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Neurologic and motor dysfunctions in *APP* transgenic mice

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Abstract

The discovery of gene mutations underlying autosomal dominant Alzheimer's disease has enabled researchers to reproduce several hallmarks of this disorder in transgenic mice, notably the formation of Aβ plaques in brain and cognitive deficits. APP transgenic mutants have also been investigated with respect to survival rates, neurologic functions, and motor coordination, which are all susceptible to alteration in Alzheimer dementia. Several transgenic lines expressing human mutated or wild-type APP had higher mortality rates than non-transgenic controls with or without the presence of Aβ plaques. Mortality rates were also elevated in APP transgenic mice with vascular amyloid accumulation, thereby implicating cerebrovascular factors in the precocious death observed in all APP transgenic models. In addition, myoclonic jumping has been described in APP mutants, together with seizure activity, abnormal limb-flexion and paw-clasping reflexes, and motor coordination deficits. The neurologic signs resemble the myoclonic movements, epileptic seizures, pathological reflexes, and gait problems observed in late-stage Alzheimer's disease.

Keywords

Alzheimer's disease; epilepsy; motor coordination; myoclonus; paw-clasping; premature death

Neurobiological characteristics of Alzheimer's disease

Neuropathology

Definite Alzheimer's disease is diagnosed after postmortem evidence of extracellular neuritic plaques and intracellular neurofibrillary tangles (Perl, 2000). In addition, there is granulovacuolar degeneration marked by intracytoplasmic vesicles (Su et al., 2002). Neuritic plaques contain A-β-protein (Aβ) and cellular debris, while Aβ-positive neurofibrillary tangles contain hyperphosphorylated τ (Perl, 2000). Cored plaques are distinguishable from diffuse ones by their β-pleated structure and later onset (Yamaguchi et al., 1988; Thal et al., 2000). Diffuse plaques contain only $A\beta_{42}$, but mature plaques contain both $A\beta_{42}$ and $A\beta_{40}$ (Iwatsubo et al., 1994). Aβ plaques are surrounded by activated microglia and astrocytes as well as inflammation-related proteins (Eikelenboom et al., 2002).

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Neuropsychological symptoms

Probable Alzheimer's disease is diagnosed when progressive loss in remembering new items occurs (anterograde amnesia) in conjunction with a deficit in language (aphasia), object use (apraxia), form recognition of faces or objects (agnosia), and step-by-step planning (McKhann et al., 1984). Memory and verbal fluency deficits are often the initial symptoms (Amieva et al., 2005). Progressive amnesia is sometimes the only sign over a considerable period, even years (Weintraub and Mesulam, 1993). Anterograde amnesia reflects a loss in factual information, called declarative memory, both for verbal and spatial items (Jacobs et al., 1995; Amieva et al., 2005; Graham et al., 2004), whereas procedural memory is relatively spared, as in the pursuit-rotor test (Eslinger and Damasio, 1986; Jacobs et al., 1999), although delay and trace conditioning of the eye-blink response, a cerebellum-mediated function, is not (Woodruff-Pak and Papka, 1996; Woodruff-Pak et al., 1996). Spatial deficits also appear in the form of constructional apraxia, defined as a difficulty in copying geometric figures or reproducing them with building blocks (Graham et al., 2004). As a result, patients are more likely than controls to be disoriented in a hospital ward (Monacelli et al., 2003) and in the streets while riding a motored vehicle (Uc et al., 2004). In addition, apathy, dysphoria, social withdrawal, and depression are common neuropsychiatric features of Alzheimer dementia (Daffner et al., 1992; Frisoni et al., 1999; Chung and Cummings, 2000; Hart et al., 2003; Senanarong et al., 2004).

Neurologic symptoms

Although usually occurring late in disease progression, neurologic symptoms are a prominent feature of patients with Alzheimer dementia. These include hallucinations (Chen et al., 1991; Frisoni et al., 1999; Chung and Cummings, 2000; Hart et al., 2003; Senanarong et al., 2004), deficient postural control (Huff et al., 1987; Pettersson et al., 2002), and myoclonus (Chen et al., 1991; Förstl et al., 1992), defined as brief, jerky movements of the arms and legs, most often bilateral (Snodgrass, 1990; Defebvre, 2006; Lanska, 2010). In addition, patients are susceptible to epileptic seizures, parkinsonian symptoms, and frontal lobe-associated release signs such as grasping and sucking in response to tactile stimuli (Huff et al., 1987; Burns et al., 1991; Chen et al., 1991; Förstl et al., 1992). Posture and gait can be impaired even in the early stages of the disease (Pettersson et al., 2002), perhaps due to vermal atrophy (Sjöbeck and Englund, 2001). Myoclonus and epileptic seizures are particularly frequent in patients with the hereditary form of the disease, marked by *APP* and *PS1* mutations (Campion et al., 1996; Furuya et al., 2003). The seizures may contribute to mental deterioration in addition to Aβ-mediated processes (Leonard and McNamara, 2007). Myoclonic twitching mostly appears in late stages, generally after extrapyramidal and psychotic symptoms (Chen et al., 1991). Unlike the sporadic form, autosomal dominant cases with myoclonus contain Aβ plaques in the cerebellum (Ishino et al., 1984; Lemere et al., 1996). Thus, anomalies of the cerebellum may contribute to both balance problems and myoclonus.

Pathological characteristics in *APP* mice

Introduction

Thanks to the discovery of pathological mutations in humans, several Alzheimer hallmarks have been attained in transgenic mice (Cole and Frautschy, 1997; Hsiao, 1998; Duff, 1999; Van Leuven, 2000; Janus and Westaway, 2001; Dodart et al., 2002). Most *APP* mutants have no neurofibrillary tangles, thereby resembling rare cases of Alzheimer dementia with amyloid deposits and hyperphosphorylated τ but without tangles (Tiraboschi et al., 2004). One exception is the transgenic model expressing *APP, PS1,* and *Mapt* (3xTg-AD) characterized by Aβ plaques and neurofibrillary tangles (Oddo et al., 2003). The genetic characteristics of mice behaviorally characterized for neurologic or motor function and

expressing mutated or wild-type (WT) *APP* or its C-terminal fragments are presented in Table 1.

APP mutations

Swedish—Several *APP* transgenic mutants have been generated with the Swedish mutation, defined as amino acid substitutions at codons 670 and 671 first reported in a Swedish family (Axelman et al., 1994; Haass et al., 1995). One of the better known transgenics of this type is APP_{695}SWE (Tg2576), containing a human *APP* transgene with the Swedish mutation of the neuron-specific 695-amino acid isoform driven by the hamster *Prp* promoter (Hsiao et al., 1996). Detergent-insoluble Congo Red-positive Aβ plaques were visible in APP_{695}SWE mice as early as 7 months, increasing with age (Kawarabayashi et al., 2001; Westerman et al., 2002). The Aβ plaques also surround vessel walls, causing micro-hemorrhages (Frackowiak et al., 2001; Fryer et al., 2003; Domnitz et al., 2005). In contrast, a previously generated transgenic mouse with the same mutation and promoter (Tg2123H) does not harbor Aβ plaques (Hsiao et al., 1995).

Another transgene with the Swedish mutation was designed with the inserted gene driven this time by the murine *Thy1* promoter on the 751-amino acid isoform (Sturchler-Pierrat et al., 1997). These APP_{751}SWE transgenic mice (APP23) accumulate Aβ in the hippocampus and neocortex, with plaque-associated Aβ peptides augmenting 5-fold from 3 to 6 months of age (Van Dam et al., 2003). As seen in Alzheimer brain, neuritic plaques are surrounded by astrocytes and activated microglia and τ is hyperphosphorylated (Sturchler-Pierrat et al., 1997; Stalder et al., 1999; Bornemann et al., 2001). In addition to parenchymal plaques, amyloid angiopathy occurs, leading to weakened vessel walls, aneurysm, vasculitis, and hemorrhage (Calhoun et al., 1999; Winkler et al., 2001; Beckmann et al., 2011).

Yet another *APP* model with the Swedish mutation driven by the murine *Thy1* promoter includes the 770-amino acid isoform (Moechars et al., 1999b). Aβ plaques were observed in the hippocampus and neocortex of these APP_{770}SWE mice. In contrast, in a model containing the *APP* transgene with the Swedish mutation driven by the endogenous *PrP* promoter of a chimeric human/murine 695-amino acid isoform, APP_{695}SWEch (Borchelt et al., 1996, 1997), few or no neuritic Aβ plaques were seen despite increased $Aβ_{42}$ and $Aβ_{40}$ levels in the brain (Savonenko et al., 2003).

Although subjects with inclusion body myopathy do not carry *APP* mutations, they are characterized by Aβ accumulation in muscles and muscle weakness. An *APP*/SWE/*Ckm* transgene was generated with the Swedish mutation driven by the murine *Ckm* (creatine kinase, muscle) promoter (Sugarman et al., 2002). As found in human muscles (Askanas and Engel, 1998, 2002), Aβ accumulated intracellularly in mouse skeletal muscles of the transgenic (Sugarman et al., 2002). As seen in sporadic but not hereditary inclusion body myopathy (Askanas and Engel, 1998), inflammation was evident, with neutrophils instead of T cells as the predominant cell type (Sugarman et al., 2002).

London—An *APP* model comprises the V717I London mutation on the 695-amino acid isoform driven by the murine *Thy1* promoter, causing diffuse and neuritic Aβ plaques (Moechars et al., 1999b; Dewachter et al., 2000a, b; Van Dorpe et al., 2000), surrounded by activated astrocytes and microglia, the neurites being linked to hyperphosphorylated τ (Moechars et al., 1999b). The angiopathy in APP_{695}LD mice leads to aneurysms but not hemorrhages (Van Dorpe et al., 2000).

Dutch and Flemish—*APP*/DU/*Thy1* and *APP*/FL/*Thy1* mice with E693Q (Dutch) and A692G (Flemish) mutations, respectively, each driven by the murine *Thy1* promoter, have

cerebral amyloid angiopathy with elevated parenchymal C-terminal fragments but not Aβ plaques (Kumar-Singh et al., 2000).

Swedish/Indiana—Several models with combined Swedish and Indiana mutations are available. *APP*$_{695}$SWE/IND mice, also known as TgCRND8 or Tg19959, express the 695-amino acid isoform regulated by the hamster *Prp* promoter (Janus et al., 2000; Chishti et al., 2001), showing Aβ plaques as early as 3 months of age (Janus et al., 2000; Chishti et al., 2001; Bellucci et al., 2006), together with early-onset angiopathy (Domnitz et al., 2005) and activated microglia and astrocytes (Bellucci et al., 2006). Two *APP*/SWE/IND constructs driven by the platelet-derived *PDGF*β promoter (J9 and J20 lines) also contain Aβ plaques (Mucke et al., 2000; Palop et al., 2003). On the contrary, the *APP*$_{751}$SWE/IND (APP-Sw, V717F/B6) model driven by the *PDGF*β promoter did not harbor plaques up to 14 months of age (Lee et al., 2004).

Swedish/London—An *APP*$_{751}$SWE/LD line with Swedish and London mutations was generated on a transgene driven by the murine *Thy1* promoter, causing Aβ plaques (Blanchard et al., 2003).

Artificial—*APP*/RK transgenic mice with an artifical double mutation at the α-secretase site were generated under the control of the murine *Thy1* promoter (Moechars et al., 1996). These mice harbor no Aβ plaques, but the neocortex and hippocampus are marked by astrocytosis and DNA fragmentation (Moechars et al., 1998, 1999a). Likewise, no Aβ plaques are seen in *APP*$_{695}$TRI*myc* mice (Tg1130H), expressing a triple mutation (V717L, V721A, and M722V) with a 3′-*myc* tag driven by the hamster *Prp* promoter (Hsiao et al., 1995).

