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ORIGINAL ARTICLE

Polymorphism in the human matrix Gla protein gene is associated with the progression of vascular calcification in maintenance hemodialysis patients

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Abstract
Background Matrix Gla protein (MGP) is one of the important proteins inhibiting vascular calcification (VC). Single nucleotide polymorphisms (SNPs) located in the promoter and coding regions of the *MGP* gene affect the transcriptional activity. In this study, we investigated the relationship between the SNPs and progression of VC in patients undergoing maintenance hemodialysis (MHD).
Methods This was a retrospective, longitudinal cohort study of 134 MHD patients whose VC could be followed by multi-detector computed tomography (MDCT) examinations. MGP-SNPs (T-138C, rs1800802 and G-7A, rs1800801) were determined. The progression speed of VC was examined by plotting the abdominal aortic calcium volume scores.
Results The progression speed of VC of patients with the CC genotype of T-138C was significantly slower than that of patients with the CT or TT genotype. Multiple regression analysis showed that CT/TT genotype, greater age at the beginning of MHD, male sex, high levels of calcium × phosphate, low levels of high-density lipoprotein cholesterol, high levels of low-density lipoprotein cholesterol, low levels of ferritin and non-use of angiotensin II receptor blockers were significantly associated with progression of VC.
Conclusions The MGP-138CC genotype may be associated with slower progression of VC in MHD patients. The genotype of the *MGP* gene will be a genomic biomarker that is predictive of VC progression.

Keywords Matrix Gla protein (MGP) · Abdominal aortic calcium volume score (AACVS) · Single nucleotide polymorphisms (SNPs)

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Introduction

Vascular calcification (VC) is a common finding in patients undergoing maintenance hemodialysis (MHD). MHD patients have a 60–80 % prevalence of moderate to severe VC [1–3]. The VC often progresses over a relatively short period of time and is a strong predictor of cardiovascular disease and all-cause mortality in MHD patients [4–6]. Abdominal aortic calcification (AAC) is reported to be a predictor for cardiovascular mortality in the general population, and was also associated with increased risk of congestive heart failure in the Framingham Study. The association between AAC and all-cause and cardiovascular mortality in MHD patients has been shown in several reports. However, the factors contributing to AAC in MHD patients are still not fully understood.

Genetic and biochemical studies have established matrix Gla protein (MGP) as the first protein known to act as a calcification inhibitor in vivo. MGP is a vitamin K-dependent protein of 84 amino acids with a molecular weight of 12 kDa [7, 8]. Although MGP knockout mice are normal at birth, they rapidly develop severe arterial calcifications and subsequent vascular ruptures leading to death within 6–8 weeks [9]. Among three types of arteriosclerosis (i.e., atherosclerosis, Mönkeberg medial calcific

sclerosis, and arteriolosclerosis), arterial medial calcification is the major cause of vascular disease and is rapidly progressive in dialysis patients [2]. Therefore, MGP would be a critical factor in the development of arteriosclerosis in patients with MHD. A few previous reports have investigated serum MGP levels in hemodialysis patients, but the relationship between the serum MGP concentration and VC is controversial [10, 11].

It has been reported that the gene encoding MGP has several single nucleotide polymorphisms (SNPs) in its promoter and coding regions. Many studies have revealed the significance of *MGP* gene polymorphisms at T-138C and G-7A [12–14]. A previous study showed that MHD patients have a different distribution of *MGP* gene polymorphisms as compared with the normal population [14]. However, the influence of MGP polymorphism with respect to the development of AAC in MHD patients is not fully understood [12, 15]. It is a fact that there are no reports which examine the association between MGP polymorphism and AAC. With regard to 'femoral artery' calcification, Herrman et al. [12] reported that it was more prevalent in carriers of the MGP A-7 allele than in MGP GG-7 homozygotes and that T-138C were unrelated to femoral artery calcification in healthy volunteers. In addition, Crosier et al. [15] reported that in males, homozygous carriers of the minor allele of T-138C, G-7A and Ala102Thr were associated with a decreased quantity of 'coronary artery calcification (CAC)', relative to major allele carriers.

To date, the exact mechanisms for accelerated VC have yet to be fully determined. In particular, it is conceivable that the speed of progression of AAC in hemodialysis patients varies widely from patient to patient. Therefore, we examined whether MGP-SNPs affect the progression speed of AAC in MHD patients.

