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Animal models of mental retardation: from gene to cognitive function

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Abstract

About 2–3% of all children are affected by mental retardation, and genetic conditions rank among the leading causes of mental retardation. Alterations in the information encoded by genes that regulate critical steps of brain development can disrupt the normal course of development, and have profound consequences on mental processes. Genetically modified mouse models have helped to elucidate the contribution of specific gene alterations and gene–environment interactions to the phenotype of several forms of mental retardation. Mouse models of several neurodevelopmental pathologies, such as Down and Rett syndromes and X-linked forms of mental retardation, have been developed. Because behavior is the ultimate output of brain, behavioral phenotyping of these models provides functional information that may not be detectable using molecular, cellular or histological evaluations. In particular, the study of ontogeny of behavior is recommended in mouse models of disorders having a developmental onset. Identifying the role of specific genes in neuropathologies provides a framework in which to understand key stages of human brain development, and provides a target for potential therapeutic intervention.

Keywords: Genetically modified; Neurodevelopmental disorders; Mental retardation; Mouse; Behavior; Development; Neuropathology; Genetic disorders

1. Introduction

Development of the central nervous system (CNS) involves the creation of numerous cell types in precise locations and at precise times, which create neural circuits that subserve sensory, motor, as well as cognitive functions [1,2]. Classically, though simplistically, CNS development is divided into three major stages: neuronal generation (neurogenesis), migration, and differentiation/maturation. Although the subject of debate, maturation of certain regions of neocortex continues likely through the teen years in humans. Aberrations in one or more of these stages lead to alterations in the course of brain development that can have long-term consequences for the integrity of higher cognitive abilities [3,4].

Approximately 2–3% of children are affected by mental retardation (MR). An individual is considered to have MR based on the following three criteria: (i) a significantly subaverage general intellectual functioning, (ii) significant limitations in adaptive functioning in at least two of the following skill areas: communication, selfcare, home living, social/interpersonal skills, use of community resources, selfdirection, functional academic skills, work, leisure, health, and safety, and (iii) the onset of cognitive disabilities must occur before age 18 years [5]. The onset of the disabilities suggests an aberration in the normal course of brain development, particularly in brain regions associated with higher cognitive functions. In one-third of the cases, the etiology of the MR is unknown. In the cases in which the etiology is known, genetic deficits rank among the leading causes [6]. Furthermore, a higher proportion of MR cases in males (25–30% than in females) suggests that an X-linked pattern of inheritance may be an important cause of MR [7]. In fact, X-linked mental retardation (XLMR) represents 5% of total diagnosed MR [8].

Genes regulating proper functioning of the nervous system and development of cognitive functions belong to

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Table 1
A selection of mouse models deficient for genes involved in critical steps of brain development

Gene	Critical step in brain development	Human disorder	Animal model references
*HESX*1	Prosencephalic midline development	Septo-optic dysplasia	[134]
*EMX*2	Specification of the cortex	Schizencephaly	[135]
*ZIC*2, *SHH*	Hemispheric cleavage	Holoprosencephaly	[136,137]
LIS 1, *DOUBLECORTIN*	Ongoing neural migration	Lissencephaly, band eteropia	[105,138]
*MeCP*2	Synaptogenesis (disruption of axon-denditic connections?)	Rett syndrome	[13,79,80]
FMRI	Synaptogenesis (spine abnormalities)	X fragile syndrome	[93–97]
alpha-GDI	Synaptogenesis (impaired neurite extension)	Non-specific mental retardation	[112]

HESX1, homeobox-containing, embrionic stemm cell t-conscription factor [x]1; EMX2, empty spiracles in factor [X]2; ZIC2, zinc finger cerebellar expressed 2; SHH, Sonic Hedgehog; LIS1, Lissencephaly 1; MeCP2, methyl-CpG binding protein 2; FMR1, fragile X mental retardation 1; alpha-GDI, Rab GDP dissociation inhibitor alpha.

highly heterogeneous group, encoding for proteins that play important roles in diverse processes. Alterations in the information these genes encode, or changes in their expression pattern can cause developmental anomalies that have a profound effect on mental processes (Table 1) [9–11]. It is very likely that many of the symptoms seen in human genetic brain disorders are the result of developmental changes [12].

Genetically modified mice are currently the most commonly used approach to investigate the role of a specific genetic alteration and to model pathologies leading to MR [13–18]. It is noteworthy that the information gained by investigating disorders in genetically modified mice is also advancing our knowledge of the role that selected genes play in regulating important aspects of normal cognitive functions.

2. Genetically modified mice: a tool to investigate developmental brain pathologies

The mouse is the most widely used laboratory species to provide insights linking specific genes to biological functions. Its wide use is primarily because among mammals, the mouse is most amenable to genetic manipulations. Furthermore, our extensive knowledge of the genome, physiology and behavior of the mouse makes it possible to interpret the effects of gene manipulations [19–21].

