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# Presenilin transgenic mice as models of Alzheimer's disease

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## Abstract

Mutations in presenilin-1 (PS1) and presenilin-2 (PS2) cause familial Alzheimer's disease (FAD). Presenilins influence multiple molecular pathways and are best known for their role in the γ-secretase cleavage of type I transmembrane proteins including the amyloid precursor protein (APP). PS1 and PS2 FAD mutant transgenic mice have been generated using a variety of promoters. PS1-associated FAD mutations have also been knocked into the endogenous mouse gene. PS FAD mutant mice consistently show elevations of A$\beta$42 with little if any effect on A$\beta$40. When crossed with plaque forming APP FAD mutant lines, the PS1 FAD mutants cause earlier and more extensive plaque deposition. Although single transgenic PS1 or PS2 mice do not form plaques, they exhibit a number of pathological features including age-related neuronal and synaptic loss as well as vascular pathology. They also exhibit increased susceptibility to excitotoxic injury most likely on the basis of exaggerated calcium release from the endoplasmic reticulum. Electrophysiologically long-term potentiation in the hippocampus is increased in young PS1 FAD mutant mice but this effect appears to be lost with aging. In most studies neurogenesis in the adult hippocampus is also impaired by PS1 FAD mutants. Mice in which PS1 has been conditionally knocked out in adult forebrain on a PS2 null background (PS1/2 cDKO) develop a


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striking neurodegeneration that mimics AD neuropathology in being associated with neuronal and synaptic loss, astrogliosis and hyperphosphorylation of tau, although it is not accompanied by plaque deposits. The relevance of PS transgenic mice as models of AD is discussed.

### Keywords

Alzheimer's disease; Familial Alzheimer's disease; Hippocampal neurogenesis; Presenilin-1; Presenilin-2; Transgenic mice

## Presenilins and Alzheimer's disease

Presenilins (PS) were discovered in the search for genes associated with familial Alzheimer's disease (FAD) (Ertekin-Taner 2007). More than 170 mutations in *presenilin-1* (*PS1*) and 14 mutations in *presenilin-2* (*PS2*) have been linked to FAD (see http://www.molgen.ua.ac.be/ADMutations). Presenilins are highly conserved in evolution having homologues in organisms as distant as *C. elegans* (Levitan and Greenwald 1995), *Drosophila* (Boulianne et al. 1997), and lower chordates (Martinez-Mir et al. 2001). A form of PS even exists in plants (Khandelwal et al. 2007).

The mammalian *PS1* and *PS2* genes encode 467 and 448 amino acid proteins, respectively, with the two human proteins sharing more than 65% sequence identity (Rogaev et al. 1995). Both PS1 and PS2 are expressed widely during development and are ubiquitously expressed in terms of tissue distribution in the adult (Rogaev et al. 1995; Sherrington et al. 1995). However, in the adult brain, PSs are expressed predominately in neurons (Elder et al. 1996; Lee et al. 1996), although they can be found in reactive astrocytes (Weggen et al. 1998), and may be expressed at lower levels in other cell types (Lee et al. 1996). PS1 is expressed at higher levels during development than PS2, although in adult brain PS1 and PS2 are expressed at relatively similar levels and in similar distributions (Lee et al. 1996). Supporting a functionally more dominant role for PS1 during development, null mutations in PS1 produce an embryonic lethal phenotype (Shen et al. 1997; Wong et al. 1997), whereas PS2 knockout mice are viable and exhibit at most a mild pulmonary phenotype (Herreman et al. 1999). While mutations in both *PS1* and *PS2* cause FAD, *PS2* mutations tend to have a later age of onset and produce a more slowly progressive disease (Bertram and Tanzi 2004).

Both PS proteins have the features of transmembrane proteins (Rogaev et al. 1995; Sherrington et al. 1995). Presenilins influence multiple molecular pathways being best known for their roles as components of the γ-secretase complex (Steiner et al. 2008; Wolfe 2009) and both PS1 and PS2 possess the conserved aspartates required for γ-secretase function (Yu et al. 2000). It is, however, clear that PS1 in particular interacts with a number of proteins (Vetrivel et al. 2006), some in manners that do not lead to the production of a γ-secretase cleavage such as PS1's well-studied interaction with β-catenin (Hass et al. 2009). PS2's interactions have been less studied than those of PS1, although it does not interact with β-catenin (Tesco et al. 1998).

## Transgenic mice expressing presenilin-associated FAD mutations

Both PS1 and PS2 FAD mutant transgenic lines have been generated by pronuclear injection using a variety of heterologous promoters including Thy1, the platelet-derived growth factor (PDGF), neuron-specific enolase (NSE), prion protein, chicken β-actin, and HMG-CoA promoters (Borchelt et al. 1996; Duff et al. 1996; Citron et al. 1997; Oyama et al. 1998; Qian et al. 1998; Chui et al. 1999; Dewachter et al. 2000; Leutner et al. 2000; Hwang et al. 2002; Wen et al. 2002a; 2004). Depending on the promoter chosen the resultant lines exhibit transgene expression patterns varying from neuron-specific to ubiquitous. Although most

studies have utilized transgenes expressing single FAD mutations, in an effort to potentiate pathological effects some investigators have engineered multiple PS1 FAD mutations into a single transgene (Leutner et al.2000). Several PS1 knock in (KI) lines have also been generated by introducing FAD mutants into the endogenous mouse gene (Guo et al. 1999; Nakano et al. 1999; Flood et al. 2002; Casas et al. 2004). PS1 FAD mutant mice have also been generated using yeast or P1 artificial chromosomes (Lamb et al. 1999; Gama Sosa et al. 2009).

Because of their ability to accentuate plaque pathology in APP FAD mutant transgenic mice (see below), PS1 FAD mutants have also been combined with APP FAD mutations such as in 5X FAD mutant mice that contain three distinct APP mutations and two PS1 FAD mutations (Oakley et al. 2006). PS1 and APP FAD mutations have also been combined with a tau mutation associated with frontotemporal dementia to generate 3X transgenic mice that exhibit a robust combination of amyloid plaques and neurofibrillary tangle (NFT)-like lesions (Oddo et al. 2003). Bigenic APP/PS1 FAD mutant mice have been widely studied to determine the pathological/pathophysiological effects of amyloid deposition and also to develop anti-amyloid strategies. Due to the focus of this review on the effects of PS FAD mutations, studies in PS/APP mice will not be further discussed.

## Effects of presenilin FAD mutants on A$\beta$ production and plaque formation in APP transgenic mice

The amyloid hypothesis postulates that shunting of APP processing towards A$\beta$ production in particular the production of the more amyloidogenic A$\beta$42 species leads to a pathophysiological cascade that produces the clinical and pathological features of AD (Pimplikar 2009). Multiple studies have shown that A$\beta$42 levels are increased in both PS1 and PS2 FAD mutant transgenic mice and rise with aging. Unlike APP FAD mutant transgenic mice, A$\beta$40 levels are typically not changed, creating a net increase in the A$\beta$42/40 ratio. This effect is not a result of elevated total levels of PS, as overexpression of wild type PS1 has no effect on either A$\beta$40 or 42 levels (Duff et al. 1996; Wen et al. 2004). Although one study has reported that overexpression of wild type PS2 increases A$\beta$42 levels as much as a PS2 FAD mutation (Hwang et al. 2002), other studies have not found any effect of wild type PS2 overexpression on A$\beta$ levels (Sawamura et al. 2000). A$\beta$42 also selectively increases in an age- and gene dosage-dependent manner in PS1 knock in mice (Nakano et al. 1999) that express wild type levels of PS1, further arguing that overexpression is not necessary for effects on A$\beta$ production.

Despite elevated A$\beta$42 and higher A$\beta$42/40 ratios PS FAD mutant mice do not develop plaque deposits even with aging. However, when overexpressing PS1 FAD mutant mice or PS1 FAD KI mice are bred with APP FAD mutant mice, compared to the parental APP FAD lines the ratio of A$\beta$42/40 increases and plaque deposition begins at an earlier age and is more extensive with aging (Borchelt et al. 1997; Citron et al. 1997; Holcomb et al. 1998; Lamb et al. 1999; McGowan et al. 1999; Dewachter et al. 2000). Indeed, APP FAD mutant KI mice that do not spontaneously develop plaque deposits can be induced to develop plaques when crossed with FAD mutant mice overexpressing PS1 or with PS1 FAD mutant KI mice (Flood et al. 2002; Kohler et al. 2005). In contrast, crossing APP FAD mutant mice with PS1 wild type transgenic animals affects neither plaque deposition nor A$\beta$ ratios compared to single transgenic APP mice. Thus, PS FAD mutants shift steady levels of A$\beta$ towards increased generation of A$\beta$42 and accelerate plaque deposition in APP FAD mice.

## Pathological effects of presenilin FAD mutations

The lack of plaque deposits in PS1 and PS2 FAD mutant mice has created the impression, sometimes noted, that PS FAD mutant mice have no phenotype. Yet, despite the lack of plaque deposits PS FAD mutant mice exhibit a variety of pathological and pathophysiological changes (see Table 1). Chui et al. (1999) were first to describe a neurodegenerative phenotype in PS1 FAD mutant mice, reporting age-related neuronal loss in the hippocampus and neocortex of mice expressing the L286V FAD mutation under the control of a PDGF promoter. These authors described a neurodegenerative phenotype that they referred to as “dark” neurons, in which abnormal shrunken neurons were identified by a silver stain. Some of these neurons were documented to be undergoing apoptosis and an age-related astrogliosis was also reported. Although no studies have further commented on the “dark” neuron phenotype and not all subsequent studies have documented age-related neuronal loss in PS1 FAD mutant mice (Schmitz et al. 2004), Sadowski et al. (2004) reported a greater than 30% loss of hippocampal pyramidal neurons at 22 month of age in the PDGF-PS1 M146L mutant mice generated by Duff et al. (1996). This loss was as severe as that in double transgenic mice in which PDGF-M146L mice were crossed with mice harboring the Swedish APP mutation (Tg2576). A layer-specific synapse decrease has also been observed in relatively young 1–3 month old A246E PS1 FAD mutant mice (Priller et al. 2007) and an age-related synapse loss has also been documented in M146L PS1 FAD mutant mice (Rutten et al. 2005) although interestingly, synaptic sprouting in the dentate molecular layer has been reported to be increased in transgenic mice that overexpress either PS1 wild type or FAD mutant transgenes (Kadish et al. 2002). By contrast dendritic spine densities on CA1 pyramidal neurons have been reported to be increased in PS1 L286V mutant mice at 4–5 months of age compared to transgenic mice expressing human wild type PS1 or non-transgenic controls (Auffret et al. 2009). However, spine densities in the FAD mutants fell to normal levels at 8–10 months of age although there were fewer ramified spines in transgenic animals overexpressing either the L286V mutation or wild type PS1 (Auffret et al. 2009). Recently an age-related vascular pathology has also been described in M146V and P117L PS1 FAD mutant mice that mimics many of the features of the vascular pathology seen in AD (Gama Sosa et al. 2009). This pathology was especially prominent in the microvasculature whose vessels became thinned and irregular with the appearance of many abnormally looped vessels as well as string vessels. Stereologic assessments revealed a reduction of the microvasculature in the hippocampus that was accompanied by hippocampal atrophy.

Tanemura et al. (2006) found Congo red- and thioflavin S-positive inclusions in hippocampal pyramidal neurons that were reminiscent of NFTs in I213T PS1 KI mice. These lesions, which appeared in an age-related fashion, were labeled with the Alz50 antibody that recognizes abnormal tau isoforms found in human NFTs. Abnormally phosphorylated forms of tau were also found by Western blotting in hippocampal extracts and sodium dodecyl sulfate (SDS)-insoluble 10 nm straight filaments, labeled with anti-phosphotau antibodies, were observed in this mouse model by electron microscopy.

Lazarov et al. (2007) have made relatively similar observations in the spinal cord of mice expressing the ΔE9 PS1 FAD mutation, finding neurons in the ventral horn of the spinal cord and the surrounding white matter that were stained with PHF-1, an antibody that like Alz50 recognizes abnormally phosphorylated forms of tau found in human NFTs. In addition, they found evidence for abnormally phosphorylated forms of the neurofilament proteins that have also been associated with neurodegenerative diseases, an observation that has also been made in PS1 L235P FAD mutant mice (Yang et al. 2009). Functionally, changes in the ΔE9 PS1 FAD mice were associated with a slowing of fast axonal transport of APP as well as Trk receptors in the sciatic nerve (Lazarov et al. 2007).

