

X-Linked Intellectual Disability (revised May 2019)

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 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
- II. New Gene Identifications
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I. New Syndromes and Localizations

- Congenital Disorders of Glycosylation, type 1s. Males and females with early onset seizures with or without somatic findings (microcephaly, hydrocephaly, optic atrophy, nystagmus, hypertelorism, soft tissue edema, contractures, scoliosis, and others) have been reported to have mutations in *ALG13*. (Timal et al. Hum Mol Genet 21:4151,2012; de Ligt et al. NEJM 367:1921,2012; Bissar-Tadmouri et al. AJMG 164A:164, 2014; Michaud et al. Hum Mol Genet 23: 4846, 2014; Dimassi et al. Clin Genet 89:198, 2015).
- Vitale et al. (Am J Med Genet 103:1, 2001) described a family in which 8 males had no speech, coarse facies, downslanting palpebral fissures, large bulbous nose, macrostomia, hypoplastic earlobes and short stature. The entity was mapped to a 16cM region in Xq24 (maximum lod score 3.61 at DSX1001). This entity looks like the condition XLID-hypogonadism-tremor (Cabezas syndrome) which results from mutations in *CUL4B*. A donor splice mutation in *CUL4B* was reported by Londin et al. (AJMG 164A:2294, 2014).
- XLID-bradykinesia-seizures. 3 reports have described splice site and synonymous variants in *ATP6AP2* in males with tremors, instability, slow motor movements, and epilepsy (Poorkaj et al. Mov Disord 25:1409, 2010; Hedera et al. Ann Neurol 51:45, 2002; Gupta et al. Park Rel Dis 21:1473, 2015).
- XLID-early onset seizures-hypotonia. Johnston et al (AJHG 90:295, 2012) reported 3 affected males with a missense mutations in *PIGA* who died in infancy. The clinical manifestations were variable but included generous fetal growth, prominent occiput, depressed nasal bridge, short nose, upslanted palpebral fissures, small mouth, micrognathia, short neck, small nails, early onset seizures, hypotonia, thin corpus callosum, small cerebellum, and immature white matter. The dysmorphology, natural history, and metabolic alterations were further delineated in subsequent reports by van

der Crabben et al. (AJMG 164A: 29, 2014) Swoboda et al. (AJMG 164A:17, 2014) and Kato et al. (Neurology 82:1587, 2014). *PIGA* is located in Xp22.2 and encodes a phosphatidylinositol involved in glycosylation.

