eQTL identification and mapping in the population isolate of Norfolk Island

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Genemappers

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Outline

1. Background
2. eQTL Mapping
3. Other Findings
4. Acknowledgements

Rationale

- eQTL's and eQTL mapping
- Why are we doing this study?
- Use the unique genetic isolate of Norfolk Island to hone in on functionally relevant loci
- using gene expression and SNP assocication

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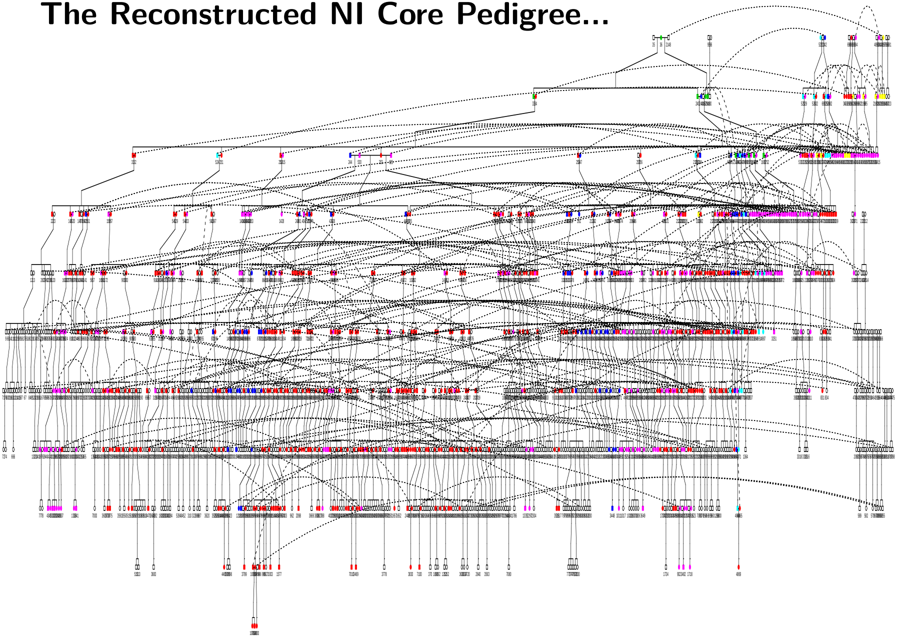
A brief history lesson...

The Reconstructed NI Core Pedigree...



Study Design

- Participants - 330 NIHS individuals
  1. Samples - Blood (circulating lymphocytes)
  2. mRNA extracted > cDNA > expression analysis
- Platforms:
  1. Expression: Illumina HT-12 beadarray
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- Normalised gene expression data (23000 transcripts)[1]
- Heritability analysis (batched using GenABEL/R: Polygenic Model)
- Heritable transcripts GWAS using SNP set
  1. mmscore function - pedigree structure analysis
  2. study-wide significance for NI pop = $1.84x10^{-7}$
  3. suggestive significance threshold = $1.0x10^{-5}$
- A series of filters were designed to identify cis/trans eQTL's
  1. SNP/CHR location, Chromosome quadrants
  2. Graphical Filter - Modified Manhattan Plots with kern smoothing to facilitate peak identification (David Eccles)

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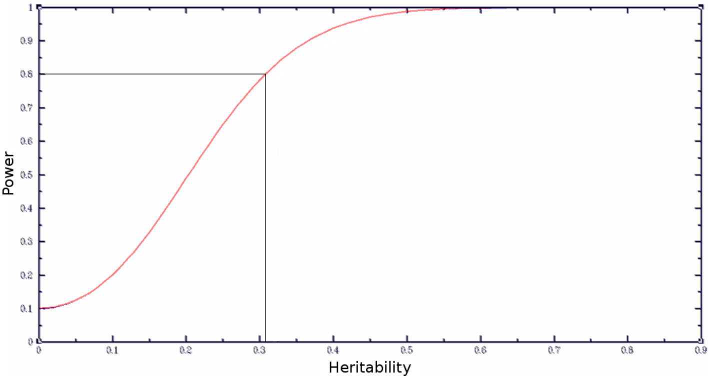
Expression Power Calculation

