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Seizures and X-linked intellectual disability

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Abstract

Intellectual disability occurs as an isolated X-linked trait and as a component of recognizable X-linked syndromes in the company of somatic, metabolic, neuromuscular, or behavioral abnormalities. Seizures accompany intellectual disability in almost half of these X-linked disorders. The spectrum of seizures found in the X-linked intellectual disability syndromes is broad, varying in time of onset, type of seizure, and response to anticonvulsant therapy. The majority of the genes associated with XLID and seizures have now been identified.

Keywords

Epilepsy; Seizures; X-chromosome; X-linked; Intellectual disability; Syndrome

1. Introduction

X-linked intellectual disability (XLID) is the most extensively studied genetic phenomenon involving the human central nervous system. Over 150 X-linked syndromes in which intellectual disability and neuromuscular, somatic, metabolic, or behavioral manifestations occur have been described [1]. Most have been mapped to defined regions of the X-chromosome and 102 of the causative genes have been identified. Seizures accompany intellectual disability in almost half of the syndromes caused by mutation of genes on the X-chromosome.

The clinical and electroencephalographic spectrum of seizure types associated with XLID is quite broad, ranging from only fever-induced seizures to recalcitrant hypsarrhythmia-associated seizures. In some XLID entities, seizures are the only manifestation other than intellectual impairment. In others, seizures are but one of a number of neurologic manifestations or other systemic findings.

Although seizures occur in one-fifth of all individuals with severe intellectual disability and one-tenth of those with mild intellectual disability, the seizure prevalence appears to be greater in the XLID syndromes [1,2]. The observation that intellectual disability occurs in the XLID syndromes, whether seizures are present or not, suggests that the seizures do not cause the intellectual disability but rather is a consequence of an underlying disturbance in the structure and/or function of the neuronal network.

2. XLID syndromes in which seizures are a defining manifestation

Six XLID syndromes are known in which seizures are a defining or near constant component of the syndrome. In these syndromes, seizures begin in infancy, often before developmental delay has been noted. The responsible gene has been identified in all six syndromes.

2.1. Christianson syndrome (OMIM 300243)

Mutations in *SLC9A6*, a gene which encodes the sodium/hydrogen exchanger NHE6, causes this distinctive syndrome [3–5]. Affected males have microcephaly (usually acquired), frontal hair upsweep, long narrow face, strabismus, impaired ocular movements, open mouth and prominence of the nose, jaw, and ears. They tend to be thin and short stature is common. Neurological findings include hypotonia, ataxia, involuntary movements, and seizures. Some develop spasticity with hyperreflexia, clonus, and Babinski signs. They fail to develop meaningful speech and have limited ability to ambulate, if at all. Profound intellectual disability is present. In some individuals, flexed elbows, hand gazing and inappropriate laughter or smiling are reminiscent of Angelman syndrome.

Generalized tonic-clonic seizures generally develop within the first two years. Commonly, these are followed by atypical absence, atonic and complex partial seizures. A poor response to anticonvulsant therapy occurs with all types of seizures. Electroencephalography shows slow rhythmic activity of high amplitude, typical of Angelman syndrome in some patients but not in others. Two major findings may be seen on brain imaging and spectroscopy [4,5]. Atrophy or hypoplasia of the cerebellum and hippocampus occurs; progression over time suggests atrophy rather than hypoplasia. Spectroscopy shows increased glutamate/glutamine peaks in the basal ganglia.

Carrier females have normal head circumference and lack neurologic abnormalities, but may have learning problems and lower intellectual function than noncarrier siblings.

