SEMINARS IN
NEPHROLOGY

Hereditary Hyperuricemia and Renal Disease

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Hyperuricemia and gout have long been known to run in families. As well as an apparently multifactorial genetic component to classic gout itself, 2 rather unusual sex-linked single-gene disorders of purine biosynthesis or recycling have been defined: deficiency of the enzyme hypoxanthine-guaninephosphoribosyl transferase (HPRT), and overactivity of PPriboseP synthase. Both result in overproduction of urate, hyperuricemia, and secondary overexcretion that may lead to acute or chronic renal damage. Familial juvenile hyperuricemic nephropathy (FJHN) and autosomal-dominant medullary cystic kidney disease (ADMCKD) are more common but less well-defined hyperuricemic conditions resulting from a decrease in the fractional excretion of filtered urate, with normal urate production. Although having features in common, ADMCKD is distinguished in particular by the presence of medullary cysts. One major group of both disorders is associated with mutations in the gene for uromodulin, but this accounts for only about one third of cases, and genetic heterogeneity is present. Whether the genes involved in these latter disorders contribute to the polygenic hyperuricemia and urate underexcretion of classic gout remains unexplored.
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A genetic basis for classic gout is suggested by the strong family association among patients with gout, which has long been known and was emphasized by Thomas Sydenham in the 17th century. The high prevalence of hyperuricemia and a low fractional excretion of filtered urate (FE_{ur}) in some races such as Polynesians[1,2] and Australian aboriginals, as well as studies of concordance in twins of 84% in monozygotic and 43% for dizygotic twins,[3,4] support this suggestion. Short[3] suggested that segregation of a major dominant gene against a polygenic background best explains their data, a cause that she hypothesizes is obscured in some studies by diet; environmental factors such as obesity, alcohol, and (probably) occult lead intoxication; and inclusion of some families with monogenic dominantly inherited familial juvenile hyperuricemic nephropathy (FJHN), as discussed later. Plasma uric acid concentrations in gouty patients are distributed smoothly in a Gaussian fashion, with the mean shifted toward higher concentrations compared with normals, a consequence of the lower FE_{ur} in this group of patients factored, but again varying with purine intake. Thus, gouty populations show a higher plasma urate concentration at each level of purine intake than normals. Although large population studies are lacking for FE_{ur}, this also is distributed approximately in a Gaussian fashion. The detailed basis of the low FE_{ur} level in classic gout in the middle-aged patient is not known because the renal tubular handling of urate is complex and bidirectional, still poorly understood, and the gene or genes in the monogenic dominant forms of renal hyperuricemia such as FJHN are only now being identified and cloned (see discussion later).

Gout, Nephropathy, and Stones Arising from Single-Gene Disorders of Purine Metabolism

A number of inherited conditions involving genetically based defects in the enzymes of purine nucleotide metabolism are known. Some of these can lead to the overproduction and overexcretion of uric acid and other purine end products: their nephrotoxicity derives from their insolubility and resultant ability of crystals formed to initiate stone formation within the urinary tract, or to generate inflammation leading to permanent renal damage within renal tissue, and sometimes both (see article by Kang in this issue). These insoluble purines include uric acid, xanthine, and 2,8-dihydroxyadenine in order of decreasing solubility. In this article we consider only uric acid.

Figure 1 shows an algorithm for the investigation of sus-

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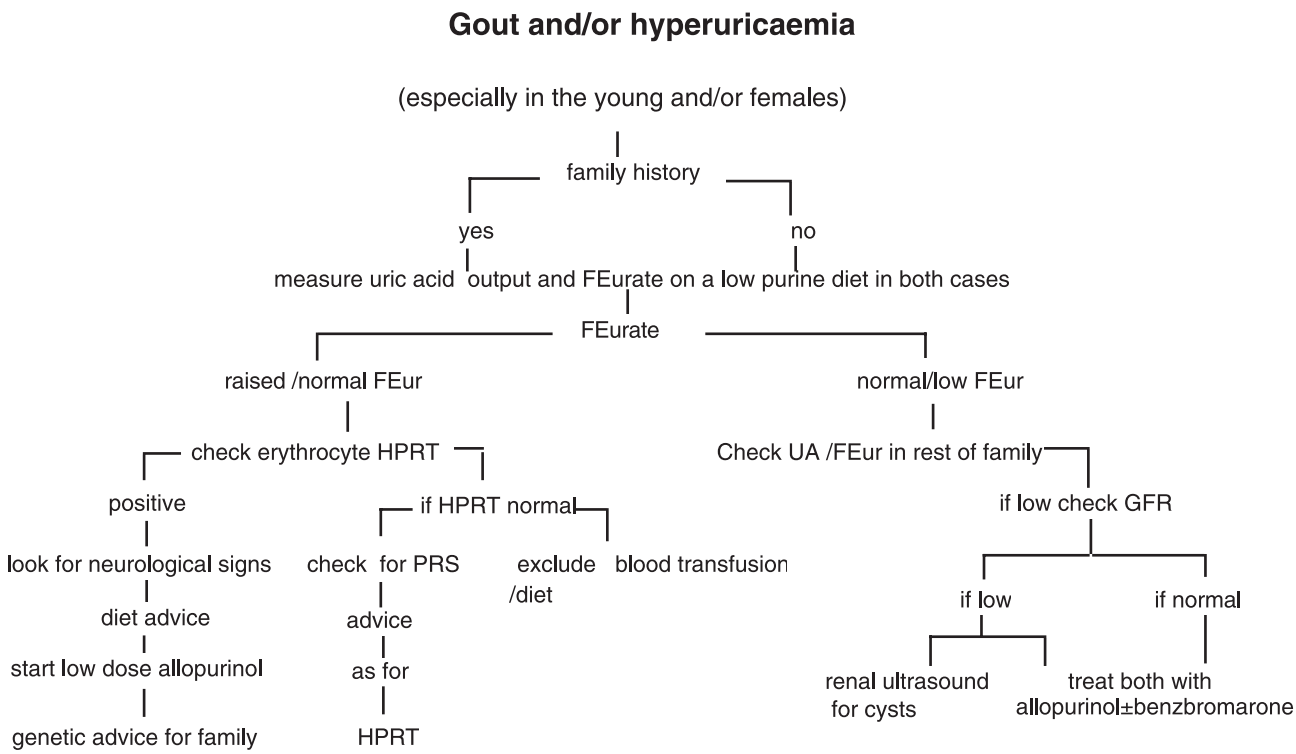

Figure 1 Gout, especially occurring in male infants or children with neurologic sequelae, should prompt measurement of PRS as well as HPRT activities in erythrocyte lysates. PRS1 complementary DNA sequencing is definitive only in the case of point mutations in PRS1. Complementary DNA and genomic sequencing may be useful in HPRT deficiency for defining mutations. Otherwise, confirmation is difficult and relies solely on studies in intact red cells, fibroblasts, or lymphoblasts Carrier detection in HPRT deficiency is best performed by using molecular methods.

pected inherited hyperuricemia, designed to differentiate those with overproduction of urate arising from genetic abnormalities of purine synthesis or recycling from those arising from mutations affecting renal tubular handling of urate, which reduce FE_{ur}. In practice, clinical clues (eg, presence or absence of affected women, associated neurologic defects, or onset in childhood or even infancy) provide valuable leads.

