

X-LINKED MENTAL RETARDATION

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Abstract | Genetic factors have an important role in the aetiology of mental retardation. However, their contribution is often underestimated because in developed countries, severely affected patients are mainly sporadic cases and familial cases are rare. X-chromosomal mental retardation is the exception to this rule, and this is one of the reasons why research into the genetic and molecular causes of mental retardation has focused almost entirely on the X-chromosome. Here, we review the remarkable recent progress in this field, its promise for understanding neural function, learning and memory, and the implications of this research for health care.

Mental retardation is one of the main reasons for referral in paediatric, child-neurological and clinical genetic practice. Often, however, despite extensive investigations, an aetiological diagnosis cannot be made, leaving families without accurate genetic counselling or reproductive options, such as prenatal diagnosis. The prevalence of mental retardation in developed countries is thought to be on the order of 2–3% (REF. 1), although estimates vary widely, particularly for mild mental retardation. In central Europe, about 8% of health-care expenditure is spent on ‘mental handicaps’ as defined by the International Classification of Disease (ICD) (BOX 1), which by far exceeds the costs that are related to all other ICD categories². Together with its high burden for society and families, this renders mental retardation one of the most important unsolved problems in medicine.

X-linked gene defects have long been considered to be important causes of mental retardation, on the basis of the observation that mental retardation is significantly more common in males than in females^{3–5}. Clinical observations and linkage studies in families revealed that X-linked mental retardation (XLMR) is a highly heterogeneous condition. The most common form of XLMR — the **Fragile X (Fra(X)) mental-retardation syndrome** — is associated with a cytogenetic marker in the distal region of the long arm of the X chromosome, which was shown to coincide with the map position of the underlying gene defect, and eventually this led to the cloning of the *FMR1* gene⁶. Since then, the number of cloned XLMR genes has been increasing exponentially. No fewer than 23 of the currently known XLMR genes have been identified since a previous review on this

subject (by Chelly and Mandel⁷) was published. Progress has been particularly spectacular for so-called non-syndromic or ‘pure’ forms of XLMR, consisting of numerous disorders that are clinically indistinguishable because cognitive impairment is their only manifestation.

In this review, we describe the strategies used to identify all genes that have been implicated in XLMR so far, emphasizing the crucial importance of large cohorts of well-characterized families. We provide a brief summary of what is currently known about the physiological and pathophysiological functions of XLMR genes, and examine the evidence for a role of these genes in cognition. Taking into account the possibility that XLMR might be less common than indicated by the observed excess of males with the condition, we discuss the potential of this research to provide new possibilities for the diagnosis, prevention and therapy of mental retardation. We conclude by discussing the importance of autosomal mental retardation genes and the challenges that will need to be overcome to identify them.

Syndromic and non-syndromic forms of XLMR

XLMR is subdivided into syndromic (S-XLMR) and non-syndromic (NS-XLMR) forms, depending on whether further abnormalities (in addition to mental retardation) are found on physical examination, laboratory investigation and brain imaging. Roughly two thirds of XLMR cases are thought to be non syndromic⁸; however, as the possibilities for classifying families through molecular studies improve, and as patients are examined in more detail, it is likely that the proportion of syndromic cases that are diagnosed will increase, with a

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Box 1 | Definition and classification of mental retardation

Mental retardation is a complex disorder, which is not easily defined in a comprehensive way. The most widely used definition¹¹⁸ comprises three criteria: significantly sub-average general intellectual functioning (Intelligence quotient (IQ) <70); significant limitations in adaptive functioning in at least two of the following skill areas — communication, self-care, ability to live independently, social and interpersonal skills, use of public services, decision making, functional academic skills, work, leisure, and health and safety; and onset before the age of 18 years. On the basis of IQ, mental retardation is subdivided into several classes. Most commonly, the WHO (World Health Organization) classification and terminology (see table) are used¹¹⁹, but numerous studies distinguish only between mild (IQ 70–50) and severe mental retardation (IQ <50).

Terminology	Intelligence quotient
Profound	<20
Severe	20–35
Moderate	35–50
Mild	50–70
Borderline	70–85

concomitant decrease in the non-syndromic cases. This is illustrated by the Fra(X) syndrome, which was initially described as non syndromic and is now considered to be the most frequent example of S-XLMR. Moreover, mutations in several XLMR genes can give rise to both non-syndromic and syndromic forms (TABLES 1,2), indicating that there is no reliable molecular basis for strictly distinguishing between genes for S-XLMR and NS-XLMR. However, for pragmatic reasons and in agreement with others (see the [XLMR Genes Update](#) web site in the Online links box), we found it useful to maintain this separation in this review.

About 140 syndromic forms of XLMR have been described so far. In 66 of these, including several that have since been found to be allelic, the causative genetic defects have been identified (TABLE 1; see online [supplementary information S1](#) (table) for a full version), and in about 50 others, the underlying defect has been mapped to a specific region of the X chromosome. By contrast, for NS-XLMR, less than 50% of the causative gene defects have been identified, as discussed below. Although progress has been made in identifying genes that are involved in NS-XLMR in the past few years (FIG. 1), the identification of other genes that are involved in these cases remains an important task.

Large-scale identification of XLMR genes

Searching for genetic defects that underlie clinically well-defined syndromic forms of XLMR is not different from gene hunting in any other monogenic condition. It has been greatly facilitated by the availability of the annotated human genome sequence and the increase in our knowledge about gene function. Between 2002 and 2004, causative mutations in 15 genes have been identified in 18 clinically different syndromic forms of XLMR, and it is safe to predict that before long, most of the 50 syndromic forms of XLMR for which mapping information is already available will also be elucidated.

Finding molecular causes of NS-XLMR is intrinsically more difficult owing to its high level of genetic heterogeneity, which precludes the pooling of linkage information from unrelated families and greatly complicates the search for mutations. To overcome these obstacles and to study the molecular basis of NS-XLMR in a systematic manner, the [European XLMR Consortium](#) was founded in 1995, and since then its members and associated groups have made important contributions

to the identification of the 20 NS-XLMR genes identified so far (TABLE 2).

Different strategies led to the identification of these genes. For example, *FMR2* was found because of its association with a fragile site, FRAXE, which is analogous to the association of *FMR1* with another such site, FRAXA, in mentally retarded males^{9,10}. Other genes were identified by breakpoint mapping and cloning in mentally retarded patients with [BALANCED REARRANGEMENTS](#) that involve the X chromosome, or by molecular characterization of small X-chromosomal deletions.

The study of chromosomal rearrangements has proved to be particularly informative in the identification of genes that are involved in XLMR. Through the systematic characterization of patients with balanced X-chromosomal rearrangements, several additional genes were found to be truncated (see for example, REFS 11,12; FIG. 2). However, these genes are not listed in TABLE 2 because subsequent screening of unrelated NS-XLMR patients failed to identify further mutations in these genes. This might be because patients with clinically complex developmental disorders are more likely to undergo karyotyping than patients with NS-XLMR, and so more balanced rearrangements will be identified that are associated with syndromic rather than with non-syndromic XLMR. Indeed, screening for mutations of the *CDKL5* (*STK9*) gene — previously identified by breakpoint cloning in two severely affected females¹³ — was unsuccessful in large cohorts of families with NS-XLMR, but several mutations of this gene were later found in patients with atypical [Rett syndrome](#)^{14,15} (a syndromic form of XLMR; TABLE 1). Therefore, many of the truncated genes that were identified by studying mentally retarded patients with balanced X-chromosomal rearrangements might still be bona fide XLMR genes, even if no mutations are detectable in unrelated patients with NS-XLMR.

Mapping the causative gene defect to a defined X-chromosomal interval, followed by mutation screening in unrelated families, is another successful strategy for identifying novel XLMR genes, particularly if the size of the relevant interval is small. For example, *ARX* — mutations in which are now known to be a common cause of syndromic and non-syndromic XLMR — was mapped to a small linkage interval as a result of pooling of linkage data from different (syndromic) families¹⁶. Similarly, *ACSL4* (*FACL4*) was one out of only four

BALANCED REARRANGEMENTS
Chromosomal rearrangements that change the chromosomal gene order but do not remove or duplicate any of the DNA from the chromosomes. The two most simple classes of balanced rearrangements are inversions and reciprocal translocations.

