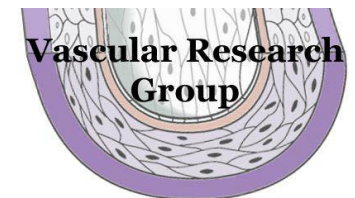
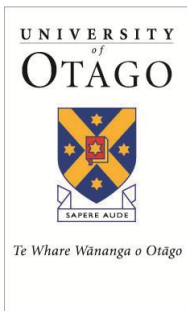


Pathway directed analysis of AAA genome wide datasets

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Vascular Research Group
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Identifying AAA Genetic Association?

The Whole Genome Approach
Measure everything!

Analysing biological pathways in genome-wide association studies

Kai Wang^{‡}, Mingyao Li[§] and Hakon Hakonarson^{*||}*

Abstract | Genome-wide association (GWA) studies have typically focused on the analysis of single markers, which often lacks the power to uncover the relatively small effect sizes conferred by most genetic variants. Recently, pathway-based approaches have been developed, which use prior biological knowledge on gene function to facilitate more powerful analysis of GWA study data sets. These approaches typically examine whether a group of related genes in the same functional pathway are jointly associated with a trait of interest. Here we review the development of pathway-based approaches for GWA studies, discuss their practical use and caveats, and suggest that pathway-based approaches may also be useful for future GWA studies with sequencing data.

Identifying AAA Genetic Association?

The Biological Pathway Approach The educated guesses!

- **Concurrent Vascular Disease** (Coronary artery disease)
- **Dyslipidemia** (Total cholesterol, LDL, HDL & Triglycerides)

Lead SNPs = Top hit for each locus.

Pathway SNPs = all SNPs with $MAF > 0.1$ in a 200kB flanking region for each locus.

Study Design

Pathway-based Genome Wide Association Analysis

New Zealand Discovery cohort

1011 AAA (mean size 58mm)

Phenotyped for concurrent disease and risk factors.

995 controls (<25mm aortic diameter)

Mean age 68 years, Gender matched.

Phenotyped for risk factors.

Genotyped using Affymetrix SNP6 &
Illumina Omni 2.5



Study Design

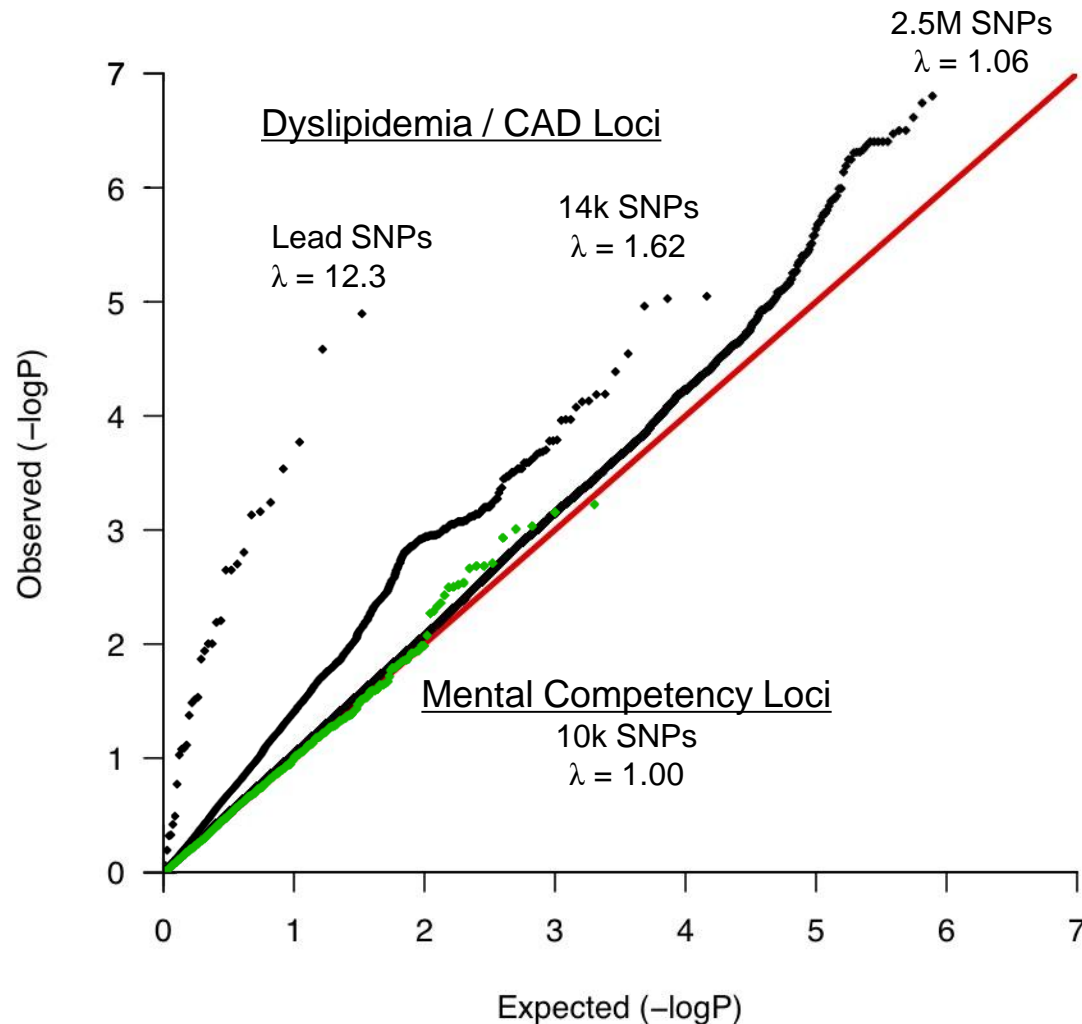
Pathway-based Genome Wide Association Analysis

