Fragile X and X-Linked Intellectual Disability: Four Decades of Discovery

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X-Linked intellectual disability (XLID) accounts for 5%–10% of intellectual disability in males. Over 150 syndromes, the most common of which is the fragile X syndrome, have been described. A large number of families with nonsyndromal XLID, 95 of which have been regionally mapped, have been described as well. Mutations in 102 X-linked genes have been associated with 81 of these XLID syndromes and with 35 of the regionally mapped families with nonsyndromal XLID. Identification of these genes has enabled considerable reclassification and better understanding of the biological basis of XLID. At the same time, it has improved the clinical diagnosis of XLID and allowed for carrier detection and prevention strategies through gamete donation, prenatal diagnosis, and genetic counseling. Progress in delineating XLID has far outpaced the efforts to understand the genetic basis for autosomal intellectual disability. In large measure, this has been because of the relative ease of identifying families with XLID and finding the responsible mutations, as well as the determined and interactive efforts of a small group of researchers worldwide.

Introduction

Mutations resulting in X-linked intellectual disability (XLID) have been described in 102 genes (Table S1, available online).[1] This work was accomplished over a 40 year period during which the term X-linked mental retardation was widely used; however, we will use intellectual disability (ID), which is emerging as the preferred terminology. Mutations in these 102 genes are responsible for 81 of the known 160 XLID syndromes and over 50 families with nonsyndromal XLID (Table S1 and Figures 1 and 2). An additional 30 XLID syndromes and 48 families with nonsyndromal XLID have been regionally mapped (Table 1 and Figures 2 and 3), but the genes not yet identified. Forty-four XLID syndromes, which remain unmapped, have also been described (Table S2). Fewer than 400 autosomal genes in which mutations resulted in ID have been identified. Of 1,640 references to ID in OMIM (as of March 2010), 316 are entities on the X chromosome. Three comparably sized chromosomes (6, 7, and 8) show 50, 58, and 60 references, respectively. Several authors have recently discussed the possibility that these striking differences might result from a relative concentration of genes that influence intelligence on the X chromosome.[2,3]

Identification of the mutations in 102 genes that cause XLID has been accomplished primarily through long-term, planned and coordinated studies from the United States, Europe, and Australia. These studies took advantage of the power of pedigrees of relatively large families to assign putative genes to the X chromosome, linkage analysis to achieve regional localizations, accumulation and sharing of large data banks of clinical details and specimens, registries of pertinent X chromosomal translocations and abnormalities, stored samples from a variety of populations around the world with ID and effective communication between numerous investigators. In this setting, the continuously developing technologies were applied and reapplied to the available clinical and specimen banks effectively and rapidly. A comparable systematic approach to autosomal ID has not been carried out.

Publication of the first family with the marker X,[4] later renamed the fragile X (MIM 300624),[5] gave an important impetus to the field by providing a laboratory tool which clearly identified the most prevalent XLID syndrome. A series of biennial international meetings on fragile X syndrome and XLID, beginning in 1983, involved about 100 investigators and provided a sense of unity and progress to the field. Papers and abstracts from these meetings and from other research were published (usually biennially) as conference reports, special issues or updates on XLID from 1984 to 2008.[6–16]

The focus of this review will be the discovery process rather than the details of the clinical or molecular findings in the individual XLID entities. Readers are referred to the recently updated excellent review of the fragile X in OMIM (MIM 300624) and OMIM entries on other XLID disorders as detailed in Tables S1 and S2. Other reviews of different aspects of XLID include the periodic XLID updates from 1984 to 2008, an Atlas of XLID Syndromes,[1] and a number of commentaries by individual investigators.[3,17–22]

XLID before Fragile X

The prelude to the current cytogenetic and molecular era covered a century (1868–1968). It encompassed descriptions of a number of clinically defined entities (Pelizaeus-Merzbacher disease [MIM 312080], Duchenne muscular dystrophy [MIM 310200], incontinentia pigmenti [MIM 308300], Goltz focal dermal hypoplasia [MIM 305600], Lenz microphthalmia syndrome [MIM 309800]), inborn errors of metabolism (Hunter syndrome [MIM 309900], Lowe syndrome [MIM 309000], Lesch-Nyhan syndrome [MIM 300322]), and large pedigrees in which ID segregated with an X-linked pattern.[23–28] During the same period, the excess of males among persons with ID was observed in

