GWAS identifies genetic variants on chromosome 9p21 as a cause of ALS in Finland

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Outline

• Introduction to amyotrophic lateral sclerosis
• Introduction to genetics
• Introduction to high throughput genomic technologies
• GWAS of ALS in Finland
• Future projects
Amyotrophic Lateral Sclerosis

- Neuro-degenerative disorder affecting upper and lower motor neurons
- Etiology poorly understood
- Median survival = 3 years
- No effective treatments

JM Charcot
1825 – 1893

Lou Gehrig
1903 - 1941
Clinical hallmarks of ALS

Introduction to genetics

- 3 billion base pairs in the human genome
- 26,564 genes (~1% of the genome)
- Genes consist of exons and introns
- Exons code for the amino acids of protein
  - 233,785 exons (Oct 2003)
  - 27.8MB of the genome
Single Nucleotide Polymorphisms (SNPs)

• DNA sequence variation involving a single nucleotide in the genome
• dbSNP: 12,017,369 SNPs
• 99% similar
  – 1% = 3 Million SNPs

Individual 1: AAG\text{C}TAGAC

Individual 1: AAG\text{T}TAGAC
Traditional gene discovery methods

- Familial
- Sporadic

Candidate gene approach

Linkage studies
Positional cloning
Candidate gene approach has been disappointing

- Schizophrenia Gene database:
  - 1,179 publications on 3,608 variants in 516 genes
  - 4 variants showed “strong epidemiological credibility

Allen et al, Nat Genetics 2008
Genome wide association studies
<table>
<thead>
<tr>
<th>Center</th>
<th>Number of cases</th>
<th>Putative loci</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH, USA</td>
<td>276 cases and 271 controls</td>
<td>-</td>
</tr>
<tr>
<td>TGEN, USA</td>
<td>386 cases and 542 controls</td>
<td>FBBY</td>
</tr>
<tr>
<td>Utrecht, The Netherlands</td>
<td>461 cases and 450 controls</td>
<td>ITPR2, DPP6</td>
</tr>
<tr>
<td>Ireland/NIH</td>
<td>221 cases and 210 controls</td>
<td>DPP6</td>
</tr>
<tr>
<td>NIH, USA</td>
<td>2,289 cases and 4,532 controls</td>
<td>SUNC1</td>
</tr>
<tr>
<td>Boston, USA</td>
<td>1,821 cases and 2,258 controls</td>
<td>Kifap3 (survival)</td>
</tr>
<tr>
<td>Utrecht, The Netherlands</td>
<td>2,532 cases and 5,940 controls</td>
<td>UNC13A, (chr 9)</td>
</tr>
</tbody>
</table>
What have we learned from GWAS?

• No large effect risk locus in ALS

• None of the loci have replicated thus far

• ALS is more genetically heterogeneous than we realized
Statement of research objectives

To discover the genetic causes of ALS in Finland by performing a genome-wide association study
Finland is ideal for GWAS

- Incidence: 8.2/100,000
- Founder population
- High prevalence of SOD1 D90A allele
- 414 Finnish ALS cases and 511 controls genotyped on 370K SNP chips
Results of Finnish ALS GWAS

MOBKL2B/IFNK/C9orf72

SOD1
Familial samples only \((n = 93)\)

Shared 42 SNP haplotype on chromosome 9p21
Chromosome 9p21 locus accounts for a sizeable proportion of ALS-FTD cases
Chromosome 9p ALS-FTD locus
Deep re-sequencing
CNV and translocations not found
Summary

• GWAS of ALS in Finland has identified the first loci in ALS that clearly exceeded bonferroni

• Narrowed the locus to 140kb region containing three genes

• Affected families shared a 42 SNP haplotype

• No variants/CNV/translocations found
Future directions: sequencing costs are beating Moore’s law

1\textsuperscript{st} human genome: $2.7$ Billion and 13 years
Today: $30,000$ and 60-90 days

C. Humphries, MIT Tech Review, April 2010
Future directions: Exome sequencing

• Ideal for discovering rare variants
• Faster
• Cheaper
• Small families and singletons
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