A *DAB2IP* genotype: sex interaction is associated with abdominal aortic aneurysm expansion

Zi Ye,[1] Erin Austin,[1,2] Daniel J Schaid,[2] Kent R Bailey,[2] Patricia A Pellikka,[1] Iftikhar J Kullo[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jim-2016-000404).

[1]Department of Cardiovascular Diseases and the Gonda Vascular Center, Mayo Clinic, Rochester, Minnesota, USA
[2]Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to
Dr Iftikhar J Kullo, Department of Cardiovascular Diseases and the Gonda Vascular Center, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA; kullo.iftikhar@mayo.edu

Accepted 25 April 2017

ABSTRACT

A faster expansion rate of abdominal aortic aneurysm (AAA) increases the risk of rupture. Women are at higher risk of rupture than men, but the mechanisms underlying this increased risk are unknown. We investigated whether genetic variants that influence susceptibility for AAA (*CDKN2A-2B*, *SORT1*, *DAB2IP*, *LRP1* and *LDLR*) are associated with AAA expansion and whether these associations differ by sex in 650 patients with AAA (mean age 70±8 years, 17% women) enrolled in the Mayo Clinic Vascular Disease Biorepository. Women had a mean aneurysm expansion 0.41 mm/year greater than men after adjustment for baseline AAA size. In addition to baseline size, mean arterial pressure (MAP), non-diabetic status, *SORT1*-rs599839[G] and *DAB2IP*-rs7025486[A] were associated with greater aneurysm expansion (all $p<0.05$). The associations of MAP and rs599839[G] were similar in both sexes, while the associations of baseline size, pulse pressure (PP) and rs7025486[A] were stronger in women than men (all $p_{sex\ interaction} \leq 0.02$). A three-way interaction of PP*sex*rs7025486[A] was noted in a full-factorial analysis ($p=0.007$) independent of baseline size and MAP. In the high PP group (≥median), women had a mean growth rate 0.68 mm/year greater per [A] of rs7025486 than men ($p_{sex\ interaction}=0.003$), whereas there was no difference in the low PP group ($p_{sex\ interaction}=0.8$). We demonstrate that variants *DAB2IP*-rs7025486[A] and *SORT1*-rs599839[G] are associated with AAA expansion. The association of rs7025486[A] is stronger in women than men and amplified by high PP, contributing to sex differences in aneurysm expansion.

Significance of this study

What is already known about this subject?

- Faster abdominal aortic aneurysm (AAA) expansion increases the risk of AAA rupture.
- There are sex differences in AAA development and progression.
- Women have higher risk of aneurysm rupture than men, but sex-specific risk factors for AAA expansion that contributes to excessive risk of AAA rupture in women are not known.

What are the new findings?

- *DAB2IP*- rs7025486[A] and *SORT1*-rs599839[G] were both associated with faster AAA expansion.
- The impact of *DAB2IP*- rs7025486[A] on AAA expansion was stronger in women than men.
- The sex difference in the association of *DAB2IP* with AAA expansion was amplified by pulse pressure (PP).

How might these results change the focus of research or clinical practice?

- Identification of genetic variants in addition to conventional risk factors for aneurysm expansion may lead to individualized management in both men and women.
- *DAB2IP*- rs7025486[A] and *SORT1*-rs599839[G] were associated with aneurysm expansion independent of baseline AAA size, suggesting the potential utility of genotyping these variants after AAA detection to optimize surveillance programs to prevent rupture.
- The stronger association of *DAB2IP*-rs7025486[A] with aneurysm expansion in women than men suggests the utility of further risk stratification by this single nucleotide polymorphism in women.
- The stronger association of *DAB2IP*-rs7025486[A] with aneurysm expansion in women than men is amplified by higher PP in women, suggesting arterial de-stiffening may have favorable impact in women to limit aneurysm expansion.

INTRODUCTION

Rupture of abdominal aortic aneurysm (AAA) is associated with a mortality as high as 80%.[1] Larger AAA size, female sex and elevated blood pressure (BP) increase the risk of rupture.[2 3] Baseline AAA size is the most important determinant of aneurysm expansion. Other reported risk factors for expansion include higher mean arterial pressure (MAP) or pulse pressure (PP), non-diabetic status and smoking.[2 4 5] Aneurysm surveillance to monitor expansion followed by elective AAA repair remains the cornerstone of management.[6 7]

AAA is a multifactorial disease with a genetic component.[8] Several susceptibility loci in pathways of lipid metabolism (*SORT1*, *LRP1* and *LDLR*) and cell survival/apoptosis (*CDKN2A-2B*, *DAB2IP*) have been reported to be associated with AAA.[9–13] Whether these variants are also associated with aneurysm

To cite: Ye Z, Austin E, Schaid DJ, *et al*. *J Investig Med* Published Online First: [*please include* Day Month Year]. doi:10.1136/jim-2016-000404

expansion is unclear. Women have fourfold higher risk of rupture than men and rupture is more likely to occur at a smaller diameter.[2 14] Whether risk factors for aneurysm expansion affect women and men differently is not known. Such knowledge will aid in understanding of sex differences in aneurysm progression and help develop therapies to slow aneurysm expansion.

