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Patient Report

Case report: Prenatal intervention for severe anterior urethral valve

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The presence of an anterior urethral valve (AUV), although uncommon compared with that of a posterior urethral valve (PUV), is one of the causes of obstructive uropathies in children. Congenital obstructive uropathies, when not severe, are rarely diagnosed during infancy, but some are diagnosed prenatally on the basis of findings such as oligohydramnios, hydronephrosis, hydroureter, urinoma and megacystis. Recently, fetal intervention has been performed in some patients with obstructive uropathies,[1–4] although its efficacy is still controversial. We herein present a patient with severe AUV on which the infusion of artificial amniotic fluid and vesico-amniotic shunting were performed. Although the long-term outcome of this patient's renal and urinary bladder functions needs to be followed up carefully, pulmonary maturation was achieved and the exacerbation of the obstructive nephropathy was prevented.

Case Report

A 25-year-old mother was introduced and admitted to The Tokyo University Hospital at 31 weeks of pregnancy because of oligohydramnios. The oligohydramnios was not noted before 30 weeks. Fetal ultrasonography at 31 weeks revealed a left perinephric urinoma, megacystis, bilateral hydronephrosis and hydroureter in the fetus. The fetus was male and had no other congenital anomalies suggesting chromosomal abnormalities. The mother had no other complications.

Lower urinary tract obstruction in the fetus was suspected. Although there was a risk of premature labor, his hydroureter deteriorated in a few days, and pulmonary immaturity was strongly suspected at this gestational age. Therefore, after obtaining informed consent from the parents, the infusion of artificial amniotic fluid followed by vesico-amniotic shunting was performed three times during the 32nd and 33rd weeks of gestation (Fig. 1). After the vesico-amniotic shunting, the hydronephrosis, hydroureter and left urinoma showed no prominent change, and the enlarged urinary bladder decreased in size markedly. The oligohydramnios improved and the volume of amniotic fluid was maintained thereafter. The sodium level of the fetal urine at first was 154 mEq/L; potassium, 0.8 mEq/L; chloride, 144 mEq/L; creatinine, <0.3 mg/dL; N-acetyl-β-D-glucosaminidase (NAG), 0.8 IU/L; and β_2-microglobulin, 0.46 mg/L. A serial chemical analysis of the fetal urine showed a rapid decrease in sodium (to 69 mEq/L) and chloride (to 59 mEql/) levels.

The amniotic membrane ruptured prematurely and a male infant was vaginally delivered at 33 weeks and 3 days of gestation weighing 2369 g with an Apgar score of 6 at 1 min and presenting with neonatal asphyxia. Because his spontaneous breathing was weak 3 min after the delivery, he was intubated immediately and an artificial surfactant was administered intratracheally. His body temperature was 36.6°C, his heart rate was 151 b.p.m., and his systemic blood pressure was 65/38 mmHg. He had no external malformations or any other abnormal clinical findings. After he was admitted to the neonatal intensive care unit, the basket catheters used for the vesico-amniotic shunting were removed.

Biochemical examination revealed: sodium, 136 mEq/L; potassium, 4.5 mEq/L; chloride, 103 mEq/L; serum creatinine, 0.56 mg/dL; and blood urea nitrogen, 5.6 mg/dL. Urinalysis showed proteinuria (2+), hematuria (occult blood [3+]), 21–50 red blood cells per high-power field and 6–10 white blood cells per high-power field. Urinary examination revealed: osmolarity, 221 mOsm/L; sodium, 89 mEq/L; chloride, 71 mEq/L; NAG, 22.4 IU/L; and α1-microglobulin, 37.2 mg/L. A chest X-ray showed no abnormalities. Ultrasonography revealed left kidney atrophy measuring 3.1 cm × 2.0 cm, left hydronephrosis and a perinephric urinoma. The right kidney was not atrophic, measuring 5.0 cm × 2.7 cm, with hydronephrosis and hydroureter. A thickening of the urinary bladder wall was detected.

He was initially ventilated with high-frequency oscillation and his respiratory condition gradually improved. He was successfully extubated on the 19th postpartum day.

A transurethral catheter (5 Fr) was smoothly inserted after birth and urine was successfully drained. Following tube-feeding with regular formula milk, his serum potassium level increased to 7.3 mEq/L on the 7th postpartum day. His serum creatinine level at that time was 1.68 mg/dL. Glucose-insulin therapy was performed and MM3 milk, a special formula for renal failure

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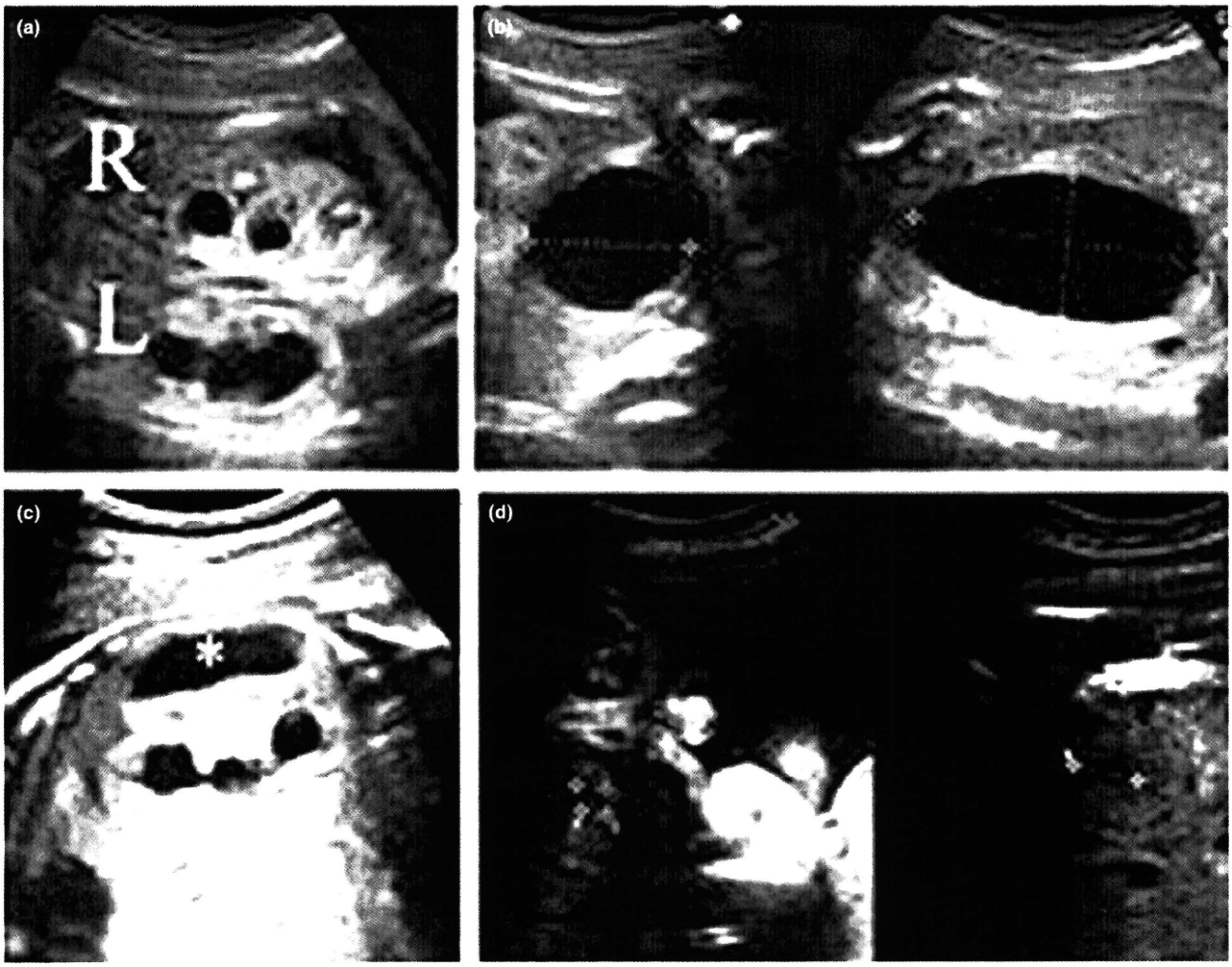

Fig. 1 Fetal ultrasonograms. (a) (Before *in utero* shunting) bilateral hydronephrosis was detected. (b) (Before *in utero* shunting) the urinary bladder was enlarged. (c) (After *in utero* shunting) the left urinoma (*) and hydronephrosis showed no change. (d) (After *in utero* shunting) the size of the urinary bladder was markedly decreased. The urinary bladder wall was markedly thickened.

ontaining a small amount of potassium (0.17 mEq/dL), was dministered. He had an episode of urinary tract infection on the 6th postpartum day. The insertion of a new transurethral catheter was unsuccessful even though the catheter with the smallest iameter (3 Fr) was used, and surgical cystostomy was performed immediately. On the 35th postpartum day, cystostomy vas performed again because of the difficulty of replacing the atheter of the initial cystostomy. The time course of his renal unction is shown in Figure 2. His creatinine clearance improved p to 50 mL/min/m^2, and the creatinine level decreased to .4 mg/dL. When the regular formula milk was restarted, his erum potassium level increased, so he was alternately fed with MM3 and regular formula milk.

