6 Syndromes and Malformations of the Urinary Tract

Chanin Limwongse

Introduction

Birth defects involving the kidney and urinary system are often encountered and frequently occur in association with other structural abnormalities. A congenital urinary tract anomaly may provide the first clue to the recognition of multiorgan developmental abnormalities. Nevertheless many renal anomalies remain asymptomatic and undiagnosed. Therefore it is critical, not only for pediatric nephrologists but also for pediatricians in general, to be familiar with the common anomalies involving the kidney and urinary system and the more complex disorders with which they may be associated.

The kidney is a pivotal organ in dysmorphology. Although the number of single malformations involving the kidney is limited, combinations of these malformations in conjunction with anomalies involving other organ systems are found in more than 500 syndromes. In addition, many well-known sequences and associations involve the kidney and urinary tract. This chapter discusses common malformations, sequences and associations involving the kidney and urinary tract, and provides a summary of conditions that have these anomalies as one of their features. In addition, *Tables 6-1–6-3* summarize more detailed information about a large number of disorders, including their phenotypic features, reported urinary tract anomalies, pattern of inheritance, causative genes and related references. These tables can be used both to provide readily available information about potential urinary tract anomalies for patients with a diagnosed genetic syndrome and to suggest a differential diagnosis when anomalies are identified. Readers interested in additional details about a specific syndrome are referred to standard reference textbooks and databases about syndromes and malformations for further reading (e.g., (5–7)).

To understand the pathophysiologic basis of structural abnormalities, it is important to be familiar with the meaning of certain terms as they are used in describing malformations and syndromes.

Malformation refers to a single structural anomaly that arises from an error in organogenesis. Such an error may be due to the failure of cells or tissues to form, to die (programmed cell death), or to induce others. Examples include renal agenesis, horseshoe kidney, and bladder exstrophy.

Deformation refers to a single structural anomaly that arises from mechanical forces, such as intrauterine constraint. Examples include many cases of metatarsus adductus, torticollis, and congenital scoliosis. The underlying tissue may be normal or abnormal, and sometimes a malformation (e.g., renal agenesis) can predispose patients to a deformation (e.g., Potter's sequence from oligohydramnios).

Disruption refers to a single structural anomaly, that results from a destructive event after normal morphogenesis. Such events can be caused by lack of vascular supply, an infectious process, or mechanical factors. Examples include limb amputation from amniotic bands and abdominal wall defect from vascular insufficiency related to maternal cocaine use.

Sequence refers to a cascade of abnormalities that result from a single initiating anomaly. Sequences can be malformational, deformational, or disruptive, and they sometimes represent more than one of these categories. Obstruction of urine flow at the level of the ureter during early gestation, for example, can cause malformation of the kidneys, intestines, and abdominal wall – a malformation sequence. At the same time, decreased urine flow will produce oligohydramnios, fetal compression, and multiple deformities of the face, limbs, and chest wall – a deformation sequence.

Syndrome refers to a consistently observed pattern of anomalies found in an individual, whether malformation, deformation, or disruption. Anomalies comprising a syndrome are thought to have a single cause, although in many cases, their causes are still unknown. Examples include Turner syndrome and fetal alcohol syndrome.

Association refers to a constellation of anomalies that occur together more often than expected by chance alone but cannot be explained by a single cause or sequence of events, and so do not represent a syndrome or sequence. VATER association, which is discussed later in this chapter, is a common example.

Table 6-1

Syndromes and disorders that have urinary tract anomalies as a frequent feature

Syndromes	Urinary tract abnormalities											Other associated anomalies	Other associated anomalies	Gene(s)	Ref.
	Renal agenesis	Ectopia/ horseshoe	Cystic/dysplasia	Duplication	Hypoplasia	Hydronephrosis/ ureter	Diverticulae	Atresia/stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephromegaly				
Abruzzo-Erickson		H										Coloboma, cleft palate, hypospadias, deafness, short stature	XR	Unk	(48)
Acrocephalopolydactylous dysplasia (Elejalde syndrome)			+		+	+						Acrodactyly, hand hexadactyly, overgrowth, visceromegaly, globular body, redundant neck skin	AR	Unk	(49)
Acrorenal (Dieker)	1	E		+	+	+	Ua					Ectrodactyly, oligodactyly, hypoplastic carpal/tarsal bones	Sporadic	Unk	(50)
Acrorenal (Johnson-Munson)	1, 2					U, Ua						Aphalangy, hemivertebrae, genital/ intestinal/anal dysgenesis	AR	Unk	(50)
Acrorenal (Siegler)		E				+		U	+			Short stature, hypoplastic radii/ ulnae/humeri, oligodactyly	Uncertain	Unk	(50)
Acro-renal-mandibular	1		+									Ectrodactyly, hypoplastic mandible	AR	Unk	(51)
Acro-renal-ocular	1	E			+		B					Hypoplastic thumb, optic coloboma, cleft lip/palate	AD	SALL4	(52)
Adrenoleukodystrophy, neonatal												See Pseudo-Zellweger			
Aglossia-adactylia	1											Micrognathia, cranial nerve palsy	Sporadic	Unk	(53)
Agnathia-holoprosencephaly		H				+						Arrhinencephaly, situs inversus, midline defects	Sporadic	Unk	(54)
Alagille	1		+	+						+		Cholestasis, peripheral pulmonic stenosis, characteristic face	AD	JAG1	(55)
Alport										+		Nephritis, proteinuria, deafness	AD, AR, XL	COL4	(56)
Alsing										+		Nephritis, nephronophthisis, optic coloboma, hip dislocation	AR	Unk	(57)
Alstrom										+		Diabetes mellitus, retinopathy, short stature, deafness	AR	ALMS1	(58)

Amelogenesis imperfecta type IG										+		Enamel hypoplasia, nephrolithiasis, enuresis	AR	Unk	(59)
Amyloidosis type 5										+		Nephropathy, proteinuria, cranial nerve palsy, cutis laxa	AD	GELSOLIN	(60)
Angiotensin converting enzyme (ACE) inhibitor, maternal use										+		IUGR, oligohydramnios, patent ductus arteriosus, limb anomalies, renal artery stenosis, progressive renal failure	Sporadic	none	(61)
Aniridia-Wilms tumor (WAGR)											+	Aniridia, ambiguous genitalia, hypospadia, short stature	AD	WT1	(62)
Axial mesodermal dysplasia	1											Bladder exstrophy, vertebral anomalies, Goldenhar-like	Uncertain	Unk	(63)
Baldellou	1											Hypoparathyroidism, ocular coloboma, MR, seizures	Uncertain	Unk	(64)
Baller-Gerold	+	E	+		+							Craniosynostosis, radial aplasia, malformed ear, anal atresia	AR	RECQL4	(65)
Barakat										+		Mesangial sclerosis, MR, optic atrophy, nystagmus	AD	GATA3	(66)
Bardet-Biedl			+	+		+	+		+	+		Obesity,polysyndactyly, MR, retinopathy, hypogonadism	AR	BBS1-12	(67, 68)
Beckwith-Wiedemann		E	+	+		+					+	Overgrowth, macroglossia, omphalocele, embryonal tumors	Sporadic, AD	CDKN1C, NSD1, H19	(69–72)
Berardinelli						+					+	Insulin resistance, lipodystrophy, acanthosis nigricans, MR	AR	BSCL2	(73)
Brachymesomelia-renal			+									Micrognathia, corneal opacity, craniofacial dysmorphism	Uncertain	Unk	(74)
Branchio-oculo-facial	1											Philtrum hypertrophy, cleft lip/palate, branchial remnant	AD	TFAP2A	(75)
Branchio-oto-renal	1, 2	E	+	+	+	+			+			Branchial remnant, preauricular pit/tag, microtia, deafness	AD	EYA1, SIX5	(76)
Braun-Bayer				+				U		+		Deafness, bifid uvula, digital anomalies	Uncertain	Unk	(77)
Cat eye												See *Table 6-3*	Chromosomal		
Caudal duplication	1, 2	E		+		+			+			Duplication of colon, sacrum, genitalia, vertebral defects	Sporadic	AXIN1	(78)
Caudal regression	1, 2	E, H			+	+	Ua		+			Atresia of colon, anus, genitalia, vertebral defects, TE fistula	AD, AR	VANGL1	(79–80)

Table 6-1 (Continued)

Syndromes	Urinary tract abnormalities											Other associated anomalies	Other associated anomalies	Gene(s)	Ref.
	Renal agenesis	Ectopia/ horseshoe	Cystic/dysplasia	Duplication	Hypoplasia	Hydronephrosis/ ureter	Diverticulae	Atresia/stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephromegaly				
Cerebro-hepato-renal (Passarge)			+									See Zellweger syndrome	AR	PEX	(81)
Cerebro-oculo-hepato-renal			+									Cerebellar hypoplasia, hepatic fibrosis, Leber amaurosis	AR	Unk	(82)
Cerebro-osteo-nephro dysplasia			+							+		Rhizomelic limb shortening, cerebral atrophy, MR, seizures	AR	Unk	(83)
CHARGE	+	E	+		+	+	+	U	+			See text for details	Sporadic, AD	CHD7	(33–37)
Chondroectodermal dysplasia (Ellis van Creveld)	1		+			+				+		Acromelic dwarfism, polydactyly, nail dystrophy, tooth hypoplasia narrow thorax, CHD	AR	EVC, EVC2	(84–85)
Cocaine, maternal use	1, 2				+	+	Ua		+			Vascular disruption anomalies affecting multiple organs	Sporadic	none	(86)
Cornelia de Lange	1		+		+	+					+	SS,microcephaly, limb defect, hirsuitism, synophrys	Sporadic	NIPBL, SMC1L1	(87)
Crossed renal ectopia-pelvic lipomatosis		E				+		U				Clubbing of fingers, gynecomastia	Uncertain	Unk	(88)
Czeizel						+		U				Ectrodactyly, spina bifida, megacystis	AD	Unk	(89)
Diabetic mother, infant of	1, 2	E, H	+	+	+	+	Ua		+			Neural tube defect, cardiac/limb anomalies, sacral agenesis	Sporadic	none	(90–91)
DiGeorge/velocardiofacial	1, 3	E		+	+	+		+	+			See *Table 6-3*	Chromosomal		
Denys-Drash		E		+						+	+	Pseudohermaphroditism, Wilms tumor, proteinuria	Sporadic	WT1	(92)
Down												See *Table 6-3*	Chromosomal		
Ectrodactyly-ectodermal dysplasia-clefting (EEC)	1		+	+		+			+			Ectrodactyly, hypohidrosis, sparse hair, cleft lip/palate	AD	Unk	(93)

Elejalde												See acrocephalopolydactylous dysplasia			
Epstein										+		Thrombocytopenia, nerve deafness, cataract	AD	MYH9	(94)
Facio-cardio-renal		H				+		U				Cardiomyopathy, conduction defect, MR, typical face	AR	Unk	(95)
Fanconi anemia	1	E, H	+	+	+	+						Pancytopenia, limb defects, leukemia, lymphoma	AR	FANCA-N	(96–97)
Fetal alcohol	1	E, H	+	+	+	+						IUGR, DD, microcephaly, short palpebral fissure	Sporadic	none	(98)
Fibromatosis, infantile					+						+	Multiple myofibromatosis, myositis ossificans	AR	Unk	(99)
Fraser cryptophthalmos	1, 2		+					U				Fused eyelids, ear/genital anomalies, syndactyly	AR	FRAS1	(100)
Frasier					+					+		Male pseudohermaphrodite, amenorrhea, ovarian cysts	AD	WT1	(101)
Goeminne			+							+		Congenital torticollis, keloids, cryptorchidism	XR	Unk	(102)
Goldenhar (oculo-auriculo-vertebral)	1	E	+	+	+	+			+			Hemifacial microsomia, ear anomalies, vertebral defects	Sporadic, AD	Unk	(103)
Goldston			+									Dandy-Walker malformation, cerebellar malformation	Uncertain	NPHP3	(104)
Graham			+								+	Cystic hamartoma of lung and kidney	Sporadic	Unk	(105)
Hemifacial microsomia (oculo-auriculo-vertebral)												See Goldenhar syndrome			
Hemihyperplasia			+								+	Asymmetry, vascular malformation, embryonal tumors	Sporadic	LIT1, H19	(106)
Hepatic fibrosis			+									Congenital hepatic fibrosis	Sporadic	PKHD1	(107)
Holzgreve	2											Potter sequence, cardiac defect, polydactyly, cleft palate	Uncertain	Unk	(108)
Hypertelorism-microtia-clefting		E		+								Microcephaly, cleft lip/palate, MR	AR	Unk	(109)
Ivemark	1		+		+	+						Poly/asplenia, complex CHD, laterality defects	Sporadic, AR	Unk	(110)
Jeune			+									Narrow chest, short limbs, polydactyly, glomerulosclerosis	AR	EVC, EVC2	(84–85)

Table 6-1 (Continued)

Syndromes	Urinary tract abnormalities											Other associated anomalies	Other associated anomalies	Gene(s)	Ref.
	Renal agenesis	Ectopia/ horseshoe	Cystic/dysplasia	Duplication	Hypoplasia	Hydronephrosis/ ureter	Diverticulae	Atresia/stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephromegaly				
Joubert			+									Vermis aplasia, apnea, jerky eyes, retinopathy, ataxia	AR	JBTS1-7	(111)
Juberg-Hayward		H			+							Microcephaly, cleft lip/palate, abnormal thumbs/toes	AR	Unk	(112)
Kabuki		H		+		+		U	+			MR, characteristic Kabuki-like face, large ears, cleft palate	Uncertain	Unk	(113)
Kallmann	1				+							Anosmia, cleft lip/palate, hypogonadotrophic hypogonadism	AD, AR, XR	KAL1-4	(114)
Kaufman-McKusick		E	+	+		+		Ua				Hydrometrocolpos, polydactyly, anal/urogenital sinus defect	AR	GLI3	(115)
Kivlin		E		+								Short stature, Peters' anomaly, MR, genital/cardiac defects	AR	B3GALTL	(116)
Klippel-Feil	1	E		+								Short neck, cervical vertebral fusion, low posterior hairline	Sporadic, AD	Unk	(117)
Kousseff	1											Sacral meningocele, hydrocephalus, cardiac defects	AR	Unk	(118)
Leprechaunism (Donohue)			+								+	Insulin resistance, lipodystrophy, hirsutism	AR	INSR	(119)
Limb-body wall complex	1	E	+			U, Ua						Lateral body wall defect, limb reduction, CHD	Sporadic	Unk	(120)
Mammo-renal				+								Ipsilateral supernumerary breasts/ nipples	Sporadic	Unk	(121)
Marden-Walker			+		+							Microcephaly, blepharophimosis, micrognathia, contractures	AR	Unk	(122)
Meckel-Gruber			+		+	U, Ua						Encephalocele, cardiac defects, cleft lip/palate, polydactyly	AR	MKS1-4	(123)
Megacystis-microcolon						+		U				Large bladder, intestinal hypoperistalsis, oligohydramnios	AR	Unk	(124)

Melnick-Needles osteodysplasty						+		U				Bowing long bones, short upper limbs, micrognathia	XR	FLNA	(125)
Mendelhall											+	Insulin resistance, acanthosis nigricans	AR	INSR	(126)
Microgastria-upper limb anomaly	1	E			+							Hypoplastic spleen, limb reduction defects	Uncertain	Unk	(127)
Miranda	+		+									Brain malformation, liver dysplasia	Uncertain	Unk	(128)
Moerman	1		+	+	+	+						Short limbs, brain malformation, cleft palate	Uncertain	Unk	(129)
MURCS association	1	E	+					U				See text for details	Sporadic	Unk	
Nager acrofacial dysostosis	+			+		+			+			Facial bone hypoplasia, cleft eyelid, radial ray defect	AD	Unk	(130)
Nail-patella										+		Absent/hypoplastic nails and patellae	AD	LMX1B	(131)
Neu-Laxova	1											IUGR,lissencephaly, CHD, pterygia, ichthyosis	AR,sporadic	Unk	(132)
Neuro-facio-digito-renal	1											Prominent forehead with vertical groove, MR, ear anomaly	Uncertain	Unk	(133)
Neurofibromatosis type I	1							Ua			+	renal artery stenosis, hypernephroma, cafe-au-lait spots	AD	NeUnkro fibromin	(134)
Nezelof			+							+		Arthrogryposis, hepatic impairment, hypotonia, club feet	AR	Unk	(135)
Noonan			+	+		+						Webbed neck, short stature, MR, pulmonic stenosis	AD	NS1	(136)
Occipital horn						+	B	Ua				Cranial exostosis, hyperextensibility, cutis laxa	XR	cUnkATPase	(137)
Ochoa				+		+	B U, Ua +					Facial grimacing with lateral displacement of mouth	Uncertain	Unk	(138)
Oculo-auriculo-vertebral												See Goldenhar syndrome			
Oculo-hepato-encephalo-renal			+		+							Encephalocele, hepatic fibrosis, coloboma	AR	Unk	(82)
Oculo-renal-cerebellar										+		MR, spastic diplegia, choreoathetosis, retinopathy	AR	Unk	(139)
Oculorenal												See Pierson syndrome			
Oculorenal (Karcher)	1				+					+		Optic nerve coloboma	AD	Unk	(140)

