eQTL identification and mapping in the population isolate of Norfolk Island

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Genemappers
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Outline

1. Background
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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 association
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A brief history lesson...
The Reconstructed N1 Core Pedigree...
Study Design

- Participants - 330 NIHS individuals
  - Samples - Blood (circulating lymphocytes)
  - mRNA extracted > cDNA > expression analysis

- Platforms:
  - Expression: Illumina HT-12 beadarray
  - SNPs: Illumina 610quad

~ 48000 mRNA probes & ~ 590000 SNPs for 330 participants

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Normalised gene expression data (23000 transcripts)\textsuperscript{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\textsuperscript{-7}
3. suggestive significance threshold = 1.0x10\textsuperscript{-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)

\textsuperscript{1}Göring et al., (2007) \textit{Discovery of expression QTLs using large-scale transcriptional profiling in human lymphocytes.} Nature Genetics
Computational Genomics

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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$^2$

**Distribution of significantly heritable transcripts**
*(age & sex adjusted, $n=1712$)*

$^2$Max sig. $H^2 = 0.84$ Min sig. $H^2 = 0.15$
Abstract

The title of the document is "Heritable eQTL’s" and it appears to be discussing eQTL mapping. The slide contains a Manhattan plot, which is a type of plot used in genome-wide association studies to identify genetic markers associated with a trait. The plot displays the -log10(p-value) on the y-axis and chromosome number on the x-axis, with points indicating the location of significant associations.

The slide also includes a section titled "Overview of eQTL Manhattan Plots," which likely provides context or interpretation of the Manhattan plot.

Acknowledgements

The document includes a section for acknowledgments, although the specific content is not visible in the image provided.
Heritable eQTL’s

Overview of eQTL Manhattan Plots

\[ p = 1.74 \times 10^{-18} \]
Heritable eQTL’s

Overview of eQTL Manhattan Plots
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Heritable eQTL’s

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\[ p = 1.74 \times 10^{-27} \]
The NI eQTL map

Linear NI eQTL map

- Chr12
  - eQTL type: cis, trans

- Chr6

Position
0.0e+00  5.0e+07  1.0e+08  1.5e+08

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eQTL mapping in NI isolate

28/08/12
The NI eQTL map

NI eQTL map

eQTL type
●
cis
trans

chr1 chr2 chr3 chr4 chr5 chr6 chr7 chr8 chr9 chr10 chr11 chr12 chr13 chr14 chr15 chr16 chr17 chr18 chr19 chr20 chr21 chr22

eQTL mapping in NI isolate

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The NI eQTL map

M Benton

eQTL mapping in NI isolate

28/08/12
200 cis & 70 trans eQTL’s identified at study wide sig.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>cis</th>
<th>trans</th>
<th>significance threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHS</td>
<td>330</td>
<td>200</td>
<td>70</td>
<td>1.84E-007</td>
</tr>
<tr>
<td>BSGS</td>
<td>852</td>
<td>1529</td>
<td>256</td>
<td>5.25E-012</td>
</tr>
<tr>
<td>San Antonio</td>
<td>1240</td>
<td>750</td>
<td>1072</td>
<td>LOD score &gt;3</td>
</tr>
</tbody>
</table>
Heritable eQTL’s: Comparison

- Overlap of several top hits with other studies:

1. BSGS\(^3\): overlap 7 of their 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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\(^4\) Göring et al., (2007) *Discovery of expression QTLs using large-scale transcriptional profiling in human lymphocytes*. Nature Genetics
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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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

<table>
<thead>
<tr>
<th>Probe_ID</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Top SNP p-value</th>
<th>eQTL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILMN_1719256</td>
<td>CKS1B</td>
<td>1</td>
<td>1.65e-10</td>
<td>trans</td>
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<td>ILMN_1675797</td>
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<tr>
<td>ILMN_1726720</td>
<td>NUSAP1</td>
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<td>8.81e-11</td>
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<td>ILMN_1728934</td>
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<tr>
<td>ILMN_1663390</td>
<td>CDC20</td>
<td>1</td>
<td>4.34e-12</td>
<td>trans</td>
</tr>
</tbody>
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- GATHER analysis suggests all 9 genes involved in possible cell division/mitosis pathway...
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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**Project Leaders:** Prof Lyn Griffiths, Dr Rod Lea

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

**Texas Biomedical Research Institute:** Melanie Carless, Claire Bellis, Matt Johnson, Harald Göring, Thomas Dyer, Jo Curran, John Blangero

**Genomics Research Centre:** Michelle Hanna, Dr Bridget Maher, Dr David Eccles

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