Autism is a Complex Genetic Disorder

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Dept. Psychiatry & Behavioral Sciences
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1. Why Genetics?

2. What does it mean autism is genetic?

3. Finding the Gene/s - Linkage

4. Finding the Gene/s - Association

5. How many genes?

6. Reducing Heterogeneity

7. Outlook
Why Genetics?

- Child Psychiatric Disorders
  - Run in Families
  - MZ concordance > DZ concordance

- Heritability estimates
  - Autism > 0.9
  - ADHD  0.6-0.8
  - Early onset Bipolar Disorder 0.8
  - Conduct Disorder 0.5
45,000 Genes
Neuronal Development

Brain Growth

Cognitive Impairments

Clinical Symptoms
Technology

CHEAP GENOTYPES
1. Why Genetics?

2. *What does it mean “autism is genetic”?*

3. Finding the Gene/s - Linkage

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7. Outlook
Genes are interacting with other molecules.
DNA

5'-end

3'-end

Base Pair

Backbone

Phosphate

Sugar

3'-end

5'-end
“The very meaning of DNA sequence is relational” (Keller, 2005)

Any phenotype is the result of interactions between a specific set of genes and specific environments

Phenotype product of Development

Prediction of the Future presence of a trait is not accomplished by identifying the trait with genes, but by understanding the developmental system

A simplified Nature-Nurture Dualism is not tenable
Why Find the Gene/s?

- Better understanding of pathophysiology
  - Function of gene/s
  - Develop models

- Psychiatric Disorders are not monogenic
  - Targeted Research
  - Targeted Treatment

- Environmental Factors

- Final Goal – Gene x Environment
1. Why Genetics?

2. What does it mean “autism is genetic”?

3. **Finding the Gene/s - Linkage**

4. Finding the Gene/s - Association

5. How many genes?

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7. Outlook
Single Nucleotide Polymorphism
Microsatellite
Human Genome

- ~3,300 million base pairs
- <1.5% are typical genes
- Number of genes
  - Estimates vary between 28,000 and 120,000
  - Best estimate - ~41,000-45,000
- 43% repetitive elements (>4.1 million)
- Locations of ~ 6 million SNPs known
Genome-wide Scan
1 SNP/20-40 kb

Candidate Region

Fine Mapping
1 SNP/2-5 kb

Candidate Genes

Gene Mining
Gene Catalog and *in silico* analysis

Disease Gene

Gene Sequencing
Polymorphism Identification

Ultra-fine Mapping
Identification of causative SNPs/haplotypes

GeneMap and Target Identification
Literature and pathway analysis
Finding the Gene/s - Linkage

- More than one affected family member
- Based on Recombination
- Power dependent upon increase in risk to relative
- Genome-wide
  - ~500 markers evenly spaced microsatellites
  - 5-10,000 SNPs
- Results have not been unequivocal
Linkage – Recombination

Gametes

Crossing-over and recombination during meiosis
Linkage

- Tests the co-segregation between a marker and a disease
- Requires families with more than one affected family member (multiplex - MPX)
- Based on Recombination
- Power dependent upon increase in risk to relative
- Markers are tested evenly spaced across the entire genome
- Lod score serves as summary statistics
- Lod>3 considered evidence for linkage
Linkage Analysis – Dominant Allele D
Linkage Analysis – What to expect

- Small number of markers
- Chromosomal Region
  - Can be large
    - >50 million base pairs
- Requires follow-up studies
- Results are restricted to multiplex families
<table>
<thead>
<tr>
<th>Chr.</th>
<th>LOD score &gt;2.0</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>D1S1656 (q42.2)</td>
<td>Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.</td>
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<tr>
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<td>D4S1647 (q23)</td>
<td>Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.</td>
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<td>D6S283 (q16.3)</td>
<td>Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.</td>
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<td>D6S1270 (q14.3)</td>
<td>Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.</td>
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<td>D7S2462 (q36.2)</td>
<td>and: Hum Molecular Genetics 2001; 10: 973–982.</td>
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</tbody>
</table>
## Linkage Studies - Autism

