Many developmental issues have a genetic basis (learning, behavior, motor skills)

- Single gene, Mendelian (fragile X – FMR1; PTEN) 20%
- Unknown cause (unidentified genes, multiple gene interactions, environment) Chromosomal 15-20%

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G-banded Karyotype Analysis

Genetic material (DNA) is organized into chromosomes

G-banded chromosome analysis:
Each chromosome (1-22,X,Y) equal to a state

Karyotype image courtesy of N. Chia, ISCN 2005
Example of Common Chromosome Abnormality

Trisomy 21
Down syndrome

Each chromosome is made up of multiple "bands" which can be rearranged, deleted or duplicated.

G-banded chromosome analysis: Each band equal to the larger cities in each state.

Could see if something is wrong with Philadelphia or Pittsburgh... but not Lewsburg.

Examples of Common Chromosome Abnormalities

2q Deletion

22q Deletion

A new technology, chromosomal microarray, allows us to look at each city for every state across the U.S.!

Resolution: Up to 100x's greater than G-banding.

One of the first clinically relevant successes of the Human Genome Project

Whole Genome by Microarray

Increasing the Resolution for Detecting Chromosome Imbalances

<table>
<thead>
<tr>
<th>Category</th>
<th>Prebanding Techniques</th>
<th>High-resolution banding</th>
<th>FISH</th>
<th>Cytogenetic range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution</td>
<td>10-20 Mb</td>
<td>5-10 Mb</td>
<td>5-5 Mb</td>
<td>50-100 kb</td>
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<tr>
<td>Known phenotype &amp; genetic basis</td>
<td>Down syndrome</td>
<td>Williams syndrome</td>
<td>Turner syndrome</td>
<td>Patau-WS syndrome</td>
</tr>
<tr>
<td>Known genetic factors</td>
<td>Trisomy 18</td>
<td>Trisomy 13</td>
<td>Smith-Magenis syndrome</td>
<td>1p deletion</td>
</tr>
<tr>
<td>(only detectable using microarray)</td>
<td>15p-</td>
<td>15p-</td>
<td>17q11.2</td>
<td>17q12</td>
</tr>
</tbody>
</table>
17q12 Deletion – Microarray Results

17q12 Region – 1.4 Mb

Similar DNA sequences mediate 17q12 del and dup

Normal pairing

Abnormal pairing

Similar DNA sequences

Normal pairing

Abnormal pairing
Since dels and dups of 17q12 are mediated by this recurrent mechanism, all individuals with these rearrangements have the EXACT same region deleted or duplicated. (This is in contrast to most chromosome rearrangements that have "random", rather than recurrent breakpoints)
17q12 Genes

Only gene in region associated with defined clinical features: Renal cysts and diabetes (RCAD)

Behavioral vs. Etiological Diagnosis

<table>
<thead>
<tr>
<th>Autism</th>
<th>Autism</th>
<th>Autism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile X syndrome</td>
<td>22q11.2 del</td>
<td>17q12 del</td>
</tr>
</tbody>
</table>

- Define etiology
- Targeted medical monitoring
- Develop etiology specific interventions

Goals of 17q12 Initiative

Identify medical, cognitive, neural and behavioral profiles shared by this genetically well defined group to inform and improve treatment and care.

Some questions to be explored:

- What explains the phenotypic heterogeneity within the group of individuals with deletion or duplication of 17q12?
- What other genes are contributing to the phenotype?
- What is the natural history and longitudinal course?

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