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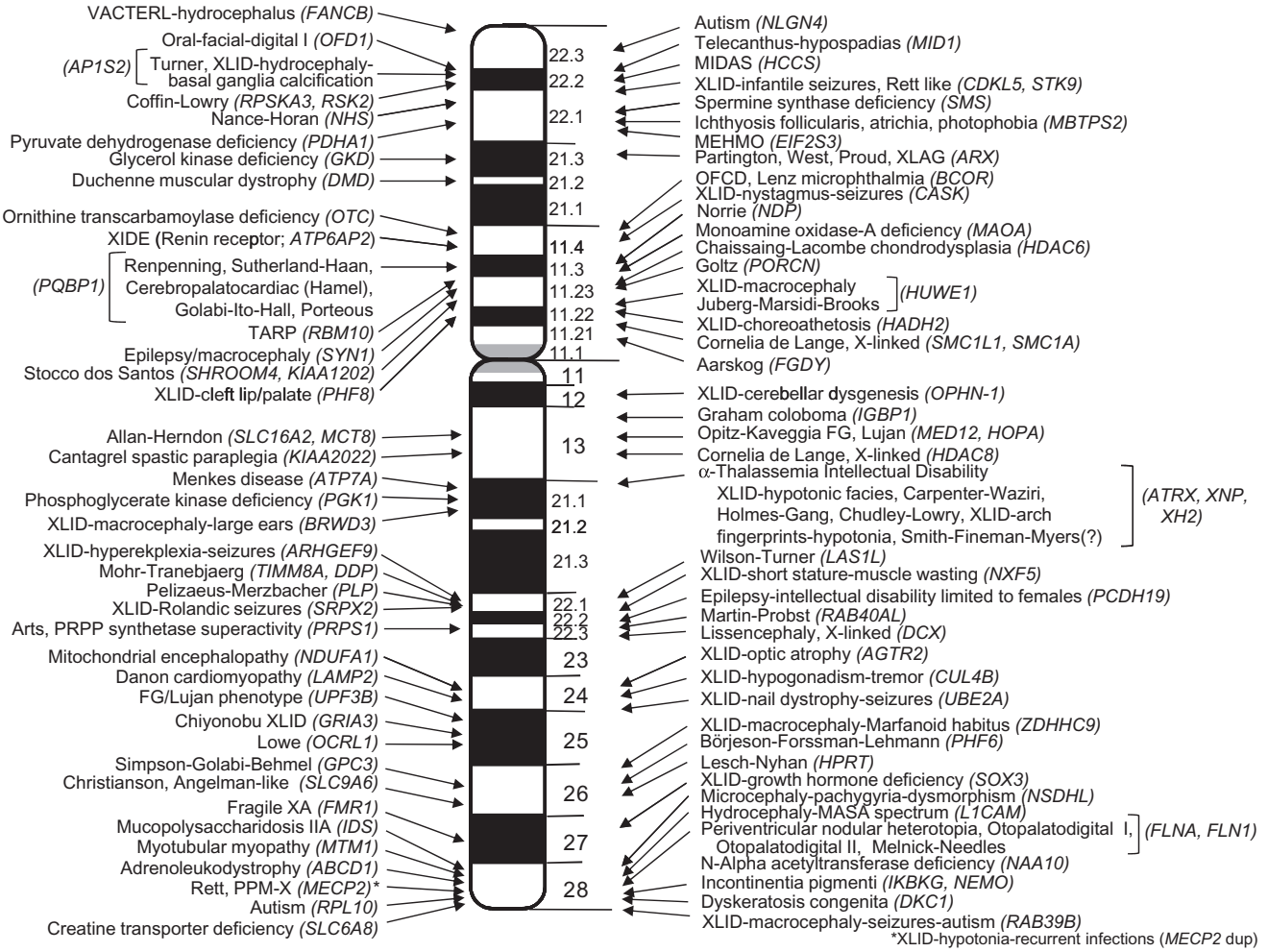


Figure 1. Genes with Identified Mutations that Cause Syndromal XLID with Chromosomal Band Location

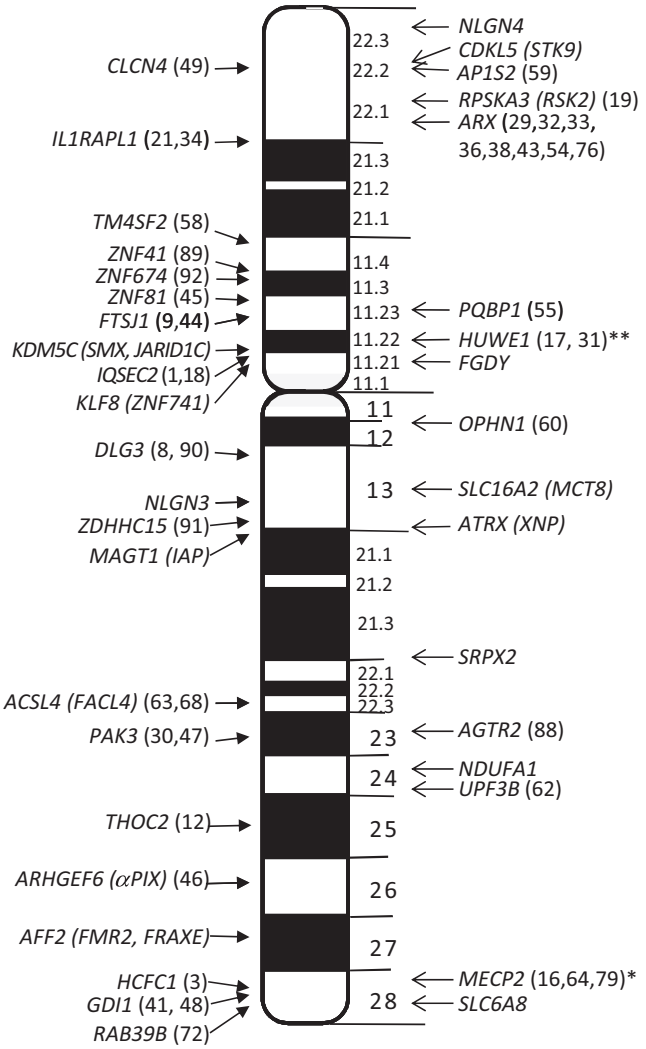
census surveys and other population studies.[29–31] The magnitude of the male excess, varied from study to study but averaged about 30 percent and was found in nearly all studies.

These two observations—the excess of males among persons with ID and clinical syndromes or families with ID that segregated with an X-linked pattern—provided compelling evidence that genes on the X chromosome were important contributors to the overall causation of ID and, hence, of individual, familial, and societal significance. By virtue of having but a single X chromosome, the male's genome was uniquely vulnerable and that vulnerability extended to brain development and function as well as to other systems.