Hypoxanthine-Guanine Phosphoribosyl Transferase Deficiency and the Kidney

Hypoxanthine-guaninephosphoribosyl transferase (HPRT) catalyzes the salvage transfer of the phosphoribosyl moiety of PP-ribose-P to hypoxanthine and guanine to form inosine monophosphate (IMP) and guanosine monophosphate, respectively (Fig. 2). HPRT is a cytoplasmic enzyme with greatest activity in the brain and testes.[5] Its importance in the normal interplay between synthesis and salvage is shown by the gross overproduction of uric acid that results from the inability to recycle either hypoxanthine or guanine in patients genetically deficient in HPRT, inducing a lack of feedback control of purine synthesis, accompanied by rapid catabolism of purines to uric acid.[5,6]

Genetics and Clinical Presentation

The gene for HPRT has been cloned and localized to Xq26-q27.2.[6,7] Male hemizygotes carrying the defective gene show a broad spectrum of presentation. This ranges from the complete enzyme defect with Lesch-Nyhan disease (LND) consisting of severe neurologic deficits, which mainly involve the function of the basal ganglia and usually present in infancy, to partial defects associated only with uric acid overproduction and its consequences (including gout), which present in adolescence or early adulthood. This is sometimes known as the Kelley-Seegmiller syndrome.[8-10] There is a wide spectrum of LND-variant neurologic abnormalities of differing severity between these 2 extremes,[7] which are related in turn to the different aberrant enzyme proteins, some of which have minor or only moderately decreased activity with different kinetic properties. Many different mutations in the gene have been described, the majority being single base substitutions.[7]

Unfortunately, there is no absolute correlation between the structural changes at the molecular level and the clinical severity of the neurologic abnormalities.[7] Although this is an X-linked disorder, LND rarely has been described in women,[11-14] probably because of an unusually large number of affected versus unaffected cells in the mosaicism that all heterozygotes of sex-linked disorders display. Kelley-Seegmiller syndrome also has been found in a girl (Sebesta et al,

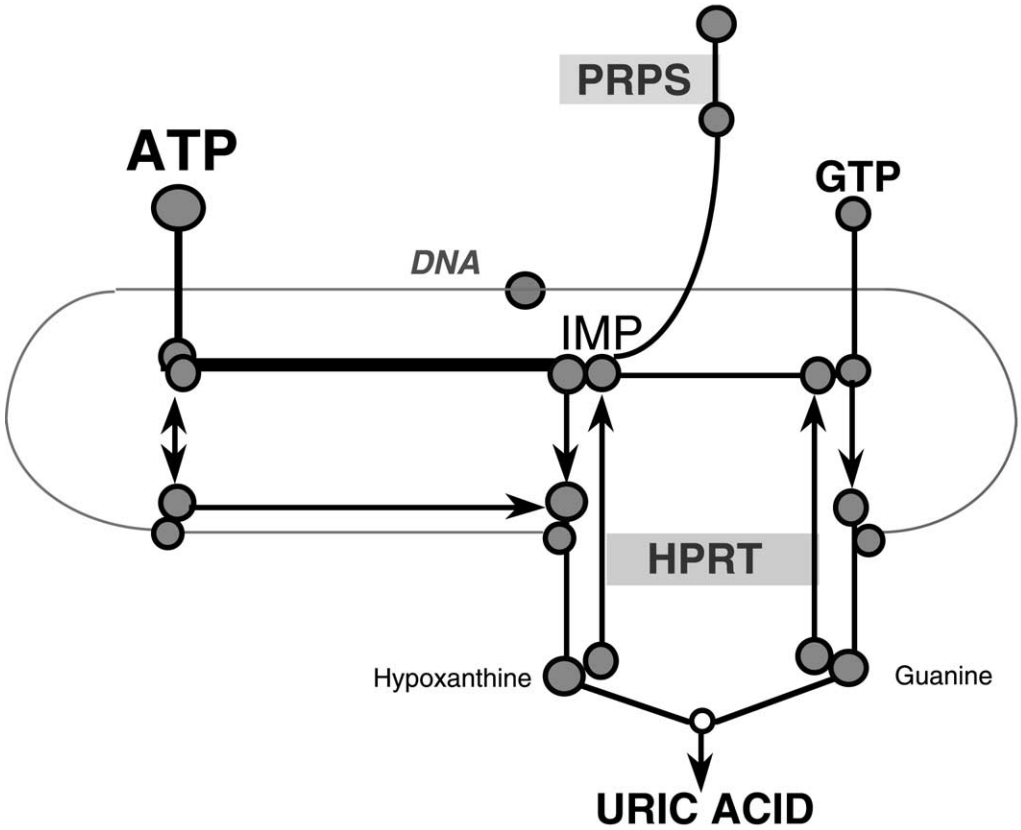

Figure 2 The biosynthesis of urate and sites of action of PRPS and HPRT. Mutations of the gene for PRPS, an enzyme in the synthetic pathway of IMP from simple molecules (top), result unusually in a gain in function, with oversynthesis of IMP, and hence uric acid its breakdown product. HPRT catalyzes the salvage of hypoxanthine and guanine into their respective monophosphates, IMP and guanosine monophosphate (GMP). This recycling strongly inhibits IMP synthesis. With loss of functional HPRT through mutations in its gene, the lack of negative feedback of IMP synthesis leads to gross overproduction of IMP, which then is degraded to hypoxanthine and then to increased amounts of uric acid.

personal communication). Thus, HPRT deficiency should not be ruled out altogether in a woman with appropriate symptoms.

All degrees of deficiency may present in the first weeks of life with crystalluria, acute renal failure, and gout, sometimes leading to dialysis, transplantation, or death in infancy.[15-17] The severe syndrome of incapacitating LND includes bizarre symptoms such as spasticity with pyramidal tract signs, compulsive self-mutilation, choreoathetosis, and developmental retardation.[5-7,18] The diagnosis in LND patients frequently is delayed for many years; although self-mutilation is present, such patients sometimes have been thought to have cerebral palsy of unknown cause because the plasma urate level—even if measured—has been normal. Urine uric acid always must be measured as well because children have a higher renal urate clearance than adults and much lower plasma urate concentrations. It is often the renal complications or gout that eventually have drawn attention to the underlying metabolic defect.[18] The same is true for partial HPRT deficiency.[19,20] Although rare, the incidence in the United Kingdom for HPRT deficiency is greater than for other genetic disorders of purine metabolism. Approximately one third of HPRT-deficient patients are new mutations, and two-thirds have had severe neurologic deficits.