Table 1 | **Syndromic forms of X-linked mental retardation***

Gene affected	Disorders associated with mental retardation	Main features	Functions of encoded protein	Refs
<i>FMR1</i>	Fragile X syndrome	Facial anomalies, macroorchidism	mRNA binding protein; mRNA transport and regulation of translation	6,101, 102
<i>MAOA</i>	MAO-A-deficiency behaviour	Aggressive and violent	MAO; serotonin metabolism	88
<i>GK</i>	Glycerol kinase deficiency [†]	Short stature, spasticity, osteoporosis, hyperglycerolaemia	Nuclear translocation of the glucocorticoid-receptor complex	63,120
<i>XNP</i> [§]	ATR-X, Juberg–Marsidi syndrome, Carpenter syndrome, Holmes–Gang syndrome, Smith–Fineman–Myers syndrome, Chudley–Lowry syndrome, Spastic paraplegia	Microcephaly, hypotonic facies, facial, urogenital and skeletal anomalies, α -thalassaemia, HbH inclusions Microcephaly, short stature, spastic diplegia	DNA helicase; chromatin remodelling, DNA methylation and regulation of gene expression; regulator of cortical size	50,51 52,121 122
<i>FGD1</i>	Aarskog–Scott syndrome [‡]	Facial, digital and genital anomalies, short stature	RhoGEF; possible role in stimulation of actin polymerization and neurite outgrowth	32,33, 123
<i>RSK2</i> [§]	Coffin–Lowry syndrome	Facial and skeletal anomalies	Serine-threonine protein kinase; CREB phosphorylation; long-term memory	65–67
<i>OPHN1</i>	Cerebellar hypoplasia or dysplasia and epilepsy	Epilepsy, cerebellar anomalies	Negative control of rhoGTPases; stabilization of dendritic arbours	34
<i>MECP2</i> [§]	Rett syndrome Male fatal neonatal encephalopathy Progressive spasticity NS-XLMR Angelman and Prader–Willi-like phenotypes	Regression, epilepsy, acquired microcephaly, hand stereotypies, autism Hypotonia, apnea, epilepsy Spasticity	Transcriptional silencer of neuronal genes	58,124, 125 53 54 57 55,56
<i>SLC6A8</i> [§]	Creatine deficiency syndrome	Epilepsy, facial anomalies	Creatine transporter, maintenance of (phospho) creatine pool in brain	126
<i>FLNA</i>	Periventricular heterotopia Otopalatodigital syndrome I and II	Epilepsy, brain anomalies Short stature, cleft palate, facial and skeletal anomalies	Actin-binding protein; neurite outgrowth; dendritic spine formation	35 35,36
<i>ARX</i> [§]	West syndrome Partington syndrome X-linked lissencephaly, ambiguous genitalia Proud syndrome	Infantile spasms, regression Epilepsy, dystonia Lissencephaly, corpus callosum agenesis, epilepsy, ambiguous genitalia Microcephaly, corpus callosum agenesis, urogenital anomalies	Transcription factor; possible role in maintenance of specific neuronal subtypes in cerebral cortex and axonal guidance in the floorplate; neuronal proliferation/differentiation of GABA-releasing neurons	16,92 16,128 127 129
<i>SMS</i>	Snyder–Robinson syndrome	Macrocephaly, palatal anomalies, scoliosis	Spermine synthase	97
<i>CDKL5 (STK9)</i>	Infantile spasms	Infantile spasms	Serine-threonine kinase; chromatin remodelling	13–15
<i>PQBP1</i> [§]	Renpenning syndrome, Sutherland–Haan syndrome, Hamel cerebro-palatocardiac syndrome, Golabi–Ito–Hall syndrome	Microcephaly, short stature, slender habitus, long face, congenital heart defect, cleft palate	Polyglutamine-binding; mRNA splicing	19
<i>PHF6</i>	Börjeson–Forssman–Lehmann syndrome	Hypogonadism, obesity, facial anomalies, epilepsy	PHD zinc-finger protein; putative role in transcription	68
<i>SLC16A2</i>	Thyroid and neurological abnormalities	Hypotonia, spasticity, dystonia, abnormal thyroid tests	Monocarboxylate transporter; T3 transport into the cytoplasm	96,130
<i>BCOR</i>	Lenz microphthalmia	Microphthalmia, skeletal and urogenital anomalies	Transcriptional co-repressor; possible role in modulation of histone acetylation and chromatin remodelling	64
<i>SYN1</i>	Epilepsy, macrocephaly, aggression [‡]	Epilepsy, macrocephaly, aggression	Synaptic-vesicle-associated protein	42–44
<i>PHF8</i>	Siderius–Hamel cleft lip or palate syndrome	Cleft lip or palate	PHD zinc-finger protein; putative role in transcription	
<i>ATP6AP2</i>	Epilepsy	Epilepsy	Renin receptor; activates ERK1 and ERK2	98
<i>KIAA1202</i>	Stocco dos Santos syndrome	Short stature, congenital hip dislocation, recurrent infections	PDZ domain-containing protein; possible role in actin remodelling	
<i>JARIDIC</i> [§] (<i>SMCX</i>)	Microcephaly, spasticity, epilepsy, short stature, facial anomalies	Microcephaly, spasticity, epilepsy, short stature, facial anomalies	Transcription factor; chromatin remodelling	22,74

*Selected forms of syndromic X-linked mental retardation (S-XLMR) that are mentioned in the text. [†]Not consistently associated with mental retardation. [§]Also mutated in non-syndromic XLMR (NS-XLMR). ^{||}X-linked dominant. See online [supplementary information S1](#) (table) for a version showing all genes identified as being involved in S-XLMR. ATR-X, X-linked α -thalassaemia mental retardation; CREB, cAMP-response-element-binding protein; ERK, extracellular-signal-regulated kinase; GABA, γ -aminobutyric acid; GEF, guanine-nucleotide exchange factor; HbH, haemoglobin H; MAO, monoamine oxidase; T3, thyroid hormone.

Table 2 | Genes that have been implicated in non-syndromic X-linked mental retardation

Gene symbol	Function	Refs
<i>FMR2</i>	Transcriptional regulator, possibly involved in long-term memory and enhanced long-term potentiation	9,10,70
<i>GDI1</i>	Regulation of Rab4 and Rab5 pools, probably involved in the maturation of synaptic vesicles	45,46
<i>PAK3</i>	Regulation of actin cytoskeleton, stimulation of neurite outgrowth	28,30
<i>IL1RAPL</i>	Regulator of dense-core-granule exocytosis, possible modulator of neurotransmitter release	131,132
<i>RSK2*</i>	Serine-threonine protein kinase, CREB phosphorylation, role in long-term memory formation	65–67
<i>MECP2*</i>	Transcriptional silencer of neuronal genes	57,58,124
<i>ARHGEF6</i>	Integrin-mediated activation of Rac and cdc42, stimulation of neurite outgrowth	31,133
<i>TM4SF2</i>	Modulation of integrin-mediated signalling, neurite outgrowth, possible role in synapse formation	134–136
<i>SLC6A8*</i>	Creatine transporter, required for maintenance of (phospho) creatine pools in the brain	94,126
<i>ARX*</i>	Transcription factor with possible role in the maintenance of specific neuronal subtypes in the cerebral cortex and axonal guidance in the floorplate, neuronal proliferation, differentiation of GABA-releasing neurons	16,92,127
<i>XNP*</i>	DNA-binding helicase that is involved in chromatin remodelling, DNA methylation and regulation of gene expression; intrinsic regulator of cortical size	50,52,137
<i>FGD1*</i>	RhoGEF, possible role in stimulation of neurite outgrowth	32
<i>ACSL4 (FACL4)</i>	Long-chain fatty-acid synthase, possible role in membrane synthesis and/or recycling	17,138
<i>AGTR2</i>	Brain-expressed angiotensin receptor 2	139,140
<i>PQBP1*</i>	Polyglutamine-binding, also has a role in mRNA splicing	19
<i>ZNF41</i>	Transcriptional regulator that is involved in chromatin remodelling	21
<i>NLGN4</i>	Postsynaptic membrane protein that is involved in induction of presynaptic structures; linked to NMDA-type glutamatergic receptors	37,41
<i>FTSJ1</i>	Role in tRNA modification and RNA translation	20,141
<i>DLG3</i>	Postsynaptic scaffolding protein linked to NMDA-type glutamatergic receptors	23
<i>JARID1C* (SMCX)</i>	Role in chromatin remodelling	22,74

*Also mutated in syndromic X-linked mental retardation (S-XLMR). CREB, cAMP-responsive element-binding protein; GABA, γ -aminobutyric acid; NMDA, *N*-methyl-D-aspartate; tRNA, transfer RNA.

candidate genes that was located in the shortest common interval of overlapping deletions¹⁷. By contrast, finding the causative mutation in isolated families with NS-XLMR turned out to be as difficult and time-consuming as expected, owing to the genetic heterogeneity of this disorder, wide linkage intervals and correspondingly large numbers of candidate genes.

Recently, semi-automated mutation-detection protocols and the availability of large cohorts of families have paved the way for large-scale mutation screening of positional or functional candidate genes. Moreover, recent studies have identified promising target regions on the X-chromosome for large-scale mutation screening. By analysing linkage intervals from 125 families with apparently non-syndromic XLMR, we showed that the underlying mutations are conspicuously clustered in three X-chromosomal regions, with the Xp11 region carrying almost 30% of all gene defects that underlie NS-XLMR (REF. 18) (see the [Max Planck Institute for Molecular Genetics — Nonsyndromic X-linked mental retardation](#) web page for an update of this analysis, including linkage data from additional families provided by other groups). Systematic mutation screening

of 50 brain-expressed genes from the Xp11 mutation hotspot has so far led to the identification of 5 novel XLMR genes — *PQBP1* (REF. 19), *FTSJ1* (REF. 20), *ZNF41* (REF. 21), *JARID1C* (REF. 22) and *PHF8* (L. S. Jensen *et al.* unpublished observations; *PHF8* was independently identified by breakpoint cloning in a patient with a balanced translocation, F. Laumonnier *et al.*, unpublished observations). Similarly, large-scale sequencing of functional candidate genes from the pericentromeric region enabled Tarpey *et al.*²³ to identify mutations in the *DLG3* gene (see below).

XLMR genes: a clue to brain function

Since the cloning of the *FMR1* gene⁶, research in many laboratories has focused on the function of its protein product, FMRP, and the pathogenesis of the Fra(X) syndrome. FMRP binds to specific mRNAs that are involved in DENDRITE development or synapse function and, in the cytoplasm of neuronal cells, it is part of large messenger ribonucleoprotein particles that contain polyribosomes. There is now evidence that FMRP mediates translational silencing of mRNAs through interaction with microRNAs and the RNA-INDUCED SILENCING COMPLEX

DENDRITE

A branching extension from the cell body that receives synaptic input from the axon of another neuron.

RNA-INDUCED SILENCING COMPLEX

A multi-component, ribonucleoprotein complex that cleaves specific mRNAs that are targeted for degradation by homologous dsRNAs during the process of RNA interference.

NEURITE

Any process that extends from the cell body of the neuron, such as the dendrite or axon.

RHO GTPases

A family of small GTPases that are components of a number of signal-transduction pathways.

DENDRITIC SPINES

Specialized regions of the dendrite that receive synaptic inputs from other neurons.

POSTSYNAPTIC DENSITY PROTEIN

An electron-dense thickening of the postsynaptic membrane that contains a high concentration of neurotransmitter receptors, scaffolding proteins and signalling molecules.

EVH1 DOMAIN

First identified in the Ena/VASP family of proteins in *Drosophila melanogaster*, EVH1 domains bind poly-proline rich regions that are recognized by various binding partners.

SYNAPTIC PLASTICITY

A change in the functional properties of a synapse as a result of use.

DENSE-CORE GRANULE

Large diameter (80–200 nm) secretory vesicles that have high electron density when visualized by electron microscopy. They usually contain neuropeptides or catecholamines (hormones that affect the sympathetic nervous system).