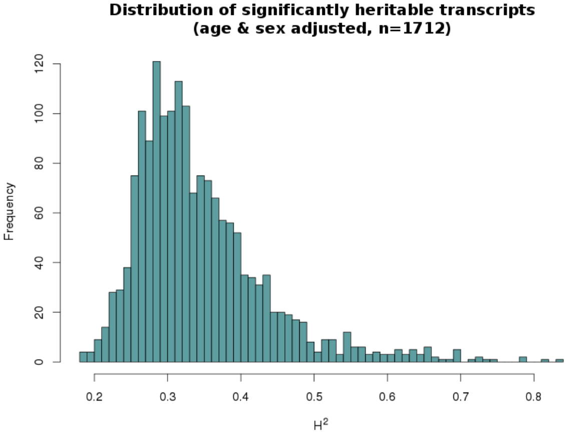
Estimation of power to detect significantly heritable transcripts in Norfolk Island pedigree was run in SOLAR



80% power to detect heritable transcripts above $H^2 = 0.3$

Heritable eQTL's

- H^2 analysis of n=23000 transcripts[2]



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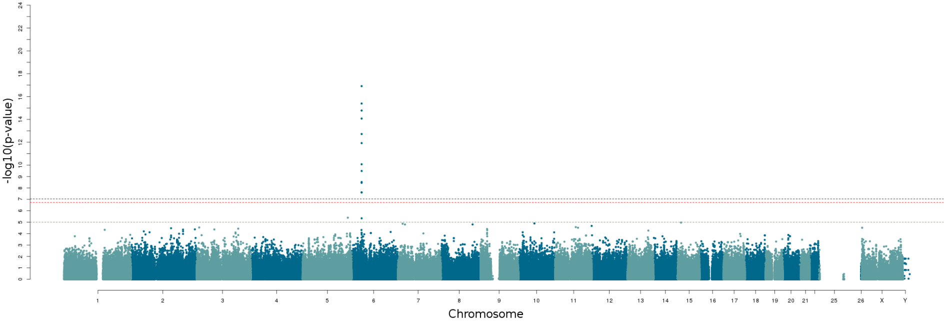
[2] Max sig. $H^2 = 0.84$ Min sig. $H^2 = 0.15$

Heritable eQTL's

Overview of eQTL Manhattan Plots



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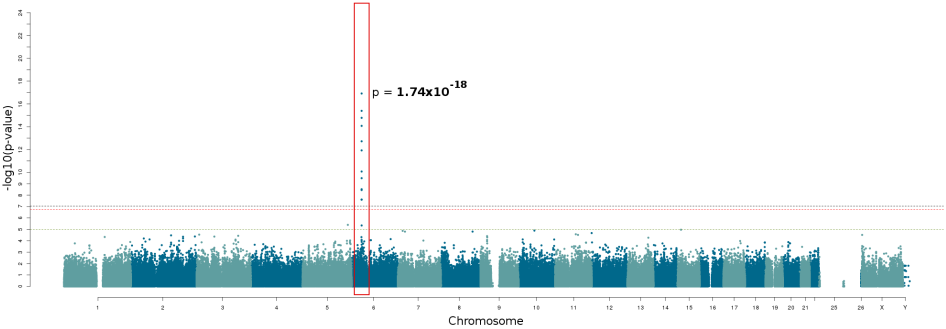

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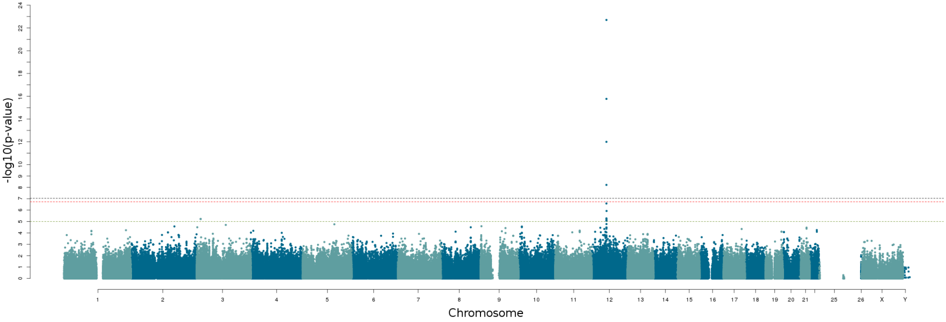