Pigino et al. (2003) also found reduced levels of PS1, APP, and synaptophysin in sciatic nerves of PS1 M146V KI mice, an observation also consistent with slowed axonal transport. Interestingly, both Lazarov et al. (2007) and Pigino et al. (2003) found increased phosphorylation of kinesin light chain in the presence of the FAD mutants, a change that would cause release of kinesin I from membrane-bound organelles leading to a reduction of kinesin based fast axonal transport. In addition, Pigino et al. (2003) observed reduced phosphorylation of serine 9 on glycogen synthase kinase 3$\beta$ (GSK-3$\beta$) in both sciatic nerve and spinal cord of M146V KI mice with no difference in total GSK-3$\beta$. Two other studies have found reduced phosphorylation of Ser 9 on GSK-3$\beta$ in brain extracts from PS1 I213T KI mice (Tanemura et al. 2006) or PS1 A246E transgenic mice (Dewachter et al. 2008). Reduced phosphorylation of GSK-3$\beta$ is associated with increased GSK-3$\beta$ enzymatic activity implying that PS1 FAD mutations lead to constitutively increased GSK-3β activity. As the kinesin light chain is among GSK-3$\beta$'s targets, a plausible explanation for the effects of PS1 FAD mutants on fast axonal transport is that increased GSK-3$\beta$ activity leads to increased phosphorylation of the kinesin light chain in turn leading to impaired fast axonal transport. Increased GSK-3$\beta$ activity would also be predicted to result in hyperphosphorylated tau which was observed in both PS1 I213T KI mice (Tanemura et al. 2006) and PS1 A246E transgenic mice (Dewachter et al. 2008). How PS1 FAD mutants affect GSK3$\beta$ activity is unknown although GSK-3$\beta$ has been reported to interact physically with PS1 (Pigino et al. 2003).

Multiple studies have shown increased lipid and protein peroxidation in PS1 FAD mutant mice (Leutner et al. 2000; Eckert et al. 2001; LaFontaine et al. 2002; Mohmmad Abdul et al. 2004; Schuessel et al. 2006), and implied increased oxidative stress either on the basis of increased production of reactive oxygen species (ROS) or reduced ROS defenses. Cu/Zn superoxide dismutase and glutathione reductase levels in brain have been reported to be normal or decreased in PS1 FAD mutants (Leutner et al. 2000; Schuessel et al. 2006). Thus, the basis for these effects remains unclear although a recent proteomic study of mitochondrial proteins in PS1 M146V KI mice found that components of the oxidative phosphorylation pathway significantly increase with age suggesting enhanced oxidative phosphorylation (Fu et al. 2009).

One study (Boeras et al. 2008) has described increased aneuploidy in splenic cells from PS1 M146V and M146L mice with a higher percentage of trisomy in cultured neurons from these mice, observations that would support suggestions from studies in cell culture that PS FAD mutants influence the cell cycle and cell division (Janicki and Monteiro 1999). Cataldo et al. (2004) have also found increased cathepsin D levels by Western blotting as well as more cathepsin D-immunoreactive neurons with aging in PS1 FAD mutant mice suggesting that PS1 FAD mutants may increase lysosomal activity with aging. Similar changes were also seen in human PS1 and PS2 FAD cases (Cataldo et al. 2004). Cathepsin D is a lysosomal acid hydrolase whose expression is increased in tangle-bearing neurons in sporadic AD. Increased cathepsin D activity could be pathophysiologically relevant by leading to increased A$\beta$ generation within the endosomal/lysosomal pathway. Cathepsin D is also a mediator of necrotic cell death and apoptosis related to calcium injury which as discussed below has been suggested to be a mechanism of cell death associated with PS FAD mutations. Recent studies have also found that PS1 FAD mutants increase levels of apolipoprotein E in the brain (Tamboli et al. 2008) as well as increase expression and activity of the $\beta$-site APP-cleaving enzyme 1 (BACE1) (Giliberto et al. 2009) and decrease acetylcholinesterase (AChE) activity and alter its glycosylation in brain (Silveyra et al. 2008). Thus, collectively despite the lack of plaque pathology, PS FAD mutant mice exhibit a variety of pathological changes relevant to AD.

## Electrophysiological changes in PS1 FAD mutant mice

Several studies have addressed the effects of PS1 FAD mutants on electrophysiological parameters in hippocampal slice cultures (Parent et al. 1999; Barrow et al. 2000; Zaman et al. 2000; Dewachter et al. 2008; Auffret et al. 2009; Wang et al. 2009). Measures of basal synaptic transmission as well as paired-pulse facilitation have been consistently found to be unaltered in PS1 FAD mutant mice (Parent et al. 1999; Barrow et al. 2000; Zaman et al. 2000). By contrast, long-term potentiation (LTP) following high-frequency stimulation has been found in multiple studies to be increased by PS1 FAD mutants (Parent et al. 1999; Barrow et al. 2000; Zaman et al. 2000; Dewachter et al. 2008; Auffret et al. 2009; Wang et al. 2009). For example, both Parent et al. (1999) and Dewachter et al. (2008) found in distinct lines of PS1 A246E FAD mutant mice that stimulation of the Schaffer collateral-CA1 synapses in hippocampus lead to larger amplitude LTP induction in the FAD mutants. PS1 ΔE9 FAD mutant mice exhibited similar changes that could be normalized by increasing inhibitory neurotransmission with a benzodiazepine (Zaman et al. 2000). Barrow et al. (2000) similarly found in two PS1 FAD lines, that medium and late after hyperpolarizations in CA3 pyramidal cells were larger and synaptic potentiation of the CA3 to CA1 projections was stronger. By contrast in none of these studies was overexpression of wild type PS1-associated with electrophysiological changes (Parent et al. 1999; Barrow et al. 2000; Dewachter et al. 2008) arguing that the effect is specific to the FAD mutant and not the result of overexpression of PS1.

Thus, multiple studies document a consistent effect of PS1 FAD mutants causing enhancement of LTP in the hippocampus. Enhancement of LTP may be seen as paradoxical as hippocampal LTP is regarded as an electrophysiological correlate of learning, whereas AD, whether sporadic or FAD, is associated with impaired learning and hippocampal function. One recent study has suggested that a possible resolution to this paradox may be that the effects are age dependent. Auffret et al. (2009) found like the other studies cited above which were all conducted in relatively young mice that in 4–5 month old PS1 L286V FAD mutant mice hippocampal LTP was enhanced in slice cultures from the FAD mutant compared to non-transgenic or mice expressing wild type PS1. By contrast at 8–10 months of age, LTP in the FAD mutant was similar to the non-transgenic while LTP was reduced in mice overexpressing wild type PS1. In 13–14 month old mice LTP was decreased in both FAD mutant and wild type PS1 over-expressing mice compared to non-transgenic mice. Pharmacological blocking studies showed like other studies (Zaman et al. 2000) that the main effects of FAD mutants were on NMDA receptor-mediated neurotransmission.

It has also been recently reported that LTP may be modulated differently in the presence of PS1 FAD mutants. In these studies, 9–12 month old PS1 M146V KI mice were found as in other studies to exhibit significantly enhanced LTP at CA1 synapses (Wang et al. 2009). However, while muscarinic receptor activation enhanced LTP in wild type mice, it impaired LTP in PS1 KI mice. Similarly, the ability of a cholinesterase inhibitor phenserine to enhance LTP was impaired in the FAD mutant, collectively suggesting that the M146V mutation impairs cholinergic modulation of LTP induction in the hippocampus.

Interestingly, hippocampal slices from PS1 heterozygous knockout (KO) mice exhibit reduced LTP in response to tetanic trains with otherwise unchanged basal responses including paired-pulse facilitation (Morton et al. 2002), suggesting that reduced PS1 levels may modulate electrophysiological responses in the hippocampus. Further supporting a role for wild type PS1 in normal hippocampal function, both LTP as well as paired-pulse facilitation are impaired in hippocampal slices from mice with a neuronal specific knockout of PS1 (Dewachter et al. 2008). Paired-pulse facilitation, LTP and NMDA receptormediated responses are also impaired in PS−/− mice in which PS1 was conditionally knocked out in

adult forebrain on a PS2 null background (PS1/2 cDKO) (Saura et al. 2004), and recent studies in which a PS cDKO was produced in either presynaptic (CA3) or postsynaptic (CA1) neurons of the hippocampal Schaffer-collateral pathway have shown that LTP induction requires PS on the presynaptic but not postsynaptic side (Zhang et al. 2009). Thus, PS1 appears essential for normal LTP induction with multiple studies indicating PS1 FAD mutants alter LTP induction in the hippocampus in likely complex ways.

## Behavioral effects of presenilin FAD mutations

Several studies have addressed whether PS FAD mutant transgenic mice exhibit behavioral abnormalities using standard batteries of tests. In general, on most tests PS FAD mutant mice have performed normally or the deficits have been subtle and inconsistent. Multiple studies have found Morris water maze performance and spontaneous Y/T maze alteration to be normal in PS1 and PS2 FAD mutant mice studied up to 9 months of age (Holcomb et al. 1999; Janus et al. 2000; Huang et al. 2003; Lalonde et al. 2003; Dewachter et al. 2008). One study found decreased anxiety in an elevated zero maze in 12-month old mice expressing a PS1 A246E FAD mutant transgene on the PS1−/− background (Lalonde et al. 2003). By contrast 6-month old male mice expressing a PS1 L235P FAD mutant transgene performed normally in an elevated zero maze but showed impaired novel object recognition (Huang et al. 2003). Altered novel object recognition has also been reported in PS1 L286V FAD mutant mice with the FAD mutants having a greater tendency to explore the novel object in a 3-h re-exposure but less of a tendency to explore the novel object at a 5-h re-exposure (Vaucher et al. 2002). In contrast, novel object recognition was normal in PS1 A246E mice, while contextual fear conditioning was augmented (Dewachter et al. 2008). While spontaneous locomotor activity in an open field was reported to be normal in several studies (Janus et al. 2000; Vaucher et al. 2002; Lalonde et al. 2003), abnormal rotarod performance has been noted in PS1 ΔE9 FAD mutant mice at 5 and 10 months of age (Lazarov et al. 2007), and impaired performance on a beam test was observed in 1 year old PS1 A246E mice (Lalonde et al. 2003).

Thus, behavioral impairments have been often observed in PS FAD mutant transgenic mice, but the deficits reported are subtle and somewhat inconsistent. However, the testing performed to date has focused mainly on relatively young PS FAD mutant mice. Yet most neurodegenerative pathology that has been described in PS FAD mutant mice has occurred in mice older than 1 year of age and indeed a recent study of greater than 1 year old N141I PS2 FAD mutant mice found impaired Morris water maze performance as well as evidence for reduced anxiety and increased locomotor activity in PS2 FAD mutant mice compared to non-transgenic or PS2 wild type transgenic mice (Yuk et al. 2009). Thus, it remains possible that other PS FAD lines which to date have exhibited only modest behavioral changes may manifest more robust effects if studied at older ages.

## Presenilin FAD mutations increase susceptibility to excitotoxic injury and alter calcium signaling

Excitotoxicity is a widely postulated mechanism for inducing cell death in a variety of chronic neurodegenerative diseases including AD. Guo et al. (1999) were the first to show that in comparison to wild type mice, intrahippocampal injections of kainate into PS1 M146V KI mice induced more necrotic cell death in CA1 and CA3 pyramidal neurons as well as in hilar neurons. Cultured hippocampal neurons from these mice were also more sensitive to glutamate induced cell death (Guo et al. 1999). Grilli et al. (2000) also found that compared to transgenic mice overexpressing wild type PS1, there was accelerated cell death in hippocampal CA3 pyramidal neurons of mice overexpressing the PS1 L286V mutation following peripheral administration of kainic acid, and Schneider et al. (2001)

made similar observations in both PS1 A246E and PS2 N146I transgenic mice. Although one study did not find increased glutamate sensitivity in cultured cortical neurons from PS1 P264L KI mice (Siman et al. 2000), both Grilli et al. (2000) and Schneider et al. (2001) found, similar to Guo et al. (1999), that excitotoxic sensitivity was greater in cultured neurons from PS1 L286V, PS1 A246E and PS2 N146I transgenic mice. Thus, multiple studies with PS transgenic mice have documented that PS FAD mutants increase neuronal sensitivity to excitotoxic damage.

