Received: 2012.11.27
Accepted: 2013.01.23
Published: 2013.01.28

Situs inversus and cystic kidney disease: Two adult patients with this Heterogeneous syndrome

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Summary

Background: Situs inversus is a rare complication of cystic kidney diseases. Only three genes, *INVS* (*NPHP2*), *NPHP3* and *PKD2* have been proved to be responsible for some cases, while the responsible genes in many others are still unknown.

Case Reports: Here we report two male patients with situs inversus combined with cystic kidney disease without any family history of polycystic kidney disease. Their renal function was normal in childhood but culminated in end stage renal disease in middle age. No pathogenic mutations were found in mutation analysis of *INVS*, *IFT88*, *PKD2, UMOD* or *NPHP3* in them.

Conclusions: Past reported cases of situs inversus and cystic kidney diseases were divided into three groups, i.e., gestational lethal renal dysplasia group, infantile or juvenile nephronophthisis group and polycystic kidney disease group. The present patients are different from each of these groups. Moreover, the renal lesions of the present two cases are quite different from each other, with one showing mildly atrophic kidneys with small numbers of cysts and the other an enlarged polycystic kidney disease, suggesting very heterogeneous entities.

key words: ADPKD • cystic kidney disease • situs inversus

Full-text PDF: http://www.amjcaserep.com/fulltxt.php?ICID=883751

Word count: 1490
Tables: 1
Figures: 4
References: 12

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Background

Since Alfzelius reported that infertile males whose sperm cilia were immortal had the triad of Kartagener syndrome, primary cilia were discovered to be the key player underlying organ laterality [1]. Here, we describe two situs inversus totalis males with cystic kidney disease who reached end stage renal disease (ESRD) in middle age in the absence of any family history of polycystic kidney disease (PKD). Situs inversus is an uncommon complication of cystic kidney diseases, with 28 such cases reported since 1981. Only three genes, *INVS* (*NPHP2*), *NPHP3* and *PKD2* have been proved to be responsible for some cases, while the responsible genes in many others are still unknown. In mutation screening analysis of *INVS, IFT88, PKD2, UMOD, NPHP3*, no pathogenic mutations were detected. Some mutations of other genes that encode protein expression in primary cilia in both node and kidney are expected to be present in these patients, and will require further investigation in future.

Case Reports

Patient 1

A 54-year-old Japanese man developed severe azotemia and anemia and required emergent hemodialysis and transfusion. On a regular chest X-ray obtained at the age of 20 years, situs inversus had been pointed out. At 47 years. bilateral kidney cysts and renal insufficiency were detected on a regular medical check-up. He had no history of sinusitis or bronchiectasis. A chest X-ray revealed dextracardia and cardiomegaly (Figure 1A). Abdominal CT scan showed situs inversus totalis of all the abdominal organs and bilateral kidney cysts, but the number and sizes of the cysts were small (Figure 1B). There were no extrarenal cysts. He has no family member with PKD or situs inversus. His parents were not consanguineous. He has two biological children. His karyotype was normal.

Patient 2

This Japanese man started regular hemodialysis at the age of 45 years. He was the third child of non-consanguineous parents. From the age of two years he developed frequent bronchitis, sinusitis and otitis media, and by his teens had developed hearing impairment that required a hearing aid. Because he refused to consult any physicians despite his long-standing ill health, situs inversus and polycystic kidneys were not detected until one year before he needed hemodialysis. At the same time bronchiectasis was detected by chest CT and he was diagnosed with Kartagener syndrome. His grandfather had situs inversus but there was no family history of PKD. He has two biological children. A chest X-ray