2.2. Epilepsy-intellectual disability in females (EIDF, OMIM 300088)

This syndrome, also known as Epilepsy Limited to Females with Intellectual Disability (EFID), is caused by mutations in *PCDH19*, a gene located in Xq22.1 which encodes a protocadherin [6,7]. Although malformations or distinctive craniofacial features do not appear to be a component of this syndrome, individual cases have had cataracts, microcephaly, syndactyly or strabismus, but are perhaps unrelated findings. Neurological manifestations typically begin during infancy (age 4–18 months) with the onset of febrile seizures that are focal or generalized tonic-clonic that cluster over a few days and may be highly refractory to therapy [8–10]. Seizures increase in frequency for a period of time but decrease by age 2–3 years. Coincident with the seizures is neurodevelopmental regression in about two-thirds of the reported cases. Ultimately, the deterioration results in severe cognitive impairment in some individuals, but mild-to-moderate intellectual impairment in others. The more severely impaired children showed stereotyped movements, handwringing, hand flapping, and some loss of fine motor skills reminiscent of an autism spectrum disorder.

Initially normal in early infancy, generalized tonic-clonic and partial clonic or tonic seizures predominate, but myoclonic, tonic, atonic and absence seizures have been described and may even resemble Dravet syndrome in presentation [9,10]. The onset is usually in infancy and may be precipitated by fever. During or following a period of neurodevelopmental and cognitive regression, patients may develop hyperreflexia, aggressive and/or obsessive behaviors, and stereotypic repetitive activities. A cohort of 14 cases showed frequent EEG

abnormalities interictally in no typical diagnostic pattern. Brain MRI and CT scans were normal in the same cohort.

Only carrier females have epilepsy and neuroregression. Later psychiatric disorders are prominent and in addition to autism spectrum disorders include obsessive-compulsion, aggression, schizophrenia, hysteria, depression, panic attacks, and self-injury. Males who carry the gene do not experience seizures or neuroregression and appear normally fertile. This sparing of males in an apparently X-linked dominant disorder is unique and is as yet not explained [11]. Girls with normal development or those with intellectual disability who present with clusters of brief febrile seizures in infancy should be considered for *PCDH19* testing [10].

2.3. Rett-like seizures-hypotonia (OMIM 300672)

XLID with early onset of multiple types of refractory seizures, hypotonia and neurodevelopmental regression predominantly in females are the hallmarks of the Rett-Like Seizures-Hypotonia syndrome [12–14]. The face appears hypotonic with tented upper lip and open mouth. Microcephaly, usually postnatally acquired, is present in half of patients. Developmental progress may appear normal prior to the onset of seizures, but thereafter usually regresses or stagnates.

Seizures usually begin in the first few months of life. Infantile spasms are typical, but generalized tonic-clonic, myoclonic, absence, and focal seizures also occur. The majority of girls have a neuroregression pattern similar to Rett syndrome, but others are atypical in that they retain speech and purposeful hand movements and may not exhibit stereotypic movements or respiratory irregularity. Muscle tone is typically decreased, especially in the early years, but may increase with age eventually resulting in spasticity. In most cases, brain imaging is normal except for small brain size. Rett-Like Seizures-Hypotonia is caused by mutations in the serine-threonine kinase gene, *CDKL5*, located in Xp22.13 [12,15,16].

2.4. XLID-infantile spasms (OMIM 308350)

This XLID syndrome, also known as West Syndrome, is allelic to several other XLID disorders [17]. Seizures in the form of infantile spasms with onset between three and eight months of age are typical. Prior to the onset of seizures, affected males usually appear normal and experience normal growth and development. Typically, infantile spasms follow a brief period of atonia and consist of clusters of flexion or extension movements of the limbs, neck and trunk. Developmental milestones slow or regress after the onset of seizures and early childhood death is not uncommon. Survivors show severe cognitive impairment.

A hypsarrhythmia pattern – multifocal spikes and high voltage slow waves throughout the cortex – is usually found on electroencephalography. Seizures respond poorly to conventional anti-epileptic drugs, but may respond to ACTH, glucocorticoids and vigabatrin therapy [18]. Cranial imaging is usually normal, except for mild dilation of the cerebral ventricles.

