Novel biomarkers of AAA derived from genetic and epigenetic studies

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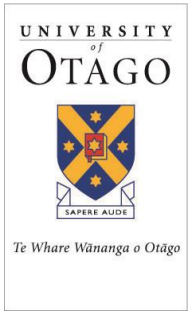
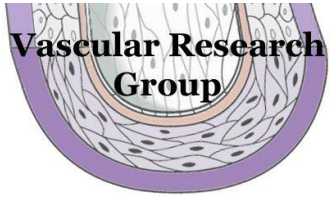
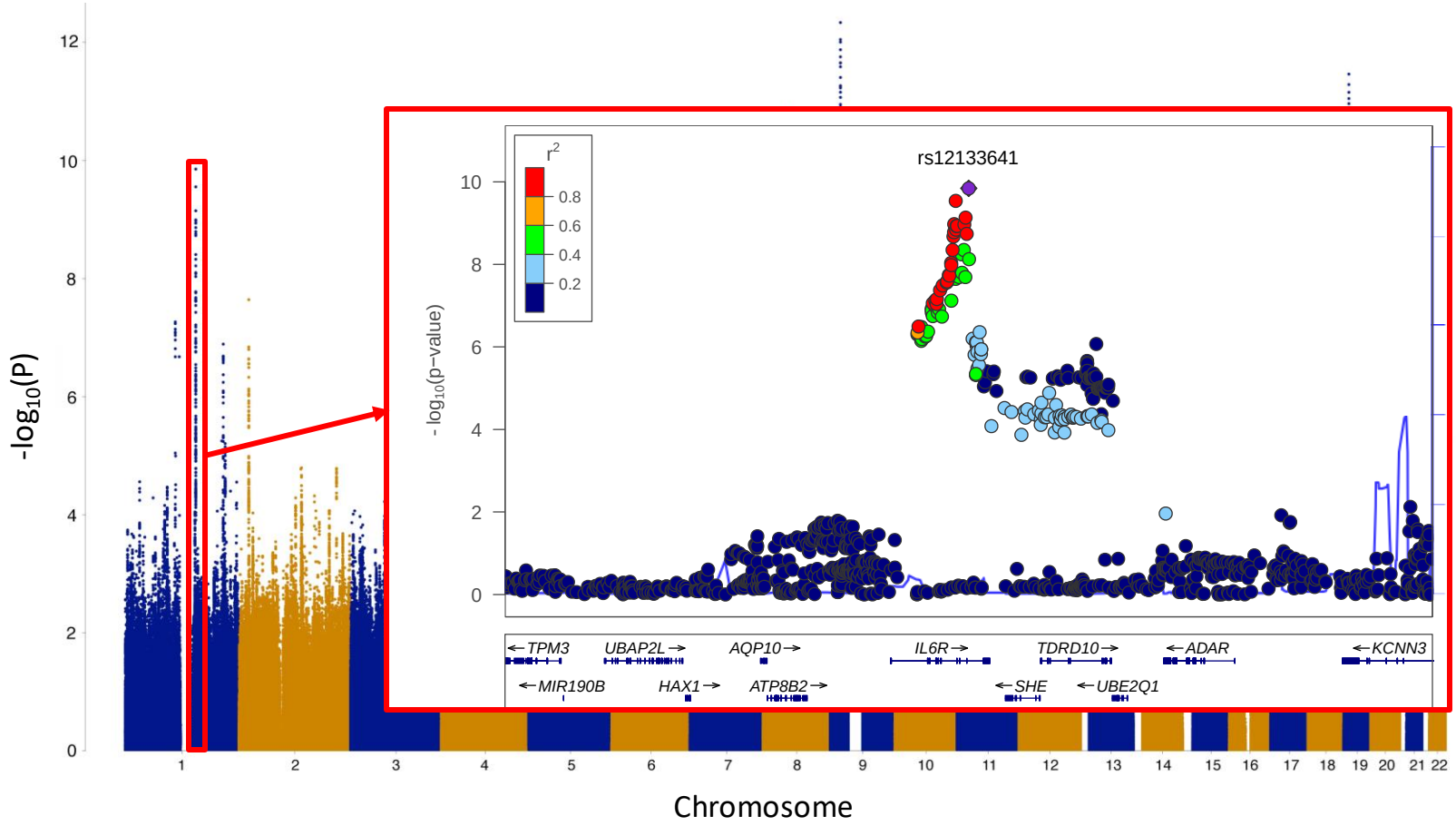


