

Inherited cerebrorenal syndromes

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Abstract | Abnormalities in the central nervous system and renal function are seen together in a variety of congenital syndromes. This Review examines the clinical presentation and the genetic basis of several such syndromes. The X-linked oculocerebrorenal syndrome of Lowe is characterized by developmental delay, blindness, renal tubular dysfunction, and progressive renal failure. This syndrome results from mutations in the *OCRL* gene, which encodes a phosphatase involved in endosomal trafficking. Mutations in *OCRL* also occur in Dent disease, which has a milder disease phenotype than Lowe syndrome. Patients with Joubert syndrome have cerebellar ataxia, pigmentary retinopathy, and nephronophthisis. Joubert syndrome is a genetically heterogeneous condition associated with mutations in at least five genes that encode ciliary proteins. Bardet–Biedl syndrome is a clinically variable condition associated with learning disabilities, progressive visual loss, obesity, polydactyly, hypogonadism, and cystic and fibrotic renal changes that can lead to renal failure. Most of the 12 genes mutated in Bardet–Biedl syndrome are also involved in ciliary function, as are the genes implicated in other ‘ciliopathies’ with similar phenotypes, including Meckel syndrome.

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Introduction

Many congenital syndromes exist in which the concomitant presence of central nervous system (CNS) and renal abnormalities has been reported in at least a subset of affected children. For example, a patient with Smith–Lemli–Opitz syndrome can have renal dysplasia, in addition to the microcephaly and mental retardation that are invariably seen; a patient with a mitochondrial disorder can have central hypotonia and some type of structural urinary tract anomaly. However, only a handful of disorders with specific structural and functional abnormalities of the CNS and kidney have defined genetic bases. This Review will focus on these disorders, highlighting in particular the clinical manifestations and genetic basis of Lowe syndrome and in ciliopathies such as Joubert and Bardet–Biedl syndromes.

Lowe syndrome

The oculocerebrorenal syndrome of Lowe is a rare X-linked recessive disorder first described in 1952.¹ The UK Lowe Syndrome Trust estimates that approximately 250 men in the US and 65 in the UK are affected, but these numbers are probably underestimates (L. Thomas, personal communication).² The disease occurs worldwide: patients from Japan, India, Europe, and North America have been described. According to the Lowe Syndrome Trust, in the absence of complications patients can be expected to live for up to 40 years, and death is often related to renal failure. Other patients succumb to respiratory infections, which sometimes complicate scoliosis or are the result of hypotonia, poor clearance of secretions and secondary atelectasis and pneumonia.

Competing interests

The authors declare no competing interests.

Mutations in the *OCRL* gene are associated with the syndrome, and the functional consequences of such mutations are coming to be understood.

Clinical features and treatment

Ophthalmologic abnormalities

All male patients with Lowe syndrome have dense cataracts at birth (Figure 1).¹ Cataracts have been demonstrated as early as 20 weeks of gestation, accompanied by necrosis and disorganization of embryonic lens epithelium.³ The cataracts should be detected by routine newborn physical examination, and the diagnosis of Lowe syndrome should be considered in any male infant in whom they are present. Early cataract removal is recommended to improve visual stimulation. However, even with immediate diagnosis and appropriate surgical intervention, visual acuity is rarely better than 20/100.³

Other ocular abnormalities also occur,⁴ and at least 50% of patients develop glaucoma in infancy or early childhood.⁵ Patients with glaucoma have an abnormal filtration angle, with decreased visibility of the scleral spur and a narrow ciliary body band.⁵ Although goniotomy would be expected to lead to improvement in these patients, such improvements seldom occur, and increased intraocular pressure is rarely relieved by surgical intervention.⁶ Loss of vision progresses, often to blindness. Thus, although glaucoma screening every 3 months in infancy and every 6 months beyond the age of 1 year is recommended,⁴ glaucoma is usually severe and refractory in these individuals.

Central neurological abnormalities

Mental retardation is seen in almost all boys with Lowe syndrome, with over one-half of cases in the range of

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Key points

- A number of rare conditions with defined genetic abnormalities are characterized by a set of specificocerebrorenal symptoms including Lowe syndrome, Joubert syndrome, and Bardet–Biedl syndrome
- Lowe syndrome is an X-linked disorder that results from mutations in *OCRL*, a gene that encodes a phosphatase involved in endosomal trafficking
- Boys with Lowe syndrome have Fanconi-type renal tubular dysfunction and progressive renal failure with developmental delay and blindness
- Joubert syndrome is a genetically heterogeneous ciliopathy; affected patients can display cerebellar ataxia, pigmentary retinopathy and nephronophthisis
- Bardet–Biedl syndrome is a clinically variable and genetically heterogeneous ciliopathy; patients can present with cystic and fibrotic renal changes that can lead to renal failure, along with learning disabilities, progressive vision loss, obesity, and hypogonadism

