Analysis of the Immunochip in a large cohort of oligo- and polyarthritis juvenile idiopathic arthritis (JIA) cases confirms previous and identifies novel associations

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Disclosures

• None to declare

Genome Wide Association Studies

• Genome-Wide Association Studies (GWAS)
  – Compare cases to controls over hundreds of thousands of Single Nucleotide Polymorphisms (SNPs) across the entire genome
  – Identified many susceptibility loci in complex diseases

Overlap of Autoimmune Disease Loci

Data source: NHGRI GWAS Catalog

Immunochip

• Custom design Illumina beadchip
• 200 known autoimmune loci
  – Chosen from previous analysis of diseases such as RA, MS, type 1 diabetes, Crohn’s disease
• 200,000 single nucleotide polymorphisms (SNPs)
  – SNPs identified from dbSNP, 1000 Genomes Project, other sequencing projects
• Cost effective method for fine-mapping autoimmune loci

Juvenile Idiopathic Arthritis

• Heterogeneous group of arthritides
  – 7 subtypes
  – Oligoarthritis and RF- polyarthritis ~70%
• Rare (prevalence 1/1000 in Caucasian populations)
• 12 genes have been validated in independent cohorts
  – HLA, PTPN22 and PTPN2 confirmed with genome-wide significance
JIA Immunochip Aims

- Immunochip provides a unique opportunity to learn more about genetic susceptibility to JIA

- Aims:
  1. Confirm regions previously associated with JIA by showing genome-wide evidence
  2. Identify novel regions not previously investigated in JIA
  3. Fine-map associated JIA susceptibility regions

Juvenile Idiopathic Arthritis (JIA) Immunochip Consortium

- Manchester, UK
  - PI: Wendy Thomson
  - Joanna Cobb, Anne Hinks
- Cincinnati, USA
  - PI: Sue Thompson
  - David Glass, Marc Sudman
  - Carl Langefeld, Miranda Marion (Wake Forest U., USA)
  - Johannes-Peter Haas (Germany)
- Salt Lake City/Atlanta, USA
  - PI: Sampath Prahalad (Emory U.)
  - John Bohnsack (Utah)

Initial Cohort

- RF negative polyarthritis and oligoarthritis subtypes

<table>
<thead>
<tr>
<th>Cohort Name</th>
<th>Description</th>
<th>Samples post QC (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>UK JIA</td>
<td>421 (469)</td>
</tr>
<tr>
<td></td>
<td>USA JIA</td>
<td>752 (818)</td>
</tr>
<tr>
<td>Cases</td>
<td>UK JIA</td>
<td>421 (469)</td>
</tr>
<tr>
<td></td>
<td>USA JIA</td>
<td>752 (818)</td>
</tr>
<tr>
<td></td>
<td>German JIA</td>
<td>436 (479)</td>
</tr>
</tbody>
</table>

Total for analysis: 1609

Caucasian Controls

- UK WTCCC: 4280 (4732)
- USA Cincinnati pediatric: 626 (658)
- USA RACI: 1481 (3249)
- German: Survey of Neonates in Pomerania (SNP) consortium: 479 (498)

Total for analysis: 7153

Analysis Methods

- Rare variants exclude
  - Analysed only SNPs with minor allele frequency greater than 5%
- Removed any SNPs which failed Hardy-Weinberg Equilibrium
- 104,108 SNPs included in analysis
- Logistic regression
  - Adjusted for first 5 principal components to account for any residual population stratification
- Set the significance threshold to genome-wide level ($P = 5 \times 10^{-8}$)
AIM 1: Confirming Previous Associations

- Regions with genome-wide evidence ($P < 5 \times 10^{-8}$)

<table>
<thead>
<tr>
<th>Gene region</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA</td>
<td>$8.9 \times 10^{-93}$</td>
</tr>
<tr>
<td>PTPN22</td>
<td>$2.1 \times 10^{-17}$</td>
</tr>
<tr>
<td>STAT4</td>
<td>$6.7 \times 10^{-14}$</td>
</tr>
<tr>
<td>PTPN2</td>
<td>$3.2 \times 10^{-13}$</td>
</tr>
<tr>
<td>IL2/IL21</td>
<td>$1.3 \times 10^{-8}$</td>
</tr>
<tr>
<td>SH2B3-ATXN2</td>
<td>$4.8 \times 10^{-8}$</td>
</tr>
</tbody>
</table>

AIM 2: Identify Novel Associations

- Tier 2 novel hits
- 37 regions associated at $P > 5 \times 10^{-8} < 1 \times 10^{-4}$
- Previously associated with JIA
  - IL2RA
  - COG6
  - IL7R
  - IL2RB
  - IRF1
- Interesting novel regions
  - RUNX1
  - RUNX3
  - IL6R
  - FAS
  - FUT2
- Important to follow-up these regions as many may prove to be true JIA susceptibility loci

AIM 3: Fine-Map Associations

Most significant SNP (Risk)

2nd SNP after conditional analysis

rs6740131 (Protective)
**Plans for Future Analysis**

- Validation cohort of oligo/RFneg poly JIA samples
- Continue our conditional fine-mapping analysis
- Future functional studies

**Validation Cohort**

<table>
<thead>
<tr>
<th></th>
<th>UK: JIA</th>
<th>oligo/RFneg/Poly</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK: Arthritis collection</td>
<td>450</td>
<td></td>
</tr>
<tr>
<td>US: JIA Utah</td>
<td>344</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>794</td>
<td></td>
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</tbody>
</table>

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<th>oligo/RFneg/Poly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian controls</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>UK: WTCCC</td>
<td>900</td>
<td></td>
</tr>
<tr>
<td>USA: Cincinnati local</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>USA: SLEGEN</td>
<td>2036</td>
<td></td>
</tr>
<tr>
<td>USA: Utah</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7586</td>
<td></td>
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</tbody>
</table>

**Conclusions**

- Evidence for 6 loci at genome-wide significance, confirming their role in JIA susceptibility
  - $STAT4$, $IL2/IL21$, $SH2B3$-$ATXN2$ for the first time
- Identified 37 regions in tier 2 with evidence at $P < 1 \times 10^{-4}$
- Fine-mapping analysis on top hit regions
  - $STAT4$ locus shows evidence of multiple independent effects

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- Childhood Arthritis Response to Medication Study (CHARMS)  
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- WTCCC  
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- Cincinnati Genomic Control Cohort  
- Immunochip Consortium  

**Arthritis Research UK**

Providing answers and treatments.