ATAXIA

Inability to coordinate movement.

ANGELMAN-LIKE SYNDROME

A genetic disorder that is caused by deletion or disruption of *UBE3A* (*E6-AP*). The symptoms of Angelman syndrome include hyperactivity, ataxia, problems with speech and language, and an unusually happy demeanour.

PRADER-WILLI-LIKE SYNDROME

A genetic disorder that is caused by loss of gene function on chromosome 15. Features of the disorder include excessive eating (hyperphagia), obesity, short stature, mental retardation or learning disabilities, and behavioural problems.

(RISC)²⁴. Moreover, several mRNA targets of FMRP and its *Drosophila melanogaster* homologue, the DFMR1 protein, have recently been identified. Several recent reviews have summarized the current knowledge in this field^{25,26}, and show the growing importance of Fra(X) research for understanding fundamental aspects of neuronal function.

Much less is known about the function of genes that are mutated in NS-XLMR, which is due in part to the fact that they have only recently been identified. Until a few years ago, most of the NS-XLMR genes that had been identified were functionally related to the formation and deconstruction of the actin cytoskeleton and to the control of NEURITE outgrowth^{7,27,28}. This holds true for *OPHN1* (REF. 29), *PAK3* (REF. 30) and *ARHGEF6* (REF. 31) (three of the few genes involved in NS-XLMR that were identified before the year 2000) and for *FGDI* (REFS 32,33), all of which code for regulators or effectors of RHO GTPases (TABLES 1,2). An explanation for why mutations in these genes lead to mental retardation has come from the recent demonstration³⁴ that inactivation of *OPHN1* reduces the length of DENDRITIC SPINES by increasing the activities of RhoA and Rho-kinase. It is noteworthy that *OPHN1* also binds to Homer, a POSTSYNAPTIC DENSITY PROTEIN with various binding partners, including the type-1 metabotropic glutamate receptors (mGluRs), which are involved in dendritic spine morphogenesis and synaptic transmission³⁴. Other functionally related genes include *FLNA*, which encodes a widely expressed actin-binding protein and is linked to three different syndromic forms of XLMR (REFS 35,36), and *KIAA1202*, which has been recently implicated in S-XLMR (O. Hagens *et al.*, unpublished observations). The *KIAA1202* protein contains an EVH1 DOMAIN, which indicates that similar to its mouse homologue, *Shroom*, it binds to actin and has a role in cytoskeletal remodelling.

Synapses have emerged as an important site of XLMR gene function, as various XLMR genes have been implicated in their induction, structure and function. For example, mutations in *NLGN4*, which encodes neuroligin 4, have been found in patients with XLMR and/or autism^{37,38}. Neuroligins localize primarily to the postsynaptic membranes of glutamatergic synapses and, through their interaction with β -neurexins in the membrane of adjacent axons, they have a central role in the induction of presynaptic structures^{39–41}.

SYN1 encodes synapsin 1, an important effector of the small Ras-like GTPase Rab3A on small synaptic vesicles^{42,43}, which has been implicated in X-linked epilepsy, with or without mental retardation (REF. 44). The *DLG3* gene encodes the synapse-associated protein 102 (SAP102), a member of the postsynaptic membrane-associated guanylate kinases (MAGUKs), which link neuroligins to N-methyl-D-aspartate (NMDA)-type glutamatergic receptors. Protein-truncating mutations in *DLG3* give rise to moderate to severe NS-XLMR (REF. 23), presumably by impairing the interaction of SAP102 with NMDA receptors and/or other proteins that function downstream in NMDA-receptor signalling pathways. Therefore, *DLG3* is the first XLMR gene to be linked directly to

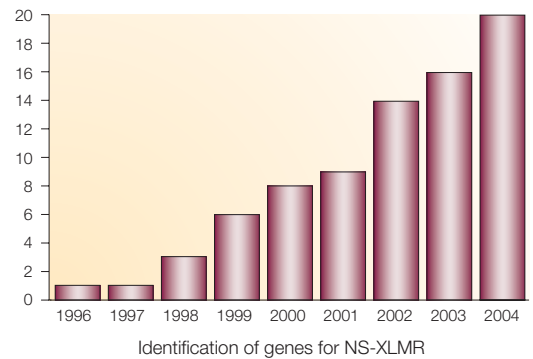


Figure 1 | Identification of genes that are involved in non-syndromic cases of X-linked mental retardation (NS-XLMR). The total number of genes identified is shown for the years 1996–2004.

NMDA receptor-mediated synaptic activity and SYNAPTIC PLASTICITY.

GDI1 mutations⁴⁵ have been shown to reduce the concentration of several Rab GTPases, including Rab4 and Rab5, which in turn seems to result in a reduction of the synaptic vesicle pool⁴⁶. Finally, results of two-hybrid screens and transfection experiments indicate that *ILIRAP1* functions as a negative regulator of DENSE-CORE GRANULE exocytosis^{47–49}. The product of this gene might therefore have a physiological role in the modulation of synaptic neurotransmitter release.

Chromatin remodelling and/or transcriptional control of gene expression are affected in numerous forms of XLMR. For example, *XNP* (REF. 50), which is mutated in various distinguishable XLMR syndromes — including X-linked α -thalassaemia-mental retardation (ATR-X) and NS-XLMR — encodes a helicase that is localized to pericentromeric heterochromatin and binds to HP1. It is part of a multiprotein complex and probably has a role in chromatin remodelling, DNA methylation and gene regulation⁵¹. By preventing apoptosis, it seems to be an intrinsic regulator of cortical size and a survival factor for hippocampal and cortical structures, which are important for learning and memory⁵².

Mutations in *MECP2* give rise to a wide range of disorders, including female-specific Rett syndrome, which is characterized by cessation and regression of development in early childhood, ATAXIA, stereotypic hand movements and other neurological features. However, *MECP2* mutations also lead to other phenotypes such as severe encephalopathy⁵³, progressive spasticity⁵⁴, ANGELMAN⁵⁵ and PRADER-WILLI-LIKE phenotypes⁵⁶, and NS-XLMR, particularly in males (REF. 57). *MeCP2* binds to methylated CpG dimer pairs in DNA, and subsequent recruitment of the transcriptional co-repressor Sin3A and incorporation of histone deacetylases (HDAC) 1 and 2 leads to chromatin condensation. Specific targets of *MeCP2* include the brain-derived neurotrophic factor (BDNF) and the *Hairy2a* gene, which are important for long-term synaptic plasticity, learning and memory^{58,59}, and for neurogenesis⁶⁰, respectively. Animal studies have

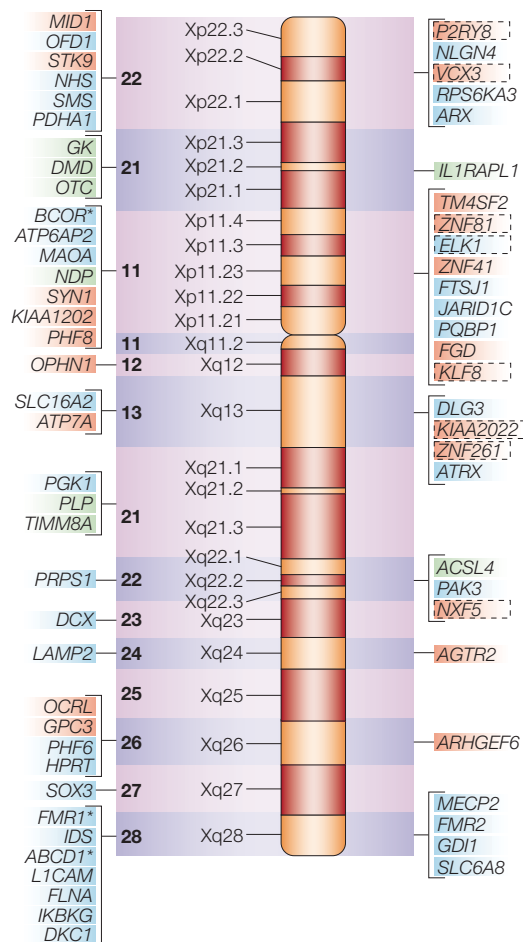


Figure 2 | **Chromosomal rearrangements: clues to the identity of X-linked mental retardation (XLMR) genes.** XLMR genes that are identified by studying balanced X-chromosome rearrangements and deletions (or duplications) are in red and green boxes, respectively; XLMR genes identified by mutation screening are in blue boxes. Boxes that have a dotted outline indicate candidate genes, the status of which is still not confirmed. For ZNF261 see REF. 9 and for P2RY8 and KIAA2022 see REF. 10; all other candidate genes are from V. Kalscheuer et al., personal communication. Genes that are implicated in NS-XLMR are shown on the right.

shown that MeCP2 is also important for neuronal survival⁶¹, and there is recent evidence for upregulation of the glucocorticoid inducible genes in brains of mouse models of Rett syndrome, indicating that the neurological abnormalities seen in these animals are related to an abnormal stress response (U. Nuber *et al.*, personal communication). It is noteworthy that altered expression of the glucocorticoid receptor gene has also been observed in Fra(X) syndrome⁶², and disrupted nuclear translocation of the glucocorticoid receptor complex seems to have a crucial role in X-linked glycerol-kinase deficiency, which is often associated with mental retardation⁶³.

As recently shown, atypical Rett syndrome in females can also result from mutations in the cyclin-dependent protein kinase-like 5 (CDKL5) gene^{14,15}. Given the strong clinical overlap between these conditions, it is conceivable that the CDKL5 protein is a modulator of

MECP2 and is therefore also involved in chromatin remodelling¹⁴. Similarly, the BCOR gene, mutated in Lenz microphthalmia (a syndromic form of XLMR; TABLE 1), is a key transcriptional regulator during early embryogenesis, with a possible role in histone acetylation and chromatin remodelling⁶⁴.

