Genetic variants in the ADAMTS13 and SUPT3H genes are associated with ADAMTS13 activity

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THROMBOSIS AND HEMOSTASIS

Key Points

- We identify rs41314453 as the strongest genetic predictor of ADAMTS13 activity, associated with a decrease of >20%.
- We present evidence of further independent associations with a common variant in SUPT3H, as well as 5 variants at the ADAMTS13 locus.

A disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) cleaves von Willebrand factor, reducing its prothrombotic activity. The genetic determinants of ADAMTS13 activity remain unclear. We performed a genome-wide association study of ADAMTS13 activity in the Rotterdam Study, a population-based cohort study. We used imputed genotypes of common variants in a discovery sample of 3443 individuals and replication sample of 2025 individuals. We examined rare exonic variant associations in ADAMTS13 in 1609 individuals using an exome array. rs41314453 in ADAMTS13 was associated with ADAMTS13 activity in both our discovery (β = −20.2%; P = 1.3 × 10−33) and replication sample (P = 3.3 × 10−36), and explained 3.6% to 6.5% of the variance. In the combined analysis of our discovery and replication samples, there were 2 further independent associations at the ADAMTS13 locus: rs3118667 (β = 3.0; P = 9.6 × 10−21) and rs139911703 (β = −11.6; P = 3.6 × 10−36). In addition, rs10456544 in SUPT3H was associated with a 4.2 increase in ADAMTS13 activity (P = 1.13 × 10−3). Finally, we found 3 independent associations with rare coding variants in ADAMTS13: rs148312697 (β = −32.2%; P = 3.7 × 10−6), rs142572218 (β = −46.0%; P = 3.9 × 10−5), and rs36222275 (β = −13.9%; P = 2.9 × 10−3). In conclusion, we identified rs41314453 as the main genetic determinant of ADAMTS13 activity, and we present preliminary findings for further associations at the ADAMTS13 and SUPT3H loci. (Blood. 2015;125(25):3949-3955)

Introduction

A disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) cleaves von Willebrand Factor (VWF) into smaller multimers.1-3 ADAMTS13 thereby greatly reduces the activity of VWF in its role in platelet adhesion and aggregation. Through this effect on VWF, ADAMTS13 has antithrombotic properties.

The role of ADAMTS13 in thrombosis is especially evident in patients with thrombotic thrombocytopenic purpura (TTP), a disorder resulting from a severe deficiency of ADAMTS13: patients with TTP have a wide range of symptoms, including thrombocytopenia and microangiopathy, which may result in stroke and myocardial infarction.4 Beyond patients with TTP, we and others recently showed that low ADAMTS13 activity and levels within the normal range are also associated with increased risk of cardiovascular outcomes.5-9

These associations between ADAMTS13 activity and arterial thrombosis raise the question of how ADAMTS13 activity is regulated. Several rare single nucleotide polymorphisms (SNPs) in the ADAMTS13 gene causing TTP have been identified along with a few common variants with more modest effects on ADAMTS13.10,11 However, it is not known whether these associations are independent of each other, or even whether they exhibit the strongest associations at the locus. Furthermore, the role of genetic variation outside of the ADAMTS13 locus remains unknown. The optimal method to identify genetic determinants is a genome-wide association (GWA) study, with a hypothesis-free approach. To date, no studies on the genetics of ADAMTS13 using this approach have been reported.

Thus, in the Rotterdam Study, a large population-based cohort study, we conducted a GWA study of ADAMTS13 activity, including a conditional analysis to identify multiple independent signals. In addition, we characterized the ADAMTS13 gene and any other genes with associated common variants by examining the role of rare variants.

Methods

Study description and population

The Rotterdam Study is a prospective, population-based cohort study of determinants of several chronic diseases in older adults.12,13 The first cohort (RS-I) includes 7983 inhabitants 55 years or older from Ommoord, a district


A.D. and M.P.M.d.M. contributed equally to this study.

The online version of this article contains a data supplement.

There is an Inside Blood Commentary on this article in this issue.