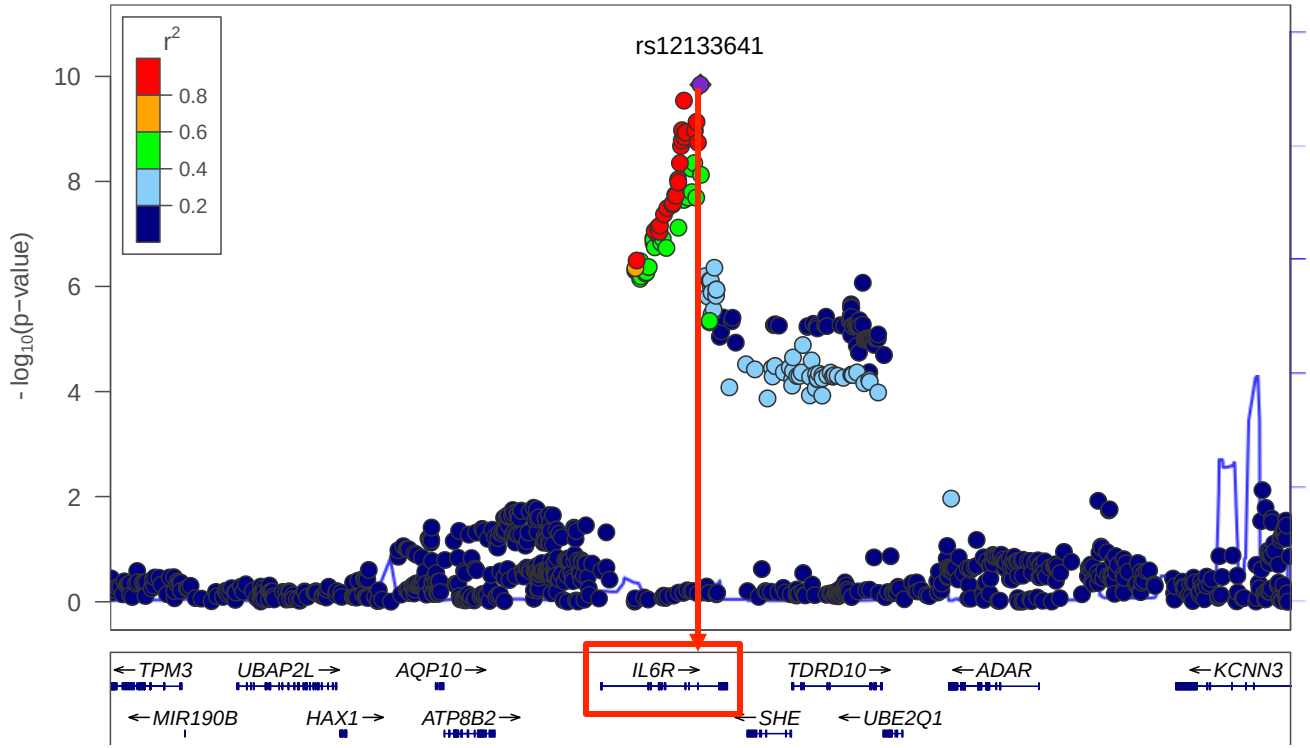


Abdominal Aortic Aneurysm Genome-Wide Association Study

5.3 million genetic markers examined in ~5000 cases and 100,000 controls



Circulation Research (2017), 120: 341-353



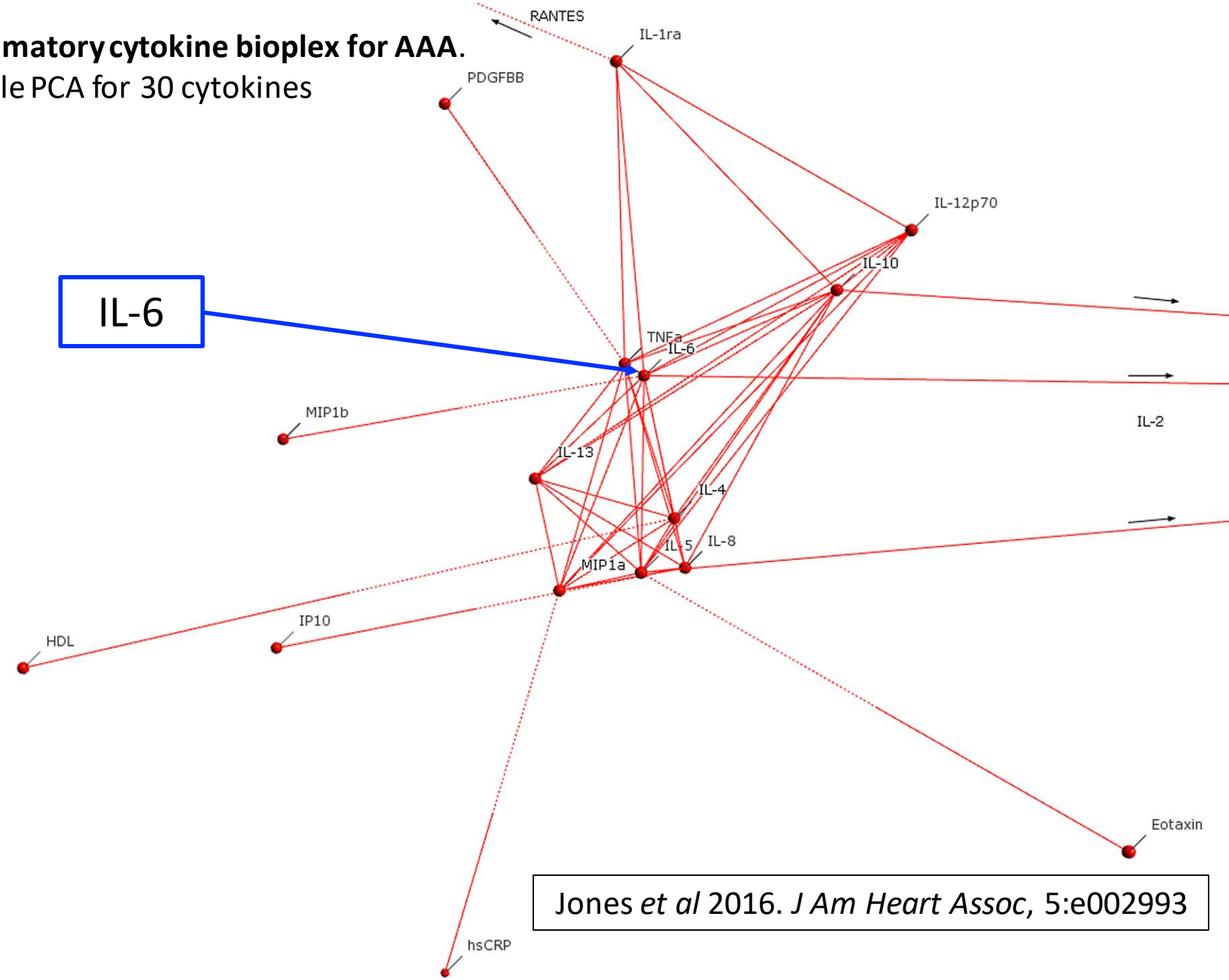
Circulating IL-6 protein

Study	SMD (95% CI)	Cases	Controls
Fowkes	0.74 (0.44, 1.04)	89	98
Jones (unpublished)	0.57 (0.38, 0.76)	166	359
Flondell-site	0.28 (0.11, 0.45)	360	218
Subtotal (I^2 = 69.5%, P = 0.003)	0.42 (0.32, 0.52)		

A Mendelian randomization approach provides robust evidence that signalling via the IL-6R is likely to be a causal pathway in AAA.
Drugs that inhibit IL-6R (tocilizumab) may play a role in AAA management.

