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Malformations Among the X-Linked Intellectual Disability Syndromes

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Abstract

Malformations are significant contributions to childhood mortality and disability. Their co-occurrence with intellectual disability may compound the health burden, requiring additional evaluation and management measures. Overall, malformations of greater or lesser severity occur in at least some cases of almost half of the 153 XLID syndromes. Genitourinary abnormalities are most common, but tend to contribute little or no health burden and occur in only a minority of cases of a given XLID syndrome. Some malformations (e.g., lissencephaly, hydranencephaly, long bone deficiency, renal agenesis/dysplasia) are not amenable to medical or surgical intervention; others (e.g., hydrocephaly, facial clefting, cardiac malformations, hypospadias) may be substantially corrected.

Keywords

Malformations; Birth Defects; X Chromosome; X-Linked Intellectual Disability

INTRODUCTION

Malformations or other structural anomalies occur in a number of the 153 X-linked intellectual disability (XLID) syndromes, and in a few instances they contribute to mortality or significant morbidity. Individually and in recognizable patterns, malformations provide substantive clues to diagnosis of several XLID syndromes (Table I). This is of particular importance in families with a single or few affected members.

Hydrocephalus, facial clefting, cardiac malformations and genitourinary anomalies are among those structural abnormalities most likely to require medical and surgical management. Malformations of the central nervous system are exceptional among the XLID syndromes and only infrequently explain the cognitive impairment or neurological manifestations.

This survey seeks to identify the structural anomalies that occur with some consistency among the XLID syndromes with emphasis on those that contribute to diagnosis and management.

MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM

Hydrocephaly (or hydranencephaly), neuronal migration abnormalities, agenesis of the corpus callosum, and cerebellar aplasia or hypoplasia are the most common and most severe of the structural anomaliesin the XLID syndromes.

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Hydrocephaly

Hydrocephaly-MASA Spectrum is the prototypic XLID syndrome with a structural alteration of the central nervous system [Schrander-Stumpel et al., 1995]. Identification of mutations in *L1CAM* has permitted inclusion of four entities – X-Linked hydrocephaly, MASA syndrome, XLID-clasp thumb, and complicated spastic paraplegia – previously considered to be separate entities in the spectrum [Jouet et al., 1993; Vits et al., 1994; Shrander-Stumpel, 1995]. Hydrocephaly, dysgenesis of the corpus callosum, adducted thumb, unsteady gait, spastic paraplegia, and intellectual disability comprise the usual clinical findings. Hypotonia is present initially, but is replaced by spasticity by late childhood or adolescence. Hydrocephaly occurs secondary to stenosis of the aqueduct of Sylvius. The degree of intellectual development appears to correlate with the severity of hydrocephaly. Truncating mutations and mutations affecting the immunoglobulin or fibronectin domains are associated with more severe phenotypic expression and mortality [Michaelis et al., 1998; Vos et al., 2010].

VACTERL-hydrocephaly occurs as autosomal and X-linked malformation syndromes [Hilger et al., 2012]. Hydrocephaly in the company of vertebral, anorectal, tracheoesophageal, renal, and limb malformations comprise the fully-expressed phenotype. Multiple vertebral anomalies, radial ray defects, imperforate anus, and tracheoesophageal fistulas with or without esophageal atresia are typical. Infant lethality is the rule. The X-linked type accounts for a minority of cases and mutations in *FANCB* occur in a minority of this type.

Hydranencephaly with abnormal genitalia represents the most severe end of *ARX*-associated XLID [Shoubridge et al., 2010]. Hydranencephaly is accompanied by abnormalities of neuronal migration, poor development of the male genitalia, hypotonia, and seizures. Microphallus, hypospadias, undescended testes and ambiguous genitalia have been described. Death typically occurs during infancy. Mild expression has been noted in female carriers.

AP1S2-associated XLID encompasses conditions described under three different names – X-Linked hydrocephaly with basal ganglia calcifications (Fried syndrome), Turner XLID syndrome, and MRX59 [Fried, 1972; Turner et al., 2003; Saillour et al., 2007]. Head size is variable and hydrocephaly and calcifications in the basal ganglia are not present in all cases. Hypotonia typically is present and aggressive behavior has been reported in several families.

