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 dysstrophy (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 groups 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.
Figure 1 Embryogenesis of bile ducts. (A) Schematic diagrams of normal embryogenesis, progressing from the ductal plate stage (gestational weeks 9 to 12) to remodelled bile ducts of the portal tract (gestational weeks 18 to 40). Remodelling is thought to be the result of epithelial-mesenchyme inductive interactions. The embryonic structures are in cross section, with a branch of the portal vein (lumen in white) and a cuff of surrounding mesenchyme (dense red dots) at the central axis. The red lines represent the ductal plate. Refer to the text for further details. (B) Examples of biliary dysgenesis, resulting in ductal plate malformations owing to incomplete remodelling. The ductal plate (red lines) is in the form of either an interrupted circle or peripheral tubular structures. The ductal plate malformation is a characteristic manifestation of a number of congenital fibrocystic syndromes that are inherited in an autosomal recessive manner.

FIBROCYSTIC DISEASES OF VISCERAL ORGANS

Polycystic kidney disease in children

“Polycystic disease” was first described as long ago as 1856, and a spectrum of disease is now known to exist. Polycystic kidney disease includes autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). Congenital hepatic fibrosis is a characteristic feature of ARPKD, but may also be associated with other conditions. Liver histology shows portal spaces enlarged by periporal fibrosis, proliferation of biliary ducts, which can be dilated and tortuous, and ductal plate malformation or insufficient remodelling of the primitive intrahepatic biliary system. In some cases, abnormal multiple bile ductules can lose connection with the biliary system and dilate to form large cysts. Patients with ARPKD tend to present with congenital hepatic fibrosis and Caroli disease (known as the “combined” form of the disease or Caroli syndrome). The “pure” form of Caroli disease is characterised by multifocal dilatations of the larger, segmental intrahepatic bile ducts. Subsequently, patients can present with recurrent bacterial cholangitis because of bile stasis at the ectopias of the intrahepatic bile tree.

The main clinical manifestation of ARPKD is both ectasia and 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. The human PKHD1 gene 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 immunoglobulin 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 recent similar findings, with the identification of a PKHD1 gene product essentially identical in both size and sequence, to fibrocystin that they name “polyductin”. 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. Adjacent parenchyma develops interstitial fibrosis and glomerulosclerosis.</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>
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<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, renal 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, polysplenia, cardiac anomalies, situs inversus, CNS abnormalities</td>
<td>Prognosis depends on the severity of renal disease</td>
<td>ARPKD, isolated MCDK</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Loci at 9q34, 1p11; AR</td>
<td>Renal changes of nephronophthisis often present in the subset of patients with renal regeneration. Also associated with multicystic dysplastic kidney.</td>
<td>Congenital hepatic fibrosis</td>
<td></td>
<td>Some patients die in infancy from breathing abnormalities; survivors have developmental delay with 25% developing renal insufficiency</td>
<td>SLS (NPHP)</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 collaganeous stroma.</td>
<td>Ductal plate malformation with periperal 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>Goldston 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, hypogenitalism</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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<td>Jeune asphyxiating thoracic dysplasia</td>
<td>Possible focus 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, renal 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 syndrome (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 \( \text{PKD1} \), localised at chromosome 16p13,\(^a\) appear to cause a more frequent and severe form of ADPKD in comparison to chromosome 16p13,\(^b\) that is implicated in 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.\(^c\) 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.\(^d\) 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.

Other renal cystic diseases in children

Medullary cystic kidney disease (MCKD) and juvenile nephronophthisis (JNP) 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.\(^e\) The juvenile form, MCKD2, has recently been shown to arise from mutations in the \( \text{UMOD} \) gene, encoding the glycoprotein uromodulin.\(^f\) In contrast, juvenile nephronophthisis is recessive and two genes (\( \text{NPHP1} \) and \( \text{NPHP4} \)) have been identified recently.\(^g\) Two other loci have been described for autosomal recessive nephronophthisis that affect children of different age groups.\(^h\) 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 \( \text{NPHP1} \) or \( \text{NPHP4} \) 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 NPHP and 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 \( \text{NPHP1} \) gene product (fig 3), appears to have a role in mediating cell adhesion.\(^i\) 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.\(^j\) 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,\(^k\) the protein product of the \( \text{NPHP4} \) gene.

\( ^{(a)} \) Johnson, Gissen, Sergi

\( ^{(b)} \) Johnson, Gissen, Sergi

\( ^{(c)} \) Johnson, Gissen, Sergi

\( ^{(d)} \) Johnson, Gissen, Sergi

\( ^{(e)} \) Johnson, Gissen, Sergi

\( ^{(f)} \) Johnson, Gissen, Sergi

\( ^{(g)} \) Johnson, Gissen, Sergi

\( ^{(h)} \) Johnson, Gissen, Sergi

\( ^{(i)} \) Johnson, Gissen, Sergi

\( ^{(j)} \) Johnson, Gissen, Sergi

\( ^{(k)} \) Johnson, Gissen, Sergi
FIBROCYSTIC CHANGES AND MALFORMATION SYNDROMES

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 primarily 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...
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, choledochal cysts, biliary cirrhosis, and renal 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. This suggests a common metabolic defect that may be consistent with a mitochondrial disorder that results from a deficiency of either electron transfer flavoprotein (ETF) or multiple acyl CoA dehydrogenase deficiency.}