To this purpose, we studied 650 patients with ≥2 measures of AAA size at least 3 months apart, who had undergone high-density genotyping. We searched the National Human Genome Research Institute-European Bioinformatics Institute Genome-Wide Association Studies (GWAS) catalog and PubMed for genetic susceptibility loci for AAA at a genome-wide level significant ($p \leq 5 \times 10^{-8}$). We aimed to assess: (1) whether variants in known susceptibility genes for AAA are associated with aneurysm expansion; and (2) whether these associations differ by sex.

METHODS

Study cohort

All subjects were from the Mayo Vascular Disease Biorepository, an electronic health records (EHR)-linked biorepository of plasma and DNA of patients referred for non-invasive vascular evaluation.[15 16] The aim of this biorepository is to identify novel biomarkers, including genetic susceptibility variants for common vascular diseases, such as AAA, peripheral artery disease and carotid artery stenosis, as well as less common vascular diseases such as fibromuscular dysplasia. The biorepository was initiated in 2006 and through August 2014, 11 814 adults had been recruited. High-density genotyping data are available in ~9300 (77 %) subjects. Demographic information, conventional risk factors and comorbidities were ascertained by algorithms based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, procedure codes, medications and laboratory data from EHR. These algorithms have been previously validated in the Electronic Medical Records and Genomics network.[15 17] All subjects gave informed consent. The study protocol was approved by the Institutional Review Board of the Mayo Clinic.

Ascertainment of AAA and aneurysm expansion

Through August 30, 2015, 1124 patients with AAA were identified from the Vascular Disease Biorepository. AAA was defined as an infrarenal abdominal aortic diameter ≥3 cm on an imaging study (ultrasound, CT, MRI or angiography reports) or a history of open or endovascular AAA repair. Based on previous reports that >85% of adults with ectasia of abdominal aorta will progress to a size ≥3 cm[18] and that infrarenal aortic diameter ≥2.5 cm was associated with significantly increased risk of cardiovascular events and mortality compared with those with a diameter <2.5 cm,[19] we included an aortic size ≥2.5 cm as the baseline measure if the subsequent measure of abdominal aorta exceeded 3 cm. We identified 651 (58%) patients with ≥2 measures of AAA size ≥3 months apart. Aneurysm expansion was estimated as (most recent/prerepair minus first diameter)/interval (mm/year, follow-up until January 24, 2016). We excluded one patient with missing BP measures, leaving 650 patients for the analyses.

Genotyping

Genomic DNA was extracted from whole blood samples drawn at recruitment. Genotyping was performed in the Mayo Clinic Genotyping Core laboratory according to standard protocols using Illumina Infimum Human core Exome Array and Illumina Human 610 and 660W Quad-v1. Sample call rates were all >95%. Out of five loci associated with AAA at genome-wide association significance ($p \leq 10^{-8}$) (see online supplementary table 1), four had been genotyped and one single nucleotide polymorphism (SNP: S*ORT1*-rs599839) was imputed based on the cosmopolitan 1000 Genomes Project reference panel using SHAPEIT2 for phasing[20] and IMPUTE2 software for imputation.[21] The IMPUTE2 information score for this SNP was 0.94. All SNPs were in Hardy-Weinberg equilibrium (all p>0.05). Risk allele frequencies in our study and those in previous GWAS are listed in online supplementary table 1.

Ascertainment of cardiovascular risk factors and atherosclerotic cardiovascular disease

Demographic information was abstracted from the EHR as structured data and conventional cardiovascular risk factors (hypertension, diabetes and dyslipidemia) and ASCVD were ascertained by algorithms validated previously.[17] Smoking status was ascertained from the study questionnaire. ASCVD was defined as a history of having any of coronary heart disease, stroke, carotid artery stenosis or peripheral arterial disease. Systolic BP (SBP) and diastolic BP (DBP) measures closest to the baseline and most recent or prerepair measure of AAA size were manually abstracted from the EHR.

Statistical methods

Comparisons between women and men were performed by t-test for continuous variables and χ^2 test for dichotomous variables. Linear regression analysis was used to assess: (1) univariate associations of conventional risk factors and genetic susceptibility variants with aneurysm expansion and (2) whether these associations differ by sex after including an interaction term of sex with each candidate risk factor. Additive models of genetic variants were assumed in the analysis. Candidate risk factors for AAA expansion included: age, sex, body mass index, baseline aneurysm size, hypertension, diabetes, dyslipidemia, current-smoking status, ASCVD and the five genetic susceptibility variants.