Mechanistically, the effects of PS FAD mutants on excitotoxic damage has been best linked to exaggerated release of intracellular calcium stores. Guo et al. (1999) found that glutamate induced greater endoplasmic reticulum (ER) calcium release in M146V KI neurons and increased mitochondrial membrane depolarization. Associated with these changes, more mitochondrial ROS as well as lipid peroxidation products were generated. Similar findings regarding increased calcium release in response to glutamate in PS FAD mutant neurons were reported by Schneider et al. (2001). Further supporting a role for calcium mediated toxicity, both dantrolene, which blocks ER calcium release, and nifedipine, an L-type voltage-dependent $Ca^{2+}$ channel blocker, largely block the toxic effect of glutamate in both wild type and FAD neurons (Guo et al. 1999) and dantrolene also blocks neuronal death, although not seizure activity, in response to kainate in vivo (Schneider et al. 2001).

Of note, the effects of PS FAD mutants on stimulusinduced calcium release are not limited to excitatory amino acids. Larger calcium responses are also triggered in PS1 FAD mutant neurons by thapsigargin and bradykinin (Schneider et al. 2001). Electrophysiologic stimulation of hippocampal slices in M146V transgenic mice also produces exaggerated calcium responses that may well explain the increased electrophysiologic responses seen in PS FAD mutant mice discussed above (Barrow et al. 2000). Interestingly, *N*-methyl-D-aspartate (NMDA) treatment of wild type cortical neurons increases PS1 RNA levels and excitotoxic damage is less in wild type neurons in which PS1 expression is knocked down with antisense RNA treatment (Grilli et al. 2000). In addition, neurons from PS1+/− or PS1−/− mice are also less sensitive to excitotoxic damage in vitro (Grilli et al. 2000). Collectively, these observations suggest a relationship between PS1 induction and excitoxic damage with PS FAD mutants exaggerating susceptibility to excitotoxic effects.

In summary, a range of studies support the view that neurons harboring PS1 FAD mutations release excessive amounts of calcium from the ER in response to diverse stimuli. They further support the notion that excessive calcium release may be a proximal cause of the accelerated cell death observed in neurons harboring FAD mutants and may also underlie the exaggerated electrophysiological responses in PS1 FAD mutant neurons. Interestingly, exaggerated calcium release from intracellular stores has also been implicated as a mechanism of cell death in sporadic AD (Marambaud et al. 2009; Small 2009). Dysregulated calcium homeostasis which has been suggested to reflect a neurotoxic effect of oligomeric A$\beta$ (Small 2009) may thus form a common pathophysiological link between sporadic AD and PS associated FAD.

PS1 FAD mutants also render mice more sensitive to trimethyltin-induced hippocampal damage (Kassed et al. 2003), and lesioning of the perforant path induces excessive neuronal loss in the entorhinal cortex in mice harboring the ΔE9 PS1 FAD mutant (Lazarov et al. 2006). Primary neuronal cultures from PS1 L286V FAD mice, in addition, show increased vulnerability to hypoxic-hypoglycemic damage in vitro, although infarct volume following middle cerebral artery occlusion was not worse in the FAD mutant mice (Grilli et al. 2000). Thus, PS FAD mutants appear to sensitize cells to a variety of insults. Whether calcium dysregulation plays a role in all these situations or other pathophysiological mechanisms are present has not been explored.

## PS1 FAD mutations and hippocampal neurogenesis

Until recently, neurogenesis in mammals was considered to occur only during embryonic and early postnatal periods and to have no significant role in the adult nervous system. However, it is now accepted that neurogenesis occurs in two brain regions in adult mammals, the hippocampus and olfactory bulb (Elder et al. 2006). In both areas, new neurons arise from a resident population of neural progenitor cells (NPCs) that are renewed throughout life. In the hippocampus, NPCs reside in a region adjacent to the granule cell layer termed the subgranular zone and give rise to new granule cells. Multiple studies have suggested that PS1 FAD mutants alter hippocampal neurogenesis, although the results have been complex with differing results reported from different investigators and sometimes seemingly discrepant results reported by the same laboratory.

Wen et al. (2002b) first suggested that PS1 and PS1 FAD mutations affect hippocampal neurogenesis in adult brain in studies using an NSE-driven wild type human PS1 cDNA or a cDNA expressing the P117L FAD mutation. An initial study in young adult mice found that neurogenesis was promoted by overexpression of wild type PS1 but not by the P117L FAD mutant (2002b). Many factors affect hippocampal neurogenesis including environmental enrichment (EE) protocols which promote neurogenesis in adult animals (Elder et al. 2006). Because the initial study suggested that modulating PS1 expression affects hippocampal neurogenesis, it was reasoned that providing adult animals with a stimulus to induce neurogenesis such as EE might accentuate differences or reveal additional differences. However, in a second study (Wen et al. 2004), also performed in young adult animals, the P117L FAD mutant clearly impaired hippocampal neurogenesis. Although NPC proliferation was mostly unaffected by increasing expression of either wild type or FAD mutant PS1, in both standard and enriched housing conditions, the FAD mutant impaired the survival of bromodeoxyuridine (BrdU)-labeled NPCs leading to fewer new $\beta$-III-tubulin-immunoreactive neurons being generated in FAD mutant animals during the 4-week postlabeling period. The effect was mutant-specific in that NPC survival and differentiation in mice overexpressing the wild type human PS1 was similar to non-transgenic mice. Two additional lines of PS1 wild type and FAD mutant transgenic mice showed similar changes, indicating that the effects were not integration site-dependent. Thus, in the second Wen et al. study (2004), overexpression of the P117L FAD mutant impaired neurogenesis in all three experiments, while overexpression of the wild type PS1 had an essentially neutral effect. What was clear, however, between the first and second study (Wen et al. 2002b, 2004) was that in four separate experiments involving two independent lines for each transgene, the fractional survival of BrdU-labeled cells in FAD mutant animals was always decreased and that FAD mutant animals were always at a deficit of new neuron production compared to either PS1 wild type transgenic or non-transgenic controls. Studies of neurospheres from adult P117L mice have also found deficits in neurogenesis in isolated NPCs (Eder-Colli et al. 2009).

Chevallier et al. (2005) investigated the effects of Thy-1 driven PS1 A246E or wild type PS1 transgenes on hippocampal neurogenesis in adult mice in which both transgenes were bred onto the PS1−/− background. These investigators found that NPC proliferation was increased in the A246E expressing mice as well as PS1+/− mice compared to mice expressing the wild type PS1 transgene. At 4 weeks after labeling, the number of BrdU-immunolabeled cells was the same in all groups indicating that the fractional survival of NPCs was less in the A246E and PS1+/− mice. However, given that the fraction of BrdU-labeled cells that differentiated into NeuN-positive neurons was similar in all groups, there was no net change in the number of new neurons generated between the groups.

Two groups have studied the effects of FAD mutations in PS1 KI mice. One study measured hippocampal neurogenesis in M146V KI mice on a heterozygous KO background comparing them to PS1+/− mice (Wang et al. 2004) finding that the M146V FAD mutant reduced NPC proliferation by ~25%. The second study examined P264L KI mice and although finding evidence of impaired hippocampal neurogenesis in double APP/PS1 KI mice, no change in the number of doublecortin (DCX)-expressing immature neurons was found in the subgranular zone of either single FAD mutant PS1 or APP KI mice (Zhang et al. 2007), suggesting that neurogenesis was not affected.

More recently, Choi et al. (2008) examined in an extensive set of studies the effects of the PS1 M146L and PS1ΔE9 FAD mutations on hippocampal neurogenesis. There investigators used mice in which a prion protein promoter drove either FAD mutant or PS1 wild type transgenes. Young adult mice were studied under standard housing or in an EE paradigm. No differences in NPC proliferation or actual neurogenesis were seen in the FAD mutant groups in standard housed mice. However, EE-induced NPC proliferation was seen in mice expressing the wild type PS1 transgene but not in M146L or ΔE9 FAD mutant mice. Supporting an effect on proliferation more multipotent neurospheres could be cultured from the hippocampus of environmentally enriched PS1 wild type transgenic mice compared to the FAD mutants. At 2 weeks postlabeling, the fraction of BrdU-immunoreactive cells that expressed DCX, $\beta$-III tubulin or NeuN tended to be less in FAD mutants and the number of new neurons that were generated was reduced in both FAD groups. Granule cell numbers did not change under either standard housing or enrichment. However, an exercise-induced (running) increase in granule cells was seen in PS1 wild type transgenic mice but not in the two FAD mutant groups.

The results of these studies are summarized in Table 2. In general, there is a clear trend that when PS1 FAD mutants affect hippocampal neurogenesis in adult brain, they impair it. These effects have been most apparent in studies where the FAD mutants were overexpressed using heterologous promoters and effects compared to similarly overexpressed wild type PS1. However, the differences between relatively similar experiments is sometimes puzzling. For example, the studies of Wen et al. (2004) and Choi et al. (2008), which studied effects under both standard housing and EE, produced different results. In Wen et al. (2004), neurogenesis was impaired under both standard housing and EE. However, in Choi et al. (2008), no effects were seen under standard housing but only following EE. Wen et al. (2004) saw increased NPC proliferation in non-transgenic, wild type PS transgenic, and FAD mutants following EE compared to standard housed mice, but Choi et al. (2008) reported increased proliferation only in PS1 wild type transgenic mice, but not FAD mutants. Both studies found that net neurogenesis was impaired, but in Wen et al. (2004) the effect was mainly one of decreased fractional survival of NPCs, whereas in Choi et al. (2008), effects were due to decreased proliferation as well as decreased fractional differentiation.

Several differences between the studies may at least in part account for the differing results. First, differences may exist among the FAD mutants in their effects, Wen et al. (2004) using P117L mice and Choi et al. (2008) M146L or ΔE9 mutants. The genetic background also differed between these studies, and genetic background effects are known to affect response to EE (Kempermann et al. 1997, 1998). There were also methodological differences in that differing BrdU injection protocols as well as different EE protocols were used. Another factor also commented on by Choi et al. (2008) is the differing promoters. The NSE promoter used by Wen et al. (2004) is not expressed in NPCs in vivo in the hippocampus and an NSE-driven wild type PS1 transgene rescues none of the abnormalities in PS1−/− mice, arguing against NPC expression in the embryo as well (Wen et al. 2005). In contrast, the PrP promoter is ubiquitously expressed and a PrP-driven FAD mutant is capable of

rescuing the embryonic lethality and developmental defects of the PS1−/− mouse (Davis et al. 1998).

Endogenous mouse PS1 is expressed in NPCs in adult hippocampus (Wen et al. 2002a) as well as in hippocampal granule cells (Elder et al. 1996). Thus, it is plausible that PS1 may have both cell autonomous effects in NPCs as well as non-cell autonomous effects on NPCs from its expression in granule neurons or other hippocampal cell types. In fact the expression pattern of the NSE driven transgene argues for non-cell autonomous effects while a PrP-driven transgene might produce effects in NPCs as well as other cells, and indeed Choi et al. (2008) showed that microglial expression of PS1 can regulate hippocampal neurogenesis in vitro.

How PS1 FAD mutants impair hippocampal neurogenesis is unclear. One possibility is that increased levels of A$\beta$42 affect hippocampal neurogenesis. Interestingly A$\beta$42 has been reported both to impair as well as stimulate NPC proliferation in vitro (Lopez-Toledano and Shelanski 2004), and to impair NPC proliferation in adult brain in vivo (Haughey et al. 2002). Consistent with a stimulatory effect, there are reports that neurogenesis is increased in APP FAD transgenic mice (Jin et al. 2004a; Lopez-Toledano and Shelanski 2007), although other studies have observed neurogenesis to be decreased (Donovan et al. 2006). Of note however, is that Choi et al. (2008) reported that when they bred the PS1 ΔE9 FAD mutation onto the APP−/− background, the deficits in EE-induced proliferation seen with the ΔE9 mutation were not rescued, indicating that the mutation's effects were independent of A$\beta$ production. PS1 affects the processing of many other type I transmembrane proteins including Notch, which is known to regulate neurogenesis (Vetrivel et al. 2006). PS1 also has effects that are not $\gamma$-secretase-dependent, such as modulating $\beta$-catenin processing, which could in turn affect hippocampal neurogenesis (Chevallier et al. 2005).