Biochemical Diagnosis

Gross overproduction and excretion of uric acid is present in all cases irrespective of the degree of enzyme deficiency, but plasma uric acid may not appear to be increased until puberty because of the greater fractional clearance (FE_{ur}) of urate in children compared with adults. In the absence of renal failure, uric acid excretion assessed relative to urinary creatinine is increased 2- to 4-fold in HPRT-deficient children and adults,[9] and urinary hypoxanthine excretion is increased similarly.[6,19]

However, excessive uric acid excretion relative to creatinine may be masked in both children and adults already presenting in acute renal failure.[15,19] In this situation, the diagnostic criterion is the grossly and disproportionately increased plasma uric acid level (often >1 mmol/L [15 mg/dL]) or even swollen gouty fingers in some neonates. Renal ultrasound provides the first clue to the correct diagnosis in the latter by displaying the bright ultrasonogram of crystal nephropathy. Uric acid stones may be the unique manifestation in other cases.

HPRT deficiency may be confirmed by the low to undetectable concentrations of HPRT activity in lysed red cells, and generally is associated with an increased adenine phos-

phoribosyl transferase (APRT) activity.[9] Because HPRT is undetectable in lysed red cells in the majority of deficient patients, intact cell studies are essential to confirm the genotype.[6,8,15] That up to 30% of cases are new mutations has presented problems for carrier detection, which until now could not be confirmed with total certainty, either by hair root analysis or biochemical methods.[21] DNA methods for carrier detection are more certain if the mutation is known. Gonosomal mosaicism (ie, a mutation in the ovary in the HPRT gene) is possible in noncarrier women with a previous HPRT-deficient child, and this carries a high risk for recurrence. Thus, antenatal testing in subsequent pregnancies may be needed. Antenatal diagnosis is possible by direct enzyme assay by using chorionic villus sampling in the first trimester, or fetal blood in the second trimester,[6,8,22] and by DNA analysis of chorionic villus samples likewise, if the mutation is known.[23,24] Preimplantation diagnosis is now possible as well,[25] thus permitting selection of unaffected blastocysts for in vitro fertilization.

Treatment

The increased uric acid concentrations in either the complete or partial deficiencies may be controlled by a high fluid intake, together with alkali and allopurinol. This drug should be used with care because urinary oxypurine excretion in all HPRT-deficient patients appears exquisitely sensitive to allopurinol, resulting in a rapid increase in concentrations of xanthine, which also is extremely insoluble. Unlike the uric acid that it replaces, the solubility of xanthine is relatively unaltered by alkalinization of the urine. Thus, patients with partial HPRT deficiency and gout may suffer a decrease in renal function from xanthine nephropathy when on long-term high-dose allopurinol. The allopurinol metabolite oxipurinol is also relatively insoluble, and both xanthine and oxipurinol calculi have been reported in patients with LND on long-term allopurinol therapy.[26,27] As in all patients with renal failure or insufficiency, the allopurinol dose must be monitored carefully, and decreased if necessary to no more than 5 mg/kg per 24 hours in children, or 100 mg per 24 hours in adults[16,19] to minimize accumulation of oxipurinol, as well as xanthine. Some patients with HPRT deficiency have progressed to end-stage renal disease and transplantation, but it should be noted that inevitably in such cases azathioprine will be ineffective (because its action depends on recycling of 6-mercaptopurine to 6-thioinosinic acid) and mycophenolate mofetil could have catastrophic consequences (by blocking guanine nucleotide synthesis from inosinic acid when guanine re-use via HPRT is absent) (Fig. 2). Cyclosporine alone has proved successful. Occasionally, very severe acute hyperuricemia and even acute renal failure have been seen, usually from tubular obstruction by a mixture of uric acid and xanthine crystals.[19] In these patients, recombinant urate oxidase (rasburicase) would appear to have a role, as in the tumor lysis syndrome, but this has not been studied yet.

The long-term prognosis is good in children and adolescents with the partial defect, but patients with complete LND rarely survive beyond adolescence. Death usually is caused by aspiration pneumonia or renal failure.[5,6,18] Sadly, no successful treatment is yet available for the severe neurologic complications, whose exact pathogenesis remains a mystery, although a defect in the basal ganglia associated with decreased dopamine concentrations seems to be central.

Phosphoribosyl Pyrophosphate Synthetase Superactivity

The enzyme phosphoribosyl pyrophosphate synthetase (PRPS) catalyzes the transfer of the pyrophosphate group of adenosine triphosphate to ribose 5-phosphate to form PP-ribose-P, and is an essential step in the synthesis of purines (Fig. 2). This defect is unusual in that overactivity of the enzyme arises from a mutant gene.

Genetics and Clinical Presentation

As with HPRT deficiency, there are 2 extremes of presentation. The more severe presents in childhood and is associated with neurologic deficits. However two thirds of the patients with this rare X-linked disorder have presented with isolated severe gout or kidney stones in adolescence or early adulthood.[28,29] Two distinct X-linked loci (PRS1 and PRS2) have been identified for the PRPS genes.[29,30] PRS1 maps to the Xq21-qter region and PRS2 maps to the short arm of X (Xp22.3-p22.3). The latter escapes X-chromosome inactivation. A third testis-specific transcript is encoded by another gene on chromosome 7.[30] Two PRS-associated proteins have been identified in the rat and may play a role in PRS regulation.[31,32] An association between the kinetic defect and the severity of the phenotypic expression, as in HPRT deficiency, is evident.

Patients may present neonatally or in childhood with severe neurodevelopmental retardation, dysmorphic features, sometimes inherited nerve deafness, a family history of repeated attacks of bronchopneumonia, and death in early infancy. In addition, there is gross purine overproduction and uric acid crystals in the kidney.[29,33] The diverse phenotypic presentations in PRPS superactivity and altered allosteric regulation is reflected in the genetic heterogeneity of mutation in the PRS1 gene. Six independent point mutations resulting in amino acid substitutions between residues 52 and 192 of the polypeptide have been identified.[29]

Although this defect is X-linked, it should be suspected in any child or young adult of either sex with marked hyperuricemia and/or hyperuricosuria, but with normal HPRT activity in lysed red cells.[28,29] Consequently (unlike HPRT deficiency), PRPS overactivity should be considered as a cause of gout and uric acid stones in premenopausal women, particularly in mothers of boys with neurologic deficits or urate overproduction. Female carriers also may have sensorineural deafness. As in HPRT deficiency, the first suspicion may derive from the finding of crystals on the diaper or the tip of the penis of a child with these neurologic deficits.[33] Reported values for PRPS activity have varied widely with the method and cell type used. Patients with the defect have had variant

enzymes that were insensitive to normal regulation or with catalytic activity 2 to 4 times greater than normal.[29]

Treatment

Prognosis is good for patients presenting in adolescence. Allopurinol, again used with care to avoid xanthine nephropathy, will control plasma uric acid levels in patients with normal renal function and gout or kidney stones. A high fluid intake and alkalinization of the urine may help, and in renal failure the dose must be decreased even further as indicated earlier. To date, no successful therapy for the associated neurologic complications in severe cases has been devised, and death in childhood is frequent.

