HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Am J Med Genet A. 2018 June ; 176(6): 1375–1388. doi:10.1002/ajmg.a.38710.

XLID Update 2017

Giovanni Neri[1,2], **Charles E. Schwartz**[1], **Hebert A. Lubs**[1], and **Roger E. Stevenson**[1]

[1]JC Self Research Institute of Human Genetics, Greenwood Genetic Center, Greenwood, South Carolina, USA

[2]Istituto di Medicina Genomica, Università Cattolica del S. Cuore, Roma

Abstract

The X-chromosome comprises only about 5 percent of the human genome but accounts for about 15 percent of the genes currently known to be associated with intellectual disability. The early progress in identifying the XLID-associated genes through linkage analysis and candidate gene sequencing has been accelerated with the use of high throughput technologies. In the 10 years since the last update, the number of genes associated with XLID has increased by 96 percent from 72 to 141 and duplications of all 141 XLID genes have been described, primarily through the application of high resolution microarrays and next generation sequencing. The progress in identifying genetic and genomic alterations associated with XLID has not been matched with insights that improve the clinician's ability to form differential diagnoses, that bring into view the possibility of curative therapies for patients, or that inform scientists of the impact of the genetic alterations on cell organization and function.

Keywords

X chromosome; intellectual disability; syndrome; genes; XLID

Introduction

Over the last three decades there has been remarkable progress in the understanding of X-linked intellectual disability (XLID). The X chromosome was targeted for study because of the excess of males among all individuals with intellectually disability (ID) and the availability of numerous families in which ID followed an X-linked pattern of inheritance. Milestones in the early history of XLID were the study of Penrose (1938) on institutionalized individuals, the description of large XLID families by Martin and Bell (1943), Allan et al. (1944) and Renpenning et al. (1962) and subsequent work by Lehrke (1972). Additional strong motivation came from the notion that the X-chromosome might harbor a disproportionate fraction of genes that influence cognitive function (Turner and Partington 1991) and the discovery of the Fragile X syndrome (*a posteriori*, rediscovery of

Correspondence to: Roger E. Stevenson, MD, J.C. Self Research Institute of Human Genetics, Greenwood Genetic Center, 113 Gregor Mendel Circle, Greenwood, SC 29646, USA, Phone: 864-941-8146, Fax: 864-388-1707, res@ggc.org.

Conflicts of Interest: All authors declare that there are no conflicts of interest.

the Martin-Bell syndrome), the first XLID entity to be regionally mapped to the X-chromosome (Lubs 1969).

Looking back at previous XLID updates published regularly every two years from 1990 to 2000 and again in 2008, it is apparent that great efforts went into classifying conditions whose phenotypes could not be more diverse. Eventually, these efforts failed, with the exception of the distinction of syndromal from nonsyndromal XLID. Even though the line dividing the two classes is blurred, sometimes arbitrary and difficult to defend from a biological standpoint, it has by now acquired quasi-historical value and deserves to be retained. In compiling the current update, no effort was made to categorize conditions and associated genes. In the practical terms of diagnosis and counseling, what is important is to know the causal genes, the mode of transmission and possibly the pathogenic mechanism.

XLID update 2017 includes the enumeration of all currently known syndromes, nonsyndromal conditions (IDX), and genes, with particular attention to the syndromes described and genes assigned since the 2007 XLID update (Chiurazzi et al. 2008). The discovery of XLID genes has, in large measure, moved from the research laboratory to the diagnostic laboratory during the past decade. Linkage analysis and candidate gene testing has been replaced with X-chromosome or exome sequencing. Various microarray technologies have identified duplications of all XLID genes, bringing attention to genomic aberrations that may even outnumber gene sequence variants. A section of this update, not present in previous editions, describes these duplications and comments on their relevance.

Finding the outstanding causal genes, possibly as many as 80, should complete the delineation of XLID at the genetic/genomic level. This may require utilizing newly emerging technologies – higher resolution microarrays, genome and RNA sequencing, metabolomics and epigenomics.

New Entries

Since the last update in 2007, 69 new XLID genes have been reported in the literature (Table I). Most of these have been associated with syndromal entities, both previously reported and novel. The identified 69 XLID genes may actually be less. As pointed out by Piton et al. (2013), for three genes (*MAGT1*, *RAB40AL*, *NXF5*) the databases utilized as “controls” contain too many loss of function mutations. For three other genes (*RPL10*, *ZMYM3*, *SIZN1*), there have been only a single report so that their inclusion as XLID genes needs replication in additional studies, as further discussed below.

Among the remaining 63 XLID validated genes identified since 2007, there are 10 (16%) which are associated with the broad process of transcription and an almost equal number, 8 (13%), are involved with either ubiquitination or metabolism. The ubiquitination category was hardly represented among genes reported prior to 2007. Additionally, there is a large group of genes, 13, whose protein function does not fit clearly into an ontology group either because the function is not yet known (e.g. *ZC4H2*), or its function is not classified (e.g. *HMGB3*), or because the function could place it into two separate groups (e.g. *STAG2*).

With the increased annotation of the genome using both genomic and RNA sequencing, at least 6 XLID genes have been found to have anti-sense transcripts (*SYP*, *PTCHD1*, *THLHE*, *USP27X*, *SLC25A5* and *HCFC1*). It is quite possible that alterations in the noncoding portions of these genes might adversely affect the function, if there is one, of their anti-sense RNA. This may be true for genes cloned before 2007, including *FMR1*.

Listing of All Known Genes

All XLID genes known to date (141) are listed by year of discovery in Supplementary Table I (S1). The position on the X chromosome of genes associated with XLID syndromes is depicted in Fig. 1. Perusal of the list calls for some comments and considerations. Three syndromes initially reported as X-linked have been found to be autosomal and have been retired. These are Zollino syndrome, initially believed to be X-linked based on one pedigree and subsequently found to be due to an unbalanced 1;12 translocation (Zollino et al. 1992, 2003), Roifman syndrome, initially reported to be X-linked and subsequently found to be caused by a deletion on 2q (Roifman 1999, Merico et al. 2015), and Wittwer syndrome, initially mapped to Xp22.3 and later found to be caused by an unbalanced 4;17 translocation (Wittwer et al. 1996, Wieland et al. 2014).

Several syndromes previously listed in XLID updates have been removed because the limited evidence that they have intellectual disability as a primary manifestation or that they are X-linked. These include XLID-retinoschisis (312700), X-linked hypoparathyroidism (307700), Giuffrè-Tsukahara (603438), Hyde-Forster (300064), Homfray seizures-contractures, XLID-precocious puberty, and XLID-thyroid aplasia-cutis verticis gyrata. Two additional syndromes have been removed because they appear to be contiguous gene syndromes (XLID-choroideremia-ectodermal dysplasia and XLID-retinitis pigmentosa).