Mutations in RSK2 (ribosomal protein S6 kinase A3; RPS6KA3) give rise to Coffin-Lowry syndrome (CLS), which sometimes resembles ATR-X syndrome (TABLE 1), and partial deficiency of this enzyme can result in NS-XLMR (REF. 65). RSK2 phosphorylates the cAMP response element-binding protein (CREB), which has an important role in learning and long-term memory and is involved in the regulation of the histone H3 acetyltransferase CBP (REF. 66). Interestingly, skeletal abnormalities that are characteristic of CLS have recently been explained by showing that ATR4, a transcription factor with a key role in OSTEOBLAST differentiation, is also regulated by RSK2-mediated phosphorylation⁶⁷.

ARX, the gene that is implicated in West syndrome, Partington syndrome and X-linked lissencephaly and absent corpus callosum and ambiguous genitalia (XLAG) (syndromic forms of XLMR; TABLE 1), encodes a homeobox-containing protein that is also a transcriptional regulator. Similarly, the PHF6 and PHF8 genes, mutated in Börjeson-Forssman-Lehmann syndrome⁶⁸ and Siderius-Hamel cleft lip and palate syndrome, respectively (REF. 69; F. Laumonier *et al.*, unpublished observations; L. S. Jensen *et al.*, unpublished observations), encode proteins with PLANT HOMEODOMAIN FINGERS and are expressed in the nucleus, which indicates a role in the control of transcription.

The same is true for FMR2 (REF. 9) and its three functionally overlapping autosomal homologues, which all function as transcriptional regulators⁷⁰. In addition, ZNF41 encodes a zinc-finger protein and has been implicated in NS-XLMR^{21,71}. The most recent addition to this category is JARID1C²² (Jumonji AT-rich interactive domain IC, formerly called SMCX⁷²), the X-chromosomal counterpart of JARIID (the gene that encodes the male-specific histocompatibility gene H-Y⁷³). All JARID proteins show strong amino-acid homology to the transcription factor RB2, and various lines of evidence indicate that they have a role in chromatin remodelling (for example, see REF. 74).

Other forms of XLMR are caused by disruptions in fundamental processes such as RNA splicing (PQBP1), translation (FTSJ1), protein degradation (MID1) and energy metabolism (SLC6A8), or by metabolic defects (for example, SMS and ACSL4) that are not confined to the brain. The precise role of many XLMR genes is still unknown, and their elucidation promises fundamentally new insights into mechanisms of brain function.

X-chromosomal genes and cognition

As is often proposed^{45,75}, allelic variants of XLMR genes might also be positive determinants of cognition and might function as ‘intelligence genes’. So far, this speculation has not been directly substantiated, but recent studies have provided circumstantial evidence for a role of X-chromosomal genes in cognition.

OSTEOBLAST
A mesenchymal cell with the capacity to differentiate into bone tissue.

HOMEODOMAIN FINGERS
A highly conserved sequence motif, usually comprising 60 amino acids, that includes a DNA-binding region.

In a large cohort of male and female monozygotic twins, Loat *et al.*⁷⁶ found that in female monozygotic twin pairs, complex behavioural traits are less closely correlated than in male monozygotic twins. Loat *et al.*⁷⁶ argued that the higher variation of cognitive traits in female twins might be due to X-chromosome inactivation, with varying proportions of cells that express functionally different alleles of cognition genes on the paternally or maternally derived X chromosome. Previous studies⁷⁷ indicated that females with a 45,X karyotype (Turner syndrome) have higher verbal and other behavioural skills if their only X chromosome is paternally derived, suggesting the existence of an imprinted gene that is inactive if carried on a maternally derived X chromosome.

Genes that have important roles in human cognition might be evolutionarily recent acquisitions or they could have undergone important changes in their spatio-temporal expression pattern during mammalian and primate evolution. It is noteworthy in this context that ZNF41 — a member of the krueppel family of zinc-finger proteins that function in transcriptional regulation and chromatin remodelling and have been implicated in XLMR — seems to have no orthologues in rodents²¹; this is particularly remarkable given the strict evolutionary conservation of the mammalian X chromosome⁷⁸.

XLMR genes with evolutionarily diverged, but still active homologues on the human Y chromosome are expected to cause functional inequalities in male and female brains. *JARIDIC* seems to be one of those genes: because *JARIDIC* mutations cause XLMR in males, the activity of the closely related *JARIID* gene is obviously not sufficient to compensate for the functional loss of its X-chromosomal homologue (which is far more active in the brain and might also be functionally different). The genetic defect underlying X-linked epilepsy that is confined to females (known as **epilepsy, female restricted, with mental retardation**) has been mapped to a region on the proximal part of Xq that is known to harbour genes that are homologous between the X and Y chromosomes^{79,80}. Although in this case males might be rescued by a Y-chromosome homologue of the (as yet unknown) X-chromosome gene, functional differences between these homologues and/or repression (or partial repression) of the X-linked gene owing to X-inactivation in females could also contribute to gender-specific differences in brain function that are unrelated to hormonal effects.

Association studies in individuals who have an exceptionally high intelligence quotient (IQ) to identify genes that enhance cognitive abilities have not been successful so far (for example, see REF. 81), but the X chromosome would be a good place to start looking for them. If there are such genes on the X chromosome, it will be interesting to see whether they are allelic to any of the known XLMR genes or to polymorphic variants with subtle effects on IQ, which have been postulated to explain the observed excess of mental retardation cases among males (see below).

XLMR: less frequent than commonly thought?

A significant excess of males has been observed in numerous large cohorts of mentally retarded patients, with male–female ratios of 1.4 for moderate to severe mental retardation (IQ < 50). Under the simplifying assumption that the male excess derives exclusively from X-linked gene defects and that no females are affected, this indicates that 28.5% of all severely retarded males have XLMR (see online **supplementary information S2** (box) for details of how this percentage is calculated).

For mild mental retardation (IQ 70–50), epidemiological data are much less robust owing to definition and ascertainment problems, but numerous studies have found even higher male–female ratios — of 1.9 on average¹ — which indicates that almost 50% of all mild forms of mental retardation are due to XLMR. So far, no plausible explanation has been provided for such a prominent role of X-linked genes, nor has it been explained why their role should be more important in mild, rather than in severe, mental retardation. Given the extent of mental retardation as a socio-economic problem, verification of these estimates is an important issue, not only for genetic services, but also for health care as a whole.

Two studies have tried to infer the frequency of XLMR from the absolute and relative frequency of affected brother and sister pairs in British Columbia, Canada⁸² and New South Wales, Australia⁸. For moderate to severe XLMR (IQ < 50), Fishburn *et al.*⁸ estimated a frequency of 5 in 10,000 males (0.05%; Herbst and Miller's estimate⁸² was almost fourfold higher, but it included mild forms of mental retardation). The frequency of XLMR can also be derived from the incidence of the Fra(X) syndrome, which is approximately 1 in 5,000 males, or 0.02% (REFS 83,84). In the study by Fishburn *et al.*⁸, roughly one quarter of the XLMR families had Fra(X) syndrome. Assuming that most males with Fra(X) syndrome have moderate to severe mental retardation, it follows that the frequency of severe XLMR in males is 0.08%, which is in good agreement with the previous estimate.

Roughly 0.4% of the general population, including both males and females, is severely mentally retarded¹, which means that the prevalence of severe mental retardation in males must be close to 0.5%. If the prevalence of moderate to severe XLMR ranges between 0.05 and 0.08%, this means that X-linked forms of mental retardation account for only 10–16% of all severely retarded patients. Finally, in cohorts of mentally retarded males, the prevalence of the Fra(X) syndrome is 2–2.5% (REFS 85,86), which also indicates that approximately 10% of these cases are due to XLMR (again assuming that one quarter of all males with severe XLMR have Fra(X) syndrome⁸ — much less than is indicated by the observed excess of mentally retarded males. Therefore, X-linked recessive forms of mental retardation cannot explain more than half of this male excess in patients with moderate to severe retardation, and can only explain a small fraction of the much larger excess in mildly affected patients (see online **supplementary information S3** (box) for details of how this is calculated).

X-linked risk factors for mental retardation?

Apart from X-linked recessive mental retardation, the skewed male–female ratio among mentally retarded patients has been attributed to behavioural differences or higher perinatal vulnerability in males¹. Another attractive possibility is the existence of X-linked risk factors that predispose to, but do not cause mental retardation⁸⁷. Indeed, it is plausible that in addition to gene defects that cause full-blown mental retardation in all male carriers, there are other mutations that reduce IQ only marginally (for example, by 15 points or 1 standard deviation). In this model, the IQ distribution in males (but not females) carrying this mutation would be shifted to the left, and the proportion of mentally retarded males in this group (that is, with IQ <70) would rise from 3% to more than 16%. If between 5% and 10% of all males carried such risk factors, this would be sufficient to account for the strong male excess observed in mild mental retardation, but the mean male IQ in the population would only be lowered by 1%, which would probably too small a change to be detectable as a sex difference. Such factors would have a much smaller effect on the incidence of severely affected males, which is in keeping with the observation that the excess of cases among males is lower for severe mental retardation. Moreover, it is conceivable that the marked intra-familial variability that is observed in numerous families with XLMR is also attributable to the independent segregation of such factors.

X-linked factors that increase the risk for mental retardation might be allelic to, or even identical to, mutations that underlie familial XLMR. Indeed, mutations in *FMR2* might have such a role, as most males with expanded trinucleotide repeats in this gene are borderline or mildly affected, and many may have normal intelligence. In the general population, mutations in *FMR2* are far too rare to have a role as a polymorphism that modulates cognitive functions, but mutations in the monoamine oxidase (*MAOA*) gene, which are associated with borderline to mild mental retardation, as well as behavioural changes⁸⁸, indicates that such polymorphisms might well exist. As shown by Caspi *et al.*⁸⁹, maltreated children with low MAOA activity resulting from a polymorphism in the promoter region have a significantly higher risk of developing antisocial behaviour than do controls with normal MAOA activity.

Allelic variants of this kind that affect cognition in a subtle way and/or increase the risk for mental retardation might also be present in genes for familial XLMR — syndromic or not — but they are not necessarily confined to these genes. In cohorts of mentally retarded males or in affected sib pairs, they should be detectable by association studies, because some of these polymorphisms might be fairly frequent owing to small effects of selection. Previously, strong linkage disequilibrium with closely linked flanking markers has been found in apparently unrelated patients with Fra(X) syndrome⁹⁰, which is also due to lack of selection against *FMR1* alleles that predispose to, but do not cause mental retardation.

