Current Clinical Research in PMS

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Seaver Autism Center for Research and Treatment
Icahn School of Medicine at Mount Sinai
### Advances in autism genetics: on the threshold of a new neurobiology

**Brett S. Abrahams and Daniel H. Geschwind**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s) associated with the syndrome</th>
<th>Proportion of patients with the syndrome that have an ASD</th>
<th>Proportion of patients with an ASD that have the syndrome</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>15q duplication — Angelman syndrome</td>
<td>UBE3A (and others)</td>
<td>&gt;40%</td>
<td>1–2%</td>
<td>101–103</td>
</tr>
<tr>
<td>16p11 deletion</td>
<td>Unknown</td>
<td>High</td>
<td>~1%</td>
<td>20, 35, 44</td>
</tr>
<tr>
<td>22q deletion</td>
<td>SHANK3</td>
<td>High</td>
<td>~1%</td>
<td>21, 22, 104</td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome</td>
<td>CNTNAP2</td>
<td>~70%</td>
<td>Rare</td>
<td>37</td>
</tr>
<tr>
<td>FragileX syndrome</td>
<td>FMR1</td>
<td>25% of males; 6% of females</td>
<td>1–2%</td>
<td>105</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Several loci</td>
<td>25%</td>
<td>Rare</td>
<td>106</td>
</tr>
<tr>
<td>Potocki-Lupski syndrome</td>
<td>Chromosome position 17p11</td>
<td>~90%</td>
<td>Unknown</td>
<td>107</td>
</tr>
<tr>
<td>Smith–Lemli–Optiz syndrome</td>
<td>DHCR7</td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>MECP2</td>
<td>All individuals have Rett syndrome</td>
<td>~0.5%</td>
<td>109</td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td>CACNA1C</td>
<td>60–80%</td>
<td>Unknown</td>
<td>24</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 and TSC2</td>
<td>20%</td>
<td>~1%</td>
<td>110</td>
</tr>
</tbody>
</table>
Novel Therapeutics

Disease → Gene Discovery → Model Systems → Pathophysiology → Drug Development → Novel Therapeutics
## Implications for treatment

<table>
<thead>
<tr>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="" alt="Before image" /></td>
<td><img src="" alt="After image" /></td>
</tr>
</tbody>
</table>

*seaver autism center for research & treatment at mount sinai*
Challenges for Clinical Trial Readiness

- Need validated measures specific to syndrome/phenotype
  - Comprehensively phenotype patients
  - Clarify natural history of illness to identify appropriate targets
  - Establish sensitivity to change over time
  - Validate across age groups and level of intellectual function

- Need new instruments
  - Adapt existing tools
  - Develop objective measures

- Need to focus on functional assessments
  - Motor skills
  - Language
  - Cognitive function
Clinical Outcome Assessments

- Patient reported
- Caregiver reported
- Clinician reported
- Composite instruments
- *Objective tests*
Potential Biomarkers for Clinical Trials

- EEG: evoked and event related potentials
- Neuroimaging
- Eye tracking, pupillometry
- Sensory gating – prepulse inhibition
- Protein synthesis assays
Electrophysiological Markers

- Identify subtypes of neurodevelopmental disorders based on excitatory/inhibitory (E/I) profiles
- Inform personalized treatment approaches
- Monitor treatment response and determine optimal responders
- Identify associations between neurophysiological responses and clinical outcomes

Paige Siper, PhD
Visual Evoked Potentials

- VEPs are extracted from ongoing EEG through signal averaging
- Reflect the sum of excitatory and inhibitory postsynaptic potentials
- Three electrodes applied to the scalp with an active electrode over the visual cortex
- $P_0$ represents activation of the primary visual cortex from the LGN
- $N_0$ represents excitatory postsynaptic activity spreading to the primary visual cortex
- $P_1$ reflects inhibitory postsynaptic activity
Transient VEPs in PMS

Siper, PM

Seaver Autism Center for Research & Treatment at Mount Sinai
Auditory Event Related Potentials

