# Patient Perspective on Genetics-Enabled Drug Development

*The View from the PWS Community*

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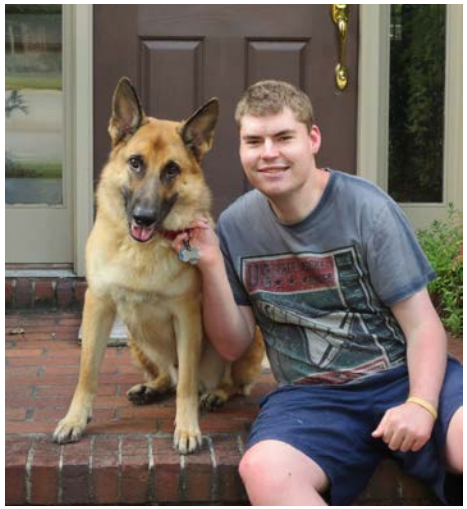
# Prader-Willi Syndrome

- 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



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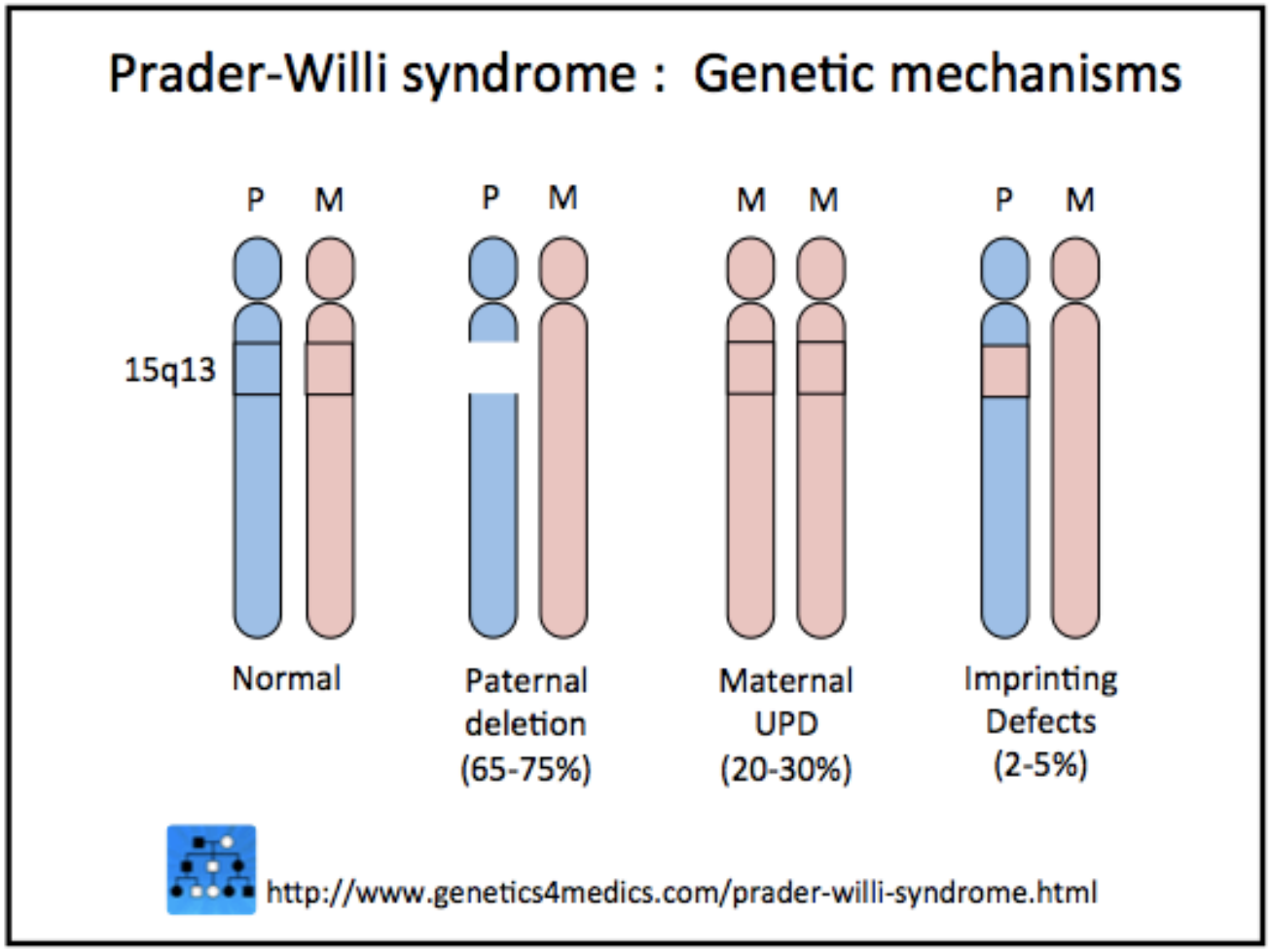
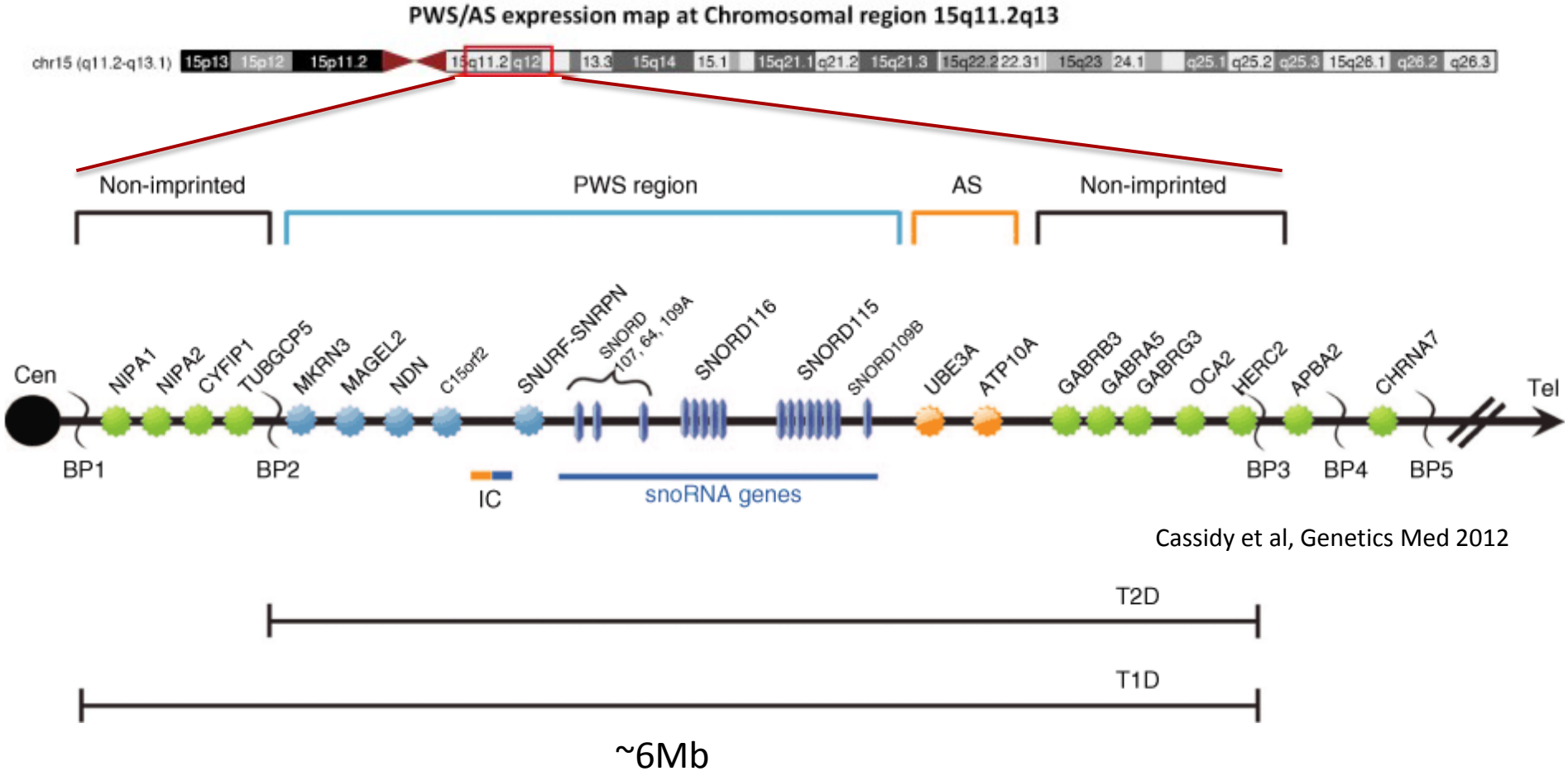