Table 6-1 (Continued)

Syndromes	Urinary tract abnormalities											Other associated anomalies	Other associated anomalies	Gene(s)	Ref.
	Renal agenesis	Ectopia/ horseshoe	Cystic/dysplasia	Duplication	Hypoplasia	Hydronephrosis/ ureter	Diverticulae	Atresia/stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephromegaly				
OEIS (omphalocoele-exstrophy of bladder-imperforate anus-spinal dysraphism) complex			+			+		Ua	+			Malrotation of colon, sacral defect, tethered spinal cord, pelvic bone abnormalities	Sporadic	Unk	
Otorenal			+			+	+	U				Renal pelvis diverticulae, nerve deafness	AD	Unk	(141)
Pallister-Hall	1, 2	E, H	+			+						Hypothalamic hamartoblastoma, polydactyly	AD	GLI3	(142–143)
Pierson			+									Hypoplastic retina, cataract, anterior chamber anomalies	AR	LAMB2	(144)
Penoscrotal transposition		E	+		+	+	B	U				Abnormal placement of external genitalia	Sporadic	Unk	(145)
Perlman			+	+		+				+	+	Early overgrowth, typical face, nephroblastomatosis	AR	Unk	(146)
Polydactyly-obstructive uropathy						+	Ua		+			Post-axial polydactyly of hands and feet	Uncertain	Unk	(147)
Potter (oligohydramnios)	1, 2		+		+			Ua				See text for details	Sporadic	Unk	
Prune belly			+	+		+	Ua		+			See text for details	Sporadic	Unk	
Pseudo-Zellweger			+								+	Hypotonia, seizures, MR, typical face, FTT, hepatomegaly	AR	PTS1	(148–150)
Pyloric stenosis		H	+	+	+	+						Cystic kidney	Sporadic	Unk	(151)
Rass-Rothschild	+					+						Klippel-Feil anomaly, sacral agenesis, cryptorchidism	Uncertain	Unk	(152)
RAPADILINO						+						Radial/patella hypoplasia, diarrhea, short stature, long nose	AR	RECQL4	(153)
Renal/Mullerian hypoplasia		H			+				+			Absent uterus, broad forehead, DD, large fontanel	AR	Unk	(154)

Renal dysplasia or adysplasia	1	E	+		+	+	Ua		+			Abnormal uterus in some patients	AD	RET, UnkPK3A	(155)
Renal-hepatic-pancreatic dysplasia			+									Pancreatic cysts, extrahepatic biliary atresia, Caroli disease	AR	EVC, EVC2	(84–85)
Retinoic acid, maternal use					+	+		U				Ear anomalies, CHD, cleft palate, neural tube defect	Sporadic	none	(156–157)
Roberts	1	H	+			+						Limb reduction, oligo/syndactyly, CHD, dysmorphic face	AR	ESCO2	(158)
Robson										+		MR,macrocephaly, deafness, proteinuria, Alport-like	XR	COL4A	(159)
Rokitansky-Mayer-Kuster-Hauser	1	E	+	U	+							Absence of vagina, uterine anomalies, amenorrhea	Sporadic	Unk	(160)
Rubella, congenital	1		+	+								CHD, MR, deafness, cataract, growth retardation	Sporadic	none	(161)
Rubinstein-Taybi	1	E	+	+	+			Ua				SS, MR, broad thumbs and great toes, typical face	Sporadic	CREBBP	(162–163)
Russell-Silver						+		Ua				SS, triangular face, asymmetry, clinodactyly, hypoglycemia	Sporadic,AD	Unk	(164)
Santos	1											Hirschsprung disease, hearing loss, postaxial polydactyly	AR	Unk	(165)
Say			+									SS,microcephaly, micrognathia, large ear, cleft palate	AD	Unk	(166)
Schimke										+		SS,spondyloepiphyseal dysplasia, immunodeficiency	AR	SMARCAL1	(167)
Schinzel-Giedion		E		U		+		U				CHD, distinctive face, figure 8 head shape, eyelid groove	AR	Unk	(168)
Senior-Loken			+							+		Nephronophthisis, tapeto retinal degeneration	AR	NPHP1,4,5	(169)
Setleis						+		U				Cutis aplasia with temporal scarring, abnormal eyelashes	AD,AR	Unk	(170)
Short rib, Beemer Langer			+		+	+		U				Hydrops, cleft lip, bowed long bones, atretic ear canal	AR	Unk	(171)
Short rib-polydactyly, type 1–3	1		+					Ua				Urethral fistula, CHD, cloacal/ urogenital sinus anomalies	AR	Unk	(171–172)
Silverman (dyssegmental dwarfism)						+		U				SS, flat face, cleft palate, generalized skeletal dysplasia	Uncertain	HSPG2	(173)
Simopoulos			+									Hydrocephalus, polydactyly	AR	Unk	(174)

Table 6-1 (Continued)

Syndromes	Urinary tract abnormalities											Other associated anomalies	Other associated anomalies	Gene(s)	Ref.
	Renal agenesis	Ectopia/ horseshoe	Cystic/dysplasia	Duplication	Hypoplasia	Hydronephrosis/ ureter	Diverticulae	Atresia/stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephromegaly				
Simpson-Golabi-Behmel			+			+					+	Overgrowth, polydactyly, typical face, arrhythmia	XR	GPC3	(175)
Sirenomelia sequence	1, 2	E	+	+	+	+	+	+	+			See text for details	Sporadic	Unk	
Smith-Lemli-Opitz	1		+		+							SS, ambiguous genitalia, 2–3 toe syndactyly, brain anomalies	AR	DHCR7	(176–177)
Sommer	1											Iris aplasia, corneal opacity, glaucoma, prominent forehead	AD	Unk	(178)
Sorsby (coloboma-brachydactyly)	1											Ocular coloboma, brachydactyly type B, bifid thumbs	AD	Unk	(179)
Sotos								Ua			+	Overgrowth, MR, embryonal tumors, advanced bone age	Sporadic	NSD1	(180)
Supernumerary nipples-renal anomalies		E	+	+	+	+						Familial polythelia	AD	Unk	(181)
Thalidomide, maternal use	1, 2	E, H	+		+	+	+		+			Limb reduction, phocomelia, neural tube defect	Sporadic	none	(182–183)
Thymic-renal-anal-lung	+		+					U				SS, absent thymus, parathyroid agenesis, urethral fistula	AR	Unk	(184)
Tolmie			+									Lethal multiple pterygia, long bone abnormalities	XR	CHRN	(185)
Townes-Brock	1		+		+			Ua	+			Triphalangeal thumb, imperforate anus, skin tag, deafness	AD	SALL1	(186)
Trimethadione, maternal use	1							U				SS, CHD, omphalocele, distinctive face	Sporadic	none	(187)
Tuberous sclerosis			+								+	MR, seizures, cortical tuber, facial angiofibroma	AD	TS1, TS2	(188)

Turner												See *Table 6-3*	Chromosomal		
Ulnar-mammary	1											Oligodactyly, ulnar ray defect, nipple aplasia, genital defects	AD	TBX3	(189)
Urogenital adysplasia	1, 2		+									Absent uterus, vaginal atresia, hydrometrocolpos	AD	RET, UnkPK3A	(190)
VATER (VACTERL) association	1	E, H	+	+	+	+	+	+	+			See text for details			
Velocardiofacial	1, 2	E, H		+	+	+		+	+			See *Table 6-3*			
von Hippel-Lindau			+								+	Cerebello-retinal angiomatosis, pheochromocytoma	AD	VHL	(191–192)
Weinberg-Zumwalt			+								+	Multiple lung cysts, ascites, accessory spleen	Uncertain	Unk	(193)
Wenstrup	1		+		+	+		U				Female pseudohermaphrodite, imperforate anus	Uncertain	Unk	(194)
Weyers		H	+	+		+		U				Oligodactyly, pterygia, sternal defect, cleft palate	AR	EVC	(195)
Williams		E			+	+	B, U	U				See *Table 6-3*	Chromosomal		
Wilms tumor-horseshoe kidney		H									+	Possible association	Sporadic	WT1	(196)
Wilms tumor-hemihypertrophy											+	Ipsilateral vascular malformation, cafe-au-lait spots	Sporadic	WT1	(106)
Wilms tumor-radial aplasia											+	Hypoplastic fibula/tibia, abnormal thumbs	Sporadic	Unk	(197)
Winter (oto-renal-genital)	1, 2		+									Middle ear anomalies, deafness, vaginal atresia	AR	Unk	(198)
Wolfram (DIDMOAD)						+			+			Diabetes mellitus/insipidus, optic atrophy, nerve deafness	AR, mitochondrial	WFS1-2	(199)
Zellweger	1		+			+						Hypotonia, seizures, hepatosplenomegaly, growth delay	AR	PEX	(148–150)

U ureter; *B* bladder; *Ua* urethra; *1* unilateral renal agenesis; *2* bilateral renal agenesis; *E* ectopia; *H* horseshoe; *ACC* agenesis of corpus callosum; *SS* short stature; *MR* mental retardation; *DD* developmental delay; *CHD* congenital heart disease; *FTT* failure to thrive; *IUGR* intrauterine growth retardation; *Unk* Gene unknown

Table 6-2

Well-known syndromes associated with occasional urinary tract anomalies

Syndromes	Renal agenesis	Ectopia/ horseshoe	Cystic/ dysplasia	Duplication	Hypoplasia	Hydro-nephrosis/ ureter	Diverticulae	Atresia/ stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephro-megaly	Other Associated Anomalies	Inheritance Pattern	Gene(s)	Reference.
Aase								Ua				Triphalangeal thumb, hypoplastic anemia	AD,AR	RPS19, 24	(200)
Achondrogenesis				+		+						Micromelic dwarfism, short trunk, fetal hydrops	AR	COL2A1	(201)
Acrocallosal	1		+									ACC, macrocephaly, polymicrogyria, polydactyly, CHD	AR	GLI3	(202)
Acro-facial dysostosis		H			+							Abnormal thumb/toe, facial bone defect,ear anomalies	AR	Unk	(203)
Acromelic frontonasal dysplasia		E		+								Polydactyly, ACC, encephalocele, Dandy-Walker anomaly	Sporadic	Unk	(204)
Adrenogenital	1			+		+						Ambiguous genitalia, vomiting,salt losing,UPJ obstruction	AR	CYP11,21	(205)
Adrenal hypoplasia-MR						+		U	+			Aminoaciduria, MR, muscular dystrophy, visual abnormality	X-linked	NROB1	(206)
Antley-Bixler		H		+								Craniosynostosis, radio-humeral synostosis, cardiac defects	AR	FGFR2	(207)
Apert (acrocephalo-syndactyly)			+			+						Acrocephaly, craniosynostosis, syndactyly	AD	FGFR2	(208)
Bloom											+	Short stature, telangiectasias, leukemia, lymphoma	AR	BLM	(209)
Bowen-Conradi		H		+								Micrognathia, arthrogryposis, cloudy cornea, brain anomaly	AR	Unk	(210)
Brachydactyly type E	1				+							Vertebral anomalies, narrow auditory canal	Uncertain	HOXD13	(211)
3C (Ritscher-Schinzel)						+						SS,Dandy-Walker anomaly,typical face, CHD	AR	Unk	(212)

C-trigonocephaly	1											Polysyndactyly, abnormal ear, hypospadias, dislocated joints	AR	CD96	(213)
Campomelic dysplasia	1		+			+						Tibial bowing, pretibial dimples, ambiguous genitalia	AD	SOX9	(214)
Carbohydrate deficient glycoprotein			+									FTT, abnormal fat pad, hepatosplenomegaly, neurodegeneration	AR	PMM2, MPI	(215)
Carpenter										+		Aminoaciduria, polysyndactyly, craniosynostosis	AD	RAB23	(216)
CHILD	1,2					+						Unilateral erythroderma, ipsilateral limb defect	X-linked	NSDHL	(217)
Chondrodysplasia punctata, non-rhizomelic			+									Flat face, microcephaly, cataract, short femora/humeri, stippled epiphyses	AR	Unk	(218)
Coffin-Siris	1					+						MR,sparse scalp hair, hirsutism,coarse face, thick lips	AR	Unk	(219)
Cutis la+a type I							B					GI tract diverticulae, emphysema, diaphragmatic defect	AR	FBLN5	(220)
Disorganization-like	+											Polydactyly, duplication of lower limbs, skin appendages	Sporadic	Unk	(221)
Duane anomaly-radial defects	1											Limited ocular abduction, radial defects, blepharophimosis	AD	SALL4	(222)
Ehlers-Danlos			+									Joint hypermobility, skin hyperextensibility, easy brusing	AD, AR, XR	COL5A, COL1A1	(223)
Epidermolysis bullosa						+		U				Skin blistering, pyloric stenosis, dystrophic nails, sparse hair	AR	LAMA3, LAMB3	(224–245)
Femoral hypoplasia-unusual facies	1											Various leg deformities, abnormal genitalia, typical face	Sporadic, AD	Unk	(226)
Floating-Harbor		E										SS, typical face, DD, delayed bone age	Uncertain	Unk	(227)

Table 6-2 (Continued)

Syndromes	Renal agenesis	Ectopia/ horseshoe	Cystic/ dysplasia	Duplication	Hypoplasia	Hydro-nephrosis/ ureter	Diverticulae	Atresia/ stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephro-megaly	Other Associated Anomalies	Inheritance Pattern	Gene(s)	Reference.
Focal dermal hypoplasia		H										Atrophy/linear skin pigmentation, hand/ vertebral anomalies	X-linked	PORCN	(228)
Freeman-Sheldon					+	+						Whistling face, ulnar deviation of hands, talipes equinovarus	AD	TNNT3, TNNI2	(229)
Fronto-metaphyseal dysplasia				+		+						Prominent supraorbital ridges, contractures, deafness	X-linked	FLNA	(230)
Frontonasal dysplasia	+	E										Hypertelorism, broad nasal tip, median cleft nose	Sporadic	Unk	(231)
Fryns			+									Digital hypoplasia, diaphragmatic defect, cleft palate	AR	Unk	(232)
G (Opitz/BBB)				+				+	+			See Opitz (G/BBB) syndrome			
Glutaric aciduria, type II			+									Cerebral anomalies, pancreatic dysplasia, biliary dysgenesis	AR	ETFA, B, DH	(233)
Grieg cephalopoly-syndactyly				+								Macrocephaly, polydactyly, hypertelorism	AD	GLI3	(234)
Hajdu-Cheney			+									SS, Wormian bones, acro-osteolysis, osteoporosis	AD	Unk	(235)
Hydrolethalus						+		Ua				Hydrocephalus, polydactyly, polyhydramnios,cleft lip	AR	HYLS1	(236)
Jarcho-Levin						+						Spondylothoracic dysplasia,fused ribs, hemivertebrae	AR	DLL3, MESP2	(237)
Johanson-Blizzard						+						Pancreatic insufficiency, spiky hair,small alae nasi	AR	UnkBR1	(238)
Killian-Pallister												See *Table 6-3*	Chromosomal		
Lacrimo-auriculo-dento-digital (LADD)	1											Nasolacrimal duct stenosis, malformed ears/enamel/digits	AD	FGFR2, 3	(239)
Larsen	1					+						Multiple joint dislocations, flat face	AD, AR	FLNB	(240, 241)

