Molecular pathology and genetics of congenital hepatorenal fibrocystic syndromes

C A Johnson, P Gissen, C Sergi

The hepatorenal fibrocystic (HRFC) syndromes are a heterogeneous group of severe monogenic conditions that may be detected before birth. Commonly, HRFC syndromes present in the neonatal and paediatric age, with consistent developmental abnormalities mostly involving the liver and kidney. The changes include the proliferation and dilatation of epithelial ducts in these tissues with abnormal deposition of extracellular matrix. In this review, we examine the clinical features and differential diagnoses of this group of syndromes, including autosomal recessive polycystic kidney disease (ARPKD), juvenile nephronophthisis (NPHP), Meckel-Gruber syndrome (MKS), Bardet-Biedl syndrome (BBS), and Jeune asphyxiating thoracic dystrophy (JATD). Extrahepatic manifestations include mostly bone and central nervous system abnormalities, dysmorphic features, and developmental delay. Previously, it has been suggested that ARPKD, JATD, and Ellis-van Creveld syndrome (EvC) may arise from defects in differentiation in a common developmental pathway. We review recent molecular advances in the recessive HRFC syndromes and discuss this hypothesis.

The congenital hepatorenal fibrocystic syndromes are a group of severe, mostly autosomal recessive, monogenic disorders that are characterised by a common pathological appearance, with the presentation of multiple defects in the liver and kidney as the most predominant feature. In the liver, increased hepatic fibrosis often associates with cysts lined with biliary epithelium and a variable degree of intrahepatic biliary tract dilatation. Cystic lesions also affect the kidneys and their severity determines the clinical presentation and long term prognosis for many HRFC syndromes. It has been suggested previously that hepatic and renal malformations in ARPKD, JATD, and EvC result from defects in developmental pathways shared by many organ systems. In this review we provide a brief update on the molecular pathology and genetics of these disorders. We examine how recent molecular genetic advances in the characterisation of the ARPKD and NPHP genes provide insights into the "common developmental pathway" hypothesis for the aetiology of these clinically heterogeneous group of disorders. The molecular basis of a number of rarer HRFC syndromes remains unknown, and it is hoped that these insights might provide a rationale for the selection of candidate genes in the future, on the basis of protein function.

PATHOLOGY OF AUTOSOMAL RECESSIVE FIBROCYSTIC DISEASES

HRFC disease is characterised by changes in the parenchymal tissues of the liver, kidney, and sometimes pancreas or other organs. They include the proliferation and dilatation of epithelial ducts, and proliferative changes in the extracellular matrix of stromal connective tissue. One of the manifestations that has received intensive study are related to the ductal plate malformation of the liver and comprise proliferation and dilatation of the intrahepatic bile ductules, with a variable degree of fibrosis and cyst formation.

The intrahepatic bile ducts develop out of sheets of primitive hepatic epithelial cells in a pattern determined by the branching of the portal vein and surrounding mesenchyme. The primitive epithelial cells that are in direct contact with the portal vein mesenchyme transform into bile duct type cells by forming a single layer and later two layers (fig 1A). Development progresses by the formation of a cleft between the two layers of cells known as the ductal plate (at gestational weeks 9 to 12). In response to unknown developmental signals, the biliary cells migrate from the ductal plate into the portal mesenchyme, with biliary structures still in partial contact with the ductal plate (the remodelling ductal plate stage at gestational weeks 13 to 17, fig 1A). Finally, remodelled bile ducts are formed that are centrally located in the portal tracts, without contact with ductal plate remnants (the remodelled bile duct stage at gestational weeks 18 to 40, fig 1A). The unincorporated epithelium of the ductal plate then disappears. Any interruption in the remodelling of the ductal plate can result in the persistence of embryonic duct structures, termed the ductal plate malformation (fig 1B). The initial lesion in the liver is thought to be excessive ductular proliferation, characterised by the formation of multiple dilated periportal biliary ductules, presumably resulting from a defect in complex epithelial-mesenchymal interactions. The ductal plate malformation is a histopathological characteristic of a number of fibrocystic syndromes, such as MKS (fig 2A, B), hepatic-pancreato-renal or Ivemark syndrome (HPRS), and JATD.