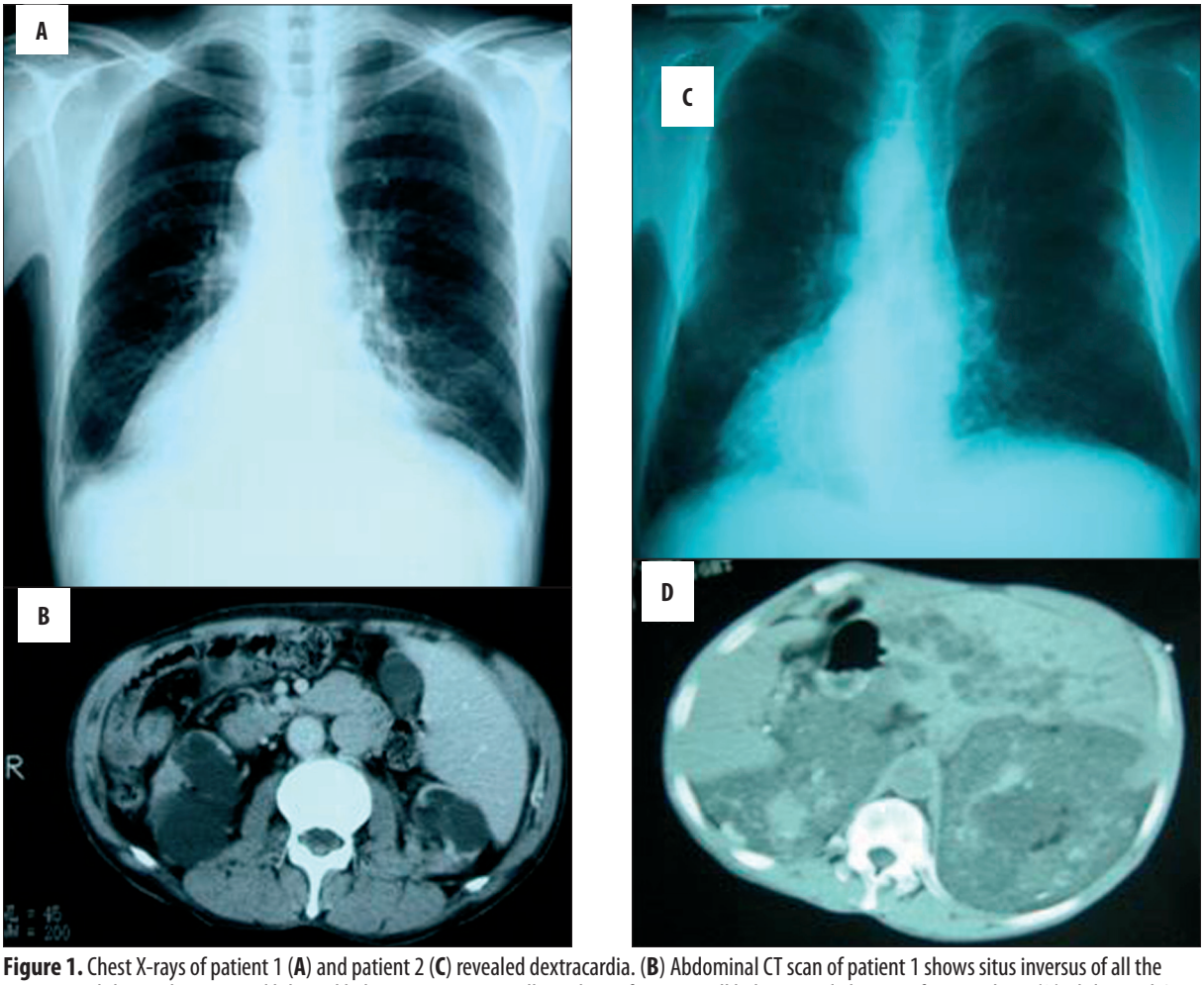

Figure 1. Chest X-rays of patient 1 (**A**) and patient 2 (**C**) revealed dextracardia. (**B**) Abdominal CT scan of patient 1 shows situs inversus of all the abdominal organs and bilateral kidney cysts. Note small numbers of cysts, small kidneys, and absence of cysts in liver. (**D**) Abdominal CT scan of patient 2 revealed situs inversus totalis and multiple bilateral renal and hepatic cysts