- XLID-movement-tone-behavior syndrome. Snijders Blok et al (AJHG 97:343, 2015) reported 38 females with de novo mutations in *DDX3X*, a gene in Xp11.4 which disturbs function of the Wnt pathway. A number of anatomical (microcephaly, hypoplasia of the corpus callosum, ventriculomegaly, polymicrogyria), neurological (hypotonia, dyskinesia, spasticity, abnormal gait, seizures), behavioral (aggression, hyperactivity, autism spectrum disorder), and other rare manifestations (cleft lip/palate, precocious puberty, pigmentary change, hearing loss, vision impairment) were noted. Several males with ID were identified in these families.
- XLID-Retinoschisis. Phadke et al. (Am J Med Genet 155A:9, 2011) reported 2 brothers with ID, short stature, microcephaly, and retinoschisis. Sequencing and microarray analysis of *RS1* were normal. The boys were concordant for 4 different regions – Xp22.33-p22.2, Xp11.3-p21.31, Xq23-q25 and Xq27.1-q28.
- X-linked Cornelia de Lange syndrome. Mutations in two genes, *SMC1A* (*SMC1L1*) in Xp11.2 and *HDAC8* in Xq13 have been implicated in X-linked Cornelia de Lange syndrome (Deardorff et al.: Am J Hum Genet 80:485, 2007 and 2011 David W. Smith Workshop on Malformations and Morphogenesis, Lake Arrowhead, CA, Sept. 9-12, 2011). An intronic variant in *HDAC8* was described in a large family with XLID, hypogonadism, short stature and facial dysmorphisms different from Cornelia de Lange syndrome by Harakalova et al. (J Med Genet 49:539, 2012.)
- X-linked Kabuki syndrome. Miyake et al. (Hum Mut 34:108, 2013) reported identified 3 mutations (2 nonsense, 1 inframe deletion) in *KDM6A* in patients with Kabuki syndrome who did not have mutations in *MLL2*. The gene is located in Xp11.3 and encodes a lysine demethylase. Lederer et al. (Am J Hum Genet 90:119, 2012) had previously reported deletion of the gene in three patients with Kabuki syndrome.
- *STAG2*-Related XLID. Duplications of Xq25 that encompass *STAG2* and adjacent genes have been reported in over 30 families (Yingjun et al., EJM 58:116, 2015; Bonnet et al., AJMG 149A:1280, 2009; Philippe et al., AJMG 161A:1370, 2013; Kumar et al., Hum Mol Genet 24:7172, 2015; and others). ID is a constant finding, ASD is frequent and some dysmorphic facial features have been reported. The adjacent genes are *XIAP*, *GRIA3*, and *THOC2*. Only one case has had deletion of *STAG2* alone. There are also unreported cases of *STAG2* mutations in males and females.
- *MSL3*-Related XLID. De novo, splice site, frameshift and nonsense variants in *MSL3* have been reported in several males and females with a “recognizable facial phenotype”, developmental delay or ID, severe constipation and in one case aphasia and cyclic neutropenia (Thevenon et al., 17th Int. Fragile X and Early-Onset Cognitive Disorders Workshop, Strasbourg, France, Sept 27-30, 2015).
- XLID-Craniofacial-Caudal. *TAF1* mutations are recognized to cause dystonia – Parkinson disease. Lyon et al. (17th Int. Fragile X and Early-Onset Cognitive Disorders Workshop, Strasbourg, France, Sept 27-30, 2015) found a missense variant in *TAF1* in two brothers with severe ID, anteverted nares, sagging cheeks, downslanted palpebrae, deep-set

eyes, thin upper lip, arched palate, prominent ears, pointed chin and a “caudal prominence”.

- XLID-Faciogenital. Vaidyanathan et al. (J Biol Chem 292:8948, 2017) reported a missense variant in OGT 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*. 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. Other 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.

II. New Gene Identifications

- *AIFM1*. Using exome sequencing, Rinaldi et al. (Am J Hum Genet 91:1095, 2012) found a missense mutation in *AIFM1* (Xq26.1) in the family originally reported with Cowchock variant of Charcot-Marie-Tooth syndrome (CMTX4).
- *BCAP31*. Cacciagli et al. (Am J Hum Genet 93:579, 2013) reported a mutation in *BCAP31* in 3 families with XLID, microcephaly, short stature, strabismus, optic atrophy, deafness, dystonia, pyramidal signs, quadriplegia, seizures and white matter hypomyelination. The gene, located in Xq28, encodes a chaperone protein involved in endoplasmic reticulum functions and programmed cell death.
- *CCDC22*. Voineagu et al. (Mol Psych 17:4, 2012) reported a missense mutation (p.T17A) in *CCDC22* (Xp11.23) that segregated with ID, cardiac anomalies, hip dislocation, scoliosis, hypoplastic distal phalanges, syndactyly, and facial abnormalities (hypertelorism, beaked nose with wide nasal tip, ear anomalies and high arched palate) in a large family with 6 affected males in 3 generations. The gene encodes a coiled-coil domain protein of unknown function.
- *CLIC2*. Takano et al. (Hum Mol Genet 21:4497, 2012) found a missense mutation (p.H101Q) in *CLIC2* in two brothers with profound ID, atrial fibrillation, cardiomegaly, congestive heart failure and seizures. Both had contractures of the large joints. Distinctive facial findings were not present. The mother was considered to be learning disabled. The gene is located in Xq28 and modulates the action of the ryanodine receptor intracellular Ca²⁺ release channels.
- *CNKSR2*. Houge et al. (Mol Syndromol 2:60, 2011) reported a 234 kb deletion of Xp22.12, which removed the first 15 exons of *CNKSR2* in a five-year-old boy with ID, microcephaly and seizures. The gene encodes the connector enhancer of KSR-2, is highly expressed in brain and localizes to the postsynaptic density. The protein may have a role in MAPK signaling. The mutation appeared to be *de novo* in the mother who was normal.