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of Rotterdam in The Netherlands. The baseline examination took place between 1990 and 1993. The third visit took place between March 1997 and December 1999 and included 4797 participants. A second cohort (RS-II) was established between February 2000 and December 2001, including another 3011 inhabitants of Ommoord who reached the age of 55 years after the baseline examination of RS-I, and individuals aged 55 years or older who had migrated into the research area. The study was approved by the Medical Ethics Committee of Erasmus University, Rotterdam, The Netherlands, and all included participants gave their written informed consent in accordance with the Declaration of Helsinki.

**ADAMTS13 measurement**

Citrated plasma samples were collected at the third visit of RS-I and the baseline examination of RS-II, and stored at −80°C. Between June 2013 and October 2013, we measured ADAMTS13 activity using a kinetic assay based on the fluorescence resonance energy transfer substrate VWF 73 (FRETsvWF73) assay. This assay uses a peptide containing the ADAMTS13 cleavage site of VWF, and thus captures variation in the VWF cleavage rate determined by ADAMTS13 levels and structure, but not by alterations in VWF.

Plasma samples were measured against a reference curve of serial dilutions of normal human plasma defined to have an ADAMTS13 activity of 1 IU/mL, and we express ADAMTS13 activity as a percentage of this. In total, the ADAMTS13 activity of 6258 participants was measured: 3791 from RS-I and 2467 from RS-II.

**Genotyping and imputation**

We used 2 sources of genetic variants: genome-wide SNPs genotyped by the Illumina Infinium HumanHap550 array or 610 quad array, and exome-wide SNPs genotyped by the Illumina HumanExome BeadChip v1.0. We genotyped 6291 participants from RS-I and 2157 participants from RS-II using the Illumina Infinium II HumanHap550 or 610 quad arrays. All genotyped participants were of European ancestry based on their self-report. Before imputation, genotyped SNPs with a call rate <98%, a minor allele frequency (MAF) <1%, or a Hardy–Weinberg equilibrium P value of <1 × 10−6 were excluded. In RS-I, 512 849 SNPs remained after filtering and these were used for imputation. In RS-II, 537 405 SNPs were used for imputation. Dosages of 19 537 258 SNPs were imputed in both studies using the Genomes of the Netherlands version 4 reference panel. We included SNPs that were functional according to the dbNSFP database that were highlighted in the common variant analysis. In addition, we only included SNPs within genes that were highlighted in the common variant analysis. In discovery, we included SNPs that were functional according to the dbNSFP database (missense, stop-gain, stop-loss, or splice site) with a MAF <0.01. We applied a genomic control correction to the combined results to account for genomic inflation. To identify secondary signals at significant loci, we performed a stepwise conditional analysis repeating the GWA analysis adjusted for the most significant variant in each locus (defined as 2 × 250 KB of the top SNP). This approach was repeated with additional adjustment for secondary signals until no further genome-wide significant signals remained.

**Rare variant analysis**

In a subset of RS-I participants, we used the exome chip to examine the effect of rare variants. To maximize our power, we included only SNPs within genes that were highlighted in the common variant analysis. In discovery, we included SNPs that were functional according to the dbNSFP database (missense, stop-gain, stop-loss, or splice site) with a MAF <0.01. We then used the seqMeta package implemented in R to determine the association between the rare variant burden in selected genes and ADAMTS13 activity, and to examine the association of individual SNPs. This package has previously been described in further detail. Rare variant burden analysis was performed using both a T1 test and a sequence kernel association test (SKAT). In T1 tests, the sum of rare variant dosages is created for each gene and associated with the traits of interest. T1 tests are unidirectional: they are more powerful when, within a gene, the effect sizes of rare variants are consistently in the same direction. SKAT is a bidirectional test and is more powerful when the effect direction of rare variants within a gene varies. Single-variant analysis was done using score tests. All analyses were adjusted for age, sex, and the independently significant common variants. In addition, the analyses were adjusted for 4 ancestry-informative principal components, because rare variants are more susceptible to population stratification. Finally, we performed stepwise conditional analysis to determine whether rare variant associations were independent from each other.

