Molecular and Comparative Genetics of Mental Retardation

Jennifer K. Inlow*,[1] and Linda L. Restifo*,†,‡,[2]

**Arizona Research Laboratories Division of Neurobiology, †Department of Neurology, ‡Genetics Graduate Interdisciplinary Program, University of Arizona, Tucson, Arizona 85721-0077*

Manuscript received August 14, 2003
Accepted for publication November 14, 2003

ABSTRACT

Affecting 1–3% of the population, mental retardation (MR) poses significant challenges for clinicians and scientists. Understanding the biology of MR is complicated by the extraordinary heterogeneity of genetic MR disorders. Detailed analyses of >1000 Online Mendelian Inheritance in Man (OMIM) database entries and literature searches through September 2003 revealed 282 molecularly identified MR genes. We estimate that hundreds more MR genes remain to be identified. A novel test, in which we distributed unmapped MR disorders proportionately across the autosomes, failed to eliminate the well-known X-chromosome overrepresentation of MR genes and candidate genes. This evidence argues against ascertainment bias as the main cause of the skewed distribution. On the basis of a synthesis of clinical and laboratory data, we developed a biological functions classification scheme for MR genes. Metabolic pathways, signaling pathways, and transcription are the most common functions, but numerous other aspects of neuronal and glial biology are controlled by MR genes as well. Using protein sequence and domain-organization comparisons, we found a striking conservation of MR genes and genetic pathways across the ~700 million years that separate *Homo sapiens* and *Drosophila melanogaster*. Eighty-seven percent have one or more fruit fly homologs and 76% have at least one candidate functional ortholog. We propose that *D. melanogaster* can be used in a systematic manner to study MR and possibly to develop bioassays for therapeutic drug discovery. We selected 42 Drosophila orthologs as most likely to reveal molecular and cellular mechanisms of nervous system development or plasticity relevant to MR.

MENTAL RETARDATION (MR) is a common form of cognitive impairment affecting between 1 and 3% of the population of industrialized countries (Roeleveld *et al.* 1997; Aicardi 1998). Although there is debate over the definition and classification of MR (Leonard and Wen 2002), it is often defined by an IQ of <70, with deficits in adaptive skills included as diagnostic criteria (Luckasson *et al.* 1992; Daily *et al.* 2000). Behavioral and cognitive therapies can help mentally retarded patients reach their maximum potential (Bathaee 2001; Butler *et al.* 2001), but they are not curative and often focus on treating habit disorders, aggression, or self-injurious behavior that can accompany MR (Long and Miltenberger 1998; Dosen and Day 2001). MR due to congenital hypothyroidism is now largely preventable through screening and hormone replacement (Gruters *et al.* 2002). Aside from this, the only molecular-based therapeutic approaches are dietary restrictions and supplements for inborn errors of metabolism such as phenylketonuria (Dashman and Sansaricq 1993; Levy 1999; Kabra and Gulati 2003). Few, if any, clinical conditions affect such large numbers of children and young adults and yet have no effective pharmacological therapy. One reason for the lack of drug treatments is the limited understanding of the molecular and cellular bases for MR.

Many environmental and genetic factors can cause MR, including premature birth, prenatal infections, chromosomal abnormalities, and single-gene mutations (Kinsbourne and Graf 2000). An etiology can be established in 60–75% of cases of severe MR, but only in 38–55% of mild cases. Estimates of genetic causes of severe MR range from 25 to 50% (McLaren and Bryson 1987). There are two categories of hereditary MR. Isolated MR with no other consistent defining features is known as nonspecific or nonsyndromal MR. To date, all but one of these (Molinari *et al.* 2002) are X-linked, but other autosomal genes may have eluded identification because of the considerably greater difficulty of mapping disorders to autosomal loci. MR also occurs, with variable penetrance and expressivity, as a phenotypic feature of numerous hereditary syndromes. The challenge of understanding the biological bases of hereditary MR is heightened by its enormous genetic heterogeneity and the limited knowledge of cellular phenotypes in the brains of mentally retarded individuals. Recent rapid progress in human genetics, however, has provided us with an opportunity for a comprehensive

[1]*Present address:* Department of Chemistry, Indiana State University, Terre Haute, IN 47809.

[2]*Corresponding author:* Arizona Research Laboratories Division of Neurobiology, 611 Gould-Simpson Bldg., 1040 E. 4th St., University of Arizona, Tucson, AZ 85721-0077. E-mail: llr@neurobio.arizona.edu

analysis of the biochemical and cellular processes underlying the MR phenotype. A search for "mental retardation" in the Online Mendelian Inheritance in Man (OMIM) database (Hamosh *et al.* 2002) yields >1000 entries, suggesting that hundreds of human genes can mutate to a MR phenotype. We conducted a detailed analysis to determine how many MR genes have been molecularly identified and what molecular and biological functions they encode.

Controversies over the definition of MR are based on both sociopolitical and biological considerations (Leonard and Wen 2002). Narrow definitions of MR restrict it to cases of nonprogressive cognitive impairment present from birth and categorize as "dementia" cases of progressive cognitive deterioration beginning some time after a period of normal development. Nonetheless, hereditary neurodegenerative disorders are often said to cause MR (see Stevenson *et al.* 2000), even when the onset is in late childhood or adolescence (*e.g.*, progressive epilepsy with mental retardation, one of the neuronal ceroid lipofuscinoses; *CLN8*). Moreover, the distinction between MR and dementia blurs in disorders such as Rett syndrome (*MECP2*), where phenotypes span a wide spectrum of severity and clinical course (Hammer *et al.* 2002). For the purpose of our analysis of hereditary MR, we chose a broader, albeit less precise, definition that includes progressive disorders with onset of cognitive impairment in childhood and, occasionally, as late as adolescence.

In parallel with human genetics research, progress in *Drosophila melanogaster* genetics and genome sequencing (Adams *et al.* 2000) allows a comparative approach to the biological study of MR. Not only do homologous mammalian and fruit fly genes share biological functions (Padgett *et al.* 1993; Bonini *et al.* 1997; Johnston *et al.* 1997; Leuzinger *et al.* 1998; Nagao *et al.* 1998; Dearborn *et al.* 2002), but also Drosophila provides useful models of human disease, including spinocerebellar ataxia (Warrick *et al.* 1998), Parkinson's disease (Feany and Bender 2000), Huntington's disease (Jackson *et al.* 1998), and type 1 diabetes (Rulifson *et al.* 2002). Moreover, neurodegeneration in the Drosophila model of Huntington's disease can be suppressed by treatment with a specific peptide (Kazantsev *et al.* 2002). Hence, we propose that this neurogenetic model system can reveal cellular phenotypes responsible for hereditary MR and will provide bioassays for potential drug therapies. By searching the Drosophila genome, we found candidate functional orthologs for the majority of molecularly identified human MR genes. Several dozen of these genes are most likely to have mutant phenotypes due to primary developmental defects of neurons or glia and thereby provide clues to the causes and treatment of MR due to single-gene mutations. Treatment strategies based on the understanding of hereditary MR may be useful for acquired MR as well.

MATERIALS AND METHODS

Databases and bioinformatics tools: The OMIM database [McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University and National Center for Biotechnology Information (NCBI), National Library of Medicine; Hamosh *et al.* 2002] was accessed online (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) to search for genes and mental retardation disorders. BLASTP (Altschul *et al.* 1997) at the NCBI (http://www.ncbi.nlm.nih.gov/BLAST/) and the Homophila Human-Disease-to-Drosophila-Gene database (Reiter *et al.* 2001; http://homophila.sdsc.edu/) were used to search for *D. melanogaster* homologs of the human MR genes. Pairwise sequence alignments were performed with LALIGN (http://www.ch.embnet.org/software/LALIGN_form.html; Huang and Miller 1991). DotPlot and TransMem of the Accelrys GCG Wisconsin Package were accessed through the Arizona Research Laboratories Biotechnology Computing Facility and were used to compare homologous protein sequences by dot matrix analysis (Maizel and Lenk 1981) and prediction of transmembrane regions, respectively. The InterPro resource for protein families, domains, and sites (Apweiler *et al.* 2001; http://www.ebi.ac.uk/interpro/scan.html) was used to determine and compare the locations of functional domains in homologous proteins. The Gene Ontology (GO) database (Gene Ontology Consortium 2001) was accessed online (http://www.geneontology.org/) to determine the molecular-function classification of MR gene products. FlyBase (FlyBase Consortium 2002) was accessed online (http://flybase.bio.indiana.edu/) to obtain information on Drosophila genes. Newly isolated *P*-element insertions were found through the P-Screen Database (http://flypush.imgen.bcm.tmc.edu/pscreen/).

Identifying human mental retardation genes through OMIM: We searched all OMIM fields on February 21, 2002, using the phrase "mental retardation" and reviewed each of the resulting 1010 entries. To include very mild MR, we also searched for "cognitive impairment" and "learning disability," obtaining 38 additional entries for evaluation. In retrospect, "developmental delay" and "psychomotor retardation" would have been useful search phrases as well. Other MR genes were identified by periodic literature searches through September 30, 2003, using NCBI's PubMed.

Careful evaluation of individual OMIM search results and cross-referencing with literature-search results revealed both false positives and false negatives. OMIM contains many partially redundant entries, which makes it impossible to equate numbers of entries obtained from a search for a specific phenotype with the number of genes that can mutate to that phenotype. OMIM entries for a genetic disorder or gene are organized into some or all of the following fields: title, MIM number, gene map, clinical synopsis, text (literature summary), allelic variants, references, and contributors. When different mutations of a single gene cause distinct disorders, there are separate OMIM entries for each disease, but only one contains a list of disease-associated alleles ("allelic variants" field). For example, mutations in the *L1CAM* gene result in one of at least three MR disorders (Weller and Gartner 2001): MASA syndrome (mental retardation, aphasia, shuffling gait, and adducted thumbs), HSAS (hydrocephalus due to congenital stenosis of the aqueduct of Sylvius), or SPG1 (spastic paraplegia 1). There is a separate OMIM entry for each of these disorders and a fourth entry for the *L1CAM* gene. There is some text redundancy among the four entries, but only the *L1CAM* entry includes the allelic variants field. On the basis of this organizational scheme, OMIM searches restricted to entries containing the allelic variants field should eliminate redundant results. However, this strategy would

cause false negatives because entries that list allelic variants do not necessarily contain complete phenotype descriptions. For example, entry 600514, which lists the allelic variants of *reelin* (*RELN*), does not contain the phrase "mental retardation," whereas entry 257320 for Norman-Roberts type lissencephaly syndrome due to *RELN* mutations contains the search phrase but does not list allelic variants. In principle, the "clinical synopsis" field could offer a useful search strategy for disease phenotypes, but some are incomplete (*e.g.*, the clinical synopsis for Norman-Roberts lissencephaly does not include MR although it is a consistent phenotype of this disorder) and many entries have no clinical synopsis at all.

Errors in the clinical synopsis fields also contributed to the many (~15%) false-positive entries (see Table 1). For example, entries 167200 and 167210 for pachyonychia congenita types 1 and 2 include MR in their clinical synopses, but the only evidence for MR is in the much rarer type 4 (Feinstein *et al.* 1988). Other false positives result from statements such as "neither [patient] had evidence of mental retardation" (entry 243605). In other entries MR is not a feature of the disorder being described, but some atypical patients are mentally retarded due to deletion of adjacent genes (*e.g.*, entry 312865). Finally, MR may be mentioned because related disorders have a MR phenotype. For instance, MR is a phenotype of a subset of hereditary spastic paraplegias, so it is mentioned in the text of the entries for most forms. Boyadjiev and Jabs (2000) noted similar difficulties in extracting information from OMIM. To obtain complete information from OMIM, one must search in a manner that yields redundant and irrelevant entries. This minimizes false negatives, but, to interpret the search results accurately, one must be willing to review individual entries carefully. Even using a broad OMIM search strategy, we missed 45 MR genes that were revealed through various literature search strategies.

Functional classification of human mental retardation genes: We searched for the 282 MR gene products in the molecular-function category of the GO database and used information from the literature to classify those not yet in the database. The GO database is composed of three parallel schemes for classifying gene function: biological process, cellular component, and molecular function (Gene Ontology Consortium 2001). Each ontology is a hierarchical classification scheme (directed acyclic graph) of structured vocabulary terms that differs from a simple hierarchical tree, such as a pedigree, in that each term may be a "child" of multiple independent "parents." There are 24 occupied top-level terms in the molecular-function ontology, *i.e.*, terms that do not have parents themselves. When GO assigned gene products to multiple molecular functions, we chose the most specific term for each. For example, we classified the α-subunit of Gs, the adenylate cyclase-stimulating guanine nucleotide-binding protein (*GNAS*), as a "nucleotide-binding protein" rather than as a "hydrolase," the other GO assignment. For genes considered by GO to have "unknown function," we found that most could be provisionally classified on the basis of data in the literature.

The "biological function(s)" assignments were based on literature reviews for each gene, including neuroimaging, gene expression, and neuropathological data from human patients, as well as studies of wild-type and mutant mice. We first designated the *basic cellular process* in which the gene is primarily involved, *e.g.*, cytoskeleton or chromosome structure. We then identified the site of primary *organ system function*, relative to MR: endocrine system, central nervous system, or neither. For those genes that directly impact central nervous system (CNS) development and/or function, we ascertained the *tissue type* (neuron, glia, or blood vessel) and the *specific cellular process* affected (*e.g.*, cell identity or differentiation). We also considered whether MR caused by mutation of the gene is *secondary to toxicity* or *secondary to energy or fuel deficiency*.

Identifying Drosophila orthologs of human mental retardation genes: We used bioinformatics tools to determine if the human MR genes have likely functional orthologs in *D. melanogaster*. For MR genes encoding tRNAs, we aligned the human and fly tRNA homologs using LALIGN and calculated the percentage identity. For each protein-coding MR gene, we searched the *D. melanogaster* sequences of the NCBI nonredundant database with NCBI's BLASTP. We used an *E*-value cutoff of 1×10^{-10} (1*e*-10), a threshold commonly used for human-fly gene comparisons (Fortini *et al.* 2000; Lloyd *et al.* 2000; Reiter *et al.* 2001). The Homophila database (Reiter *et al.* 2001) is designed for such comparisons but, due to its organizational features and infrequent updates, we found it easier and more reliable to do our own BLAST searches. For one MR gene, we concluded that Drosophila does not have a biologically meaningful homolog despite a published claim of one. *Grunge* (FBgn0010825) is the most similar fly gene to human *DRPLA* (Zhang *et al.* 2002), but has a BLASTP *E*-value of 5E-2, which does not meet our threshold. Moreover, sequence similarity is limited to the extreme C terminus and the Grunge protein does not possess the same domain organization as DRPLA.

For protein-coding MR genes, we also conducted a "reverse" BLASTP search using the top-scoring Drosophila BLASTP result as a query against the human sequences of the NCBI nonredundant database. A Drosophila gene was considered an ortholog of a human MR gene only if this reverse analysis (sometimes supplemented with dot-matrix plot and protein-domain comparison; see below) revealed that it was more similar to the human MR gene (or a paralog) than to another gene. For example, the Drosophila proteins most similar to human glial fibrillary acidic protein (*GFAP*) are the products of *Lamin* and *Lamin C*. A reverse BLASTP search revealed that, although these two proteins share a single common domain with GFAP, they are more similar over their full lengths to members of the human lamin family. In addition, both human and Drosophila lamins are localized to the nucleus (Goldman *et al.* 2002), whereas GFAP is cytoplasmic (Eng *et al.* 2000). Hence, *GFAP* does not have an ortholog in Drosophila.

When compared with mammals, Drosophila has relatively few duplicated genes (Durand 2003), so in some cases a Drosophila gene is the single ortholog of a paralogous set of human genes. For example, *FMR1*, which causes fragile X syndrome, is a member of a gene family that also includes *FXR1* and *FXR2*, the autosomal fragile X-related genes. Drosophila *dfmr1* is the only homologous fly gene, sharing significant sequence similarity and domain structure with all three human genes, suggesting that it is the sole ortholog.

To determine if orthologous genes are likely to share the same molecular and biological functions in humans and flies, we used dot matrix plots (GCG DotPlot) to assess the extent of protein sequence similarity and searched the InterPro database for known functional domains in each protein. GCG TransMem was used to predict transmembrane regions in the human and fly proteins. If the proteins share sequence similarity over most of their lengths and have similar organization of known functional domains, we considered them to be candidate functional orthologs. In some cases we also considered expression patterns, mutant phenotypes, and subcellular localization. In cases of "computed genes" predicted from the Drosophila genome sequence, the absence of experimental data made the evaluation of ortholog status more difficult.

RESULTS AND DISCUSSION

The 282 mental retardation genes have been molecularly identified: Analysis of OMIM and literature search

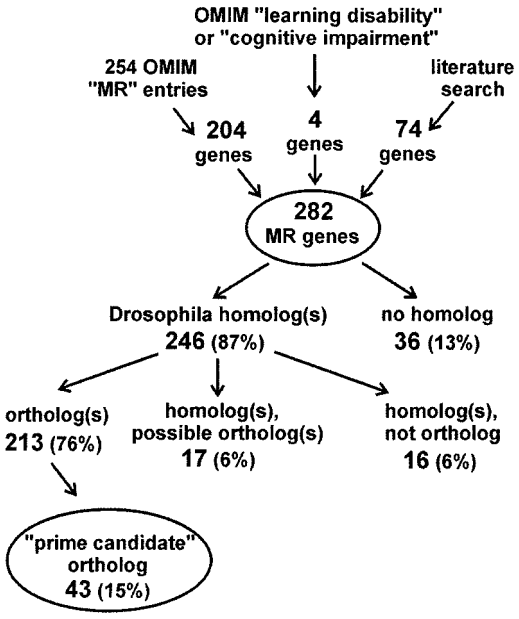

FIGURE 1.—Diagram of the identification of human mental retardation genes and their comparison to *D. melanogaster* genes. The OMIM searches were performed on February 21, 2002. The literature search was completed on September 30, 2003.

results allows us to present a status report on the genetics of MR. From the 1010 OMIM "mental retardation" entries obtained on February 21, 2002, we found 204 human genes that cause MR either in isolation or as part of a syndrome. Through literature searches we found 45 additional MR genes whose OMIM entries did not contain the search phrase "mental retardation." About a quarter of these "false-negative" entries contained the phrases "psychomotor retardation" and/or "developmental delay." To include disorders causing very mild MR, we also searched OMIM for entries containing "cognitive impairment" or "learning disability" but not "mental retardation." Most of these 38 entries describe adult-onset, progressive cognitive impairment disorders, but literature review identified 4 of them as MR genes. Finally, literature searches between March 2002 and September 30, 2003 revealed 29 recently identified MR genes for a total of 282 human genes known to cause MR (Figure 1). On the basis of these and subsequent publications, we estimate that new MR genes are being identified at a rate of 1–2 per month. The APPENDIX lists the 282 MR genes in alphabetical order by their gene symbols, along with their associated MR disorders, chromosomal locations, OMIM numbers, and other information explained below. As will be discussed in later sections, the MR genes control an extraordinary range of molecular and cellular functions.

We classified the 1010 OMIM "mental retardation" entries, based on data available in spring 2002, according to the following scheme (Table 1):

Category 1: The disorder has been mapped to a specific gene *and* allelic variants have been identified (this category includes OMIM entries for the MR disorders as well as separate entries describing the genes themselves).

Category 2: The disorder has been mapped to one or more candidate genes in a chromosomal region (contiguous gene deletion syndromes, *e.g.*, Prader-Willi, are in this category).

Category 3: The disorder has been mapped to a chromosomal region.

Category 4: The disorder has been mapped to a candidate chromosome.

Category 5: The disorder has not yet been mapped to a chromosome.

Category 6: The disorder is caused by a gross chromosomal abnormality and no single gene determines the MR phenotype (Down syndrome is one example).

Category 7: MR is not a phenotype of the disorder.

Category 8: The disorder does not exist.

TABLE 1

OMIM mental retardation entries

Category	Description	No. of entries	% of entries
1	Known gene	254	25.1
2	Candidate gene	55	5.4
3	Chromosomal region	98	9.7
4	Candidate chromosome	26	2.6
5	Not mapped	416	41.2
6	Chromosomal abnormality	9	0.9
7	No MR phenotype	149	14.8
8	Nonexistent disorder	3	0.3
	Total:	**1010**	**100**

This table is based on analysis of a search done on February 21, 2002.

The number of OMIM entries in category 1 ("known gene"), 254, is greater than the number of genes, 204, because of OMIM database redundancy (see MATERIALS AND METHODS). The nearly 600 OMIM entries in categories 2–5 represent MR disorders in which the causative genes were unknown (see below). Of the 29 recently discovered MR genes, half had "advanced" from "candidate gene" (1 gene), "chromosomal region" (9 genes), or "unmapped" (5 genes) categories. Thirteen represent new loci that can cause a known disorder. One (*FKRP*) causes a form of muscular dystrophy, not previously associated with MR, that had been in category 7.

Entries in category 6 ("chromosomal abnormality") describe *bona fide* MR disorders, but we have not considered them further in this analysis because they appear to involve many genes (*e.g.*, SHAPIRO 1999). It remains to be determined whether individual genes that contribute to MR in cases of aneuploidy or other chromosomal defects can mutate to an MR phenotype individually. The 149 OMIM entries in category 7 ("no MR pheno-

type") represent false positives in which MR is not a phenotype (see MATERIALS AND METHODS). Most of these false-positive errors could be eliminated by the adoption of a controlled vocabulary for OMIM clinical synopses, with the previously mentioned caveat that MR definitions vary. The three entries in category 8 ("nonexistent disorders") do not represent distinct clinical entities, and one was subsequently removed from the OMIM database.

With ~600 OMIM MR entries in categories 2–5 (Table 1), it is obvious that many more MR genes remain to be identified—but how many? Some of these disorders, particularly those in categories 4 ("candidate chromosome") and 5 ("not mapped"), are likely to represent MR genes that are already known. This is because of both practical difficulties in mapping human phenotypes and the phenomenon of phenotypic divergence; *i.e.*, different mutant alleles of the same gene cause distinct MR disorders (*e.g.*, different *DKC1* mutations result in dyskeratosis congenita or Hoyeraal-Hreidarsson syndrome). Similarly, novel MR genes that remain to be identified may each explain more than one disorder, especially within the large unmapped group. Hence, this set of OMIM entries is likely to represent <595 genes.

On the other hand, what MR disorders might be "missing" from our analysis? First, we know that some genes, or their corresponding disorders, are present in the OMIM database but fail to appear in MR-related search results because of inconsistent use of terminology in the medical literature, curatorial errors, or differing opinions on what constitutes mental retardation (see MATERIALS AND METHODS). Second, MR mutations occurring in small families likely represent a large number of genes not yet listed in OMIM. Some families never reach the attention of medical genetics research teams. Small pedigrees represent significant challenges for gene mapping, even on the X chromosome (ROPERS *et al.* 2003). The X-Linked Mental Retardation Genes Update Site (http://xlmr.interfree.it/home.htm; CHIURAZZI *et al.* 2001) lists 57 nonspecific MR families and 110 X-linked MR syndromes for which the genes remain elusive. However, only 80 OMIM entries described X-linked MR disorders (syndromes and nonspecific) for which genes have not been identified (Table 1, X-linked entries in categories 2–4).

A third "missing" or underrecognized category is composed of essential genes of which most deleterious mutations cause early prenatal lethality and only exceptional alleles with specific molecular consequences permit viability along with an MR phenotype. In genetic model systems, complementation testing can easily show that a viable "memory mutation" is allelic to mutations causing early death with profound neuroanatomical defects (*e.g.*, PINTO *et al.* 1999), but comparable mapping studies are much more difficult in humans.