As alluded to above, in 2013, Piton et al. challenged the validity of 25 of the 106 genes then reported to be associated with XLID. Five of the challenged genes were considered highly questionable, five questionable and fifteen in need of replication. None of the 5 highly questionable gene assignments has been confirmed. Of the 5 questionable genes, only *ATP6AP2* has been confirmed. Of the 15 assignments in need of replication, additional cases with *MAOA, HCFC1, CCDC22, CNKSR2, KIAA2022, NAA10* and *SHROOM4* sequence variants have now been published, leaving 17 of the 25 challenged genes unresolved. These genes are identified by an asterisk (*) in Table S1.

Furthermore, a comment on penetrance is in order. Although 183 conditions are classified as XLID syndromes, it is appropriate to note that not all individuals with one of these diagnoses will have ID. Exemplifying this is the inconsistent or even infrequent occurrence of intellectual disability among individuals with Incontinentia Pigmenti, Dyskeratosis Congenita, Oralfacialdigital I, Duchenne Muscular Dystrophy, Simpson-Golabi-Behmel, Aarskog and Nance-Horan syndromes among others. In similar fashion, the severity of ID may vary considerably within certain syndromes e.g., Pelizaeus-Merzbacher, Hunter and Christian syndromes.

In Fig. 2, a histogram illustrates the growing knowledge of XLID syndromes and respective causal genes from 1988 to date. The number of known syndromes has increased from 83 to 183, and the number of cloned genes associated with XLID syndromes from 5 to 113. If we inspect the last column (but this is also true for the others), the apparent discrepancy between 136 syndromes with gene assigned and only 113 genes cloned, requires an explanation. This is due to the fact that a number of genes were found to be responsible for more than one syndrome. Genes that have been linked to three or more XLID syndromes include *PQBP1, ATRX, ARX, FLNA, AP1S2* and *MED12*. The allelic *PQBP1*-associated disorders include Renpenning, Sutherland-Hann, Hamel Cerebro-Palato-Cardiac, Golabi-Ito-Hall, and Porteous syndromes, all of which have a degree of phenotypic concordance. Strong phenotypic overlap may also be noted among the entities associated with *ATRX* variants (Alpha-Thalassemia Intellectual Disability, Chudley-Lowry, Holmes-Gang, Carpenter-Waziri, and Arch Fingerprints-Hypotonia syndromes) and the entities associated with *AP1S2* variants (Fried syndrome, XLID-Hydrocephaly-Basal Ganglia Calcifications, and Turner XLID syndrome). This is not the case for *ARX* variants, which have been found in the disparate phenotypes of Partington syndrome, West syndrome, X-linked lissencephaly with abnormal genitalia, hydranencephaly with abnormal genitalia, Proud syndrome, Ohtahara syndrome as well as nonsyndromal XLID (IDX 29, 32, 33, 36, 38, 43, 54, 76, 87). Similar phenotypic discordance has been found among the *FLNA*-associated disorders (otopalatodigital I and II syndromes, periventricular heterotopias, spondylometaphyseal dysplasia and Melnick-Needles syndrome) and the *MED12*-associated disorders (Opitz FG, Lujan, and Ohdo syndromes). As to the mapped and unmapped syndromes, totaling 47, some were described in families now lost to follow-up and do not imply that another 47 genes await discovery. It is quite possible that a number of these syndromes could be explained by genes discovered after their initial description.

As to the families with nonsyndromal XLID which have received IDX numbers, their total is currently 105 (Figure 3). For 67 of these families, the genes have been cloned, 33 have been mapped but the genes have not been identified and 5 have reserved IDX numbers (IDX8, 50, 69, 83 and 86) but have not been published. Twenty-eight of the “IDX genes” in Figure 3 have also been associated with XLID syndromes. Sequence variants in 11 genes (*KLF8, AFF2, SLC6A8, NDUFA1, ALG13, SRPX2, ATRX, NLGN3, FGDY, CDKL5,* and *NLGN4*) have been found in families with IDX but in whom IDX numbers were never assigned.

Duplication of Xlid Of Genes

Segmental duplications involving all protein-coding regions of XLID-associated genes on the p and q arms of the X chromosome have been reported. They vary in size from a few kilobases to many megabases and do not cross the centromere. Relative to phenotypic consequences of duplications, their informativeness is inversely proportional to the length and the number of genes encompassed within the duplicated segment. Among those duplications which appear to be clinically important, marked skewing of X-inactivation in females is typical.

Duplication of 137 of the 141 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, has been found only in large duplications that involve the entire p arm (Tuck-Muller et al. 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*, *HUWE1* and *OCRL* (van Esch et al. 2005; Friez et al. 2006, 2016; Froyen et al. 2007, 2008; Leroy et al. 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. 2009).

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. 2014; Popovici et al. 2014; Maurin et al. 2017).

Duplication of *PLP1*

Sequence variants in the coding or splice site regions of *PLP1* are found in less than half of families with Pelizaeus-Merzbacher syndrome. More commonly, the condition is caused by duplications of the entire gene (Mimault et al. 1999; Regis et al. 2008). The severity of the signs and symptoms – nystagmus, initial hypotonia progressing to spastic paraplegia, ataxia, tremors, dystonia and other abnormal movements of the limbs, white matter dysmyelination, and basal ganglia deposits – do not appear to be related to the size of the duplications.

Duplication of *HUWE1*

Sequence variants in *HUWE1* have been associated with Juberg-Marsidi syndrome, Brooks syndrome, Turner XLID-macrocephaly syndrome, and a family in which males had moderate ID and normal facial appearance (Friez et al 2016; Turner et al. 1994; Froyen et al. 2008). Duplication of *HUWE1*, usually associated with a *HSD17B10* duplication, has been associated with ID of moderate severity, limited speech or dysarthria, facial dysmorphism (hypertelorism, upslanted palpebral fissures, synophrys, open mouth) and usually normal prenatal and postnatal growth measurements (Froyen et al 2008; Whibley et al. 2010; Orivoli et al. 2016). Two families (IDX17 and IDX31) had no distinctive dysmorphism and had normal growth. Seizures occurred in several patients, one individual had submucous cleft palate and two boys had first-degree hypospadias.

Duplication of *STAG2*

A number of duplications of Xq25, a gene poor region have been reported in males and females. *STAG2*, which encodes a subunit of the cohesin complex, is completely duplicated in these cases and adjacent genes *(XIAP, THOC2, GRIA3, SH2D1A, and TENM1)* are variably duplicated completely or partially (Kumar et al. 2015). The phenotype is dominated by ID of variable severity. Other common features include normal stature and head circumference, malar flatness, thick lip vermilion, prognathism, facial hypotonia and behavioral problems. Seizures and autism occur in a third or less. In contrast, individuals with deletions or sequencing variants of *STAG2* have more severe developmental failure, growth impairment, microcephaly and midline malformations including holoprosencephaly or other CNS anomalies, facial clefting, and ocular colobomas.