Hepatic fibrosis may manifest either as a consequence of ductal plate malformation within
a monogenic fibrocystic disorder, in response to hepatocyte damage and subsequent necrosis, or as necrosis independent hyperstimulation of matrix producing cells. In the liver, the major cellular sources of extracellular matrix are activated Ito or hepatic stellate cells. These are fat storing cells that resemble fibroblasts, and in response to chronic hepatocyte damage they differentiate into myofibroblasts. These cells then secrete matrix proteins, such as interstitial collagen types I, III, IV, and laminin, and are responsible for the deposition and accumulation of the majority of the excess extracellular matrix in the fibrotic liver. In most cases, fibrosis consists of broad, collagenous fibrous bands surrounding normal hepatic lobules. The increase of the periportal connective tissue may compress portal vein radicles, leading to hypertension in the portal system. Cirrhosis is a common end stage for a number of monogenic disorders that result in hepatic insult owing, in part, to fibrotic and cystic changes.

Renal cysts can occur as manifestations of both non-genetic and genetic disorders. In the former case, non-hereditary lesions, consisting of an enlarged kidney filled with large cystic structures, can occur in response to ureteral atresia or obstruction. "Renal dysplasia" is the usual term to describe the abnormal differentiation of renal parenchyma, with the occurrence of microscopic abnormalities such as cystic dilatation of the renal collecting tubules in the kidney that prevents the normal development of nephrons, so that they remain as primitive ducts lined by undifferentiated epithelium and sheathed with thick layers of connective tissue. The kidney appears spongy, and there is no clear separation of the cortex and medulla (fig 2D). The prognosis of ARPKD is dependent on the degree of renal involvement and speed of disease progression to renal insufficiency and end stage renal failure (ESRF). A number of long term survivors have been reported.

The PCK rat model of polycystic kidney disease also develops renal and hepatic cysts, but in addition also displays ductal plate malformation of the intrahepatic bile ducts and overgrowth of portal connective tissue that resembles human ARPKD. Genetic analysis of the PCK rat has recently led to the identification of the human orthologue, PKHD1, of the rat gene. PKHD1 is predicted to encode a large protein of approximately 450 kDa, named fibrocystin, of unknown function (fig 3). Fibrocystin contains at least 10 copies of an immunoglobin fold-like domain (the IPT/TIG domain) found in plexins, transcription factors, and extracellular regions of receptor proteins that appear to regulate cell proliferation and cellular adhesion. Another group reported similar recent findings, with the identification of a PKHD1 gene product essentially identical, in both size and sequence, to fibrocystin that they name "polycystin-1". It will be interesting to elucidate the normal role of fibrocystin in the development and differentiation of collecting ducts in the kidney and bile ducts in the liver. Fibrocystin may be a receptor of growth signals because of the predicted extracellular domain, but could also participate in mediating cell adhesion. The unusual multiplicity of splicing variants for PKHD1 may be an important mechanism in regulating these functions by different protein isoforms.

