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Polycystic Liver Disease: the interplay of genes causative for hepatic and renal cystogenesis

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Polycystic liver disease (PLD) is a group of genetic disorders characterized by development of hepatic cysts derived from cholangiocytes as a result of mutations in disease-related genes. PLD can present as liver manifestations of autosomal dominant polycystic kidney disease (ADPKD) caused by mutations in *PKD1* and *PKD2* genes, and autosomal recessive PKD (ARPKD) caused by mutations in *PKHD1* gene. In autosomal dominant polycystic liver disease [ADPLD; also called dominantly inherited isolated polycystic liver disease (PCLD)], a form of PLD confined to the liver, mutations in the two most common genes, *PRKCSH* and *SEC63*, account for ~35% of clinically diagnosed cases. In addition, two other genes, *LRP5* and *GANAB*, have been implicated in development of ADPLD.^{1, 2} Recently, analyzing a cohort of 102 patients with no mutations in *PRKCSH* and *SEC63* Besse et al³ found two novel genes, *ALG8* and *SEC61B*, also responsible for hepatic cystogenesis in isolated PLD (Fig. 1A). Besides, this group confirmed the causative role of *GANAB*, and described a novel role for *PKHD1* in hepatic cystogenesis.

ADPKD and ARPKD belong to a group of diseases commonly termed ciliopathies. We named PKD-associated PLD as “cholangiociliopathy” emphasizing the nature of disease-targeted cells (i.e., cholangiocytes) and altered organelles (i.e., primary cilia).⁴ Indeed, while protein products of *PKD1* (polycystin-1 [PC-1]), *PKD2* (polycystin-2 [PC-2]) and *PKHD1* (fibrocystin [FC]) are localized to different cellular compartments, common place of their expression is the primary cilium of renal epithelial cells and cholangiocytes (Fig. 1).⁵ Mutations in PKD/PLD-associated genes lead to structural and functional abnormalities of primary cilia, altered expression and localization of PC-1, PC-2 and FC, and disrupted formation of their functional complexes; all subsequently initiate tissue remodeling resulting in renal and hepatic cystogenesis.

In contrast, the protein products of ADPLD-related genes, *PRKCSH* (glucosylase IIβ [GIIβ]) and *SEC63* (SEC63), were shown to be localized in the endoplasmic reticulum (ER) where they are involved in protein modifications and translocations.^{6, 7} Because isolated PLD clinically and pathophysiologically are similar to PKD-associated PLD, the ER was an unexpected organelle for localization of protein products of mutated genes. But accumulated evidence that PC-1 and PC-2 are clients of GIIβ and SEC63 resolved the mystery. Elegant

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work by Stefan Somlo's group at Yale University showed that $GII\beta$ and *SEC63* are required for expression of a functional complex of PC-1 and PC-2 with PC-1 being the rate-limiting component of this complex.⁸ They also demonstrated that the level of functional PC-1 following mutation of *PRKCSH* or *SEC63* is a major determinant of disease severity. Thus, a connection between genes causing ADPKD and ADPLD has been established.

Approximately 65% of clinically ascertained PLD patients had no mutations in *PRKCSH*, *SEC63* and *LRP5* implying the existence of un-identified causative genes of this disease. Indeed, a recent study by Besse et al. reported *ALG8*, *GANAB*, and *SEC61B* as well as an ARPKD-associated gene, *PKHD1*, as PLD-causative. The mutations in these four genes explained an additional 15% of cases in analyzed 102 probands in whom mutations in *PRKCSH* and *SEC63* were not found.³

ALG8, *GANAB* and *SEC61B* encode, respectively, α -1,3-glucosyltransferase, catalytic glucosidase II subunit α ($GII\alpha$, also known as PKD3), and β subunit of the SEC61. All of these proteins are integral ER membrane proteins and all three influence biogenesis and trafficking of PC-1 (Fig. 1B). Mutations in *ALG8*, *GANAB* and *SEC61B* reduce steady-state levels of PC-1 (Fig. 1C). However, among all these novel genes, *SEC61B* causes the most severe quantitative reduction of PC-1. Importantly, cholangiocytes appear to have a lower tolerance for reduced PC-1 level compared to renal epithelial cells. This finding may explain why cysts are formed in the liver but not in the kidney when loss-of-function mutations in PLD genes affect biogenesis of PC-1. The exception is *GANAB* since mutations in this gene result in cyst development not only in the liver but in the kidney as well. This is in agreement with a previously published observation that mutations in *GANAB* cause both ADPKD and ADPLD, and that the renal and hepatic cystogenesis is most likely driven by defects in maturation of PC-1.¹

In contrast to *ALG8*, *GANAB* and *SEC61B*, mutations in the ARPKD gene, *PKHD1*, contribute to isolated PLD without affecting biogenesis of PC-1, likely through aberrant interaction of PC-1 with FC.

Previously loss-of function mutations and pathogenic missense variants in *LRP5* gene were found in patients with isolated PLD.² *LRP5* encodes a low-density lipoprotein receptor-related protein 5 which functions as a co-receptor for Frizzled in the canonical Wnt signaling pathway. Despite the fact that Besse et al.³ did not discover any loss-of function *LRP5* mutations in the cohort of analyzed patients, missense variants in *LRP5* were found to co-exist with *PKHD1* variants suggesting that interaction of these two genes may contribute to hepatic cystogenesis in patients with mutated *PKHD1*.

Thus, as of today, the genetic landscape of isolated PLD or PKD-associated PLD includes nine causative genes (Fig. 1). Accumulating evidence suggests that *PKD1* and its protein product PC-1 are the key players in development of PLD. It is clear now that the hepatic cystogenesis as a result of mutations in 5 genes (i.e., *PRKCSH*, *SEC63*, *ALG8*, *SEC61B*, and *GANAB*) is associated with steady-state levels of PC-1 supporting the current hypothesis that PC-1 dosage determines cyst formation in the kidney and liver, as well as the severity of both PKD and PLD. However, described mutations can explain only 50% of

clinical cases of PLD suggesting that other genes and mechanisms might contribute to disease development and progression.

In summary, discovery of novel causative genes for isolated PLD and the interaction of their protein products with PC-1 suggest the complexity of PLD genetics and further support the hypothesis that PC-1 is a master regulator of intersecting pathways of renal and hepatic cystogenesis. Taking into account that mutations in a specific PLD-causative gene might underlie the degree of abnormalities of disturbed intracellular functions and, subsequently, the severity of disease, therapeutic approaches of individualized medicine for this disease could provide significant benefits for PLD/PKD patients.

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Fig. 1. Polycystic liver disease (PLD): interactions of genes and proteins. (A). Hepatic cystogenesis in isolated PLD and in PLDs associated with either ADPKD or ARPKD could be triggered by mutation in nine genes. Mutations in *PKHD1* cause ARPKD and isolated PLD; mutations in *GANAB* cause isolated PLD and ADPKD. Despite the genetic heterogeneity, all forms of PLD are characterized by the presence of multiple liver cysts. Scanning electron microscopic image shows the liver cysts in animal model of PLD, the PCK rat. (B). Schematic diagram depicts the site of localization of PLD-related proteins. Mutations in PLD-causative genes disrupt functional complexes formed by PLD-related proteins (i.e., PC-1 and PC-2; FC and PC-2) leading to hepatic cystogenesis. Proteins implicated in hepatic cystogenesis in isolated form of PLD are localized to ER where they involved in co- and posttranslational protein modifications. (C) Mutations in genes causative for isolated PLD lead to defective biogenesis of PC-1 resulting in its functional dosage. Abbreviations: PC – polycystin, FC- fibrocystin.