Haptoglobin 2-1 phenotype predicts rapid growth of abdominal aortic aneurysms

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Background: **Haptoglobin (Hp) polymorphism is associated with the prevalence and clinical evolution of many inflammatory diseases and atherosclerosis. Circulating neutrophils and neutrophil-associated proteases are an important initial component of experimental abdominal aortic aneurysm (AAA) formation. Elastase and C-reactive protein (CRP) levels are elevated in patients with AAAs. This study assessed the relationship between AAA expansion and Hp phenotypes, neutrophil count, elastase, and CRP levels.**

Methods: **Eighty-three consecutive AAA patients underwent annual ultrasound scans. Three major Hp phenotypes (1-1, 2-1, and 2-2) were determined, and the neutrophil count, serum elastase, and high-sensitivity (hs) CRP levels were measured at the initial examination. After initial screening, patients were rescanned at 6- to 12-month intervals up to a period of 2 to 7 years. The mean yearly growth of the AAA largest transverse diameter was estimated for each group of Hp patients. The results are presented as median (interquartile range).**

Results: **Hp 2-1 patients had a significantly higher growth rate (3.69 [2.40] mm/y) of AAA compared with patients with Hp 2-2 (1.24 [0.79], $P < .00001$) and Hp 1-1 (1.45 [0.68], $P = .00004$). This association remained significant in the multivariate analysis. Elevated elastase serum activity was also evident in AAA patients with Hp 2-1 (0.119 [0.084] arbitrary units) in contrast to Hp 2-2 (0.064 [0.041], $P < .00001$) and Hp 1-1 (0.071 [0.040], $P = .0006$) patients. CRP serum levels (mg/L) were significantly higher in patients with Hp 2-1 (7.2 [7.1]) than in Hp 2-2 (3.4 [3.1], $P = .0058$) and Hp 1-1 (2.8 [4.1], $P = .044$). The neutrophil count was not significantly different among Hp groups.**

Conclusions: **The Hp 2-1 phenotype showed a strong association with increased rates of the expansion of AAAs and may be a useful independent predictor of growth rate. Further large follow-up studies will be needed to investigate the pathomechanisms of association and the role of elastase and inflammation in the progression of AAA. (J Vasc Surg 2010; 52:691-6.)**

Clinical Relevance: **Elective surgical or endovascular repair is recommended for large aneurysms, whereas small aneurysms are managed by watchful waiting. The diameter and rate of growth of the AAA are the most important determinants of the risk of rupture and in deciding when elective repair is justified. In the present study, the Hp 2-1 phenotype predicted rapid aneurysm expansion. This may have implications for the frequency of follow-up and timing of repair of AAA in patients with the Hp 2-1 phenotype.**

Although abdominal aortic aneurysm (AAA) is an important cardiovascular disease, the genetic and environmental risk factors that contribute to an increase in the likelihood that an aneurysm will develop in an individual are nonetheless still poorly understood. Ongoing research into the genetic components of AAA using a candidate gene approach has been generally unsuccessful. However, significant evidence has emerged in recent years to suggest that chronic aortic wall inflammation causes connective tissue remodeling. Observational studies have highlighted a familial trend toward AAA development among the relatives of individuals with AAA, and it is thought that such inflammatory genes may influence an individual's susceptibility. Genetic influences may also be crucial in the regulation of inflammatory responses.[1] Heredity and inflammation appear to be important factors in the development of AAA.[2]

Haptoglobin (Hp) is a hemoglobin-binding protein expressed by a genetic polymorphism as three major phenotypes: Hp 1-1, Hp 2-1, and Hp 2-2, that are the products of two alleles (*Hp 1* and *Hp 2*). The Hp 1-1 protein is biologically the most effective in binding free hemoglobin and suppressing inflammatory responses, Hp 2-2 is the least active, and Hp 2-1 is moderately active.[3] Most attention has been paid to determining the Hp phenotype as a genetic fingerprint used in forensic medicine. Several functional differences between Hp phenotypes have also been shown to have important biologic and clinical consequences.[4] Hp 2-2 is reported to be associated with the risk of atherosclerosis and coronary heart disease, including myocardial infarction.[5] The frequency of the *Hp 1* allele was significantly increased in patients with aneurysms compared with