In contrast, patients with ADPKD tend to present with large hepatic cysts (fig 2C), and the number of hepatic cysts can
<table>
<thead>
<tr>
<th>Inherited disorder</th>
<th>Gene(s) or loci, (protein product); mode of inheritance</th>
<th>Renal abnormalities: imaging and histopathology</th>
<th>Hepatic abnormalities</th>
<th>Other associated features</th>
<th>Prognosis</th>
<th>Differential diagnosis</th>
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<tr>
<td>AR or juvenile polycystic kidney disease, congenital hepatic fibrosis</td>
<td>PKHD1 (fibrocystin), AR</td>
<td>Antenatally diagnosed by ultrasonography with grossly enlarged bilaterally echogenic kidneys, absent urine, oligohydramnios and pulmonary hypoplasia. Cysts less than 3 mm in diameter extend from papillary tips to the surface of the cortex; lined by flattened epithelium representing dilated collecting tubules.</td>
<td>Congenital hepatic fibrosis, Caroli’s disease, and biliary dysgenesis. Hepatic disease more prominent if patients present as older children, and results in cirrhosis and portal hypertension</td>
<td>Neonatal presentation often with pulmonary hypoplasia</td>
<td>Majority of neonatally presenting patients die within 6 weeks of pulmonary disease and renal failure; 80% of survivors live until 15 years of age. All will develop ESRF by 20 years</td>
<td>Caroli’s disease</td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>NPHP1 (nephrocystin), loci NPHP2-4, AR</td>
<td>Ultrasound will detect small kidneys, uniformly increased echogenicity and cysts at the corticomedullary junction. Histology shows cortical atrophy with variable numbers of cysts at the corticomedullary junction (up to 1 cm in size). Histology shows tubular atrophy, interstitial fibrosis, and chronic inflammation; progression to glomerulosclerosis with markedly thickened basement membrane</td>
<td>Congenital hepatic fibrosis</td>
<td>Cone shaped epiphyses, retinal degeneration [Senior-Løken syndrome]</td>
<td>Patients develop ESRF within 5–10 years after presentation</td>
<td></td>
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<tr>
<td>Renal-hepatic-pancreatic dysplasia (Ivemark syndrome)</td>
<td>Autosomal recessive</td>
<td>May be detected on antenatal ultrasound showing bilaterally enlarged polycystic kidneys. Histology usually reveals cystic dysplasia</td>
<td>Congenital hepatic fibrosis and Caroli’s disease</td>
<td>Dilated pancreatic ducts, short ribs, polydactyly, polysyndactyly, cardiac anomalies, situs inversus, CNS abnormalities</td>
<td>Prognosis depends on the severity of renal disease</td>
<td>ARPKD, isolated MCDK</td>
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<tr>
<td>Joubert syndrome</td>
<td>Loci at 9q34, 17p11, AR</td>
<td>Renal changes of nephronophthisis often present in the subset of patients with retinal degeneration. Also associated with multicystic dysplastic kidney</td>
<td>Congenital hepatic fibrosis</td>
<td>Age progression or dysgenesis of cerebellar vermis with or without Dandy-Walker malformation, hypotonia, developmental delay and hyperpnoea/apnoea</td>
<td>Some patients die in infancy from breathing abnormalities; survivors have developmental delay with 25% developing renal insufficiency</td>
<td>SLS (NPHP), ARPKD, Joubert syndrome</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome</td>
<td>Loci at 13q13, 17q21-24, AR</td>
<td>Antenatal ultrasound diagnosis: bilateral gross renal enlargement, variable size cysts. In the peripheral cortex the cysts are very small, thin walled, with a thin zone of normal glomeruli, more centrally the cysts are larger. The largest cysts are in the medulla, up to several millimetres with thick fibromuscular walls separating them from collagenous stroma</td>
<td>Ductal plate malformation with peripartal fibrosis and biliary dysgenesis</td>
<td>Occipital encephalocele, other CNS malformations, polydactyly, cardiac malformations</td>
<td>Lethal in the neonatal period from respiratory and renal insufficiency</td>