**Estimation of the heritability**

In RS-I, we estimated the proportion of variance of ADAMTS13 activity explained by all SNPs together. First, we constructed a matrix of pairwise genetic relationships based on common (MAF ≥0.01), well-imputed (imputation quality >0.3) SNPs. We excluded 1 individual from each pair with a pairwise relationship >0.025, reducing the number of included individuals to 2455. We then used a restricted maximum likelihood model to estimate the proportion of variance explained by the genetic relationships. The result can be interpreted as the lower bound of the heritability. The estimated heritability is expected to be lower than the true heritability because it is based on imperfectly imputed SNPs that may in turn be only partially correlated to the underlying causal variants.

We then calculated the variance explained by the combination of independently significant variants using the adjusted R² resulting from a linear regression model in R. We did this separately for RS-I and RS-II.

In addition, to place genetic determinants of ADAMTS13 into a wider context, we estimated the variance of ADAMTS13 activity explained by genome-wide significant SNPs, as well as by baseline characteristics including age, sex, total and high density lipoprotein (HDL) cholesterol, prevalent type 2 diabetes, current smoking status, body mass index (BMI), and systolic and diastolic blood pressure. We used the partial2 function from the asbio package in R. All variables were included in a single linear regression model, and the resulting partial coefficients of determination indicate the variance explained on top of the other variables in the model.

**Results**

**Discovery in RS-I and replication in RS-II**

Participant characteristics are shown in Table 1. Participants in RS-I were older (mean age, 72.4 years ±7.0 standard deviation [SD]) than participants in RS-II (mean age, 64.6 years ±7.9 SD). The mean...
ADAMTS13 activity was 89.5% in RS-I and 95.0% in RS-II, with a range of 5% to 198% across the 2 cohorts. After removing rare and poorly imputed SNPs, 8,237,900 SNPs were included in the discovery GWA analysis, of which 329 were significantly associated with ADAMTS13 activity (supplemental Figures 1 and 2). All of these SNPs mapped to the ADAMTS13 locus. The minor allele of the lead SNP, rs14314453, was associated with a 20.2% decrease in ADAMTS13 activity ($P = 1.3 \times 10^{-8}$). The signal was successfully replicated in RS-II: the minor allele of rs14314453 was associated with a 23.5% decrease in ADAMTS13 activity ($P = 3.3 \times 10^{-8}$).

**Combined analysis of RS-I and RS-II**

In the combined analysis of RS-I and RS-II, rs14314453 was also the lead variant at the ADAMTS13 locus (Table 2 and Figure 1A). There was 1 genome-wide significant SNP outside of the ADAMTS13 locus: rs10456544, an intronic SNP in the SUPT3H gene (Table 2 and Figure 1B). The minor allele was associated with a 4.2% increase in ADAMTS13 activity. After adjustment for rs14314453 and rs10456544, there were no significant variants remaining at the SUPT3H locus, but there was a second signal at the ADAMTS13 locus. The minor allele of lead variant rs3118667 was associated with a 3.0% increase in ADAMTS13 activity ($P = 4.9 \times 10^{-5}$). When additionally adjusting for rs3118667, there was a third genome-wide significant signal at the ADAMTS13 locus. The minor allele of the lead variant, rs13991703, was associated with an 11.6% decrease in ADAMTS13 activity ($P = 3.6 \times 10^{-6}$).

**Rare variant analyses**

There were 11 functional SNPs with MAF <0.01% in ADAMTS13 and 4 in SUPT3H. For single-variant analysis, we thus used a $P$ value threshold of .0033. Three rare variants were associated with ADAMTS13 activity: rs48312697 (beta = −32.8; $P = 3.6 \times 10^{-6}$; frequency, 0.16%), rs142572218 (beta = −46.0; $P = 3.9 \times 10^{-5}$; frequency, 0.06%), and rs36222275 (beta = −14.7; $P = 2.2 \times 10^{-3}$; frequency, 0.34%). The association of these variants was independent of the 3 associated common variants in ADAMTS13 (Table 3), and stepwise conditional analysis suggests that the associations are also independent of each other (supplemental Table 1). The spread across the functional domains of ADAMTS13 of these associated rare nonsynonymous variants, as well as the associated common nonsynonymous variant (rs41314453), is shown in Figure 2. None of the rare variants in SUPT3H was significantly associated with ADAMTS13 activity.