Fourth, mutations in genes controlling thyroid development or function rarely cause MR in industrialized societies because of neonatal screening and treatment for hypothyroidism (GRUTERS *et al.* 2002). Hence, while a dozen known genes have been associated with MR secondary to hypothyroidism (APPENDIX), mutations in other similar genes may not have had the "opportunity" to reveal whether they would cause MR in untreated patients. Finally, syndromal MR genes for which the MR phenotype has very low penetrance present a significant ascertainment challenge. For example, eight DNA repair genes/disorders are associated with MR in a modest fraction of patients. It seems likely that more such disorders (*e.g.*, the rarer Fanconi anemia complementation groups) have MR as a *bona fide* phenotype, but, presumably because the phenotype depends on chance somatic mutations during brain development (GILMORE *et al.* 2000), it is difficult to confidently assign MR to their clinical descriptions.

Given all these considerations, predicting the true number of human MR genes is difficult. A complete and accurate count may be beyond the capacity of medical science to determine directly. We believe that 282 represents substantially less than half of the total. It is easy to imagine that human MR genes could number ~1000.

X-linked mental retardation genes: To date, eight X-linked genes are known to cause exclusively nonspecific MR (MRX genes), and 31 X-linked genes cause exclusively syndromal forms of MR (Table 2). Nonspecific MR has been the focus of much attention, in part because of the idea that genes with "pure" behavioral phenotypes, unaccompanied by gross brain abnormalities or other organ system defects, may provide greater insight into the molecular basis of cognition than the syndromal MR genes (CHELLY 1999; TONIOLO 2000). Indeed, several MRX genes figure prominently in Rho-type G-protein pathways (*ARHGEF6*, *GDI1*, *OPHN1*, *PAK3*, *FGD1*; RAMAKERS 2002) or are regulated by neuronal activity (*PAK3*, *IL1RAPL1*, *RSK2*, *TM4SF2*; BODA *et al.* 2002). However, with the discovery that mutations of five MR genes can cause either nonspecific or syndromal MR (Table 2), the distinction between the two categories may not be as meaningful as originally proposed (see discussion in FRINTS *et al.* 2002).

For *RSK2* (*RPS6KA3*), the phenotype difference is explained by allele type and severity. The R383W mutation that causes MRX19 is a partial loss-of-function allele, encoding a protein with 20% of wild-type kinase activity (MERIENNE *et al.* 1999). In contrast, null mutations of *RSK2* cause Coffin-Lowry syndrome with prominent skeletal and connective tissue involvement (HANAUER and YOUNG 2002). For several genes, the structure-function relationships are inferred but not directly demonstrated. The T1621M mutation of *ATRX* (also known as *XH2* or *XNP*) causes nonspecific MR in the mild-to-moderate range (YNTEMA *et al.* 2002). Although residue 1621 is within the highly conserved

TABLE 2

X-linked mental retardation genes

Type of MR disorder	No. of XLMR genes	% of XLMR genes	Gene symbols (see also APPENDIX)
Nonspecific only	8	18.2	*ARHGEF6*, *FACL4*, *FMR2*, *GDI1*, *IL1RAPL1*, *OPHN1*, *PAK3*, *TM4SF2*
Syndromal only	31	70.5	All other X-linked genes in the APPENDIX
Both	5	11.4	*ARX*, *ATRX*, *FGD1*, *MECP2*, *RSK2*
Total	**44**	**100**	

XLMR, X-linked mental retardation.

SNF2-related domain, it is not conserved, suggesting that some alterations at that site are compatible with partial function of this nuclear protein involved in chromatin structure and transcription regulation. Missense mutations just 7 and 12 residues upstream, however, cause a more severe, syndromal phenotype with hematologic, skeletal, and genital defects (GIBBONS *et al.* 1995), suggesting greater disruption of ATRX function. A variety of *FGD1* mutations, most of which truncate the encoded putative Rho GEF, cause Aarskog-Scott syndrome, which includes highly penetrant skeletal and genital anomalies but infrequent, and only mild, MR. In contrast, one particular missense mutation in a region of unknown function, P312L, causes severe, fully penetrant nonspecific MR (LEBEL *et al.* 2002).

Genotype-phenotype relationships are even more complex for *MECP2* and *ARX*. Within and among Rett syndrome families, females with *MECP2* mutations show great clinical heterogeneity, with X-inactivation patterns and mutation sites believed to explain the severity differences (CHEADLE *et al.* 2000; HAMMER *et al.* 2002). In addition, at least seven different missense mutations in *MECP2*, scattered over the length of the protein, cause nonspecific MR (ORRICO *et al.* 2000; COUVERT *et al.* 2001); several of these are very close to sites of Rett-syndrome-causing missense mutations (CHEADLE *et al.* 2000; HAMMER *et al.* 2002). For *ARX*, identical mutations, resulting in polyalanine tract expansion of this homeodomain protein, caused nonspecific MR in one family, but distinct neurological syndromes (West or Partington or MR with hypsarrhythmia) in various other families (STROMME *et al.* 2002). This suggests a major effect of genetic background on *ARX* phenotypes. Other *ARX* mutations cause a unique lissencephaly syndrome with abnormal genitalia (KITAMURA *et al.* 2002).

Complex genotype-phenotype relationships are also a feature of some autosomal MR disorders (*e.g.*, *FGFR1*, *GLI3*, *PEX1*, *PTEN*, *PTPN11*). On the basis of X-linked MR, it is possible that some alleles of the one known autosomal nonspecific MR gene (*PRSS12*; MOLINARI *et al.* 2002) will be found to cause a syndromal MR phenotype. Conversely, autosomal genes presently known to cause MR syndromes may be able to mutate to a nonspecific MR phenotype.

Chromosomal distribution of human mental retardation genes: Of the 282 human MR genes, 11 are encoded by the mitochondrial genome. Figure 2A shows the chromosomal distribution of the 271 nuclear MR genes compared to the chromosomal distribution of all known and predicted human genes based on the human genome sequence (VENTER *et al.* 2001). While ~4% of known and predicted genes are on the X chromosome, ~16% of the MR genes reside there—a fourfold overrepresentation. In contrast, the distribution of MR genes among the autosomes roughly parallels their relative gene contents (Figure 2A). An even greater X-chromosome overrepresentation is found among the MR disorders mapped to candidate loci (6-fold), chromosomal regions (14-fold), and chromosomes (15-fold), which correspond to categories 2, 3, and 4, respectively, of Table 1.

It has been proposed that the human X chromosome contains a disproportionately high density of genes for cognitive ability (LEHRKE 1972; TURNER and PARTINGTON 1991). This proposal generated controversy as well as speculation concerning possible underlying evolutionary mechanisms, including the intriguing suggestion that female mate selection for high male intelligence helped accelerate the rapid rise of human cognitive abilities (TURNER 1996; ZECHNER *et al.* 2001). The identification of numerous MRX genes and X-linked MR syndromes (CHIURAZZI *et al.* 2001) seemed to support the proposal. Opponents, however, argued that all X-linked recessive mutations are simply easier to map and identify because their phenotypes are revealed in hemizygous males (MORTON 1992; LUBS 1999). Countering this view is an OMIM-based analysis (ZECHNER *et al.* 2001) showing a 7.2-fold X-chromosome bias for MR genes, whereas genes causing common morphological phenotypes (polydactyly, cleft palate, facial dysplasia, skeletal dysplasia, and growth retardation) have, on average, only a 2.4-fold X-chromosome bias. [ZECHNER *et al.* (2001) did not take OMIM errors, such as false positives and negatives, into consideration, but such errors may be comparable across phenotypes.]

To take this question one step further, we asked whether the apparent X-chromosome overrepresentation among the molecularly identified human MR genes

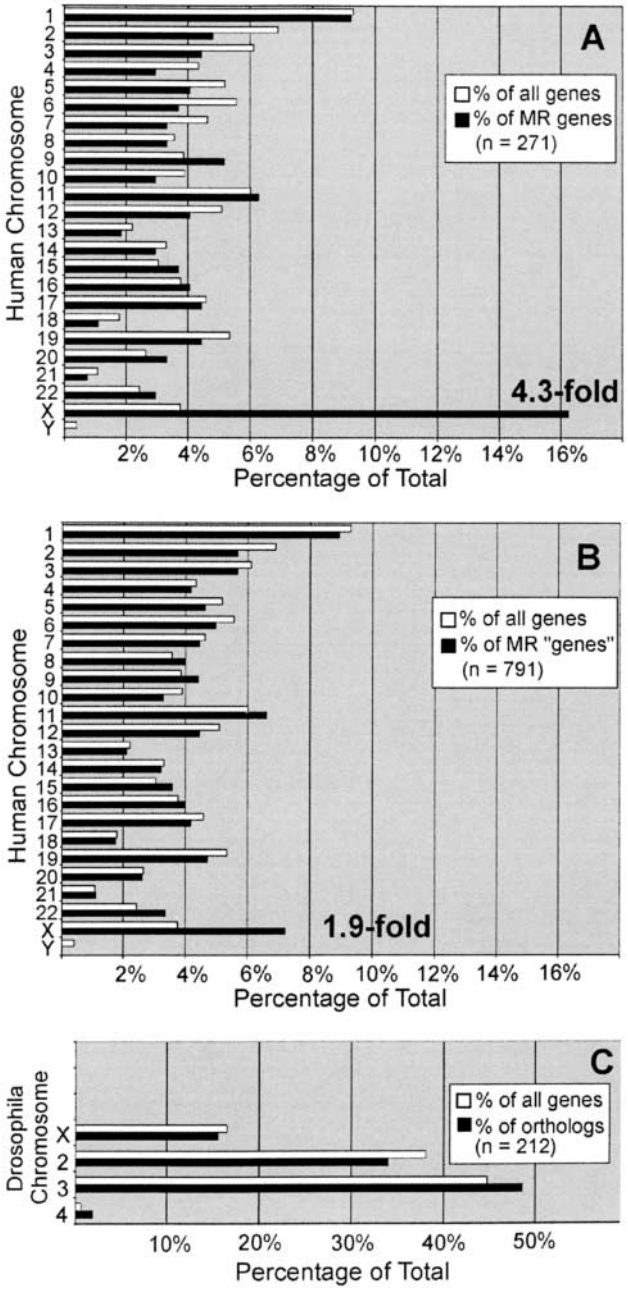

FIGURE 2.—Chromosomal distribution of human mental retardation genes and *D. melanogaster* orthologs. (A) The chromosomal distribution of the 271 molecularly identified nuclear MR genes is compared to the chromosomal distribution of all nuclear, protein-coding human genes based on human genome sequence analysis (VENTER *et al.* 2001). Note the striking overrepresentation of X-linked MR genes. (B) The predicted chromosomal distribution of known and potential MR genes based on maximizing the assignment of genes to autosomes (see RESULTS and DISCUSSION), compared to all nuclear human genes as in A. The X-chromosome overrepresentation has been reduced, but remains almost twofold. (C) The chromosomal distribution of the Drosophila MR gene orthologs is compared to the chromosomal distribution of all nuclear, protein-coding Drosophila genes on the basis of Drosophila genome sequence analysis (ADAMS *et al.* 2000; see FlyBase at http://flybase.bio.indiana.edu/ for Release 3). Drosophila homologs of human MR genes that are not orthologs were not included in this analysis.

(Figure 2A) would disappear if we accounted for the plausible possibility that numerous autosomal loci are "hiding" among the unmapped MR genes (represented by the OMIM entries in category 5, Table 1). We attempted to overcome the ascertainment bias that favors identification of X-linked genes by making simplifying assumptions that maximize the estimate of autosomal MR genes and minimize the estimate of X-linked MR genes. First, we assumed that one OMIM entry equals one gene. Second, for the unmapped MR disorders (category 5, Table 1), we assumed that each represents a different, novel autosomal gene and that these are distributed in proportion to the overall gene distribution on those chromosomes (VENTER *et al.* 2001). Third, for those disorders whose genes map to chromosomal regions and candidate chromosomes (categories 3 and 4, Table 1), we assumed that there will be no new X-linked genes, *i.e.*, that each potential X-linked gene is identical to an X-linked gene already known to cause MR. However, all candidate genes (category 2, Table 1), including the X-linked genes, were assumed to be new MR genes.

Even when these very conservative (*i.e.*, biased toward autosomal) assumptions are used to estimate the chromosomal distribution of the unknown MR genes, a 1.9-fold overrepresentation of MR genes on the X chromosome remains (Figure 2B). This result supports the hypothesis that the X chromosome contains a disproportionately high density of genes influencing cognitive ability. One caveat is the possibility discussed above that many autosomal MR genes may be so rare or difficult to study that they never appear in the medical literature and, hence, in OMIM. We also agree with the suggestion of LUBS (1999) that resolution of this issue would be enhanced by analyzing genome-wide brain expression data and by searching for allelic variation in single genes responsible for the high end of the intelligence spectrum.

***D. melanogaster* homologs of human mental retardation genes:** We found that 87% of known MR genes (246/282) have at least one Drosophila homolog with a BLASTP *E*-value of 1×10^{-10} or better (Figure 1; APPENDIX). Similarly, REITER *et al.* (2001) found that 75% of ~1400 human disease genes, representing all major disease categories, have Drosophila homologs at this level of sequence similarity. More important, 76% (213) of the MR genes, including syndromal and nonsyndromal types, have at least one Drosophila ortholog (see MATERIALS AND METHODS and APPENDIX). In fact, a handful of the human genes were named for their Drosophila orthologs, in most cases prior to their identification as MR genes (*ASPM*: *abnormal spindle-like, microcephaly-associated*; *EMX2*: *homolog 2 of empty spiracles*; *PTCH*: *homolog of patched*; *PTCH2*: *homolog 2 of patched*; *SHH*: *sonic hedgehog*; *SIX3*: *homolog 3 of sine oculis*).

The APPENDIX lists the Drosophila homologs and orthologs of the MR genes, their FlyBase accession num-

bers, and the BLASTP *E*-values (see also Figure 1 for overview). As discussed below, several dozen Drosophila orthologs (designated "¶" in the APPENDIX) are prime candidates for cellular and molecular study of MR. Seventeen MR genes (6%; designated with asterisk) have one or more homolog(s) that may be orthologs, but it is not possible to make a determination on the basis of sequence analysis in the absence of experimental data. Another 16 MR genes (6%; in brackets) have one or more Drosophila homolog(s) that are not orthologs on the basis of reverse BLAST results or other sequence analysis (see MATERIALS AND METHODS). There are 36 MR genes (13%) with no Drosophila homolog, although this number may decline as final gene identification for the Drosophila genome is completed.

Some of the Drosophila genes are functional orthologs of human MR genes on the basis of experimental data. For instance, mutations of *dfmr1*, the Drosophila ortholog of *fragile X mental retardation 1* (*FMR1*; WAN *et al.* 2000), cause specific disruptions of neuronal morphology (ZHANG *et al.* 2001; MORALES *et al.* 2002; LEE *et al.* 2003; C. MICHEL, R. KRAFT, B. HASSAN and L. RESTIFO, unpublished results) and behavioral defects (DOCKENDORFF *et al.* 2002; INOUE *et al.* 2002). Genetic and biochemical data suggest that Drosophila dFMR1 is a regulator of translation (ZHANG *et al.* 2001; ISHIZUKA *et al.* 2002), as has been shown for mammalian FMRP (KAYTOR and ORR 2001; LAGGERBAUER *et al.* 2001; MAZROUI *et al.* 2002; ZALFA *et al.* 2003). Although learning phenotypes of *dfmr1* mutant flies have not yet been reported, four of the fruit fly MR gene orthologs are "learning and memory genes" on the basis of behavioral data: *G protein sα60A* (CONNOLLY *et al.* 1996), the ortholog of *GNAS*; *Neurofibromin 1* (GUO *et al.* 2000), the ortholog of *NF1*; *cheerio* (see DUBNAU *et al.* 2003, online supplement), the ortholog of *FLNA*; and *S6kII* or *ignorant* (G. PUTZ, T. ZARS, and M. HEISENBERG, personal communication), the ortholog of *RSK2*. Additional Drosophila learning and memory genes have been proposed as candidates for MR disorders that are not yet mapped (MORLEY and MONTGOMERY 2001).

The Drosophila orthologs of the human MR genes do not have a skewed chromosomal distribution (Figure 2C). Approximately 16% of all fly genes and 16% of MR gene orthologs are on the X chromosome. Of the first two dozen Drosophila "learning and memory genes" identified, almost 50% are X-linked (reviewed in DUBNAU and TULLY 1998; MORLEY and MONTGOMERY 2001). However, the recent isolation of 60 new autosomal memory genes (DUBNAU *et al.* 2003) indicates that the older results reflect the previous tendency to design X-chromosome screens for behavioral and neuroanatomical phenotypes.

Molecular functions of mental retardation genes: Each of the 282 MR genes was classified in a single molecular-function category, primarily on the basis of the GO database (Figure 3; APPENDIX; see MATERIALS AND METHODS). The MR genes are distributed over a broad range of functions, indicating that disruption of any of a wide array of molecular processes can impair brain function so as to cause MR. Several categories are prominently represented, such as enzymes (143 genes; 51%), mediators of signal transduction (32 genes; 12%) and transcription regulation (19 genes; 7%), binding proteins (23 genes; 8%), and transporters (21 genes; 8%). Enzymes, especially those expressed in accessible peripheral tissues, make gene identification easier than that for many other proteins, so their relative representation may decline as new MR genes are discovered. Other categories with smaller numbers of MR genes include cell adhesion molecule, structural molecule, motor protein, tRNAs, apoptosis regulator, chaperone, and enzyme regulator. GO classifies ~9% of the MR genes (25) in the "unknown function" category, but published data suggest functions for all but 10 of them (see APPENDIX).

Within the GO molecular-function ontology, top-level categories include fundamental molecular functions (*e.g.*, binding activity, of which there are many subcategories), as well as others related to a specific cellular process (*e.g.*, cell adhesion molecule), and in many cases, genes could be assigned to more than one. This makes classification, analysis, and comparison to other sets of genes somewhat difficult. We did not classify any MR gene products as "defense/immunity proteins," but *IKBKG* encodes a subunit of a signal transducer (our category choice) that regulates NF-κB in the immune and inflammatory response pathway (WALLACH *et al.* 2002). We also did not use the "translation regulator" category, but *EIF2AK3* encodes a kinase (our category choice) that indirectly regulates translation by phosphorylating eukaryotic translation initiation factor-2 (MA *et al.* 2002). Similarly, we classified *FMR1* as "RNA binding," but considerable data demonstrate that it regulates translation (JIN and WARREN 2003). In addition, we could have classified some genes in the "protein stabilization" (*e.g.*, *PPGB*), cytoskeletal regulator (*e.g.*, *TBCE*), or "protein tagging" (*e.g.*, *UBE3A*) categories. However, anticoagulant, antifreeze, antioxidant, chaperone regulator, nutrient reservoir, and toxin are top-level categories in which none of the 282 MR genes could be placed.

Figure 3 indicates the Drosophila-homolog status of the MR genes in each molecular-function category. The 213 MR genes with Drosophila ortholog(s) (solid bars) are distributed among the GO categories in roughly the same pattern as that of all the MR genes, with two exceptions. More than half of the "receptor binding" genes (4 of 7) and 36% (9 of 25) of the "unknown function" MR genes have no Drosophila homolog.

Biological functions of mental retardation genes: We devised a "biological function(s)" classification scheme for the 282 MR genes that considers both cellular- and

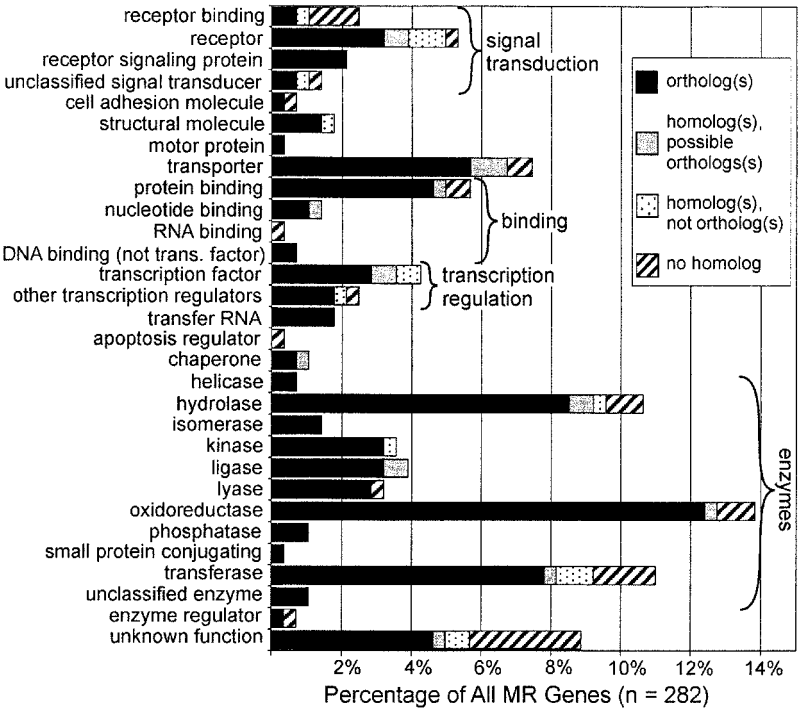

FIGURE 3.—Molecular function classification of mental retardation genes. Genes were classified on the basis of GO categories (see MATERIALS AND METHODS). In cases where the top-level parent terms include large numbers of genes (signal transduction, binding, transcription regulation, enzyme), we show the distribution of genes among the children terms. For many of the genes that have not yet been classified by the GO Consortium, we used information from the literature to assign them to a GO term. For some of the genes designated "unknown function" by GO, we were able to assign provisional functions on the basis of published literature (see APPENDIX), but these genes are included in the "unknown function" category of this figure. As indicated by the boxed legend, each bar indicates classification of the human MR genes based on the degree of similarity to Drosophila genes.

systems-level perspectives (Figure 4; APPENDIX; see MATERIALS AND METHODS). The *basic cellular processes* controlled by MR genes take place in the nucleus, in the cytoplasm (including within organelles), and at the interface among cells, cell compartments, and the extracellular milieu. In the nucleus, MR genes affect chromosome structure (*e.g.*, *DNMT3B*), DNA repair (*e.g.*, *NBS1*), basal and regulated transcription (*e.g.*, *ERCC2* and *SIX3*, respectively), as well as rRNA processing (*e.g.*, *DKC1*).

In the cytoplasm, many MR genes have metabolic functions (see also KAHLER and FAHEY 2003), involving a wide range of pathways [citric acid cycle (*e.g.*, *FH*), gluconeogenesis (*e.g.*, *GK*), glycolysis (*e.g.*, *PDHA1*), oxidation (*e.g.*, the *PEX* genes), oxidative phosphorylation (*e.g.*, *MTCO1*), urea cycle (*e.g.*, *OTC*), and general cell integrity (*e.g.*, *GSS*)] and biologically critical compounds [amine (*e.g.*, *MAOA*), amino acid (*e.g.*, *OAT*), carbohydrate (*e.g.*, *GALE*), cholesterol (*e.g.*, *SC5DL*), creatine (*e.g.*, *GATM*), fatty acid (*e.g.*, *ALDH3A2*), heme (*e.g.*, *PPOX*), lipid (*e.g.*, *DIA*), methionine (*e.g.*, *MAT1A*), purine (*e.g.*, *HPRT*), pyrimidine (*e.g.*, *DPYD*), and cofactors (*e.g.*, *TC2*)]. MR genes involved in macromolecular synthesis and modification include those required for mitochondrial translation (*e.g.*, *MTTK*), translation regulation (*e.g.*, *FMR1*), protein folding (*e.g.*, *BBS6*), protein stability (*e.g.*, *PPGB*), protein glycosylation (*e.g.*, *PPM2*), and lipid synthesis (*FACL4*). Macromolecular degradation in lysosomal (*e.g.*, *HEXA*) and proteasomal (*e.g.*, *UBE3A*) pathways is also commonly disrupted by mutations in MR genes. MR genes have major effects on the cytoskeleton, including its actin (*e.g.*, *FLNA*), microtubule (*e.g.*, *DCX*), and intermediate filament (*e.g.*, *GFAP*) components.

