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REVIEW

XLMR genes: update 2000

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This is the sixth edition of the catalogue of XLMR genes, ie X-linked genes whose malfunctioning causes mental retardation. The cloning era is not yet concluded, actually much remains to be done to account for the 202 XLMR conditions listed in this update. Many of these may eventually prove to be due to mutations in the same gene but the present number of 33 cloned genes falls surely short of the actual total count. It is now clear that even small families or individual patients with cytogenetic rearrangements can be instrumental in pinning down the remaining genes. DNA chip technology will hopefully allow (re)screening large numbers of patients for mutations in candidate genes or testing the expression levels of many candidate genes in informative families. Slowly, our knowledge of the structure and functioning of the proteins encoded by these genes is beginning to cast some light on the biological pathways required for the normal development of intelligence. Correlations between the molecular defects and the phenotypic manifestations are also being established. In order to facilitate the exchange of existing information and to allow its timely update, we prepared the first edition of the XLMR database (available at http://homepages.go.com/~xlmr/home.htm) and invite all colleagues, expert in the field, to contribute with their experience. *European Journal of Human Genetics* (2001) **9,** 71–81.

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Introduction

Mental retardation (MR) can be defined as a failure to develop cognitive abilities and achieve a level of intelligence that would be appropriate for the age group. In most cases MR causes a deficit in the 'adaptive behaviour'. A percentage of the general population, variably estimated between 0.5 and 2%, is reported to be functioning two standard deviations below the average (ie to have an IQ of less than 70). Genetic determinants underlie many of these conditions[1] and an excess of affected males has often been reported,[2,3] especially in the mild-to-moderate MR range (IQ between 70 and 35). This phenomenon was eventually interpreted as being due to X-linked mutations, whose effects become more apparent in the hemizygous males who cannot compensate for deleterious mutations present on their X chromosome.[2,4] Herbst and Miller[5] estimated the frequency of X-linked mental retardation (XLMR) at 1.8/1000 males in British Columbia. Recently the prevalence of the fragile X syndrome, probably the commonest of XLMR conditions, has been re-estimated at 1/4000 males at most[6] and may represent up to 15–20% of the total XLMR. Neri *et al*[7] prepared the first XLMR update in 1990 and tried to include all X-linked forms of mental retardation in their listing, which steadily grew to the total number of 179 entries in the previous update.[8] This XLMR update 2000 now lists 202 conditions subdivided in different nosological classes that will be illustrated in the next section.

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Information sources and classification of XLMR conditions

The information sources employed to compile this listing have been many and diverse. First of all, we have regularly scanned the published literature, ie articles in scientific journals and abstracts presented at the American Society of Human Genetics, the European Society of Human Genetics and the biannual International Workshop on Fragile X and