Human brain disorders of suspected genetic origin can be modeled in the mouse using standardized procedures, such as knocking out genes by the homologous recombination technique, or random insertion of wild-type or mutant transgenes. These specific genes (or the lack of specific genes) then induce alterations of protein products that lead downstream to pathological events that mimic the human disorder [19,20]. If the genetically modified mice display symptoms reminiscent of the human disorder, they represent an important tool to study the molecular basis of specific pathologies and test potential therapeutic interventions. Not surprisingly, a considerable effort has been undertaken by many laboratories to develop genetically modified mice that display key features of specific human brain disorders (see the web site of Neuroscience Mutagenesis Facility at Jackson Laboratory, http://www.jax.org/nmf).

With the rapid and dramatic increase in the types of genetically modified mice available [22], it is clear that appropriate phenotyping, including behavioral characterization, is critical [19,23–26]. Behavioral analysis can provide crucial information about the integrity of CNS functions that is not detectable following commonly used molecular, cellular or histological evaluations [12,27]. Most laboratories involved in the testing of genetically modified mice subject adult animals to a battery of behavioral tests that assess motor and sensory, as well cognitive functions. Several learning tests including olfactory-based paradigms (e.g. social transmission of food preferences), which are extremely relevant in macrosmatic mammals such as mice [28], are used to characterize cognitive impairment [29–31].

However, there is still skepticism towards the idea that human cognitive impairment can be modeled in the mouse. This skepticism arises erroneously from the expectation that specific symptoms will have the same physical manifestation across species. However, different species have species-specific behavioral repertoires shaped by their evolutionary history [32]. Thus, modeling of human-like symptoms in animals should be based primarily on an expectation of functional similarity of the displayed behavioral strategy, rather than on one of behavior equivalency. The crucial point is not whether a mouse would show a given cognitive impairment, but rather, how a cognitive impairment would manifest itself in a mouse [23,33]. Ethological studies have provided detailed descriptions of the mouse behavioral repertoire that allow an accurate analysis of its behavioral profile in order to identify deficits in specific behavioral abilities [12,19,20,34].

3. Genetically modified mouse models of neurodevelopmental pathologies

The genetic defects causing neurodevelopmental pathologies have been classified in different categories:

chromosome aneusomies, partial chromosome aberrations, subchromosomal anormalities, monogenic disorders and polygenic predispositions [9]. These defects result in altered metabolism of proteins, carbohydrates or lipids, enzymatic deficits or mitochondrial disorders. These alterations then lead to aberrations in nervous system development and/or functioning, and to impairments in cognitive performance. The nature and severity of cognitive impairments, however, are diverse. Several genetically modified mouse models of neurodevelopmental pathologies have been developed. Here, we describe models of three different human genetic disorders that present MR, selected amongst those having a higher incidence in the population.

3.1. Down syndrome

Down syndrome (DS), or trisomy 21, is the most common genetic cause of MR, occurring once in every 700 births [18]. The etiological cause of DS is a total or partial triplication of human chromosome 21 (HC21) [35]. Individuals with trisomy 21 display muscular hypotonia, MR and deposition of Alzheimer-like plaques and neurofibrillar tangles in brain in the third decade of life. DS individuals may also show a wide range of other pathological features such as congenital heart disease, sterility, higher incidence of leukemia, immune system perturbations, and premature aging [36,37]. Brains of DS individuals shows several morphological alterations, including reduced cortical size, increased neuronal density, loss of cholinergic neurons in the basal forebrain, and a disproportionately small cerebellum [36,38,39]. Within neocortex, alterations in dendritic spines are reported [40]. This combination of abnormalities suggests that several stages of normal brain development are altered in DS individuals.

Because mouse chromosome 16 (MC16) has considerable synteny with HC21 [21,41], full and segmental trisomy 16 mice have been developed, by means of selected Robertsonian chromosome translocation, as models for DS. The first model, developed in 1975, is the trisomy 16 (Ts16) mouse which has three copies of MC16 in its genome (Fig. 1) [42]. During prenatal development, Ts16 mice display numerous phenotypic abnormalities including some pathological characteristics similar to those displayed by DS individuals, such as a reduced brain weight, a relatively small cerebellum, a reduced neuronal number in selected cortical regions, and abnormal electrophysiological properties of the hippocampus [43–45]. Unfortunately, these mice die in utero, which precludes study of their postnatal development. Another factor limiting their usefulness as a model for DS is that MC16 contains genes that are not located on HC21. Triplication of some of the non-syntenic genes likely accounts for the death of the mice in utero.

