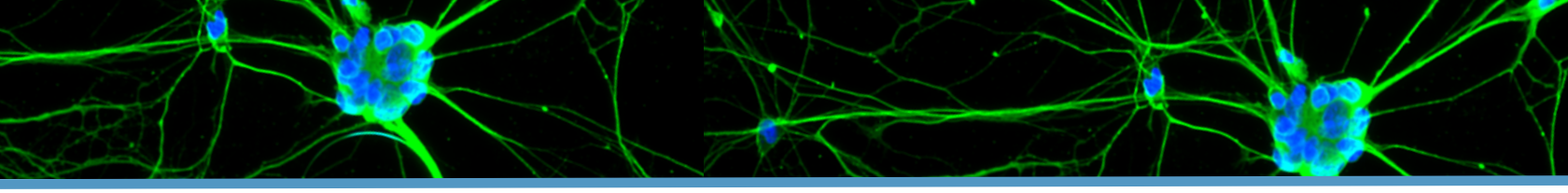

Prader-Willi Syndrome
Mental Health Research Strategy Workshop

March 1-3, 2015
DoubleTree Hotel
Bethesda, MD

FOUNDATION FOR PRADER-WILLI RESEARCH
Working Toward an Independent Future

FOUNDATION FOR PRADER-WILLI RESEARCH CANADA

COLORADO PRADER-WILLI SYNDROME ASSOCIATION
Still hungry for a cure.

*The **mission of the Foundation for Prader-Willi Research** is to eliminate the challenges of Prader-Willi syndrome through the advancement of research.*

Organizing Committee

Elisabeth Dykens, Ph.D.	Vanderbilt University
Anthony Holland, MRCP, FRCPsych	University of Cambridge
Elizabeth Roof, M.A.	Vanderbilt University
Lauren Schwartz Roth, Ph.D.	University of Washington
Theresa V. Strong, Ph.D.	University of Alabama at Birmingham

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Theresa V. Strong, Ph.D.	Scientific Advisory Board, Chair, FPWR Member FPWR Board of Directors, FPWR
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Susan Hedstrom	Executive Director, FPWR
Tanya Johnson	Member Board of Directors, FPWR

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PRADER WILLI SYNDROME MENTAL HEALTH RESEARCH STRATEGY WORKSHOP

Sunday, March 1, 2015 - Tuesday March 3, 2015
DoubleTree Hotel And Executive Meeting Center, Bethesda Maryland

***Purpose*:** To develop a focused research strategy to advance the science for mental health issues in Prader Willi syndrome. Mental health and behavioral problems remain a major challenge and o for individuals with the syndrome and their caretakers, with significant impacts on quality of life. Workshop participants will identify and prioritize key research questions in this area, as well as highlight current opportunities and needs. Recommendations will be made with respect to resource development, collaborative opportunities, and targeted research initiatives to facilitate the accomplishment of the mental health research goals identified during the workshop.

Sunday March 1st:

3:00 pm - **Hotel Check-In:** DoubleTree Hotel
8120 Wisconsin Avenue
Bethesda, MD 20814

4:00 – 5:00 pm Workshop Registration **Location:** 2nd Floor Foyer

5:00 - 7:00 pm **Welcome Reception** **Location**: Ballroom A
Cocktails and Hors d'oeuvres

Welcoming Remarks
Elisabeth Dykens, Ph.D., Psychology Professor, Director and Annette Schaffer Eskind Professor, Vanderbilt Kennedy Center, Co-Director for the University Center for Excellence in Developmental Disabilities

Perspectives from a PWS Parent and Psychologist
Lauren Schwartz Roth, Ph.D., Associate Professor, Department of Rehabilitation Medicine, University of Washington
FPWR Scientific Advisory Board and Board of Directors

Poster Session

Dinner on Your Own

Monday, March 2nd:

8:00 am	**Continental Breakfast**	**Location:** Imagination Break
8:30-5:00 pm	**Setting the Stage: Needs & Opportunities**	**Location:** Ballroom A

***8:30 to 12:00 pm**: Morning Session will include a Key Note presentation on the "state of the field" regarding mental health research in PWS, emphasizing areas of need and opportunity. This will be followed by presentations from experts in related fields of mental health/disability focusing on how research in other areas dovetail with PWS and how one might apply this knowledge towards new ways of conceptualizing and addressing mental health issues in PWS.*