Materials and methods

Study design, setting and participants

This is a retrospective, longitudinal cohort study of MHD patients. As a setting, patients with end-stage kidney disease (ESKD) who started hemodialysis therapy after 2001 at Kawashima Hospital were recruited between August 2009 and November 2010. All of the procedures were performed in accordance with the guidelines of the Helsinki Declaration on Human Experimentation and the Ethical Guidelines on Clinical Research published by the Japanese Health, Labour and Welfare Ministry. This study was approved by the Ethics Committee of Tokushima University and Kawashima Hospital, and written informed consent was obtained from all patients.

The exclusion criteria were (1) past operation for abdominal aortic aneurysms and (2) renal transplantation.

Finally 145 participants were recruited and provided samples which we assayed for two SNPs in the *MGP* gene promoter region—T-138C (rs1800802) and G-7A (rs1800801). Routine abdominal computed tomography (CT) examination is performed once a year in each patient, and we used these data. We enrolled 134 of the 145 patients whose VC could be followed in consecutive multidetector CT (MDCT) examinations; 11 patients were excluded from additional analysis because they underwent MDCT examination once or not at all.

Identification of *MGP* gene genotypes

We selected two common SNPs on the *MGP* gene promoter—T-138C (rs1800802) and G-7A (rs1800801). Whole blood samples were obtained via vascular access at the start of routine hemodialysis treatment, and were used for the extraction of genomic DNA with a Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA). First, T-138C (rs1800802) polymorphism was genotyped using a mismatch polymerase chain reaction (PCR) fragment amplified with the primers for 142 bp region as a pilot study—5′-AAGCATACGATGGCCAAAACTTCTGCA-3′ and 5′-GAACTAGCATTGGAACTTTTCCCAACC-3′ [13]. These PCR products were purified with DNA Clean & Concentrator-5 kit (Zymo Research, Orange, CA, USA) and were digested with the restriction enzyme *Bsr*I, and analyzed in polyacrylamide gel (Fig. 1).

The following primers were designed for a 408 bp region that included T-138C (rs1800802) and G-7A (rs1800801)—5′-TCTGTCCCCAAGCATACGAT-3′ and 5′-ACACAGAGAAATGGGAGAAAAG-3′. These primers were verified by sequencing and PCR was carried out. Purified PCR products were subjected to direct sequencing by using 3730xl DNA Analyzer (Applied Biosystems).

Serum MGP assay

Serum MGP concentrations were quantified with a kit from Biomedica (Vienna, Austria) as described previously [16].

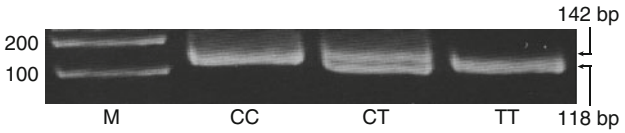

Fig. 1 Genotyping of the T-138C polymorphism using mismatch PCR followed by digestion with the restriction enzyme *Bsr*I. The presence of a T nucleotide at position −138 produced a *Bsr*I restriction endonuclease site giving fragments of 118 and 24 bp. The presence of a C nucleotide at position −138 did not produce a restriction endonuclease site for *Bsr*I. M: 100 bp DNA Ladder

Detection and measurement of VC

In order to evaluate the VC of each patient, we gathered data from the past abdominal CT examinations of each patient and calculated the abdominal aortic calcium volume score (AACVS). The plain abdominal MDCT imaging was performed using an 8-slice Aquarion scanner (Toshiba, Japan). The images from the bifurcation at the beginning of the common iliac artery to the 70-mm cranial interval were transferred to a workstation. Quantification of aortic calcification was carried out with ZIO Workstation software (ZIO, Japan). VC was defined as >130 Hounsfield units of CT value on this workstation, and counted as pixel data. The AACVS was defined according to the following formula—(pixel) × (pixel) × (slice thickness) × (quantity of voxel) [mm^3]. In this formula, (1 pixel) × (1 pixel) × (slice thickness) expresses (1 voxel). The volumetric scoring method named the calcium volume score was referred to in previous articles [17–19].

Statistical methods

We considered two-tailed p values <0.05 as statistically significant. All of the statistical analyses were performed using JMP 9.02 (SAS Institute, Cary, NC, USA). Statistical analysis of continuous variables was performed with Kruskal–Wallis analysis because assumptions of normality of the distribution were not verified. Post hoc multiple comparisons were made using the Steel–Dwass method. In addition, statistical analysis of nominal variables was performed with the chi-squared test.