The relevance of hippocampal neurogenesis to the pathophysiology of AD is a subject of interest. Hippocampal neurogenesis is required for some types of hippocampusdependent learning and neurogenesis is also enhanced by learning a hippocampus-dependent task (Elder et al. 2006), suggesting that impaired hippocampal neurogenesis might contribute to AD related memory dysfunction and constitute a therapeutic target. Pathologically, the hippocampus is affected early in AD with pyramidal cell loss and disruption of perforant path connections from the entorhinal cortex to the dentate granule cell layer (Hyman et al. 1984; Hof et al. 2003). Granule cell neurons also exhibit cytoskeletal changes that are similar to those found in other neurons in AD (Thal et al. 2000). However, within the hippocampus the brunt of the earliest pathology is in the pyramidal cell layer, a neuronal population currently thought to be non-neurogenic. Thus, the degree to which enhancing granule cell neurogenesis would benefit AD patients in the absence of correcting pathology in other non-neurogenic regions is unclear.

Interestingly, some studies have reported that paradoxically hippocampal neurogeneis is increased in sporadic AD (Jin et al. 2004b), based on finding increased numbers of neurons that express immature neuronal markers such as DCX, polysaturated nerve cell adhesion molecule (PSA-NCAM), and TUC-4 (TOAD [Turned On After Division]/Ulip/CRMP) in the hippocampal granule cell layer of sporadic human cases. These findings have been interpreted as indicating that neurogenesis is increased in AD. However, given the lack of any method for tracking the fate of these immature neurons and, in particular, whether they ever progress to become mature neurons, these results could also be interpreted as showing that in AD hippocampal neurogenesis is blocked at the stage of immature neuron generation. In addition, more recent studies have failed to identify increased numbers of proliferating cells in the dentate gyrus as judged by the number of Ki67-immunolabeled cells (Boekhoorn et al. 2006).

## PS1 conditional knockout mice and AD

Mice with a null mutation of the *PS1* gene die during late intrauterine life or shortly after birth and exhibit a combination of CNS and non-CNS abnormalities (Shen et al. 1997; Wong et al. 1997). *PS2*−/− mice, in contrast, are viable (Donoviel et al. 1999; Herreman et al. 1999) and exhibit at most a mild pulmonary phenotype manifested as a tendency to develop pulmonary fibrosis and hemorrhages with age (Herreman et al. 1999). Brain development in *PS2*−/− mice proceeds normally and adult *PS2*−/− mice have not been reported to exhibit any neuroanatomic changes.

To circumvent the embryonic lethality of the *PS1*−/− mouse, PS1 conditional knockouts (cKO) were generated (Feng et al. 2001; Yu et al. 2001; Dewachter et al. 2002). In each case, mice with a floxed PS1 gene were created and then crossed with mice expressing Cre recombinase under the control of the calcium-calmodulin kinase II (CamKII) promoter, which drives Cre expression postnatally in forebrain neurons including the neocortex and hippocampus. Inactivation of PS1 in homogenates of cortex is evident by 3 weeks postnatally. Dramatic reductions occur by 6 weeks with minimal PS1 expression remaining at 6 months, as judged by Western blotting (Yu et al. 2001).

Curiously, despite extensive forebrain inactivation of PS1, the phenotype of the PS1 cKO mice is mild. PS1 cKO mice exhibit no gross abnormalities. As would be expected, due to the loss of γ-secretase activity, both α- and β-cleaved carboxy-terminal fragments (CTFs) of APP accumulate while α-cleaved, secreted APP products are normal. However, despite elevated CTFs, there is less Aβ40 and Aβ42 with an increased 42/40 ratio (Yu et al. 2001; Dewachter et al. 2002). Electrophysiologically, basal synaptic transmission, paired-pulse facilitation, and LTP in the hippocampal CA1 field were normal (Feng et al. 2001; Yu et al. 2001). Behaviorally, in the studies of Yu et al. (2001), cKO mice exhibited subtle deficits in spatial learning and memory, although Feng et al. (2001) found no change in novel object recognition or spatial learning as well as no change in cued or contextual fear conditioning. Feng et al. (2001) did find that enrichment-induced NPC proliferation was less in PS1 cKO mice, although there were no differences in standard housed mice.

Two studies have crossed APP FAD mutant transgenes onto the PS1 cKO background (Dewachter et al. 2002; Saura et al. 2005). Both groups found that the lack of PS1 prevented accumulation of amyloid deposits. Aβ levels sharply decreased and APP CTFs accumulated. Associated with these biochemical changes, was a variable and age-dependent rescue of the behavioral and electrophysiological abnormalities seen in these mice. Thus, inactivating PS1 eliminates plaque pathology in APP FAD mutant mice but does not completely prevent age-dependent effects of the APP FAD mutation on behavior and electrophysiology.

The mildness of the PS1 cKO phenotype was at first surprising. However, it immediately brought attention to the possibility that PS2 expression in adult brain might be sufficient to ameliorate largely the effect of the PS1 cKO. As the PS2 KO produces at most a mild phenotype, it was possible to inactivate both PSs in adult forebrain by breeding the PS1 cKO onto the PS2 null background, thereby creating a conditional double KO (cDKO) of PS in adult forebrain (Feng et al. 2004; Saura et al. 2004). These mice develop a striking neurodegeneration that is most apparent in the cerebral cortex but affects all forebrain regions generally. The degenerative process is grossly apparent by 6 months of age, and as aging proceeds, leads to global forebrain atrophy with massive enlargement of the lateral and third ventricles. At the microscopic level, the atrophy is accompanied by neuronal loss, dendritic atrophy, reduced synaptophysin immunoreactivity, astrogliosis, and in some regions a strong microglial activation. Biochemically, the neurodegeneration is accompanied by abnormal levels of hyperphosphorylated tau by 9 months of age, with one report

describing that NFT-like structures can be revealed by silver staining and intracellular straight filaments by electron microscopy (Chen et al. 2008b). Behaviorally, mild impairments in spatial memory and contextual fear are evident at 2 months of age, which become severe by 6 months. Changes in presynaptic and postsynaptic NMDA receptor NR2A subunits have also been noted in PS cDKO mice as early as two months of age (Dewachter et al. 2008; Aoki et al. 2009) and impairments in basal synaptic transmission, paired-pulse facilitation, and LTP are present early and worsen as the degenerative process progresses (Saura et al. 2004).

Mechanistically, the basis for the neurodegeneration remains unclear. PS cDKO mice do not develop plaque deposits (Beglopoulos et al. 2004). A$\beta$ levels are reduced and are similar to the A$\beta$ levels in PS1 cKO mice. Reduced expression of cAMP-binding protein (CBP) and CREB/CBP target genes, such as c-fos and brain-derived neurotrophic factor (BDNF) have been documented as early as 2 months of age, when levels of CREB and p-CREB are normal (Saura et al. 2004). Some degenerating neurons in these cDKO mice are TUNEL-positive and there are also increased levels of the activated form of caspase 3 suggesting that apoptosis may play a role in cell death (Feng et al. 2004). An increased inflammatory response is found in both the brain and periphery of cDKO mice (Beglopoulos et al. 2004; Jiang et al. 2009). There is also evidence for increased lipid peroxidation and protein oxidation in the cerebral cortex at 2–4 months of age before the onset of the more pronounced pathology (Gu et al. 2008; Zhu et al. 2008)

Unlike PS1 cKO mice and PS1 FAD mutant transgenic mice, hippocampal neurogenesis has been reported to be increased in the early stages of neurodegeneration in PS cDKO mice with increased NPC proliferations and more BrdU/NeuN-immunolabeled neurons as well as BrdU/GFAP-positive astrocytes being produced at 7-9 months of age (Chen et al. 2008a). However, with aging, neurogenesis decreased becoming normal in 18–20 month old mice. Associated with these changes, dentate granule cell numbers, although normal at 7–9 months of age, are decreased by 30% at 19–20 months of age, suggesting that enhanced neurogenesis compensates for the neurodegenerative process early but eventually fails with aging (Chen et al. 2008a).

Interestingly, two recent studies have found that the neurodegenerative phenotype of cDKO mice can be ameliorated by either caloric restriction (CR) or EE (Dong et al. 2007; Wu et al. 2008). Wu et al. (2008) investigated the effects of a 4-month CR regimen on PS cDKO mice and found that CR improved novel object recognition and contextual fear conditioning, and was accompanied by less ventricle enlargement, caspase-3 activation, and astrogliosis, as well as reduced induction of hyperphosphorylated tau and a decreased inflammatory response. In a separate study, this same group found that an EE protocol enhanced memory and partially rescued forebrain atrophy in PS cDKO mice (Dong et al. 2007). Mechanistically, how CR and EE protect PS cDKO mice against neurodegeneration is uncertain. The studies nonetheless suggest that PS is not necessary for mediating at least some of the beneficial effects of EE or CR.

## Relevance of PS FAD mutant mice as models of AD

Due to the lack of a plaque pathology, PS FAD mutant mice have been less studied than APP or APP/PS FAD mutant transgenic mice that develop robust plaque pathology. One immediate question is why do PS FAD mutant transgenic mice not develop a more AD-like pathology given the potency of especially the PS1 FAD mutations in humans, which typically induce disease at younger ages than APP FAD mutations (Bertram and Tanzi 2004). Why PS FAD mutant mice do not develop the full spectrum of AD pathology is unclear. Indeed, plaque pathology has only been prominent with overexpression of APP

FAD transgenes at levels far above those found in the human disease. Even in the setting of plaque pathology, neuronal loss has typically been at most modest compared to the human condition, and mice only develop a plaque- and NFT-like pathology when APP with or without PS1 FAD mutations are expressed along with mutations in tau associated with frontotemporal dementia (Lewis et al. 2001; Oddo et al. 2003), a distinct disorder that does not naturally occur in combination with AD.

Yet, despite the lack of a full AD-like pathology as discussed above, PS FAD mutant mice exhibit phenotypes that mimic features of human AD. The basis for these abnormalities remains incompletely understood. PS FAD mutations elevate levels of A$\beta$42 and increase the ratio of A$\beta$42/40 in transgenic mice. Thus, the mutant phenotypes in the absence of plaque pathology can be seen as support for the current model of the amyloid hypothesis that postulates soluble forms of oligomeric Ab rather than plaque amyloid as the critical toxic species. The fact that PS mutations typically affect A$\beta$ levels less than APP mutations could also explain the generally milder pathology in PS FAD mutant transgenic mice, although, as noted above, PS1 FAD mutations produce, in humans, a typically more aggressive disease than APP FAD mutations. In contrast, suggestions that not all PS1 FAD mutants alter A$\beta$ production would support the possibility that PS FAD mutants produce effects independent of A$\beta$ production and, therefore, be seen as a challenge to the amyloid hypothesis (Shioi et al. 2007). However, the dependence of pathological changes in PS FAD mutant transgenic mice on A$\beta$ production has never been experimentally tested. Another nuance in considering PS FAD models is that when PS FAD mutant transgenics are studied without the presence of a human APP transgene, A$\beta$ dependent effects must result from overproduction of mouse A$\beta$. Mouse A$\beta$ differs from human A$\beta$ in its aggregation properties (Jankowsky et al. 2007), specifically in its tendency not to form fibrillar aggregates and these differences may underlie some of the apparent lack of pathology seen in PS FAD mutant transgenic mice.

## Are PS FAD mutations gain of function or loss of function?

Whether PS FAD mutations result in toxic gain or loss of function is an issue that has generated much debate (Shen and Kelleher 2007). PS FAD mutations were initially suggested to exert their effect through a toxic gain of function based on their leading to elevation of the more amyloidogenic and toxic forms of A$\beta$ (Duff et al. 1996). However, recently, a general consensus has emerged that relative to $\gamma$-secretase function, PS FAD mutants are in fact hypofunctional, having impaired enzymatic activity against a range of substrates including APP, Notch and cadherins (Song et al. 1999; Marambaud et al. 2002; De Strooper 2007; Wolfe 2007). When Tg2576 mice are crossed with PS1 M146 V KI mice, the pathology is worse when the remaining wild type PS1 allele is removed (Wang et al. 2006) consistent with the notion that further reduction in $\gamma$-secretase activity caused by removal of the wild type allele makes the pathology worse. Mice in which the PS1 loop region is deleted also have lowered $\gamma$-secretase activity but produce elevated A$\beta$42/40 ratios and accelerate plaque deposition when crossed to the Tg2576 mice (Deng et al. 2006). Thus, a series of observations support the notion that with respect to $\gamma$-secretase activity PS FAD mutants are hypofunctional.