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healthy controls. It has been documented in vitro that Hp 2-1 and Hp 1-1 possess a far higher activity to stimulate elastin hydrolysis by leucocyte elastase than that of Hp 2-2.[6] In fact, Hp 2-2 has no effect on elastin hydrolysis by neutrophil elastase, indicating that Hp 2-1 and Hp 1-1 specifically affect elastin by making it more susceptible to degradation. Corresponding to these data, Hp 2-2 patients had the highest mean age at aneurysm resection.[6] Variation in the Hp gene appears to influence the dilatation of the abdominal aorta and probably has a direct effect on the degradation of elastin in the atherosclerotic aorta.[6]

This study tested the hypothesis that the Hp phenotype affects the growth rate of aneurysm, serum elastase activity, and markers of inflammation in patients with newly diagnosed AAA.

METHODS

The Bioethical Committee of the Pomeranian Medical University, Szczecin, Poland, approved the study protocol. The nature of the study was explained to the patients, and their written consent was obtained.

Patients. The study enrolled 83 consecutive patients (73 men, 10 women) with a recent diagnosis of AAA referred to the outpatient clinic of the Department of Vascular Surgery and Angiology of Pomeranian Medical University between February 2000 and January 2006. Patients were 66.9 ± 7.7 years old and had a body mass index of 25.8 ± 4.1 kg/m^2. The study excluded individuals with symptomatic or ruptured AAA.

Shortly after enrollment, the initial examination was arranged and ultrasound imaging was performed to confirm the AAA diagnosis and measure the initial aneurysm diameter. A blood sample was also taken, and patients were queried about comorbidities, which were confirmed by medical documentation, smoking, and pharmacologic treatment, including β-blockers, statins, and antiplatelet drugs.

An AAA was defined as a focal dilation of the abdominal aorta with a diameter >30 mm, which is a standard criterion for many clinical trials. The patients were prospectively observed and underwent repeat ultrasound scans (maximal anteroposterior diameter) at 6- to 12-month intervals to monitor the growth of the aneurysm during a period of 2 to 7 years, or until AAA operation, loss of contact, or the end of the study. Operative intervention was considered for patients with AAA ≥55 mm. The follow-up was continued in the AAA patients with large aneurysms (≥55 mm) when they did not consent to have surgery at the time.

The same experienced radiologist examined all of the patients. The maximal anteroposterior diameter of the aorta was measured using VOLUSON 730Pro with CONVEX probe (General Electric Medical Systems, Wien, Austria) in color Doppler mode.

The average rate of growth was calculated as the change in aortic diameter over time, using the formula:

$$\text{Growth rate (mm/y)} = (\text{max diameter at last scan} - \text{max diameter at first scan})/\text{time interval}.$$

Table I. Distribution of haptoglobin *(Hp)* phenotypes in patients with abdominal aortic aneurysm *(AAA)* and in healthy controls[a]

Hp phenotype	*Controls*	*AAA group*
	No. (%)	No. (%)
1-1	136 (13)	13 (16)
2-1	448 (43)	41 (49)
2-2	459 (44)	29 (35)

[a]The distributions are not significantly different ($P = .27$, χ^2 test).

Laboratory analysis. The methods for Hp phenotyping, estimation of serum elastase activity, and neutrophil count in the peripheral blood have been previously described in detail.[7] The blood was sampled from the peripheral vein of fasting patients. One tube (without anticoagulant) was centrifuged ≤1 hour, and the serum samples were stored at –20°C. The second tube (containing ethylenediaminetetraacetic acid) was used for neutrophil count. Hp phenotyping was performed by starch-gel electrophoresis. The serum, which contains free hemoglobin added in excess, provides a haptoglobin-hemoglobin complex of one of three phenotypes, which is observed after benzidine staining.[7]

Serum elastase activity was measured using a kit (Enzymatic Assay of ELASTASE, Leukocyte, E-8140, Sigma-Aldrich, Poznan, Poland) according to the manufacturer's instructions with an ultraviolet-visible spectrophotometry Lambda 40 P spectrophotometer (Perkin Elmer, Turku, Finland) and expressed in arbitrary units based on change of absorbance at 347.5 nm.

High-sensitivity CRP (hsCRP) serum concentration was measured using the sandwich enzyme immunoassay test CRP (EUROIMMUNN-ELISA, Medizinische Labordiagnostika AG, Lübeck, Germany) with EnVision 2104 Multilabel Reader (Perkin Elmer). The detection limit for hsCRP was 0.8 ng/mL and intra-assay precision (CV%) was 5.0% to 5.8 %. The neutrophil count was determined by the automated hematology analyser CELLDYN 3700 (Abbott Laboratories, Abbot Park, Ill).

