X-Linked Intellectual Disability (revised February 2021)

Information posted on these pages are intended to complement and update the *Atlas of X-Linked Intellectual Disability Syndromes,* Edition 2, by Stevenson, Schwartz, and Rogers (Oxford University Press, 2012) and the XLID Update 2017 (Neri et al. Am J Med Genet 176A:1375, 2018)

New X-linked intellectual disability syndromes, new gene localizations, revised gene localizations, and gene identifications are presented in abbreviated form with appropriate references. Three graphics show syndromal XLID genes, IDX genes, and linkage limits. A table gives gene identifications in chronological order.

I. New Syndromes and Localizations (2017 – Present)

- Linear skin defects. Indrieri et al. (AJHG 91:942, 2012) discovered *COX7B* (Xq21.1) alterations in 2 girls with linear skin defects, intellectual disability, microcephaly and facial dysmorphisms. One girl, an isolated case, also had cardiac, renal, and diaphragmatic anomalies and short stature. In the second case with a nonsense alteration, the mother carried the gene alteration and the linear skin defect but no cognitive impairment. In a separate family, a girl with a frameshift change in *COX7B* had linear skin defects, microcephaly, and short stature but normal developmental milestones.
- UDP-Galactose Transporter Deficiency. Three females, ages 8-12 years, with early onset epileptic encephalopathy, facial dysmorphism, absent speech, and variable MRI findings were found to have alterations in *SLC35A2* by Kodera et al. (Hum Mutat 34:1708, 2013). This condition with a gene locus at Xp11.23 has been overlooked in previous XLID updates. Three other patients (1 female, 2 males) with *SLC35A2* alterations were reported by Ng et al. (AJHG 92:632, 2013). All three had developmental delay, ocular abnormalities, brain malformations, and hypotonia. Two had infantile spasms, two had microcephaly and dysmorphic facies, and two had shortened limbs. Improvement in clinical and biochemical abnormalities were reported with galactose supplements by Verheijen et al. (Genet Med 22:268, 2020).
- Ataxia-seizures-hearing loss. Jazayeri et al. (Arch Iranian Med 18:670, 2015) reported 2 males with severe ID, seizures, gait disturbance and sensorineural hearing loss in a consanguineous family who carried a one base deletion in *RIPPLY1* (Xq22.3) leading to a frameshift change.

- XLID-spasticity. Hu et al. (Mol Psychiat 21:133, 2016) found a 2 bp deletion in *CDK16* (Xp11.3) in 4 males with ID and spastic diplegia in a single kindred.
- XLID-Faciogenital. Vaidyanathan et al. (J Biol Chem 292:8948, 2017) reported a missense variant in *OGT* (Xq13) in three males in a family with genital anomalies (hypospadias, small testes), fifth finger clinodactyly and variable craniofacial features (microcephaly, frontal upsweep, synophrys, open mouth).
- Isoleucine Degradation Defect – HSD10 Deficiency. Su et al. (Metab Brain Dis 32:2063, 2017) reported two boys with missense mutations in *HSD17B10* (Xp11.21). After 8 month and 24 month periods of normal development, they developed seizures and were found to have elevated lactate and lactate/pyruvate ratios and other markers of disturbed isoleucine degradation. The gene encodes a mitochondrial enzyme with multiple metabolic functions. Additional patients have been reported by Zschocke (J Inherit Metab Dis 35:81, 2012, Ensenauer (Ann Neurol 51:656, 2002), Perez-Cerda et al. (Pediatr Res 58:488, 2015) and others.
- GABRA3-related seizures. Niturad et al. (Brain 140:2879, 2017) identified 7 families in which alterations in *GABRA3* (Xq28) were present. In family 1 from a cohort of 15 families with epilepsy, 2 males had a variety of pharmacoresistant seizures and severe ID and 2 females with less severe seizures and learning problems. In family 2 from the 480 families in the EURO-MRX consortium, three of four males with a missense variant in *GABRA3* had intellectual disabilities of variable degree, two had seizures and one was asymptomatic. Female carriers had absence seizures. In family 3 from a cohort of patients with seizures (198), ID (299) or both (103), a microduplication encompassing exons 1-3 of *GABRA3*, was found in one male with epilepsy and borderline intellectual function. A single female from family 4 and family 5 with seizures and mild-moderate ID were found to have de novo missense variants in *GABRA3* in a diagnostic sequencing effort. A variant of uncertain significance was found in one of 2 brothers in family 6 with autism and severe ID but no seizures. In family 7 from a cohort of 238 families with generalized genetic epilepsy, a missense variant was found in a female and her unaffected mother. Her sister and father who also had epilepsy did not carry the *GABRA3* variant.
- Galloway-Mowat syndrome 2. Braun et al. (Nat Genet 49:1529, 2017) reported alterations in *LAGE3* (Xq28) in 4 males from 3 kindreds with delayed development, microcephaly, gyral brain anomalies, minor facial dysmorphism, renal disease, and early childhood lethality. Carrier mothers were not affected and showed skewed X-inactivation.
- Osteopathia striata congenita with cranial sclerosis. Females with osteopathia striata may have mild learning disabilities in addition to macrocephaly, cleft palate, hearing loss, and sclerosis of the long bones and calvaria. The condition is generally lethal in males during the fetal or neonatal periods. More significant developmental delay has been noted among surviving males (Hague et al. AJMG 173A:1931, 2017; Holman et al. AJMG 155A:2397, 2011; Joseph et al. J Clin Endc Med 95:1506, 2016; Lazar et al. J Bone Mineral Res 14:152, 1999). The associated gene is *AMER1* located in Xq11.2; surviving males typically have mosaicism for the gene alteration.