When he was 2 months old, voiding cystourethrography VCUG) (Fig. 3), renal diethylene triamine pentaacetic acid DTPA) scintigraphy, and magnetic resonance imaging (MRI) vere performed. The initial contrast study was postponed to this ime because his general condition had been unstable, that is, urinary tract infection had repeated, and his serum potassium level was unstable. VCUG demonstrated left vesicoureteral regurgitation (VUR) with severe dilation of the left ureter but no right VUR. An anterior urethral diverticulum was also identified. Renal DTPA scintigraphy (not shown) revealed a nonfunctional pattern in the left kidney and delayed washout in the right kidney. The glomerular filtration rates (GFR) of the left and right kidneys were 36.4 and 63.7%, respectively. MRI results (not shown) showed bilateral hydronephrosis, hydroureters, and a thickened urinary bladder wall. The anterior urethra showed a water density area 16 mm in diameter. These findings strongly suggested the presence of AUV. Cystourethroscopic examination was not performed at that time because the urethra was too narrow. At 3 months of age, his bodyweight reached 4.4 kg, and he was definitively diagnosed as having AUV by cystourethroscopy. Temporary diversion with cutaneous vesicostomy was conducted, and transurethral incision of diverticulum or open urethral reconstruction will be undergone when his weight increases.

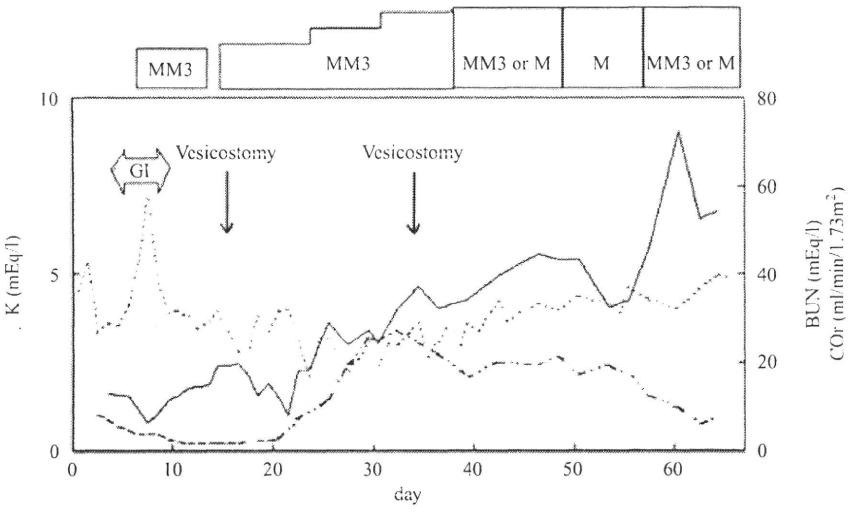

Fig. 2 Time course of renal function and treatment. With a series of treatments including prenatal intervention, postnatal cystostomy, and electrolyte management, the patient's renal function showed improvement during the first two postpartum months. K (dotted line), BUN (dotted and solid line), CCr (solid line). BUN, blood urea nitrogen; CCr, creatinine clearance; GI, glucose-insulin therapy; K, potassium; M, regular formula milk; MM3, special formula milk containing a small amount of potassium.

Discussion

Recently, Merrot *et al.*[5] reported a patient with AUV managed by prenatal urinary ascites evacuation. To our knowledge, this is the first report on a patient with AUV treated by vesico-amniotic shunting. There are several reports on the *in utero* treatment of obstructive uropathies other than AUV, but there are no randomized or large multicenter studies regarding the long-term outcome of *in utero* treatment. Antenatal vesico-amniotic shunting aims at relieving urinary obstruction and providing adequate amniotic fluid to improve renal and urinary bladder functions as well as lung maturation. According to several reports,[1–4] the overall survival rate is 40–91% in the cases treated with *in utero* shunting. Approximately 35% of patients who underwent *in utero* shunting developed renal failure. The complication rate was 10–45%. It is difficult to definitely assess whether prenatal intervention is effective, because the patients who underwent *in utero* shunting might have represented the worst end of the spectrum of obstructive uropathies. Even so, the above rate of renal failure suggests a possible benefit from *in utero* shunting. When the chemical analysis of fetal urine indicates sodium < 100 mEq/L, chloride < 90 mEq/L, osmolarity < 200 mOsm/L, β_2-microglobulin < 6 mg/L, calcium < 8 mg/dL and total protein < 20 mg/dL, the renal function of the fetus is regarded as good.[6]

In this patient, oligohydramnios, hydronephrosis and hydroureter were observed prenatally and lower urinary tract obstruction was suspected. Such urethral obstruction may lead to urinary tract rupture, resulting in ascites or perinephric urinoma.[7] This patient exhibited a left perinephric urinoma suggesting that the urethral obstruction was very severe. When severe urethral obstruction was suspected at 31 weeks of gestation, we had only two possible options: fetal intervention or an emergency cesarean section. Considering the pulmonary immaturity and possible respiratory complications such as respiratory distress syndrome and dry lung syndrome, we performed vesico-amniotic shunting to decompress the urinary tract and maintain an adequate volume of amniotic fluid for lung maturation. Vesico-amniotic shunting is superior to single vesicocentesis for the continuous drainage of fetal urine.

After the vesico-amniotic shunting and infusion of artificial amniotic fluid, the chemical analysis of the fetal urine showed a rapid improvement in sodium and chloride levels. The enlarged urinary bladder decreased in size, and the volume of amniotic fluid was maintained. The patient showed the symptom of acute respiratory distress after birth, but he was successfully extubated and developed no chronic lung disease. The function of the right kidney was maintained. Although it might be partly due to the "pop-off" phenomenon, he does not require dialysis treatment at the moment as a result of a series of treatments including prenatal intervention, postnatal cystostomy, and electrolyte management.

As for an expert and critical treatment for the anterior urethral valve, urethroscopic treatment during the neonatal period should be taken into account. Our patient will undergo transurethral incision of diverticulum or open urethral reconstruction after weight gain.

Because AUV is a very rare obstructive uropathy, there has been no report regarding the prognostic factors of AUV. According to Ylinen *et al.*,[8] who investigated the prognosis of PUV, the initial serum creatinine level, the maximum level of serum creatinine during the first year, the presence of bilateral VUR, and breakthrough urinary tract infections are prognostic factors of PUV. Bajpai *et al.*[9] showed that children with a normal or near normal serum creatinine level (0.8 mg/dL or less) at 1 year of age are able to maintain good renal function at the time of final evaluation (1.0 mg/dL or less). Lopez *et al.*[10] reported that the most significant prognostic factor is GFR at 1 year of age. The onset of proteinuria during the follow-up period is also associated with a poor prognosis. Our patient showed the following poor prognostic factors such as: left unilateral VUR, proteinuria, and an episode of urinary tract infection. The long-term outcome of his renal and urinary bladder functions should be followed up

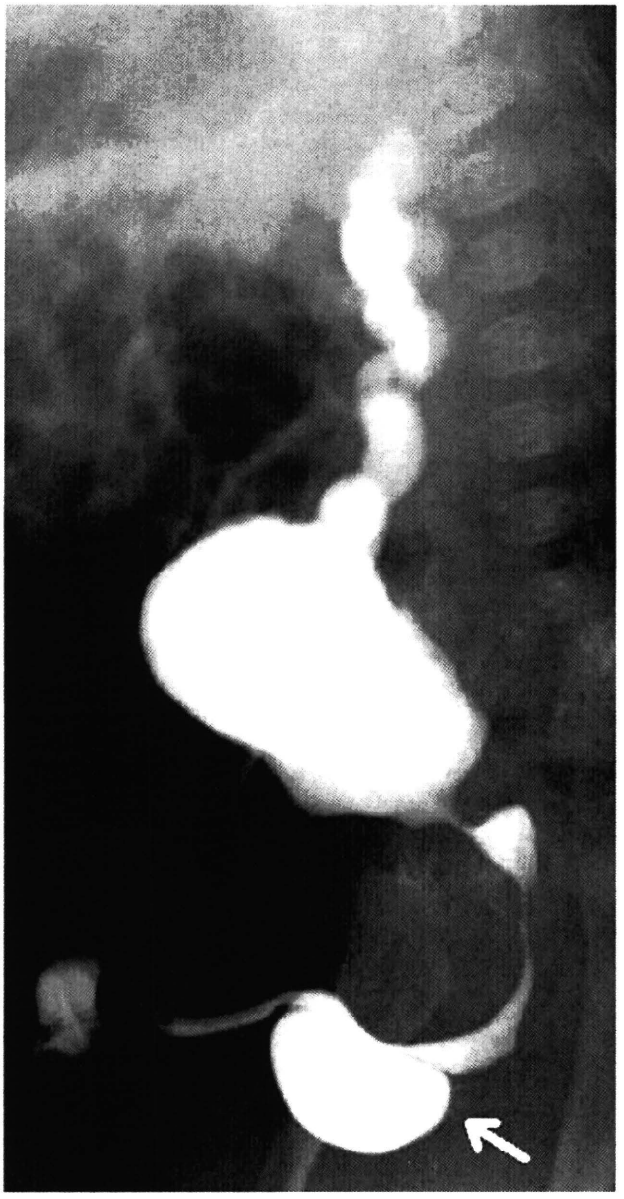

Fig. 3 Voiding cystourethrography demonstrated left vesicoureteral regurgitation with severe dilation of the left ureter. The anterior urethral diverticulum is indicated by an arrow.

paying particular attention to ultrasonographic findings, and serum creatinine level.

In conclusion, we performed prenatal intervention for a patient with severe AUV. Although the efficacy of this intervention on renal function awaits further evaluation, we believe that pulmonary maturation was successfully attained, and the exacerbation of renal function problems was prevented. There are some controversies regarding prenatal intervention and postnatal management; thus, it is important for pediatricians to cooperate with obstetricians and pediatric surgeons to preserve renal function in such cases of severe urinary tract obstruction.