Further insights during this early period of time were that XLID comprised syndromal entities (ID plus somatic, metabolic, or neuromuscular manifestations) and nonsyndromal entities (ID alone or with inconsistent abnormalities). It also became clear that some females in XLID pedigrees had intellectual limitations, albeit with neither the consistency nor the severity of males. Technological limitations (lack of tools for linkage analysis and gene isolation) precluded a more precise genetic characterization of XLID disorders and delayed the clinical delineation.

The Setting of the Initial Observation of the Marker X

In 1966, when a one-year-old boy and his brother were referred to the Yale chromosome laboratory for study because of delayed development, medical cytogenetics was in a period of transition. The major trisomies as well as translocations and large deletions had been defined by nonspecific orcein or Giemsa staining. Prenatal cytogenetic diagnosis had begun and in order to provide more predictive developmental information to families, there was a need for both better, less biased clinical information about X and Y aneuploidy and the several types of smaller variations in the short arms of the acrocentric chromosomes and variant heterochromatic regions on 1, 9, 16, and Y. The Yale laboratory had selected a minimal media (199) for both routine diagnostic studies and for a year-long study of 4,500 consecutive cord blood and 500 maternal samples. Special attention was given to breaks, gaps, and chromosome variants in the year-long study. The study also sought to identify cytogenetic markers



*MRX64 is due to a dup *MECP2*
**MRX17 and MRX31 are due to dup *HUWE1* and 2 adjacent genes

Figure 2. Location of Genes with Mutations that Cause Nonsyndromal XLID
Twenty-two genes shown on the left of the chromosome with solid arrows cause nonsyndromal XLID only. Numbers in parentheses adjacent to the gene symbols are assigned MRX numbers. Seventeen genes shown on the right of the chromosome with open arrows cause both syndromal and nonsyndromal XLID.

Table 1. Nonsyndromal XLID families (MRX1 – MRX95) with linkage or gene identification[a]

1	*IQSEC2*	33	*ARX*	65	Xp11.3-q21.33
2	Xp22.1-p22.3	34	del *IL1RAPL1*	66	Xq21.33-q23
3	*HCFC1*	35	Xq21.3-q26	67	Xq13.1-q21.31
4	Xp11.22-q21.31	36	*ARX*	68	*ACSL4*
5	Xp21.1-q21.3	37	Xp22.31-p22.32	69	Xp11.21-q22.1
6	Xq27	38	*ARX*	70	Xq23-q25
7	Xp11.23-q12	39	Xp11	71	Xq24-q27.1
8	*DLG3*	40	Xq21	72	*RAB39B*
9	*FTSJ1*	41	*GDI1*	73	Xp22-p21
10	Xp11.4-p21.3	42	Xp11.3-q13.1; Xq26	74	Xp11.3-p11.4
11	Xp11.22-p21.3	43	*ARX*	75	Xq24-q26
12	*THOC2*	44	*FTSJ1*	76	*ARX*
13	Xp22.3-q22	45	*ZNF81*	77	Xq12-q21.33
14	Xp21.2-q13	46	*ARHGEF6*	78	Xp11.4-p11.23
15	Xp22.1-q12	47	*PAK3*	79	*MECP2*
16	*MECP2*	48	*GDI1*	80	Xq22-q24
17	*dup HUWE1*	49	*CLCN4*	81	Xp11.2-q12
18	*IQSEC2*	50	Xp11.3-p11.21	82	Xq24-q25
19	*RPSKA3*	51	Xp11.23-p11.3	83	*Not published*
20	Xp21.1-q23	52	Xp11.21-q21.32	84	Xp11.3-q22.3
21	*IL1RAPL1*	53	Xq22.2-q26	85	Xp21.3-p21.1
22	Xp21.1-q21.31	54	*ARX*	86	*Not published*
23	Xq23-q24	55	*PQBP1*	87	*ARX*
24	Xp22.2-p22.3	56	Xp21.1-p11.21	88	*AGTR2*
25	Xq27.3	57	Xq24-q25	89	*ZNF41*
26	Xp11.4-q23	58	*TM4SF2*	90	*DLG3*
27	Xq24-q27.1	59	*AP1S2*	91	*ZDHHC15*
28	Xq27.3-qter	60	*OPHN1*	92	*ZNF674*
29	*ARX*	61	Xq13.1-q25	93	*BRWD3*
30	*PAK3*	62	*UPF3B*	94	*GRIA3*
31	*dup HUWE1*	63	*ACSL4*	95	*MAGT1/OSTb*
32	ARX	64	*dup MECP2*		

[a]Mutations in *NLGN4, CDKL5, KDM5C, FGD1, SLC16A2, ATRX, AFF2* and *SLC6A8* have been found in other families with nonsyndromal XLID.

that might correlate directly with clinical conditions.[32] Thus, the initial observation that the two brothers referred to the laboratory because of ID had a consistent chromatid break or constriction in the distal long arm of a large C group chromosome was very pertinent to the research goals of the laboratory. Further study revealed that their normal mother and two maternal relatives with ID (an uncle and great uncle of the boys) had the same marker X chromosome.