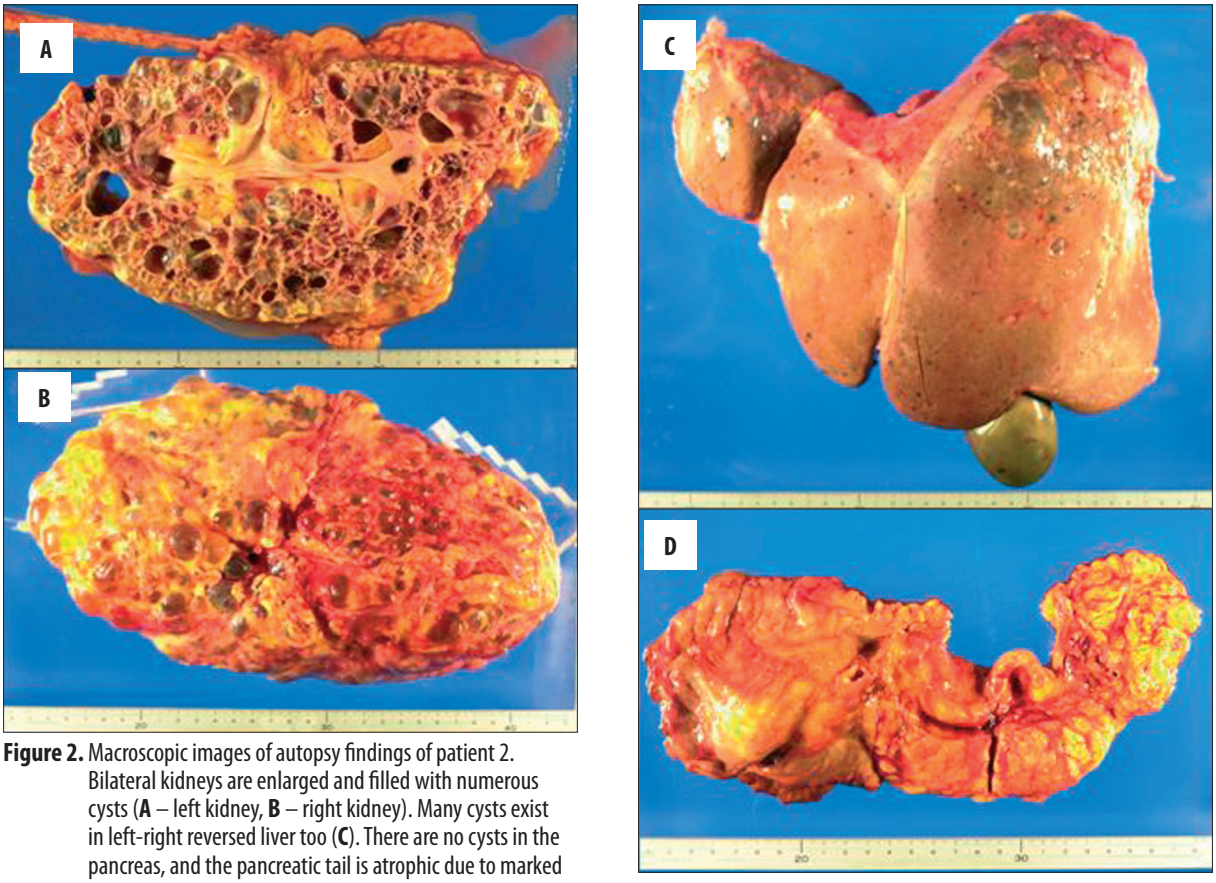

Figure 2. Macroscopic images of autopsy findings of patient 2. Bilateral kidneys are enlarged and filled with numerous cysts (**A** – left kidney, **B** – right kidney). Many cysts exist in left-right reversed liver too (**C**). There are no cysts in the pancreas, and the pancreatic tail is atrophic due to marked fat infiltration (**D**).