Human WT APP murine WT App

The 695 splice variant was used for generating mice expressing human WT *APP*$_{695}$ under the control of the metallothionein IIA (*Mt2*) promoter (Yamaguchi et al., 1991). A similar *APP*$_{695}$WT construct driven by the murine *Thy1* promoter is available (*APP*$_{695}$WT/*Thy*) (Moechars et al., 1999b). Mice expressing human *APP*$_{695}$*myc* WT with a 3′-*myc* tag (Tg6209) and murine *APP*$_{695}$WT (Tg1874) driven by the hamster *Prp* promoter have also been generated (Hsiao et al., 1995).

APP C-terminal fragments

APP/C99 mice (Tg13592) expressing the human 99-amino acid C-terminal fragment in the brain and skeletal muscles driven by a CMV enhancer/chicken *Actb* (β-actin promoter) mimic inclusion body myopathy in that Aβ accumulates in muscles but not in the brain (Fukuchi et al., 1996, 1998, 2000).

Aβ$_{42}$

Transgenic mice overexpressing human Aβ$_{42}$ driven by the murine *Nefl* promoter have increased intracellular levels of the peptide (LaFerla et al., 1995, 1996). These mice are marked by DNA fragmentation, increased p53 levels, and morphological markers of apoptosis in the neocortex, hippocampus, amygdala, and thalamus.

APP+PS1 mutations

The above-described *APP*$_{695}$SWE mice (Tg2576) were interbred with mutated *PS1* line 5.1, yielding the *APP*$_{695}$SWE+*PS1*/M146L bigenic, characterized by earlier Aβ plaque onset than the single transgenic (Duff et al., 1996; Holcomb et al., 1998, 1999; Westerman et al., 2002; Kurt et al., 2003), with the same features of astrocytosis and microgliosis (Holcomb et

al., 1998, 1999; Gordon et al., 2002), Aβ plaques surrounding vessel walls (Christie et al., 2001; Domnitz et al., 2005), and reduced vasodilatation properties (Christie et al., 2001). The same *APP*$_{695}$SWE line was bred with a *PS1/*A246E strain crossed with a null mutant for the murine *Ps1* gene (Qian et al., 1998), yielding Aβ plaques with earlier onset than the single transgenic (Dineley et al., 2002).

A co-injected bigenic contains the 695-amino acid chimeric human/murine *APP* transgene with the Swedish mutation combined with a *PS1* transgene with the ΔE9 mutation driven by the murine *Prp* promoter (Jankowsky et al., 2004). These *APP*$_{695}$SWE/co+*PS1/*ΔE9 mice (line 85) harbor Aβ plaques at 6 months of age (Jankowsky et al., 2004; Garcia-Alloza et al., 2006) and possess fewer capillary segments than controls in the neocortical white matter (Lee et al., 2005).

The *APP*$_{751}$SWE/LD line with Swedish and London mutations on a transgene driven by the murine *Thy1* promoter (section 2.2.6) was crossed with a *PS1*/M146L line on a transgene driven by the human 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (*HMGCR*) promoter, causing Aβ plaques (Blanchard et al., 2003). The *APP*$_{751}$SWE/LD line was also crossed with a *PS1*/M233T+L235P knockin, yielding a bigenic with Aβ plaque onset at 2.5 months of age, glial activation, and pyramidal cell loss in the hippocampus (Casas et al., 2004), as well as dentate gyrus granule cells (Cotel et al., 2008). The *APP*$_{751}$SWE/LD+*PS1*/M233T+L235P mice are marked by spinal axonopathy and thoracolumbar kyphosis, i.e., spine curvature, not a feature of Alzheimer's disease (Wirths and Bayer, 2008).

A 5-fold transgenic model exists with Swedish/Florida/London mutations on *APP* and M146L and L286V mutations on *PS1* with the murine *Thy1* promoter (Oakley et al., 2006). These 5xFAD transgenic mice have Aβ plaques as early as 2 months of age, accompanied by astrogliosis and microgliosis. As mentioned above, the only model with Aβ plaques and neurofibrillary tangles is the triple *APP*/SWE+*PS1*/M146V+*Mapt*/P301L mutant (Oddo et al., 2003). These 3xTg-AD mice were generated by co-injecting *APP* with the Swedish mutation and four-repeat *Mapt* with the P301L mutation into single-cell embryos of *PS1*/M146V knockin mice.

Neurologic symptoms and survival rates in *APP* mice

Although several reviews of murine Alzheimer models have appeared (Van Leuven, 2000; Ashe, 2001; Morgan, 2003; Sant' Angelo et al., 2003; German and Eisch, 2004; Mineur et al., 2005; Spires and Hyman, 2005; McGowan et al., 2006; Gimenez-Llort et al., 2007; Duyckaerts et al., 2008; Howlett and Richardson, 2009; Kokjohn et al., 2009; Ashe and Zahs, 2010; Wirths and Bayer, 2010; Scearce-Levie, 2011; Lalonde et al., 2012), the authors mostly describe the effects of accumulating Aβ concentrations on synaptic activity or learning abilities in various spatial and non-spatial tasks. We present in-depth task-by-task effects of *APP* transgenesis on survival and basic neurologic functions regarding pathological reflexes, myoclonus, and epilepsy. In particular, the SmithKline-Harwell Imperial College Royal Hospital Phenotype Assessment (SHIRPA) multi-test battery, first described by Rogers et al. (1997), has been used to provide information on the general neurologic function in *APP* mutants (Lalonde et al., 2005). We also present the effects of *APP* transgenesis on motor coordination, a neglected aspect of behavior but justified on the basis of the deficient postural control reported in patients with Alzheimer's disease (Huff et al., 1987), sometimes even during early stages (Pettersson et al., 2002).

Premature death

Premature death has been described in several *APP* transgenic models relative to mice of the same background strain. In most of these reports, qualitative descriptions were provided

without the backing of statistical analyses. Nevertheless, such reports are of interest in providing data on overall biological functions, not being limited to the impact of Aβ on synaptic activity and learning.

King and Arendash (2002) first reported that the often used *APP*$_{695}$SWE transgenic mutant (Tg2576) bearing Aβ plaques dies prematurely. Relative to the WT strain of the same genetic background, fewer *APP*$_{695}$SWE transgenic mice survived between the ages of 6 and 12 months, dying from unknown causes. This finding was confirmed at other age ranges (Lewis et al., 2004; Kim et al., 2007). The same result was found in the *APP*$_{695}$SWE+*PS1*/A246E bigenic derived from the same monogenic (Lewis et al., 2004) as well as a second Aβ plaque-bearing bigenic derived from different monogenics, *APP*$_{695}$SWE/co*+PS1/*ΔE9 (Gimbel et al., 2010).

The susceptibility of *APP* transgenesis to premature death was further documented in a second monogenic with the Swedish mutation resulting in Aβ plaques, *APP*$_{770}$SWE (Moechars et al., 1999a). In contrast to the 4% mortality rate recorded in normal mice during the first year of life, from 21% to 70% of *APP*$_{770}$SWE mice (depending on specific lines) died from undetermined causes. Of note is the equally high death rate (from 53% to 68%) of *APP*$_{695}$*WT/Thy1* mice without Aβ plaques (Moechars et al., 1999a), thus indicating that *APP* overexpression alone or high Aβ concentrations cause precocious death, independently of Aβ plaques. In confirmation of this hypothesis, death occurred earlier than normal in six other *APP* transgenic models without Aβ plaques. Indeed, while 7% of normal mice died within the first year, from 44% to 69% of *APP/RK* mice did so (Moechars et al., 1996). Mortality rates were augmented as well in the following mutants: *APP*$_{751}$SWE/IND (Lee et al., 2004), *APP*$_{695}$*myc*WT (Tg6209), *APP*$_{695}$WT (Tg1874), *APP*$_{695}$TRI*myc*WT (Tg1130H), *APP*$_{695}$SWE (Tg2123H) (Hsiao et al., 1995; Carlson et al., 1997), and Aβ$_{42}$ (LaFerla et al., 1995).

A key insight into the underlying cause of death is provided by data showing higher mortality rates in *APP* transgenic mice with vascular but not parenchymal amyloid accumulation. In contrast to the 3% mortality rate found in non-transgenic controls over the first 6 months of life, from 8% to 32% of *APP*/DU*/Thy1* mutants (depending on specific lines) and from 21% to 31% of *APP*/FL*/Thy1* mutants died (Kumar-Singh et al., 2000). Therefore, cerebrovascular factors are likely to be at work in most if not all *APP* transgenic models. In confirmation of this hypothesis, the death rate among *APP*$_{695}$*myc*WT mice was potentiated by overexpression of the *FGF2* gene, encoding basic fibroblast growth factor, a protein involved in vascular smooth muscle hypertrophy (Carlson et al., 1997). How vascular angiopathy causes death in rodents remains to be determined.

Myoclonus

Myoclonus refers to involuntary, jerky, large-amplitude movements distinct from lower amplitude muscle tics (Snodgrass, 1990; Defebvre, 2006; Lanska, 2010). Like seizure activity displayed in the form of clonic movements, myoclonic movements are rhythmical but of briefer duration. Myoclonus is considered as part of a pre-epileptic state. Some drug treatments of human and animal epileptic seizures are also effective anti-myoclonic agents by protecting neurons from synchronized repetitious moto-neuron firing as the main therapeutic target. Myoclonic movements may originate from abnormal neural activity of several brain regions, especially the brainstem and the cerebellum.

In a manner reminiscent of the myoclonus observed in late-stage Alzheimer's disease (Chen et al., 1991; Förstl et al., 1992), a species-specific form of myoclonus occurring in mice, myoclonic jumping (Table 2), was described in *APP*$_{751}$SWE mutants (APP23) bearing Aβ plaques (Lalonde et al., 2005). *APP*$_{751}$SWE mutants often rear against the walls of their

home-cage and hop continuously, the hindpaws are on and off the ground, the forepaws are with wall support, and the snout is facing upward. This stereotyped response was not observed in WT mice of the same C57BL/6J background strain when first compared to the mutants. However, one may occasionally see this behavior when looking at large groups of normal mice of the C57BL/6J strain, and likely other strains, although this has never to our knowledge been assessed in a systematic fashion.

The neurochemical basis of myoclonic jumping likely involves 5-hydroxytryptamine (5HT). Drugs potentiating 5HT neurotransmission cause myoclonic jumping in guinea pigs, such as peripheral administration of the immediate metabolic precursor of 5HT, 5-hydroxytryptophan (Weiner et al., 1979), as well as L-tryptophan combined with pargyline, a monoamine oxidase inhibitor (Luscombe et al., 1983). The stereotyped response was antagonized by both $5HT_1$ or $5HT_2$ receptor antagonists (Luscombe et al., 1982; Pappert et al., 1998). However, this maladaptive behavior is more difficult to be elicited in mice and rats (Carvey et al., 1986), possibly as a result of species-specific distributions of 5HT receptors. Nevertheless, in support of the hypothesis that 5HT is involved in the mutant response, 5HT concentrations of APP_{751}SWE mutants were higher than those of WT controls in the neocortex (Van Dam et al., 2005) and possibly in the brainstem. Moreover, myoclonic symptoms in humans can be caused by 5HT-enhancing agents (Radomski et al., 2000).