Ten overlapping phenotypes, linked by having intellectual disability in common, are caused by mutations in human ortholog of the aristaless gene, *ARX*, located at Xp21.3 [17,19,20]. These phenotypes include a seizure subgroup (XLID-Infantile Spasms or West Syndrome, X-Linked Myoclonic Epilepsy, Infantile Epilepsy-Dyskinesia, Ohtahara Syndrome or Early Infantile Epileptic Encephalopathy), a brain malformation subgroup (Proud Syndrome or Agenesis of the Corpus Callosum with Abnormal Genitalia, X-Linked Lissencephaly with Abnormal Genitalia and Hydranencephaly with Abnormal Genitalia), a dystonia subgroup (Partington Syndrome and Tonic Seizures with Dystonia), and nonsyndromal XLID. Among these disorders, the nonsyndromal XLID presentation is most common accounting for over

one-third of cases. Next in order of frequency are X-linked lissencephaly with abnormal genitalia, XLID-Infantile Spasms and Partington syndrome. Seizures occur less commonly in Partington syndrome and nonsyndromal XLID than in the other *ARX*-associated phenotypes.

2.5. XLID-Epilepsy (OMIM 300423)

ATP6AP2, a gene in Xp11.4 that encodes the renin receptor, is responsible for XLID with Infancy-Onset Epilepsy [21,22]. Seizures and neurodevelopmental delay dominate the clinical presentation. Growth, including head circumference, and craniofacial features are usually normal. Malformations do not occur. Motor and speech development are moderately delayed, but neuroregression does not occur. Seizures are the first evidence of abnormalities, begin between four and 14 months of age, and are primarily generalized tonic-clonic, brief atonic and myoclonic seizures without status epilepticus or infantile spasms. Scoliosis, ataxia and hyporeflexia occur in a minority. Neurological signs may also include clumsiness and muscle rigidity. Brain MRIs are normal. The EEG shows generalized polyspike and waves discharges before seizures.

2.6. XLID-Rolandic Seizures (OMIM 300643)

The presentation in XLID-Rolandic Seizures is neurodevelopmental and neurologic in nature. Speech and language development is primarily affected with males and females showing overall speech delay, oro-facial dyspraxia, impaired comprehension, and inattention. Cognitive function is low average to variably impaired generally in the mild-to-moderate range. The seizures originate adjacent to the rolandic or sylvian fissures and are characterized electroencephalographically by clusters of centro-temporal spikes that are usually activated during sleep.

Typically nocturnal, the seizure wakes the child and causes paresthesias and/or twitching of mouth/face and pharynx resulting in drooling and speech arrest. Consciousness is preserved and the seizures last one to 2 min. In the under five year old age group, the nocturnal seizures frequently generalize into tonic-clonic seizures. Females appear to be affected with equal severity as males. Mutations in the gene, *SRPX2*, which is located at Xq22.1 and encodes a sushi-repeat containing protein expressed in neurons of the human adult brain including the rolandic area, are responsible for XLID-Rolandic Seizures [23].

2.7. Other XLID syndromes with seizures

In addition to these six prototypic XLID-seizure disorders, seizures occur as a frequent, but not defining, feature of a large number of other XLID syndromes (Tables 1–4). The better known of these disorders are Rett and Börjeson-Forssman-Lehmann syndromes. In Rett syndrome, well over half of patients have seizures. With the notable exception of infantile spasms and petit mal, a wide variety of other seizure types have been reported. Other findings of Rett syndrome – regression or loss of purposeful hand movements – generally precede the onset of seizures. Although seizures were described as a component feature in the original family with Börjeson-Forssman-Lehmann syndrome, more recent reports note seizures to be an uncommon finding [24–26]. When present, the seizures are generalized and can be well controlled. Seizures occur in less than half of individuals of other well known XLID disorders: Allan-Herndon-Dudley, Coffin-Lowry, Fragile X, Incontinentia Pigmenti, Lesch-Nyhan, Opitz FG, Oral-Facial-Digital I, Pelizaeus-Merzbacher, Renpenning, and Simpson-Golabi-Behmel syndromes. The responsible gene in each of these disorders has been identified (Table 1).