The distribution of Hp phenotypes in AAA patients was compared with 1043 healthy Polish men (aged 19 to 48 years) from northwestern Poland (Table I) who underwent Hp phenotyping as part of a paternity test in the Department of Forensic Medicine at the same time as the AAA patients were having their follow-up. Their health status was assessed on the basis of interview and available medical documentation. No aneurysms or any other comorbidities were found in this group except 26 with diabetes mellitus.

Statistical analysis. The studied quantitative parameters were compared among the Hp phenotype groups by Kruskal-Wallis and Mann-Whitney tests. Qualitative parameters were analyzed with χ^2. The Spearman rank correlation coefficient (r) was used to measure the strength of correlations. A general linear model was used for multivariate analysis with logarithmic transformation of variables with log-normal distribution for AAA diameter and growth

Table II. Characteristics of 83 patients with abdominal aortic aneurysm *(AAA)*[a]

Variable	*Mean ± SD*	*Median (IQR)*
Age at initial examination, y	66.9 ± 7.7	68 (11)
Initial AAA diameter, mm	40.8 ± 8.7	39 (11)
Final AAA diameter, mm	52.2 ± 8.7	52 (8)
Follow-up, mon	54.7 ± 15.1	52 (28)
	No. (%)	—
Male gender	73 (88)	—
Hypertension	42 (51)	—
Coronary artery disease	37 (31)	—
COPD	11 (13)	—
Hernia repair	15 (18)	—
Peripheral vascular disease	17 (21)	—
Cerebrovascular disease	10 (12)	—
Diabetes	7 (8)	—
Active smokers	73 (88)	—
Statins	74 (89)	—
β-blockers	31 (37)	—
Antiplatelet drugs	83 (100)	—

COPD, Chronic obstructive pulmonary disease; *IQR,* interquartile range.
[a]Comorbidities and drugs taken at the initial examination are presented.

rate, elastase activity, and CRP concentration. A value of $P < .05$ was considered statistically significant.

RESULTS

The distribution of Hp phenotypes in patients with AAA was similar to the control group (Table I). The characteristics of the AAA patients are reported in Table II. The Hp phenotype groups were not significantly different in age, gender, and pharmacologic treatment ($P > .05$ for all comparisons, data not shown). The only comorbidity significantly associated with the Hp phenotype was coronary artery disease, present in 1 Hp 1-1 patient (8%), 16 Hp 2-1 patients (39%), and 20 Hp 2-2 patients (69%; $P = .0007$, χ^2). At the last scan the AAA diameter was 30 to 49 mm in 21 patients (25%), 50 to 54 mm in 33 (40%), and ≥ 55 mm in 29 (35%).

The comparison of AAA diameter, growth rate, serum elastase activity, and inflammation markers among the Hp phenotypes is reported in Table III. Univariate analysis showed that the Hp 2-1 phenotype was associated with a lower initial AAA diameter, a higher increase of diameter between the initial and final study, a higher AAA growth rate (Fig), and shorter time of observation until the last follow-up visit compared with the Hp 1-1 and Hp 2-2 phenotypes. Hp 2-1 was also associated with higher serum elastase activity and CRP concentration than both homozygous phenotypes. There were no significant differences in final AAA diameter and neutrophil count. No differences were found between Hp 1-1 and Hp 2-2 patients.

Table IV presents correlations of studied blood parameters with AAA growth rate and initial diameter. The AAA growth rate correlated positively with serum elastase activity and CRP concentration in the entire group. A positive correlation with elastase was also present within the Hp 2-1 subgroup. The growth rate correlated positively with the neutrophil count in Hp 2-1 patients. No correlations were significant in Hp 1-1 and Hp 2-2 groups.

The initial AAA diameter correlated negatively with serum elastase activity, but this association was significant only in the entire AAA group. No significant associations between AAA growth rate or inflammation markers and age, gender, smoking, comorbidities, and pharmacologic treatment were found (data not shown).