Table 2

<table>
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<tr>
<th>Metabolic condition</th>
<th>Deficient enzyme</th>
<th>Renal abnormalities</th>
<th>Hepatic abnormalities</th>
<th>Associated features</th>
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<td>Polyacetyl-CoA dehydrogenase deficiency</td>
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<td>Peroxisome biogenesis disorders: (a) Defect in function of all peroxisomal enzymes (b) Peroxisomal plasmalogen biosynthesis and branch chain fatty acid oxidation defects</td>
<td>Various peroxisomal enzymes</td>
<td>Congenital disorder of glycerolipid metabolism (Zellweger syndrome spectrum disorders, neonatal adrenoleukodystrophy, ZS, NALD, IRD, PMM2, phosphomannomutase)</td>
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or ETF-ubiquinone oxidoreductase (ETF-QO). Both are inter-
mediate 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 misdagnosis of
MKS in the past. CNS anomalies include dysplasia of the cer-
bral cortex and abnormal neuronal migration, and liver his-
tology typically shows microvesicular steatosis and fibrosis.66
Bile duct hypoplasia and cholestasis may also occur.

Zellweger syndrome (ZS), or cerebrohepaticrenal syndrome,
is the most severe variant of the Zellweger spectrum of
disorders.72 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-
rhois 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 mutationαα or
gene targetingαα 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.82 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),83 and a third, the bpk mutation in BALB/c mice,
associates with renal cysts and epithelial hyperplasia of the
intra- and extrahepatic biliary tracts.84

Transgenic mouse embryos that overexpress keratinoocyte
growth factor (KGF) develop hepatomegaly, biliary hyperpla-
sia, and cystic dilatation of renal collecting tubules resulting in
polycystic kidneys.68 The correct expression of KGF is thought to be important for the mesenchymal-epithelial signalling
required during normal embryogenesis.66 However, transgenic
mice that overexpress the c-myc proto-oncogene, a regulator of
cell proliferation, develop polycystic kidneys,67 as do knock out
mice homozygous for deletions of the bcl-2 gene, which
normally regulates apoptosis.74 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 cell death 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,10 but that then subsequently diverge in
terms of disease progression and clinical outcome, with vari-
able presentations of fibrosis, hepatocyte damage, cirrhosis,
nephritis, 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
liver and kidney development that define tubular structures in
epithelial cells.12,13 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
progression 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
energy 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 process is perturbed by a number of genetic lesions; (2) different proteins interact directly with each other to mediate either
adhesion or signal transduction events, or to form a
multi-subunit complex; (3) different proteins participate in
distinct but complementary pathways. These hypotheses are
now testable following the recent identification of the PKHD1,
Pkd1, Pkd2, NPHP1, and NPHP4 genes. The encoded proteins
(fibrocystin, polycystin-1 and polycystin-2, nephrocystin and
nephrocystin-4, fig 3) appear to have pivotal functional roles
in renal epithelial differentiation and organisation by mediating
interactions between epithelial cells and extracellular
components.

Defects in direct protein-protein interactions are now
thought to be the primary cause of the cystic changes of the
various types of polycystic kidney diseases and juvenile neph-
ronophthisis (NPHP), but the precise mechanisms remain
unclear at present. The loss of contact points and signalling
events between cells and either the extracellular matrix (at focal adhesions) or other cells (at adherens junctions) may be
the defect that underlies NPHP. Nephrocystin, the product of
nephronophthisis type I gene (NPHP1), appears to have a
fundamental role in mediating cell adhesion.71 In addition, the C-terminal region of polycystin-1 has been shown to form
multi-subunit complexes with focal adhesion proteins that
include the structural and actin binding proteins vinculin,
talin, tensin, and α-actinin, the adaptor proteins paxillin and
p130(Cas), and the signalling kinase c-src.69 Polycystin-1 is
also thought to form a heterodimeric ion channel with
polycystin-2 (see above). The complex of focal adhesion
proteins links the extracellular matrix to the actin cytoskel-
on through the cell membrane. It is possible that mutations
in other proteins of the polycystin-1 complex may lead to
either cystic kidney disease or additional extrarenal fibrocystic
changes. Familial focal segmental glomerulosclerosis, for
example, is thought to be caused by mutations in the focal
adhesion protein, α-actinin-4.9 The very recent demonstra-
tion, by a series of immunoprecipitation experiments, that
nephrocystin and nephrocystin-4 interact directly68 suggests
that these proteins are either in the same multi-subunit com-
plex, or interact in a developmental pathway to mediate either
adhesion or signal transduction events. Defects in either of
the proteins will therefore result in NPHP. A similar molecular
explanation has been suggested for the existence of at least six

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J Med Genet: first published as 10.1136/jmg.40.5.311 on 1 May 2003. Downloaded from http://jmg.bmj.com/ on June 14, 2021 by guest. Protected by copyright.
...or genes for Bardet-Biedl syndrome. BBBS6 encodes a protein that has significant sequence homologies to a class of chaperonins that facilitate protein folding, and other BBBS proteins could either form part of a chaperonin complex or interact with BBBS6 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 intrahepatic 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.

ACKNOWLEDGEMENTS

The authors wish to thank Professor Deirdre A Kelly and Dr David Milford for helpful discussion and for critical reading of the manuscript. CAJ receives financial support from the Birmingham Children's Hospital Endowment Fund and the Birth Defects Foundation (grant 02/02). PG is a Royal College Birmingham Children's Hospital Endowment Fund and the David Milford for helpful discussion and for critical reading of the manuscript.

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