- *CXorf56*. A single large family with mild nonsyndromal XLID 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.
- *DDX3X*. Snijders Blok (ASHG 97: 343, 2015) reported mutations on *DDX3X* at Xp11.4, which encodes a helicase that functions in a variety of cellular processes in IDX102 and in other patients with XLID accompanied by neurological manifestations. The mutations were primarily de novo, loss of function variants in girls.
- *EBP*. Hartill et al. (J Med Genet Suppl 1 49:SP05, 2012) reported a missense mutation (p.W47R) in *EBP* in a kindred with 4 affected males in three generations. Affected males had aggressive behavior, toe 2-3 syndactyly and "soft dysmorphic signs." The gene, located at Xp11.23, encodes an enzyme (3-beta-hydroxysteroid-delta 8, delta 7-isomerase) involved in cholesterol metabolism and is known to be the cause of X-linked dominant chondrodysplasia punctata. This family had no signs of chondrodysplasia punctata.
- *EFHC2*. A missense mutation was reported in IDX74 by deBrouwer et al. (Hum Mut 28:207, 2007). The gene, located at Xp11.3, has been considered important in fear recognition and harm avoidance. It contains a Ca-binding motif.
- *FAM50A*. The family reported by Armfield et al. (AJMG 85:236, 1995) has been found to have a missense variant in *FAM50A* (Schwartz et al. 39th David W. Smith Workshop, Banff Canada, August 28, 2018). The gene locates to Xq28 and the protein is a member of the spliceosome complex. Four other unrelated males were presented at the same workshop.
- *FRMPD4* (*PDZ10*, *PDZK10*). Hu et al. (Mol Psychiatry 21:133, 2016) reported a truncating mutation in *FRMPD4* in 5 males in 1 family with variable ID, absent or limited speech, seizures and abnormal behavior. An unrelated male with no speech, autism, and developmental delay was found to have a de novo missense mutation. In the mouse, *FRMPD4* depletion results in decreased spine density and excitatory synaptic transmission. Piard et al. (Hum Mol Genet doi:10.1093/hmg/ddx426) published findings in this gene in another three families with XLID. Functional studies indicated the mutations adversely affected dendritic spine morphogenesis.
- *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 in *HMGB3*, located in Xq28.
- *HNRNPH2*. Bain et al. (AJHG 99:1, 2016) described de novo sequence variants in 6 unrelated females with ID, autism, seizures and hypotonia. The facial features were variable as were growth and skeletal abnormalities. The gene, located at Xq22.1, is involved in pre-RNA processing and trafficking between the nucleus and cytoplasm.