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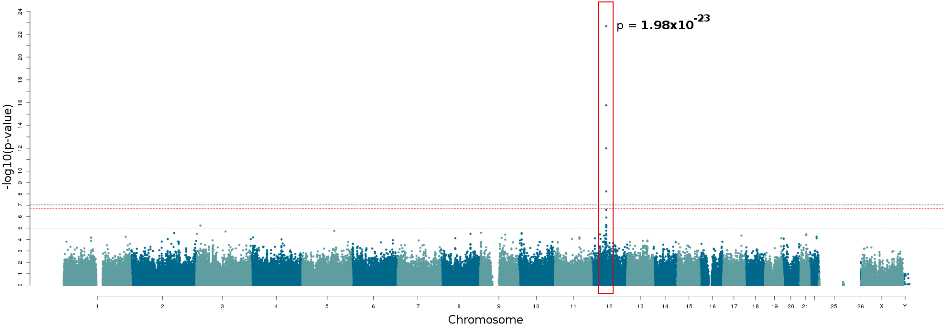

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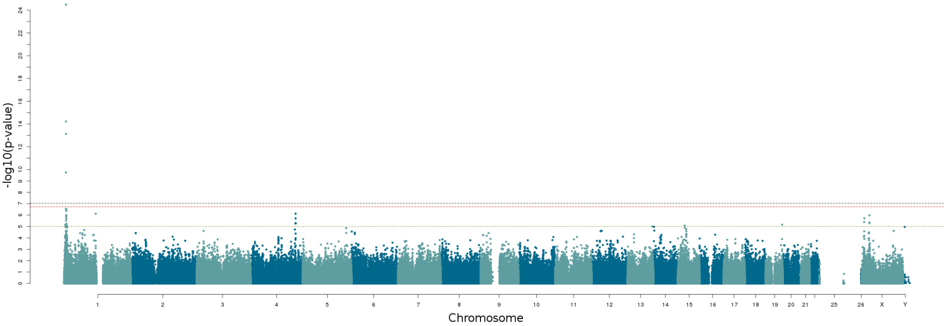

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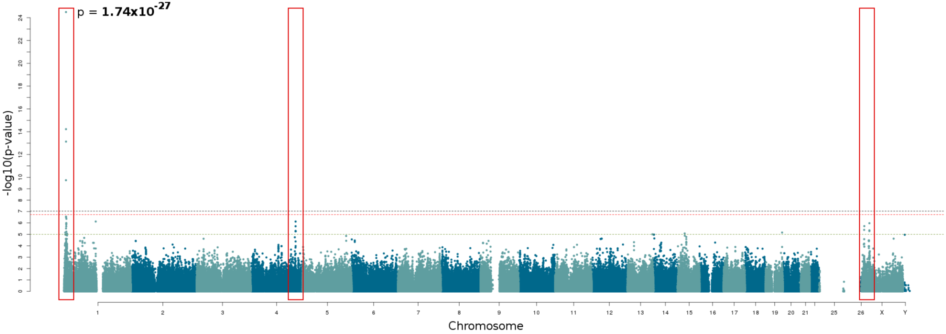
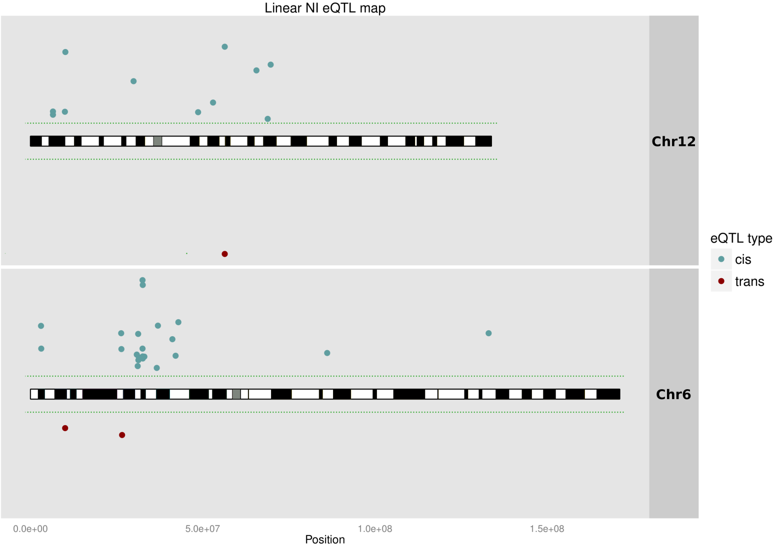