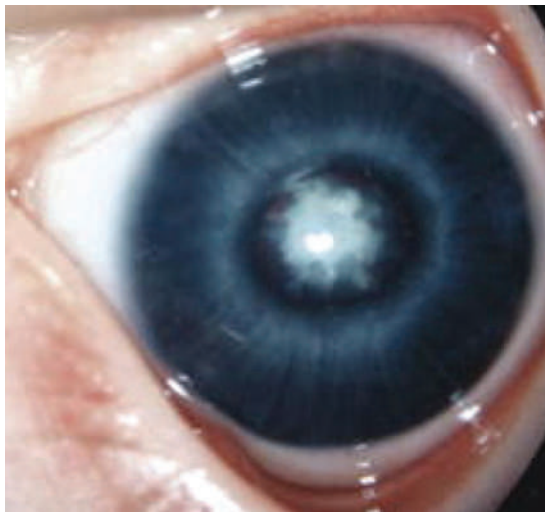


Figure 1 | Discoid cataract in an infant with Lowe syndrome. Permission obtained from Wolters Kluwer Health © Walton, D. S., Katsavounidou, G. & Lowe, C. U. Glaucoma with the oculocerebrorenal syndrome of Lowe. *J. Glaucoma* **14**, 181–185 (2005).

severe to profound handicap and only about 10% in the range of low to normal intellectual function.⁷ In addition, many patients demonstrate maladaptive behaviors, including temper tantrums and self-abuse. Stereotypic and obsessive–compulsive behavior is also common.⁷ Approximately half of patients eventually develop generalized motor seizures that require anticonvulsants.⁸ Early intervention programs should be considered to maximize psychomotor development and redirect maladaptive impulses, if possible. Antipsychotic therapy can be prescribed in an effort to help control these behaviors. These developmental and behavioral problems often prove to be the most disabling aspect of Lowe syndrome.

At birth or shortly thereafter, boys with Lowe syndrome demonstrate central hypotonia, with absence of deep-tendon reflexes. Early manifestations of central hypotonia can include poor suck and swallowing with gastroesophageal reflux; as a result, nasogastric or gastrostomy tube placement and feeding are sometimes

necessary in infancy. Poor motor tone persists during growth and these boys demonstrate severe delay in motor milestones. Only 25% and 75% of 6 and 13-year-olds, respectively, walk independently.⁸ Poor muscle tone leads to multiple complications. Specifically, decreased abdominal tone can contribute to chronic constipation, umbilical and inguinal hernias,⁴ and to cryptorchidism, which is observed in one-third of these boys;⁸ in addition, poor truncal tone leads to scoliosis in 50% of patients;⁸ reduced extremity tone can lead to hip and knee dislocation.

Renal tubular dysfunction and renal failure

Careful characterization of the resorptive defects observed in Lowe syndrome has revealed that they do not resemble a classic Fanconi syndrome.^{9,10} Unlike patients with this syndrome, those with Lowe syndrome do not have glycosuria. Rather, the renal dysfunction is a specific tubulopathy in which low-molecular-weight proteinuria, aminoaciduria, and hypercalciuria predominate, although renal tubular acidosis can also be observed.^{9,11} The tubulopathy of Lowe syndrome closely resembles that of Dent disease, although renal tubular acidosis is not a feature of the latter.¹⁰ Genetic overlap between these two syndromes is discussed below.

Elevated urinary excretion of low-molecular-weight proteins is the earliest renal manifestation of Lowe syndrome and can be seen in neonates.¹² This increased excretion reflects the failure of the proximal tubule to reabsorb filtered plasma proteins, including albumin; albuminuria is typically in the non-nephrotic range. The urinary proteome pattern observed in Lowe syndrome resembles that seen in Dent disease and other forms of proximal tubulopathy, with excessive excretion of low-molecular-weight proteins of plasma origin and reduced excretion of some proteins, such as uromodulin, that originate in the renal epithelium.¹³ However, in two studies, excessive excretion of *N*-acetyl- β -D-glucosaminidase and other lysosomal enzymes was observed in 14 of 14 patients with Lowe syndrome.^{9,14} These observations are possibly a manifestation of abnormal membrane trafficking, as discussed below.

Other proximal renal tubular defects of varying severity become evident in infancy and the first several years of life.¹⁵ Urinary concentrating capacity is impaired, and patients are, therefore, vulnerable to volume depletion, although generally not to the degree seen in patients with cystinosis-associated Fanconi syndrome.¹⁵ Generalized aminoaciduria is common, but renal glycosuria is usually absent.⁹ Roughly half of patients have low serum levels of bicarbonate and require replacement therapy with alkali;^{1,9,15} in most other patients, serum bicarbonate levels are within the low range of normal.⁹ Abnormal urinary losses of potassium and phosphate also occur, although they are usually modest. However, in some patients, severe phosphate losses lead to rickets.^{5,15} Even when the absolute doses of bicarbonate or phosphate required are modest, three to four doses per day are

generally optimal to mimic physiologic ionic losses and minimize risk of secondary hyperparathyroidism. Given the developmental delays and behavior difficulties, many patients require gastrostomy tubes beyond infancy to assure consistent and complete delivery of medication.

Urinary calcium excretion is typically elevated, often considerably so, even in patients not receiving calcitriol for treatment of hypophosphatemia and rickets.^{9,16} Nephrocalcinosis or stones have been reported in as many as two-thirds of patients.⁹ According to anecdotal evidence, urinary calcium excretion can be normalized with thiazide diuretics.¹⁶ Calcium metabolism has not been characterized fully in many patients, but isolated descriptions of elevated parathyroid hormone levels and normal vitamin D levels¹⁶ suggest that the pattern is different from that seen in Dent disease.