- *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 on Xp11.22.
- *IQSEC2*. Mau-Them et al. (Eur J Hum Genet 22: 289-292, 2014) reported 3 unrelated males with postnatal onset microcephaly, midline stereotypic hand movements, hypotonia, hyperactivity, strabismus and seizures with mutations (2 intragenic dups, 1 nonsense) in *IQSEC2*. Prior cases with mutations in *IQSEC2* have been considered to be nonsyndromal (Nat Genet 42:486, 2010; AJMG 30:485, 1988). The phenotype has broadened considerably with additional reports. ID and seizures appear to be the most consistent components. Males and females may be affected. All different types of alterations affecting *IQSEC2* have been reported (Mignot et al. Genet Med online Sept 2018).
- *KDM6A*. Lindgren et al. (Hum Genet 132:537, 2013) reported a female with an X:5 translocation which disrupted *KDM6A*, a histone 3 lysine 27 demethylase and histone 3 lysine 4 methyltransferase gene. The 19-year-old had global developmental delay, microcephaly, short stature, large posteriorly-rotated ears, downslanted palpebral fissures, arched eyebrows, myopia, short columella, short philtrum, cleft palate, abnormally-shaped dysplastic teeth, pectus excavatum, clinodactyly, short metacarpals and metatarsals, puffy fingers, hyperconvex nails, ventriculomegaly, hypotonia and seizures. The authors found reports of 7 duplications and 2 deletions of *KDM6A* in other individuals with some phenotypic overlap. They also noted that individuals with Kabuki syndrome have similar clinical findings and some have had deletions or point mutations in *KDM6A*.
- *KIF4A*. Willemsen et al. (J Med Genet 51:487, 2014) reported a missense mutation in this gene, located at Xq13.1, that encodes Kinesin family member 4A in 5 males in 3 generations of one family. No distinctive clinical findings were present. The condition has been assigned IDX100.
- *KLHL15*. Hu et al. (Mol Psychiatry 21:133, 2016) found a truncating variant in *KLHL15* in 8 males in 3 generations of a single family. The males are reported to have mild to moderate ID and facial dysmorphism which was not described. Another unpublished family with a truncating variant has been found by Gecz et al. 2015. The gene is a member of the kelch-like protein family but is poorly characterized.
- *MID2*. Geetha et al. (Hum Mut 35:41, 2014) reported a family with 10 males in 3 generations with ID who had a missense mutation in *MID2*, located at Xq22.3, which encodes a U3 ubiquitin ligase. There were no findings similar to those found in Telecanthus-hypospadias syndrome (Opitz G/BBB syndrome due to *MID1* mutations), no distinctive craniofacial or growth abnormalities, and the condition was assigned IDX101.
- *MSL3*. Males and females with nonsense, frameshift and splice site variants in *MSL3* were reported by Thevenon et al. (17th Int. Fragile X and Early-Onset Cognitive Disorders

Workshop, Strasbourg, France, Sept 27-30, 2015). The phenotype was variable but includes severe ID, facial dysmorphism and severe constipation. The gene, located at Xp22.2, is a regulator of transcription.

- *NONO*. Mircsof et al. (Nature Neurosc. 18:1731, 2015) reported a de novo splice mutation and a one base pair insertion in two unrelated males with ID, slender build, macrocephaly, hypotonia, facial dysmorphism, thick corpus callosum and small cerebellum. The gene, located at Xq13.1, encodes a regulator of transcription.
- *OGT*. Vaidyanathan et al. (JBC March 16, 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 Niranjana et al. (PLoS One 10:e0116454, 2015).
- *PIGA*. Three reports since 2012 have implicated *PIGA* at Xp22 as an XLID gene. Johnston et al. (Am J Hum Genet 90:295, 2014) reported 3 males in one family with an infancy lethal disorder characterized by central hypotonia, seizures, small nose with depressed nasal bridge, upslanting palpebral fissures, gingival overgrowth, short neck, small nails, short digits, hyperreflexia, thin corpus callosum and small cerebellum. Swoboda et al. (Am J Med Genet 164A:17, 2013) reported 3 related males with neurological degeneration, systemic iron storage, brown skin papules and scattered areas of hyperpigmentation with an inframe deletion in *PIGA*. They suggested the name Ferro-Cerebro-Cutaneous syndrome. Affected males also showed acquired microcephaly, alveolar ridge overgrowth, seizures, muscle atrophy, spasticity, contractures, hepatomegaly and splenomegaly. Van der Crabben et al. (AJMG 164A:29, 2014) reported a missense mutation in this phosphatidylinositol glycan class A gene in a boy with severe developmental delay and regression, central hypotonia, seizures, high frontal hairline, long philtrum, alveolar overgrowth, unerrupted teeth, accelerated statural growth, deep plantar creases, thin corpus callosum, cerebral atrophy and elevated alkaline phosphatase. Maternal X-inactivation was markedly skewed.
- *POLA1*. Van Esch et al. (AJHG 2019 <https://doi.org/10.1016/j.ajhg.2019.03.006>, Epub ahead of print), 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.
- *PTCHD1*. Pinto et al. (Nature 466:368, 2010), Noor et al. (Sci Transl Med 2:49ra68, 2010) and Chaudhry et al. (Clin Genet 88:224, 2015) have reported deletions of *PTCHD1* (Xp22.11) in individuals with autism spectrum disorder and intellectual disability. Functional studies have not been reported.
- *RAB40AL*. Bedoyan et al. (J Med Genet 49:332, 2012) reported a missense mutation in *RAB40AL*, which encodes a RAS-like GTPase protein in the family reported by Martin et al. (J Med Genet 37:836, 2000). Evidence against this being the correct gene assignment has been provided by Oldak et al. (Hum Mut 35:1171, 2014).
- *RBMX*. Shashi et al. (Clin Genet. 88:386, 2015) reported a 23 bp deletion in this gene in the original family with Shashi XLID – coarse facies.