Results

This study was carried out to examine the effects of *MGP* gene promoter polymorphisms (T-138C and G-7A) on the progression of VC in patients undergoing MHD. The T-138C and G-7A polymorphisms are located in the promoter region of the *MGP* gene (Fig. 2). Sequencing results of these polymorphisms are also shown in Fig. 2. The distribution of the T-138C genotype in this study was TT (35.1 %, $n = 47$), CT (52.2 %, $n = 70$) and CC (12.7 %, $n = 17$) (Fig. 3a). Similarly, the frequency of the G-7A genotype was GG (85.1 %, $n = 114$), GA (12.7 %, $n = 17$) and AA (2.2 %, $n = 3$) (Fig. 3b). We then compared the T-138C allele frequency of this study with that from the database of the genome-wide association study (GWAS); a chi-squared test showed no significant differences between them ($p = 0.73$, data not shown). In contrast, we could get no information on the G-7A allele frequency in GWAS. For that reason, we decided to place the primary focus on the analyses of the T-138C genotype.

Clinical characteristics of all patients of each genotype of T-138C are presented in Table 1. We found that the CC genotype was associated with significantly higher concentrations of high-density lipoprotein (HDL) cholesterol ($p = 0.03$).

Figure 4a shows the progression of the AACVS throughout the study (mean $R^2 = 0.87$), and Fig. 4b, c and d show the scores for the CC ($n = 17$), CT ($n = 70$) and TT ($n = 47$) genotypes, respectively. The dashed line shows the mean scores for all patients in each genotype group.

In order to investigate the effect of the T-138C genotype on the serum MGP concentration, we analyzed the MGP concentrations in the sera of MHD patients. There were no

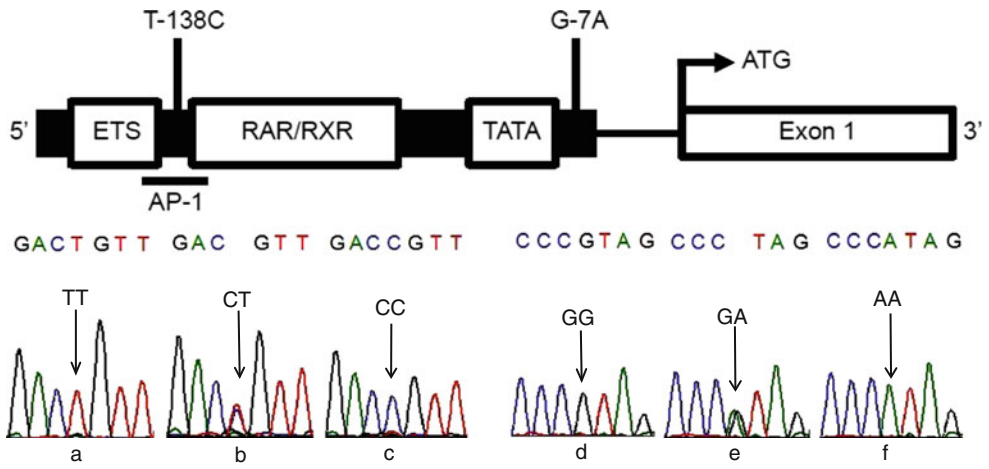

Fig. 2 DNA sequences of the polymorphic region in the MGP (T-138C, G-7A). **a** DNA sequence from individual homozygous for the TT genotype of T-138C. **b** heterozygous for the CT genotype of T-138C. **c** Homozygous for the CC genotype of T-138C. **d** DNA sequence from individual homozygous for the GG genotype of G-7A. **e** heterozygous for the GA genotype of G-7A. **f** homozygous for the AA genotype of G-7A. *ETS* Ets transcription factor family, *AP-1* activating protein-1, *RAR/RXR* retinoid A and X receptor, *TATA* TATA box

