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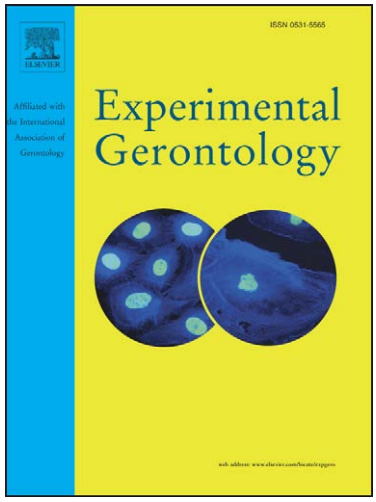

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Complement factor H 402His variant confers an increased mortality risk in Finnish nonagenarians: The Vitality 90+ Study

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Abstract

Ageing is characterized by chronic low-grade inflammation and the expected lifespan may be affected by several immunological and inflammatory mediators. In this study, we investigated whether the functional Tyr402His polymorphism (rs1061170) on complement factor H (CFH) gene, which is a key inflammatory downregulator, modulates the longevity of 491 nonagenarians in the Vitality 90+ study. Logistic regression analysis and Kaplan-Meier method with the log rank test were used to examine the effect of the CFH Tyr402His polymorphism on 4-year mortality. After follow-up, we observed that risk factor-adjusted mortality was significantly higher among the carriers of CFH 402His allele compared to non-carriers (OR 1.78, 95% CI 1.19-2.67, p=0.005) and that the survival curves of CFH 402His carriers and non-carriers deviated significantly (p=0.016). We propose that the increased mortality is inflammation-related and mediated by aberrant complement regulation by the CFH 402His variant.

Keywords: nonagenarians, longevity, complement factor H, inflammation, mortality

1. Introduction

Determination of human lifespan, especially in old age, is largely affected by the antigenic burden that the immune system encounters and has to deal with (reviewed in Franceschi et al. 2007 and Vasto et al., 2007). Age-related low-grade inflammation is characterized by a 2 to 4 -fold increase in inflammatory mediators and this increase has often predicted a shorter life expectancy (reviewed in Franceschi et al. 2007 and Vasto et al., 2007). In addition to physiological factors such as BMI, sex hormones, plasma lipids, smoking and chronic diseases that modulate the systemic inflammatory state, genetics has frequently been reported to contribute to the immunosenescence and ensuing mortality. The polymorphisms of the key immune mediators which affect the level or the function of the protein have gained recent interest as predictors of longevity (Balistreri et al., 2004; reviewed in Christensen et al., 2006). Nevertheless, the results have frequently been contradictory - either due to confounding co-morbidity, case-control bias, too liberal p-values or insufficient power. Moreover, the majority of the reported associations are limited to certain populations and have not been replicated by others (reviewed in Christensen et al., 2006 and Budovsky et al., 2007).

Complement is a sophistically ordered cascade functioning at the heart of the immune system by stimulating the inflammation, participating in waste and pathogen disposal as well as interlinking the components of innate and adaptive immunity. Vigorous complement activators include CRP, amyloid proteins, antibodies, oxidized lipoproteins and cell debris, all of which are abundant in old age. Complement activity is regulated by the complement factor H (CFH) which downregulates the activation cascade when bound to CRP. The Tyr402His tagging polymorphism on CFH creates a proinflammatory functional variant (402His) which has a markedly reduced CRP-binding capability and thus an inability to downregulate the complement sufficiently (Laine et al., 2007). In brief, the CFH 402His variant loses its anti-inflammatory properties, which leads to unbalanced and excessive inflammatory reaction (Laine et al., 2007). Therefore, we wanted to examine whether this polymorphism is associated with increased mortality during 4-year follow-up

in the oldest-old population. Along these lines, since the CFH 402His variant has been consistently linked with age-related macula degeneration (AMD) (Edwards et al., 2005; Thakkinstian et al., 2006; Skerka et al., 2007) it is conceivable that CFH may be a candidate gene in other inflammation-related processes, such as age-associated mortality.