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Patients with Epstein–Fechtner syndromes owing to *MYH9* R702 mutations develop progressive proteinuric renal disease

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Recent linkage analyses of nondiabetic African-American patients with focal segmental glomerulosclerosis (FSGS) have identified *MYH9*, encoding nonmuscle myosin heavy chain IIA (NMMHC-IIA), as a gene having a critical role in this disease. Abnormalities of the *MYH9* locus also underlie rare autosomal dominant diseases such as May–Hegglin anomaly, and Sebastian, Epstein (EPS), and Fechtner (FTNS) syndromes that are characterized by macrothrombocytopenia and cytoplasmic inclusion bodies in granulocytes. Among these diseases, patients with EPS or FTNS develop progressive nephritis and hearing disability. We analyzed clinical features and pathophysiological findings of nine EPS–FTNS patients with *MYH9* mutations at the R702 codon hot spot. Most developed proteinuria and/or hematuria in early infancy and had a rapid progression of renal impairment during adolescence. Renal histopathological findings in one patient showed changes compatible with FSGS. The intensity of immunostaining for NMMHC-IIA in podocytes was decreased in this patient compared with control patients. Thus, *MYH9* R702 mutations display a strict genotype–phenotype correlation, and lead to the rapid deterioration of podocyte structure. Our results highlight the critical role of NMMHC-IIA in the development of FSGS.

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KEYWORDS: Epstein syndrome; FSGS; *MYH9*; NMMHC-IIA; podocyte

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May–Hegglin anomaly and Sebastian syndrome are rare autosomal dominant disorders characterized by thrombocytopenia, giant platelets, and granulocyte cytoplasmic inclusion bodies called Döhle body-like inclusion bodies.[1] There are two related disorders, namely, Fechtner syndrome (FTNS) and Epstein syndrome (EPS), in which progressive hearing disability and nephritis are observed.[1] In FTNS, cataract is also present. Recently, *MYH9*, a gene encoding nonmuscle myosin heavy chain IIA (NMMHC-IIA), has been identified as the causative gene for these four disorders.[2–3] Several mutations in *MYH9* have been identified, and the existence of mutational hot spots in *MYH9*, that is, codons R702, R1165, D1424, E1841, and R1933, has been reported.[5–9]

As mutations in a single gene cause four distinct disorders, a novel nomenclature, *MYH9* disorders, has been proposed.[6,8,10] However, the mechanisms by which mutations in a single gene cause a variety of phenotypes remain to be elucidated.[1] Certain mutations in *MYH9* have been associated with the development of renal phenotypes, and R702 mutation is one of these.[7–10] Nevertheless, detailed information on renal manifestations, renal histology, and prognosis has been lacking.

In addition to macrothrombocytopenic diseases due to *MYH9* mutations, a significant association between the development of idiopathic focal segmental glomerulosclerosis (FSGS) or end-stage renal disease (ESRD) in African-American individuals and single-nucleotide polymorphisms in *MYH9* was identified in 2008.[11,12] This finding shows that NMMHC-IIA is responsible for not only EPS–FTNS, but also FSGS. Structural or functional abnormalities of NMMHC-IIA are considered to be critical in the development of FSGS in the African-American population.

In this study, we analyzed nine cases with R702 mutation in *MYH9*. Most cases with R702 mutation in *MYH9* develop nephritis characterized by proteinuria and/or hematuria in early infancy, and the deterioration of renal function accelerates in early adolescence. Hearing disability also manifests in early infancy and progresses to deafness at approximately 30 years of age. Findings of a serial renal biopsy in one case indicated that the pathological feature underlying this progressive nephritis is FSGS.

RESULTS

Clinical presentation and *MYH9* mutations

The clinical backgrounds of each case are summarized in Table 1. The age at the latest examination ranges from 4 to 33 years. Most of the cases were diagnosed as having idiopathic thrombocytopenic purpura at first presentation.

Genetic analysis revealed R702H mutation in case 1 and R702C mutation in the remaining 8 cases. All the R702 mutations identified in this study were *de novo* mutations. No disease-related family histories were noted.

Urinary abnormalities and development of renal dysfunction

The renal manifestations of nine cases are described in Table 1. Except for case 1, all the other cases developed proteinuria and/or hematuria before 12 years of age. Case 2 developed significant proteinuria (1+; urine protein/gCr = 310 mg/g creatinine (Cr)) as early as 2 years and 7 months of age. It is notable that four cases over 15 years old developed ESRD between 15 and 20 years of age. Distinct from another progressive hereditary nephritis, that is, Alport's syndrome, none of the cases showed macroscopic hematuria at presentation. For cases 6, 7, 8, and 9 who developed ESRD, their serum Cr levels are plotted in Figure 1. Each case progressed to ESRD shortly after the serum Cr level exceeded 1.0 mg/dl. The clinical status at the latest evaluation is described in Table 1 along with age at final evaluation.

Extrarenal manifestations

Among these cases, only case 1 showed cataract (Table 2). A hearing disability was observed in most of the cases by approximately 5 years of age, which progressed rapidly. Over 30 years old, all of the cases in this study became deaf.

Renal histopathological analysis of case 6

Light and electron microscopy findings of serial renal biopsies of specimens from case 6 are shown in Figure 2. The first biopsy was performed at 9 years of age by surgical operation, when the serum Cr level was 0.4 mg/dl. Twenty-four glomeruli were obtained, and mild mesangial cell proliferations and expansion were observed in most glomeruli (Figure 2a). Sclerotic lesions were not observed in any glomeruli, and tubulointerstitial changes were minimal. Immunofluorescence studies using immunoglobulins G, A, M, and C1q, C3, and C4 antibodies showed negative or no significant findings. Electron microscopy of these specimens revealed focal lesions of podocyte foot process effacement (indicated by an arrow in Figure 2c). Focal glomerular basement membrane (GBM) thickening lesions were observed (up to 1000–1500 nm in diameter), whereas most GBM show normal appearance (thickness ranges from 300 to 400 nm). The other GBM abnormalities, such as splitting, attenuation, or reticulation, were not observed. The second biopsy was performed by needle biopsy when the case was 11 years and 9 months of age. Only four glomeruli were obtained; one glomerulus showed global sclerosis, and two of the remaining three glomeruli showed segmental sclerosis.

Table 1 | Clinical backgrounds and renal manifestations in patients with R702 mutation in *MYH9*

Case no.	Sex	Ethnic background	*MYH9* mutation	First clinical diagnosis	Age and urinalysis findings when urine abnormalities were first noted			Age at latest evaluation and each clinical status				
					Age	Proteinuria	Hematuria	Age	Clinical status	Age at CKD 5 onset	Proteinuria	Hematuria
1	F	Japanese	R702H	ITP		(−)	(−)	4y11m	w.n.l		(−)	(−)
2	F	Japanese	R702C	MHA	2y7m	(1+)	(−)	4y2m	CKD stage 1		(−)	(−)
3	F	Chinese	R702C	ITP	6y8m	(−)	(1+)	6y8m	CKD stage 1		(−)	(1+)
4	M	Japanese	R702C	ITP	5y8m	(2+)	(3+)	12y3m	CKD stage 1		(3+)	(3+)
5	M	Japanese	R702C	ITP	11y8m	(+)	(+/−)	11y8m	CKD stage 1		(+)	(+/−)
6	F	Japanese	R702C	ITP	8y8m	(1+)	(1+)	21y3m	Transplant	15y		
7	M	Japanese	R702C	MHA	9y	(1+)	(1+)	20y7m	Transplant	17y		
8	F	Japanese	R702C	ITP	Unknown		Unknown	33y	PD/HD	16y		
9	F	Japanese	R702C	ITP	5y8m	(+/−)	Unknown	32y	Transplant	20y		

Abbreviations: HD, hemodialysis; HPF, high power fields; ITP, idiopathic thrombocytopenic purpura; MHA, May-Hegglin anomaly; m, month; PD, peritoneal dialysis; y, year.
In the urinalysis, stages of proteinuria and hematuria were defined as follows:
Proteinuria: +/−, 15 mg/dl; +, 30 mg/dl; 2+, 100 mg/dl; 3+, 300 mg/dl or over 300 mg/dl.
Hematuria: +/−, RBC ~ 5/HPF; 1+, 5–10/HPF; 2+, 10 ~ 50/HPF; 3+, >50–100/HPF.

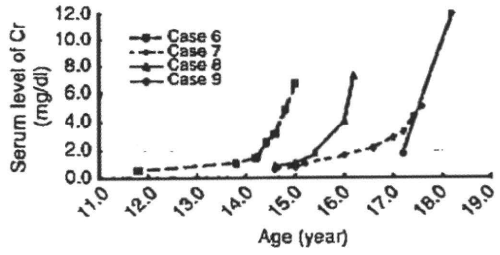

Figure 1 | Rapid progression of renal dysfunction in cases 6, 7, 8, and 9. Serum Cr levels (mg/dl) of cases 6, 7, 8, and 9 are plotted. The rapid deterioration of renal function is apparent in these cases. Each case progressed to end-stage renal disease shortly after Cr levels exceeded 1.0 mg/dl.

The glomeruli were not enlarged. Interstitial fibrosis, cellular infiltration, and tubular atrophy were observed around the impaired glomeruli. At the time of the second renal biopsy, the serum Cr level was 0.6 mg/dl, and the estimated glomerular filtrate rate calculated by Schwartz's formula was 107 ml/min per 1.73 m^2. The findings of the second biopsy of case 6 are compatible with the diagnosis of FSGS. Considering an almost normal glomerular filtrate rate at the time of the second renal biopsy, absence of enlarged glomeruli in the kidney specimen, and the subsequent rapid progression to ESRD in this patient, focal segmental sclerosis is considered to be the primary lesion due to *MYH9* mutation rather than a phenomenon secondary to nephron mass reduction.