<td>Goldenhar syndrome, ARPKD, Joubert syndrome</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td>Genes BBS2, BBS4, BBS5, loci at 11q13, 3p13, 2q31, AR or possible triallelic inheritance</td>
<td>Persistent fetal lobulation, small kidneys with clubbed calyces, cystic dysplasia; may be diagnosed on antenatal ultrasound scanning. Histology changes of nephronophthisis</td>
<td>Congenital hepatic fibrosis</td>
<td>Retinal degeneration, obesity, polydactyly and other limb deformities, hypogonadism</td>
<td>Renal disease leads to a need for dialysis and transplantation during adolescence and early adulthood</td>
<td>Prader-Willi syndrome</td>
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<tr>
<td>Jeune asphyxiating thoracic dysplasia</td>
<td>Possible locus at 12p, AR</td>
<td>Histology may show cystic renal tubular dysplasia, with or without glomerular sclerosis; could also have similar findings to nephronophthisis</td>
<td>May have neonatal cholestasis, Caroli’s disease, and congenital hepatic fibrosis</td>
<td>Short stature, narrow, long thorax with short ribs, micromelia, other skeletal malformations, lung hypoplasia, retinal degeneration, pancreatic cysts and insufficiency</td>
<td>Severity of thoracic involvement variable and improves with age; patients who survive beyond infancy may develop renal involvement and ESRF, which determines prognosis</td>
<td>Ellis-van Creveld syndrome, short rib-polydactyly syndromes (SRPS) types I, II, III</td>
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AR, autosomal recessive; MCKD, medullary cystic kidney disease; MCDK, multicystic dysplastic kidney; SLS, Senior-Løken syndrome; ESRF, end stage renal failure.
increase with the age of the patient, but the biliary malformations and hepatic fibrosis that are characteristic of ARPKD are absent in the majority of cases. Defects in two genes have been implicated in ADPKD. Mutations in \textit{PKD1}, localised at chromosome 16p13,\textsuperscript{12} appear to cause a more frequent and severe form of ADPKD in comparison to chromosome 16p13,\textsuperscript{13} that is implicated in autosomal dominant polycystic kidney disease (ADPKD). The juvenile form, \textit{PKD2}, has recently been shown to arise from mutations in \textit{UMOD}, encoding the glycoprotein uromodulin.\textsuperscript{14} In contrast, juvenile nephronophthisis is recessive and two genes \textit{(NPHP1 and NPHP4)} have been identified recently.\textsuperscript{27–29} Two other loci have been described for autosomal recessive nephronophthisis that affect children of different age groups.\textsuperscript{30} It is interesting to note that patients with Senior-Loken syndrome (SLS), which is an association of nephronophthisis and retinal dystrophy, were found to have identical mutations in either the \textit{NPHP1} or \textit{NPHP4} genes to the affected children with purely renal involvement. This variable phenotype may indicate the action of some modifier locus, although the presence of intrafamilial variation suggests that all patients may have some degree of retinal involvement. Both \textit{NPHP} and \textit{MCKD} share characteristic features, such as tubular atrophy, cyst development, and fibrosis of interstitial cells, although the kidneys are usually of normal size. Cyst formation tends to occur close to the papillary tips in MCKD and at the corticomedullary border in NPHP. Nephrocystin, the \textit{NPHP1} gene product (fig 3), appears to have a role in mediating cell adhesion.\textsuperscript{31} Functional studies of the murine homologue of nephrocystin indicate that it can interact with Crk associated substrate, p130(Cas), a protein known to participate in integrin mediated signal transduction and organisation of the actin cytoskeleton at sites of cell adhesion.\textsuperscript{32} Nephrocystin also contains a c-src homology 2 (SH2) domain, that is implicated in signal transduction (fig 3). In addition, nephrocystin has been shown to interact with nephrocystin-4,\textsuperscript{33} the protein product of the \textit{NPHP4} gene.