2. Methods

The study population (n=491; 380 females, 111 males) consisted of two population-based cohorts of people living in the city of Tampere, Finland, who were studied in the Vitality 90+ project at the age of 90, those born in 1907-08 were studied in 1998 (n= 212), and those born in 1909-10 were studied in 2000 (n=279). The study design was approved by the local ethics committee and all participants gave their informed consent. The physical examination and clinical parameters have been described elsewhere (Goebeler et al., 2003). Smoking habits and plasma concentrations of CRP, IL-6 and HDL-cholesterol were determined as previously described (Goebeler et al., 2003; Jylhä et al., 2007) and CRP and IL-6 were log-transformed prior to analyses due to their skewed distributions. Genotyping of the CFH Tyr402His polymorphism (+1277T>C, rs1061170) was performed with Assay-By-Design from Applied Biosystems under standard conditions using the ABI Prism 7900HT Sequence Detection System (Taqman, Applied Biosystems, Foster City, CA, USA).

The subjects with either His/His (CC) or His/Tyr (CT) genotype were classified as 402His carriers and the subjects with Tyr/Tyr (TT) genotype as non-carriers. The division into CFH 402His carriers and non-carriers was based on the observation that when the genotypes (Tyr/Tyr, Tyr/His and His/His) were tested separately, identical behaviour was observed for Tyr/His and His/His genotypes in Kaplan-Meier analysis. Statistical analyses were carried out with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Logistic regression analysis and Kaplan-Meier method with the log rank test were used to examine the effect of the CFH Tyr402His polymorphism on 4-year

mortality. Risk factor adjustment included cardiovascular diseases, diabetes and sex (available for 491 individuals) as well as smoking, BMI, CRP, IL-6, HDL-cholesterol and sex (available for 210 individuals).

3. Results

Genotype frequencies of the CFH +1277T>C polymorphism in this cohort followed the Hardy-Weinberg equilibrium and were TT 27.3%, TC 52.3% and CC 20.4%. A significant risk of increased mortality was observed for the 402His carriers in logistic regression analysis (OR 1.78, 95% CI 1.19-2.67, p=0.005, Table 1) and Kaplan-Meier analysis with the log rank test revealed that death rate during 4-year follow-up was significantly higher among the carriers of the CFH 402His variant than among non-carriers (p=0.016; Figure 1). Risk factor adjustment in logistic regression analysis with sex, cardiovascular diseases and diabetes (p= 0.001; OR 2.06; 95% CI 1.33-3.20) or smoking, BMI, CRP, IL-6, HDL-cholesterol, sex, cardiovascular diseases and diabetes (p=0.015; OR 2.05; 95% CI 1.08-3.81) did not change the result.

4. Discussion

The results of this population-based study show that the CFH 402His variant confers a significant risk of mortality in old age when inflammatory mechanisms, especially those of innate immunity, are known to play a crucial role in determining the remaining lifespan. Importantly, as being a longitudinal follow-up study, the potentially biased case-control setting was circumvented. Moreover, the fact that risk factor-adjustment did not attenuate this effect, indicates that the higher mortality rate of the CFH 402His carriers is not affected by confounding factors or co-morbidities. However, since smoking and BMI data as well as the plasma concentrations of CRP, IL-6 and HDL-

cholesterol were only available from 210 individuals, their effect on mortality could only be analyzed for this sub-cohort instead of the whole cohort (n=491).

Using this same follow-up approach and partially same cohort, we have previously shown that 1) the high CRP producing haplotypes of the CRP gene (Hurme et al., 2007) and 2) the high IL-6 producing genotypes (Hurme et al., 2005) are less prevalent in nonagenarians surviving the 4-year follow-up time. These data are in line with the reports by Bonafe et al. 2001 and Rea et al. 2004, who have shown that pro-inflammatory genotypes are associated with increased mortality in the elderly populations. As hypothesized, this phenomenon is likely to be the result of the "trade-off" from effective resistance to infectious diseases earlier in life (reviewed in Franceschi et al. 2007). Regarding the CFH Tyr402His polymorphism, Mooijaart et al. (2007) have recently demonstrated in the Leiden 85-plus Study that the 402His allele associates in a gene dose dependent fashion with increased inflammation and cardiovascular mortality but not with all-cause mortality in old population. Since our results concern all-cause mortality and are independent of gene dose, direct comparison of these results is not feasible. In addition, as the data concerning this polymorphism and longevity are so far scarce, we cannot exclude the possibility that a population-specific character is involved in the association. Further research and functional studies are thus required in order to clarify the exact role of the CFH in age-associated inflammation.