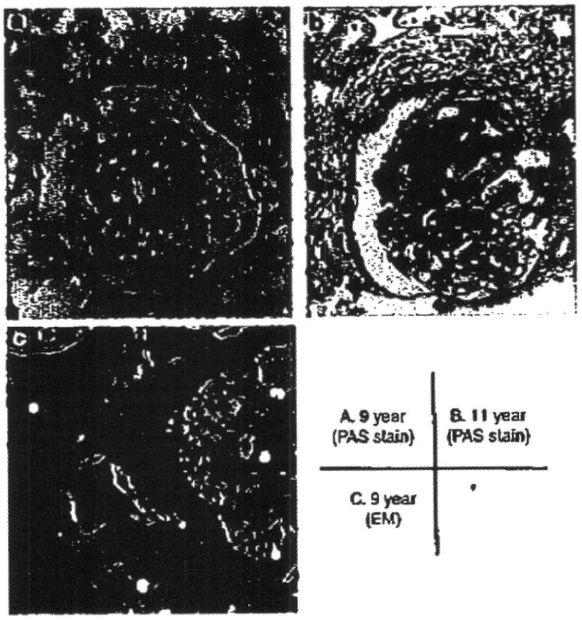

Figure 2 | Histopathological analysis of renal specimen from case 6. Light and electron microscopies of the renal specimen from case 6. (a) Periodic acid Schiff (PAS) staining of typical glomerulus and surrounding tubules of the renal specimen of case 6 at 9 years of age (first biopsy). (b) Findings of the same case at 11 years of age (second biopsy). This glomerulus shows typical morphological changes compatible with focal segmental glomerulosclerosis. (c) Electron microscopy of first biopsy specimen shows a nearly normal appearance of the glomerular basement membrane with focal podocyte foot process effacement (arrow) and focal thickening of GBM (arrowhead).

Immunohistochemical analyses of NMMHC-IIA in control and case 6 kidney samples

Figure 3 shows the immunostaining data of NMMHC-IIA in the glomerulus in normal control and case 6 kidney samples. In the glomeruli of the control sample, the intensity of NMMHC-IIA immunostaining is very strong in podocytes (Figure 3a and b). In the first biopsy specimen from case 6, the intensity of immunostaining of NMMHC-IIA is already significantly decreased (Figure 3c and d). The second biopsy specimen from case 6 (Figure 3e and f) also shows a decreased NMMHC-IIA immunostaining intensity.

In the normal kidney sample, NMMHC-IIA is also expressed in renal tubular cells, particularly those of the distal tubule, Henle's loop, and proximal tubular cells (Figure 4a-d). Endothelial cells of interlobular arteries and arterioles, and peritubular capillaries also express NMMHC-IIA (Figure 4a-c). In case 6, NMMHC-IIA expression in renal tubular cells and endothelial cells did not change significantly (Figure 4e and f).

NMMHC-IIA distribution in peripheral blood neutrophils

The NMMHC-IIA distribution pattern in peripheral blood neutrophils was examined by immunofluorescence analysis. In normal blood neutrophils, NMMHC-IIA distributes diffusely in the cytoplasm (Figure 5, control 1, 2, and 3). In all the cases with *MYH9* R702 mutations, NMMHC-IIA was condensed and localized in the peripheral region of neutrophils (Figure 5, cases 1–9; condensation of NMMHC-IIA is indicated by an arrowhead). This granular pattern (type II) was observed in neutrophils from all the cases with R702 mutations (Figure 5 and Table 2, see Methods and Discussion sections for the definition of NMMHC-IIA distribution patterns in neutrophils).

Effect of ARB/ACEI on urinary abnormalities and renal function in three cases

Three cases, namely cases 2, 4, and 7, were treated with angiotensin receptor blockers (ARB) and/or angiotensin-converting enzyme inhibitors (ACEIs) for progressive nephritis. Figure 6 shows the effect of ARB/ACEI on urinary protein level in case 2. The urinary protein level evaluated in terms of urine protein/Cr was decreased from 500–700 mg/gCr to approximately 100 mg/gCr by administration of 20 mg of valsartan (Figure 6). In cases 4 and 7, the effect of ARB/ACEI was not very conclusive (data not shown). In case 4, other drugs such as cyclosporine A were used simultaneously; therefore, the effect of only ARB/ACEI could not be determined. In case 7, the effect of ARB/ACEI was transient.

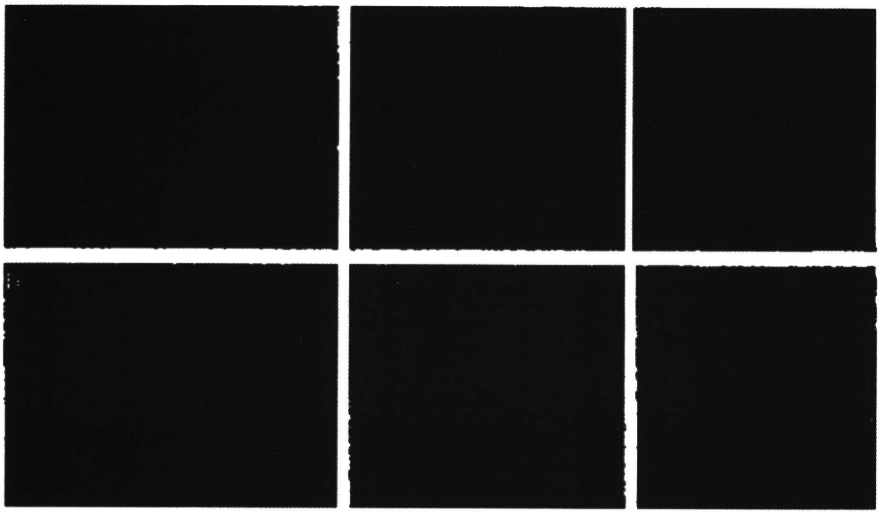

Figure 3 | Expression of NMMHC-IIA in the glomerulus from normal control and case 6 kidney samples. (a and b) NMMHC-IIA expression in the glomerulus from normal control sample. NMMHC-IIA is strongly expressed in podocytes. (c and d) First biopsy specimen from case 6. The intensity of immunostaining of NMMHC-IIA is already decreased. (e and f) Second biopsy specimen from case 6. The intensity of immunostaining of NMMHC-IIA is decreased.

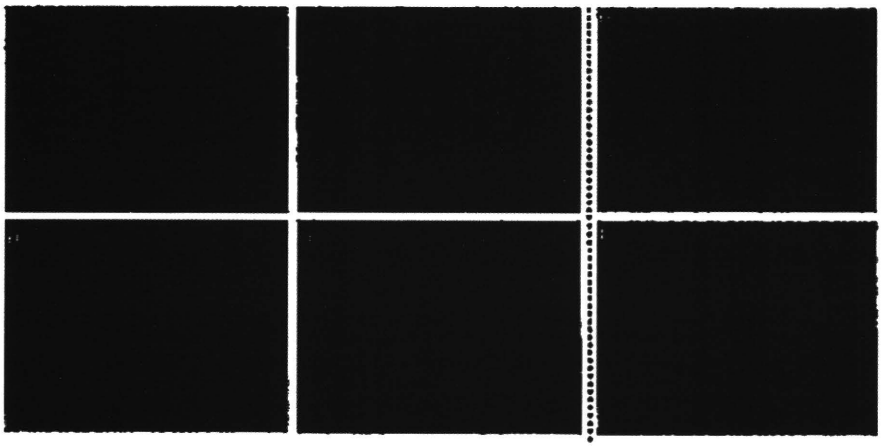

Figure 4 | Expression of NMMHC-IIA in normal control and case 6 kidney samples. (a–d) NMMHC-IIA expression in normal control kidney sample. Compared with the strong staining of NMMHC-IIA in podocytes, its expression in other renal tissues is relatively weak. Weak expression of NMMHC-IIA is observed in the distal nephron (b and d) and loop of Henle (b). Endothelial cells of arteries also express NMMHC-HHA (c). In the first (e) and second (f) renal biopsy specimen from case 6, expression of NMMHC-IIA in tubular cells and endocapillary cells is not remarkably changed compared with the controls, whereas decreased staining of podocytes is noted.

DISCUSSION

In this study, we showed that cases with *MYH9* R702 mutation show a very rapid deterioration of renal function with concurrent progressive hearing disability. Proteinuria and/or hematuria was detected in early infancy, and ESRD developed during adolescence. To date, several mutations including S96L, R702C, R702H, R1165C, and D1424 have been associated with the development of nephritis.[7–10] Pecci *et al.*[9] showed that mutations in the motor domain of NMMHC-IIA are associated with severe thrombocytopenia and the development of nephritis and deafness before 40 years of age, whereas patients with mutations in the tail domain not only have a much lower risk of developing such impairments but also significantly higher platelet counts. Heath *et al.*[7] and Dong *et al.*[8] described the development of nephritis in patients with R702 mutations. However, description of the clinical course of nephritis in these reports was very limited. In this study, we examined the precise clinical manifestations in nine patients with *MYH9* R702 mutations, and showed a definite genotype–phenotype correlation in both renal impairment and hearing disability.

