How to Conquer a Chromosome Abnormality

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Disclosure

Jannine Cody has no relationships with commercial companies to disclose.

Learning Objectives

At the end of this presentation the participant will be able to:
1. Define the 5 main chromosome 18 abnormalities.
2. Discuss reasons that these conditions are not syndromes.
3. Improve care of chromosome 18 patients by understanding where to go for the latest information.

Our Goal

To make the chromosome 18 conditions the first completely treatable chromosome abnormalities.
The Chromosome 18 Conditions

18q-

18p-

Ring 18

Tetrasomy 18p

Trisomy 18

Trisomy 18

Trisomy 18

Trisomy 18

Prevalence of Chromosome 18 Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>1 / # of births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 18</td>
<td>1,710</td>
</tr>
<tr>
<td>18q-</td>
<td>54,764</td>
</tr>
<tr>
<td>18p+</td>
<td>56,336</td>
</tr>
<tr>
<td>Ring 18</td>
<td>300,129</td>
</tr>
<tr>
<td>Tetrasomy 18p</td>
<td>625,000</td>
</tr>
<tr>
<td>All non-trisomy</td>
<td>24,450</td>
</tr>
<tr>
<td>chromosome 18 conditions</td>
<td></td>
</tr>
<tr>
<td>All chromosome abnormalities</td>
<td>230</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>434</td>
</tr>
</tbody>
</table>

Wellesley et al., 2012

Pediatric Grand Rounds

UT Health San Antonio
Prevalence of chromosome abnormalities

Prevalence of a new chromosome abnormality

664/ year in Bexar Co.
Prevalence of a chromosome abnormalities

>100,000 bp = ~10/ individual
>50 bp = ~50 / individual

Population Frequency

Normal Variation  Disease Risk Factors  Disease Causing

It’s The Genes That Matter

Teenage girl
Deletion = 100,000 bp
1 gene
Developmental age of 11 months

Gene dosage is:
– common mechanism
– amenable to treatment

Teenage girl
Deletion = 6,000,000 bp
27 genes
IQ 120
Our Approach

- **Clinical**
  - Investigative
  - Defining standards of care

- **Molecular**
  - Identifying key genes
  - Defining gene action
  - Regulating gene action

Then; 1990

Smith's Recognizable Patterns of Human Malformations

- Small stature
- Long hands
- Obnoxious behavior
- Growth deficiency
- Wide mouth
- Alopecia
Genotype / Phenotype

Subject 1
A
B
C
Subject 2
A
B
C
Subject 3
A
B
C
Subject 4

Phenotype Regions

1. High resolution genotypes
2. In-depth phenotypes
3. A large cohort

Enrollment Numbers

347 18q-
118 18p-
73 Tetrasomy 18p
39 Ring 18
34 Trisomy 18
5 18q+
3 18p+
619 Total

Enrollment Distribution

North American Continent - 532
US (49 states) - 463
Canada (7 provinces) - 44
Mexico - 2
Barbados - 1
Puerto Rico - 1
Dominican Republic - 1
South American Continent - 5
Brazil - 4
Columbia - 1
Europe (16 countries) - 48
Asia (3 countries) - 5
Australia - 21
New Zealand - 6
Africa (1 country) - 2

Team 18

Chromosome 18 Clinical Research Center Investigators

Director: Jannine Cody, Ph.D.
Medical Director: Daniel Hale, M.D.
Neuropsychology: Louise O'Donnell, Ph.D.
Bio-informatics: Jon Gelfond, MD, PhD
Endocrinology: Daniel Hale, M.D.
Psychiatry: Catherine Larson, M.D.
Child Neurology: Sid Atkinson, M.D.
MRI: Peter Fox, MD
 ENT: Jack Lancaster, Ph.D.
Cytogenetics: Brian Perry, M.D.
Ophthalmology: Martha Schatz, M.D.
Gait: Ann Menéttre, Ph.D.
 Gail: Gail Walden
Allergy/Immunology: Edward Brooks, MD
Bone health: Alvaro Moreira, MD
Platelet function: Andrew Meyer, MD
Mouse behavior/neurophysiology: Georgina Gould, Ph.D.
Mouse electrophysiology: Sun Hee Kim, Ph.D.
Cell-based assays: Donna Lehman, Ph.D.
Chromosome 18 Clinical Research Center Staff

**Administrative**
- Gloria Matthews
- Linda Ancira

**Laboratory**
- Patty Heard

**Research**
- Annice Hill
- Mimi Hasi
- David Rupert
- Bridgette Soileau
- Courtney Sebold

Research Center Activities

- DNA & cell bank
- Medical records
- Surveys
- DNA analysis
- Clinical evaluations
- Information for families

Website
Chromosome 18 Registry
Physician Referral
Primary Enrollment
- Consent forms
- Medical Records
- Blood

Annual Developmental Survey (BASC)
Clinical Assessment in San Antonio

Autism survey
Allergy survey
Seizure survey

Clinical Assessment

- Endocrine testing
- MRI
- Neuropsychological testing
- Genetic/ Dysmorphology
- Behavioral Audiology/ ABR / ENT
- Psychiatric Evaluation
- Neurological Assessment
- Dental Examination
- Ophthalmology
- Orthopedics
- GI

Our Approach

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De-identification
Data for statistical analysis
DNA for sequencing
Cell lines for drug testing
Ongoing Assessment

• Development
  – BASC
  – Social Impairment
  – Executive Function
  – Autism

• Natural History
  – Education
  – Living situation (location, marriage, children)
  – Employment

• Medical Records

Next Gen Phenotyping

• All conditions
  – Seizures Sid Atkinson
  – Autoimmune disorders Ed Brooks
  – Autism Louise O’Donnell

• 18q-
  – Brain volumes, DMN, DTI Jack Lancaster

• Tetrasomy 18p
  – Bone density Alvaro Moreira

www.pediatrics.uthscsa.edu/centers/chromosome18

Management Guides

18q- Molecular Variability
Individually useful information

97% dysmyelination of the brain

What is the chance that this person has dysmyelination?

\[ \text{Chance of dysmyelination} = 97\% \]

= population risk

Our Approach

- Clinical
  - Investigative
  - Defining standards of care
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  - Identifying key genes
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Molecular breakpoint data
Molecular breakpoint data

18q-

Pitt-Hopkins syndrome
- Severe intellectual disability
- <18mo. skills
- Microcephaly
- Autistic behaviors
- Epilepsy
- Hyperventilation

TCF4

Genotype / Phenotype

Subject 1

Subject 2

Subject 3

Subject 4
18q Phenotype Regions

Gene Profiling
- Eliminate normal variants
- Animal models
- Single gene disorders

Chromosome 18 Dosage Sensitive Genes

263 Genes
194 variants
24 risk factors
24 dosage sensitive
(21 unknown)

The Role of Key Genes

18p = 18p- & Tetrasomy 18p
- EMILIN2
  Andrew Meyer
- SMCHD1 - FSHD2
  Silvere Van der Maarl
- AFG3L2 - SCA28
  Sarah Hunt

18q = 18q-
- NET01 – executive function
  Georgianna Gould
- MBP + ?
  Danna Lehman
- TCF4
  Steve Haggarty