Replication cohort

Wellcome Trust (UK), 1846 AAA, 5605 controls

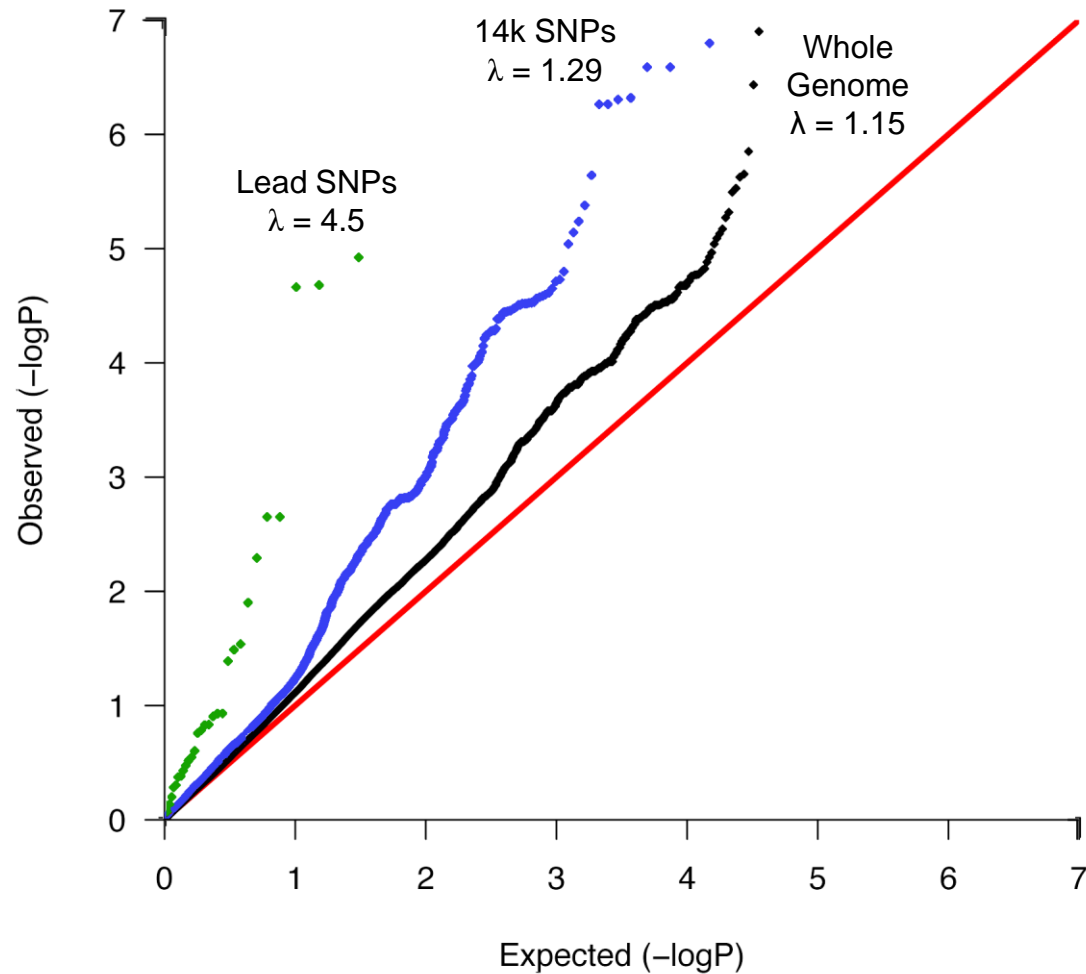
Whole Genome versus Pathway approaches

New Zealand cohort



WTCCC AAA GWAS

Dyslipidemia / CAD Loci



