YH	175 (51.9)	1,418 (47.1)	0.2	48 (51.6)	679 (46.8)	0.2	153 (52.0)	1,006 (47.5)	0.3
HH	39 (11.6)	413 (13.7)	0.6	14 (15.1)	195 (13.4)	0.4	32 (10.9)	294 (13.9)	0.3
	Overall cohort			**Baseline normotensives**			**Period prevalent hypertensives**		
CFH genotype	**ISC cases (*n*, %)**	**Noncases (*n*, %)**	***P****	**ISC cases (*n*, %)**	**Noncases (*n*, %)**	***P****	**ISC cases (*n*, %)**	**Noncases (*n*, %)**	***P****
White									
YY	90 (33.3)	3,469 (38.1)	Ref	47 (32.9)	2,629 (38.2)	Ref	61 (32.4)	1,525 (37.6)	Ref
YH	124 (45.9)	4,232 (46.4)	0.4	65 (45.4)	3,202 (46.6)	0.5	87 (46.3)	1,877 (46.4)	0.4
HH	56 (20.8)	1,414 (15.5)	0.01	31 (21.7)	1,044 (15.2)	0.03	40 (21.3)	648 (16.0)	0.04
African American									
YY	78 (36.6)	1,214 (39.2)	Ref	20 (35.7)	588 (39.8)	Ref	71 (36.8)	845 (38.6)	Ref
YH	112 (52.6)	1,459 (47.1)	0.2	28 (50.0)	691 (46.7)	0.6	103 (53.4)	1,039 (47.5)	0.3

	Overall cohort			Baseline normotensives			Period prevalent hypertensives		
CFH genotype	**CHD cases (*n*, %)**	**Noncases (*n*, %)**	***P****	**CHD cases (*n*, %)**	**Noncases (*n*, %)**	***P****	**CHD cases (*n*, %)**	**Noncases (*n*, %)**	***P****
HH	23 (10.8)	425 (13.7)	0.5	8 (14.3)	200 (13.5)	0.7	19 (9.8)	304 (13.9)	0.3

ARIC, Atherosclerosis Risk in Communities; CFH, complement factor H; CHD, coronary heart disease.

** P* value comparing genotype frequencies between cases and noncases.

Table 4

Carotid IMT measures by CFH genotype, in the overall ARIC cohort and by hypertension status

	Overall cohort			Baseline normotensives			Period prevalent hypertensives		
CFH genotype	***N***	**Carotid IMT (mm)**	***P***	***N***	**Carotid IMT (mm)**	***P***	***N***	**Carotid IMT (mm)**	***P***
White									
YY	3,383	0.727 (0.003)	Ref	2,545	0.711 (0.003)	Ref	1,495	0.762 (0.005)	Ref
YH	4,144	0.734 (0.002)	0.08	3,122	0.712 (0.003)	0.8	1,859	0.776 (0.004)	0.03
HH	1,407	0.742 (0.004)	0.003	1,031	0.720 (0.005)	0.1	656	0.787 (0.007)	0.003
African American									
YY	1,175	0.735 (0.004)	Ref	559	0.705 (0.005)	Ref	828	0.751 (0.005)	Ref
YH	1,434	0.735 (0.004)	1.0	667	0.703 (0.005)	0.8	1,030	0.753 (0.005)	0.7
HH	398	0.729 (0.008)	0.5	191	0.717 (0.009)	0.3	280	0.736 (0.009)	0.2

Values are presented as mean (s.e.m.) and adjusted for age and gender; adjustments for additional covariates did not alter the means and *P* values presented here (data not shown).

ARIC, Atherosclerosis Risk in Communities; CFH, complement factor H; IMT, intima-media thickness.