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Romanian Prader-Willi Association

ASOCIACIÓN MADRILEÑA  
PARA EL SÍNDROME DE  
PRADER-WILLI



## WHAT CAN WE LEARN FROM MOUSE MODELS TO BETTER UNDERSTAND PWS?

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**INTRODUCTION:** Mouse model is a powerful force in elucidating the genetic basis of human disease and in analysing the mechanisms of this disease at the physiological, cellular and molecular levels.

PWS is a complex disease resulting from a lack of expression of several genes located in the 15q11-q13 region. Because there is no reported PWS patient with a normal paternal copy of 15q11-q13 and an inheritance consistent with a single mutated gene, it is assumed that PWS is a multigenic syndrome. PWS results from the loss of expression of several paternally expressed genes including SNURF-SNRPN, NDN, MAGEL2, MKRN3, C15ORF, the C/D-box small nucleolar RNAs (snosRNAs) and some other non coding transcripts. The mouse 7C chromosomal region has conserved synteny with the human 15q11-q13 region: the genes, their organization and their imprinted regulation are conserved. Thus, mouse appears a good model to study the regulation and function of those genes, in regard to PWS.

**RESULTS:** Two types of mouse models have been generated. The first type is characterized by a global deficiency of paternal gene expression in the 7C chromosomal region. Four such potential mouse models, have so far been reported as PWS model. In all cases, the main feature of the observed phenotype is lethality during the first post-natal week, associated with various degrees of poor feeding, hypotonia and growth retardation. These observations are consistent with the feeding difficulties and failure to thrive that characterize PWS infants. Such models do not allow us to determinate the role of each gene in the PWS phenotype. The second type of mouse models is defined by specific inactivation of each candidate gene separately, in order to determine the role of each gene in the aetiology of PWS. Among all knock-out mouse models created, *Necdin* knock-out mouse models show postnatal respiratory distress leading to lethality in a fraction of pups at birth. Surviving *Necdin*-KO mice present phenotypic characteristics such as respiratory defects, a high level of scraping, a particular cognitive profile, sensory-motor defects which reveal striking parallels with some of the phenotypic manifestations in PWS patients. The *Necdin*-KO model is consequently a good model for specific symptoms of PWS. The physiological and cellular defects leading to these symptoms will be discussed.

**DISCUSSION:** The foreseeable consequences of such studies on mouse models will be to associate the clinical symptoms of PWS with specific genes and signalling pathways that are deficient in PWS and to suggest appropriate therapies for PWS or other pathologies that share symptoms with PWS (obesity, compulsive behavior...).