Lenz microphthalmia	1		+			+						Ocular coloboma, ear/facial anomalies, syndactyly/camptodactyly	X-linked	Unk	(242)
LEOPARD (multiple lentigines)	1											Hypertelorism, deafness, abnormal ECG, genital anomalies	AD	PTPN11, RAF1	(243)
Marfan			+							+		Tall thin habitus, aortic root dilatation, lens sublu+ation, arachnodactyly	AD	FBN1	(244, 245)
Marshall-Smith						+						MR, FTT, accelerated bone maturation, broad phalanges	Sporadic	Unk	(246)
Miller-Dieker (lissencephaly)	1		+									See *Table 6-3*	Microdeletion	LIS1	
Moebius-peripheral neuropathy				+								Peripheral neuropathy, anosmia, hypogonadism	Sporadic	Unk	(247)
Mohr-Majewski												See Oro-facio-digital syndrome type IV			
Multiple pterygium					+							Multiple soft tissue contractures, camptodactyly	AR	CHRNG	(248)
Myotonic dystrophy			+									Myotonia, muscle weakness, cataract, arrhythmia, diabetes	AD	DMPK	(249, 250)
Nijmegen breakage						+						MR, SS, microcephaly, immunodeficiency	AR	NBS1	(251)
Opitz (G/BBB)												Hypertelorism, hypospadias, cleft lip/palate, dysphagia	AD, X-linked	MID1	(252, 253)
Oro-facio-digital, type I			+			+						Midline cleft lip, multiple frenulae, polydactyly, tongue nodules	X-linked	CXORF5	(254)
Oro-facio-digital, type IV	1		+									Cleft palate, multiple frenulae, polysyndactyly, lobed tongue	AR	Unk	(254, 255)
Oro-facio-digital, type VI	1		+									Midline cleft lip, multiple frenulae, polydactyly, tongue nodules	AR	Unk	(254)
Pallister-Killian												See *Table 6-3*	Chromosomal		

Table 6-2 (Continued)

Syndromes	Renal agenesis	Ectopia/ horseshoe	Cystic/ dysplasia	Duplication	Hypoplasia	Hydro-nephrosis/ ureter	Diverticulae	Atresia/ stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephro-megaly	Other Associated Anomalies	Inheritance Pattern	Gene(s)	Reference.
Peutz-Jeghers			+									Hamartomatous intestinal polyposis, lip hyperpigmentation	AD	STK11	(257)
Poland anomaly	1			+	+							Hypoplastic pectoralis, ipsilateral upper limb reduction	Sporadic	Unk	(258, 259)
Restrictive dermopathy				U								Aplasia cutis, rigid skin, contractures, typical face	AR	LMNA, ZMPSTE24	(260)
Robinow				+		+						Mesomelic dwarfism, typical face, abnormal genitalia	AD, AR	ROR2	(261)
Rothmund-Thomson										+		Poikiloderma, alopecia, dysplastic nails, photosensitivity	AR	RECQL4	(262)
Serpentine fibula			+									Elongated curved fibulae, hirsutism, hypertelorism	Uncertain	Unk	(263)
Spondylocostal dysostosis	1		+									Sacral agenesis, anal atresia, bifid thumb, skin tags	Uncertain	Unk	(264)
Spondyloepimeta-physeal dysplasia						+		U				Joint laxity, kyphoscoliosis, talipes equinovarus, CHD	AR	COL2A1	(265)
Spondylometa-physeal dysplasia										+		SS, platyspondyly, co+a vara, vertebral/long bone anomalies	AD	Unk	(266)
Syndactyly, type V		E			+							Bladder exstrophy, fusion of 4th and 5th metacarpal bones	AD	HOXD13	(267)

U ureter, *B* bladder, *Ua* urethra, *1* unilateral renal agenesis, *2* bilateral renal agenesis, *E* ectopia, *H* horseshoe, *ACC* agenesis of corpus callosum, *SS* short stature, *MR* mental retardation, *DD* developmental delay, *CHD* congenital heart disease, *FTT* failure to thrive, *IUGR* intrauterine growth retardation, *Unk* Gene unknown

Table 6-3

Chromosomal disorders and their consistent associated urinary tract anomalies

Chromosomal disorders	Renal agenesis	Ectopia/ horseshoe	Cystic/ dysplasia	Duplication	Hypoplasia	Hydro-nephrosis/ ureter	Diverti-culae	Atresia/ stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephro-megaly	Other Associated Anomalies	Reported Familial Cases	Ref.
3p deletion		E,H				+						MR, growth delay, ptosis, postaxial polydactyly, micrognathia	No	(270)
3q duplication		H		+	+	+						MR, SS, seizures, hirsutism, typical face, cardiac defects	No	(271)
Williams syndrome (7q deletion)		E			+	+	B,U	U				SS, typical face, supravalvar aortic stenosis, hypercalcemia	Yes	(268)
Trisomy 9 mosaicism			+			+	B					MR, joint contractures, cardiac defects, brain anomalies	No	(269)
10q duplication		H	+									MR, ptosis, short palpebral fissures, camptodactyly	Yes	(270
Aniridia-Wilms tumor (WAGR) (11p13 deletion)											+	Ambiguous genitalia, hypospadias,short stature	AD	(271)
Pallister-Killian syndrome (tetrasomy 12p)			+									SS, MR, hypogonadism, seizures, diaphragmatic defect	No	(271)
Patau syndrome (trisomy 13)	1,2	H	+	+		+						Holoprosencephaly, midline anomalies, cleft lip/palate	No	(269)

Table 6-3 (Continued)

Chromosomal disorders	Renal agenesis	Ectopia/ horseshoe	Cystic/ dysplasia	Duplication	Hypoplasia	Hydro-nephrosis/ ureter	Diverti-culae	Atresia/ stenosis	Reflux	Nephritis/ sclerosis	Tumor/ nephro-megaly	Other Associated Anomalies	Reported Familial Cases	Ref.
Miller-Dieker syndrome (17p13 deletion)	1		+									MR, lissencephaly, microgyria, agyria, typical face, seizures	No	(272)
Edward syndrome (trisomy 18)	+	E,H	+	+		+						IUGR, CHD, clenched hands, rocker bottom feet	Yes	(269)
18q deletion		H										SS, MR, microcephaly, narrow external ear canals,long hands	Yes	(273)
Down syndrome (trisomy 21)	1	H	+	+								MR,hypotonia, CHD, typical face, clinodactyly	Yes	(274)
Cat eye syndrome (tetrasomy 22p)	1	H	+			+		U				MR, CHD, colobomas, anal/digital anomalies	Yes	(275)
Velocardiofacial syndrome (22q11 deletion)	1,2	E,H	+	+	+	+		+	+			Conotruncal CHD, thymic aplasia, typical face, cleft palate	Yes	(276, 277)
Turner syndrome (45,+ or 46,+,i (+q))	1	E,H	+	+	+	+			+			SS,amenorrhea, webbed neck, cubitus valgus, hypogonadism	No	(278)
Triploidy		H	+			+						Large molar placenta, IUGR, syndactyly of 3rd and 4th digit, others	No	(271)

U ureter; *B* bladder; *Ua* urethra, *1* unilateral renal agenesis, *2* bilateral renal agenesis, *E* ectopia, *H* horseshoe, *ACC* agenesis of corpus callosum, *SS* short stature, *MR* mental retardation, *DD* developmental delay, *CHD* congenital heart disease; *FTT* failure to thrive, *IUGR* intrauterine growth retardation

Prevalence of Urinary Tract Anomalies

The true incidence of urinary tract anomalies is difficult to ascertain because many anomalies are asymptomatic and therefore undetected. Many reported statistics have apparent bias of ascertainment because they are derived from symptomatic individuals. Furthermore, inconsistent terminology and clustering of data have decreased the power of much of the epidemiologic data. Long-term analysis of data collected through major national birth defect registries showed increasing prevalence of reported statistics for many congenital birth defects, not only from an actual increment but also from increased tendency to report several isolated and associated anomalies (1–4). For this reason, the practical use of the derived prevalence seems not to be meaningful. However, there currently are quite a number of reliable estimates for prevalence of specific isolated anomalies and of those associated with a specific syndrome. A large number of European birth cohorts during 1996–1998 (EUROSCAN) was prenatally studied and recently reported (4). *Table 6-4* shows a comparison of prevalence figures among various studies.

Approach to the Child with a Urinary Tract Anomaly

The approach to the child with a urinary tract anomaly is similar to that for other birth defects. The initial step is to make a specific diagnosis based on history taking, physical examination, and laboratory investigation. A thorough *family history* for both urinary tract anomalies and for any other type of congenital or developmental anomalies that may have occurred in the family must be obtained. Many genetic disorders have variable expression even within the same family. A careful *physical examination* looking specifically for major and minor anomalies should be performed. Sometimes, a pattern of multiple anomalies can be recognized immediately as a well-described syndrome. Patterns of anomalies that cannot be recognized may require a literature or database search, or referral to an expert in syndrome recognition, such as a clinical geneticist. The search for a specific diagnosis is optimally accomplished by identifying the least common and most distinctive anomalies, for which the list of differential diagnoses is limited. Many excellent textbooks, atlases, and databases are available (5–7). To aid

Table 6-4

Prevalence of urinary tract anomalies detected by various surveys

Anomalies	Rates per 1,000 births			
	EUROSCAN 1996–1998[a]	CBDMP 1983–1994[b]	WSBDR 1987–1989[c]	MACDP 1983–1988[d]
Total renal malformation	*~1.6*	*~2.31*	*~2.33*	~1.5
Unilateral renal agenesis	0.08			
Bilateral renal agenesis/dysplasia	0.13			
Unilateral multicystic dysplasia	0.14			
All renal agenesis /dysplasia	0.36	0.48	0.58	0.47
Horseshoe/ectopic kidney	0.04	0.04	0.16	No data
Cystic kidney	0.04	0.03	0.05	No data
Obstruction of kidney/ureter	0.43	1.27	1.27	0.8
Double ureter	no data	0.004	0.05	No data
Exstrophy of bladder	0.03	0.03	0.02	0.03
Obstruction of bladder/urethra	0.04	0.16	0.2	0.2
VATER, CHARGE, and MURCS associations	No data	0.21	No data	No data
Sirenomelia	No data	0.09	No data	No data

[a]European Renal Anomaly Detection Program (total 709,030 births)
[b]California Birth Defect Monitoring Program
[c]Washington State Birth Defect Registry
[d]Metropolitan Atlanta Congenital Defects Program

Table 6-5

Syndromes associated with unilateral renal agenesis

Acrocallosal syndrome
Acrorenal syndrome, Dieker type
Acro-renal-mandibular syndrome
Acro-renal-ocular syndrome
Adrenogenital syndrome
Aglossia-adactylia syndrome
Alagille syndrome (arterio-hepatic dysplasia)
Branchio-oto-renal syndrome
C-trigonocephaly syndrome
Campomelic dysplasia
Cat-eye syndrome
Chondroectodermal dysplasia
Coffin-Siris syndrome
Cornelia de Lange syndrome
Ectrodactyly-ectodermal dysplasia-clefting (ECC) syndrome
Femoral hypoplasia-unusual facies syndrome
Fetal alcohol syndrome
Goldenhar syndrome
Ivemark syndrome
Kallmann syndrome
Klippel-Feil anomaly
Lacrimo-auriculo-dento-digital syndrome
Larsen syndrome
Lenz microphthalmia syndrome
LEOPARD syndrome (multiple lentigenes)
Limb-body wall complex
Miller-Dieker syndrome
MURCS association
Neu-Laxova syndrome
Oro-facio-digital syndrome, types IV andVI
Pfeiffer syndrome
Poland anomaly
Renal dysplasia
Roberts syndrome
Rokitansky-Mayer-Kuster-Hauser syndrome
Rubella syndrome, congenital
Rubinstein-Taybi syndrome
Russell-Silver syndrome
Short rib polydactyly syndrome, types 1–3
Smith-Lemli-Opitz syndrome
Sorsby coloboma-brachydactyly syndrome
Spondylocostal dysostosis
Townes-Brocks syndrome
Trisomy 22
Turner syndrome
Ulnar-mammary syndrome
VATER (VACTERL) association
Zellweger syndrome

Table 6-6

Syndromes associated with unilateral or bilateral renal agenesis

Acrorenal, Johnson-Munson type
Alkylating agent, maternal use
Caudal duplication syndrome
Caudal regression syndrome
Cocaine, maternal use
CHARGE syndrome
Diabetic mother, infant of
DiGeorge syndrome
Fraser (cryptophthalmos) syndrome
Holzgreve syndrome
Pallister-Hall syndrome
Potter (oligohydramnios) sequence
Sirenomelia sequence
Thalidomide embryopathy
Urogenital abysplasia
Velocardiofacial syndrome
Winter syndrome

in this effort, refer to *Tables 6-1–6-3* in addition to a table listing the differential diagnosis that accompanies the description of each of the major urinary tract anomalies below (*Tables 6-5–6-15*). For example, it is preferable to search for syndromes with urethral agenesis (22 syndromes) rather than renal dysplasia (more than 80 syndromes) when the two anomalies coexist. A search based on the more common anomalies can be performed if the first search does not reveal a match. Even after careful evaluation, a substantial number of children with multiple congenital anomalies remain undiagnosed.

When a suspected syndrome is known to be caused by a gene mutation, confirmatory molecular genetic testing can be performed. DNA-based test is currently available on either a clinical service or research basis. Knowledge regarding a pathogenic mutation specific for each

Table 6-7
Syndromes associated with ectopic kidney

Acromelic frontonasal dysplasia
Acrorenal syndrome, Dieker type
Acrorenal syndrome, Siegler type
Acro-renal-ocular syndrome
Baller-Gerold syndrome
Beckwith-Wiedemann syndrome
Branchio-oto-renal syndrome
Caudal regression syndrome
CHARGE syndrome
Crossed ectopia-pelvic lipomatosis syndrome
DiGeorge syndrome
Drash (Denys-Drash) syndrome
Fanconi anemia syndrome
Fetal alchhol syndrome
Floating-Harbor syndrome
Frontonasal dysplasia
Goldenhar syndrome
Kaufman-McKusick syndrome
Klippel-Feil anomaly
Limb-body wall complex
MURCS association
Pallister-Hall syndrome
Penoscrotal transposition
Renal adysplasia
Rokitansky-Mayer-Kuster-Hauser syndrome
Rubinstein-Taybi syndrome
Schinzel-Giedion syndrome
Sirenomelia sequence
Turner syndrome
VATER (VACTERL) association
Velocardiofacial syndrome
Williams syndrome

Table 6-8
Syndromes associated with horseshoe kidney

Acro-facial dysostosis syndrome
Agnathia-holoprosencephaly syndrome
Antley-Bixler syndrome
Bowen-Conradi syndrome
Caudal regression syndrome
Diabetic mother, infant of
Fanconi anemia syndrome
Fetal alcohol syndrome
Focal dermal hypoplasia
Juberg-Hayward syndrome
Kabuki syndrome
Pallister-Hall syndrome
Pyloric stenosis
Roberts syndrome
Thalidomide embryopathy
Trisomy 13, 18, 21, and 22
Turner syndrome
VATER (VACTERL) association
Weyers syndrome
Wilms tumor

proband may potentially be useful for genetic counseling and future reproductive option in order to avoid intrafamilial recurrence. *Tables 6-1* and *6-2* list currently known causative gene(s) for each of the disorder.

A chromosome analysis is indicated in any child who has at least two major congenital anomalies or one isolated anomaly that is a pertinent feature of a chromosome abnormality, such as aniridia (microdeletion 11p). Growth or developmental delay and dysmorphic features or lack of familial resemblance should also prompt a chromosome analysis. Chromosome abnormalities are found in approximately 10–12% of all renal anomalies (3, 8). *Table 6-3* lists common and distinct chromosomal disorders with their reported urinary tract anomalies.

For a child with no known urinary tract anomaly, findings that should prompt an evaluation of the urinary tract are oligohydramnios, undefined abdominal mass, abnormal genitalia, aniridia, hypertension, preauricular pits or tags, branchial cleft cyst or sinus, imperforate anus, or symptoms indicative of renal dysfunction, urinary tract infection, or obstructive uropathy (3). For patients with known syndromes, the type of potentially associated urinary tract anomalies are listed in *Tables 6-1* and *6-2*.