- XLID-Craniofacioskeletal Syndrome. Ten males from eight families with Marfanoid habitus, dysmorphic facies, hypotonia, and developmental delay/intellectual disability were found to have missense variants in *NKAP*, a gene in Xq24 that is involved in transcriptional regulation (AJHG 105:987, 2019).
- XLID-autism-dysmorphic features. Shukla et al. (ASMG 179A:870, 2019) reported missense variants in the *BCORL1* gene (Xq26.1) in 5 males from 3 families with autism spectrum disorder, variable ID (1 mild, 3 severe), seizures (3), hypotonia (2), and variable craniofacial findings (macrocephaly in 2, tall forehead in 4, hypertelorism in 3, downslanting palpebral fissures in 2, and dysmorphic ears in 3).
- Keipert syndrome. Amor et al. (AJHG 104:914, 2019) found a *GPC4* variant (Xq26.1) in the original kindred with Keipert syndrome (craniofacial and digital anomalies, sensorineural hearing loss and variable learning disability) and three additional kindreds. The craniofacial features were macrocephaly, prominent forehead, midface flattening, hypertelorism, broad nose, downturned corners of the mouth, prominent lips and simple or low set ears. Brachydactyly, clinodactyly, broad thumbs and broad halluces were present in over half of the cases described. Intellectual disability or borderline cognitive function was present in 8 of the ten cases.
- XLID-mitochondrial myopathy. Benincá et al. (J Med Genet 2020) reported a missense variant in *APOO* (Xp22.1) in 3 females and 5 males in three generations of kindred with muscle weakness, neurologic signs and elevated blood lactate. The most severely affected was a male with hypotonia, dysautonomia, recurrent infections, cognitive impairment and autistic behavior.
- XLID-Trigonocephaly. Seven males with intellectual disability in five different Japanese families were reported to have a missense alteration in *PJA1* in Xq13.1 (Ann Clin Transl Neurology 7:1117, 2020). Six had autistic manifestations and five had trigonocephaly. In one family, the maternal grandfather, who did not have developmental abnormalities, also carried the missense change (p.R376C), calling into question the pathogenicity of the variant.
- XLID-hydrocephaly plus. Tripolszki (Clin Genet 99:303, 2021) described a family with 13 affected males in 3 generations with IUGR, hydrocephaly, hypotonia, short stature, visual impairment, cardiac defects, hypospadias and severe developmental delay. Most affected males died in infancy of sepsis. Female carriers were asymptomatic. The syndrome is caused by a missense alteration in *OTUD5* (Xp11.23). The gene has a deubiquitination function. Two prior males with de novo missense alterations reported by Beck et al. (bioRXIV 2020) had a similar phenotype with early lethality but did not have hydrocephaly.

II. New Gene Identifications (2017 – Present)

- *AMER1*. Alterations in *AMER1* (Xq11.2) cause osteopathia striata with cranial sclerosis, an X-linked dominant skeletal dysplasia. Although most cases reported are female, the males identified tend to be more severely affected with macrocephaly and craniofacial malformations including clefting and, in some cases, developmental delay or intellectual disability (Clin Genet 83:251, 2013).