Multivariate analysis adjusted for age, gender, and variables significantly associated with Hp phenotype or growth rate (AAA initial diameter, elastase activity, CRP, and presence of coronary artery disease) showed that the Hp 2-1 phenotype was the only independent predictor of a higher AAA growth rate (significantly positive β coefficient) compared with Hp 1-1 and 2-2 phenotypes (Table V). Another multivariate analysis adjusted for age, gender, elastase activity, CRP, and presence of coronary artery disease (Table VI) showed that the Hp 2-1 phenotype was the only independent predictor of a lower initial AAA diameter (significantly negative β coefficient) compared with the Hp 2-2 phenotype; however, no association was significant in the model when Hp 2-1 was compared with Hp 1-1. This was probably due to a low number of Hp 1-1 patients. No significant predictors of AAA growth rate or initial diameter were found in multivariate models comparing Hp 1-1 and Hp 2-2 phenotypes (data not shown).

DISCUSSION

AAA has a prevalence of 1.3% to 8.9% in men and 1.0% to 2.2% in women aged >55 years and is a life-threatening disease characterized by the progressive aortic dilation and rupture. The rupture of a large AAA has a mortality rate of up to 90%. Elective surgical or endovascular repair is recommended for large aneurysms, whereas small aneurysms are managed by careful monitoring and patience. AAA diameter and growth rate are the most important determinants of the risk of rupture and the need for elective repair. Therefore, systemic biomarkers associated with faster aneurysm growth would be useful in clinical practice.

To the best of our knowledge, this is the first prospective study to analyze the association of AAA growth rate with Hp phenotype. We showed that the Hp 2-1 phenotype is associated with the highest mean growth rate of AAA. The association also remains significant after adjustment for other variables correlating with the Hp phenotype or growth rate. Moreover, the Hp 2-1 phenotype was associated with the highest absolute AAA diameter increase in the shortest period, proving that the association with the highest growth rate is not solely dependent on the shortest follow-up time. We therefore postulate that the Hp 2-1 phenotype is a strong independent risk factor of faster AAA growth.

An increased frequency of the Hp 2-1 phenotype was previously reported among AAA patients,[8] but we did not confirm this finding in our study patients. However, our study confirmed the *Hp 2* allele is associated with coronary artery disease.[5] Different values of mean annual rate of AAA expansion have been reported, including 1.3,[9] 1.6,[10] 2.6,[11]

Table III. Comparison of abdominal aortic aneurysm *(AAA)* parameters, serum elastase activity, and inflammation markers among patients with various haptoglobin *(Hp)* phenotypes

	Hp phenotype, median (IQR)			P *value*[a]		
Parameters	*1-1*	*2-1*	*2-2*	*2-1 vs 1-1*	*2-1 vs 2-2*	*2-2 vs 1-1*
Age at initial examination, y	68 (10)	68 (14)	69 (11)	.89	.77	.91
AAA diameter, mm						
Initial	43 (15)	38 (6)	44 (12)	.023	.0081	.52
Final	56 (10)	52 (7)	51 (15)	.38	.79	.27
Increase[b]	8 (5)	15 (9)	8 (4)	.0074	.00007	.77
Follow-up, mon	66 (26)	45 (13)	62 (12)	.0028	<.00001	.81
Growth rate, mm/y	1.45 (0.68)	3.69 (2.40)	1.24 (0.79)	.00004	<.00001	.14
Elastase activity, AU[c]	0.071 (0.040)	0.119 (0.084)	0.064 (0.041)	.0006	<.00001	.65
CRP, mg/L	2.8 (4.1)	7.2 (7.1)	3.4 (3.1)	.044	.0058	.79
Neutrophil count, G/L	5.5 (2.0)	5.7 (2.5)	5.4 (1.8)	.55	.95	.57

CRP, C-reactive protein; *IQR*, interquartile range.
[a]Mann-Whitney test.
[b]Difference between final and initial AAA diameter.
[c]Arbitrary units based on absorbance change.