Harrison *et al. European Heart Journal* (2013), 34: 3707-3716

Inflammatory cytokine bioplex for AAA.
Variable PCA for 30 cytokines

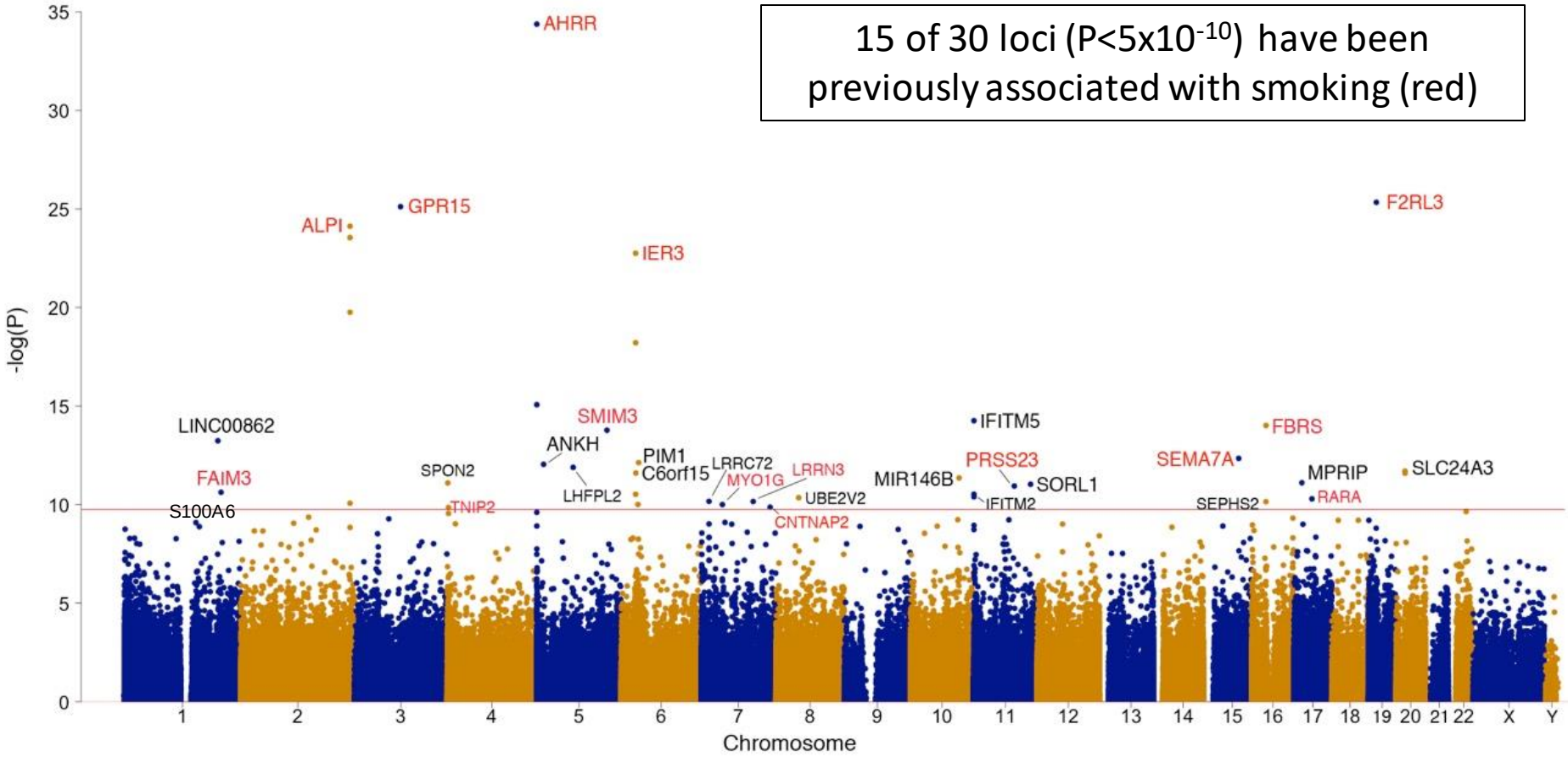


Jones *et al* 2016. *J Am Heart Assoc*, 5:e002993

AAA Epigenome-Wide Associations

(adjusted for age & blood cell composition)

15 of 30 loci ($P<5x10^{-10}$) have been previously associated with smoking (red)