The major signaling pathways are represented among the MR genes, including those regulated by Sonic Hedgehog (*e.g.*, *SHH*), the TGF-β family of growth factors (*e.g.*, *GPC3*), Notch (*e.g.*, *JAG1*), and calcium (*e.g.*, *ATP2A2*). MR-related signaling cascades are mediated by diverse cell surface proteins, such as integrins (*e.g.*, *ITGA7*), G protein-coupled receptors (*e.g.*, *AGTR2*), receptor tyrosine kinases (*e.g.*, *NTRK1*), and intracellular proteins, including small G proteins (*e.g.*, *GDI1*), heterotrimeric G proteins (*e.g.*, *GNAS*), and phosphatidylinositol (*e.g.*, *PTEN*). Moreover, genes in a common pathway can share MR as a phenotype. SHH (MING *et al.* 1998), through its receptors encoded by *PTCH* and *PTCH2*, regulates *GLI3*, some of whose targets are also regulated by *GPC3*.

MR genes also control communication and transport across cell and organelle membranes. These include cation-chloride cotransporters (*SLC12A1*, *SLC12A6*) that may be critical for inhibitory neurotransmission (PAYNE *et al.* 2003). The transmembrane linkage (*ITGA7*, *TM4SF2*) between the extracellular matrix (*LAMA2*) and the cytoskeleton is strongly implicated in MR, as is cell adhesion (*L1CAM*).

The overlap between MR and muscle disease is striking and appears to arise from at least three distinct mechanisms: reduced membrane/cytoskeletal stability (*DMD*, *ITGA7*, *LAMA2*); glycosylation defects associated with abnormal neuronal migration (*FCMD*, *FKRP*, *LARGE*, *POMGNT1*, *POMT1*); and mitochondrial dysfunction (*MTCO3* and many others). The biological basis of myotonic dystrophy (*DM1*) is unknown.

An integrative view of MR biology: The hereditary MR disorders can be approached from two somewhat

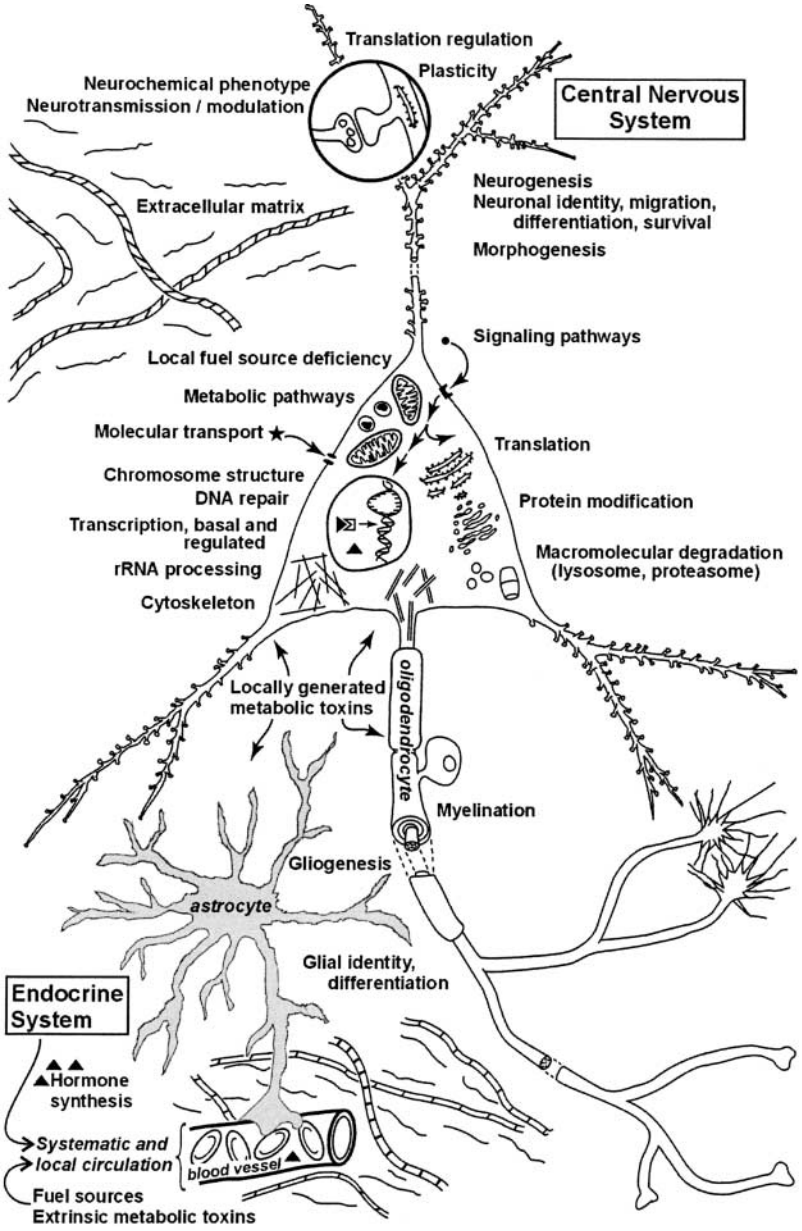

FIGURE 4.—Biological functions that underlie mental retardation. Diagram of a mammalian cortical neuron and associated structures in the central nervous system. The physiological connection to the endocrine system via the bloodstream is indicated in the bottom left. Sizes are not to scale. Solid triangles represent hormone molecules. Each of the unboxed terms, in roman type, is a biological function regulated by one or more MR genes or results from mutation of an MR gene (see APPENDIX).

independent perspectives: (i) where the genes are expressed and function and (ii) the relationship between the mutation and pathogenesis of the MR phenotype. Genes may act selectively within the brain ("intrinsic or selective function") or primarily outside the CNS ("extrinsic or generalized function"). MR may result from fundamental cellular defects that impair many tissues ("generic effect"), with the brain sometimes having a higher sensitivity, or MR can result from selective impairment of unique features of brain development or physiology ("selective effect"). With the caveat that MR pathogenesis is incompletely understood and that spatial expression data are limited, we consider examples of MR genes in these major categories.

Extrinsic or generalized function/generic effect: ABCC8 (*SUR1*) and *KCNJ11* gene products work together in the pancreas to regulate ATP-dependent, exocytotic insulin secretion. Mutations in either gene cause excess insulin release and hypoglycemia which, if inadequately treated, disrupts brain development and function due to systemic fuel deficiency (VANNUCCI and VANNUCCI 2001; HUOPIO *et al.* 2002). Similarly, the brain's energy requirements make it very sensitive to genetic disruptions of mitochondrial function (CHOW and THORBURN 2000). Mutations in mitochondrial genes (*MTATP6*, *MTCO1*, *MTCO2*, *MTCO3*, *MTCYB*, *MTTE*, *MTTK*, *MTTL1*, *MTTS1*) or in nuclear genes encoding mitochondrial proteins (*BCS1L*, *SCO2, SURF1, TIMM8A*) cause MR due to local energy (ATP) deficiency in neurons and glia (SERVIDEI 2001).

Extrinsic or generalized function/selective effect: In the endocrine system, locally synthesized hormones enter the

circulation and affect distant organs. MR genes include several tissue-specific regulators of thyroid gland development (*TTF2*, *PAX8*) or thyroid hormone synthesis (*DUOX2*, *TG*, *TPO*; Kopp 2002). Mutations in these cause congenital hypothyroidism, and mutations in a receptor (*THRB*) cause thyroid hormone resistance. In either case, brain cells cannot initiate the transcriptional cascade that controls neuronal size, migration, and dendritic morphology, as well as oligodendrocyte differentiation (Thompson and Potter 2000). Hence, neuronal circuitry and myelination are disrupted.

Many metabolic MR genes fall into this category as well. *AASS* is expressed in most tissues and encodes a key enzyme in lysine metabolism (Sacksteder *et al.* 2000). In patients lacking AASS function, lysine accumulates and inhibits arginase, causing excess circulating ammonia, which interferes with neuronal and glial functions (Felipo and Butterworth 2002). Similarly, *PAH* is expressed mainly in nonneural tissues (Lichter-Konecki *et al.* 1999), with mutations causing elevated circulating phenylalanine. This systemic toxin impairs myelination, synaptogenesis (Bauman and Kemper 1982; Huttenlocher 2000), and possibly aminergic neurotransmission (Surtees and Blau 2000). The lysosomal storage disorders, which cause macromolecules to accumulate in many tissues, may also belong to this category. Most represent degradative enzyme deficiencies, but some of the genes encode transport, stabilizer, or activator proteins (Wisniewski *et al.* 2001). They are classified by the compounds that accumulate in lysosomes, such as sphingolipidoses (*e.g.*, *ARSA*), neuronal ceroid lipofuscinoses (*e.g.*, *CLN1*), glyoproteinoses (*e.g.*, *PPGB*), and mucolipidoses (*e.g.*, *NEU1*). The traditional view that the progressive brain phenotypes result "simply" from local toxicity is countered by reports of specific neurodevelopmental defects (Walkley 1998; Altarescu *et al.* 2002).

Intrinsic function/selective effect: For genes with selective expression or function within the CNS, the consequences of mutations are also primarily CNS selective, with variation in cell-type involvement and severity (Pomeroy and Kim 2000). The coexistence of neuropathology and cognitive deficits supports the view of MR as a disorder of brain development or plasticity. At one end of the spectrum are MR disorders with gross brain malformations. Holoprosencephaly, a failure of the right and left brain halves to form distinct hemispheres, results from mutations in genes controlling cellular identity of forebrain neuronal precursors (*PTCH*, *SHH*, *SIX3*, *TDGF1*, *TGIF*, *ZIC2*; Wallis and Muenke 2000). Schizencephaly ("cleft brain") is due to dominant missense mutations in *EMX2*, which encodes a homeodomain-containing transcription factor (Faiella *et al.* 1997). Abnormal neuronal migration in the rostral forebrain (the region of *EMX2* expression) causes gross morphogenetic as well as more subtle lamination defects. Neuronal migration defects also cause lissencephaly ("smooth brain") due to mutations in *LIS1*, *DCX*, and *RELN*, as well as *ARX* (some alleles) and *FLNA* (Olson and Walsh 2002). Agenesis (partial or complete) and dysgenesis of the interhemispheric corpus callosum (Davila-Gutierrez 2002) are relatively common MR-associated phenotypes (*e.g.*, *CXORF5*, *GLI3*, *OCRL*, *SLC12A6*, *TSC1*, *TSC2*) and may be isolated or accompany holoprosencephaly and other abnormalities.

A handful of MR genes and their primary cellular phenotypes are glia specific. Dominant missense mutations in *GFAP* cause Alexander disease due to astrocytic accumulation of abnormal intermediate filaments and secondary demyelination (Johnson 2002). In contrast, *PLP1* is expressed solely in oligodendrocytes and encodes the most abundant CNS myelin protein. Myelin integrity is very sensitive to *PLP1* gene dosage, with duplications, deletions, and missense mutations all causing Pelizaeus-Merzbacher disease (Koeppen and Robitaille 2002).

At the other end of the spectrum are the many hereditary MR disorders for which routine neuropathological data are unavailable or fail to show consistent defects. Higher-resolution Golgi staining has revealed dendritic abnormalities of cortical neurons in fragile-X (*FMR1*; Irwin *et al.* 2000) and Rett syndromes (*MECP2*; Armstrong 2001) and possibly in Rubinstein-Taybi syndrome (*CREBBP*; Kaufmann and Moser 2000). All three likely result from misregulated gene expression in the brain, but which target genes are responsible for the dendritic defects remain to be determined.

For MR disorders with no known anatomical lesions, such as nonsyndromal MRX, gene function in the CNS is inferred from molecular analyses. For example, *GDI1* (MRX41, MRX48; Bienvenu *et al.* 1998) encodes a brain-specific regulator of Rab-type G proteins. One of its targets is believed to be Rab3A, which controls activity-dependent synaptic vesicle recruitment to axon terminals (Leenders *et al.* 2001). Given the structure-function relationships underlying developmental synaptic plasticity (Cohen-Cory 2002), it seems likely that neuroanatomical phenotypes for this and other MRX disorders will eventually be found.

Regardless of the scheme used, many disorders defy straightforward classification. For example, the role of homocysteine in CNS development and function (Mattson and Shea 2003) belies the "metabolic" classification of the MR genes *CBS*, *MTHFR*, *MTR*, *MTRR*, and *TC2*. The MR genes *SC5DL* and *DHCR7* encode enzymes in cholesterol biosynthesis, making them also primarily "metabolic." However, because Sonic Hedgehog protein function is absolutely dependent on covalent linkage to cholesterol (Ingham and McMahon 2001), the enzymatic deficiencies may impair SHH signaling. It may be that, with sufficient research on molecular and cellular pathogenesis, few if any MR genes will be considered "just metabolic."

TABLE 3

Human mental retardation genes: prime candidates for study in *D. melanogaster*

Human gene[a]	Human disease[b]	Mammalian brain phenotype includes:[c]	Mouse mutant/MR[d]	Drosophila ortholog			
				Gene name[e]	Gene location	Mutants	Biological function in Drosophila[f]
ARHGEF6 (1)	MRX46	Presumed to have no obvious defects	None	*rtGEF*	38C	NP	[Rho pathway; actin cytoskeleton; morphogenesis]
ASPM (2)	Primary microcephaly 5	Microcephaly	None	*abnormal spindle*	96A	Yes, N	Spindle formation; cytokinesis
ATP2A2 (3)	Darier-White disease	Unknown	Yes/?	*Calcium ATPase 60A*	60A	Yes	Protein trafficking/post-translational processing
ATRX (4)	α-Thalassemia/MR syndrome; nonspecific MR	Mild cerebral atrophy; microcephaly; ACC	None	*XNP*	96E	UP	[Transcription regulation; chromatin structure]
CREBBP (5)	Rubinstein-Taybi syndrome	ACC; decreased dendritic arborization	Yes/yes	*nejire*	9A	Yes, N	TGF-β/Wnt signaling; NMJ structure/function
DCX (6)	X-linked lissencephaly	Abnormal cortical lamination: heterotopia, pachygyria	Yes/yes	*CG17528*	41AC	None	[Microtubule cytoskeleton; neurite outgrowth]
DKC1 (7)	Dyskeratosis congenita; HHS	ACC; cerebellar hypoplasia; slow myelination	Yes/?	*Nucleolar protein 60B*	60C	Yes	rRNA processing; cell and organismal growth
DMD (8)	Duchenne/Becker m. dystrophy	Neuron loss; abnormal dendrites; astrocytosis	Yes/yes	*dystrophin*	92A	NP	[Plasma membrane-cytoskeleton linkage]
FGFR-1,-2, -3 (9)	Apert and other craniosynostosis syndromes	ACC; abnormal limbic and pyramidal tract; heterotopia	Yes/?	*breathless*	70C	Yes, N	Glial cell migration
			Yes/?	*heartless*	90E	Yes, N	Axon outgrowth, guidance, and wrapping by glia
FLNA (10)	Periventricular nodular heterotopia	Periventricular heterotopia; ACC; cerebellar hypoplasia	None	*cheerio*	89E	Yes, N	Actin filament organization; long-term memory
FMR1 (11)	Fragile X mental retardation syndrome	Abnormal dendritic spines, ?immature	Yes/yes	*dfmr1*	85F	Yes, N	Translation regulation; neuron structure/function
FOXP2 (12)	Developmental verbal dyspraxia	Abnormal frontal lobe motor areas	None	*CG16899*	85E	NP	[Transcription regulation]
GDI1 (13)	MRX41, MRX48	No obvious defects	Yes/yes	*GDI*	30B	Yes	Rab GTPase binding; growth; pupariation
GLI3 (14)	Acrocallosal syndrome; others	ACC; ↓ neural tube apoptosis; abnormal DV pattern	Yes/?	*cubitus interruptus*	102A	Yes, N	Hh pathway; transcription; neuron differentiation
GNAS (15)	Albright hereditary osteodystrophy	Cerebral calcification	Yes/?	*G protein sα60A*	60A	Yes, N	Locomotor behavior; learning; phototransduction
GPC3 (16)	Simpson-Golabi-Behmel syndrome type I	Unknown	Yes/?	*dally*	66E	Yes, N	Wnt pathway; cell cycle; neurogenesis
GPH (17)	Molybdenum cofactor deficiency type C	Cerebral atrophy; ↓ GlyR and GABA-R clustering	Yes/yes	*cinnamon*	1A	Yes	Molybdenum cofactor biosynthesis
GPI (18)	Hemolytic anemia	?Loss of neurotrophic activity	Yes/?	*pgi*	44F	Yes	Glucose metabolism; [neuronal survival]
ITGA7 (19)	Congenital myopathy	Cortical atrophy; abnormal white matter	None	*mew*	11E	Yes, N	Tissue adhesion; cell migration; axon pathfinding

(*continued*)

TABLE 3

(Continued)

Human gene[a]	Human disease[b]	Mammalian brain phenotype includes:[c]	Mouse mutant/MR[d]	Drosophila ortholog			
				Gene name[e]	Gene location	Mutants	Biological function in Drosophila[f]
JAG1 (20)	Alagille syndrome	Abnormal vessels (moyamoya) and neuronal patterning	Yes/?	*Serrate*	97E	Yes, N	Notch pathway; cell fate; neurogenesis
L1CAM (21)	MASA syndrome; HSAS; SPG1	ACC; hydrocephalus	Yes/yes	*neuroglian*	7F	Yes, N	Neuron adhesion/morphology; axon pathfinding
LAMA2 (22)	Congenital muscular dystrophy	Abnormal lamination and white matter; ↓ cerebellum	Yes/yes	*wing blister*	35A	Yes	Cell migration and adhesion
LIS1 (23)	Lissencephaly; periventricular heterotopia	↓ Cortical lamination: pachy/agyria, heterotopia	Yes/yes	*Lissencephaly-1*	52F	Yes, N	Neurogenesis; dendritogenesis; axonal transport
MID1 (24)	Opitz syndrome type I	ACC and other midline defects; cortical atrophy	None	*CG31721* (*CG6256*)	32A	NP	?Embryonic CNS development
MYO5A (25)	Elejalde syndrome	Cerebellar hypoplasia; abnormal dendritic spines	Yes/yes	*didum*	43D	UP	Embryogenesis
NF1 (26)	Neurofibromatosis	Megencephaly; abnormal white matter; glial tumors	Yes/yes	*Neurofibromin 1*	96F	Yes, N	Ras pathway; glial growth; learning/memory
NSD1 (27)	Nijmegen breakage syndrome	ACC; polygyria; dilated ventricles	None	*Mes-4*	98B	NP	[Transcription regulation]
OCRL (28)	Lowe oculocerebrorenal syndrome	ACC; abnormal white matter	Yes/no	*EG:86E4.5*	2B	NP	[Inositol phosphate pathway; ?protein sorting]
OPHN1 (29)	MRX60	Presumed to have no obvious defects	None	*Graf*	13E	NP; R; N	Axon stability
PAK3 (30)	MRX 30; MRX47	No obvious defects	None	*Pak*	83E	Yes, N	Axon pathfinding
PRSS12 (31)	Autosomal recessive nonspecific MR	Presumed to have no obvious defects	None	*Tequila*	66F	NP	[Serine protease]
PTEN (32)	Cowden syndrome; Bannayan-Zonana syndrome	Megencephaly; abnormal lamination; ↑ neuron size	Yes/yes	*Pten*	31B	Yes	Cell size and proliferation; insulin pathway
PTPN11 (33)	Noonan syndrome; LEOPARD syndrome	Unknown	Yes/?	*corkscrew*	2D	Yes, N	RTK pathways; cell fate, migration, pathfinding
RSK2 (34)	Coffin-Lowry syndrome; MRX19	ACC; dilated ventricles	Yes/yes	*S6kII*	20A	Yes, N	[Signaling pathways]; learning and memory
SHH (35)	Holoprosencephaly 3	Holoprosencephaly; ventral fate failure	Yes/yes	*hedgehog*	94E	Yes, N	Morphogen expression; patterning; neurogenesis
SIX3 (36)	Holoprosencephaly 2	Holoprosencephaly	None	*Optix*	44A	NP	Induces eye development
SOX3 (37)	MR with growth hormone deficiency	Unknown	None	*SoxNeuro*	29F	Yes, N	Cell fate; neurogenesis; axon guidance
TBCE (38)	HRD syndrome (see APPENDIX)	Unknown; ?axon degeneration	Yes/yes	*CG7861*	42A	UP	[Chaperone; tubulin folding and dimerization]

(*continued*)

TABLE 3

(Continued)

Human gene[a]	Human disease[b]	Mammalian brain phenotype includes:[c]	Mouse mutant/MR[d]	Drosophila ortholog			
				Gene name[e]	Gene location	Mutants	Biological function in Drosophila[f]
TSC2 (39)	Tuberous sclerosis 2	Cortical tubers; subcortical nodules; astrocytomas	Yes/yes	*gigas*	76F	Yes, N	Cell size; cell cycle; axon pathfinding
UBE3A (40)	Angelman syndrome	"Atrophy"; abnormal gyral pattern; ↓ dendritic arbors	Yes/yes	*CG6190*	68B	UP	[Selective protein degradation]
ZIC2 (41)	Holoprosencephaly 5	Holoprosencephaly; defective neurulation	Yes/yes	*odd paired*	82E	Yes	Tissue morphogenesis; [interacts with Hh pathway]

ACC, agenesis, dysgenesis, or hypoplasia of the corpus callosum; DV, dorsal-ventral; UP, uncharacterized *P*-element insertion in the gene; NP, nearby *P* elements; None, no mutants and no *P* elements known to be nearby; R, function assessed by double-stranded RNA interference; N, behavioral and/or neuroanatomical phenotype results from disruption by mutation or RNAi; Hh, hedgehog; NMJ, neuromuscular junction; RTK, receptor tyrosine kinase. ?, precedes phenotypes suggested but not conclusively demonstrated.