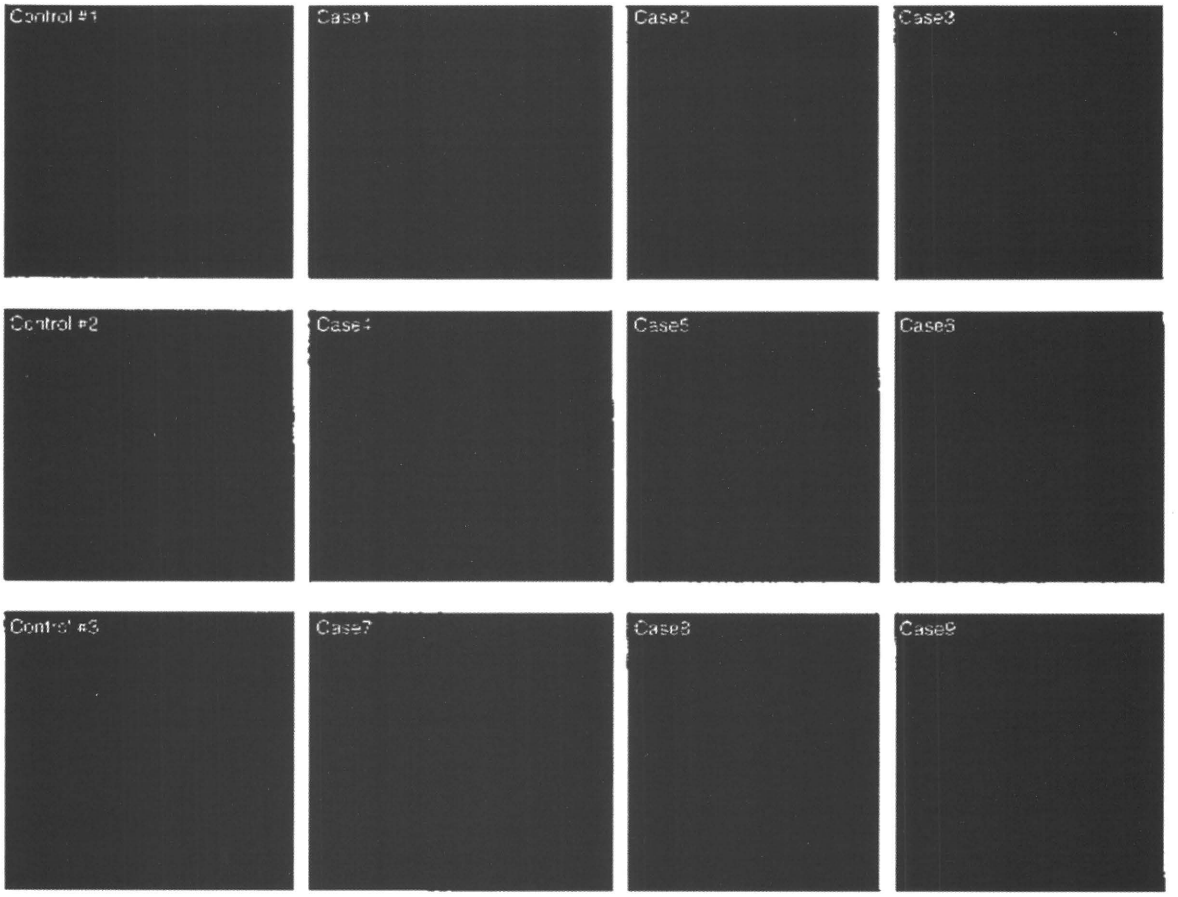

Figure 5 | Distribution of NMMHC-IIA in the cytoplasm of neutrophils in control and cases with R702 mutations. Controls 1, 2, and 3: Normal distribution of NMMHC-IIA in the cytoplasm of neutrophils. NMMHC-IIA is diffusely distributed in the cytoplasm. Cases 1 to 9: In all the cases with *MYH9* R702 mutations, NMMHC-IIA was condensed and localized in a granular pattern in the cytoplasm as indicated by gray arrowheads.

Table 2 | Extrarenal manifestations in each patient

Case no.	Type of cytoplasmic distribution of NMMHC-IIA	Hearing disability: Age of presentation and severity	Hearing disability: Latest hearing level	Cataract
1	II	2y2m: 50 db	NT	+
2	II	(−)	(−)	(−)
3	II	(−)	(−)	(−)
4	II	4y	NT	(−)
5	II	4y	40–50 dB	(−)
6	II	8y10m: 30 dB	40–55 dB	(−)
7	II	10y	70–80 dB	(−)
8	II	9y	Deaf	(−)
9	II	5y	Deaf	(−)

Abbreviations: m, month; NMMHC-IIA, nonmuscle myosin heavy chain IIA; NT, not tested; y, year.
Note: Abnormal distributions of NMMHC-IIA are classified into three types according to the number, size, and shape of accumulated NMMHC-IIA granules (see also the Materials and Methods section).[16] Type II is characterized by the presence of up to 20 circular to oval NMMHC-IIA-positive spots (≤1 μm).

In Epstein–Fechtner syndrome, renal biopsy is principally contraindicated because of the accompanying thrombocytopenia. There have been few reports on the morphological changes of renal histology in Epstein–Fechtner syndrome. Only three reports on renal pathological findings are available in the literature.[13–15] Epstein *et al.*[13] described the renal morphology in a 13-year-old patient with Epstein syndrome. Their study revealed interstitial fibrosis, focal mesangial proliferation, and global sclerotic changes when the serum Cr level was 0.6 mg/dl. A recent genetic study by Heath *et al.*[7] identified *MYH9* R702C mutation in this patient. Moxey-Mims *et al.*[14] performed renal biopsy twice in an African-American female with Fechtner's syndrome. The type of *MYH9* mutation in this patient was not identified in the literature. The first biopsy at 7 years of age showed proliferation of mesangial cells and matrix with alterations in the GBM, such as effacement, thickening, and splitting; the second biopsy at 10 years of age revealed global sclerotic changes in 75% of glomeruli.[14] Moxey-Mims *et al.*[14] concluded that these renal changes are similar to those in Alport syndrome. Ghiggeri *et al.*[15] performed renal biopsy in FTNS patients with D1424H mutation, and electron microscopy showed focal and segmental effacement of podocytes and loss

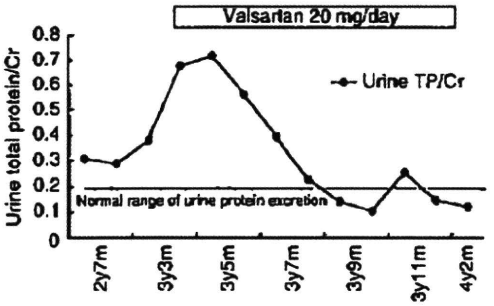

Figure 6 | Effect of valsartan on urinary protein excretion. The effect of 20 mg of valsartan on urinary protein excretion (urine protein g/urine creatinine mg) in case 2 is shown. The start of treatment with valsartan in case 6 was immediately after the age of 3 years (y) and 4 months (m), when the urinary protein level was nearly 0.7 g/g Cr.

of the interpodocyte slit diaphragm. The histopathological changes reported so far could occur in various types of glomerulonephritis. In this study, renal biopsy was performed twice in case 6 with platelet transfusion. The second renal biopsy specimen from case 6 showed that the pathological diagnosis is FSGS. In Epstein–Fechtner's syndrome with R702 mutation, progressive proteinuria and rapid deterioration of renal function are the common characteristics, as shown in this study, and the renal histology in case 6 is compatible with the clinical features of Epstein–Fechtner's syndrome with *MYH9* R702 mutation.

Epstein syndrome has been considered to be a variant of Alport syndrome, because of their very similar phenotypes, except for macrothrombocytopenic purpura, which is observed only in Epstein syndrome. However, the following two lines of evidence make them distinct from each other. The first is the different types of urinary abnormality. As shown in Table 1, proteinuria is equivalent or predominant in patients with Epstein syndrome; in contrast, hematuria is predominant, and macroscopic hematuria is often observed in patients with Alport syndrome much earlier than proteinuria. The second is the differences in the expression of causative genes in the glomeruli. The type IV collagen α5 chain gene responsible for Alport syndrome encodes an essential structural component of GBM; in contrast, NMMHC-IIA encoded by *MYH9* is exclusively expressed in podocytes, renal tubular cells and endothelial cells, as shown in Figure 3. In general, GBM abnormalities could occur secondary to podocyte dysfunction. Taken together, we consider that the alterations of GBM in Epstein syndrome are a phenomenon secondary to the dysfunction NMMHC-IIA molecule in podocytes owing to *MYH9* mutation.

Kunishima *et al.*[16] reported that the abnormal distributions of NMMHC-IIA in blood neutrophils in cases with *MYH9* disorders are classified into three types: type I, NMMHC-IIA is condensed into one or two granular masses; type II, NMMHC-IIA is present as granular masses of up to 20; type III, NMMHC-IIA is diffusely distributed as fine granules throughout the cytoplasm. Kunishima *et al.*[16] also indicated that the type of abnormal distribution of NMMHC-IIA is closely related to the site of the *MYH9* mutation.[16] In all the cases in this study, NMMHC-IIA distribution in neutrophils was of type II (Figure 5 and Table 2).