The best initial evaluation to screen for urinary tract anomalies in general is an ultrasound examination because this study is noninvasive and gives good anatomic information about the urinary tract. It is also the only method routinely used for the prenatal diagnosis of urinary tract anomalies. Specific investigations such as intravenous pyelogram, voiding cystourethrogram, radionuclide renal and urinary system scan, and specialized genetic testing may then be used, depending on the working diagnosis. The type

Table 6-9
Syndromes associated with renal dysplasia/cystic kidney

Acro-renal-mandibular syndrome
Alagille syndrome (arterio-hepatic dysplasia)
Baller-Gerold syndrome
Bardet-Biedl syndrome
Beckwith-Wiedemann syndrome
Branchio-oto-renal syndrome
Campomelic dysplasia
Carbohydrate deficient glycoprotein syndrome
CHARGE syndrome
Chondrodysplasia punctata, non-rhizomelic
Cloacal exstrophy
Cornelia de Lange syndrome
Diabetic mother, infant of
Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome
Fanconi anemia syndrome
Fetal alcohol syndrome
Fraser (cryptophthalmos) syndrome
Fryns syndrome
Glutaric aciduria, type II
Goldenhar syndrome
Hajdu-Cheney syndrome
Ivemark syndrome
Jeune syndrome
Joubert syndrome
Kaufman-McKusick syndrome
Lenz microphthalmia syndrome
Leprechaunism (Donohue) syndrome
Limb-body wall complex
Marden-Walker syndrome
Marfan syndrome
Marshall-Smith syndrome
Meckel-Gruber syndrome
MURCS association
Noonan syndrome
Omphalocele-Exstrophy of bladder-Imperforate anus-Spinal dysraphism (OEIS) complex
Oral-facial-digital syndrome, types I and VI
Pallister-Hall syndrome
Pallister-Killian syndrome
Potter (oligohydramnios) sequence
Prune belly syndrome
Renal adysplasia
Roberts syndrome
Rokitansky-Mayer-Kuster-Hauser syndrome
Rubella syndrome, congenital
Short rib-polydactyly syndrome
Smith-Lemli-Opitz syndrome
Thalidomide embryopathy
Trisomy 8, 9, 13, 18, 21, and 22
Tuberous sclerosis
VATER (VACTERL) association
Von Hippel-Lindau diesease
Zellweger and pseudo-Zellweger syndromes

of anomaly generally guides treatment. Corrective or reparative treatments are available for many anomalies (stenosis or atresia, bladder exstrophy, duplication. diverticula, and tumors). Symptomatic treatment for complications is often necessary.

Families who have a child with a urinary tract anomaly should be informed of the diagnosis when possible. A search for a related anomaly in first-degree relatives is automatically indicated only when the proband has renal agenesis by ultrasound examination (9). Otherwise, the decision to investigate family members should be based on a thorough family history and/or physical examination, and whether the child's disorder is a well described inherited syndrome. Genetic counseling should be provided to the family and should include a discussion of the manifestations of the disorder, the natural history, complications, available treatments, cause, and recurrence risk when these are known. Reproductive options should be discussed in a nondirective fashion. For an isolated anomaly without a family history of similar or related anomalies, an empiric risk can be provided. Accurate risk figures can be determined for Mendelian disorders, and estimated risks are available for associations.

All children with congenital anomalies need long-term, periodic follow-up to detect new abnormalities or complications of their birth defects. This is especially the case for children with undiagnosed multiple congenital anomalies, for whom follow-up examination may lead to a specific diagnosis. Additional relevant family information should be specifically sought for any newly affected member. Finally, for patients with a urinary tract anomaly who reach reproductive age, the recurrence risk for their offspring and reproductive options should be discussed.

The remainder of this chapter contains descriptions of the major types of urinary tract anomalies, including the etiology, pathogenesis, and associated disorders. First, a review of the embryology of the normal urinary tract

Table 6-10

Syndromes associated with hydronephrosis or hydroureter

Acro-cephalo-polysyndactylous dysplasia
Acrorenal syndrome, Dieker snd Johnson-Munson types
Barbet-Biedl syndrome
Branchio-oto-renal syndrome
Campomelic dysplasia
Caudal duplication and regression syndromes
CHARGE syndrome
Cloacal exstrophy
Coffin-Siris syndrome
Crossed ectopia-pelvic lipomatosis syndrome
Cornelia de Lange syndrome
Diabetic mother, infant of
Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome
Fanconi anemia syndrome
Fetal alcohol syndrome
Goldenhar syndrome
Hydrolethalus syndrome
Kabuki syndrome
Kaufman-McKusick syndrome
Megacystis-microcolon syndrome
Noonan syndrome
Ochoa syndrome
Omphalocoele-Exstrophy of bladder-Imperforate anus-Spinal dysraphism (OEIS) complex
Pallister-Hall syndrome
Polydactyly-obstructive uropathy syndrome
Pyloric stenosis
Roberts syndrome
Sirenomelia sequence
Schinzel-Giedion syndrome
VATER (VACTERL) association

Table 6-11

Syndromes associated with duplication of ureters or collecting systems

Achondrogenesis
Acromelic frontonasal dysplasia
Adrenogenital syndrome
Antley-Bixler syndrome
Bardet-Biedl syndrome
Bowen-Conradi syndrome
Branchio-oto-ureteral syndrome
Braun-Bayer syndrome
Caudal duplication syndrome
Diabetic mother, infant of
Drash (Denys-Drash) syndrome
Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome
Fanconi anemia syndrome
Fetal alcohol syndrome
Frontometaphyseal dysplasia
G (Opitz-Frias) syndrome
Goldenhar syndrome
Kabuki syndrome
Kaufman-McKusick syndrome
Mammo-renal syndrome
Noonan syndrome
Ochoa syndrome
Perlman syndrome
Poland anomaly
Prune belly syndrome
Robinow syndrome
Rubinstein-Taybi syndrome
Trisomy 8, 9, 13, 18, and 21
Turner syndrome
Weyers syndrome

will be useful in understanding structural urinary tract abnormalities.

Overview of Normal Embryogenesis of the Urinary System

Renal organogenesis is reviewed in chapter 1. Embryogenesis of the lower urinary tract includes development of the mesonephric duct and urogenital sinus. The mesonephric duct from which the ureteric bud arose inserts into the lower allantois, just above the terminal part of the hindgut, the cloaca. During the fourth to seventh weeks, mesoderm proliferates and forms the transverse mesodermal ridge, the urorectal septum that divides the cloaca into the anterior portion, the primitive urogenital sinus, and the posterior portion, the cloacal sinus or anorectal canal. The mesonephric ducts open into the urogenital sinus and later become the ureters. The urorectal septum develops caudally and fuses with the cloacal membrane, dividing it into the urogenital membrane (anterior) and the anorectal membrane (posterior) by the end of the

Table 6-12

Syndromes associated with bladder exstrophy

Axial mesodermal dysplasia
Caudal duplication syndrome
Caudal regression syndrome
Cloacal exstrophy
Frontonasal dysplasia
Omphalocoele-Exstrophy of bladder-Imperforate anus-Spinal dysraphism (OEIS) complex
Trisomy 18
Sirenomelia sequence
Syndactyly, type V

Table 6-13

Syndromes associated with urethral agenesis

Aase syndrome
Acrorenal syndrome, Dieker and Johnson-Munson types
Adrenogenital syndrome
Caudal regression syndrome
Cocaine, maternal use
Diabetic mother, infant of
Hydrolethalus syndrome
Kaufman-McKusick syndrome
Limb-body wall complex
Meckel-Gruber syndrome
Occipital horn syndrome
Ochoa syndrome
Omphalocoele-Exstrophy of bladder-Imperforate anus-Spinal dysraphism (OEIS) complex
Potter (oligohydramnios) Sequence
Prune belly syndrome
Renal adysplasia
Russell-Silver syndrome
Short rib-polydactyly syndrome, types 1–3
Sirenomelia sequence
Sotos syndrome
Townes-Brocks syndrome
Trisomy 21

Table 6-14

Syndromes associated with urethral duplication

Amniotic band disruption sequence
Limb-body wall complex
Omphalocoele-Exstrophy of bladder-Imperforate anus-Spinal dysraphism (OEIS) complex
Prune belly syndrome

Table 6-15

Syndromes associated with posterior urethral valves

Acrorenal syndrome, Johnson-Munson type
Caudal regression syndrome
Diabetic mother, infant of
Kaufman-McKusick syndrome
Limb-body wall complex
Neurofibromatosis, type I
Ochoa syndrome
Omphalocoele-Exstrophy of bladder-Imperforate anus-Spinal dysraphism (OEIS) complex
Polydactyly-obstructive uropathy syndrome
Potter (oligohydramnios) sequence
Prune belly syndrome
Renal adysplasia
Rubinstein-Taybi syndrome
Sirenomelia sequence
Townes-Brocks syndrome
VATER (VACTERL) association

seventh week. The primitive perineal body forms at the site of fusion.

The primitive urogenital sinus develops primarily into the urinary bladder. The superior portion, originally continuous with the allantois, later becomes a solid fibrous cord, the urachus or median umbilical ligament, which connects the bladder to the umbilicus. The inferior portion of the urogenital sinus in the male divides into a pelvic portion, containing the prostatic and membranous urethra, and the long phallic portion, containing the penile urethra. The inferior portion in the female forms a small portion of the urethra and the vestibule. At the same time, the distal portion of the mesonephric ducts is incorporated into the endodermal vesicoureteral primordium, forming the trigone of the bladder. A part of the distal end of both mesonephric ducts just proximal to the trigone develops into the seminal vesicles and ductus deferens in the male. Finally, at the end of the twelfth week, the epithelium of the superior portion of the prostatic urethra proliferates to form buds that penetrate the surrounding mesenchyme. In the male, these buds form

the prostate gland; in the female, they form the urethral and paraurethral glands.

Anomalies Involving the Urinary Tract

Kidney Defects

Renal Agenesis

By definition, renal agenesis refers to complete absence of one of both kidneys without identifiable rudimentary tissue. Renal agenesis is usually associated with agenesis of the ipsilateral ureter. The pathogenesis of renal agenesis is failure of formation of the metanephros. Causal heterogeneity has been shown, by both animal studies and human observations (10–12), including failure of ureteric bud formation, failure of the bud to reach the metanephric blastema, or failure of the bud and the metanephric blastema to create mutual inductive influence on one another. In addition, interruption in vascular supply and regression of a multicystic kidney can lead to renal agenesis in the fetal period (11).

Unilateral renal agenesis is usually asymptomatic and found incidentally, whereas bilateral renal agenesis results in severe oligohydramnios and fetal or perinatal loss. Renal agenesis can occur in either side without predilection. Birth prevalence in the United States for renal agenesis/hypoplasia ranges between 0.30 and 9.61 per 10,000 live births (3). Several studies have demonstrated that unilateral renal agenesis is associated with an increased frequency of anomalies in the remaining kidney (9, 13). Moreover, renal agenesis is often detected in conjunction with anomalies of other organ systems. These anomalies can occur both in contiguous structures (e, g., vertebrae, genital organs, intestines, and anus) and also in noncontiguous structures (e.g., limbs, heart, trachea, ear, and central nervous system). The diagnosis of renal agenesis is made by abdominal ultrasound. Care must be taken to exclude the possibility of ectopic kidney. Intravenous pyelography, computerized tomography scan, and radionuclide studies can be helpful in equivocal cases.

The recurrence risk for renal agenesis can be provided if the pattern of inheritance is known or if the proband has a recognizable syndrome. For nonsyndromic renal agenesis, an empiric risk of 3% can be used for families in which renal anomalies in first-degree relatives (siblings, parents) have been excluded (3). First-degree relatives of patients with nonsyndromic renal agenesis have an increased prevalence of related urogenital anomalies. In one study, 9% of first- degree relatives of infants with agenesis or dysgenesis of both kidneys had a related urogenital anomaly, and 4.4% had an asymptomatic renal malformation (13). In another recent retrospective review, empiric risks were 7% in offspring, 2.5% in siblings and 4.5% in parents (14). Moreover, offspring of an individual with unilateral agenesis is at a slightly increased risk for bilateral renal agenesis. Therefore renal ultrasound is recommended for the first-degree relatives of the proband unless renal agenesis in the proband is clearly sporadic or a specific cause without an increased recurrence risk is identified.

Tables 6-5 and *6-6* list the syndromes commonly associated with unilateral and bilateral renal agenesis, respectively. See also *Tables 6-1–6-3* for more information about these disorders and other less known conditions with renal agenesis.

Ectopic Kidney

The ectopic kidney derives from an error of ascent. Most are pelvic kidneys that fail to ascend out of the pelvic cavity. Rare case reports of thoracic kidney exist (15). Ectopic kidney can be unilateral or bilateral. In bilateral pelvic kidneys, the kidneys often fuse into a midline mass of renal tissue, with two pelves and a variable number of ureters, which is referred to as a pancake or discoid kidney. Fused pelvic kidney may in fact be due to fusion of ureteric buds or metanephric blastema. *Crossed renal ectopia* refers to an ectopic kidney whose ureter crosses the midline. It often fuses with the normal kidney. The embryogenesis of crossed renal ectopia is not well understood, but presumably involves abnormal migration of the ectopic kidney to the contralateral side. An ectopic kidney is usually hypoplastic, is rotated, and has numerous small blood vessels and associated ureteric anomalies. Ectopic kidneys may be asymptomatic and incidentally found, but complications from ureteral obstruction, infection, and calculi can occur. In a recent study, ectopic kidney without hypoplasia or hydronephrosis seems not to be associated with an appreciable increase frequency of associated anomaly and complication thus making further urologic investigation such as vesicourethrography unnecessary (16). *Table 6-7* provides a list of syndromes that include ectopic kidney. These are described in *Tables 6-1–6-3*.

Horseshoe Kidney

Horseshoe kidney refers to a condition in which both kidneys are fused at the lower poles with a renal parenchymal or, less commonly, fibrous isthmus.

The embryogenesis of horseshoe kidney with parenchymal isthmus is thought to be migration of nephrogenic cells across the primitive streak before the fifth gestational week. Horseshoe kidney with fibrous isthmus is believed to originate from mechanical fusion of the two developing kidneys at or after the fifth week before renal ascent (17). The concept of a narrow vascular fork leading to approximation and fusion of the two kidneys is no longer considered valid. Most horseshoe kidneys are located in the pelvis or at the lower lumbar vertebral level because ascent is further prevented when the fused kidney reaches the junction of the aorta and inferior mesenteric artery.

Complications of horseshoe kidneys include obstructive uropathy primarily related to ureteropelvic junction obstruction, calculi and urinary tract infection. Similar to other urinary tract anomalies, a horseshoe kidney is often associated with other genitourinary anomalies. In addition, there is an increased risk of various types of renal tumors developing in the horseshoe kidney compared with the normal kidney (18). Renal cell carcinoma is the most common, but Wilms' tumor, adenocarcinoma, transitional cell carcinoma, malignant teratoma, oncocytoma, angiomyolipoma, and carcinoid have all been reported. Horseshoe kidneys also carry an increased risk for renal pelvis carcinoma and higher proportion of squamous cell carcinoma than those in normal kidneys (19).

Table 6-8 lists syndromes associated with horseshoe kidney. See *Tables 6-1* and *6-2* for more details of these disorders.