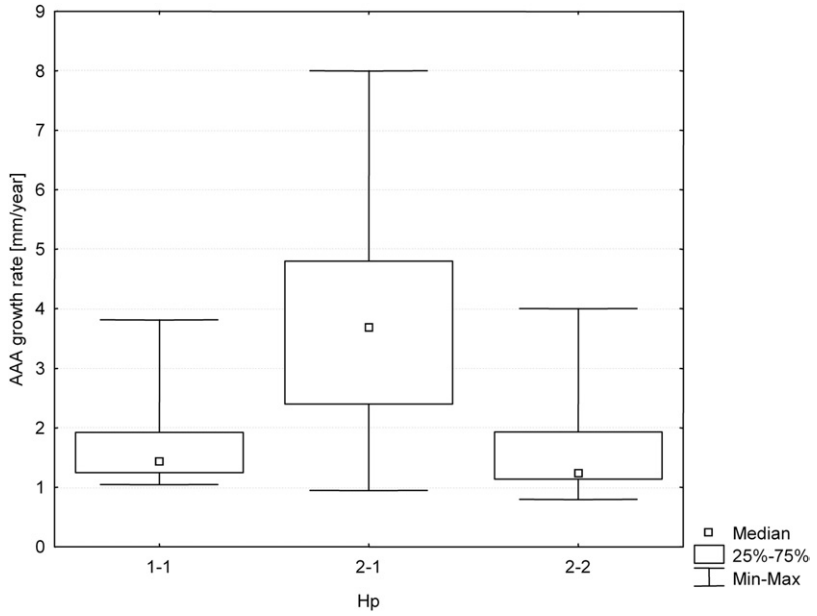

Fig. Abdominal aortic aneurysm *(AAA)* growth rate is shown in patients with various haptoglobin *(Hp)* phenotypes.

3.2,[12] and 7.9 mm/y,[13] but none of these studies analyzed Hp phenotype.

It is difficult to explain why the Hp 2-1 heterozygous phenotype was different from both homozygous phenotypes, and no differences were found between Hp 1-1 and Hp 2-2 homozygotes. However, such mode of association was previously reported in relation to other diseases. In Crohn's disease, patients with Hp 2-1 had a higher risk of the inflammatory form compared with the other two homozygous phenotypes.[14] A significant number of individuals with Parkinson's disease were carrying the Hp 2-1 phenotype,[15] as were patients with a family history of ovarian carcinoma.[4] It could be speculated that Hp 2-1 phenotype might cumulate harmful features associated with allele *Hp 1* (stimulation of the elastin hydrolysis)[6] and allele *Hp 2* (increased risk of atherosclerosis)[5] to yield a combination that is particularly efficient in promoting AAA growth, but much more evidence is needed to support this hypothesis.

Aneurysmal dilatation was linked with a significant increase in aortic stiffness or inelasticity and with decreased medial elastin content.[16] Neutrophil elastase is a proteinase in granulocytes that is important in the pathogenesis of inflammatory disorders because it causes medial degeneration.[17] The neutrophil count and elastase contribute to the progression of vascular disease.[18] Moreover, elastin-derived peptides

Table IV. Correlations of studied blood parameters with abdominal aortic aneurysm *(AAA)* growth rate and initial diameter in all AAA patients and in subgroups with various haptoglobin *(Hp)* phenotypes[a]

	AAA group (n = 83)		*Hp 1-1 (n = 13)*		*Hp 2-1 (n = 41)*		*Hp 2-2 (n = 29)*	
Parameter	*r*	P *value*	*r*	P *value*	*r*	P *value*	*r*	P *value*
Correlations with AAA growth rate								
Elastase activity	+0.42	.00009	+0.24	.43	+0.45	.0033	−0.23	.23
CRP level	+0.32	.0031	+0.14	.64	+0.25	.11	−0.03	.86
Neutrophil count	+0.17	.12	−0.04	.90	+0.33	.035	−0.10	.62
Correlations with initial AAA diameter								
Elastase activity	−0.29	.0068	−0.50	.079	−0.08	.64	−0.19	.32
CRP level	−0.05	.63	−0.11	.72	+0.15	.34	+0.09	.64
Neutrophil count	−0.01	.92	+0.07	.82	+0.06	.69	−0.12	.53

CRP, C-reactive protein.
[a]Values of Spearman rank correlation coefficients (*r*) with corresponding values of *P* are presented.

Table V. Multivariate analysis of predictors of abdominal aortic aneurysm *(AAA)* growth rate[a]

	Hp 2-1 vs Hp 1-1		*Hp 2-1 vs Hp 2-2*	
Parameter	β-*Coefficient*	P *value*	β-*Coefficient*	P *value*
Age	−0.06	.60	−0.07	.48
Male gender	−0.03	.81	+0.09	.37
Coronary artery disease	−0.10	.40	−0.11	.28
AAA initial diameter[b]	−0.04	.74	+0.01	.89
Serum elastase activity[b]	+0.28	.055	+0.09	.44
Serum CRP[b]	+0.19	.14	+0.13	.20
Hp 2-1 phenotype	+0.34	.021	+0.48	.00026

CRP, C-reactive protein; *Hp*, haptoglobin.
[a]A general linear model was used with the logarithm of growth rate as the dependent variable and seven independent variables. Models for comparison of Hp 2-1 with each of the homozygous phenotypes are presented.
[b]This variable was transformed logarithmically before analysis.