- *RLIM*. Missense variant in this gene that encodes RING-H2 zinc finger protein 12 (Xq13.2) were reported in 3 families by Hu et al. (Mol Psychiatry 21:133, 2016). These families were considered to have nonsyndromal XLID but with variable ID, microcephaly, micrognathia, cryptorchidism and behavioral abnormalities. One of the families reported (Rodríguez Criado: An Pediatr (Barc) 76:184, 2012) included eight males in one family with ID, short stature, microcephaly, hypertelorism, genital hypoplasia and variable skeletal findings. The gene mapped to Xp11.23-q21.32 (LOD 2).
- *RNF113A*. Corbett et al. (JMG 52:269, 2015) reported nonsense variants in *RNF113A*, located at Xq24, in related males with trichothiodystrophy type 5.
- *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.
- *SSR4*. Losfeld et al. (Hum Mol Genet 23:1602, 2014) reported a *de novo* single base deletion in *SSR4*, a gene located in Xq28, which encodes a protein in the heterotetrameric translocon-associated protein complex in a 16 year old teenager with microcephaly, ID, seizures and gastroesophageal reflux. The protein is involved in N-glycosylation, hence represents a new congenital disorder of glycosylation.
- *STAG2*. Duplications in *STAG2* and adjacent genes have been reported in numerous families (Review by Yingjun et al., EJMG 58:116, 2015). Deletions and point mutations, known in both males and females show more severe developmental failure, growth, failure, microcephaly and midline malformations (Mullegama et al. Am J Med Genet 173A:1329, 2017). The gene, located at Xq25, regulates cohesion of sister chromatids and transcription.
- *SYP*. Tarpey et al. (Nat Genet 41:535, 2009) reported 4 mutations, three of them truncating, in *SYP* which encodes an integral membrane protein of small synaptic vesicles. The ID was mild to moderate. Some affected males had seizures, but other findings were inconsistent. Phillips et al. (Orphanet J Rare Diseases 9:49, 2014) reported a missense variant in *SYP* (Xp22.2) in 9 males (3 generations) with mild-moderate ID, prominent supraorbital ridges, deep-set eyes, short philtrum and prominent chin. Three males had hypoplasia of the corpus callosum and mild cortical atrophy. The authors considered this to be a syndromal presentation; mutations in this gene have been previously reported in nonsyndromal XLID.
- *TAF1*. Lyon et al. (17th Int. Fragile X and Early-Onset Cognitive Disorders Workshop, Strasbourg, France, Sept 27-30, 2015) reported a missense mutation in two brothers with severe ID, , anteverted nares, sagging cheeks, downslanted palpebrae, deep-set eyes, thin upper lip, arched palate, prominent ears, pointed chin and a “caudal prominence”.
- *TMLHE*. Alterations in this gene, located adjacent to *PAR2* in Xq28, has been implicated as a risk factor for autism. Some of the affected males also have ID, others have normal intelligence. The gene encodes 6-N-trimethyllysine dioxygenase, the first enzyme in carnitine synthesis. A deletion of exon 2 is the most common alteration and is found 2.8 fold more frequently in male siblings with autism than in sporadic autism or in controls

(Celestino-Soper et al. Proc Nat'l Acad Sci USA 109:7974, 2012). Nonsense and missense mutations have also been reported (Nava et al. Transl Psychiatry 2:e179, 2012).

