Patient Perspective on Genetics-Enabled Drug Development

*The View from the PWS Community*

Theresa V. Strong, PhD

Director of Research Programs

Foundation for Prader-Willi Research
Prader-Willi Syndrome

• Complex neurodevelopmental disorder
• Prevalence 1/15,000 – 1/30,000
• Occurs spontaneously, affects males/females equally, all races and ethnicities
• Accurate diagnostic test - DNA Methylation detects >99% cases
• Defining feature: Hyperphagia

photos used with permission
Regardless of mechanism – unmethylated (paternal) allele is not represented

Hyperphagia, obesity, metabolic changes are similar across genetic subtypes

Genetic subtype differences: most striking with respect to risk of mental illness
**PWS region: 15q11-13**

Cassidy et al, Genetics Med 2012

~6Mb

2 common deletion breakpoints: +/- haploinsufficiency of 4 additional genes
Infancy and Early Childhood

- Hypotonia at birth - improves over time but never normalizes
- Assisted feeding typically necessary to ensure adequate nutritional intake
- Decreased muscle mass and increased fat mass apparent from infancy
- Developmental delay
- Weight begins to increase ~ 2 years old, even without a change in calories
Onset of hyperphagia is variable [4 -13+, average age 8]
Caloric requirement is lower than normal
Behavioral issues increase: OCD, cognitive rigidity, temper outbursts, anxiety
Underlying mechanism(s) driving hunger is incompletely understood; reliable biomarkers not available
Strict environmental control is needed to maintain acceptable weight
Burden of Disease

- PWS is life-threatening: morbid obesity and associated complications, accidents, choking, stomach rupture
- Individual with PWS and their family/caregivers typically limit social engagement and opportunities for independence, employment
- Significant impact on quality of life:
  - High caregiver burden by multiple measures
  - Individuals with PWS have high rates of depression
How can we ensure that genetic information is fully utilized to improve the quality of life for those with PWS?
Clinical Issues

- Growth hormone deficiency (100%)
- Hypogonatropic hypogonadism (~90%)
- Hypothyroidism (15-20%)
- Central adrenal insufficiency (15%)
- Hypoglycemia (10-20%)
- Osteopenia / osteoporosis (~50%)
- Scoliosis (50-70%)
- Sleep disturbance / narcolepsy
- Strabismus
- Developmental delay / intellectual disability
- Autism (30%)
- Seizures (~25%)
- Mental Illness – Bipolar disorder / psychosis, major depression
<table>
<thead>
<tr>
<th>Drug</th>
<th>Sponsor</th>
<th>Proposed target</th>
<th>Phase</th>
<th>Status</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin</td>
<td>Various</td>
<td>OXTR Appetite/behavior</td>
<td>1, 2</td>
<td>various</td>
<td>All</td>
</tr>
<tr>
<td>Carbetocin</td>
<td>Ferring Levo</td>
<td>OXTR Appetite/behavior</td>
<td>2</td>
<td>Completed, planning</td>
<td>Children</td>
</tr>
<tr>
<td>Tesomet</td>
<td>Saniona</td>
<td>Neurotransmitters Appetite/weight</td>
<td>2a</td>
<td>Q2 2017</td>
<td>Adults</td>
</tr>
<tr>
<td>AZP-531</td>
<td>Alize</td>
<td>Ghrelin, Appetite/weight</td>
<td>2</td>
<td>Completed, Ph3 planning</td>
<td>Adults</td>
</tr>
<tr>
<td>Beloranib</td>
<td>Zafgen</td>
<td>MetAP2, Weight/appetite</td>
<td>3</td>
<td>halted</td>
<td>12 &amp; up</td>
</tr>
<tr>
<td>Setmelanotide</td>
<td>Rhythm</td>
<td>MC4R, Weight/appetite</td>
<td>2</td>
<td>Completed</td>
<td>16 &amp; up</td>
</tr>
<tr>
<td>Diazoxide -CCR</td>
<td>Essentialis</td>
<td>K–ATP channel --appetite, behavior</td>
<td>2</td>
<td>Completed, Ph3 planning</td>
<td>5-20</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>INSYS</td>
<td>Endocannabinoid system, Appetite/weight</td>
<td>2</td>
<td>Planning</td>
<td>8-65</td>
</tr>
<tr>
<td>VNS</td>
<td>Holland</td>
<td>Vagus nerve – behavior</td>
<td>Pilot</td>
<td>Ongoing</td>
<td>Adults</td>
</tr>
<tr>
<td>tDCS</td>
<td>Butler</td>
<td>Electric stimulation - appetite</td>
<td>Pilot</td>
<td>Ongoing</td>
<td>Adults</td>
</tr>
</tbody>
</table>
Practical Challenges

- Limited population
- No quantitative biomarkers
- Genetic subtype influences
- Environmental influences on phenotype
  - Quality of care
  - Weight management
  - Access to interventions (e.g., GH)
Drug Efficacy

• Small population (Phase 3 ~100 participants), not likely to be powered for GWAS
• May be able to examine how known genetic variants impact efficacy
• Examine efficacy and/or stratify patients or dose prospectively
  – Oxytocin – small studies, mixed responses to date $OXTR$ variants
Clinical Experience - Phase 3 study of a drug designed to impact hyperphagia and weight in PWS

• Unexpected serious adverse event – fatal embolism

• Some indication that risk of thromboembolism is increased in PWS – insufficient data

• Known gene variants impact blood clot formation

• No stored DNA on trial participants, no consent

• Second fatal incident led to the company’s decision to suspend development
“PWS Genomes” Project

- Pilot - WGS of individuals with PWS
- Link data to information in Global PWS Registry
- Inform clinical management and drug selection (e.g., psychiatric drugs)
- Available to stratify for clinical trials
- Efficacy
- Safety
Family Engagement and Education - Challenges

- Complex genetics of the disorder
- Array of medical problems, terms
- Education about clinical trials, expectations
- Who are you educating? Parent/guardian or Participant (IDD)
- Reaching entire population - diversity
- Informed consent - conveying information that is useful, while not increasing burden
Opportunities

- Tight knit community with active advocacy organizations
- Advocacy organizations have a unique role and are often trusted partners
- This population is used to connecting through technology; and learning about PWS this way
- High level of motivation - Genetics has the potential to impact other aspects of clinical care in the short term
Strategies for Engaging and Educating

- Community advisory board
- Written materials aimed at different groups and educational levels – Information accessible in multiple ways:
  - Webinars, videos, live stream/recordings of conference proceedings, social media, downloadable reference materials
- In person – annual conferences, PWS clinics
Needs

• Patient friendly, graphical representations of genetic variants, risk assessment, etc, from definitive sources – adaptable to different disorders

• Need for best practices and ‘off the shelf’ models that can be widely used for education in rare disease communities

• Genetic information that stays with the individual
  – To understand disease variability, risk over the lifetime
  – To understand efficacy – most drugs will fail in clinical trials, and many patients will participate in more than one study
  – To understand longterm safety (Phase IV)
Summary and Lessons

- Genetic information, beyond diagnosis, has tremendous potential to improve clinical trial efficiency in rare disease
  - Trial design
  - Interpretation of findings
  - Safety
- Many challenges remain
  - Educating rare disease communities using approaches that are accessible, informative
  - Reporting back information in a responsible, useable manner
  - Limiting burden
  - Operational challenges if genetic information resides with patients
Acknowledgements

Foundation Prader-Willi Research
Jessica Bohonowych
Nathalie Kayadjanian
Lauren Schwartz

University of Alabama at Birmingham
Bruce Korf

Those with PWS and their families