The pedigree was, of course, consistent with X-linked ID. Studies with H^3 thymidine showed that the late replicating, large C group chromosome was the same as the chromosome with the apparent breaks and secondary constrictions. The data led to the conclusion that "either the secondary constriction itself or a closely linked recessive gene may account for the pattern of X-linked inheritance".[4] This was, in fact, probably the first precise localization of a gene associated with human disease. The fragile X locus was subsequently defined as an uncoiled region (secondary constriction) by electron microscopy.[33] Studies from a number of laboratories would provide a more precise confirmation and molecular characterization

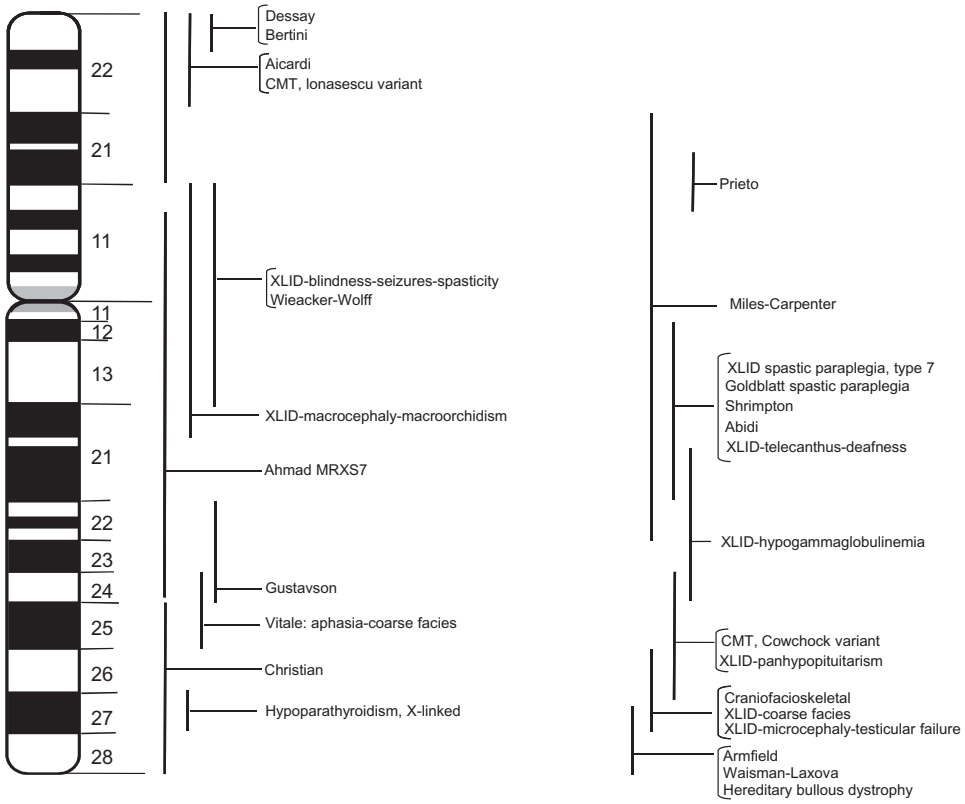


Figure 3. Approximate Linkage Limits for XLID Syndromes for which the Genes Have Not Been Identified

of the location in the ensuing decade[34–36] and identification of the gene itself in 1991.[37–40]

In addition, the juxtaposition and timing of the family study and the population survey permitted us to look for the marker X in 5,000 individuals and over 30,000 cells and to conclude tentatively that it was not a common marker or variant because not even one marker X cell was observed. Another family with a similar chromosomal appearance at distal 16q was also ascertained in this same interval. This was inherited in an autosomal-dominant manner and not associated with a disease. We were, therefore, able to make the preliminary conclusion that such markers did not necessarily indicate disease but that the marker X was a significant clinical marker for a Mendelian disease and hence a new and useful tool.

Observations in the 1970s and 1980s

More complex and folic-acid-enriched media become popular during the 1970s and presumably made detection of the fragile X increasingly difficult. Most early studies gave variable results and were not published. The initial report was confirmed by Giraud et al.[34] and Harvey et al.[35] These articles and the report by Sutherland[36] established that folic acid in the culture media prevented the expression and detection of the fragile X.

During the 1980s it became clear that a majority of XLID families did not have fragile X, and the identification and study of large non-fragile X XLID families with linkage analysis began in earnest. Large scale studies began across the globe at this time. The results summarized in Table 1, Tables S1 and S2, and Figures 1, 2, and 3 are, therefore, based on about 20 years of clinical and molecular studies.

Methodologies Quicken the Pace of Gene Discovery

Besides the cytogenetic methods used in the diagnosing and confirmation of fragile X, a number of strategies have been utilized to identify XLID genes (Table S1 and Figures 1 and 2). Prior to 1990, these were limited to the pursuit of genes in cases where the gene products (enzymes in all cases: *HPRT* [MIM 308000], *PGK1* [MIM 311800], *OTC* [MIM 311250] , and *PDHA1* [MIM 300582]) were known, the molecular pathway was known (*PLP* [MIM 300401]) or a chromosome aberration had localized the candidate region (*DMD* [MIM 300377]). Over the next decade and a half, exploitation of chromosome rearrangements and linkage coupled with candidate gene testing dominated the field. In the past several years, X chromosome sequencing, microarrays (expression and genomic), and exploration of molecular pathways have added to the range of technologies available for XLID gene identification. Five of the first seven gene identifications were accomplished with a combination of known metabolic pathways and tissue culture studies in families with inborn errors of metabolism (Figure 4). The first identification, Lesch-Nyhan syndrome due to mutations in *HPRT*, was reported in 1983[41] and the most recent was the creatine