Hydrocephaly-Cerebellar Agenesis has been afforded XLID syndrome status, but only one family has been reported [Riccardi and Marcus, 1978]. In addition to the CNS anomalies, hypotonia, areflexia or hyporeflexia, and seizures occur. All infants have died in the neonatal period. Focal glomerulosclerosis and visceral hemosiderin deposits have been noted at postmortem. The gene locus is not known and allelism with another of the XLID-hydrocephaly syndromes is possible.

In addition to these syndromes in which hydrocephaly is a defining malformation, seven other XLID syndromes include hydrocephaly or hydranencephaly as a finding, at least in some cases (Table II).

Abnormalities of Neuronal Migration

Disturbance in neuronal migration in the form of lissencephaly, cortical dysplasia or heterotopia occurs in seven XLID syndromes. Detection, which requires CNS imaging, provides an important diagnostic finding.

Lissencephaly, X-Linked presents as a central nervous system phenotype without malformations in other systems [Gleeson et al., 1998]. Frontal pachygyria is typical in males, but agyria, polymicrogyria, hypoplasia of the cerebellar vermis, dilated ventricles and dysgenesis of the corpus callosum may also occur. The brain is small and associated with hypotonia, spasticity, seizures and underdevelopment of the genitalia. Subcortical band heterotopia is typical in females and may be associated with mild-moderate intellectual disability, behavioral problems and seizures. Mutations in *DCX* are responsible [Gleeson et al., 1998; Sossay-Alaoui et al., 1998].

Lissencephaly with Abnormal Genitalia is one of a spectrum of XLID syndromes caused by mutations in *ARX* [Kitamura et al., 2002; Shoubridge et al., 2010]. The posterior cerebral cortex is more severely affected. Small overall brain size, dilated ventricles, and absent corpus callosum accompany the thickened smooth cortex. The abnormal genitalia may present as microphallus, undescended testes and hypospadias or be completely undifferentiated. Death usually occurs in infancy. Carrier may have dysgenesis of the corpus callosum, seizures and learning disabilities.

FLNA-Associated XLID syndromes present with variably severe skeletal findings and intellectual disability, if present, tends to be mild [Robertson, 2005]. Periventricular Nodular Heterotopia is the exception. This XLID syndrome primarily affects females, skeletal manifestations are absent, and seizures dominate the clinical picture. Truncating mutations of *FLNA* are generally found. Although less commonly identified in males, similar MRI findings and clinical course have been reported.

Disturbances of neuronal migration also occur in Aicardi syndrome (cortical dysplasia plus agenesis of the corpus callosum and cerebellar hypoplasia), CK syndrome (pachygyria and polymicrogyria), Kang syndrome (gyral dysplasia plus agenesis of the corpus callosum and hydrocephaly) and hydranencephaly with abnormal genitalia (thin cortex with simplified gyral pattern plus hydranencephaly) [Stevenson et al., 2012].

Dysgenesis of the Corpus Callosum

Dysgenesis of the corpus callosum is the most common structural anomaly of the central nervous system among all individuals and competes with hydrocephaly as the most common among the XLID syndromes (Table I). The impact of this anomaly on cognitive ability is debated. Certainly, dysgenesis or agenesis of the corpus callosum may be found incidentally among persons who appear to have normal cognitive and neurological function. It is found rather consistently in some XLID syndromes (e.g., Aicardi and Opitz FG syndromes) and less consistently in many others (Table II). In neither circumstance does it cause distinguishing manifestations in the neurological examination or neuropsychological testing profile.

Cerebellar Agenesis

Underdevelopment or absence of part or all of the cerebellum is a characteristic of several XLID syndromes (Table II). Neurological signs in the form of hypotonia, ataxia, choreoathetosis, or spasticity result. Other structural abnormalities of the nervous system are invariably present and may contribute to the neurological phenotype.

OCULAR MALFORMATIONS

Anophthalmia/microphthalmia and coloboma are the ocular malformations of note in the XLID syndromes [Stevenson et al., 2012]. Absence of the eyes or extreme microphthalmia occurs in Graham anophthalmia syndrome; less severe degrees of microphthalmia occur in Aicardi, cerebro-oculo-genital, Chassaing-Lacombe chondrodysplasia, Goltz,

incontinentiapigmenti, Lenz, MIDAS, Nance-Horan, and VACTERL-hydrocephaly syndromes. Abnormalities of the anterior chamber, iris or retinal colobomas, and cataracts may accompany the microphthalmia. Retinal colobomas or lacunae occur in Aicardi and cerebro-cerebello-coloboma syndromes; iris colobomas are more typical in the other XLID syndromes with ocular anomalies.