Glycogen Storage Disease Type I

Another nonpurine metabolic defect that can present as acute renal failure in infancy, childhood, or early adult life associated with hyperuricemia is glycogen storage disease type I. This results from a deficiency of glucose 6-phosphatase.[34] The disorder must be considered when there is evidence of overproduction of uric acid in the face of normal purine enzymes. The purine overproduction arises from a combination of accelerated adenosine triphosphate breakdown and increased synthesis. The associated lactic acidosis affects the tubular transport of uric acid, thereby greatly exaggerating the appearance and severity of hyperuricemia (see article by Kang in this issue).[35]

Inherited Hyperuricemias of Renal Tubular Origin

Hyperuricemia is also the presenting manifestation of a group of familial disorders that have received little attention until recently, and that equally affect young men or young women, and even children of either sex.

FJHN

Although first described over 40 years ago,[36] this group of patients had been characterized poorly in the past.[37,38] They are now usually given the clinical description of *familial nephropathy with gout* or *familial juvenile hyperuricemic nephropathy* (FJHN). The condition may be associated with juvenile onset of gout and frequently progressive renal disease, and is distinguished clearly from the classic primary gout of the middle-aged man[39] or the gouty Polynesian population.[2] In both of these groups, obesity is a frequently associated characteristic, and renal function usually is normal for age. It is now clear that FJHN is a syndrome, not the result of defects in a single gene (see discussion of genetics later).

Clinical Presentation and Evolution

The onset of FJHN is common in childhood, adolescence, or early adult life, although cases presenting later have been seen. Renal failure often is recognized between 20 and 40 years of age. Autosomal-dominant inheritance is suggested by the presentation in consecutive generations, the equal ratio of sexes, and transmission from father to son.

FJHN was considered rare until recently, but about 70 kindreds have now been studied in the United Kingdom alone. The condition often has been missed in the past, and a diagnosis of *familial renal disease* of undetermined type was made until—and only if—an isolated attack of gout (which is rare in uncomplicated renal failure or young women) appeared in 1 or more family members. Because gout is an inconstant feature,[38,41] the term *hyperuricemia* is preferable although gout is clearly an important factor in drawing attention to such kindreds.[38,40] Importantly and in contrast to medullary cystic kidney disease (MCKD) (see later), the majority of patients are normotensive, but hypertension may be found, usually of late onset in those with renal dysfunction.

Diagnosis

There are 2 biochemical hallmarks for FJHN: the first is hyperuricemia disproportionate to the age, sex, or degree of renal dysfunction (although in occasional affected family members the diagnosis may be masked by a low purine intake); the second and crucial finding is that the degree of renal hypoexcretion of urate is extreme, with an absence of the usual sex and age differences—figures as low as 1% excretion of FE_{ur} have been published. The mean FE_{ur} in FJHN is only 5.1% and is equally low in young men, women, and children.[42] This value is lower even than the 5.4% found in middle-aged gouty men, and clearly explains the associated hyperuricemia and tendency to gout found even in young women and children in these kindreds.[42] The grossly decreased mean FE_{ur} found in affected children is even more striking when compared with the normally high FE_{ur} of their healthy counterparts (range, 12% to 30%). However, the very low FE_{ur} in FJHN increases if renal failure supervenes,[37,40] and in consequence in early uremia the FE_{ur} may be normal for a while[37] and thus confuse diagnosis. Symptomless members of affected families may show similar defects in urate and even decreased renal function and should be screened. A crucial point in terms of understanding possible pathogenesis is that the low FE_{ur} precedes all other manifestations of the disease in some patients in affected families who are apparently normal to begin with.[42,43] Proteinuria is minimal or absent and the sediment is nonspecific with hyaline and granular casts. Minor degrees of microscopic hematuria may be present.

Pathology and Pathogenesis

Histologically, the kidney usually shows patchy areas of tubular atrophy and fibrosis, with focal interstitial infiltration of lymphocytes and histiocytes and globally or segmentally sclerosed glomeruli. Associated gross thickening and sometimes reduplication of the basement membrane in distal tubules and collecting ducts has been observed.[42,44-46] These histologic features are nonspecific but similar to those reported in families linked to the autosomal-dominant MCKD (ADMCKD2) locus (see later),[47,48] in whom microcysts may

be present on histology, and larger cysts on echography. However, in a few patients with FJHN, the paucity of any abnormal features in the biopsy examination has been remarkable, despite an already significantly decreased renal function. Uric acid crystals have been reported in only 3 of more than 50 biopsy specimens,[45,49] but the absence of crystals does not exclude their presence in the past because in experimental models they may be re-absorbed or translocate.[45]

The manner in which the renal failure, the low FE_{ur}, and hyperuricemia may relate to one another in FJHN has been the subject of much debate. Urate production is normal in all cases as judged by urinary excretion on a purine-free diet. A decreased FE_{ur} for age and sex precedes any decrease in the glomerular filtration rate in otherwise apparently healthy patients,[42,43] **s**uggesting a primary defect in urate handling with secondary (or late associated) renal damage. Lhotta et al[50] suggested a gain-of-function mutation of the luminal anion exchanger of the proximal tubule would be consistent with decreased uric acid excretion, dominant inheritance, and the observed apoptosis of tubular epithelial cells. A low FE_{ur} might damage the tubules in some way through an increased transtubular flux of urate.[51] This suggestion seems less likely now that the exchanger (URAT-1) has been cloned and localized to chromosome 11q,[52] a region that has not yet been associated with FJHN. Alternatively, hyperuricemia induced in a rat model was implicated directly in renal fibrosis through a crystal-independent mechanism[53] (see article by Johnson in this issue). The beneficial effect of allopurinol in families studied for up to 36 years, and the retention of normal renal function in children treated sufficiently early, also provides support for the primacy of urate in the renal damage.[54]

Conversely, it has been suggested that abnormal urate handling may be an early manifestation of an underlying renal disease resulting from abnormal regulation of nephrogenesis, perhaps mediated by a defective G protein–coupled receptor.[47] A further proposal is that the disorder arises from a primary intrarenal vasoconstriction, with a secondary decrease in FE_{ur},[41] an extension of the work of Messerli et al[55] in general gout. This hypothesis, however, has a major weakness in that measurements of renal vascular resistance rest on the assumption of normal tubular handling of the para-aminohippurate used to derive renal plasma flow and hence blood flow indirectly—an unsafe assumption because urate and para-aminohippurate share renal tubular transporters and urate transport is grossly disturbed. However, there is also some echo Doppler evidence for vasoconstriction in FJHN,[56] and vasoconstrictive purinergic nerves are present within the kidney. Ischemic changes may be seen also in the histology of FJHN (eg, glomerular collapse), but are relatively nonspecific.