Although we only examined 2 genes, we used a $P$ value threshold of .013 to adjust for doing both SKAT and T1 tests. The 11 variants in ADAMTS13 had a cumulative minor allele frequency of 1.1%. Rare variant burden in ADAMTS13 was associated with ADAMTS13 activity according to both the T1 ($P = 5.7 \times 10^{-8}$) and SKAT test ($P = 1.5 \times 10^{-8}$). These associations remained significant after adjusting for the 3 associated common variants in ADAMTS13 (supplemental Table 2). When we additionally adjusted the burden tests for the 3 rare SNPs in a stepwise manner, the association diminished with each step and finally lost significance upon adjustment for all 3 rare SNPs (supplemental Table 2). The rare variant burden in SUPT3H was not associated with ADAMTS13 activity according to the T1 ($P = .5$) and SKAT tests ($P = .7$).

**Estimation of the heritability**

The variance of ADAMTS13 activity explained by all SNPs in RS-I was 35.2% ($P = .009$), which can be interpreted as the lower bound of the heritability. The variance explained by the 4 independently significant common SNPs was 5.8% to 8.2%. The variance of ADAMTS13 activity explained by each of the 4 independently significant common SNPs on top of other baseline characteristics is shown in supplemental Table 3. This table also shows the variance explained by other baseline characteristics. The variance explained by rs41314453 (3.6%-6.5%) is comparable with the variance explained by sex (4.5%-6.7%). The variance explained by rs3118667 (1.3%-2.1%) is comparable with the variance explained by current smoking status (1.5%-1.7%). Because the estimates for SNPs are based on imputed dosages rather than on directly measured genotypes, the actual variance explained by the SNPs is likely to be higher.

**Discussion**

In this first-ever GWA study of ADAMTS13 activity, we robustly identified rs41314453 within the ADAMTS13 gene as the main genetic

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**Table 1. Characteristics of the participants included in the discovery in the Rotterdam Study I (RS-I) and in the replication in the Rotterdam Study II (RS-II)**

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Age (y)</th>
<th>Sex (% males)</th>
<th>ADAMTS13 activity (%)</th>
<th>BMI (kg/m²)</th>
<th>Current smoking (%)</th>
<th>Total cholesterol (mmol/L)</th>
<th>HDL cholesterol (mmol/L)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Prevalent type 2 diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-I</td>
<td>3423</td>
<td>72.4 ± 7.0</td>
<td>64.6 ± 7.9</td>
<td>26.8 ± 3.9</td>
<td>15.8</td>
<td>5.8 ± 1.0</td>
<td>1.4 ± 0.4</td>
<td>143.3 ± 21.0</td>
<td>75.2 ± 11.2</td>
<td>14.1</td>
</tr>
<tr>
<td>RS-II</td>
<td>2025</td>
<td>64.6 ± 7.9</td>
<td>45.1</td>
<td>27.2 ± 4.0</td>
<td>19.5</td>
<td>5.8 ± 1.0</td>
<td>1.4 ± 0.4</td>
<td>143.3 ± 21.3</td>
<td>78.9 ± 10.8</td>
<td>11.5</td>
</tr>
</tbody>
</table>

BMI, body mass index; HDL, high-density lipoprotein. Continuous variables are summarized by their mean ± SD.
determinant of ADAMTS13 activity in both our discovery and replication cohort, explaining between 3.6% and 6.5% of the variance. Through the combined analysis of our discovery and replication samples, we present preliminary evidence of independent associations with 2 further SNPs in ADAMTS13 (rs3118667 and rs139911703), and with an SNP in the SUPT3H gene (rs10456544). Furthermore, in a subset of our discovery sample, we found 3 independently associated rare variants in ADAMTS13 (rs148312697, rs142572218, and rs36222275). Finally, we established a lower bound for the heritability of ADAMTS13 activity at 35%.

The most significant SNP, rs41314453, is a nonsynonymous exonic variant in the thrombospondin type1 repeat 2 domain that is also known...
as Ala732Val. It is in linkage disequilibrium with several intronic SNPs in ADAMTS13, as well as with SNPs in regulatory regions of neighboring genes. However, among these SNPs, rs41314453 remains the most promising SNP, because it has previously been shown in vitro to reduce ADAMTS13 levels by 40% and ADAMTS13 activity by 29%. The decrease in activity appeared to be mediated completely by the decrease in protein concentration rather than by a decrease in the specific activity (activity per milligram of ADAMTS13), and the decrease in levels was not linked to decreased synthesis. This suggests that the underlying mechanism is a decreased secretion of ADAMTS13.