Duplication of *MECP2*

Rett syndrome, due to deletions or sequence variants in *MECP2* and characterized by a period of normal development in infancy followed by microcephaly and episodic but unrelenting course of neurological deterioration, loss of purposeful hand use, seizures, and spasticity, differs quite substantially from the manifestations of patients with *MECP2* duplications. From birth, patients with duplications have hypotonia which later in childhood progresses to spasticity, absent or limited speech and ambulation, and recurrent respiratory infections which often requires tracheostomy and ventilator care. They have severe ID often complicated by seizures, and most die prior to age 25 years (Meins et al. 2005; van Esch et al. 2005; Friez et al. 2006, Vignoli et al. 2012; Lim et al. 2017). Although initially described as an X-linked recessive syndrome in males, more recent reports have confirmed occurrence in females, generally expressed as infantile hypotonia progressing to spasticity, severe ID and neurodevelopmental manifestations including autism spectrum disorder (Scott Schwoerer et al. 2014; Fieremans et al. 2014).

Duplication of *OCRL*

Lowe syndrome, caused by sequence variants or deletions of *OCRL*, is characterized by early onset cataracts, depressed muscle tone and reflexes, aminoaciduria, and ID. Duplication of *OCRL* has been described in 3 families, all in the company of duplications of adjacent genes (Møller et al. 2014; Schroer et al. 2012). They have had neurodevelopmental abnormalities, ID, autism, and seizures but in no other respect has the phenotype of Lowe syndrome been seen among these boys.

Concluding Remarks

In spite of the progress made over the past 30 years, much remains to be done before the XLID field may be considered fully defined. Perhaps as many as 80 additional genes could still be implicated in XLID. Discovery of pathogenic mechanisms probably represents the next biggest challenge, requiring intense efforts by several laboratories and proportionately large financial support. Is this justifiable? The question is legitimate, in view of the rarity of each individual condition, with the exception of the fragile X syndrome and a small number of other XLID syndromes, and of the limited resources available. On the other hand, if the effort conducted so far were meant to be, as in fact it is, preparatory to the ultimate goal,

namely the cure, or at least the improvement, of XLID, it would not make sense to halt studies now. The current state of XLID knowledge has little to offer to further such an ultimate goal. As for most genetic diseases, few are the therapeutic successes. Enzyme infusions, stem cell and bone marrow transplantation, drugs and dietary management have been partially effective in a small number of conditions, e.g. ornithine transcarbamoylase deficiency, Hunter syndrome, adrenoleukodystrophy and phosphoglycerate kinase deficiency. A more widely applicable intervention, gene therapy, is on the horizon, with the recent development of delivery vectors that appear to reach target tissues and avoid safety concerns of the past (Hocquemuller et al. 2016), but at the present time it continues to be a hope for the future.

In the meanwhile, a number of outstanding issues continue to challenge clinicians, scientists and families alike. Clinicians must consider in the differential diagnosis a large number of syndromes when evaluating a male with ID and somatic, neurologic, or behavior manifestations and an almost equally large number of possibilities when evaluating a male with ID and no other manifestations. Family history does not help in isolated cases, but can be very informative in kindreds with multiple affected individuals. Physical examination continues to be the basic tool of clinical diagnosis, now aided by a number of genetic databases, including OMIM, POSSUM and Face2Gene. Recognition and use of the human phenotype ontology will bring consistency in describing the clinical manifestations of the various XLID disorders (Robinson et al. 2008).

For scientists, the unresolved issues are no less daunting. While acknowledging the disproportionate progress of identifying ID-associated alterations on the X-chromosome in comparison to ID-associated alterations on the autosomes, knowledge about the impact of these alterations on cellular organization and functions remains limited (Vissers et al. 2010, Dekker and Mirny 2016, Kochinke et al. 2016, Schwarzer et al. 2017). Although sequence variants of uncertain pathogenicity continue to distress laboratory and clinical geneticists, a more systematic approach to their resolution with functional studies including protein modeling, enzyme analysis, metabolomics, RNAseq, immunofluorescence studies of the protein in cell cultures and animal models is being formulated in many laboratories. Recently emerged technologies promise to identify alterations of the X-chromosome, especially involving the noncoding regions of the genome, for those XLID entities which have not been resolved with currently used technologies. These include whole genome sequencing, higher resolution microarray analysis, and structural rearrangement detection (Bionano Genomics).

As to the families, the main services which can be offered continue to be estimation of recurrence risks, preimplantation and prenatal diagnosis, ultrasonographic monitoring of at risk pregnancies, best possible neonatal treatment in cases requiring intensive care, habilitation therapies and advocacy for their needs. The development of treatments which significantly ameliorate the signs and symptoms of the XLID disorders has been disappointingly slow and current clinical trials have limited outcome goals. Abandonment of the notion that the brain is not accessible and development of methods to produce adequate amounts of native genes or CRISPR-cas engineered genes are only two of the major hurdles

that gene therapy must overcome before reaching the bedside of patients with XLID disorders (Hocquemiller et al. 2016).

Most X-linked disorders are rare and thus access to multiple cases will be limited. Utilization of GeneMatcher to locate other cases with variants in XLID genes helps to connect researchers and clinicians which stimulate the pursuit of functional studies. In the end, it should not be forgotten that the alliance between physicians, scientists and families has spawned some of the greatest successes in discovering the causes of genetic diseases and delineating their phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

Allan W, Herndon CN, Dudley FC. Some examples of the inheritance of mental deficiency: apparently sex-linked idiocy and microcephaly. American Journal of Mental Deficiency. 1944; 48:325–334.

Chiurazzi P, Schwartz CE, Gecz J, Neri G. XLMR genes: update 2007. European Journal of Human Genetics. 2008; 16:422–434. [PubMed: 18197188]

Dekker J, Mirny L. The 3D Genome as Moderator of Chromosomal Communication. Cell. 2016; 164:1110–1121. [PubMed: 26967279]

Fieremans N, Bauters M, Belet S, Verbeeck J, Jansen AC, Seneca S, et al. Froyen G. De novo MECP2 duplications in two females with intellectual disability and unfavorable complete skewed X-inactivation. Human Genetics. 2014; 133:1359–1367. [PubMed: 25037250]

Friez MJ, Brooks SS, Stevenson RE, Field M, Basehore MJ, Ades LC, et al. Schwartz CE. HUWE1 mutations in Juberg-Marsidi and Brooks syndromes: the results of an X-chromosome exome sequencing study. BMJ Open. 2016; 6:e009537.