If mutations of the UMOD gene (see later) leading to synthesis of mutant forms of uromodulin (Tamm-Horsfall protein) underlie from approximately one quarter to one half of cases of FJHN in different series, it is difficult to find an explanation of how a low FE_{ur} might come about. The general view has been that in mammals the bidirectional exchange of urate is complete by the end of the mammalian proximal tubule,[57] although direct observation of this is of course lacking in primates, including humans. In contrast, uromodulin normally is localized rather strictly to the thick ascending loop of Henle.[58] Although the luminal, partially sodium-linked anion exchanger responsible for urate re-absorption is confined to the proximal tubule in humans as well as rodents,[52,57] it may be that the voltage-dependent pathways that contribute to urate secretion may be found at a more distal site as well. Hisatome et al[59] interpreted their pharmacologic observations in FJHN to suggest a defect in secretion, but the basis of this type of interpretation now seems insecure.[57] Until more is known of the renal tubular handling of urate, it is difficult to say more.

A final possibility is that the low FE_{ur} is the result of polyuria and salt loss, leading to volume contraction, of which low FE_{ur} and hyperuricemia is a consequence. However, neither polyuria nor salt loss are features of FJHN, and in autosomal-dominant medullary cystic kidney disease (ADMCKD) (see later) in which both are prominent features (unlike in FJHN), hyperuricemia is found only in a minority of affected individuals. Finally, in nephronophthisis resulting from mutations in the NPH1 gene, in which polyuria is universal, hyperuricemia is not found and in the few such cases in which it has been measured, FE_{ur} was normal or increased, not decreased.

Treatment

The management of FJHN likewise includes therapies about which there is little disagreement, and others that remain contentious. Aggressive control of high blood pressure, where present, generally is thought to be crucial for a successful outcome. The role of allopurinol (and hence a decrease of hyperuricemia) in ameliorating the progression of the renal disease has been stressed by some,[46] including ourselves for some 2 decades now,[42,54] but is disputed by others.[40,41,60] An important point is that efficacy of allopurinol clearly relates to the degree of renal damage at the time of treatment initiation, as well as patient compliance. In compliant patients from 21 FJHN kindreds studied for up to 36 years and treated sufficiently early (ie, before the onset of renal disease), improvement was seen;[45] whereas in those treated later it was ineffective, as in the study of Puig et al.[41] The cohort studied by Farebrother et al[45] included families now known to have the UMOD mutation (see later). If decreased uric acid excretion is caused by a gain-of-function mutation of a proximal tubule anion exchanger, then treatment with a combination of allopurinol to decrease the renal urate load, together with benzbromarone to block the tubular anion exchanger,[50] may be even more beneficial, and is effective even in renal failure.[59,81] Benzbromarone has a possible advantage over allopurinol because it restores the FE_{ur} toward normal, whereas FE_{ur} remains unchanged under allopurinol treatment.

Renal transplantation has been performed in some first-generation cases either undiagnosed or not diagnosed sufficiently early. Approximately 50% of these grafts have failed,

but no consistent explanation is present for this high failure rate. As would be expected if this is a disorder of renal urate transport, the remainder have retained stable graft function for 15 years or more, free of clinical gout or hyperuricemia. However, most have been treated with continued allopurinol treatment in doses appropriate to renal function because gout is common in the transplant population, particularly in those treated with cyclosporin and diuretics together.

ADMCKD

MCKD was first described in 1945,[62] and in 1951 Fanconi et al[63] noted the features of what they called *nephronophthisis* in children. During the 1960s it generally was thought[64,65] that these 2 conditions were part of a single complex, but subsequent decades have shown that they are 2 quite distinct groups of disorder, after the identification of recessive medullary cystic diseases associated with mutations in a gene now called NPH1,[66] located on chromosome 2q12 to 13, which codes for the 83-kd intracellular protein nephrocystin. Further varieties of recessive nephronophthisis with infantile and adolescent onset are associated with mutations in genes NHP2 (9q 22-31) and NHP3 (3q21-22) and possibly NHP4. The important fact for the present argument concerning these polyuric, volume-contracted patients is that they do not show hyperuricemia (except in very advanced renal failure), and similar to most forms of renal insufficiency, do not develop clinical gout. Even early in the disease, the few observations of FE_{ur} have shown increased or normal levels.

In parallel, the much rarer dominantly inherited forms of medullary cystic disease have been described and explored. The main clinical characteristics are an onset in early or later adult life rather than in childhood as in nephronophthisis, with a generally slow evolution into chronic renal insufficiency. The kidneys are small and echogenic and usually (but not invariably) display small medullary cysts on echography. Despite the presence of polyuria, hypertension is common and often precocious, in contrast to FJHN in which it is inconstant and late in presentation. Microscopically, the characteristic appearance is tubulointerstitial nephritis with thickened tubular basement membranes—a nonspecific appearance seen also in FJHN. However, tubular dilation is present and microcyst formation can be seen. Twenty years ago, 2 families were identified[67,68] that could be described clinically as having FJHN, but whose members had medullary cysts also. Much later, Scolari et al[69] in 1999 and Christodoulou et al[70] in 1998 emphasized that a proportion of the affected members of their families with MCKD of either 1q or 16p linkage (see later) showed hyperuricemia, and a few showed clinical gout. Some affected members did not show cysts on echography, but did have all the other features including hyperuricemia. They thus resemble patients categorized as having FJHN. Unfortunately, little data on FE_{ur} in MCKD1 are available,[71] and none at all on affected patients of either type of MCKD before signs (including cysts) and symptoms develop. One must not forget either that a low FE_{ur} may be present even when plasma uric acid concentration is within normal limits, as in some affected patients described by Bleyer et al,[40] if purine intake is low. Thus, the absence of hyperuricemia does not exclude abnormal renal handling of urate.

Clinical Genetics of FJHN and MCKD

The first observations of a genetic linkage was in MCKD, to chromosome 1q21, described in 1998 in a Cypriot family with MCKD,[70] with other local families showing similar results later.[71] In these families, hyperuricemia was common and gout occurred occasionally.[71] Then Kamatani et al[72] reported in 2000 a linkage to 16p12 in a large Japanese family with FJHN who presented with gouty arthritis, renal failure, and (unusually) hypertension;[61] no medullary cysts were noted. Linkage to 16p11.2 was shown also in 2 of 3 Czech families with FJHN with hyperuricemia, decreased FE_{ur}, gouty arthritis, and renal insufficiency.[73] At almost the same time in 2001, an additional localization for MCKD at 16p12, which was termed *MCKD2* by Scolari et al[69] was found in a family with occasional small medullary cysts (in 1 of 7 patients), but typical small fibrotic kidneys. Hyperuricemia and gouty arthritis consistent with a diagnosis of FJHN were also a feature of the clinical presentation. Hateboer et al[74] studied a large Welsh family with linkage to this site, although no members of this family showed hyperuricemia or gout.

Studies in a large Belgian FJHN family[47] refined the critical region of the 16p11-12 locus further, as has the work of Stacey et al[75] in 7 FJHN families. In view of the striking clinical and pathologic resemblance between MCKD families linked to the MCKD2 locus in their FJHN family, several observers, especially Dahan et al,[47] have suggested that the 2 disorders might be allelic at the same mutation, but an alternative hypothesis is that 2 separate but closely linked disease-associated genes are at the MCKD2 locus.