Table 1 Malformation syndromes

MIM No.	*Name*	*Locus*	*Gene*	*Description*
*305400	Aarskog-Scott	Xp11.21	*FGDY*	Hypertelorism, short stature, downslanting palpebral fissures, anteverted nostrils, shawl scrotum, joint hyperlaxity
304200	Akesson			Cutis verticis gyrata, thyroid aplasia
#301040	ATR-X	Xq13	*XH2/XNP* *300032	Microcephaly, 'coarse' face, genital and skeletal anomalies, alpha-thalassemia. **It includes Juberg-Marsidi (#309590), Carpenter-Waziri,[15] Holmes-Gang,[16] a family with spastic diplegia[17] and possibly[18] Smith-Fineman-Myers (309580)**
*301900	Borjeson-Forssman-Lehmann	Xq26-q27		Obesity, hypogonadism, round face, narrow palpebral fissures, epilepsy
301950	Branchial arch			Short stature, downslanting eyes, lowset ears, webbed neck, highly arched palate
308830	Cantu'			Macrocephaly, dwarfism, keratosis follicularis
*309620	Christian	Xq27-q28		Skeletal dysplasia, VI nerve palsy
*300243	Christianson	Xq23-q27.3		Profound MR, mutism despite normal hearing, craniofacial dysmorphism, grand-mal epilepsy, ophthalmoplegia, cerebellar atrophy
309490	Chudley-Lowry			Short stature, obesity, small genitalia
#303600	Coffin-Lowry	Xp22.2-p22.1	*RSK2* *300075	'Coarse' face, drumstick phalanges, skeletal anomalies. **It includes MRX19[12]**
#305000	Dyskeratosis congenita	Xq28	*DKC1* *300126	Skin pigmentation, nail dystrophy, leukoplakia of oral mucosa
*305450	FG	Xq12-q21.3		Macrocephaly, agenesis of corpus callosum, gastrointestinal anomalies, deafness
*309550	Fragile X	Xq27.3	*FMR1*	Macrocephaly, long face and ears, macro-orchidism
301590	Graham			Anophthalmos, ankyloblepharon, orbital underdevelopment
*302000	Hereditary bullous dysfunction	Xq27.3-q28		Short stature, microcephaly, alopecia, bullous dystrophy, hypogenitalism
300064	Hyde-Forster			Craniofacial anomalies with plagiocephaly, flattened occiput
307010	Hydrocephalus with cerebellar agenesis			Hydrocephalus, cerebellar agenesis, absence of Magendie and Luschka's foramina
*309800	Lenz	Xq27-q28		Microphthalmia, thumb and skeletal anomalies, urogenital and cardiovascular anomalies. **It includes Siber *et al*.[21]**
*309520	Lujan-Fryns			Marfanoid habitus, triangular face, narrow palate, hypernasal voice
*309605	Miles/MRXS4	Xp11.2-q23		Microcephalus, asymmetric face, hypogonadism, joint hypermobility, 10 digital arches
*302350	Nance-Horan	Xp22.31-p22.13		Cataract, microcornea, cone-shaped incisors, supernumerary teeth
*300000	Opitz G/BBB	Xp22	*MID1*	Hypertelorism, midline abnormalities, heart defects, hypospadias
*311300	Oto-palato-digital	Xq27-q28		Short stature, hearing loss, cleft palate, characteristic face
*309510	Partington/MRXS1	Xp22.2-p22.1		Dysarthria, dystonic hand movements, ataxia, seizures
*304340	Pettigrew/MRXS5	Xq26-q27.1		Long 'coarse' face, hydrocephalus, hypotonia, spasticity, ataxia, seizures, iron accumulation in basal ganglia, Dandy-Walker anomaly
300055	PPM-X	Xq28		Psychosis, pyramidal signs, macro-orchidism
*309610	Prieto/MRXS2	Xp21.1-p11.3		Peculiar face, dental anomalies, sacral dimple, joint dysplasia, epilepsy
300004	Proud			Microcephaly, agenesis of corpus callosum, arthrogryposis, renal dysplasia, hypospadias
*309500	Renpenning/MRXS8	Xp11.4-p11.2		Microcephaly, short stature
308200	Rud	Xp22		Ichthyosis, epilepsy, nystagmus, hypogonadism
314320	Say-Meyer			Trigonocephaly, short stature
312840	Schimke			Early onset choreoathetosis with later spasticity, microcephaly, growth failure, external ophthalmoplegia, variable deafness
#312870	Simpson-Golabi-Behmel	Xq26	*GPC3* *300037	Macrosomia, 'coarse' face, polydactyly, extra nipples, heart defects
309580	Smith-Fineman-Myers			Peculiar face, microcephaly, short stature, seizures
*309583	Snyder-Robinson	Xp22.2-p21.2		Macrocephaly, long thin face, high narrow/cleft palate, asthenic body build, scoliosis
*309470	Sutherland/MRXS3	Xp11.3-q12		Microcephaly, short stature, small testes, spastic diplegia
309480	Tranebjaerg I			Epilepsy, psoriasis
*314390	VACTERL with hydrocephalus			Vertebral, anal, tracheo-esophageal, renal and radial defects, hydrocephalus