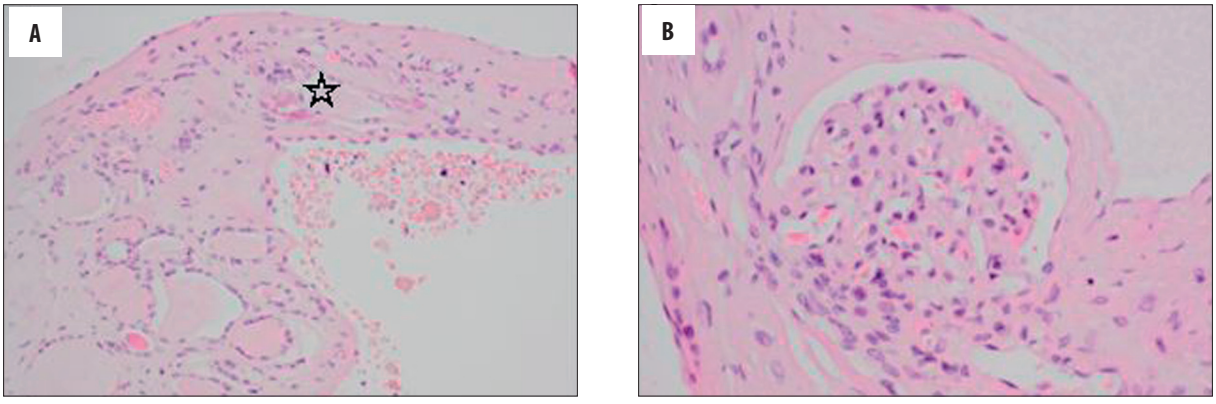

Figure 3A,B. Microscopic images of autopsy findings of patient 2. (**A**) Kidneys are filled with cysts of various sizes, among which atrophic and dilated tubules and calcified veins (☆) persist. (**B**) Only a few glomeruli remain with no signs of glomerulonephritis.

(Figure 1C) and an abdominal CT scan (Figure 1D) revealed situs inversus totalis and bilateral multiple renal and hepatic cysts. After 10 years of regular hemodialysis, he died of acute myocardial infarction at the age of 55 years. Autopsy was performed then. Figures 2 and 3 shows the macroscopic and microscopic findings of the postmortem autopsy of patient 2. The kidneys were enlarged to 28×11 cm (left) and 28×13cm (right) and contained numerous and variously sized cysts separated by very thin parenchyma. Variously sized cysts were present in the left-right reversed liver too. The pancreatic tail was atrophic, but the pancreas contained no cysts. In kidney specimens cysts of various sizes were prominent, with few glomeruli with no particular features. In the interstitium, atrophic and dilated tubules and calcified veins were present. All of these findings were compatible with those of end-stage kidneys due to Autosomal dominant polycystic kidney disease (ADPKD). The liver showed variously sized cysts, which consisted of a layer of biliary epithelium. The pancreas showed mild fibrotic change that was attributed to the chronic pancreatitis associated with the renal failure. There was no dysplastic change in the pancreas. In the lungs there were many bronchiectatic regions, the result of repeated inflammation characteristic of Kartagener syndrome. Figure 4 shows cilia staining of patient 2 kidney (Figure 4A) along with that of an ESRD patient due to non-cystic kidney disease (Figure 4B) and ESRD patients receiving hemodialysis due to ADPKD (Figure 4C). In patient 2, decreased and shortened primary cilia were observed in