Studies in *Drosophila* have also suggested that compared to human wild type PS1, PS1 FAD mutations are hypofunctional in their ability to rescue PS loss of function mutations with FAD mutants being less efficient at generation of the Notch intracellular domain (Seidner et al. 2006). Wild type human PS1 has also been shown to rescue the egg-laying defects in Sel12 null mutants (the *C. elegans* homolog of PS), while 6 human FAD mutants had reduced ability to rescue the phenotype (Levitan et al. 1996). The multiplicity of mutations in the PS1 gene with more than 170 mutations identified to date (see http://

www.molgen.ua.ac.be/ADMutations) is also more suggestive of loss rather than gain of function.

The effects of FAD mutants are however not explicable as simple loss of function. Indeed, PS1 FAD mutants can rescue the embryonic lethality of the PS1 KO (Davis et al. 1998; Qian et al. 1998), and PS1 heterozygous null mice produce less of both A$\beta$40 and 42 (Wang et al. 2006), unlike PS FAD mutants that elevate A$\beta$42 and only variably affect A$\beta$40. In addition, unlike the enhanced plaque deposition seen when APP FAD mutant mice are crossed with PS1 FAD mutant mice, crossing an APP FAD mutant transgene onto a PS1+/− background has no effect on plaque deposition (Jankowsky et al. 2004).

PS cDKO develop a frank neurodegenerative phenotype. However, these mice produce little A$\beta$40 or 42 and do not develop plaque pathology. In addition, a clear degenerative phenotype is only seen when all four PS genes (i.e., both copies of PS1 and PS2) are removed. In contrast, neither PS1 cKO mice nor PS2 KO mice have ever been observed to develop a neurodegenerative phenotype. Nevertheless, a single copy of an FAD mutant, including mutations in the less functionally important PS2, are sufficient to produce FAD. Microarray studies have also found that when PS1 cKO and PS1 FAD mutant datasets are compared, 23 out of the 30 transcripts that were altered in both data sets were altered in opposite directions in the cKO and FAD mutant brain, suggesting that the FAD-linked PS1 variants act through molecular mechanisms different from loss of function mutations (Mirnics et al. 2005).

The genetics of PS-associated FAD thus argues very strongly that PS FAD mutations are dominant mutations genetically but with respect to $\gamma$-secretase activity are loss of function mutations enzymatically. Thus, PS FAD mutants are most similar to what are usually described as dominant-negative mutations. What remains to be explored is the molecular basis for their dominant-negative effect on $\gamma$-secretase activity, as well as whether $\gamma$-secretase-independent functions of PS may be compromised as well.

AD is also a disease in which select neuronal populations and circuits are more vulnerable (Hof and Morrison 2004). Both PS1 and PS2 are widely expressed in adult brain both in highly vulnerable (e.g., hippocampal) as well as less or non-vulnerable (e.g., cerebellar and brainstem) circuits (Elder et al. 1996; Lee et al. 1996). There is currently no basis to suggest why PS FAD mutants make some circuits vulnerable to degeneration but not others although data from sporadic AD has suggested that neurons with higher PS1 expression seem to be protected from neurodegeneration (Giannakopoulos et al. 1997). A better understanding of the biology of PS FAD mutations and how they affect specific neuronal circuits will likely be needed to resolve this paradox.

## Concluding remarks

It has been more than a decade since the discovery that mutations in PS1 and PS2 can cause FAD. Due to their lack of a plaque pathology, PS transgenic mice have been less studied than APP or APP/PS FAD mutant mice. Yet PS FAD mutant mice exhibit a range of pathological as well as physiological changes that mimic many aspects of AD and merit a fuller examination as models of AD, particularly given the shift in the focus of the amyloid hypothesis away from plaque amyloid towards oligomeric A$\beta$ as the most toxic species.

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## References


Aoki C, Lee J, Nedelescu H, Ahmed T, Ho A, Shen J. Increased levels of NMDA receptor NR2A subunits at pre- and postsynaptic sites of the hippocampal CA1: An early response to conditional double knockout of presenilin 1 and 2. J Comp Neurol. 2009; 517:512–523. [PubMed: 19795494]

Auffret A, Gautheron V, Repici M, Kraftsik R, Mount HT, Mariani J, Rovira C. Age-dependent impairment of spine morphology and synaptic plasticity in hippocampal CA1 neurons of a presenilin 1 transgenic mouse model of Alzheimer's disease. J Neurosci. 2009; 29:10144–10152. [PubMed: 19675248]

Barrow PA, Empson RM, Gladwell SJ, Anderson CM, Killick R, Yu X, Jefferys JG, Duff K. Functional phenotype in transgenic mice expressing mutant human presenilin-1. Neurobiol Dis. 2000; 7:119–126. [PubMed: 10783295]

Beglopoulos V, Sun X, Saura CA, Lemere CA, Kim RD, Shen J. Reduced beta-amyloid production and increased inflammatory responses in presenilin conditional knock-out mice. J Biol Chem. 2004; 279:46907–46914. [PubMed: 15345711]

Bertram L, Tanzi RE. The current status of Alzheimer's disease genetics: what do we tell the patients? Pharmacol Res. 2004; 50:385–396. [PubMed: 15304236]

Boekhoorn K, Joels M, Lucassen PJ. Increased proliferation reflects glial and vascular-associated changes, but not neurogenesis in the presenile Alzheimer hippocampus. Neurobiol Dis. 2006; 24:1–14. [PubMed: 16814555]

Boeras DI, Granic A, Padmanabhan J, Crespo NC, Rojiani AM, Potter H. Alzheimer's presenilin 1 causes chromosome missegregation and aneuploidy. Neurobiol Aging. 2008; 29:319–328. [PubMed: 17169464]

Borchelt DR, Thinakaran G, Eckman CB, Lee MK, Davenport F, Ratovitsky T, Prada CM, Kim G, Seekins S, Yager D, Slunt HH, Wang R, Seeger M, Levey AI, Gandy SE, Copeland NG, Jenkins NA, Price DL, Younkin SG, Sisodia SS. Familial Alzheimer's disease-linked presenilin 1 variants elevate A$\beta$1–42/1–40 ratio in vitro and in vivo. Neuron. 1996; 17:1005–1013. [PubMed: 8938131]

Borchelt DR, Ratovitski T, van Lare J, Lee MK, Gonzales 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]

Boulianne GL, Livne-Bar I, Humphreys JM, Liang Y, Lin C, Rogaev E, St. George-Hyslop P. Cloning and characterization of the Drosophila *presenilin* homologue. Neuroreport. 1997; 8:1025–1029. [PubMed: 9141085]

Casas C, Sergeant N, Itier JM, Blanchard V, Wirths O, van der Kolk N, Vingtdeux V, van de Steeg E, Ret G, Canton T, Drobecq H, Clark A, Bonici B, Delacourte A, Benavides J, Schmitz C, Tremp G, Bayer TA, Benoit P, Pradier L. 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]

Cataldo AM, Peterhoff CM, Schmidt SD, Terio NB, Duff K, Beard M, Mathews PM, Nixon RA. Presenilin mutations in familial Alzheimer disease and transgenic mouse models accelerate neuronal lysosomal pathology. J Neuropathol Exp Neurol. 2004; 63:821–830. [PubMed: 15330337]

Chen Q, Nakajima A, Choi SH, Xiong X, Sisodia SS, Tang YP. Adult neurogenesis is functionally associated with AD-like neurodegeneration. Neurobiol Dis. 2008a; 29:316–326. [PubMed: 17980611]

Chen Q, Nakajima A, Choi SH, Xiong X, Tang YP. Loss of presenilin function causes Alzheimer's disease-like neurodegeneration in the mouse. J Neurosci Res. 2008b; 86:1615–1625. [PubMed: 18189321]

Chevallier NL, Soriano S, Kang DE, Masliah E, Hu G, Koo EH. Perturbed neurogenesis in the adult hippocampus associated with presenilin-1 A246E mutation. Am J Pathol. 2005; 167:151–159. [PubMed: 15972961]

Choi SH, Veeraraghavalu K, Lazarov O, Marler S, Ransohoff RM, Ramirez JM, Sisodia SS. Non-cell-autonomous effects of presenilin 1 variants on enrichment-mediated hippocampal progenitor cell proliferation and differentiation. Neuron. 2008; 59:568–580. [PubMed: 18760694]

Chui DH, Tanahashi H, Ozawa K, Ikeda S, Checler F, Ueda O, Suzuki H, Araki W, Inoue H, Shirotani K, Takahashi K, Gallyas F, Tabira T. Transgenic mice with Alzheimer presenilin 1 mutations show accelerated neurodegeneration without amyloid plaque formation. Nat Med. 1999; 5:560–564. [PubMed: 10229234]

Citron M, Westaway D, Xia W, Carlson G, Diehl T, Levesque G, Johnson-Wood K, Lee M, Seubert P, Davis A, Kholodenko D, Motter R, Sherrington R, Perry B, Yao H, Strome R, Lieberburg I, Rommens J, Kim S, Schenk D, Fraser P, St. George Hyslop P, Selkoe DJ. Mutant presenilins of Alzheimer's disease increase production of 42- residue amyloid beta-protein in both transfected cells and transgenic mice. Nat Med. 1997; 3:67–72. [PubMed: 8986743]

Davis JA, Naruse S, Chen H, Eckman C, Younkin S, Price DL, Borchelt DR, Sisodia SS, Wong PC. An Alzheimer's disease-linked PS1 variant rescues the developmental abnormalities of PS1-deficient embryos. Neuron. 1998; 20:603–609. [PubMed: 9539132]

De Strooper B. Loss-of-function presenilin mutations in Alzheimer disease. Talking Point on the role of presenilin mutations in Alzheimer disease. EMBO Rep. 2007; 8:141–146.

Deng Y, Tarassishin L, Kallhoff V, Peethumnongsin E, Wu L, Li YM, Zheng H. Deletion of presenilin 1 hydrophilic loop sequence leads to impaired gamma-secretase activity and exacerbated amyloid pathology. J Neurosci. 2006; 26:3845–3854. [PubMed: 16597739]

Dewachter I, Van Dorpe J, Smeijers L, Gilis M, Kuiperi C, Laenen I, Caluwaerts N, Moechars 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. J Neurosci. 2000; 20:6452–6458. [PubMed: 10964951]

Dewachter I, Reverse D, Caluwaerts N, Ris L, Kuiperi C, Van den Haute C, Spittaels K, Umans L, Serneels L, Thiry E, Moechars D, Mercken M, Godaux E, Van Leuven F. Neuronal deficiency of presenilin 1 inhibits amyloid plaque formation and corrects hippocampal long-term potentiation but not a cognitive defect of amyloid precursor protein [V717I] transgenic mice. J Neurosci. 2002; 22:3445–3453. [PubMed: 11978821]

Dewachter I, Ris L, Croes S, Borghgraef P, Devijver H, Voets T, Nilius B, Godaux E, Van Leuven F. Modulation of synaptic plasticity and Tau phosphorylation by wild-type and mutant presenilin1. Neurobiol Aging. 2008; 29:639–652. [PubMed: 17222948]

Dong S, Li C, Wu P, Tsien JZ, Hu Y. Environment enrichment rescues the neurodegenerative phenotypes in presenilins-deficient mice. Eur J Neurosci. 2007; 26:101–112. [PubMed: 17614943]

Donovan MH, Yazdani U, Norris RD, Games D, German DC, Eisch AJ. Decreased adult hippocampal neurogenesis in the PDAPP mouse model of Alzheimer's disease. J Comp Neurol. 2006; 495:70–83. [PubMed: 16432899]

Donoviel DB, Hadjantonakis AK, Ikeda M, Zheng H, Hyslop PS, Bernstein A. Mice lacking both presenilin genes exhibit early embryonic patterning defects. Genes Dev. 1999; 13:2801–2810. [PubMed: 10557208]

Duff K, Eckman C, Zehr C, Yu X, Prada CM, Perez-tur J, Hutton M, Buée L, Harigaya Y, Yager D, Morgan D, Gordon MN, Holcomb L, Refolo L, Zenk B, Hardy J, Younkin S. Increased amyloid-beta42(43) in brains of mice expressing mutant presenilin 1. Nature. 1996; 383:710–713. [PubMed: 8878479]