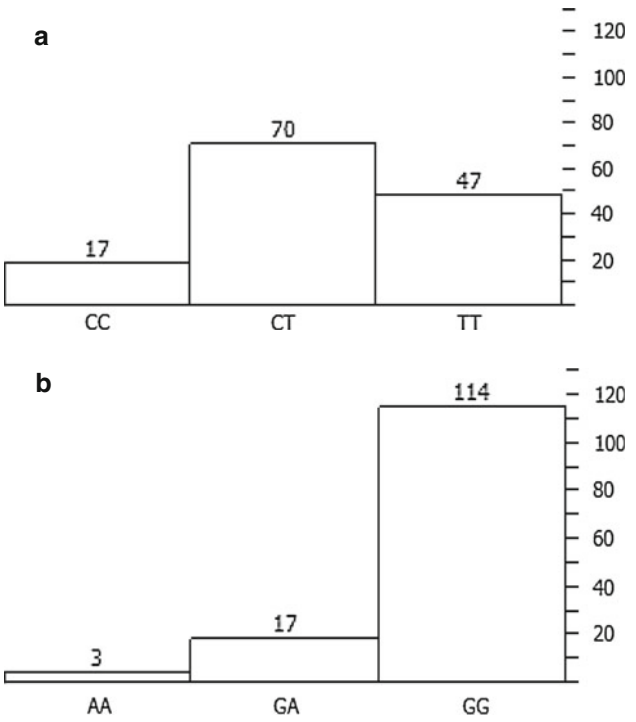

Fig. 3 The distribution of T-138C and G-7A genotype. **a** The distribution of the T-138C genotype ($n = 134$). **b** The distribution of the G-7A genotype ($n = 134$)

significant differences in the serum MGP concentration among the genotypes [CC: 22.57 (21.41, 28.43), CT: 25.10 (21.23, 26.87), TT: 25.01 (23.07, 26.45); unit: nmol/L, $p = 0.72$].

We compared the result of the slope value of the absolute AACVS plots as a linear function among the T-138C genotypes (Fig. 5a). The slope value for the CC genotype [53.00 (12.11, 254.90)] was significantly smaller than that for the CT genotype [319.85 (110.70, 647.80)] and TT genotype [261.00 (85.50, 626.56)] ($p = 0.003$, 0.03). Figure 5b shows the results of the comparison of the *y*-intercepts among the T-138C genotypes; there were no significant differences among them ($p = 0.52$). It is generally believed that the progression of VC at the beginning of MHD would contribute to the acceleration of VC and long-term survival of MHD patients [20]. Interestingly, however, our results indicate that the CC genotype of T-138C significantly contributes to the slowing of VC progression, regardless of differences in the VC volume at the beginning of MHD.

Multiple regression analysis by the best subset regression method between the progression speed of AACVS and related parameters revealed that CT/TT genotypes, greater age at the beginning of MHD, male sex, high levels of calcium × phosphate (Ca × P), low levels of HDL cholesterol, high levels of low-density lipoprotein (LDL) cholesterol, low levels of ferritin and non-use of angiotensin receptor blockers (ARBs) contributed to the progression of VC (Table 2).

Discussion

Although AAC is reported as a predictor for cardiovascular mortality in the general population, it is unknown whether this is also true in MHD patients. In addition, although many studies have focused on coronary calcification, there have been very few studies assessing the progression of AAC in MHD patients. A system for quantification of calcification was described by Kauppila et al. [21] in a subgroup of participants of the Framingham heart study. It relies on lateral lumbar radiographs and the calculation of the AAC score. Its predictive value for cardiovascular events and mortality was validated in the Framingham heart study [22, 23]. Recently, the AAC score was shown to correlate well with electron beam CT scores of the coronary arteries in MHD patients [24]. AAC may also be associated with all-cause and cardiovascular mortality in ESKD [25]. More recently, VC scores determined by MDCT were shown to be useful for evaluating the volume of VC [18]. For that reason, we used MDCT examinations for evaluation of the progression of VC in MHD patients.

The progression speed of VC differed among the MHD patients, and we hypothesized that MGP polymorphisms had some effect on this variation. Our study proved that MHD patients with the MGP T-138C CC genotype exhibited slower progression of VC than those with other genotypes. To our knowledge, this is the first study to reveal that the MGP T-138C polymorphism is closely linked to differences in the progression speed of VC among MHD patients.