Given the effect of PP and MAP on aneurysm expansion and rupture,[2 4] we included PP and MAP (2/3 DBP+1/3 PP) as risk factors for aneurysm expansion (the average of baseline and most recent or prerepair BP variables and baseline BP variables were both used in separate models). Stepwise regression analyses with backward elimination were used to identify variables significantly associated with aneurysm expansion, using the criteria p<0.1 to enter and p<0.05 to retain in the model, starting with all candidate variables and interaction terms with sex if it was statistically significant (p<0.05) in the univariate analysis. Multivariable regression models were built to assess associations of variables identified from stepwise approach with aneurysm expansion. Additional analyses were performed to assess impact of BP control over time with aneurysm expansion.

Table 1 Patient characteristics stratified by sex

	Women (n=113)	Men (n=537)
Age, years	70±8	70±9
BMI, kg/m^2	28.4±5.5*	29.3±4.6
Hypertension, %	89	84
Diabetes, %	18*	27
Current smoking, %	39	42
Dyslipidemia, %	91	92
ASCVD, %	87	90
PP, mm Hg	64±15*	60±13
MAP, mm Hg	92±11	92±10
Baseline AAA size, mm	35.5±7.2*	37.2±7.7
Time interval between two imaging studies, year	5.0±3.2	5.5±3.7
AAA expansion, mm/year† (adjusted for baseline size)	2.9 (0.23)*	2.6 (0.10)

*p<0.05 for comparisons between women and men by t-test or χ^2 test.
†AAA expansion from linear regression model, expressed as least square mean (SE). PP and MAP: average of BP variables measured at baseline size and most recent or prerepair size.
AAA, abdominal aortic aneurysm; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; MAP, mean arterial pressure; PP, pulse pressure.

RESULTS

Patient characteristics are shown in table 1. The majority (98%) of subjects were whites (by self-report). Age and prevalence of hypertension, smoking, dyslipidemia and ASCVD were similar in men and women, whereas the prevalence of diabetes was higher in men. Mean PP was higher in women than men, while mean MAP was similar. The mean time interval between two imaging studies was 5.42 (0.14) years and was similar in women and men. The mean growth rate was 2.44 (0.1) mm/year. Women had faster aneurysm expansion than men after adjustment for the baseline aneurysm size. Diabetics had slower expansion than non-diabetics (mean±SE: 2.02±0.15 vs 2.58±0.13 mm/year, p=0.01); the mean growth rate was 1.18 mm/year greater for 1 cm increase in baseline size and 0.4 mm/year greater per 10 mm Hg increase in MAP (both p<0.001). None of the other conventional risk factors were associated with aneurysm expansion.

Of five genetic susceptibility variants for AAA (table 2), *DAB2IP*-rs7025486[A] and *SORT1*-rs599839[G] were associated with aneurysm expansion: the mean aneurysm expansion was 0.5 mm/year greater per A allele of *DAB2IP*-rs7025486 and 0.44 mm/year greater per G allele of *SORT1*-rs599839 (both p<0.01). After adjustment for multiple testing (for five SNPs), the associations of *DAB2IP*-rs7025486[A] and *SORT1*-rs599839[G] remained significant (p<0.001 and p=0.025, respectively).

The association of *SORT1*-rs599839[G] was similar in women and men. Associations of age, baseline aneurysm size, PP and *DAB2IP*-rs7025486[A] with aneurysm expansion were different in women and men: older age, higher PP and greater baseline aneurysm size were more strongly associated with faster aneurysm expansion in women than men (table 2). Women had a mean growth rate 0.47 mm/year greater than men per A allele of *DAB2IP*-rs7025486 (p=0.02). In other words, compared with a man homozygous for 'A' at *DAB2IP*-rs7025486, the mean growth rate was 0.94 mm /year faster in a woman homozygous for 'A' at this locus.

Multivariable stepwise regression analysis identified baseline aneurysm size, MAP, PP, PP*sex, *DAB2IP*-rs7025486[A], *DAB2IP*-rs7025486[A]*sex and *SORT1* to be independently associated with aneurysm expansion (table 3): the association of *DAB2IP*-rs7025486[A] (per risk allele) with aneurysm expansion was stronger in women than men; higher PP was associated with greater aneurysm expansion in women only. The mean growth rate was 0.44 mm/year greater in women than men, per A allele of *DAB2IP*-rs7025486, and 0.30 mm/year greater in women than men for each 10 mm

Table 2 Sex modification of associations of variables with AAA expansion (mm/year)