In addition to APP_{751}SWE mutants, myoclonic jumping was observed in a second Aβ plaque-bearing monogenic, this time with combined Swedish and Indiana mutations, APP_{695}SWE/IND, also known as TgCRND8 or Tg19959 (Ambrée et al., 2006). In the same mutant, twitching and vocalizations were enhanced after peripheral administration of pentylenetetrazole, the γ-amino butyric acid (GABA) receptor antagonist (Jolas et al., 2002). The involvement of GABA in myoclonic jumping is indicated by the finding that this maladaptive behavior can be elicited after intracerebroventricular administration of Zn^{2+}, inhibitor in the activity of glutamic acid decarboxylase, the GABA-synthesizing enzyme, and that the Zn^{2+}-induced behavior was reversed by intracerebroventricular GABA (Itoh and Ebadi, 1982). The same effect occurred after Zn^{2+} injections inside the hippocampus but not inside the amygdala, hypothalamus, thalamus, or caudate, implicating reduced GABA transmission in the hippocampus as an important mediator of myoclonic jumping.

Despite these observations of the two Alzheimer-like mutants, myoclonic jumping is not a feature of all *APP* mutants. Indeed, despite elevated Aβ plaque load, it was not observed in two mutants, APP_{695}SWE/co+*PS1*/ΔE9 (Lalonde et al., 2004) and APP_{695}SWE (Lalonde et al., 2003), or in only 3% of the latter when larger groups are available (Westmark et al., 2008). This may be due to an insufficient increase of 5HT neurotransmission, or to an insufficient decline in GABA transmission, or to some other neurochemical anomaly to which APP_{751}SWE and APP_{695}SWE/IND mutants are susceptible but not the other two. In any event, the importance of *APP* overexpression in myoclonic jumping is underlined by the finding that such movements are a phenotypic feature of Ts65Dn mice, a murine model of Down syndrome, overexpressing several genes from mouse chromosome 16, analogous to human chromosome 21, one of which is *APP* (Turner et al., 2001). Like Alzheimer patients, late-stage Down syndrome subjects often display myoclonic symptoms (Möller et al., 2002).

Convulsive seizures

In addition to myoclonus, APP_{751}SWE mutants exhibit spontaneous tonic-clonic seizures (Table 2), thereby indicating that myoclonic movements may appear simultaneously with clonic movements in the same mutant (Lalonde et al., 2005). The seizures are described as being spontaneous in the sense of being unprovoked by an experimenter-controlled stimulus, often audiogenic in nature. Spontaneous tonic-clonic seizures were also observed in four

other models harboring Aβ plaques: *APP*$_{695}$SWE (although 'a small percentage only' according to Westmark et al., 2008), *APP*$_{710}$SWE (Moechars et al., 1999b), *APP*$_{695}$LD mice (Moechars et al., 1999b), and *APP*$_{695}$SWE/co+*PS1*/ΔE9 (Minkeviciene et al., 2009). The same phenotype was evident in four Alzheimer-like *APP* mutants not harboring Aβ plaques: *APP*$_{695}$WT/*Thy1* (Moechars et al., 1999b), *APP*/RK (Moechars et al., 1996), *APP*$_{695}$TRI*myc* (Hsiao et al., 1995), and Aβ$_{42}$ (LaFerla et al., 1995). Moreover, the same phenotype appeared in *APP*/DU/*Thy1* and *APP*/FL/*Thy1* mutants with vascular angiopathy (Kumar-Singh et al., 2000), thus implicating vascular factors in all the mutants, as is the case with the premature death syndrome presented in section 3.1, and perhaps revealing a relation between the two. Indeed, a high mortality rate in *APP*$_{695}$SWE/co+*PS1*/ΔE9 mutants is attributed to their epileptic seizures (Mink-eviciene et al., 2009).

In one mutant carrying Aβ plaques, *APP*/SWE/IND/J20, no overt seizures were observed, but the EEG showed convulsive features (Palop et al., 2007), indicating that this phenotype is likely to be more prominent than believed. Two mutants, *APP*$_{695}$SWE (Westmark et al., 2008) and *APP*/SWE/IND/J20 (Palop et al., 2007), were more susceptible than normal mice to pentylenetetrazole-induced convulsions, implicating subnormal GABA transmission as the key underlying factor behind EEG anomalies and likely the overt seizures found in other models.

The susceptibility of APP mutants to convulsions is another point of resemblance with Alzheimer patients, susceptible to epileptic seizures, as well as pathological reflexes (Huff et al., 1987; Burns et al., 1991; Chen et al., 1991; Förstl et al., 1992), described in mice in the next section.

Abnormal reflexes: limb-flexion and paw-clasping

When WT C57BL/6J mice are held by the tail and slowly lowered towards a horizontal surface, they all exhibit the normal placing response marked by extension of all four limbs. On the contrary, 8 of 17 (47%) Aβ plaque-bearing *APP*$_{751}$SWE mutants (APP23) on the same genetic background exhibited hindlimb-flexion and 2 of 17 (12%) exhibited the hindpaw-clasping response, in which the paws are linked together while suspended in the air (Lalonde et al., 2005). The same pathological reflexes were seen in Aβ plaque-bearing *APP*$_{695}$SWE mutants (Tg2576) on the C57B6/SJL genetic background, with 13 of 14 (93%) of them displaying hindlimb-flexion and 5 of 14 (36%) displaying hindpaw-clasping (Lalonde et al., 2003). However, some WT C57B6/SJL littermates displayed the same sign, hindlimb-flexion noted in 10 of 21 (48%) and hindpaw-clasping in 2 of 21 (10%), presumably as a consequence of 'abnormal' unidentified genes on the SJL background. Although the number of mutants showing abnormal flexion reflexes might be higher than WT, the presence of these phenotypes in 'normal' mice rendered them ambiguous in a theoretical sense and useless for identifying them in conjunction with genotyping of tail biopsies. Nevertheless, hindlimb-flexion and paw-clasping were reported in *APP*$_{751}$SWE/LD+*PS1*/M233T+L235P mutants on a B6/CBA/129SV background, also characterized by parenchymal Aβ plaques but unlike the other two mutants by axonal neuropathology in the brain and spinal cord (Wirths et al., 2007). On the contrary, despite the presence of Aβ plaques, *APP*$_{695}$SWE/co+*PS1*/ΔE9 mutants did not exhibit paw-clasping, indicating that amyloid pathology does not necessarily lead to this phenotype (Lalonde et al., 2004).

Because paw-clasping appears in *5htt* mutants lacking the 5HT transporter (Lira et al., 2003), elevated 5HT concentrations at the synapse may be responsible for triggering it. This may be one mechanism underlying paw-clasping in mice with Alzheimer-like pathology, because, as mentioned in section 3.2 regarding myoclonus, *APP*$_{751}$*SWE* mice were reported as having higher neocortical 5HT concentrations than those of WT (Van Dam et al., 2005).

Motor coordination

In view of impaired posture and gait even in early stages of Alzheimer's disease (Pettersson et al., 2002), it is of interest to examine *APP* mutants with respect to motor skills. The main measure used in motor coordination tests (Table 3) is the time elapsed before falling from various types of apparatus requiring balance and equilibrium (Lalonde and Strazielle, 1999).

Stationary beam

In the stationary beam test, mice are placed on a narrow beam obstructed at either end to prevent escapes and latencies before falling are measured (Lalonde and Strazielle, 1999). Alternate measures include distance travelled and, when one obstacle is removed, the time taken to escape from the beam towards a platform. On one hand, five *APP* mutants have been shown to fall sooner than controls from the stationary beam: APP_{695}SWE (Arendash et al., 2001b, 2004; King and Arendash, 2002), APP_{695}SWE+*PS1*/M146L(Arendash et al., 2001a, b), APP_{751}SWE/LD (Le Cudennec et al., 2008), APP_{751}SWE/LD+*PS1*/M233+L235P (Cotel et al., 2012), and 5xFAD (Jawhar et al., 2011). The result for the latter mutant is not surprising in view of its spinal axonopathy, not part of Alzheimer symptomatology. On the other hand, latencies before falling were equivalent to those of controls in the APP_{695}SWE mutant in a separate study (Lalonde et al., 2003), as well as three other *APP* mutants bearing Aβ plaques in the brain: APP_{751}SWE (Lalonde et al., 2002b), APP_{695}SWE/co+*PS1*/ΔE9 (Lalonde et al., 2004), and 3xTg-AD (Gimenez-Llort et al., 2007; Gulinello et al., 2009), as well as one with Aβ plaques in skeletal muscles, *APP/*C99, part of inclusion body myopathy but not Alzheimer symptomatology (Lalonde et al., 2002a). When latencies before escaping from the beam are considered, APP_{695}SWEch (Savonenko et al., 2003) mutants were slower than controls, but such a result was not found in a mutant carrying Aβ plaques, APP_{695}SWE+*PS1*/M146L (Sadowski et al., 2004), although, as mentioned above, this bigenic was impaired in terms of falling latencies (Arendash et al., 2001a, b).

One possible reason for these discrepancies is the unequal distribution of Aβ plaques or soluble Aβ accumulation in motor-related areas such as the motor cortex, dorsal striatum, and cerebellum. In addition, different results may be due to methodological factors such as the age of mice, the genetic background, the specific measure used, and the width of the bar. In particular, the APP_{695}SWE mutant was impaired only when the width of the bar was narrow (Arendash et al., 2001a, 2004; King and Arendash, 2002), but the same mutant was not impaired on a wider bar, making the task easier (Lalonde et al., 2003).

Suspended bar or coat-hanger

Like the stationary beam test, the mouse locomotes along a narrow surface and its latencies before falling are measured in the suspended bar test (Lalonde and Strazielle, 1999). Unlike the previous test, the narrowness of the wire is such that the animal is suspended upside-down, thereby requiring a greater degree of muscle strength to support its body weight. In the coat-hanger version, various movement time measures are added as to the time taken to reach either end of the bar and to climb atop the diagonal bar found at each end.

Relative to controls, three *APP* mutants harboring Aβ plaques were found to be impaired in the suspended bar test: APP_{695}SWE (King and Arendash, 2002), APP_{695}SWE+*PS1*/M146L (Arendash et al., 2001a), and 5xFAD (Jawhar et al., 2011). However, no impairment was found in the APP_{695}SWE mutant in two other studies (Chapman et al., 1999; Arendash et al., 2004). In the study with the positive result, 14- and 19-month-old animals were used (King and Arendash, 2002), whereas in the one with a null result from the same laboratory, 5-month-old mutants with few or no Aβ plaques were used (Arendash et al., 2004).

Nevertheless, a null result appeared at 16 months of age when Aβ plaques are apparent (Chapman et al., 1999), a discrepancy that might be due to the mixed genetic background of the mutant, which differs according to local husbandry practices.

In any event, two other *APP* mutants with Aβ plaques were reported as being impaired in the suspended bar test: APP_{751}SWE/LD (Le Cudennec et al., 2008; Blanchard et al., 2009) and APP_{751}SWE/LD+*PS1*/M233+L235P (Cotel et al., 2012), the latter marked by spinal axonopathy. On the contrary, there was no impairment in three others with Aβ plaques, APP_{751}SWE (Lalonde et al., 2002b, 2005), APP_{695}SWE/co+*PS1*/ΔE9 (Lalonde et al., 2004), and 3xTg-AD (Gimenez-Llort et al., 2007), as well as three more without Aβ plaques in the brain, APP_{695}SWEch (Savonenko et al., 2003), APP_{751}WT (Moran et al., 1995), and *APP*/C99 (Lalonde et al., 2002a).

