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## ***Clinical Science***

# Common Y402H variant in complement factor H gene is not associated with susceptibility to myocardial infarction and its related risk factors

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## Abstract

Recently, the genetic variant Y402H in complement factor H gene (*CFH*) was associated with increased risk for myocardial infarction (MI) in a prospective Caucasian cohort. In another nested case-control study, however, the *CFH*-Y402H variant did not carry susceptibility to MI. The aim of the present study was to test for association between the *CFH*-Y402H variant and MI in a large case-control sample with familial background for coronary artery disease (CAD). A total of 2,161 individuals from the German MI family study were studied by questionnaire, physical examination and biochemical analyses. MI patients (n=1,188; 51.4 ± 8.6 years at first MI) were recruited from families with at least two members affected by MI and/or severe CAD. Spouses, sisters-in-law, and brothers-in-law, respectively, without MI/CAD were included as unaffected controls (n=973; 56.9 ± 9.8 years). Genotyping was performed using a TaqMan assay. Common Y402H variant in the *CFH* gene was not associated with classical cardiovascular risk factors (diabetes, hypercholesterolemia, hypertension, obesity, smoking, and C-reactive protein serum levels). No association could be found between the *CFH*-Y402H variant and susceptibility to MI. Separate analyses in both men and women revealed no gender-specific influence of the gene variant on cardiovascular risk factors or MI. This investigation could not replicate the association between the common *CFH*-Y402H variant and susceptibility to MI in our large Caucasian population which is enriched for genetic factors. We conclude that the *CFH*-Y402H variant has no relevant risk modifying effect in our population.

Word count: 240

## Introduction

Coronary artery disease (CAD) and myocardial infarction (MI) are the leading causes of morbidity and mortality in the Western world [1]. In epidemiological studies, factors like smoking, obesity, high blood pressure, elevated cholesterol levels, and diabetes have been identified to increase cardiovascular risk. Additionally, a strong genetic component was also documented in the etiology of CAD [2,3]. To unravel the underlying genes, several genome-wide analyses have been performed and revealed chromosomal loci with linkage to CAD or MI [4-12]. However, until today only few genes and variants responsible for prevalence to MI in the general population are known [9,13].

In the pathophysiology of atherosclerosis, inflammation is hypothesized to play an important role for plaque formation and its destabilization and therefore causing CAD and MI [14,15]. Complement factor H (CFH) as a part of innate immunity contributes to inflammation processes. CFH provides binding sites for C3b, heparin as well as sialic acids, and also interacts with C-reactive protein (CRP) [16], which has been linked in several studies to CAD, MI and stroke [17].

Recently, an association between a common *CFH* gene variant and increased risk for MI was reported in a prospective cohort study: Single nucleotide polymorphism (SNP) rs1061170, representing a tyrosine-histidine change at amino acid position 402 in the CFH protein, showed hazard ratios up to 1.77 in 226 MI cases during a mean of 8.4 years of follow-up of 5,237 individuals from the Rotterdam Study [18]. However, another prospective study with 335 MI cases did not show an influence of Y402H variant on susceptibility to MI [19].

The German MI family study [4,20-22] provides well-characterized MI patients as well as unrelated, healthy controls for association studies. Here, we investigated the association between the *CFH*-Y402H genetic variant and susceptibility to MI and known cardiovascular risk factors, as well as CRP serum levels.

## Methods

### Study sample

The study sample consisted of individuals from the German MI family study. Selection criteria have been described previously [4,20]. All participants were studied by standardized questionnaire, physical examination and biochemical analyses at inclusion (n=2,161) and five-year follow-up (n=1,780).

Baseline characteristics of the 2,161 investigated participants in this study at the time point of inclusion are summarized in Table 1. The present analyses included independent MI cases (n=1,188) with a positive family history (at least one additional family member who had suffered from MI or severe CAD, defined as treatment with percutaneous coronary intervention or coronary artery bypass graft). Control individuals (n=973) consisted of married-in spouses, sisters-in-law, and brothers-in-law, respectively. Thereof, 617 controls were confirmed to be free of any cardiovascular symptoms and events during the follow-up period. Of the remaining 356 control individuals follow-up examination was not completed from the time of the present study. Consanguineous individuals were excluded. Research has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Written informed consent was obtained from all subjects, and the ethics committee of the University of Regensburg approved the study.

### Definition of risk factors

Diabetes was defined as a history of diabetes mellitus or intake of antidiabetic medication. Individuals with former or current smoking habit were classified as smokers. Obesity was defined as body mass index  $\geq 30$  kg/m<sup>2</sup>. Study subjects receiving antihypertensive therapy or with a systolic blood pressure (BP)  $\geq 140$  mmHg or diastolic BP  $\geq 90$  mmHg were classified as hypertensive. Hypercholesterolemia was defined as low-density lipoprotein (LDL) cholesterol  $\geq 160$  mg/dL or use of a lipid lowering therapy.