MGP T-138C polymorphisms lie in the promoter region of the *MGP* gene, which is critical for the transcriptional activity. Farzaneh-Far et al. [13] previously showed that the −138C variant provides higher levels of MGP transcriptional activity in vascular smooth muscle cells. Therefore, our clinical data imply that the −138C allele increases MGP promoter activity in the arterial vessel and works more protectively against the progression of VC in MHD patients with the CC genotype. Furthermore, a previous study demonstrated that the −138C variant is associated with higher serum MGP levels (+30 %) [13]. On the other hand, the serum MGP level was not correlated with T-138C polymorphisms in another study [26]. Our results in this study also showed no relation between the MGP polymorphisms and serum MGP levels. Several reports have demonstrated that MGP expression was increased in atherosclerotic arteries [27, 28]. From in situ hybridization, it was shown that MGP mRNA transcription takes place in the arterial vessel wall, and is particularly upregulated in atherosclerotic arteries [27]. Thus, local MGP upregulation

Table 1 Clinical characteristics of all the patients of each genotype of T-138C

	Characteristic	CC ($n = 17$)	CT ($n = 70$)	TT ($n = 47$)	p value[a]
Basic	Age at the beginning of HD (years)	61 (44, 72)	57 (49, 69)	57 (50, 68)	0.90
	Age at the time of this study	62 (48, 74)	63 (53.8, 74)	60 (53, 70)	0.85
	Male % (n)	82.4 (14)	68.6 (48)	70.2 (33)	0.53
	Body mass index (kg/m^2)	21.6 (19.0, 24.2)	22.4 (20.4, 24.9)	22.6 (20.0, 23.9)	0.53
	HD duration (month)	26 (18, 39)	42 (23, 74)	41 (22, 77)	0.10
	Diabetes % (n)	23.5 (4)	47.1 (33)	40.4 (19)	0.20
Medications (po)	Statin % (n)	23.5 (4)	11.4 (8)	10.6 (5)	0.35
	Antihypertensives				
	Calcium channel blocker % (n)	13.3 (2)	30.0 (21)	36.2 (17)	0.17
	ACE inhibitor % (n)	0.0 (0)	1.4 (1)	2.1 (1)	0.82
	ARB % (n)	17.7 (3)	31.4 (22)	27.7 (13)	0.52
	Vitamin K % (n)	5.9 (1)	1.4 (1)	4.3 (2)	0.51
	Antiplatelet % (n)	29.4 (5)	37.1 (26)	31.9 (15)	0.76
	Warfarin % (n)	0.0 (0)	4.3 (3)	4.3 (2)	0.69
	Calcium carbonate % (n)	70.6 (12)	81.4 (57)	85.1 (40)	0.42
	Active vitamin D % (n)	82.4 (14)	60.0 (42)	57.5 (27)	0.17
	Sevelamar hydrochloride % (n)	17.7 (3)	27.1 (19)	23.4 (11)	0.70
	Cinacarcet % (n)	0.0 (0)	1.4 (1)	4.3 (2)	0.48
	Lanthanum carbonate % (n)	11.8 (2)	14.3 (10)	12.8 (6)	0.95
	Steroid % (n)	5.9 (1)	5.7 (4)	2.1 (1)	0.63
HD-related parameters	Kt/V	1.49 (1.41, 1.62)	1.46 (1.30, 1.67)	1.48 (1.33, 1.60)	0.80
	HD (hours)	4 (4, 4)	4 (4, 4)	4 (4, 4)	0.69
Laboratory data (blood)	Total protein (mg/dL)	6.3 (6.1, 6.5)	6.2 (5.9, 6.6)	6.2 (6.0, 6.6)	0.54
	Albumin (mg/dL)	3.6 (3.5, 3.9)	3.6 (3.4, 3.8)	3.7 (3.5, 3.8)	0.14
	Total cholesterol (mg/dL)	163 (136, 184)	154 (136, 180)	156 (139, 176)	0.97
	HDL cholesterol (mg/dL)	54 (40, 62)	42 (33, 51)	38 (32, 53)	0.03*
	LDL cholesterol (mg/dL)	67 (55, 104)	78 (67, 100)	78 (66, 97)	0.62
	Triglyceride (mg/dL)	123 (63, 156)	105 (70, 158)	119 (85, 223)	0.32
	Blood glucose (mg/dL)	128 (113, 151)	126 (102, 146)	125 (96, 151)	0.88
	HbA1c (%): only diabetic patients (n = 4:33:19)	5.7 (5.4, 8.3)	5.8 (5.5, 7.6)	6.2 (5.5, 6.7)	0.98
	GA (%): only diabetic patients (n = 4:33:19)	19.7 (17.2, 29.5)	19.5 (16.7, 23.6)	22.0 (20.3, 24.6)	0.12
	C-reactive protein (mg/dL)	0.1 (0.0, 0.2)	0.1 (0.0, 0.4)	0.1 (0.0, 0.2)	1.00
	Calcium (mg/dL)	9.0 (8.2, 9.5)	8.9 (8.6, 9.4)	9.1 (8.6, 9.7)	0.41
	Phosphate (mg/dL)	4.6 (3.8, 5.4)	4.9 (4.0, 5.6)	4.8 (4.2, 5.6)	0.46
	Calcium × phosphate	40.9 (32.0, 48.6)	43.4 (34.0, 49.6)	44.2 (36.9, 53.0)	0.30
	Intact-PTH (pg/mL)	75 (36, 105)	74 (39, 129)	63 (39, 145)	0.86
	Hemoglobin (g/dL)	11.2 (10.7, 11.7)	11.1 (10.5, 11.7)	10.9 (10.4, 11.8)	0.79
	Ferritin (ng/mL)	126 (94, 158)	132 (79, 192)	130 (55, 173)	0.64
	β2 microglobulin (mg/L)	23.9 (20.1, 26.0)	25.8 (22.0, 30.9)	25.8 (23.1, 30.6)	0.16
	Blood urea nitrogen (mg/dL)	64.8 (51.5, 81.9)	63.8 (56.5, 76.2)	69.1 (60.6, 80.0)	0.39
	Creatinine (mg/dL)	11.40 (9.33, 13.58)	11.73 (9.61, 13.39)	11.63 (10.22, 14.02)	0.70