<table>
<thead>
<tr>
<th>Chr.</th>
<th>LOD &gt;2.0</th>
<th>References</th>
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<tbody>
<tr>
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<td>D10S1412 (p14)</td>
<td>Buxbaum JD, Mol Psychiatry 2004; 9: 144–150.</td>
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<tr>
<td></td>
<td>D11S1392 (p13)</td>
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</table>
Increasing Sample Size

- Power in Linkage Studies
  - $\lambda_r = \text{Risk increases in siblings/Risk in population}$
- Risk increase of conferred by mutations in specific gene may be low due to heterogeneity
- Solution – Increase Sample Size
Finding the Genes

- Large-Scale Collaborative Studies
  - AGP – Consortium of 13 Groups (>20 Universities)
    - >1500 Multiplex families
    - ~ 2000 Trios
    - Phase 1: Affymetrix 10k SNP Chip
    - Phase 2: Fine Mapping
AGP – Phase 1

- Genotypes from TGEN (contract service)
- 10,112 SNPs
  - Completion rate of genotypes/SNP ≥ 90%
  - Completion of genotypes/individual ≥ 80%
- Hardy Weinberg tested in “Europeans”
- Discordant call rate: ≈ 5/10,000 (from duplicates)
AGP – Phase 1

Diagnostic Groups
- Narrow: ADI + ADOS = Autism (all)
- Broad: ADI + ADOS = Autism for ≥ 1 sib
- hASD: ADOS missing or both sibs ASD by ADI and ADOS
- Broad + hASD families = Total MPX families
Lod Scores and Sample Size

- Replication - the “holy grail”
- Reality for complex disorders
  - “Strong evidence” diminishes with more data
- Many genes
  - Different samples will maximize at different locations
  - Very large sample sizes are required
- Large samples allow to subdivide phenotype
Linkage analysis by diagnostic group.

# multiplex

N = 522

N = 739

N = 1168

11p12-p13
1. Why Genetics?

2. What does it mean “autism is genetic”?

3. Finding the Gene/s - Linkage

4. *Finding the Gene/s - Association*

5. How many genes?

6. Reducing Heterogeneity

7. Outlook
Finding the Gene/s - Association

- Singleton Families
- Based on increased number of allele in disease population compared to control population
- Power dependent upon increase of risk conferred by the allele
- To cover genome
  - 500,000 to 1,000,000 markers
  - Under way - None published for child psychiatric disorder
  - Most studies so far - Candidate Genes
# Candidate Genes - Autism

<table>
<thead>
<tr>
<th>Chr.</th>
<th>Association</th>
<th>References</th>
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<tr>
<td>7</td>
<td>GABA (A) receptor sub-units GABRB3 and GABRA5 (q12) ATP10C (q12) - Aminophospholipid-transporting ATPase gene UBE3A-gene (q12) - E6-AP ubiquitin ligase</td>
<td>Serajee FJ, et al., Journal of Medical Genetics 2003; 40: e119.</td>
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<tr>
<td>17</td>
<td>Serotonin transporter gene (5-HTT)</td>
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</tbody>
</table>
### Table 1.

Significant Pooled Odds Ratios for Gene Variants Examined in Three or More Case-Control or Family-Based Studies

<table>
<thead>
<tr>
<th>Gene</th>
<th>Study Design</th>
<th>Pooled OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Dopamine D4 Receptor (exon III VNTR, 7-repeat)</td>
<td>Family</td>
<td>1.16</td>
<td>1.03–1.31</td>
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<tr>
<td>Dopamine D4 Receptor (exon III VNTR, 7-repeat)</td>
<td>Case-control</td>
<td>1.45</td>
<td>1.27–1.65</td>
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<td>Dopamine D5 Receptor (CA repeat, 148 bp)</td>
<td>Family</td>
<td>1.24</td>
<td>1.12–1.38</td>
</tr>
<tr>
<td>Dopamine Transporter (VNTR, 10-repeat)</td>
<td>Family</td>
<td>1.13</td>
<td>1.03–1.24</td>
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<tr>
<td>Dopamine β-Hydroxylase (TaqI A)</td>
<td>Case-control</td>
<td>1.33</td>
<td>1.11–1.59</td>
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<tr>
<td>SNAP-25 (T1065G)</td>
<td>Family</td>
<td>1.19</td>
<td>1.03–1.38</td>
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<tr>
<td>Serotonin Transporter (5-HTTLPR long)</td>
<td>Case-control</td>
<td>1.31</td>
<td>1.09–1.59</td>
</tr>
<tr>
<td>HTR1B (G861C)</td>
<td>Family</td>
<td>1.44</td>
<td>1.14–1.83</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; VNTR, variable number of tandem repeats.

