

Oral Presentation

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## Linkage analysis for hydrocephalus in the LEW/Jms rat strain

H Jones\*, C Totten and D Mayorga

Address: Department of Pharmacology, University of Florida, Gainesville, Florida, USA

Email: H Jones\* - [hjones@college.med.ufl.edu](mailto:hjones@college.med.ufl.edu)

\* Corresponding author

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The Lew/Jms rat is an inbred strain with severe inherited hydrocephalus. The hydrocephalus starts in late gestation and occurs twice as often in males as females. The aim of this study was to locate the genetic loci linked to the hydrocephalus on the rat genome. Methods: Progeny were generated from two different backcrosses with Fischer F344 rats: one bred using male LEW/Jms rats for each pairing and the other using female LEW/Jms rats. Tissue was collected for DNA extraction and the brains were fixed and sliced for measurement of ventricular dilatation. Quantitative trait locus (QTL) mapping is a method whereby genetic loci for a quantitative trait are localized to specific chromosomal regions. A two-stage genome scan was performed on the hydrocephalic progeny and the same number of non-hydrocephalic progeny from both crosses, using a panel of DNA microsatellite markers previously determined to be polymorphic between the LEW/Jms and F344 strains. Linkage of chromosomal regions to hydrocephalus was determined from statistical association between genotype and phenotype ( $\chi^2$  and LOD score). Results: The backcross using male LEW/Jms rats resulted in 918 progeny of which 167 had severe or mild hydrocephalus (18.2%) and there were significantly more affected males than females (109:58,  $P < 0.001$ ). The backcross using female rats resulted in a total of 910 rats of which 182 had severe or mild hydrocephalus (19.9%). Again, there were more males than females with hydrocephalus (102:80) but it was not significant. The mean severity of ventricular dilatation was significantly different for the two crosses ( $0.58 \pm 0.01$ ,  $0.61 \pm 0.01$ ,  $P < 0.05$ ), and both groups had significantly smaller ventricles than the parental LEW/Jms strain ( $0.66 \pm 0.01$ ,  $P < 0.01$  and  $0.05$ ). QTL mapping produced different results for the two crosses. The backcross using two male LEW/Jms rats showed possible linkage on chromosomes 1, 5, 17 and 19. None reached the full significance required for a genome-wide scan and only Chrs 5 and 19 were sugges-

tive for significance. The backcross using two female rats showed possible linkage on Chrs 2, 4, and 17. There was full significance on Chr 2 with a LOD score of 3.91. Combining the data for both crosses also resulted in a locus that was close to full significance on Chr 17, LOD = 2.71. The linkage data for Chrs 1 and 2 showed sex specificity when analysed separately for males and females. Although not fully x-linked, investigations are ongoing to determine if there is partial linkage with the X chromosome. It is concluded that the expression of hydrocephalus in this strain is dependent on different genetic loci for male and female rats.