Glomerular filtration rate declines with age at a variable rate but renal failure is common by early adulthood. Renal biopsies performed in the first decade of life can show interstitial fibrosis and tubular dilatation but not primary glomerular abnormality. Biopsies performed past the age of 10 years show interstitial disease of increased severity with secondary glomerulosclerosis.^{6,15} The mechanism of renal failure is not known. Norden and colleagues¹⁷ observed that in Lowe and similar tubulopathies, the low-molecular-weight proteins excreted in excess include chemokines and other bioactive proteins, and have speculated that these proteins contribute to interstitial inflammation and fibrosis.¹⁷ Whether nephrocalcinosis contributes to the gradual decline in glomerular filtration rate is unclear.¹⁵ Notably, successful renal transplantations in patients with Lowe syndrome have been described.⁶

Other clinical manifestations

Clinical manifestations in organs other than the eye, the CNS, and kidneys are variable in frequency. For instance, superficial cysts in the mouth and skin occur in some patients.¹⁸ These cysts are often painful and can become infected.¹⁸ Skin fibroblasts from patients with the Lowe syndrome have elevated phosphatidylinositol (4,5) bisphosphate (PI(4,5)P₂) concentrations, which might disrupt epithelial migration and explain cyst formation. Subcutaneous benign fibromas, especially involving the hands and feet, are also occasionally noted, as are non-inflammatory arthritis and tenosynovitis.¹⁹ Decreased dentin formation and subsequent dental caries and need for restorative dental care are also reported.⁵ In addition, boys with Lowe syndrome have a distinct facial dysmorphism with microcephaly, deep-set small eyes and frontal bossing in the context of an elongated face (Figure 2).²⁰

Molecular genetics

Lowe syndrome is consistently associated with mutations in *OCRL*; mutations in other genes have not been reported. *OCRL*-1, the enzyme encoded by the gene, is one of ten inositol 5-phosphatases, and its preferred



Figure 2 | A boy with the typical facies of Lowe syndrome. Courtesy of Lorraine Thomas, chair of Lowe Syndrome Trust. Written consent for publication of this photo was obtained from the patient's mother.

substrate is PI(4,5)P₂.²¹ Low levels of *OCRL*-1 result in elevated cellular levels of PI(4,5)P₂.²² *OCRL*-1 localizes to the Golgi complex and endosomes, and regulation of PI(4,5)P₂ concentration has a potentially important role in cell signaling, actin polymerization, and protein trafficking between these two compartments.²³

More than 100 *OCRL* mutations, most of them unique, have been reported in patients with Lowe syndrome. Many are missense mutations—single base changes that lead to the substitution of a single amino acid—and most of them occur within the phosphatase domain of *OCRL*-1, which suggests that interference with the phosphatase function of *OCRL*-1 is critical to the phenotype of Lowe syndrome. This hypothesis is supported by observations in mice deficient in the mouse *OCRL*-1 homolog *Ocrl*. Mice that lack *Ocrl* do not have any eye, kidney, or neurologic abnormalities. However, when these mice were crossbred with mice deficient in another homologous phosphatase encoded in the autosomal gene *Inpp5d*, no progeny were born lacking both enzymes. This observation suggests that deficiency of both enzymes is lethal to the fetus.²⁴ Overall, evidence thus strongly suggests that one phosphatase can complement the function of another, which might explain why mutations in *OCRL*, which is expressed in a wide range of tissues, only results in dysfunction of the eye, brain, and kidney. In these tissues, expression of complementary phosphatases might be different from that in other tissues.

OCRL-1 also interacts directly with clathrin and other proteins important in the motility of endocytic vesicles in renal tubular cells and the brain.^{25,26} The ASH-RhoGAP domains near the C-terminus of *OCRL*-1 interact with proteins involved in membrane trafficking and the

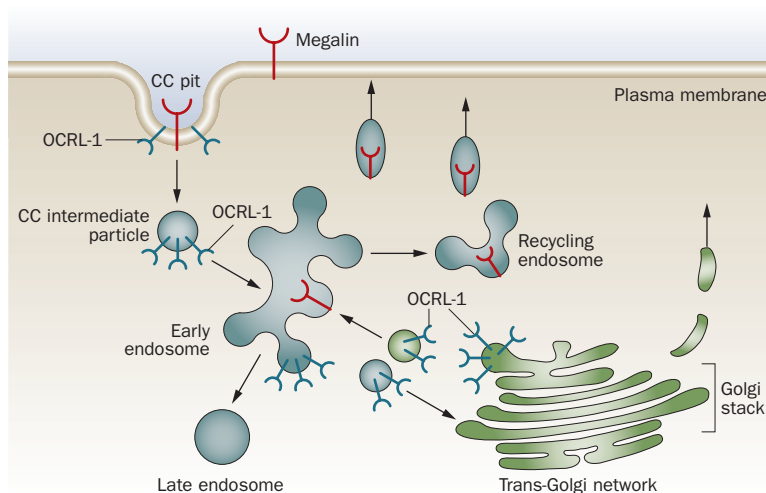


Figure 3 | Role of OCRL-1 in endosome and trans-Golgi network trafficking. OCRL-1 is a phosphatase present on the trans-Golgi network and seems to regulate traffic between this network, early endosomes and clathrin-coated intermediate particles. OCRL-1 could also influence other processes, such as the delivery of cargo from the trans-Golgi network to the plasma membrane and the recycling of receptors from early or recycling endosomes back to the cell surface. Trafficking between recycling endosomes and the cell surface is of particular importance in the proximal tubule, where the multiligand receptors megalin and cubilin (not shown) undergo rapid cycles of internalization and recycling to remove proteins from urine. OCRL-1 deficiency could result in reduced numbers of plasma membrane receptors, which would be consistent with the protein absorption defect associated with the OCRL-1 mutations that lead to Lowe syndrome. Abbreviation: CC, clathrin-coated. Permission obtained from Wiley-Blackwell © Lowe, M. *Traffic* 6, 711–719 (2005).²²

endosomal pathway. Some of the mutations identified in patients with Lowe syndrome are located in the ASH-RhoGAP domains, and each of these mutations alters the interaction between OCRL-1 and a specific endocytic adaptor protein, DCC-interacting protein 13- α .²⁷