	β (SE)	p Value	β (SE) for interaction term with male sex	p for interaction term with male sex
Age, years	0.02 (0.02)	0.3	−0.04 (0.02)	**0.01**
BMI, kg/m^2	−0.01 (0.03)	0.7	−0.02 (0.03)	0.3
Current-smoking	−0.15 (0.14)	0.3	0.15 (0.14)	0.3
Hypertension	−0.07 (0.22)	0.7	−0.08 (0.22)	0.7
Diabetes	−0.33 (0.17)	0.05	0.07 (0.17)	0.7
Dyslipidemia	−0.03 (0.25)	1.0	−0.27 (0.23)	0.3
ASCVD	−0.16 (0.21)	0.4	−0.11 (0.20)	0.6
PP, mm Hg	0.01 (0.01)	0.5	−0.03 (0.01)	**<0.001**
MAP, mm Hg	0.06 (0.01)	<0.001	−0.02 (0.01)	0.08
Baseline AAA size, cm	1.47 (0.17)	<0.001	−0.40 (0.17)	**0.02**
DAB2IP-rs702586[A]	0.85 (0.21)	<0.001*	−0.47 (0.21)	**0.02**
SORT1-rs599839[G]	0.63 (0.22)	0.005*	−0.69 (0.46)	0.1
CDKN2A-2B-rs2383207[G]	0.41 (0.20)	0.04*	−0.22 (0.43)	0.3
LRP1-rs1466535[C]	−0.16 (0.21)	0.5*	−0.16 (0.21)	0.4
LDLR-rs6511720[A]	−0.06 (0.30)	0.8*	−0.38 (0.30)	0.2

*p Values for five SNPs were not adjusted for multiple testing. After adjustment for multiple testing, only associations of DAB2IP-rs7025486 [A] and SORT1-rs599839 [G] remained significant.
†Regression coefficient, SE, β of genetic susceptibility variants per risk allele, PP and MAP (average of BP variables measured at baseline size and most recent or prerepair size).
AAA, abdominal aortic aneurysm; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; MAP, mean arterial pressure; PP, pulse pressure.

Table 3 Multivariable regression model of abdominal aortic aneurysm expansion (mm/year) after stepwise selection

	Total (adjusted R^2=0.21)	
	Regression β (SE)	p Value
Baseline size, cm	1.13 (0.12)	<0.001
Male sex	1.69 (0.53)	0.001
PP, mm Hg	−0.01 (0.01)	0.1
PP*male sex	−0.03 (0.01)	0.001
MAP, mm Hg	0.06 (0.01)	<0.001
DAB2IP-rs7025486 (per A allele)	0.74 (0.19)	<0.001
DAB2IP-rs7025486*male sex	−0.44 (0.19)	0.02
SORT1-rs599839 (per G allele)	0.34 (0.16)	0.03

PP and MAP: average of blood pressure variables measured at baseline size and most recent or prerepair size.
MAP, mean arterial pressure; PP, pulse pressure.

Hg increase in PP, after adjustment for MAP, baseline size and *SORT1*. Given that sex modified the associations of PP and *DAB2IP*-rs7025486[A] with aneurysm expansion in the same model, we assessed whether PP modified the association of sex**DAB2IP*-rs7025486[A] with aneurysm expansion by including a three-way interaction term of PP*sex**DAB2IP*-rs7025486[A]. The interaction was significantly associated with greater aneurysm expansion independent of MAP and baseline size (regression coefficient β=0.034, p=0.007, see online supplementary table 2). Women had a mean growth rate 0.68 mm/year greater than men per A allele of rs7025486 in high PP (≥median) group, but not in low PP group (figure 1).

In additional analyses, we found that SBP, DBP and MAP, but not PP, decreased over time (see online supplementary figure 1). Change in BP did not modify the association of *DAB2IP* with aneurysm expansion. When baseline PP and MAP were used in the analysis, results were similar (see online supplementary table 3).

DISCUSSION

In this study of 650 patients with AAA and with ≥2 measures of AAA size, we confirmed the associations of baseline AAA size, BP measures and non-diabetic status with aneurysm expansion. In addition, we report for the first time that: a) *DAB2IP*-rs7025486[A] and *SORT1*-rs599839[G] are associated with AAA expansion and b) there are sex differences in the association of *DAB2IP*-rs7025486[A] with AAA expansion: the association is stronger in women than men and amplified by higher PP in women.

Prior studies of the genetic basis of AAA expansion included the UK Small Aneurysm Trial,[13] which assessed whether rs10757278[G] at the 9p21 locus was associated with aneurysm expansion in 400 patients with aneurysm diameter 4.5 to 5.5 cm at baseline. The study did not find this locus to be associated with aneurysm growth rate or aneurysm rupture (n=24). In a study of 168 controls and 141 cases of AAA that investigated associations of candidate genes (*LRP1, MMP-9, IL-10, AT1R, and MTHFR*) with aneurysm expansion,[22] borderline significant associations of *MMP-9* and *LRP1* were noted (p=0.046 and p=0.048, respectively). To the best of our knowledge, our study is the first to report associations of variants in *SORT1* and *DAB2IP* with aneurysm expansion and sex-specific genetic susceptibility which is additionally modified by PP.