The abnormal distribution of NMMHC-IIA in Epstein–Fechtner syndrome could be directly associated with the pathogenesis in the kidney. Arrondel *et al.*[17] showed the expression of NMMHC-IIA in podocytes, endocapillary cells, and proximal tubular cells in the human kidney. In this study, we show that NMMHC-IIA is expressed in the glomerulus, tubular cells including the distal tubule, loop of Henle, and the proximal tubule, endothelial cells of the interlobular arteries and arterioles, and peritubular capillaries. Ghiggeri *et al.*[15] discussed that the aggregation and compartmentation of NMMHC-IIA in podocytes might be associated with podocin dysfunction. In addition, there is another possibility. Two hereditary types of FSGS with an autosomal dominant trait are known, and one is caused by mutations in the gene encoding α-actinin-4 (*ACTN4*).[18] Several studies have indicated the following possible mechanisms: mutations in *ACTN4* increased the ability of binding of mutated α-actinin-4 to actin filaments, alter their intracellular localization, and finally cause FSGS.[19,20] Michaud *et al.*[20] showed that when mutated α-actinin-4 is expressed in cultured podocytes, and the localization of α-actinin-4 changes; that is, aberrant sequestering of α-actinin-4 impairs podocyte spreading and motility and decreases the number of peripheral projections. They suggested that these cytoskeletal derangements may underlie podocyte damage and foot process effacement. Recently, several studies have indicated that NMMHC-II has important roles in cell polarity, cell adhesion, and cell migration.[21] Podocytes are highly differentiated epithelial cells, and are connected to each other through a specific cell–cell adhesion molecule complex, that is, a slit diaphragm, which is crucial for glomerular filtration. NMMHC-IIA is considered to be located at the scaffolding underneath the plasma membrane and in the cytoplasm, and to have a role in maintaining and disassembling the adhesion junction complex.[21] It is plausible that mutated NMMHC-IIA would impair the function and structure of the slit diaphragm, which would result in proteinuria and the development of FSGS.

It has been reported that human immunodeficiency virus-related or hypertension-related FSGS are common in the African-American populations. Recently, two groups have independently identified a highly significant association between the development of FSGS or ESRD and single-nucleotide polymorphisms in *MYH9* in African-American individuals using an admixture-mapping linkage-disequilibrium genome scan method.[11,12] The development of ESRD was associated with hypertension, not with diabetes mellitus. This evidence strongly indicates that NMMHC-IIA is responsible for the development of not only Epstein–Fechtner

syndrome, but also idiopathic FSGS. There is no information on why specific single-nucleotide polymorphisms in *MYH9* increase the susceptibility of African-American individuals to FSGS or ESRD. Clarification of the pathophysiological mechanisms underlying the development of FSGS in Epstein–Fechtner syndrome would provide clues elucidating the molecular mechanisms underlying the development of FSGS.

Just recently, Pecci *et al.*[22] have reported a favorable effect of ACEI and/or ARB on proteinuria in patients genetically diagnosed with Epstein–Fechtner syndrome. In this study, three cases among the nine enrolled were treated with ARB and/or ACEI. In case 2, administration of 20 mg of valsartan markedly reduced the amount of protein in the urine (Figure 3). In cases 4 and 7, ARB and ACEI partially reduced the amount of proteinuria. These findings, as well as those of Pecci *et al.*, suggest the protective effect of ARB and ACEI on the kidney in cases with D1424H and N93K mutations. As the susceptibility to ESRD or FSGS caused by certain single-nucleotide polymorphisms in *MYH9* in African Americans is also associated with hypertension, ARB and ACEI presumably showed a protective effect on the progression of renal dysfunction owing to their direct effects on podocytes. This is another important issue in the elucidation of the mechanisms underlying the development of FSGS related to NMMHC-IIA.

In conclusion, in this study, we showed a rapid deterioration of renal function in cases with *MYH9* R702 mutation, and the pathological findings in one case were consistent with FSGS; apparent changes in NMMHC-IIA expression in podocytes were observed in this patient. Further studies are required to elucidate the possible pathophysiological mechanisms by which podocyte dysfunction occurs because of R702 mutations in *MYH9*, which is cardinal in the development of FSGS in African-American populations. Such studies could provide us clues to the mechanisms underlying the development of idiopathic FSGS.

MATERIALS AND METHODS

Cases

We performed genetic analysis in approximately 100 patients suspected of having *MYH9* disorders. Among those 100 patients, we selected all unrelated patients with R702 mutation and enrolled them in this study (Table 1). Some of the clinical and hematological data of patients 1, 2, 4, and 5 were previously published:[23] except for case 4, there were no symptoms of nephritis in these patients previously reported. The other cases are all new.

Details of clinical data and courses, the treatment for nephritis, the treatment for ESRD, and the latest clinical data were obtained by the attending physician in each case. Ocular abnormalities and hearing disabilities were evaluated by ophthalmologists and otolaryngologists, respectively.

The renal biopsy specimens from case 6 were evaluated by light microscopy and electron microscopy using conventional techniques. Immunohistochemical analysis was carried out as described below.

Genetic analysis of *MYH9* was approved by the institutional review boards of Nagoya Medical Center and each of the hospitals where the patients were enrolled, and was performed after informed consent was obtained from the patients and/or their parents. The IRB of the National Hospital Organization Nagoya Medical Center also approved the publication of the case reports and the obtained experimental data. Mutational analysis of *MYH9* was performed as previously described.[6]

Immunohistochemical analysis of renal specimens from control and case 6 kidney samples

Renal biopsy specimens from normal control and case 6 kidney samples were also subjected to immunohistochemical analysis. This was performed using 3 μm-thick sections of a paraffin-embedded sample. A renal specimen derived from a 51-year-old renal transplantation donor kidney, which was excised from the donor with immediate perfusion (0 h), was used as a control. Each renal section was autoclaved for 15 min at 121 °C in a citrate buffer of pH 6.0. After washing with water and phosphate-buffered saline, each section was incubated with an anti-NMMHC-IIA antibody (BT561, Biomedical Technologies, Stoughton, MA, USA, 1:100) for 2 h at room temperature. After washing, each section was further incubated with a secondary antibody (ENVISION, Dako, Kyoto, Japan) for 20 min. Subsequently, each section was treated with streptavidin-horseradish peroxidase and diaminobenzidine. The sections were then counterstained with hematoxylin.

Immunofluorescence analysis of NMMHC-IIA in peripheral blood neutrophils

Immunofluorescence analysis was performed to evaluate the subcellular localization of NMMHC-IIA in peripheral blood neutrophils as previously described.[16] The cytoplasmic distribution patterns of NMMHC-IIA in neutrophils can be classified according to the number, size, and shape of accumulated NMMHC-IIA granules, into types I, II, and III. Type I comprises one or two large (0.5–2 μm), intensely stained, oval- to spindle-shaped cytoplasmic NMMHC-IIA-positive granules. Type II comprises up to 20 circular to oval cytoplasmic granules (≤1 μm). Type III appears as a speckled staining. The pattern of localization correlates with the site of *MYH9* mutation. Mutations in exons 16, 26, and 30 are associated with type II localization.[16]

DISCLOSURE

All the authors declared no competing interests.

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ACEI/ARB fetopathy*

五十嵐隆**

はじめに

胎児の腎機能と構造が発育するためにアンジオテンシンⅡの作用とそれに引き続くアンジオテンシンタイプⅠ受容体を介する情報伝達が維持されることが必要である[1]。胎児腎へのアンジオテンシンⅡの作用を阻害する母体へのACEI（アンジオテンシン変換酵素阻害薬）やARB（アンジオテンシンⅡタイプ1受容体拮抗薬）の投与は胎児にさまざまな有害事象を起こす。妊娠中のすべての時期においてACEI/ARBの投与は禁忌であるが，妊娠中の母体にACEIまたはARB（ACEI/ARB）が投与されたために生じる胎児病をACEI/ARB fetopathyと呼ぶ[2~6]。本稿では，ACEI/ARB fetopathyの動物実験における解析と症例報告例を中心に，本症の病態生理について解説する。

Ⅰ 動物実験におけるACEI/ARB fetopathy

ヒトの腎のネフロン形成（metanephrogenesis）は在胎5週から始まり在胎36週までにほぼ完成する。一方，ラットでは在胎11ないし12日からネフロン形成が始まり，出生時にはネフロンは完成しておらず出生後10日目頃まで形成が続く。したがって腎の成熟段階の観点からラットとヒトとを比較すると，生後10日目までのラットの腎はヒトの妊娠中期・末期の腎に相当する。腎への影響という点で，出生後から出生10日までのラットにACEI/ARBを投与することは妊娠中期・末期の妊婦・胎児に同薬剤を投与することにほぼ相当する。

新生児ラットにARBを投与すると，組織学的には腎乳頭部が萎縮（形成不全）して尿細管が萎縮しその周囲の間質が拡大する。同部位の萎縮はHenle上行脚の電解質再吸収を阻害し髄質部の高浸透圧環境が形成されない。その結果，永続的な尿濃縮力障害（抗利尿ホルモンADHに無反応の腎性尿崩症）をきたす[1,7,8]。さらに，尿細管におけるNaとKの再吸収能も低下する[1,7,8]。

ARBを投与された新生児ラットの糸球体濾過率（GFR）と腎血漿流量は15%程度低下し，平均動脈血圧は正常と差がみられない。GFRの低下はネフロン数の減少による[1,7,8]。また，皮質血管壁の肥厚がみられ，これもGFRを低下させる一因となる[1,7,8]。さらに，尿管の平滑筋形成が障害され，尿管の蠕動運動が低下し尿管の機能的閉塞をきたす[9]。

Ⅱ 分子レベルでのACEI/ARB fetopathy

動物実験では，ロサルタン（ARBの一種）はアンジオテンシンⅡの作用を抑制し，腎における細

* ACEI/ARB fetopathy
key words：ACEI，ARB，胎児毒性
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表　出生直後の ACEI/ARB fetopathy の臨床症状