FACIAL CLEFTING

Facial clefting has been reported in 16 XLID syndromes, although it is a consistent finding in only half of these. Cleft lip is less frequent than cleft palate (Table III). In almost all cases, malformations affecting other systems will be present (Fig 1).

Otopalatodigital syndrome I and Otopalatodigital syndrome II are caused by mutations in *FLNA* [Robertson et al., 2003]. OPD I is less severe in both physical and functional characteristics. Craniofacial findings include prominent occiput, frontal prominence with overhanging brow, broad and depressed nasal root, hypertelorism, downslanting palpebral fissures, small mouth and chin, and cleft palate. The thumbs and great toes are short and broad and the other digits blunted with bulbous tips and short nails. Other skeletal findings include irregular curvature and spacing of the digits, limited elbow movement, bowed long bones, pectus excavatum, short trunk and short stature. Conductive hearing loss accompanies these physical findings. Intellectual disability tends to be mild. Carrier females may have many of the same craniofacial and digital manifestations.

OPD II is more severe in all phenotypic aspects and may be stillborn or lethal during the first year or so. The face shows greater prominence of the forehead, flattening of the midface and nasal root, hypertelorism, small mouth, micrognathia and cleft palate. Skeletal manifestations are likewise more pronounced with short stature, underossification of the cranium, sclerotic and bowed long bones, flat vertebrae, rockerbottom feet, and irregular spacing and flexion of the blunted digits. The great toes and fibulas may be absent. Mixed hearing loss accompanies these physical findings. Many of the same findings, albeit less pronounced, may be seen in carrier females.

Oral-Facial-Digital Syndrome I is found almost exclusively in females. The facial findings include dystopia canthorum, flattened midface with underdevelopment of the alar cartilages, milia, and pseudocleft of the lip [Thauvin-Robinet et al., 2006]. Oral manifestations are more notable with lobation and hamartomas of the tongue, unusual hypertrophied frenula, hypodontia, malocclusion, and highly arched or irregularly cleft palate. The digits are short with proximal syndactyly and clinodactyly, especially fingers 2 and 5. Hydrocephaly, porencephaly, agenesis of the corpus callosum, adult-type polycystic kidney, alopecia or dry sparse scalp hair may occur. The syndrome is due to mutations in *CXORF5*.

Telecanthus-Hypospadias syndrome (Opitz BBB/G syndrome) is caused by mutations in *MID1* [Quaderi et al., 1997]. The face is characterized by telecanthus, epicanthus, high broad nasal root, dysplastic or posteriorly-rotated ears and cleft lip [Stevens and Wilroy, 1988]. The forehead may be narrow with metopic ridge, and the cranium small, abnormally configured, or asymmetric. Cleft palate or uvula and other anomalies of the pharynx, larynx and trachea occur. A variety of cardiac defects have been reported, but only in a minority. Hypospadias occurs in most males and hypoplastic or cleft scrotum, undescended testes, inguinal hernia, and imperforate anus less frequently. Skeletal defects are uncommon, but short stature occurs in one-third of cases. Cognitive deficits tend to be mild. Carrier females may have telecanthus, but lack other malformations.

XLID-cleft lip/cleft palate (Siderius syndrome) typically has cleft lip and cleft palate [Siderius et al., 1999]. The face tends to be long, the nose broad, the ears cupped and the

hands large. Synophrys may be present. Short attention span occurs. Behavior may be unpredictable with bouts of aggression. Mutations have been found in *PHF8*, a histone deacetylase [Laumonnier et al., 2005].

CARDIAC MALFORMATIONS

Structural anomalies of the cardiovascular system occur in several XLID syndromes; only in TARP syndrome do they appear to be a defining manifestation [Johnston et al., 2010]. Septal defects, valvular stenosis or incompetence and anomalies of major vessels rather than life-threatening complex cardiac malformations are typical. Septal defects are most common, occurring at least occasionally in nine XLID syndromes (Table IV). Tetralogy of Fallot, hypoplastic left heart, and other complex cardiac malformations have been reported in individual cases of alpha-thalassemia intellectual disability, Renpenning syndrome and Opitz FG syndrome. Cardiomyopathy occurs in five XLID syndromes and arrhythmias with or without cardiomyopathy in seven (Table III). Malformations in other systems commonly accompany the cardiovascular anomalies (Fig 1).