Mutations in *OCRL* could, therefore, impair trafficking between membrane compartments through alterations in PI(4,5)P₂ levels and disturbances in direct interactions between OCRL-1 and trafficking proteins. These mechanisms provide a potential explanation for proteinuria and other disturbances in renal tubular reabsorption observed in patients with the Lowe syndrome. Proteins filtered at the glomerulus bind to the membrane surface receptors megalin and cubilin and are internalized into endocytic vesicles as the first step in degradation; the receptors are then recycled to the apical surface. Alterations in this receptor recycling process, or in the delivery of newly synthesized receptors from the trans-Golgi network to subapical endosomes or, potentially, directly to the plasma membrane, would result in reduced apical abundance of megalin and cubilin, and would, in principle, decrease the amount of protein that can be degraded by glomerular cells (Figure 3).²² The hypothesis that mutations in *OCRL* could result in depletion of megalin and cubilin is consistent with the observation that urinary megalin level is decreased in patients with Lowe syndrome.²⁸ Such

disturbances in trafficking might also affect the apical abundance of other membrane proteins, such as those involved in sodium-dependent transport of phosphate and amino acids, although this idea remains speculative. How a defective *OCRL* gene causes the ophthalmic or neurologic abnormalities in these patients is not understood, although the enzymatic activity and localization of OCRL-1 might both be important in proper epithelial migration and differentiation in the eye.²⁹

Although no genetic heterogeneity has been associated with Lowe syndrome, mutations in *OCRL* are associated with phenotype heterogeneity. Some patients with Dent disease (type 2) have mutations in this gene rather than in *CLCN5*, which encodes the chloride transporter more commonly associated with Dent disease (type 1). Other than the absence of renal tubular acidosis in Dent disease, the two syndromes have similar renal features. Eye or neurologic abnormalities, which are never present in type 1 Dent disease, are occasionally present in subtle form in type 2 Dent disease. Type 2 Dent disease could, therefore, be considered a very mild variant of Lowe syndrome. The spectrum of *OCRL* mutations in type 2 Dent disease differs substantially from that in Lowe syndrome, consistent with the hypothesis that the clinical differences between the diseases reflect tissue-specific expression of OCRL-1 splice variants that might preserve phosphatase expression in the eye and brain of patients with Dent disease.^{30,31}

Diagnostic testing

As noted above, the diagnosis of Lowe syndrome should be pursued in newborn boys with cataracts, particularly in the context of central hypotonia. The overlap of these clinical features with those of other disorders is limited. In particular, congenital cataracts are rare and tend to be seen in disorders that have distinctive phenotypes, such as trisomy 13, Pierre Robin syndrome, Down syndrome, and congenital rubella.

The diagnosis of Lowe syndrome is made on the basis of reduced (<10% of normal) inositol polyphosphate 5-phosphatase activity of OCRL-1 in cultured skin fibroblasts. Although such diagnosis is highly reliable, molecular genetic testing often is desirable, generally to assess the risk of a patient's mother, sister, or maternal family member having another affected son. In fact, 32% of Lowe-syndrome-causing mutations in *OCRL* are spontaneous,^{32,33} which means that only approximately two-thirds of mothers of a son with Lowe syndrome are carriers of the condition. In addition, approximately 5% of carrier females over the age of 15 years do not have the characteristic punctate lens opacities visible through direct and retroillumination. A kit for the sequence analysis of *OCRL* is commercially available in the US and Europe, and it identifies mutations in approximately 95% of males with Lowe syndrome. The mutation thus identified can then be tested for in the mother. Notably however, approximately 5% of carrier females have germline mosaicism, so the mutation might not be detected

even if present.^{32,33} In this circumstance, linkage analysis can prove insightful and will provide an exhaustive, though not absolute, evaluation of carrier status.

Prenatal diagnosis can be made by chorionic villus sampling at 10–12 weeks of gestation. If the karyotype is 46,XY, enzyme activity can be measured in cultured cells. Alternatively, if previous mutation analysis in the family proved informative, such analysis can be performed. Even if carrier testing has proven negative, prenatal enzymatic diagnosis should be offered to women who are known to be carriers.

Ciliopathies

A group of inherited cerebrenal syndromes share a common link: their causative genes encode proteins that are important in the structure or function of immotile (primary) cilia.^{34,35} Cilia are conserved cellular structures that comprise a microtubule-based axoneme anchored in the basal body by a centrosome. Cilia are found in most vertebrate tissues, during both cell development and maturation, and are responsive to mechanosensory and chemosensory cues.³⁴ Cilia are linked to sensing of morphogenetic signals and the regulation of many key signaling pathways, which seem to be important in both differentiation and maintenance of tissues.^{36,37} Individuals with diseases that result from mutations causing loss-of-function of a particular protein important in primary cilia function—the so-called ciliopathies—display certain symptoms that appear at birth and others that gradually manifest over time.