The NI eQTL map



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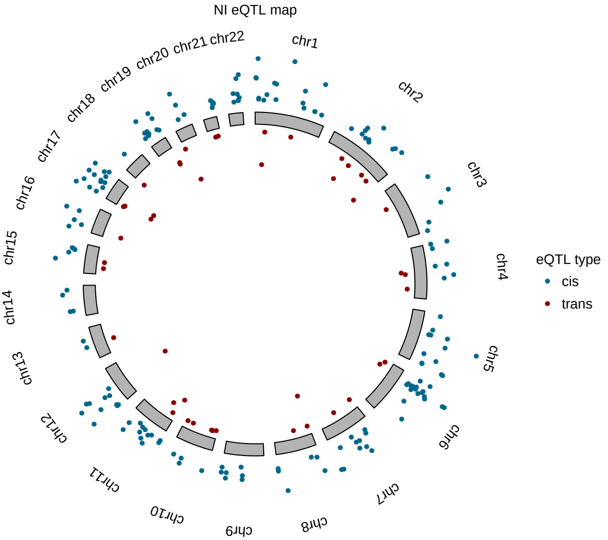

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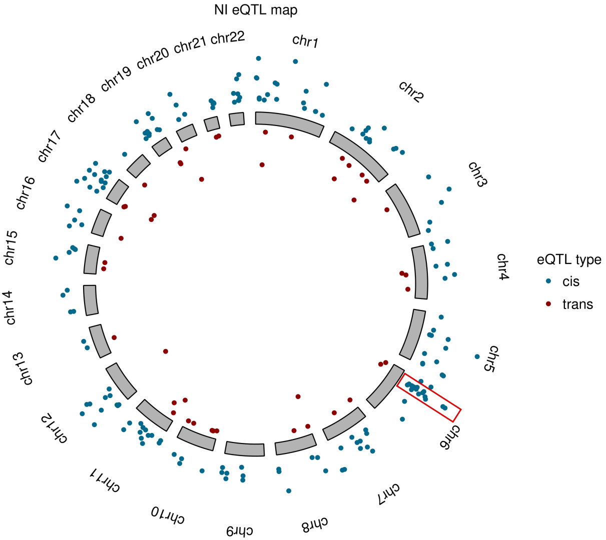

Heritable eQTL's: Comparison

200 cis & 70 trans eQTL's identified at study wide sig.

	n	cis	trans	significance threshold
NIHS	330	200	70	1.84E-007
BSGS	852	1529	256	5.25E-012
San Antonio	1240	750	1072	LOD score >3

Heritable eQTL's: Comparison

- Overlap of several top hits with other studies:
    1. BSGS[3]: overlap 7 of there top 12 cis-eQTL results
    (genes: HLA-DRB1, HLA-DQB1, ERAP2, RPS26, CLEC12A, TUBB2A, PAM)
    2. some overlap with San Antonio Family Heart Study[4]
    An overlap of 7 of the top 20 cis-eQTL results:
    (genes: UTS2, RPS26, TIMM10, LGALS2, RPL14, HLA-DRB3, HLA-DRB5)

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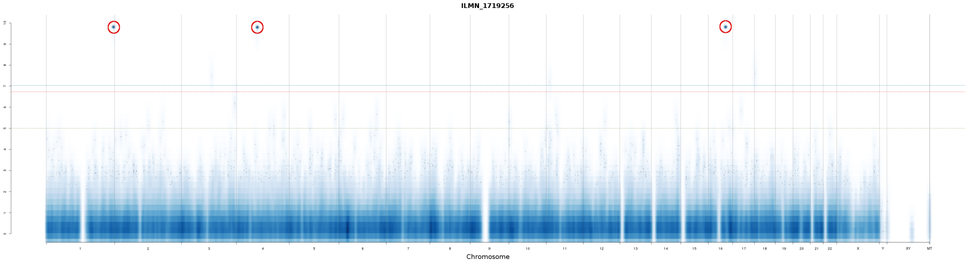
[3] Powell et al., (2012) *The Brisbane Systems Genetics Study: Genetical Genomics Meets Complex Trait Genetics.* PLoS ONE

[4] Göring et al., (2007) *Discovery of expression QTLs using large-scale transcriptional profiling in human lymphocytes.* Nature Genetics

eQTL with Genomewide SNP signature?