Friez MJ, Jones JR, Clarkson K, Lubs H, Abuelo D, Bier JA, et al. Stevenson RE. Recurrent infections, hypotonia, and mental retardation caused by duplication of MECP2 and adjacent region in Xq28. Pediatrics. 2006; 118:e1687–1695. [PubMed: 17088400]

Froyen G, Corbett M, Vandewalle J, Jarvela I, Lawrence O, Meldrum C, et al. Gecz J. Submicroscopic duplications of the hydroxysteroid dehydrogenase HSD17B10 and the E3 ubiquitin ligase HUWE1 are associated with mental retardation. American Journal of Human Genetics. 2008; 82:432–443. [PubMed: 18252223]

Froyen G, Van Esch H, Bauters M, Hollanders K, Frints SG, Vermeesch JR, et al. Marynen P. Detection of genomic copy number changes in patients with idiopathic mental retardation by high-resolution X-array-CGH: important role for increased gene dosage of XLMR genes. Human Mutation. 2007; 28:1034–1042. [PubMed: 17546640]

Hocquemiller M, Giersch L, Audrain M, Parker S, Cartier N. Adeno-Associated Virus-Based Gene Therapy for CNS Diseases. Human Gene Therapy. 2016; 27:478–496. [PubMed: 27267688]

Kochinke K, Zweier C, Nijhof B, Fenckova M, Cizek P, Honti F, et al. Schenck A. Systematic Phenomics Analysis Deconvolutes Genes Mutated in Intellectual Disability into Biologically Coherent Modules. American Journal of Human Genetics. 2016; 98:149–164. [PubMed: 26748517]

Kumar R, Corbett MA, Van Bon BW, Gardner A, Woenig JA, Jolly LA, et al. Gecz J. Increased STAG2 dosage defines a novel cohesinopathy with intellectual disability and behavioral problems. Human Molecular Genetics. 2015; 24:7171–7181. [PubMed: 26443594]

Lehrke R. A theory of X-linkage of major intellectual traits. Response to Dr. Anastasi and to the Drs. Nance and Engel. American Journal of Mental Deficiency. 1972; 76:626–631. [PubMed: 5031083]

Leroy C, Jacquemont ML, Doray B, Lamblin D, Cormier-Daire V, Philippe A, et al. Malan V. Xq25 duplication: the crucial role of the STAG2 gene in this novel human cohesinopathy. Clinical Genetics. 2016; 89:68–73. [PubMed: 25677961]

Lim Z, Downs J, Wong K, Ellaway C, Leonard H. Expanding the clinical picture of the MECP2 Duplication syndrome. Clinical Genetics. 2017; 91:557–563. [PubMed: 27247049]

Lubs HA. A marker X chromosome. American Journal of Human Genetics. 1969; 21:231–244. [PubMed: 5794013]

Lugtenberg D, de Brouwer AP, Oudakker AR, Pfundt R, Hamel BC, van Bokhoven H, Bongers EM. Xq13.2q21.1 duplication encompassing the ATRX gene in a man with mental retardation, minor facial and genital anomalies, short stature and broad thorax. American Journal of Medical Genetics Part A. 2009; 149A:760–766. [PubMed: 19291773]

Martin JP, Bell J. A Pedigree of Mental Defect Showing Sex-Linkage. Journal of neurology and psychiatry. 1943; 6(3-4):154–157. [PubMed: 21611430]

Maurin ML, Arfeuille C, Sonigo P, Rondeau S, Vekemans M, Turleau C, et al. Malan V. Large Duplications Can Be Benign Copy Number Variants: A Case of a 3.6-Mb Xq21.33 Duplication. Cytogenetic and Genome Research. 2017; 151:115–118. [PubMed: 28273668]

Meins M, Lehmann J, Gerresheim F, Herchenbach J, Hagedorn M, Hameister K, Epplen JT. Submicroscopic duplication in Xq28 causes increased expression of the MECP2 gene in a boy with severe mental retardation and features of Rett syndrome. Journal of Medical Genetics. 2005; 42:e12. [PubMed: 15689435]

Merico D, Roifman M, Braunschweig U, Yuen RK, Alexandrova R, Bates A, et al. Scherer SW. Compound heterozygous mutations in the noncoding RNU4ATAC cause Roifman Syndrome by disrupting minor intron splicing. Nature Communications. 2015; 6:8718.

Mimault C, Giraud G, Courtois V, Cailloux F, Boire JY, Dastugue B, Boespflug-Tanguy O. Proteolipoprotein gene analysis in 82 patients with sporadic Pelizaeus-Merzbacher Disease: duplications, the major cause of the disease, originate more frequently in male germ cells, but point mutations do not. The Clinical European Network on Brain Dysmyelinating Disease. American Journal of Human Genetics. 1999; 65:360–369. [PubMed: 10417279]

Møller RS, Jensen LR, Maas SM, Filmus J, Capurro M, Hansen C, et al. Kleefstra T. X-linked congenital ptosis and associated intellectual disability, short stature, microcephaly, cleft palate, digital and genital abnormalities define novel Xq25q26 duplication syndrome. Human Genetics. 2014; 133:625–638. [PubMed: 24326587]

Orivoli S, Pavlidis E, Cantalupo G, Pezzella M, Zara F, Garavelli L, et al. Piccolo B. Xp11.22 Microduplications Including HUWE1: Case Report and Literature Review. Neuropediatrics. 2016; 47:51–56. [PubMed: 26587761]

Penrose LS. Genetic Linkage in Graded Human Characters. Annals of Eugenics. 1938; 8:233–237.

Piton A, Redin C, Mandel JL. XLID-causing mutations and associated genes challenged in light of data from large-scale human exome sequencing. American Journal of Human Genetics. 2013; 93:368–383. [PubMed: 23871722]

Popovici C, Busa T, Boute O, Thuresson AC, Perret O, Sigaudy S, et al. Philip N. Whole ARX gene duplication is compatible with normal intellectual development. American Journal of Medical Genetics Part A. 2014; 164A:2324–2327. [PubMed: 25044608]

Regis S, Biancheri R, Bertini E, Burlina A, Lualdi S, Bianco MG, et al. Filocamo M. Genotype-phenotype correlation in five Pelizaeus-Merzbacher disease patients with PLP1 gene duplications. Clinical Genetics. 2008; 73:279–287. [PubMed: 18190592]

Renpenning H, Gerrard JW, Zaleski WA, Tabata T. Familial sex-linked mental retardation. Canadian Medical Association Journal. 1962; 87:954–956. [PubMed: 13981686]

Robinson PN, Kohler S, Bauer S, Seelow D, Horn D, Mundlos S. The Human Phenotype Ontology: a tool for annotating and analyzing human hereditary disease. American Journal of Human Genetics. 2008; 83:610–615. [PubMed: 18950739]

Roifman CM. Antibody deficiency, growth retardation, spondyloepiphyseal dysplasia and retinal dystrophy: a novel syndrome. Clinical Genetics. 1999; 55:103–109. [PubMed: 10189087]

Schroer RJ, Beaudet AL, Shinawi M, Sahoo T, Patel A, Sun Q, et al. Stevenson RE. Duplication of OCRL and adjacent genes associated with autism but not Lowe syndrome. American Journal of Medical Genetics Part A. 2012; 158A:2602–2605. [PubMed: 22965764]

Schwarzer W, Abdennur N, Goloborodko A, Pekowska A, Fudenberg G, Loe-Mie Y, Fonseca NA, et al. Spitz F. Two independent modes of chromatin organization revealed by cohesin removal. Nature. 2017; 551:51–56. [PubMed: 29094699]

Scott Schwoerer J, Laffin J, Haun J, Raca G, Friez MJ, Giampietro PF. MECP2 duplication: possible cause of severe phenotype in females. American Journal of Medical Genetics Part A. 2014; 164A: 1029–1034. [PubMed: 24458799]