In the renal tubule, primary cilia sense fluid movement and transmit through the basal body signals linked to maintenance of normal tubular development and morphology.^{38,39} Wnt proteins are important regulators of these cellular responses through either the canonical β -catenin pathway or the noncanonical pathway.⁴⁰ Canonical signaling occurs in the absence of tubular flow and stabilizes intracellular β -catenin, which, via β -catenin response elements, increases expression of the gene encoding Disheveled, the nuclear and cytoplasmic protein that regulates the Wnt signaling pathway.⁴¹ By contrast, tubular flow increases expression of inversin and, eventually, of the β -catenin destruction complex.^{40,42} Noncanonical signaling predominates in the presence of tubular flow and is important in maintaining proper apical–basolateral polarity of the renal epithelium.⁴²

Defects in ciliary or basal body proteins result in the disruption of renal tubular mechanosensation or regulation of these complex signaling pathways, which alters the balance between cell proliferation and apoptosis.³⁴ For example, defects in *PKD1* and in its ciliary protein product, polycystin 1, lead over time to tubular cell hyperproliferation and autosomal-dominant polycystic kidney disease.⁴³ Defects in genes that encode other ciliary or basal body proteins alter signaling in a way that seems to dysregulate apoptosis and lead to fibrosis and the clinical picture of nephronophthisis seen in many of the ciliopathies.⁴⁴

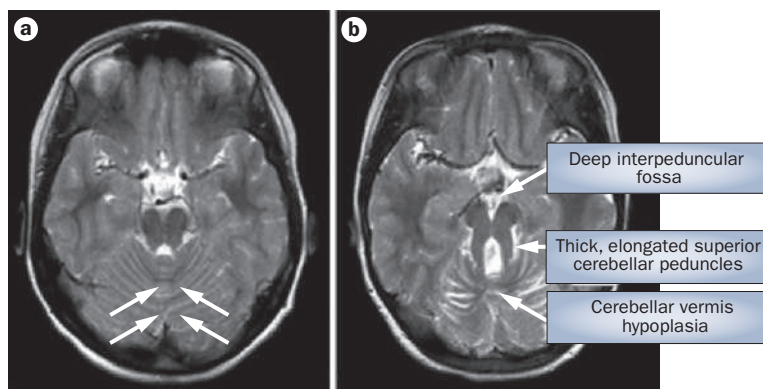


Figure 4 | The ‘molar tooth sign’ associated with Joubert syndrome. **a** | An axial MRI image through the cerebellum and brainstem of a healthy person shows the intact cerebellar vermis (white arrows). **b** | An axial MRI image through the cerebellum and brainstem of a child with Joubert syndrome shows the three components of the molar tooth sign. Parisi, M. & Glass, I. (Updated March 8, 2007). Joubert Syndrome. In *GeneReviews at GeneTests: Medical Genetics Information Resource* (database online). © University of Washington, Seattle. 1997–2009. Available at <http://www.genetests.org>. Accessed June 22, 2009.

Cilia are also involved in photosensation.³⁴ Thus, patients with defects in genes that encode proteins essential to ciliary function can develop degenerative retinal disease. However, ciliopathies are generally characterized by both degenerative and developmental abnormalities. Structural defects of the brain, craniofacial structures, limbs, and gonads occur with varying frequency.³⁴

Antegrade and retrograde transport along the ciliary axoneme of the so-called intraflagellar transport proteins is essential for proper Sonic Hedgehog (SHH) signaling.^{36,37} SHH signaling in vertebrates is not fully understood, but SHH proteins probably regulate activity of Gli proteins, which can act as transcriptional activators or repressors.³⁷ Through this pathway, SHH proteins seem to regulate tissue patterning and are required for various developmental processes, including dorsalization of the nervous system,³⁶ migration of neural crest cells to form the craniofacial skeleton,⁴⁵ and limb formation.³⁷ Abrogation of function of ciliary intraflagellar transport proteins in mice leads to defects in neuronal patterning in the spinal cord and mid-face skeleton and polydactyly.⁴⁵

Joubert syndrome

Joubert syndrome is a rare autosomal-recessive disease characterized by a distinctive cerebellar and brainstem malformation and cerebellar ataxia.⁴⁶ A prevalence of one in 100,000 live births is estimated.⁴⁷

Clinical features

Patients with Joubert syndrome have hypoplasia of the cerebellar vermis, a deep interpeduncular fossa, and thick, elongated superior cerebellar peduncles. Axial MRI through the junction of the midbrain and pons produces images that resemble the section of a tooth. This ‘molar tooth sign’ is diagnostic of Joubert syndrome (Figure 4),⁴⁸

Table 1 | Genetic loci and genes associated with Joubert syndrome

Locus	Gene	Protein	Detected mutation frequency*	Nephronophthisis	Retinal disease	Other associated syndromes [‡]
9q34	Unknown	Unknown	Unknown	No	Present in ~50% of patients	None
11p12–q13	Unknown	Unknown	Unknown	Present in a minority of patients	Present in a minority of patients	Meckel syndrome?
6q23.2	<i>AHI1</i>	Jouberin	7–11%	Present in a minority of patients	Present in a majority of patients	None
12q21.33	<i>CEP290</i>	Nephrocystin 6	~10%	Present in almost all patients	Present in almost all patients	Senior–Løken syndrome (common cause), Meckel syndrome
2q13	<i>NPHP1</i>	Nephrocystin 1	2–3%	Present in almost all patients	Present in a minority of patients	Senior–Løken syndrome (rare cause), Cogan oculomotor apraxia
8q22.1	<i>TMEM67</i>	Meckelin	~10%	No, cystic kidneys reported	Not reported	Meckel syndrome, COACH syndrome
16q12.2	<i>RPGRIPL</i>	RPGRIPL 1-like protein	~1%	Present in almost all patients	Rarely present	Meckel syndrome, COACH syndrome?