Candidate genes in the 16p11-12 region were examined, but initially none appeared to be involved in FJHN[76] and in MCKD, including the UMOD gene coding for uromodulin (Tamm-Horsfall protein).[76] However, Hart et al[78] clearly described a mutation in UMOD in 2 large families with a phenotype of FJHN[40] and also in a single family with MCKD, and re-examination of data from the Italian family of Pirulli et al[77] revealed that they, too, had a UMOD mutation.[79] Recently, Turner et al[80] also found UMOD mutations in 3 families with FJHN, Dahan et al[48] in 11 families with FJHN, and Wolf et al[81] in 3 further families, this time stated to have MCKD although the brief clinical details given suggest that cyst formation was minimal. Most of these mutations occur in exon 4 of the UMOD gene. A quarter of a century ago, abnormal distribution of uromodulin within the kidney had been noted in interstitial disease,[82,83] thus strengthening the suggestion of a pathogenetic role for uromodulin. Dahan et al[48] in FJHN and Rampoldi et al[84] in MCKD showed also that mutant forms of uromodulin accumulate within the tubular cells of the ascending limb, with low urinary excretion of the protein, and postulated defective translocation of uromodulin as the central event in these diseases. Rampoldi et al[84] also extended the syndrome of FJHN-MCKD uromodulin–associated disor-

ders to include some patients with dominantly inherited glomerulocystic disease.

However, a number of families with both FJHN and MCKD2,[73,76,85-87] and all families with MCKD1 and hyperuricemia, localized on chromosome 1[71] do not show a linkage to 16p11-12. Of families studied in our unit, exons 4 and 5 of the uromodulin gene have been sequenced in 13 kindreds, and UMOD mutations were found in only 4 of them (AM Marinaki, personal communication, 2003). These data suggest that the clinical variation seen in affected families may reflect an underlying genetic heterogeneity. The proportion of families showing UMOD mutation in either FJHN or MCKD seems to be less than 50% at most. Wolf et al[81] detected these in only 3 of 19 families studied with FJHN, and Dahan et al[48] in 11 of 25 families studied. Recently, a new locus was noted in another family from the United Kingdom that was studied clinically by us, and also in a Belgian family (Hodañová et al, personal communication, 2003). Onset of diabetes type 2 in another of our families with FJHN led to the diagnosis of a mutation in the hepatocyte nuclear factor-1β gene on chromosome 17.[88]

Clearly, despite the importance of UMOD mutations and the likelihood that it, or closely related genes, account for the disease in the majority or all 16p-linked families, there is considerable genetic heterogeneity in both FJHN and MCKD. It is, of course, possible that the additional mutations identified by us on chromosomes 1 and 17 could affect folding, translocation, or glycophosphoinositol (GPI) anchoring of (normal) uromodulin; this possibility is under study. In the study by Dahan et al,[48] however, patients with FJHN not related to UMOD mutations failed to show decreased uromodulin excretion.

This genetic heterogeneity makes the understanding of the pathogenesis of the hyperuricemia and the renal failure all the more difficult. What exactly is the relationship between the 2 phenotypes described so far? At a clinical level, we have never observed evolution of cysts or cysts at post mortem in any of our families diagnosed as having FJHN and who were followed-up for many years, and in fact have yet to encounter a family in the United Kingdom with hyperuricemia and medullary cysts, despite extensive referral of patients with uric acid problems to our laboratory for investigation. However, the resolution of current imaging techniques may not be sufficient to show microcysts, and often renal biopsy examinations do not sample the whole depth of the renal medulla to show them. Despite the similarities, there are clinical differences, particularly in relation to the age at onset, and the timing and frequency of hypertension. The genetic basis for this heterogeneity will emerge as more data become available. Finally, how the decreasing of FE_{ur} occurs and what role hyperuricemia plays in the genesis of the disease remain controversial: chronic hypovolemia from polyuria[40] does not appear to us to be an adequate explanation for the low FE_{ur}.

References

1. Gibson T, Waterworth P, Hatfield P, et al: Hyperuricaemia, gout and kidney function in young New Zealand Maori men. Br J Rheumatol 23:276-282, 1984
2. Simmonds HA, McBride MB, Hatfield PJ, et al: Polynesian women are also at risk for hyperuricaemia and gout because of a defect in renal urate handling. Br J Rheumatol 33:932-937, 1994
3. Short EG: Gout and hyperuricemia, in King RA, Rutter JI, Mitulsky G (eds): The Genetic Basis of Common Diseases. Oxford, Oxford University Press, 1992, pp 482-506
4. Emmerson BT, Nagel SL, Duffy DL, et al: Genetic control of the renal clearance of urate: A study of twins. Ann Rheum Dis 51:375-377, 1992
5. Watts RWE: Defects of tetrahydrobiopterin synthesis and their possible relationship to a disorder of purine metabolism, the Lesch-Nyhan syndrome. Adv Enzyme Regul 23:25-58, 1985
6. Jinnah HA, Friedmann T: Lesch-Nyhan disease and its variants, in Scriver CR, Beaudet AL, Sly WS, et al (eds): The Metabolic and Molecular Basis of Inherited Disease (ed 8). New York, McGraw Hill, 2001, pp 2537-2570
7. Jinnah HA, De Gregorio L, Harris JC, et al: The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases. Mutat Res 463:309-326, 2000
8. Page T, Nyhan WL: The spectrum of HPRT deficiency: An update. Adv Exp Med Biol 253A:129-133, 1989
9. Wyngaarden JM, Kelley WN: Gout and hyperuricemia. New York, Grune and Stratton, 1976
10. Khattak FH, Morris IM, Harris K: Kelley-Seegmiller syndrome: A case report and review of the literature. Br J Rheumatol 37:580-581, 1998
11. Ogasawara N, Stout JT, Goto H, et al: Molecular analysis of a female Lesch-Nyhan patient. J Clin Invest 84:1024-1027, 1989
12. Van Bogaert P, Ceballos I, Desguerre I, et al: Lesch-Nyhan syndrome in a girl. J Inherit Metab Dis 15:790-791, 1992
13. Aral B, de Saint Basile G, Al-Garawi S, et al: Novel nonsense mutation in the hypoxanthine guanine phosphoribosyltransferase gene and nonrandom X-inactivation causing Lesch-Nyhan syndrome in a female patient. Hum Mutat 7:52-58, 1996
14. De Gregorio L, Nyhan WL, Serafin E, et al: An unexpected affected female patient in a classical Lesch-Nyhan family. Mol Genet Metab 69:263-268, 2000
15. Cameron JS, Simmonds HA, Webster DR, et al: Problems of diagnosis in an adolescent with hypoxanthine-guanine phosphoribosyltransferase deficiency. Adv Exp Med Biol 165A:7-13, 1984
16. Simmonds HA, Cameron JS, Morris GS, et al: Allopurinol in renal failure and the tumour lysis syndrome. Clin Chim Acta 160:189-195, 1986
17. Stapleton FB: Uric acid nephropathy, in Edelmann CM Jr (ed): Pediatric Nephrology (ed 3). Boston, Little Brown, 1992, pp 1647-1659
18. McCarthy GT: Medical diagnosis, management and treatment of Lesch-Nyhan Disease. Nucleosides, nucleotides and nucleic acids. 2004 (in press)
19. Simmonds HA, Cameron JS, Barratt TM, et al: Purine enzyme defects as a cause of acute renal failure in childhood. Pediatr Nephrol 3:433-437, 1989
20. Augoustides-Savvopoulou P, Papachristou F, Fairbanks LD, et al: Partial hypoxanthine-guanine phosphoribosyltransferase deficiency as the unsuspected cause of renal disease spanning three generations: A cautionary tale. Pediatrics 109:E17, 2002
21. Puig JG, Mateos FA, Torres RJ, et al: Purine metabolism in female heterozygotes for hypoxanthine-guanine phosphoribosyltransferase deficiency. Eur J Clin Invest 28:950-957, 1998
22. Simmonds HA, Duley JA, Davies, PM: Analysis of purines and pyrimidines in blood, urine and other physiological fluids, in Hommes F (ed): Techniques in diagnostic human biochemical genetics. A laboratory manual. New York, Wiley-Liss, 1991, pp 397-425
23. Yamada Y, Suzumori K, Tanemura M, et al: Molecular analysis of a Japanese family with Lesch-Nyhan syndrome: Identification of mutation and prenatal diagnosis. Clin Genet 50:164-167, 1996
24. Torres RJ, Mateos FA, Molano J, et al: Molecular basis of hypoxanthine-guanine phosphoribosyltransferase deficiency in thirteen Spanish families. Hum Mutat 15:383, 2000
25. Ray PF, Harper JC, Ao A, et al: Successful preimplantation genetic diagnosis for sex linked Lesch–Nyhan Syndrome using specific diagnosis. Prenat Diagn 19:1237-1241, 1999