As in the previous test, it remains to be determined whether different results are caused by unequal distribution of Aβ accumulation in brain regions associated with motor coordination. An age-related study must be undertaken in the same mutant performing various motor coordination tests, with analyses of the distribution of Aβ plaques in the hindbrain in addition to the forebrain, focusing on brain regions known to be involved in both suspended bar and stationary beam tests such as the cerebellum (Lalonde and Strazielle, 1999).

Inclined screen

In one of the few Alzheimer models tested to date, APP_{695} SWEch mice without Aβ plaques were slower than non-transgenic controls before turning upward on an inclined screen (Savonenko et al., 2003). APP_{751}SWE mice were not less likely to turn and climb the inclined grid, but speed was not measured (Lalonde et al., 2005).

Rotorod

The rotorod task is equivalent to the stationary beam task, except that the beam is moving, usually at an accelerated pace, augmenting the difficulty of mice to stay upright without falling (Lalonde and Strazielle, 1999). Rotorod performance was reported to be impaired in APP_{751}SWE transgenic mice bearing Aβ plaques (Van Dam et al., 2003; Dumont et al., 2004). This result was found in mutants prior to Aβ plaque formation, at 3 and 6 months of age, but was not reproduced after plaques had formed, at 16 and 24 months of age (Lalonde et al., 2002b), perhaps because of the declining abilities of older normal mice, causing a floor effect (no significant decrease is possible because normal values are too low). Nevertheless, one other *APP* mutant with Aβ plaques was impaired in this test, APP_{695}SWE +*PS1*/M146L (Ewers et al., 2006), as well as one without Aβ plaques, APP_{751}SWE/IND (Lee et al., 2004). On the contrary, five models with Aβ plaques performed normally on the rotorod: APP_{695}SWE (Dineley et al., 2002; Lalonde et al., 2003; Gil-Bea et al., 2007; Perucho et al., 2010), APP_{695}SWE+*PS1*/A246E (Dineley et al., 2002), APP_{695}SWE/IND (Hyde et al., 2005; Bellucci et al., 2006), and APP_{695}SWE/co+*PS1*/ΔE9 (Lalonde et al., 2004), as well as the APP_{751}WT mutant without plaques (Moran et al., 1995). Thus, different results are found in mutants irrespective of whether they bear Aβ plaques. As mentioned in the previous section, these questions can only be resolved by analyzing the distribution of Aβ accumulation in brain regions known to be involved in rotorod performance, such as the cerebellum and the dorsal striatum (Lalonde and Strazielle, 1999,2007).

As expected from an experimental model of inclusion body myopathy, rotorod performance worsened in mice expressing the *APP*/SWE/*Ckm* transgene in muscles relative to WT (Sugarman et al., 2002; Kitazawa et al., 2006). However, despite Aβ plaques in muscles,

APP/C99 mice performed as well as controls in this test (Lalonde et al., 2002a). If confirmed within a single study, these contrasting data offer the possibility of examining the reason why Aβ accumulation in muscles leads to motor deterioration in one model but not in the other.

Concluding remarks

Several hallmarks of Alzheimer's disease and inclusion body moyopathy have been reproduced in transgenic mice overexpressing the human *APP* gene, notably Aβ plaque-related pathology in the brain or muscles, respectively, and, in the case of the former, anterograde amnesia during maze testing. In addition, *APP* transgenics have been examined with respect to survival rates, various neurologic functions comprising myoclonus, seizure activity, and pathological reflexes, as well as motor coordination, all susceptible to be altered in Alzheimer dementia, together with inclusion body myopathy in the case of the latter. Several *APP* mutants expressing mutated or WT *APP* had higher mortality rates than non-transgenic controls with or without the presence of Aβ plaques, seen as well in those with vascular amyloid accumulation, thereby implicating cerebrovascular factors in all of them. In addition, myoclonic jumping and seizure activity have been described in *APP* mutants, likely the result of deficient neuronal inhibitory processes, as well as pathological reflexes such as limb-flexion and paw-clasping when mice are suspended in the air by the tail. Moreover, motor coordination deficits have been found in several *APP* mutants. However, as seen with myoclonic jumping and paw-clasping, some *APP* mutants with Aβ plaques do not display motor deficits. These conflicting results may be resolved by examining the role of Aβ-related pathologies in hindbrain regions.

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References

Ambrée O, Touma C, Gortz N, Keyvani K, Paulius W, Palme R, Sachser N. Activity changes and marked stereotyped behavior precede Aβ pathology in TgCRND8 Alzheimer mice. Neubiol Aging. 2006; 27:955–964.

Amieva H, Phillips LH, Della Sala S, Henry JD. Inhibitory functioning in Alzheimer's disease. Brain. 2004; 127:949–964. [PubMed: 14645147]

Amieva H, Jaqmin-Gadda H, Orgogozo JM, Le Carret N, Helmer C, Letenneur L, Barberger-Gateau P, Fabrigoule C, Dartigues JF. The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. Brain. 2005; 128:1093–1101. [PubMed: 15774508]

Arendash GW, King DL, Gordon MN, Morgan D, Hatcher JM, Hope CE, Diamond DM. Progressive, age-related behavioral impairments in transgenic mice carrying both mutant amyloid precursor protein and presenilin-1 transgenes. Brain Res. 2001a; 891:42–53. [PubMed: 11164808]

Arendash GW, Gordon MN, Diamond DM, Austin LA, Hatcher JM, DiCarlo G, Wilcock D, Morgan D. Behavioral assessment of Alzheimer's transgenic mice following long-term Aβ vaccination: task specificity and correlations between Aβ and spatial memory. DNA Cell Biol. 2001b; 20:737–744. [PubMed: 11788052]

Arendash GW, Lewis J, Leighty RE, McGowan E, Cracchiolo JR, Hutton M, Garcia MF. Multi-metric behavioral comparison of APPsw and P301L models for Alzheimer's disease: linkage of poorer cognitive performance to τ pathology in forebrain. Brain Res. 2004; 1012:29–41. [PubMed: 15158158]

Ashe KH. Learning and memory in transgenic mice modeling Alzheimer's disease. Learn Mem. 2001; 8:301–308. [PubMed: 11773429]

Ashe KH, Zahs KR. Probing the biology of Alzheimer's disease in mice. Neuron. 2010; 66:631–645. [PubMed: 20547123]

Askanas V, Engel WK. Sporadic inclusion-body myositis and hereditary inclusion-body myopathies: curent concepts of diagnosis and pathogenesis. Curr Opin Rheumatol. 1998; 10:530–542. [PubMed: 9812213]

Askanas V, Engel WK. Inclusion-body myositis and myopathies: different etiologies, possibly similar pathogenic mechanisms. Curr Opin Neurol. 2002; 15:525–531. [PubMed: 12351995]

Axelman K, Basun H, Winblad B, Lannfelt L. A large Swedish family with Alzheimer's disease with a codon 670/671 amyloid precursor protein mutation. A clinical and genealogical investigation. Arch Neurol. 1994; 51:1193–1197. [PubMed: 7986173]

Beckmann N, Gérard C, Abramowski D, Cannet C, Staufenbiel M. Noninvasive magnetic resonance imaging detection of cerebral amyloid angiopathy-related microvascular alterations using superparamagnetic iron oxide particles in APP transgenic mouse models of Alzheimer's disease: application to passive Aβ immunotherapy. J Neurosci. 2011; 31:1023–1031. [PubMed: 21248127]

Bellucci A, Luccarini I, Scali C, Prosperi C, Giovannini MG, Pepeu G, Casamenti F. Cholinergic dysfunction, neuronal damage and axonal loss in TgCRND8 mice. Neurobiol Dis. 2006; 23:260–272. [PubMed: 16766197]

Blanchard J, Moussaoui S, Czech C, Touchet N, Bonici B, Planche M, Canton T, Jedidi I, Gohin M, Wirths O, et al. Time sequence of maturation of dystrophic neurites associated with Aβ deposits in APP/PS1 transgenic mice. Exp Neurol. 2003; 184:247–263. [PubMed: 14637096]

Blanchard J, Decorte L, Noguès X, Micheau J. Characterization of cognition alteration across the course of the disease in APP751SL mice with parallel estimation of cerebral Aβ deposition. Behav Brain Res. 2009; 201:147–157. [PubMed: 19428628]

Borchelt DR, Thinakaran G, Eckman CB, Lee MK, Davenport F, Ratovitsky T, Prada CM, Kim G, Seekins S, Yager D, et al. Familial Alzheimer's disease-linked presenilin 1 variants elevate Aβ1–42/1–40 ratio *in vitro* and *in vivo*. Neuron. 1996; 17:1005–1013. [PubMed: 8938131]

Borchelt DR, van Lare J, Lee MK, Gonzalez V, Jenkins NA, Copeland NG, Price DL, Sisodia SS. Accelerated amyloid deposition in the brains of transgenic mice coexpressing mutant presenilin 1 and amyloid precursor proteins. Neuron. 1997; 19:939–945. [PubMed: 9354339]

Bornemann KD, Wiederhold KH, Pauli C, Ermini F, Stalder M, Schnell L, Sommer B, Jucker M, Staufenbiel M. Aβ-induced inflammatory processes in microglia cells of APP23 transgenic mice. Am J Pathol. 2001; 158:63–73. [PubMed: 11141480]

Burns A, Jacoby R, Levy R. Neurological signs in Alzheimer's disease. Age Ageing. 1991; 20:45–51. [PubMed: 2028851]

Calhoun ME, Burgermeister P, Phinney AL, Stalder M, Tolnay M, Wiederhold KH, Abramaowski D, Sturchler-Pierrat C, Sommer B, Staufenbiel M, et al. Neuronal overexpression of mutant amyloid precursor protein in prominent deposition of cerebrovascular amyloid. Proc Natl Acad Sci USA. 1999; 96:14088–14093. [PubMed: 10570203]

Campion D, Brice A, Dumanchin C, Puel M, Baulac M, De la Sayette V, Hannequin D, Duyckaerts C, Michon A, Martin C, et al. A novel presenilin 1 mutation resulting in familial Alzheimer's disease with an onset age of 29 years. Neuroreport. 1996; 7:1582–1584. [PubMed: 8904759]

Carlson GA, Borchelt DR, Dake A, Turner S, Danielson V, Coffin JD, Eckman C, Meiners J, Nilsen SP, Younkin SG, et al. Genetic modification of the phenotypes produced by amyloid precursor protein overexpression in transgenic mice. Hum Mol Genet. 1997; 6:1951–1959. [PubMed: 9302276]

Carvey P, Paulseth JE, Goetz CG, Klawans HL. L-5-HTP-induced myoclonic jumping behavior in guinea pigs: an update. Adv Neurol. 1986; 43:509–517. [PubMed: 3484857]

Casas C, Sergeant N, Itier JM, Blanchard V, Wirths O, van der Kolk N, Vingtdeux V, van de Steeg E, Ret G, Canton T, et al. Massive CA1/2 neuronal loss with intraneuronal and N-terminal truncated $A\beta_{42}$ accumulation in a novel Alzheimer transgenic model. Am J Pathol. 2004; 165:1289–1300. [PubMed: 15466394]

Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, Younkin L, Good MA, Bliss TVP, Hyman BT, et al. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. Nat Neurosci. 1999; 2:271–276. [PubMed: 10195221]

Chen JY, Stern Y, Sano M, Mayeux R. Cumulative risks of developing extrapyramidal signs, psychosis, or myoclonus in the course of Alzheimer's disease. Arch Neurol. 1991; 48:1141–1143. [PubMed: 1953398]

Chishti MA, Yang DS, Janus C, Phinney AL, Horne P, Pearson J, Strome R, Zuker N, Loukides J, French J, et al. Early-onset amyloid deposition and cognitive deficits in transgenic mice expressing a double mutant form of amyloid protein 695. J Biol Chem. 2001; 276:21562–21570. [PubMed: 11279122]

Christie R, Yamada M, Moskowitz M, Hyman B. Structural and functional disruption of vascular smooth cells in a transgenic mouse model of amyloid angiopathy. Am J Pathol. 2001; 158:1065–1071. [PubMed: 11238054]

Chung JA, Cummings JL. Neurobehavioral and neuropsychiatric symptoms in Alzheimer's disease. Neurol Clin. 2000; 18:829–846. [PubMed: 11072263]

Cole GM, Frautschy SA. Animal models for Alzheimer's disease. Alzheimer Dis Rev. 1997; 2:33–41.