Jennifer Foss-Feig, PhD
Sensory Reactivity in PMS (Short Sensory Profile)

Mieses et al., 2016

<table>
<thead>
<tr>
<th>Category</th>
<th>SSP Scores</th>
<th>PMS</th>
<th>ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tactile Sensitivity</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste/Smell Sensitivity</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual/Auditory Sensitivity</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Movement Sensitivity</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory Filtering</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Energy/Weak</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underresponsive/Seeks Sensation</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: * indicates a statistically significant difference.
Sensory Assessment for Neurodevelopmental Disorders (SAND)

Clinician-administered observation and corresponding caregiver interview capturing DSM-5 sensory reactivity symptoms in children with neurodevelopmental disorders

Siper, PM et al., 2017
Sensory Reactivity in PMS – SAND

Siper, PM

Seaver Autism Center for Research & Treatment at Mount Sinai
Communicative vocal sounds elicited greater activation in right superior temporal gyrus (STG) compared to non-communicative vocal sounds in the PMS but not idiopathic ASD group.
Tracts with reduced FA in the PMS group relative to idiopathic ASD in red-yellow (yellow = higher statistical significance; green = not significantly different between groups). No regions of increased FA in PMS group.
18 subjects with PMS underwent comprehensive evaluations.

Over 542 hours of audio recording from the home environment was collected using LENA.

3 hours of audio was randomly selected for each participant and analyzed by human transcribers.
Findings

How accurately does LENA distinguish the Key Child from all others?

<table>
<thead>
<tr>
<th>Human Transcriber</th>
<th>LENA System</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Key Child</td>
</tr>
<tr>
<td>Key Child</td>
<td>12,229 (40%)</td>
</tr>
<tr>
<td>All Other Sound Sources</td>
<td>2,662 (3%)</td>
</tr>
</tbody>
</table>

$k = 0.449 \ (p < 0.001), \ \text{95\% CI (0.443, 0.455)}.$

Rankine et al., 2017
Findings

How accurately does LENA distinguish Key Child speech-related vocalizations from non-speech sounds?

$\text{LENA System}$

<table>
<thead>
<tr>
<th>Human Transcriber</th>
<th>Child Vocalizations</th>
<th>Child Non-Speech Sounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Vocalizations</td>
<td>6,800 (84%)</td>
<td>1,313 (16%)</td>
</tr>
<tr>
<td>Child Non-Speech Sounds</td>
<td>1,609 (39%)</td>
<td>2,507 (61%)</td>
</tr>
</tbody>
</table>

$k = 0.455 \ (p < .001), \ 95\% \ CI \ (0.437, \ 0.473).$

Rankine et al., 2017
### Findings

#### What factors impact LENA performance?

<table>
<thead>
<tr>
<th>Key Child Inter-rater Agreement</th>
<th>Vocalization Inter-rater Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
</tr>
<tr>
<td>Age</td>
<td>.618 *</td>
</tr>
<tr>
<td>ADOS-2 Total Score</td>
<td>.125</td>
</tr>
<tr>
<td>ABC Inappropriate Speech Subscale Score</td>
<td>.247</td>
</tr>
<tr>
<td>RBS Total Score</td>
<td>.242</td>
</tr>
<tr>
<td></td>
<td>-577 *</td>
</tr>
<tr>
<td></td>
<td>-.134</td>
</tr>
<tr>
<td></td>
<td>-.567 *</td>
</tr>
<tr>
<td></td>
<td>-.242</td>
</tr>
<tr>
<td></td>
<td>.012</td>
</tr>
<tr>
<td></td>
<td>.596</td>
</tr>
<tr>
<td></td>
<td>.014</td>
</tr>
<tr>
<td></td>
<td>.333</td>
</tr>
</tbody>
</table>
Gait Analysis

Performed in real time and captured at 240 Hz using 16 electro-magnetic sensors. All output kinematic features of movement trajectories are analyzed from the head and upper/lower extremities. Gait is measured during two exercises: 1) walking spontaneously along a six foot marked path; 2) walking along the identical path circumventing a waist-high obstacle.
Characterization of the Statistical Signatures of Micro-Movements Underlying Natural Gait Patterns in Children with Phelan McDermid Syndrome: Towards Precision-Phenotyping of Behavior in ASD