Continued

Table 1 *(Continued)*

MIM No.	*Name*	*Locus*	*Gene*	*Description*
*314500	Van den Bosch			Choroideremia, acrokeratosis verruciformis, anhydrosis, skeletal deformities
311450	W syndrome			Characteristic face, clefting, subluxed elbow, camptodactily
308400	Warkany			Intrauterine growth retardation, microcephaly
*309545	Wilson	(Xp11-Xq27)		Aphasia, growth failure, brachycephaly, large mouth with thick lips, seizures, frequent infections
*309585	Wilson/MRXS6	Xp21.1-q22		Obesity, gynecomastia, tapering fingers, emotional lability
	Abidi[22]	Xq12-q21		Short stature, small head, sloping forehead, hearing loss
	Ahmad/MRXS7[23]	Xp11.3-q22		Obesity, hypogonadism, tapered fingers
	Aldred[24]			Retinitis pigmentosa, microcephaly
	Armfield[25]	Xq28		Macrocephaly, glaucoma, cleft palate, seizures, short stature, small hands and feet
	Atkin-Flaitz[26]			Macrocephaly, 'coarse' face, short stature, macroorchidism
	Baraitser[27]			Macrocephaly, large ears, broad nasal tip, thick lower lip, teeth anomalies, obesity, macroorchidism
	Brzustowicz[14]	Xp22		Early lethal, multiple congenital anomalies, hydrops fetalis, Simpson-Golabi-Behmel like
	Carpenter[28]	Xq23-q24		Congenital hip dislocation, microcephaly, hypertelorism and dysmorphic facial features, short neck and sternum
	Chudley[29]	Xq21.2-q23		Prognathism, synophrys, hirsutism, seizures, abnormal gait and weakness
	Golabi-Ito-Hall[30]			Short stature, triangular face, epicanthic folds, microcephaly, brittle hair
	Hall[31]			Cleft lip/palate, facial dysmorphism, inguinal hernia, digital defects
	Hamel[32]			Congenital heart defect, cleft palate, short stature, facial anomalies
	Hockey[33]			Precocious puberty, progressive IQ deterioration (mild to moderate)
	Homfray[34]			Coarse facial features, epilepsy, progressive joint contractures
	Johnson[35]	Xq12-q21		Macrocephaly, macroorchidism, midface hypoplasia, triangular face
	Kang[36]			Microcephaly, dysgenesis of corpus call., hydrocephalus, spasticity, short broad hands, facial anomalies
	Lubs[37]	Xq28		Hypertelorism, short nose, seizures, hearing loss, early demise, cardiomegaly at autopsy
	MEHMO[38]	Xp22.13-p21.1		Epilepsy, hypogonadism and hypogenitalism, microcephaly, obesity
	Oosterwijk[39]	(Xp11.4-q24) excluded		A/synphalangism of hands and feet, hearing loss, verrucosis and hypertrichosis, immunodeficiency
	Porteous[40]	Xp11.4-q13		Short stature, high-pitched voice, high forehead, receding hairline
	Reish[41]			Multiple congenital anomalies, growth retardation, ectodermal dysplasia
	Seemanova[42]			Microcephaly, microphthalmia, growth retardation
	Shashi[43]	Xq26-q27		Coarse facial features, puffy eyelids, obesity, large ears and testes
	Shrimpton/MRXS9[44]	Xq12-q21.31		Microcephaly, variably short stature
	Siderius-Hamel[45]	Xp11.3-q21.3		Cleft lip and palate, broad nasal tip, large hands
	Sklower-Brooks[46]			Peculiar face, growth retardation, optic atrophy, spastic diplegia, atrophic hydrocephalus
	Stevenson[47]	Xq12-q21.2		Hypotonia, areflexia, tapered fingers, arches increased, genu valgum
	Stocco dos Santos[48]			Short stature, hip luxation, precocious puberty
	Stoll[49]			Short stature, prominent forehead, hypertelorism, broad nasal tip, anteverted nares
	Tariverdian[50]			Acromegaly, CNS anomalies, macroorchidism
	Turner[51]	Xp21.2-q13		Macrocephaly, heterozygote expression
	Vasquez[52]			Hypogonadism, gynecomastia, short stature, obesity
	Vitale[53]	Xq24		Short stature, brachydactyly, narrow downslanted palpebral fissures, large bulbous nose, macrostomia
	Vles[54]			Corpus callosum agenesis, spastic quadriparesis, irregular lining of lateral ventricles
	Wittwer[55]			Square face, high broad forehead, frontal bossing, hypertelorism, downslanting palpebral fiss., anteverted nares
	Young-Hughes[56]			Short stature, obesity, hypogonadism

XLMR. The On-line Mendelian Inheritance in Man (OMIM) catalogue was often checked and provided valuable information and references (available at http://www.ncbi.nlm.nih.gov/omim/). For approximately 560 entries listed in the OMIM catalogue, MR is mentioned in the clinical synopsis and 90 (16%) of these are X-linked (as per June 30, 2000). Lastly, some inclusions and exclusions were suggested to us by many colleagues, whose advice was extremely helpful. It is