From Lowe et al., 2004; Faraone et al., 2006
1. Why Genetics?

2. What does it mean “autism is genetic”?

3. Finding the Gene/s - Linkage

4. Finding the Gene/s - Association

5. How many genes?

6. Reducing Heterogeneity

7. Outlook
Mapping genes - complex diseases

- depends on number and frequency of susceptibility alleles
- only feasible if common diseases influenced by one or a few susceptibility alleles at each locus, but not so if there is a high degree of allelic heterogeneity.
Linkage Disequilibrium

Chromosome: 7
Position: 98857311-98883707
Gene Symbol: CYP3A5
Common Disease – Common Variant

- Common disease-common variant hypothesis predicts
  - Common disease causing alleles will be found in all populations
  - Complex polygenic diseases
    - which are evolutionary neutral
    - Caused by common variants
    - Each variation will have a small effect
    - additive or multiplicative effect of many alleles

- Examples
  - ApoeE (Alzheimer Disease)
  - IL23R (Crohn Disease)
Common Disease – Common Variant

- Strongest Argument in favor of the CD-DV hypotheses
  - Milder Phenotypes in first degree relatives
  - Endophenotypes
Parents of Children with Autism

- **Experimental**
  - Bias towards detail-focus
  - This is seen across tasks of
    - Perceptual judgment
    - Visuo-spatial construction
    - Problem solving
    - Verbal semantics

- **Real-life Skills**
  - Preference for solitary pastimes
  - Less interest in social interaction
  - Detail-focus interests
## Autism Spectrum Quotient

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Index</th>
<th>Control</th>
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<tr>
<td></td>
<td>Mo</td>
<td>Fa</td>
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<tr>
<td>Social skills</td>
<td>(65)</td>
<td>(46)</td>
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<tr>
<td>Attention switching</td>
<td>2.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Attention to detail</td>
<td>3.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Communication</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Imagination</td>
<td>2.0</td>
<td>3.2</td>
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</tbody>
</table>
Autism and Single Gene Disorders

- Single Gene disorders associated with autism
  - Rett syndrome
  - Tuberous sclerosis
  - Timothy syndrome
  - Many more
Autism and Single Gene Disorders

- Cytogenetic abnormalities
  - Many individual case reports
    - Most often
      - Fragiles X
      - Duplication chromosome 15q11-q13
      - 22q11 deletion syndrome
    - Turner syndrome
Can the autism phenotype be explained by multiple single gene mutations?
Copy Number Variation

- CNV
  - Gains and Losses of pieces of DNA sequence consisting of between ten thousand and five million base pairs
  - Loss = Deletion
  - Gain = Insertion
Deletion

Deletion in the blue chromosome

1  1
2  2
3  3
4  4
5  5
6  6
7  7
8  8

9  9
10 10
11 11
12 12
13 13
14 14
15 15
Insertion

DNA replication

Recombination between sister chromosomes

Duplication of sequences between direct repeats
High Frequency CNVs

- Wong et al. (2007)
  - Genome-wide search using BAC array
    - Sensitivity 40kb
    - Minimum of 40 Mb
    - 1.5% of mapped human autosomes
  - 800 loci
  - 77% are novel
  - Greatest difference between two individuals
    - 228 clones
    - > 9Mb
High Frequency CNV - Genes