8:30 - 9:30 am	**Key Note Presentation: Characterizing Behaviours to Understanding Mechanisms: Investigating and Developing Interventions for the Problem Behaviours and Mental Ill-Health Associated with PWS** Tony Holland, MRCP, FRCPsych., Health Foundation Chair, Professor Department of Psychiatry, University of Cambridge	
9:30 - 10:15 am	**Cognitive-Affective Interactions and Psychosis Risk (and Protection?): The Case of Chromosome 22q11.2 Deletion Syndrome** Tony Simon, Ph.D., MIND Institute and Professor, Department of Psychiatry, University of California, Davis	
10:15 - 10:30 am	**Break**	**Location:** Imagination Break
10:30 - 11:15 am	**The Polyvagaltheory and Autonomic Nervous System Function: Implications for the Understanding of the Behavioral Phenotype of PWS** Stephen Porges, Ph.D., Professor, Department of Psychiatry, University of North Carolina, Chapel Hill	
11:15 - 12:00 pm	**Outcome Measures for Treatment Trials in Fragile X Syndrome: Hurdles, Lessons and Progress** Elizabeth Berry Kravis, MD., Ph.D., Professor Departments of Pediatrics, Neurological Sciences, and Biochemistry, Rush University Medical Center	
12:00 – 1:15 pm	**Lunch**	**Location:** Hotel Restaurant

Monday, March 2nd Continued:

1:15 - 5:00 pm **Afternoon Session**

1:15 – 2:30 pm **Can We Prevent or Mitigate Psychosis in PWS?**
Moderator: Tony Holland, M.D.

Brief summary of the state of the field by the moderator and group discussion focused on highlighting similarities and differences with other genetic syndromes, how to best characterize, measure and intervene; and how to develop a research strategy to impact the onset, severity, or recurrence of psychosis symptoms in PWS.

2:30 – 5:00 pm **Identification of Key Issues and Research Priorities**
Break out working groups

Workshop participants will break into pre-assigned working groups. Groups will include representatives from a spectrum of mental health and disability research. Each group will identify research strategies to address several specific mental health and behavioral challenges in PWS previously identified to be the most pressing issues in the field. Participants will be asked to evaluate the identified issue, propose concrete research strategies/goals and develop actionable steps towards achieving those goals. Each group will meet for 1 hour. Each participant will be involved in 2 different working groups during this session.

2:30-3:30 pm	**Working Group I**	**Location:** to be announced
3:30-4:00 pm	**Break**	**Location:** Imagination Break
4:00- 5:00 pm	**Working Group II**	**Location:** to be announced
6:30- 8:00 pm	**Group Dinner – off site** 4930 Cordell Ave, Bethesda 0.45 mi from hotel	**Location:** Trattoria Sorrento

Tuesday, March 3rd

8:00 am	**Continental Breakfast**	**Location:** Imagination Break
8:30 - 2:00 pm	**Summary and Research Stategy Development**	**Location:** Ballroom A
8:30-9:30 am	**The Oxytocin Conundrum** *Moderator*: Sue Carter, PhD A brief review of the state of the field will be followed by a focused discussion among participants. The goal of this session is to identify next steps and facilitate research towards understanding oxytocin's potential role in regulating anxiety, behavioral and social issues in PWS.	
9:30- 10:00 am	**Break**	**Location:** Imagination Break
10:00- 12:00	**Overview of Working Group Discussions** Presentation of the Working Group recommendations from the previous day. Full group discussion to refine key issues and determine actionable next steps.	
12:00-1:00 pm	**Working Lunch** *(on site)*	
1:00-2:00 pm	**Research Plan Development** Final summary and development of recommendations for future research initiatives, fully utilizing existing assets and providing a plan to develop needed resources. This summary session will be the basis for a final report on key research questions and strategies to address mental health issues in PWS which have been identified during the workshop.	