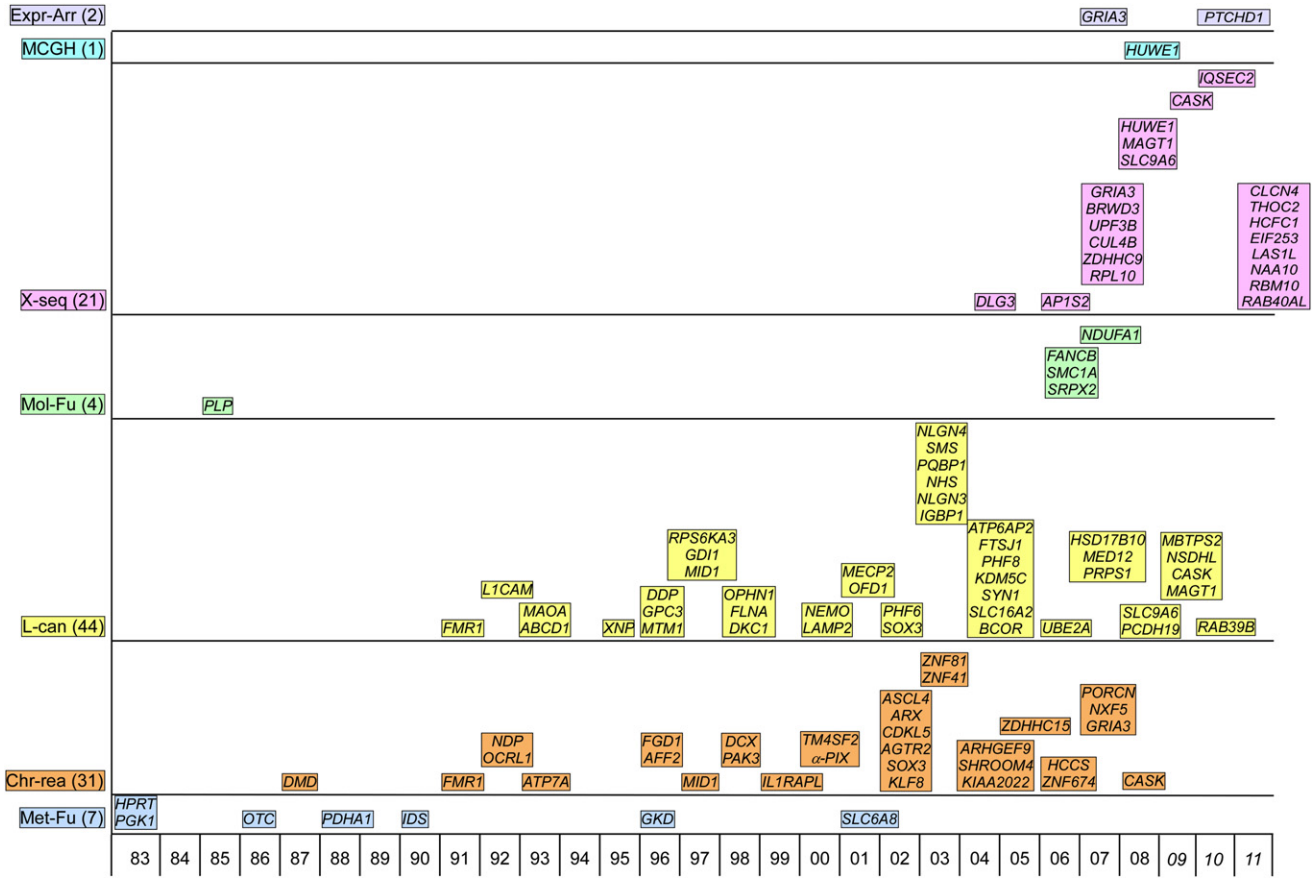


Figure 4. The Year and Methodology Used to Identify Genes Associated with XLID
The following abbreviations are used: Exp-Arr = expression microarray. MCGH = genomic microarray. X-seq = gene sequencing. Mol-Fu = follow up of a known molecular pathway. L-can = candidate gene testing within a linkage interval. Chr-rea = positional cloning based on a chromosome rearrangement. Met-Fu = follow up of a known metabolic pathway.

transporter syndrome (MIM 300352) due to mutations in *SLC6A8* [MIM 300036].[42] Mutations in seven genes were identified by this methodology.

Two workhorse approaches have been responsible for the great majority of subsequent gene identifications. The first of these, based on the ascertainment of a patient with both ID and a chromosomal rearrangement involving the X chromosome, was used successfully in identifying the gene associated with Duchenne muscular dystrophy in 1987. A total of 31 genes (Table S1 and Figure 4) had been identified by the middle of 2011 with this approach. The second and most productive "workhorse" approach, linkage study of XLID families followed by molecular analysis of appropriate candidate genes, was employed initially by a number of investigators in detecting and characterizing *FMR1* (MIM 309550). Subsequently, its use has resulted in the identification of 43 mutant X genes. With increasing ease of sequencing, the pace of gene identification by this route accelerated after 2003, as shown in Table S1 and Figure 4.

The availability of brute force sequencing capability after completion of the Human Genome Project has brought an additional effective method of gene identification, and 21 have been reported since 2006 (Table S1 and Figure 4). Whether sequencing of large series of sporadic males, male siblings, or families with clear XLID will prove to be the most effective use of this resource remains to be determined. The selection of pedigree-based subjects for sequencing, however, has the advantage that segregation of gene alterations can be tested. Since this approach often permits a relatively straight-forward path to gene identification, continued collection of both clinical data and blood samples remains important. Exploitation of a specific molecular finding has accounted for four gene identifications (*FANCB* [MIM 300515], *PORCN* [MIM 300651], *SMC1A/SM1L1* [MIM 300040], *NDUFA1* [MIM 300078]).