\textbf{Other renal cystic diseases in children}\n
Medullary cystic kidney disease (MCKD) and juvenile nephronophthisis (JNPH) have different modes of inheritance and different age of onset, but otherwise resemble one another. Corticomedullary cysts, fibrosis, and progressive renal failure are common features of MCKD. MCKD1 affects mainly adults, has an autosomal dominant inheritance pattern, and maps to chromosome 1q21.\textsuperscript{34} The juvenile form, MCKD2, has recently been shown to arise from mutations in the \textit{UMOD} gene, encoding the glycoprotein uromodulin.\textsuperscript{35}

![Figure 2](https://jmedgenet.bmj.com) Examples of the ductal plate malformation and cystic changes in the liver and kidney for a range of congenital fibrocystic disorders. Panels (A) and (B) show immunohistochemical detection of a mixture of cytokeratin epitopes to visualise ductal and bile duct cells. (A) Normal control, showing a portal vein branch surrounded by connective tissue and cells expressing cytokeratin forming a discontinuous, partially double layered ductal plate. (B) A ductal plate malformation (type I). Two mid to large sized portal tracts are shown that are close to the hilum hepatic and with central portal veins. The portal tracts show a cystic dilatation of the primitive biliary structures that are located at the limiting plate. There is a moderate increase in intraportal connective tissue between the endothelium of the portal vein and the ductal epithelium. Panels (C) to (E) show examples of cystic changes in the liver and kidney for a range of fibrocystic disorders. (C) Liver cysts or polycystic liver disease of an adult affected with autosomal dominant polycystic kidney disease (ADPKD). Cysts in ADPKD can be derived from any segment of the nephrons, from glomerular capsule to collecting ducts. The cysts can be numerous to countless, fluid or blood filled, and range in size from millimetres to centimetres in diameter. (D) The cut surface of a kidney from a child affected with autosomal recessive polycystic kidney disease (ARPKD). The kidney shows a sponge-like appearance, with dilated elongated channels at right angles to the cortical surface. The dilated elongated channels almost completely replace the medulla and cortex. (E) Diffuse cystic kidney dysplasia of a fetus (2nd trimester of pregnancy) affected with Meckel-Gruber syndrome, showing cysts throughout the cortex and the medulla. There are small and medium sized thin walled cysts that vary greatly in size. The lobar organisation of the kidneys is preserved but corticomedullary differentiation is mostly absent.
Skeletal malformation syndromes

Renal, hepatic, and pancreatic abnormalities are common features of Jeune asphyxiating thoracic dystrophy (JATD), although the consistent features are skeletal abnormalities, including a long and narrow thorax, metaphyseal irregularities, and shortness of the ribs and long bones. Polydactyly of both hands and feet is an occasional feature. Most severely affected cases have a fatal outcome in the perinatal period owing to asphyxia arising from a small thorax and hypoplastic lungs. Chronic renal failure occurs in the 20% of patients with JATD who survive beyond the neonatal period. Hepatic involvement can be severe, and can manifest as neonatal cholestasis or hepatic fibrosis, which leads to biliary cirrhosis and portal hypertension.

JATD appears to overlap with other chondrodysplasias in a phenotypic spectrum (table 1). There are particularly striking similarities between JATD and Ellis-van Creveld syndrome (EvC), which is characterised by short limbs, short ribs, postaxial polydactyly, and dysplastic nails and teeth. A differential diagnosis of JATD or EvC, on the basis of radiology alone, may not be possible. However, polydactyly, fingernail dysplasia, and congenital cardiac defects, usually a defect of primary atrial septation that forms a common atrium, are the primary features of EvC. In contrast, the main abnormality of JATD is renal. As for JATD, there are occasional developmental defects and dysplasias in the kidneys and liver for EvC. It has been suggested previously that JATD, EvC, and hepatic-pancreato-renal (HPRS) syndrome have overlapping features from one disease spectrum. The EvC gene has been mapped recently to chromosome 4p16 and the EvC protein has distant homology to the serine/threonine protein kinase family of proteins and contains a potential transmembrane region, but has at the present time no known function.

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder that displays pronounced phenotypic variability, with both developmental and progressive defects. The clinical manifestations are difficult to classify, but are characterised by retinal dystrophy, obesity, and postaxial polydactyly. Renal structural abnormalities, such as multicystic dysplasia, are a minor clinical feature of BBS and may not give rise to clinical evidence of renal disease. At least seven BBS loci have been identified, and the BBS6, BBS2, and BBS4 genes have been identified. The BBS4 gene product has significant homology to O-linked N-acetylglucosamine transferases, and the BBS4 protein may glycosylate proteins to modulate signal transduction during normal development.

