Advances in Pediatrics 63 (2016) 47–77

ADVANCES IN PEDIATRICS

Prader Willi Syndrome

Genetics, Metabolomics, Hormonal Function, and New Approaches to Therapy

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Keywords

• Imprinting defect • Hyperphagia • Childhood obesity syndrome
• Growth hormone

Key points

- Prader Willi syndrome (PWS) has a unique phenotypic and metabolic profile and remains the most common cause of syndromic obesity.
- Diagnostic advances have resulted in early detection of PWS in infants and young children, allowing for early treatment and improved outcomes.
- Growth hormone (GH) therapy has been shown to have therapeutic benefits in PWS, and requires close monitoring for adverse events.
- Several top priority areas for GH research in PWS include determination of optimal timing and dosage of GH treatment initiation in early life, longer-term data on safety and efficacy of GH in PWS populations across international databases and registries, further evaluation of GH effects on behavior and cognition across development, longer-term data on appropriate monitoring for sleep-disordered breathing post-GH initiation, and randomized controlled trials to evaluate the effects of GH therapy in concert with other novel therapeutic strategies including bariatric surgery.

Disclosures: None.

Funding: The authors are supported in part by a grant from the Foundation for Prader-Willi Research (A.M. Haqq, M. Freemark), grant from the Canadian Institutes of Health Research MOP 119504 (A.M. Haqq), and NIH 5T32HD043029-12 (K.A. Irizarry) to the Duke Department of Pediatrics.

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0065-3101/16/$ – see front matter
http://dx.doi.org/10.1016/j.yapd.2016.04.005

Learning objectives

1. Identify physical, hormonal, and biochemical features of Prader Willi syndrome (PWS).
2. Discuss the use of growth hormone therapy and risks and benefits of this and other treatments in PWS.
3. Review advances in therapeutic strategies for common comorbid conditions in PWS, including sleep disturbance, hyperphagia, and skin picking.

INTRODUCTION

Advances in clinical assessment, epidemiology, metabolomics, and genomics have provided new insights into the pathogenesis of obesity comorbidities, including insulin resistance, fatty liver disease, type 2 diabetes mellitus (T2DM), and cardiovascular disease; yet, we know very little about the factors causing people to become obese in the first place. In that regard, studies of genetic obesity models in humans and experimental animals are of critical value. Here we provide a review and update on Prader Willi syndrome (PWS), a unique genetic model of obesity associated with hypotonia, sarcopenia, cognitive dysfunction, hyperphagia, progressive fat deposition, and varying degrees of hypopituitarism.

GENETICS OF PRADER WILLI SYNDROME

Chromosomal localization

PWS is the most common syndromic obesity disorder, with a prevalence of 1 in 10,000 to 1 in 15,000 live births annually. Occurring equally in male and female individuals and detected in all races [1], it is characterized by infantile hypotonia and failure to thrive, followed by progressive obesity and hyperphagia in childhood. PWS results from lack of expression of paternally inherited genes in the region of chromosome 15q11.2-q13 [1]. Seventy percent of patients have a deletion of the paternally inherited region, whereas 25% have inherited 2 copies of the critical region on chromosome 15 from the mother; the latter is called maternal uniparental disomy. Five percent have abnormal imprinting or methylation that silences paternal genes in the PWS region.

Candidate genes

Chromosome 15q11.2 to 13 contains a number of genes that contribute to the PWS phenotype (Fig. 1).

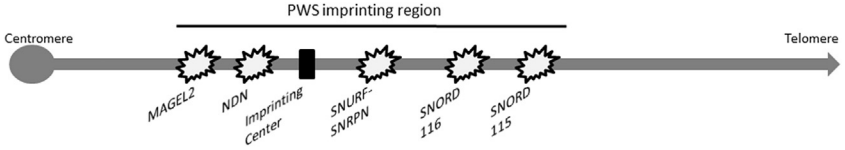

Fig. 1. Representation of chromosome 15q11 to 13.