Health Research Council of New Zealand

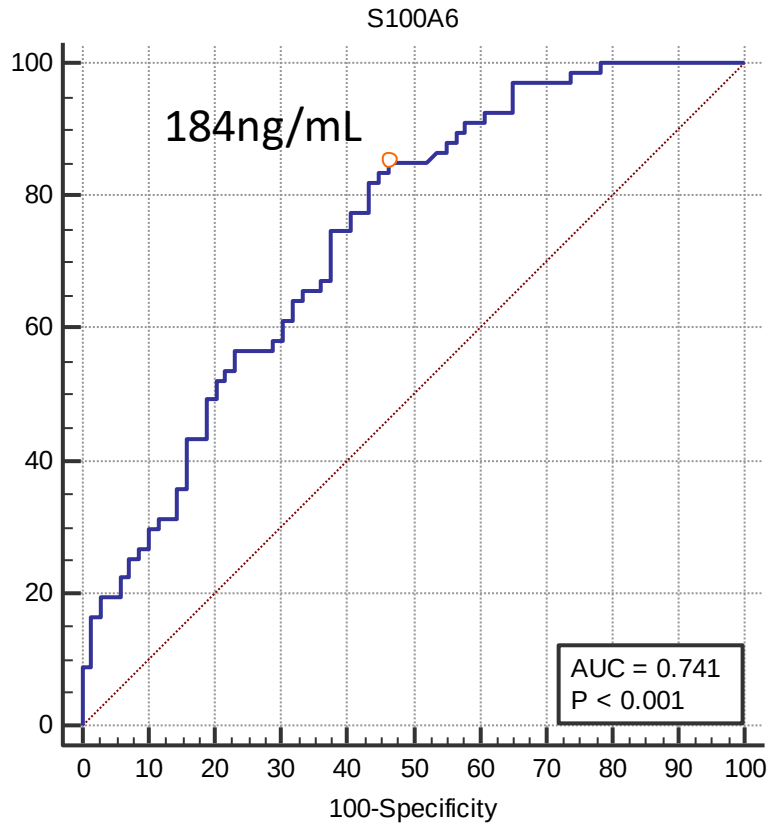
S100 CALCIUM-BINDING PROTEIN A6 (S100A6)

5% hypomethylated in AAA

Gene Functions:
Endothelial cells which overexpress S100A6 have enhanced tube formation and angiogenesis marker expression.

Endothelial S100A6 depletion (by RNA interference) results in cell-cycle arrest.

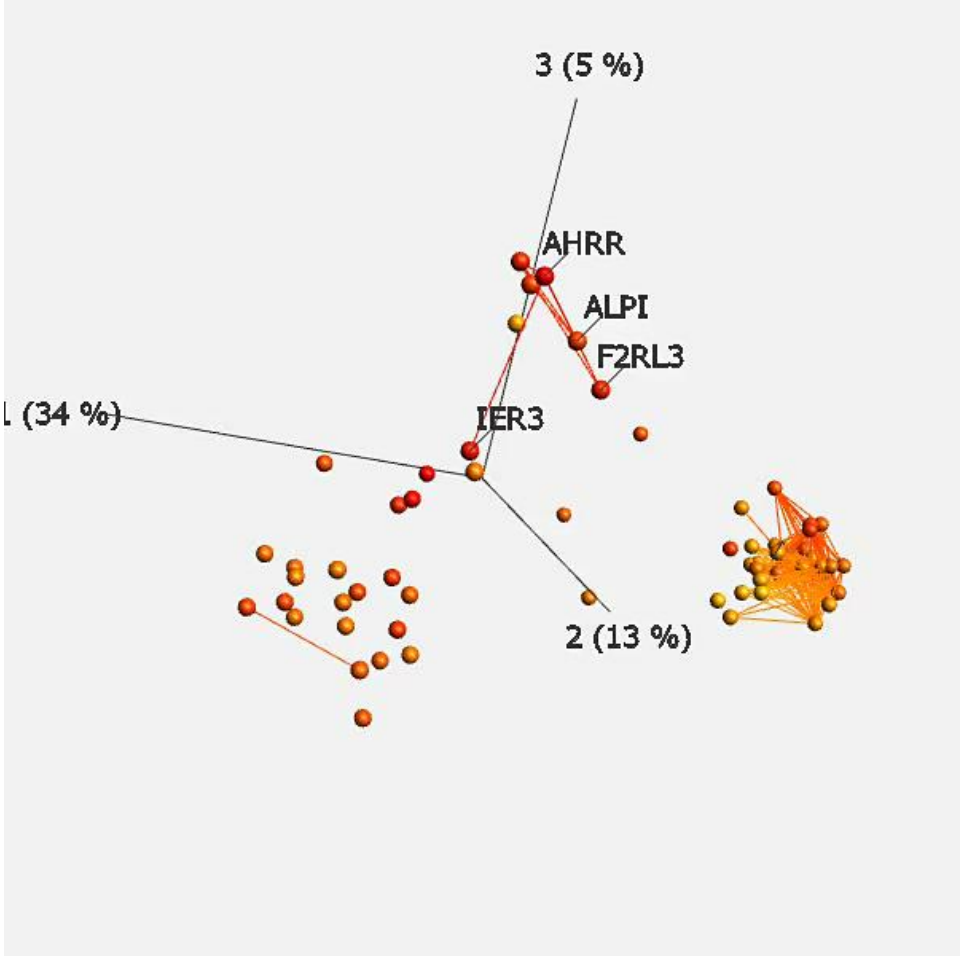
Mechanical strain enhances smooth muscle S100A6 expression.



