The TAGA Study: a new family study for the genetic analysis of aortic abdominal aneurysm

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Introduction

Abdominal aortic aneurysms (AAA) are characterized by structural deterioration of the vascular wall leading to progressive dilatation and, potentially, rupture of the abdominal aorta. Disease prevalence is approximately 5% in men and 1% in women, with no current effective medical therapies beyond surgical repair. We have designed and collected the TAGA Study (Triple–A Genetic Analysis), a family study aiming to understand the genetic factors predisposing to AAA.

Methods

The TAGA Study comprises 407 individuals in 12 large Spanish families. Cases were defined as those with dilation in abdominal aortic diameter (AAOD) higher than 30 mm in adults. All participants underwent clinical questionnaire, ultrasound measures of the main arteries, and measurements of an extensive number of intermediate phenotypes. We applied variance component methods to calculate heritabilities and phenotypic correlations (split into genetic and environmental correlations) between AAOD and all phenotypes.

Results

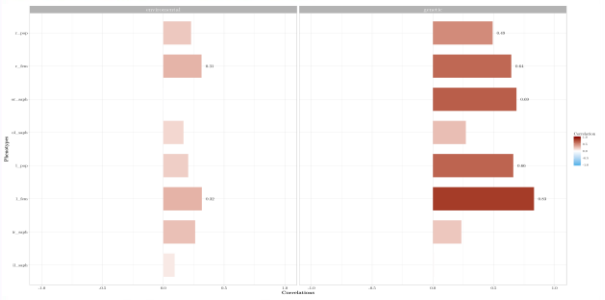
Heritability of AAOD was 0.34 ± 0.1 (Table 1). Among the main related arteries, the strongest genetic correlation was observed between AAOD and the diameter of left femoral artery (r^2 = 0.82; p = $1.8 \cdot 10^{-5}$) (Figure 1). We also observed significant phenotypic correlations between AAOD and serum creatinine levels (r^2 = 0.32; p = $2.1 \cdot 10^{-10}$), and lung function tests, the strongest being with forced vital capacity observed (FVC) (r^2 = 0.39, p = $7.8 \cdot 10^{-14}$) forced expiratory volume in 1 second (FEV1) (r^2 = 0.38; p = $3.9 \cdot 10^{-13}$), and post dilator FVC (r^2 = 0.31; p = $7.9 \cdot 10^{-8}$).

Table 1. Herabilities of the artery diameters measured by eco-doppler ultrasonography.

Phenotypes*	h^2 ± SE#	p–val#
l_pop	0.46 ± 0.09	$1.3 \cdot 10^{-11}$
r_fem	0.43 ± 0.08	$7.2 \cdot 10^{-13}$
r_pop	0.41 ± 0.08	$3.8 \cdot 10^{-10}$
l_fem	0.35 ± 0.08	$4.3 \cdot 10^{-9}$
aaod	0.34 ± 0.10	$3.7 \cdot 10^{-5}$
ol_saph	0.32 ± 0.10	$1.8 \cdot 10^{-4}$
ir_saph	0.22 ± 0.09	0.002
il_saph	0.21 ± 0.09	0.001
or_saph	0.15 ± 0.09	0.029

(*) diameter of the arteries: left popliteal, femoral and inner and outer saphenous (l_pop, l_fem, il_saph and ol_saph); right popliteal, femoral and inner and outer saphenous (r_pop, r_fem, ir_saph and or_saph); and abdominal aortic diameter (aaod).
(#) The heritabilities (h^2), standard errors (SE) and p–values. Models were adjusted for sex, age and age square (l_pop, r_fem, r_pop, l_fem and aaod), and age and age squared for rest of the phenotypes.

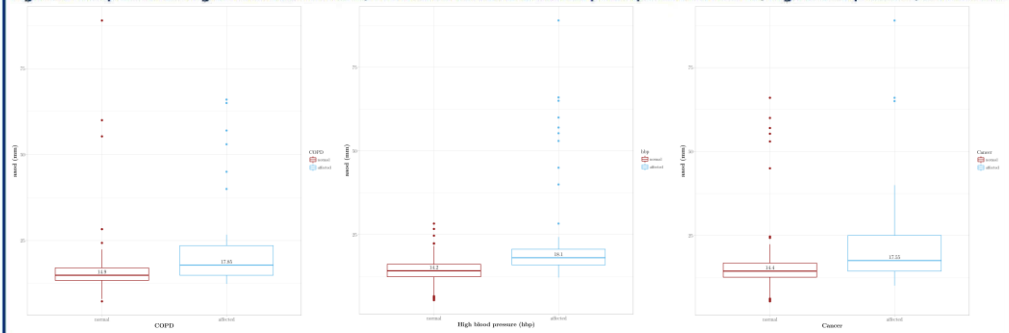
Figure 1: The main results of the enviromental, and genetic correlations between AAOD and diameter of related arteries.



Numbers show the correlations between AAOD and phenotypes upper 0.3. The y axis show the phenotypes abbreviations as follow: diameters of the righ popliteal, femoral, outer and inner saphenous areties (r_pop, r_fem, or_saph and ir_saph); diameters of the left popliteal, femoral, outer and inner saphenous areties (l_pop, l_fem, ol_saph and il_saph). The x axis show the ranges of the correlation between -1.0 and 1.0.

Our results also show significant associations between AAOD and other related diseases, such as Chronic Obstructive Pulmonar Disease (COPD), high blood pressure, and cancer (Figure 2).

Figure 2: Boxplots showing differences in AAOD, in affected versus unaffected participants with COPD, high blood pressure, and cancer.



Conclusions

- Our results indicate that one third of the variability in AAOD is explained by genes.
- Well–design genetic studies may be a suitable tool to elucidate novel biological mechanisms underlying AAA.
- Common genetic factors regulate normal variation in the diameter of the related arteries.
- We found strong phenotypic correlations between some markers of respiratory alterations and AAOD; these were mainly driven by non-genetic factors independent of smoking.
- In–depth study of novel intermediate phenotypes genetically correlated with AAOD can be a powerful tool to prioritize the main biological traits and mechanisms underlying AAA formation and development.

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