Cotel MC, Bayer TA, Wirths O. Age-dependent loss of dentate gyrus granule cells in APP/PS1KI mice. Brain Res. 2008; 1222:207–213. [PubMed: 18585693]

Cotel MC, Jawhar S, Christensen DZ, Bayer TA, Wirths O. Environmental enrichment fails to rescue working memory deficits, neuron loss, and neurogenesis in APP/PS1KI mice. Neurobiol Aging. 2012; 33:96–107. [PubMed: 20359774]

Daffner KR, Scinto LFM, Weintraub S, Guinessey JE, Mesulam MM. Diminished curiosity in patients with probable Alzheimer's disease as measured by exploratory eye movements. Neurology. 1992; 42:320–328. [PubMed: 1736159]

Defebvre L. Myoclonies et syndromes extrapyramidaux. Neurophysiol Clin. 2006; 36:319–325. [PubMed: 17336776]

Dewachter I, Van Dorpe J, Spittaels K, Tesseur I, Van Den Haute C, Moechars D, Van Leuven F. Modeling Alzheimer's disease in transgenic mice: effect of age and of Presenilin on amyloid biochemistry and pathology in APP/London mice. Exp Gerontol. 2000a; 35:831–841. [PubMed: 11053674]

Dewachter I, Van Dorpe J, Smeijers L, Gilis M, Kuipéri C, Laenen I, Caluwaerts D, Checler F, Vanderstichele H, Van Leuven F. Aging increased amyloid peptide and caused amyloid plaques in brain of old APP(V717I transgenic mice by a different mechanism than mutant presenilin1. Eur J Neurosci. 2000b; 20:6452–6458.

Dineley KT, Xia X, Bui D, Sweatt JD, Zheng H. Accelerated plaque accumulation, associative learning deficits, and up-regulation of α7 nicotinic receptor protein in transgenic mice co-expressing mutant human presenilin 1 and amyloid precursor proteins. J Biol Chem. 2002; 277:22768–22780. [PubMed: 11912199]

Dodart JC, Mathis C, Bales KR, Paul SM. Does my mouse have Alzheimer's disease? Genes Brain Behav. 2002; 1:142–155. [PubMed: 12884970]

Domnitz SB, Robbins EM, Hoang AW, Garcia-Alloza M, Hyman BT, Rebeck GW, Greenberg SM, Bacskai BJ, Frosch MP. Progression of cerebral amyloid angiopathy in transgenic mouse models of Alzheimer disease. J Neuropathol Exp Neurol. 2005; 64:588–594. [PubMed: 16042310]

Duff, K. Transgenic mouse models of Alzheimer's disease. In: Crusio, W.; Gerlai, R., editors. Handbook of Molecular-Genetic Techniques for Brain and Behavior Research (Techniques in the Behavioral and Neural Sciences). Vol. 13. Amsterdam: Elsevier; 1999. p. 888-894.

Duff K, Eckman C, Zehr C, Yu X, Prada CM, Perez-tur J, Hutton J, Buee L, Harigaya Y, Yager D, et al. Increased β-amyloid42(43) in brains of mice expressing mutant *presenilin 1*. Nature. 1996; 383:710–713. [PubMed: 8878479]

Dumont M, Strazielle C, Staufenbiel M, Lalonde R. Spatial learning and exploration of environmental stimuli in 24-month-old female APP23 transgenic mice with the Swedish mutation. Brain Res. 2004; 1024:113–121. [PubMed: 15451372]

Duyckaerts C, Potier MC, Delatour B. Alzheimer disease models and human neuropathology: similarities and differences. Acta Neuropathol. 2008; 115:5–38. [PubMed: 18038275]

Eikelenboom P, Bate C, Van Gool WA, Hoozemans JJM, Rozemuller JM, Veerhuis R, Williams A. Neuroinflammation in Alzheimer's disease and prion disease. Glia. 2002; 40:232–239. [PubMed: 12379910]

Eslinger PJ, Damasio AR. Preserved motor learning in Alzheimer's disease: implications for anatomy and behavior. J Neurosci. 1986; 6:3006–3009. [PubMed: 3760945]

Ewers M, Morgan DG, Gordon MN, Woodruff-Pak DS. Associative and motor learning in 12-month-old transgenic APP+PS1 mice. Neurobiol Aging. 2006; 27:1118–1128. [PubMed: 15993985]

Förstl H, Burns A, Levy R, Cairns N, Luthert P, Lantos P. Neurologic signs in Alzheimer's disease: results of a prospective clinical and neuropathologic study. Arch Neurol. 1992; 49:1038–1042. [PubMed: 1417511]

Frackowiak J, Mazur-Kolecka B, Kaczmarski W, Dickson D. Deposition of Alzheimer's disease vascular amyloid-β is associated with decreased expression of brain L-3-hydroxyacyl-coenzyme A dehydrogenase (ERAB). Brain Res. 2001; 907:44–53. [PubMed: 11430884]

Frisoni GB, Rozzini L, Gozetti A, Binetti G, Zanetti O, Bianchetti A, Trabucchi M, Cummings JL. Behavioral syndromes in Alzheimer's disease: description and correlates. Dement Geriatr Cogn Disord. 1999; 10:130–138. [PubMed: 10026387]

Fryer JD, Taylor JW, DeMattos RB, Bales KR, Paul SM, Parsadanian M, Holtzman DM. Apolipoprotein E markedly facilitates age-dependent cerebral amyloid angiopathy and spontaneous hemorrhage in amyloid precursor protein transgenic mice. J Neurosci. 2003; 23:7889–7896. [PubMed: 12944519]

Fukuchi K, Ho L, Younkin SG, Kunkel DD, Ogburn CE, LeBoeuf RC, Furlong CE, Deeb SS, Nochlin D, Wegiel J, et al. High levels of circulating β-amyloid peptide do not cause cerebral β-amyloidosis in transgenic mice. Am J Pathol. 1996; 149:219–227. [PubMed: 8686746]

Fukuchi K, Pham D, Hart M, Li L, Lindsey JR. Amyloid-β deposition in skeletal muscle of transgenic mice: possible model of inclusion body myopathy. Am J Pathol. 1998; 153:1687–1693. [PubMed: 9846958]

Fukuchi K, Li L, Hart M, Lindsey JR. Accumulation of amyloid-β protein in exocrine glands of transgenic mice overexpressing a carboxyl terminal portion of amyloid protein precursor. Int J Exp Pathol. 2000; 81:231–239. [PubMed: 10971744]

Furuya H, Yasuda M, Terasawa KJ, Tanaka K, Murai H, Kira J, Ohyagi Y. A novel mutation (L250V) in the presenilin 1 gene in a Japanese familial Alzheimer's disease with myoclonus and generalized convulsion. J Neurol Sci. 2003; 209:75–77. [PubMed: 12686406]

Garcia-Alloza M, Robbins EM, Zhang-Nunes SX, Purcell SM, Betensky RA, Raju S, Prada C, Greenberg SM, Bacskai BJ, Frosch MP. Characterization of amyloid deposition in the APPswe/PS1dE9 mouse model of Alzheimer disease. Neurobiol Dis. 2006; 24:516–524. [PubMed: 17029828]

German DC, Eisch AJ. Mouse models of Alzheimer's disease: insight into treatment. Rev Neurosci. 2004; 15:353–369. [PubMed: 15575491]

Gil-Bea FJ, Aisa B, Schliebs R, Ramirez MJ. Increase of locomotor activity underlying the behavioral dishinhibition in Tg2576 mice. Behav Neurosci. 2007; 121:340–344. [PubMed: 17469923]

Gimbel DA, Nygaard HB, Coffey EE, Gunther EC, Laurén J, Gimbel ZA, Strittmatter SM. Memory impairment in transgenic Alzheimer mice requires cellular prion protein. J Neurosci. 2010; 30:6367–6374. [PubMed: 20445063]

Gimenez-Llort L, Blasquez G, Canete T, Johansson B, Oddo S, Tobena A, LaFerla FM, Fernandez-Teruel A. Modeling behavioral and neuronal symptoms of Alzheimer's disease in mice: a role for intraneuronal amyloid. Neurosci Biobehav Rev. 2007; 31:125–147. [PubMed: 17055579]

Gordon MN, Holcomb LA, Jantzen PT, DiCarlo G, Wilcock D, Boyett KW, Connor K, Melachrino J, O'Callaghan JP, Morgan D. Time course of the development of Alzheimer-like pathology in the doubly transgenic mice PS1 + APP mouse. Exp Neurol. 2002; 173:183–195. [PubMed: 11822882]

Graham NL, Emery T, Hodges JR. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. J Neurol Neurosurg Psychiatry. 2004; 75:61–71. [PubMed: 14707310]

Gulinello M, Gertner M, Mendoza G, Schoenfeld BP, Oddo S, LaFerla F, Choi CH, McBride SM, Faber DS. Validation of a 2-day water maze protocol in mice. Behav Brain Res. 2009; 196:220–227. [PubMed: 18831990]

Haass C, Lemere CA, Capell A, Citron M, Seubert P, Schenk D, Lannfelt L, Selkoe DJ. The Swedish mutation causes early-onset Alzheimer's disease by bold β-secretase cleavage within the secretory pathway. Nat Med. 1995; 1:1291–1296. [PubMed: 7489411]

Hart DJ, Craig D, Compton SA, Critchlow S, Kerrigan BM, McIlroy SP, Passmore AP. A retrospective study of the behavioural and psychological symptoms of mid and late phase Alzheimer's disease. Int J Geriatr Psychiatry. 2003; 18:1037–1042. [PubMed: 14618556]

Holcomb LA, Gordon MN, McGowan E, Yu X, Benkovic S, Jantzen P, Wright K, Saad I, Mueller R, Morgan D, et al. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant *amyloid precursor protein* and *presenilin* transgenes. Nat Med. 1998; 4:97–100. [PubMed: 9427614]

Holcomb LA, Gordon MN, Jantzen P, Hsaio K, Duff K, Morgan D. Behavioral changes in transgenic mice expressing both amyloid precursor protein and presenilin-1 mutations: lack of association with amyloid deposits. Behav Genet. 1999; 29:177–185. [PubMed: 10547924]

Howlett DR, Richardson JC. The pathology of APP transgenic mice: a model of Alzheimer's disease or simply overexpression of APP? Histol Histopathol. 2009; 24:83–100. [PubMed: 19012248]

Hsiao K. Transgenic mice expressing Alzheimer amyloid precursor proteins. Exp Gerontol. 1998; 33:883–889. [PubMed: 9951631]

Hsiao K, Borchelt DR, Olson K, Johannsdottir R, Kitt C, Yunis W, Xu S, Eckman C, Younkin S, Price D, et al. Age-related CNS disorder and early death in transgenic FVB-N mice overexpressing Alzheimer amyloid precursor proteins. Neuron. 1995; 15:1203–1218. [PubMed: 7576662]

Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G. Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice. Science. 1996; 274:99–102. [PubMed: 8810256]

Huff FJ, Boller F, Lucchelli F, Querriera R, Beyer J, Belle S. The neurologic examination in patients with probable Alzheimer's disease. Arch Neurol. 1987; 44:929–932. [PubMed: 3619712]

Hyde LA, Kazdoba TM, Grilli M, Lozza G, Brussa R, Zhang Q, Wong GT, McCool MF, Zhang L, Parker EM, et al. Age-progressing cognitive impairments and neuropathology in transgenic CRND8 mice. Behav Brain Res. 2005; 160:344–355. [PubMed: 15863231]

Ishino H, Higashi S, Chuta M, Ohta H. Juvenile Alzheimer's disease with myoclonus: amyloid plaques and grumose alteration in the cerebellum. Clin Neuropathol. 1984; 3:193–198. [PubMed: 6499295]

Itoh M, Ebadi M. The selective inhibition of hippocampal glutamic acid decarboxylase in zinc-induced epileptic seizures. Neurochem Res. 1982; 7:1287–1298. [PubMed: 7155279]

Iwatsubo T, Odaka A, Suzuki N, Mizusawa H, Nukina N, Ihara Y. Visualization of Aβ42(43) and Aβ40 in senile plaques and end-specific Aβ monoclonals: evidence that an initially deposited species is Aβ42(43). Neuron. 1994; 13:45–53. [PubMed: 8043280]

Jacobs DM, Sano M, Dooneief G, Marder K, Bell KL, Stern Y. Neuropsychological detection and characterization of preclinical Alzheimer's disease. Neurology. 1995; 45:957–962. [PubMed: 7746414]

Jacobs DH, Adair JC, Williamson DJ, Na DL, Gold M, Foundas AL, Shuren JE, Cibula JE, Heilman KM. Apraxia and motor-skill acquisition in Alzheimer's disease are dissociable. Neuropsychologia. 1999; 37:875–880. [PubMed: 10408654]

Jankowsky JL, Fadale DJ, Anderson J, Xu GM, Gonzales V, Jenkins NA, Copeland NG, Lee MK, Younkin LH, Wagner SL, et al. Mutant presenilins specifically elevate the levels of the 42 residue β-amyloid peptide *in vivo*: evidence for augmentation of a 42-specific γ secretase. Hum Mol Genet. 2004; 13:159–170. [PubMed: 14645205]

Janus C, Westaway D. Transgenic mouse models of Alzheimer's disease. Physiol Behav. 2001; 73:873–886. [PubMed: 11566220]

Janus C, Pearson J, McLaurin J, Matthews PM, Jiang Y, Schmidt SD, Chishti MA, Horne P, Heslin D, French J, et al. Aβ peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. Nature. 2000; 408:979–982. [PubMed: 11140685]

Jawhar S, Wirths O, Schilling S, Graubner S, Demuth HU, Bayer TA. Overexpression of glutaminyl cyclase, the enzyme responsible for pyroglutamate Aβ formation, induces behavioral deficits, and

glutaminyl cyclase knock-out rescues the behavioral phenotype in 5XFAD mice. J Biol Chem. 2011; 286:4454–4460. [PubMed: 21148560]

Jolas T, Zhang XS, Zhang Q, Wong G, Del Vecchio R, Gold L, Priestly T. Long-term potentiation is increased in the CA1 area of the hippocampus of APPswe/ind CRND8 mice. Neurobiol Dis. 2002; 11:394–409. [PubMed: 12586549]

Kawarabayashi T, Younkin LH, Saido TC, Shoji M, Ashe KH, Younkin SG. Age-dependent changes in brain, CSF, and amyloid β protein in the Tg2576 transgenic mouse model of Alzheimer's disease. J Neurosci. 2001; 21:372–381. [PubMed: 11160418]

Kim J, Onstead L, Randle S, Price R, Smithson L, Zwizinski C, Dickson DW, Golde T, McGowan E. Aβ inhibits amyloid deposition *in vivo*. J Neurosci. 2007; 27:627–633. [PubMed: 17234594]

King DL, Arendash GW. Behavioral characterization of the Tg2576 transgenic model of Alzheimer's disease through 19 months. Physiol Behav. 2002; 75:627–642. [PubMed: 12020728]

Kitazawa M, Green KN, Caccamo A, LaFerla FM. Genetically augmenting Aβ42 levels in skeletal muscle exacerbates inclusion body myositis-like pathology and motor deficits in transgenic mice. Am J Pathol. 2006; 168:1986–1997. [PubMed: 16723713]

Kokjohn TA, Roher AE, Kokjohn TA, Roher AE. Amyloid precursor protein transgenic mouse models and Alzheimer's disease: understanding the paradigms, limitations, and contributions. Alzheimers Dement. 2009; 5:340–347. [PubMed: 19560104]

Kumar-Singh S, Dewachter I, Moechars D, Lübke U, De Jonghe C, Ceuterick C, Checler F, Naidu A, Cordell B, Cras P, et al. Behavioral disturbances without amyloid deposits in mice overexpressing human amyloid precursor protein with Flemish (A692G) or Dutch (E693Q) mutation. Neurobiol Dis. 2000; 7:9–22. [PubMed: 10671319]

Kurt MA, Davies DC, Kidd M, Duff K, Howlett DR. Hyperphosphorylated τ and paired helical filament-like structures in the brains of mice carrying mutant amyloid precursor protein and mutant presenilin-1 transgenes. Neurobiol Dis. 2003; 14:89–97. [PubMed: 13678670]

LaFerla FM, Tinkle BT, Bieberich CJ, Haudenschild CC, Jay G. The Alzheimer's Aβ peptide induces neurodegeneration and apoptotic cell death in transgenic mice. Nat Genet. 1995; 9:21–30. [PubMed: 7704018]

LaFerla FM, Hall CK, Ngo L, Jay G. Extracellular deposition of β-amyloid upon p53-dependent neuronal cell death in transgenic mice. J Clin Invest. 1996; 98:1626–1632. [PubMed: 8833912]

Lalonde, R.; Strazielle, C. Motor performance of spontaneous murine mutations with cerebellar atrophy. In: Crusio, W.; Gerlai, R., editors. Handbook of Molecular-Genetic Techniques for Brain and Behavior Research (Techniques in the Behavioral and Neural Sciences). Vol. 13. Amsterdam: Elsevier; 1999. p. 627-637.

Lalonde R, Strazielle C. Brain regions and genes affecting postural control. Prog Neurobiol. 2007; 81:45–60. [PubMed: 17222959]

Lalonde R, Dumont M, Fukuchi K, Strazielle C. Transgenic mice expressing the human C99 terminal fragment of βAPP: effects on spatial learning, exploration, anxiety, and motor coordination. Exp Gerontol. 2002a; 37:1399–1410.

Lalonde R, Dumont M, Staufenbiel M, Sturchler-Pierrat C, Strazielle C. Spatial learning, exploration, anxiety, and motor coordination in female APP23 transgenic mice with the Swedish mutation. Brain Res. 2002b; 956:36–44. [PubMed: 12426044]

Lalonde R, Lewis TL, Strazielle C, Kim H, Fukuchi K. Transgenic mice expressing the βAPP_{695}SWE mutation: effects on exploratory activity, anxiety, and motor coordination. Brain Res. 2003; 977:38–45. [PubMed: 12788511]

Lalonde R, Kim HD, Fukuchi K. Exploratory activity, anxiety, and motor coordination in bigenicAPPswe+PS1/ΔE9 mice. Neurosci Lett. 2004; 369:156–161. [PubMed: 15450687]

Lalonde R, Dumont M, Staufenbiel M, Strazielle C. Neurobehavioral characterization of APP23 transgenic mice with the SHIRPA primary screen. Behav Brain Res. 2005; 157:91–98. [PubMed: 15617775]

Lalonde R, Fukuchi K, Strazielle C. *APP* transgenic mice for modelling behavioral and psychological symptoms of dementia (BPSD). Neurosci Biobehav Rev. 2012; 36:1357–1375. [PubMed: 22373961]

Lanska DJ. The history of movement disorders. Handb Clin Neurol. 2010; 95:501–546. [PubMed: 19892136]

Le Cudennec C, Faure A, Ly M, Delatour B. One-year longitudinal evaluation of sensorimotor functions in APP751SL transgenic mice. Genes Brain Behav. 2008; 7(Suppl 1):83–91. [PubMed: 18184372]

Lee KW, Lee SH, Kim H, Song JS, Yang SD, Paik SG, Han PL. Progressive cognitive impairment and anxiety induction in the absence of plaque deposition in C57BL/6 inbred mice expressing transgenic amyloid precursor protein. J Neurosci Res. 2004; 76:572–580. [PubMed: 15114629]

Lee GD, Aruna JH, Barrett PM, Lei DL, Ingram DK, Mouton PR. Stereological analysis of microvascular parameters in a double transgenic model of Alzheimer's disease. Brain Res Bull. 2005; 65:317–322. [PubMed: 15811597]

Lemere CA, Lopera F, Kosik KS, Lendon CL, Ossa J, Saido TC, Yamaguchi H, Ruiz A, Martinez A, Madrigal L, et al. The E280A presenilin 1 Alzheimer mutation produced increased Aβ42 deposition and severe cerebellar pathology. Nat Med. 1996; 2:1146–1150. [PubMed: 8837617]

Leonard AS, McNamara JO. Does epileptiform activity contribute to cognitive impairment in Alzheimer's disease? Neuron. 2007; 55:677–678. [PubMed: 17785172]

Lewis HD, Beher D, Smith D, Hewson L, Cookson N, Reynolds DS, Dawson GR, Jian M, Van der Ploeg LHT, Qian S, et al. Novel aspects of accumulation dynamics and Aβ composition in transgenic models of AD. Neurobiol Aging. 2004; 25:1175–1185. [PubMed: 15312963]

Lira A, Zhou M, Castanon N, Ansorge MS, Gordon JA, Francis JH, Bradley-Moore M, Lira J, Underwood MD, Arango V, et al. Altered depression-related behaviors and functional changes in the dorsal raphe nucleus of serotonin transporter-deficient mice. Biol Psychiatry. 2003; 54:960–971. [PubMed: 14625138]

Luscombe G, Jenner P, Marsden CD. Tryptamine-induced myoclonus in guinea-pigs pretreated with a monoamine oxidase inhibitor indicates pre- and post-synaptic actions of tryptamine upon central indoleamine systems. Neuropharmacology. 1982; 21:1257–1265. [PubMed: 6130489]

Luscombe G, Jenner P, Marsden CD. Alterations in brain 5HT and tryptamine content during indoleamine-induced myoclonus in guinea pigs. Biochem Pharmacol. 1983; 32:1857–1864. [PubMed: 6192824]

McGowan E, Eriksen J, Hutton M. A decade of modeling Alzheimer's disease in transgenic mice. Trends Genet. 2006; 22:281–289. [PubMed: 16567017]

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRA work group under the Department of Health and Human Services task force on Alzheimer's disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]

Mineur YS, McGoughlin D, Crusio WE, Sluyter F. Genetic models of Alzheimer's disease. Neural Plast. 2005; 12:299–310. [PubMed: 16444901]

Minkeviciene R, Rheims S, Dobszay MB, Zilberter M, Hartikainen J, Fülöp L, Penke B, Zilberter Y, Harkany T, Pitkänen A, et al. Amyloid β-induced neuronal hyperexcitability triggers progressive epilepsy. J Neurosci. 2009; 29:3453–3462. [PubMed: 19295151]

Moechars D, Lorent K, De Strooper B, Dewachter I, Van Leuven F. Expression in brain of amyloid precursor protein mutated in the α-secretase site causes disturbed behavior, neuronal degeneration and premature death in transgenic mice. EMBO J. 1996; 15:1265–1274. [PubMed: 8635459]

Moechars D, Lorent K, Dewachter I, Baekelandt V, De Strooper B, Van Leuven F. Transgenic mice expressing an α-secretion mutant of the amyloid precursor protein in the brain develop a progressive CNS disorder. Behav Brain Res. 1998; 95:55–64. [PubMed: 9754877]

Moechars D, Lorent K, Van Leuven F. Premature death in transgenic mice that overexpress a mutant amyloid precursor protein is preceded by severe neurodegeneration and apoptosis. Neuroscience. 1999a; 92:819–830.