### Genetic analysis

Genomic DNA was isolated from whole blood samples using the PureGene DNA Purification System Blood Kit (Gentra, Minneapolis, MN, USA). DNA samples were genotyped using 5' exonuclease TaqMan<sup>®</sup> technology (Applied Biosystems, Foster City, CA, USA) with differently fluorescence labeled probes including non-fluorescence quencher and minor groove binder (MGB) [23,24]. For SNP rs1061170, a Custom TaqMan<sup>®</sup> SNP Genotyping Assay (Applied Biosystems) was used with forward primer: 5'- CTT TAT TTA TTT ATC ATT GTT ATG GTC CTT AGG AAA ATG TTA TTT -3', reverse primer: 5'- GGC AGG CAA CGT CTA TAG ATT TAC C -3', probe 1: VIC-5'- TTT CTT CCA TAA TTT TG -3'-MGB, probe 2:

FAM-5'- TTT CTT CCA TGA TTT TG -3'-MGB (fluorophore VIC<sup>®</sup> and 6FAM<sup>™</sup>, respectively, and MGB are quoted; SNP position is underlined; probes were designed on the reverse chromosomal strand).

For each genotyping experiment 10 ng DNA was used in a total volume of 5 µl containing 1x TaqMan<sup>®</sup> Universal PCR Master Mix (Applied Biosystems). PCR reaction and post-PCR endpoint plate read was carried out according to the manufacturer's instructions using the Applied Biosystems 7900HT Real-Time PCR System. Sequence Detection System software version 2.2 (Applied Biosystems) was used to assign genotypes applying the allelic discrimination test [24]. Case and control DNA was genotyped together on the same plates. Duplicates of samples (15 %) were employed to assess intraplate and interplate genotype quality. No genotyping discrepancies were detected. Assignment of genotypes was performed by a person without knowledge of the affection status.

### Statistical analysis

Genotype distribution within the groups of cases and controls, respectively, was compared with values predicted by Hardy-Weinberg equilibrium using the  $\chi^2$ -test. Differences in allele frequencies between dichotomous traits were calculated with the same method. Genotype distribution between cases and controls assuming dominant or recessive genetic models were performed using logistic regression analysis. Linear regression analysis was employed for comparison of genotype distributions with continuous variables, whereas ln(CRP) serum levels were used. Potential interaction between each traditional cardiovascular risk factor and genotype was tested in separate logistic regression analyses including cross-product term. Prevalence odds ratios (OR) with their 95% confidence intervals (CI) were reported. A two-sided *P* value  $\leq 0.05$  was considered statistically significant. All analyses were carried out using JMP IN 5.1 (SAS Institute, Cary, NC, USA). Power analysis was performed applying the G\*Power program [25].

## Results

From 2,187 DNA specimens, a total of 2,161 individuals were genotyped successfully and therefore the overall call rate was 98.8 %. Baseline characteristics of this study sample are shown in Table 1. The proportion of women was lower in the patient group (n=375) than in the control group (n=636). As expected, the MI patients (n=1,188) had a higher prevalence of classical cardiovascular risk factors (hypercholesterolemia, hypertension, obesity, diabetes, and smoking habit) than did the control subjects (n=973). In MI patients, the mean age at first MI was  $51.4 \pm 8.4$  years. Anthropometric and biochemical measurement were performed at time-point of inclusion at a mean age of  $57.9 \pm 9.2$  years ( $58.7 \pm 8.6$  years for MI patients,  $56.9 \pm 9.8$  years for controls).

Genotype distribution of *CFH* gene variant Y402H was analyzed in the whole population and in sub-groups separately. The Hardy-Weinberg equilibrium was always fulfilled. Hence, test for allele frequency difference and co-dominant model gave nearly the same *P* values (not shown). Therefore, additional to the allele frequency comparisons we reported results from dominant and recessive genetic models (Table 2). In our study with 2,161 different DNA samples, the frequency of the H allele was 36.7%. Genotype frequencies in the whole study group were 40.4%, 45.8%, and 13.8% for YY, YH, and HH, respectively.

### ***CFH*-Y402H variant and susceptibility to MI and risk factors**

The observed allele frequency and genotype distributions of the *CFH*-Y402H variant were not significantly different between 1,188 MI cases and 973 unaffected controls. In addition, no association could be found between the Y402H variant and classical cardiovascular risk factors, namely diabetes, hypercholesterolemia, hypertension, obesity, and smoking habit (Table 2). We also performed adjusted analyses to exclude confounding effects of the differently distributed risk factors between MI cases and controls and found no significant association between *CFH*-Y402H variant and MI (data not shown).