Elizabeth B. Torres, Jillian Nguyen, Sejal Mistry, Caroline Whyatt, Vilemni Kalampratsidou and Alexander Kolevzon

n = 16 PMS; 11 controls

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Eye Tracking in PMS

Visual Paired Comparison
Rose et al, 2013

Gap-Overlap Task
Elison et al, 2013

Flicker Detection
Farzin et al, 2011

Pilar Trelles, MD
Dose-dependent effect of risperidone treatment in a case of 22q13.3 deletion syndrome

Augusto Pasini*, Elisa D'Agati, Livia Casarelli, Paolo Curatolo
Brain & Development (2009)

Lithium as a rescue therapy for regression and catatonia features in two SHANK3 patients with autism spectrum disorder: case reports

Sylvie Serret*, Susanne Thummier, Emmanuelle Dior, Stephanie Vesperini, Andrea Santos and Florence Askenazy

A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome

Alexander Kolevzon1,2,3,4,5,10*, Lauren Bush1,4,9, A Ting Wang1,2,4,5,10, Danielle Hapern1,4,10, Yitzchok Frank1,4,5,10, David Grodberg1,4,10, Robert Rapoport5,10, Teresa Tavassoli1,4,10, William Chaplin1, Latha Soony1,9 and Joseph D Buxbaum1,2,3,4,5,10
Molecular Autism 2014, 5:54

Is there an effect of intranasal insulin on development and behaviour in Phelan-McDermid syndrome? A randomized, double-blind, placebo-controlled trial

Renée J Zwanenburg1, Gianni Bosca1, Selma AJ Ruiter1, Jan H Dillingh1, Boudien CT Flapper2, Edwin R van den Heuvel3 and Conny MA van Ravenswaaij-Arts4,1
European Journal of Human Genetics (2016), 1–6

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A Double-Blind Placebo-Controlled Crossover Trial of IGF-1
A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome

Alexander Kolevzon1,2,3,4,5,10*, Lauren Bush1,4,10, A Ting Wang1,2,4,6,10, Danielle Halpern1,4,10, Yitzchak Frank1,4,5,7,10, David Grodberg1,4,10, Robert Rapoport5,9,10, Teresa Tavassoli1,4,10, William Chaplin11, Latha Soorya12 and Joseph D Buxbaum1,2,3,4,6,8,10

Mean Change in ABC Social Withdrawal

Mean Change in RBS-R Restricted Behavior Score
Can we use telehealth platforms to increase access to high quality behavioral/communication interventions for children with rare neurodevelopmental diseases?

- Surmount barriers to care
- Increase parent knowledge and efficacy
- Use as a platform for studying integrated treatments

Stages of PMSF Fellowship:

1. Training in rare disease research and assessment/treatment
2. Examine current “landscape” of behavioral/communication interventions for individuals with PMS
   - Literature review; Archival data analysis; Descriptive data collection to inform telehealth intervention development
3. Develop & pilot an integrated intervention
4. Conduct a larger trial of the integrated intervention

Allison Wainer, PhD
Complete a series of questionnaires related to perceptions about early intervention and parent-mediated intervention.

Watch short clips about existing telehealth interventions and progress monitoring tools.

Data will then be used to select and adapt the most acceptable & appropriate telehealth intervention.

The adapted intervention will serve as the behavioral approach for the multimodal intervention in Stages 3 & 4.

Stage #2: Community Based Participatory Research (in progress)
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- Yitzchak Frank
- Reymundo Lozano
- Hala Harony-Nicolas
- Silvia De Rubeis

*Dr. Buxbaum and Mount Sinai hold a shared patent for the use of IGF-1 in PMS

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- Thomas Frazier

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- Audrey Thurm
- Jon Bernstein
- Craig Powell
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- Lauren Ethridge

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- April Levin
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