Table 2 Neuromuscular disorders

MIM No.	*Name*	*Locus*	*Gene*	*Description*
*309600	Allan-Herndon-Dudley	Xp11.4-q22		Severe hypotonia, joint contractures, muscular atrophy
*302500	Apak			Spinocerebellar ataxia, nystagmus, dysarthria
*301835	Arts	Xq21.33-q24		Early death, hypotonia, ataxia, deafness, loss of vision, recurrent infections
301840	Ataxia-dementia			Ataxia, pyramidal tract signs, adult-onset dementia
312890	Baar-Gabriel			Athetotic spastic paraplegia
309660	Bergia			Cardiomyopathy (lethal), scapuloperoneal muscular dystrophy, myopia
*302801	CMTX2	Xp22.3-1		Motor-sensory neuropathy, formerly listed as Ionasescu (Family 1)
*310490	Cowchock-Fishbeck	Xq24-q26.1		Motor-sensory neuropathy and deafness. **It is possibly allelic to CMTX3 [*302802]**
*310200	Duchenne muscular dystrophy	Xp21.3-1	*DMD*	Pseudohypertrofic muscular dystrophy
309560	Fitzsimmons			Spastic paraplegia, pes cavus, palmoplantar hyperkeratosis
#312920	Goldblatt	Xq13-q21.1		Complicated spastic paraplegia with nystagmus and optic atrophy
*309555	Gustavson	Xq25-q26		Optic atrophy, hearing loss, epilepsy, spasticity, restricted joint mobility, early death
#307000	HSAS	Xq28	*L1CAM* *308840	Hydrocephalus with stenosis of the aqueduct of Silvius. **It includes spastic paraplegia I [#312900] and MASA [#303350]**
*304100	Menkes-Kaplan			Partial agenesis of corpus callosum, seizures
*304700	Mohr-Tranebjaerg	Xq22	*DDP*	Hearing loss, visual impairment, ataxia, spastic paraplegia. **It includes Jensen [#311150]**
*310600	Norrie	Xp11.3	*NDP*	Blindness, hearing loss
*311050	OPA-2	Xp11.4-p11.21		Optic atrophy, abnormal reflexes, dysarthria, tremor
311400	Paine & Seemanova			Spastic diplegia, myoclonic seizures, cerebellar hypoplasia
*312080	Pelizaeus-Merzbacher	Xq21.33-q22	*PLP*	Spasticity, cerebellar ataxia, parkinsonism. **It includes spastic paraplegia II [#312920]**
308850	Plott			Laryngeal abductor paralysis
*300220	Reyniers/MRXS10	Xp22.1-q21.3		Choreoathetosis, dysarthria, psychosis
301790	Schmidley			Hypotonia, ataxia, sensorineural deafness, optic atrophy, early demise
#300067	SCLH/XLIS	Xq22.3-q23	*DCX* *300121	Subcortical laminar heterotopia in females, lissencephaly and epilepsy in males
*311510	Waisman-Laxova	Xq27.2-qter		Parkinsonism, seizures, apparent basal ganglia degeneration
*308350	West	Xp21.3-p22.1		Infantile spasms, hypsarrythmia, early death
*314580	Wieacker-Wolff	Xp11.3-q13		Contractures, distal muscular atrophy, dyspraxia of ocular and facial muscles
	Arena[57]			Spastic paraplegia, ataxia, titubation, iron deposits in basal ganglia
	Berry-Kravis (XLAG)[58]			Lissencephaly with frontal pachygiria and posterior agyria, agenesis of corpus callosum, neonatal epilepsy and hypotonia, hypothermia, ambiguous genitalia
	Bertini[59]	Xp22.3		Ataxia, hypotonia, recurrent infections
	Cabezas[60]	Xq22.3-q25		Short stature, small testes, muscle wasting, tremor
	Claes[61]			Slowly progressive spastic paraplegia, maxillary hypoplasia, facial hypotonia
	Fried[62]	Xp22		Hydrocephaly, spastic diplegia, calcification of basal ganglia
	Garcia[63]	Xp11-q13		Learning difficulty, epilepsy, intermittent aggressive behaviour
	Hamel BCD[64]	Xp11.3-q21.3		Blindness, convulsions, hypomyelination, spasticity, early death
	SPG7[65]	Xq11.2-q23		Quadriplegia, motor aphasia, reduced vision, dysfunction of bowel and bladder
	Tranebjaerg II[66]			Dyspraxia, ataxia, seizures, pes equinovarus, macroorchidism
	XMRE[67]	Xp21.1-p11.4		Generalized tonic-clonic and atonic seizures, moderate MR, normal electromyography and nerve conduction

inevitable that some items may have been missed or erroneously included in this listing. Any suggestions or corrections will be gratefully accepted and it is now possible to do so in real time by contributing to the on-line XLMR database. We excluded small pedigrees with uncertain X-linkage (eg a mother with two affected sons), but such 'uncertain' families may still be extremely valuable for genetic studies and could be included in a dedicated section of the on-line XLMR database. Two affected half-brothers or an affected nephew and uncle have been considered sufficient proof of X linkage.

In the nosology of XLMR, a major distinction has been made between 'nonspecific' and 'specific' or 'syndromal' conditions. According to the HUGO Nomenclature Commit-

Table 3 Metabolic conditions

MIM No.	*Name*	*Locus*	*Gene*	*Description*
*300100	Adrenoleukodystrophy	Xq28	*ALD*	Spastic quadriparesis, impaired vision, ataxia, dementia
*300123	MRGH	Xq24-q27.3		Isolated GH deficiency, short stature, small sella turcica, **overlap with *312000 ?**
*307030	Hyperglycerolemia	Xp21.3	*GK1*	Glyceroluria, poor growth, esotropia, osteoporosis
*309900	Hunter disease	Xq28	*IDS*	'Coarse' face, dysostosis multiplex, dwarfism, hepato-splenomegaly, heart involvement
*308000	Lesch-Nyhan	Xq26	*HPRT*	Cerebral palsy, choreoathetosis, self-destructive biting
*309000	Lowe	Xq25-q26.1	*OCRL1*	Hydrophthalmia, cataract, vitamin D-resistant rickets
*309850	MAO-A deficiency	Xp11.3	*MAOA*	Aggressive behaviour, disturbance in monoamine metabolism
#309400	Menkes	Xq13	*ATP7A* *300011	Growth retardation, peculiar hair, focal cerebral & cerebellar degeneration. **It includes occipital horn syndrome or cutis laxa [#304150]**
*311250	OTC deficiency	Xp21.1	*OTC*	Hyperammonemia
*312000	Panhypopituitarism	Xq25-q26		Combined deficiency of pituitary hormones, **overlap with *300123?**
*311800	PGK1 deficiency	Xq21.1	*PGK1*	Myoglobinuria, epilepsy, hemolytic anemia
*312170	Pyruvate DH complex E1a subunit deficiency	Xp22.1	*PDHA1*	Lactic acidosis, ataxia