[a] See APPENDIX for alternate gene symbols. Numbers in parentheses following individual genes refer to representative references from the mammalian and Drosophila genetics literature: (1) KUTSCHE *et al.* (2000); WERNER and MANSEAU (1997); (2) BOND *et al.* (2002); WAKEFIELD *et al.* (2001); (3) JACOBSEN *et al.* (1999); PERIZ and FORTINI (1999); (4) GIBBONS and HIGGS (2000); (5) CANTANI and GAGLIESI (1998); NEWFELD and TAKAESU (2002); MAREK *et al.* (2000); (6) FRIOCOURT *et al.* (2003); (7) AKABOSHI *et al.* (2000); GIORDANO *et al.* (1999); (8) ANDERSON *et al.* (2002); GREENER and ROBERTS (2000); (9) PASSOS-BUENO *et al.* (1999); KLAMBT *et al.* (1992); GARCIA-ALONSO *et al.* (2000); SHISHIDO *et al.* (1997); (10) FOX *et al.* (1998); LI *et al.* (1999); DUBNAU *et al.* (2003); (11) IRWIN *et al.* (2000); ZHANG *et al.* (2001); DOCKENDORFF *et al.* (2002); ISHIZUKA *et al.* (2002); MORALES *et al.* (2002); C. MICHEL, R. KRAFT, B. HASSAN and L. RESTIFO (unpublished results); (12) VARGHA-KHADEM *et al.* (1998); (13) BIENVENU *et al.* (1998); RICARD *et al.* (2001); (14) ELSON *et al.* (2002); HUANG and KUNES (1998); (15) ALDRED and TREMBATH (2000); CONNOLLY *et al.* (1996); CHYB *et al.* (1999); WOLFGANG *et al.* (2001); (16) LI *et al.* (2001); NAKATO *et al.* (1995); TSUDA *et al.* (1999); (17) REISS *et al.* (2001); WITTLE *et al.* (1999); (18) LUO *et al.* (2002); KUGLER and LAKOMEK (2000); see FlyBase ID FBgn0003074; (19) BOKEL and BROWN (2002); PEGORARO *et al.* (2002); HOANG and CHIBA (1998); (20) WOOLFENDEN *et al.* (1999); KRANTZ *et al.* (1998); TSAI *et al.* (2001); GU *et al.* (1995); FLEMING *et al.* (1990); (21) WELLER and GARTNER (2001); GARCIA-ALONSO *et al.* (2000); HALL and BIEBER (1997); (22) JONES *et al.* (2001); MARTIN *et al.* (1999); (23) CARDOSO *et al.* (2002); LIU *et al.* (2000); (24) COX *et al.* (2000); BRODY *et al.* (2002); (25) SANAL *et al.* (2000); TAKAGISHI *et al.* (1996); MACIVER *et al.* (1998); (26) LYNCH and GUTMANN (2002); YAGER *et al.* (2001); GUO *et al.* (2000); (27) DOUGLAS *et al.* (2003); (28) LIN *et al.* (1998); (29) BILLUART *et al.* (1998, 2001); (30) BIENVENU *et al.* (2000); ALLEN *et al.* (1998); HING *et al.* (1999); (31) MOLINARI *et al.* (2002); (32) MARSH *et al.* (1998); LI *et al.* (2003); OLDHAM *et al.* (2002); (33) MUSANTE *et al.* (2003); PERKINS *et al.* (1996); (34) JACQUOT *et al.* (2002); G. PUTZ, T. ZARS and M. HEISENBERG (personal communication); (35) ODENT *et al.* (1999); INGHAM and MCMAHON (2001); (36) PASQUIER *et al.* (2000); SEIMIYA and GEHRING (2000); (37) LAUMONNIER *et al.* (2002); BUESCHER *et al.* (2002); OVERTON *et al.* (2002); (38) PARVARI *et al.* (2002); MARTIN *et al.* (2002); (39) MIZUGUCHI and TAKASHIMA (2001); TAPON *et al.* (2001); CANAL *et al.* (1998); (40) CLAYTON-SMITH and LAAN (2003); (41) BROWN *et al.* (2001); NAGAI *et al.* (2000); CIMBORA and SAKONJU (1995).

[b] Additional disorders may be caused by mutation of these genes; see the APPENDIX.

[c] Based on neuropathology, neurophysiology, and/or brain imaging of human patients. In some cases, data from mouse mutants were also considered.

[d] Yes/yes, mouse mutant displays a neurological or behavioral phenotype relevant to MR; yes/?, mouse mutant has not yet been characterized neurologically; yes/no, mouse mutant has no known neurological phenotype; none, no mouse mutant.

[e] The Drosophila genes with prefixes "CG" and "EG" have been identified only by genome sequencing projects (see FlyBase at http://flybase.bio.indiana.edu/ for details). See APPENDIX for BLASTP *E*-values.

[f] Biological functions in brackets are inferred from molecular data (including gene expression and biochemistry) or sequence homology to proteins of known function. All others are based on mutant phenotypes.

The role of *D. melanogaster* in MR research: In terms of primary amino acid sequence and protein-domain organization, the degree of MR gene conservation between humans and Drosophila is remarkable (Figure 1; APPENDIX). Not only individual genes but also whole pathways have been retained through ~700 million years of evolution. These include protein glycosylation (*ALG3*, *ALG6*, *B4GALT1*, *DPM1*, *FUCT1*, *GCS1*, *MGAT2*, *MPDU1*, *PMI*, *PPM2*), as well as signaling pathways, notably the Hedgehog pathway (*SHH*, *PTCH*, *PTCH2*, *GLI3*, *GPC3*) and those mediated by small G proteins (*ARHGEF6*, *GDI1*, *OPHN1*, *PAK3*, *FGD1*, *GPH*, *RSK2*, and others).

Given this remarkable conservation of MR genes, we propose that Drosophila genetics can be used in a systematic manner to study MR. We have selected 42 fly genes (the orthologs of 43 human MR genes) as "prime candidates" for such analyses (Table 3). These genes most likely act selectively within the brain during development to establish the anatomical and physiological substrates for experience-dependent plasticity. The majority of prime-candidate orthologs currently have fly mutants available (about the same fraction as have mouse mutants available) and the rest can be mutagenized through the mobilization of nearby transposable elements or studied using RNA interference methods (ADAMS and SEKELSKY 2002). About half are already known to have neural phenotypes, behavioral or anatomical, in Drosophila (Table 3 and references therein). The anatomical defects involve neurons (*e.g.*, *cubitus interruptus*), glia (*e.g.*, *Neurofibromin 1*), and neural precursor cells (*e.g.*, *division abnormally delayed*) and result from problems with proliferation (*e.g.*, *hedgehog*), migration (*e.g.*, *breathless*), and process extension or arborization (*e.g.*, *Pak*, *dfmr1*). For a few genes, neuronal defects in the mushroom bodies, an arthropod learning and memory center (ZARS 2000), have been demonstrated (*e.g.*, *Lissencephaly 1*; *Drosophila fragile-X mental retardation 1*).

How will the Drosophila developmental neurogenetics system contribute to the understanding and treatment of these challenging human disorders? First, cellular phenotypes, including those detected in primary neuronal culture (KRAFT *et al.* 1998; R. KRAFT, J. KURTIS and L. RESTIFO, unpublished results), could provide bioassays for drug testing. Second, genetic interaction studies will likely identify novel MR genes, as well as reveal the interconnected structure of MR gene pathways.

The degree to which fly mutant phenotypes "match" those of human patients remains to be seen, but it may not matter nearly as much as the genetic pathways involved, as these are likely to guide targeted drug discovery. For example, the fly ortholog of the MR gene *ATP2A2* was identified in a screen for enhancers of *Notch* (PERIZ and FORTINI 1999). The role of the Notch pathway in MR is revealed by Alagille syndrome due to mutations in *JAG1* (KRANTZ *et al.* 1998), which encodes a ligand of Notch (the Drosophila ligand is Serrate). The biological relevance of genetic interactions in human MR is well demonstrated by some of the Bardet-Biedl syndromes (*BBS2* and *BBS6*; see APPENDIX) in which clinical manifestations result from "triallelic inheritance," homozygosity at one locus and heterozygosity at another (KATSANIS *et al.* 2001). Genetic interaction tests in Drosophila could help clarify the functional relevance of the physical interaction between mammalian ZIC2 and GLI3 proteins (KOYABU *et al.* 2001).

The number of MR genes is very large, but they may be involved in a relatively small number of interconnected pathways. If so, a modest number of pharmacological treatment strategies might be effective for many MR patients. In fact, some types of acquired MR might benefit from the same drugs. Diagnoses of hereditary MR are typically made early in life at a time when developmental brain plasticity provides an opportunity for therapeutic intervention. The widespread functional conservation of MR genes in Drosophila indicates that this genetic model system could play a critical role in the discovery of novel treatment strategies for MR.

The authors thank Brian Blood for recent literature searches and BLAST analyses to update the list of human MR genes and their Drosophila homologs. The authors are grateful to colleagues David Mount for advice on bioinformatics methods, Terrill Yuhas and Nirav Merchant for computer support, Charles Hedgecock for assistance with computer graphics, and John Meaney and Robert Erickson for helpful discussions about human genetic disease. This work was funded by the National Institutes of Health (grant no. P01 NS028495).

Note added in proof: Evaluation of recently updated OMIM entries revealed three more MR genes whose molecular identifications were published prior to September 30, 2003. They are *AAAS* (OMIM 605378), *COH1* (OMIM 607817), and *MLC1* (OMIM 605908).

LITERATURE CITED

ADAMS, M. D., and J. J. SEKELSKY, 2002 From sequence to phenotype: reverse genetics in *Drosophila melanogaster*. Nat. Rev. Genet. **3:** 189–198.

ADAMS, M. D., S. E. CELNIKER, R. A. HOLT, C. A. EVANS, J. D. GOCAYNE *et al.*, 2000 The genome sequence of *Drosophila melanogaster*. Science **287:** 2185–2195.

AICARDI, J., 1998 The etiology of developmental delay. Semin. Pediatr. Neurol. **5:** 15–20.

AKABOSHI, S., M. YOSHIMURA, T. HARA, H. KAGEYAMA, K. NISHIKWA *et al.*, 2000 A case of Hoyeraal-Hreidarsson syndrome: delayed myelination and hypoplasia of corpus callosum are other important signs. Neuropediatrics **31:** 141–144.

ALDRED, M. A., and R. C. TREMBATH, 2000 Activating and inactivating mutations in the human *GNAS1* gene. Hum. Mutat. **16:** 183–189.

ALLEN, K. M., J. G. GLEESON, S. BAGRODIA, M. W. PARTINGTON, J. C. MACMILLAN *et al.*, 1998 *PAK3* mutation in nonsyndromic X-linked mental retardation. Nat. Genet. **20:** 25–30.

ALTARESCU, G., M. SUN, D. F. MOORE, J. A. SMITH, E. A. WIGGS *et al.*, 2002 The neurogenetics of mucolipidosis type IV. Neurology **59:** 306–313.

ALTSCHUL, S. F., T. L. MADDEN, A. A. SCHAFFER, J. ZHANG, Z. ZHANG *et al.*, 1997 Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. Nucleic Acids Res. **25:** 3389–3402.

ANDERSON, J. L., S. I. HEAD, C. RAE and J. W. MORLEY, 2002 Brain function in Duchenne muscular dystrophy. Brain **125:** 4–13.

Apweiler, R., T. K. Attwood, A. Bairoch, A. Bateman, E. Birney *et al.*, 2001 The InterPro database, an integrated documentation resource for protein families, domains and functional sites. Nucleic Acids Res. **29:** 37–40.

Armstrong, D. D., 2001 Rett syndrome neuropathology review 2000. Brain Dev. **23** (Suppl. 1): S72–S76.

Bat-haee, M. A., 2001 A longitudinal study of active treatment of adaptive skills of individuals with profound mental retardation. Psychol. Rep. **89:** 345–354.

Bauman, M. L., and T. L. Kemper, 1982 Morphologic and histoanatomic observations of the brain in untreated human phenylketonuria. Acta Neuropathol. **58:** 55–63.

Bienvenu, T., V. des Portes, A. Saint Martin, N. McDonell, P. Billuart *et al.* 1998 Non-specific X-linked semidominant mental retardation by mutations in a Rab GDP-dissociation inhibitor. Hum. Mol. Genet. **7:** 1311–1315.

Bienvenu, T., V. des Portes, N. McDonell, A. Carrie, R. Zemni, *et al.* 2000 Missense mutation in *PAK3*, R67C, causes X-linked nonspecific mental retardation. Am. J. Med. Genet. **93:** 294–298.

Billuart, P., T. Bienvenu, N. Ronce, V. des Portes, M. C. Vinet, *et al.* 1998 *Oligophrenin-1* encodes a rhoGAP protein involved in X-linked mental retardation. Nature **392:** 923–926.

Billuart, P., C. G. Winter, A. Maresh, X. Zhao and L. Luo, 2001 Regulating axon branch stability: the role of p190 RhoGAP in repressing a retraction signaling pathway. Cell **107:** 195–207.

Boda, B., C. Mas and D. Muller, 2002 Activity-dependent regulation of genes implicated in X-linked non-specific mental retardation. Neuroscience **114:** 13–17.

Bokel, C., and N. H. Brown, 2002 Integrins in development: moving on, responding to, and sticking to the extracellular matrix. Dev. Cell **3:** 311–321.

Bond, J., E. Roberts, G. H. Mochida, D. J. Hampshire, S. Scott *et al.*, 2002 *ASPM* is a major determinant of cerebral cortical size. Nat. Genet. **32:** 316–320.

Bonini, N. M., Q. T. Bui, G. L. Gray-Board and J. M. Warrick, 1997 The Drosophila *eyes absent* gene directs ectopic eye formation in a pathway conserved between flies and vertebrates. Development **124:** 4819–4826.

Boyadjiev, S. A., and E. W. Jabs, 2000 Online Mendelian Inheritance in Man (OMIM) as a knowledge base for human developmental disorders. Clin. Genet. **57:** 253–266.

Brody, T., C. Stivers, J. Nagle and W. F. Odenwald, 2002 Identification of novel Drosophila neural precursor genes using a differential embryonic head cDNA screen. Mech. Dev. **113:** 41–59.

Brown, L. Y., S. Odent, V. David, M. Blayau, C. Dubourg *et al.*, 2001 Holoprosencephaly due to mutations in *ZIC2*: alanine tract expansion mutations may be caused by parental somatic recombination. Hum. Mol. Genet. **10:** 791–796.

Buescher, M., F. S. Hing and W. Chia, 2002 Formation of neuroblasts in the embryonic central nervous system of *Drosophila melanogaster* is controlled by *SoxNeuro*. Development **129:** 4193–4203.

Butler, F. M., S. P. Miller, K. H. Lee and T. Pierce, 2001 Teaching mathematics to students with mild-to-moderate mental retardation: a review of the literature. Ment. Retard. **39:** 20–31.

Canal, I., A. Acebes and A. Ferrus, 1998 Single neuron mosaics of the Drosophila *gigas* mutant project beyond normal targets and modify behavior. J. Neurosci. **18:** 999–1008.

Cantani, A., and D. Gagliesi, 1998 Rubinstein-Taybi syndrome. Review of 732 cases and analysis of the typical traits. Eur. Rev. Med. Pharmacol. Sci. **2:** 81–87.

Cardoso, C., R. J. Leventer, J. J. Dowling, H. L. Ward, J. Chung *et al.*, 2002 Clinical and molecular basis of classical lissencephaly: mutations in the *LIS1* gene (*PAFAH1B1*). Hum. Mutat. **19:** 4–15.

Cheadle, J. P., H. Gill, N. Fleming, J. Maynard, A. Kerr *et al.*, 2000 Long-read sequence analysis of the *MECP2* gene in Rett syndrome patients: correlation of disease severity with mutation type and location. Hum. Mol. Genet. **9:** 1119–1129.

Chelly, J., 1999 Breakthroughs in molecular and cellular mechanisms underlying X-linked mental retardation. Hum. Mol. Genet. **8:** 1833–1838.

Chiurazzi, P., B. C. Hamel and G. Neri, 2001 XLMR genes: update 2000. Eur. J. Hum. Genet. **9:** 71–81.

Chow, C. W., and D. R. Thorburn, 2000 Morphological correlates of mitochondrial dysfunction in children. Hum. Reprod. **15** (Suppl. 2): 68–78.

Chyb, S., W. Hevers, M. Forte, W. J. Wolfgang, Z. Selinger *et al.*, 1999 Modulation of the light response by cAMP in Drosophila photoreceptors. J. Neurosci. **19:** 8799–8807.

Cimbora, D. M., and S. Sakonju, 1995 Drosophila midgut morphogenesis requires the function of the segmentation gene *odd-paired*. Dev. Biol. **169:** 580–595.

Clayton-Smith, J., and L. Laan, 2003 Angelman syndrome: a review of the clinical and genetic aspects. J. Med. Genet. **40:** 87–95.

Cohen-Cory, S., 2002 The developing synapse: construction and modulation of synaptic structures and circuits. Science **298:** 770–776.

Connolly, J. B., I. J. Roberts, J. D. Armstrong, K. Kaiser, M. Forte *et al.*, 1996 Associative learning disrupted by impaired Gs signaling in Drosophila mushroom bodies. Science **274:** 2104–2107.

Couvert, P., T. Bienvenu, C. Aquaviva, K. Poirier, C. Moraine *et al.*, 2001 *MECP2* is highly mutated in X-linked mental retardation. Hum. Mol. Genet. **10:** 941–946.

Cox, T. C., L. R. Allen, L. L. Cox, B. Hopwood, B. Goodwin *et al.*, 2000 New mutations in *MID1* provide support for loss of function as the cause of X-linked Opitz syndrome. Hum. Mol. Genet. **9:** 2553–2562.

Daily, D. K., H. H. Ardinger and G. E. Holmes, 2000 Identification and evaluation of mental retardation. Am. Fam. Physician **61:** 1059–1067.

Dashman, T., and C. Sansaricq, 1993 Nutrition in the management of inborn errors of metabolism. Clin. Lab. Med. **13:** 407–432.

Davila-Gutierrez, G., 2002 Agenesis and dysgenesis of the corpus callosum. Semin. Pediatr. Neurol. **9:** 292–301.

Dearborn, R., Q. He, S. Kunes and Y. Dai, 2002 Eph receptor tyrosine kinase-mediated formation of a topographic map in the Drosophila visual system. J. Neurosci. **22:** 1338–1349.

Dockendorff, T. C., H. S. Su, S. M. McBride, Z. Yang, C. H. Choi *et al.*, 2002 Drosophila lacking dfmr1 activity show defects in circadian output and fail to maintain courtship interest. Neuron **34:** 973–984.

Dosen, A., and K. Day (Editors), 2001 *Treating Mental Illness and Behavior Disorders in Children and Adults with Mental Retardation*. American Psychiatric Press, Washington, DC.

Douglas, J., S. Hanks, I. K. Temple, S. Davies, A. Murray *et al.*, 2003 *NSD1* mutations are the major cause of Sotos syndrome and occur in some cases of Weaver syndrome but are rare in other overgrowth phenotypes. Am. J. Hum. Genet. **72:** 132–143.

Dubnau, J., and T. Tully, 1998 Gene discovery in Drosophila: new insights for learning and memory. Annu. Rev. Neurosci. **21:** 407–444.

Dubnau, J., A. S. Chiang, L. Grady, H. Barditch, S. Gossweiler *et al.*, 2003 The staufen/pumilio pathway is involved in Drosophila long-term memory. Curr. Biol. **13:** 286–296.

Durand, D., 2003 Vertebrate evolution: doubling and shuffling with a full deck. Trends Genet. **19:** 2–5.

Elson, E., R. Perveen, D. Donnai, S. Wall and G. C. M. Black, 2002 De novo *GLI3* mutation in acrocallosal syndrome: broadening the phenotypic spectrum of *GLI3* defects and overlap with murine models. J. Med. Genet. **39:** 804–806.

Eng, L. F., R. S. Ghirnikar and Y. L. Lee, 2000 Glial fibrillary acidic protein: GFAP-thirty-one years (1969–2000). Neurochem. Res. **25:** 1439–1451.

Faiella, A., S. Brunelli, T. Granata, L. D'Incerti, R. Cardini *et al.*, 1997 A number of schizencephaly patients including two brothers are heterozygous for germline mutations in the homeobox gene *EMX2*. Eur. J. Hum. Genet. **5:** 186–190.

Feany, M. B., and W. W. Bender, 2000 A Drosophila model of Parkinson's disease. Nature **404:** 394–398.

Feinstein, A., J. Friedman and M. Schewach-Millet, 1988 Pachyonychia congenita. J. Am. Acad. Dermatol. **19:** 705–711.

Felipo, V., and R. F. Butterworth, 2002 Neurobiology of ammonia. Prog. Neurobiol. **67:** 259–279.

Fleming, R. J., T. N. Scottgale, R. J. Diederich and S. Artavanis-Tsakonas, 1990 The gene *Serrate* encodes a putative EGF-like transmembrane protein essential for proper ectodermal development in *Drosophila melanogaster*. Genes Dev. **4:** 2188–2201.

FlyBase Consortium, 2002 The FlyBase database of the Drosophila genome projects and community literature. Nucleic Acids Res. **30:** 106–108.

Fortini, M. E., M. P. Skupski, M. S. Boguski and I. K. Hariharan,

2000 A survey of human disease gene counterparts in the Drosophila genome. J. Cell Biol. **150:** F23–F30.

Fox, J. W., E. D. Lamperti, Y. Z. Eksioglu, S. E. Hong, Y. Feng *et al.*, 1998 Mutations in *filamin 1* prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron **21:** 1315–1325.

Frints, S., G. Froyen, P. Marynen and J. P. Fryns, 2002 X-linked mental retardation: vanishing boundaries between non-specific (MRX) and syndromic (MRXS) forms. Clin. Genet. **62:** 423–432.

Friocourt, G., A. Koulakoff, P. Chafey, D. Boucher, F. Fauchereau *et al.*, 2003 Doublecortin functions at the extremities of growing neuronal processes. Cereb. Cortex **13:** 620–626.

Garcia-Alonso, L., S. Romani and F. Jimenez, 2000 The EGF and FGF receptors mediate neuroglian function to control growth cone decisions during sensory axon guidance in Drosophila. Neuron **28:** 741–752.

Gene Ontology Consortium, 2001 Creating the gene ontology resource: design and implementation. Genome Res. **11:** 1425–1433.

Gibbons, R. J., and D. R. Higgs, 2000 Molecular-clinical spectrum of the ATR-X syndrome. Am. J. Med. Genet. **97:** 204–212.

Gibbons, R. J., D. J. Picketts, L. Villard and D. R. Higgs, 1995 Mutations in a putative global transcriptional regulator cause X-linked mental retardation with alpha-thalassemia (ATR-X syndrome). Cell **80:** 837–845.

Gilmore, E. C., R. S. Nowakowski, V. S. Caviness and K. Herrup, 2000 Cell birth, cell death, cell diversity and DNA breaks: How do they all fit together? Trends Neurosci. **23:** 100–105.

Giordano, E., I. Peluso, S. Senger and M. Furia, 1999 *minifly*, a Drosophila gene required for ribosome biogenesis. J. Cell Biol. **144:** 1123–1133.

Goldman, R. D., Y. Gruenbaum, R. D. Moir, D. K. Shumaker and T. P. Spann, 2002 Nuclear lamins: building blocks of nuclear architecture. Genes Dev. **16:** 533–547.

Greener, M. J., and R. G. Roberts, 2000 Conservation of components of the dystrophin complex in Drosophila. FEBS Lett. **482:** 13–18.

Gruters, A., A. Jenner and H. Krude, 2002 Long-term consequences of congenital hypothyroidism in the era of screening programmes. Best Pract. Res. Clin. Endocrinol. Metab. **16:** 369–382.

Gu, Y., N. A. Hukriede and R. J. Fleming, 1995 *Serrate* expression can functionally replace *Delta* activity during neuroblast segregation in the Drosophila embryo. Development **121:** 855–865.

Guo, H. F., J. Tong, F. Hannan, L. Luo and Y. Zhong, 2000 A neurofibromatosis-1-regulated pathway is required for learning in Drosophila. Nature **403:** 895–898.

Hall, S. G., and A. J. Bieber, 1997 Mutations in the Drosophila *neuroglian* cell adhesion molecule affect motor neuron pathfinding and peripheral nervous system patterning. J. Neurobiol. **32:** 325–340.

Hammer, S., N. Dorrani, J. Dragich, S. Kudo and C. Schanen, 2002 The phenotypic consequences of *MECP2* mutations extend beyond Rett syndrome. Ment. Retard. Dev. Disabil. Res. Rev. **8:** 94–98.

Hamosh, A., A. F. Scott, J. Amberger, C. Bocchini, D. Valle *et al.*, 2002 Online Mendelian Inheritance in Man (OMIM), a knowledge base of human genes and genetic disorders. Nucleic Acids Res. **30:** 52–55.

Hanauer, A., and I. D. Young, 2002 Coffin-Lowry syndrome: clinical and molecular features. J. Med. Genet. **39:** 705–713.