Table VI. Multivariate analysis of predictors of abdominal aortic aneurysm initial diameter[a]

	Hp 2-1 vs Hp 1-1		*Hp 2-1 vs Hp 2-2*	
Parameter	β-*Coefficient*	P *value*	β-*Coefficient*	P *value*
Age	+0.19	.15	+0.14	.22
Male gender	+0.20	.12	+0.09	.47
Coronary artery disease	−0.08	.55	−0.03	.80
Serum elastase activity[b]	−0.28	.076	−0.13	.37
Serum CRP[b]	+0.05	.72	+0.09	.48
Hp 2-1 phenotype	−0.23	.13	−0.31	.035

CRP, C-reactive protein; *Hp,* haptoglobin.
[a]A general linear model was used with the logarithm of initial diameter as the dependent variable and six independent variables. Models for comparison of Hp 2-1 with each of the homozygous phenotypes are presented.
[b]Variable was transformed logarithmically before analysis.

stimulate the release of elastase in the aortic wall by circulating neutrophils.[19] Circulating neutrophils and neutrophil-associated proteinases are an important initial component of AAA formation.[20,21] In addition, the serum elastase activity is associated with arterial stiffness and may be involved in the process of aortic elasticity loss.[22]

The elasticity of the large arteries was significantly lower in diabetic patients with Hp 2-1 and Hp 2-2 phenotype compared with Hp 1-1.[23] The highest elastase activity in our AAA patients was seen in the Hp 2-1 group, and the AAA expansion rate significantly positively correlated with serum elastase activity in the entire group and within those with the Hp 2-1 phenotype. Some have suggested that neutrophil elastase is a better and more accurate marker of inflammation than CRP.[24] This is consistent with our results: a much stronger association with AAA growth rate was found for elastase than for CRP.

Increased serum hsCRP levels have been reported during the formation of AAA.[25] Serum CRP concentrations were threefold higher in patients with increased arterial stiffness than in healthy controls.[26] It is therefore probable that the increased serum hsCRP levels are related to the enhanced elastin degradation within aneurysm wall. Norman et al[10] demonstrated that the CRP levels do not appear to be associated with rapid expansion. In our study, CRP correlated with AAA growth rate in the entire group, but the association was not significant in the multivariate model.

Although the Hp 2-1 group had the highest elastase activity, the neutrophil count was similar in all the Hp groups. This is consistent with the observation that neutrophil elastase did not correlate with the leucocyte count in vascular disease.[18] Biologically active peptides generated from CRP by neutrophil elastase promote neutrophil apoptosis,[27] and this phenomenon might explain the lack of association between Hp and neutrophil count. The neutrophil count in our patients correlated positively with aneurysm growth rate only in the Hp 2-1 group.

Our study has several limitations that should be accounted for when interpreting the results. Patients in the study group had a wide range of initial AAA diameters and follow-up times. We could not establish the outcome of patients after the last examination.

The AAA diameter was measured with ultrasound imaging and not computed tomography, because computed tomography is not convenient for repeated measurements.

Elastase activity and inflammation markers were measured only at the initial examination and were not monitored during follow-up. No serum lipids were assessed. Further studies with a larger and a more homogenous group of AAA patients are needed to confirm our results.

CONCLUSIONS

We suggest that the Hp 2-1 phenotype is a strong independent predictor of rapid aneurysm growth. This may have implications for the frequency of follow-up and timing of repair of AAA in patients with Hp 2-1 phenotype. The pathomechanisms of the association of haptoglobin, elastase, and inflammation with AAA growth need further research.

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AUTHOR CONTRIBUTIONS

Conception and design: IW
Analysis and interpretation: IW, KS, JP
Data collection: IB, JP
Writing the article: IW, KS
Critical revision of the article: KS
Final approval of the article: PG
Statistical analysis: KS
Obtained funding: IW
Overall responsibility: IW

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