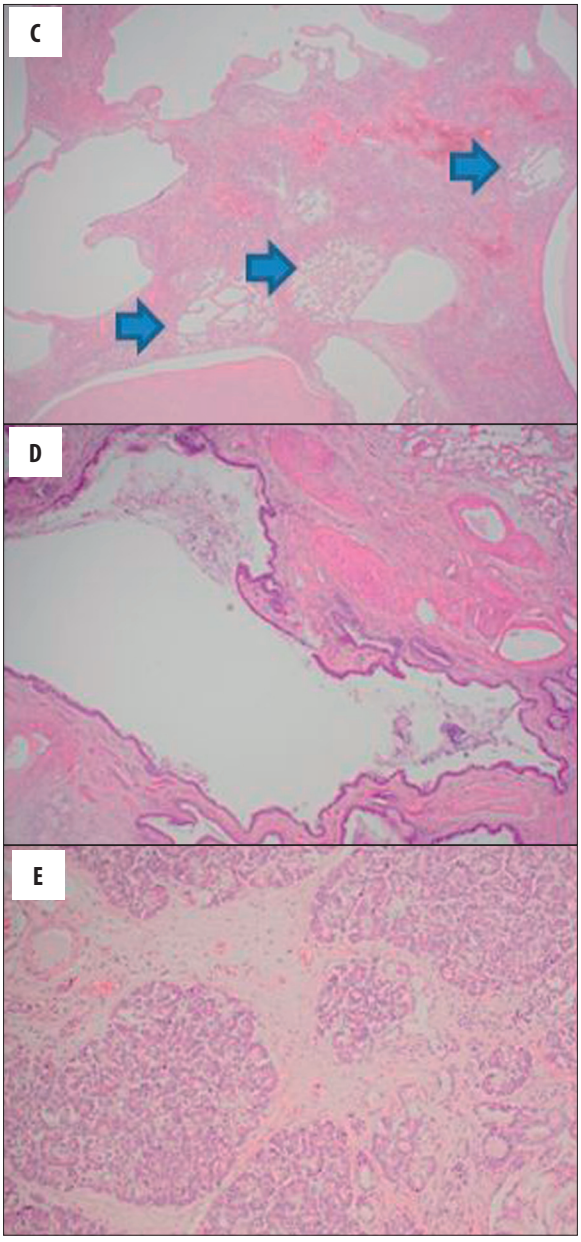

Figure 3C–E. Microscopic images of autopsy findings of patient 2. (**C**) Liver has variously sized cysts consisting of a layer of biliary epithelium. Among the cysts there are many biliary micro hamartomas (arrow) and a subtle fibrous interstitium. (**D**) Bronchiectasis is present in the lungs. (**E**) Pancreas has mild fibrotic change and atrophy of lobules.

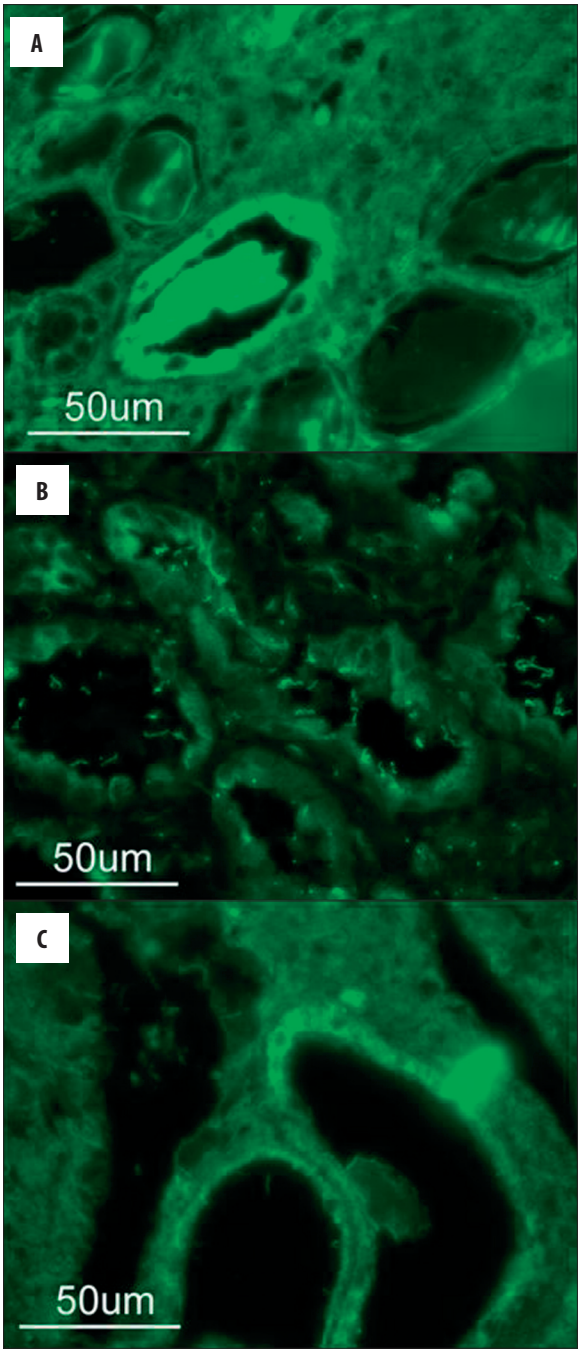

Figure 4. Cilia staining of patient 2 (**A**) and ESRD patient due to non-cystic kidney disease (**B**) and ESRD patient receiving HD due to ADPKD (**C**). In patient 2 and the ADPKD patient, decreased and shortened primary cilia were observed compared with the non-cystic kidney disease patient.

dilated renal tubular epithelial cells, although this finding is similar to that in ADPKD patients receiving hemodialysis.