Two other new technologies, expression array and array-comparative genomic hybridization have, surprisingly, been applied successfully in only two and one instance, respectively. Expression array was used in combination with two other methods to discover the role of *GRIA3* (MIM 305915) and *PTCHD1* (MIM 300828) in ID. Array-CGH was used in the isolation of the mutant gene in one nonsyndromal family (*HUWE1* [MIM 300697]).[43] Many potentially valuable combinations of array technologies for screening followed with brute force sequencing can

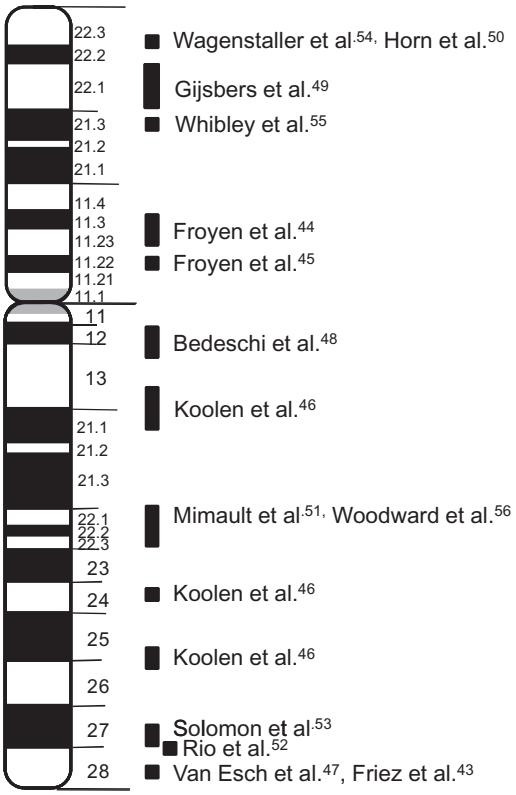


Figure 5. Location of Segmental Duplications Associated with Syndromal or Nonsyndromal XLID[43–56]

be envisioned. Detection of a consistent up or downregulation or other abnormality in two or more XLID family members can certainly be envisioned as a fruitful approach to the selection of subjects for partial or complete X sequencing. Two or more approaches were used in combination in six instances among the 102 gene identifications shown in Table S1 and Figure 1 (*FMR1*, *MID1* [MIM 602148], *SOX3* [MIM 313430], *HUWE1*, *CASK* [MIM 300172], and *GRIA3*). The application of CGH and related methods in conjunction with a variety of molecular technologies has increasingly been used to detect duplications and deletions of genes associated with XLID (Figure 5).[1,43–56]

In spite of the identification of mutations in 102 genes that result in XLID, the fragile X syndrome continues to be by far the most frequent XLID syndrome. Whether the gradual but continuous expansion of the number of triplet repeats in the large bank of premutation carriers, which vary from 1/113 in Israel to 1/313–382 in the United States) plays a role in maintaining its relatively high gene frequency is unknown.[57]

Lumping, Splitting, and Reclassification Based on Gene Discovery: A Model for Future Research

Given the variability and imprecision with which clinical evaluations are carried out, it is inevitable that some individuals with X-linked ID will be incorrectly included in existing diagnostic categories, whereas others will be incorrectly excluded. The extent to which individuals and families can be evaluated is dependent on the setting, access to historical information, availability and ages of affected and nonaffected family members, and the experience and expertise of the observers. Differences in phenotype can result from mutations in different domains of a gene and by contributions from the balance of the genome. The identification of mutations in many genes associated with XLID has provided the opportunity to compensate for some of these variables, resulting in the lumping of entities previously considered to be separate and the splitting of other entities previously considered the same. In addition, the phenotypic limits of some XLID entities were established with some degree of objectivity.

Several XLID entities have been most instructive. Discovery that mutations in *ATRX* (MIM 300032) (Xq21.1) cause alpha-thalassemia ID allowed testing of large number of males with hypotonic facies, ID, and other features.[58–60] Currently, as shown in Table S1, four other named XLID syndromes (Carpenter-Waziri, Holmes-Gang, XLID-Hypotonia-Arch Fingerprints, and Chudley-Lowry syndromes [MIM 309580]) have been found to be allelic variants of alpha-thalassemia ID as have certain families with spastic paraplegia and nonsyndromal XLID.[1,61–65] One family clinically diagnosed as Juberg-Marsidi syndrome was found to have an *ATRX* mutation.[66,67] This is now known to be based on misdiagnosis of Juberg-Marsidi syndrome (MIM 300612); indeed, the original family with this syndrome has a mutation in *HUWE1* at Xp11.22 (Friez et al., 2011, 15th International Workshop on Fragile X and Other Early-Onset Cognitive Disorders). One family clinically diagnosed as Smith-Fineman-Myers syndrome was also found to harbor an *ATRX* mutation, but the gene has not been analyzed in the original family.[68–70] A clinically similar condition, Coffin-Lowry syndrome (MIM 303600), was found to be separate from alpha-thalassemia ID and due to mutations in *RPS6KA3* (MIM 300075), which encodes a serine-threonine kinase.[71]

Kalscheuer et al.[72] found mutations in *PQBP1* (MIM 300463) (Xp11.2) in two named XLID syndromes – Sutherland-Haan syndrome (MIM 309470) and Hamel cerebropalatocardiac syndrome (MIM 309500)—in MRX55 and two other families with microcephaly and other findings. Lenski et al.,[73] Stevenson et al.,[74] and Lubs et al.[75] added Renpenning, Porteous, and Golabi-Ito-Hall syndromes to the list of XLID syndromes caused by mutations in *PQBP1*.[73–75] The six phenotypes now attributed to mutations in *PQBP1* are now summarized in the allelic variants of OMIM 300463. As with the *ATRX* phenotypes, a wide variety of phenotypic expressions result from different mutations in *PQBP1* and we remain challenged to better understand the molecular and developmental mechanisms leading to these differences.