*Proportion of patients with Joubert syndrome who have defects in the gene or locus. [‡]Other clinical syndromes associated with defects in these genes. Abbreviations: COACH, cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis; JS, Joubert syndrome.

although the syndrome is otherwise clinically heterogeneous. CNS manifestations are invariably present, but the clinical spectrum and severity vary both within and between families. Different CNS phenotypes have even been reported in a set of monozygotic twins.⁴⁹

At birth, hypotonia and irregular breathing, with alternating tachypnea and apnea, are common.⁴⁶ Use of apnea monitors and pharmacologic therapy can be necessary. During the first year of life, abnormal eye movements are often noted, usually in the form of oculomotor apraxia or difficulty in smooth visual pursuit.⁵⁰ Signs of delayed fine and gross motor development, including cerebellar ataxia, are generally evident and most children have cognitive impairment, although the degree of mental retardation is variable.⁴⁷ Early diagnosis of Joubert syndrome is important, as intervention programs focused on motor and cognitive performance show maximal benefit when started in the first year of life. In particular, many patients have verbal apraxia and require intensive speech therapy.⁵¹

In addition to the CNS manifestations, at least 25% of patients with Joubert syndrome have characteristic retinal and renal abnormalities. Pigmentary retinopathy similar to classic retinitis pigmentosa is sometimes present. Impairment in visual acuity is often severe and always irreversible.⁴⁶

Patients with retinal disease often have renal disease. Although some patients display cystic dysplasia at birth,⁴⁶ the most common renal manifestation is nephronophthisis.³⁴ This chronic tubulointerstitial nephropathy is characterized pathologically by atrophic, sometimes dilated, renal tubules with thickened

basement membranes. As interstitial disease predominates, patients with renal disease invariably have a renal concentrating defect and present with polyuria and polydipsia. Development of secondary segmental glomerulosclerosis is followed by global glomerulosclerosis and slowly progressive renal disease. The rate of progression of the renal disease is variable, with some patients requiring renal replacement before 5 years of age and others not until their third decade of life.^{52,53} In patients with nephronophthisis in the context of Joubert syndrome, end-stage renal disease occurs at the average age of 13 years.⁵⁴

Clinical manifestations other than those discussed above are rarer, but they can include hepatic fibrosis with bile duct proliferation. This condition is often associated with the CNS manifestations of Joubert syndrome and with chorioretinal colobomas, but rarely with renal disease. Although this presentation is a variant of Joubert syndrome, it is sometimes referred to as cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis (COACH) syndrome.⁵⁵ Polydactyly has also been reported and can be unilateral or bilateral.⁵⁵ Some male patients have a micropenis, similar to that seen in children with Bardet–Biedl syndrome (see below).⁴⁷

Genetics

Unsurprisingly, given its heterogeneous clinical presentation, Joubert syndrome is a genetically heterogeneous condition (Table 1). The cause of Joubert syndrome has been traced to seven gene loci, and the specific genes have been identified in five cases.^{46,56} Other causative genes are likely to be discovered, as the mutation

detection frequency for any one of the identified genes is only approximately 10%.⁴⁷ The proteins encoded by the identified genes localize in primary cilia in multiple tissues, particularly the CNS, photoreceptors in the eye, renal tubular cells, liver, and in developing limbs.³⁴

Certain genotype–phenotype patterns have emerged in Joubert syndrome and can be explained in part by the relative importance in various organs of the different protein products in regulating ciliary function. In all but one of 22 families of individuals with Joubert syndrome and an *AH11* defect, the syndrome presented with retinal dystrophy, whereas the syndrome presented with nephronophthisis in only three of these families.^{57,58} In most families with a defect in *CEP290* (the gene that encodes nephrocystin 6; also known as *NPHP6*) Joubert syndrome presents with retinal disease and nephronophthisis, and the renal, retinal, and cerebellar phenotype of the syndrome can be reproduced in Zebrafish by abrogating function.⁵⁹ Mutations in *NPHP1* (which encodes nephrocystin 1) have been identified in 50–85% of patients with nephronophthisis, but fewer than 10% of these patients exhibit retinal or CNS abnormalities consistent with Joubert syndrome.⁵⁷ Moreover, when present, these manifestations are mild. In fact, of the eight genes known to cause nephronophthisis, only four have been associated with neurologic findings consistent with the Joubert syndrome phenotype.³⁴

