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Dissertations-Kurzfassung

Characterisation of a modifier locus and gene expression profiling in the *cy* rat, a model of autosomal dominant polycystic kidney disease

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Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most common monogenetic human disorders. The cause of the disease progression in ADPKD is very variable even within the same family. This points to the existence of modifier genes. The aim of the present study was to investigate the existence of modifier loci influencing PKD severity and related quantitative renal phenotypes in the PKD/Mhm (cy/+) rat, a model for ADPKD. Furthermore, we wanted to identify possible candidates for modifier genes affecting disease progression and severity. In addition, gene expression profiling was performed in order to detect differentially expressed genes in PKD-affected and unaffected animals. For this purpose a backcross generation (BC1) was obtained by crossing PKD/Mhm (cy/+) and Lewis rats. Pheno- and genotype analysis was performed using the animals of the BC1 generation. The obtained data were compared with previously obtained results from WOK and BN backcrosses. In this work we succeeded to identify a modifier locus involved in the control of the PKD severity in our PKDxLew backcross on rat chromosome 10. In addition, we found a significant genetic linkage with the PKD grade on the distal part of rat chromosome 8. From 305 genes listed in the region of the QTL loci we selected 48 candidates for modifier genes based on their possible involvement in PKD pathogenesis and results of the gene expression analysis. The gene expression profiling of PKD-affected vs PKD-unaffected animals was performed using Affymetrix microarray rat set (RAE230A). Our analysis identified 318 misregulated genes in the PKD-affected animals. Moreover, using a gene set enrichment analysis, we have identified several major pathways misregulated in PKD. These pathways are apoptosis, cilia, complement activation, inflammatory response, hypoxia, JAK-STAT, TGF-beta signaling, Wnt, ribosomal proteins, proteasome degradation and solute carriers. Most of these pathways are well known to be involved in PKD pathogenesis while some have not been described yet in relation to PKD and this may give an additional information to better understand the disease development. The fact that two modifier loci controlling PKD grading were identified on two chromosomes suggests the existence of at least two modifier genes influencing PKD severity. It is possible that epistatic interactions between these modifier genes and between modifiers and PKDr1 gene determine the severity of PKD in this animal model. Identification and characterisation of possible modifier genes as well as misregulated molecular pathways should provide new insights into the PKD pathogenesis, development and disease variability. Moreover, the identified modifier genes might be candidates for a potential gene therapy while identification of misregulated genes/pathways might lead to development of new pharmacological or dietary interventions.