Mutations in *ARX* (MIM 300382) (Xp22.2) were also found to be an important cause of XLID encompassing

multiple phenotypes. Alterations, most commonly a 24 bp expansion of a polyalanine tract, were found in a number of families with nonsyndromal XLID (MRX29, 32, 33, 36, 38, 43, 54, and 76), an X-linked dystonia (Partington syndrome [MIM 309510]), X-linked infantile spasms (MIM 308350) (West syndrome), X-linked lissencephaly with abnormal genitalia (MIM 300215), hydranencephaly and abnormal genitalia (MIM 300215), and Proud syndrome (MIM 300215).[76–83]

Perhaps the most prominent example of syndrome splitting is FG syndrome (MIM 305450). This syndrome, initially described in 1974 by Opitz and Kaveggia,[84] is manifest by macrocephaly (or relative macrocephaly), downslanting palpebral fissures, imperforate anus or severe constipation, broad and flat thumbs and great toes, hypotonia, and ID. In the ensuing years, the manifestations attributed to FG syndrome have become protean, but none was pathognomonic or required for the diagnosis.[85–88] As a result, a number of different localizations on the X chromosome were proposed for FG syndrome.[89–95]

In 2007, Risheg et al.[96] found a recurring mutation, c.2881C>T (p.Arg961Trp), in *MED12* (MIM 300188) in six families with the FG phenotype, including the original family reported by Opitz and Kaveggia.[84] In addition to the above noted manifestations, two other findings, small ears and friendly behavior, were consistently noted.

Although most individuals who have carried the FG diagnosis have one or more findings that overlap with those in FG syndrome, they do not have *MED12* mutations.[97,98] Some have been found to have mutations in other X-linked genes (*FMR1, FLNA* [MIM 300017], *ATRX*, *CASK*, and *MECP2* [MIM 300005]), whereas others have duplications or deletions of the autosomes.[97] So great is the currently existing heterogeneity within FG syndrome that the vast majority of individuals so designated should best be considered to have ID of undetermined cause.

In a number of instances, certain gene mutations have been associated with nonsyndromal XLID, whereas other mutations within the same genes have caused syndromal XLID. Mutations in 17 genes that may cause either type of XLID, depending on the mutation, have been identified (Figure 2). In some cases (e.g., those with *OPHN1* [MIM 300127] and *ARX* mutations) re-examination has found syndromal manifestations in families previously considered to have nonsyndromal XLID.[79,99,100]

The frequency with which the process of lumping and splitting in this limited field of investigation has occurred has been extremely instructive to both clinical and molecular investigators. Moreover, the process of reclassifying and refining the XLID syndromes in light of the gene identifications may be one of the most important contributions by medical genetics to clinical medicine. The underlying mechanisms or pathways by which mutations in different genes result in similar phenotypes and different mutations in a single gene result in disparate phenotypes, however, remain to be fully elucidated.

Improved Understanding of Disease Mechanisms in XLID Disorders

Analysis of the presently known 102 genes associated with XLID lends some insight into the numerous molecular functions in which disruption can lead to cognitive impairment and impaired brain development.[17] Three major functions are almost equally represented in proteins encoded by this panel of 102 genes: 22% are involved in regulation of transcription, 19% in signal transduction, and 15% in metabolism. Additionally, 15% are components of membrane-associated functions. The remainder are equally distributed (~3%–5%) in seven other cellular functions: cytoskeleton, RNA processing, DNA metabolism, protein synthesis, ubiquitinization, cell cycle, and cell adhesion. Regarding their localization within a cell, the proteins encoded by genes associated with XLID are almost equally distributed among the four major subcellular fractions: 30% in the nucleus, 28% in the cytoplasm, 18% in the membranes, and 16% in cellular organelles.[17]

The XLID disorders offer many opportunities for understanding the functions of specific genes and their interactions with other genes in producing disease. Studies involving control of gene expression will necessarily be especially complex. These have just begun, in part because of their complexity and the rapid development of new techniques. Only recently, for example, has a preliminary expression microarray analysis been carried out in two affected fragile X males.[101] The study identified over 90 genes with a greater than 1.5-fold change in expression. Overrepresented genes were involved in signaling (both under- and overexpression), morphogenesis (underexpression), and neurodevelopment and function (overexpression). Although not addressed in this study, the possibility that a hallmark finding in the fragile X syndrome, enlargement of the testes, might result from altered control of tubular growth by a specific target gene is intriguing. One of the 90 genes identified, *NUT* (nuclear protein in testis [MIM 608963]), which is normally only expressed in the testis, should be a candidate gene in future studies because the *BRDA-NUT* fusion oncogenes are critical growth promoters in certain aggressive carcinomas.[102] Alternatively, a more general growth-controlling gene might also explain the prognathism, macrocephaly and large hands which occur in some individuals with the fragile X syndrome.

Studies directed at understanding the mechanisms underlying recurring clinical problems in XLID disorders such as short stature, microcephaly or macrocephaly, autistic behavior, and structural CNS abnormalities[103] are also particularly appealing because they provide an opportunity both to simultaneously understand critical pathways, such as in dendrite development and the development of XLID structural abnormalities, gene expression, and phenotype. The association of autism spectrum disorder with mutations in at least eight of the 102 genes listed in Table S1 is of particular current interest. This has been reported most frequently in the fragile X syndrome and Rett syndrome but also in disorders resulting from

mutations in *NLGN3* (MIM 300336), *NLGN4* (MIM 300427), *RPL10* (MIM 312173), *RAB39B* (MIM 300774), *PTCHD1*, and *MED12*. These genes, however, affect a wide range of functions (Table S1), and the cause of the clinical overlap is not clear. In nonsyndromal XLID, for example, mutations have been identified in five genes involved in the RhoGTPase cycle that affect dendritic outgrowth (*OPHN1*, *PAK3* [MIM 300142], *ARHGEF6* [MIM 300267], *TM4SF2* [MIM 300096], and *GDI1* [MIM 300104]) and are central to the development of the nonsyndromal phenotype.[1,17,104]

The limited imaging and direct studies of macrocephaly, microcephaly, and cerebellar hypoplasia have recently been summarized,[104] but more extensive application of anatomical and functional brain imaging and spectroscopy techniques that can identify variations in specific brain regions for each disorder, in conjunction with both clinical observations and psychometric studies, is critically needed.