Additionally, no association between *CFH*-Y402H variant and CRP serum levels at date of inclusion was observed (*P* = 0.16). Due to the limited sample size with CRP data points at inclusion date (497 of 2,161 individuals; 471 of them classified as MI patients) we used five-year follow-up values (mean age  $62.9 \pm 8.7$  years), where 1,284 CRP values were measured. Again, no association between *CFH*-Y402H variant and CRP serum level could be found (*P* = 0.97). From the follow-up examination, the available CRP measurements were from 855 MI patients (mean age  $63.2 \pm 8.1$  years, i. e. on the average of 11.8 years after first MI) and 429 controls (mean age  $62.5 \pm 9.1$  years), respectively. No significant association between CRP serum levels at follow-up examination and MI was observed (*P* = 0.09).

To test for gender-specific influences of *CFH*-Y402H variant, we performed the analyses in

both men and women separately. Neither susceptibility to MI nor cardiovascular risk factors (diabetes, hypercholesterolemia, hypertension, obesity, and smoking habit) showed gender-specific association with Y402H variant. Likewise, no gender-related association between *CFH*-Y402H genotypes and CRP serum levels from the follow-up examination could be found (data not shown).

Additional analysis in a age- and sex-matched sub-sample (n=1,200) with 300 cases and 300 controls from both men and women also showed no association between risk factors, MI and *CFH*-Y402H genotypes (data not shown).



## Discussion

Inflammation and components of the innate immunity - and thereby potentially complement activation - play a major role in the pathophysiology of atherosclerosis [26]. The *CFH* gene, encoding a plasma protein essential for regulation of the alternative complement pathway, is a good candidate for genetic susceptibility to MI. Two recent studies showed inconsistent results on the association of *CFH*-Y402H variant with MI in prospective cohorts [18,19]. Thus, additional data is needed to assess the impact of this variant to the genetic etiology of MI.

In the present case-control association study, the *CFH*-Y402H variant was neither associated with an increased risk for MI in patients with a strong familial background for cardiovascular disease nor with classical cardiovascular risk factors, such as diabetes mellitus, hypercholesterolemia, hypertension, obesity, and smoking (Table 2). Serum CRP as a non-specific indicator of inflammation has gained great importance as a risk marker in cardiovascular disease, although the magnitude of its risk stratification potential has been debated [27]. Since the CRP binding site of CFH protein is localized within the region of Y402H variant [28] and its genotype potentially determine CRP levels [29], we analyzed a possible association of *CFH*-Y402H and CRP serum levels in our study group. At follow-up, CRP serum levels were available from 1,284 participants. No association between serum CRP and Y402H genotypes was detectable, indicating that CRP serum levels are not influenced by the *CFH* gene variant in a measurable fashion in our cohort. Additionally, CRP serum level at follow-up examination is not associated with susceptibility to MI in our study. However, it has to be noted that in this study group baseline as well as follow-up values for serum CRP are measured after a mean of 7.3 and 11.8 years, respectively, after suffering from MI. It is thus questionable whether these values can be related to the pathophysiology of the MI event.

Within the *CFH* gene the amino acid position 402 is encoded in exon 9. This region is part of a strong linkage disequilibrium (LD) block that did not cover the whole gene with respect to a  $r^2$  value of 0.8 by analyzing data from the HapMap project [30]. However, Y402H variant is the only one so far showing positive association with MI in a prospective cohort study [18]. In upcoming genome-wide association (GWA) studies on MI, e. g. using Affymetrix® GeneChip® Human Mapping 500K Array Set, *CFH*-Y402H variant will not be analyzed directly due to absence of this SNP on the chips. Altogether, information of 18 SNPs within the 95.5-kb *CFH* gene will be available from these GWA studies. Recent studies on the *CFH* gene dealing with association between the Y402H variant and age-related macular degeneration showed that other polymorphisms within the *CFH* gene also contribute to disease susceptibility independent from Y402H genotype [31,32]. This emphasises the relevance of analyzing the

Y402H variant separately. Additionally, in the background of GWA studies future focus should be given on remaining part of *CFH* gene as a potential candidate locus for MI susceptibility.

Our non-replication of the recently reported association between *CFH*-Y402H variant and MI is unlikely to be a result of insufficient power. The sample size with 1,188 MI cases and 973 controls has greater than 96% power to detect a weak to moderate gene effect with an effect size = 0.2 at a significance level of 0.05.