3. Seizures and XLID associated with brain anomalies

Aicardi syndrome and the *ARX*-associated XLID syndromes are considered the prototypes for seizures and XLID associated with structural brain anomalies. Other XLID syndromes with seizures and structural anomalies of the brain are shown in Table 2. Brain abnormalities associated with XLID syndromes are under-ascertained because of the reluctance to use anesthesia which is often required in these patients.

3.1. Aicardi syndrome (OMIM 304050)

As a rule, Aicardi syndrome occurs sporadically and almost exclusively in females. The tetrad of dysgenesis of the corpus callosum, lacunar chorioretinopathy, costovertebral anomalies and seizures is typical. After birth, cephalic growth slows and may result in acquired microcephaly and neurodevelopment is severely globally delayed. A wide variety of seizures occur, although infantile spasms with the EEG findings of burst-suppression pattern of hypsarrhythmia are common, other seizure types and asymmetry between the cerebral hemispheres can occur. In addition to dysgenesis of the corpus callosum, other structural brain abnormalities include asymmetry of the cerebral hemispheres, cerebellar hypoplasia, neural migration disturbances (heterotopia, poly-microgyria), enlarged lateral ventricles, and cysts of the posterior fossa and choroid plexus.

3.2. *ARX*-associated XLID (OMIM 309510)

As noted above, the *ARX*-Associated XLID syndromes include ten overlapping phenotypes: a seizure subgroup (four phenotypes), a brain malformation subgroup (three phenotypes), a dystonia subgroup (two phenotypes), and nonsyndromal XLID. The three subtypes with structural anomalies of the brain include Agenesis of the Corpus Callosum with Abnormal Genitalia (Proud syndrome), X-Linked Lissencephaly with Abnormal Genitalia and Hydranencephaly with Abnormal Genitalia. Each of these subtypes has seizures, generally of intractable nature, often with onset soon after birth.

3.3. Periventricular nodular heterotopia (OMIM 300049)

Periventricular nodular heterotopia (PVNH) is an X-linked dominant condition caused by mutations in the filamin-A (*FLNA*) gene [27]. The vast majority of patients are females who present with partial or secondary generalized seizures, but rarely have intellectual disability. Affected males usually die in utero. However, there are rare cases where males with hemizygous *FLNA* mutations have survived [28,29]. Depending on the location of the mutation within the genes (conserved or nonconserved residue) the severity of the seizures and intellectual impairment can be quite variable.

4. Seizures resulting from X-linked metabolic disturbances

Most patients with Menkes Syndrome, Creatine Transporter Deficiency, Phosphoglycerate Kinase Deficiency, Pyruvate Dehydrogenase Deficiency and Ornithine Transcarbamoylase Deficiency have seizures as a usual manifestation (Table 3). Generalized and myoclonic seizures occur in Menkes Syndrome, often in association with hypothermia and hypoglycemia. This fatal disorder of copper transport due to mutations in *ATP7A*, is characterized by growth impairment, abnormality of the hair (pili torti), widespread skeletal changes, arterial tortuosity, progressive cerebral deterioration and childhood death. Creatine Transporter Deficiency also appears to be a progressive disorder [30]. It is due to mutations in *SLC6A8* in Xq28. It appears to cause more severe impairment of speech and language than of motor skills. Seizures occur in about half of patients, are usually of generalized type, and are readily controlled with anticonvulsants. Phosphoglycerate Kinase Deficiency interferes with glycolysis in muscle resulting in weakness, depressed deep tendon reflexes,

myoglobinemia, developmental delay and seizures, usually of the generalized type [31]. Pyruvate Dehydrogenase Deficiency produces lactic acidosis which may be fatal in infancy or present as a more chronic neurologic disease with hypotonia, lethargy, seizures, and intellectual disability [32]. Ornithine Transcarbamoylase Deficiency leads to chronic or intermittent hyperammonemia that in turn may result in changes in sensorium, slurred speech, ataxia, hemiparesis, seizures, and coma. Survivors have intellectual disability and cerebral palsy [33,34]. Lesch-Nyhan Syndrome, XLID-Thyroxine Binding Globulin Deficiency, and other X-linked metabolic disorders listed in Table 3 have seizures less commonly.

