X-Linked Intellectual Disability (revised March 2024)

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 (2021 – Present)

- TCEAL1-related XLID. Hijazi et al. (Am J Hum Genet 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 three 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)
- SLITRK2. XLID disorder III, caused by alterations in *SLITRK2*, is manifest by variable ID, neurobehavioral malfunctions, movement and tone abnormalities and seizures (El Chehadeh et al., Nat Comm 13:4112, 2022). Kyphoscoliosis white matter anomalies and feeding difficulties may affect half of patients. Seven male and one female from seven families have been reported.
- ATP2B3-related XLID. A missense alteration in *ATP2B3* has been found in a male and his uncle with severe ID and signs (Mir et al., BMC Med Genomics 16:239, 2023). The boy had global and severe development delay, hearing impairment, strabismus, hypotrichosis and low eyebrows. The uncle had long face, low

eyebrows and broad nasal tip.

- Pilorge XLID. A number of males with XLID, seizures, ocular abnormalities, and behavioral manifestations with alteration in *GLRA2* has been reported by Pilorge (Mol Psychiatry 21:936, 2016), Marcogliese et al. (Cell Rep 38:110517, 2022), Pitron et al. (Mol Psychiatry 16:867, 2011), and Mir et al. (BMC Med Genomics 16:239, 2023). Both males and females have been affected.
- SH3KBP1-related XLID. Deletion of *SH3KBP1* have been found in a family of 6 males and 1 female (compound heterozygous) affected with intellectual disability, global developmental delay, attention deficit hyperactivity disorder and partial agenesis of corpus collosum. Seizures and immunodeficiency related features such as asthma, allergy and eczema occurred in some affected individuals. Carrier females were unaffected.
- IL1RAPL2-related XLID. Loss of function variants in *IL1RAPL2* have been identified in seven males in four families affected with intellectual disability and autism. Ataxia may affect half of these patients.
- ZFX-related XLID. Shepherdson et al. (Am J Hum Genet 111:1, 2024) described 18 patients with variants in *ZFX*, located in Xp22.1, who also had a facial gestalt, neurodevelopmental disorder, and behavioral abnormalities. Patients with ZFX-related XLID appeared to be at an increased risk for congenital anomalies and hyperparathyroidism.
- SMARCA1-related XLID. Picketts et al. (Res Sq. 2023 Spe 29:rs.3.rs-331798) reported 40 patients from 30 families with pathogenic variants in *SMARCA1* (Xq25-26.1). The patients had variable intellectual delay/developmental delay, microcephaly and delayed or regressive speech development.

II. A. New Gene Identifications (2021 - Present)

- *TCEAL1.* Hijaz et al. (Am J Hum Genet 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 six families by Kury et al. (Genet Med 24:1941, 2022). Included among these was the family of six 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.

- *SLITRK2*. Missense variants in *SLITRK2* have been identified in seven males and one female from seven families have been reported as XLID disorder-III by El Chehadeh et al. (Nat Comm 13:4112, 2022). The gene located at Xq27.3 is a transmembrane protein that regulates neurite outgrowth and maintenance of excitatory synapses.
- *ATP2B3*. Mir et al. (BMC Med Genomics 16:239, 2023) and reported a missense alteration in *ATP2B3* (p.Asp847glu) in a male and his uncle with severe ID, seizures, and dysmorphic faces. The gene located on Xq28, controls calcium levels at the presynaptic terminals and have been associated with X-linked cerebellar ataxia.
- *GLRA2*. Pilorge et al. (Mol Psychiatry 21:936, 2016 and Marcogliese et al. (Cell Rep 38:110517, 2022) have reported a deletion and missense alterations in *GLRA2*, a gene at Xp22.2 that has a role in glycinergic signaling. Affected males have variable cognition skills, behavioral abnormalities, seizures and ocular manifestations. The disorder has been termed Pilorge type XLID.
- *SH3KBP1*. Deletion of *SH3KBP1* have been identified in 6 males and 1 female (compound heterozygous) in 4 generations in a family. Clinical findings include intellectual disability, global developmental delay, and partial agenesis of corpus collosum. The gene is located at Xp22.12, encodes an adapter protein that facilitates protein-protein interactions and is implicated in apoptosis, cytoskeletal rearrangement, cell adhesion and in the regulation of clathrin-dependent endocytosis.
- *IL1RAPL2.* Deletion of *IL1RAPL2* have been identified in four males in two generations in a family. Clinical findings include intellectual disability, ataxia and seizures. Additionally, three unrelated males with ID and autism have been identified to carry hemizygous truncating variant or deletion of *IL1RAPL2*. The gene is located Xq22.3, encodes a member of the interleukin 1 receptor family, most closely related to *IL1RAPL1* that is associated with XLID.
- *ZFX.* This X-linked zinc finger protein, located at Xp22.1 is a transcription factor involved in oncogenesis and development as well as neurodevelopment (Shepherdson et al. Am J Hum Genet 111:1, 2024).
- *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).

