



6th International IPWSO Conference  
Cluj-Napoca 21.06.07 - 24.06.07  
"Coming here, you will discover yourself, discovering others"  
Romanian Prader-Willi Association

ASOCIACIÓN MADRILEÑA  
PARA EL SÍNDROME DE  
PRADER-WILLI



## PHENOTYPING OF ADULT MICE WITH A DELETION OF THE PRADER-WILLI SYNDROME IMPRINTING CENTER

Anthony P. Goldstone <sup>1\*</sup>, Karen A. Johnstone <sup>2</sup>, Christopher R. Futtner <sup>2</sup>, Xeve Silver <sup>3</sup>, Clive Wasserfall <sup>4</sup>, Margaret L. Stoll <sup>5</sup>, Roger L. Reep <sup>5</sup>, Mark A. Atkinson <sup>4</sup>, Jim L. Resnick <sup>2</sup> & Daniel J. Driscoll <sup>1,2</sup>

<sup>1</sup> Division of Pediatric Genetics, <sup>2</sup> Dept. of Molecular Genetics, <sup>3</sup> AMRIS Facility, McKnight Brain Institute, <sup>4</sup> Dept. of Pathology, University of Florida; <sup>5</sup> Dept. of Physiological Sciences, University of Florida College of Veterinary Medicine; Gainesville, USA. \*Current address: MRC Clinical Sciences Centre, Imperial College, Hammersmith Hospital, London, UK

**INTRODUCTION:** PWS is caused by the loss of imprinted gene expression on chr 15q11-q13. The PWS-imprinting center (PWS-IC) is a positive regulatory element required for bidirectional activation of a number of paternally expressed genes in this region. Until recently, all mouse models of PWS were post-natally lethal, precluding them from studies of late onset phenotypes, such as obesity. We have established a strain-specific survival model of PWS through paternally inherited deletion of the PWS-IC on an FVB-B6 F1 background.

**METHODS:** PWS-IC<sup>+/-del</sup> mice were compared to wild-type littermates. Mice were housed in groups by sex and genotype. Body weight and food intake were measured twice weekly from weaning at 3 weeks until 22 weeks, and then weekly until 48 weeks. At 50 weeks, after a 6 hour fast, organs were removed for histology, and blood taken for measurement of insulin, leptin, ghrelin and IGF-1. Adult mice had *in vivo* brain (11 Tesla) and *ex vivo* whole body (4.7 Tesla) magnetic resonance imaging (MRI) to examine brain and body composition.

**RESULTS AND DISCUSSION:** Body weights for both male and female PWS-IC<sup>+/-del</sup> mice remained reduced compared to wild-type mice throughout the post-weaning period into adulthood (n = 10-16 per group). Compared to wild-type littermates, the body weight of male PWS-IC<sup>+/-del</sup> mice was 54% at 3 weeks and 52% at 48 weeks (mean ± SEM: 29.5 ± 0.8 vs. 55.8 ± 1.8g, P<0.001), and of female PWS-IC<sup>+/-del</sup> mice was 55% at 3 weeks and 63% at 48 weeks (21.5 ± 0.6 vs. 39.2 ± 3.1g, P<0.001). Female PWS-IC<sup>+/-del</sup> mice had delayed vaginal opening compared to wild-type females (39 vs. 27 days, n = 7, P<0.001).

Both sexes of adult PWS-IC<sup>+/-del</sup> mice had a large reduction in inguinal adipose tissue weight (by 45-83% at 50 weeks of age), and fat content was visibly reduced on MRI. PWS-IC<sup>+/-del</sup> mice had significantly reduced plasma insulin, leptin and IGF-1 levels compared to wild-type littermates, but no significant difference in plasma ghrelin (n = 6-12 per group). Post-weaning food intake (corrected for body weight) was in fact reduced in male PWS-IC<sup>+/-del</sup> mice up to 14 weeks of age, and in female PWS-IC<sup>+/-del</sup> mice up to the 48 week point.

At 50 weeks of age, PWS-IC<sup>+/-del</sup> mice had reduced body length (by 9-10%, P<0.001), reduced brain, liver, stomach, kidney and testes weights (by 10-54%, P<0.02) compared to wild-type mice. No histological abnormalities in the liver, stomach, duodenum, pancreas, kidney, salivary gland, ovary or testis were seen in PWS-IC<sup>+/-del</sup> mice on hematoxylin and eosin staining. No gross brain defects were seen in adult PWS-IC<sup>+/-del</sup> mice using MRI except for mild ventriculomegaly (n = 4 of each sex, aged 54 to 77 weeks), nor with thionine or myelin staining (n = 7 of each sex, aged 48 to 109 weeks).



IPWGO  
6th International IPWSO Conference  
Cluj-Napoca 21.06.07 - 24.06.07  
"Coming here, you will discover yourself, discovering others"  
Romanian Prader-Willi Association

ASOCIACIÓN MADRILEÑA  
PARA EL SÍNDROME DE  
PRADER-WILLI



**CONCLUSION:** As in humans with PWS, PWS-IC<sup>+/del</sup> mice display pre-weaning failure-to-thrive and growth retardation which persist into adulthood. However, by contrast these mice do not develop hyperphagia, obesity or infertility. In fact, adult PWS-IC<sup>+/del</sup> mice are resistant to the development of age-related adiposity. Current studies are addressing abnormalities in brain morphology or behavior, as they are observed in humans with PWS.