5. XLID syndromes with somatic manifestations and seizures

Abnormalities in every anatomical system have been described in one or more of the XLID syndromes. In some cases, these somatic manifestations collectively comprise a recognizable pattern that may be diagnostic. Although seizures may occur in many of these syndromes, seldom does the presence or absence of seizures add substantively to the diagnostic search.

Table 4 gives selected XLID syndromes with somatic manifestations and note whether seizures may be anticipated in these syndromes.

6. Seizures and nonsyndromal XLID

Table 5 lists the six XLID genes associated with nonsyndromal XLID and seizures. Two of these genes are also associated with syndromal XLID. As already mentioned, *ARX* is responsible for EIEE1 and is the gene most closely associated with seizures in males with nonsyndromal XLID [35]. Patients with a mutation in *OPHN1* can present with epilepsy or seizures without much of a phenotype and thus, without brain imaging, would appear to be nonsyndromal [36,37]. The other four genes in Table 5 are only associated with nonsyndromal XLID. *KD5MC* (*JARID1C*) mutations are responsible for perhaps 1% of nonsyndromal XLID, but only 50% of families with mutation exhibit seizures [38]. Relative to *HUWE1*, seizures are observed in some patients with a duplication of this gene [39]. Although mutations in *AGTR2* are not common, 50% patients are reported to have seizures [40]. With respect to *IQSEC2*, although seizures have been noted in patients with mutations, it is a rare occurrence [41].

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XLID syndromes associated with seizures.

Table 1

Common	Less than 50% of patients
Alcardi [304050]	Allan-Hemdon-Dudley [300253, <i>SLC16A2</i>]
Armfield [300261]	Atkin-Flaitz [300431]
Arts [301835, <i>PRPS1</i>]	ATRX-Associated XLID [301040, 309580, <i>ATRX</i>]
ARX-Associated XLID [309510, <i>ARX</i>]	Coffin-Lowry [303600, <i>RPS6KA3</i>]
Börjeson-Forsssman-Lehmann [301900, <i>PHF6</i>]	Cornelia de Lange, X-linked [300580, <i>SMC1L1</i>]
Cantu [308830]	Fragile X [309550, <i>FMR1</i>]
Cerebro-Cerebello-Coloboma	Hyde-Forster [300064]
Christianson [300243, <i>SLC9A6</i>]	Hydrocephaly-MASA Spectrum [303350, 304100, 307000, <i>L1CAM</i>]
CK [<i>NSDHL</i>]	Incontinentia pigmenti [308310, <i>IKBK1</i>]
Creatine Transporter Deficiency [300352, <i>SLC6A8</i>]	Lesch-Nyhan [300322, <i>HPR1</i>]
Epilepsy-Intellectual Disability in Females [300088, <i>PCDH19</i>]	Lujan [309520, <i>MED12</i>]
<i>FLNA</i> -Associated XLID [300077, <i>FLNA</i>]	MIDAS [309801, <i>HCCS</i>]
Gustavson [309555]	Opitz FG [305450, <i>MED12</i>]
Homfray Seizures-Contractures	Oral-Facial-Digital I [311200, <i>OFD1</i>]
Hydrocephaly-Cerebellar Agenesis [307010]	Pelizaeus-Merzbacher [312080, <i>PLP1</i>]
Juberg-Marsidi-Brooks [300612, <i>HUWE1</i>]	Prieto [309610]
Lissencephaly and Abnormal Genitalia [300215, <i>ARX</i>]	Renpenning [309500, <i>PQBPI</i>]
Lissencephaly, X-Linked [300067, <i>DCX</i>]	Simpson-Golabi-Behmel [312870, <i>GPC3</i>]
MEHMO [300148, <i>EIF2S3</i>]	Snyder-Robinson [309583, <i>SM5</i>]
Menkes [309400, <i>ATP7A</i>]	Vasquez
<i>OPHN1</i> -Associated XLID [300486, <i>OPHN1</i>]	Waisman-Laxova [311510]
Ornithine Transcarbamoylase Deficiency [311250, <i>OTC</i>]	XLID-Ataxia-Apraxia
Paine [311400]	XLID-Nystagmus-Seizures [300740, <i>CASK</i>]
Pallister W [311450]	XLID-Retinitis Pigmentosa
Pettigrew [304340]	XLID-Thyroxine Binding Globulin Deficiency [314200]
Phosphoglycerokinase Deficiency [311800, <i>PGK1</i>]	
PPM-X [300055, <i>MECP2</i>]	
Pyruvate Dehydrogenase Deficiency [312170, <i>PDHA1</i>]	
Rett [312750, <i>MECP2</i>]	