II. B. New XLID Disorder-Gene Associations (2021-Present)

- *RBMX* and Gustavson syndrome. Johansson et al. (Eur J Hum Genet 32:333, 2024) reported an in-frame deletion of *RBMX* in the original 5-generation Swedish family with XLID reported by Gustavson et al. (Am J Med Genet 45:654, 1993).
- *WNK3* and Prieto syndrome. Kury et al. (Genet Med 24:1991, 2022) reported a missense alteration in *WNK3* in the 3-generation family reported by Prieto et al. (Clin

Genet 32:326, 1987).

- *DLG3* and IDX20. Huyghebaert et al. (Eur J Hum Genet 32:317, 2024) reported a stop alteration in *DLG3* in the 2-generation family (IDX20) reported by Lazzarini et al. (Am J Med Genet 57:552, 1995).

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.
- *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 two 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., Am J Hum Genet 96: 640-650, 2015).
- *PLXNA3*. Steele et al. (Pediatr Nuerol 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. (Am J Med Genet 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 (Am J Hum Genet 67:563, 2000).

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. Am J Med Genet 30:473, 1988)
- IDX5: Xp21.1-Xq21.3 (Samanns C, et al. Am J Med Genet 38:224, 1991)
- IDX6: Xq27 (Kondo I, et al. Cytogenet Cell Genet 58:2071, 1991)
- IDX7: Xp11.23-Xq12 (Jedele KB, et al. Am J Med Genet 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. Am J Med Genet 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, 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: *RPS6KA3* (RSK2), Xp22.2-Xp22.1 (Merienne et al. Nat Genet 22:13, 1999)
- IDX20: *DLG3*, Xq13.1 (Huyghebaert et al. Eur J Hum Genet 32:317, 2024)
- 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. Am J Med Genet 55:387, 1995)
- IDX25: *SLC6A8*, Xq27.3 (*unpublished*, Friez 2019)
- IDX26: Xp11.4-Xq23 (Robledo R, et al. Am J Med Genet 64:107, 1996)
- IDX27: *PQBP1*, Xq24-Xq27.1

- IDX28: Xq27.3-qter (Holinski-Feder E, et al. Am J Med Genet 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. Am J Med Genet, 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. Am J Med Genet 85:283, 1999)
- IDX52: *ARX*, Xp11.21-q21.32 (DeBrouwer 2019, not published)
- IDX53: Xq22.2-q26 (Ahmad W, et al. Am J Hum Genet 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 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: 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. Am J Med Genet A 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. Am J Med Genet 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 March 2024)

As of December 2022, 164 genes on the X-chromosome have been associated with X-linked intellectual disability (XLID). The association of nine of these genes are considered uncertain (Piton et al. Am J Hum Genet 93:368, 2013). In addition, there are seven 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, usually 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).

Sahajpal et al. (Clin Genet 105:123, 2023) have described the clinical findings associated with duplication of 22 individual genes.

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).

VI. Summary of XLID (Updated March 2024)

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 1C – Location of genes associated with syndromic XLID and nonsyndromic XLID combined.
- 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. Note that IDX56 has been withdrawn by HUGO (2018) and IDX83 and IDX86 have not been published. IDX69 has also not been published but the linkage internal is known.
- Table - Listing of XLID genes and gene functions chronologically by year of discovery.