TARP syndrome is defined by four key findings – talipes equinovarus, atrial septal defect, Robin sequence, and persistence of the left superior vena cava [Gripp et al., 2011]. Structural anomalies are, however, more widespread involving most systems. The face is distinctive with small head, upslanted palpebral fissures, low-set posteriorly-rotated ears, small jaw and cleft palate. Dysgenesis of the corpus callosum, cerebellar dysgenesis, mega cisterna magna, optic atrophy and hearing loss affect the nervous system. Cryptorchidism occurs in a majority of cases. Arrhythmias occur and contribute to early demise, generally in infancy. Mutations in *RBM10,* which encodes an RNA binding motif protein, are causative.

GENITOURINARY MALFORMATIONS

Almost one-third of the XLID syndromes will have genitourinary anomalies at least in a minority of cases (Table V). In many instances, the anomalies are trivial without associated morbidity; in a few instances the anomalies require medical or surgical management. Incompletely differentiated genitalia represents the most severe end of the spectrum of genital anomalies, shawl scrotum and undescended testes the least severe. Hydronephrosis is the most severe co-occurring urinary system anomaly.

Lissencephaly with abnormal genitalia and hydranencephaly with abnormal genitalia are allelic conditions caused by mutations in *ARX* [Kitamura et al., 2002; Shoubridge et al., 2010]. The genitalia may be undifferentiated or be less severely affected with microphallus, hypospadias and undescended testes. Microcephaly generally accompanies the brain malformations. Profound developmental failure, hypotonia and seizures dominate the clinical presentation and death occurs in the neonatal period or later in infancy.

Alpha-thalassemia intellectual disability commonly has some form of genital abnormality [Gibbons et al., 2008]. Undifferentiated genitalia is the most severe but least common anomaly. Genital hypoplasia, hypospadias and undescended testes are said to occur in most cases. This may represent a biased view since males with more typical phenotype are more likely to be diagnosed. For example, only 20% of males with the p.R37X mutation in *ATRX* have genital anomalies [Basehore et al., unpublished].

GASTROINTESTINAL MALFORMATIONS

Gastrointestinal malformations are rarely found among the XLID syndromes. Tracheoesophageal fistula and esophageal atresia are sentinel findings in VACTERL-

Hydrocephaly syndrome (Table I). Imperforate anus or other anorectal malformations occur in VACTERL-Hydrocephaly, Opitz FG and Telecanthus-Hypospadias syndromes.

SKELETAL MALFORMATIONS AND DYSPLASIAS

Malformations involving the chondroosseous structures are distinctly rare among the XLID syndromes. The skeletal features can be divided into two main classifications: 1) anatomical, defined as primary malformations and 2) functional, defined as secondary and include most cases of joint contractures and other positional deformities. These functional anomalies are typically secondary to poor fetal or postnatal movement and sometimes accompanying primary central nervous system malformations which lead to spasticity, contractures, and even scoliosis. The primary anatomic abnormalities, which provide diagnostic clues to the specific syndrome and its etiology, can be further divided into generalized skeletal dysplasias and specific focal skeletal malformations (Tables VI and VII).

Long bone deficiencies occur only in VACTERL-hydrocephaly (radial aplasia) and otopalatodigitalsyndrome II (fibular aplasia) [Robertson et al., 2003; Stevenson and Hunter, 2013]. Oligodactyly occurs in VACTERL-Hydrocephaly (absent thumbs) and Goltz syndrome (absence of any digits). Polydactyly occurs in Lenz Microphthalmia and rarely in Opitz FG, otopalatodigital II and Simpson-Golabi-Behmel syndromes. Some cases of Aarskog, oral-facial-digital II, and otopalatodigital II syndromes have incomplete cutaneous syndactyly. Brachydactyly of greatest severity is present in oral-facial-digital syndrome I. Less severe shortening of the digits occurs in alpha-thalassemia intellectual disability, Aarskog, Atkin-Flaitz, Simpson-Golabi-Behmel, hereditary bullous dystrophy, and the Otopalatodigital syndromes [Stevenson et al., 2012]. Broad thumbs typically occur in Opitz FG and otopalatodigital I syndromes. Carpal and tarsal coalitions may be seen in otopalatodigitalsyndrome II and radioulnarsynostosis in Giuffre-Tsukahara syndrome. Abnormalities of vertebral segmentation are usually present in VACTERL-hydrocephaly and Christian syndrome; less commonly in Aicardi and Goltz syndromes. Most of these syndromes are readily diagnosed on the basis of clinical findings (Table VI). The clinical diagnosis may be confirmed in most cases with molecular testing.