How many genes?

Roughly 40% of the 885 protein-coding genes that have been identified on the human X chromosome are expressed in the brain (see [e!project ENSEMBL MartView](#) web site), and in principle, XLMR could result from mutations in any of these. 125 X-linked genes, most of which are expressed in the brain, have already been screened for mutations in patients of the EURO-MRX cohort (H. van Bokhoven, personal communication), and collective efforts of many groups have implicated 59 genes in S-XLMR and/or NS-XLMR (TABLES 1,2; and see online [supplementary information S1](#) (table)). Until now, causative genetic defects have been detected in 26 of the 80 families with NS-XLMR for which details have been published (designated MRX, for 'mental retardation, X-linked'⁹¹; see also the XLMR Genes Update web site). This indicates that the 20 genes listed in TABLE 2 might account for almost one third of all mutations that underlie NS-XLMR. However, it is highly likely that the proportion of these families that carry mutations in known genes is even higher, because several of these genes have been identified only recently and have still not been screened for mutations in all MRX families with overlapping linkage intervals.

Mutations in *ARX* have been identified in 8 (or 10%) of the 80 published MRX families; this is far more frequent than mutations in other NS-XLMR genes. However, compared with the Fra(X) syndrome, the incidence of *ARX* mutations seems to be low. In a recent study of 697 males with sporadic mental retardation, Grønskov *et al.*⁸⁶ detected 15 cases of Fra(X) — in keeping with other studies that have indicated that 2–2.5% of the mentally retarded males have Fra(X) (for example, see REF. 85) — but found only a single patient with an *ARX* mutation. This is all the more surprising because mutations in *ARX* are not only common in families with NS-XLMR, but also in those with S-XLMR. Several (mostly unpublished) studies of other groups have yielded similar results, including a search for *ARX* mutations in 148 kindreds with 2 mentally retarded males⁹². Mandel and Chelly⁸⁷ speculated that X-linked risk factors would be a more likely cause of mental retardation in kindreds with two affected males than in large XLMR pedigrees, and that this might explain the low proportion of known gene defects in brother pairs. However, the recently reported high frequency of *JARID1C* and *SLC6A8* mutations in patients from the EURO-MRX cohort^{22,93}, which consists mostly of small families or mentally retarded brother pairs, seems to argue against this speculation.

Diagnosis, prevention and therapy

Many of the syndromic forms of XLMR were previously considered to be non-syndromic, until specific clinical patterns could be defined in cohorts of patients with the same genetic lesion. In a significant number of cases, the syndromic character of the disorder is only apparent at puberty or later in life. Therefore, in clinical practice, with only a single child or a small family affected, it will often not be possible to arrive at a specific clinical diagnosis, and most of these cases will

seem to be non-syndromic, thereby increasing the apparent heterogeneity of NS-XLMR.

Having excluded chromosomal disorders, it is common practice to perform Fra(X) testing in all non-microcephalic males with mental retardation of unknown cause, although *FMR1* mutations are only found in 2–2.5% of these patients. In large families with XLMR, clinical examination might reveal distinguishing features, and linkage mapping might focus mutation screening on a subset of the known XLMR genes. If no such information can be obtained, it will also be justified to screen for mutations in *ARX*, which are the most common cause of NS-XLMR (10% of the MRX families carry a mutation in this gene), or for mutations in *JARID1C*, which was found to be mutated in 12 of the 340 families that were screened (REF. 22; L. S. Jensen *et al.* unpublished observations). Furthermore, mutations in several other recently identified genes should be screened for, including *SLC6A8*, *DLG3* and *FTSJ1*, each of which might account for more than 1% of the mutations that underlie NS-XLMR.

Up to 50% of the patients from MRX families might have mutations in one of the genes that have been implicated in NS-XLMR so far, but current methods are generally too expensive or too unreliable — or both — to justify mutation screening of all known NS-XLMR genes in a diagnostic setting. This might soon change, owing to the introduction of DNA arrays or related methods that allow affordable re-sequencing of many genes in a single experiment. However, given the size of many genes and the possible involvement of unknown regulatory sequences, methods that assay the function of genes — by measuring the activity of enzymes or using other specific functional parameters that can be reliably measured in samples from patients — have many advantages, and if available, they will eventually replace DNA-based mutation screening. For some of the relevant genes, such as *ACSL4* (*FACLA*), *SMS*, *SLC6A8* and *SLC16A2*, functional assays are already available^{94–98} and a few of these are suitable for clinical screening tests.

X-linked polymorphisms that modulate IQ in a more subtle way — which have been postulated to explain the relative excess of males who are affected by mental retardation — might be responsible for much of the clinical variability that is observed in XLMR families. Therefore, typing of such modifier genes might greatly improve the accuracy of predictions about the severity and course of the disorder. In males with sub-average, but still normal IQ, such mutations might be expected to result in borderline to mild mental handicaps. So, these mutations might also represent important risk factors for mental retardation in the general population, and their existence would create previously unforeseen problems for genetic counselling⁸⁷.

Owing to the complexity of the human brain and the early onset of mental retardation, it is generally believed that the chances of developing curative therapies for monogenic XLMR are low. Although this might be the case for syndromic disorders that involve developmental defects of the brain, patients with NS-XLMR do not

show such gross anatomical changes, and histological examination has often identified aberrant length and density of dendritic spines as the only abnormality. Confocal-timelapse imaging, and more recently, TWO PHOTON IMAGING, have both revealed conspicuous plasticity of dendrite formation, maintenance and synaptic interaction with upstream axons, thereby replacing the concept of hard-wired connections in the central nervous system (reviewed in REFS 99,100). These findings indicate that in patients with genetic defects that cause mental retardation, therapeutic intervention might be possible even after birth, and they open up new and unexpected possibilities for drug treatment of these disorders. For example, it has been shown that loss of the *FMR1* protein in Fra(X) mental retardation leads to overexpression of group 1 mGluRs, which then results in protein-dependent long-term depression (LTD), altered synaptic plasticity and dysgenesis of dendritic spines^{101,102}. This indicates a possible role of mGluR antagonists in the treatment of Fra(X) syndrome.

Conclusions

Towards the identification of all XLMR genes. Both for clinical reasons and to increase our understanding of the function of the brain, identifying genes that are involved in XLMR will remain an important task. Breakpoint mapping and cloning in mentally retarded patients with balanced rearrangements of the X chromosome has been a successful strategy for identifying novel XLMR genes, but subsequent screening of patients with NS-XLMR has often failed to identify other mutations in these genes, or have shown that such mutations are rare. Therefore, alternative approaches to identify the molecular causes of NS-XLMR will be required.

The sequencing and annotation of the human genome and the availability of large cohorts of patients and families have together paved the way for candidate-gene approaches to identify the molecular causes of XLMR. Known XLMR genes and emerging pathways will aid in the identification of novel promising candidate genes for mutation screening. The identification of X-chromosomal regions that are frequently involved in XLMR will further facilitate the search for these genes¹⁸. However, in view of the importance of mental retardation for health care and the substantial contribution of XLMR to these cases, even the screening of all brain-expressed X-chromosomal genes would be justified, and should be considered. The molecular elucidation of all monogenic forms of XLMR might also pave the way for the identification of polymorphic variants that affect cognition in a more subtle way, as it is conceivable that such variants are allelic to fully penetrant mutations in XLMR genes. Systematic association studies in large cohorts of mentally retarded males or in affected brother pairs would be another promising strategy to prove the existence of such subtle X-linked mutations.

Finally, although mutation screening has so far been confined to protein-coding genes, it is becoming clear that most mRNAs do not code for protein, both in the brain and in other tissues. Therefore, these 'RNA genes'

TWO PHOTON IMAGING

A form of imaging in which a fluorochrome that would normally be excited by a single photon is stimulated quasi-simultaneously by two photons of lower energy. This allows reduced light scattering and less photodamage of the sample.

promise to become a fertile field for future research into the primary causes of XLMR.

Autosomal causes of mental retardation: the new frontier.

Although far more is known about the role of X-linked genes in mental retardation, autosomal gene mutations and subtle chromosomal rearrangements have a principal role in the aetiology of mental retardation. Small subtelomeric deletions have been found in up to 7% of patients with mental retardation of unknown cause^{103,104}, and there is increasing evidence that they are not confined to the chromosome ends. Recently, genome-wide screening for submicroscopic deletions and duplications has become possible owing to the introduction of high-resolution array CGH (comparative genomic hybridization)¹⁰⁵, and screening of large cohorts of mentally retarded patients is underway in several laboratories^{106,107}.

Characterization of autosomal microdeletions should soon reveal novel candidate genes for autosomal-dominant mental retardation, thereby expanding a list

of genes which have been recently identified by cloning of chromosome breakpoints in mentally retarded patients with balanced chromosomal rearrangements^{108–113}. Autosomal recessive forms of mental retardation (ARMR) might be even more common, but in developed countries, large families with several affected patients are rare, which has hampered their investigation. No more than three different genes for ARMAR have been identified so far^{114–116}, including forms that are associated with microcephaly, although it is clear that this is just the proverbial tip of the iceberg. In analogy to the observation that *connexin 26* mutations are found in about 50% of patients with autosomal recessive, non-syndromic childhood deafness (reviewed in REF 117), it is quite possible that mutations in relatively few genes account for most cases of non-syndromic ARMAR. Homozygosity mapping in large consanguineous families is the strategy of choice for identifying such genes, and their detection could have far-reaching implications for the diagnosis, prevention and eventually even the treatment of mental retardation.