Detection of Possible Advantageous Cognitive and Behavioral Genes

The identification of 102 X-linked genes affecting intelligence has raised the probability that X chromosomal genes (including XLID genes) might play a particularly important role in brain structure and function as well as a specific role in intelligence and certain cognitive abilities. Clearly, as discussed at the beginning of this paper, the research planned and carried out to identify XLID genes and syndromes over the last several decades might account for part or even all of this relative excess compared to autosomal loci. A number of papers, however, have addressed the issue of active selection during evolution for X chromosomal localization of important brain and cognitive genes.[2,105,106] The finding that human and mouse X chromosome genes are hyperexpressed in the CNS compared to autosomal genes provided additional important confirmatory data for the hypothesis of positive evolutionary selection.[107] These studies showed not only that there was a doubling of X chromosome expression (compared to autosomes) early in development (leading to dosage compensation), but overexpression in human CNS tissue and in mouse CNS tissue increased by 2.8× and 2.5×, respectively, compared to expression in somatic tissues. These observations also support the general idea that X genes are particularly important for brain development and function. Mutations significantly improving intellectual, creative, perceptive, and leadership qualities would be fully expressed in males and reasonably could have been positively selected for in a relatively short period of time in contrast to the negative selection for XLID mutations.[108–112] In essence, the XY males may have been the experimental animal and the XX female, the storage facility for both advantageous and deleterious mutations.

Medical investigations generally focus on adverse effects and no organized searches for X-linked pedigrees with particularly high intellectual or special cognitive talents have been reported. Thus, the same approach that has been effective in identifying XLID syndrome genes, investigating families with an X-linked pattern of intellectual outliers, might also prove rewarding for studies at the other end of the intellectual spectrum. What if we selected for families with an X-linked pattern of high intellectual accomplishment; special talents in art or music; unique types of cognitive behavior involving memory, problem solving, or, indeed, any type of special intellectual accomplishment such as Nobel awards in Economics or Physics? Such families will certainly be uncommon but so are most XLID disorders. Yet families might be identified if academicians asked the pertinent family history questions during lunch with colleagues, a dedicated, interactive home page was available, or notices were placed in journals asking for information about possible families. The same group of laboratories that contributed to the data in Table S1 would be logical sources for referral and molecular studies because the necessary cognitive and molecular studies are already in place. A positive result might be even be more important to society than XLID disease description and provide important insight into human evolution.

Although there is a wide array of pertinent cognitive tests, these were not designed to detect specific familial talents. The coapplication of a pedigree analysis with pertinent laboratory tests should provide sufficiently precise initial diagnosis of the affected to carry out linkage and array or other screening tests successfully. One family with four to five outstanding individuals over several generations could provide sufficient data to warrant testing other families (or even other species) and to begin an identification process similar to that described in this paper that has proven successful for XLID. Imagine the prospects for investigating specific gene-environmental interactions during learning and development!

Why, other than not having looked seriously, have we not stumbled upon such families? Perhaps we have. In the Inaugural Book of the new National Museum of the American Indian, *Native Universe, Voices of Indian America*,[113] in which tribal leaders, writers, scholars, and story tellers describe Indian traditions and heritages, the following is recounted:

"Story tells us that a group split from the Lenni Lenape, perhaps a thousand years ago or more. The people then settled on the Eastern Shore of the Chesapeake, and were one and the same as the Nanticoke. Then, for some reason, the first Tayac, Uttapoingassenum, led his people to the other side of the bay. Upon their arrival, they encountered peoples who had been living on the land for more than 8,000 years, according to various archeological estimates. For thirteen generations prior to English settlement, as told to Jesuit and Moravian missionaries, the Tayac's inheritance passed from brother to brother and then to the sister's sons. Each led the people until his death."

The possibility that the Nanticoke had intuitively recognized and employed a quality of leadership that followed an X-linked pattern of inheritance is intriguing to consider.

Although much progress has been made during the past four decades, the clinical and molecular delineation of XLID is far from complete. Perhaps little more than half of the genes in which mutations will result in XLID have been identified. The molecular pathways are incompletely understood, the mechanisms by which brain structure and function are deranged have not been identified, and with few exceptions the neurobehavioral profiles and natural history of the XLID entities have received insufficient attention. These deficiencies notwithstanding, considerable benefits have been gained for individuals with XLID and their families. Specific molecular tests, including multigene panels, are now available to more efficiently reach a diagnosis. Carrier testing, donor eggs, prenatal diagnosis, and preimplantation genetic testing may be used to prevent recurrence when a specific gene mutation is found. Through these measures, reproductive confidence may be restored for families in which XLID has occurred.[114]

Supplemental Data

Supplemental Data include two tables and can be found with this article online at http://www.cell.com/AJHG/.

Web Resources

The URLs for data presented herein are as follows:

Greenwood Genetic Center, XLID Update, http://www.ggc.org/research/molecular-studies/xlid.html

Online Mendelian Inheritance in Man (OMIM), http://www.omim.org/

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