The X-linked skeletal dysplasias with intellectual disability include Chassaing-Lacombe chondrodysplasia, *FLNA*-Associated XLID (otopalatodigital Syndromes I and II), Roifman syndrome and XLID-spondyloepimetaphyseal dysplasia (Table VII). Chassaing-Lacombe chondrodysplasia is lethal in males as are most cases of otopalatodigital syndrome II. The nonskeletal findings are useful in differentiating the few XLID syndromes with chondroosseous dysplasias (Table VI). The responsible genes are known for Chassaing-Lacombe Chondrodysplasia (*HDAC6*) and the Otopalatodigital Syndromes (*FLNA*) [Stevenson et al., 2012; Robertson et al., 2003].

SUMMARY

Major malformations occur in 2–5% of all infants and comprise the most common cause of death during infancy. The prevalence of malformations of varying severity among the XLID syndromes exceeds this rate, being found at least in some cases of almost half (72) of the 153 XLID syndromes. Malformations of the central nervous system occur in 14% (21/153), facial clefting in 10% (16/153), cardiovascular malformations or cardiomyopathy in 12% (18/153), genitourinary anomalies in 31% (48/153) and skeletal malformations or dysplasias in 8% (12/153). Malformations play a significant health role in over half of the 18 XLID syndromes with infant or early childhood lethality.

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Malformation	Total Number of Syndromes with Malformations	Syndromes with Malformations Isolated to Single Organ System	Syndromes with Malformations in more than one Organ System					
			ORO	CV	SK	GU	GI	OC
CNS	21	13	3	1	2	7	1	3
ORO	16	2		5	6	8	2	3
CV	18	5	5		3	9	3	3
SK	12	4	6	3		4	2	4
GU	48	28	8	9	4		3	3
GI	3	0	2	3	2	3		1
OC	11	3	3	3	4	3	1	

CNS-central nervous system, ORO-orofacial clefting, CV-cardiovascular, SK-skeletal, GU-genitourinary, GI-gastrointestinal, OC-ocular

Figure 1.
Numbers of XLID syndromes with malformations in a single organ system and in multiple organ systems.

Table I

Malformations indicative of specific XLID syndromes

Periventricular heterotopia	*FLNA*-associated XLID
Lissencephaly	*ARX*-associated XLID CK syndrome X-linked lissencephaly
Hydranencephaly	*ARX*-associated XLID Hydrocephaly-MASA spectrum
Retinal lacunae	Aicardi syndrome
Cleft lip	XLID cleft lip/cleft palate Telecanthus-hypospadias
Tracheoesophageal fistula/esophageal atresia	VACTERL-hydrocephaly
Imperforate anus	VACTERL-hydrocephaly Opitz FG syndrome
Renal agenesis	Lenz microphthalmia
Cystic kidneys	Oral-Facial-Digital syndrome I Simpson-Golabi-Behmel
Ambiguous genitalia	*ARX*-associated XLID *ATRX*-associated XLID
Radial aplasia	VACTERL-hydrocephaly
Radioulnar synostosis	Guiffre-Tsukahara
Vertebral segmentation	VACTERL-hydrocephaly Christian syndrome

Table II

XLID Syndromes with Central Nervous System Malformations

Syndrome	Hydrocephaly/Hydranencephaly	Neuronal Migration Abnormality	Dysgenesis of the Corpus Callosum	Cerebellar Agenesis/Hypoplasia
Hydrocephalus-MASA Spectrum	+		+	
VACTERL-Hydrocephaly	+			
Hydranencephaly with Abnormal Genitalia (*ARX*-Associated XLID)	+	+		
Hydrocephaly-Cerebellar Agenesis	+			+
Agenesis of the Corpus Callosum			+	
Aicardi		+	+	+
AP1S2-Associated XLID	+			
Armfield	+			+
Bertini			+	+
Cerebro-Cerebello-Coloboma	+			+
CK		+		
Christianson				+
FLNA-Associated XLID		+		
Gustavson	+			+
Juberg-Marsidi-Brooks	+		+	
Kang	+	+	+	
Lissencephaly, X-Linked		+	+	+
Lissencephaly with Abnormal Genitalia (*ARX*-Associated XLID)		+	+	
Oral-Facial-Digital I	+		+	
Pettigrew	+			
Schimke				+