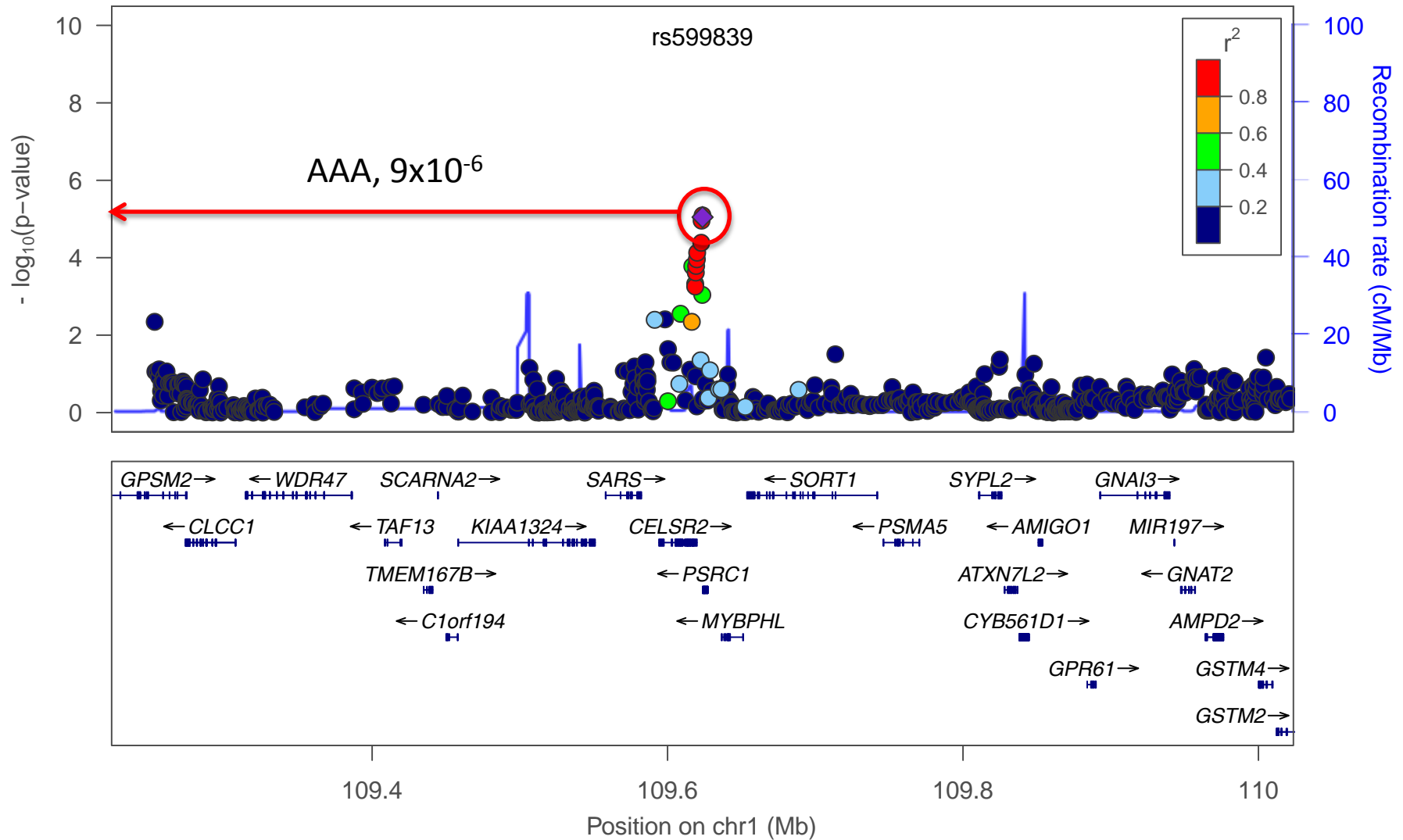
Whole Genome versus Pathway approaches

	Inflation Factor	
	NZ GWAS	WTCCC
Whole Genome	1.06	1.15
CAD + Lipid loci	1.62 (+0.56)	1.29 (+0.14)

Atherosclerosis (CAD) or Dyslipidemia loci?