Prader-Willi SyndromeOverview: Problem Behaviours and Psychopathology

PWS is a genetically determined neurodevelopmental disorder associated with a phenotype that changes across the lifespan. As an infant, s/he fails to thrive and is unable to suckle. As a child s/he may be slow to develop with evidence of an intellectual impairment. Over-eating /hyperphagia also begins to develop due to an impaired satiety response and/or because of the high reward value of food for PWS (Hinton et al 2006; Miller et al 2007). As the child develops, the characteristic physical features of PWS, which can be largely minimized by growth and sex hormone replacement, become apparent (de Souza et al 2013). As a teenager and adult, because of the propensity for over eating, the individual is at risk of severe obesity. This life course is also associated with a high risk for specific maladaptive behaviours and psychiatric disorders, which are not unique to PWS, but are more prevalent than is found in those with other neurodevelopmental disorders also associated with developmental intellectual disabilities. Rates of psychopathology are high and generally remain so over time (Einfeld et al 1999). This PWS 'behavioural phenotype' includes: a) repetitive and ritualistic behaviours (Dykens 2004) similar in character to those found in autistic spectrum conditions (Greaves et al 2006); b) temper outbursts that tend to occur at times of unexpected or unwanted change (Woodcock et al 2009); c) skin picking or other forms of picking that vary in nature and intensity over time; d) mood disorders that can be cyclical in nature and characterised by both hypomanic and depressive phases (Soni et al 2008); and e) psychotic illness that is predominately affective in nature and may develop as early as the teenage years with the occurrence of abnormal mental beliefs and experiences (Boer et al 2002; Soni et al 2008; Vogels et al 2003).

With some exceptions in terms of intensity and degree, and some differences across the lifespan (Butler et al 2004; Dykens and Roof 2008), the behavioural and psychiatric problems are found across PWS genotypes (Type I or II deletions at 15q11-13, maternal UPD of chromosome 15), with the most striking exception being the very high risk (~60%) for affective psychosis seen in adults with PWS mUPD (Boer et al 2002; Vogels et al 2006). Psychotic illness in those with PWS due to deletion is lower (~10%) and has been found to be associated with a maternal history of depression (Soni et al, 2008) and an interstitial chromosomal duplication of maternal origin (Webb et al 2008).
However Sinnema et al (2011) did not find a relationship between maternal depression and psychosis in PWS deletion subjects. The increased liability to non-psychotic mood disorders in PWS may be due to the absence of the snoRNA,SNORD115 (previously called HBII-52) and the effect on the serotonin 2C receptor (Kishore and Stamm 2006; Doe et al 2009). An extra expressed copy of a gene of the opposite imprint to that of the PWS gene(s) at the distal end of the PWS critical region has been proposed to account for the increased risk of psychotic illness in those with PWS mUPD (Webb et al 2008). In terms of treatment for these symptoms, Larsen et al 2013, found good clinical outcomes with on-going use of psychotropic medications. The two main genetic subtypes of PWS also differ in intellectual profiles and social functioning. The deletion group have better visuo-spatial skills and the mUPD group have higher verbal functioning (Roof et al 2000, Whittington et al 2004). Those with mUPD who have more features of autism spectrum disorders (Veltman et al 2005) have also been shown to be slower at cognitive processing (Stauder et al 2005).

The PWS behavioural phenotype is well recognised. The question now is to identify the shared or separate mechanisms that directly or indirectly link the PWS genotype to different aspects of the behavioural phenotype. Factor analysis suggests three groupings of behaviours: a) eating disorder, lying and stealing; b) repetitive and ritualistic behaviours and temper outbursts; and c) skin picking and mood disorders. Each of these three groups may have different causal mechanisms (Holland et al 2003). Impaired set-shifting ability and different patterns of brain activation have been shown to be associated with increased temper outbursts, when routines are disrupted, and to repetitive and ritualistic behaviours (Woodcock et al 2009, 2010, 2011). However, recent research suggests that, strict adherence to routines in childhood may lead to greater problems in later life (Bull et al 2014). Incidental findings of marked improvements in these behaviours in a pilot study of vagus nerve stimulation (VNS), which was undertaken to investigate its effect on eating behaviour, may indicate that the thresholds for when these behaviours are triggered by environmental events may be moderated through manipulation of the autonomic nervous system (Manning et al, in submission; Porges and Furman 2011). Tauber et al 2011, found positive effects in their study of intra-nasal oxytocin on social functioning and behaviour. However, no differences were found in a double blind placebo controlled trial (Einfeld et al 2014). The usefulness of intra-nasal oxytocin in PWS remains uncertain. Mechanisms that underpin skin picking behaviour are also unclear but are most often conceptualised as part of the obsessive

compulsive disorder. In an open label study of N-acetylcysteine, a modulator of the glutaminergic pathway, Miller et al (2014) found positive results in terms of reductions in the extent and severity of skin picking. Hall et al 2013, 2014, have proposed a functional explanation for self-injurious behaviours based on applied behavioural analysis. As possible neural and psychological mechanisms linking genotype to the PWS behavioural phenotype are identified, more targeted and effective treatments should become possible. Clinical assessment and formulation of the problem is essential to identify the interplay between behaviours of developmental origin, acquired co-morbid illness, or other disturbances (e.g. sleep disorders) with factors in the environment that might predispose to, precipitate and maintain the behaviours (e.g., Woodcock et al 2009).