Table III

Orofacial Clefts in the XLID Syndromes

Syndrome	Cleft Lip		Cleft Palate	
	Occasional	Frequent	Occasional	Frequent
Armfield				+
ATRX			+	
Goltz	+		+	
Hall Orofacial	+		+	
Lenz Microphthalmia	+		+	
Oral-Facial-Digital I		P		+
Otopalatodigital I				+
Otopalatodigital II				+
Pallister W		P		+
Renpenning			+	
Simpson-Golabi-Behmel			+	
Snyder-Robinson			+	
TARP			+	
Telecanthus-Hypospadias		+		+
VACTERL-Hydrocephaly			+	
XLID-Cleft Lip/Palate		+		+

P=pseudocleft or incomplete cleft

Table IV

Cardiovascular Abnormalities Reported in XLID Syndromes

Syndrome	ASD	VSD	Other Malformations	Valve Disease	Major Vessel Anomaly	Cardio-myopathy	Arrhyth-mias
TARP	+				+		+
MIDAS	+	+			+	+	+
Bergia Cardiomyopathy						+	+
Renpenning	+	+	T/F, other complex defects		+		
Craniofacioskeletal (males)	+	+			+		
Myotubular Myopathy						+	+
ATRX	+	+	T/F, D	+	TGV		
Creatine Transporter Deficiency						+	+
Duchenne Muscular Dystrophy						+	+
Hereditary Bullous Dystrophy				+			
Lenz Microphthalmia				+	C		
Lujan	+						
Opitz FG		+	Hypoplastic left heart		C		
Simpson-Golabi-Behmel							
Telecanthus-Hypospadias	+	+		+	C, +		
Mucopolysaccharidosis II				+			
n-Alpha-Acetyl Transferase Deficiency							+
VACTERL-Hydrocephalus	+	+			C		

C=coarctation of the aorta, T/F=Tetralogy of Fallot, TGV=Transposition of Great Vessels, D=Dextrocardia

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Table V

Abnormalities of the Genitourinary System in XLID Syndromes

	Anomalies of Genitalia				Anomalies of Urinary System		
Syndrome	**Undifferentiated**	**Hypospadias**	**Minor Anomalies**	**Macroorchidism/ Microorchidism**	**Renal Dysplasia**	**Hydro-nephrosis**	**Renal Agenesis**
Aarskog			S, UT				
Ahmad			MP	Mi			
Alpha-Thalassemia Intellectual Disability	+	+	UT, MP	Mi			
Armfield			UT				
ARX-Associated XLID	+	+	MP, UT				
Atkin-Flaitz				Ma			
Börjesson-Forssman-Lehman			MP	Mi			
Branchial Arch			UT				
Cerebro-Oculo-Genital		+	MP, UT				
Cornelia de Lange				Mi			
Craniofacioskeletal		+	UT			+	
Dyskeratosis Congenita			MP	Mi			
Fragile X				Ma			
Hall Orofacial			UT		+		
Hereditary Bullous Dystrophy			UT	Mi			
Juberg-Marsidi-Brooks			MP	Mi			
Lenz Microphthalmia		+	UT			+	+
Lissencephaly, X-Linked			MP	Mi			
Lujan				Ma			
Martin-Probst			MP	Mi			
MEHMO			MP, UT				
Myotubular Myopathy			UT				
Opitz FG		+	UT				
Oral-Facial-Digital I					+		
Pettigrew				Mi			
PPMX				Ma			

	Anomalies of Genitalia				Anomalies of Urinary System		
Syndrome	**Undifferentiated**	**Hypospadias**	**Minor Anomalies**	**Macroorchidism/ Microorchidism**	**Renal Dysplasia**	**Hydro-nephrosis**	**Renal Agenesis**
Prieto			UT				
Renpenning		+		Mi			Horseshoe kidney
Shashi				Ma			
Simpson-Golabi-Behmel			UT		+	+	
Smith-Fineman-Myers			UT				
Telecanthus-Hypospadias		+	UT, S				
Urban			MP, UT	Ma			
VACTERL-Hydrocephalus			MP	Mi			Horseshoe kidney
Vasquez			MP	Mi			
Wilson-Turner			MP, UT	Mi			
Wittwer		E	UT			+	
XLID-Cleft Lip/Palate				Mi			
XLID-Hypogamma-globulinemia			UT				
XLID-Hypogonadism-Tremor				Mi			
XLID-Hypospadias		+					
XLID-Ichthyosis-Hypogonadism		+	MP, UT	Mi			
XLID-Macrocephaly-Macroorchidism				Ma			
XLID-Microcephaly-Testicular Failure		+	UT	Mi			
XLID-Panhypopituitarism			MP	Mi			
XLID-Precocious Puberty				Ma			
XLID-Psoriasis			UT				
Young-Hughes			MP	Mi			