Data are presented in % (n) for categorical variables, and as median (25th, 75th percentile) for continuous variables

We analyzed the MGP concentrations in the sera of 48 MHD patients (CC: $n = 7$, CT: $n = 26$, TT: $n = 15$) because of discontinuation of the kit from Biomedica. There were no significant differences in the serum MGP concentration among the genotypes (CC: 22.57 (21.41, 28.43), CT: 25.10 (21.23, 26.87), TT: 25.01 (23.07, 26.45), unit: nmol/L, $p = 0.72$)

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, GA glycated albumin, *HD* hemodialysis, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein *PTH* parathyroid hormone

* $p < 0.05$

[a] Chi-squared test was used for categorical variables, and Kruskal–Wallis tests were used for continuous variables

in arterial walls may be a central mechanism counteracting the progression of excessive VC. Furthermore, a recent study reported that gremlin, one of the bone morphogenetic protein (BMP) antagonists, binds to precursors of BMP and inhibits their function [29]. BMP is an osteoinductive factor expressed in atherosclerotic lesions and MGP is

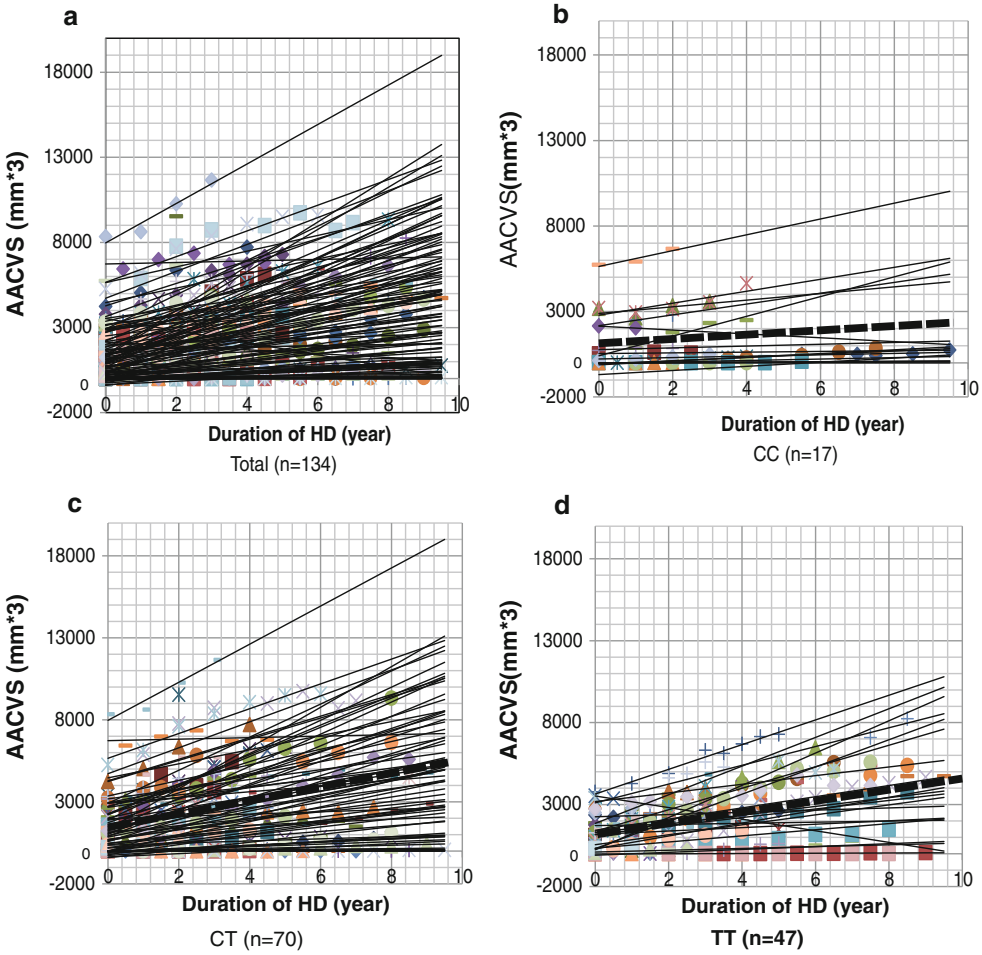

Fig. 4 Plots of the abdominal aortic calcium volume score (AACVS) as a linear function of each patients. **a** Plots of total patients (mean $R^2 = 0.87$). **b** Plots of only patients with the CC genotype of T-138C. **c** Plots of only patients with the CT genotype of T-138C. **d** Plots of only patients with the TT genotype of T-138C. The *dashed line* shows the mean scores for all patients in each genotype group

thought to be a BMP inhibitor. Therefore, the intracellular function to block BMP activation may be true of MGP and MGP may prevent arteries from calcification. Together with these findings, our study suggests that the CC genotype of T-138C may enhance the local activation of MGP independently of the serum MGP concentration, and may have the potential to inhibit VC in MHD patients.