SORT1, located at 1p13 locus, encodes protein sortilin, a membrane protein typically localized to vesicles in the Golgi body, and a sorting molecule that in conjunction with the Golgi network transports lipoproteins and regulates lipoprotein degradation.[23] In animal studies, macrophage *SORT1* was associated with the degree of atherosclerosis[24–26]; while in humans, overexpression of *SORT1* decreased LDL cholesterol.[27 28] Recent GWAS have identified multiple genetic variants associated with total/LDL cholesterol[29–32] and ASCVD[33–35] in a non-coding region near gene-3[30 33–35] close to *SORT1* or in a non-coding region[29 31 32] that can bind to the enhancer to disrupt sortilin transcription.

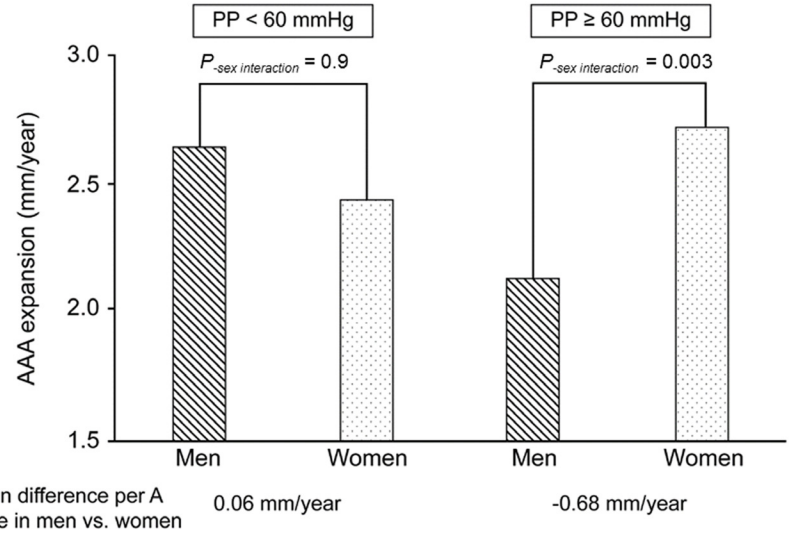

Figure 1 Mean difference in aneurysm expansion rate between women and men for each A allele of rs7025486 of *DAB2IP* stratified by the median of pulse pressure (PP) of the cohort. Differences in aneurysm expansion rates adjusted for sex, baseline AAA size and MAP. Differences adjusted for baseline size, sex and MAP; p for sex interaction with *DAB2IP*-rs7025486[A]. The association of sex interaction was significant in high-PP group only, suggesting a faster growth rate in women than men in this group.

SORT1-rs599839[G] has been shown to be associated with coronary heart disease/stroke[35] and LDL-C levels.[36 37] The association of this genetic variant with AAA expansion and lack of an association of dyslipidemia in our study (regression coefficient±SE: −0.19±0.18, p=0.3) suggest that the association may be independent of lipid levels.

DAB2IP encodes *DAB* interacting protein, also known as apoptosis signal-regulating kinase 1-interacting protein, or *AIP1* (anti-inflammatory protein 1), has 14 exons, and is located at *9q33.1-q33.3*. The protein is a GTPase-activating protein that regulates cell cycle checkpoint,[38] mediates tumor necrosis factor (TNF)-induced cell apoptosis,[39] inhibits JAK-STAT-pathway-dependent vascular smooth cell proliferation[40] and vascular endothelial growth factor receptor signaling pathway-dependent endothelial cell migration and angiogenesis.[41] These pathways are associated with extracellular matrix remodeling and inflammation, and therefore could influence aneurysm expansion.

Genetic susceptibility variants in *DAB2IP* are associated with prostate cancer[42] and ASCVD.[12 43] In particular, rs7025486[A] is associated with coronary heart disease,[12 43] peripheral artery disease and AAA.[12] In contrast to *SORT1*, *LRP1* or *LDLR*, *DAP2IP* is not associated with any conventional risk factor, such as hypertension, diabetes or lipids, suggesting that it contributes to aneurysm formation and progression independent of conventional risk factors. Animal studies suggest that estrogen may have protective effect on the integrity of aortic wall through antiapoptotic,[44] anti-inflammatory effects, inhibition of extracellular matrix remodeling,[45 46] promoting cell growth by altering estrogen receptor-*DAB2IP* pathway.[47] The sex difference in the effect of this variant on aneurysm expansion may be due to lack of protective effect of estrogen in postmenopausal women.[48]