E=epispadias, S=shawl scrotum or cleft scrotum, MP=microphallus, UT=undescended testes, Mi=small testes, Ma=macroorchidism

Table VI

XLID Syndromes with Skeletal Malformations

Syndrome (gene)	Long bones	Digits	Associated features
Giuffre-Tsukahara	Radioulnar synostosis	Fifth finger clinodactyly	Microcephaly in males and females
Goltz (*PORCN*)	Asymmetry, longitudinal striations of metaphyses	Reduction defects with missing digital rays	Dermal hypoplasia, ectodermal dysplasia, cleft lip/palate, renal anomalies
Lenz Microphthalmia (*BCOR*)	–	Duplicated and/or hypoplastic thumbs, syndactyly, camptodactyly	Microphthalmia and anterior chamber defects, cleft lip/palate, urogenital anomalies
Opitz FG (*MED12*)	–	Broad flat thumbs, rarely duplicated	Macrocephaly, dysplastic corpus callosum, cardiac defects, imperforate anus, constipation, hypotonia
Oral-Facial-Digital (*OFD1*)	–	Asymmetrically shortened fingers, syndactyly	Cleft lip, lingual hamartomas, accessory frenulae, CNS anomalies
Otopalatodigital II (*FLNA*)	Fibular deficiency, bowing of long bones	Short digits, broad thumbs and great toes, variable absence of thumbs, polydactyly and syndactyly	Prominent forehead, hypertelorism, flat midface, downslanting palpebral fissures, small mouth, micrognathia, cleft palate, spondylobrachydactyly, poor calvarial ossification, abnormally formed carpals and tarsals, narrow thorax
VACTERL-Hydrocephaly (*FANCB*)	Radial deficiency	Absent thumbs	Early lethality, hydrocephalus, vertebral, tracheoesphageal, cardiac, renal, and anal anomalies

Table VII

XLID Syndromes with Generalized Skeletal Dysplasias

Syndrome (gene)	Type of Skeletal Dysplasia	Other Skeletal Features	Associated Features
Chassaing-Lacombe Chondrodysplasia (*HDAC6*)	Spondylometaphyseal	Platyspondyly, metaphyseal flaring, 11 ribs, poor mineralization, brachydactyly	Hydrocephaly, microphthalmia, male lethality, females affected
Christian	Spondylobrachydactyly	Prominent metopic ridge, hemivertebrae, scoliosis, sacral hypoplasia, brachydactyly with short middle phalanges	Abducens palsy, downslanting palpebral fissures, glucose intolerance
Otopalatodigital I (*FLNA*)	Spondylobrachydactyly	Short trunk with pectus excavatum, brachydactyly, short and broad thumbs and halluces, abnormal carpals and tarsals	Pugilistic facies, downslanting palpebral fissures, cleft palate, large anterior fontanel with delayed closure
Otopalatodigital II (*FLNA*)	Spondylobrachydactyly (more severe, but similar skeletal findings to those seen in OPD1)	Short trunk with pectus excavatum, brachydactyly, short and broad thumbs and halluces, abnormal carpals and tarsals, bowed long bones, hypoplastic/absent fibulae	Prominent forehead, downslanting palpebral fissures, large anterior fontanel with delayed closure, hypertelorism, small mouth, cleft palate, micrognathia
Roifman	Spondyloepiphyseal	Wavy and irregular vertebral endplates, generalized epiphyseal changes, short tapered digits	Microcephaly, downslanting palpebral fissures, long philtrum, thin upper lip, pigmentary retinopathy, immune deficiency with frequent infections
XLID-SEMD	Spondyloepimetaphyseal	Progressive dysplasia of spine, metaphyses, and epiphyses, chest deformation	Coarse facies, progressive mental deterioration