A second model is the Ts(17^{16})65Dn or Ts65Dn mouse, which has a partial trisomy [46]. Among trisomic mouse models created, this one carries triplication of the MC16 region that is most syntenic to HC21 (Fig. 1). Not surprisingly, these mice display more DS-like symptoms than the other models. In particular, a behavioral analysis in early phases of ontogeny has revealed a delayed sensory-motor and behavioral development [47]. Furthermore, Ts65Dn mice display hyperactivity, altered emotional behavior, and learning and memory impairments in adulthood [46,48,49]. Neuroanatomical alterations in Ts65Dn mice include decreased volume of CA2 region and reduced neuronal number in the dentate gyrus of the hippocampus when compared to their control littermates [50]. These results are consistent with alterations in neuronal neurogenesis and/or migration. Neurochemical studies have revealed functional abnormalities in the noradrenergic projections to the cerebral cortex and hippocampus, but not in the cerebellum [51]. Because these mice show a marked loss of basal forebrain cholinergic neurons, they have been considered also an animal model for Alzheimer's disease [47].

More recently, two other partial trisomy models have been developed: the Ts1Cje and Ms1Ts65 models. Ts1Cje mice carry an extra copy of MC16 segment spanning from *Sod1* (not expressed) to *Mx1* (Fig. 1). These mice display less severe learning deficits than those of Ts65Dn, namely a slight impairment in spatial learning and a slight hypoactivity profile [52,53]. No basal forebrain cholinergic neuronal degeneration has been found in Ts1Cje mice. Ms1Ts65 mice carry an extra copy of a shorter MC16 segment spanning from *App* to *Sod 1* (not expressed; Fig. 1) and show very subtle behavioral deficits in a spatial navigation task [53].

A specific region of HC21 of 2 Mb surrounding D21S55 at 21q22.2, the Down syndrome Critical Region 1 (DCR-1), may be responsible for several phenotypical features present in DS individuals, including MR [54–56]. However, other authors have challenged this hypothesis suggesting that a larger region of chromosome 21 could be responsible for cognitive impairment, though not excluding the crucial role played by DCR-1 [57]. In order to evaluate the effect of triplication of different genes or groups of genes located on this region, transgenic mice have been developed by inserting yeast artificial chromosomes (YACs) bearing a fragment of the human DCR-1 into the murine genome. Specifically, four YAC mouse lines have been created [58], each one bearing a different fragment that is either contiguous or partially overlapping with the others. Two out of the four YAC lines, the 230E8 and 152F7 lines, the latter containing among others the *DYRK1A* gene, show learning and memory impairments in a spatial navigation task (the Morris water maze) in adulthood. Furthermore, 152F7 mice are hypoactive in a 1 h activity test performed in the dark. Histopathological analysis reveals that the 152F7 line show no neuropathological correlates for the reported learning and memory impairments and hypoactivity. In contrast, the 230E8 line displays a significantly greater cortical neuronal density [58].