Table 4 Dominant conditions

MIM No.	*Name*	*Locus*	*Gene*	*Description*
*304050	Aicardi	Xp22		Agenesis of corpus callosum, chorioretinopathy, microphthalmia, seizures
#300049	BPNH	Xq28	*FLN1* *300017	Epilepsy, periventricular nodular heterotopia, mild hypoplasia of corpus callosum and/or cerebellum in females; syndactyly and severe MR in rare affected males
*300088	EFMR	Xq21.3-q22.2		MR and epilepsy in females only, males spared
*305600	Goltz			Focal dermal hypoplasia, short missing digits, polysyndactyly, microphthalmia
#308310	Incontinentia pigmenti Type II	Xq28	*NEMO* *300248	Incontinentia pigmenti, incomplete dentition, retinal abnormalities
*309801	MIDAS	Xp22		Microphthalmia, dermal aplasia, sclerocornea
*311200	OFD1	Xp22.2-3		Midline clefting of face, tongue nodules, syndactyly
#312750	Rett	Xq28	*MeCP2* *300005	Ataxia, autism, dementia

tee (http://www.gene.ucl.ac.uk/nomenclature/), the former are indicated by the acronym MRX and the latter by the acronym MRXS, where 'S' stands for 'syndromal'. The terms 'syndromal' and 'specific' are currently used interchangeably to indicate conditions that are clinically recognizable because of a specific pattern of physical, neurological, or metabolic abnormalities.[4] A dedicated survey of MRXS conditions, compiled by some of the authors of this update 2000, was recently published.[9] Sometimes MRX numbers were assigned to pedigrees that were eventually described as 'syndromal' and this has created some confusion. The MRX designation is actually intended for families whose only consistent clinical manifestation is X-linked MR. MRXS conditions have been somewhat arbitrarily subdivided into four classes: malformation syndromes (Table 1), neuromuscular disorders (Table 2), metabolic (Table 3) and dominant (Table 4) conditions. By 'malformation syndrome' we mean a condition characterised by MR and multiple congenital anomalies. A 'neuromuscular disorder' is one with a major involvement of the nervous system and/or muscles. 'Metabolic' conditions are considered separately because their pathophysiology is known and due to the abnormal functioning of specific enzymes. 'Dominant' conditions have been set apart because of their peculiar inheritance, with near absence of affected males (males die before birth, with the notable exception of one form with epilepsy and MR restricted to females) and presence of affected females. The distinction between specific and nonspecific conditions should intuitively have a molecular correlate. Actually, one can speculate that MRXS genes code for proteins with a broad range of molecular targets (eg transcriptional regulators such as XNP/ATR-X or protein kinases such as RSK2), while most of

Table 5 MRX cloned genes

MIM No.	*Name*	*Locus*	*Gene*	*Includes*	*Excludes*
*309548	FRAXE	Xq28	*FMR2*		
*300104	RABGDIA	Xq28	*GDI1*	**MRX41 and 48**	**MRX3, 25, 28 and 16**
*300127	Oligophrenin-1	Xq12	*OPHN1*	**MRX60**	**MRX14 and 52**
*300142	p21 Act. Kinase 3	Xq22	*PAK3*	**MRX30 and 47**	
*300206	IL1 Rec acc. Protein	Xp22.1-p21.3	*IL1RAPL*	**MRX34 (deletion at DXS1218)**	**MRX2, 36, 43, 54**
*300096	Tetraspanin	Xp11.4	*TM4SF2*		**MRX15 and 55**
*300267	αPIX	Xq26	*ARHGEF6*	**MRX46**	

Table 6 XLMR genes: update 2000

	Total	*Mapped*	*Cloned*
Malformations syndromes	79	34	7
Neuromuscular disorders	37	18	6
Metabolic conditions	12	2	10
Dominant conditions	8	4	3
Total MRXS	**136**	**58**	**26**
MRX	**66**	**59**	**7**
Total entries	**202**	**117**	**33**

the MRX genes now cloned seem to produce proteins with more limited and specific tasks[10,11] (eg regulating the shuttling of synaptic vesicles or modulating the establishment of synaptic contacts between neurons). This hypothesis will need further experimental support, also to explain such discrepancies as observed for the *RSK2* gene mutated in the Coffin-Lowry syndrome and in the nonspecific MRX19 family,[12] or for the *MeCP2* gene responsible for the Rett syndrome but also mutated in a small MRX family.[13]