- *APOO*. A variable phenotype with muscle weakness, neurological signs and increased blood lactate was expressed in three females and five males in three generations having a missense variant in *APOO* (Benincá et al. J Med Genet 2020, online ahead of print). The most severely affected included a male who also had hypotonia, dysautonomia, recurrent infections, cognitive impairment and autistic behavior. The gene, located in Xp22.11, may be involved in the maintenance and assembly of the inner mitochondrial membrane.
- *BCORL1*. Two brothers with severe intellectual disability, coarse facies and hypotonia were reported in association with a missense mutation in *BCORL1* (J Med Genet 50:802, 2013). The gene, located in Xq25-q26.1, functions as a transcriptional corepressor. Five additional males in three families were reported by Shukla et al. (AJMG 179A:820, 2019).
- *CDK16*. The gene, located in Xp11.3 encodes a protein kinase which acts as cell cycle regulator. In a study based on massive parallel sequencing of all X chromosome exons of 405 families with unresolved XLID, a dinucleotide deletion causing a premature stop codon was found in one family with four affected male cousins (Hu et al. Mol Psychiatry 21:133-148, 2016).
- *COX7B.* The protein encoded by this gene, located in Xq21.1, is a subunit of the cytochrome oxidase complex. Mutations in the gene have been found in females with MIDAS syndrome (Indrieri A et al. Am J Hum Genet 91:942-9, 2012).
- *CSTF2*. Four males from a single kindred with mild intellectual disability primarily affecting communication skills have been associated with a missense variant in *CSTF2* (Nucleic Acids Res 48:9804, 2020). The gene, in Xq22.1, encodes an RNA binding protein that is involved in mRNA cleavage and polyadenylation.
- *CXorf56*. A single large family with mild nonsyndromal XLID (IDX107) and behavioral problems has been reported with a 2 base pair deletion of *CXorf56*. Verkerk et al. (Eur J Hum Genet 36:552, 2018) reported this candidate XLID gene. The causative role of alterations in CXorf56 was confirmed in two families by Rocha et al. (EJHG 28:367, 2020).
- *FAM50A.* The family reported by Armfield et al. (AJMG 85:236, 1995) has been found to have a missense variant in *FAM50A* (Lee et al. Nat Comm 11:3698, 2020). The gene locates to Xq28 and the protein is a member of the spliceosome complex. Four other unrelated males were presented.
- *GABRA3*. The gene, located in Xq28, encodes the GABA receptor A3. Five missense variants and one microduplication were detected in four families and two sporadic cases presenting with a range of epileptic seizure types, a varying degree of intellectual disability and developmental delay, sometimes with dysmorphic features or nystagmus. Overall, males were more severely affected and there were three asymptomatic female mutation carriers compared to only one male without a clinical phenotype. (Niturad et al. Brain 140:2879-2894, 2017).
- *GPC4.* Located in Xq26.2, the protein of *Glypican-4* is a heparan sulfate proteoglycan located on the cell surface. Amor et al. (Am J Hum Genet 104:914; 2019) described a truncating mutation in *GPC4* that was associated with Keipert syndrome (OMIM

#301026) in an Australian family. In follow-up studies, they identified additional truncating mutations in seven males in five families.