An interesting finding is the stronger association of *DAB2IP*-rs7025486[A] with aneurysm expansion in women in the setting of elevated PP. Higher PP increases shear stress and aortic wall stress, thereby increasing risk for aneurysm expansion,[49] likely mediated through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kβ) and mitogen-activated protein kinase (MAPK) pathways[50]—pathways that underlie cell survival/apoptosis and are regulated by *DAB2IP*.[51] Previous studies found significant apoptosis in the stiffened aortic segment located within AAA[52] and a greater impact of activation of MAPK pathway on aneurysm expansion in hypertensive female versus male mice.[53] Aortic wall tension[54] and rupture rates of AAA[2] are greater in women than men. PP, a determinant of aortic wall tension that correlates with aneurysm expansion[6] and rupture,[2 6] is higher in women than men.[55 56] Our results suggest that wider PP increases the genetic susceptibility to aneurysm expansion in women and may contribute to the increased risk for rupture.

Several limitations need mention. The majority of subjects (98%) were whites referred to a tertiary medical center. We were unable to perform analyses stratified by the ethnicity since only 10 patients did not self-report as white. Not all patients had follow-up visits in the Mayo Clinic. We compared the characteristics of patients with AAA included in this analysis versus those not included (n=473). Patients included in the current analysis were older, more likely to have hypertension and dyslipidemia than those not included. Prevalence of men, ASCVD, diabetes, smoking history and family history and numbers of risk alleles were similar (analyses not shown). We did not find current smoking to be associated with aneurysm expansion in contrast to what was reported in clinical trials.[2] This may be because the time frame we used to ascertain smoking status was based on the recruitment date and the dates of first and most recent measures of AAA size were not in this time window. We used measures of AAA size assessed by different imaging modalities given that in the clinical setting, smaller AAA were often followed by ultrasound and not until the size reached certain threshold would the CT be performed. The use of two measures, latest and baseline, to calculate growth rate may simplify the complex trajectory of AAA expansion. However, the average growth rate in our cohort was similar to previous reports. Our results could be considered as preliminary and hypothesis generating until replication in additional cohorts.

In conclusion, in 650 patients with AAA (113 women), in addition to baseline AAA size, BP measures and diabetic status, we found two genetic susceptibility variants for AAA to be associated with aneurysm expansion: *DAB2IP*-rs7025486[A] and *SORT1*-rs599839[G]. The association of rs599839[G] is similar in women and men, while the association of rs7025486[A] is stronger in women than men and amplified by higher PP, suggesting that sex modifies genetic susceptibility to aneurysm expansion and this effect is enhanced in women with higher PP . Further study is needed to assess the clinical implication of incorporating genetic variants into clinical variables to construct sex-specific predictive models of AAA expansion.

Acknowledgements All authors have approved submission of the manuscript. We thank study subjects and the staff of the Mayo non-invasive vascular laboratory and the Medical Genome Facility Genotyping Core at the Mayo Clinic for carrying out the genotyping for this study. We gratefully acknowledge Diane Vrieze (deceased) for her dedication to recruiting patients to the Mayo Vascular Disease Biorepository.

Contributors ZY contributed to study design, analysis and manuscript writing. IJK contributed to study design and manuscript writing and supervised the entire study. EA and DJS contributed to analysis and manuscript revision. KRB contributed to analysis. PAP contributed to manuscript revision.

Funding IJK is supported by grant U01 HG-06379 from the National Human Genome Research Institute. The publication was made possible by the Center for Translational Science Activities Grant UL1 TR000135 from the National Center for Advancing Translational Sciences, a component of the NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

Competing interests None declared.

Patient consent A Mayo clinic patient consent form approved for this study was signed by each patient at the time of recruitment.

Ethics approval The Mayo IRB has approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional unpublished data from the study.

REFERENCES

1 Norman PE, Powell JT. Abdominal aortic aneurysm: the prognosis in women is worse than in men. *Circulation* 2007;115:2865–9.
2 Sweeting MJ, Thompson SG, Brown LC, *et al*. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. *Br J Surg* 2012;99:655–65.

