Communicating Pharmacogenetic Test Results to Patients – What do They Want to Know?

The View from the PWS Community

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www.fpwr.org
Prader-Willi Syndrome

- Rare, 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
- Loss of paternally expressed, imprinted genes on chromosome 15q11-13

Cassidy et al, Genetics Med 2012
- 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
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 / mild to moderate ID
- Growth hormone - FDA approved therapy – improves linear growth and body composition
Late Childhood to Adult

- Onset of hyperphagia is variable [~8 yo]
- Caloric requirement is lower than normal
- Underlying mechanism(s) driving hunger is not well understood
- Currently no effective treatment for hyperphagia - Strict environmental control is needed to avoid morbid obesity
- Other clinical symptoms: Daytime sleepiness / sleep disruptions, scoliosis, incomplete sexual development, etc.
Mental Health and Behavioral Issues

- Behavioral issues: Cognitive rigidity, temper outbursts, anxiety, repetitive questioning, OCD symptoms
- As individuals enter adulthood - highly susceptible to psychosis (bipolar affective psychosis, espec UPD); major depression (deletion)
- Medication use common - SSRI, atypical antipsychotic, wake-promoting, ADHD—individuals may be very sensitive to dose (mood activation)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Sponsor</th>
<th>Proposed target</th>
<th>Phase</th>
<th>Status</th>
<th>Age</th>
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<tbody>
<tr>
<td>Oxytocin</td>
<td>Various</td>
<td>OXTR Appetite/behavior</td>
<td>1, 2</td>
<td>Various</td>
<td>All</td>
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<tr>
<td>Carbetocin</td>
<td>Levo</td>
<td>OXTR Appetite/behavior</td>
<td>3</td>
<td>Planning</td>
<td>Children</td>
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<tr>
<td>Tesomet</td>
<td>Saniona</td>
<td>Triple reuptake inhib Appetite/weight</td>
<td>2a</td>
<td>Completed, high drop out</td>
<td>Adults</td>
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<tr>
<td>Livoletide</td>
<td>Millendo</td>
<td>Ghrelin, Appetite / weight</td>
<td>3</td>
<td>Planning</td>
<td>12 &amp; up</td>
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<td>Beloranib</td>
<td>Zafgen</td>
<td>MetAP2, Weight / appetite</td>
<td>3</td>
<td>halted</td>
<td>12 &amp; up</td>
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<td>Rhythm</td>
<td>MC4R, Weight / appetite</td>
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<td>Completed</td>
<td>16 &amp; up</td>
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<tr>
<td>Diazoxide -CCR</td>
<td>Soleno</td>
<td>K –ATP channel --appetite, behavior</td>
<td>3</td>
<td>Planning</td>
<td>8 &amp; up</td>
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<tr>
<td>Cannabidiol</td>
<td>INSYS</td>
<td>Endocannabinoid system, Appetite/weight</td>
<td>2</td>
<td>Planning</td>
<td>7-17</td>
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<tr>
<td>GLWL-01</td>
<td>GLWL</td>
<td>Ghrelin, appetite / weight</td>
<td>2</td>
<td>Ongoing</td>
<td>16-65</td>
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</table>
Integration of Pharmacogenetic Information

• High level of interest from families
• Inform clinical management - drug selection and optimization of available psychiatric drugs
• Novel Therapeutics - **Efficacy**: Impact of known genetic variants on efficacy (eg OXTR variants)
• Novel Therapeutics – **Safety**: Impact of genetic variants on side effect profile (eg, drug metabolism, drug-specific risks)
Use of Pharmacogenetic Information - Challenges

• Complex genetics of the disorder - Array of medical problems, terms
• Conveying information that is useful, while not increasing burden
• Education - realistic expectations re: genomic testing
• Some physicians may not be comfortable interpreting pharmacogenomics results
Opportunities – rare disease communities

• 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 – Long term engagement
Rare Disease Community 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
  - Optimize clinical care / medical management
  - Understand disease variability, risk over the lifetime
  - Understand efficacy – most drugs will fail in clinical trials, and many patients will participate in more than one study
  - Understand longterm safety of new agents (Phase IV)
Future Plan: PWS Genome Analysis

• Genetic information, beyond diagnosis, has tremendous potential to improve clinical trial efficiency and optimize care in rare disease
  – Clinical management
  – New therapeutic development
• Incorporating genomic information into an ongoing natural history study
• Many challenges remain
  – Educating rare disease communities using approaches that are accessible, informative
  – Limiting burden
  – Reporting back information in a responsible, useable manner
  – Operational challenges if genetic information resides with patients
Thank you!

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Those with PWS and their families