- *GPKOW*. Carroll et al. (EJHG 25:1078, 2017) reported 5 males in a single family with a male lethal syndrome with IUGR and microcephaly. Only one male was available and showed a splice site variant in *GPKOW*.
- *GRASP1.* Mutations in *GRASP1* which encodes a neuron-specific endosomal protein have been reported in two families (Chiu et al. Neuron 93:1405, 2017). Two males in the first family had severe ID, short stature and spastic paraplegia. The gene is located at Xp11.23.
- *HMGB3*. One male in a family with microphthalmia type 13 was found to have a truncating sequence variant (2 bp insertion) in *HMGB3*, located in Xq28 (Scott et al. JAMA Ophthalmol 132:1215, 2014). The male was a member of the kindred with 4 affected males reported by Goldberg and McKusick (Am J Ophthal 71:1128, 1971).
- *HS6ST2.* Male twins with a missense mutation in the *HS6ST2* gene (Xq26.2) which encodes a heparan sulfate sulfotransferase reported by Paganini et al. (Clin Genet 95:368-374, 2019) showed severe ID, seizures, ventricular enlargement, myopia, chorioretinopathy, and some facial dysmorphism.
- *HSD17B10.* Mutations in HSD17B10, which encodes with multiple metabolic functions have been associated with neurodeterioration and seizures after variable periods of normal development (Su et al. Metab Brain Dis 32:2063, 2017). The gene is located in Xp11.22.
- *LAGE3*. The gene, located in Xq28, encodes a subunit of the highly conserved kinase, endopeptidase, and other proteins of small size (KEOPS) complex, that regulates the second biosynthetic step in the formation of N-6-threonylcarbamoyladenosine (t6A) in the cytosol. This gene is responsible for the X-linked variant of the Galloway-Mowat syndrome (OMIM 301006) consisting of nephrotic syndrome, microcephaly, gyral abnormalities, delayed psychomotor development (Braun et al. Nature Genet 49:1529-1538, 2017).
- *NKAP*. Intellectual disability has been reported in association with *de novo* and inherited missense variants in *NKAP*, a gene located in Xq24 that plays a role in transcriptional regulation (AJHG 105:987, 2019). In addition to variable intellectual disability, affected males had marfanoid habitus with pectus anomalies and scoliosis, open mouth appearance, short philtrum, midface hypoplasia, and prominent ears.
- *OGT.* Vaidyananthan et al. (JBC 292:8948, 2017) reported three males in one family with a missense mutation in OGT, located in Xq13.1. The gene is involved in posttranslational modification of nuclear and cytosolic proteins. Other cases have been reported by Willems et al. (JBC 292:12621, 2017), Bouazzi et al. (Clin Case Rep 3:604, 2015) and Niranjan et al. (PLoS One 10:e0116454, 2015). Has been assigned to MRX106.
- *OTUD5*. Located in Xp11.23, the gene is a deubiquitinating enzyme that cleaves ubiquitin linkages. A missense variant was identified in a single patient with XLID and another missense variant was found in three male siblings with moderate ID (Kosmicki et al. Nat Genet:49:504, 2017). Recently Tripolszki et al. (Clin Genet 2020) reported a large family with 13 male patients who had a missense variant which segregated in the 10 males they tested. The affected males presented with an apparent syndrome

consisting of low birth weight, short stature, hydrocephalus, hypospadias, severe neurodevelopmental delay and early death.

- *PJA1*. A missense variant in *PJA1* (Xq13.1) has been reported in seven Japanese patients with intellectual disability and hyperactivity, six of whom had autistic traits and five of whom had trigonocephaly (Ann Clin Transl Neurol 7:1117, 2020). The p.R376C variant was also found in one maternal grandparent who was healthy, introducing concern about the pathogenicity of the variant.
- *POLA1.* Van Esch et al. (AJHG 104:957, 2019) reported 5 families with XLID and missense or splice site variants in *POLA1*. Affected males had microcephaly, short stature, hypogonadism, and variable minor facial manifestations. The gene, located at Xp22.1-p21.3, encodes a subunit of the heterotetrameric DNA polymerase, alpha-primase.
- *RIPPLY1*. The gene, located in Xq22.3, encodes a Ripply protein expressed in somites of zebra fish embryos. In one consanguinous family two brothers with ID carried a deletion of a nucleotide (C) near the end of the 3rd exon resulting in a frameshift change from amino acid position 93 and causing a premature stop codon that affects the protein product, which is a developmental transcription regulator. It is to be noted that this family was recruited in a search of new autosomal recessive ID genes (Jazayeri et al. Arch Iranian Medicine 18:670-682, 2015).
- *SLC35A2*. This XLID gene, which encodes a UPD-galactose transporter, has been missed in prior XLID updates. The gene alterations (frameshift and missense) lead to galactose-deficient glycoproteins, thus adding to the number of X-linked disorders of glycosylation (Kodera at al. Hum Mutat 34:1208, 2013, Ng et al. AJHG 92:632, 2013).
- *SLC9A7*. Khayat et al. (Hum Mol Genet 28:598, 2019) reported 2 unrelated families with the same missense variant in *SLC9A7*. The gene located at Xp11.3, encodes an alkali cation (Na+, K+)/proton (H+) exchange factor that resides in the Golgi. Affected males had variable ID, hypotonia, brisk reflexes, muscle weakness, and bilateral clinodactyly. The authors considered the disorder to be nonsyndromal (IDX108).
- *USP9X*. Homan et al. (Am J Hum Genet 94:470, 2014) reported 2 missense and one truncating mutation in *USP9X,* located at Xp11.4, in 3 families with XLID. The ID was mild to moderate, hypotonia was present in the 5 males studied, but all other findings were inconsistent. IDX99 has been assigned for the entity.
- *ZFP92*. Schwartz et al. (ASHG Annual Meeting 2018, San Diego) reported a family with a missense mutation and a single male with a deletion in *ZFP92* (Xq28). The four males had ID, hypotonia, and behavioral problems.