3 Nordon IM, Hinchliffe RJ, Loftus IM, *et al*. Pathophysiology and epidemiology of abdominal aortic aneurysms. *Nat Rev Cardiol* 2011;8:92–102.
4 Bhak RH, Wininger M, Johnson GR, *et al*. Factors associated with small abdominal aortic aneurysm expansion rate. *JAMA Surg* 2015;150:44–50.
5 De Rango P, Farchioni L, Fiorucci B, *et al*. Diabetes and abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2014;47:243–61.
6 Guirguis-Blake JM, Beil TL, Sun X, *et al*. Primary Care Screening for abdominal aortic aneurysm: a systematic evidence review for the U. S. Preventive Services Task Force. *AHRQ* 2014.
7 Dua A, Kuy S, Lee CJ, *et al*. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg* 2014;59:1512–7.
8 Saratzis A, Bown MJ. The genetic basis for aortic aneurysmal disease. *Heart* 2014;100:916–22.
9 Bradley DT, Hughes AE, Badger SA, *et al*. A variant in LDLR is associated with abdominal aortic aneurysm. *Circ Cardiovasc Genet* 2013;6:498–504.
10 Bradley DT, Hughes AE, Badger SA, *et al*. A variant in LDLR is associated with abdominal aortic aneurysm. *Circ Cardiovasc Genet* 2013;6:498–504.
11 Bown MJ, Jones GT, Harrison SC, *et al*. Abdominal aortic aneurysm is associated with a variant in low-density lipoprotein receptor-related protein 1. *Am J Hum Genet* 2011;89:619–27.
12 Gretarsdottir S, Baas AF, Thorleifsson G, *et al*. Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. *Nat Genet* 2010;42:692–7.
13 Helgadottir A, Thorleifsson G, Magnusson KP, *et al*. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nat Genet* 2008;40:217–24.
14 Bown MJ, Sweeting MJ, Brown LC, *et al*. Surveillance intervals for small abdominal aortic aneurysms: a meta-analysis. *JAMA* 2013;309:1720–1.
15 Ye Z, Kalloo FS, Dalenberg AK, *et al*. An electronic medical record-linked biorepository to identify novel biomarkers for atherosclerotic cardiovascular disease. *Glob Cardiol Sci Pract* 2013;2013:10–90.
16 Ye Z, Austin E, Schaid DJ, *et al*. A multi-locus genetic risk score for abdominal aortic aneurysm. *Atherosclerosis* 2016;246:274–9.
17 Kullo IJ, Fan J, Pathak J, *et al*. Leveraging informatics for genetic studies: use of the electronic medical record to enable a genome-wide association study of peripheral arterial disease. *J Am Med Inform Assoc* 2010;17:568–74.
18 Devaraj S, Dodds SR. Ultrasound surveillance of ectatic abdominal aortas. *Ann R Coll Surg Engl* 2008;90:477–82.
19 Freiberg MS, Arnold AM, Newman AB, *et al*. Abdominal aortic aneurysms, increasing infrarenal aortic diameter, and risk of total mortality and incident cardiovascular disease events: 10-year follow-up data from the Cardiovascular Health Study. *Circulation* 2008;117:1010–7.
20 Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. *Nat Methods* 2011;9:179–81.
21 Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* 2009;5:e1000529.
22 Duellman T, Warren CL, Matsumura J, *et al*. Analysis of multiple genetic polymorphisms in aggressive-growing and slow-growing abdominal aortic aneurysms. *J Vasc Surg* 2014;60:613–21.
23 Dubé JB, Johansen CT, Hegele RA. Sortilin: an unusual suspect in cholesterol metabolism: from GWAS identification to in vivo biochemical analyses, sortilin has been identified as a novel mediator of human lipoprotein metabolism. *Bioessays* 2011;33:430–7.
24 Patel KM, Strong A, Tohyama J, *et al*. Macrophage sortilin promotes LDL uptake, foam cell formation, and atherosclerosis. *Circ Res* 2015;116:789–96.
25 Mortensen MB, Kjolby M, Gunnersen S, *et al*. Targeting sortilin in immune cells reduces proinflammatory cytokines and atherosclerosis. *J Clin Invest* 2014;124:5317–22.
26 Strong A, Ding Q, Edmondson AC, *et al*. Hepatic sortilin regulates both apolipoprotein B secretion and LDL catabolism. *J Clin Invest* 2012;122:2807–16.
27 Musunuru K, Strong A, Frank-Kamenetsky M, *et al*. From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. *Nature* 2010;466:714–9.
28 Linsel-Nitschke P, Heeren J, Aherrahrou Z, *et al*. Genetic variation at chromosome 1p13.3 affects sortilin mRNA expression, cellular LDL-uptake and serum LDL levels which translates to the risk of coronary artery disease. *Atherosclerosis* 2010;208:183–9.
29 Teslovich TM, Musunuru K, Smith AV, *et al*. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010;466:707–13.
30 Willer CJ, Sanna S, Jackson AU, *et al*. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nat Genet* 2008;40:161–9.