Eckert A, Schindowski K, Leutner S, Luckhaus C, Touchet N, Czech C, Muller WE. Alzheimer's disease-like alterations in peripheral cells from presenilin-1 transgenic mice. Neurobiol Dis. 2001; 8:331–342. [PubMed: 11300728]

Eder-Colli L, Abad-Estarlich N, Pannetier C, Vallet PG, Walzer C, Elder GA, Robakis NK, Bouras C, Savioz A. The presenilin-1 familial Alzheimer's disease mutation P117L decreases neuronal differentiation of embryonic murine neural progenitor cells. Brain Res Bull. 2009; 80:296–301. [PubMed: 19555743]

Elder GA, Tezapsidis N, Carter J, Shioi J, Bouras C, Li H-C, Johnston JM, Efthimiopoulos S, Friedrich VL, Robakis NK. Identification and neuron specific expression of the S182/presenilin I protein in human and rodent brains. J Neurosci Res. 1996; 45:308–320. [PubMed: 8841992]

Elder GA, De Gasperi R, Gama Sosa MA. Research update: neurogenesis in adult brain and neuropsychiatric disorders. Mt Sinai J Med. 2006; 73:931–940. [PubMed: 17195878]

Ertekin-Taner N. Genetics of Alzheimer's disease: a centennial review. Neurol Clin. 2007; 25:611–667. [PubMed: 17659183]

Feng R, Rampon C, Tang YP, Shrom D, Jin J, Kyin M, Sopher B, Martin GM, Kim SH, Langdon RB, Sisodia SS, Tsien JZ. Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. Neuron. 2001; 32:911–926. [PubMed: 11738035]

Feng R, Wang H, Wang J, Shrom D, Zeng X, Tsien JZ. Forebrain degeneration and ventricle enlargement caused by double knockout of Alzheimer's presenilin-1 and presenilin-2. Proc Natl Acad Sci USA. 2004; 101:8162–8167. [PubMed: 15148382]

Flood DG, Reaume AG, Dorfman KS, Lin YG, Lang DM, Trusko SP, Savage MJ, Annaert WG, De Strooper B, Siman R, Scott RW. FAD mutant PS-1 gene-targeted mice: increased A$\beta$42 and A$\beta$ deposition without APP overproduction. Neurobiol Aging. 2002; 23:335–348. [PubMed: 11959395]

Fu YJ, Xiong S, Lovell MA, Lynn BC. Quantitative proteomic analysis of mitochondria in aging PS-1 transgenic mice. Cell Mol Neurobiol. 2009; 29:649–664. [PubMed: 19241155]

Gama Sosa MA, De Gasperi R, Rocher AB, Wang AC-J, Janssen WGM, Flores T, Perez GM, Schmeidler J, Dickstein DL, Hof PR, Elder GA. Age-related vascular pathology in transgenic mice expressing presenilin 1-associated familial Alzheimer's disease mutations. Am J Pathol. 2009 doi: 10.3233/JAD-2009-1164.

Giannakopoulos P, Bouras C, Kovari E, Shioi J, Tezapsidis N, Hof PR, Robakis NK. Presenilin-1-immunoreactive neurons are preserved in late-onset Alzheimer's disease. Am J Pathol. 1997; 150:429–436. [PubMed: 9033258]

Giliberto L, Borghi R, Piccini A, Mangerini R, Sorbi S, Cirmena G, Garuti A, Ghetti B, Tagliavini F, Mughal MR, Mattson MP, Zhu X, Wang X, Guglielmotto M, Tamagno E, Tabaton M. Mutant presenilin 1 increases the expression and activity of BACE1. J Biol Chem. 2009; 284:9027–9038. [PubMed: 19196715]

Grilli M, Diodato E, Lozza G, Brusa R, Casarini M, Uberti D, Rozmahel R, Westaway D, St. George-Hyslop P, Memo M, Ongini E. Presenilin-1 regulates the neuronal threshold to excitotoxicity both physiologically and pathologically. Proc Natl Acad Sci USA. 2000; 97:12822–12827. [PubMed: 11070093]

Gu F, Zhu M, Shi J, Hu Y, Zhao Z. Enhanced oxidative stress is an early event during development of Alzheimer-like pathologies in presenilin conditional knock-out mice. Neurosci Lett. 2008; 440:44–48. [PubMed: 18539391]

Guo Q, Fu W, Sopher BL, Miller MW, Ware CB, Martin GM, Mattson MP. Increased vulnerability of hippocampal neurons to excitotoxic necrosis in presenilin-1 mutant knock-in mice. Nat Med. 1999; 5:101–106. [PubMed: 9883847]

Hass MR, Sato C, Kopan R, Zhao G. Presenilin: RIP and beyond. Semin Cell Dev Biol. 2009; 20:201–210. [PubMed: 19073272]

Haughey NJ, Liu D, Nath A, Borchard AC, Mattson MP. Disruption of neurogenesis in the subventricular zone of adult mice, and in human cortical neuronal precursor cells in culture, by amyloid beta-peptide: implications for the pathogenesis of Alzheimer's disease. Neuromolecular Med. 2002; 1:125–135. [PubMed: 12025858]

Herreman A, Hartmann D, Annaert W, Saftig P, Craessaerts K, Serneels L, Umans L, Schrijvers V, Checler F, Vanderstichele H, Baekelandt V, Dressel R, Cupers P, Huylebroeck D, Zwijsen A, Van Leuven F, De Strooper B. Presenilin 2 deficiency causes a mild pulmonary phenotype and no changes in amyloid precursor protein processing but enhances the embryonic lethal phenotype of presenilin 1 deficiency. Proc Natl Acad Sci USA. 1999; 96:11872–11877. [PubMed: 10518543]

Hof PR, Morrison JH. The aging brain: morphomolecular senescence of cortical circuits. Trends Neurosci. 2004; 27:607–613. [PubMed: 15374672]

Hof PR, Bussière T, Gold G, Kovari E, Giannakopoulos P, Bouras C, Perl DP, Morrison JH. Stereologic evidence for persistence of viable neurons in layer II of the entorhinal cortex and the CA1 field in Alzheimer disease. J Neuropathol Exp Neurol. 2003; 62:55–67. [PubMed: 12528818]

Holcomb L, Gordon MN, McGowan E, Yu X, Benkovic S, Jantzen P, Wright K, Saad I, Mueller R, Morgan D, Sanders S, Zehr C, O'Campo K, Hardy J, Prada CM, Eckman C, Younkin S, Hsiao K,

Duff K. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. Nat Med. 1998; 4:97–100. [PubMed: 9427614]

Holcomb LA, Gordon MN, Jantzen P, Hsiao 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]

Huang XG, Yee BK, Nag S, Chan ST, Tang F. Behavioral and neurochemical characterization of transgenic mice carrying the human presenilin-1 gene with or without the leucine-to-proline mutation at codon 235. Exp Neurol. 2003; 183:673–681. [PubMed: 14552909]

Hwang DY, Chae KR, Kang TS, Hwang JH, Lim CH, Kang HK, Goo JS, Lee MR, Lim HJ, Min SH, Cho JY, Hong JT, Song CW, Paik SG, Cho JS, Kim YK. Alterations in behavior, amyloid beta-42, caspase-3, and Cox-2 in mutant PS2 transgenic mouse model of Alzheimer's disease. FASEB J. 2002; 16:805–813. [PubMed: 12039862]

Hyman BT, Van Horsen GW, Damasio AR, Barnes CL. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science. 1984; 225:1168–1170. [PubMed: 6474172]

Janicki SM, Monteiro MJ. Presenilin overexpression arrests cells in the G1 phase of the cell cycle. Arrest potentiated by the Alzheimer's disease PS2(N141I)mutant. Am J Pathol. 1999; 155:135–144. [PubMed: 10393846]

Jankowsky JL, Slunt HH, Gonzales V, Jenkins NA, Copeland NG, Borchelt DR. APP processing and amyloid deposition in mice haplo-insufficient for presenilin 1. Neurobiol Aging. 2004; 25:885–892. [PubMed: 15212842]

Jankowsky JL, Younkin LH, Gonzales V, Fadale DJ, Slunt HH, Lester HA, Younkin SG, Borchelt DR. Rodent A$\beta$ modulates the solubility and distribution of amyloid deposits in transgenic mice. J Biol Chem. 2007; 282:22707–22720. [PubMed: 17556372]

Janus C, D'Amelio S, Amitay O, Chishti MA, Strome R, Fraser P, Carlson GA, Roder JC, St. George-Hyslop P, Westaway D. Spatial learning in transgenic mice expressing human presenilin 1 (PS1) transgenes. Neurobiol Aging. 2000; 21:541–549. [PubMed: 10924767]

Jiang X, Zhang D, Shi J, Chen Y, Zhang P, Mei B. Increased inflammatory response both in brain and in periphery in presenilins conditional double knock-out mice. J Alzheimer's Dis. 2009 (in press).

Jin K, Galvan V, Xie L, Mao XO, Gorostiza OF, Bredesen DE, Greenberg DA. Enhanced neurogenesis in Alzheimer's disease transgenic (PDGF-APPSw, Ind) mice. Proc Natl Acad Sci USA. 2004a; 101:13363–13367. [PubMed: 15340159]

Jin K, Peel AL, Mao XO, Xie L, Cottrell BA, Henshall DC, Greenberg DA. Increased hippocampal neurogenesis in Alzheimer's disease. Proc Natl Acad Sci USA. 2004b; 101:343–347. [PubMed: 14660786]

Kadish I, Pradier L, van Groen T. Transgenic mice expressing the human presenilin 1 gene demonstrate enhanced hippocampal reorganization following entorhinal cortex lesions. Brain Res Bull. 2002; 57:587–594. [PubMed: 11927360]

Kassed CA, Butler TL, Navidomskis MT, Gordon MN, Morgan D, Pennypacker KR. Mice expressing human mutant presenilin-1 exhibit decreased activation of NF-κB p50 in hippocampal neurons after injury. Mol Brain Res. 2003; 110:152–157. [PubMed: 12573544]

Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature. 1997; 386:493–495. [PubMed: 9087407]

Kempermann G, Brandon EP, Gage FH. Environmental stimulation of 129/SvJ mice causes increased cell proliferation and neurogenesis in the adult dentate gyrus. Curr Biol. 1998; 8:939–942. [PubMed: 9707406]

Khandelwal A, Chandu D, Roe CM, Kopan R, Quatrano RS. Moonlighting activity of presenilin in plants is independent of gamma-secretase and evolutionarily conserved. Proc Natl Acad Sci USA. 2007; 104:13337–13342. [PubMed: 17684101]

Kohler C, Ebert U, Baumann K, Schroder H. Alzheimer's disease-like neuropathology of gene-targeted APP-SLxPS1mut mice expressing the amyloid precursor protein at endogenous levels. Neurobiol Dis. 2005; 20:528–540. [PubMed: 15921918]

LaFontaine MA, Mattson MP, Butterfield DA. Oxidative stress in synaptosomal proteins from mutant presenilin-1 knock-in mice: implications for familial Alzheimer's disease. Neurochem Res. 2002; 27:417–421. [PubMed: 12064358]

Lalonde R, Qian S, Strazielle C. Transgenic mice expressing the PS1–A246E mutation: effects on spatial learning, exploration, anxiety, and motor coordination. Behav Brain Res. 2003; 138:71–79. [PubMed: 12493631]

Lamb BT, Bardel KA, Kulnane LS, Anderson JJ, Holtz G, Wagner SL, Sisodia SS, Hoeger EJ. Amyloid production and deposition in mutant amyloid precursor protein and presenilin-1 yeast artificial chromosome transgenic mice. Nat Neurosci. 1999; 2:695–697. [PubMed: 10412057]

Lazarov O, Peterson LD, Peterson DA, Sisodia SS. Expression of a familial Alzheimer's disease-linked presenilin-1 variant enhances perforant pathway lesion-induced neuronal loss in the entorhinal cortex. J Neurosci. 2006; 26:429–434. [PubMed: 16407539]

Lazarov O, Morfini GA, Pigino G, Gadadhar A, Chen X, Robinson J, Ho H, Brady ST, Sisodia SS. Impairments in fast axonal transport and motor neuron deficits in transgenic mice expressing familial Alzheimer's disease-linked mutant presenilin 1. J Neurosci. 2007; 27:7011–7020. [PubMed: 17596450]