A possible limitation of the study is the recruitment of our MI patients: only patients who survived at least one MI and had an affected sibling with CAD or MI were included. Hence, there was a selection bias for both MI surviving patients and familial form of the disease. On the other hand, however, due to the family-based character of our patient selection, the genetic background for etiology of MI is high in our study group thus enabling us to investigate even small genetic effects. Using married-in spouses or their relatives as control subjects, the risk of population stratification between affected MI patients and unaffected individuals is minimized. Additionally, main part of control group was validated as being free of any cardiovascular symptoms and events during the five-year follow-up period.

Like other candidate genes, *CFH* should be included to analyses in upcoming association studies of CAD and MI to reveal more information about the contribution of this gene and its variants to the genetic etiology of the disease.

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The authors declare no conflict of interest.

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## Tables

**Table 1.** Characteristics of study sample from the German MI family study

Variable	MI cases ( <i>n</i> = 1,188)	Controls ( <i>n</i> = 973)
Five-year follow-up available ( <i>n</i> )	1,163	617
Age at first MI, years (range)	51.4 ± 8.6 (24 - 77)	-
Age at inclusion, years (range)	58.7 ± 8.6 (29 - 87)	56.9 ± 9.8 * (29 - 80)
Gender, % male ( <i>n</i> )	68.4 (813)	34.6 (337) *
Hypercholesterolemia <sup>†</sup> , % ( <i>n</i> )	82.9 (985)	39.8 (386) *
Total cholesterol, mg/dL	227.2 ± 47.1	238.2 ± 42.8 *
HDL cholesterol, mg/dL	50.1 ± 13.2	60.7 ± 15.4 *
LDL cholesterol, mg/dL	151.3 ± 43.3	146.9 ± 34.9 *
Triglycerides, mg/dL	199.6 ± 139.0	152.5 ± 109.3 *
Hypertension <sup>‡</sup> , % ( <i>n</i> )	93.7 (1,113)	57.2 (554) *
Systolic blood pressure, mm Hg	137.6 ± 19.5	133.8 ± 17.7 *
Diastolic blood pressure, mm Hg	82.2 ± 10.1	82.0 ± 9.8
Obesity <sup>§</sup> , % ( <i>n</i> )	22.8 (269)	18.5 (180) *
Body mass index, kg/m <sup>2</sup>	27.5 ± 3.6	26.7 ± 4.2 *
Diabetes mellitus <sup>  </sup> , % ( <i>n</i> )	16.8 (199)	5.4 (53) *
Smoking <sup>¶</sup> , % ( <i>n</i> )	69.3 (823)	49.8 (484) *

Values denote means ± standard deviations unless indicated otherwise.

\* Significant different between the groups (*P* < 0.05)

<sup>†</sup> Defined as LDL ≥ 160 mg/dL or lipid lowering therapy

<sup>‡</sup> Defined as blood pressure ≥ 140/90 mm Hg or intake of antihypertensive medication

<sup>§</sup> Defined as body mass index ≥ 30 kg/m<sup>2</sup>

<sup>||</sup> Defined as history of diabetes mellitus or intake of antidiabetic medication

<sup>¶</sup> Former or current smoking habit

To convert values for total cholesterol, HDL cholesterol, and LDL cholesterol to millimoles per liter, divide by 38.66.

**Table 2.** *CFH*-Y402H genotype distribution according to affection status

	Affected				Unaffected				Difference in		Dominant model		Recessive model	
	Genotype (n)				Genotype (n)				allele frequency		(genotype HH+YH vs. YY)		(genotype HH vs. YH+YY)	
	YY	YH	HH	MAF	YY	YH	HH	MAF	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
Myocardial infarction	484	540	164	0.365	390	449	134	0.368	0.83	0.99 (0.87-1.12)	0.76	0.97 (0.82-1.16)	0.98	1.00 (0.78-1.28)
Diabetes mellitus *	104	115	33	0.359	770	874	265	0.368	0.71	0.96 (0.79-1.17)	0.78	0.96 (0.74-1.26)	0.73	0.93 (0.62-1.36)
Hypercholesterolemia *	558	637	176	0.361	316	349	122	0.377	0.29	0.93 (0.82-1.06)	0.80	0.98 (0.82-1.17)	0.08	0.80 (0.63-1.03)
Hypertension *	679	758	230	0.365	193	229	68	0.372	0.68	0.97 (0.84-1.12)	0.59	0.77 (0.86-1.16)	0.96	0.99 (0.75-1.34)
Smoking *	507	617	183	0.376	366	372	115	0.353	0.12	1.11 (0.97-1.26)	0.06	1.19 (1.00-1.41)	0.73	1.04 (0.81-1.35)
Obesity *	186	210	53	0.352	686	775	242	0.370	0.33	0.96 (0.79-1.08)	0.66	0.95 (0.77-1.18)	0.19	0.81 (0.58-1.10)

MAF: minor allele frequency

Unadjusted odds ratios (OR) are given

\* Definition is given in Table 1