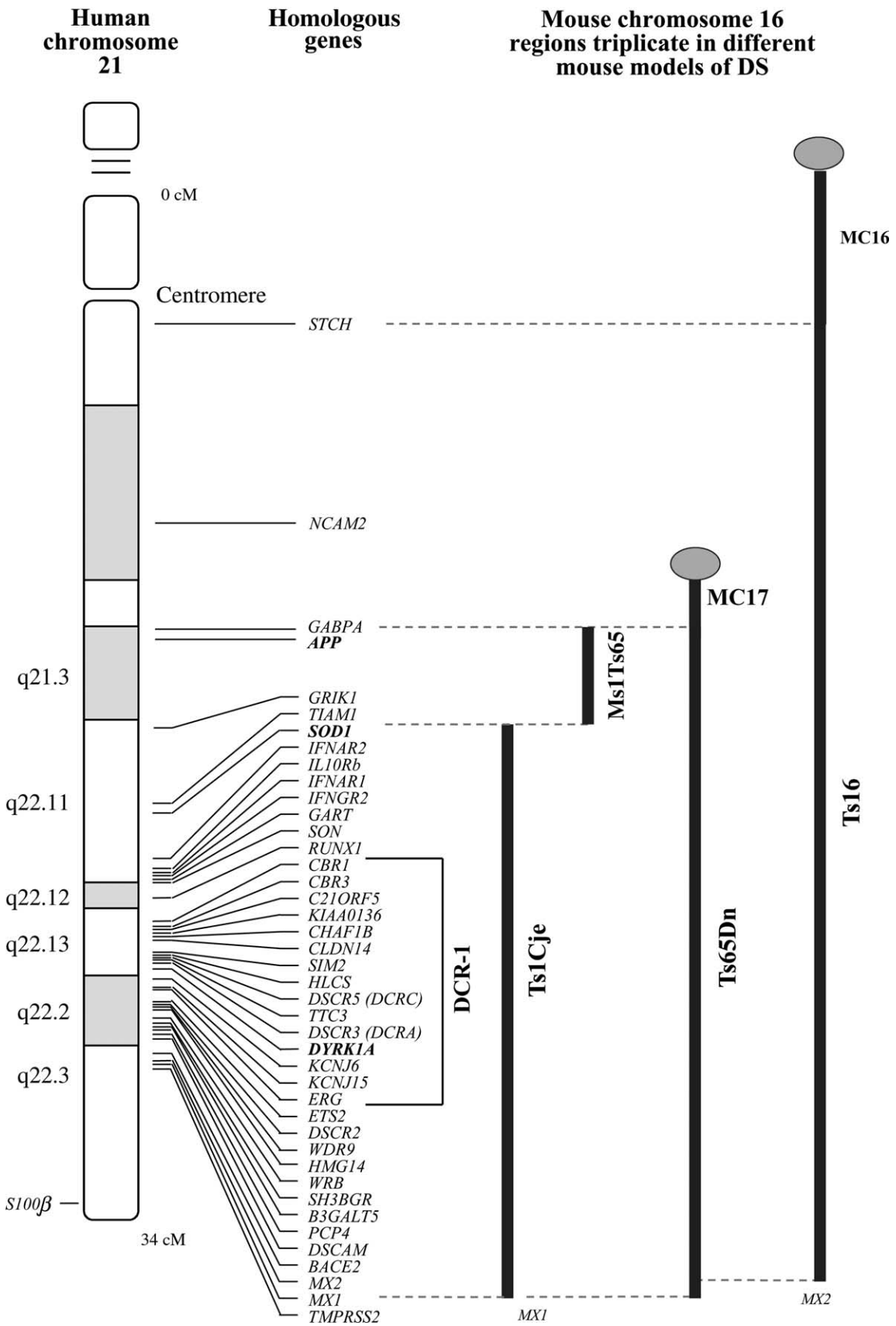

Fig. 1. Left side: schematic view of genes located on human chromosome 21 region syntenic to mouse chromosome 16. Mouse gene homologue to human *S100β* is located on mouse chromosome 10. Right side: mouse chromosome 16 regions triplicate in different mouse models of Down syndrome [53,139].

In order to identify the effects due to the presence of the three copies of each gene located on HC21, mouse models having three copies of a single gene have been also generated. Transgenic mice overexpressing *SOD1* (superoxyde dismutase) human gene have been developed [59,60]. These mice display neuromuscular junctions abnormalities and premature aging by oxidative damage in the brain, the latter symptom suggests that *SOD1* may be responsible for the premature aging of the brain associated with DS [60,61]. Another single gene mouse model overexpresses the *Dyrk1a* gene [62]. The *DYRK1A* gene, *Drosophila minibrain* homologous, plays a crucial role in brain development and function [63,64]. In particular, the DYRK1A protein, a serine–threonine kinase, phosphorylates a variety of substrates, such as the microtubule-associated protein tau [65], the transcription factors of the Forkhead family [66], and the cyclic-AMP response element binding protein (CREB) [67], which play a key roles in different biochemical pathways. Transgenic mice overexpressing the murine *Dyrk1a* gene in the forebrain exhibit several developmental alterations, including a delay in the appearance of selected motor responses. In adulthood, these mice display hyperactivity in an open field, and impairments in learning and memory processes in a Morris water-maze task [62]. Recently, a targeted disruption of the *Dyrk1a* gene has been performed [68]. Whereas the loss of both *Dyrk1a* copies in mice induces embryonic mortality, heterozygotes exhibit decreased brain and body size, and a delayed neurobehavioral development [68].

Several other DS mouse models have been developed targeting different genes, such as *Sim2*, involved in CNS development. Mice with an extra-copy of *SIM2* displayed reduced exploratory behavior and sensitivity to pain [69]. In addition, mice overexpressing genes associated with Alzheimer-like phenotypes, which are seen almost invariably in older DS individuals, have also been generated. For example, mice overexpressing *APP* [70], a mutated form of *APP* [71–73], or S100β gene have been tested [74,75].

3.2. Rett syndrome

Classic Rett syndrome (RTT) is a neurodevelopmental disorder found almost solely in females, with prevalence of 1:10,000–20,000. Clinical characteristics of the syndrome include abnormal motor gait, stereotypic hand wringing movements, and autistic-like behavior. Affected girls also exhibit speech abnormalities and severe cognitive deficits in most cases [76]. One peculiar aspect of this disorder is that individuals appear normal at birth, then between 6 and 18 months they begin to lose some already acquire skills, such as communication, language and motor coordination.

The apparent cause of RTT is the mutation of an X-linked gene encoding MeCP2 (methyl-CpG binding protein 2), a protein that binds specifically to methylated CpG pairs of DNA sequences and, in association with the co-repressor *sin 3a* and histone deacetylases, condenses chromatin structure making DNA inaccessible to transcriptional machinery. The protein is found ubiquitously, suggesting that it is responsible for DNA silencing in different tissues. This evidence, however, appears difficult to reconcile with the fact that most of the RTT phenotype lays within the neurological field [76–78].