Lee MK, Slunt HH, Martin LJ, Thinakaran G, Kim G, Gandy SE, Seeger M, Koo E, Price DL, Sisodia SS. Expression of presenilin 1 and 2 (PS1 and PS2) in human and murine tissues. J Neurosci. 1996; 16:7513–7525. [PubMed: 8922407]

Leutner S, Czech C, Schindowski K, Touchet N, Eckert A, Muller WE. Reduced antioxidant enzyme activity in brains of mice transgenic for human presenilin-1 with single or multiple mutations. Neurosci Lett. 2000; 292:87–90. [PubMed: 10998555]

Levitan D, Greenwald I. Facilitation of lin-12-medlated signalling by sel-12, a *Caenorhabditis elegans* S182 Alzheimer's disease gene. Nature. 1995; 377:351. [PubMed: 7566091]

Levitan D, Doyle TG, Brousseau D, Lee MK, Thinakaran G, Slunt HH, Sisodia SS, Greenwald I. Assessment of normal and mutant human presenilin function in *Caenorhabditis elegans*. Proc Natl Acad Sci USA. 1996; 93:14940–14944. [PubMed: 8962160]

Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, Hardy J, Hutton M, McGowan E. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science. 2001; 293:1487–1491. [PubMed: 11520987]

Lopez-Toledano MA, Shelanski ML. Neurogenic effect of beta-amyloid peptide in the development of neural stem cells. J Neurosci. 2004; 24:5439–5444. [PubMed: 15190117]

Lopez-Toledano MA, Shelanski ML. Increased neurogenesis in young transgenic mice overexpressing human APP(Sw, Ind). J Alzheimer's Dis. 2007; 12:229–240. [PubMed: 18057556]

Marambaud P, Shioi J, Serban G, Georgakopoulos A, Sarner S, Nagy V, Baki L, Wen P, Efthimiopoulos S, Shao Z, Wisniewski T, Robakis NK. A presenilin-1/gamma-secretase cleavage releases the E-cadherin intracellular domain and regulates disassembly of adherens junctions. EMBO J. 2002; 21:1948–1956. [PubMed: 11953314]

Marambaud P, Dreses-Werringloer U, Vingtdeux V. Calcium signaling in neurodegeneration. Mol Neurodegen. 2009; 4:20.

Martinez-Mir A, Canestro C, Gonzalez-Duarte R, Albalat R. Characterization of the amphioxus presenilin gene in a high gene-density genomic region illustrates duplication during the vertebrate lineage. Gene. 2001; 279:157–164. [PubMed: 11733140]

McGowan E, Sanders S, Iwatsubo T, Takeuchi A, Saido T, Zehr C, Yu X, Uljon S, Wang R, Mann D, Dickson D, Duff K. Amyloid phenotype characterization of transgenic mice overexpressing both mutant amyloid precursor protein and mutant presenilin 1 transgenes. Neurobiol Dis. 1999; 6:231–244. [PubMed: 10448051]

Mirnics K, Korade Z, Arion D, Lazarov O, Unger T, Macioce M, Sabatini M, Terrano D, Douglass KC, Schor NF, Sisodia SS. Presenilin-1-dependent transcriptome changes. J Neurosci. 2005; 25:1571–1578. [PubMed: 15703411]

Mohmmad Abdul H, Wenk GL, Gramling M, Hauss-Wegrzyniak B, Butterfield DA. APP and PS-1 mutations induce brain oxidative stress independent of dietary cholesterol: implications for Alzheimer's disease. Neurosci Lett. 2004; 368:148–150. [PubMed: 15351438]

Morton RA, Kuenzi FM, Fitzjohn SM, Rosahl TW, Smith D, Zheng H, Shearman M, Collingridge GL, Seabrook GR. Impairment in hippocampal long-term potentiation in mice under-expressing the

Alzheimer's disease related gene presenilin-1. Neurosci Lett. 2002; 319:37–40. [PubMed: 11814648]

Nakano Y, Kondoh G, Kudo T, Imaizumi K, Kato M, Miyazaki JI, Tohyama M, Takeda J, Takeda M. Accumulation of murine amyloid$\beta$42 in a gene-dosage-dependent manner in PS1 'knock-in' mice. Eur J Neurosci. 1999; 11:2577–2581. [PubMed: 10383647]

Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, Guillozet-Bongaarts A, Ohno M, Disterhoft J, Van Eldik L, Berry R, Vassar R. Intraneuronal beta-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. Tripletransgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron. 2003; 39:409–421. [PubMed: 12895417]

Oyama F, Sawamura N, Kobayashi K, Morishima-Kawashima M, Kuramochi T, Ito M, Tomita T, Maruyama K, Saido TC, Iwatsubo T, Capell A, Walter J, Grunberg J, Ueyama Y, Haass C, Ihara Y. Mutant presenilin 2 transgenic mouse: effect on an age-dependent increase of amyloid beta-protein 42 in the brain. J Neurochem. 1998; 71:313–322. [PubMed: 9648880]

Parent A, Linden DJ, Sisodia SS, Borchelt DR. Synaptic transmission and hippocampal long-term potentiation in transgenic mice expressing FAD-linked presenilin 1. Neurobiol Dis. 1999; 6:56–62. [PubMed: 10078973]

Pigino G, Morfini G, Pelsman A, Mattson MP, Brady ST, Busciglio J. Alzheimer's presenilin 1 mutations impair kinesin-based axonal transport. J Neurosci. 2003; 23:4499–4508. [PubMed: 12805290]

Pimplikar SW. Reassessing the amyloid cascade hypothesis of Alzheimer's disease. Int J Biochem Cell Biol. 2009; 41:1261–1268. [PubMed: 19124085]

Priller C, Dewachter I, Vassallo N, Paluch S, Pace C, Kretzschmar HA, Van Leuven F, Herms J. Mutant presenilin 1 alters synaptic transmission in cultured hippocampal neurons. J Biol Chem. 2007; 282:1119–1127. [PubMed: 17088253]

Qian S, Jiang P, Guan XM, Singh G, Trumbauer ME, Yu H, Chen HY, Van de Ploeg LH, Zheng H. Mutant human presenilin 1 protects presenilin 1 null mouse against embryonic lethality and elevates A$\beta$1–42/43 expression. Neuron. 1998; 20:611–617. [PubMed: 9539133]

Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, Mar L, Sorbi S, Nacmias B, Piacentinl S, Amaducci L, Chumakov I, Cohen D, Lannfelt L, Fraser PE, Rommens JM, St. George-Hyslop PH. Familial Alzheimer's disease In kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature. 1995; 376:775–778. [PubMed: 7651536]

Rutten BP, Van der Kolk NM, Schafer S, van Zandvoort MA, Bayer TA, Steinbusch HW, Schmitz C. Age-related loss of synaptophysin immunoreactive presynaptic boutons within the hippocampus of APP751SL, PS1M146L, and APP751SL/PS1M146L transgenic mice. Am J Pathol. 2005; 167:161–173. [PubMed: 15972962]

Sadowski M, Pankiewicz J, Scholtzova H, Ji Y, Quartermain D, Jensen CH, Duff K, Nixon RA, Gruen RJ, Wisniewski T. Amyloid-beta 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]

Saura CA, Choi SY, Beglopoulos V, Malkani S, Zhang D, Shankaranarayana Rao BS, Chattarji S, Kelleher RJ 3rd, Kandel ER, Duff K, Kirkwood A, Shen J. Loss of presenilin function causes impairments of memory and synaptic plasticity followed by age-dependent neurodegeneration. Neuron. 2004; 42:23–36. [PubMed: 15066262]

Saura CA, Chen G, Malkani S, Choi SY, Takahashi RH, Zhang D, Gouras GK, Kirkwood A, Morris RG, Shen J. Conditional inactivation of presenilin 1 prevents amyloid accumulation and temporarily rescues contextual and spatial working memory impairments in amyloid precursor protein transgenic mice. J Neurosci. 2005; 25:6755–6764. [PubMed: 16033885]

Sawamura N, Morishima-Kawashima M, Waki H, Kobayashi K, Kuramochi T, Frosch MP, Ding K, Ito M, Kim TW, Tanzi RE, Oyama F, Tabira T, Ando S, Ihara Y. Mutant presenilin 2 transgenic mice. A large increase in the levels of A$\beta$42 is presumably associated with the low density

membrane domain that contains decreased levels of glycerophospholipids and sphingomyelin. J Biol Chem. 2000; 275:27901–27908. [PubMed: 10846187]

Schmitz C, Rutten BP, Pielen A, Schafer S, Wirths O, Tremp G, Czech C, Blanchard V, Multhaup G, Rezaie P, Korr H, Steinbusch HW, Pradier L, Bayer TA. Hippocampal neuron loss exceeds amyloid plaque load in a transgenic mouse model of Alzheimer's disease. Am J Pathol. 2004; 164:1495–1502. [PubMed: 15039236]

Schneider I, Reverse D, Dewachter I, Ris L, Caluwaerts N, Kuiperi C, Gilis M, Geerts H, Kretzschmar H, Godaux E, Moechars D, Van Leuven F, Herms J. Mutant presenilins disturb neuronal calcium homeostasis in the brain of transgenic mice, decreasing the threshold for excitotoxicity and facilitating long-term potentiation. J Biol Chem. 2001; 276:11539–11544. [PubMed: 11278803]

Schuessel K, Frey C, Jourdan C, Keil U, Weber CC, Muller-Spahn F, Muller WE, Eckert A. Aging sensitizes toward ROS formation and lipid peroxidation in PS1M146L transgenic mice. Free Rad Biol Med. 2006; 40:850–862. [PubMed: 16520237]

Seidner GA, Ye Y, Faraday MM, Alvord WG, Fortini ME. Modeling clinically heterogeneous presenilin mutations with transgenic *Drosophila*. Curr Biol. 2006; 16:1026–1033. [PubMed: 16713961]

Shen J, Kelleher RJ 3rd. The presenilin hypothesis of Alzheimer's disease: evidence for a loss-of-function pathogenic mechanism. Proc Natl Acad Sci USA. 2007; 104:403–409. [PubMed: 17197420]

Shen J, Bronson RT, Chen DF, Xia W, Selkoe DJ, Tonegawa S. Skeletal and CNS defects in presenilin-1-deficient mice. Cell. 1997; 89:629–639. [PubMed: 9160754]

Sherrington R, Rogaev EI, Llang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, Tsuda T, Mar L, Foncin J-F, Bruni AC, Montesil MP, Sorbi S, Rainero I, Pinessi L, Nee L, Chumakov I, Pollen D, Brookes A, Sanseau P, Polinsky RJ, Wasco W, Da Silva HAR, Haines JL, Pericak-Vance MA, Tanzi RE, Roses AD, Fraser PE, Rommens JM, St. George Hyslop PH. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature. 1995; 375:754–760. [PubMed: 7596406]

Shioi J, Georgakopoulos A, Mehta P, Kouchi Z, Litterst CM, Baki L, Robakis NK. FAD mutants unable to increase neurotoxic A$\beta$42 suggest that mutation effects on neurodegeneration may be independent of effects on A$\beta$. J Neurochem. 2007; 101:674–681. [PubMed: 17254019]

Silveyra MX, Evin G, Montenegro MF, Vidal CJ, Martinez S, Culvenor JG, Saez-Valero J. Presenilin 1 interacts with acetylcholinesterase and alters its enzymatic activity and glycosylation. Mol Cell Biol. 2008; 28:2908–2919. [PubMed: 18299393]

Siman R, Reaume AG, Savage MJ, Trusko S, Lin YG, Scott RW, Flood DG. Presenilin-1 P264L knock-in mutation: differential effects on A$\beta$ production, amyloid deposition, and neuronal vulnerability. J Neurosci. 2000; 20:8717–8726. [PubMed: 11102478]

Small DH. Dysregulation of calcium homeostasis in Alzheimer's disease. Neurochem Res. 2009; 34:1824–1829. [PubMed: 19337829]

Song W, Nadeau P, Yuan M, Yang X, Shen J, Yankner BA. Proteolytic release and nuclear translocation of Notch-1 are induced by presenilin-1 and impaired by pathogenic presenilin-1 mutations. Proc Natl Acad Sci USA. 1999; 96:6959–6963. [PubMed: 10359821]

Steiner H, Fluhrer R, Haass C. Intramembrane proteolysis by gamma-secretase. J Biol Chem. 2008; 283:29627–29631. [PubMed: 18650432]

Tamboli IY, Prager K, Thal DR, Thelen KM, Dewachter I, Pietrzik CU, St. George-Hyslop P, Sisodia SS, De Strooper B, Heneka MT, Filippov MA, Muller U, van Leuven F, Lutjohann D, Walter J. Loss of gamma-secretase function impairs endocytosis of lipoprotein particles and membrane cholesterol homeostasis. J Neurosci. 2008; 28:12097–12106. [PubMed: 19005074]

Tanemura K, Chui DH, Fukuda T, Murayama M, Park JM, Akagi T, Tatebayashi Y, Miyasaka T, Kimura T, Hashikawa T, Nakano Y, Kudo T, Takeda M, Takashima A. Formation of tau inclusions in knock-in mice with familial Alzheimer disease (FAD) mutation of presenilin 1 (PS1). J Biol Chem. 2006; 281:5037–5041. [PubMed: 16377636]

Tesco G, Kim TW, Diehlmann A, Beyreuther K, Tanzi RE. Abrogation of the presenilin 1/beta-catenin interaction and preservation of the heterodimeric presenilin 1 complex following caspase activation. J Biol Chem. 1998; 273:33909–33914. [PubMed: 9852041]

Thal DR, Holzer M, Rub U, Waldmann G, Gunzel S, Zedlick D, Schober R. Alzheimer-related tau-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]

Vaucher E, Fluit P, Chishti MA, Westaway D, Mount HT, Kar S. Object recognition memory and cholinergic parameters in mice expressing human presenilin 1 transgenes. Exp Neurol. 2002; 175:398–406. [PubMed: 12061869]

Vetrivel KS, Zhang YW, Xu H, Thinakaran G. Pathological and physiological functions of presenilins. Mol Neurodegen. 2006; 1:4.