Tuck-Muller CM, Martinez JE, Batista DA, Kearns WG, Wertelecki W. Duplication of the short arm of the X chromosome in mother and daughter. Human Genetics. 1993; 91:395–400. [PubMed: 8500796]

Turner G, Gedeon A, Mulley J. X-linked mental retardation with heterozygous expression and macrocephaly: pericentromeric gene localization. American Journal of Medical Genetics. 1994; 51:575–580. [PubMed: 7943042]

Turner G, Partington MW. Genes for intelligence on the X chromosome. Journal of Medical Genetics. 1991; 28:429.

van Asbeck E, Ramalingam A, Dvorak C, Chen TJ, Morava E. Duplication at Xq28 involving IKBKG is associated with progressive macrocephaly, recurrent infections, ectodermal dysplasia, benign tumors, and neuropathy. Clinical Dysmorphology. 2014; 23:77–82. [PubMed: 24721901]

Van Esch H, Bauters M, Ignatius J, Jansen M, Raynaud M, Hollanders K, et al. Froyen G. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. American Journal of Human Genetics. 2005; 77:442–453. [PubMed: 16080119]

Vignoli A, Borgatti R, Peron A, Zucca C, Ballarati L, Bonaglia C, Canevini MP. Electroclinical pattern in MECP2 duplication syndrome: eight new reported cases and review of literature. Epilepsia. 2012; 53:1146–1155. [PubMed: 22578097]

Vissers LE, de Vries BB, Veltman JA. Genomic microarrays in mental retardation: from copy number variation to gene, from research to diagnosis. Journal of Medical Genetics. 2010; 47:289–297. [PubMed: 19951919]

Whibley AC, Plagnol V, Tarpey PS, Abidi F, Fullston T, Choma MK, et al. Raymond FL. Fine-scale survey of X chromosome copy number variants and indels underlying intellectual disability. American Journal of Human Genetics. 2010; 87:173–188. [PubMed: 20655035]

Wieland I, Schanze D, Schanze I, Volleth M, Muschke P, Zenker M. A cryptic unbalanced translocation der(4)t(4;17)(p16.1;q25.3) identifies Wittwer syndrome as a variant of Wolf-Hirschhorn syndrome. American Journal of Medical Genetics Part A. 2014; 164A:3213–3214. [PubMed: 25251057]

Wittwer B, Kircheisen R, Leutelt J, Orth U, Gal A. New X-linked mental retardation syndrome with the gene mapped tentatively in Xp22.3. American Journal of Medical Genetics. 1996; 64:42–49. [PubMed: 8826447]

Zollino M, Colosimo C, Zuffardi O, Rossi E, Tosolini A, Walsh CA, Neri G. Cryptic t(1;12)(q44;p13.3) translocation in a previously described syndrome with polymicrogyria, segregating as an apparently X-linked trait. American Journal of Medical Genetics Part A. 2003; 117A:65–71. [PubMed: 12548742]

Zollino M, Mastroiacovo P, Zampino G, Mariotti P, Neri G. New XLMR syndrome with characteristic face, hypogenitalism, congenital hypotonia and pachygyria. American Journal of Medical Genetics. 1992; 43:452–457. [PubMed: 1605225]

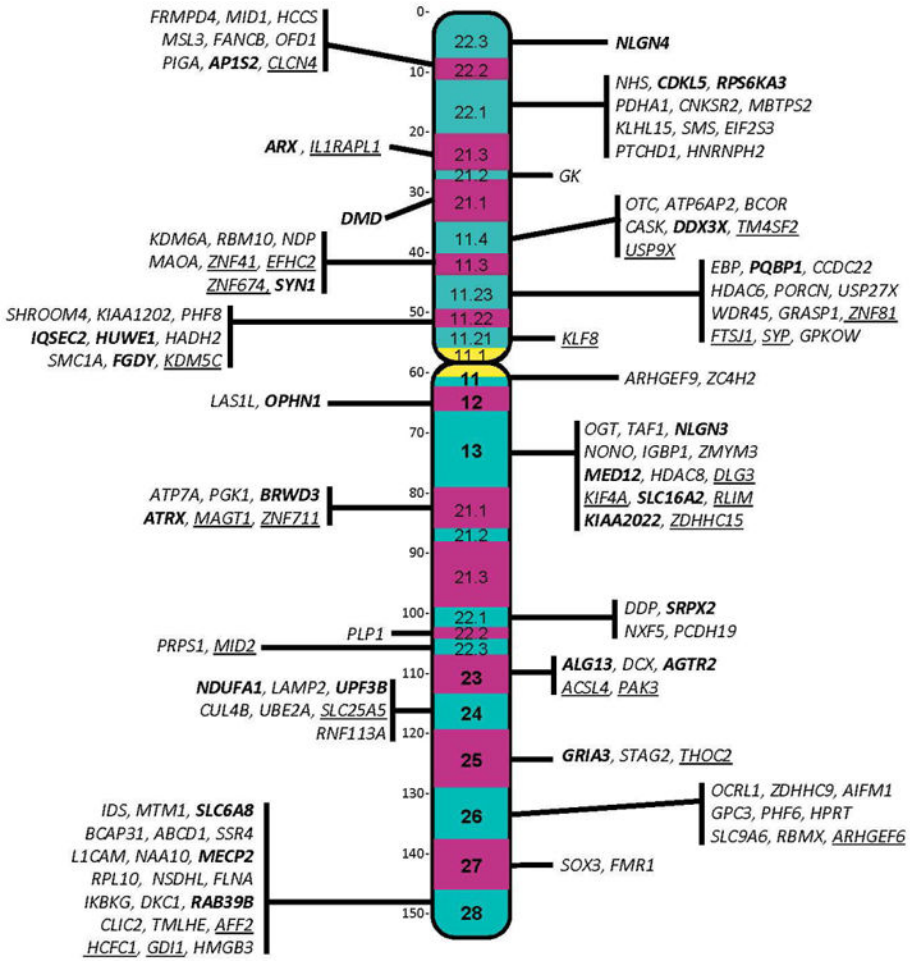
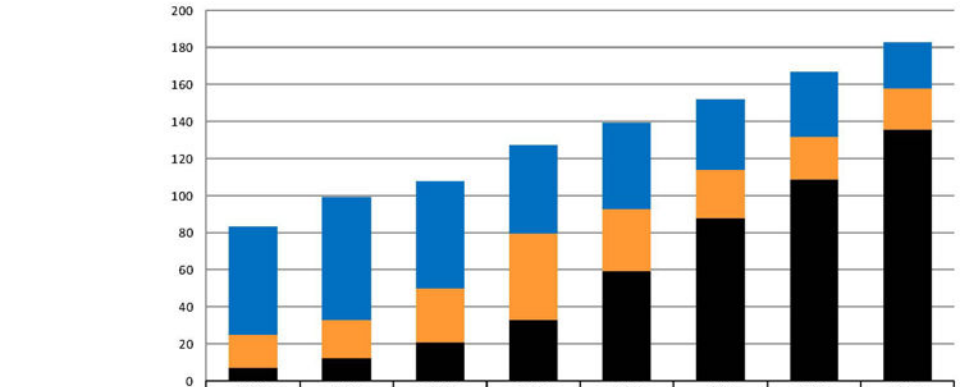


Figure 1.