Central nervous system malformation syndromes

Johann F Meckel first described an unusual association of renal cysts, polydactyly, and posterior encephalocele in 1822. Subsequently, this association was studied further by Georg B Gruber who used the label “dysencephalia splanchnocystica”. Meckel-Gruber syndrome (MKS) is a lethal malformation syndrome characterised by a frequent...
triad of central nervous system malformations (prosencephalic dysgenesis, occipital encephalocele, and rhombic roof dysgenesis), large multicystic kidneys, bilateral postaxial polydactyly, and fibrocystic changes of the liver\textsuperscript{42–46} (fig 2B, E). The rates of both cell proliferation and apoptosis were high in the remodelling ductal plate, and moderate in remodelled bile ducts.\textsuperscript{47} However, the malformed ductal plates in fetal livers with MKS had a low rate of apoptosis, and a lower expression of Fas, a transmembrane receptor that mediates apoptotic signals. In addition, MKS ductal plates had a dramatic increase in proliferative activity and high expression of Bcl-2, an anti-apoptotic protein, in comparison to control livers.\textsuperscript{48} It is particularly interesting that MKS, JATD, and HPRS syndromes are associated with postaxial polydactyly.\textsuperscript{49} This common malformation is suggestive that an imbalance between proliferative activity and cell death exists in these HRFC syndromes, since this could induce the apical ridge to produce an additional digit during limb morphogenesis. There appears to be considerable clinical and genetic heterogeneity in MKS,\textsuperscript{50–52} with at least three loci linked to the typical MKS phenotype of CNS malformations, cystic kidneys, and polydactyly,\textsuperscript{53–55} but none of the MKS genes have yet been identified. An alternative, although uncommon, neuropathological anomaly in MKS is a posterior fossa cyst in the form of a cerebellar Dandy-Walker malformation.\textsuperscript{56} Both the Dandy-Walker malformation and survival beyond the perinatal period are unusual findings in MKS, and may be characteristic of a distinct entity, such as cerebra-reno-digital or Goldston syndromes.”\textsuperscript{57–59}

The Dandy-Walker malformation, in association with aplasia or severe hypoplasia of the cerebellar vermis, is a feature of other conditions such as HPRS (table 1),\textsuperscript{60} short rib-polydactyly syndrome type II,\textsuperscript{61} and Joubert syndrome (JS).\textsuperscript{62–64} In JS, which is characterised by cerebellar hypoplasia, retinal dystrophy, and impaired psychomotor development, 35% of the subset of JS patients with retinal dystrophy develop renal cysts. The developmental link between the kidney and the CNS may depend upon inductive intercellular interactions during organogenesis\textsuperscript{65} and a complex interplay between the \textit{c-ret} proto-oncogene product, fibroblast growth factor receptor (FGF-R), and glial derived nerve factor (GDNF). All of these proteins are expressed in the embryonic renal and CNS tissues and appear to be important during organogenesis.\textsuperscript{66–68}

### FIBROCYSTIC CHANGES AND METABOLIC CONDITIONS

The association of renal cystic changes and liver disease is also a feature of a number of inherited metabolic disorders (table 2), and it is therefore important to differentiate these syndromes, which can be readily tested by biochemical means, from recessive HRFC syndromes. For example, Smith-Lemli-Opitz syndrome (SLOS) is caused by the deficiency of 7-dehydrocholesterol reductase (DHCR7), and the clinical features of SLOS include structural brain anomalies such as holoprosencephaly, microcephaly, cleft palate, syndactyly and postaxial polydactyly, cholestatic liver disease, and renal multicystic disease. Renal disease is characterised by microcysts or tubular dilations. It is particularly interesting that the pattern of anomalies seen for Smith-Lemli-Opitz syndrome (SLOS), such as cerebellar vermis aplasia and renal cystic changes, are similar to those for MKS.\textsuperscript{69–74} SLOS forms frustes subjects appear to have an even closer overlap with MKS. The discovery of the biochemical defect in this condition has led to the improved management of affected patients and emphasised the importance of sterols in embryogenesis, namely that cholesterol has a direct involvement in the hedgehog embryonic signalling pathway.\textsuperscript{75}