Chr1p13 locus (CAD, Dyslipidemia)

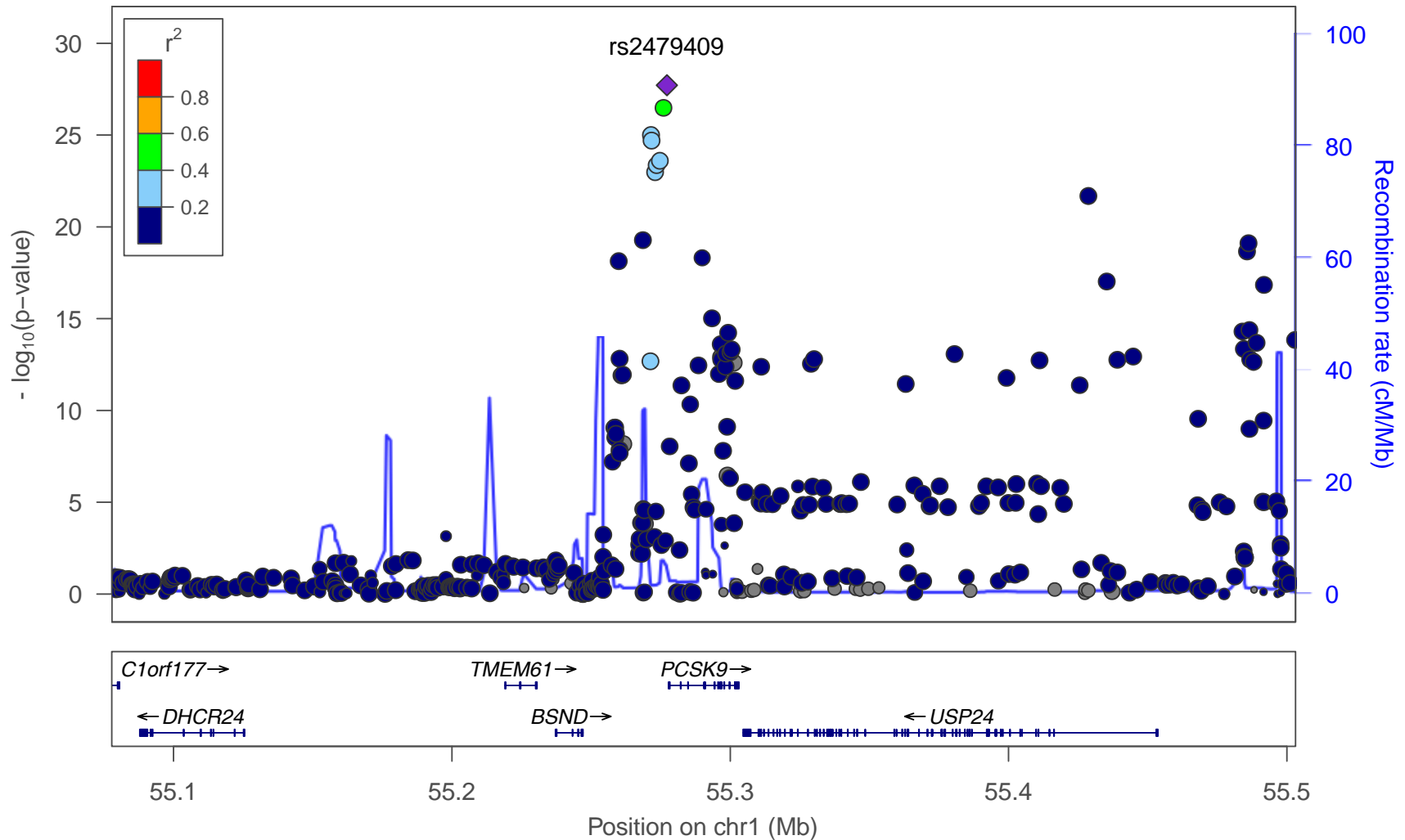
AAA



Does the top hit pick up all the association?

GLGC_2010_IdI

Plotted SNPs



Abdominal Aortic Aneurysm Genetic Loci

Whole genome approaches have the potential of making novel discovery.

Pathway analysis is a pragmatic compromise between candidate and whole genome approaches.



Abdominal Aortic Aneurysm Genetic Loci

CAD pathway-based genetic markers have an inflated association with AAA.

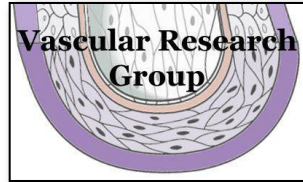
Using knowledge of the pathobiology of AAA may help identify genetic association within genome wide datasets.





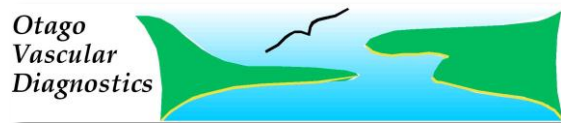
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