- Regardless of mechanism – unmethylated (paternal) allele is not represented
- Hyperphagia, obesity, metabolic changes are similar across genetic subtypes
- Genetic subtype differences: most striking with respect to risk of mental illness

# PWS region: 15q11-13




Cassidy et al, Genetics Med 2012

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

# Childhood to Adult Transition

- 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-threating: 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

# Where can genetics/precision medicine help?

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 hypgonadism (~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

Endocrinopathies

# Clinical Trials for PWS

| Drug | Sponsor | Proposed target | Phase | Status | Age |
|---|---|---|---|---|---|
| Oxytocin | Various | OXTR Appetite/behavior | 1, 2 | various | All |
| Carbetocin | Ferring Levo | OXTR Appetite/behavior | 2 | Completed, planning | Children |
| Tesomet | Saniona | Neurotransmitters Appetite/weight | 2a | Q2 2017 | Adults |
| AZP-531 | Alize | Ghrelin, Appetite / weight | 2 | Completed, Ph3 planning | Adults |
| Beloranib | Zafgen | MetAP2, Weight / appetite | 3 halted | suspended | 12 & up |
| Setmelanotide | Rhythm | MC4R, Weight / appetite | 2 | Completed | 16 & up |
| Diazoxide -CCR | Essentialis | K –ATP channel --appetite, behavior | 2 | Completed, Ph3 planning | 5-20 |
| Cannabidiol | INSYS | Endocannabinoid system, Appetite/ weight | 2 | Planning | 8-65 |
| VNS | Holland | Vagus nerve – behavior | Pilot | Ongoing | Adults |
| tDCS | Butler | Electric stimulation - appetite | Pilot | Ongoing | Adults |

# 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

# Drug Safety Profiling

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 thromoboembolism 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

GLOBAL PRADER-WILLI SYNDROME REGISTRY

# 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 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

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