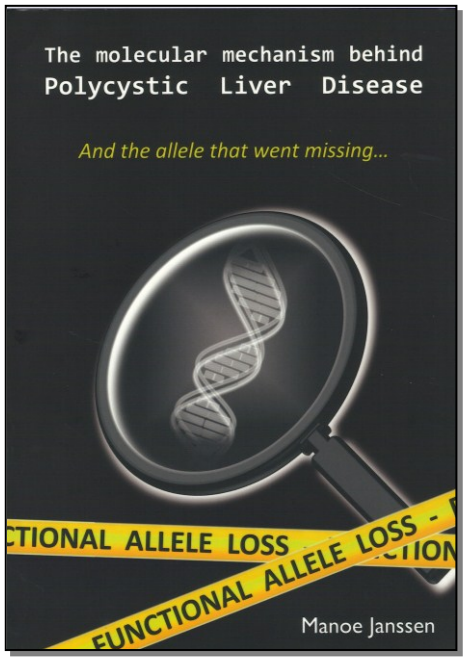

Samenvatting proefschrift
Manoe J. Janssen

'The molecular mechanism behind polycystic liver disease. And the allele that went missing…'

Promotiedatum: 20 maart 2013
Radboud Universiteit Nijmegen

Promotor:
Prof. dr. J.P.H. Drenth

Polycystic liver disease is a genetic disease in which patients develop many (>20) fluid filled liver cysts. These liver cysts are formed by the abnormal development of bile duct epithelial cells into closed structures which slowly expand over time. Although the liver function remains intact, these cysts can cause a strong increase in liver volume resulting in pain and pressure on abdominal organs. There are four genes known to be involved in liver cyst formation: PRKCSH, SEC63, PKD1 and PKD2. Patients in which one of the alleles of these genes is mutated have a genetic predisposition for cyst formation and a high risk to develop polycystic liver disease.
In this thesis we have studied the molecular mechanism underlining liver cyst formation. By analysing liver cyst tissue samples from 8 patients with a PRKCSH germline mutation we found that, in contrast to blood DNA, the PRKCSH wild type allele was no longer present in 76% of liver cysts. To understand the type of somatic mutation underlying cyst formation we used a genome wide array to identify changes in copy number and regions with LOH in cyst DNA. We obtained samples from three polycystic liver disease patients with different genetic backgrounds and found that LOH was caused by either telomeric copy number neutral (CNN) LOH or interstitial deletions, depending on the gene involved. Furthermore, this analysis showed that the breakpoints were unique in each cyst, indicating that each cyst developed independently through a separate somatic mutation.
Together these data show that somatic mutations play an important role in liver cyst formation and that cyst formation is recessive on a cellular level. A loss of function model may therefore be used to study cyst formation and to test potential medications in vitro. ◄

Aan de publicatie van dit proefschrift werd een financiële bijdrage geleverd door de Nederlandse Vereniging voor Hepatologie.

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