Listing and maps

In Tables 1–4, which list the specific conditions, the name, the OMIM number or reference and a brief description are provided for every entry, while the gene localisation and the name of the gene are obviously indicated only where available. Table 1 contains several additions of syndromes described in the last 2 years. The presence of a second Simpson-Golabi-Behmel locus in Xp22 should be noted,[14] as it underlines the possibility of genetic heterogeneity of clinically similar/identical conditions. On the other hand, a clear example of clinical variability is represented by the ATR-X syndrome. Mutations in the *XNP* gene have now been found in at least four other conditions, namely Juberg-Marsidi (#309590), Carpenter-Waziri,[15] Holmes-Gang,[16] and a family with spastic diplegia, microcephaly and short stature.[17] An *XNP* mutation was also found in a family reported as Smith-Fineman-Myers,[18] though a separate entry for this latter condition is still included in Table 1. In this case 'lumping' of clinically distinguishable conditions has been possible after the gene cloning and re-screening of patients belonging to families with either a resembling phenotype or linkage to the same chromosomal interval. Until mutational screening allows more lumping, we are convinced that the wisest approach is 'splitting', ie considering as different any similar but not quite identical conditions, until proven otherwise. Linkage exclusion is sometimes very useful for splitting two conditions segregating in two small families that will not reach the threshold of LOD score significance. In Table 2, another example of lumping is offered by the spectrum of *L1CAM* mutations listed under HSAS (#307000), but the most extreme example of clinical variability is presently represented by the *RSK2* mutations causing either the Coffin-Lowry syndrome or a nonspecific MRX.[12] It is instructive to note that the Zollino syndrome of pachygyria and MR,[19] which was present in the 1998 update, has been excluded from this update because it was found to be due to a cryptic subtelomeric translocation. Table 3 lists metabolic conditions whose genes have almost all been cloned, while Table 4 summarises the information on eight X-linked dominant disorders; genes for three of these were recently cloned. Only one of these conditions, EFMR (*300088), is not lethal in males: actually it affects exclusively females and it has been hypothesised that the responsible gene may have a homologue on the Y chromosome. A brief note should be made here to remember that a skewed X-inactivation is often observed in carrier females of these dominant mutations. One may hypothesise that cells which inactivate the normal allele die preferentially during embryogenesis or divide less than those with the normal allele on the active X chromosome. Sometimes skewage of X-inactivation is observed also in female carriers of conditions which are not lethal in males (such as ATR-X). However, in many cases there is random X-inactivation, probably because no selection occurs during early development, and female carriers may have different degrees of involvement depending on the fraction of mutant alleles on the active X chromosome. In heterozygous females two distinct cell populations will exist side by side, as nicely demonstrated, for instance, by the formation of a 'double cortex' in female carriers of the *XLIS* (#300067) mutant gene (Table 2). For reasons of space Table 5 lists only the cloned MRX genes; the complete listing of MRX conditions with their localisation can be retrieved from the on-line XLMR database. Several of these genes encode proteins involved in the control of the cytoskeleton

