X-Linked Intellectual Disability (revised January 2020)

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.

New Syndromes and Localizations (2017 – Present)

- 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. 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.

New Gene Identifications (2017 – Present)

- *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.
- *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.

- *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. 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.
- *OGT.* Vaidyananthan 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 Niranjan et al. (PLoS One 10:e0116454, 2015). Has been assigned to MRX106.
- *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.
- *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.

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, 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: 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 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 (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 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)
- 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*

I. Segmental X Chromosome Duplications (Updated January 2020)

As of January 2020, 146 genes on the X-chromosome have been associated with X-linked intellectual disability (XLID). Variants in 118 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).