In the past year, three laboratories have produced mice with genetically altered *MeCP*2 that display some features of RTT—Jaenisch and colleagues [79], Bird and colleagues [13], and Zoghbi and colleagues [80]. Numerous laboratories are characterizing the biochemical, pathological, and, of course, behavioral features of these mice, and comparing them to the human condition. The mouse model described recently by Zoghbi's group has a truncated form of *MeCP2*. These mice appear normal until 6 weeks of age, and then exhibit progressive motor abnormalities (associated with RTT) and increased anxiety-related behaviors (associated with RTT), quite strikingly they also display stereotypic forelimb movements (associated with RTT), but only when suspended by the tail. These mice, however, do not display cognitive deficits on a water maze or contextual fear conditioning task, and so do not reproduce the severe MR that is a hallmark of RTT. Another mouse model described by Jaenisch's group appears normal at birth, and begins to exhibit motor abnormalities (associated with RTT) and weight gain (not associated with RTT) at 5 weeks [79]. Most of the male mice, who are hemizygous for the mutation, die by 10 weeks of age. Preliminary results suggest that these mice do exhibit some cognitive deficits, unlike the Zoghbi model [81]. A third mouse model described by Bird's group begins to exhibit motor abnormalities (associated with RTT), irregular breathing (associated with RTT), and weight gain (not associated with RTT) between 3 and 8 weeks of age. Cognitive testing in these mice has not yet been described. The different mouse lines are likely modeling different aspects of RTT syndrome, a syndrome that includes a wide range of forms and severity [82]. In this enigmatic syndrome, which results from alterations in a protein that is fundamental to regulation of gene expression, it seems likely that multiple neurotransmitters, brain regions and behavioral processes are interrupted, each with different developmental timecourses [83].

On the basis of a series of clinical and neuropathological evidence pointing to RTT as a disorder of neuronal development and primarily of pre- and post-synaptic components of synapses [84,85], Johnston et al. proposed a unifying hypothesis [86]. The major effect of the *MeCP2* mutations could be to disrupt synaptic proliferation and pruning in a restricted developmental window coinciding with the peak of synaptic proliferation in cerebral cortex (7–18 months in humans, and the first weeks of life in the mouse). This would suggest that aberrations in neuronal maturation are a primary cause of the behavioral phenotype in RTT. Such an hypothesis could be tested by detailed neuroanatomical and behavioral phenotyping of *MeCP2* mice during very early phases of postnatal development.

Thus far, studies of this nature have not been carried out in any of these three RTT models.

3.3. X-linked mental retardation

Since genes located on the X chromosome are in an haploid status in males, X-linked neuropathologies have a significantly higher incidence in males than in females. In particular, XLMR with different grades of cognitive impairment, represents 5% of all MR cases, and occurs 20–30% more frequently in males [7,8]. For diagnostic and clinical purposes, X-linked forms of MR are classified as syndromal or non-specific. In the first case, cognitive impairment is one of symptoms of a complex syndrome that is characterized by clear signs of developmental abnormalities, such as alterations in the normal pattern of brain organization or connectivity. By contrast, individuals affected by non-specific forms of MR, display cognitive impairment only as symptom of disease [87].

Among syndromal forms of XLMR, Fragile X syndrome is the most frequently inherited cause of MR (it accounts for 15–20% of all XLMR) [88]. The molecular basis of this pathology is an alteration in the number of copies of a CGG trinucleotide repeat at the 5′ untranslated region of the *FMR1* gene. Normal individuals have 6–50 trinucleotide repeats, whereas individuals with Fragile X have more than 230 units [89]. As a consequence, an hypermethylation of the repeat and promoter regions occurs, leading to a lack of expression of the *FMR1* gene product: the Fragile X Mental Retardation Protein (FMRP) [90]. This protein is a member of a family of RNA-binding proteins that appears to play a central role in brain development, in particular during synaptogenesis [91,92]. In *Fmr1* knockout mice, the *Fmr1* wild-type gene is replaced by a non-functional *Fmr1* gene leading to the absence of FMRP [93–98]. These mice exhibit subtle cognitive and behavioral impairments. In particular, the mice show reduced flexibility in spatial orientation; they are impaired in learning to locate the hidden platform during the reversal phase of spatial navigation testing, after a period of intensive acquisition training [93,94,97]. More recently, *Fmr1* knockouts bred to a different genetic background (C57BL/6 instead of 129Re/J) only partially replicate previous results [96,98]. It is noteworthy that for behavioral studies C57BL/6 mice are usually more suitable than 129 on several behavioral tasks including spatial and emotional learning and memory paradigms [19,20,99]. The C57BL/6 *Fmr1* mice display increased exploratory behavior. An histopathological analysis, using Golgi impregnation techniques, reveals abnormal dendritic spines, as well as greater spine density along the apical dendrite in layer V pyramidal cells of occipital cortex in *Fmr1* knockouts [100]. These findings, which parallel alterations found in individuals with Fragile X, suggest that FMRP is involved in synaptic maturation and pruning. These structural anomalies are likely to be one of the neural substrates for the cognitive impairment associated with Fragile X [101].