Dysplasia and Polycystic Kidney

Renal dysplasia is the most common congenital urinary tract anomaly and the most common cause of an abdominal mass in children (3). Unilateral dysplasia is reported to occur in 1:1,000, whereas the prevalence of bilateral disease is estimated to be 1:5,000 (20). It may be unilateral or bilateral, and diffuse, segmental, or focal. Symptoms are variable from silent in unilateral or focal dysplasia to progressive renal dysfunction in diffuse or bilateral dysplasia. Dysplasia refers to abnormal differentiation or organization of cells in the tissue. Renal dysplasia is characterized histologically by the presence of primitive ducts and nests of metaplastic cartilage (20, 21). Although cysts are not always present in a dysplastic kidney, the dysplastic process often results in the formation of cysts that are variable in size and number. Several hypotheses are proposed for the embryogenesis of the dysplastic kidney. The most likely pathogenesis is an error of the mutual induction between the ureteric bud and the metanephric blastema. The molecular pathogenesis of cystic kidney, especially polycystic kidney, has been one of the most extensively studied aspects of nephrology and recent studies discovered few genes and pathways critical for renal cyst formation such as TCF2/hepatocyte nuclear factor 1ss (HNF1beta), PAX2 and uroplakins. Dysplastic kidneys are usually identified as enlarged bright kidneys on prenatal ultrasonography. If there is associated functional renal impairment, alteration in amniotic fluid volume could potentially be detected and signifies a poor prognosis. (22) Unilateral dysplasia carries an overall better postnatal prognosis than that of bilateral disease. However, up to 30–50% of those with unilateral dysplasia have associated contralateral urinary anomalies (22). Multicystic renal dysplasia is the most common among many causes of renal dysplasia and it is usually unilateral. Polycystic kidney diseases, both autosomal dominant (ADPKD) and autosomal recessive (ARPKD) forms, are in general far more common than other syndromic causes of renal dysplasia. *Table 6-9* summarizes well-known syndromes with renal dysplasia/cystic kidney. See also *Tables 6-1–6-3*.

Obstruction and Hydronephrosis

Urinary obstruction is a complication of a primary anomaly, which can be stenosis or atresia of the ureteropelvic junction, ureter, or urethra; a poorly functional bladder causing reflux; a malformed dilated ureteral end (ureterocele); or extrinsic compression by other structures, such as anomalous blood vessels or tumors. Hydronephrosis and pyelectasis (dilated renal pelvis) are the most common urinary tract abnormalities on prenatal ultrasound examination. Early diagnosis of collecting system dilatation can be achieved by ultrasound examination in the second trimester (23). Persistent dilatation almost always indicates an underlying anomaly. Isolated obstructive uropathies diagnosed prenatally may not require antenatal or immediate postnatal surgical intervention. Postnatally diagnosed obstructive uropathies are almost always symptomatic and require thorough investigation to delineate the anatomy of the urinary tract and to exclude associated anomalies.

Table 6-10 provides a list of syndromes commonly associated with obstruction and hydronephrosis. See also *Tables 6-1–6-3*.

Ureter Defects

Duplication

Double ureters or collecting systems are caused by duplication of the ureteric bud. Early duplication results in

duplicated kidney, which is usually smaller and fused with the ipsilateral kidney and has ureters that enter into the bladder separately. Duplication that occurs later results in double ureters that may have separate openings into the bladder or may join each other before the opening. On rare occasion, one of the ureters may have an ectopic opening into the vagina, vestibule, or urethra. In most double ureters, the two ureters cross each other, and that from the higher pelvis enters the bladder more caudally. Duplication anomalies are common but usually asymptomatic; therefore they often remain undetected. One autopsy study reported the prevalence of duplication anomalies to be as high as 1 in 25, with females about four times more likely to be affected than males (24). Unilateral duplication is five to six times more common than bilateral duplication (3). Double ureters are commonly associated with vesico-ureteral reflux due to their ectopic opening into the urinary bladder and/or the ureterocele (23). In addition, ureteric obstruction can occur at the level of vesico-ureteric junction or that of uretero-pelvic junction.

Table 6-11 summarizes syndromes associated with duplication, and *Tables 6-1–6-3* provide clinical information about these disorders.

Hydroureter

Hydroureter, or magaloureter, is caused by distal obstruction and is usually found with hydronephrosis, except in ureteropelvic junction obstruction. Hydroureter has the same etiology as hydronephrosis (see Obstruction and Hydronephrosis).

Bladder Defects

Anomalies of the bladder are rare. These include agenesis, hypoplasia, diverticulae, and dilatation or megacystis caused by distal obstruction or by non-obstructive causes. Agenesis of the bladder is usually associated with severe developmental anomalies of the urinary tract, such as in sirenomelia and caudal regression syndrome. Hypoplastic bladder can be found in conditions associated with bilateral renal agenesis because no urine is produced. Bladder diverticulae have heterogeneous causes. They result from an intrinsic defect in the bladder wall, such as in cutis laxa, or Ehlers-Danlos, Ochoa, occipital horn, and Williams syndromes. They can also be caused by increased intravesicular pressure from distal obstruction or by persistent urachus. See *Tables 6-1–6-3* for information about specific syndromes associated with bladder diverticulae.

Bladder Exstrophy

Bladder exstrophy refers to a urinary bladder that is open anteriorly because of the lack of an abdominal wall closure. It is usually associated with anomalies of the contiguous structures including epispadias and separation of the pubic rami. This anomaly is thought to result from an overdeveloped cloacal membrane that interferes with inferolateral abdominal mesenchymal closure. Therefore, when the cloacal membrane ruptures, the inferior abdominal wall has not completely closed and the bladder cavity is exposed. It has been suggested that bladder exstrophy belongs to the spectrum of omphalocele-cloacal exstrophy-imperforate anus-spinal dysraphism (OEIS) complex (25–27). The extent of anomalies is determined by the timing of the cloacal membrane rupture. Rupture that occurs after the separation of cloaca by the urorectal septum results in bladder exstrophy, whereas one that occurs before the separation results in the more severe cloacal exstrophy and OEIS complex. Bladder exstrophy is six times more common in males.

Table 6-12 lists syndromes associated with bladder exstrophy, and *Tables 6-1–6-3* provide information about these disorders.

Urethral Defects

Agenesis and Atresia

Urethral agenesis is rare, and its predominant occurrence in males probably reflects the greater complexity of embryogenesis of the male urethra. Urethral agenesis is often associated with bladder obstruction sequence. *Table 6-13* lists syndromes associated with urethral agenesis, and clinical information about these disorders is summarized in *Tables 6-1–6-3*.

Duplication

Duplication refers to complete or partial duplication of the urethra, which is a rare anomaly found only in a few syndromes. Those syndromes associated with urethral duplication are listed in *Table 6-14* and their findings are provided in *Tables 6-1–6-3*.

Posterior Urethral Valves

Posterior urethral valves refer to abnormal mucosal folds that function as a valve to obstruct urine flow. This is the

most common childhood cause of obstructive uropathy leading to renal failure. Posterior urethral valves can be suspected prenatally when a dilated bladder is seen in association with obstructive uropathy. A "keyhole" sign has been demonstrated in prenatal ultrasound of fetuses with subsequently confirmed posterior urethral valves (28). A voiding cystourethrogram or endoscopy is usually required for a definitive diagnosis. The embryogenesis of posterior urethral valves is unknown. Proposed hypotheses include an overdeveloped posterior urethral fold, a remnant of the mesonephric duct, and an anomalous opening of the ejaculatory duct. *Table 6-15* lists syndromes in which posterior urethral valves can be seen, and the other findings in these disorders are provided in *Tables 6-1*–*6-3*.

Associations and Sequences Involving the Urinary Tract

A number of associations and sequences involve anomalies of the urinary tract that may be important to both diagnosis and management. For this reason, such conditions are described in more detail in this section, in addition to the information presented in *Tables 6-1* and *6-2*.

VATER Association

VATER association is an acronym used to designate a non-random occurrence of Vertebral defects, imperforate Anus, Tracheo-Esophageal fistula, Radial and Renal anomalies (29, 30). An acronym VACTERL has been proposed to broaden the spectrum of VATER to include Cardiac defects and Limb anomalies. The term VATER is not a diagnosis per se, but the designation provides clues for potentially associated anomalies and for recurrence risk counseling when no specific syndromic diagnosis can be made. Patients with VATER association need a careful physical examination and investigation for potential multiorgan anomalies. A specific diagnosis should be sought. Causes of VATER association include: chromosomal disorders, such as trisomy 18; genetic syndromes, such as Goldenhar and Holt-Oram syndromes; and teratogenic exposures, such as infants of diabetic mothers and fetal alcohol syndrome. A family with a mitochondrial DNA mutation was identified in which the daughter was born with VACTERL association, and her mother and sister had classic mitochondrial cytopathy (31). Thus all patients suspected to have VATER association should have a chromosome analysis, a careful family and prenatal exposure history, and a thorough examination for dysmorphic features. The spectrum of anomalies seen in VATER is broad. Associated renal anomalies are usually agenesis, ectopy, or obstruction (29, 30).

Because there is apparent causal heterogeneity for VATER association, the inheritance pattern and recurrence risk vary with the cause. VATER association is usually sporadic with an empirical recurrence risk of 1 to 3% when a specific cause cannot be identified (32). Autosomal recessive and X-linked inheritance have been reported for subsets of patients, such as for VATER with hydrocephalus, and recurrence risk in these families can be as high as 25% (32).

CHARGE Syndrome (CHARGE Association)

CHARGE syndrome – previously designated as an association but now recognized to have a major causative gene- is an acronym used to designate an association of Coloboma of iris, choroid or retina, Heart defects, Atresia choanae, Retarded growth and development, Genital anomalies or hypogonadism, and Ear anomalies or deafness (33–36). In addition, unilateral facial palsy is a common finding. Renal anomalies occasionally found in CHARGE syndrome include ectopy, dysplasia, renal agenesis, and ureteric anomalies. The presence of two or more anomalies associated with CHARGE syndrome should prompt a search for the others. To prevent overuse of the term, it was suggested that at least three anomalies are required for the term CHARGE to be applied, and one of the anomalies should be either coloboma or choanal atresia (34). To date, consistent features in CHARGE syndrome have been ocular coloboma, choanal atresia and semicircular canal hypoplasia (37). Conditions with anomalies in the spectrum of CHARGE include trisomy 13, trisomy 18, and Wolf-Hirschhorn (deletion 4p), cat-eye, Treacher-Collins, velocardiofacial, Apert, Crouzon, and Saethre-Chotzen syndromes. Therefore, a careful physical examination for malformations and dysmorphic features should be conducted. Recently, *CHD7* mutation has been found by an array CGH study to be the cause of this syndrome in about 60 percent of typical patients thus making a molecular confirmation possible. In those without *CHD7* mutation, chromosome analysis including specific fluorescence in situ hybridization (FISH) probes for velocardiofacial syndrome (deletion 22q) and 4p deletion should be performed. Because most cases of CHARGE association are sporadic, the empirical recurrence risk in sibling is low (33, 36).

MURCS Association

MURCS association refers to a rare occurrence of Mullerian duct aplasia, Renal aplasia and Cervicothoracic Somite dysplasia (38). Anomalies include absence of the proximal two thirds of the vagina; uterine hypoplasia or aplasia; unilateral renal agenesis; ectopic kidney; renal dysplasia; C5-T1 vertebral anomalies (hypoplasia of vertebrae, fusion, hemivertebrae, and butterfly vertebrae); and short stature. Additional anomalies are common, including rib defects, facial asymmetry, limb anomalies, hearing loss, and brain anomalies, such as encephalocoele and cerebellar cyst (39).

The pathogenesis of MURCS association is unknown, but is thought to be related to defects in the paraxial mesoderm, which gives rise to the cervicothoracic somites and the adjoining intermediate mesoderm. Most patients are diagnosed because of primary amenorrhea or infertility associated with normal secondary sexual characteristics, followed by recognition of reproductive organ atresia. MURCS association is usually sporadic. A report of vertebral and renal anomalies associated with azoospermia was proposed to represent the male version of MURCS association (40).

Oligohydramnios Sequence

Oligohydramnios of whatever cause leads to a recurrent pattern of abnormalities that has been called the oligohydramnios sequence (3, 6). Oligohydramnios may be caused by decreased production of fatal urine from bilateral renal agenesis or dysplasia or by urinary obstruction, or it can result from amniotic fluid leakage. When the oligohydramnios is prolonged and severe, the condition is lethal because of pulmonary hypoplasia. Moderate oligohydramnios from amniotic fluid leakage may result in a liveborn child with multiple congenital anomalies. These anomalies are both malformations and deformations. Intrauterine constraint leads to mechanical compression that leads to the characteristic flat facial profile (Potter's facies), limb deformities (e.g., talipes equinovarus), and intrauterine growth retardation (IUGR). Decreased fetal movement as a result of intrauterine constraint causes multiple joint contractures (arthrogryposis). Breech presentation is common. Pulmonary hypoplasia can be the consequence of compression of the chest cavity coupled with decreased inspiration of amniotic fluid. Liveborns have respiratory distress caused by pulmonary hypoplasia, and the lungs may have insufficient volume to support life.

Because the initial defect has many causes, recurrence risk is based on the underlying defect. When oligohydramnios is due to nonsyndromic bilateral renal agenesis or dysgenesis, related renal malformations occur at an increased frequency in first-degree relatives (13), and recurrence risk can be as high as 4–9%. The recurrence risk can be as high as 25% for an autosomal recessive disorder causing bilateral renal agenesis or dysplasia.

Urethral Obstruction Sequence

The initial defect in this sequence is obstruction of the urethra leading to dilation of the proximal urinary tract, bladder distension, and hydroureter (3, 6, 41). Obstruction of urine flow interferes with normal nephrogenesis, resulting in renal dysplasia. Other potential anomalies related to bladder distension include cryptorchidism, malrotation of colon, persistent urachus, and limb deficiency caused by iliac vessel compression. In addition, oligohydramnios results from lack of urine and leads to the oligohydramnios sequence.

Prune-belly syndrome (41, 42) is a rare entity referring to a constellation of anomalies that includes megacystis, abdominal wall muscle deficiency, hydroureter, renal dysplasia, and characteristic wrinkled abdominal skin. This condition, previously thought to be a form of urethral obstruction sequence, is in fact a non-obstructive cause of bladder distension that results from a malformation, thus now being properly designated a syndrome (28).

The most common cause of urethral obstruction is posterior urethral valves, but urethral agenesis/atresia or bladder neck obstruction can also be the cause. This anomaly occurs mostly in males, with a male: female ratio of 20:1. Survival is rare in fetuses with complete obstruction, and severe urinary tract dysfunctions are always present in those that are liveborn. Prenatal diagnosis by ultrasound examination can detect the abnormally dilated bladder at the beginning of the second trimester (43), and intrauterine urinary decompression procedures, such as vesicoamniotic shunts, are options for treatment in order to decrease the occurrence of pulmonary hypoplasia, although their benefits have not been unequivocally shown (44, 45).

Sirenomelia Sequence

Sirenomelia is a malformation characterized by the presence of a single lower extremity with posterior alignment of the knees and feet, sacral agenesis and other lower vertebral defects, imperforate anus and rectal agenesis,

and absence of external and internal genitalia (46). The current view of the embryogenesis is that sirenomelia results from a vascular steal phenomenon (47). This is supported by the presence of abnormal vasculature in the caudal part of affected embryos. A single large vessel originating from the aorta, a derivative of the vitelline artery complex, connects the iliac arteries to the placenta rather than the two normal umbilical arteries. The area caudal to the origin of this vessel has minimal blood supply because of the lack of aortic branches. Therefore, a "vascular steal phenomenon" is generated, leading to a vascular disruption sequence. Alternatively, since sirenomelia shares a number of anomalies with caudal regression syndrome, it is thought to potentially be causally similar and represent different patterns in the same spectrum.

Sirenomelia is a rare condition and has a broad spectrum of anomalies. Virtually any urinary tract anomaly can occur in sirenomelia sequence. Renal agenesis occurs in two-thirds of cases and a variable degree of renal dysplasia is present in one-third of cases (3). Absence of the ureter and bladder are common. All cases of sirenomelia are sporadic and almost uniformly fatal because of pulmonary hypoplasia. Sirenomelia has been noted with an increased frequency among monozygotic twins in which only one of the twins in usually affected.

