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

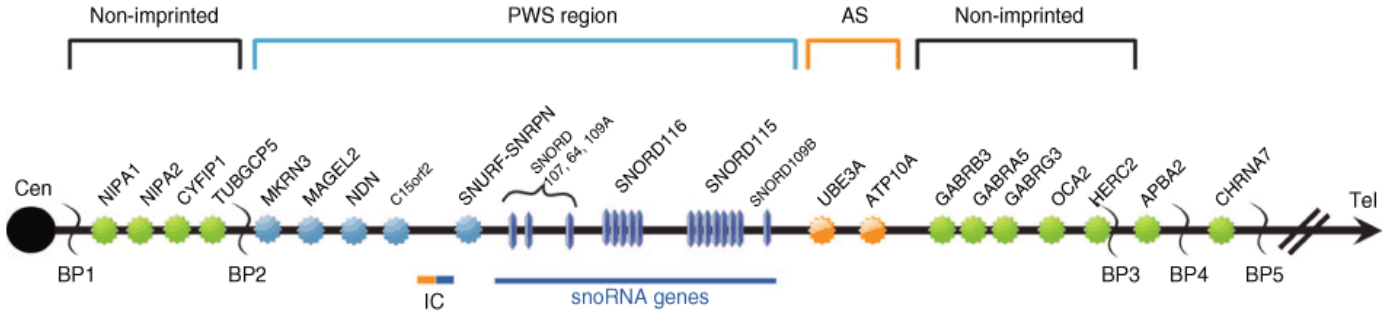
The View from the PWS Community

Theresa V. Strong, PhD
Director of Research Programs
Foundation for Prader-Willi Research

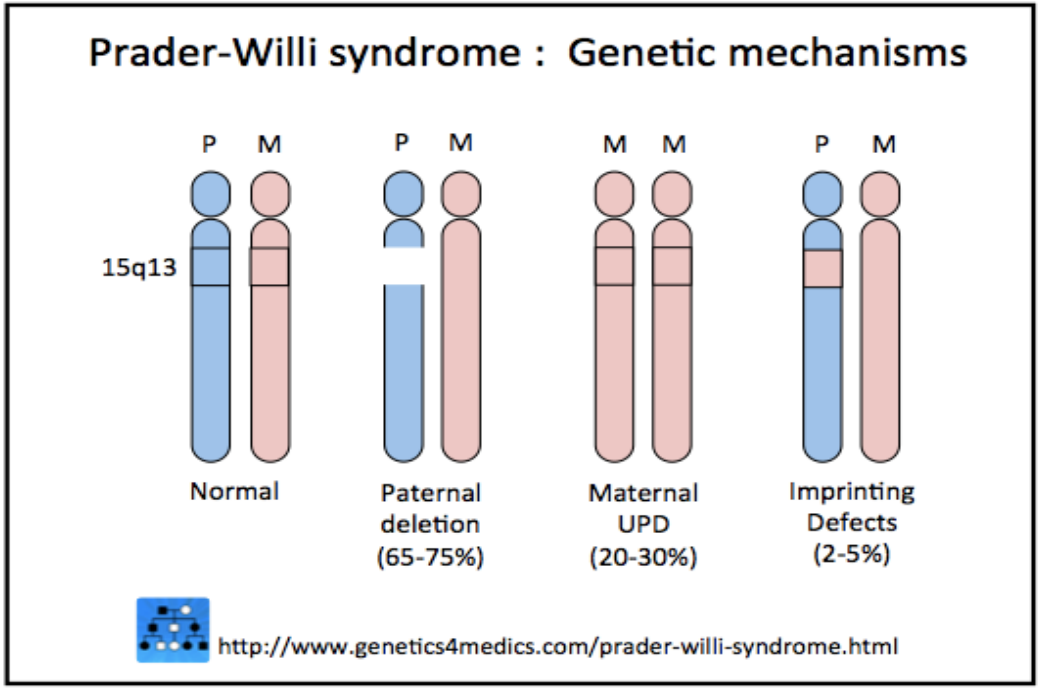
FOUNDATION FOR PRADER-WILLI RESEARCH
www.fpwr.org

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)

Active Clinical Trial Landscape

Drug	Sponsor	Proposed target	Phase	Status	Age
Oxytocin	Various	OXTR Appetite/behavior	1, 2	Various	All
Carbetocin	Levo	OXTR Appetite/behavior	3	Planning	Children
Tesomet	Saniona	Triple reuptake inhib Appetite/weight	2a	Completed, high drop out	Adults
Livoletide	Millendo	Ghrelin, Appetite / weight	3	Planning	12 & up
Beloranib	Zafgen	MetAP2, Weight / appetite	3 halted	Suspended	12 & up
Setmelanotide	Rhythm	MC4R, Weight / appetite	2	Completed	16 & up
Diazoxide -CCR	Soleno	K –ATP channel --appetite, behavior	3	Planning	8 & up
Cannabidiol	INSYS	Endocannabinoid system, Appetite/ weight	2	Planning	7-17
GLWL-01	GLWL	Ghrelin, appetite / weight	2	Ongoing	16-65

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

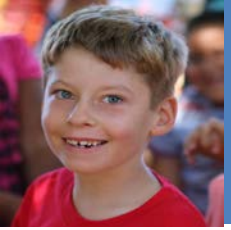
- Tight knit community with active advocacy organizations
- Advocacy organizations have a unique role and are often trusted partners
- This population is used to connecting through technology; and learning about PWS this way
- High level of motivation – Long term engagement

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!

<u>Foundation Prader-Willi Research Research Team</u>

Jessica Bohonowych

Priya Balasubramanian

Nathalie Kayadjanian

Lauren Schwartz

Those with PWS and their families

FOUNDATION FOR PRADER-WILLI RESEARCH