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

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (95% CI)</th>
<th>Cases</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Fowkes</td>
<td>0.74 (0.44, 1.04)</td>
<td>89</td>
<td>98</td>
</tr>
<tr>
<td>Jones (unpublished)</td>
<td>0.57 (0.38, 0.76)</td>
<td>166</td>
<td>359</td>
</tr>
<tr>
<td>Flondell-site</td>
<td>0.28 (0.11, 0.45)</td>
<td>360</td>
<td>218</td>
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<tr>
<td>Subtotal (I² = 69.5%, P = 0.003)</td>
<td>0.42 (0.32, 0.52)</td>
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</tbody>
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Harrison et al. European Heart Journal (2013), 34: 3707-3716
Inflammatory cytokine bioplex for AAA.
Variable PCA for 30 cytokines

AAA Epigenome-Wide Associations
(adjusted for age & blood cell composition)

15 of 30 loci ($P<5\times10^{-10}$) have been previously associated with smoking (red)
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
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.
Aotearoa New Zealand Life-Course Epigenetics Consortium

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