Candidate XLID Genes

- *EFNB1*. The *EFNB1* gene (Xq12) is associated with craniofrontonasal syndrome, a disorder expressed more completely in females with males usually showing only a widened midface. Intellectual disability in either sex is exceptional and possibly unrelated.
- *FAM120C.* This gene is an unannotated open reading frame located in Xp11.22. Its association with XLID is based on circumstantial evidence: a deletion in a patient with

ASD and its presumed involvement with the FMRP complex (De Wolf et al. Am J Med Genet 160A:3035-41, 2014).

- *GSPT2.* This gene, located in Xp11.22, binds GTP. It plays a role in the G1- to S-phase transition in the cell cycle. The association of the gene with XLID is based on its presence in deletions in Xp11.22 which also include at least three other genes (Grau et al. PLoS One 12:e0175962, 2017). No concrete evidence was presented specifically linking *GSPT2* to the XLID in the patients.
- *ITIH6.* This gene is located in Xp11.22 and was previously known as *ITIH5L*. It is a candidate XLID gene based on a single report of a variant being present in a Saudi family with ASD (Al-Mabarak et al. Sci Rep. July 18:7(1):5679, 2017).
- *MAGED2.* Mutations in *MAGED2*, located in Xp11, causes Bartter syndrome Type 5 (BARTS5; OMIM #300971), which is an antenatal, transient form of the syndrome. Although BARTS5 can be lethal because of prematurity, polyhydramnios and postnatal renal salt wasting, there have been no reports of ID in affected males.
- *NDUFB11*. The gene, located in Xp11.3, encodes a component of mitochondrial complex I. Complex I catalyzes the first step in the electron transport chain, the transfer of 2 electrons from NADH to ubiquinone, coupled to the translocation of 4 protons across the membrane. Mutations in *NDUFB11* cause microphthalmia with linear skin defects syndrome. One affected girl was also found to have severe psychomotor delay (van Rahden et al. AJHG 96: 640-650, 2015).
- *PNPLA4* and *HDHD1*. Labonne et al. (J Clin Med 9:274, 2020) reviewed five microdeletions in Xp22.31 in males with developmental delay or intellectual disability and ichthyosis. Three had craniofacial anomalies, two had seizures, and one had hearing loss. The five microdeletions include *HDHD1* and four included *PNPLA4*, two genes highly expressed in brain and which the authors considered as candidate XLID genes. Microduplications incorporating the two genes have also been reported with developmental delay/intellectual disability. *VCX3A* has also been considered to be a candidate XLID gene located in deletions in this Xq22.31 region (AJHG 67:563, 2000).
- *SMARCA1*. The gene was cloned from a Xq25-q26 deletion derived from a t(X;3) translocation. Its protein product is a transcriptional regulator in yeast. A missense variant (c.G2897T; G966V) was found in one female patient from a cohort of 19 patients with a Rett-like phenotype (Lopes et al. J Med Genet 53:190-199, 2015).

III. IDX (formerly MRX) Families, Loci and Genes

- IDX1: *IQSEC2*, Xp11.2 (Shoubridge et al. Nat Genet 42:486, 2010)
- IDX2: *PQBP1*, Xp22.3 (Kalscheuer et al. Nat Genet 35:313, 2003)
- IDX3: *HCFC1*, Xq28-qter (Gedeon et al. J Med Genet 28:372, 1991; Huang et al. Am J Hum Genet 91:694, 2012)
- IDX4: Xp11.22-Xq21.31
- IDX5: Xp21.1-Xq21.3

