# Alzheimer's disease: a tale of two diseases?

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## Abstract

Sporadic late-onset Alzheimer's disease (SLOAD) and familial early-onset Alzheimer's disease (FEOAD) associated with dominant mutations in *APP*, *PSEN1* and *PSEN2*, are thought to represent a spectrum of the same disorder based on near identical behavioral and histopathological features. Hence, FEOAD transgenic mouse models have been used in past decades as a surrogate to study SLOAD pathogenic mechanisms and as the gold standard to validate drugs used in clinical trials. Unfortunately, such research has yielded little output in terms of therapeutics targeting the disease's development and progression. In this short review, we interrogate the widely accepted view of one, dimorphic disease through the prism of the *Bmi1*$^{+/-}$ mouse model and the distinct chromatin signatures observed between SLOAD and FEOAD brains.

**Key Words:** aging; Alzheimer's disease; BMI1; epigenetics; familial; late-onset; sporadic

## Overview of Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia in the world affecting up to 35 million people worldwide (Cacace et al., 2016). AD cases can be categorized according to the age of onset and the presence of a family history of the disease or lack thereof. Early-onset AD (EOAD) designates cases that manifest before 65 years old whereas AD at and after 65 years old is considered late-onset AD (LOAD). Familial AD (FAD) indicates a positive family history while sporadic AD (SAD) indicates no familial history of the disease. Differentiating familial and sporadic cases can prove difficult, especially in large cohorts, when family history is missing or incomplete. Nonetheless, LOAD is by far the most predominant form of AD, accounting for 90–99% of all AD patients, depending on the estimate (Bird, 2008; Cacace et al., 2016) (**Figure 1**). Of the total LOAD cases, according to one study, approximately 40% were familial LOAD (FLOAD) whereas the remaining 60% were sporadic LOAD (SLOAD) (Jarvik et al., 1993) (**Figure 1**). On the other hand, EOAD, representing only 1–10% of total AD cases, is comprised of up to 60% familial EOAD (FEOAD) cases and thus approximately 40% sporadic EOAD (SEOAD) cases (Bird, 2008; Cacace et al., 2016). Unfortunately, comprehensive statistics such as these remain very limited given that often studies employ only one axis (e.g. late *vs*. early onset). Moreover, family history may be unobtainable to researchers. Thus, even though these estimates are based on relatively small populations, they provide a useful overview of the disease. Further study of diverse AD populations would greatly improve our understanding of this challenging disorder.

LOAD and EOAD are neurodegenerative diseases affecting primarily the cortex and the hippocampus, and are generally considered the same disease, despite the different age of onset, with the amyloid beta peptide ($A\beta_{42}$) considered as the central etiological factor (Nussbaum and Ellis, 2003). In all cases, patients' episodic memory deteriorates as the pathologies progress, and so do the main cognitive functions, e.g. critical judgment, orientation, language, eventually leading to a loss of autonomy (Blennow et al., 2006). The pathological hallmarks comprise extracellular senile plaques formed by the aggregation of $A\beta_{42}$, intracellular tangles of the hyperphosphorylated form of Tau protein, neuronal loss and synaptic degeneration (Blennow et al., 2006).

## Genetics of Alzheimer's Disease

### FEOAD

The discovery of highly penetrant mutations in the amyloid beta precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) genes has revealed important aspects of the mechanisms underlying FEOAD. However, these known mutations can only explain between 5% and 10% of FEOAD cases (Cacace et al., 2016). Some EOAD families also present a duplication of one allele of *APP*, resulting in three gene copies (Van Cauwenberghe et al., 2016). FEOAD-associated genes are all involved in the amyloid cascade: APP can either be cleaved by β-secretase (BACE1) in the amyloidogenic pathway or follow the non-amyloidogenic pathway and be processed by α-secretase. The products of both pathways are subsequently cleaved by γ-secretase. The former pathway leads to the production of the non-physiologic $A\beta_{42}$ peptide, which is fibrillogenic and aggregation-prone, causing the formation of the characteristic extracellular plaques (Blennow et al., 2006). Therefore, according to the amyloid cascade hypothesis, an imbalance between the production and clearance of $A\beta_{42}$ is the triggering cause of the disease (Yin and Wang, 2018). *PSEN1* and *PSEN2* are highly homologous genes which encode for the catalytic subunits of γ-secretase. Mutations in these loci therefore impair the enzymatic activity, the localization and the conformation of the complex, leading to an aberrant