1. Leonard, H. & Wen, X. The epidemiology of mental retardation: challenges and opportunities in the new millennium. *Ment. Retard. Dev. Disabil. Res. Rev.* **8**, 117–134 (2002).
A comprehensive meta-analysis on the aetiology and prevalence of mental retardation in males and females.
2. Polder, J. J., Meerding, W. J., Koopmanschap, M. A., Bonneux, L. & van der Maas, P. J. The cost of sickness in the Netherlands in 1994. *Ned. Tijdschr. Geneesk.* **142**, 1607–1611 (1998).
A comparative evaluation of disease-related costs, concluding that mental retardation is the most important cost factor in health care.
3. Penrose, L. S. *A Clinical and Genetic Study of 1280 Cases of Mental Defect* Vol. 229 (HMSO, London, 1938).
4. Lehrke, R. A theory of X-linkage of major intellectual traits. *Am. J. Ment. Defic.* **76**, 611–619 (1972).
5. Lehrke, R. G. X-linked mental retardation and verbal disability. *Birth Defects Orig. Artic. Ser.* **10**, 1–100 (1974).
References 4 and 5 are influential early publications that postulate an important role for X-linked genes in cognition and mental retardation.
6. Verkerk, A. J. et al. Identification of a gene (*FMR-1*) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in Fragile X Syndrome. *Cell* **65**, 905–914 (1991).
This is a landmark paper that describes the cloning of the gene for Fra(X) mental retardation, one of the first trinucleotide-repeat expansion disorders.
7. Chelly, J. & Mandel, J. L. Monogenic causes of X-linked mental retardation. *Nature Rev. Genet.* **2**, 669–680 (2001).
8. Fishburn, J., Turner, G., Daniel, A. & Brookwell, R. The diagnosis and frequency of X-linked conditions in a cohort of moderately retarded males with affected brothers. *Am. J. Med. Genet.* **14**, 713–724 (1983).
The only available study that provides empirical data on the relative frequency of syndromic and non-syndromic XLMR.
9. Geetz, J., Gedeon, A. K., Sutherland, G. R. & Mulley, J. C. Identification of the gene *FMR2*, associated with FRAXE mental retardation. *Nature Genet.* **13**, 105–108 (1996).
10. Gu, Y., Shen, Y., Gibbs, R. A. & Nelson, D. L. Identification of *FMR2*, a novel gene associated with the FRAXE CCG repeat and CpG island. *Nature Genet.* **13**, 109–113 (1996).
11. van der Maarel, S. M. et al. Cloning and characterization of DXS6673E, a candidate gene for X-linked mental retardation in Xq13.1. *Hum. Mol. Genet.* **5**, 887–897 (1996).
12. Cantagrel, V. et al. Disruption of a new X-linked gene highly expressed in brain in a family with two mentally retarded males. *J. Med. Genet.* **41**, 736–742 (2004).
13. Kalscheuer, V. M. et al. Disruption of the serine/threonine kinase 9 gene causes severe X-linked infantile spasms and mental retardation. *Am. J. Hum. Genet.* **72**, 1401–1411 (2003).
14. Tao, J. et al. Mutations in the X-linked cyclin-dependent kinase-like 5 (*CDKL5/STK9*) gene are associated with severe neurodevelopmental retardation. *Am. J. Hum. Genet.* **75**, 1149–1154 (2004).
15. Weaving, L. S. et al. Mutations of *CDKL5* cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. *Am. J. Hum. Genet.* **75**, 1079–1093 (2004).
16. Stromme, P. et al. Mutations in the human ortholog of *Aristalless* cause X-linked mental retardation and epilepsy. *Nature Genet.* **30**, 441–445 (2002).
This paper describes the identification of the ARX gene, which is mutated in several XLMR syndromes and in many families with NS-XLMR.
17. Meloni, I. et al. *FACL4*, encoding fatty acid-CoA ligase 4, is mutated in nonspecific X-linked mental retardation. *Nature Genet.* **30**, 436–440 (2002).
18. Ropers, H. H. et al. Nonsyndromic X-linked mental retardation: where are the missing mutations? *Trends Genet.* **19**, 316–320 (2003).
Meta-analysis of published linkage intervals reveals regional clustering of mutations that underlie NS-XLMR.
19. Kalscheuer, V. M. et al. Mutations in the polyglutamine binding protein 1 gene cause X-linked mental retardation. *Nature Genet.* **35**, 313–315 (2003).
20. Freude, K. et al. Mutations in the *FTSJ1* gene coding for a novel S-adenosylmethionine-binding protein cause nonsyndromic X-linked mental retardation. *Am. J. Hum. Genet.* **75**, 305–309 (2004).
21. Shoichet, S. A. et al. Mutations in the *ZNF41* gene are associated with cognitive deficits: identification of a new candidate for X-linked mental retardation. *Am. J. Hum. Genet.* **73**, 1341–1354 (2003).
22. Jensen, L. R. et al. Mutations in the *JARID1C* gene, encoding a protein involved in transcriptional regulation and chromatin remodeling, cause X-linked mental retardation. *Am. J. Hum. Genet.* (in press).
23. Tarpey, P. et al. Mutations in the *DLG3* gene cause nonsyndromic X-Linked mental retardation. *Am. J. Hum. Genet.* **75**, 318–324 (2004).
24. Jin, P. et al. Biochemical and genetic interaction between the fragile X mental retardation protein and the microRNA pathway. *Nature Neurosci.* **7**, 113–117 (2004).
25. Jin, P., Alish, R. S. & Warren, S. T. RNA and microRNAs in fragile X mental retardation. *Nature Cell Biol.* **6**, 1048–1053 (2004).
26. Willemsen, R., Oostra, B. A., Bassell, G. J. & Dichtenberg, J. The fragile X syndrome: from molecular genetics to neurobiology. *Ment. Retard. Dev. Disabil. Res. Rev.* **10**, 60–67 (2004).
27. Chelly, J. Breakthroughs in molecular and cellular mechanisms underlying X-linked mental retardation. *Hum. Mol. Genet.* **8**, 1833–1838 (1999).
28. Ramakers, G. J. Rho proteins, mental retardation and the cellular basis of cognition. *Trends Neurosci.* **25**, 191–199 (2002).
29. Billuart, P. et al. *Oligophrenin-1* encodes a rhoGAP protein involved in X-linked mental retardation. *Nature* **392**, 923–926 (1998).
This is a seminal paper on the cloning of OPHN1, then considered as one of the first genes for NS-XLMR.
30. Allen, K. M. et al. *PAK3* mutation in nonsyndromic X-linked mental retardation. *Nature Genet.* **20**, 25–30 (1998).
31. Kutsche, K. et al. Mutations in *ARHGGEF6*, encoding a guanine nucleotide exchange factor for Rho GTPases, in patients with X-linked mental retardation. *Nature Genet.* **26**, 247–250 (2000).
32. Lebel, R. R. et al. Non-syndromic X-linked mental retardation associated with a missense mutation (*P312L*) in the *FGD1* gene. *Clin. Genet.* **61**, 139–145 (2002).
33. Pasteris, N. G. et al. Isolation and analysis of the faciogenital dysplasia (Aarskog-Scott syndrome) gene: a putative, rho/rac guanine nucleotide exchange factor. *Cell* **79**, 669–678 (1994).
34. Govek, E. E. et al. The X-linked mental retardation protein oligophrenin-1 is required for dendritic spine morphogenesis. *Nature Neurosci.* **7**, 364–372 (2004).
An important paper providing insights into the pathomechanism of OPHN1.
35. Fox, J. W. et al. Mutations in *filamin 1* prevent migration of cerebral cortical neurons in human periventricular heterotopia. *Neuron* **21**, 1315–1325 (1998).
36. Robertson, S. P. et al. OPD-spectrum Disorders Clinical Collaborative Group. Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. *Nature Genet.* **33**, 487–491 (2003).
37. Laumonnier, F. et al. X-linked mental retardation and autism are associated with a mutation in the *NLGN4* gene, a member of the neuroligin family. *Am. J. Hum. Genet.* **74**, 552–557 (2004).
This paper establishes a link between defective synapse induction and mental retardation.
38. Jamain, S. et al. Mutations of the X-linked genes encoding neuroligins *NLGN3* and *NLGN4* are associated with autism. *Nature Genet.* **34**, 27–29 (2003).
39. Scheiffele, P., Fan, J., Choih, J., Fetter, R. & Serafini, T. Neuroligin expressed in nonneuronal cells triggers presynaptic development in contacting axons. *Cell* **101**, 657–669 (2000).
40. Dean, C. et al. Neurexin mediates the assembly of presynaptic terminals. *Nature Neurosci.* **6**, 708–716 (2003).
41. Chih, B., Afridi, S. K., Clark, L. & Scheiffele, P. Disorder-associated mutations lead to functional inactivation of neuroligins. *Hum. Mol. Genet.* **13**, 1471–1477 (2004).
42. Giovedi, S. et al. Synapsin is a novel Rab3 effector protein on small synaptic vesicles: I. Identification and characterization of the synapsin I-Rab3 interactions *in vitro* and in intact nerve terminals. *J. Biol. Chem.* **279**, 43760–43768 (2004).