Another syndromal form of XLMR is due to mutations in *DCX* gene, whose product is *DOUBLECORTIN*. This protein is a microtubule-associated protein expressed in migrating and differentiating neurons, and plays a crucial role in neocortical and hippocampal development [102]. Mutations of *DCX* gene in hemizygous males cause lissencephaly, whose main pathological features are a smooth cerebral surface with a paucity of gyri and an abnormally thick cortex. By contrast, a single mutant allele of *DCX* in females causes a double cortex phenotype consisting of a heterotopic band of neurons in the white matter underlying the normal cortex [103,104].

Recently, *Dcx* knockout mice have been developed [105]. Surprisingly, despite the profound cortical alteration found in humans with *DCX* mutations, these mice showed normal neocortical lamination and normal patterns of neocortical neurogenesis and neuronal migration. It is possible that there are species differences in proteins involved in neuronal migration between the two species, or that the mouse has more redundancy and/or compensations for these effects [105]. However, *Dcx* knockouts do display a profound disruption of hippocampal lamination, which is most severe in the CA3 region, paralleling the structural alterations found in humans with this syndrome. The mice show behavioral impairments in context and cued conditioned fear, which probes an animal's ability to associate a fearful stimulus with a defensive response, that may be due to the abnormal hippocampal cytoarchitecture [105].

Contrary to syndromic forms of XLMR, where cognitive impairment is a secondary feature of gross brain developmental abnormalities, non-specific XLMR might provide further insight into dysregulation of biological mechanisms that underlie cognitive impairments. Therefore, they represent a precious tool to identify genes and molecular and cellular processes involved in cognitive functions, opening new perspectives into the biology of cognition [87,106,107].

Mutations in the *FMR2* gene cause FRAXE a non-specific form of XLMR with an incidence of 1:50,000 [108]. Expansion and methylation of a CCG trinucleotide repeat located in exon 1 of the X-linked *FMR2* gene results in transcriptional silencing and subsequently in a lack of expression of its product, the FMR2 protein. This protein has been hypothesized to be a transcriptional activator [109].

In *Fmr2* knockout mice, the gene has been partially replaced and subsequently silenced [110]. These mice showed a delay-dependent conditioned fear impairment, a slight deficit in spatial learning in a Morris water-maze task, and increased pain threshold in the hot plate test. Surprisingly, long-term potentiation (LTP), a physiological model of the synaptic plasticity that may underlie learning and memory formation, was found to be enhanced in hippocampal slices of *Fmr2* knockouts as compared to

wild-type littermates. Taken together, the behavioral and electrophysiological results suggest that enhanced LTP may be as detrimental to cognitive processes as previous reports of diminished LTP [110]. These findings indicate *Fmr2* as a key factor in the development and/or regulation of synaptic plasticity because its absence can alter neuronal functioning and memory formation.

A second gene involved in non-specific XLMR is *GDI1* which encodes αGdi, a rabGDP-dissociation inhibitor regulating vesicle fusion and intracellular trafficking [111]. This protein seems to be essential for neuronal maturational processes, such as outgrowth of axons and dendrites [112].

Gdi1 knockout mice show a normal profile in several behavioral tasks, however, they are impaired in hippocampal-dependent tasks that test for short-term temporal associations, suggesting that the mice have a defect in short-term memory. Also, these mice show altered social behavior and, in particular, lowered aggression levels [112,113]. In electrophysiological studies, *Gdi1* knockouts show a selected deficit in synaptic plasticity specific to the 5 Hz stimulation protocol, suggesting that a specific pattern of neuronal activity may be responsible for the cognitive impairments [113].

Several other genes responsible for XLMR have been identified [106]. Though these genes encode an heterogeneous group of proteins, virtually all of the proteins are involved in signal transduction pathways. Most of the genes, including *GDI1*, encode proteins that regulate members of the Ras superfamily of small GTPases or their effectors [87,106].

4. The need of studying behavior during ontogeny in mouse models of neurodevelopmental disorders

Analysis of behavior during the developmental period (within the first weeks of life) can be extremely informative when applied to genetically modified mice modeling human neurodevelopmental disorders. During early postnatal development in the mouse, several important processes that will shape brain structure and function are proceeding (Fig. 2). Neurogenesis in the hippocampus, a structure associated with higher cognitive functions such as learning and memory, occurs during the early postnatal period. Additionally, neuronal differentiation, maturation and synaptogenesis continue in this critical window of early postnatal development. Aberrant brain development has long been considered a neural substrate for many forms of MR. It stands to reason that a detailed analysis of specific sensory-motor and behavioral responses during ontogeny may help to detect the onset of pathogenetic events or identify a specific functional alteration before compensatory effects in adulthood mask it [12].

As mentioned earlier, some of the studies on murine models of Down syndrome investigating early phases of behavioral development, have reported significant neurobehavioral deficits already within the first two postnatal weeks [47,62]. These findings are consistent with the behavioral profile of Down syndrome children, and provide validation of both the mouse model and the sensitivity of early phenotyping. Early behavioral testing also provides a behavioral phenotype on which potential therapeutic strategies could be tested, starting from the early phases of development, when recovery could be more likely.