The secondary signal at the ADAMTS13 locus, rs3118667, is a synonymous SNP that has not previously been reported to be associated with ADAMTS13. It is not in strong linkage disequilibrium with other SNPs. Thus, the mechanism behind this signal is unclear. The third signal at the ADAMTS13 locus, rs139911703, is an intronic SNP in SUPT3H, which encodes the protein Spt3, a part of the SPT3-TAF9-GCN5 acetyltransferase (STAGA) complex, Spt3 is involved in transcription activation. The STAGA complex acetylates histones, reconforming the DNA around the histones into a more accessible structure, allowing for increased transcription. The STAGA complex acetylates histones, reconfiguring the DNA around the histones into a more accessible structure, allowing for increased transcription. The main role of the Spt3 subunit in STAGA is to recruit the transcription factor II D complex (TFIID), which then binds to TATA box motifs in promoters, enabling RNA polymerase II to position itself appropriately for transcription. The ADAMTS13 promoter does not have a known TATA box motif, but it does have an Sp1 binding site, which can allow TFIID to bind to TATA-less promoters. We thus hypothesize that rs10456544 is associated with ADAMTS13 activity through a disturbance to these basal transcription activation processes. Because ADAMTS13 does not appear to be heavily regulated by transcription factors, the sensitivity to these processes might be increased. The possible relationship between Spt3 and ADAMTS13 activity should be confirmed through replication of the association and functional work.

Of the 3 associated rare SNPs, rs148312697 (Asp187His), located in the metalloprotease domain, has been shown in mice to reduce ADAMTS13 activity and secretion and to cause TTP. Another variant at the same position (Asp187Ala) has also been shown to reduce proteolytic function. rs142572218 (Arg1060Trp) has been identified as a causal mutation for late-onset adult TTP and has been shown to profoundly decrease secretion, but not the specific activity. rs36222275 (Gly982Arg) has not previously been associated with ADAMTS13 activity. The effect size is smaller than that of the other 2 rare variants and rs41314453, the lead common variant. We were able to identify this rare variant with an intermediate effect size because of our hypothesis-driven approach, but it will need to be confirmed either in vitro or through replication in other association studies.

Nonsynonymous variant rs28647808, or Pro618Ala, has previously been used as a genetic proxy for ADAMTS13 activity. Indeed, several lines of experimental evidence support a causal role for Pro618Ala. In the combined analysis of our discovery and replication samples, Pro618Ala was well-imputed (imputation quality > 0.9) and was associated with ADAMTS13 activity (β = −4.5; P = 7.3 × 10⁻16, frequency, 9.8%). However, this association disappeared after adjusting for the lead variant, rs41314453, with which it is in modest linkage disequilibrium (R² = 0.18). In line with our results, studies by Miyata et al and Kokame et al have found no association between Pro618Ala and ADAMTS13 activity in the Japanese general population. Our results therefore do not support a causal role of rs28647808 in the regulation of ADAMTS13 activity, and suggest that rs41314453 may be a more suitable genetic proxy for future studies.

Similarly, another polymorphism that has been associated with ADAMTS13 activity in the literature, rs2301612 or Gln448Glu, was not strongly associated with ADAMTS13 activity in our study (β = 1.6; P = 1.4 × 10⁻10; frequency, 43.6%). The effect direction was...
consistent with the literature. Interestingly, the association became stronger upon adjustment for ADAMTS13 lead variant rs41314453 (β, 2.6; \(P = 1.1 \times 10^{-15}\)) but was again attenuated when further adjusted for secondary variant rs3118667 (β, 1.3; \(P = 1.4 \times 10^{-3}\)).