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Common	Less than 50% of patients
Rett-like Seizures-Hypotonia [300672, <i>CDKL5</i>]	
Say-Meyer [314320]	
Shashi [300238]	
Smith-Fineman-Myers	
Wittwer [300421]	
XLID-Ataxia-Deafness-Dementia [301790]	
XLID-Blindness-Seizures-Spasticity	
XLID-Epilepsy [300423, <i>ATP6AP2</i>]	
XLID-Hypogonadism-Tremors [300354, <i>CUL4B</i>]	
XLID-Hypotonia-Recurrent Infections [300260, dup <i>MECP2</i>]	
XLID-Infantile Spasms [308350, <i>ARX</i>]	
XLID-Nail Dystrophy-Seizures [312180, <i>UBE2A</i>]	
XLID-Psoriasis [309480]	
XLID-Rolandic Seizures [300643, <i>SRPX2</i>]	
Young-Hughes	

Table 2

XLID syndromes with seizures and structural brain anomalies.

Syndrome	OMIM	Gene	Brain anomalies
Aicardi ^a	304050	–	ACC
<i>ARX</i> -Associated ^a	309510	<i>ARX</i>	ACC, lissencephaly, hydranencephaly
Cerebro-Cerebello-Coloboma	–	–	ACC, hydrocephaly, heterotopias, cysts, cerebellar hypoplasia
Cerebro-Oculo-Genital ^b	–	–	ACC
Christianson ^a	300243	<i>SLC9A6</i>	Cerebellar and brain stem atrophy
<i>FLNA</i> -Associated ^a	307077	<i>FLNA</i>	Lissencephaly, heterotopias
Hydrocephaly-Cerebellar Agenesis ^a	307010	–	Cerebellar agenesis, hydrocephaly
Hydrocephaly-MASA Spectrum, X-Linked ^b	303350, 304100, 307000	<i>L1CAM</i>	Hydrocephaly, ACC
Lissencephaly, X-Linked ^a	300067	<i>DCX</i>	Lissencephaly
Lujan ^b	309520	<i>MED12</i>	ACC
MIDAS ^b	309801	<i>HCCS</i>	ACC, enlarged ventricles, cysts of cerebrum
<i>OPHN1</i> -Associated ^a		<i>OPHN1</i>	Cerebellar hypoplasia
Opitz FG ^b	305450	<i>MED12</i>	ACC
Oral-Facial-Digital 1 ^b	311200	<i>OFD1</i>	ACC, heterotopias, cysts, porencephaly, hydrocephaly, cerebellar hypoplasia
Pettigrew ^a	304340	–	Dandy-Walker, hydrocephaly
XLID-Hydrocephaly-Basal Ganglia Calcification ^b	300630	<i>AP1S2</i>	Hydrocephaly
XLID-Nystagmus-Seizures ^b	300749	<i>CASK</i>	ACC, cerebellar and midbrain hypoplasia, pachygyria

ACC - Agenesis or dysgenesis of corpus callosum.

Certain other syndromes (e.g. VACTERL-Hydrocephaly) die early which may preclude assessment of propensity for seizures.

^aSeizures commonly associated.^bSeizures in less than half of patients.