Currently neurobehavioural characterization of genetically modified mice during ontogeny is sporadic. Most of the studies on animal models of neurodevelopmental disorders, including X-linked forms of MR and RTT, are focused on adulthood, without considering the neonatal or adolescent behavioral phenotype [13,93,114,115].

The lack of behavioral characterization of the developmental period is surprising because these animal models are supposed to mimic neurological and cognitive symptoms in humans that emerge already during infancy. It would be considered inexcusable to define an animal model of Alzheimer's disease with behavioral characterization only in the pre-weaning phase; it is similarly limiting to describe only adult behavior in animal models of neurological disorders with early onset and developmental pathology. Moreover, methods for studying mouse neurobehavioral development are now readily available [12]. Behavioral competencies of rodent pups have been described extensively in the last decades. These studies have used several behavioral endpoints, appropriate for each maturational stage, and standardized the methodological procedures to assess the ontogeny of sensory-motor, emotional and cognitive abilities [12,116,117].

5. Environmental factors modulate cognitive deficits in genetic disorders

Exposure to a stimulating, enriched environment exerts a profound effect on brain structure and function, enhancing neurogenesis, gliogenesis, synaptogenesis and angiogenesis, stimulating the activity of several neurotransmitter systems and increasing the gene expression of growth factors, such as Nerve Growth Factor and Brain derived Growth Factor [118,119]. It also improves memory function in several learning tasks [118,120].

Furthermore, environmental enrichment can facilitate recovery from brain insults. Recovery from brain lesions can be facilitated by pre- and post-operative enrichment [121]. More recently, a 3 week exposure to an enriched environment has been shown to reduce apoptosis by 45% in the hippocampus, and prevent the development of seizures triggered by administration of kainic acid [122].

In genetically modified mouse models of genetic diseases, exposure to enrichment can delay the onset of neurological symptoms. Huntington's disease is a genetic