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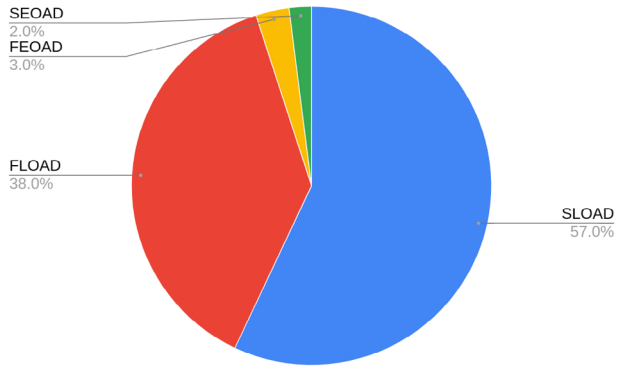


**Figure 1** | **Breakdown of total AD cases.**
Each percentage value is based on the total number of AD cases. From largest to smallest, SLOAD is 57%, FLOAD is 38%, FEOAD is 3% and SEOAD is 2%. For the purposes of this figure, LOAD is considered 95% of the total (Bird, 2008; Cacace et al., 2016), 60% of which is SLOAD and 40% is FLOAD (Jarvik et al., 1993). EOAD, here 5% of the total cases, is made up of 60% FEOAD and 40% SEOAD cases (Bird, 2008; Cacace et al., 2016). AD: Alzheimer's disease; EOAD: early-onset Alzheimer's disease; FEOAD: familial early-onset Alzheimer's disease; FLOAD: familial late-onset Alzheimer's disease; LOAD: late-onset Alzheimer's disease; SEOAD: sporadic early-onset Alzheimer's disease; SLOAD: sporadic late-onset Alzheimer's disease.

accumulation and further aggregation of $A\beta_{42}$ (Escamilla-Ayala et al., 2020). The proteins have different biological roles, demonstrated by the different impacts they have once mutated; missense mutations in *PSEN1* are responsible for the most serious form of FEOAD, with an onset as early as 25 years old. Whereas those occurring in *PSEN2* might not have complete penetrance and are linked to older age of onset (Van Cauwenberghe et al., 2016).

### SLOAD

While the modes of transmission of FEOAD are generally understood, those responsible for SLOAD are much less clear. Interestingly, mutations in the *APP* gene have been identified in small populations of cortical neurons from SAD patients, attributed to seemingly random somatic mutations (Lee et al., 2019). However, it is unclear what the prevalence of such somatic gene mosaicism is and whether it is sufficient to provoke AD. Thus, SLOAD is thought to be the result of complex interactions between both environmental and human genetic factors (Chouraki and Seshadri, 2014).

Apolipoprotein E (*APOE*) is the gene most robustly associated with the risk of developing LOAD, both familial and sporadic. APOE is the main apolipoprotein present in the brain, which is involved, amongst other things, in the transport of lipids and responsible for their internalization through specific binding to cell-surface lipoprotein receptors (Huang and Mahley, 2014). Three *APOE* allelic variants exist, which differ by nucleotides at two sites in the gene: E2 is considered protective (the rarest allele, ~8.5% worldwide frequency), E3 is considered neutral (the most common allele, ~78% worldwide) and E4 increases LOAD risk by 3-fold in carriers and 15-fold in E4 homozygotes (Corder et al., 1993; Saunders et al., 1993). In patients, these figures of allelic frequency are overturned, since E4 is the dominant allele both in LOAD, found in ~50% of the subjects affected, and in EOAD, carried by 44.31% of the patients enrolled in one study (Verghese et al, 2011; Jia et al., 2020). It should also be taken into account that the percentages here listed slightly vary between different ethnic groups. However, different studies evidenced a notable disparity concerning the effect of *APOE4* on disease progression in EOAD *vs.* LOAD (van der Vlies et al., 2009; Jochemsen et al., 2012). LOAD *APOE4*-carriers experience more rapid disease progression than LOAD *APOE4*-negative individuals, whereas EOAD *APOE4* carriers exhibit a slower disease progression than EOAD *APOE4*-negative individuals. The biological reasons behind this effect are yet to be elucidated and are more likely to be found in the interaction of the genotype with environmental cues and other factors, rather than in the genetic background solely. It is indeed well-known that *APOE4* modulatory effect on the clinical AD features strongly correlates with the age of onset of the disease (van der Flier et al., 2011).