Tony Holland, January 2015

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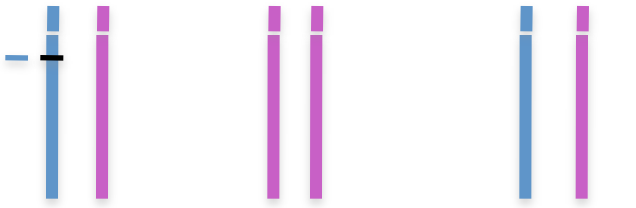
Genetics of Prader-Willi Syndrome

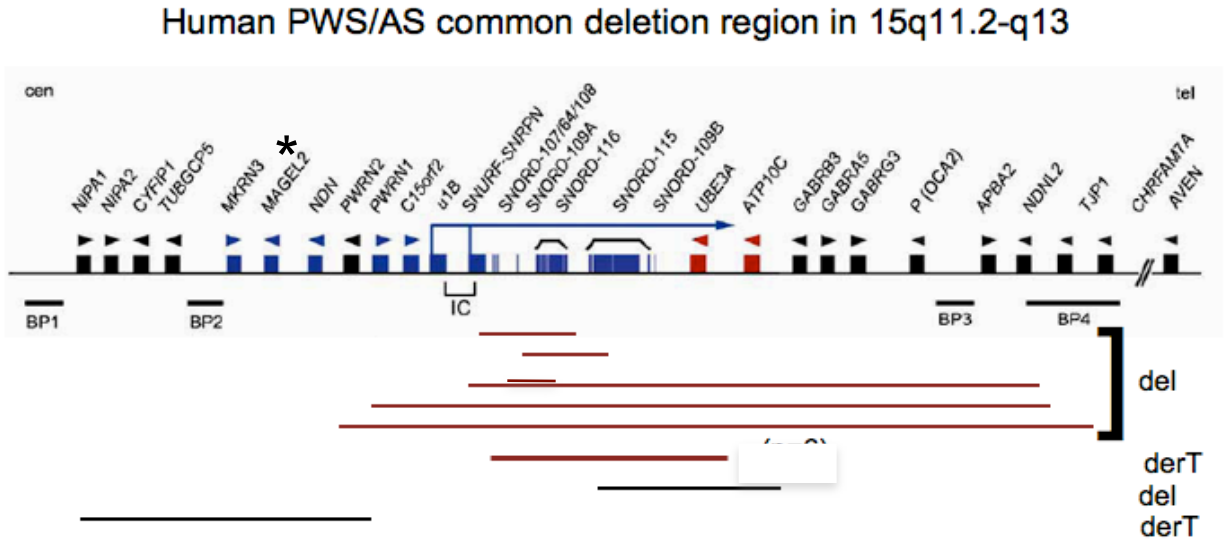


Paternal Deletion ~70%

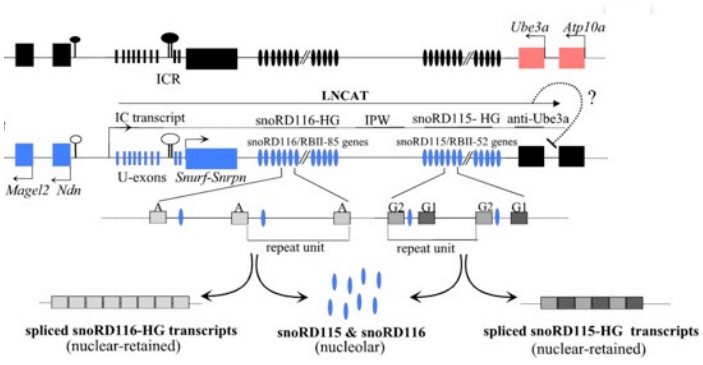
Maternal Uniparental disomy 25-30%

Imprinting defect 2-5%

PWS results when paternally active genes on chromosome 15q11-13 are lost. Generally, this occurs one of three ways: through deletion of the paternally derived chromosome 15, maternal uniparental disomy (where the paternal chromosome is lost upon rescue of a trisomy 15 conception), or a mutation at the Imprinting Center, which results in a paternal chromosome that carries a maternal imprint.