26. Brock WA, Golden J, Kaplan GW: Xanthine calculi in the Lesch-Nyhan syndrome. J Urol 130:157-159, 1983
27. Kenney IJ: Renal sonography in long standing Lesch Nyhan syndrome. Clin Radiol 43:39-41, 1991
28. Zoref E, de Vries A, Sperling O: Mutant feedback resistant phosphoribosyl-pyrophosphate synthetase associated with purine overproduction and gout. J Clin Invest 56:1093-1099, 1975
29. Becker MA: Hyperuricemia and gout, in Scriver CR, Beaudet AL, Sly WS, et al (eds): The Metabolic and Molecular Basis of Inherited Disease (ed 8). New York, McGraw Hill, 2001, pp 2513-2535
30. Ishizuka T, Iizasa T, Taira M, et al: Promoter regions of the human X-linked housekeeping genes PRPS1 and PRPS2 encoding phosphoribosylpyrophosphate synthetase subunit I and II. Biochim Biophys Acta 1130:139-148, 1992
31. Kita K, Ishizuka T, Ishijima S, et al: A novel 39-kDa phosphoribosylpyrophosphate synthetase-associated protein of rat liver. Cloning, high sequence similarity to the catalytic subunits, and a negative regulatory role. J Biol Chem 269:8334-8340, 1994
32. Sonoda T, Ishizuka T, Kita K, et al: Cloning and sequencing of rat cDNA for the 41-kDa phosphoribosylpyrophosphate synthetase-associated protein has a high homology to the catalytic subunits and the 39-kDa associated protein. Biochim Biophys Acta 1350:6-10, 1997
33. Christen H-J, Hanefeld F, Duley JA, et al: Distinct neurological syndrome in two brothers with hyperuricaemia. Lancet 340:1167-1168, 1992
34. Chen Y-T: Glycogen storage diseases, in Scriver CR, Beaudet AL, Sly WS, et al (eds): The Metabolic and Molecular Basis of Inherited Disease (ed 8). New York, McGraw Hill, 2001, pp 1521-1551
35. Stone TW, Simmonds HA: Purines: Basic and clinical aspects. London, Kluwer, 1991
36. Duncan H, Dixon A. Gout, familial hyperuricaemia, and renal disease. QJM 29:127-136, 1960
37. Calabrese G, Simmonds HA, Cameron JS: Precocious familial gout with reduced fractional excretion of urate and normal purine enzymes. QJM 75:441-450, 1990
38. Cameron JS, Moro F, Simmonds HA: Gout, uric acid and purine metabolism in paediatric nephrology. Pediatr Nephrol 7:105-118, 1993
39. Berger L, Yü T-F: Renal function in gout. IV. An analysis of 524 gouty subjects including long-term studies. Am J Med 59:605-613, 1975
40. Bleyer AJ, Woodward AS, Shibabi Z, et al: Clinical characterization of a family with a mutation in the uromodulin (Tamm-Horsfall glycoprotein) gene. Kidney Int 64:36-42, 2003
41. Puig JG, Miranda ME, Mateos FA, et al: Hereditary nephropathy associated with hyperuricaemia and gout. Arch Intern Med 153:357-365, 1993
42. McBride MB, Simmonds HA, Ogg CS, et al: Presymptomatic detection of familial juvenile hyperuricaemic nephropathy in children. Pediatr Nephrol 12:359-364, 1998
43. Moro F, Ogg CS, Simmonds HA, et al: Familial juvenile gouty nephropathy with renal urate hypoexcretion preceding renal disease. Clin Nephrol 35:263-269, 1991
44. Simmonds HA, Warren DJ, Cameron JS, et al: Familial gout and renal failure in young women. Clin Nephrol 14:176-182, 1980
45. Farebrother DA, Simmonds HA, Warren D, et al: Uric acid crystal-induced nephropathy: Evidence for a specific renal lesion in a gouty family. J Pathol 135:159-168, 1981
46. Richmond JM, Kincaid-Smith P, Whitworth JA, et al: Familial urate nephropathy. Clin Nephrol 16:163-168, 1981
47. Dahan K, Fuchshuber A, Adamis S, et al: Familial juvenile hyperuricemic nephropathy and autosomal dominant medullary cystic kidney disease type 2: Two facets of the same disease? J Am Soc Nephrol 12:2348-2357, 2001
48. Dahan K, Devuyst O, Smaers M, et al: A cluster if mutations in the UMOD gene causes familial juvenile hyperuricemic nephropathy with abnormal expression of uromodulin. J Am Soc Nephrol 14:2883-2893, 2003
49. Reiter L, Brown MA, Edmonds J: Familial hyperuricemic nephropathy. Am J Kidney Dis 25:235-241, 1995
50. Lhotta K, Gruber J, Sgonc R, et al: Apoptosis of tubular epithelial cells in familial juvenile gouty nephropathy. Nephron 79:340-344, 1998
51. Gresser U, Zöllner N (eds): Urate deposition in man and its clinical consequences. Berlin, Springer-Verlag, 1999
52. Enomoto A, Kimura H, Chairoungdua A, et al: Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature 417:447-452, 2002
53. Mazzali M, Hughes J, Kim YG, et al: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 38:1101-1106, 2001
54. Fairbanks LD, Cameron JS, Venkat-Raman G, et al: Early treatment with allopurinol in familial juvenile hyperuricaemic nephropathy ameliorates progression of renal disease in long-term studies. QJM 95:597-607, 2002
55. Messerli FH, Frolich ED, Dreslemski ER, et al: Serum uric acid in essential hypertension: An indicator of renal vascular involvement. Ann Intern Med 93:817-821, 1980
56. Prieto C, Berrocal T, on behalf of the Spanish group for the study of FNAH. Ultrasound imaging and colour Doppler studies in familial nephropathy associated with hyperuricemia (FNAH). Adv Exp Med Biol 370:65-68, 1995
57. Roch-Ramel F: Renal transport of organic anions. Curr Opin Nephrol Hypertens 7:17-24, 1998
58. Kumar S, Muchmore A: Tamm-Horsfall protein-uromodulin (1950-1990). Kidney Int 37:1395-1401, 1990
59. Hisatome I, Kosaka H, Ohtahara K, et al: Renal handling of urate in a patient with familial juvenile gouty nephropathy. Intern Med 35:564-568, 1996
60. Yakota N, Yamanaka H, Yamamoto Y, et al: Autosomal dominantly transmission of gouty arthritis with renal disease in a large Japanese family. Ann Rheum Dis 50:108-111, 1991
61. Lhotta K: Stopping progression in familial juvenile hyperuricemic nephropathy with benzbromarone? Kidney Int 64:1920-1921, 2003 (letter)
62. Smith CH, Graham YB: Congenital medullary cystic disease of the kidney with severe refractory anemia. Am J Dis Child 69:369-377, 1945
63. Fanconi G, Hanhart E, von Albertini A, et al: Die familiäre juvenile nephronophthise. Helv Paediatr Acta 6:1-9, 1951
64. Mongeau JG, Worthen HG: Nephronophthisis and medullary cystic kidney disease. Am J Med 43:345-355, 1967
65. Gardner KD: Evolution of clinical signs in adult-onset cystic disease of the renal medulla. Ann Intern Med 74:47-54, 1971
66. Antignac C, Arduy CH, Beckmann JS, et al: A gene for familial juvenile nephronophthisis (recessive medullary cystic kidney disease) maps to chromosome 2p. Nat Genet 3:342-345, 1993
67. Thompson GR, Wess JJ, Goldman RT, et al: Familial occurrence of hyperuricemia, gout and medullary cystic disease. Arch Intern Med 138:1614-1617, 1978
68. Burke JR, Inglis JA, Craswell PW: Juvenile nephronophthisis and medullary cystic disease: The same disease. Report of a large family with medullary cystic disease associated with gout and epilepsy. Clin Nephrol 18:1-8, 1981
69. Scolari F, Puzzer F, Amoroso A, et al: Identification of a new locus for medullary cystic disease, on chromosome 16p12. Am J Hum Genet 64:1655-1660, 1999
70. Christodoulou K, Tsingis M, Stavrou C, et al: Chromosome 1 localization of a gene for autosomal dominant medullary cystic kidney disease. Hum Mol Genet 7:905-911, 1998
71. Stavrou C, Koptides M, Tombazos C, et al: Autosomal-dominant medullary cystic kidney disease type 1: Clinical and molecular findings in six large Cypriot families. Kidney Int 62:1385-1394, 2002
72. Kamatani, N. Moritani M, Yamanaka H, et al: Localization of a gene for familial juvenile hyperuricemic nephropathy causing underexcretion-type gout to 16p12 by genome-wide linkage analysis of a large family. Arthritis Rheum 43:925-929, 2000
73. Stibùrková B, Majewski J, Hodaňová K, et al: Familial juvenile hyperuricemic nephropathy: Localization of the gene on chromosome