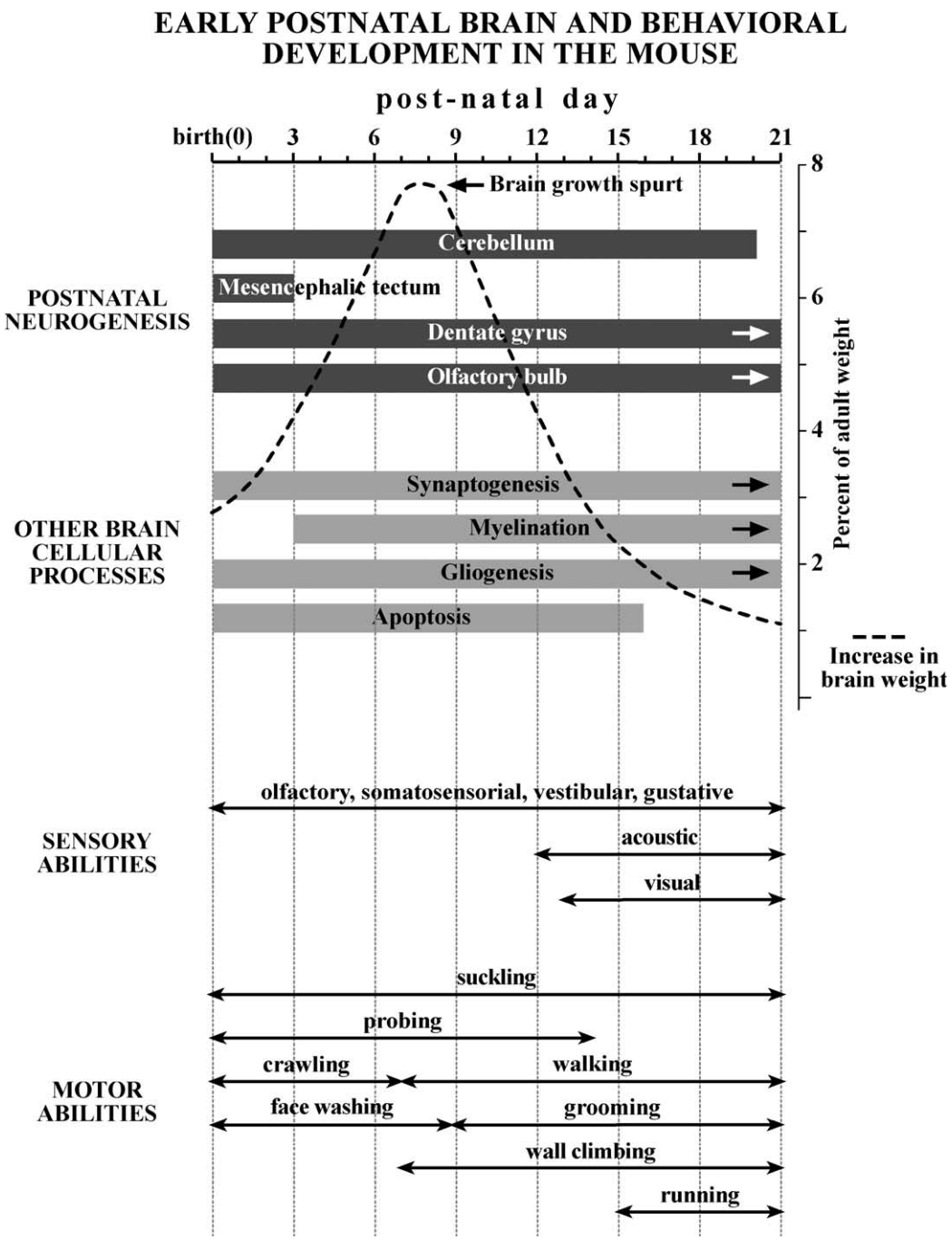

Fig. 2. Thick lines: age phases relative to the occurrence of specific postnatal brain cellular processes [140,141]. The dashed curve represents the increase of brain weight as percentage of adult brain weight [142]. Thin lines: age phases relative to the appearance of different mouse pup sensory and motor capabilities.

disorder characterized by progressive neurodegeneration in the corpus striatum and cerebral cortex [123]. Transgenic mice have been developed that display a neurodegenerative syndrome that closely models the human disease [124]. The exposure of these mice to an enriched environment during the late developmental phase (from the fourth postnatal-week) partially prevents the loss of cerebral volume and delays the onset of motor disorders [125]. This effect may be due to increased sensory input and/or motor activity having a direct influence on the synaptic number and neuronal morphology in the striatum, or to increased cortical input that counteracts the reduction in activity occurring in selected cortical areas in Huntington's disease. These findings parallel human data from studies performed on monozygotic twins with Huntington's disease having the same genetic alteration but different grades of cognitive impairments, suggesting that environmental factors may significantly modulate the course of this pathology [126].

In another genetically modified mouse, an interaction between environmental and gene effects has been noted

[31]. Mice with the *N*-methyl-D-aspartate receptor 1 subunit knocked out in CA1 of the hippocampus, exhibit cognitive impairments. These cognitive impairments can be counteracted by exposing the knockouts at 45–60 days of age to an enriched environment for 3 h daily for 2 months. It is tempting to speculate that a modification as simple as enriching the environment could improve the outcome for individuals with neurodevelopmental disorders. This is an idea that is very amenable to testing in mouse models.

Amongst most relevant environmental factors influencing adult behavior, maternal behavior should be taken into account in animal models of neurodevelopmental disorders. Mother–offspring interactions shape physiology and behavior and have long-term consequences on the animal's behavior [127,128]. Furthermore, maternal responsiveness is markedly modulated by behavior of the pups [129,130]. Therefore, alterations of pup behavioral profile and of mother–offspring interactions may have profound long-term consequences on neurobehavioral analysis in adulthood.

6. Conclusions

Studies of different forms of MR in humans implicate a great number of genes in their etiology (search for 'mental retardation' at Online Mendelian Inheritance in Man web site, http://www3.ncbi.nlm.nih.gov/Omim/searchomim.html). The identification of these genes in the mouse provides a relevant tool for investigating their role in regulating cognitive functions. Although cognitive impairment may arise from a large repertoire of mutations of a diverse set of genes involved in CNS development, the cellular processes that are targeted in brain developmental disorders are more limited in number [9,11]. During brain development, a series of critical steps, including neurogenesis, migration, differentiation, synaptogenesis, regressive events-cell death, and synapse rearrangement, must be orchestrated accurately in order to give rise to a proper brain structure and function [1,2,4,131]. Mutations in genes encoding different proteins may exert a similar effect during a critical time period on a crucial step of brain development, which lead to similar brain alterations (Table 1). Lissencephaly represents a telling example: mutations in two genes encoding proteins having different structures and functions, DCX and LIS1, disrupt ongoing cortical neuronal migration, leading to a similar brain pathologies [132]. The identification of specific pathways and critical timing of developmental events may provide relevant information for developing therapeutic interventions.

Furthermore, a comparison between conditional and constitutive knockouts can aid in dissociating developmental effects from adult dysfunctions. For example, mice lacking serotonin 1A receptor constitutively display increased anxiety-like behavior. Mice who lack the serotonin 1A receptor conditionally, during the early postnatal period but who have serotonin 1A receptor functioning restored in adulthood, also exhibit increased anxiety. Restoration of the receptor functioning in early postnatal development does restore normal anxiety-related functions. These results underscore the idea that early postnatal serotonin functioning shapes the anxiety related behavioral repertoire in adulthood [133].

An appropriate analysis of adult behavior of mouse models of neurodevelopmental disorders represents a powerful tool to identify critical pathways for brain development, and the functional consequences of their disruption [19,26,80,96,113]. However, for genetically modified mice modeling neural disorders occurring during development, a detailed characterization of behavioral ontogeny is advisable. Detailed behavioral analysis during the critical time period when some of these critical steps in development become derailed is crucial to identify endpoints of early brain dysfunction, and to develop interventions at a time when the brain has a high degree of functional plasticity [12,47,62].

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