No pathogenic mutation was discovered in the sequencing analysis of *INVS*, *PKD2*, *IFT88*, *UMOD* or *NPHP3* in both patients. Prior to the genetic analysis, informed consent was obtained from both patients. Detailed methods of genetic and pathological testing are available upon request.

Discussion

Table 1 shows reported cases of situs inversus and cystic kidney diseases from the PubMed database. There have been a total of 28 comorbid cases reported so far, which can be divided into three groups: Renal dysplasia group (12 cases), Nephronophthisis (NPHP) group (13 cases) and PKD group (3 cases). The biggest difference between the groups is the age at renal disease onset. Renal dysplasia patients are found mostly in the gestational period with all of them dying in the fetal or neonatal period and none surviving for longer than 10 days. Nephronophthisis groups are diagnosed in the infantile or juvenile periods. ADPKD patients reach ESRD in adulthood. *INVS* and *NPHP3* mutations were

Table 1. Reported cases of situs inversus comorbid with cystic kidney disease.

Case No	Sex	CS	Ethnic origin	Age[a]	Other complications	Responsible gene	Category[b]	Ref
1	F	N.D.	Japan	–/35 gw/–/1 hr	COA, PDA, aortic stenosis, pulmonary stenosis	unknown	D	(Yoshikawa et al., 1981)
2	F	N.D.	USA	–/40 gw/–/1 day		unknown	D	(Bernstein et al., 1987)
3	M	No	Japan	–/35 gw/–/10 days		unknown	D	(Hiraoka et al., 1988)
4	M	N.D.	Canada	–/32 gw/–/3 min	Chondrodysplasia, absent right kidney, polydactyly	unknown	D	(Fraser et al., 1989)
5	F	N.D.	USA	–/37 gw/–/stillborn	Multisystem fibrosis	unknown	D	(Pinar and Rogers, 1992)
6	M	Yes	Turkey	–/38 gw/–/stillborn	Ventriculomegaly of brain, bowing of the lower limbs and clavicles	unknown	D	(Balci et al., 1999)
7	F	Yes	Turkey	–/18 gw/–/ terminated	Same as No 6 (sibling)	unknown	D	(Balci et al., 1999)
8	F	Yes	Turkey	–/20 gw/–/ terminated	Same as No 6 (sibling)	unknown	D	(Balci et al., 2000)
9	M	N.D.	Taiwan	–/20 gw/–/stillborn	Potters sequences, agenesis of bilateral ureters	unknown	D	(Huang and Chen, 2000)
10	F	No	Turkey	1 mo/1 mo/1 mo/–	Capillary hemangioma	unknown	D	(Mir and Akil, 2003)
11	N.D	Yes	Turkey	–/–/14 mo/–	VSD	INVS	N	(Otto et al., 2003)
12	N.D	No	France	–/29 gw/–/–	Asplenia,CNS malformation[c], DWM	*CEP260*(?)[d]	D	(Baala et al., 2007)
13	M	No	Japan	21 y/11 y/Cr 1.62/–	Asphyxiating thoracic dystrophy	unknown	N	(Okada et al., 2008)
14	F	N.D.	Vietnam	12 y/1 mo/3 mo/–	Postaxial polydactyly,	*NPHP3*	N (D)[e]	(Bergmann et al., 2008)
15	M	No	India	10 mo/10 mo/Cr 0.7/–		unknown	P[f]	(Jayakrishnan and Devarajan, 2008)
16	N.D	No	France	–/18 mo/18 mo/–		INVS	N	(Tory et al., 2009)
17	N.D	No	Switzerland	–/–/9 mo/–	Absence epilepsy	unknown	N	(Tory et al., 2009)
18	N.D	Yes	Old Amish Community	–/34 gw/34 gw/29 days		*NPHP3*	N (D)[e]	(Simpson et al., 2009)
19	F	N.D.	Reunion Island	–/31 gw/–/ terminated	VSD	unknown	D	(Alessandri et al., 2009)
20	F	No	Belgium	31 y/10 y/11 y/–	Corrected TGA	*INVS*	N	(Bellavia et al., 2010)
21	F	No	France	64 y/35 y/59 y/–		*PKD2*	P	(Bataille et al., 2011)
22	M	No	France	54 y/54 y/Cr 2.0/–		PKD2	P	(Bataille et al., 2011)