The mechanisms linking APOE to the etiology of AD are unclear, but it has been implicated in amyloid clearance and p-Tau pathology as well as neuroinflammation (Carter, 2005; Castellano et al., 2011; Dorey et al., 2014; Tai et al., 2015; Rebeck, 2017; Buckley et al., 2019; Fernandez et al., 2019). More recently, expression of *APOE4* in cultured human neurons was shown to induce degeneration of GABAergic neurons, suggesting that APOE4 entails toxic gain-of-function activities (Wang et al., 2018). Conversely, the protective role of *APOE2* has been explained with a weaker ability of this isoform to stimulate Aβ synthesis by neurons via the engagement of a MAPK signaling pathway; APOE4, APOE3, APOE2 respectively exhibit a decreased potency in doing so (Huang et al., 2017). Further, the protective genotype also correlates with specific morphological features in the brain of healthy heterozygous individuals, i.e. a wider entorhinal cortex in children (Shaw et al., 2007) and a thicker hippocampus in the adults (Fennema-Notestine et al. 2011), while the homozygotes exhibit even more prominent characteristics, such as a larger volume of the grey matter in the anterior cingulate and medial prefrontal areas and less severe tau tangles and Aβ plaques (Reiman et al., 2020).

Since the discovery of the correlation between *APOE4* and AD decades ago, at least 20 new alleles of other genes have been reported to have an impact on the risk of developing the disease (Dong et al., 2017). Different strategies have been used to identify new hits, mainly GWAS, the candidate gene approach, statistical testing of SNPs, the study of the structural variants as a genetic marker and gene-environment interactions (Chouraki and Seshadri, 2014; Van Cauwenberghe et al., 2016). In the end, many of the variants described in these studies occur in loci either involved in the processing of APP, or in the modulation of Tau toxicity. Nevertheless, they are also part of broader biochemical processes, i.e. the immune response (e.g. *CR1* (Lambert et al., 2009), *TREM2* (Jonsson et al., 2013) and *CD33* (Naj et al., 2011)), cholesterol and lipid metabolism (e.g. *ABCA7* (Hollingworth et al., 2011), *CLU* (Harold et al., 2009)), apoptosis (e.g. *HRK* (Bis et al., 2012)), trafficking of endosomal vesicles (e.g. *PICALM* (Harold et al., 2009), *SORL1* (Rogaeva et al., 2007), *BIN1* (Harold et al., 2009, Chapuis et al., 2013)), and the regulation of the cytoskeleton (e.g. FERMT2 (Lambert et al., 2013)), expanding the number of dysregulated pathways in AD. However, each of these alleles only mildly modulates the risk of the disease (effect sizes with odds ratio ≤ 2.0), implying that APOE4 remains the most relevant LOAD susceptibility gene (Van Cauwenberghe et al., 2016). Nonetheless, there is no mutation that can be uniquely and directly associated with LOAD and it is difficult to distinguish between genetic causal mutations and biomarkers (Lutz et al., 2016). Concluding, none of the risk alleles described so far is necessary nor sufficient to explain the insurgence of the pathology, although models of combinatorial risk variants have been developed (Sims et al., 2020). For this reason, we advance an epigenetic framework underlying the development or progression of SLOAD based on seeming disparate epigenetic signatures between FEOAD and SLOAD.

## Non-Genetic Alzheimer's Disease Risk Factors

Among many other risk factors for AD, ageing is by far the most relevant (Hou et al., 2019). In 2019, 5.8 million Americans were living with AD, 81% of whom were aged 75 or older (Alzheimer's Association, 2019). Meta-analysis studies showed that the incidence rate is 7 times higher in subjects

aged 85–89 years compared to individuals from 70 to 74 years old (Petersen et al., 2001).

Other risk factors include family history and female sex. Having a relative who is affected by AD more than doubles the chances of developing the pathology (Alzheimer's Association, 2019) and in every age group considered, the percentage of females affected is higher of that of the males (Viña and Lloret, 2010). Moreover, both cardiovascular diseases and risk factors of developing them are associated with AD (de Bruijn and Ikram, 2014; Reitz and Mayeux, 2014), as well as a number of environmental factors. For instance, viral infections, aluminum and other trace metals, and an unhealthy diet all have been demonstrated to increase the risk of AD (Grant et al., 2002; Armstrong, 2019). Similarly, lifestyle habits such as lack of sleep, high blood pressure and sedentary behavior affect AD risk (Reitz and Mayeux, 2014), while education and intellectual engagement in old age are protective factors (Sando et al., 2008; Stern, 2012).