- IDX6: Xq27
- IDX7: Xp11.23-Xq12
- IDX8: *DLG3*, Xq13.1 (unpublished, Schwartz et al.)
- IDX9: *FTSJ1,* Xp11.23 (Ramser et al. J Med Genet 41:679, 2004)
- IDX10: *ILRAPL1*, Xp11.4-Xp21.3 (deBrouwer et al. Hum Mutat 28:207, 2007)
- IDX11: Xp11.22-Xp21.3
- IDX12: *THOC2*, Xp21.2-Xq12 (Kumar et al. Am J Hum Genet 97:302, 2015)
- IDX13: *KDM5C*, Xp11.22 (Rujirabanjerd et al. Eur J Hum Genet 18:330, 2010)
- IDX14: Xp11.22-Xq12
- IDX15: *CLCN4, Xp*22.2 (Hu et al. Mol Psychiat, Feb 2015).
- IDX16: *MECP2,* Xq28 (Couvert et al. Hum Mol Genet 15:941, 2002)
- IDX17: Duplication of Xp11.22 - *RIBC1, HSD17B10*, and *HUWE1* (Froyen et al. Am J Hum Genet 82:432, 2008)
- IDX18: *IQSEC2*, Xp11.2 (Shoubridge et al. Nat Genet 42:486, 2010)
- IDX19: *RPSKA3* (RSK2), Xp22.2-Xp22.1 (Merienne et al. Nat Genet 22:13, 1999)
- IDX20: Xp21.1-Xq23
- IDX21: *IL1RAPL1*, Xp22.1 (Tabolacci et al., Am J Med Genet 140A:482, 2006)
- IDX22: *SLC16A2*, Xp13.2 (Maranduba et al., J Med Genet 43:457, 2006)
- IDX23: Xq23-Xq24
- IDX24: Xp22.2-Xp22.3,
- IDX25: *SLC6A8*, Xq27.3 (unpublished, Friez 2019)
- IDX26: Xp11.4-Xq23
- IDX27: *PQBP1*, Xq24-Xq27.1
- IDX28: Xq27.3-qter
- IDX29: *ARX*, Xp22.13 (Stepp et al. MBC Med Genet 6:16, 2005)
- IDX30: *PAK3,* Xq21.3-Xq24 (Allen et al. Nat Genet 20:25, 1998)
- IDX31: Duplication of Xp11.22 - *RIBC1, HSD17B10*, and *HUWE1* (Froyen et al. Am J Hum Genet 82:432, 2008)
- IDX32: *ARX,* Xp22.13 (Stepp et al. MBC Med Genet 6:16, 2005)
- IDX33: *ARX,* Xp22.13 (Stepp et al. MBC Med Genet 6:16, 2005)
- IDX34: *IL1RAPL1*, Xp22.1 (Raeymaekers et al., Am J Med Genet 64:16, 1996)
- IDX35: *THOC2*, Xq21.3-Xq26 (Kumar et al. Am J Hum Genet 97:302, 2015)

- IDX36: *ARX*, Xp22.13 (Frints et al., Am J Med Genet 112:427, 2002)
- IDX37: Xp22.31-Xp22.32
- IDX38: *ARX,* Xp22.13 (Stepp et al. MBC Med Genet 6:16, 2005)
- IDX39: Xp11
- IDX40: Xq28
- IDX41: *GDI1,* Xq28 (Bienvenu et al. Hum Mol Genet 7:1311, 1998)
- IDX42: Xq26
- IDX43: *ARX*, Xp22.13 (Bienvenu et al., Hum Mol Genet 11:981, 2002)
- IDX44: *FTSJ1,* Xp11.23 (Freude et al. Am J Hum Genet 75:305, 2004)
- IDX45: *ZNF81,* Xp22.1-Xp11 (Kleefstra et al. J Med Genet 41:394, 2004)
- IDX46: *ARHGEF6*, Xq26 (Kutsche et al. Nat Genet 26:247, 2000)
- IDX47: *PAK3,* Xq21.3-Xq24 (Bienvenu et al. Am J Med Genet 93:294, 2000)
- IDX48: *GDI1,* Xq28 (D'Adamo et al. Nat Genet 19:134, 1998, Bienvenu et al. Hum Mol Genet 7:1311, 1998)
- IDX49: *CLCN4,* Xp22.2 (Palmer et al. Mol Psychiatric, 2015)
- IDX50: *SYN1*, Xp11.4-p11.21 (not published, pathogenicity?)
- IDX51: Xp11.4-p11.3
- IDX52: *ARX*, Xp11.21-q21.32 (DeBrouwer 2019, not published)
- IDX53: Xq22.2-q26
- IDX54: *ARX*, Xp22.13 (Bienvenu et al., Hum Mol Genet 11:981, 2002)
- IDX55: *PQBP1*, Xp11.2 (Kalscheuer et al., Nat Genet 35:313, 2003)
- IDX56: Xp21.1-p11.21
- IDX57: Xq24-q25
- IDX58: *TM4SF2 (TSPAN7)*, Xp11.4 (Zemni et al., Nat Genet 24:167, 2000)
- IDX59: *AP1S2*, Xp22 (Tarpey et al., Am J Hum Genet 79:1119, 2006)
- IDX60: *OPHN1*, Xq12 (Billuart et al., Nature 392:923, 1998)
- IDX61: *RLIM*, Xq13.1-q25 (Tonne et al., Eur J Hum Gent 23:1652, 2015)
- IDX62: *UPF3B*, Xq24 (Laumonnier et al., Mol Psychiatry 15:767, 2010)
- IDX63: *FACL4*, Xq22 (Meloni et al., Nat Genet 30:436, 2002)
- IDX64: Xq28, *MECP2* dup, same as Pai syndrome (Pai et al., J Med Genet 34:529, 1997; Friez et al., Pediatrics 118:e1687, 2006).