- Olfactory receptor genes
- Genes affected with taste
- Cancer-related Genes
- Others
  - Diabetes mellitus
  - Alzheimer Disease
  - Coronary artery disease
  - Schizophrenia (COMT)
- 21 microRNAs reside within 14 of CNVs
Copy Number Variants by signal intensity

Chromosome fragment with SNP locations | Signal Intensities

[Diagram of chromosome fragments with signal intensities indicated by different symbols]
Copy Number Variants by signal intensity

Chromosome fragment with SNP locations

Signal Intensities ARE NOISY
Copy Number Variants

2p16: 2 affected siblings
NRX1

17p12: three families
Smith Magenis,
Charcot-Marie Tooth

1q21: three families
Previously implicated in MR

22q11.2: two families
Interpretation complicated

- 14 de novo CNVS found in both ASP
- 18 CNVs overlap ASD-related rearrangements
- Numerous overlapping/recurrent CNVs
- Families with transmission of maternal 15q gains
Sebat et al. (2007)

<table>
<thead>
<tr>
<th></th>
<th>No Indiv.</th>
<th>CNV</th>
<th>Proportion</th>
<th>$x^2$</th>
<th>Mplx vs. Splx</th>
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<tr>
<td>Simplex Autism</td>
<td>118</td>
<td>12</td>
<td>0.102</td>
<td>0.0005</td>
<td>0.043</td>
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<tr>
<td>Multiplex Autism</td>
<td>77</td>
<td>2</td>
<td>0.026</td>
<td>0.59</td>
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<tr>
<td>Splx/Mplx Combined</td>
<td>195</td>
<td>14</td>
<td>0.072</td>
<td>0.0035</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>196</td>
<td>2</td>
<td>0.010</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.1 Mb Deletion
20p13
27 genes
Incl. Oxytocin
<table>
<thead>
<tr>
<th>Individual</th>
<th>Locus</th>
<th>Start position</th>
<th>Length</th>
<th>change</th>
<th>Family type</th>
<th>Diagnosis</th>
<th>Gender</th>
<th>Validation</th>
<th># Genes</th>
<th>Single gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>63-144-2575 &amp; 2667</td>
<td>2q24.2</td>
<td>162,212,720</td>
<td>99,252</td>
<td>loss</td>
<td>Simplex</td>
<td>Autism</td>
<td>female</td>
<td>A</td>
<td>1</td>
<td>SLC4A10</td>
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<tr>
<td>61-2710-3</td>
<td>2q37.2-q37.3</td>
<td>236,414,455</td>
<td>6,286,648</td>
<td>loss</td>
<td>Simplex</td>
<td>Autism</td>
<td>male</td>
<td>A,B,D</td>
<td>50</td>
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<tr>
<td>Van69</td>
<td>2q37.3</td>
<td>238,217,066</td>
<td>4,484,037</td>
<td>loss</td>
<td>Simplex</td>
<td>Autism</td>
<td>male</td>
<td>A,D</td>
<td>43</td>
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<tr>
<td>89-3507-1</td>
<td>3p14.2</td>
<td>60,746,033</td>
<td>101,507</td>
<td>loss</td>
<td>Simplex</td>
<td>Autism</td>
<td>male</td>
<td>A</td>
<td>1</td>
<td>FHIT</td>
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<tr>
<td>63-562-6612</td>
<td>3p14.2</td>
<td>61,072,100</td>
<td>293,096</td>
<td>gain</td>
<td>Simplex</td>
<td>Autism</td>
<td>male</td>
<td>A</td>
<td>1</td>
<td>FHIT</td>
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<tr>
<td>AU010604</td>
<td>6p23</td>
<td>13,997,280</td>
<td>1,264,651</td>
<td>loss</td>
<td>Simplex</td>
<td>Autism</td>
<td>male</td>
<td>A,D</td>
<td>2</td>
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<tr>
<td>89-3507-100</td>
<td>20p13</td>
<td>1,169,205</td>
<td>1,193,737</td>
<td>loss</td>
<td>Simplex</td>
<td>Autism</td>
<td>male</td>
<td>A</td>
<td>13</td>
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<tr>
<td>AU072203</td>
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<td>151,880</td>
<td>loss</td>
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<td>Autism</td>
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<td>AU032903</td>
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<td>50,562,149</td>
<td>10,916,362</td>
<td>gain</td>
<td>Simplex</td>
<td>Autism</td>
<td>male</td>
<td>A,B</td>
<td>23</td>
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<tr>
<td>60-3061-4</td>
<td>15q11-q13.33</td>
<td>18,526,971</td>
<td>12,229,800</td>
<td>gain</td>
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<td>Autism</td>
<td>male</td>
<td>A,B</td>
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<td>AU077504</td>
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<td>5,992,836</td>
<td>207,980</td>
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<td>Autism</td>
<td>female</td>
<td>A,B,C,D</td>
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<td>A2BP1</td>
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<td>CG2061</td>
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<td>29,578,715</td>
<td>502,574</td>
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<td>Simplex</td>
<td>Aspergers</td>
<td>female</td>
<td>A,C,D</td>
<td>27</td>
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<tr>
<td>SK-135-C</td>
<td>20p13</td>
<td>2,785,194</td>
<td>1,169,205</td>
<td>loss</td>
<td>Simplex</td>
<td>Aspergers</td>
<td>male</td>
<td>A,D</td>
<td>23</td>
<td></td>
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<tr>
<td>89-3524-100</td>
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<td>45,144,027</td>
<td>4,321,856</td>
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<td>Simplex</td>
<td>Autism</td>
<td>female</td>
<td>A,B,C,D</td>
<td>30</td>
<td></td>
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<tr>
<td>NA10857</td>
<td>2p16.1</td>
<td>58,394,177</td>
<td>2,786,284</td>
<td>gain</td>
<td>Control</td>
<td>Unaffected</td>
<td>Unaffected</td>
<td>A</td>
<td>7</td>
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<tr>
<td>AU070807</td>
<td>20p13-p12.3</td>
<td>111,824</td>
<td>5,316,286</td>
<td>gain</td>
<td>Simplex</td>
<td>Unaffected</td>
<td>Unaffected</td>
<td>A</td>
<td>69</td>
<td></td>
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</tbody>
</table>