References

1. Schulman J, Edmonds LD, McClearn AB et al. Surveillance for and comparison of birth defect prevalences in two geographic areas-United States, 1983–88. *MMWR* 1993;42:1–7.
2. National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention. Birth defects surveillance data from selected states, 1999–2003. *Birth Defects Res A Clin Mol Teratol* 2006;76(12):894–960.
3. Van Allen MI. Urinary tract. In Human Malformations and Related Anomalies. Stevenson RE, Hall JG, Goodman RM (eds.). New York, Oxford University Press, 1993, 11:pp. 501–550.
4. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C, EUROSCAN Study Group. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. *Eur J Med Genet* 2005;48 (2):131–144.
5. Gorlin RJ, Cohen MM, Hennekam RCM. Syndromes of the Head and Neck, 4th edn. New York, Oxford University Press, 2001.
6. Jones KL. Smith's Recognizable Patterns of Human Malformation, 6th edn. Philadelphia, WB Saunders, 2005.
7. Winter RM, Baraitser M. London Dysmorphology Database. London, Oxford University Press, 1995.
8. Nicolaides KH, Cheng HH, Abbas A et al. Fetal renal defects: Associated malformations and chromosomal defects. *Fetal Diagn Ther* 1992;7:1–11.
9. Robson WLM, Leung AKC, Rogers RC. Unilateral renal agenesis. *Adv Pediatr* 1995;42:575–592.
10. Ekblom P. Genetics of kidney development. *Curr Opin Nephrol Hypertens* 1996;5:282–287.
11. Mesrobian HG, Rushton HG, Bulas D. Unilateral renal agenesis may result from in utero regression of multicystic renal dysplasia. *J Urol* 1993;150(2 Pt 2):793–794.
12. Atiyeh B, Husmann D, Baum M. Contralateral renal abnormalities in patients with renal agenesis and noncystic renal dysplasia. *Pediatrics* 1993;91:812–815.
13. Roodhooft AM, Birriholz JC, Holmes LB. Familial nature of congenital absence and severe dysgenesis of both kidneys. *N Engl J Med* 1984;310:1341–1345.
14. McPherson E. Renal anomalies in families of individuals with congenital solitary kidney. *Genet Med* 2007;9(5):298–302.
15. N'Guessen G, Stephens FD, Pick J. Congenital superior ectopic (thoracic) kidney. *Urology* 1984;24:219–228.
16. Calisti A, Perrotta ML, Oriolo L, Ingianna D, Miele V. The risk of associated urological abnormalities in children with pre and postnatal occasional diagnosis of solitary, small or ectopic kidney: Is a complete urological screening always necessary? *World J Urol* 2008.
17. Domenech-Mateu JM, Gonzalez-Compta X. Horseshoe kidney: A new theory on its embryogenesis based on the study of a 16-mm human embryo. *Anat Rec* 1988;244:408–417.
18. Stimac G, Dimanovski J, Ruzic B, Spajic B, Kraus O. Tumors in kidney fusion anomalies – report of five cases and review of the literature. *Scand J Urol Nephrol* 2004;38(6):485–489.
19. Mizusawa H, Komiyama I, Ueno Y, Maejima T, Kato H. Squamous cell carcinoma in the renal pelvis of a horseshoe kidney. *Int J Urol* 2004;11(9):782–784.
20. Winyard P, Chitty LS. Dysplastic Kidneys. *Semin Fetal Neonatal Med* 2008;13(3):142–151.
21. Fisher C, Smith JF. Renal dysplasia in nephrectomy specimens from adolescents and adults. *J Clin Pathol* 1975;28:879–890.
22. Winyard P, Chitty LS. Dysplastic and polycystic kidneys: Diagnosis, associations and management. *Prenat Diagn* 2001;21:924–935.
23. Whitten SM, Wilcox DT. Duplex systems. *Prenat Diagn* 2001;21:952–957.
24. Campbell MF, Harrison JH (eds.). Anomalies of the ureter. In Urology, vol 2, 3rd edn. Philadelphia, PA, WB Saunders, 1970, pp. 1488–1800.
25. Pang D. Sacral agenesis and caudal spinal cord malformations. *Neurosurgery* 1993;32:755–778.
26. Carey JC, Greenbaum B, Hall BD. The OEIS complex (omphalocoele, imperforate anus, exstrophy and spinal defects). *Birth Defects Orig Artic Ser* 1978;14(6B):253–263.
27. Keppler-Noreuil K, Gorton S, Foo F, Yankowitz J, Keegan C. Prenatal ascertainment of OEIS complex/cloacal exstrophy – 15 new cases and literature review. *Am J Med Genet A* 2007;143 (18):2122–2128.
28. McHugo J, Whittle M. Enlarged fetal bladders: Aetiology, management and outcome. *Prenat Diagn* 2001;21:958–963.
29. Ueliling DT, Gilbert E, Chesney R. Urologic implications of the VATER association. *J Urol* 1983;129:352–354.
30. Evans JA, Stranc LC, Kaplan P et al. VACTERL with hydrocephalus: Further delineation of the syndrome(s). *Am J Med Genet* 1989;34:177–182.
31. Damian MS, Seibel P, Schachenmayr W et al. VACTERL with the mitochondrial np 3243 point mutation. *Am J Med Genet* 1996;62:398–403.
32. Harper PS. Practical Genetic Counseling, 3rd edn. London, Butterworth, 1988.

33. Pagon RA, Graham JM, Zonana J et al. Coloboma, congenital heart disease and choanal atresia with multiple anomalies, CHARGE association. *J Pediatr* 1981;99:223–227.
34. Harris J, Robert E, Kallen B. Epidemiology of choanal atresia with special reference to the CHARGE association. *Pediatrics* 1997;99: 363–367.
35. Davenport SLH, Hefner MA, Mitchell JA. The spectrum of clinical features in CHARGE syndrome. *Clin Genet* 1986,29: 298–310.
36. Toriello HV. CHARGE association. *J Am Acad Audiol* 1995;6:47–53.
37. Sanlaville D, Verloes A. CHARGE syndrome: An Update. *Eur J Hum Genet* 2007;15(4):389–399.
38. Braun-Quentin C, Billes C, Bowing MURCS. association: Case report and review. *J Med Genet* 1996,33:618–620.
39. Lin HJ, Cornford ME, Hu B et al. Occipital encephalocele and MURCS association: case report and review of central nervous system anomalies in MURCS patients. *Am J Med Genet* 1996;61: 59–62.
40. Wellesley DG, Slaney SF. MURCS in a male? *J Med Genet* 1995;32: 314–315.
41. Terada S, Suzuki N, Uchide K et al. Etiology of prune belly syndrome: Evidence of megalocystic origin in an early fetus. *Obstet Gynecol* 1994;83:865–868.
42. Sutherland RS, Mevorach RA, Kogan BA. The Prune belly syndrome: Current insights. *Pediatr Nephrol* 1995;9:770–778.
43. Cazorla E, Ruiz F, Abad A et al. Prune belly syndrome: Early antenatal diagnosis. *Eur J Obstet Gynecol Reprod Biol* 1997;72:31–33.
44. Freedman AL, Bukowski TP, Smith CA. Fetal therapy for obstructive uropathy: diagnosis specific outcome. *J Urol* 1996;156: 720–723.
45. Agarwal SK, Fisk NM. In utero therapy for lower urinary tract obstruction. *Prenat Diagn* 2001;21:970–976.
46. Langer B, Stoll C, Nicolau R et al. Sirenomelia and situs inversus: Case report and review of the literature. *Fetal Diagn Ther* 1996;11:79–84.
47. Stevenson RE, Jones KL, Phelan MC et al. Vascular steal: The pathogenetic mechanism producing sirenomelia and associated defects of the viscera and soft tissues. *Pediatrics* 1986;78:451–457.
48. Abruzzo MA, Erickson RP. A new syndrome of cleft palate associated with coloboma, hypospadia, deafness, short stature, and radial synostosis. *J Med Genet* 1977;14:76–80.
49. Nevin NC, Herron B, Armstrong MJ. An 18 week fetus with Elejalde syndrome (acrocephalopolydactylous dysplasia). *Clin Dysmorphol* 1994;3:180–184.
50. Evans JA, Vitez M, Czeizel A. Pattern of acrorenal malformation associations. *Am J Med Genet* 1992;44:413–419.
51. Halal F, Desgranges M-F, Leduc B et al. Acro-renal-mandibular syndrome. *Am J Med Genet* 1980;5:277–284.
52. Kohlhase J, Schubert L, Liebers M, Rauch A, Becker K, Mohammed SN, Newbury-Ecob R, Reardon W. Mutations at the SALL4 locus on chromosome 20 result in a range of clinically overlapping phenotypes, including Okihiro syndrome, Holt-Oram syndrome, acro-renal-ocular syndrome, and patients previously reported to represent thalidomide embryopathy. *J Med Genet* 2003;40:473–478.
53. Schuhl H. Aglossia-adactylia. A propos of a case. Review of the literature. *Ann Pediatr (Paris)* 1986;33:137–140.
54. Pauli RM, Pettersen JC, Arya S. Familial agnathia-holoprosencephaly. *Am J Med Genet* 1983;14:677–698.
55. Krantz ID, Piccoli DA, Spinner NB. Alagille syndrome. *J Med Genet* 1997;34:152–157.
56. Kashtan CE. Alport syndrome: An inherited disorder of renal, ocular, and cochlear basement membranes. *Medicine* 1999;78:338–360.
57. Alsing A, Christensen C. A typical macular coloboma (dysplasia) associated with familial juvenile nephronophthisis and skeletal abnormality. *Ophthal Paed Genet* 1988.9:149–155.
58. Marshall JD, Beck S, Maffei P, Naggert JK. Alstrom syndrome. *Europ J Hum Genet* 2007;15:1193–1202.
59. Hall RK, Phakey P, Palamara J, McCredie DA. Amelogenesis imperfecta and nephrocalcinosis syndrome: Case studies of clinical features and ultrastructure of tooth enamel in two siblings. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995;79:583–592.
60. DelaChapelle A, Kere J, Sack GH, Jr, Tolvanen R, Maury CPJ. Familial amyloidosis, Finnish type: G654-to-A mutation of the gelsolin gene in Finnish families and an unrelated American family. *Genomics* 1992;13:898–901.
61. Barr M Jr. Teratogen update: angiotensin-converting enzyme inhibitors. *Teratology* 1994;50:399–409.
62. Clericuzio CL. Clinical phenotypes and Wilms' tumor. *Med Pediatr Onco suppl* 1993;21:182–187.
63. Stewart FJ, Nevin NC, Brown S. Axial mesodermal dysplasia spectrum. *Am J Med Genet* 1993;45:426–429.
64. Baldellou A, Bone J, Tamparillas M et al. Congenital hypoparathyroidism, ocular coloboma, unilateral renal agenesis and dysmorphic features. *Genetic Couns* 1991;2:245–247.
65. Van Maldergem L, Siitonen HA, Jalkh N, Chouery E, De Roy M, Delague V, Muenke M, Jabs EW, Cai J, Wang LL, Plon SE, Fourneau C, Kestila M, Gillerot Y, Megarbane A, Verloes A. Revisiting the craniosynostosis-radial ray hypoplasia association: Baller-Gerold syndrome caused by mutations in the RECQL4 gene. *J Med Genet* 2006;43:148–152.
66. Muroya K, Hasegawa T Ito Y, Nagai T, Isotani H, Iwata Y, Yamamoto K, Fujimoto S, Seishu S, Fukushima Y, Hasegawa Y, Ogata T. GATA3 abnormalities and the phenotypic spectrum of HDR syndrome. *J Med Genet* 2001;38:374–380.
67. Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. *J Med Genet* 1999;36:437–446.
68. O'dea D, Parfrey PS, Harnett JD et al. The importance of renal impairment in the natural history of Bardet-Biedl syndrome. *Am J Kidney Dis* 1996;27:776–783.
69. Elliot M, Bayly R, Cole T et al. Clinical features and natural history of Beckwith-Wiedemann syndrome: Presentation of 74 new cases. *Clin Genet* 1994;46:168–174.
70. Mulvihill DM, Mercado MG, Boineau FG. Beckwith-Wiedemann syndrome and its association with type 3 polycystic kidney disease. *Pediatr Nephrol* 1989;3:286–289.
71. Ponte P, Katz SM, FaIkner B. Beckwith-Wiedemann syndrome. Renal pathology at 4 months of age. *Clin Pediatr* 1990;29:393–397.
72. Watanabe H, Yamanaka T. A possible relationship between Beckwith-Wiedemann syndrome, urinary tract anomaly and prune belly syndrome. *Clin Genet* 1990;38:410–415.
73. Moller DE, Flier JS. Insulin resistance-mechanisms, syndromes, and implications. *N Engl J Med* 1991;325:938–948.
74. Langer LO Jr, Nishino R, Yamaguchi A et al. Brachymesomelia-renal syndrome. *Am J Med Genet* 1983;15:57–65.
75. Milunsky JM, Maher TA, Zhao G, Roberts AE, Stalker HJ, Zori RT et al. TFAP2A mutations result in branchio-oculo-facial syndrome. *Am J Hum Genet* 2008;82(5):1171–1177.
76. Chitayat D, Hodgkinson KA, Chen MY et al. Branchio-oto-renal syndrome: further delineation of an underdiagnosed syndrome. *Am J Med Genet* 1992;43:970–975.