CS – consanguineous; N.D. – no data available; COA – Coarctation of Aorta; PDA – Patent ductus arteriosus; VSD – Ventricular septal defect; CNS – central nervous system; DWM – Dandy-Walker malformation; TGA – Transposition of the great arteries.
Six NPHP cases with no clinical data available are not shown (Otto et al., 2008). Cases diagnosed with known cilia-related syndromes (Syndromes such as Bardet-Biedl syndrome, Ellis-van Creveld syndrome, hemifacial microsomia) are not included.
a – Age at report/diagnosis/ESRF/death. When patient has not reached ESRF, the serum Cr value (mg/dl) is shown; b – Category of kidney disease D: Renal Dysplasia N: Nephronophthisis P: Polycystic kidney disease; c – Occipital meningocele, Hydrocephaly, arhinencephaly, cerebellar vermis hypoplasia, cystic V4; d – Although his DNA was not available, his sibling with Meckel syndrome without situs inversus had compound heterozygous mutations of *CEP260*; e – Renal lesion of case No 14 was reported to be renal dysplasia. So the two cases with *NPHP3* mutation might be more appropriately included in the renal dysplasia category; f – Bilateral kidneys enlarged to about 10cm. He is assumed to have ARPKD.

detected in 3 and 2 NPHP patients respectively. Although almost all *invs* mutated mice manifest situs inversus [2], the incidence of situs inversus is not high in humans with *INVS* mutation. Only 3 of 32 NPHP patients carrying *INVS* mutation showed situs inversus.

It would be natural to conclude a diagnosis of ADPKD in the present two patients who started hemodialysis therapy at the age of 54 and 45 years respectively. However some features in the present patients differ from those usually seen in ADPKD including absence of family history of ADPKD in both patients. Sizes of kidneys and numbers of kidney cysts in patient 1 were small for age as compared to usual ADPKD. Patient 2 had features of typical Kartagener syndrome. Extra renal cysts are common in ADPKD, but none were noted in patient 1. So the present two patients do not meet the criteria of ADPKD and differ from the two ADPKD patients reported by Bataille [3]. Besides, the phenotypes of the two present patients are quite different.

The phenotype of Medullary cystic kidney disease (MCD) is similar to that of nephronophthisis. Affected patients reach ESRD in their forties to fifties. It is caused by at least two genes, one of which is Uromodulin (*UMOD*). *UMOD* has been found to be located in cilia[4], although no mutations in *UMOD* gene were found in the present cases.

A striking point is that even the same gene mutation in the same family may cause different phenotypes. Among 12 related individuals with renal dysplasia carrying the same homozygous *NPHP3* mutation, only one had situs inversus[5]. Both of the two pairs of independent *PKD2* family siblings sharing the same mutation had discordance of situs inversus in the report of Bataille[3]. The same homozygous *INVS* mutation (Arg899X) in two siblings caused situs inversus discordantly and another independent patient with the same mutation did not show situs inversus either [6]. On the other hand, all of three siblings manifested situs inversus in the report of Balci [7] with unknown genetic abnormalities. So it is difficult to assume the mutated gene from the phenotype of a patient because syndromes of cystic kidney diseases combined with situs inversus comprise a very heterogeneous disease spectrum.