Table 3

XLID syndromes associated with metabolic disturbances.

Allan-Herndon-Dudley ^b
Creatine transporter deficiency ^a
Glycerol kinase deficiency ^c
Lesch-Nyhan ^b
Menkes ^a
Mucopolysaccharidosis II (Hunter) ^c
Ornithine transcarbamylase deficiency ^a
Phosphoglycerate kinase deficiency ^a
Pyruvate dehydrogenase deficiency ^a
Snyder-Robinson (spermine synthase deficiency) ^b
XLID-thyroxine binding globulin deficiency ^a

^aDisorders commonly with associated seizures.

^bDisorders with seizures in less than half of patients.

^cSeizures not associated or rarely so.

Table 4

Selected XLID syndromes with somatic manifestations and seizures.

Ocular	Facial Cleft	Urogenital	Limb
Anophthalmia/microphthalmia			
Aicardi [304050] ^a	Aicardi (CL/P) [304050] ^a	Aarskog [305400, <i>FGD1</i>] ^c	Goltz [305600, <i>PORCN</i>] ^c
Cerebro-oculo-genital ^a	Armfield (P) [300261] ^a	Abidi [300262] ^c	Hydrocephaly-MASA spectrum, X-linked [303350, 304100, 307000, <i>LICAM</i>] ^b
Chassaign chondrodysplasia ^c	ATRX-Associated XLID (P) [301040, 309580, <i>ATRX</i>] ^b	Armfield [300261] ^a	Lenz microphthalmia [309800] ^c
Goltz [305600, <i>PORCN</i>] ^c	Comelia de Lange, X-linked (P) [300590, <i>SMC1L1</i>] ^b	ARX-Associated XLID [309510, <i>ARX</i>] ^a	VACTERL-hydrocephaly [314390, <i>FANCB</i>] ^d
Incontinentia pigmenti [308310, <i>IKBKG</i>] ^b	Craniofaciockeletal (P) [300712] ^c	Atkin-Flaitz [300431] ^b	
Lenz [309800] ^c	FLNA-Associated XLID (P) [300077, <i>FLNA</i>] ^a	ATRX-Associated XLID [301040, 309580, <i>ATRX</i>] ^b	Cutaneous
MIDAS [309801, <i>HCCS</i>] ^b	Goltz (CL/P) [305600, <i>PORCN</i>] ^c	Borjeson-Forsman-Lehmann [301900, <i>PHF6</i>] ^a	Cantu [308830] ^a
Nance-Horan [302350, <i>NHS</i>] ^c	Hall Orofacial (P) ^d	Branchial Arch syndrome, X-linked [301950] ^c	Dyskeratosis congenita [305000, <i>DKC1</i>] ^c
Colobomas/retinal lacunae	Lenz (CL/P) [309800] ^c		Fitzsimmons [309560] ^c
Aicardi [304050] ^a	Oral-facial-digital I (P) [311200, <i>OFD1</i>] ^b		Goltz [305600, <i>PORCN</i>] ^c
Cerebro-cerebello-coloboma ^a	Pallister W (CL/P) [311450] ^a		Hereditary bullous dystrophy, X-linked [302000] ^c
Goltz [305600, <i>PORCN</i>] ^c	Renpenning (P) [309500, <i>PQBP1</i>] ^b		Incontinentia pigmenti [308310, <i>IKBKG</i>] ^b
Graham anophthalmia [301590] ^c	Simpson-Golabi-Behmel (P) [312870, <i>GPC3</i>] ^b		MIDAS [309801, <i>HCCS</i>] ^b
Graham coloboma [300472, <i>IGBP1</i>] ^c	Telecanthus-hypospadias (CL/P) [300000, <i>MID1</i>] ^c		Oral-facial-digital I [311200, <i>OFD1</i>] ^b
Lenz [309800] ^c	VACTERL-hydrocephalus (P) [314390, <i>FANCB</i>] ^d		XLID-nail dystrophy-seizures [312180, <i>UBE2A</i>] ^a
MIDAS [309801, <i>HCCS</i>] ^b	CL-cleft lip; P-palate		Young-Hughes ^a
Renpenning [309500, <i>PQBP1</i>] ^b			
Wittwer [300421] ^a			
Cardiac			
	ATRX-Associated XLID [301040, 309580, <i>ATRX</i>] ^b		
	Bergia cardiomyopathy (CM) ^c		
	Craniofaciockeletal (in males) [300712] ^d		
	Duchenne muscular dystrophy (CM) [310200, <i>DMD</i>] ^c		
	Hereditary bullous dystrophy, X-linked [302000] ^c		
	Lenz microphthalmia [309800] ^c		
	Lujan [309520, <i>MED12</i>] ^b		
	MIDAS [309801, <i>HCCS</i>] ^b		
	Myotubular myopathy (CM)		
	Aarskog [305400, <i>FGD1</i>] ^c		
	Abidi [300262] ^c		
	Armfield [300261] ^a		
	ARX-Associated XLID [309510, <i>ARX</i>] ^a		
	Atkin-Flaitz [300431] ^b		
	ATRX-Associated XLID [301040, 309580, <i>ATRX</i>] ^b		
	Borjeson-Forsman-Lehmann [301900, <i>PHF6</i>] ^a		
	Branchial Arch syndrome, X-linked [301950] ^c		
	Cerebro-oculo-genital ^a		
	Clark-Baraitser [300602]		
	Dyskeratosis congenita [305000, <i>DKC1</i>] ^c		
	Fragile X [309550, <i>FMR1</i>] ^b		
	Goltz [305600, <i>PORCN</i>] ^c		
	Hall Orofacial ^d		
	Hereditary bullous dystrophy, X-linked [302000] ^c		
	Lenz microphthalmia [309800] ^c		
	Lissencephaly and abnormal genitalia [300215, <i>ARX</i>] ^a		
	Lujan [309520, <i>MED12</i>] ^b		
	MEHMO [300148, <i>EIF2S3</i>] ^a		
	Myotubular myopathy [310400, <i>MTM1</i>] ^a		
	Oral-facial-digital I [311200, <i>OFD1</i>] ^b		
	PPM-X [300055, <i>MECP2</i>] ^a		
	Prieto [309610] ^c		
	Renpenning [309500, <i>PQBP1</i>] ^b		
	Shashi [300238] ^a		
	Simpson-Golabi-Behmel [312870, <i>GPC3</i>] ^b		
	Telecanthus-hypospadias [300000, <i>MID1</i>] ^c		
	Urbard		