Regional locations of genes associated with XLID syndromes. Bolded genes have also been associated with nonsyndromal XLID. Genes underlined have been challenged by Piton et al. 2013. Color figure can be viewed in the online issue.



	1988	1992	1996	2000	2004	2008	2012	2017
Syndromes not mapped/cloned	58	66	58	47	46	38	35	25
Syndromes mapped	18	21	29	47	34	26	23	22
Syndromes with genes assigned	7	12	21	33	59	88	109	136
Syndrome genes cloned	5	10	19	30	47	71	90	113
Syndromes described	83	99	108	127	139	152	167	183

Figure 2.

Progress in identifying XLID syndromes and associated genes, 1988-2017. Color figure can be viewed in the online issue.

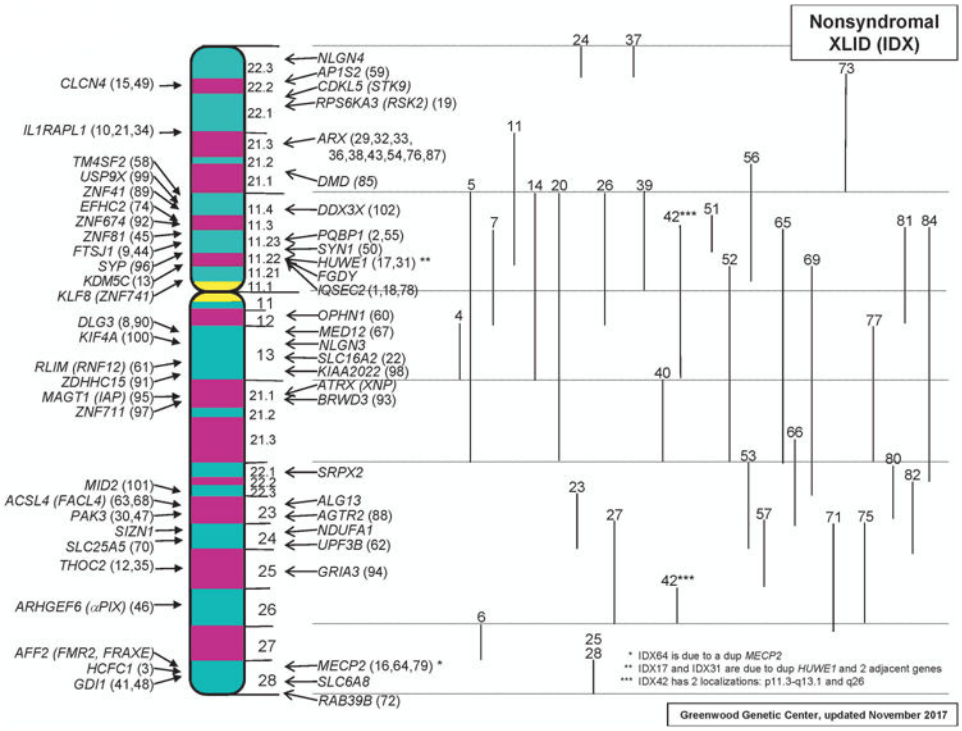


Figure 3.

Families with nonsyndromal XLID which have received IDX numbers. Their total is currently 105. Linkage limits for IDX families for which the genes have not been identified are shown to the right. Color figure can be viewed in the online issue.

Table I

XLID genes identified 2007-2017

Year	Gene Symbol	Gene Name	Locus	Gene OMIM	How Discovered	Clinical Description	Function	References
2007	*BRWD3*	BROMODOMAIN- AND WD REPEAT-CONTAINING PROTEIN 3	Xq21.1	300553	X-seq	XLID-Macrocephaly-Large Ears, IDX93	Transcription factor	Field et al. 2007
2007	*CUL4B*	CULLIN 4B	Xq24	300304	X-seq	XLID-Hypogonadism-Tremor	Cell cycle, ubiquitin cycle, E3 ubiquitin ligase	Tarpey et al. 2007
2007	*GRIA3*	GLUTAMATE RECEPTOR, IONOTROPIC, AMPA 3	Xq25	305915	Chr-rea, Exp-Arr, X-seq	Chiyonobu XLID, IDX94	Signal transduction, ion transport, glutamate signaling pathway	Wu et al. 2007
2007	*HSD17B10 (HADH2)*	17-BETA-HYDROXYSTEROID DEHYDROGENASE X	Xp11.22	300256	L-can	XLID-Choreoathetosis	Lipid metabolism	Lenski et al. 2007
2007	*MED12 (HOPA)*	MEDIATOR COMPLEX SUBUNIT 12NOTE: MEDIATOR COMPLEX SUBUNIT 12	Xq13.1	300188	L-can	Opitz FG, Lujan, IDX67	Transcription regulation, RNA polymerase II transcription mediator activity, ligand-dependent nuclear receptor transcription coactivator activity, vitamin D receptor and thyroid hormone receptor binding	Risheg et al. 2007
2007	*NDUFA1*	NADH-UBIQUINONE OXIDOREDUCTASE 1 ALPHA SUBCOMPLEX, 1	Xq24	300078	Mol-Fu	Mitochondrial Complex 1 Deficiency	Energy production, oxidoreductase activity	Fernandez-Moreira et al. 2007
2007	*NXF5* *	NUCLEAR RNA EXPORT FACTOR 5	Xq22.1	300319	Chr-rea	XLID-Short Stature-Muscle Wasting	mRNA processing, mRNA export from nucleus	Froyen et al. 2007
2007	*PORCN*	PORCUPINE, DROSOPHILA, HOMOLOG	Xp11.23	300651	Chr-rea (del)	Goltz	Wnt receptor signaling pathway, acyltransferase activity, integral to membrane of endoplasmic reticulum	Wang et al. 2007
2007	*PRPS1*	PHOSPHORIBOSYLPYROPHOSPHATE SYNTHETASE I	Xq22.3	311850	L-can	Arts, PRPS1 Superactivity	Ribonucleotide monophosphate biosynthesis	de Brouwer et al. 2007
2007	*RPL10* *	RIBOSOMAL PROTEIN L10	Xq28	312173	X-seq	Autism	Protein synthesis, ribosomal protein	Klauck et al. 2006
2007	*UPF3B*	UPF3, YEAST, HOMOLOG OF, B	Xq24	300298	X-seq	Lujan/FG Phenotype, IDX62	mRNA catabolism, nonsense-mediated decay	Tarpey et al. 2007
2007	*ZDHHC9*	ZINC FINGER DHHC DOMAIN-CONTAINING PROTEIN 9	Xq26.1	300646	X-seq	XLID-Macrocephaly-Marfanoid Habitus		Raymond et al. 2007
2008	*HUWE1*	HECT, UBA, AND WWE DOMAINS-CONTAINING PROTEIN 1	Xp11.22	300697	CMA	XLID-Macrocephaly, Juberg-Marsidi-Brooks, IDX17, IDX31	Ubiquitin-protein ligase, mRNA transport	Froyen et al. 2008
2008	*PCDH19*	PROTOCADHERIN 19	Xq22.1	300460	L-can	Epilepsy-Intellectual Disability Limited to Females		Dibbens et al. 2008
2008	*SLC9A6*	SOLUTE CARRIER FAMILY 9, MEMBER 6	Xq26.3	300231	L-can	Christianson, X-linked Angelman-like	Sodium-hydrogen antiporter activity, lysosome organization and biogenesis, regulation of endosome volume	Gilfillan et al. 2008