31 Kathiresan S, Willer CJ, Peloso GM, *et al*. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nat Genet* 2009;41:56–65.
32 Lettre G, Palmer CD, Young T, *et al*. Genome-wide association study of coronary heart disease and its risk factors in 8,090 African Americans: the NHLBI CARe Project. *PLoS Genet* 2011;7:e1001300.
33 Reilly MP, Li M, He J, *et al*. Identification of ADAMTS7 as a novel locus for coronary atherosclerosis and association of ABO with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies. *Lancet* 2011;377:383–92.
34 Schunkert H, König IR, Kathiresan S, *et al*. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet* 2011;43:333–8.
35 Dichgans M, Malik R, König IR, *et al*. Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants. *Stroke* 2014;45:24–36.
36 Sandhu MS, Waterworth DM, Debenham SL, *et al*. LDL-cholesterol concentrations: a genome-wide association study. *Lancet* 2008;371:483–91.
37 Wallace C, Newhouse SJ, Braund P, *et al*. Genome-wide association study identifies genes for biomarkers of cardiovascular disease: serum urate and dyslipidemia. *Am J Hum Genet* 2008;82:139–49.
38 Xie D, Gore C, Liu J, *et al*. Role of DAB2IP in modulating epithelial-to-mesenchymal transition and prostate cancer metastasis. *Proc Natl Acad Sci USA* 2010;107:2485–90.
39 Ji W, Li Y, Wan T, *et al*. Both internalization and AIP1 association are required for tumor necrosis factor receptor 2-mediated JNK signaling. *Arterioscler Thromb Vasc Biol* 2012;32:2271–9.
40 Yu L, Qin L, Zhang H, *et al*. AIP1 prevents graft arteriosclerosis by inhibiting interferon-γ-dependent smooth muscle cell proliferation and intimal expansion. *Circ Res* 2011;109:418–27.
41 Zhou HJ, Chen X, Huang Q, *et al*. AIP1 mediates vascular endothelial cell growth factor receptor-3-dependent angiogenic and lymphangiogenic responses. *Arterioscler Thromb Vasc Biol* 2014;34:603–15.
42 Duggan D, Zheng SL, Knowlton M, *et al*. Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. *J Natl Cancer Inst* 2007;99:1836–44.
43 Harrison SC, Cooper JA, Li K, *et al*. Association of a sequence variant in DAB2IP with coronary heart disease. *Eur Heart J* 2012;33:881–8.
44 Ding Q, Hussain Y, Chorazyczewski J, *et al*. GPER-independent effects of estrogen in rat aortic vascular endothelial cells. *Mol Cell Endocrinol* 2015;399:60–8.
45 Laser A, Ghosh A, Roelofs K, *et al*. Increased estrogen receptor alpha in experimental aortic aneurysms in females compared with males. *J Surg Res* 2014;186:467–74.
46 Lu G, Su G, Zhao Y, *et al*. Dietary phytoestrogens inhibit experimental aneurysm formation in male mice. *J Surg Res* 2014;188:326–38.
47 Yeh CR, Ou ZY, Xiao GQ, *et al*. Infiltrating T cells promote renal cell carcinoma (RCC) progression via altering the estrogen receptor β-DAB2IP signals. *Oncotarget* 2015;6:44346–59.
48 Makrygiannis G, Courtois A, Drion P, *et al*. Sex differences in abdominal aortic aneurysm: the role of sex hormones. *Ann Vasc Surg* 2014;28:1946–58.
49 Li ZY, Sadat U, U-King-Im J, *et al*. Association between aneurysm shoulder stress and abdominal aortic aneurysm expansion: a longitudinal follow-up study. *Circulation* 2010;122:1815–22.
50 Lemarié CA, Tharaux PL, Lehoux S. Extracellular matrix alterations in hypertensive vascular remodeling. *J Mol Cell Cardiol* 2010;48:433–9.
51 Zhang J, Zhou HJ, Ji W, *et al*. AIP1-mediated stress signaling in atherosclerosis and arteriosclerosis. *Curr Atheroscler Rep* 2015;17:503.
52 Raaz U, Zöllner AM, Schellinger IN, *et al*. Segmental aortic stiffening contributes to experimental abdominal aortic aneurysm development. *Circulation* 2015;131:1783–95.
53 Schmit BM, Yang P, Fu C, *et al*. Hypertension overrides the protective effect of female hormones on the development of aortic aneurysm secondary to Alk5 deficiency via ERK activation. *Am J Physiol Heart Circ Physiol* 2015;308:H115–25.
54 Shang EK, Nathan DP, Gorman RC, *et al*. 2014. Increased Peak Wall Stress in Women with Abdominal Aortic Aneurysms. Society for Clinical Vascular Surgery 42nd Annual Symposium; March 18-22. La Costa Hotel, Carlsbad, CA.
55 Mitchell GF, Gudnason V, Launer LJ, *et al*. Hemodynamics of increased pulse pressure in older women in the community-based age, Gene/Environment Susceptibility-Reykjavik Study. *Hypertension* 2008;51:1123–8.
56 Mitchell GF. Arterial stiffness and wave reflection in hypertension: pathophysiologic and therapeutic implications. *Curr Hypertens Rep* 2004;6:436–41.