- Another interesting finding... a group of trans eQTL that were originally filtered out appear to form a genome-wide 'signature' associated with 9 separate transcripts:



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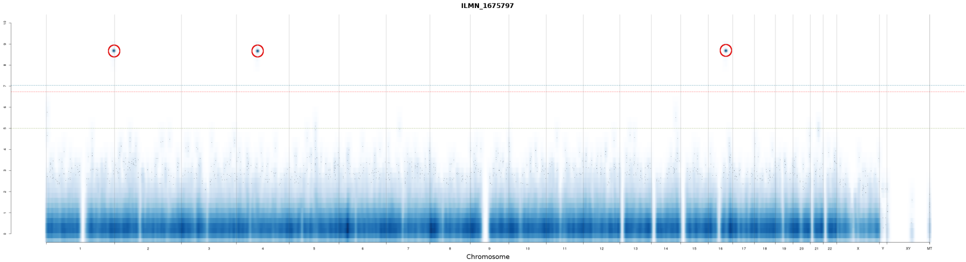

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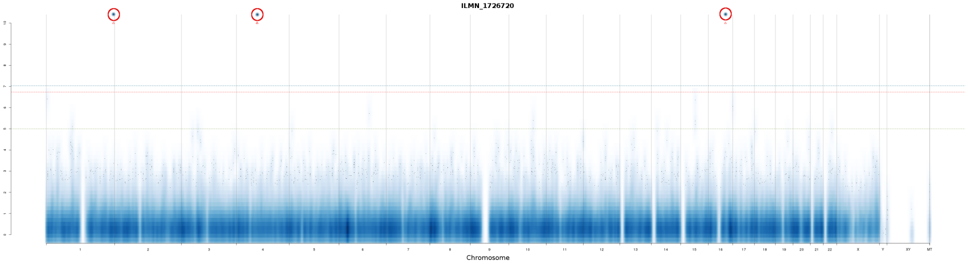

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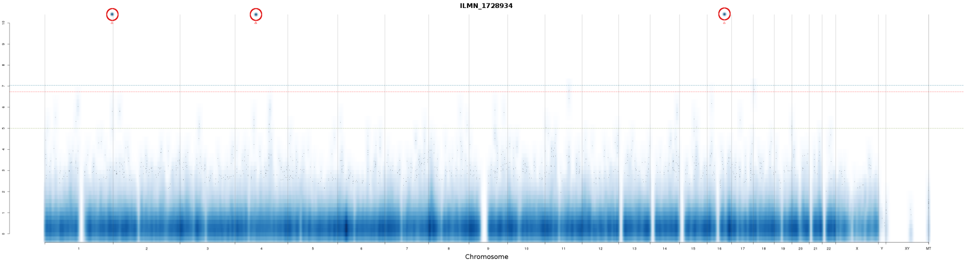

eQTL with Genomewide SNP signature?

- No SNP peaks, but potential genomewide SNP signature:
  1. 3 locus SNP signature
  2. 9 transcripts, 9 genes from 6 different chromosomes

Probe_ID	Gene	Chromosome	Top SNP p-value	eQTL
ILMN_1719256	CKS1B	1	1.65e-10	trans
ILMN_1675797	EPDR1	7	2.05e-09	trans
ILMN_1726720	NUSAP1	15	8.81e-11	trans
ILMN_1709634	CMBL	5	7.74e-09	trans
ILMN_1741133	NME1	17	1.28e-09	trans
ILMN_1786125	CCNA2	4	3.54e-06	trans
ILMN_1800197	MRPL36	5	3.64e-07	trans
ILMN_1728934	PRC1	15	2.39e-11	trans
ILMN_1663390	CDC20	1	4.34e-12	trans

- GATHER analysis suggests all 9 genes involved in possible cell division/mitosis pathway...

Conclusions & Future Directions

In conclusion...

- Identified a genomewide eQTL map in NI.
- 1712 expression transcripts were found to be significantly H^2
- GWAS identified 200 cis & 70 trans eQTL (study wide threshold).
- potentially novel SNP/eQTL signatures have been identified.

Future Directions...

- More comprehensive meta-analysis of current eQTL maps/databases
- **should facilitate the detection of novel (NI/population specific?) eQTL's**
- linkage analysis with SOLAR (STR & SNP??) for comparison
- more comprehensive analysis of trans-acting eQTL's

We've identified a trans-eQTL mapping to a gene which associates with an obesity related phenotype (COMP3) with associated kidney dysfunction.

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Acknowledgements

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Co Supervisors: Dr Donia Macartney-Coxson, Dr Geoff Chambers

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