As it has been reported that the CFH 402His variant has a reduced capacity to downregulate complement activation and control the inflammation (Laine et al., 2007), it is conceivable that the fine-tuning of systemic inflammation could be compromised among the carriers of the CFH 402His variant. We suggest that the novel finding reported here about all-cause mortality among the CFH 402His carriers is related to this phenomenon and that these individuals are predisposed to a chronic proinflammatory state which manifests as an increased risk of mortality in very old age.

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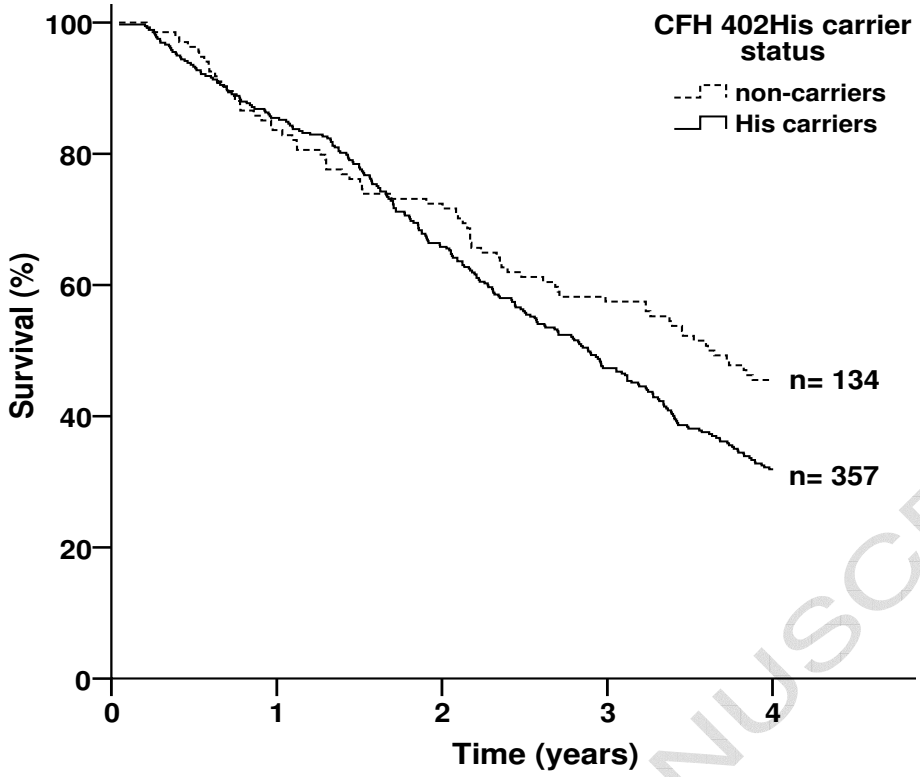

Figure 1. Survival curves of 402His carriers and non-carriers in Kaplan-Meier analysis during 4-year follow-up among Finnish nonagenarians. The mortality rates differ markedly (p=0.016) between the carrier and non-carrier groups: the 402His carriers have higher mortality count and decreased survival compared to the non-carriers.

Table 1. Effect of CFH 402His carrier status on the mortality of Finnish nonagenarians in logistic regression analysis during the 4-year follow-up. The mortality count among 402His carriers is significantly higher than among 402His non-carriers.

	Survivors		Nonsurvivors				
	n	**(%)**	**n**	**(%)**	**P**	**OR**	**95% CI**
402His carriers	114	(31.9)	243	(68.1)	0.005	1.78	1.19-2.67
402His non-carriers	61	(45.6)	73	(54.5)			