Hing, H., J. Xiao, N. Harden, L. Lim and S. L. Zipursky, 1999 Pak functions downstream of Dock to regulate photoreceptor axon guidance in Drosophila. Cell **97:** 853–863.

Hoang, B., and A. Chiba, 1998 Genetic analysis on the role of integrin during axon guidance in Drosophila. J. Neurosci. **18:** 7847–7855.

Huang, X., and W. Miller, 1991 A time-efficient, linear-space local similarity algorithm. Adv. Appl. Math. **12:** 337–357.

Huang, Z., and S. Kunes, 1998 Signals transmitted along retinal axons in Drosophila: hedgehog signal reception and the cell circuitry of lamina cartridge assembly. Development **125:** 3753–3764.

Huopio, H., S.-L. Shyng, T. Otonkoski and C. G. Nichols, 2002 K_{ATP} channels and insulin secretion disorders. Am. J. Physiol. Endocrinol. Metab. **283:** E207–E216.

Huttenlocher, P. R., 2000 The neuropathology of phenylketonuria: human and animal studies. Eur. J. Pediatr. **159** (Suppl. 2): S102–S106.

Ingham, P. W., and A. P. McMahon, 2001 Hedgehog signaling in animal development: paradigms and principles. Genes Dev. **15:** 3059–3087.

Inoue, S. B., M. Shimoda, I. Nishinokubi, M. C. Siomi, M. Okamura *et al.*, 2002 A role for the Drosophila fragile X-related gene in circadian output. Curr. Biol. **12:** 1331–1335.

Irwin, S. A., R. Galvez and W. T. Greenough, 2000 Dendritic spine structural anomalies in fragile-X mental retardation syndrome. Cereb. Cortex **10:** 1038–1044.

Ishizuka, A., M. C. Siomi and H. Siomi, 2002 A Drosophila fragile X protein interacts with components of RNAi and ribosomal proteins. Genes Dev. **16:** 2497–2508.

Jackson, G. R., I. Salecker, X. Dong, X. Yao, N. Arnheim *et al.*, 1998 Polyglutamine-expanded human *huntingtin* transgenes induce degeneration of Drosophila photoreceptor neurons. Neuron **21:** 633–642.

Jacobsen, N. J. O., I. Lyons, B. Hoogendoorn, S. Burge, P.-Y. Kwok *et al.*, 1999 *ATP2A2* mutations in Darier's disease and their relationship to neuropsychiatric phenotypes. Hum. Mol. Genet. **8:** 1631–1636.

Jacquot, S., M. Zeniou, R. Touraine and A. Hanauer, 2002 X-linked Coffin-Lowry syndrome (CLS, MIM 303600, *RPS6KA3* gene, protein product known under various names: $pp90^{rsk2}$, RSK2, ISPK, MAPKAP1). Eur. J. Hum. Genet. **10:** 2–5.

Jin, P., and S. T. Warren, 2003 New insights into fragile X syndrome: from molecules to neurobehaviors. Trends Biochem. Sci. **28:** 152–158.

Johnson, A., 2002 Alexander disease: a review and the gene. Int. J. Dev. Neurosci. **20:** 391–394.

Johnston, S. H., C. Rauskolb, R. Wilson, B. Prabhakaran, K. D. Irvine *et al.*, 1997 A family of mammalian *Fringe* genes implicated in boundary determination and the Notch pathway. Development **124:** 2245–2254.

Jones, K. J., G. Morgan, H. Johnston, V. Tobias, R. A. Ouvrier *et al.*, 2001 The expanding phenotype of laminin α2 chain (merosin) abnormalities: case series and review. J. Med. Genet. **38:** 649–657.

Kabra, M., and S. Gulati, 2003 Mental retardation. Indian J. Pediatr. **70:** 153–158.

Kahler, S. G., and M. C. Fahey, 2003 Metabolic disorders and mental retardation. Am. J. Med. Genet. **117C:** 31–41.

Katsanis, N., S. J. Ansley, J. L. Badano, E. R. Eichers, R. A. Lewis *et al.*, 2001 Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. Science **293:** 2256–2259.

Kaufmann, W. E., and H. W. Moser, 2000 Dendritic anomalies in disorders associated with mental retardation. Cereb. Cortex **10:** 981–991.

Kaytor, M. D., and H. T. Orr, 2001 RNA targets of the fragile X protein. Cell **107:** 555–557.

Kazantsev, A., H. A. Walker, N. Slepko, J. E. Bear, E. Preisinger *et al.*, 2002 A bivalent Huntingtin binding peptide suppresses polyglutamine aggregation and pathogenesis in Drosophila. Nat. Genet. **30:** 367–376.

Kinsbourne, M., and W. D. Graf, 2000 Disorders of mental development, pp. 1155–1211 in *Child Neurology*, edited by J. H. Menkes and H. B. Sarnat. Lippincott Williams & Wilkins, Philadelphia.

Kitamura, K., M. Yanazawa, N. Sugiyama, H. Miura, A. Iizuka-Kogo *et al.*, 2002 Mutation of *ARX* causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. Nat. Genet. **32:** 359–369.

Klambt, C., L. Glazer and B. Z. Shilo, 1992 breathless, a Drosophila FGF receptor homolog, is essential for migration of tracheal and specific midline glial cells. Genes Dev. **6:** 1668–1678.

Koeppen, A. H., and Y. Robitaille, 2002 Pelizaeus-Merzbacher disease. J. Neuropathol. Exp. Neurol. **61:** 747–759.

Kopp, P., 2002 Perspective: genetic defects in the etiology of congenital hypothyroidism. Endocrinology **143:** 2019–2024.

Koyabu, Y., K. Nakata, K. Mizugishi, J. Aruga and K. Mikoshiba, 2001 Physical and functional interaction between Zic and Gli proteins. J. Biol. Chem. **276:** 6889–6892.

Kraft, R., R. B. Levine and L. L. Restifo, 1998 The steroid hormone 20-hydroxyecdysone enhances neurite growth of Drosophila mushroom body neurons isolated during metamorphosis. J. Neurosci. **18:** 8886–8899.

Krantz, I. D., R. P. Colliton, A. Genin, E. B. Rand, L. Li *et al.*, 1998 Spectrum and frequency of *jagged1* (*JAG1*) mutations in Alagille syndrome patients and their families. Am. J. Hum. Genet. **62:** 1361–1369.

Kugler, W., and M. Lakomek, 2000 Glucose-6-phosphate isomerase deficiency. Bailliere's Best Pract. Res. Clin. Haematol. **13:** 89–101.

Kutsche, K., H. Yntema, A. Brandt, I. Jantke, H. G. Nothwang *et al.*, 2000 Mutations in *ARHGEF6*, encoding a guanine nucleotide exchange factor for Rho GTPases, in patients with X-linked mental retardation. Nat. Genet. **26:** 247–250.

Laggerbauer, B., D. Ostareck, E.-M. Keidel, A. Ostareck-Lederer and U. Fischer, 2001 Evidence that fragile X mental retardation protein is a negative regulator of translation. Hum. Mol. Genet. **10:** 329–338.

Laumonnier, F., N. Ronce, B. C. Hamel, P. D. Thomas, J. Lespinasse *et al.*, 2002 Transcription factor *SOX3* is involved in X-linked mental retardation with growth hormone deficiency. Am. J. Hum. Genet. **71:** 1450–1455.

Lebel, R. R., M. May, S. Pouls, H. A. Lubs, R. E. Stevenson *et al.*, 2002 Non-syndromic X-linked mental retardation associated with a missense mutation (P312L) in the *FGD1* gene. Clin. Genet. **61:** 139–145.

Lee, A., L. Wenjun, K. Xu, B. A. Bogert, K. Su *et al.*, 2003 Control of dendritic development by the *Drosophila fragile X-related* gene involves the small GTPase Rac1. Development **130:** 5543–5552.

Leenders, A. G., F. H. Lopes da Silva, W. E. Ghijsen and M. Verhage, 2001 Rab3a is involved in transport of synaptic vesicles to the active zone in mouse brain nerve terminals. Mol. Biol. Cell **12:** 3095–3102.

Lehrke, R., 1972 Theory of X-linkage of major intellectual traits. Am. J. Ment. Defic. **76:** 611–619.

Leonard, H., and X. Wen, 2002 The epidemiology of mental retardation: challenges and opportunities in the new millennium. Ment. Retard. Dev. Disabil. Res. Rev. **8:** 117–134.

Leuzinger, S., F. Hirth, D. Gerlich, D. Acampora, A. Simeone *et al.*, 1998 Equivalence of the fly *orthodenticle* gene and the human *OTX* genes in embryonic brain development of Drosophila. Development **125:** 1703–1710.

Levy, H. L., 1999 Phenylketonuria: old disease, new approach to treatment. Proc. Natl. Acad. Sci. USA **96:** 1811–1813.

Li, L., F. Liu and A. H. Ross, 2003 PTEN regulation of neural development and CNS stem cells. J. Cell. Biochem. **88:** 24–28.

Li, M., M. Serr, K. Edwards, S. Ludmann, D. Yamamoto *et al.*, 1999 Filamin is required for ring canal assembly and actin organization during Drosophila oogenesis. J. Cell Biol. **146:** 1061–1073.

Li, M., C. Shuman, Y. L. Fei, E. Cutiongco, H. A. Bender *et al.*, 2001 *GPC3* mutation analysis in a spectrum of patients with overgrowth expands the phenotype of Simpson-Golabi-Behmel syndrome. Am. J. Med. Genet. **102:** 161–168.

Lichter-Konecki, U., C. M. Hipke and D. S. Konecki, 1999 Human phenylalanine hydroxylase gene expression in kidney and other nonhepatic tissues. Mol. Genet. Metab. **67:** 308–316.

Lin, T., B. M. Orrison, S. F. Suchy, R. A. Lewis and R. L. Nussbaum, 1998 Mutations are not uniformly distributed throughout the *OCRL1* gene in Lowe syndrome patients. Mol. Genet. Metab. **64:** 58–61.

Liu, Z., R. Steward and L. Luo, 2000 Drosophila Lis1 is required for neuroblast proliferation, dendritic elaboration and axonal transport. Nat.. Cell Biol. **2:** 776–783.

Lloyd, T. E., P. Verstreken, E. J. Ostrin, A. Phillippi, O. Lichtarge *et al.*, 2000 A genome-wide search for synaptic vesicle cycle proteins in Drosophila. Neuron **26:** 45–50.

Long, E. S., and R. G. Miltenberger, 1998 A review of behavioral and pharmacological treatments for habit disorders in individuals with mental retardation. J. Behav. Ther. Exp. Psychiatry **29:** 143–156.

Lubs, H. A., 1999 The other side of the coin: a hypothesis concerning the importance of genes for high intelligence and evolution on the X chromosome. Am. J. Med. Genet. **85:** 206–208.

Luckasson, R., D. L. Coulter, E. A. Polloway, S. Reiss, R. L. Schalock *et al.*, 1992 *Mental Retardation: Definition, Classification, and Systems of Support.* American Association on Mental Retardation, Washington, DC.

Luo, Y., J. M. Long, C. Lu, S. L. Chan, E. L. Spangler *et al.*, 2002 A link between maze learning and hippocampal expression of neuroleukin and its receptor gp78. J. Neurochem. **80:** 354–361.

Lynch, T. M., and D. H. Gutmann, 2002 Neurofibromatosis 1. Neurol. Clin. **20:** 841–865.

Ma, K., K. M. Vattem and R. C. Wek, 2002 Dimerization and release of molecular chaperone inhibition facilitate activation of eukaryotic initiation factor-2 kinase in response to endoplasmic reticulum stress. J. Biol. Chem. **277:** 18728–18735.

MacIver, B., A. McCormack, R. Slee and M. Bownes, 1998 Identification of an essential gene encoding a class-V unconventional myosin in *Drosophila melanogaster*. Eur. J. Biochem. **257:** 529–537.

Maizel, J. V., Jr., and R. P. Lenk, 1981 Enhanced graphic matrix analysis of nucleic acid and protein sequences. Proc. Natl. Acad. Sci. USA **78:** 7665–7669.

Marek, K. W., N. Ng, R. Fetter, S. Smolik, C. S. Goodman *et al.*, 2000 A genetic analysis of synaptic development: pre- and postsynaptic dCBP control transmitter release at the Drosophila NMJ. Neuron **25:** 537–547.

Marsh, D. J., V. Coulon, K. L. Lunetta, P. Rocca-Serra, P. L. Dahia *et al.*, 1998 Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline *PTEN* mutation. Hum. Mol. Genet. **7:** 507–515.

Martin, D., S. Zusman, X. Li, E. L. Williams, N. Khare *et al.*, 1999 wing blister, a new Drosophila laminin alpha chain required for cell adhesion and migration during embryonic and imaginal development. J. Cell Biol. **145:** 191–201.

Martin, N., J. Jaubert, P. Gounon, E. Salido, G. Haase *et al.*, 2002 A missense mutation in *Tbce* causes progressive motor neuropathy in mice. Nat. Genet. **32:** 443–447.

Mattson, M. P., and T. B. Shea, 2003 Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends Neurosci. **26:** 137–146.

Mazroui, R., M. E. Huot, S. Tremblay, C. Filion, Y. Labelle *et al.*, 2002 Trapping of messenger RNA by fragile X mental retardation protein into cytoplasmic granules induces translational repression. Hum. Mol. Genet. **11:** 3007–3017.

McLaren, J., and S. E. Bryson, 1987 Review of recent epidemiological studies of mental retardation: prevalence, associated disorders and etiology. Am. J. Ment. Retard. **92:** 243–254.

Merienne, K., S. Jacquot, S. Pannetier, M. Zeniou, A. Bankier *et al.*, 1999 A missense mutation in *RPS6KA3* (*RSK2*) responsible for non-specific mental retardation. Nat. Genet. **22:** 13–14.

Ming, J. E., E. Roessler and M. Muenke, 1998 Human developmental disorders and the Sonic hedgehog pathway. Mol. Med. Today **4:** 343–349.

Mizuguchi, M., and S. Takashima, 2001 Neuropathology of tuberous sclerosis. Brain Dev. **23:** 508–515.

Molinari, F., M. Rio, V. Meskenaite, F. Encha-Razavi, J. Auge *et al.*, 2002 Truncating *neurotrypsin* mutation in autosomal recessive nonsyndromic mental retardation. Science **298:** 1779–1781.

Morales, J., P. R. Hiesinger, A. J. Schroeder, K. Kume, P. Verstreken *et al.*, 2002 Drosophila fragile X protein, DFXR, regulates neuronal morphology and function in the brain. Neuron **34:** 961–972.

Morley, K. I., and G. W. Montgomery, 2001 The genetics of cognitive processes: candidate genes in humans and animals. Behav. Genet. **31:** 511–531.

Morton, N. E., 1992 Genes for intelligence on the X chromosome. J. Med. Genet. **29:** 71.

Musante, L., H. G. Kehl, F. Majewski, P. Meinecke, S. Schweiger *et al.*, 2003 Spectrum of mutations in *PTPN11* and genotype-phenotype correlation in 96 patients with Noonan syndrome and five patients with cardio-facio-cutaneous syndrome. Eur. J. Hum. Genet. **11:** 201–206.

Nagai, T., J. Aruga, O. Minowa, T. Sugimoto, Y. Ohno *et al.*, 2000 *Zic2* regulates the kinetics of neurulation. Proc. Natl. Acad. Sci. USA **97:** 1618–1623.

Nagao, T., S. Leuzinger, D. Acampora, A. Simeone, R. Finkelstein *et al.*, 1998 Developmental rescue of Drosophila cephalic defects by the human *Otx* genes. Proc. Natl. Acad. Sci. USA **95:** 3737–3742.

Nakato, H., T. A. Futch and S. B. Selleck, 1995 The *division abnormally delayed* (*dally*) gene: a putative integral membrane proteoglycan required for cell division patterning during postembryonic development of the nervous system in Drosophila. Development **121:** 3687–3702.

Newfeld, S. J., and N. T. Takaesu, 2002 An analysis using the *hobo* genetic system reveals that combinatorial signaling by the Dpp

and Wg pathways regulates dpp expression in leading edge cells of the dorsal ectoderm in *Drosophila melanogaster*. Genetics **161:** 685–692.

Odent, S., T. Attie-Bitach, M. Blayau, M. Mathieu, J. Auge *et al.*, 1999 Expression of the *Sonic hedgehog* (*SHH*) gene during early human development and phenotypic expression of new mutations causing holoprosencephaly. Hum. Mol. Genet. **8:** 1683–1689.

Oldham, S., H. Stocker, M. Laffargue, F. Wittwer, M. Wymann *et al.*, 2002 The Drosophila insulin/IGF receptor controls growth and size by modulating PtdInsP(3) levels. Development **129:** 4103–4109.

Olson, E. C., and C. A. Walsh, 2002 Smooth, rough and upside-down neocortical development. Curr. Opin. Genet. Dev. **12:** 320–327.

Orrico, A., C. Lam, L. Galli, M. T. Dotti, G. Hayek *et al.*, 2000 *MECP2* mutation in male patients with non-specific X-linked mental retardation. FEBS Lett. **481:** 285–288.

Overton, P. M., L. A. Meadows, J. Urban and S. Russell, 2002 Evidence for differential and redundant function of the Sox genes *Dichaete* and *SoxN* during CNS development in Drosophila. Development **129:** 4219–4228.

Padgett, R. W., J. M. Wozney and W. M. Gelbart, 1993 Human BMP sequences can confer normal dorsal-ventral patterning in the Drosophila embryo. Proc. Natl. Acad. Sci. USA **90:** 2905–2909.

Parvari, R., E. Hershkovitz, N. Grossman, R. Gorodischer, B. Loeys *et al.*, 2002 Mutation of *TBCE* causes hypoparathyroidism-retardation-dysmorphism and autosomal recessive Kenny-Caffey syndrome. Nat. Genet. **32:** 448–452.

Pasquier, L., C. Dubourg, M. Blayau, L. Lazaro, B. Le Marec *et al.*, 2000 A new mutation in the six-domain of *SIX3* gene causes holoprosencephaly. Eur. J. Hum. Genet. **8:** 797–800.

Passos-Bueno, M. R., W. R. Wilcox, E. W. Jabs, A. L. Sertie, L. G. Alonso *et al.*, 1999 Clinical spectrum of fibroblast growth factor receptor mutations. Hum. Mutat. **14:** 115–125.

Payne, J. A., C. Rivera, J. Voipio and K. Kaila, 2003 Cation-chloride co-transporters in neuronal communication, development and trauma. Trends Neurosci. **26:** 199–206.

Pegoraro, E., F. Cepollaro, P. Prandini, A. Marin, M. Fanin *et al.*, 2002 Integrin alpha 7 beta 1 in muscular dystrophy/myopathy of unknown etiology. Am. J. Pathol. **160:** 2135–2143.

Periz, G., and M. E. Fortini, 1999 Ca^{2+}-ATPase function is required for intracellular trafficking of the Notch receptor in Drosophila. EMBO J. **18:** 5983–5993.

Perkins, L. A., M. R. Johnson, M. B. Melnick and N. Perrimon, 1996 The nonreceptor protein tyrosine phosphatase corkscrew functions in multiple receptor tyrosine kinase pathways in Drosophila. Dev. Biol. **180:** 63–81.

Pinto, S., D. G. Quintana, P. Smith, R. M. Mihalek, Z. H. Hou *et al.*, 1999 *latheo* encodes a subunit of the origin recognition complex and disrupts neuronal proliferation and adult olfactory memory when mutant. Neuron **23:** 45–54.

Pomeroy, S. L., and J. Y. H. Kim, 2000 Biology and pathobiology of neuronal development. Ment. Retard. Dev. Disabil. Res. Rev. **6:** 41–46.

Ramakers, G. J., 2002 Rho proteins, mental retardation and the cellular basis of cognition. Trends Neurosci. **25:** 191–199.

Reiss, J., S. Gross-Hardt, E. Christensen, P. Schmidt, R. R. Mendel *et al.*, 2001 A mutation in the gene for the neurotransmitter receptor-clustering protein gephyrin causes a novel form of molybdenum cofactor deficiency. Am. J. Hum. Genet. **68:** 208–213.

Reiter, L.T ., L. Potocki, S. Chien, M. Gribskov and E. Bier, 2001 A systematic analysis of human disease-associated gene sequences in Drosophila melanogaster. Genome Res. **11:** 1114–1125.

Ricard, C. S., J. M. Jakubowski, J. W. Verbsky, M. A. Barbieri, W. M. Lewis *et al.*, 2001 Drosophila rab GDI mutants disrupt development but have normal rab membrane extraction. Genesis **31:** 17–29.

Roeleveld, N., G. A. Zielhuis and F. Gabreels, 1997 The prevalence of mental retardation: a critical review of recent literature. Dev. Med. Child Neurol. **39:** 125–132.

Ropers, H.-H., M. Hoeltzenbein, V. Kalscheuer, H. Yntema, B. Hamel *et al.*, 2003 Nonsyndromic X-linked mental retardation: Where are the missing mutations? Trends Genet. **19:** 316–320.

Rulifson, E. J., S. K. Kim and R. Nusse, 2002 Ablation of insulin-producing neurons in flies: growth and diabetic phenotypes. Science **296:** 1118–1120.

Sacksteder, K. A., B. J. Biery, J. C. Morrell, B. K. Goodman, B. V. Geisbrecht *et al.*, 2000 Identification of the alpha-aminoadipic semialdehyde synthase gene, which is defective in familial hyperlysinemia. Am. J. Hum. Genet. **66:** 1736–1743.

Sanal, O., L. Yel, T. Kucukali, E. Gilbert-Barnes, M. Tardieu *et al.*, 2000 An allelic variant of Griscelli disease: presentation with severe hypotonia, mental-motor retardation, and hypopigmentation consistent with Elejalde syndrome (neuroectodermal melanolysosomal disorder). J. Neurol. **247:** 570–572.

Seimiya, M., and W. J. Gehring, 2000 The Drosophila homeobox gene *optix* is capable of inducing ectopic eyes by an *eyeless*-independent mechanism. Development **127:** 1879–1886.

Servidei, S., 2001 Mitochondrial encephalomyopathies: gene mutation. Neuromuscul. Disord. **11:** 332–337.

Shapiro, B. L., 1999 The Down syndrome critical region. J. Neural. Transm. **57** (Suppl.): 41–60.

Shishido, E., N. Ono, T. Kojima and K. Saigo, 1997 Requirements of DFR1/Heartless, a mesoderm-specific Drosophila FGF-receptor, for the formation of heart, visceral and somatic muscles, and ensheathing of longitudinal axon tracts in CNS. Development **124:** 2119–2128.

Stevenson, R. E., C. E. Schwartz and R. J. Schroer, 2000 *X-Linked Mental Retardation.* Oxford University Press, New York.

Stromme, P., M. E. Mangelsdorf, M. A. Shaw, K. M. Lower, S. M. Lewis *et al.*, 2002 Mutations in the human ortholog of *Aristaless* cause X-linked mental retardation and epilepsy. Nat. Genet. **30:** 441–445.

Surtees, R., and N. Blau, 2000 The neurochemistry of phenylketonuria. Eur. J. Pediatr. **159** (Suppl. 2): S109–S113.

Takagishi, Y., S. Oda, S. Hayasaka, K. Dekker-Ohno, T. Shikata *et al.*, 1996 The *dilute-lethal* (*dl*) gene attacks a Ca2+ store in the dendritic spine of Purkinje cells in mice. Neurosci. Lett. **215:** 169–172.

Tapon, N., N. Ito, B. J. Dickson, J. E. Treisman and I. K. Hariharan, 2001 The Drosophila tuberous sclerosis complex gene homologs restrict cell growth and cell proliferation. Cell **105:** 345–355.