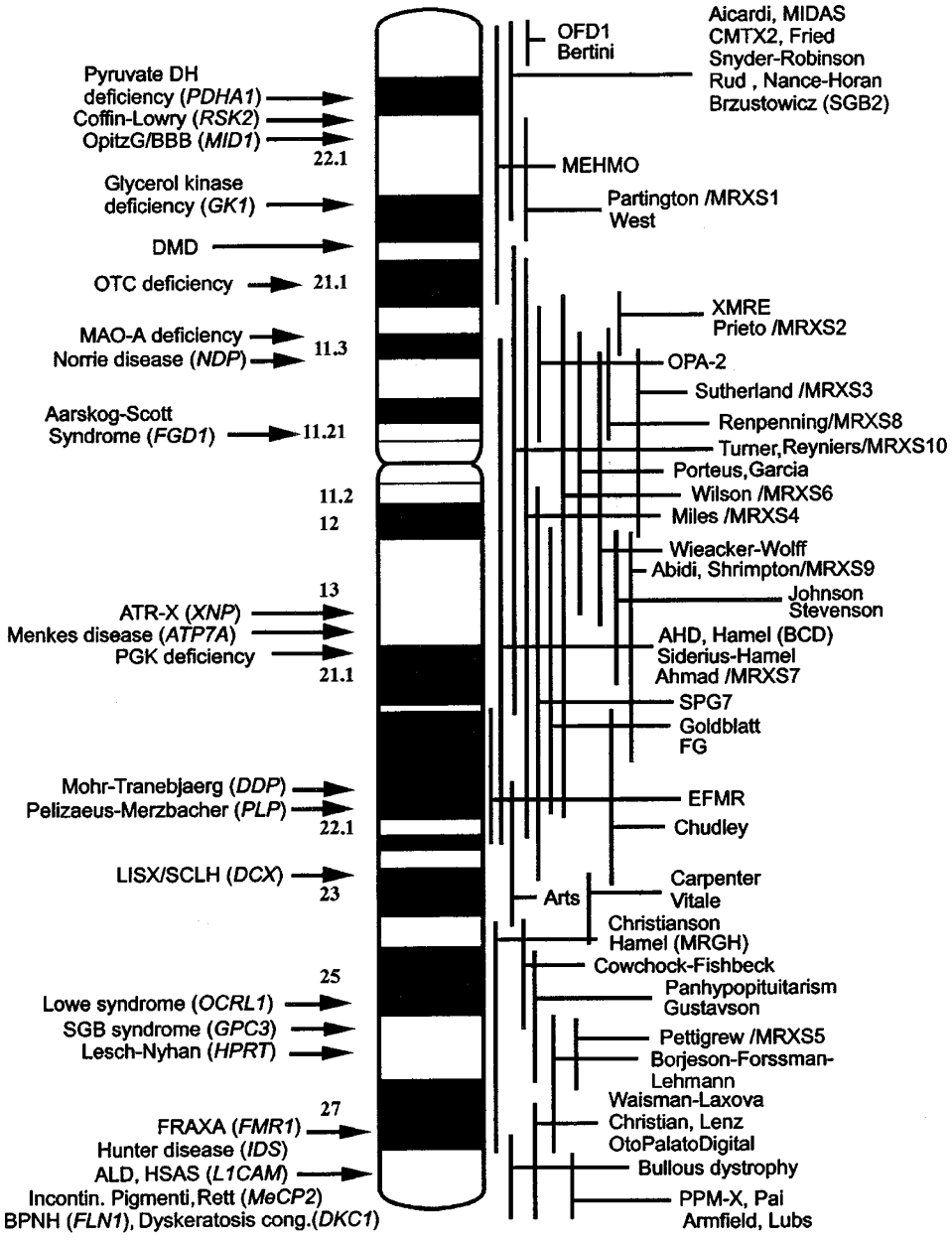

Figure 1 Ideogram of the X chromosome (G-banding) with the localisation of the 26 cloned (arrows) and 58 mapped (bars) MRXS genes.

and neurite outgrowth or in synaptic vesicle cycling,[10] ie proteins that have a specific and limited task in the functioning of the central nervous system[20] and will not disturb development nor impair cell viability. Table 6 has the total counts. A total of 202 conditions (136 MRXS and 66 MRX) have been included in this update (as of October 19, 2000). The genes of 117 of these (58 MRXS and 59 MRX) have been regionally mapped and 33 (26 MRXS and seven MRX) cloned. Figures 1 and 2 depict the cloned/mapped MRXS and MRX genes, respectively.

The on-line XLMR database

To integrate the published XLMR update we designed a simple on-line catalogue, the XLMR database, which is now available on the Internet at http://homepages.go.com/~xlmr/home.htm. This is obviously no substitute for information derived from journals, books, expert systems and clinical experience, but it could become a useful tool if most of the fellow researchers will help to improve it and to keep it updated. Potentially, it offers a number of advantages over any published document: it can be updated as