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Ocular	Facial Cleft	Urogenital	Limb
	[310400, <i>MTM1</i>] ^c Opitz FG [305450, <i>MED12</i>] ^b Renpenning [309500, <i>PQBP1</i>] ^b Simpson-Golabi-Behmel [312870, <i>GPC3</i>] ^b Telecanthus-hypospadias [300000, <i>MID1</i>] ^c CM – cardiomyopathy	VACTERL-hydrocephalus [314390, <i>FANCB</i>] ^d Wilson-Turner [309585] ^c Wittwer [300421] ^a XLID-hypogonadism-tremor [300354, <i>CUL4B</i>] ^a XLID-hypospadias XLID-macrocephaly-macroorchidism [309530] ^c XLID-microcephaly-testicular failure ^d XLID-nail dystrophy-seizures ^a XLID-precocious puberty ^d	

^aDisorders commonly associated with seizures

^bDisorders with seizures in less than half of patients

^cSeizures not associated or rarely so

^dSeizure propensity not known

Table 5

Genes associated with seizures in nonsyndromal XLID.

<i>AGTR</i> ^b
<i>ARX</i> ^a
<i>HUWE1</i> (dup) ^b
<i>IQSEC2</i> ^c
<i>KD5MC</i> ^b
<i>OPHN1</i> ^b

^aDisorders commonly associated with seizures.^bSeizures sometimes associated.^cSeizures are present in a small percentage of patients.