In some animals with cilia-related gene mutations there have been descriptions of the presence of no cilia or extremely short primary cilia, [8,9], and this prompted us to check the cilia of patient 2. An extremely decreased number of and shortened primary cilia were detected in the kidneys of patient 2. However, this finding cannot be considered specific for this patient, since a similar picture is observed in the kidneys of ADPKD patients receiving hemodialysis.

The occurrence of situs inversus is decided by the direction of nodal ciliary movement during embryogenesis [10]. Although the situs abnormality can be caused by mutation of a ciliary gene, other modifier genes or environmental factors also likely contribute. The existence of another mutation in another gene may be one explanation for the phenomenon[11]. Numerous genes that express proteins in cilium and centrosome have been discovered and the numbers of such genes are still increasing. 13 genes have been proven to be responsible for NPHP, but account for only about 30% of cases, which implicates other as yet undiscovered genes in NPHP [12]. However the mechanisms of such gene complexes are still equivocal.

CONCLUSIONS

We describe two patients with situs inversus comorbid with cystic kidney disease that are different from any other previously reported cases. Although no genetic evidence was obtained, this syndrome may fall into a kind of cilia dysfunction syndrome. To prove this, analysis of a greater range of cilia related genes will be required in future, Such studies may also provide hints to the formation of left-right asymmetry.

Acknowledgments

We thank the patients and their families for providing clinical information, Mr. J. S. Gelblum for his critical reading of the manuscript and Mrs. Y. Kubo for her secretarial assistance.

Disclosure

None of the authors have declared any competing interests.

REFERENCE:

1. Afzelius BA: A human syndrome caused by immotile cilia. Science, 1976; 193: 317–19
2. Mochizuki T, Saijoh Y, Tsuchiya K et al: Cloning of inv, a gene that controls left/right asymmetry and kidney development. Nature, 1998; 395: 177–81
3. Bataille S, Demoulin N, Devuyst O et al: Association of PKD2 (Polycystin 2) Mutations With Left-Right Laterality Defects. Am J Kidney Dis, 2011; 58: 456–60
4. Zaucke F, Boehnlein JM, Steffens S et al: Uromodulin is expressed in renal primary cilia and UMOD mutations result in decreased ciliary uromodulin expression. Hum Mol Genet, 2010; 19: 1985–97
5. Simpson MA, Cross HE, Cross L et al: Lethal cystic kidney disease in Amish neonates associated with homozygous nonsense mutation of NPHP3. Am J Kidney Dis, 2009; 53: 790–95
6. Bellavia S, Dahan K, Terryn S, Cosyns JP et al: A homozygous mutation in INVS causing juvenile nephronophthisis with abnormal reactivity of the Wnt/beta-catenin pathway. Nephrol Dial Transplant, 2010; 25: 4097–102
7. Balci S, Bostanoglu S, Altinok G, Ozaltin F: New syndrome?: Three sibs diagnosed prenatally with situs inversus totalis, renal and pancreatic dysplasia, and cysts. Am J Med Genet, 2000; 90: 185–87
8. Takeda S, Yonekawa Y, Tanaka Y et al: Left-right asymmetry and kinesin superfamily protein KIF3A: new insights in determination of laterality and mesoderm induction by kif3A-/- mice analysis. J Cell Biol, 1999; 145: 825–36
9. Pazour GJ, Dickert BL, Vucica Y et al: Chlamydomonas IFT88 and its mouse homologue, polycystic kidney disease gene tg737, are required for assembly of cilia and flagella. J Cell Biol, 2000; 151: 709–18
10. Sutherland MJ, Ware SM: Disorders of left-right asymmetry: heterotaxy and situs inversus. Am J Med Genet C Semin Med Genet, 2009; 151C: 307–17
11. Hoefele J, Wolf MT, O'Toole JF et al: Evidence of oligogenic inheritance in nephronophthisis. J Am Soc Nephrol, 2007; 18: 2789–95
12. Hildebrandt F, Attanasio M, Otto E: Nephronophthisis: disease mechanisms of a ciliopathy. J Am Soc Nephrol, 2009; 20: 23–35