The relationship between genotype and phenotype of Joubert syndrome and other ciliopathies is complex. For instance, mutations in the ciliary gene *RPGRIPII* can cause the Joubert syndrome phenotype of the molar tooth sign, cerebellar ataxia, retinal dysplasia, and nephronophthisis.⁶⁰ However, defects in this gene were also found in infants with Meckel syndrome, a condition that leads to death in infancy and is characterized by severe CNS malformation (typically, occipital encephalocele), postaxial polydactyly, hepatic fibrosis with bile duct proliferation, and cystic renal dysplasia.^{60,61} *RPGRIPII* is one of four genes identified in association with the Meckel phenotype and the third of these (along with *TMEM67* and *CEP290*) in which defects have also been described in patients diagnosed with Joubert syndrome.⁵⁶ In addition, defects at one gene locus linked to Joubert syndrome in which the gene has not been identified have been noted in infants with a phenotype similar to Meckel syndrome.⁴⁶ The variation in phenotype between Joubert and Meckel syndromes could be explained in part by the type of gene defect. Analysis of *RPGRIPII* revealed that infants with Meckel syndrome had loss of function mutations, and transgenic mice that lack the *RPGRIPII* mouse ortholog *Rpgrip1l* exhibit a similar phenotype to patients.⁶⁰ By contrast, a hypomorphic allele is often seen in patients with Joubert syndrome.

Bardet–Biedl syndrome

The Bardet–Biedl syndrome is an autosomal-recessive disorder that has substantial clinical variability within and among affected families.⁶²



Figure 5 | A girl with wide midface and upward nasal displacement characteristic of Bardet–Biedl syndrome. Courtesy of Mary Morris, Vice President of Lawrence–Moon Bardet–Biedl Association. Written consent for publication of this photo was obtained from the patient's mother.

Clinical features

Clinical diagnosis of Bardet–Biedl syndrome is established by the presence of at least three of six primary clinical features. These features comprise postaxial polydactyly (present in 60–70% of patients),⁶³ truncal obesity, learning disabilities, hypogonadism in males or genital abnormalities in females, renal anomalies, and cone–rod dystrophy.⁶⁴ Although the latter is a feature of all patients and its presence is necessary to make the diagnosis, this retinal abnormality is progressive rather than developmental, and visual dysfunction is generally not apparent until the age of approximately 7 years, when night blindness arises.⁶³ Consequently, diagnosis of Bardet–Biedl syndrome is often not made until late in the first decade of life when the visual disturbance progresses; such disturbance includes early involvement of the macula and progressive loss of visual acuity, with patients becoming legally blind at the mean age of 15 years.⁶³

Although all patients with Bardet–Biedl syndrome develop obesity, and striking weight gain is apparent in the first year of life in most patients, birthweight and resting metabolic rate are normal. Anecdotal reports indicate that abnormal satiety might be responsible for obesity.⁶⁵ Severe mental retardation is unusual, but cognitive impairment is seen in virtually all children with this syndrome,^{63,64} and early intervention to address these learning difficulties is important. Patients with Bardet–Biedl syndrome have a characteristic facial dysmorphism with a wide midface and upward nasal displacement (Figure 5).⁴⁵ The majority of male patients have hypogonadism and micropenis and small-volume testicles.⁶⁴ Female genitourinary malformations such as hydrometrocolpos and persistent urogenital sinus have been described but are seen in a minority of patients.⁶⁴

Table 2 | Genes associated with Bardet–Biedl syndrome

Gene	Locus	Cellular localization	Putative function
<i>BBS1</i>	11q13	Basal body and cilium	Cilia function
<i>BBS2</i>	16q21	Basal body and cilium	Cilia function and flagellum formation
<i>ARL6 (BBS3)</i>	3q11.2	Basal body and cilium	Vesicle trafficking
<i>BBS4</i>	15q22.3-q23	Pericentriolar region and basal body	Microtubule transport
<i>BBS5</i>	2q31	Basal body and cilium	Cilia function and flagellum formation
<i>MKKS (BBS6)</i>	20p12	Basal body and cilium	Cilia function and flagellum formation
<i>BBS7</i>	4q27	Basal body and cilium	IFT particle assembly
<i>TTC8 (BBS8)</i>	14q31.3	Basal body and cilium	IFT particle assembly
<i>BBS9</i>	7p14	Unknown	Unknown (expressed in bone cells)
<i>BBS10</i>	12q21.2	Unknown	Unknown
<i>TRIM32 (BBS11)</i>	9q33.1	Unknown	E3 ubiquitin ligase
<i>BBS12</i>	4q27	Unknown	Type II chaperonin

Abbreviation: IFT, intraflagellar transport. Adapted from Tobin, J. L. & Beales, P. L. *Pediatr. Nephrol.* **22**, 926–936 (2007), which was published by Springer DE.

Renal anomalies are often described. Beales *et al.*⁶³ reported that the results of renal imaging were abnormal in 27 (46%) of 59 patients with Bardet–Biedl syndrome. Hyperechoic kidneys and cystic dysplasia are the most common anomalies, and have been seen on prenatal ultrasound scans in fetuses affected by the syndrome.⁶⁶ However, renal histology can show similarities to nephronophthisis, with tubular dilatation, interstitial fibrosis and secondary focal glomerulosclerosis.³⁵ Not surprisingly, renal concentrating defects have been reported in 70% of cases, and polyuria and polydipsia are often present.⁶⁷ Patients can develop progressive renal failure, and 10–30% require renal replacement therapy.^{35,68}