Plasma S100A6 >184ng/mL,
AAA odds ratio 6.8* (95% CI 2.9-15.9, P<0.0001),
*Adjusted for age and history of heart disease

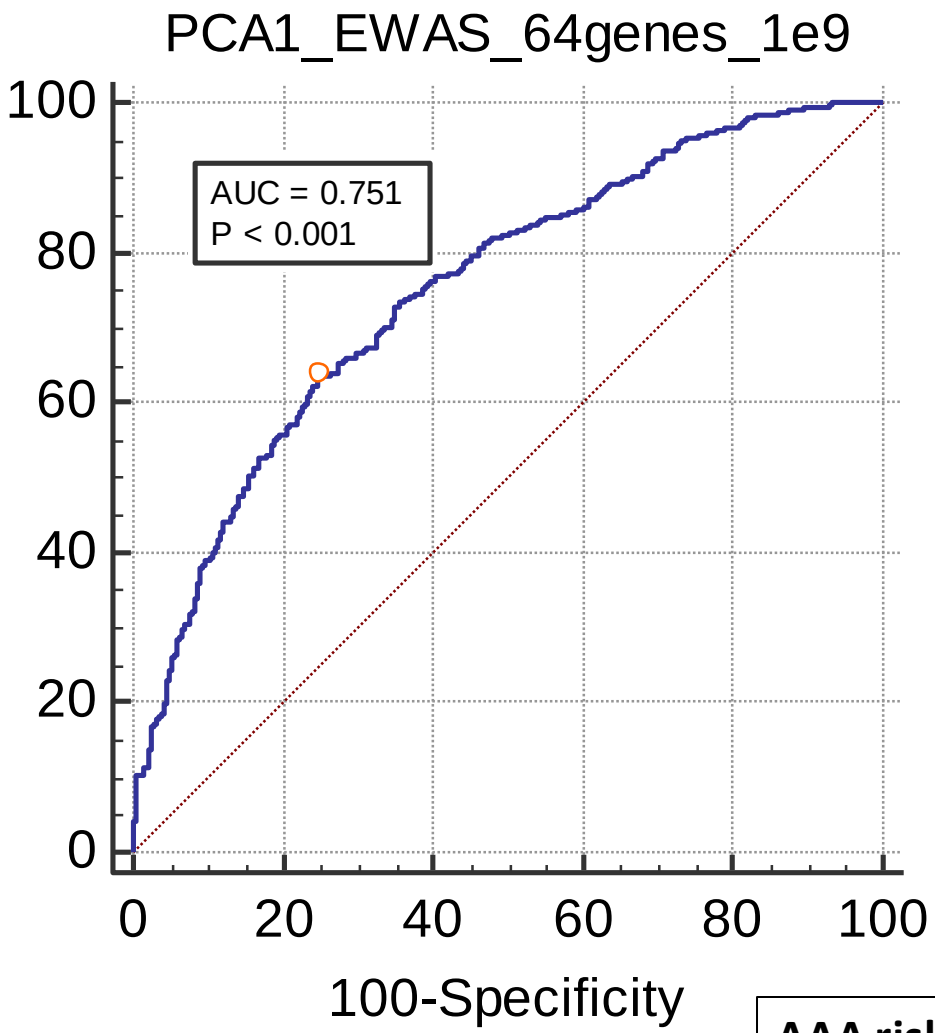
Variable Principal Component Analysis

(Solid lines Euclidean threshold >60%)



Methylation sites associated with AAA

64 differentially methylated gene regions ($P<1x10^{-9}$, adjusted for age and blood cell composition)



Methylation first principal component for AAA

*Adjusted for age and cell composition

Based on 64 CpG sites ($P<1x10^{-9}$)

470 Aneurysm Cases

478 Non-aneurysm Controls

Methylation PCA1

Logistic regression: independently associated with AAA in a model including age, hypertension, dyslipidaemia and smoking.

AAA risk model: age, hypertension, dyslipidaemia and smoking. R^2=0.30

AAA risk model plus Methylation PCA1. R^2=0.42

Conclusions

Genome-wide association studies have the potential to identify novel AAA risk prediction markers or therapeutic targets.

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Heart Foundation™