Year	Gene Symbol	Gene Name	Locus	Gene OMIM	How Discovered	Clinical Description	Function	References
2008	*SIZN1* *(ZCCHC12)*	SMAD-INTERACTING ZINC FINGER PROTEIN 1	Xq24	300701	L-can	IDX	Modulates BMP signalling influences forebrain cholinergic neurons	Cho et al. 2008
2009	*MAGT1* *	MAGNESIUM TRANSPORTER 1	Xq21.1	300715	L-can, X-seq	IDX95	Magnesium transporter with N-glycosylation sites and putative phosphorylation sites	Molinari et al. 2008
2009	*MBTPS2*	MEMBRANE-BOUND TRANSCRIPTION FACTOR PROTEASE, SITE 2	Xp22.12	300294	L-can	Ichthyosis Follicularis, Atrichia, Photophobia (IFAP)	Protease activity, activates signaling proteins	Oeffner et al. 2009
2009	*NSDHL*	NAD(P)H STEROID DEHYDROGENASE-LIKE PROTEIN	Xq28	300275	L-can	CK (microcephaly, pachygyria, facial dysmorphism, seizures), also in CHILD syndrome	Sterol metabolism	du Souich et al. 2009
2009	*SYP*	SYNAPTOPHYSIN	Xp11.23	313475	X-seq	IDX96	Membrane protein of small synaptic vesicles	Tarpey et al. 2009
2009	*ZNF711*	ZINC FINGER PROTEIN 711	Xq21.1	314990	X-seq	IDX97	Binds to a subset of PHF8 target genes	Tarpey et al. 2009
2010	*IQSEC2*	IQ MOTIF- AND SEC7 DOMAIN-CONTAINING PROTEIN 2	Xp11.22	300522	X-seq	IDX1, IDX18, and other Nonsyndromal XLID	Regulation of vesicular transport and organelle structure	Shoubridge et al. 2010
2010	*PTCHD1*	PATCHED DOMAIN-CONTAINING PROTEIN 1	Xp22.11	300828	CMA	Autism-XLID	Transmembrane protein related to hedgehog receptors	Noor et al. 2010
2010	*RAB39B*	RAS-ASSOCIATED PROTEIN	Xq28	300774	L-can	XLID-Macrocephaly-Seizures -Autism, Waisman-Laxova, IDX72	Formation and maintenance of synapse	Giannandrea et al. 2010
2011	*CLCN4*	CHLORIDE CHANNEL 4	Xp22.2	302910	X-seq	IDX15, IDX49	Chloride transport	Veeramah et al. 2013
2011	*CNKSR2*	CONNECTOR ENHANCER OF KSR 2	Xp22.12	300724	CMA	XLID-Microcephaly-Seizures	Stimulates MAPK signalling	Houge et al. 2012
2011	*EIF2S3*	EUKARYOTIC TRANSLATION INITIATION FACTOR 2, SUBUNIT 3	Xp22.11	300161	X-seq	MEHMO	Initiates translation	Borck et al. 2012
2011	*HCFC1*	HOST CELL FACTOR C1	Xq28	300019	X-seq	IDX3	Cell proliferation	Huang et al. 2012
2011	*HDAC6*	HISTONE DEACETYLASE 6	Xp11.23	300272	L-can	Chassaing-Lacombe Chondrodysplasia	Tubulin deacetylase	Simon et al. 2010
2011	*HDAC8*	HISTONE DEACETYLASE 8	Xq13.1	300269	Mol-Fu, X-seq	Cornelia de Lange, X-linked	Chromatin cohesion	Deardorff et al. 2012; Harakalova et al. 2012
2011	*LAS1L*	LAS1-LIKE RIBOSOME BIOGENESIS FACTOR	Xq12	300964	X-seq	Wilson-Turner	Nucleolar protein, cell proliferation and ribosome biogenesis	Hu et al. 2016
2011	*NAA10*	N-ALPHA-ACETYLTRANSFERASE 10, NatA CATALYTIC SUBUNIT	Xq28	300013	X-seq	N-Alpha-Acetyltransferase Deficiency	N-terminal acetylation	Rope et al. 2011
2011	*RAB40AL*	RAS-ASSOCIATED PROTEIN RAB40A-LIKE	Xq22.1	300405	X-seq	Martin-Probst (?) Questioned: Hum Mutat 35:1171, 2014	Ras-like GTPase protein	Bedoyan et al. 2012