Genetics

Bardet–Biedl syndrome has been associated with mutations in 12 genes (Table 2),³⁵ although no correlation between genotype and phenotype seems to exist. The proteins encoded by these genes might participate in a common cellular process. In fact, eight of the 12 proteins have been localized to the basal body of primary cilia, and the others could be important in proper folding of these eight proteins.^{33,35} Cilia lack ribosomes, and thus all proteins involved in their function must be transported along the axoneme via so-called intraflagellar transport.⁶⁹ The proteins implicated in Bardet–Biedl syndrome are thought to be involved in the intraflagellar transport of proteins such as those associated with autosomal-dominant kidney disease, polycystin 1 and polycystin 2.^{70,71}

As noted above, intraflagellar transport proteins are essential for normal tissue patterning and development, probably because of their effect on intracellular signaling pathways.^{36,37,45} For example, mice deficient in the homologs of the proteins encoded by *BBS4* and *MKKS* in humans, respectively, demonstrate a SHH-dependent defect in migration of neural crest cells, which results in skeletal defects and facial anomalies comparable to those observed in children with Bardet–Biedl syndrome.⁴⁵

However, the reason why mutations in certain ciliary proteins produce the Bardet–Biedl syndrome phenotype whereas others produce phenotypes consistent with Joubert or Meckel syndromes is unclear. The issue is further complicated by the observation that defects in three Bardet–Biedl syndrome genes (*BBS2*, *BBS4* and *MKKS*) can be associated with a phenotype very similar to that of Meckel syndrome.⁷²

Other ciliopathies

Other autosomal-recessive syndromes have genetic homology with Joubert and Bardet–Biedl syndromes and have been associated with mutations in genes that encode proteins expressed in primary cilia.

Meckel syndrome

As noted above, Meckel syndrome is characterized by severe forms of many of the developmental abnormalities typical of ciliopathies. In particular, the severity of CNS malformation (which classically comprises occipital encephalocele) is responsible for death during infancy.^{60,61} Mutations in four genes that encode ciliary proteins have been described in patients with Meckel syndrome; notably, mutations in three of these genes have also been associated with Joubert syndrome.⁵⁶ In addition, a phenotype similar to Meckel syndrome has been associated with defects in three genes involved in Bardet–Biedl syndrome.⁷²

Senior–Løken syndrome

Senior–Løken syndrome is characterized by retinitis pigmentosa and nephronophthisis.⁷³ Patients generally present late in the first decade of life with progressively reduced night vision. Some patients with Senior–Løken syndrome display the same neurologic abnormalities as those seen in patients with Joubert syndrome, including the molar tooth sign.⁵⁷ Of the eight genes associated with nephronophthisis, mutations in all but one

have been detected in patients with Senior–Løken syndrome, although mutations in *IQCB1* and *CEP290* (also associated with Joubert and Meckel syndromes) are most common.⁷⁴ The protein products of these genes—nephrocystin 5 and 6—with the retinitis pigmentosa GTPase regulator interacting protein 1 form a multimeric complex that is expressed in photoreceptor cilia.⁷⁵

Cogan oculomotor apraxia

Mutations in *NPHP1* have been identified in some patients with Cogan oculomotor apraxia.⁷⁶ Patients present in infancy with defective visual fixation and horizontal pathologic nystagmus. Neurologic abnormalities associated with Joubert syndrome and the molar tooth sign have also been reported in these individuals and patients usually manifest motor and cognitive delays.⁷⁷ The renal disease associated with cogan oculomotor apraxia is nephronophthisis.

Conclusions

Molecular genetic observations provide insight to the potential mechanisms of inherited diseases. The X-linked oculocerebrorenal syndrome of Lowe results from mutations in *OCRL*, which encodes a phosphatase involved in endosomal trafficking; a mechanism for proteinuria and other renal tubular abnormalities in boys with Lowe syndrome can then be inferred. Correlation between this genetic abnormality and the other predominant characteristics of Lowe syndrome, that is developmental delay, blindness, and progressive renal failure remains speculative.

Ciliopathies are autosomal recessive diseases caused by defects in genes encoding proteins that are important in

the structure or function of immotile cilia. Abnormalities of the CNS, kidney, eye, and limbs are most commonly seen, and they can be congenital or developmental.

Joubert syndrome is a genetically heterogeneous condition associated with mutations in at least five genes that encode ciliary proteins. Patients have a characteristic abnormality on MRI of the brain, which is known as the ‘molar tooth sign’. Clinical manifestations are variable, though patients generally have motor and cognitive delay and often display cerebellar ataxia. The renal manifestation is nephronophthisis.

Bardet–Biedl syndrome is clinically variable and genetically heterogeneous. Mutations in 12 genes with protein products isolated to immotile cilia have been described. Patients generally present with progressive vision loss. Other potential manifestations include learning disabilities, obesity, hypogonadism, and post-axial polydactyly. Renal manifestations include cystic and fibrotic disease, which can lead to renal failure.

Review criteria

A PubMed search was performed using the search terms “Lowe syndrome”, “oculocerebrorenal syndrome”, “Joubert syndrome”, “Bardet–Biedl syndrome”, “nephronophthisis”, “Meckel syndrome”, “Senior–Løken syndrome”, “retinitis pigmentosa”, “ciliary diseases”, “inherited mental retardation”, and “cystic kidney disease”. The search was restricted to papers published in English. Relevant publications were identified and reviewed. Other supporting information and referenced works are derived from the authors’ knowledge of the published literature and personal experience.

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