Variability of cholestatic liver disease in a family with 11 siblings and an ABCB4 defect

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Index Patient with biliary type cirrhosis

- 34y old female with biliary type cirrhosis was referred for liver transplantation
- First symptoms (pruritus, mild icterus) at age of 26 years
- All serological and virological markers unremarkable
- Initial histology showed fibrosis with ductopenic pattern => referred for idiopathic adulthood ductopenia
Marked clustering of cholestatic disease was present in the family.
Any known players in cholestatic disease?

- The following were dismissed:
  - IAD was dismissed since two siblings were likely to be affected in childhood
  - PFIC 1+2 due to late onset of disease and histopathological findings
  - PFIC 3 due to late onset of disease and normal/+ GGT and normal serum bile acid concentration
  - Allagille‘s syndrome, no features except ductopenia

- => Search for a new player was initiated
SNP Genotyping and Genome-Wide Linkage Analysis was Performed

Initial analysis (under the assumption that no consanguinity was present) revealed a variety of loci across the genome with a maximum lod-score of only 1.5
What to do next?

• More samples or more detailed pedigree information could enhance linkage:
• Fly to Transylvania?
• Dig in churches for old records?
• Suck more blood?
SNP Genotyping and autozygousity mapping demonstrated a segment on chromosome 7q21.

Genome-wide linkage of disease to 7q21.1-7q22, with lod-score of 3.01 and 3.88 was revealed. This computational data analysis used the information that the parents were consanguinous as fourth-degree once removed.
The identified haploblocks contained 149 annotated genes.

Severely affected family members were homozygous across this interval, mildly or unaffected were heterozygous.

All other genomic regions could be excluded to be linked to disease.

Among the 149 genes were \textit{ABCB1} and \textit{ABCB4}.
A mutation of p.R788 is predicted to affect PC transport activity.

p.R788 lies in the intracellular loop domain of the 2nd subunit of ABCB4, which is considered essential for coupling with the NBD-domain.
PC is reduced in bile

- Cholesterol / BA ratio normal
- PC / BA ratio reduced by 40%
- Indicating a reduced PC secretion in the patients

Gotthardt et al Hepatology 2008, in press
Allelic status correlates with severity of liver disease in 12 patients.
Cholestasis parameters from first symptoms until transplantation

Marked improvement of cholestasis with beginning of UDCA

Gotthardt et al Hepatology 2008, in press
Conclusions

- Allelic status of c.2362C>T / Arg788Trp is associated with ICP, subtle histopathological changes and severe cholestasis
- pArg788Trp causes cholestasis, ductopenia and biliary cirrhosis in adulthood
- Other genomic loci were excluded by linkage analysis
- PC content in bile is moderately reduced in these patients
- UDCA improved parameters of cholestasis in all affected patients studied
- Other factors may cause the variable course of disease in mutation homozygous