- IDX65: Xp11.3-Xq21.33, *ZNF711* (Yntema et al., Am J Med Genet 85:205, 1999; van der Werf et al., Gene 605:92, 2017)
- IDX66: Xq21.33-q23
- IDX67: *MED12,* Xq13.1 (Hu et al., Mol Psychiatry 21:133, 2016)
- IDX68: *FACL4*, Xq23 (Longo et al., J Med Genet 40:11, 2003)
- IDX69: Xp11.21-q22.1 (not published)
- IDX70: *del SLC25A5*, Xq24 (Vandewalle et al., Hum Genet 132:1177, 2013)
- IDX71: Xq24-q27.1
- IDX72: *RAB39B*, Xq28 (Giannandrea et al., Am J Hum Genet 86:185, 2010)
- IDX73: Xp22-p21 (Martinez et al., Am J Med Genet 102:200, 2001)
- IDX74: *EFHC2*, Xp11.3-p11.4 (de Brouwer et al., Hum Mut 28:207, 2007)
- IDX75: Xq24-q26 (Caspari et al., Am J Med Genet 93:290, 2000)
- IDX76: *ARX*, Xp22.13 (Bienvenu et al., Hum Mol Genet 11:981, 2002)
- IDX77: Xq12-q21.33 (Sismari et al., Am J Med Genet 122A:46, 2003)
- IDX78: *IQSEC2* (Kalscheuer et al. Front Mol Neurosci 8:85, 2016); Xp11.4-p11.23 (DeVries et al., Am J Med Genet 111:443, 2002)
- IDX79: *MECP2*, Xq28 (Winnepenninckx et al., Hum Mutat 20:249, 2002)
- IDX80: Xq22-q24 (Verot et al., Am J Med Genet 122A:37, 2003)
- IDX81: Xp11.2-Xq12 (Annunziata et al., Am J Med Genet 118A:217, 2003)
- IDX82: Xq24-q25 (Martinez et al., Am J Med Genet A 131:174, 2004)
- IDX83: (not published)
- IDX84: Xp11.3-q22.3 (Zhang et al., Am J Med Genet 129A:286, 2004)
- IDX85: *DMD*, Xp21.3-p21.1 (DeBrouwer et al., Hum Mutat 28:207, 2007)
- IDX86: (not published)
- IDX87: *ARX*, Xp22.13 (LaPeruta et al., BMC Med Genet 8:25, 2007)
- IDX88: *AGTR2*, Xq24 (Vervoort et al., Science 296:20401, 2002)
- IDX89: *ZNF41*, Xp11.3 (Shoichet et al., Am J Hum Genet 73:1341, 2003)
- IDX90: *DLG3*, Xq13 (Tarpey et al., Am J Hum Genet 75:318, 2004)
- IDX91: t(X:15)(q13.3; cent) in female patient; *ZDHHC15* mutation? (Mansouri et al., Eur J Hum Genet 13:970, 2005)
- IDX92: *ZNF674*, Xp11.3 (Lugtenberg et al., Am J Hum Genet 78:215, 2006)
- IDX93: *BRWD3*, Xq21.1 (Field et al., Am J Hum Genet 81:367, 2007)

- IDX94: *GRIA3*, Xq25 (Wu et al., PNAS 104:18163, 2007)
- IDX95: *MAGT1 (IAP*) Xq21.1 (Molinari et al., Am J Hum Genet 82:1150, 2008)
- IDX96: *SYP*, Xp11.23 (Tarpey et al., Nat Genet 41:535, 2009)
- IDX97: *ZNF711*, Xq21.1 (Tarpey et al., Nat Genet 41:535, 2009; van der Werf et al., Gene 605:92, 2017)
- IDX98: *KIA2022*, Xq13 (Cantagrel et al., J Med Genet 41:736, 2004; Van Maldergem et al., Hum Mol Genet 22:3306, 2013)
- IDX99: *USP9X*, Xp11.4 (Homan et al., Am J Hum Genet 94:470, 2014)
- IDX100: *KIF4A*, Xq13.1 (Willemsen et al., J Med Genet 51:487, 2014)
- IDX101: *MID2*, Xq22.3 (Geetha et al., Hum Mut 35:41, 2014)
- IDX102: *DDX3X,* Xp11.4 (Snijders Blok et al., Am J Hum Genet 97:343, 2015)
- IDX103: *KLHL15*, Xp22 (Mignon-Ravix et al., AJMG 164A:1991, 2014)
- IDX104: *FRMPD4*, Xp22.2 (Hu et al., Mol Psychiatry 21:133, 2016)
- IDX105: *USP27X*, Xp11.23 (Hu et al., Mol Psychiatry 21:133, 2016)
- IDX106: *OGT*, Xq13.1 (Willems et al., J Biol Chem 292:12621, 2017)
- IDX107: *CXorf56*, Xq24 (Verkerk et al., Eur J Hum Genet 26:552, 2018)
- IDX108: *SLC9A7*, Xp11.3 (Khayat et al., Hum Mol Genet 28:598, 2019)