**Table 1.** Spontaneous CNVs detected by ROMA. A description of 17 de novo CNVs in 16 subjects is provided, along with the methods used for its validation. The number of unique RefSeq genes within each CNV region are indicated, and when the locus apparently encompasses only a single gene, the gene symbol is listed. Types of validation included (A) Higher-resolution microarray scans by 390K ROMA or Agilent 244K CGH, (B) G-banded karyotype, (C) FISH, and (D) microsatellite genotyping. References are listed for four cases where similar de novo CNVs were previously reported in the literature.

FLJ1647 – Sterol desaturase  
SLC4A10 – Sodium bicarbonate cotransporter  
FHIT – Fragile Histidine Triad  
A2BP1 – Ataxin-2 binding protein 1  
All four genes are in the top 3% of the human genes by length
Autism – How many Genes

- 10-20%
  - CNVs
    - Large number of different genes
- Is there a more common allele predisposing to autism?
1. Why Genetics?

2. What does it mean “autism is genetic”?

3. Finding the Gene/s - Linkage

4. Finding the Gene/s - Association

5. How many genes?

6. *Reducing Heterogeneity*

7. Outlook
Removing MPX families with CNVs.

Broad Sample:
N= 739 MPX

N= 641

N= 603

N= 567

11p13

15q23 & 15q25.3
Removing MPX families with CNVs & Partitioning by sex

<table>
<thead>
<tr>
<th>Female–containing Families</th>
<th>Male–only Families</th>
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<tbody>
<tr>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
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<table>
<thead>
<tr>
<th>No. of Broad MPX families</th>
</tr>
</thead>
<tbody>
<tr>
<td>233</td>
</tr>
<tr>
<td>221</td>
</tr>
<tr>
<td>208</td>
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<table>
<thead>
<tr>
<th>FC families</th>
<th>MO families</th>
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</thead>
<tbody>
<tr>
<td>11p12-p13, 15q23</td>
<td>11p12-p13, 15q23</td>
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Autism