Year	Gene Symbol	Gene Name	Locus	Gene OMIM	How Discovered	Clinical Description	Function	References
2011	*RBM10*	RNA-BINDING MOTIF PROTEIN 10	Xp11.3	300080	X-seq	TARP	RNA-binding	Johnston et al. 2014
2011	*THOC2*	THO COMPLEX, SUBUNIT 2	Xq25	300395	X-seq	IDX12, IDX35	mRNA transcription or export	Kumar et al. 2015
2012	*AIFM1*	APOPTOSIS-INDUCING FACTOR, MITOCHONDRIA-ASSOCIATED, 1	Xq26.1	300169	X-seq	Charcot-Marie-Tooth disease, Cowchock variant and XLID-spondyloepimetaphyseal dysplasia	Induces apoptosis	Rinaldi et al. 2012
2012	*ALG13*	ALG13, S. CEREVISIAE, HOMOLOG	Xq23	300776	WES	CDG1s	Glycosylation	Timal et al. 2012; de Ligt et al. 2012
2012	*CCDC22*	COILED-COIL DOMAIN-CONTAINING PROTEIN 22	Xp11.23	300859	X-seq	Cardiofacioskeletal (like 3C/Ritscher-Schinzel)	Unknown	Voineagu et al. 2012
2012	*CLIC2* *	CHLORIDE INTRACELLULAR CHANNEL 2	Xq28	300138	X-seq	XLID-Cardiomegaly-Seizures	Regulating ryanodine receptor channel activity	Takano et al. 2012
2012	*EBP*	EMOPAMIL-BINDING PROTEIN	Xp11.23	300205	Met-Fu	Variable manifestations but XLID-Aggression in one family	Enzyme in cholesterol metabolism	Furtado et al. 2010
2012	*KDM6A*	LYSINE-SPECIFIC DEMETHYLASE 6A	Xp11.3	300128	Chr-rea	Kabuki syndrome 2	Histone demethylase and methyltransferase	Lederer et al. 2012
2012	*PIGA*	PHOSPHATIDYLINOSITOL GLYCAN ANCHOR BIOSYNTHESIS CLASS A PROTEIN	Xp22.2	311770	X-seq	XLID-Brain iron accumulation	Enzyme, signal transduction pathway, adhesion molecules	Johnston et al. 2012
2012	*TMLHE*	EPSILON-TRIMETHYLLYSINE HYDROXYLASE	Xq28	300777	X-seq	Autism-ID	Enzyme in carnitine synthesis	Celestino-Soper et al. 2011
2013	*BCAP31*	B-CELL RECEPTOR-ASSOCIATED PROTEIN 31	Xq28	300398	X-seq	XLID-microcephaly-dystonia	ER & golgi structure and metabolism	Cacciagli et al. 2013
2013	*SSR4*	SIGNAL SEQUENCE RECEPTOR, DELTA	Xq28	300090	WES	XLID-glycosylation defect	Glycosylation	Losfeld et al. 2014
2013	*WDR45*	WD REPEAT-CONTAINING PROTEIN 45	Xp11.23	300526	WES	Neurodegeneration with brain iron accumulation-XLID	Autophagy and other cellular functions	Haack et al. 2012; Saitsu et al. 2013
2013	*ZC4H2*	ZINC FINGER C4H2 DOMAIN-CONTAINING PROTEIN	Xq11.2	300897	WES, Chr-rea, CMA	Wieacker-Wolff, Miles-Carpenter	Axon guidance	Hirata et al. 2013
2014	*HMGB3*	HIGH MOBILITY GROUP BOX 3	Xq28	300193	WES	Microphthalmia 13	DNA replication, transcription, nucleosome assembly	Scott et al. 2014
2014	*KIF4A*	KINESIN FAMILY MEMBER 4A	Xq13.1	300521	WES	IDX100	Moves proteins along microtubule	Willemsen et al. 2014
2014	*MID2*	MIDLINE 2	Xq22.3	300204	L-can, WES	IDX101	Enzyme, ubiquity ligase E3 microtubule stabilization	Geetha et al. 2014
2014	*USP9X*	UBIQUITIN-SPECIFIC PROTEASE 9, X-LINKED	Xp11.4	300072	X-seq	IDX99	Neuronal migration growth	Homan et al. 2014

Year	Gene Symbol	Gene Name	Locus	Gene OMIM	How Discovered	Clinical Description	Function	References
2014	*ZMYM3* *	ZINC FINGER, MYM-TYPE 3	Xq13.1	300061	X-seq	XLID-aortic stenosis-hypospadias	Component of histone deacetylase-containing multiple protein complexes	Philips et al. 2014
2015	*KLHL15*	KELCH-LIKE 15	Xp22.11	300980	X-seq	Mild to moderate cognitive impairment, facial dysmorphism, IDX103	Uncertain	Mignon-Ravix et al. 2014
2015	*DDX3X*	DEAD/H BOX 3, X-LINKED	Xp11.4	300160	WES	Variable cognitive, neurologic and nonneurologic manifestations, IDX102	RNA helicase	Snijders Blok et al. 2015
2015	*FRMPD4* *	FERM AND PDZ DOMAINS-CONTAINING PROTEIN 4	Xp22.2	300838	X-seq	XLID-Aphasia-seizures, IDX104	Regulates spine morphogenesis	Hu et al. 2016
2015	*MSL3*	MALE-SPECIFIC LETHAL 3, DROSOPHILA, HOMOLOG	Xp22.2	300609	WES	MSL3-Related XLID	Transcription regulation, chromatin modifier	Thevenon et al. 2015
2015	*NONO*	NON-POU DOMAIN-CONTAINING OCTAMER-BINDING PROTEIN	Xq13.1	300084	WES	Mircsof-Langouët	Regulation of transcription (activation, repression, splicing, pre-mRNA processing, RNA transport)	Mircsof et al. 2015
2015	*RBMX*	RNA-BINDING MOTIF PROTEIN, X CHROMOSOME	Xq26.3	300199	WES	Shashi	RNA binding	Shashi et al. 2015
2015	*RLIM (RNF12)*	RING FINGER PROTEIN, LIM DOMAIN-INTERACTING	Xq13.2	300379	X-seq	IDX with variable microcephaly, behaviour abnormalities and other manifestation, IDX61	Enzyme, ubiquity ligase E3	Tonne et al. 2015
2015	*RNF113A*	RING FINGER PROTEIN 113A	Xq24	300951	WES	Trichothiodystrophy 5	Gene regulation, DNA repair	Corbett et al. 2015
2015	*TAF1*	TAF1 RNA POLYMERASE II, TATA BOX-BINDING PROTEIN-ASSOCIATED FACTOR, 250-KD	Xq13.1	313650	WGS	XLID-Craniofacial-Caudal	Key role in initiating transcription	O'Rawe et al. 2015
2015	*USP27X*	UBIQUITIN-SPECIFIC PROTEASE 27, X-LINKED	Xp11.23	3000975	X-seq	Variable cognitive and speech impairment and behavioural abnormalities, IDX105	Peptidase	Hu et al. 2016
2016	*EFHC2*	EF-HAND DOMAIN (C-TERMINAL)-CONTAINING PROTEIN 2	Xp11.3	300817	L-can	IDX74	Calcium binding and other unknown functions	Startin et al. 2015
2016	*GRASP1*	GRIP1-ASSOCIATED PROTEIN 1	Xp11.23	300408	X-seq	XLID-Short Stature-Spasticity	Synaptic function and neuronal connectivity	Chiu et al. 2017
2016	*HNRNPH2*	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN H2	Xp22.1	300610	WES	Bain XLID, Female Limited	Nuclear localization	Bain et al. 2016
2016	*SLC25A5*	SOLUTE CARRIER FAMILY 25 (MITOCHONDRIAL CARRIER, ADENINE NUCLEOTIDE TRANSLOCATOR), MEMBER A5	Xq24	300150	CMA	IDX70	Mitochondrial exchange of ADP/ATP	Vandewalle et al. 2013
2016	*STAG2*	STROMAL ANTIGEN 2	Xq25	300826	CMA	STAG2-Related XLID	Chromatin cohesion	Leroy et al. 2016
2017	*GPKOW*	G-PATCH DOMAIN AND KOW MOTIFS	Xp11.23	301003	X-seq	XLID-Microcephaly-Early lethality	Spliceosome component	Carroll et al. 2017
2017	*OGT*	O-LINKED N-ACETYLGLUCOSAMINE TRANSFERASE	Xq13.2	300255	WES	XLID-Faciogenital	Post translational modification of nucleocytoplasmic proteins	Vaidyanathan et al. 2018

*Association with XLID has been challenged (Piton et al. 2013) and not subsequently resolved (n=7)

Chr-rea = chromosome rearrangement
WES = whole exome sequencing
WGS = whole genome sequencing
Exp-Arr = expression array
L-can = linkage and candidate gene testing
CMA = array-comparative genomic hybridization
Met-Fu = exploitation of metabolic alteration
Mol-Fu = exploitation of molecular finding
X-seq = sequencing of X-chromosome exons