

X-Linked Intellectual Disability (revised December 2022)

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 2022 (Schwartz et al. *Am J Med Genet* 191:144, 2023).

New X-linked intellectual disability syndromes, new gene localizations, revised gene localizations, and gene identifications are presented in abbreviated form with appropriate references. Five graphics (1A, 1B, 1C, 2, 3) 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
- III. Candidate XLID genes
- IV. IDX Families, Genes and Loci
- V. Segmental X Chromosome Duplications
- VI. Summary of XLID: Figures (5) and Table of Gene Identifications

I. New Syndromes and Localizations (2021 – Present)

- TCEAL1-related XLID. Hijazi et al. (*AJHG* 109:2270, 2022) reported males and females with deletions and sequence alterations in *TCEAL1* located in Xq22.2. Major findings included DD/ID, hypotonia, abnormal gait, and autistic mannerisms. The facies were described as mildly dysmorphic and some individuals had ocular abnormalities, brain malformations, GI symptoms, seizures and recurrent infections.
- Prieto syndrome. Kury et al. (*Genet Med* 24:1941, 2022) reported alterations in *WNK3*, located in Xp11.22, in 14 individuals including the 3 generation family reported by Prieto et al. (*Clin Genet* 32:326, 1987). Major clinical findings included variable facial dysmorphism, hypotonia, DD/ID and brain anomalies. New Gene Identifications (2021 – Present)

II. New Gene Identifications (2021 - Present)

- *TCEAL1*. Hijaz et al. (*AJGH* 109:2270, 2022) reported males and females with hemizygous truncating variants, a hemizygous missense variant, a heterozygous frameshift variant, a heterozygous deletion of *TCEAL1*, and a heterozygous contiguous gene deletion which included *TCEAL1*. Patients had DD/ID autistic behaviors, hypotonia, abnormal gait, and mildly abnormal facial features (broad forehead, deep set eyes, bow-shaped upper lip). Some patients had ocular abnormalities, brain anomalies, seizures, recurrent infections, and gastrointestinal symptoms. The gene, located at Xq22.2, may play a role in regulation of transcription.

- *WNK3*. Pathogenic sequence variants in *WNK3* were reported in 6 families by Kury et al. (Genet Med 24:1941, 2022). Included among these was the family of 6 males in three generations with Prieto syndrome (Prieto et al. Clin Genet 32:326, 1987). Clinical findings in the majority of 14 cases included DD/ID, hypotonia, variable facial dysmorphism (trigonocephaly, hypertelorism, tubular/prominent nose, retrognathia) and abnormalities on brain imaging. Less than half had microcephaly, seizures and abnormal behavior. The gene, located at Xp11.22 is involved in phosphorylation of a neuronal-specific chloride transporter.

III. 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. (Wieland et al., Hum Mut 26:113, 2005).
- *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).
- *PLXNA3*. Steele et al. (Pediatr Neurol 126:65, 2022) reported 14 boys with variable ID, ASD, and missense alterations in *PLXNA3*, a gene in Xq28 that encodes a plexin receptor in fetal brains. Six patients had seizures and most had fine motor dyspraxia, ADHD and aggressive behavior. Two other males had been previously reported by Athanasakis et al. (AJMG 1640:170, 2014).
- *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).

IV. 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 (Arveiler B, et al. AJMG 30:473, 1988)
- IDX5: Xp21.1-Xq21.3 (Samanns C, et al. AJMG 38:224, 1991)
- IDX6: Xq27 (Kondo I, et al. Cytogenet Cell Genet 58:2071, 1991)
- IDX7: Xp11.23-Xq12 (Jedele KB, et al. AJMG 43:436, 1992)
- IDX8: *DLG3*, Xq13.1 (*unpublished*, Schwartz et al.)
- IDX9: *FTSJ1*, Xp11.23 (Ramser et al. J Med Genet 41:679, 2004)
- IDX10: *IL1RAPL1*, Xp11.4-Xp21.3 (deBrouwer et al. Hum Mutat 28:207, 2007)
- IDX11: Xp11.22-Xp21.3 (Kerr B, et al. AJMG 43:392, 1992)
- 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: *FTSJ1*, Xp11.22-Xq12 (Gendrot C, et al. Clin Genet 45:145, 1994; Toutain A, personal communication 2021))
- 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: *RPS6KA3* (*RSK2*), Xp22.2-Xp22.1 (Merienne et al. Nat Genet 22:13, 1999)
- IDX20: Not published as of 12/1/2021, Xp21.1-Xq23 (Lazzarini A, et al. AJMG

57:552, 1995; Kooy F., *personal communication*, 2021)

- 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 (Gregg RG, et al. Hum Mol Genet 5:411, 1996)
- IDX24: Xp22.2-Xp22.3 (Martinez F, et al. AJMG 55:387, 1995)
- IDX25: *SLC6A8*, Xq27.3 (*unpublished*, Friez 2019)
- IDX26: Xp11.4-Xq23 (Robledo R, et al. AJMG 64:107, 1996)
- IDX27: *PQBP1*, Xq24-Xq27.1
- IDX28: Xq27.3-qter (Holinski-Feder E, et al. AJMG 64:125, 1996)
- 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 (Bar-David S, et al. AJMG, 64:83, 1996)
- IDX38: *ARX*, Xp22.13 (Stepp et al. MBC Med Genet 6:16, 2005)
- IDX39: Xp11 (Teboul M, et al. J Genet Hum 37:179, 1989)
- IDX40: Contiguous Gene Deletion, Xq28 (May et al. 1995; van der Maarel et al. 1995)
- IDX41: *GDI1*, Xq28 (Bienvenu et al. Hum Mol Genet 7:1311, 1998)
- IDX42: Xq26 (Holinski-Feder E, et al. Eighth International Workshop on Fragile X and X- Linked Mental Retardation. Picton, Canada, 1997)
- 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 (Claes et al. AJMG 85:283, 1999)
- IDX52: *ARX*, Xp11.21-q21.32 (DeBrouwer 2019, not published)
- IDX53: Xq22.2-q26 (Ahmad W, et al. AJHG 61:A265, 1997)
- 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 (Withdrawn by HUGO, 2019)
- IDX57: Xq24-q25 (Holinski-Feder E, et al. Eighth International Workshop on Fragile X and X-Linked Mental Retardation. Picton, Canada, 1997)
- 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 (Laumonier 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: ZNF711, Xp11.3-Xq21.33, (Yntema et al. Am J Med Genet 85:205, 1999; van der Werf et al. Gene 605:92, 2017)
- IDX66: *PAK3*, Xq21.33-q23 (Raynaud, *personal communication*, 2016)
- 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 (Sismani 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: *UPF3B*, Xq24-q25 (Martinez et al. AJMGA 131A:170, 2020; Tejada et al. Front Genet 10:1074, 2019)
- 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: *KIAA2022*, 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 genes associated with nonsyndromal XLID families without IDX numbers.

- *ALG13*
- *NLGN4*
- *CDKL5 (STK9)*
- *ATRX (XNP)*
- *AFF2 (FMR2)*
- *SLC6A8*
- *KLF8*
- *NDUFA1*
- *SRPX2*
- *NLGN3*
- *ZFP92*
- *SIZN1 (ZCCHC12)*

V. Segmental X Chromosome Duplications (Updated December 2022)

As of December 2022, 164 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 (*IKBK*, *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).