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Dissertations-Kurzfassung

Gene Expression Profiling in two substrains of the cy rat, a model of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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The Han:SPRD (cy/+) rat is a well described ADPKD animal model. Two substrains of this rat have been derived in 1990: the PKD/Mhm substrain in the Medical Research Center of University of Hedelberg, Germany and the PKD/US substrain in the Animal Care Facility at the University of Kansas Medical Center, US. The gene locus responsible for PKD has been mapped on chromosome 5 in both substrains. In this study a systematic analysis of the morphological data from 2 backcrosses derived form PKD/Mhm and PKD/US animals was performed. All animals were kept under identical conditions and examined at the same age. Statistical analysis of the extent of cyst formation assessed by histological examination and grading revealed that animals of the (PKD/Mhm x Lew) x Lew backcross have significantly more severe disease progression than animals of the (PKD/US x Lew) x Lew backcross. Thus, extrapolating results from one substrain to the other might be difficult. There was a clear influence of gender on disease severity in both crosses with males having more severe histological grades and higher kidney to body weight ratio. Maternal transmission of the PKD gene resulted in a more pronounced disease severity which supports evidence for the genetic imprinting effect in this PKD model. The main purpose of this study was to identify genes and molecular pathways whose expression patterns are altered in animals with PKD as well as expression differences in the two substrains of animals with different disease severity. Gene expression profiling using Affymetrix Rat Expression Set 230 A and Affymetrix defined protocols was performed in inbred PKD/US and PKD/Mhm animals. The SAS System version 8.02 was used for the statistical analysis of the data which included quality control (correlation analysis), normalization (mixed linear modeling) and identification of differentially expressed genes (gene-specific mixed model ANOVA analysis). Clustering analysis was performed on the genes with significant difference in expression levels. Gene expression profiling of PKD-affected animals and controls revealed 14 molecular pathways which had an increased percentage of misregulated genes when compared to the whole chip: apoptosis, TGF-ß, cilia structure, WNT-signaling, complement activation, solute carriers, cell cycle, JAK/STAT signaling, matrix metalloproteinases, inflammatory response, cysteine metabolism, eicosanoid synthesis, fatty acid degradation and hypoxia response. Most of these pathways have already been described in connection with PKD pathogenesis but the precise mechanism and the time-course of these expression changes remains to be elucidated in future experiments. Analysis of the expression differences between the two substrains of Han:SPRD (cy/+) rat (PKD/US and PKD/Mhm) revealed that there might be a difference in steroid metabolism between these lines. This might explain the observed difference in the disease severity in these substrains, but further investigations are required to confirm that.