Thompson, C. C., and G. B. Potter, 2000 Thyroid hormone action in neural development. Cereb. Cortex **10:** 939–945.

Toniolo, D., 2000 In search of the MRX genes. Am. J. Med. Genet. **97:** 221–227.

Tsai, H., R. E. Hardisty, C. Rhodes, A. E. Kiernan, P. Roby *et al.*, 2001 The mouse *slalom* mutant demonstrates a role for Jagged1 in neuroepithelial patterning in the organ of Corti. Hum. Mol. Genet. **10:** 507–512.

Tsuda, M., K. Kamimura, H. Nakato, M. Archer, W. Staatz *et al.*, 1999 The cell-surface proteoglycan Dally regulates Wingless signaling in Drosophila. Nature **400:** 213–215.

Turner, G., 1996 Intelligence and the X chromosome. Lancet **347:** 1814–1815.

Turner, G., and M. W. Partington, 1991 Genes for intelligence on the X chromosome. J. Med. Genet. **28:** 429.

Vannucci, R. C., and S. J. Vannucci, 2001 Hypoglycemic brain injury. Semin. Neonatol. **6:** 147–155.

Vargha-Khadem, F., K. E. Watkins, C. J. Price, J. Ashburner, K. J. Alcock *et al.*, 1998 Neural basis of an inherited speech and language disorder. Proc. Natl. Acad. Sci. USA **95:** 12695–12700.

Venter, J. C., M. D. Adams, E. W. Myers, P. W. Li, R. J. Mural *et al.*, 2001 The sequence of the human genome. Science **291:** 1304–1351.

Wakefield, J. G., S. Bonaccorsi and M. Gatti, 2001 The Drosophila protein Asp is involved in microtubule organization during spindle formation and cytokinesis. J. Cell Biol. **153:** 637–647.

Walkley, S. U., 1998 Cellular pathology of lysosomal storage disorders. Brain Pathol. **8:** 175–193.

Wallach, D., T. U. Arumugam, M. P. Boldin, G. Cantarella, K. A. Ganesh *et al.*, 2002 How are the regulators regulated? The search for mechanisms that impose specificity on induction of cell death and NF-kappaB activation by members of the TNF/NGF receptor family. Arthritis Res. **4:** S189–S196.

Wallis, D., and M. Muenke, 2000 Mutations in holoprosencephaly. Hum. Mutat. **16:** 99–108.

Wan, L., T. C. Dockendorff, T. A. Jongens and G. Dreyfuss, 2000 Characterization of dFMR1, a Drosophila melanogaster homolog

of the fragile X mental retardation protein. Mol. Cell. Biol. **20:** 8536–8547.

Warrick, J. M., H. L. Paulson, G. L. Gray-Board, Q. T. Bui, K. H. Fischbeck *et al.*, 1998 Expanded polyglutamine protein forms nuclear inclusions and causes neural degeneration in Drosophila. Cell **93:** 939–949.

Weller, S., and J. Gartner, 2001 Genetic and clinical aspects of X-linked hydrocephalus (L1 disease): mutations in the *L1CAM* gene. Hum. Mutat. **18:** 1–12.

Werner, L. A., and L. J. Manseau, 1997 A Drosophila gene with predicted rhoGEF, pleckstrin homology and SH3 domains is highly expressed in morphogenic tissues. Gene **187:** 107–114.

Wisniewski, K. E., N. Zhong and M. Philippart, 2001 Pheno/genotypic correlations of neuronal ceroid lipofuscinoses. Neurology **57:** 576–581.

Wittle, A. E., K. P. Kamdar and V. Finnerty, 1999 The Drosophila *cinnamon* gene is functionally homologous to Arabidopsis *cnx1* and has a similar expression pattern to the mammalian *gephyrin* gene. Mol. Gen. Genet. **261:** 672–680.

Wolfgang, W. J., A. Hoskote, I. J. H. Roberts, S. Jackson and M. Forte, 2001 Genetic analysis of the Drosophila *Gs*α Gene. Genetics **158:** 1189–1201.

Woolfenden, A. R., G. W. Albers, G. K. Steinberg, J. S. Hahn, D. C. C. Johnston *et al.*, 1999 Moyamoya syndrome in children with Alagille syndrome: additional evidence of a vasculopathy. Pediatrics **103:** 505–508.

Yager, J., S. Richards, D. S. Hekmat-Scafe, D. D. Hurd, V. Sundaresan *et al.*, 2001 Control of Drosophila perineurial glial growth by interacting neurotransmitter-mediated signaling pathways. Proc. Natl. Acad. Sci. USA **98:** 10445–10450.

Yntema, H. G., F. A. Poppelaars, E. Derksen, A. R. Oudakker, T. Van Roosmalen *et al.*, 2002 Expanding phenotype of *XNP* mutations: mild to moderate mental retardation. Am. J. Med. Genet. **110:** 243–247.

Zalfa, F., M. Giorgi, B. Primerano, A. Moro, A. Di Penta *et al.*, 2003 The fragile X syndrome protein FMRP associates with *BC1* RNA and regulates translation of specific mRNAs at synapses. Cell **112:** 317–327.

Zars, T., 2000 Behavioral functions of the insect mushroom bodies. Curr. Opin. Neurobiol. **10:** 790–795.

Zechner, U., M. Wilda, H. Kehrer-Sawatzki, W. Vogel, R. Fundele *et al.*, 2001 A high density of X-linked genes for general cognitive ability: A run-away process shaping human evolution? Trends Genet. **17:** 697–701.

Zhang, S., L. Xu, J. Lee and T. Xu, 2002 Drosophila atrophin homolog functions as a transcriptional corepressor in multiple developmental processes. Cell **108:** 45–56.

Zhang, Y. Q., A. M. Bailey, H. J. Matthies, R. B. Renden, M. A. Smith *et al.*, 2001 Drosophila fragile X-related gene regulates the MAP1B homolog Futsch to control synaptic structure and function. Cell **107:** 591–603.

Communicating editor: R. S. Hawley

APPENDIX

Human mental retardation genes and *D. melanogaster* homologs

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
AASS	α-Aminoadipic semialdehyde synthase	7q	Hyperlysinemia	605113	Oxidoreductase	Metabolic (amino acid): MR 2° systemic toxicity	*BEST:CK02318*	0025687	−300
ABAT	4-Aminobutyrate aminotransferase	16p	Inborn error of GABA metabolism	137150	Transferase	CNS development/ function: neurotransmission (GABA)	*CG7433* (&)	0036927	−147
ABCC8 (*SUR1*)	ATP-binding cassette, subfamily C, member 8	11p	Hyperinsulinemic hypoglycemia of infancy	600509	Receptor	Endocrine (pancreas): MR 2° systemic fuel deficiency	[*CG7627*, others]	0032026	−151
ACOX1	Acyl-coenzyme A oxidase 1	17q	Pseudoneonatal adrenoleukodystrophy	264470	Oxidoreductase	Metabolic (fatty acid): MR 2° local toxicity (glia: myelin)	*BcDNA:GH07485*, others	0027572	−155
ADA •••	Adenosine deaminase	20q	ADA-severe combined immunodeficiency	102700	Hydrolase	Metabolic (purine): ?MR 2° local toxicity; ?neuromodulation	*Adenosine deaminase*	0037661	−14
ADSL	Adenylosuccinate lyase	22q	Succinylpurinemic autism	103050	Lyase	Metabolic (purine synthesis): ?MR 2° systemic toxicity	*CG3590*	0038467	−179
AGA	Aspartylglucosaminidase	4q	Aspartylglucosaminuria	208400	Hydrolase	Lysosomal pathway (glycoprotein): MR 2° local toxicity (neuron)	*CG1827*, *CG10474*	0033431	−83
AGTR2	Angiotensin II receptor type 2	Xq	X-linked MR	300034	Receptor	Signaling pathway (GPCR): fluid balance; CNS development/ function	[*Takr99D*, others]	0004622	−18
AK1	Adenylate kinase 1	9q	Hemolytic anemia due to AK1 deficiency	103000	Kinase	Metabolic (purine homeostasis): MR cause unknown	*Adenylate kinase-1* (&)	0022709	−45
ALDH3A2	Aldehyde dehydrogenase 3A2	17p	Sjogren-Larsson syndrome	270200	Oxidoreductase	Metabolic (fatty acid synthesis): CNS development/ function	*Aldh-III* (&)	0010548	−105
ALDH4A1	Aldehyde dehydrogenase 4A1	1p	Hyperprolinemia type II	606811	Oxidoreductase	Metabolic (amino acid): MR cause unknown	*CG7145* (&)	0037138	−300
ALDH5A1	Aldehyde dehydrogenase 5A1	6p	Inborn error of GABA metabolism	271980	Oxidoreductase	Neurotransmission (GABA)	*CG4685* (&)	0039349	−128

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
ALDOA	Aldolase A	16q	Hemolytic anemia due to ALDOA deficiency	103850	Lyase	Metabolic: general cell integrity	*Aldolase*, *CG5432*	0000064	−131
ALG2	Homolog of yeast *Asparagine Linked Gene 2*	9q	Congenital disorder of glycosylation type Ii	607905	Transferase	Protein modification (glycosylation): CNS development/ function	*CG1291* (&)	0035401	−104
ALG3 (*NOT65L*)	Homolog of yeast *Asparagine Linked Gene 3*	3q	Congenital disorder of glycosylation type Id	601110	Transferase	Protein modification (glycosylation): CNS development/ function	*lethal (2) neighbor of tid*	0011297	−55
ALG6	Homolog of yeast *Asparagine Linked Gene 6*	1p	Congenital disorder of glycosylation type Ic	604566	Transferase	Protein modification (glycosylation): CNS development/ function	*CG5091*	0032234	−76
ALG12	Homolog of yeast *Asparagine Linked Gene 12*	22q	Congenital disorder of glycosylation type Ig	607144	Transferase	Protein modification (glycosylation): CNS development/ function	*CG8412*	0037743	−98
AMT	Aminomethyltransferase	3p	Glycine encephalopathy	238310	Transferase	Metabolic (amino acid): MR 2° neuro/glial toxicity (neurotransmission)	*CG6415*	0032287	−100
ARG1	Arginase	6q	Argininemia	207800	Hydrolase	Metabolic (urea cycle): MR 2° systemic toxicity	*arginase*	0023535	−60
ARHGEF6 (*PIXA*)	Rho guanine nucleotide exchange factor 6	Xq	MRX46	300267	Receptor signaling protein	Signaling pathway (integrin): neuronal development/ plasticity	*rtGEF* (&¶)	0015803	−90
ARSA	Arylsulfatase A	22q	Metachromatic leukodystrophy	250100	Hydrolase	Lysosomal pathway (glycolipid): MR 2° local toxicity (glia: myelin)	*CG32191*, others (*)	0052191	−23
ARX	Aristaless-related homeobox, X-linked	Xp	MRX36; West syndrome; Partington syndrome; lissencephaly	300382	Transcription regulator	CNS development/ function: neuronal migration	*PvuII-PstI homology 13*, others	0023489	−29
ASAH	*N*-Acylsphingosine amidohydrolase (ceramidase)	8p	Farber lipogranulomatosis	228000	Hydrolase	Lysosomal pathway (glycolipid): MR 2° local toxicity (neuron)	None	—	—

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
ASL	Argininosuccinate lyase	7q	Argininosuccini-caciduria	207900	Lyase	Metabolic (urea cycle): MR 2° systemic toxicity	*CG9510*	0032076	−106
ASPA	Aspartoacyclase	17p	Canavan disease	271900	Hydrolase	Metabolic: glial development/ function; MR 2° local toxicity (myelin)	None	—	—
ASPM	Abnormal spindle-like, microcephaly-associated	1q	Primary microcephaly 5	605481	Protein binding	CNS development/ function: neurogenesis	*abnormal spindle* (&¶)	0000140	−54
ASS	Argininosuccinate synthetase	9q	Classic citrullinemia (type I)	603470	Ligase	Metabolic (urea cycle): MR 2° systemic toxicity	*BG:DS00004.14*	0026565	−121
ATP2A2	ATPase, $Ca^{(2+)}$-transporting, slow-twitch	12q	Darier-White disease	108740	Transporter	Signaling pathway (calcium): cell adhesion (skin); MR cause unknown	*Calcium ATPase at 60A* (&¶)	0004551	−300
ATP7A	Cu^{2+}-transporting ATPase, α-polypeptide	Xq	Menkes syndrome; occipital horn syndrome	300011	Transporter	Metabolic: CNS development/ function	*CG1886* (&)	0030343	−300
ATR	Ataxia-telangiectasia and RAD3-related	3q	Seckel syndrome	601215	Kinase	DNA repair: CNS development/ function	*mei-41* (&)	0004367	−300
ATRX (*XH2, XNP*)	X-linked helicase 2	Xq	α-Thalassemia/MR syndrome; nonspecific MR; others	300032	Helicase	Chromosome structure and transcription regulation	*XNP* (&¶)	0039338	−300
AVPR2	Arginine vasopressin receptor 2	Xq	X-linked nephrogenic diabetes insipidus	304800	Receptor	Signaling pathway (GPCR): MR 2° systemic toxicity	*CG6111*, others (*)	0039396	−30
B4GALT1	β-1,4-Galactosyltransferase 1	9p	Congenital disorder of glycosylation type IId	137060	Transferase	Protein modification (glycosylation): CNS development/ function	*BcDNA:GH13356, CG14517*	0027538	−60
B4GALT7 (*XGPT1*)	β-1,4-Galactosyltransferase 7	5q	Ehlers-Danlos syndrome, progeroid form	604327	Transferase	Protein modification (glycosylation): ?CNS development/ function	*CG11780* (&)	0039258	−73
BBS1	Bardet-Biedl syndrome 1	11q	Bardet-Biedl syndrome 1	209901	Unknown function	Unknown	*CG14825*	0035741	−62
BBS2	Bardet-Biedl syndrome 2	16q	Bardet-Biedl syndrome 2	606151	Unknown function	Unknown	None	—	—

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
BBS4	Bardet-Biedl syndrome 4	15q	Bardet-Biedl syndrome 4	600374	[Transferase]	?Protein modification (glycosylation): MR cause unknown	*CG13232* (&)	0033578	−54
BBS6 (*MKKS*)	Bardet-Biedl syndrome 6	20p	Bardet-Biedl syndrome 6	604896	Chaperone	Protein modification (folding): MR cause unknown	*Tcp1-like*, *Cct*γ (*)	0003676	−11
BCKDHA	Branched-chain keto acid dehydrogenase E1α	19q	Maple syrup urine disease type IA	248600	Oxidoreductase	Metabolic (amino acid): MR 2° systemic and local toxicity	*CG8199* (&)	0037709	−136
BCKDHB	Branched-chain keto acid dehydrogenase E1β	6p	Maple syrup urine disease type IB	248611	Oxidoreductase	Metabolic (amino acid): MR 2° systemic and local toxicity	*CG17691* (&)	0039993	−124
BCS1L	Yeast *BCS1* homolog-like	2q	Tubulopathy, encephalopathy, and liver failure	603647	[Nucleotide binding]	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*CG4908* (&)	0032195	−146
BSCL2	Seipin	11q	Berardinelli-Seip congenital lipodystrophy	606158	Unknown function	?CNS development/function: hypothalamic-pituitary axis	*EG:BACR7C10.1*	0040336	−45
BSND	Barttin	1p	Bartter syndrome with sensorineural deafness	606412	Transporter	MR cause unknown: ?systemic toxicity	None	—	—
BTD	Biotinidase	3p	Multiple carboxylase deficiency	253260	Ligase	Metabolic (various): MR 2° systemic and local toxicity	*vanin-like*, others	0040069	−40
CA2	Carbonic anhydrase II	8q	Osteopetrosis with renal tubular acidosis	259730	Lyase	CNS development/function: CSF, neurotransmission, ?myelination	*Carbonic anhydrase 1*, others	0027844	−59
CBS	Cystathionine β-synthase	21q	Homocystinuria	236200	Lyase	Metabolic: CNS development/function; systemic and local toxicity	*CG1753*	0031148	−163
CGI58	Comparative gene identification 58	3p	Ichthyotic neutral lipid storage disease	604780	Hydrolase	Metabolic (fatty acid): ?MR 2° local toxicity	*CG1882*	0033226	−81

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
CIAS1	Cryopyrin	1q	Chronic neurologic cutaneous and articular syndrome	606416	Apoptosis regulator	?Signaling pathway (unknown): immune response; ?MR 2° inflammation	None	—	—
CKN1 (*CSA*)	Cockayne syndrome type I	5q	Cockayne syndrome type I	216400	Transcription factor	DNA repair (transcription-coupled): CNS development/function (myelin)	[*will die slowly*, others]	0040066	−14
CLCNKB	Chloride channel, kidney, B	1p	Bartter syndrome type III	602023	Transporter	MR cause unknown: ?systemic toxicity	*CG31116* (&)	0051116	−108
CLN1 (*PPT1*)	Palmitoyl-protein thioesterase 1	1p	Neuronal ceroid ipofuscinosis, infantile	600722	Hydrolase	Lysosomal pathway (lipoprotein): MR 2° local toxicity (neuron)	*Ppt1* (&)	0030057	−74
CLN2	Ceroid lipofuscinosis, neuronal 2	11p	Neuronal ceroid lipofuscinosis, late infantile	204500	Hydrolase	Lysosomal pathway (peptide): MR 2° local toxicity (neuron)	None	—	—
CLN3	Ceroid lipofuscinosis, neuronal 3	16p	Batten disease	607042	Unknown function	Lysosomal pathway: MR 2° local toxicity (neuron); ?synaptic function	*CG5582*	0036756	−69
CLN5	Ceroid lipofuscinosis, neuronal 5	13q	Neuronal ceroid lipofuscinosis, late infantile	256731	Unknown function	Lysosomal pathway: MR 2° local toxicity (neuron)	None	—	—
CLN6	Ceroid lipofuscinosis, neuronal 6	15q	Neuronal ceroid lipofuscinosis, late infantile	606725	Unknown function	?Lysosomal pathway: MR 2° local toxicity (neuron)	None	—	—
CLN8	Ceroid lipofuscinosis, neuronal 8	8p	Progressive epilepsy with MR	600143	Unknown function	?Lysosomal pathway: MR 2° local toxicity (neuron)	None	—	—
COX10	Cytochrome *c* oxidase subunit 10	17p	Progressive mitochondrial encephalopathy	602125	Transferase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*CG5037*	0032222	−80
CPS1	Carbamoylphosphate synthetase 1	2q	Hyperammonemia due to CPS1 deficiency	237300	Ligase	Metabolic (urea cycle): MR 2° systemic toxicity	*rudimentary*	0003189	−300
CREBBP (*CBP*)	CREB-binding protein	16p	Rubinstein-Taybi syndrome	600140	Transcription regulator	Transcription regulation: CNS development/function; ?chromosome structure	*nejire* (&¶)	0015624	−300

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
CXORF5	Chromosome X open reading frame 5	Xp	Oral-facial-digital syndrome type I	300170	[Protein binding]	CNS development/ function: neuronal migration/ differentiation (?microtubule)	None	—	—
CYP27A1	Cytochrome P450 27A1 (sterol 27-hydroxylase)	2q	Cerebrotendinous xanthomatosis	606530	Oxidoreductase	Metabolic (lipid): MR 2° systemic and local toxicity	*Cyp49a1*, others	0033524	−42
DBT	Dihydrolipoamide branched-chain transacylase	1p	Maple syrup urine disease type II	248610	Transferase	Metabolic (amino acid): MR 2° systemic and local toxicity	*CG5599* (&)	0030612	−115
DCX	Doublecortin	Xq	Lissencephaly; subcortical laminar heterotopia	300121	Protein binding	Cytoskeleton (microtubule): neuronal migration and differentiation	*CG17528* (&¶)	0032999	−47
DHCR7	7-Dehydrocholesterol reductase	11q	Smith-Lemli-Opitz syndrome types I, II	602858	Oxidoreductase	Metabolic (cholesterol): signaling pathway (Hh): CNS development/ function	None	—	—
DIA1	Diaphorase (NADH-cytochrome b5 reductase)	22q	Methemoglobinemia type II	250800	Oxidoreductase	Metabolic (lipid): CNS development and function	*CG5946*	0036211	−92
DKC1	Dyskerin	Xq	Dyskeratosis congenita; Hoyeraal-Hreidarsson syndrome	300126	RNA binding	RNA processing (rRNA): CNS development/ function; ?chromosome structure	*Nucleolar protein at 60B* (¶)	0023184	−174
DLD	Dihydrolipoamide dehydrogenase	7q	Maple syrup urine disease type III	246900	Oxidoreductase	Metabolic (glycolysis): MR 2° local energy deficiency	*CG7430* (&)	0036762	−300
DM1	Dystrophia myotonica protein kinase	19q	Congenital myotonic dystrophy 1	605377	Kinase	?CNS development/ function; neighboring genes may contribute to phenotype	[*genghis khan*, others]	0023081	−119
DMD	Dystrophin	Xp	Duchenne, Becker muscular dystrophies	300377	Structural molecule	Cytoskeleton (actin): CNS development/ function (neurons, glia, blood vessel)	*dystrophin* (&¶)	0024242	−300

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
DNMT3B	DNA methyltransferase 3B	20q	Immunodeficiency, centromeric instability syndrome	602900	Transferase	Chromosome structure: MR cause unknown	None	—	—
DPAGT1	GlcNAc 1-P transferase	11q	Congenital disorder of glycosylation type Ij	191350	Transferase	Protein modification (glycosylation): CNS development/ function	*CG5287*	0032477	−97
DPM1	Dolichyl-phosphate mannosyltransferase 1	20q	Congenital disorder of glycosylation type Ie	603503	Transferase	Protein modification (glycosylation): CNS development/ function	*CG10166* (&)	0032799	−106
DPYD	Dihydropyrimidine dehydrogenase	1p	Dihydropyrimidinuria due to DPYD deficiency	274270	Oxidoreductase	Metabolic (pyrimidine): ?MR 2° neurotoxicity	*Rhythmically expressed gene 3* (&)	0016718	−300
DPYS (*DHP*)	Dihydropyrimidinase	8q	Dihydropyrimidinuria due to DPYS deficiency	222748	Hydrolase	Metabolic (pyrimidine): ?MR 2° neurotoxicity	*collapsin response mediator protein*	0023023	−141
DRPLA	Atrophin-1	12p	Progressive myoclonus epilepsy syndrome	125370	Protein binding	Transcription regulation (neuron)	None (see MATERIALS AND METHODS)	—	—
DUOX2 (*THOX2*)	Dual oxidase 2	15q	Congenital hypothyroidism	606759	Oxidoreductase	Hormone synthesis: endocrine function (thyroid): CNS development/ function	*CG3131* (&)	0031464	−300
EIF2AK3 (*PEK*)	Eukaryotic translation initiation factor 2α kinase 3	2p	Wolcott-Rallison syndrome	604032	Kinase	Translation: CNS development/ function	*EIF2-like* (&)	0037327	−44
EMX2	Homolog 2 of Drosophila *empty spiracles*	10q	Schizencephaly	600035	Transcription factor	Transcription regulation: CNS development/ function (neuron)	*empty spiracles, E5*	0000576	−25
ERCC2 (*XPD*)	Xeroderma pigmentosum type D	19q	Trichothiodystrophy; XPD/Cockayne syndrome	126340	Protein binding	Transcription (basal): CNS development/ function (neuron, glia)	*Xeroderma pigmentosum D* (&)	0015844	−300
ERCC3 (*XPB*)	Xeroderma pigmentosum type B	2q	XPB/Cockayne syndrome	133510	Helicase	Transcription/DNA repair: CNS development/ function	*haywire*	0001179	−300