Wang R, Dineley KT, Sweatt JD, Zheng H. Presenilin 1 familial Alzheimer's disease mutation leads to defective associative learning and impaired adult neurogenesis. Neuroscience. 2004; 126:305–312. [PubMed: 15207348]

Wang R, Wang B, He W, Zheng H. Wild-type presenilin 1 protects against Alzheimer disease mutation-induced amyloid pathology. J Biol Chem. 2006; 281:15330–15336. [PubMed: 16574645]

Wang Y, Greig NH, Yu QS, Mattson MP. Presenilin-1 mutation impairs cholinergic modulation of synaptic plasticity and suppresses NMDA currents in hippocampus slices. Neurobiol Aging. 2009; 30:1061–1068. [PubMed: 18068871]

Weggen S, Diehlmann A, Buslei R, Beyreuther K, Bayer TA. Prominent expression of presenilin-1 in senile plaques and reactive astrocytes in Alzheimer's disease brain. Neuroreport. 1998; 9:3279–3283. [PubMed: 9831464]

Wen PH, Friedrich VL Jr, Shioi J, Robakis NK, Elder GA. Presenilin-1 is expressed in neural progenitor cells in the hippocampus of adult mice. Neurosci Lett. 2002a; 318:53–56. [PubMed: 11796184]

Wen PH, Shao X, Shao Z, Hof PR, Wisniewski T, Kelley K, Friedrich VL Jr, Ho L, Pasinetti GM, Shioi J, Robakis NK, Elder GA. Overexpression of wild type but not an FAD mutant presenilin-1 promotes neurogenesis in the hippocampus of adult mice. Neurobiol Dis. 2002b; 10:8–19. [PubMed: 12079399]

Wen PH, Hof PR, Chen X, Gluck K, Austin G, Younkin SG, Younkin LH, DeGasperi R, Gama Sosa MA, Robakis NK, Haroutunian V, Elder GA. The presenilin-1 familial Alzheimer disease mutant P117L impairs neurogenesis in the hippocampus of adult mice. Exp Neurol. 2004; 188:224–237. [PubMed: 15246822]

Wen PH, De Gasperi R, Sosa MA, Rocher AB, Friedrich VL Jr, Hof PR, Elder GA. Selective expression of presenilin 1 in neural progenitor cells rescues the cerebral hemorrhages and cortical lamination defects in presenilin 1-null mutant mice. Development. 2005; 132:3873–3883. [PubMed: 16079160]

Wolfe MS. When loss is gain: reduced presenilin proteolytic function leads to increased Abeta42/Abeta40. Talking Point on the role of presenilin mutations in Alzheimer disease. EMBO Rep. 2007; 8:136–140. [PubMed: 17268504]

Wolfe MS. Gamma-Secretase in biology and medicine. Semin Cell Dev Biol. 2009; 20:219–224. [PubMed: 19162210]

Wong PC, Zheng H, Chen H, Becher MW, Sirinathsinghji DJ, Trumbauer ME, Chen HY, Price DL, Van der Ploeg LH, Sisodia SS. Presenilin 1 is required for Notch1 and DII1 expression in the paraxial mesoderm. Nature. 1997; 387:288–292. [PubMed: 9153393]

Wu P, Shen Q, Dong S, Xu Z, Tsien JZ, Hu Y. Calorie restriction ameliorates neurodegenerative phenotypes in forebrain-specific presenilin-1 and presenilin-2 double knockout mice. Neurobiol Aging. 2008; 29:1502–1511. [PubMed: 17499883]

Yang X, Yang Y, Luo Y, Li G, Wang J, Yang ES. Hyperphosphorylation and accumulation of neurofilament proteins in transgenic mice with Alzheimer presenilin 1 mutation. Cell Mol Neurobiol. 2009; 29:497–501. [PubMed: 19137424]

Yu G, Chen F, Nishimura M, Steiner H, Tandon A, Kawarai T, Arawaka S, Supala A, Song YQ, Rogaeva E, Holmes E, Zhang DM, Milman P, Fraser PE, Haass C, George-Hyslop PS. Mutation of conserved aspartates affects maturation of both aspartate mutant and endogenous presenilin 1 and presenilin 2 complexes. J Biol Chem. 2000; 275:27348–27353. [PubMed: 10856299]

Yu H, Saura CA, Choi SY, Sun LD, Yang X, Handler M, Kawarabayashi T, Younkin L, Fedeles B, Wilson MA, Younkin S, Kandel ER, Kirkwood A, Shen J. APP processing and synaptic plasticity in presenilin-1 conditional knockout mice. Neuron. 2001; 31:713–726. [PubMed: 11567612]

Yuk DY, Lee YK, Nam SY, Yun YW, Hwang DY, Choi DY, Oh KW, Hong JT. Reduced anxiety in the mice expressing mutant (N141I) presenilin 2. J Neurosci Res. 2009; 87:522–531. [PubMed: 18803281]

Zaman SH, Parent A, Laskey A, Lee MK, Borchelt DR, Sisodia SS, Malinow R. Enhanced synaptic potentiation in transgenic mice expressing presenilin 1 familial Alzheimer's disease mutation is normalized with a benzodiazepine. Neurobiol Dis. 2000; 7:54–63. [PubMed: 10671322]

Zhang C, McNeil E, Dressler L, Siman R. Long-lasting impairment in hippocampal neurogenesis associated with amyloid deposition in a knock-in mouse model of familial Alzheimer's disease. Exp Neurol. 2007; 204:77–87. [PubMed: 17070803]

Zhang C, Wu B, Beglopoulos V, Wines-Samuelson M, Zhang D, Dragatsis I, Sudhof TC, Shen J. Presenilins are essential for regulating neurotransmitter release. Nature. 2009; 460:632–636. [PubMed: 19641596]

Zhu M, Gu F, Shi J, Hu J, Hu Y, Zhao Z. Increased oxidative stress and astrogliosis responses in conditional double-knockout mice of Alzheimer-like presenilin-1 and presenilin-2. Free Rad Biol Med. 2008; 45:1493–1499. [PubMed: 18822370]

**Table 1**

Pathological effects of presenilin FAD mutations observed in transgenic mice

| Effect | References |
|---|---|
| Age-related neuronal loss | Chui et al. (1999); Sadowski et al. (2004)) |
| Age-related synapse loss | Priller et al. (2007) |
| Increased synaptic sprouting in dentate gyrus following entorhinal cortex lesioning | Kadish et al. (2002) |
| Increased dendritic spine densities on CA1 pyramidal neurons at 4–5 months, densities becoming normal at 8–10 months | Auffret et al. (2009) |
| Age-related vascular pathology especially prominent in the microvasculature with thinned and irregular vessels; appearance of abnormally looped vessels as well as string vessels | Gama Sosa et al. (2009) |
| Age-related Congo red- and thioflavin S-positive inclusions and Alz50 labeling of hippocampal pyramidal neurons; abnormally phosphorylated forms of tau by Western blotting; insoluble 10 nm straight filaments that label with antiphosphotau antibodies; PHF-positive neurons in ventral horn of the spinal cord | Tanemura et al. (2006); Lazarov et al. (2007); Dewachter et al. (2008) |
| Reduced phosphorylation of serine 9 on glycogen synthase kinase 3$\beta$ (GSK-3$\beta$) in sciatic nerve, spinal cord and hippocampus | Pigino et al. (2003); Tanemura et al. (2006) |
| Abnormally phosphorylated neurofilament proteins | Lazarov et al. (2007); Yang et al. (2009) |
| Slowed axonal transport associated with increased phosphorylation of the kinesin light chain. | Pigino et al. (2003); Lazarov et al. (2007) |
| Increased lipid and protein peroxidation products in brain; enhanced expression of components of the oxidative phosphorylation pathway | Leutner et al. (2000); Eckert et al. (2001); LaFontaine et al. (2002); Mohmmad Abdul et al. (2004); Schuessel et al. (2006); Fu et al. (2009) |
| Increased aneuploidy in spleen cells | Boeras et al. (2008) |
| Increased cathepsin D levels by Western blotting and more cathepsin D-immunoreactive neurons with aging | Cataldo et al. (2004) |
| Decreased acetylcholinesterase (AChE) activity and alteration of AChE glycosylation | Silveyra et al. (2008) |
| Elevated levels of apolipoprotein E in the brain | Tamboli et al. (2008) |
| Increased expression and activity of BACE1 | Giliberto et al. (2009) |
| Larger and more sustained induction of LTP in hippocampal slices | Parent et al. (1999); Barrow et al. (2000); Zaman et al. (2000); Dewachter et al. (2008); Auffret et al. (2009); Wang et al. (2009) |
| Decreased anxiety; altered novel object recognition; augmented contextual fear conditioning; impaired motor performance; Morris water maze-normal in most studies but impaired in one study of >1 year old PS2 FAD mutant mice | Vaucher et al. (2002); Lalonde et al. (2003); Lazarov et al. (2007); Dewachter et al. (2008); Yuk et al. (2009) |

| Effect | References |
|---|---|
| Increased sensitivity to kainate-induced excitotoxic hippocampal injury | Guo et al. (1999); Grilli et al. (2000); Schneider et al. 2001) |
| Increased sensitivity to trimethyltin-induced hippocampal damage | Kassed et al. (2003) |
| Excessive neuronal loss in the entorhinal cortex following lesioning of the perforant path | Lazarov et al. (2006) |
| Impaired hippocampal neurogenesis in adult brain | Wen et al. (2002b); Wang et al. ( 2004); Wen et al. (2004); Chevallier et al. (2005); Zhang et al. (2007); Choi et al. (2008) |

**Table 2**

Studies of the effects of PS1 FAD mutations on hippocampal neurogenesis in adult brain

| Promoter | FAD mutation | Standard housing | Enriched housing | Reference |
|---|---|---|---|---|
| Neuron-specific enolase | PS1 P117L | Neurogenesis promoted by overexpression of wild type PS1 but not by FAD mutant | | Wen et al. (2002b) |
| Neuron-specific enolase | PS1 P117L | FAD mutant impaired survival of NPCs leading to fewer new neurons produced. | FAD mutant impaired survival of NPCs leading to fewer new neurons produced | Wen et al. (2004) |
| Thy-1 | A246E on PS1−/− background | NPC proliferation increased, fractional survival of NPCs less, no net change in new neuron production | | Chevallier et al. (2005) |
| Native mouse | M146V KI on PS1−/− background | Reduced NPC proliferation by ~25% in FAD mutant | | Wang et al. (2004) |
| Native mouse | P264L KI | No change in DCX-positive immature neurons | | Zhang et al. (2007) |
| Prion protein (PrP) | M146L or PS1ΔE9 | No difference in NPC proliferation or neurogenesis in FAD mutants | Enrichment-induced NPC proliferation and neurogenesis less in FAD mutants | Choi et al. (2008) |