Other IDX Genes

- *ALG13*
- *NLGN4*
- *CDKL5 (STK9)*
- *FGDY*
- *ATRX (XNP)*
- *AFF2 (FMR2)*
- *SLC6A8*
- *KLF8*
- *NDUFA1*
- *SRPX2*
- *NLGN3*
- *ZFP92*

IV. Segmental X Chromosome Duplications (Updated February 2021)

As of February 2021, 160 genes on the X-chromosome have been associated with X-linked intellectual disability (XLID). The association of 9 of these genes are considered uncertain (Piton et al. AJHG 93:368, 2013). In addition, there are 7 candidate genes awaiting confirmation. Variants in 129 of these genes have been associated with XLID syndromes and 31 exclusively with nonsyndromal XLID (IDX). Duplication of every gene associated with XLID has been identified in one or more individuals. Typically, in these cases, the entire XLID gene is duplicated, often with complete or partial duplication of adjacent genes. Duplication of *KLF8*, the XLID gene on the p arm closest to the centromere also been found only in large duplications that involve the entire p arm (Tuck-Muller et al., Hum Genet 91:395, 1993).

The phenotypic consequences of duplication of XLID genes are protean. In the first instance, the duplication may be associated with a phenotype identical or similar to that associated with a loss of function mutation or deletion of the gene. Such is the case for duplication of the *PLP1* gene which results in Pelizaeus-Merzbacher syndrome. In the second instance, duplication of an XLID gene may result in a distinct phenotype but one quite different from loss of function mutations in the same gene. Duplication of *MECP2* appears to be the most common duplication of this type but others include duplication of *STAG2, OCRL1* and *HUWE1* (van Esch et al., Am J Hum Genet 77:442, 2005; Friez et al., Pediatrics 118:e1687, 2006; Friez et al., BMJ Open 6:e009537, 2016; Froyen et al., Hum Mut 28:1034, 2007; Schroer et al., Am J Med Genet 158A:2602, 2012; Leroy et al., Clin Genet 89:68, 2016). Intermediate between these phenotypic consequences are duplications of the *ATRX* gene which are associated with some manifestations of the Alpha-Thalassemia Intellectual Disability syndrome (short stature, genital anomalies, intellectual disability, hypotonia) but lack the typical facial features seen with loss of function variants in *ATRX* (Lugtenberg et al., Am J Med Genet 149A:760, 2009). Among those duplications which appear to be clinically important, marked skewing of X-inactivation in females is typical.

Duplications of certain XLID-associated genes *(IKBKG, ARX*) and certain X chromosome regions (Xp21.33, Xq21.33) do not appear to be associated with neurodevelopmental abnormalities although they may be associated with other somatic manifestations (van Asbeck et al., Clin Dysmorphol 23:77, 2014; Popovici et al., Am J Med Genet 164A:2324, 2014; Maurin et al., Cytogenet Genome Res 151:115, 2017).

V. Summary of XLID (Updated February 2021)

The linkage limits for XLID syndromes and IDX and the band locations for cloned XLID genes are provided in the accompanying illustrations. Click to download figures as pdfs. A table is also available showing the genes associated with X-linked intellectual disability in order of their discovery.

- Figures 1A and 1B - Location of genes associated with XLID syndromes which have been cloned and mutations demonstrated.
- Figure 2 - Linkage limits for XLID syndromes which have been mapped (lod score >2), but the genes not yet cloned.

- Figure 3 – Location of genes associated with IDX and linkage limits for IDX families which have been mapped (lod score >2), but the genes not yet cloned. The locations of the IDX genes which have been cloned are indicated on the left with solid arrows, genes that cause both IDX and XLID syndromes are shown on the right with open arrows.
- Table - Listing of XLID genes and gene functions chronologically by year of discovery.