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
ERCC5 (*XPG*)	Xeroderma pigmentosum type G	13q	XPG/Cockayne syndrome	133530	Hydrolase?, other?	DNA repair (transcription-coupled): CNS development/ function	*mutagen-sensitive 201* (&)	0002887	−64
ERCC6 (*CSB*)	Excision repair cross-complementing 6	10q	Cockayne syndrome type II; cerebrooculofacio-skeletal syndrome	133540	Hydrolase	DNA repair (transcription coupled), transcription: CNS development/ function	[*Helicase 89B*, others]	0022787	−79
FACL4	Fatty acid CoA ligase, long-chain 4	Xq	MRX63, MRX68	300157	Ligase	Lipid synthesis: CNS development/ function (neuron)	*l(2)44DEa* (&)	0010609	−177
FANCA	Fanconi anemia complementation group A	16q	Fanconi anemia complementation group A	227650	[Protein binding]	DNA repair: ?CNS development/ function	None	—	—
FANCC	Fanconi anemia complementation group C	9q	Fanconi anemia complementation group C	227645	[Protein binding]	DNA repair: ?CNS development/ function	None	—	—
FBN1	Fibrillin 1	15q	Shprintzen-Goldberg craniosynostosis syndrome	134797	Structural molecule	Extracellular matrix (microfibrils): MR cause unknown	*dumpy* (&)	0000488	−50
FCMD	Fukutin	9q	Fukuyama congenital muscular dystrophy	253800	[Transferase]	Protein modification (glycosylation): CNS development (neuron migration, glia)	None	—	—
FGD1	Faciogenital dysplasia 1	Xp	Nonspecific MR; Aarskog-Scott syndrome	305400	Receptor signaling protein	Signaling pathway (phosphoinositide, Rho-type G protein)	*CG2008*, others	0037287	−23
FGFR1	Fibroblast growth factor receptor 1	8p	Craniosynostosis; Apert syndrome; others	136350	Receptor	Signaling pathway (receptor tyrosine kinase): ?CNS development/ function	*heartless*, *breathless* (¶)	0010389	−123
FGFR2	Fibroblast growth factor receptor 2	10q	Apert and other cranio-synostosis syndromes	176943	Receptor	Signaling pathway (receptor tyrosine kinase): CNS development/ function	*breathless*, *heartless* (¶)	0005592	−130

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
FGFR3	Fibroblast growth factor receptor 3	4p	Craniosynostoses, chondrodysplasias	134934	Receptor	Signaling pathway (receptor tyrosine kinase): ?CNS development/ function	*heartless*, *breathless* (¶)	0010389	−127
FH	Fumarate hydratase	1q	Fumaricaciduria due to FH deficiency	136850	Lyase	Metabolic (citric acid cycle): CNS development/ function (?neuronal migration)	*CG4094*, others	0029889	−300
FKRP	Fukutin-related protein	19q	Muscular dystrophy with MR and cerebellar cysts	606596	Unknown function	?Protein modification (glycosylation): CNS development/ function	*CG15651*	0034567	−33
FLJ90130	Dymeclin	18q	Dyggve-Melchior-Clausen disease	223800	Unknown function	?Protein modification (proteoglycan): MR cause unknown	*BcDNA:GH02536*	0027607	−127
FLNA	Filamin A	Xq	Periventricular nodular heterotopia; others	300017	Protein binding	Cytoskeleton (actin): CNS development/ function (neuronal migration)	*cheerio* (&¶)	0014141	−300
FMR1	Fragile X mental retardation 1	Xq	Fragile X mental retardation syndrome	309550	RNA binding	Translation regulation: CNS development/ function (?neuronal differentiation)	*dfmr1* (¶)	0028734	−95
FMR2	Fragile site mental retardation 2	Xq	X-linked nonspecific MR	309548	[Transcription regulator]	Transcription regulation: CNS development/ function (?neuronal differentiation)	*lilliputian* (*)	0041111	−19
FOXP2 •••	Forkhead box P2	7q	Developmental verbal dyspraxia	605317	Transcription regulator	Transcription regulation: CNS development/ function	*CG16899* (&¶)	0037735	−32
FRAS1	Fraser syndrome gene 1	4q	Fraser syndrome	607830	Unknown function	?Extracellular matrix: CNS development/ function	[*fur2*, others]	0004598	−65

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
FUCA1	α-L-Fucosidase 1	1p	Fucosidosis	230000	Hydrolase	Lysosomal pathway (glycoprotein): MR 2° local toxicity (neuron, glia)	*CG6128*	0036169	−129
FUCT1	GDP-fucose transporter 1	11p	Congenital disorder of glycosylation type IIc	605881	Transporter	Protein modification (glycosylation): CNS development/function	*CG9620*	0037567	−76
G6PD	Glucose-6-phosphate dehydrogenase	Xq	Nonspherocytic hemolytic anemia; kernicterus	305900	Oxidoreductase	Metabolic (glycolysis): MR 2° systemic toxicity	*Zwischenferment* (&)	0004057	−300
GALE	Galactose epimerase	1p	Epimerase-deficiency galactosemia	606953	Isomerase	Metabolic (carbohydrate): ?CNS development/function	*CG12030* (&)	0035147	−124
GALT	Galactose-1-phosphate uridylyltransferase	9p	Transferase-deficiency galactosemia	606999	Transferase	Metabolic (carbohydrate): MR 2° local toxicity	*CG9232*	0031845	−118
GAMT	Guanidinoacetate methyltransferase	19p	Reversible brain creatine deficiency	601240	Transferase	Metabolic (creatine): CNS development/function; MR 2° systemic energy deficiency	None	—	—
GATM (*AGAT*)	L-Arginine:glycine amidinotransferase	15q	Inborn error of creatine metabolism	602360	Transferase	Metabolic (creatine): CNS development/function; MR 2° systemic energy deficiency	None	—	—
GCDH •••	Glutaryl-CoA dehydrogenase	19p	Glutaricacidemia I	231670	Oxidoreductase	Metabolic (amino acid): CNS development/function; ?neurotoxicity	*CG9547* (&)	0031824	−163
GCH1	GTP cyclohydrolase 1	14q	Atypical hyperphenylalaninemia	600225	Hydrolase	Metabolic (BH_4 synthesis): neurotransmission (amines); systemic toxicity	*Punch*	0003162	−75
GCS1	Glucosidase I	2p	Congenital disorder of glycosylation type IIb	601336	Hydrolase	Protein modification (glycosylation): CNS development/function	*CG1597*	0030289	−138

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
GCSH	Glycine cleavage system H protein	16q	Glycine encephalopathy	238330	Transferase	Metabolic (amino acid): MR 2° neuro/glial toxicity (neurotransmission)	*pumpless*	0027945	−26
GDI1	Guanine dissociation inhibitor 1 (Rab GDI α)	Xq	MRX41, MRX48	300104	Receptor signaling protein	Signaling pathway (small G): neuronal development/function (neurotransmission)	*GDP dissociation inhibitor* (&¶)	0004868	−156
GFAP	Glial fibrillary acidic protein	17q	Alexander disease	137780	Structural molecule	Cytoskeleton (intermediate filament): glial development/function (astrocyte)	[*Lamin*, *Lamin C*]	0002525	−40
GK	Glycerol kinase	Xp	Hyperglycerolemia due to GK deficiency	307030	Kinase	Metabolic (gluconeogenesis): ?MR 2° local/systemic energy deficiency	*Glycerol kinase*, others	0025592	−155
GLB1	β-Galactosidase 1	3p	GM1-gangliosidosis types I, II	230500	Hydrolase	Lysosomal pathway (glycolipid): MR 2° local toxicity (neuron)	*CG3132*, *CG9092*	0037977	−139
GLDC	Glycine decarboxylase	9p	Glycine encephalopathy	238300	Oxidoreductase	Metabolic (amino acid): MR 2° neuro/glial toxicity (neurotransmission)	*CG3999*	0037801	−300
GLI3	GLI-Kruppel family member 3	7p	Acrocallosal syndrome; Greig cephalopolysyndactyly	165240	Transcription factor	Transcription regulation: CNS development/function (neuronal differentiation)	*cubitus interruptus* (&¶)	0004859	−93
GM2A	Ganglioside GM2-activator	5q	Tay-Sachs disease, AB variant	272750	Enzyme regulator	Lysosomal pathway (glycolipid): MR 2° local toxicity (neuron, glia)	None	—	—
GNAS	Stimulatory G protein, α-subunit	20q	Albright hereditary osteodystrophy	139320	Nucleotide binding	Signaling pathway (GPCR → cAMP): CNS function (?neuronal plasticity)	*G protein sα60A* (&¶)	0001123	−163
GNPAT	Glyceronephosphate *O*-acyltransferase	1q	Rhizomelic chondrodysplasia punctata type II	602744	Transferase	Lipid synthesis: CNS development/function (glia: myelin)	*Dhap-at* (&)	0040212	−74
GNS (*G6S*)	*N*-Acetylglucosamine-6-sulfatase	12q	Mucopolysaccharidosis IIID (Sanfillipo syndrome D)	607664	Hydrolase	Lysosomal pathway (glycosaminoglycan): MR 2° local toxicity	*CG18278* (&)	0033836	−110

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
GPC3	Glypican 3	Xq	Simpson-Golabi-Behmel syndrome type I	300037	Signal transducer	Signaling pathways (TGFβ, RTK, Wnt): ?CNS development/function	*division abnormally delayed* (&¶)	0011577	−23
GPH	Gephyrin	14q	Molybdenum cofactor deficiency type C	603930	Protein binding	CNS development/function: neurotransmission and metabolic (see *MOCS1,2*)	*cinnamon* (¶)	0000316	−59
GPI	Glucose-6-phosphate isomerase (neuroleukin)	19q	Hemolytic anemia due to GPI deficiency	172400	Isomerase	CNS development/function (neuron survival, differentiation, ?plasticity)	*Phosphoglucose isomerase* (¶)	0003074	−300
GSS	Glutathione synthetase	20q	5-Oxoprolinuria due to GSS deficiency	601002	Ligase	Metabolic (general cell integrity): ?MR 2° local/systemic toxicity	*CG32495* (&)	0052495	−92
GUSB	β-Glucuronidase	7q	Mucopolysaccharidosis type VII (Sly syndrome)	253220	Hydrolase	Lysosomal pathway (glycosaminoglycan): MR 2° local toxicity	*CG15117, CG2135*	0034417	−146
HESX1	Homeobox gene expressed in ES cells	3p	Septooptic dysplasia	601802	Transcription factor	Transcription regulation: CNS and endocrine (pituitary) development/function	[*PHDP*, others]	0025334	−14
HEXA •••	Hexosaminidase A	15q	Tay-Sachs disease	606869	Hydrolase	Lysosomal pathway (glycolipid): MR 2° local toxicity (neuron)	*Hexo2*, others	0041629	−62
HEXB	Hexosaminidase B	5q	Sandhoff disease (GM2-gangliosidosis)	606873	Hydrolase	Lysosomal pathway (glycolipid): MR 2° local toxicity (neuron)	*Hexo2*, others	0041629	−64
HLCS	Holocarboxylase synthetase	21q	Biotin-responsive multiple carboxylase deficiency	253270	Ligase	Metabolic (various): MR 2° systemic and local toxicity (see also *PC, PCC*)	*CG14670*	0037332	−67
HMGCL	3-Hydroxy-3-methylglutaryl-CoA lyase	1p	3-Hydroxy-3-methylglutaric aciduria	246450	Lyase	Metabolic (various): systemic neurotoxicity; glial development/function (myelin)	*CG10399*	0031877	−99
HPD	4-Hydroxyphenyl-pyruvate dioxygenase	12q	Tyrosinemia type III	276710	Oxidoreductase	Metabolic (amino acid): ?MR 2° systemic toxicity	*CG11796*	0036992	−140

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
HPRT	Hypoxanthine phosphoribosyltransferase	Xq	Lesch-Nyhan syndrome	308000	Transferase	Metabolic (purine): ?neurotransmission (DA); ? CNS devel (neuron)	None	—	—
IDS	Iduronate 2-sulfatase	Xq	Mucopolysaccharidosis type II (Hunter syndrome)	309900	Hydrolase	Lysosomal pathway (glycosaminoglycan): MR 2° local toxicity	*CG12014*	0035445	−118
IDUA	α-L-Iduronidase	4p	Mucopolysaccharidosis type I (Hurler syndrome)	252800	Hydrolase	Lysosomal pathway (glycosaminoglycan): MR 2° local toxicity	*CG6201*	0032343	−64
IGF1	Insulin-like growth factor 1	12q	Growth retardation with deafness and MR	147440	Ligand	Signaling pathway (RTK): CNS development/function (neuron, glia)	None	—	—
IKBKG (*NEMO*)	Inhibitor of KB kinase, γ-subunit	Xq	Incontinentia pigmenti type II	300248	Signal transducer	Signaling pathway (multiple): ?CNS development/function (?cell survival)	None	—	—
IL1RAPL1	Interleukin 1 receptor accessory protein-like 1	Xp	MRX34	300206	Signal transducer	Signaling pathway (cytokine): ?CNS development/function	[*Tehao*, others]	0026760	−13
ITGA7	Integrin α-7	12q	Congenital myopathy	600536	Receptor	Signaling pathway (integrin): ?CNS development/function	*multiple edematous wings* (&¶)	0004456	−83
JAG1	Jagged 1	20p	Alagille syndrome	601920	Ligand	Signaling pathway (Notch): CNS development/function (neuron, glia, ?blood vessel)	*Serrate* (&¶)	0004197	−168
KCNJ1 (*ROMK*)	Potassium channel J1, inwardly rectifying	11q	Bartter syndrome type II, antenatal hypercalciuric form	600359	Transporter	MR cause unknown: ?systemic toxicity	*Ir, Irk2* (*)	0039061	−76
KCNJ11 (*Kir6.2*)	Potassium channel J11, inwardly rectifying	11p	Hyperinsulinemic hypoglycemia of infancy	600937	Transporter	Endocrine (pancreas): MR 2° systemic fuel deficiency	*Ir, Irk2* (*)	0039061	−86
L1CAM	L1 cell adhesion molecule	Xq	MASA syndrome; HSAS; SPG1	308840	Cell adhesion molecule	Cell adhesion: CNS development/function (neuron migration, differentiation, ?survival)	*neuroglian* (&¶)	0002968	−136

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
LAMA2	Laminin α-2 (merosin)	6q	Congenital merosin-deficient muscular dystrophy	156225	Structural molecule	Extracellular matrix: CNS development/function (neuronal migration; myelin)	*wing blister* (&¶)	0004002	−300
LAMP2	Lysosome-associated membrane protein 2	Xq	Glycogen storage disease IIB	309060	Protein binding	Lysosomal pathway: MR cause unknown; ?local toxicity (neuron, glia)	None	—	—
LARGE	Acetylglucosaminyltransferase-like protein	22q	Congenital muscular dystrophy ID	603590	Transferase	Protein modification (glycosylation): CNS development/function	*CG3253*, others (*)	0041706	−19
LIS1 (*PAFAH-1B1*)	Platelet-activating factor acetylhydrolase 1Bα	17p	Lissencephaly; subcortical laminar heterotopia	601545	Unclassified enzyme	Cytoskeleton (microtubule): CNS development/function (neuron migration, ?proliferation)	*Lissencephaly-1* (&¶)	0015754	−300
LRPPRC	Leucine-rich PPR motif-containing protein	2p	Leigh syndrome, French-Canadian type	607544	[DNA binding]	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*bicoid stability factor* (&)	0032679	−79
MAN2B1	α-Mannosidase 2B1, lysosomal	19q	α-Mannosidosis	248500	Hydrolase	Lysosomal pathway (glycoprotein): MR 2° local toxicity (neuron, glia) vessel	*BcDNA:GH02419*, others	0027611	−300
MANBA	β-Mannosidase	4q	β-Mannosidosis	248510	Hydrolase	Lysosomal pathway (glycoprotein): MR 2° local toxicity (neuron, glia)	*CG12582*	0037215	−72
MAOA	Monoamine oxidase A	Xp	Brunner syndrome	309850	Oxidoreductase	Metabolic (amine): CNS development/function: neurotransmission (DA, 5HT)	None	—	—
MAT1A	Methionine adenosyltransferase	10q	Methionine adenosyltransferase I/III deficiency	250850	Transferase	Metabolic (methionine): CNS development/function (glia: myelin)	*M(2)21AB*	0005278	−162
MCCC1 (*MCCA*)	3-Methylcrotonyl-CoA carboxylase 1	3q	3-Methylcrotonylglycinuria I	210200	Ligase	Metabolic (amino acid): MR 2° local and systemic neuroglial toxicity	*CG2118* (&)	0039877	−300

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
MCCC2 (*MCCB*)	3-Methylcrotonyl-CoA carboxylase 2	5q	3-Methylcrotonyl-glycinuria II	210210	Ligase	Metabolic (amino acid): MR 2° local and systemic neuroglial toxicity	*CG3267* (&)	0042083	−300
MCOLN1	Mucolipin 1	19p	Mucolipidosis IV	605248	Transporter	Lysosomal pathway (glycolipid): MR 2° local toxicity (neuron)	*CG8743*	0036904	−100
MCPH1	Microcephalin	8p	Primary microcephaly 1	607117	[DNA binding]	(?DNA repair): CNS development/function: neurogenesis	[*CG8981*]	0033664	−12
MECP2	Methyl-CpG-binding protein 2	Xq	Rett syndrome; MRX16; neonatal encephalopathy; other	300005	DNA binding	Transcription regulation; CNS development/function: neuron differentiation	None	—	—
MGAT2	β-1,2-*N*-Acetylglucosaminyltransferase II	14q	Congenital disorder of glycosylation type IIa	602616	Transferase	Protein modification (glycosylation): CNS development/function	*Mgat2*	0039738	−57
MID1	Midline 1	Xp	Opitz syndrome type I	300000	Protein binding	Cytoskeleton (microtubule): CNS development/function (?proliferation)	*CG31721* (¶)	0051721	−30
MLYCD	Malonyl-CoA decarboxylase	16q	MLYCD deficiency	606761	Lyase	Metabolic (?fatty acid): ?CNS development/function	none	—	—
MOCS1 (*orfs A, B*)	Molybdenum cofactor synthesis 1	6p	Molybdenum cofactor deficiency type A	603707	Unclassified enzyme	Metabolic (amino acids and others): MR 2° local toxicity (neuron, glia)	orfs A and B: *Mocs1*	0036122	−123, −32
MOCS2 (*orfs A, B*)	Molybdopterin synthase, small and large subunits	5q	Molybdenum cofactor deficiency type B	603708	Unclassified enzyme	Metabolic (amino acids and others): MR 2° local toxicity (neuron, glia)	orfs A and B: *CG10238*[i]	0039280	−13, −29
MPDU1 (*Lec35*)	Mannose-P-dolichol utilization defect 1	17p	Congenital disorder of glycosylation type If	604041	[Chaperone]	Protein modification (glycosylation): CNS development/function	*CG3792*	0031662	−45

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
MTATP6	ATP synthase subunit 6	Mt	Leigh syndrome; neuropathy, ataxia, retinitis pigmentosa	516060	Transporter	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*mt:ATPase6*	0013672	−16
MTCO1	Cytochrome *c* oxidase subunit I	Mt	Mitochondrial syndromic encephalopathy	516030	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*mt:CoI*	0013674	−300
MTCO2	Cytochrome *c* oxidase subunit II	Mt	Mitochondrial encephalopathy	516040	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*mt:CoII*	0013675	−52
MTCO3	Cytochrome *c* oxidase subunit III	Mt	Leigh-like encephalopathy; MELAS	516050	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*mt:CoIII*	0013676	−79
MTCYB	Cytochrome b of complex III	Mt	Multisystem mitochondrial disorder	516020	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*mt:Cyt-b*	0013678	−107
MTHFR	Methylenetetrahydrofolate reductase	1p	Homocystinuria due to MTHFR deficiency	607093	Oxidoreductase	Metabolic (methionine): CNS development/function (myelin)	*CG7560*	0036157	−21
MTND5	NADH-ubiquinone oxidoreductase subunit 5	Mt	Leigh syndrome, MELAS syndrome	516005	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*mt:ND5*	0013684	−65
MTR	Methionine synthase	1q	Methylcobalamin deficiency, cblG type	156570	Transferase	Metabolic (methionine): CNS development/function (myelin)	None	—	—
MTRR	Methionine synthase reductase	5p	Homocystinuria-megaloblastic anemia	602568	Transferase	Metabolic (methionine): CNS development/function (myelin)	[*Cpr*, others]	0015623	−46
MTTE	Mitochondrial glutamic acid transfer RNA	Mt	Encephalomyopathy with diabetes mellitus	590025	Transfer RNA	Metabolic (mitochondrial translation): MR 2° local energy deficiency	*mt:tRNA:E*	0013692	51% id
MTTK	Mitochondrial lysine transfer RNA	Mt	MERRF syndrome; MERRF/MELAS overlap syndrome; others	590060	Transfer RNA	Metabolic (mitochondrial translation): MR 2° local energy deficiency	*mt:tRNA:K*	0013697	50% id

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
MTTL1	Mitochondrial leucine transfer RNA 1	Mt	MELAS syndrome	590050	Transfer RNA	Metabolic (mitochondrial translation): MR 2° local energy deficiency	*mt:tRNA:L:UUR*	0013699	56% id
MTTS1	Mitochondrial serine transfer RNA 1	Mt	MERRF/MELAS overlap syndrome	590080	Transfer RNA	Metabolic (mitochondrial translation): MR 2° local energy deficiency	*mt:tRNA:S:UCN*	0013706	47% id
MTTV	Mitochondrial valine transfer RNA	Mt	Leigh syndrome	590105	Transfer RNA	Metabolic (mitochondrial translation): MR 2° local energy deficiency	*mt:tRNA:V*	0013708	48% id
MYO5A	Myosin VA	15q	Elejalde syndrome (neuroectodermal melanolysosomal disease)	160777	Motor protein	Cytoskeleton: CNS development/function: ?neurotransmission (pre/postsynaptic)	*didum* (&¶)	0015933	−300
NAGLU	*N*-acetyl-α-D-glucosaminidase	17q	Mucopolysaccharidosis type IIIB	252920	Hydrolase	Lysosomal pathway (glycosaminoglycan): MR 2° local toxicity	*ESTS:172F5T*	0014417	−145
NBS1	Nibrin	8q	Nijmegen breakage syndrome	602667	Protein (DNA?) binding	DNA repair: CNS development/function	*nbs*	0026198	−33
NDP	Norrin	Xp	Norrie disease	310600	Ligand	?Signaling pathway (?growth factor): ?neuronal survival	None	—	—
NDUFS1	NADH-ubiquinone oxidoreductase Fe-S p. 1	2q	Mitochondrial complex I deficiency	157655	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*ND75*	0017566	−300
NDUFS2	NADH-ubiquinone oxidoreductase Fe-S p. 2	1q	Encephalomyopathy	602985	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*CG1970, CG111913*	0039909	−300
NDUFS4	NADH-ubiquinone oxidoreductase Fe-S p. 4	5q	Leigh syndrome	602694	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*CG12203*	0031021	−36
NDUFS7	NADH-ubiquinone oxidoreductase Fe-S p. 7	19p	Leigh syndrome	601825	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*CG2014, CG9172*	0039669	−66