77. Braun FC, Bayer JF. Familial nephrosis associated with deafness and congenital urinary tract anomalies in siblings. *J Pediatr* 1962;60:33–41.
78. Oates NA, VanVliet J, Duffy DL, Kroes HY, Martin NG, Boomsma DI et al. Increased DNA methylation at the AXIN1 gene in a monozygotic twin from a pair discordant for a caudal duplication anomaly. *Am J Hum Genet* 2006;79:155–162.
79. Kibar Z, Torban E, McDearmid JR, Reynolds A, Berghout J, Mathieu M et al. Mutations in VANGL1 associated with neural-tube defects. *New Eng J Med* 2007;356:1432–1437.
80. Adra A, Cordero D, Mejides A et al. Caudal regression syndrome: Etiopathogenesis, prenatal diagnosis, and perinatal management. *Obstet Gynecol Surv* 1994;49:508–516.
81. Passarge E, MeAdams AJ. Cerebro-hepato-renal syndrome. A newly recognized hereditary disorder of multiple congenital defects, including sudanophilic leukodystrophy, cirrhosis of the liver, and polycystic kidneys. *J Pediatr* 1967;71:691–702.
82. Matsuzaka T, Sakuragawa N, Nakayama H et al. Cerebro-oculo-hepato-renal syndrome (Arima's syndrome), a distinct clinicopathological entity. *J Child Neurol* 1986;1:338–346.
83. Opitz JM, Lowry RE, Holmes TM et al. Hutterite cerebro-osteonephrodysplasia; autosomal recessive trait in a Lehrerleut Hutterite family from Montana. *Am J Med Genet* 1985;22:521–529.
84. Caraballo A, Lopez Barrios A, Martin Govantes J et al. Thoracic asphyxiant dystrophy and renal disease. *An Esp Pediatr* 1977;10: 88–95.
85. Brueton LA, Dillon MJ, Winter RM. Ellis van Creveld syndrome, Jeune syndrome, and renal-hepatic-pancreatic dysplasia: Separate entities or disease spectrum? *J Med Genet* 1990;27:252–255.
86. Chasnoff IJ, Chisum GM, Kaplan WE. Maternal cocaine use and genitourinary tract malformations. *Teratology* 1988;37:201–204.
87. Jackson L, Kline AD, Barr MA et al. De Lange syndrome: A clinical review of 310 individuals. *Am J Med Genet* 1993;147:940–946.
88. Goswami RK, Rangnekar GV, Varshney S et al. Crossed renal ectopia with pelvic lipomatosis: A new syndrome involving chromosome 1. *Hum Genet* 1992;89:666–670.
89. Czeizel A, Losonei A. Split hand, obstructive urinary anomalies and spina bifida or diaphragmatic defect syndrome with autosomal dominant inheritance. *Hum Genet* 1987;77:203–204.
90. Lynch SA, Wright C. Sirenomelia, limb reduction defects, cardiovascular malformation, renal agenesis in an infant born to a diabetic mother. *Clin Dysmorphol* 1997;6:75–80.
91. Grix A, Jr, Curry C, Hall BD. Patterns of multiple malformations in infants of diabetic mothers. *Birth Defects Orig Artic Ser* 1982;18:55–77.
92. Mueller RF. Syndrome of the month. Denys-Drash syndrome. *J Med Genet* 1994;31:471–477.
93. London R, Heredia RM, Israel J. Urinary tract involvement in EEC syndrome. *Am J Dis Child* 1985;l39:1191–1193.
94. Turi S, Kobor J, Erdos A et al. Hereditary nephritis, platelet disorders and deafness- Epstein's syndrome. *Pediatr Nephrol* 1992;6:38–43.
95. Nevin NC, Hill AE, Carson DJ. Facio-cardio-renal (Eastman-Bixler) syndrome. *Am J Med Genet* 1991;40:31–33.
96. Glaze A, Fraser FC. Spectrum of anomalies in Fanconi anemia. *J Med Genet* 1982;19:412–416.
97. Joenje H, Patel KJ. The emerging genetic and molecular basis of Fanconi anaemia. *Nature Rev Genet* 2001;2:446–457.
98. Taylor CL, Jones KL, Jones MC et al. Incidence of renal anomalies in children prenatally exposed to ethanol. *Pediatrics* 1994;94:209–212.
99. Davies RS, Carty H, Pierro A. Infantile myofibromatosis-A review. *Br J Radiol* 1994;67:619–623.
100. Gattuso J, Patton MA, Baraitser M. The clinical spectrum of the Fraser syndrome: Report of three new cases and review. *J Med Genet* 1987;24:549–555.
101. Klamt B, Koziell A, Poulat F, Wieacker P, Scambler P, Berta P, Gessler M. Frasier syndrome is caused by defective alternative splicing of WT1 leading to an altered ratio of WT1+/−KTS splice isoforms. *Hum Molec Genet* 1998;7:709–714.
102. Goeminne L. A new probably X-linked inherited syndrome: Congenital muscular torticollis, multiple keloids, cryptorchidism and renal dysplasia. *Acta Genet Med Gemeloll* 1968;17:439–467.
103. Ritchey NIL, Norbeck J, Huang C et al. Urologic manifestations of Goldenhar syndrome. *Urology* 1994;43:88–91.
104. Goldston AS, Burke EC, DAgostino A et al. Neonatal polycystic kidney with brain defect. *Am J Dis Child* 1963;106:484–488.
105. Graham J, Jr, Boyle W, Troxell J et al. Cystic harmartomata of lung and kidney: A spectrum of developmental abnormalities. *Am J Med Genet* 1987;27:45–59.
106. Hennessy WT, Cromie WJ, Duckett JW. Congenital hemihypertrophy and associated abdominal lesions. *Urology* 1981;18:576–579.
107. Lipschitz B, Berdon WE, Defelice AR et al. Association of congenital hepatic fibrosis and autosomal dominant polycystic kidney disease. Report of a family with review of the literature. *Pediatr Radiol* 1993;23:131–133.
108. Thomas IT, Honore GM, Jewett T et al. Holzgreve syndrome: Recurrence in sibs. *Am J Med Genet* 1993;45:767–769.
109. Verloes A. Hypertelorism-microtia-clefting (HMC syndrome). *Genetic Coun* 1994;5:283–287.
110. Larson RS, Rudloff MA, Liap H et al. The Ivemark syndrome: Prenatal diagnosis of an uncommon cystic renal lesion with heterogeneous associations. *Pediatr Nephrol* 1995;9:594–598.
111. Cantani A, Lucenti P, Ronzani GA et al. Joubert syndrome: Review of the fifty-three cases so far published. *Ann Genet* 1990;33:96–98.
112. Verloes A, Le Mercer M, Davin J-C et al. The orocraniodigital syndrome of Juberg and Hayward. *J Med Genet* 1992;29:262–265.
113. Niikawa N, Matsuura N, Fukushima Y et al. The Kabuki-make up syndrome. *J Pediatr* 1981;99:565–569.
114. Honiball S, Snadler M. Kallmann syndrome with unilateral renal agenesis: A case report. *S Afr Med J* 1986;70:489–491.
115. Schaap C, de Die-Smulder CEM, Kuijten RH et al. McKusick-Kaufmann syndrome: the diagnostic challenge of abdominal distension in the neonatal period. *Eur J Pediatr* 1992;151:583–585.
116. Hennekam RCM, Van Schooneveld MJ, Ardinger HH et al. The Peters' plus syndrome: description of 16 patients and review of the literature. *Clin Dysmorphol* 1993;2:283–300.
117. Grise P, Lefort J, Dewald M et al. Urinary malformations in synostoses of the cervical vertebrae (Klippel-Feil syndrome). Apropos of 35 cases. *Ann Uro(Paris)* 1984;18:232–235.
118. Kousseff EG. Sacral meningocoele and conotruncal heart defects: A possible autosomal recessive trait. *Pediatrics* 1984;74:395–398.
119. Ellis EN, Kemp SF, Frindik JP et al. Glomerulopathy in patients with Donohue syndrome (Leprechaunism). *Diabetes Care* 1991;14: 413–414.
120. Russo R, D'Armiento M, Angrisami P et al. Limb body wall complex: A critical review and a nosological proposal. *Am J Med Genet* 1993;47:893.
121. Goeminne L. Synopsis of mammorenal syndrome. *Humangenetik* 1972;14:170–171.
122. Schrander-Stumpel C, DeDieSchmulder C, DeKrom M et al. Marden-Walker syndrome: case report, literature review and nosologic discussion. *Clin Genet* 1993;43:303–308.

123. Blankenberg TA, Ruebner BH et al. Pathology of renal and hepatic anomalies in Meckel-Gruber syndrome. *Am J Med Genet* 1987; 3(Suppl):395–410.
124. Penman DG, Lilford RJ. The megacystis-microcolon -intestinal hypoperistalsis syndrome: A fatal autosomal recessive condition. *J Med Genet* 1989;26:66.
125. LaMontagne AE. Urologic manifestations of Melnick-Needles syndrome: A case report and review of the literature. *J Urol* 1991;145: 1020–1021.
126. Robinson S, Kessling A. Diabetes secondary to genetic disorders. *Baillieres Clin Endocrinol Metab* 1992;6:867–898.
127. Cunniff C, Williamson-Kruse L, Olney AH. Congenital microgastria and limb reduction defects. *Pediatrics* 1993;91:1192–1194.
128. Miranda D, Schjnella RA, Finegold MJ. Familial renal dysplasia. *Arch Pathol* 1972;93:483–491.
129. Moerman P, Vandenberghe K, Fryns JP et al. A new lethal chondrodysplasia with spondylocostal dysostosis, multiple internal anomalies and Dandy-Walker cyst. *Clin Genet* 1985;27: 160–164.
130. McDonald MT, Gorski JL. Syndrome of the month. Nager acrofacial dysostosis. *J Med Genet* 1993;30:779–782.
131. Rizzo R, Pavone L, Micali G et al. Familial bilateral antecubital pterygia with severe renal involvement in nail-patella syndrome. *Clin Genet* 1993;44:1–7.
132. King JA, Gardner V, Chen S et al. Neu-Laxova syndrome: Pathological evaluation of a fetus and review of the literature. *Pediatr Pathol Lab Med* 1995;15:57–79.
133. Freire-Maia N, Pinheiro M, Opitz JM, The neurofaciodigitorenal (NFDR) syndrome. *Am J Med Genet* 1982;11:326–336.
134. Demierre MF, Gerstein W. Segmental neurofibromatosis with ipsilateral renal agenesis. *Int J Dermatol* 1996;35:445–447.
135. Saraiva JM, Lemos C, Goncalves I et al. Arthrogryposis multiplex congenita with renal and hepatic abnormalities in a female infant. *J Pediatr* 1990;117:761–763.
136. George CD, Patton MA, el Sawi M et al. Abdominal ultrasound in Noonan syndrome: A study in 44 patients. *Pediatr Radiol* 1993;23: 316–318.
137. Tsukahara M, Imaizumi K, Kawai S et al. Occipital horn syndrome: Report of a patient and review of the literature. *Clin Genet* 1994;45: 32–35.
138. Teebi AS, Hassoon MM. Urofacial syndrome associated with hydrocephalus due to aqueductal stenosis. *Am J Med Genet* 1991;40:199–200.
139. Hunter AGW, Jurenka S, Thompson D et al. Absence of the cerebellar granular layer, mental retardation, tapetoretinal degeneration and progressive glomerulopathy: An autosomal recessive oculorenal-cerebellar syndrome. *Am J Med Genet* 1982;11:383–395.
140. Weaver RG, Cashwell LP, Lorentz W et al. Optic nerve coloboma associated with renal disease. *Am J Med Genet* 1988;29:597–605.
141. Morse MJ, Lirenman DS, Johnson HW. The association of renal pelviocaliceal dysmorphism with sensorineural deafness: A new syndrome. *J Urol* 1981;125:625–627.
142. Hall JG, Pallister M, Clarren SK et al. Congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus and postaxial polydactyly-A new syndrome. *Am J Med Genet* 1980;7:47–83.
143. Biesecker LG, Graham JM Jr. Pallister-Hall syndrome. *J Med Genet* 1996;33:585–589.
144. Hasselbacher K, Wiggins RC, Matejas V, Hinkes BG, Mucha B, Hoskins BE et al. Recessive missense mutations in LAMB2 expand the clinical spectrum of LAMB2-associated disorders. *Kidney Int* 2006;70:1008–1012.
145. MacKenzie J, Chitayat D, McLorie G et al. Penoscrotal transposition: A case report and review. *Am J Med Genet* 1994;49:103–107.
146. Henneveld HT, van Lingen RA, Hamel BCJ, Stolte-Dijkstra I, Van Essen AJ. Perlman syndrome: Four additional cases and review. *Am. J. Med. Genet* 1999;86:439–446.
147. Halal F. Distal obstructive uropathy with polydactyly: A new syndrome? *Am J Med Genet* 1986;24:753–757.
148. Singh I, Johnson GH, Brown FRILL. Peroxisomal disorders Biochemical and clinical diagnostic consideration (Review). *Am J Dis Child* 1988;142:1297–1301.
149. Moser AB, Rasmussen M, Naldu S et al. Phenotype of patients with peroxisomal disorders subdivided into sixteen complementation groups. *J Pediatr* 1995;127:13–22.
150. Suzuki Y, Shimozawa N, Takahashi Y et al. Peroxisomal disorders: Clinical aspects. *Ann N Y Acad Sci* 1996;804:442–449.
151. Bidair M, Kalota SJ, Kaplan GW. Infantile hypertrophic pyloric stenosis and hydronephrosis: Is there an association? *J Urol* 1993;150:153–155.
152. Raas-Rothchild A, Goodman RM, Grunbaum M et al. Klippel-Feil anomaly with sacral agenesis: an additional subtype, type IV. *J Cranio Genet Dev Biol* 1988;8:297–301.
153. Vargas FR, Carbral de Almeida JC, Llrena JC Jr et al. Brief clinical report: RAPADILINO syndrome. *Am J Med Genet* 1992;44:716–719.
154. Davee MA, Moore CA, Bull MJ et al. New syndrome? Familial occurrence of renal and Mullerian duct hypoplasia, craniofacial anomalies, severe growth and developmental delay. *Am J Med Genet* 1992;44:293–296.
155. Moerman P, Fryns J-P, Sastrowijoto HS et al. Hereditary renal adysplasia: New observation and hypotheses. *Pediatr Pathol* 1994;14:405–410.
156. Rosa FW, Wilk AL, Ketsey FO. Teratogen update: Vitamin A congeners. *Teratology* 1986;34:366.
157. Rothman M, Moore LL, Singer MR et al. Teratogenicity of high vitamin A intake. *N Engl J Med* 1995;333:1369–1373.
158. VanDenBerg DJ, Francke U. Roberts syndrome: A review of 100 cases and a new rating system for severity. *Am J Med Genet* 1993;47:1104–1123.
159. Robson WLM, Lowry RB, Leung AM. X-linked recessive nephritis with mental retardation, sensorineural hearing loss and macrocephaly. *Clin Genet* 1994;45:314–317.
160. Strubbe EH, Cremers CWRJ, Willensen P et al. The Mayer-Rokitansky-Kuster-Hauser syndrome without and with associated features: two separate entities. *Clin Dysmorphol* 1994;3:192–199.
161. Menser MA, Robertson SE, Dorman DC et al. Renal lesions in congenital rubella. *Pediatrics* 1967;40:901–904.
162. Prosperi P, Ricotti Chessa G. Rubinstein-Taybi syndrome with renal malformations. *Minerva Pediatr* 1975;27:2230–2238.
163. Wallerstein R, Anderson CE, Hay B et al. Submicroscopic deletions at 16p13.3 in Rubinstein-Taybi syndrome: Frequency and clinical manifestations in a North American population. *J Med Genet* 1997;34:203–206.
164. Patton MA. Syndrome of the month. Russell-silver syndrome. *J Med Genet* 1988;25:557–560.
165. Santos H, Mateus J, Leal MJ. Hirschsprung disease associated with polydactyly, unilateral renal agenesis, hypertelorism and congenital deafness: a new autosomal recessive syndrome. *J Med Genet* 1988;25:204–208.
166. Abu-Libdeh B, Fujimoto A, Ehinger M. Syndrome of cleft palate, microcephaly, large ears and short stature (Say syndrome). *Am J Med Genet* 1993;45:358–360.