16p11.2-and evidence for genetic heterogeneity. Am J Hum Genet 66:1989-1994, 2000
74. Hateboer N, Gumbs C, Teare MD, et al: Confirmation of a gene locus for medullary cystic kidney disease (MCKD2) on chromosome 16p12. Kidney Int 60:1233-1239, 2001
75. Stacey JM, Turner JJ, Harding B, et al: Genetic mapping studies of familial hyperuricemic nephropathy on chromosome 16p11-13. J Clin Endocrinol Metab 88:464-470, 2003
76. Stibůrková B, Majewski J, Hodaňová K, et al: Familial juvenile hyperuricaemic nephropathy (FJHN): Linkage analysis in 15 families, physical and transcriptional characteristics of the FJHN critical region and analysis of 7 candidate genes. Eur J Hum Genet 11:145-154, 2003
77. Pirulli D, Puzzer D, De Fusco M, et al: Molecular analysis of uromodulin and SAH genes, positional candidates for autosomal medullary cystic kidney disease linked to 16p12. J Nephrol 14:392-396, 2001
78. Hart TC, Gorry MC, Hart MC, et al: Mutations of the UMOD gene are responsible for medullary cystic disease 2 and familial juvenile hyperuricaemic nephropathy. J Med Genet 39:882-892, 2002
79. Casari G, Amoroso A: Molecular analysis of uromodulin and SAH genes, positional candidates for autosomal dominant medullary cystic kidney disease linked to 16p12. J Nephrol 16:459, 2003
80. Turner JJ, Stacey JM, Harding B, et al: UROMODULIN mutations cause familial juvenile hyperuricemic nephropathy. J Clin Endocrinol Metab 88:1398-1401, 2003
81. Wolf MTF, Mucha BE, Attanasio M, et al: Mutations of the Uromodulin gene in MCKD type 2 patients cluster in exon 4, which encodes three EGF-like domains. Kidney Int 64:1580-1587, 2003
82. Resnick JS, Sisson S, Vernier RL: Tamm-Horsfall protein: Abnormal localization in renal disease. Lab Invest 38:550-555, 1978
83. Zager RA, Cotran RS, Hoyer JR: Pathologic localization of Tamm-Horsfall protein in interstitial deposits in interstitial disease. Lab Invest 38:52-57, 1978
84. Rampoldi L, Caridi G, Santon D, et al: Allelism of MCKD, FJHN and GCKD caused by impairment of uromodulin export dynamics. Hum Med Genet 12:3369-3384, 2003
85. Kroiss S, Huck K, Berthold S, et al: Evidence of further genetic heterogeneity in autosomal dominant medullary cystic kidney disease. Nephrol Dial Transplant 15:818, 2000
86. Auranen M, Ala-Mello S, Turunen JA, et al: Further evidence for linkage of autosomal-dominant medullary cystic kidney disease on chromosome 1q21. Kidney Int 60:1225-1232, 2001
87. Ohno I, Ichida K, Okabe H, et al: Familial juvenile gouty nephropathy: Exclusion of 16p12 from the candidate locus. Nephron 92:573-575, 2002
88. Bingham C, Ellard S, van't Hoff WG, et al: Familial juvenile hyperuricemic nephropathy associated with hepatocyte nuclear factor 1β gene mutation. Kidney Int 63:1645-1651, 2003