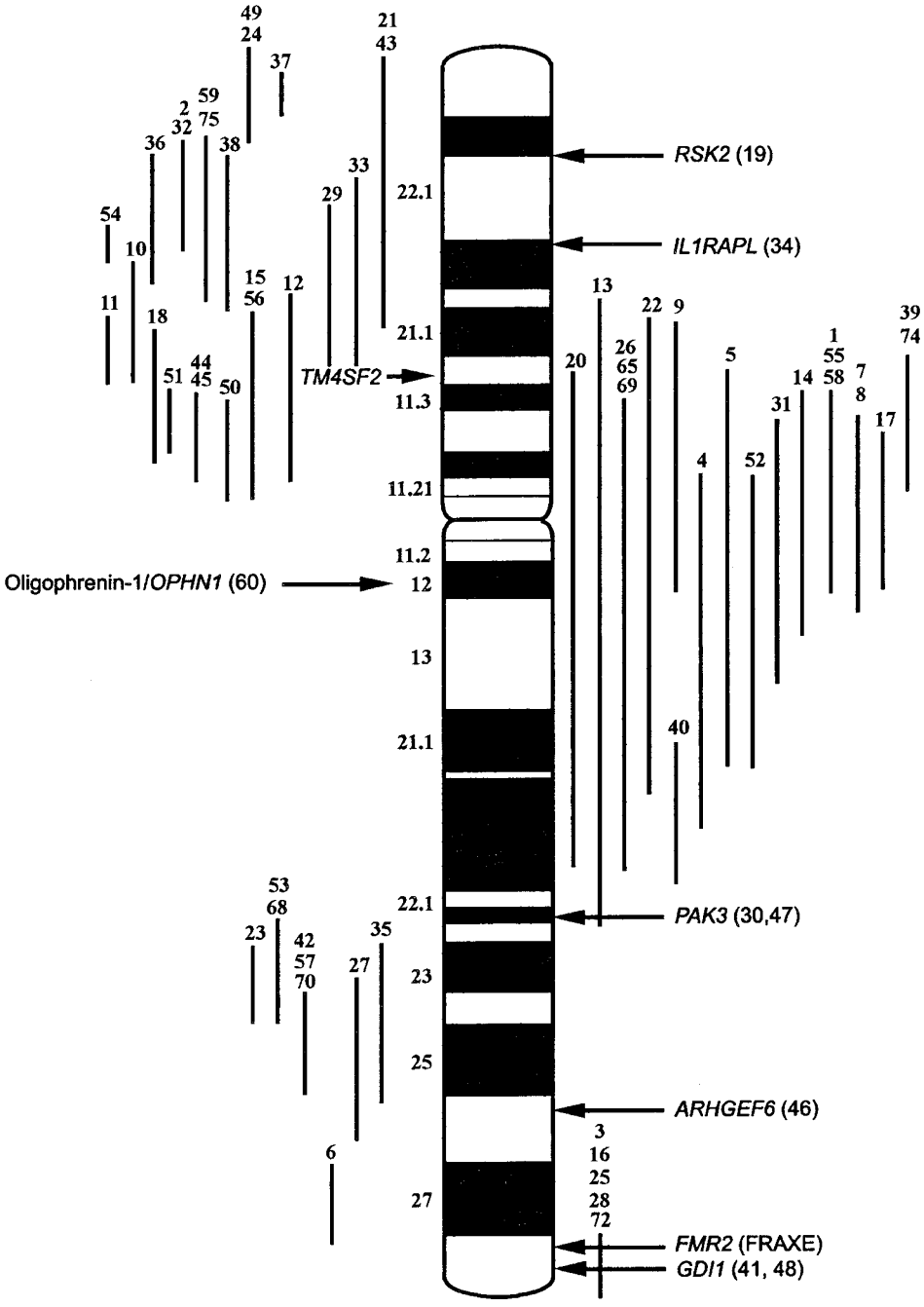

Figure 2 Ideogram of the X chromosome (G-banding) with the localisation of the seven cloned MRX genes (arrows) and of the 59 mapped MRX families (bars). The extra cloned gene indicated is *RSK2*, which is also depicted in Figure 1 and most often mutated in the Coffin-Lowry syndrome (Table 1).

frequently as needed and there is much more space for additional information that may never be published. Presently, the on-line catalogue contains an expanded version of Tables 1–6 of this update (extra columns are available and the OMIM numbers and references are hyperlinked). A colour-coded version of Figures 1 and 2 is also available and we plan to hyperlink the conditions mentioned there with the corresponding Tables. An individual record for every condition would be highly desirable, possibly with more information on the cloned genes (with a link to Locuslink of NCBI, at least). Also, thanks to the space available, the complete linkage data might be attached and

information on all tested loci (and not only recombinant ones) could be compared between overlapping conditions. Negative linkage data, which are not easily publishable but still very relevant and useful, may be stored. Eventually, images could be attached to the card describing each specific XLMR condition. Finally, a listing of available DNA from small families or individual cases with cytogenetic rearrangements in the various laboratories researching on XLMR may be envisaged, which would certainly boost the opportunity for collaboration. In brief, this informal Web site could become a 'meeting point' for the XLMR community.

Future research

Although the primary sequence of the human genome will soon be completed, the cloning era is far from being concluded and much 'sequence mining' and 'traditional' cloning remains to be done to account for the 202 XLMR conditions listed in this update. Many of these may eventually prove to be due to mutations in the same gene but the present number of 33 cloned XLMR genes definitely falls short of the actual amount. Unexpectedly, mutations in already cloned genes were not found to account for mental retardation in families mapping to the same narrow intervals where these genes are located. Therefore, new strategies will have to be designed to exploit even small families and individual patients for the identification of new XLMR genes. Some recent observations are encouraging. We now appreciate the value that even small families or individual patients with cytogenetic rearrangements can have in helping to pin down the remaining genes. For example, the MRX genes *IL1RAPL* and *TM4SF2* were identified thanks to the observation of patients with a microdeletion and an X;autosome translocation, respectively, and confirmatory mutations were found in small families that could not reach a linkage significance. DNA chip technology will hopefully allow (re)screening of large numbers of patient DNAs for mutations in several candidate genes at the same time, as well as testing the expression of these genes in informative families. Finally, the next challenge awaiting us will be the unravelling of the structure and function of the proteins encoded by the XLMR genes. This will be a daunting task belonging to the new era of 'proteomics' but will surely lead us to a better understanding of the biological pathways required for the normal development of intelligence.

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