PWS region of chromosome 15: Paternally expressed genes are shown in blue, maternally expressed genes in red, and biallelically expressed genes in black. The bipartite imprinting center (IC) is proximal to the SNURF-SNRNP locus. Commonly, PWS deletions occur at one of two proximal breakpoints (BP); type I deletions encompass ~7Mb from BP1-BP3, type II deletions extend ~5Mb from BP2-BP3. **Below:** Rare cases with partial deletions (del) or reciprocal translocations (derT) that do (red) or do not (black) cause PWS narrow the causative region to the SNORD116 (previously called HBII-85) snoRNA cluster. Truncating mutations in the paternally active MAGEL2 gene (asterisk) lead to a "PWS-like" phenotype, including cognitive disability and autistic symptoms. Maternally inherited duplication of this region (Dup15) is the most common copy number variation associated with autism in the general population, accounting for ~1% of autism cases, and has also been associated with schizophrenia (Ingason et al AJPsych 166:408, 2011). Figure modified from Kanber et al EJHG 17:582 (2008); See also: de Smith et al Hum Mol Genet 18:3257 (2008), Sahoo et al Nat Genet 40:719, (2008), Duker et al, EJHG 18:1196 (2010) Bieth et al, EJHG 23:252, (2015).



Long noncoding RNAs and processed RNAs generated from the PWS region. Small nucleolar RNAs (snoRNAs) are generated from intronic sequences of the SNORD116 and 115 host genes: additional processed RNAs may include sno-lncRNAs and processed snoRNAs (not shown).

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FPWR Highlights

In 2014 alone, FPWR invested over $1.2 Million in Prader-Willi Research. Over the past 10 years, FPWR has supported nearly 100 high-quality research projects at top medical and research institutions around the world. At the heart of our research program is scientific collaboration which is encouraged through scientific workshops and meetings, resource development and resource sharing grants. Below are just a few of FPWR's accomplishments to date.

- FPWR has committed more than $5 million in PWS research, supporting projects ranging from basic science to clinical studies, and covering a variety of fields including genetics, obesity, neuroscience, model systems, behavioral research and therapeutics development and evaluation.
- FPWR supported projects have generated more than 70 publications in the medical literature to date, including publications in Nature Neuroscience, Journal of Clinical Investigation, Proceedings of the National Academy of Sciences, Molecular Cell, and Human Molecular Genetics.
- FPWR funded investigators have received more than $5 million in additional support from NIH and other government granting agencies to continue/ expand studies started with FPWR funds.
- FPWR has drawn new scientists into the PWS field, helping to launch several investigators in independent research careers.
- FPWR has developed the OneSMALL Step global fundraising campaign for PWS research, which raised over $1.5 million in 65 events around the globe in 2014. Over 8,000 participants attend One SMALL Step events each year.
- FPWR has supported scientific workshops and meetings to prioritize research [Resnick, 2013] and build consensus on clinical issues [Deal, 2013].
- FPWR supported projects have led to the development of key resources for use across the scientific community (new mouse models of PWS, the generation of induced pluripotent stem cell models; bioinformatics).
- We are supported by a strong global patient community; with over 900 members and a reach of more than 5,500 on social media outlets.

FPWR has developed the **Global PWS Registry** to aggregate clinical data, facilitate the completion of clinical trials, and guide the development of standards of care.

The purpose of the Global PWS Registry is to enhance the understanding of PWS by describing the full spectrum of PWS characteristics. The Registry will facilitate the completion of clinical trials and other research studies in the field of PWS. The Global PWS Registry is a comprehensive, secure database, compliant with U.S. Health Information privacy laws, FDA regulations. The registry is open to all individuals with PWS and can be completed by a parent /guardian, or by the person with PWS, if s/he is able. Registry participants will be asked to update their registry data annually. The information in the registry will be made anonymous and can be made available to researchers conducting clinical trials or research studies, companies developing potential drugs or other treatments for PWS. The Global PWS Registry is governed by a board that includes scientists, doctors and parent advocates, which will review and approve research studies. Patient data collection is set to start March 2015 with the goal of enrolling 1000 patients with PWS by the beginning of 2016.

GLOBAL PRADER-WILLI SYNDROME REGISTRY

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Thank you for your participation.