Moechars D, Dewachter I, Lorent K, Reversé D, Baekelandt V, Naidu A, Tesseur I, Spittaels K, Van Den Haute C, Checler F, et al. Early phenotypic changes in transgenic mice that overexpress different mutants of amyloid precursor protein in brain. J Biol Chem. 1999b; 274:6483–6492. [PubMed: 10037741]

Möller JC, Hamer HM, Oertel WH, Rosenow F. Late-onset myoclonic epilepsy in Down's syndrome (LOMEDS). Seizure. 2002; 11(Suppl A):303–305.

Monacelli AM, Cushman LA, Kavcic V, Duffy CJ. Spatial disorientation in Alzheimer's disease: the remembrance of things passed. Neurology. 2003; 61:1491–1497. [PubMed: 14663030]

Moran PM, Higgins LS, Cordell B, Moser PC. Age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β-amyloid protein precursor protein. Proc Natl Acad Sci USA. 1995; 92:5341–5345. [PubMed: 7777509]

Morgan D. Learning and memory deficits in APP transgenic mouse models of amyloid deposition. Neurochem Res. 2003; 28:1029–1034. [PubMed: 12737527]

Mucke L, Masliah E, Yu GQ, Mallory M, Rockenstein EM, Tatsuno G, Hu K, Kholodenko D, Johnson-Wood K, McConlogue L. High-level neuronal expression of $A\beta_{1-42}$ in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. J Neurosci. 2000; 20:4050–4058. [PubMed: 10818140]

Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, Guillozet-Bongaarts A, Ohno M, Disterhoft JF, Van Eldik L, et al. Intraneuronal β-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. J Neurosci. 2006; 26:10129–10140. [PubMed: 17021169]

Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Aβ and synaptic dysfunction. Neuron. 2003; 39:409–421. [PubMed: 12895417]

Palop JJ, Jones B, Kekonius L, Chin J, Yu GQ, Raber J, Masliah E, Mucke L. Neuronal depletion of calcium-dependent proteins in the dentate gyrus is tightly linked to Alzheimer's disease-related cognitive deficits. Proc Natl Acad Sci USA. 2003; 100:9572–9577. [PubMed: 12881482]

Palop JJ, Chin J, Roberson ED, Wang J, Thwin MT, Bien-Ly N, Yoo J, Ho KO, Yu GQ, Kreitzer A, et al. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. Neuron. 2007; 55:697–711. [PubMed: 17785178]

Pappert EJ, Goetz CG, Stebbins GT, Belden M, Carvey PM. 5-Hydroxytryptamine-induced myoclonus in guinea pigs: mediation through $5\text{-}HT_{1/2}$ receptor subtypes. Eur J Pharmacol. 1998; 347:51–56. [PubMed: 9650847]

Perl DP. Neuropathology of Alzheimer's disease and related disorders. Neurol Clin. 2000; 18:847–864. [PubMed: 11072264]

Perucho J, Casarejos MJ, Rubio I, Rodriguez-Navarro JA, Gómez A, Ampuero I, Rodal I, Solano RM, Carro E, García de Yébenes J, et al. The effects of parkin suppression on the behaviour, amyloid processing, and cell survival in APP mutant transgenic mice. Exp Neurol. 2010; 221:54–67. [PubMed: 19815012]

Pettersson AF, Engardt M, Wahlund LO. Activity and balance in subjects with mild Alzheimer's disease. Dement Geriatr Cogn Dis. 2002; 13:213–216.

Qian S, Jiang P, Guan XM, Singh G, Trumbauer ME, Yu H, Chen HY, Van der Ploeg LHT, Zheng H. Mutant human presenilin-1 protects *presenilin 1* null mouse against embryonic lethality and elevates Aβ1–42/43 production. Neuron. 1998; 20:611–617. [PubMed: 9539133]

Radomski JW, Dursun SM, Reveley MA, Kutcher SP. An exploratory approach to the serotonin syndrome: an update of clinical phenomenology and revised diagnostic criteria. Med Hypotheses. 2000; 55:218–224. [PubMed: 10985912]

Rogers DC, Fisher EMC, Brown SDM, Peters J, Hunter AJ, Martin JE. Behavioral and functional analysis of mouse phenotype: SHIRPA, a proposed protocol for comprehensive phenotype assessment. Mamm Genome. 1997; 8:711–713. [PubMed: 9321461]

Sadowski M, Pankiewicz J, Scholtzova H, Ji Y, Quartermain D, Jensen CH, Duff K, Nixon RA, Gruen RJ, Wisniewski T. Amyloid-β deposition is associated with decreased hippocampal glucose metabolism and spatial memory impairment in APP/PS1 mice. J Neuropathol Exp Neurol. 2004; 63:418–428. [PubMed: 15198121]

Sant' Angelo A, Trinchese F, Arancio O. Usefulness of behavioral and electrophysiological studies in transgenic models of Alzheimer disease. Neurochem Res. 2003; 28:1009–1015. [PubMed: 12737525]

Savonenko AV, Xu GM, Price DL, Borchelt DR, Markowska AL. Normal cognitive behavior in two distinct congenic lines of transgenic mice hyperexpressing APPSWE. Neurobiol Dis. 2003; 12:194–211. [PubMed: 12742740]

Scearce-Levie, K. Monitoring spatial learning and memory in Alzheimer's disease mouse models using the Morris water maze. Alzheimer's disease and frontotemporal dementia. In: Roberson, ED., editor. Methods in Molecular Biology. Vol. 670. Berlin: Springer; 2011. p. 191-205.

Senanarong V, Cummings JL, Fairbanks L, Mega M, Masterman DM, O'Connor SM, Strickland TL. Agitation in Alzheimer's disease is a manifestation of frontal lobe dysfunction. Dement Geriatr Cogn Disord. 2004; 17:14–20. [PubMed: 14560060]

Sjöbeck M, Englund E. Alzheimer's disease and the cerebellum: a morphologic study on neuronal and glial changes. Dement Geriatr Cogn Disord. 2001; 12:211–218. [PubMed: 11244215]

Snodgrass SR. Myoclonus: analysis of monoamine, GABA, and other systems. FASEB J. 1990; 4:2775–2788. [PubMed: 2165012]

Spires TL, Hyman BT. Transgenic models of Alzheimer's disease: learning from animals. NeuroRx. 2005; 2:423–437. [PubMed: 16389306]

Stalder M, Phinney A, Probst A, Sommer B, Staufenbiel M, Jucker M. Association of microglia with amyloid plaques in brains of APP23 transgenic mice. Am J Pathol. 1999; 154:1673–1684. [PubMed: 10362792]

Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mislt C, Rothacher S, Ledermann B, Bürki K, Frey P, Paganetti PA, et al. Two precursor protein transgenic mouse models with Alzheimer disease-like pathology. Proc Natl Acad Sci USA. 1997; 94:13287–13292. [PubMed: 9371838]

Su JH, Kesslak JP, Head E, Cotman CW. Caspase-cleaved amyloid precursor protein and activated caspase-3 are co-localized in the granules of granulovacuolar degeneration in Alzheimer's disease and Down's syndrome brain. Acta Neuropathol. 2002; 104:1–6. [PubMed: 12070657]

Sugarman MC, Yamasaki TR, Oddo S, Echegoyen JC, Murphy MP, Golde TE, Jannatipour M, Leissring MA, LaFerla FM. Inclusion body myositis-like phenotype induced by transgenic overexpression of βAPP in skeletal muscle. Proc Natl Acad Sci USA. 2002; 99:6334–6339. [PubMed: 11972038]

Thai DR, Holzer M, Rüb U, Waldmann G, Günzel S, Zedlick D, Schober R. Alzheimer-related τ-pathology in the perforant path target zone and in the hippocampal stratum oriens and radiatum correlates with onset and degree of dementia. Exp Neurol. 2000; 163:98–110. [PubMed: 10785448]

Tiraboschi P, Sabbagh MN, Hansen LA, Salmon DP, Merdes A, Gamst A, Masliah E, Alford M, Thai LJ, Corey-Bloom J. Alzheimer disease without neocortical neurofibrillary tangles: "a second look". Neurology. 2004; 62:1141–1147. [PubMed: 15079014]

Turner CA, Presti MF, Newman HA, Bugenhagen P, Crnic L, Lewis MH. Spontaneous stereotypy in an animal model of Down syndrome: Ts65Dn mice. Behav Genet. 2001; 31:393–400. [PubMed: 11720125]

Uc EY, Rizzo M, Anderson SW, Shi Q, Dawson JD. Driver route-following and safety errors in early Alzheimer disease. Neurology. 2004; 63:832–837. [PubMed: 15365132]

Van Dam D, D'Hooge R, Staufenbiel M, Van Ginneken C, Van Meir F, De Deyn PP. Age-dependent cognitive decline in the APP23 model precedes amyloid deposition. Eur J Neurosci. 2003; 17:388–396. [PubMed: 12542676]

Van Dam D, Marescau B, Engelborghs S, Cremers T, Mulder J, Staufenbiel M, De Deyn PP. Analysis of cholinergic markers, biogenic amines, and amino acids in the CNS of two APP overexpression mouse models. Neurochem Int. 2005; 46:409–422. [PubMed: 15737439]

Van Dorpe J, Smeijers L, Dewachter I, Nuyens D, Spittaels K, Van Den Haute C, Mercken M, Moechars D, Laenen I, Kuiperi C, et al. Prominent cerebral amyloid angiopathy in transgenic mice overexpressing the london mutant of human APP in neurons. Am J Pathol. 2000; 157:1283–1298. [PubMed: 11021833]

Van Leuven FF. Single and multiple transgenic mice as models for Alzheimer's disease. Prog Neurobiol. 2000; 61:305–312. [PubMed: 10727777]

Weiner WJ, Carvey PM, Nausieda PA, Klawans HL. Dopaminergic antagonism of L-5-hydroxytryptophan-induced myoclonic jumping behavior. Neurology. 1979; 29:1622–1625. [PubMed: 41197]

Weintraub, S.; Mesulam, MM. Four neuropsychological profiles in dementia. In: Spinnler, H.; Boller, F., editors. Handbook of Neuropsychology. Vol. 8. Amsterdam: Elsevier; 1993. p. 253-282.