- *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.
- *USP27X*. Hu et al. (Mol Psychiatry 21:133, 2016) reported a truncating variant and a missense variant in 2 families with 12 affected males. Cognitive function was borderline to moderately impaired, speech absent or limited and behavioral problems were present in some males. The function of this ubiquitin specific protein is unknown but may have a serotonergic function.
- *WDR45*. Saitsu et al. (Nat Genet 45:445, 2013) reported 5 females with globally delayed development in childhood and neurodegeneration with seizures, dystonia, rigidity, tremors, brain iron accumulation and cerebral atrophy in early adulthood. The *WDR45* gene, located at Xp11.23, may have diverse cellular functions including autophagy. Prior reports of this distinctive form of neurodegeneration with brain iron accumulation include those of Gregory et al. (J Med Genet 46:73, 2009) and Haack et al. (Am J Hum Genet 91:1144, 2012).
- *ZC4H2*. Hirata et al. (Am J Hum Genet 92:681, 2013) reported mutations in the zinc-finger gene *ZC4H2* in four families with arthrogryposis and 1 family with cerebral palsy. Carrier females were affected but to a lesser degree. The gene is located in Xq11.2. Miles-Carpenter syndrome (Am J Med Genet 38:215, 1991) also harbors a mutation in this gene May et al. (Hum Mol Genet 24:4848, 2015).
- *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.
- *ZMYM3*. Phillips et al. (Orphanet J Rare Diseases 9:49, 2014) reported a nonsense mutation in this Xq13.1 gene in 3 brothers with microcephaly, large ears, aortic valve abnormalities, hypospadias and sleep disorder. The intellectual disability was moderate.
- *ZNF711*. Tarpey et al. (Nat Genet 41:535, 2009) reported truncating mutations in *ZNF711*, located at Xq21.1, in 2 families. Both families were said to have moderate ID without other distinctive findings.

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 (de Brouwer 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*, Xp22.2 (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: Xq27.3
- IDX26: Xp11.4-Xq23
- IDX27: 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: Xp11.21-q21.32
- 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 Genet* 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 (Yntema et al., *Am J Med Genet* 85:205, 1999)
- 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 Mutat 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)
- 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* (Mignon-Ravix et al. AJMG 164A:1991, 2014)
- IDX104: *FRMPD4* (Hu et al. Mol Psychiatry 21:133, 2016)
- IDX105: *USP27X* (Hu et al. Mol Psychiatry 21:133, 2016)

Other IDX Genes

- *ALG13*
- *NLGN4*
- *CDKL5 (STK9)*
- *FGDY*
- *ATRX (XNP)*
- *AFF2 (FMR2)*
- *SLC6A8*
- *KLF8*
- *NDUFA1*
- *SRPX2*
- *NLGN3*
- *CXorf56*
- *ZFP92*
- *SLC9A7*

IV. Segmental X Chromosome Duplications (Updated May 2019)

As of May 2019, 146 genes on the X-chromosome have been associated with X-linked intellectual disability (XLID). Variants in 116 of these genes have been associated with XLID syndromes and 28 exclusively with nonsyndromal XLID (IDX). Duplication of every gene associated with XLID has been identified in one or more individuals. Duplication of 142 of the XLID genes have been identified in males and duplications of 4 XLID genes (*KDM6A*,

ZNF674, *RBM10*, and *KLF8*) have been found only in females. 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 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).