We performed multiple regression analysis by the best subset regression method between the progression speed of VC and related parameters (Table 2), suggesting that the CC genotype of T-138C would function as a preventive factor for VC. Moreover, greater age at the beginning of MHD, high levels of Ca × P, low levels of HDL cholesterol, high levels of LDL cholesterol, and non-use of ARBs are all classic factors contributing to the progression of VC. With regard to gender, Yamada et al. [30] previously showed that the progression of AAC was negatively associated with the premenopausal status in women, which was considered to be due to female sex hormones. In our study, however, 34 of 39 (87.2 %) female participants were >50 years. Additionally, in our study, the CC genotype of T-138C was associated with higher concentrations of HDL cholesterol in the cross-sectional data (Table 1), and low levels of HDL cholesterol were significantly associated with progression of VC (Table 2). Yao et al. [31] previously reported in vitro that an increasing concentration of HDL cholesterol progressively enhanced expression of the activin-like kinase receptor 1 (ALK1) in human aortic endothelial cells, and that induction of ALK1 was associated with increased levels of MGP as determined by real-time PCR. This report supports our present data because high levels of HDL cholesterol may induce upregulation of focal MGP expression in the artery wall and subsequently halt the progression of VC. However, further investigations are needed to fully understand the mechanisms of regulation of HDL level in the CC genotype. Additionally, we tried taking the presence of diabetes, blood glucose and dialysis vintage (month) into the multiple regression analysis by the conventional model and the best subset regression method (stepwise method). These parameters were found not to influence the progression speed of VC in our analysis. Collectively, the most important finding in our study was that the MGP genotype was an invariable parameter related to the longitudinal VC progression.