Impairment in the Development of

Social Interaction
Communication including Language
Stereotypies Restricted Interests
Table I. Summary of Peaks in Stratification Analysis in ALL and DELAYED Families

<table>
<thead>
<tr>
<th>Region</th>
<th>All families</th>
<th>Stratified by PD</th>
<th>Stratified by WD</th>
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</thead>
<tbody>
<tr>
<td>Chr</td>
<td>cM</td>
<td>NPL</td>
<td>NPL</td>
</tr>
<tr>
<td>1</td>
<td>131.34</td>
<td>1.12</td>
<td>1.70*</td>
</tr>
<tr>
<td>2</td>
<td>136.34</td>
<td>0.48</td>
<td>2.07*</td>
</tr>
<tr>
<td>2</td>
<td>153.65</td>
<td>-0.039</td>
<td>1.78*</td>
</tr>
<tr>
<td>2</td>
<td>191.87a</td>
<td>0.14</td>
<td>1.82*</td>
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<td>1.81*</td>
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<td>2.53**</td>
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<tr>
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ni, no increase.
* P ≤ 0.05.
** P ≤ 0.01.

Spence et al. (2006)
**Nature modifies Nature**

$G \times E$ interactions = genes modify environmental effects

Caspi & Moffitt (2006), Legrand et al. (2005)

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**Nuture modifies Nature**

Epigenesis = environments modify gene expression
1. Why Genetics?

2. What does it mean “autism is genetic”?

3. Finding the Gene/s  - Linkage

4. Finding the Gene/s  - Association

5. How many genes?

6. Reducing Heterogeneity

7. Outlook
Genetics the Second Wave

- The Bigger – The Better
- Large number of markers to cover genome
  - 500,000 – 1,000,000
- Very close to disease related mutation
- Several Studies Ongoing
  - BROAD
  - Johns Hopkins
  - AGP
- Combined with Genome-Wide Search for CNVs
Genetics the Second Wave

- Ongoing Studies are based on Common Disease – Common Variation Model
  - Low hanging fruits – Common alleles
  - Genes implicated will not account for autism in a substantial fraction
  - Predisposing alleles on its own will only contribute a small increase in risk
  - Risk will be unspecific and overlap with other disorders
  - It will require major efforts to define the predictive value of each one of the variants

- A better understanding of the relationship between genetic factors, cognitive deficits, neuropathology and clinical symptoms will be paramount
Conclusions

- Autism is a complex genetic disorder and most likely influenced by a combination of mutations in single genes, deletions and duplications, and by more common alleles

- Linkage: 11p13-12 is a good place to look for liability loci (Also, All: 15q; FO: 9p, 5p, 6q, 15q, 2q; MO: 7q, 5q)
Conclusions

- Could dysregulated glutamate be a major pathway to risk for ASD?
  - Linkage results → Any striking coincidences?
    - 11p13-12: SLC1A2 – Glutamate transporter member 2
    - 9p24.2: SLC1A1 - Glutamate transporter member 1
    - 2q31: SLC25A12 - Mitochondrial aspartate/glutamate carrier
    - 4q28.3: SLC7A11 - Cystine-glutamate transporter
    - 7q21.3: SLC25A13 - Aspartate-glutamate transporter in mitochondria

- Striking pattern of CNVs
  - Chromosomal abnormalities not rare
  - 10k does not cover genome.
Genotype \rightarrow \text{Gene expression} \rightarrow \text{Synapse}

Neural substrate reactivity
Autism Genome Project

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International Molecular Genetic Study of Autism Consortium (IMGSAC)
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Autism Speaks, CIHR, CAN, Genome Canada, HHMI, Hospital for Sick Children Foundation, INSERM, MRC, NICHD, NIDCD, NIMH, NINDS, NLM Family Foundation, Swedish National Medical Council, Wellcome Trust, EU