(1) 肺低形成（による死亡）
(2) 四肢可動性の制限，四肢関節の拘縮
(3) 頭蓋骨の一部欠損
(4) 低血圧
(5) 腎不全
(6) 早産（超低出生体重児）
(7) 動脈管開存症

註：子宮内胎児死亡も報告されている。

胞間および細胞と細胞周囲組織（マトリックス）間の相互作用に関係する分子の発現を抑制し，腎尿細管と腎内血管系の成熟を抑制する[10]。Syndecan 2, α-smooth muscle actin, NHC class Ⅱ, leukocyte type 12-lipoxygenase の発現が低下する。また，ロサルタンはヘンレ上行脚管腔側膜の type Ⅰ bumetanide-sensitive Na^+-K^+-$2Cl^-$ cotransporter の発現量を減少させ，管腔内の Na，Cl などの Henle 上行脚での再吸収が低下する。その結果，抗利尿ホルモンが分泌されて水チャネルであるアクアポリン 2 が動員されても，集合管周囲組織の高浸透圧環境が形成されないために集合管内の水は管腔内から尿細管細胞・集合管周囲の間質に移動できず，腎性尿崩症が発症する[10]。また，髄質の integrin α6 の発現や髄質の尿細管細胞の増殖も抑制される。さらに，糸球体原基ならびに間質細胞の TGF-β の発現が増加し，糸球体基底膜の部分的な肥厚や尿細管細胞の apoptosis が生じる[11]。これらの一連の変化は，腎の発生段階における細胞間および細胞と周辺部のマトリックス間の相互作用の重要性を示しており，ACEI/ARB がこれらの相互作用を阻害することにより尿細管と糸球体の発育が障害される。

Ⅲ ヒトの ACEI/ARB fetopathy[12～14]

1．出生直後の ACEI/ARB fetopathy の臨床症状

表に，出生直後の ACEI/ARB fetopathy の臨床症状を示す。ACEI/ARB fetopathy は腎にのみ限局する疾患ではなく，早産での出産などによる合併症を含め，全身性の重篤な新生児疾患である。

2．長期的臨床症状と予後

ACEI/ARB fetopathy の患児は妊娠中に死亡（胎児死亡）するか，早産と羊水過少による肺形成障害に起因する出生時の著しい呼吸障害により，あるいは出生後早期から認められる低血圧，腎不全により死亡することが多い[15]。出生後早期に腎不全となり治療により腎不全状態から回復しても永続的な腎機能低下や高血圧を呈する[16,17]。ただし，生存例の長期的予後やその詳しい臨床症状についての報告がなく，不明な点が多い。腎性尿崩症については動物実験でもヒトでも報告されている[1,7,8,18]。Angiotensin Ⅱ は胎児期の腎形成において重要な成長促進因子であるとともにそのほかの臓器の形成にも必要である。母体を介しての胎児への ACEI/ARB の投与は胎児の腎のみでなく全身臓器の成長を阻害する[19,20]。

新生児期に典型的な ACEI/ARB fetopathy の症状を呈し，新生児期の腎不全を治療により脱した後，本症の患児はその後，① 腎性尿崩症，糸球体機能障害，② 顔が細く，耳が大きいという独特の顔貌，③ 成長障害，④ 中枢神経障害（脳質周囲白質軟化症・精神運動発達障害・てんかん）などの永続的合併症が生じる。また，糸球体機能障害の観点からみて，新生児期の腎不全から回復しても糸球体機能障害が残存し，成長とともに腎機能障害が進行して長期的には末期腎不全に至る可能性もある。

Ⅳ ACEI/ARB を服用している妊娠中の母親への対応

妊婦または妊娠している可能性のある婦人への ACEI/ARB の投与は禁忌である。ACEI/ARB の添付文書には，「妊娠中期・末期の服用は羊水過少症，胎児・新生児の死亡，新生児の低血圧，腎不全，高カリウム血症，頭蓋に形成不全および羊水過少症によると推測される四肢の拘縮，頭蓋顔

面の変形などが現れたとの報告がある」と記述されている[2]。ACEI/ARB は高血圧治療薬あるいは腎機能障害を有する患者での腎保護薬として有効性が示されており，多数の患者に使用されている。したがって，ACEI/ARB を服用中の女性には（未成年の女児には保護者にも）ACEI/ARB の胎児毒性について説明する。妊娠予定の患者には，胎児毒性が少ないとされるメチルドパ（アルドメット：中等度～高度の慢性高血圧の妊娠女性のための選択薬）やクロニジン（カタプレス），ヒドララジン（アプレゾリン），ラベタロール（トランデート）などに変更する[21]。

ACEI/ARB を服用中に妊娠が判明した場合，速やかに ACEI/ARB の服薬を中止する。ただし，妊娠初期よりも妊娠中期・後期に ACEI/ARB を服用した場合のほうが胎児毒性は強く，妊娠初期の段階で同剤の服用を中止できれば胎児毒性は出現しない可能性がある。妊娠初期に ACEI/ARB を使用した母体から出生した新生児のうち，口蓋裂，動脈管開存，軽度の大動脈狭窄を呈した者が 1 人みられただけで，30 名の新生児のなかに腎障害はみられなかった[17]。したがって，妊娠のすべての時期において ACEI/ARB の母体への投与は原則禁忌であるが，妊娠初期にのみ ACEI/ARB を使用したことは必ずしも妊娠中絶の絶対的な適応にはならないとされる[17]。

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Hospital acquired hyponatremia

Hospital acquired hyponatremia とは？

入院や外来で行われる経静脈輸液療法によって生じる低 Na 血症のこと。Hospital induced hyponatremia とも呼ばれる。

脱水症や呼吸器感染症などにて入院した患児に低張液（血清 Na が 135 mEq/L よりも低い液）を用いて輸液を行うことが多い[1]（表）。欧米にてもこれまで同様であった。トロント小児病院では入院時に低 Na 血症（血清 Na 値＜136 mEq/L）のない患児 1,490 名に低張液による輸液療法を行ったところ 40 名（2.7%）に低 Na 血症をきたした[1]。うち 2 名に重篤な中枢神経障害が残り，1 名が死亡した。低 Na 血症となった理由は低張液を用いたためで，血清 Na 値が 138 mEq/L 未満の小児には低張液を使用するべきではないとしている。その後も同様な報告がある[2]。

重篤な低 Na 血症（血清 Na 値 125 mEq/L 以下）は脳浮腫をきたし，脳内圧を上昇させ，痙攣，意識障害などの中枢神経障害や脳ヘルニアによる死亡の原因となる。したがって，重篤な低 Na 血症は medical emergency である。

表　浸透圧上昇以外の ADH 分泌刺激となる原因

1）すぐに除去し得る原因
- 脳下垂体への有効循環血液量の低下
- 不安，ストレス，痛み（扁桃腺摘出術後，腎生検後など），吐き気
- 吐き気をきたす薬剤：抗悪性腫瘍薬（シクロホスファミドなど）
- ADH 放出刺激となる薬剤：モルヒネ，バルビツレート，麻薬
- ADH の腎での作用を増強する薬剤：経口血糖降下薬，非ステロイド性消炎薬，抗痙攣薬（カルバマゼピンなど）
- 内分泌疾患：甲状腺機能低下症，副腎不全
- 外因性の dDAVP（抗利尿ホルモン），オキシトシン

2）すぐには除去できない原因
- ADH 産生腫瘍
- 脳炎，脳症，脳腫瘍などの中枢神経病変
- 細気管支炎，肺炎，肺腫瘍などの肺病変
- 肉芽腫症
- 代謝性疾患：ポルフィリア

Hospital acquired hyponatremia の原因：nonosmotic antidiuretic hormone (ADH) secretion stimuli と低張液の使用

抗利尿ホルモン（antidiuretic hormone：ADH）は主として血漿の高浸透圧（ほとんどは高 Na 血症）により脳下垂体から分泌され腎集合管にて水の保持を行う。高濃度の ADH は血管平滑筋細胞の V1a receptor に結合し血管を収縮させ血圧を上昇させる。この作用は腎では Na 排泄増加をきたす[3]。一方，高浸透圧血症以外のさまざまな病態も ADH 分泌刺激（nonosmotic stumuli）となる（表）。このような疾患の患者に輸液を行う際には低 Na 血症がない場合でも ADH 分泌刺激による低 Na 血症のリスクを考慮することが必要である。

SIADH あるいはその準備状態を証明するには，体液量が減少していないこと（尿量は減少），低 Na 血症があること，そして血漿 ADH 値が上昇していることが必要である。しかし，血漿 ADH 値は RIA 法による測定のため結果を知るのに 3 日

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が必要で，臨床現場で血漿 ADH 値を診断の根拠として利用できない。この問題を補うため，SIADH あるいはその準備状態が疑われる患者では輸液開始時の尿中 Na 濃度あるいは尿浸透圧を測定し，尿 Na が 40 mEq/L 以上あるいは 100 mOsm/kg H_2O 以上のときには SIADH あるいはその準備状態と判断する。ただし，副腎不全，利尿薬使用中，尿細管機能障害の可能性を否定することが必要である。さらに，乳幼児では尿中 Na 濃度が増加している点を SIADH の根拠としにくい。

輸液療法時の hospital acquired hyponatremia の予防

輸液療法は理想的には患者の病態に応じた輸計画をたて，さまざまな合併症の危険を考慮しながら行うべきである[4]。しかしながら，わが国では経静脈輸液療法はソリタ T1，(T2)，T3 の順に使用するプロトコールが広く用いられている。また，ソリタ T2 を使用せず T1 から T3 に移行することも多い。