In the discovery GWA analysis, we only found associations with SNPs within the ADAMTS13 gene itself. In the combined analysis of the discovery and replication samples, only 1 SNP at another locus was genome-wide–significant. Although this is likely related to the small sample size, the unbalanced genetic architecture is not surprising. ADAMTS13 is constantly synthesized and secreted in its active form. Previous work suggests that ADAMTS13 transcription is stable and not significantly regulated by transcription factors. This leaves little room for strong regulators. Furthermore, although several factors are known to influence the rate at which ADAMTS13 cleaves VWF, these are not captured by the measurement of ADAMTS13 activity. The measurement is based on the rate at which an introduced peptide similar to VWF is cleaved. However, in vivo, alterations to VWF that disrupt its interactions with ADAMTS13 may also affect the cleavage rate. For example, mutations involved in type 2A von Willebrand disease have been shown to increase the cleavage rate.\(^{45}\)

Apart from synthesis and secretion, ADAMTS13 activity is further determined by degradation and the specific activity. ADAMTS13 degradation is known to occur in the presence of thrombin and plasmin.\(^{46}\) However, the level of ADAMTS13 degradation is minimal, because coagulation and fibrinolysis normally only occur at a very low level. We therefore expect the regulation of ADAMTS13 degradation to explain a very small part of the genetic associations with ADAMTS13 activity.

In patients with congenital ADAMTS13 deficiency, who often suffer from TTP, the main underlying mechanisms are changes in secretion and specific activity.\(^{1,11}\) This is in line with our results in this population-based study. Functional work has previously been done for 3 of the variants associated with ADAMTS13 activity in our study, and two of these reduce secretion, whereas one reduces the specific activity.\(^{29,40,41}\)

The strengths of this study include our genome-wide hypothesis-free approach, which, in contrast to the targeted genotyping of a few candidate SNPs, allowed us to systematically examine the ADAMTS13 locus. Second, the use of Genomes of the Netherlands as a reference panel for the imputation of unmeasured SNPs was particularly appropriate, because this reference panel is based specifically on the Dutch population. Third, we were able to replicate our common variant results in a nonoverlapping sample that was ethnically similar to the discovery sample and used the same assay to measure ADAMTS13 activity. Finally, the rare variant and conditional analyses we performed allowed us to gain a detailed view of the ADAMTS13 locus.

However, although 2 of the rare variant associations were backed up by previous functional work, we were not able to replicate our rare variant associations because participants in RS-II were not genotyped using the exome chip. Neither were we able to replicate the associations with rs3118667 and rs139911703 in ADAMTS13, nor rs10456544 in SUPT3H, because these associations were identified by combining our discovery and replication samples. In addition, the limited sample size allowed us to detect only the strongest associations with ADAMTS13 activity. This will be improved as more studies with genome-wide SNP array data measure ADAMTS13 activity or levels. Although we replicated our results in a nonoverlapping sample, both samples were from the Rotterdam Study and were measured together. Thus, the samples were not completely independent from one another. Finally, our estimate of the heritability should be interpreted as the lower bound of the heritability for 2 reasons. First, it is based on imperfectly imputed SNPs that may in turn be only partially correlated to the underlying causal variants. Second, it is only based on common SNPs, whereas a portion of the heritability is likely to stem from rare variants. Estimates from twin and family studies are required for further precision.

In conclusion, in our study we robustly identified a strong association between rs41314453 in the ADAMTS13 gene and ADAMTS13 activity, and we present preliminary evidence of association with another 5 genetic variants in ADAMTS13 and 1 variant in the SUPT3H gene. Explaining between 3.6% and 6.5% of the variance, rs41314453 appears to be the main genetic determinant of ADAMTS13 activity.

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Authorship

Contribution: P.S.d.V., F.W.G.L., O.H.F., M.P.M.d.M., and A.D. designed the research; F.R., M.A.I., H.R., A.H., and A.G.U. collected data; J.B. and M.A.H.S. analyzed and interpreted data; P.d.V. performed statistical analysis; P.d.V., M.P.M.d.M., and A.D. wrote the manuscript; and all authors were involved in the revision of the manuscript.

Conflict-of-interest disclosure: H.R. is a full-time employee of Baxter Innovations GmbH, Vienna, Austria. O.H.F. works in ErasmusAGE, a center for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd.), Metagenics Inc., and AXA. Nestlé Nutrition (Nestec Ltd.), Metagenics Inc., and AXA had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, nor in the preparation, review or approval of the manuscript.

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Genetic variants in the *ADAMTS13* and *SUPT3H* genes are associated with ADAMTS13 activity