Glutaric acidaemia type II (GA2 or multiple acyl CoA dehydrogenase deficiency) is a mitochondrial disorder that results from a deficiency of either electron transfer flavoprotein (ETF)
or ETF-ubiquinone oxidoreductase (ETF-QO). Both are inter-
emediate electron carriers to ubiquinone in the mitochondrial 
respiratory chain. The complete deficiency of ETF-QO is asso-
ciated with multiple congenital anomalies, including cystic 
dysplasia of the kidneys, which has led to the misdiagnosis of 
MKS in the past. CNS anomalies include dysplasia of the cere-
bral cortex and abnormal neuronal migration, and liver his-
tology typically shows microvesicular steatosis and fibrosis.80 
Bile duct hypoplasia and cholestasis may also occur.

Zellweger syndrome (ZS), or cerebrohepatorenal syndrome, 
is the most severe variant of the Zellweger spectrum of dis-
orders.79 Patients have severe neurological deficit, progres-
sive hepatic and renal dysfunction, and skeletal abnormalities. 
Renal cysts can vary from glomerular microcysts to large cor-
tical cysts of glomerular or tubular origin. The liver includes 
architectural abnormalities that disrupt the arrangement and 
spacing of portal and central areas, with multiple central veins 
in each hepatic lobule. There may be a paucity of the intrahe-
patic bile ducts, and either severe fibrosis or micronodular cir-
rhosis in more advanced cases.

ANIMAL MODELS OF FIBROCYSTIC SYNDROMES

A number of animal models of fibrocystic diseases have been 
developed, including models of polycystic diseases that involve 
the liver and biliary tree. Mice with an insertional mutation79 
or gene targeting79 of the Pkd1 gene have a phenotype similar 
to human autosomal recessive polycystic kidney disease 
(ARPKD). The cpk (congenital polycystic kidneys) mutation 
on chromosome 12 in mice produces a lethal recessive form of 
PKD that is associated with hepatic cysts, and has been used 
as an animal model of human polycystic disease.80 The mouse 
cpk mutation is also associated with biliary ductal plate 
malformations, although the expression of the defect was 
modulated by the genetic background. A second, spontaneous 
recessive polycystic kidney mutation is jck (juvenile cystic 
kidneys),79 and a third, the bpk mutation in BALB/c mice, 
associates with renal cysts and epithelial hyperplasia of the 
infra- and extrahepatic biliary tracts.79

Transgenic mouse embryos that overexpress keratinocyte 
growth factor (KGF) develop hepatomegaly, biliary hyperpla-
sia, and cystic dilatation of renal collecting tubules resulting in 
polycystic kidneys.80 The correct expression of KGF is thought 
to be important for the mesenchymal-epithelial signalling 
required during normal embryogenesis.80 However, transgenic 
mice that overexpress the c-myc proto-oncogene, a regulator 
of cell proliferation, develop polycystic kidneys,80 as do knock out 
mice homozygous for deletions of the bcl-2 gene, which 
normally regulates apoptosis.80 In the latter two model 
systems, disruption of apoptosis or proliferation would be a 
reasonable primary cause of cystogenesis. However, the renal 
cystic abnormalities could equally arise as a pleiotropic effect 
of the genetic lesion in the mouse model. Until the molecular 
mechanisms that regulate epithelial differentiation and the 
balance of cell proliferation or apoptosis are known in more 
detail, it is difficult to assess the importance of the phenotypes 
in these models.

