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Romanian Prader-Willi Association

ASOCIACIÓN MADRILEÑA
PARA EL SÍNDROME DE
PRADER-WILLI



BEHAVIOURAL ANALYSIS OF A MOUSE MODEL OF PWS

Dinko Relkovic^{1,2}, Trevor Humby², Karen A. Johnstone³, Jim L. Resnick³, Anthony J. Holland⁴, Lawrence S. Wilkinson² and Anthony R. Isles^{2,4}

¹The Babraham Institute, Cambridge, UK; ²Behavioural Genetics Group, Psychological Medicine, Cardiff University, Cardiff, UK ³Department of Molecular Genetics and Microbiology, Center for Mammalian Genetics, University of Florida, Gainesville, USA; ⁴Developmental Psychiatry, University of Cambridge, Cambridge, UK

INTRODUCTION: Prader-Willi syndrome (PWS) is a developmental disorder characterized by the lack of expression of maternally imprinted genes on chromosome 15q11-q13 either through paternally inherited deletion, chromosome 15 maternal uniparental disomy (mUPD) or imprinting centre (IC) mutations. Individuals are prone to a number of neuropsychiatric problems, including obsessive compulsive behaviour, mood instability, non-psychotic depression and psychosis. Exactly which genes in the PWS interval contribute to these behavioural phenotypes is not clear, and indeed the finding that those PWS patients with either IC mutation or mUPD are more likely to develop psychotic illness than deletion subtypes suggests that some psychiatric problems may not be due to loss of maternally imprinted gene expression, but the over-expression of paternally imprinted genes in or close to the PWS interval (Boer *et al.* 2001).

METHODS: We are using an established mouse model (PWS-IC^{del}) which recapitulates the molecular features of the IC mutation PWS genetic subtype. The work is focused on examining behavioural endophenotypes of relevance to PWS, including sensorimotor gating (prepulse inhibition and acoustic startle), reactivity to novel and fear inducing environments (locomotor activity and open field) and cognitive aspects of psychosis, such as preservation (reversal learning).

RESULTS: Gene expression analysis of brain samples confirms the absence of maternally imprinted gene expression in the PWS-IC^{del} mice. Additionally there is a relative over-expression of the paternally imprinted gene *Ube3a* and differences in the relative abundance of functional *5Ht2cr* splice variants. PWS-IC^{del} mice were generally hypolocomotor compared to wild type littermates, but also showed greater motoric skill on the rotarod test. There were no apparent difference in sensory motor gating, nor were there any differences in emotional behaviour in the open field test. Cognitive testing using a Y-maze based task indicated that PWS-IC^{del} mice made less errors-to-criteria in reversal learning. Analysis of latency data also suggested that during initial acquisition of the task the PWS-IC^{del} were quicker at key decision points of the task.

DISCUSSION: For the first time we have examined behavioural endophenotypes of relevance to the neuropsychiatric problems seen in PWS in a mouse model. The PWS-IC^{del} mice show specific differences in aspects of locomotor function, particularly a general hypolocomotor phenotype, something that is consistent with the condition. Furthermore we have demonstrated a cognitive difference in that the PWS-IC^{del} mice actually perform a Y-maze reversal learning task *better* than wild-type littermates. We suggest this may be due to altered motivational processes with respect to the food reinforcer in the PWS-IC^{del} mice.