低張液を中心とする静脈療法を行うことに多くの場合，問題はない。しかしながら，急性の低 Na 血症の患者や高浸透圧血症以外の理由で ADH が分泌される病態を有する患者では，SIADH あるいはその準備状態の可能性を考え輸液組成や投与量などについて配慮する。一方，軽症から重症までのすべての脱水症患者あるいは血清 Na が 138 mEq/L 以下の患者の初期輸液には生理食塩液などの等張液を使用すべきとする主張がある[5]。すべての脱水症患者に生理食塩液を bolus injection する場合，肺水腫，高 Na 値血症，低血糖などの危険性がある。

血清 Na 濃度が不明の脱水症患者には，乳酸リンゲルや重炭酸リンゲルにて輸液を開始し，血清 Na 値が判明したときに原疾患と患者の全身状態とを考慮して，輸液の Na 濃度を決める。特に高浸透圧血症以外の理由で ADH が分泌される恐れのある患者の初期輸液の際に，ソリタ T1 などの低張液を用いた急速補液を行わない。さらに，Holiday-Segar 法から計算される維持輸液量は健康小児から導きだされたデータのため，脱水症などの病的小児の場合の維持輸液量はその 2/3 量程度とする。また，初期輸液終了後の輸液にはソリタ T3 (Na 35 mEq/L) ではなくソリタ T2 (Na 84 mEq/L) を用いて，輸液開始時からの 24 時間まで使用する。なお，英国では Na 30.8 mEq/L の NaCl 0.18% with dextrose 4%液は小児の輸液療法には原則として使用しない[6]。近年，英国，オーストラリア，ニュージーランド，シンガポールなどでは初期輸液には 0.45% NaCl with 5% dextrose 液を用い，状態が改善したらそれに 12 mmol/kg/day の KCl を加えた液にすることが提唱されている。

初期輸液終了時にも低 Na 血症が改善しない場合には糖を付加した乳酸または重炭酸リンゲル液を維持輸液として用いることも考慮する。輸液中には患者の全身状態，尿量，血清 Na 濃度を評価する。

できるだけ経口補液療法を併用して，経静脈輸液による投与量を減らすことも安全な治療法である[7]。

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● 総 説

腎疾患と電解質異常を来す疾患の遺伝子学

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要 旨

腎疾患と電解質異常を来す疾患の原因遺伝子とその遺伝子座を示す一覧表を掲載した．X染色体性 Alport 症候群において遺伝子型と表現型の相関関係は明らかであるが，アデニンホスホリボシルトランスフェラーゼ（APRT）欠損症ではそれは明らかではない．欧米ではステロイド抵抗性ネフローゼ症候群患児の約2/3は *NPHS1*, *NPHS2*, *WT1*, *LAMB2* の4つの遺伝子異常によって占められているが，我が国ではそのようなことはない．小児の末期腎不全の原因として重要なネフロン癆は，遺伝的多様性の高い疾患である．

はじめに

現在では数多くの遺伝性腎疾患の原因遺伝子が同定されている（表1）．疾患の原因が1つの遺伝子異常に起因する単一遺伝子疾患は少なくないが，生後3ヵ月以内に発症する先天性ネフローゼ症候群，遺伝性巣状糸球体硬化症，Bartter 症候群，ネフロン癆などほぼ同一の表現形を示す疾患において，複数の原因遺伝子が同定されつつある．医学の進歩は単一遺伝子疾患を今後さらに減少させるであろう．さら

キーワード：遺伝子型と表現型の相関，X染色体性 Alport 症候群，
アデニンホスホリボシルトランスフェラーゼ欠損症，
ステロイド抵抗性ネフローゼ症候群，ネフロン癆

表1　腎疾患と電解質異常を来す疾患の原因遺伝子と遺伝子座

疾患	原因遺伝子（略号）	遺伝子座
【糸球体疾患】		
先天性ネフローゼ症候群		
フィンランド型	nephrin（*NPHS1*）	19q13.1
Pierson syndrome	laminin β2（*LMB2*）	3p14-22
diffuse mesangial sclerosis	Wilms tumor gene 1（*WT1*）	11p13
	phospholipase C epsilon protein（*PLCE1*）	10q23.32-24.1
infantile sialic acid storage disorder	sialin（*SLC17A5*）	6p14-15
遺伝性巣状糸球体硬化症		
常染色体優性	α-actinin-4（*ACTN4*）	19q13
	canonical transient reveptor protein 6（TRPC6）ion channel（*TRPC6*）	11q
	CD2-associate protein（*CD2AP*）	6p12
常染色体劣性	podocin（*NPHS2*）	1q25-31
	phospholipase C epsilon（*PLCE1*）	10q23.32-24.1
	coenzyme Q2 homologue, prenyltransferase（*COQ2*）	4q21.22
	integrin β4（*ITGβ4*）	17q25.1
hereditary multiple exostoses	86.3 kD endoplasmic reticulum-localized type Ⅱ transmembrane glycoprotein（*EXT1 / 2*）	8q24.11-24.13
Alport 症候群		
X 染色体性	Ⅳ型 collagen α5 鎖（*COL4A5*）	Xq22
常染色体劣性または優性	Ⅳ型 collagen α3 鎖（*COL4A3*）or Ⅳ型 collagen α4 鎖（*COL4A4*）	2q35-37
IgA 腎症　常染色体優性	?	6q22-23
MPGN type Ⅱ	Factor H（*CFH*）	1q32
glomerulopathy with fibronectin deposits	fibronectin（*FN1*）	2q34
lipoprotein glomerulopathy	apolipoprotein E（*APOE*）	19q13.2
atypical HUS	Factor H（*CFH*）	1q32
	Factor I（*CFI*）	4q25
	membrane cofactor protein（*MCP*）	1q32
familial TTP	ADAM metallopeptidase with thrombospondine type 1 motif, 1313（*ADAMTS 13*）	9q34
【尿細管機能異常症】		
autosomal recessive renal glucosuria	Na^+ / gucose cotransporter（*SLC5A2*）	16p11.2
高シュウ酸尿症		
type Ⅰ	alanine：glyoxylate aminotransferase（*AGT*）	2q36-37
type Ⅱ	glyoxylate reductase / hydroxypyruvate reductase（*GRHPR*）	9q11
シスチン尿症		
type Ⅰ	amino acid transporter（rBAT heavy chain）（*SLC3A1*）	2p16.3
type non-Ⅰ	amino acid transporter（rBAT light chain）（*SLC7A9*）	19q13.1
hypoxanthine-guanine phosphoribosyltransferase deficiency	hypoxanthine-guanine phosphoribosyltransferase（*HPRT1*）	Xq26.1

疾患	原因遺伝子（略号）	遺伝子座
adenine phosphoribosyltransferase deficiency	adenine phosphoribosyltransferase（*APRT*）	16q24.3
xanthine dehydrogenase / xanthine oxidase deficiency	xanthinedehydrogenase / xanthine oxidase（*XO*）	2q22
Fanconi-Bickel syndrome	glucose transporter 2（*GLUT2*）	3q26.1-26.3
痛風	ATP-binding cassette, sub-family G, member 2（*ABCG2*）	4q22
Dent 病（特発性尿細管性タンパク尿症）		
	chloride channel-5（*CLCN5*）	Xp11.22
	oculocerebrorenal syndrome-1（*OCRL-1*）	Xq25-26
腎性低尿酸血症		
type 1	urate transporter 1（*SLC22A12*）	11q13
type 2	glucose transporter 9（*SLC2A9*）	4p16-15
familial juvenile hyperuricemic nephropathy (autosomal dominant medullary cystic kidney disease type 2)		
	uromodulin（*UMOD*）	16p12
家族性低カルシウム尿性高カルシウム血症		
	calcium-sensing-receptor（*CASR*）	3q13.3-21
家族性高カルシウム尿性低カルシウム血症		
	calcium-sensing-receptor（*CASR*）	3q13.3-21
Liddle 症候群	amiloride-sensitive Na channel（*SCNN1A*） (gain of function) β or γ subunit	16q12.2-13.11
Bartter 症候群		
type 1（neonatal）	bumetanide-sensitive Na-K-2Cl cotransporter（*SLC12A1*）	15q15-21
type 2（neonatal）	ATP-sensitive K channel（*KCNJ1*）	11q24
type 3（classic）	renal chloride channel（*CLCNKB*）	1q36
type 4（deafness, renal failure）	barttin（*BSND*）	1p31
type 5	calcium-sensing-receptor（*CASR*）	3q13.3-21
type 6	chloride channel-5（*CLCN5*）	Xp11.22
Gitelman 症候群	thiazide-sensitive Na-Cl cotransporter（*SLC12A3*）	16q13
腎尿細管性アシドーシス		
persistent isolated pRTA		
dRTA	Na^+ / HCO_3^- cotransporter（*SLC4A4*）	4q21
autosomal dominant	Cl^- / HCO_3^- exchanger（*SLC4A1*）	17q21-22
autosomal recessive	H^+-ATPase, B1 subunit（*ATP6V1B1*）	2q13
dRTA + pRTA	H^+-ATPase, a4 subunit（*ATP6V0A4*）	7q33-34
炭酸脱水酵素 II 異常症	carbonic anhydrase II（*CA2*）	8q22
低 P 血症性くる病		
X 染色体性	neutral endopeptidase family of proteins（*PHEX*）	Xp22.1
常染色体優性	fibroblast growth factor（*FGF23*）	12p1
hyperostosis-hyperphosphatemic syndrome（HHS）	a peptide involved in mucin-type O-glycosylation（*GALNT3*）	2q24-31
autosomal dominant hypomagnesemia	Na^+, K^+-ATPase γ subunit（*FXYD2*）	11q23

（次頁に続く）