DISCUSSION

In this review, we have compared the variable pathological 
processes and phenotypes that are associated with several 
recessive HRFC syndromes. Several reviews have postulated a 
spectrum of “fibrocystic syndromes” that have a more or less 
similar aetiology,80 but that then subsequently diverge in 
terms of disease progression and clinical outcome, with var-
iable presentations of fibrosis, hepatocyte damage, cirrhosis, 
nefritis, and end stage organ failure. The suggestion has 
been made that the initial phenotypic similarity of HRFC syn-
dromes, at least in terms of histopathology, may arise from 
similar causative defects in the embryological pathways of 
life and kidney development that define tubular structures in 
epithelial cells.12 14 Developmental defects could therefore 
involve the disruption of cell-cell or cell-matrix interactions of 
epithelium and mesenchyme. In particular, biliary dysgenesis 
appears to be a key manifestation that distinguishes the HRFC 
syndromes (table 1) from the fibrocystic changes of metabolic 
conditions. Although renal cystic dysplasia is a common (but 
not obligate) feature of many conditions (table 1), the co-occurrence of biliary dysgenesis, in a form suggestive of 
ARPKD, appears to be limited to the group of HRFC 
syndromes that are inherited in an autosomal recessive 
pattern. In contrast, biliary dysgenesis is not a feature of 
metabolic conditions, but congenital hepatic fibrosis, cirrhosis, 
and renal cystic dysplasia are common end points in the pro-
gression of metabolic conditions (table 2). This probably indi-
cates that the latter features are the result of any form of insult 
to the liver and kidney, whether it is congenital or acquired. 
Renal cyst formation, for example, could be induced by an 
ergy deficit in the tubular epithelial cells, perhaps by 
disturbing the balance of cell proliferation and apoptosis, 
rather than by a specific defect in a developmental pathway. 
Clinical manifestations in Smith-Lemli-Opitz syndrome (table 
2) could be a result of cholesterol deficiency during fetal 
development.

Three plausible molecular mechanisms could explain the 
common features of HRFC syndromes: (1) the diverse proteins 
participate in a default developmental pathway for 
tubulo-epithelial differentiation during embryogenesis of different 
organ systems, and the specific expression of a lethal recessive form of 
PKD that is associated with hepatic cysts, and has been used 
as an animal model of human polycystic disease.80 The mouse 
cpk mutation is also associated with biliary ductal plate 
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in these models.
loci or genes for Bardet-Biedl syndrome.\footnote{3} BB56 encodes a protein that has significant sequence homologies to a class of chaperonins that facilitate protein folding, and other BB56 proteins could either form part of a chaperonin complex or interact with BB56 while still unfolded polypeptides. It will be interesting to determine the causes of genetic heterogeneity in Meckel-Gruber syndrome and Joubert syndrome: do the different encoded proteins interact or participate in the same developmental pathways?

In the future, further study of the structure and function of known proteins, such as fibrocystin and nephrocystin, will contribute to our knowledge of renal cystic dysplasia and biliary dysgenesis. It will then be clear whether or not a common pathogenetic pathway is involved in the range of congenital fibrocystic syndromes, and perhaps provide molecular mechanisms to explain the variability in the rates of disease progression and the severity of clinical phenotype. Understanding these mechanisms may allow novel pharmacological interventions or gene therapy procedures to be designed that would prevent renal cyst development, dysgenesis of the biliary tree, and hepatic fibrosis.

CONCLUSION

This review has identified a number of hepatorenal fibrocystic (HRFC) syndromes that are a group of severe malformation syndromes that cause fibrocystic changes in the liver and kidney, and that are inherited in an autosomal recessive manner. Biliary dysgenesis is a common feature of these conditions, which appears to differentiate them from metabolic conditions with fibrocystic changes. This diversity emphasizes the common nature of the embryogenesis in different organ systems, and suggests that tubulo-epithelial differentiation in the kidney and intrahepatic biliary system has a common molecular mechanism. The possible functions of the gene products in these pathways may involve signal transduction by both the extracellular matrix and soluble growth factors, and regulation of epithelial cell proliferation and complex epithelial-mesenchymal interactions that are disrupted in HRFC syndromes. The identification of these genes, and the assessment of the role of mutations, will be an important step in describing critical developmental pathways in molecular detail. Recent work has identified a number of integral membrane proteins that appear to participate in these pathways, but their exact molecular functions remain to be elucidated.

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Congenital fibrocystic syndromes