Westerman MA, Cooper-Blacketer D, Mariash A, Kotilinek L, Kawarabayashi T, Younkin LH, Carlson GA, Younkin SG, Ashe KH. The relationship between Aβ and memory in the Tg2576 mouse model of Alzheimer's disease. J Neurosci. 2002; 22:1858–1867. [PubMed: 11880515]

Westmark CJ, Westmark PR, Beard AM, Hildebrandt SM, Malter JS. Seizure suseptibility and mortality in mice that over-express amyloid precursor protein. Int J Clin Exp Pathol. 2008; 1:157–168. [PubMed: 18784809]

Winkler DT, Bondolfi L, Herzig MC, Jann L, Calhoun ME, Wiederhold KH, Tolnay M, Staufenbiel M, Jucker M. Spontaneous hemorrhagic stroke in a mouse model of cerebral amyloid angiopathy. J Neurosci. 2001; 21:1619–1627. [PubMed: 11222652]

Wirths O, Bayer TA. Motor impairment in Alzheimer's disease and transgenic Alzheimer's disease mouse models. Genes Brain Behav. 2008; 7(Suppl 1):1–5. [PubMed: 18184365]

Wirths O, Bayer TA. Neuron loss in transgenic mouse models of Alzheimer's disease. Int J Alzheimers Dis. 2010 Aug 12.:723782. pii. [PubMed: 20871861]

Wirths O, Weis J, Kayed R, Saido TC, Bayer TA. Age-dependent axonal degeneration in an Alzheimer mouse model. Neurobiol Aging. 2007; 28:1689–1699. [PubMed: 16963164]

Wirths O, Breyhan H, Schäfer S, Roth C, Bayer TA. Deficits in working memory and motor performance in the APP/PS1ki mouse model for Alzheimer's disease. Neurobiol Aging. 2008; 29:891–901. [PubMed: 17215062]

Woodruff-Pak DS, Papka M. Alzheimer's disease and eyeblink conditioning: 750 ms trace vs. 400 ms delay paradigm. Neurobiol Aging. 1996; 17:397–404. [PubMed: 8725901]

Woodruff-Pak DS, Romano S, Papka M. Training to criterion in eyeblink classical conditioning in Alzheimer's disease, Down's syndrome with Alzheimer's disease, and healthy elderly. Behav Neurosci. 1996; 110:22–29. [PubMed: 8652068]

Yamaguchi H, Hirai S, Morimatsu M, Shoji M, Ihara Y. A variety of cerebral amyloid deposits in the brains of the Alzheimer-type dementia demonstrated by β protein immunostaining. Acta Neuropathol. 1988; 76:541–549. [PubMed: 3059748]

Yamaguchi F, Richards SJ, Beyruther K, Salbaum M, Carlson GA, Dunnett SB. Transgenic mice for the amyloid precursor protein 695 isoform have impaired spatial memory. Neuroreport. 1991; 2:781–784. [PubMed: 1686563]

Biographies

Prof. Robert Lalonde graduated from the University of Montreal, Department of Psychology, with a PhD degree in 1982. After postdoctoral training at the Clinical Research Institute of Montreal, he obtained a position as an Assistant Professor at the Department of Medicine at the University of Montreal. In 1996, he obtained a position as a Professor at the Department of Psychology at the University of Rouen. His main research work concerns the behavioral characterization of mutant mice as well as psychopharmacological studies. He has published 214 research articles.

Dr. Ken-ichiro (Ken) Fukuchi graduated from the Osaka University Medical School with a Medical Degree in 1979 and a PhD in 1985 in the field of medical genetics. He is a neuroscientist, molecular biologist and trained as a geriatrician who has dedicated his life to biomedical research. The Fukuchi Laboratory research has been focused on studying the molecular mechanisms underlying age-associated diseases such as Alzheimer's disease and developing new preventive and therapeutic measures for over 20 years. Dr. Fukuchi is the Principal Investigator and recipient of numerous research grants from various resources including National Institutes of Health (NIH). Dr. Fukuchi has published over 70 scientific peer reviewed articles in this research area.

Dr. Catherine Strazielle graduated from the University of Lorraine with a MSc in Nutrition and a PhD in 1995 in Neuroscience, in the field of functional neuroanatomy. After postdoctoral training in Montreal in 1995, she began to collaborate with Robert Lalonde concerning the phenotypic characterization of animal models of human neurodegenerative diseases, particularly Alzheimer's disease and cerebellar ataxia, evaluating by means of brain cartographies, the neurochemical changes linked to behavioral performances. She has published more than 60 articles in this field.

Table 1

Description of behaviorally characterized mice expressing human mutated or WT *APP* transgenes or $A\beta_{42}$ with or without mutated *PS1.*

Name	Mutation	Promoter	Parenchymal Aβ plaques	References
APP_{695}SWE Tg2576	Swedish	Hamster *Prp*	Yes	Hsiao et al., 1996
APP_{695}SWE Tg2123H	Swedish	Hamster *Prp*	No	Hsiao et al., 1995
APP_{695}SWEch	Swedish	Murine *PrP*	No	Borchelt et al., 1996, 1997
APP_{751}SWE TgAPP23	Swedish	Murine *Thy1*	Yes	Sturchler-Pierrat et al., 1997
APP_{770}SWE	Swedish	Murine *Thy1*	Yes	Moechars et al., 1999b
APP/SWE/*Ckm*	Swedish	Murine *Ckm*	No	Sugarman et al., 2002
APP_{695}LD	London	Murine *Thy1*	Yes	Moechars et al., 1999b
APP/DU/*Thy1*	Dutch	Murine *Thy1*	No	Kumar-Singh et al., 2000
APP/FL/*Thy1*	Flemish	Murine *Thy1*	No	Kumar-Singh et al., 2000
APP_{695}SWE/IND TgCRND8 or Tg19959	Swedish+Indiana	Hamster *Prp*	Yes	Chishti et al., 2001
APP/SWE/IND/J20	Swedish+Indiana	Platelet-derived *PDGF*β	Yes	Mucke et al., 2000; Palop et al., 2003
APP_{751}SWE/IND TgAPP-Sw, V717F/B6	Swedish+Indiana	Platelet-derived *PDGF*β	No	Lee et al., 2004
APP_{751}SWE/LD	Swedish+London	Murine *Thy1*	Yes	Blanchard et al., 2003
APP/RK	Artificial 684+687 codons	Murine *Thy1*	No	Moechars et al., 1996
APP_{695}TRI*myc* Tg1130H	Artificial	Hamster *Prp*	No	Hsiao et al., 1995
APP_{695}WT/*Mt2*	None	*Mt2*	No	Yamaguchi et al., 1991
APP_{695}WT/*Thy1*	None	Murine *Thy1*	No	Moechars et al., 1999b
APP_{695}WT Tg1874	None	Hamster *Prp*	No	Hsiao et al., 1995
APP_{695}*myc*WT Tg6209	None	Hamster *Prp*	No	Hsiao et al., 1995
APP/C99 Tg13592	None	CMV enhancer/chicken *Actb*	No	Fukuchi et al., 1996
$A\beta_{42}$	None	Murine *Nefl*	No	LaFerla et al., 1995

Name	Mutation	Promoter	Parenchymal Aβ plaques	References
APP$_{695}$SWE+*PS1*/M146L	Bigenic	Hamster *Prp*+PDGFβ2	Yes	Duff et al., 1996; Holcomb et al., 1998
APP$_{695}$SWE+*PS1*/A246E	Bigenic	Hamster *Prp*+human *THY1*	Yes	Qian et al., 1998; Dineley et al., 2002
APP$_{695}$SWEch+*PS1*/A246E	Bigenic	Murine *PrP*	Yes	Borchelt et al., 1996
APP$_{695}$SWE/co+*PS1*/ΔE9	Co-Injected bigenic	Murine *PrP*	Yes	Jankowsky et al., 2004
APP$_{751}$SWE/LD+*PS1*/M146L	Bigenic	Murine *Thy1*+human *HMGCR*	Yes	Blanchard et al., 2003
APP$_{751}$SWE/LD+*PS1*/M233T+L235P	Bigenic	Murine *Thy1*	Yes	Casas et al., 2004
3xTg-AD	Trigenic	Murine *Thy1*+endogenous control+murine *Thy1*	Yes	Oddo et al., 2003
5xFAD	Five-time mutated	Murine *Thy1*	Yes	Oakley et al., 2006

Table 2

Myoclonic and epileptic phenotypes in mice expressing human mutated or WT *APP* transgenes with or without mutated *PS1.*

Name	Myoclonic jumping	Tonic-clonic seizures	Parenchymal Aβ plaques	References to behavior
APP_{695}SWE Tg2576	Yes (3%)	Yes (small number)	Yes	Lalonde et at., 2003; Westmark et al., 2008
APP_{751}SWE TgAPP23	Yes	Yes	Yes	Lalonde et al., 2005
APP_{770}SWE	Not reported	Yes	Yes	Moechars et al., 1999b
APP_{695}LD	Not reported	Yes	Yes	Moechars et al., 1999b
APP/DU/*Thy1*	Not reported	Yes	No	Kumar-Singh et al., 2000
APP/FL/*Thy1*	Not reported	Yes	No	Kumar-Singh et al., 2000
APP_{695}SWE/IND TgCRND8 orTg19959	Yes	Not reported	Yes	Ambrée et al., 2006
APP/SWE/IND/J20	Not reported	Yes (EEG only)	Yes	Palop et al., 2007
APP_{695}TRI*myc* Tg1130H	Not reported	Yes	No	Hsiao et al., 1995
APP/RK	Not reported	Yes	No	Moechars et al., 1996
APP_{695}WT/*Thy1*	Not reported	Yes	No	Moechars et al., 1999b
$A\beta_{42}$	Not reported	Yes	No	LaFerla et al., 1995
APP_{695}SWE/co+*PS1*/ΔE9	No	Yes	Yes	Lalonde et al., 2004; Minkeviciene et al., 2009

Table 3

Motor coordination in mice expressing human mutated or WT *APP* transgenes with or without mutated *PS1* (↓=deficit or normal vs. controls).

Name	Stationary beam	Suspended bar	Rotorod	References
APP_{695}SWE Tg2576	↓ or normal	↓ or normal	Normal	Chapman et at., 1999; Arendash et al., 2001b, 2004; Dineley et al., 2002; King and Arendash, 2002; Lalonde et al., 2003; Gil-Bea et al., 2007; Perucho et al., 2010
APP_{751}SWE APP23	Normal	Normal	↓ or normal	Lalonde et al., 2002b, 2005; Van Dam et at., 2003; Dumont et al., 2004
APP_{695}SWEch	↓	Normal	Not reported	Savonenko et al., 2003
APP_{695}SWE/IND TgCRND8 or Tg19959	Not reported	Not reported	Normal	Hyde et al., 2005; Bellucci et al., 2006
APP_{751}SWE/IND	Not reported	Not reported	↓	Lee et al., 2004
APP_{751}SWE/LD	↓	↓	Not reported	Le Cudennec et al., 2008; Blanchard et al., 2009
APP_{751}WT	Not reported	Normal	Normal	Moran et al., 1995
APP/SWE/*Ckm*	Not reported	Not reported	↓	Sugarman et al., 2002; Kitazawa et al., 2006
APP/C99	Normal	Normal	Normal	Lalonde et al., 2002a
APP_{695}SWE+*PS1*/M146L	↓ or normal	↓	↓	Arendash et al., 2001a, b; Sadowski et al., 2004; Ewers et al., 2006
APP_{695}SWE+*PS1*/A246E	Not reported	Not reported	Normal	Dineley et al., 2002
APP_{695}SWE/co+*PS1*/ΔE9	Normal	Normal	Normal	Lalonde et al., 2004
APP_{751}SWE/LD+*PS1*/M233+L235P	↓	↓	Not reported	Cotel et al., 2012
3xTg-AD	Normal	Normal	Not reported	Gimenez-Llort et al., 2007; Gulinello et al., 2009
5xFAD	↓	↓	Not reported	Jawhar et al., 2011