43. Giovedi, S., Darchen, F., Valtorta, F., Greengard, P. & Benfenati, F. Synapsin is a novel Rab3 effector protein on small synaptic vesicles: II. Functional effects of the Rab3A-synapsin I interaction. *J. Biol. Chem.* **279**, 43769–43779 (2004).
44. Garcia, C. C. *et al.* Identification of a mutation in synapsin I, a synaptic vesicle protein, in a family with epilepsy. *J. Med. Genet.* **41**, 183–187 (2004).
45. D'Adamo, P. *et al.* Mutations in *GDI1* are responsible for X-linked non-specific mental retardation. *Nature Genet.* **19**, 134–139 (1998).
46. D'Adamo, P. *et al.* Deletion of the mental retardation gene *Gdi1* impairs associative memory and alters social behavior in mice. *Hum. Mol. Genet.* **11**, 2567–2580 (2002).
47. McFerran, B. W., Graham, M. E. & Burgoyne, R. D. Neuronal Ca²⁺ sensor 1, the mammalian homologue of frequenin, is expressed in chromaffin and PC12 cells and regulates neurosecretion from dense-core granules. *J. Biol. Chem.* **273**, 22768–22772 (1998).
48. McFerran, B. W., Weiss, J. L. & Burgoyne, R. D. Neuronal Ca²⁺ sensor 1. Characterization of the myristoylated protein, its cellular effects in permeabilized adrenal chromaffin cells, Ca²⁺-independent membrane association, and interaction with binding proteins, suggesting a role in rapid Ca²⁺ signal transduction. *J. Biol. Chem.* **274**, 30258–30265 (1999).
49. Ferrante, M. I., Ghiani, M., Bulfone, A. & Franco, B. *IL1RAPL2* maps to Xq22 and is specifically expressed in the central nervous system. *Gene* **275**, 217–221 (2001).
50. Gibbons, R. J., Picketts, D. J., Villard, L. & Higgs, D. Mutations in a putative global transcriptional regulator cause X-linked mental retardation with α -thalassaemia (ATR-X syndrome). *Cell* **80**, 837–845 (1995).
- The authors describe the identification of the ATR-X gene that later turned out to be mutated in a wide variety of XLMR syndromes.**
51. Villard, L. & Fontes, M. α -Thalassaemia/mental retardation syndrome, X-Linked (ATR-X, MIM #301040, ATR-X/NXP/XH2 gene MIM #300032). *Eur. J. Hum. Genet.* **10**, 223–225 (2002).
52. Picketts, D. J. *et al.* The ATR-X mental retardation syndrome gene is required for neuronal survival during corticogenesis. *Genet. Couns.* **15**, 252 (2004).
53. Villard, L. *et al.* Two affected boys in a Rett syndrome family: clinical and molecular findings. *Neurology* **55**, 1188–1193 (2000).
54. Meloni, I. *et al.* A mutation in the Rett syndrome gene, *MECP2*, causes X-linked mental retardation and progressive spasticity in males. *Am. J. Hum. Genet.* **67**, 982–985 (2000).
55. Watson, P. *et al.* Angelman syndrome phenotype associated with mutations in *MECP2*, a gene encoding a methyl CpG binding protein. *J. Med. Genet.* **38**, 224–228 (2001).
56. Kleefstra, T. *et al.* *De novo* *MECP2* frameshift mutation in a boy with moderate mental retardation, obesity and gynaecomastia. *Clin. Genet.* **61**, 359–362 (2002).
57. Orrico, A. *et al.* *MECP2* mutation in male patients with non-specific X-linked mental retardation. *FEBS Lett.* **481**, 285–288 (2000).
58. Chen, W. G. *et al.* Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science* **302**, 885–889 (2003).
- This paper identifies the BDNF gene as a specific target for the Rett gene, MECP2.**
59. Pang, P. T. *et al.* Cleavage of proBDNF by tPA/Plasmin is essential for long-term hippocampal plasticity. *Science* **306**, 487–491 (2004).
- The authors link BDNF and tPA/plasmin to late-phase long-term potentiation**
60. Stancheva, I., Collins, A. L., van den Veyver, I. B., Zoghbi, H. & Meehan, R. R. A mutant form of MeCP2 protein associated with human Rett syndrome cannot be displaced from methylated DNA by notch in *Xenopus* embryos. *Mol. Cell* **12**, 425–435 (2003).
61. Young, J. I. & Zoghbi, H. Y. X-Chromosome inactivation patterns are unbalanced and affect the phenotypic outcome in a mouse model of Rett syndrome. *Am. J. Hum. Genet.* **74**, 511–520 (2004).
62. Miyashiro, K. Y. *et al.* RNA cargoes associating with FMRP reveal deficits in cellular functioning in Fmr1 null mice. *Neuron* **37**, 417–431 (2003).
- Establishes the role of the FMR protein in the intracellular transport of specific mRNAs.**
63. Eastman, K., Martinez, J. A. & McCabe, E. R. B. Glycerol kinase: Role in nuclear translocation of the activated glucocorticoid receptor complex (GRC). *ASHG Abstracts* **257**, 69 (2004).
64. Ng, D. *et al.* Oculofaciocardiodental and Lenz microphthalmia syndromes result from distinct classes of mutations in *BCOR*. *Nature Genet.* **36**, 411–416 (2004).
65. Merienne, K. *et al.* A missense mutation in *RPS6KA3* (*RSK2*) responsible for non-specific mental retardation. *Nature Genet.* **22**, 13–14 (1999).
66. Ginty, D. D., Bonni, A. & Greenberg, M. E. Nerve growth factor activates a Ras-dependent protein kinase that stimulates c-fos transcription via phosphorylation of CREB. *Cell* **77**, 713–725 (1994).
67. Yang, X., Matsuda, K. *et al.* ATF4 is a substrate of RSK2 and an essential regulator of osteoblast biology: implication for Coffin-Lowry syndrome. *Cell* **117**, 387–398 (2004).
68. Lower, K. M. *et al.* Mutations in *PHF6* are associated with Börjesjö-Forsman-Lehmann syndrome. *Nature Genet.* **32**, 661–665 (2002).
69. Siderius, L. E. *et al.* X-linked mental retardation associated with cleft lip/palate maps to Xp11.3-q21.3. *Am. J. Med. Genet.* **85**, 216–220 (1999).
70. Gu, Y. & Nelson, D. L. FMR2 function: insight from a mouse knockout model. *Cytogenet. Genome Res.* **100**, 129–139 (2003).
71. Kleefstra, T. *et al.* Zinc finger 81 (*ZNF81*) mutations associated with X-linked mental retardation. *J. Med. Genet.* **41**, 394–399 (2004).
72. Agulnik, A. I. *et al.* A novel X gene with a widely transcribed Y-linked homologue escapes X-inactivation in mouse and human. *Hum. Mol. Genet.* **3**, 879–884 (1994).
73. Scott, D. M. *et al.* Identification of a mouse male-specific translocation antigen, H-Y. *Nature* **376**, 695–698 (1995).
74. Ciissold, P. M. & Ponting, C. P. Mjic: cupin metalloenzyme-like domains in jumonji, hairless and phospholipase A₂. *Trends Biochem. Sci.* **26**, 7–9 (2001).
75. Turner, G. & Partington, M. W. Genes for intelligence on the X chromosome. *J. Med. Genet.* **28**, 429 (1991).
76. Loat, C. S., Asbury, K., Galsworthy, M. J., Plomin, R. & Craig, I. W. X inactivation as a source of behavioural differences in monozygotic female twins. *Twin Res.* **7**, 54–61 (2004).
77. Skuse, D. H. *et al.* Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature* **387**, 652–653 (1997).
78. Ohno, S. Ancient linkage groups and frozen accidents. *Nature* **244**, 259–262 (1973).
79. Ryan, S. G. *et al.* Epilepsy and mental retardation limited to females: an X-linked dominant disorder with male sparing. *Nature Genet.* **17**, 92–95 (1997).
80. Sargent, C. A. *et al.* The sequence organization of Yp/proximal Xq homologous regions of the human sex chromosomes is highly conserved. *Genomics* **32**, 200–209 (1996).
81. Plomin, R. & Spinath, F. M. Intelligence: genetics, genes, and genomics. *J. Pers. Soc. Psychol.* **86**, 112–129 (2004).
82. Herbst, D. S. & Miller, J. R. Nonspecific X-linked mental retardation II: the frequency in British Columbia. *Am. J. Med. Genet.* **7**, 461–469 (1980).
- Another classical study that infers the prevalence of (mild and severe) XLMR from the frequency of affected brother and sister pairs.**
83. de Vries, B. B. *et al.* Screening and diagnosis for the fragile X syndrome among the mentally retarded: an epidemiological and psychological survey. *Am. J. Hum. Genet.* **61**, 660–667 (1997).
84. Turner, G., Webb, T., Wake, S. & Robinson, H. Prevalence of fragile X syndrome. *Am. J. Hum. Genet.* **64**, 196–197 (1996).
- References 83 and 84 are two studies which document that the prevalence of Fra(X) mental retardation is much lower than previously estimated.**
85. Biancalana, V. *et al.* Five years of molecular diagnosis of Fragile X syndrome (1997–2001): a collaborative study reporting 95% of the activity in France. *Am. J. Med. Genet.* **129A**, 218–224 (2004).
86. Gronskov, K., Hjalgrim, H., Nielsen, I. M. & Brondum-Nielsen, K. Screening of the *ARX* gene in 682 retarded males. *Eur. J. Hum. Genet.* **12**, 701–705 (2004).
87. Mandel, J. L. & Chelly, J. Monogenic X-linked mental retardation: is it as frequent as currently estimated? The paradox of the *ARX* (*Aristaless X*) mutations. *Eur. J. Hum. Genet.* **12**, 689–693 (2004).
- This paper contains an interesting speculation on the existence of X-chromosomal risk factors for mental retardation.**
88. Brunner, H. G., Nelen, M., Breakefield, X. O., Ropers, H. H. & van Oost, B. A. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science* **262**, 578–580 (1993).
89. Caspi, A. *et al.* Role of genotype in the cycle of violence in maltreated children. *Science* **297**, 851–854 (2002).
90. Smits, A. P. *et al.* The fragile X syndrome: no evidence for any recent mutations. *J. Med. Genet.* **30**, 94–96 (1993).
91. Mulley, J. C., Kerr, B., Stevenson, R. & Lubbs, H. Nomenclature guidelines for X-linked mental retardation. *Am. J. Med. Genet.* **43**, 383–391 (1992).
92. Bienvenu, T. *et al.* *ARX*, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. *Hum. Mol. Genet.* **11**, 981–991 (2002).
93. Rosenberg, E. H. *et al.* High prevalence of *SLC6A8* deficiency in X-linked mental retardation. *Am. J. Hum. Genet.* **75**, 97–105 (2004).
94. Salomons, G. S. *et al.* X-linked creatine-transporter gene (*SLC6A8*) defect: a new creatine-deficiency syndrome. *Am. J. Hum. Genet.* **68**, 1497–1500 (2001).
95. Longo, I. *et al.* A third MRX family (*MRX68*) is the result of mutation in the long chain fatty acid-CoA ligase 4 (*FACL4*) gene: proposal of a rapid enzymatic assay for screening mentally retarded patients. *J. Med. Genet.* **40**, 11–17 (2003).
96. Friesema, E. C. H. *et al.* Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet* **364**, 1435–1437 (2004).
97. Carson, A. L. *et al.* X-linked spermine synthase gene (*SMS*) defect: the first polyamine deficiency syndrome. *Eur. J. Hum. Genet.* **11**, 937–944 (2003).
98. Ramser, J. *et al.* Impairment of the renin receptor prevents ERK1/2 activation in a patient suffering from mental retardation and epilepsy. *Eur. J. Hum. Genet.* **12**, 72–73 (2004).
99. Bonhoeffer, T. & Yuste, R. Spine motility. Phenomenology, mechanism, and function. *Neuron* **35**, 1019–1027 (2002).
100. Yuste, R. & Bonhoeffer, T. Genesis of dendritic spines: insights from ultrastructural and imaging studies. *Nature Rev. Neurosci.* **5**, 24–34 (2004).
- References 99 and 100 are two articles that illustrate the unexpected plasticity of dendritic-spine formation and maintenance.**
101. Jin, P. & Warren, S. T. New insights into fragile X syndrome: from molecules to neurobehaviors. *TIBS* **28**, 152–158 (2003).
102. Huber, K., Gallagher, S. M., Warren, S. T. & Bear, M. F. Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proc. Natl Acad. Sci. USA* **99**, 7746–7750 (2002).
103. Flint, J. *et al.* The detection of subtelomeric chromosomal rearrangements in idiopathic mental retardation. *Nature Genet.* **9**, 132–140 (1995).
104. Knight, S. J. *et al.* Subtle chromosomal rearrangements in children with unexplained mental retardation. *Lancet* **354**, 1676–1681 (1999).
105. Ishkanian, A. S. *et al.* A tiling resolution DNA microarray with complete coverage of the human genome. *Nature Genet.* **36**, 299–303 (2004).
106. Vissers, L. E. *et al.* Array-based comparative genomic hybridization for the genomewide detection of submicroscopic chromosomal abnormalities. *Am. J. Hum. Genet.* **73**, 1261–1270 (2003).
- This is the first application of array CGH to screen patients with unexplained mental retardation for submicroscopic genomic imbalances.**
107. Shah-Smith, C. *et al.* Microarray based comparative genomic hybridisation (array-CGH) detects submicroscopic chromosomal deletions and duplications in patients with learning disability/mental retardation and dysmorphic features. *J. Med. Genet.* **41**, 241–248 (2004).
108. Bhalla, K. *et al.* The *de novo* chromosome 16 translocations of two patients with abnormal phenotypes (mental retardation and epilepsy) disrupt the *AZBP1* gene. *J. Hum. Genet.* **49**, 308–311 (2004).
109. Fernandez, T. *et al.* Disruption of contactin 4 (*CNTN4*) results in developmental delay and other features of 3p deletion syndrome. *Am. J. Hum. Genet.* **74**, 1286–1293 (2004).
110. Nothwang, H. G. *et al.* Functional hemizygosity of *PAFAH1B3* due to a *PAFAH1B3-CLK2* fusion gene in a female with mental retardation, ataxia and atrophy of the brain. *Hum. Mol. Genet.* **10**, 797–806 (2001).
111. Bonaglia, M. C. *et al.* Disruption of the *ProSAP2* gene in a t(12;22)(q24.1;q13.3) is associated with the 22q13.3 deletion syndrome. *Am. J. Hum. Genet.* **69**, 261–268 (2001).
112. Endris, V. *et al.* The novel Rho-GTPase activating gene *MEGAP/srGAP3* has a putative role in severe mental retardation. *Proc. Natl Acad. Sci. USA* **99**, 11754–11759 (2002).
113. Giorda, R. *et al.* Selective disruption of muscle and brain-specific *BPAG1* isoforms in a girl with a 6;15 translocation, cognitive and motor delay, and tracheo-oesophageal atresia. *J. Med. Genet.* **41**, e71 (2004).
114. Molinari, F. *et al.* Truncating neurotrophin mutation in autosomal recessive nonsyndromic mental retardation. *Science* **298**, 1779–1781 (2002).
- Identification of the first gene defect that underlies autosomal-recessive mental retardation.**
115. Bond, J. *et al.* ASPM is a major determinant of cerebral cortical size. *Nature Genet.* **32**, 316–320 (2002).
116. Sheen, V. L. *et al.* Mutations in *ARFGEF2* implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. *Nature Genet.* **36**, 69–76 (2004).
117. Cohn, E. S. & Kelley, P. M. Clinical phenotype and mutations in connexin 26 (*DFNB1/GJB2*), the most common cause of childhood hearing loss. *Am. J. Med. Genet.* **89**, 130–136 (1999).

118. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 4th edn (Washington DC, 1994).
119. World Health Organization. International classification of impairments, disabilities and handicaps. (World Health Organization, Geneva, 1980).
120. Guo, W. *et al.* Genomic scanning for expressed sequences in Xp21 identifies the glycerol kinase gene. *Nature Genet.* **4**, 367–371 (1993).
121. Gibbons, R. J. & Higgs, D. R. Molecular-clinical spectrum of the ATR-X syndrome. *Am. J. Med. Genet.* **97**, 204–212 (2000).
122. Lossi, A. M. *et al.* Mutation of the *XNP/ATR-X* gene in a family with severe mental retardation, spastic paraplegia and skewed pattern of X inactivation: demonstration that the mutation is involved in the inactivation bias. *Am. J. Hum. Genet.* **65**, 558–562 (1999).
123. Pasteris, N. G. *et al.* Cloning and regional localization of the mouse faciogenital dysplasia (*Fgdl*) gene. *Mamm. Genome* **6**, 658–661 (1995).
124. Shahbazian, M. D. & Zoghbi, H. Y. Rett syndrome and MeCP2: linking epigenetics and neuronal function. *Am. J. Hum. Genet.* **71**, 1259–1272 (2002).
125. Amir, R. E. *et al.* Rett syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG-binding protein 2. *Nature Genet.* **23**, 185–188 (1999).
- The authors describe the identification of the gene that is involved in Rett syndrome.**
126. Salomons, G. S. *et al.* X-linked creatine transporter defect: an overview. *J. Inher. Metab. Dis.* **26**, 309–318 (2003).
127. Kitamura, K. *et al.* Mutation of *ARX* causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. *Nature Genet.* **32**, 359–369 (2002).
128. Frints, S. G., Borghgraef, M., Froyen, G., Marynen, P. & Fryns, J. P. Clinical study and haplotype analysis in two brothers with Partington syndrome. *Am. J. Med. Genet.* **112**, 361–368 (2002).
129. Kato, M. *et al.* Mutations of *ARX* are associated with striking pleiotropy and consistent genotype-phenotype correlation. *Hum. Mutat.* **23**, 147–159 (2004).
130. Friesema, E. C. H. *et al.* Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. *J. Biol. Chem.* **278**, 40128–40135 (2003).
131. Bahi, N. *et al.* IL1 receptor accessory protein like, a protein involved in X-linked mental retardation, interacts with Neuronal Calcium Sensor-1 and regulates exocytosis. *Hum. Mol. Genet.* **12**, 1415–1425 (2003).
132. Carrie, A. *et al.* A new member of the IL-1 receptor family highly expressed in hippocampus and involved in X-linked mental retardation. *Nature Genet.* **23**, 25–31 (1999).
133. Kuchenbecker, K. *et al.* *Arhgef6*-deficient mice, a model for non-specific X-linked mental retardation, show a decrease of mature dendritic spines. *Eur. J. Hum. Genet.* **12**, 73 (2004).
134. Kopczyński, C. C., Davis, G. W. & Goodman, C. S. A neural tetraspanin, encoded by late bloomer, that facilitates synapse formation. *Science* **271**, 1867–1870 (1996).
135. Fradkin, L. G., Kamphorst, J. T., DiAntonio, A., Goodman, C. S. & Noordermeer, J. N. Genomewide analysis of the *Drosophila* tetraspanins reveals a subset with similar function in the formation of the embryonic synapse. *Proc. Natl Acad. Sci. USA* **99**, 13663–13668 (2002).
136. Zerni, R. *et al.* A new gene involved in X-linked mental retardation identified by analysis of an X;2 balanced translocation. *Nature Genet.* **24**, 167–170 (2000).
137. Bérubé, N. G., Smeenk, C. A. & Picketts, D. J. Cell cycle-dependent phosphorylation of the ATRX protein correlates with changes in nuclear matrix and chromatin association. *Hum. Mol. Genet.* **9**, 539–547 (2000).
138. Meloni, I. *et al.* *FACL4* and mental retardation: protein characterization and cellular knock-out model. *Eur. J. Hum. Genet.* **12**, 334 (2004).
139. Ichiki, T. *et al.* Effects on blood pressure and exploratory behaviour of mice lacking angiotensin II type-2 receptor. *Nature* **377**, 748–750 (1995).
140. Vervoort, V. S. *et al.* *AGTR2* mutations in X-linked mental retardation. *Science* **296**, 2401–2403 (2002).
141. Ramser, J. *et al.* A splice site mutation in the methyltransferase gene *FTSJ1* in Xp11.23 is associated with non-syndromic mental retardation in a large Belgian family (MRX9). *J. Med. Genet.* **41**, 679–683. (2004).
142. Fukami, M. *et al.* A member of a gene family on Xp22.3, *VCX-A*, is deleted in patients with X-linked nonspecific mental retardation. *Am. J. Hum. Genet.* **67**, 563–573 (2000).
143. Schroer, A. *et al.* Cosegregation of T108A Elk-1 with mental retardation. *Am. J. Med. Genet.* **95**, 404–405 (2000).
144. Lossi, A. M. *et al.* Abnormal expression of the *KLF8* (*ZNF741*) gene in a female patient with an X;autosome translocation t(X;21)(p11.2;q22.3) and non-syndromic mental retardation. *J. Med. Genet.* **39**, 113–117 (2002).
145. Frints, S. G. *et al.* Inv(X)(p21.1;q22.1) in a man with mental retardation, short stature, general muscle wasting, and facial dysmorphism: clinical study and mutation analysis of the *NXF5* gene. *Am. J. Med. Genet.* **119A**, 367–374 (2003).

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Competing interests statement

The authors declare no competing financial interests.

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