There were several limitations to our study. The sample size of the study population was relatively small for a genetic association study. Therefore, further studies with a larger

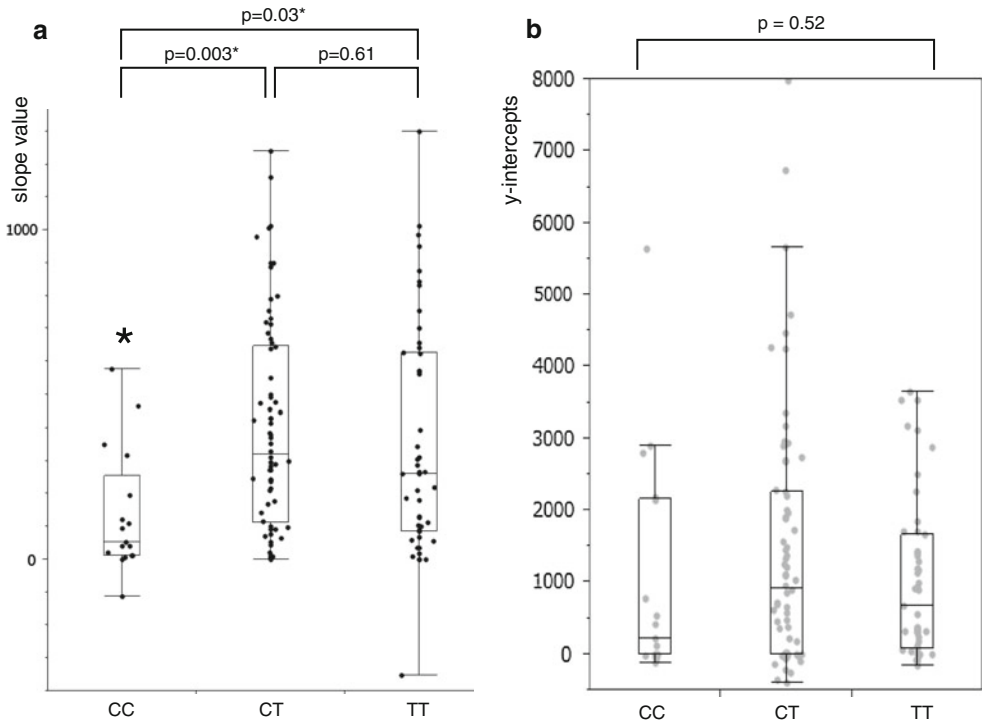

Fig. 5 The comparison of the progression speed of vascular calcification among the T-138C genotype. **a** The differences of the progression speed of the abdominal aortic calcium volume score (AACVS). **b** The comparison result of the vascular calcification (VC) at the beginning of HD (*y*-intercepts). Both were analyzed by Kruskal–Wallis test and Steel–Dwass test

Table 2 Multiple regression analysis between the progression speed of AACVS and related parameters

Covariate	Coefficient	95 % CI	Standardized β	*p* value
CT/TT genotype of T-138C	87.06	(19.04, 155.07)	0.25	0.01*
Age at the beginning of HD (years)	9.10	(5.14, 13,07)	0.38	<0.001*
Female sex	−73.30	(−127.38, −19.22)	−0.20	0.008*
Ca × P	9.15	(4.61, 13.70)	0.33	<0.001*
HDL cholesterol (mg/dL)	−3.44	(−6.60, −0.28)	−0.16	0.03*
LDL cholesterol (mg/dL)	3.09	(1.10, 5.07)	0.23	0.003*
Ferritin (ng/mL)	−0.65	(−1.13, −0.16)	−0.20	0.01*
ARBs	−63.70	(−117.61, −9.78)	−0.18	0.02*

$n = 134$, $R^2 = 0.34$, $F = 7.1936$, $p < 0.001$, Durbin–Watson ratio 1.9365483

ARBs angiotensin receptor blockers, *Ca* × *P* calcium × phosphate, *HD* hemodialysis, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

* $p < 0.05$

number of subjects in different groups with different characteristics are needed. We need to continue this study prospectively in order to investigate relationships to cardiovascular events and long-term mortality. In addition, large-scale follow-up studies with high-risk CKD patients would enhance and vary the information about the genetic background.

Conclusions

This study emphasizes that MGP T-138C polymorphism is closely linked to the progression speed of VC in MHD patients. VC is very common in MHD patients and is a strong predictor of cardiovascular disease and all-cause mortality. In particular, accelerated progressive VC strongly deteriorates the prognosis of MHD patients. We propose here that the genotype of the *MGP* gene might be a genomic biomarker that is predictive of VC progression. Furthermore, this inalterable biomarker may be helpful for disease detection and classification, treatment response prediction, treatment efficacy, and prognosis.

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Conflict of interest The authors have declared that no conflict of interest exists.

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