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
NDUFS8	NADH-ubiquinone oxidoreductase Fe-S p. 8	11q	Leigh syndrome	602141	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*ND23*	0017567	−75
NDUFV1	NADH-ubiquinone oxidoreductase flavoprotein 1	11q	Leigh syndrome, Alexander syndrome	161015	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*CG9140*, others	0031771	−300
NEU1	Neuraminidase	6p	Sialidosis type II	256550	Hydrolase	Lysosomal pathway (glycolipid): MR 2° local toxicity	*CG7447* (*)	0035539	−19
NF1	Neurofibromin	17q	Neurofibromatosis type I	162200	Receptor signaling protein	Signaling pathway (small/heterotrimeric G proteins): ?synaptic plasticity	*Neurofibromin 1* (&¶)	0015269	−300
NP	Nucleoside phosphorylase	14q	Purine NP deficiency	164050	Transferase	Metabolic (purine): ?MR 2° local toxicity	*CG16758* (&)	0035348	−81
NPC1	Niemann-Pick disease type C1	18q	Niemann-Pick disease types C1, D	607623	Transporter	Lysosomal pathway (cholesterol): MR 2° local toxicity (neuron, glia)	*NPC1, NPC1b*	0024320	−300
NPC2	Niemann-Pick disease type C2	14q	Niemann-Pick disease type C2	601015	Transporter	Lysosomal pathway (cholesterol): MR 2° local toxicity (neuron, glia)	*CG7291* (&)	0031381	−24
NSD1	Nuclear receptor binding SET domain protein 1	5q	Sotos syndrome (cerebral gigantism)	606681	Transcription regulator	Transcription regulation: CNS development/function	*Mes-4* (&¶)	0039559	−113
NTRK1 (*TRKA*)	Neurotrophic tyrosine kinase receptor type 1	1q	Congenital insensitivity to pain with anhydrosis	191315	Receptor	Signaling pathway (RTK): CNS development/function (neuron)	[*Ror*, others]	0010407	−73
OAT	Ornithine ketoacid aminotransferase	10q	Gyrate chorioretinal atrophy	258870	Transferase	Metabolic (amino acid): ?MR 2° local energy deficiency	*CG8782* (&)	0036898	−168
OCRL	Oculocerebrorenal syndrome of Lowe	Xq	Lowe oculocerebrorenal syndrome	309000	Phosphatase	Signaling pathway (PI) and/or protein sorting: CNS development/function (myelin)	*EG:86E4.5* (&¶)	0023508	−105

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
OPHN1	Oligophrenin 1	Xq	MRX60	300127	Receptor signaling protein	Signaling pathway (small G): cytoskeleton (actin); CNS development/function	*Graf* (&¶)	0030685	−82
OTC	Ornithine transcarbamylase	Xp	Hyperammonemia due to OTC deficiency	311250	Transferase	Metabolic (urea cycle): MR 2° systemic toxicity	[*rudimentary*]	0003189	−17
PAH	Phenylalanine hydroxylase	12q	Phenylketonuria	261600	Oxidoreductase	Metabolic (amino acid): MR 2° systemic toxicity (neuron, glia)	Henna (&)	0001208	−153
PAK3	p21-activated protein kinase 3	Xq	MRX30, MRX47	300142	Kinase	Signaling pathway (small G): ?cytoskeleton (actin); CNS development/function	Pak (&¶)	0014001	−148
PANK2	Pantothenate kinase 2	20p	Hallervorden-Spatz disease	606157	Kinase	Metabolic (various): MR 2° local energy deficiency	fumble	0011205	−87
PAX8	Paired box gene 8	2q	Thyroid dysgenesis	167415	Transcription factor	Transcription regulation: endocrine development/function (thyroid)	shaven (&)	0005561	−59
PC	Pyruvate carboxylase	11q	Leigh necrotizing encephalopathy	266150	Ligase	Metabolic: local & systemic toxicity; neurotransmission (glutamate)	*BcDNA: GH06348* (&)	0027580	−300
PCCA	Propionyl-CoA carboxylase, α-subunit	13q	Propionicacidemia	232000	Ligase	Metabolic (amino acid): MR 2° systemic toxicity	*CG2118* (* &)	0039877	−123
PCCB	Propionyl-CoA carboxylase, β-subunit	3q	Propionicacidemia	232050	Ligase	Metabolic (amino acid): MR 2° systemic toxicity	*CG3267* (* &)	0042083	−61
PDHA1	Pyruvate dehydrogenase, E1-α	Xp	PDHA1 deficiency	312170	Oxidoreductase	Metabolic (glycolysis): ?CNS development/function; MR 2° local energy deficiency	*CG7010, CG7024*	0029721	−118
PEPD	Peptidase D (prolidase)	19q	PEPD deficiency	170100	Hydrolase	Protein degradation (?extracellular matrix): MR cause unknown	*Dipeptidase C* (&)	0000455	−139

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
PEX1	Peroxin 1 (peroxisome biogenesis factor 1)	7q	Zellweger syndrome; infantile Refsum disease; NALD	602136	Nucleotide binding	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*l(3)70Da* (&)	0013563	−85
PEX2 (*PXMP3*)	Peroxisomal membrane protein 3	8q	Zellweger syndrome; infantile Refsum disease	170993	Protein binding	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*CG7081*	0035876	−31
PEX3	Peroxin 3 (peroxisome biogenesis factor 3)	6q	Zellweger syndrome	603164	[Protein binding]	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*CG6859*	0036484	−51
PEX5 (*PXR1*)	Peroxisome receptor 1	12p	Zellweger syndrome; NALD	600414	Receptor	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*EG:63B12.5*	0023516	−102
PEX6	Peroxin 6 (peroxisome biogenesis factor 6)	6p	Zellweger syndrome	601498	Nucleotide binding	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*CG11919* (&)	0033564	−82
PEX7	Peroxin 7 (peroxisome biogenesis factor 7)	6q	Rhizomelic chondrodysplasia punctata type I	601757	Receptor	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*CG6486* (&)	0035922	−71
PEX10	Peroxin 10 (peroxisome biogenesis factor 10)	1p	Zellweger syndrome; NALD	602859	Protein binding	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*CG7864*	0035233	−26
PEX12	Peroxin 12 (peroxisome biogenesis factor 12)	17p	Zellweger syndrome	601758	Protein binding	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*CG3639*	0031282	−23
PEX13	Peroxin 13 (peroxisome biogenesis factor 13)	2p	Zellweger syndrome; NALD	601789	Protein binding	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*CG4663*	0033812	−29
PEX16	Peroxin 16 (peroxisome biogenesis factor 16)	11p	Zellweger syndrome	603360	[Protein binding]	Metabolic (oxidation): CNS development/ function (neuron migration, glia)	*CG3947*	0037019	−32

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
PEX19	Peroxin 19 (peroxisome biogenesis factor 19)	1q	Zellweger syndrome	600279	[Protein binding]	Metabolic (oxidation): CNS development/function (neuron migration, glia)	CG5325	0032407	−13
PGK1	Phosphoglycerate kinase 1	Xq	Hemolytic anemia and MR due to PGK1 deficiency	311800	Kinase	Metabolic (glycolysis): ?CNS development/function (?synaptic plasticity)	*Pgk*, *CG9961*	0003075	−164
PHF6	Plant homeodomain-like finger 6	Xq	Börjeson-Forssman-Lehmann syndrome	300414	Transcription regulator	?Transcription: ?CNS development/function	None	—	—
PLP1	Proteolipid protein 1	Xq	Pelizaeus-Merzbacher disease	300401	Structural molecule	CNS development/function: oligodendrocyte (myelin)	*M6*	0037092	−16
PMM2	Phosphomannomutase 2	16p	Congenital disorder of glycosylation type Ia	601785	Isomerase	Protein modification (glycosylation): CNS development/function	*CG10688*	0036300	−74
POMGNT1	*N*-Acetylglucosaminyl-transferase I.2	1p	Muscle-eye-brain disease	606822	Transferase	Protein modification (glycosylation): CNS development/function (neuronal migration)	[*Mgat1*]	0034521	−29
POMT1	Protein *O*-mannosyl-transferase 1	9q	Walker-Warburg syndrome	607423	Transferase	Protein modification (glycosylation): CNS development/function (neuronal migration)	*rotated abdomen* (&)	0003292	−158
POU1F1 (*PIT1*)	POU domain class 1 transcription factor 1	3p	Combined pituitary hormone deficiency	173110	Transcription factor	Transcription: endocrine dev/function (pituitary) → CNS development/function	*ventral veins lacking*, others (*)	0003995	−47
PPGB	β-Galactosidase protective protein (cathepsin A)	20q	Galactosialidosis	256540	Protein binding	Lysosomal pathway (glycolipid): MR 2° local toxicity (neuron)	*CG4572*, others (*)	0038738	−35
PPOX	Protoporphyrinogen oxidase	1q	Variegate porphyria	600923	Oxidoreductase	Metabolic (heme synthesis): MR cause unknown	*protoporphyrinogenoxidase*	0020018	−79
PRPS1	Phosphoribosylpyrophosphate synthetase 1	Xq	PRPS1-related gout	311850	Kinase	Metabolic (purine, pyrimidine synthesis): MR cause unknown	*CG6767* (&)	0036030	−161

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
PRSS12	Serine protease 12 (neurotrypsin)	4q	Autosomal recessive nonspecific MR	606709	Hydrolase	Protein degradation: CNS development/function (synapse)	*Tequila* (&¶)	0023479	−71
PSAP	Prosaposin	10q	Metachromatic leukodystrophy, PSAP deficiency	176801	Enzyme regulator	Lysosomal pathway (glycolipid): MR 2° local toxicity (glia: myelin)	*Saposin-related*	0000416	−27
PTCH	Homolog of Drosophila *patched*	9q	Holoprosencephaly 7; basal cell nevus syndrome	601309	Receptor	Signaling pathway (Hh): CNS development/function (?neuron identity, proliferation)	*patched* (&)	0003892	−127
PTCH2	Homolog 2 of Drosophila *patched*	1p	Nevoid basal cell carcinoma syndrome	603673	Receptor	Signaling pathway (Hh): CNS development/function (?neuron identity, proliferation)	*patched* (&)	0003892	−300
PTEN	Phosphatase and tensin homolog	10q	Cowden syndrome; Bannayan-Zonana syndrome; others	601728	Phosphatase	Signaling pathway (PI): CNS development/function (neuron migration/differentiation)	*Pten* (&¶)	0026379	−72
PTPN11 (*SHP2*)	Protein-tyrosine phosphatase, nonreceptor type 11	12q	Noonan syndrome 1; LEOPARD syndrome	176876	Phosphatase	Signaling pathway (various): ?CNS development/function	*corkscrew* (&¶)	0000382	−114
PTS	6-Pyruvoyltetrahydropterin synthase	11q	Hyperphenylalaninemia due to PTS deficiency	261640	Lyase	Metabolic (BH_4 synthesis): neurotransmission (amines); systemic toxicity	*purple*	0003141	−40
PVRL1	Poliovirus receptor-like 1 (nectin 1)	11q	Cleft lip/palate-ectodermal dysplasia syndrome; others	600644	Cell adhesion molecule	Cell-cell adhesion: CNS development/function (synaptogenesis, ?plasticity)	None	—	—
PYCS	δ-1-Pyrroline-5-carboxylate synthetase	10q	Hyperammonemia	138250	Oxidoreductase	Metabolic (amino acid): MR 2° systemic toxicity; ?neuromodulation	*CG7470*	0037146	−300
QDPR	Quinoid dihydropteridine reductase	4p	Atypical phenylketonuria	261630	Oxidoreductase	Metabolic (BH_4): neurotransmission (amines); systemic toxicity	*Dihydropteridine reductase*	0035964	−70
RAI1	Retinoic acid induced 1	17p	Smith-Magenis syndrome	607642	[Transcription regulator]	?Transcription regulation; CNS development/function: ?neuron differentiation	none	—	—

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
RELN	Reelin	7q	Norman-Roberts lissencephaly syndrome	600514	Ligand	Signaling pathway (various): CNS development (neuron migration, differentiation)	none	—	—
RSK2 (*RPS6KA3*)	Ribosomal S6 kinase 2	Xp	Coffin-Lowry syndrome; MRX19	300075	Kinase	Signaling pathway (growth factor): ?CNS development/function	*S6kII* (&¶)	0011285	−300
SARA2 (*SAR1B*)	Sar1-ADP-ribosylation factor 2	5q	Chylomicron retention disease with Marinesco-Sjogren syndrome	607690	Nucleotide binding	Transport (lipids): MR cause unknown	*sar1* (* &)	0038947	−80
SC5DL (*SC5D*)	Sterol C5-desaturase (lathosterol dehydrogenase)	11q	Lathosterolosis	602286	Oxidoreductase	Metabolic (cholesterol): signaling pathway (Hh); ?CNS development/function	None	—	—
SCO2	Homolog of yeast *SCO2*	22q	Fatal infantile cardioencephalomyopathy	604272	Chaperone	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*CG8885*	0031656	−56
SDHA	Succinate dehydrogenase complex subunit A	5p	Leigh syndrome	600857	Oxidoreductase	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*Scs-fp, CG5718*	0017539	−300
SGSH (*HSS*)	*N*-Sulfoglucosamine sulfohydrolase	17q	Mucopolysaccharidosis type IIIA	605270	Hydrolase	Lysosomal pathway (glycosaminoglycan): MR 2° local toxicity	*CG14291* (&)	0038660	−139
SHH	Sonic hedgehog	7q	Holoprosencephaly 3	600725	Ligand	Signaling pathway(Hh): CNS development (neuron and glia identity, differentiation)	*hedgehog* (&¶)	0004644	−83
SIX3	Homolog 3 of Drosophila *sine oculis*	2p	Holoprosencephaly 2	603714	Transcription factor	Transcription reg: CNS development (cell fate, differentiation; morphogenesis)	*Optix* (&¶)	0025360	−87
SLC4A4 (*NBC1*)	Solute carrier 4A4 (Na-HCO_3 cotransporter)	4q	Renal tubular acidosis II	603345	Transporter	Transport (pH regulation): ?CNS development/function (neuron, glia)	*Na^+-driven anion exchanger 1* (&)	0031899	−300

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
SLC5A5	Solute carrier 5A5 (Na-I symporter)	19p	Genetic defect in thyroid hormonogenesis I	601843	Transporter	Transport (iodide): endocrine function (thyroid): CNS development/function	*CG2187*, others	0017448	−84
SLC6A8 (*CRTR*)	Solute carrier 6A8 (creatine transporter)	Xq	X-linked creatine deficiency syndrome	300036	Transporter	Transport (creatine): CNS development/function; MR 2° local energy deficiency	*CG1732*, others (*)	0039915	−156
SLC7A7	Solute carrier 7A7 (y + L amino acid transporter 1)	14q	Lysinuric protein intolerance	603593	Transporter	Transport (dibasic amino acids): ?MR 2° systemic toxicity	*CG1607*, others	0039844	−124
SLC12A1 (*NKCC2*)	Solute carrier 12A1 (Na-K-Cl transporter 2)	15q	Bartter syndrome type I, antenatal hypercalciuric form	600839	Transporter	Transport (ions): MR cause unknown; ?systemic toxicity	*CG4357*, others	0036279	−300
SLC12A6 (*KCC3*)	Solute carrier 12A6 (K-Cl cotransporter)	15q	Agenesis of corpus callosum (ACCPN)	604878	Transporter	Transport (ions): CNS development/function (myelin, neuron)	*BEST:CK01510* (&)	0025698	−300
SLC17A5	Solute carrier 17A5 (sialin)	6q	Infantile sialic acid storage disorder; Salla disease	604322	Transporter	Lysosomal pathway (various): MR 2° local toxicity (neuron, glia)	*CG4288*, others	0038799	−94
SLC25A15 (*ORNT1*)	Solute carrier 25A15 (ornithine transporter 1)	13q	HHH syndrome	603861	Transporter	Transport (ornithine): MR 2° systemic toxicity ?and CNS development/function	*CG1628* (&)	0030218	−71
SMPD1 (*ASM*)	Sphingomyelin phosphodiesterase 1	11p	Niemann-Pick disease, type A	257200	Hydrolase	Lysosomal pathway (glycolipid): MR 2° local toxicity (neuron)	*CG3376* (&)	0034997	−124
SMS	Spermine synthase	Xp	Snyder-Robinson syndrome	300105	Transferase	Metabolic (polyamine): ?CNS development/function (neuron excitability)	*CG4300*	0036272	−64
SOX3	SRY-related HMG-box 3	Xq	MR with growth hormone deficiency	313430	Transcription factor	Transcription regulation: CNS development/function (neurogenesis)	*SoxNeuro* (&¶)	0029123	−25
SOX10	SRY-related HMG-box 10	22q	Waardenburg-Shah syndrome, neurologic variant	602229	Transcription factor	Transcription regulation: CNS development (myelin: oligodendrocyte differentiation)	*Sox100B* (&)	0024288	−29

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
SUOX	Sulfite oxidase	12q	Sulfocysteinuria	606887	Oxidoreductase	Metabolic (amino acids): MR 2° local toxicity	*CG7280*	0030966	−130
SURF1	Surfeit 1	9q	Leigh syndrome	185620	[Protein binding]	Metabolic (oxidative phosphorylation): MR 2° local energy deficiency	*Surfeit 1*	0029117	−57
TAT	Tyrosine aminotransferase	16q	Tyrosinemia type II	276600	Transferase	Metabolic (amino acids): ?MR 2° systemic toxicity	*CG1461* (&)	0030558	−127
TBCE	Tubulin-specific chaperone E	1q	Hypoparathyroidism-retardation-dysmorphism syndrome	604934	Chaperone	Cytoskeleton (microtubule): ?CNS development/function	*CG7861* (&¶)	0033055	−61
TC2	Transcobalamin II	22q	TC2 deficiency	275350	Transporter	Transport (cofactor): CNS development/function and ?local neurotoxicity	None	—	—
TDGF1 (*CRIPTO*)	Teratocarcinoma-derived growth factor 1	3p	Holoprosencephaly, other forebrain defects	187395	Receptor	Signaling pathway (nodal): CNS development/function	None	—	—
TG	Thyroglobulin	8q	Genetic defect in thyroid hormonogenesis V	188450	Ligand	Hormone synthesis: endocrine function (thyroid): CNS development/function	[*Acetylcholinesterase*, others]	0000024	−33
TGIF	TG-interacting factor	18p	Holoprosencephaly 4	602630	Transcription regulator	Transcription regulation: CNS development/function (morphogenesis, ?proliferation)	*vismay*, *achintya*	0033748	−25
THRB	Thyroid hormone receptor β	3p	Thyroid hormone resistance	190160	Receptor	Transcription regulation: endocrine function (thyroid): CNS development/function	*E75B*, others (*)	0000568	−37
TIMM8A (*DDP1*)	Translocase of inner mitochondrial membrane 8	Xq	Mohr-Tranebjaerg syndrome	300356	Transporter	Transport (mitochondria): metabolic; MR 2° local energy deficiency	*Tim8*	0027359	−15

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
TM4SF2	Transmembrane 4 superfamily, member 2	Xq	MRX58	300096	Signal transducer	Signaling pathway (integrin): ?actin cytoskeleton; ?CNS development/function	*Tetraspanin 29Fb*, others	0032075	−22
TPI1	Triosephosphate isomerase 1	12p	Nonspherocytic hemolytic anemia	190450	Isomerase	Metabolic (glycolysis): MR 2° local energy deficiency ?and local toxicity	*Triose phosphate isomerase*	0003738	−88
TPO	Thyroid peroxidase	2p	Thyroid hormone or total iodide organification defect	606765	Oxidoreductase	Hormone synthesis: endocrine function (thyroid): CNS development/function	*Peroxidasin* (* &)	0011828	−148
TSC1	Hamartin	9q	Tuberous sclerosis 1	605284	Protein binding	Cytoskeleton: CNS development/function (neuron/glia proliferation, differentiation)	*Tsc1*	0026317	−43
TSC2	Tuberin	16p	Tuberous sclerosis 2	191092	Receptor signaling protein	Signaling pathway (small G): CNS development/function (neuron/glia proliferation, differentiation)	*gigas* (&¶)	0005198	−151
TSHB	Thyroid-stimulating hormone, β-chain	1p	Congenital hypothyroidism due to TSHB deficiency	188540	Ligand	Signaling pathway (heterotrimeric G): endocrine function: CNS development/function	None	—	—
TSHR	Thyroid-stimulating hormone receptor	14q	Congenital hyperthyroidism, hypothyroidism	603372	Receptor	Signaling pathway (heterotrimeric G): endocrine function: CNS development/function	*Fsh* (&)	0016650	−113
TTF1 (*NKX2A*)	Thyroid transcription factor 1	14q	Congenital hypothyroidism with choreoathetosis	600635	Transcription factor	Transcription regulation: endocrine development/function (thyroid): CNS development/function	*scarecrow* (&)	0028993	−44

(*continued*)

APPENDIX

(Continued)

Gene symbol[a]	Gene name	Chr. arm[b]	Clinical disorder[c]	OMIM no.	Molecular-function GO category[d]	Biological function(s)[e]	Drosophila homolog(s)[f]	FlyBase no.[g]	BLASTP *E*-value[h]
TTF2 (*FOXE1*)	Thyroid transcription factor 2	9q	Congenital hypothyroidism	602617	Transcription factor	Transcription regulation: endocrine development/ function (thyroid): CNS development/ function	*crocodile*, others (*)	0014143	−30
UBE3A	Ubiquitin-protein ligase E3A	15q	Angelman syndrome	601623	Small protein conjugating	Protein degradation (proteasome): CNS development/ function (neuron differentiation)	*CG6190* (&¶)	0036148	−175
XPA	Xeroderma pigmentosum type A	9q	Xeroderma pigmentosum type A	278700	Protein (DNA?) binding	DNA repair: CNS development/function	*Xpac*	0004832	−50
ZFHX1B (*SIP1*)	Zinc-finger homeobox 1B	2q	Hirschsprung disease-mental retardation syndrome	605802	Transcription regulator	Transcription regulation: CNS development/function; ?signaling pathway	[*Kr-h1*, others]	0028420	−17
ZIC2	Zinc-finger protein of cerebellum 2	13q	Holoprosencephaly 5	603073	Transcription factor	Transcription regulation: CNS development (cell fate, differentiation; morphogenesis)	*odd paired* (&)	0003002	−83

?, precedes functions suggested but not conclusively demonstrated.

[a] Alternative gene symbols used commonly in the literature are in parentheses. Genes marked "•••" were found by the OMIM search for "cognitive impairment" or "learning disability."

[b] Mt indicates a gene in the mitochondrial genome.

[c] Additional disorders may also be caused by mutation of these genes.

[d] Bracketed entries represent a proposed function, on the basis of the available literature, for genes that are not listed in GO or have been classified by GO as "unknown molecular function."

[e] 2° means "secondary to."

[f] The Drosophila genes with prefixes CG, BG, EG, ESTS, BEST, or BcDNA have been identified only by genomic sequencing projects (see FlyBase at http://flybase.bio.indiana.edu/ for details). An asterisk (*) following a gene name indicates a homolog that may be an ortholog, but it was not possible to assign ortholog status only on the basis of BLAST results and functional domain alignments. Gene names in brackets are homologous to the human gene, but are not likely to be orthologs on the basis of reverse BLAST analysis. All other Drosophila genes listed are orthologs. The ampersand symbol (&) after an ortholog indicates that it was selected from among two or more homologous genes. The paragraph symbol (¶) after an ortholog indicates that it is a "prime candidate" (Table 3).

[g] The prefix FBgn before each accession number is required to access the entry in FlyBase. If two or more homologs are listed, only the FlyBase accession number of the gene producing the top-scoring BLASTP alignment is given.

[h] Only the exponent of the forward BLASTP *E*-value is shown. If two or more homologs are listed, only the exponent of the top-scoring BLASTP alignment is shown. For tRNA genes, the percentage identity, based on a pairwise alignment between the Drosophila and human sequences (using LALIGN), is shown in lieu of a BLAST score.

[i] The gene-sequencing software used by the Drosophila genome sequencing project (releases 2 and 3) has failed to recognize that homologs of both *MOCS2* open reading frames are present.