167. Ludman MD, Cole DEC, Crocker JFS et al. Schimke immuno-osseous dysplasia: Case report and review. *Am J Med Genet* 1993;47:793–796.
168. Okamoto N, Takeuchi M, Kitajinia H et al. A patient with Schinzel-Giedion syndrome and a review of 20 patients. *Jpn J Hum Genet* 1995;40:189–193.
169. Cantani A, Bamonte G, Ceccoli D et al. Familial juvenile nephronophthisis. A review and differential diagnosis. *Clin Pediatr* 1986;25:90–95.
170. Clark RD, Golabi M, Lacassie Y et al. Expanded phenotype and ethnicity in Setleis syndrome. *Am J Med Genet* 1989;34:354–357.
171. Tsai Y-C, Chang J-M, Changchien CC et al. Unusual short rib-polydactyly syndrome. *Am J Med Genet* 1992;44:31–36.
172. Silence D, Kozlowski K, Bar-Ziv J et al. Perinatally lethal short rib-polydactyly syndromes 1. Variability in known syndromes. *Pediatr Radiol* 1987;17:474–480.
173. Aleck KA, Grix A, Clericuzio C et al. Dyssegmental dysplasia: Clinical, radiographic and morphologic evidence of heterogeneity. *Am J Med Genet* 1987;27:295–312.
174. Simoupoulos A, Brennan GC, Alivan A et al. Polycystic kidneys, internal hydrocephalus, polydactylism in newborn siblings. *Pediatrics;*1967;39:931–934.
175. Verloes A, Massart B, Dehalleux I et al. Clinical overlap of Beckwith-Wiedermann, Perlman and Simpson-Golabi-Behmel syndromes: A diagnostic pitfall. *Clin Genet* 1995;47:257–262.
176. Cunniff C, Kratz LE, Moser A et al. Clinical and biochemical spectrum of patients with RSH/Smith-Lemli-Opitz syndrome and abnormal cholesterol metabolism. *Am J Med Genet* 1997;68: 263–269.
177. Curry JCR, Carey JC, Holland JS et al. Smith-Lemli-Opitz syndrome type II: Multiple congenital anomalies with male pseudohermaphroditism and frequent early lethality. *Am J Med Genet* 1987;26:45–57.
178. Sommer A, Rathbun MA, Battles ML. A syndrome with partial aniridia, unilateral renal agenesis and mild psychomotor retardation. *J Pediatr* 1974;85:870–872.
179. Thompson EM, Baraitser M. Sorsby syndrome: A report on further generations of the original family. *J Med Genet* 1988;25:313–321.
180. Sotos JF. Syndromes and other disorders associated with overgrowth. *Clin Pediatr* 1997;36:89–103.
181. Jejart G, Seres E. Supernumerary nipples and renal anomalies. *Int Urol Nephrol* 1994;26:141–144.
182. McBride WG. Thalidomide embryopathy. *Teratology* 1977;16: 79–82.
183. Smithells BW, Newman CGH. Recognition of thalidomide defects. *J Med Genet* 1992;29:716–723.
184. Rudd NL, Curry C, Chen KTK et al. Thymic-renal-anal-lung dysplasia in sibs: A new autosomal recessive error of early morphogenesis. *Am J Med Genet* 1990;37:401–405.
185. Tolmie JL, Patrick A, Yates JRW. A lethal multiple pterygium syndrome with apparent X-linked inheritance. *Am J Med Genet* 1987;27:913–919.
186. O'Callaghan M, Young ID. Syndrome of the month. Townes-Brocks syndrome. *J Med Genet* 1990;27:457–461.
187. Kelly TE. Teratogenicity of anticonvulsant drugs. I: Review of the literature. *Am J Med Genet* 1984;19:413–434.
188. Bernstein J, Robbins TO. Renal involvement in tuberous sclerosis. *Ann N Y Acad Sci* 1991;615:36–49.
189. Bamshad M, Root S, Carey JC. Clinical analysis of a large kindred with the Pallister ulnar-mammary syndrome. *Am J Med Genet* 1996;65:325–331.
190. Battin J, Lacombe B, Leng JJ. Familial occurrence of hereditary renal adysplasia with Mullerian anomalies. *Clin Genet* 1993;43: 23–24.
191. Neumann HP, Zbar B. Renal cyst, renal cancer and von Hippel-Lindau disease. *Kidney Int* 1997;51:16–26.
192. Maher ER, Yates JRW, Harries R et al. Clinical features and natural history of von Hippel-Lindau disease. *Q J Med* 1990;77:1151–1163.
193. Weinberg AG, Zumwalt RE. Bilateral nephromegaly and multiple pulmonary cysts. *Am J Clin Pathol* 1976;67:284–288.
194. Wenstrup RJ, Pagon RA. Female pseudohermaphroditism with anorectal, Mullerian duct, and urinary tract malformations: Report of four cases. *J Pediatr* 1985;107:751–754.
195. Turnpenny PD, Dean JCS, Dufty P et al. Syndrome of the month: Weyers' ulnar ray/oligodactyly and the association of midline malformations and ulnar ray defects. *J Med Genet* 1992;29:659–662.
196. DelPapa M, Attardo S, Mobilli M et al. Critical considerations on a case of nephroblastoma in a horseshoe kidney. *G Chir* 1991;12:549–552.
197. Hewitt M, Lunt PW, Oalchill A. Wilms' tumor and a de novo (1;7) translocation in a child with bilateral radial aplasia. *J Med Genet* 1991;28:411–412.
198. King LA, Sanchez-Ramos L, Talledo OE et al. Syndrome of genital, renal and middle ear anomalies: a third family and report of a pregnancy. *Obstet Gynecol* 1986;69:891–893.
199. Monller Gisberg J, Tano Pino F, Rodriguez Arteaga G et al. Urologic manifestations in Wolfram syndrome. *Acta Urol Esp* 1996;20: 474–477.
200. Hing AV, Dowton SB. Aase syndrome: Novel radiographic feature, *Am J Med Genet* 1993;45:413–415.
201. Schulte JM, Lenz W, Vogel M. Lethale Achondrogenesis: Eine Ubersicht uber 56 Falle. *Klin Padiatr* 1978;191:327–340.
202. Casamassima AC, Beneck D, Gewitz MH et al. Acrocallosal syndrome: Additional manifestations. *Am J Med Genet* 1989;32:311.
203. Petit P, Moerman P, Fryns J-P. Acrofacial dysostosis syndrome type Rodriguez: A new lethal MCA syndrome. *Am J Med Genet* 1992;42:343–345.
204. Toriello HV, Radecki LL, Sharda J et al. Frontonasal 'dysplasia', cerebral anomalies and polydactyly: Report of a new syndrome and discussion from a developmental field perspective. *Am J Med G* 1986;2(Suppl):89–96.
205. McMillan DD, McArthur RG, Williams JA et al. Upper urinary tract anomalies in children with adrenogenital syndrome. *J Pediatr* 1976;89:953–955.
206. Petrykowski WV, Beckmann R, Bohm N et al. Adrenal insuff'iciency, myotonic hypotonia, severe psychomotor retardation, failure to thrive, constipation, and bladder ectasia in 2 brothers: Adrenomyodystrophy. *Helv Paediatr Acta* 1982;37:387–400.
207. Hassell S, Butler MG. Antley-Bixler syndrome: Report of a patient and review of the literature. *Clin Genet* 1994;46:372–376.
208. Cohen MM Jr, Kreiborg S. Visceral anomalies in the Apert syndrome. *Am J Med Genet* 1993;45:758–760.
209. Cairney AEL, Andrews M. Wilms' tumor in three patients with Bloom syndrome. *J Pediatr* 1987;111:414–416.
210. Bowen P, Conradi GJ. Syndrome of skeletal and genitourinary anomalies with unusual facies and failure to thrive in Hutterite sibs. *Birth Defects Orig Artic Ser* 1976;12(6):101–108.
211. Temtamy SA, McKusick VA. The Genetics of Hand Malformations. 1978; 261–262.
212. Kosaki K, Curry C, Roeder E et al. Ritscher-Schinzel (3C) syndrome: Delineation of the phenotype. *Am J Med Genet* 1997;68:421–427.

213. Antley RM, Hwang DS, Theopold W et al. Further delineation of the C (trigonocephaly) syndrome. *J Med Genet* 1981;9:147–163.
214. Houston CS, Opitz JM, Spranger JW et al. The campomelic syndrome. *J Med Genet* 1983;15:3–28.
215. Jaeken J, Carchon R. The carbohydrate deficient glycoprotein syndromes: An overview. *J Inherit Metab Dis* 1993;16:813–820.
216. Robinson LK, James HE, Mubarak SJ et al. Carpenter syndrome: Natural history and clinical spectrum. *Am J Med Genet* 1985;20: 461–469.
217. Cullen SI, Harris DE, Carter CH et al. Congenital unilateral ichthyosiform erythroderma. *Arch Dermatol* 1969;199:724–729.
218. Nuoffer J11, Pfammatter JP, Spahr A et al. Chondrodysplasia punctata with a mild clinical course. *J Inherit Metab Dis* 1994;17:60–66.
219. Levy P, Baraitser M. Syndrome of the month. Coffin-Siris syndrome. *J Med* 1991;28:338–341.
220. Janik JS, Shandling B, Mancer K. Cutis laxa and hollow viscus diverticula. *J Pediatr Surg* 1982;17:318–320.
221. Woods CG, Treleaven S, Betheras FR et al. Disorganization-like syndrome with 47,XXY and unilateral narrowing of the common iliac artery. *Clin Dysmorphol* 1995;4:82–86.
222. Cullen P, Rodgers CS, Callen CF et al. Association of familial Duane anomaly and urogenital abnormalities with a bisatellited marker derived from chromosome 22. *Am J Med Genet* 1993;47:925–930.
223. Levard G, Aigrain Y, Ferkadji L et al. Urinary bladder diverticula and the Ehlers-Danlos syndrome in children. *J Pediatr Surg* 1989;24:1184–1186.
224. Berger TG, Detlefs RL, Donatucci CF. Junctional epidermolysis bullosa, pyloric atresia, and genitourinary disease. *Pediatr Dermatol* 1986;3:130–134.
225. Eklof O, Parkkulainen K. Epidermolysis bullosa dystrophica with urinary involvement. *J Pediatr Surg* 1984;19:215–217.
226. Burn J, Winter RM, Baraitser M et al. The femoral hypoplasia-unusual facies syndrome. *J Med Genet* 1984;21:331–340.
227. Patton RA, Hurst J, Donnai D et al. Syndrome of the month. Floating-Harbor syndrome. *J Med Genet* 1991;28:201–204.
228. Suskan E, Kurkcuoglu N, Uluoglu O. Focal dermal hypoplasia (Goltz syndrome) with horseshoe kidney abnormality. *Pediatr Dermatol* 1990;7:283–286.
229. Hashemi C, Mahloudji M. The whistling face syndrome: Report of a case with a renal anomaly. *Birth Defects Orig Artic Ser* 1974;10:265–267.
230. Kanemura T, Orii T, Olitani M. Frontometaphyseal dysplasia with congenital urinary tract malformations. *Clin Genet* 1979;16: 399–404.
231. Roizenblatt J, Wajntal A, Diament AJ. Median cleft face syndrome or frontonasal dysplasia: A case report with associated renal malformations. *J Pediatr Ophthalmol Strabismus* 1979;16:16–20.
232. Siebert JR, Benjamin DR, Jutil S et al. Urinary tract anomalies associated with congenital diaphragmatic defects. *Am J Med Genet* 1990;37:1–5.
233. Hockey A, Knowles S, Davies D et al. Glutaric aciduria type II, an unusual cause of prenatal polycystic kidneys: Report of prenatal diagnosis and confirmation of autosomal recessive inheritance. *Birth Defects Orig Artic Ser* 1993;29:373–382.
234. Gallop TR, Fontes LR. The Grieg cephalopolysyndactyly syndrome: Report of a family and review of the literature. *Am J Med Genet* 1985;22:59–68.
235. Kaplan P, Ramos F, Zackai EH et al. Cystic kidney disease in Hajdu-Cheney syndrome. *Am J Med Genet* 1995;56:25–30.
236. Salonen R, Herva R. Syndrome of the month: Hydrolethalus syndrome. *J Med Genet* 1990;27:756–759.
237. Devos EA, Leroy JG, Braeckman JJ et al. Spondylocostal dysostosis and urinary tract anomaly: Definition and review of the entity. *Eur J Pediatr* 1978;128:7–15.
238. Gershoni-Baruch R, Lemer A, Braun J et al. Johanson-Blizzard syndrome: Clinical spectrum and further delineation of the syndrome. *Am J Med Genet* 1990;35:546–551.
239. Horn D, Wakowski R. Phenotype and counseling in lacrimo-auriculodento-digital (LADD) syndrome. *Genetic Couns* 1993;4: 305–309.
240. Raff ML, Byers PH. Joint hypermobility syndromes. *Curr Opin Rheumatol* 1996;8:459–466.
241. Silverman FN. Larsen syndrome: Congenital dislocation of the knees and other joints, distinctive facies, and frequently, cleft palate. *Ann Radiol* 1972;15:297–328.
242. Traboulsi EI, Lenz W, GonzalesRamos M et al. The Lenz microphthalmia syndrome. *Am J Ophthalmol* 1988;105:40–45.
243. Swanson SL, Santen RJ, Smith DW. Multiple lentigines syndrome: New findings of hypogonadotrophism, hyposmia, and unilateral renal agenesis. *J Pediatr* 1971;78:1037–1039.
244. Sbar GR, Venkataseshan VS, Huang Z et al. Renal disease in Marfan syndrome. *Am J Nephrol* 1996;16:320–326.
245. Biermann CW, Rutishauser G. Polycystic kidneys associated with Marfan syndrome in an adult. *Scand J Urol Nephrol* 1994;28: 295–296.
246. Sharon A, Gillerot Y, Van Maldergem L et al. The Marshall-Smith syndrome. *Eur J Pediatr* 1990;150:54–55.
247. Kawai M, Momoi T, Fujii T et al. The syndrome of Moebius sequence, peripheral neuropathy and hypogonadotropic hypogonadism. *Am J Med Genet* 1990;37:578–582.
248. Willems PJ, Colpaert C, Vaerenbergh M et al. Multiple pterygium syndrome with body asymmetry. *Am J Med Genet* 1993;47:106–111.
249. Roig M, Balliu PR, Navarro C et al. Presentation, clinical course and outcome of the congenital form of myotonic dystrophy. *Pediatr Neurol* 1994;11:208–213.
250. Emery AEH, Oleesky S, Williams RT. Myotonic dystrophy and polycystic disease of the kidneys. *J Med Genet* 1967;4:26–28.
251. Taalman RDHM, Hustinx TWJ, Weemaes CM et al. Further delineation of the Nijmegen breakage syndrome. *Am J Med Genet* 1989;32:425–431.
252. Robin NH, Opitz JM, Muenke M. Opitz/GBBB syndrome: Clinical comparisons of families linked to Xp22 and 22q, and review of the literature. *Am J Med Genet* 1996;62:305–317.
253. Cappa M, Borrelli P, Marini R et al. The Opitz syndrome: A new designation for clinically indistinguishable BBB and G syndromes. *Am J Med Genet* 1987;28:303–310.
254. Toriello HV. Review Oral-facial-digital syndromes, 1992. *Clin Dysmorphol* 1993;2:95–105.
255. Meinecke P, Hayek H. Orofaciodigital syndrome type IV (Mohr-Majewski) with severe expression expanding the known spectrum of anomalies. *J Med Genet* 1990;27:200–202.
256. Kieselstein M, Herman G, Wahrman J et al. Mucocutaneous pigmentation and intestinal polyposis (Peutz-Jeghers syndrome) in a family of Iraqi Jews with polycystic kidney disease, with a chromosome study. *Isr J Med Sci* 1969;5:81–90.
257. Kuwada SK, Burt RW. The clinical features of the hereditary and nonhereditary polyposis syndromes. *Surg Oncol Clin N Am* 1996;5:553–567.
258. Bouvet J, Maroteaux P, Briand-Guillemot M. Le syndrome de Poland: Etudes clinique et genetique considerations physiopathologiques. *Presse Med* 1976;5:185–190.

259. Bamforth JS, Fabian C, Machin G et al. Poland anomaly with a limb body wall disruption defect: case report and review. *Am J Med Genet* 1992;43:780–784.
260. Verloes A, Mulliez N, Gonzales M et al. Restrictive dermopathy, a lethal form of arthrogryposis multiplex with skin and bone dysplasias: three new cases and review of the literature. *Am J Med Genet* 1992;43:539–547.
261. Butler MG, Wadlington WB. Robinow syndrome: report of two patients and review of the literature. *Clin Genet* 1987;31:77.
262. Vennos EM, Collins M, James WD. Rothmund-Thomson syndrome: Review of the world literature. *J Am Acad Dermatol* 1992;27:750–762.
263. Majewski F, Enders H, Ranke MB et al. Serpentine fibula-polycystic kidney syndrome and Melnick-Needles syndrome are different disorders. *Eur J Pediatr* 1993;152:916–921.
264. Murr MM, Waziri MH, Schelper RL et al. Case of multivertebral anomalies, cloacal dysgenesis, and other anomalies presenting prenatally as cystic kidneys. *Am J Med Genet* 1992;42:761–765.
265. Beighton P. Syndrome of the month. Spondyloepimetaphyseal dysplasia with joint laxity (SEMWL). *J Med Genet* 1994;31:136–140.
266. Carter P, Burke JR, Searle J. Renal abnormalities and spondylometaphyseal dysplasia. *Austr Paediatr J* 1985;21:115–117.
267. Robinow M, Johnson GF, Broock W. Syndactyly type V. *Am J Med Genet* 1982;11:475–482.
268. Pankau R, Partsch CJ, Winter M et al. Incidence and spectrum of renal abnormalities in Williams-Beuren syndrome. *Am J Med Genet* 1996;63:301–304.
269. Sandoval R, Sepulveda W, Gutierrez J, Be C, Altieri E. Prenatal diagnosis of nonmosaic trisomy 9 in a fetus with severe renal disease. *Gynecol Obstet Invest* 1999;48:69–72.
270. Barakat AY, Butler MG. Renal and urinary tract abnormalities associated with chromosome aberrations. *Int J Pediatr Nephrol* 1987;8:215–226.
271. Jones KL. Smith's Recognizable Patterns of Human Malformation. 6th edn. Philadelphia, WB Saunders, 2005.
272. Van Zelderen-Bhola SL, Breslau-Siderius EJ, Beveratocks GC et al. Prenatal and postnatal investigation in a case of Miller-Dieker syndrome due to a familial cryptic translocation t(17;20) (p13.3; q13.3) detected by prenatal fluorescence in situ hybridization. *Prenat Diagn* 1997;17:173–179.
273. Gorlin RJ, Cohen MM, Hennekam RCM. Syndromes of the Head and Neck. 4th edn. New York, Oxford University Press, 2001.
274. Kupferman JC, Stewart CL, Kaskel FJ et al. Posterior urethral valves in patients with Down syndrome. *Pediatr Nephrol* 1996;10:143–146.
275. VanBuggenhout GJ, Verbruggen J, Fryns JP. Renal agenesis and trisomy 22: Case report and review. *Arm Genet* 1995;38:44–48.
276. Goldberg R, Motzkin B, Scambler PJ et al. Velo-cardio-facial syndrome: A review of 120 patients. *Am J Med Genet* 1993;45: 313–319.
277. Greenberg F. DiGeorge syndrome: A historical review of clinical and cytogenetic features. *J Med Genet* 1993;30:803–806.
278. Flynn MT, Ekstrom L, DeArce M et al. Prevalence of renal malformation in Turner syndrome. *Pediatr Nephrol* 1996;10:498–500.