## Mouse Models of AD

### FEOAD models

To date, there are 184 mouse models of AD according to Alzforum (Alzforum.org). However, because causal mutations associated with SLOAD are not known, there is a relative dearth of such models. Given the high penetrance of FEOAD-associated mutations, many AD models utilize one or more of them. In some cases, FEOAD-associated mutations are introduced in conjunction with SLOAD-associated risk genes however, assessments of AD-related pathologies remain incomplete or absent in these mouse strains. For thorough reviews of the current FEOAD-associated genetic mouse models, see Onos et al. (2016) and Esquerda-Canals et al. (2017).

Characterized in 2003, the 3xTg-AD mouse continues to be a popular preclinical AD model and can help illustrate the advantages and disadvantages of such FEOAD models. This strain contains three human transgenes coding for the mutant $APPS^{we}$, $PS1^{m146V}$ and $Tau^{P301L}$ proteins (Oddo et al., 2003). The most notable AD-related pathologies are replicated in this mouse, with some important caveats. Firstly, Aβ plaques are detectable in the hippocampus at 6 months, with severity increasing with age; cortical Aβ plaques appear at 12 months and also exhibit an age-dependent progression (Oddo et al., 2003; Belfiore et al., 2019). In fact, Tau phosphorylation shows the same pattern of age- and region-specific appearance (Belfiore et al., 2019). Tau tangles have been shown at 12 months in the hippocampus particularly in pyramidal neurons of the CA1 region (Oddo et al., 2003). However, there are important considerations concerning the 3xTg-AD mouse tauopathy. Firstly, mutations of the *MAPT* gene are exceedingly rare in human cases of AD; in fact, they are more often associated with frontotemporal dementia (Strang et al., 2019). Secondly, Tau isolated from 3xTg-AD mouse brains fails to replicate important characteristics of Tau isolated from human AD brains. Notably, human AD-related Tau has the prion-like ability to transform normal Tau into the pathological, filamentous form both *in vitro* and *in vivo*, it often lacks the N-terminal domain and it is hyperphosphorylated to a much greater extent than 3xTg-AD mouse-derived Tau (Li et al., 2019). In terms of cognitive decline, the 3xTg-AD mouse presents cognitive impairment as early as 4 months which persists with age (Oddo et al., 2003). At last, the 3xTg-AD mouse model contains an aberrant gene copy number for *APP*, *PSEN1* and *MAPT*, a condition that does not reflect AD genetics, even in those rare FEOAD patients carrying three wild type alleles of *APP*.

As we will highlight, recent studies elaborate a particular epigenetic profile of SLOAD in terms of markers of heterochromatin and DNA damage response machinery. In contrast to analyses of human SLOAD samples, the 3xTg-AD mouse shows increased levels of the heterochromatin mark $H3K9^{me3}$ compared to non-transgenic mice, a trend that is consistent from young to old age (Walker et al., 2013). Lardenoije et al. (2019) review epigenetic aspects of multiple, prominent FEOAD mouse models even though the available data focus on DNA methylation, hydroxymethylation and the related genes. More broadly, divergent protein homology between humans and mice may have disparate effects on mouse models of FEOAD and SLOAD. For example, all three FEOAD-associated proteins have an amino acid sequence homology greater than 90% between mice and humans. However, LOAD risk-related proteins APOE and TREM2 exhibit approximately 70% and 50% sequence homology, respectively (Liao et al., 2015; Penney et al., 2020). Moreover, mouse ApoE is more amyloidogenic than any of the human isoforms (Fagan et al., 2002). For these reasons, AD therapeutics tested on FEOAD-associated genetic mouse models may have little to no efficacy in the case of SLOAD pathogenesis.

### LOAD models

Recently reviewed in Zhang et al. (2020), several LOAD mouse models exist. In these various models, AD phenotypes are induced via metabolic dysregulation, traumatic brain injury, Adeno-associated virus 1 (AAV1) gene transduction, toxin exposure, perturbed metal ion homeostasis or aging. Of particular interest is the final category, aging, and the corresponding model, the senescence-accelerated mouse prone 8 (SAMP8) model. Although the exact cause of accelerated senescence has not yet been determined, this model may shed light on the relationship between aging and AD (Griñán-Ferré et al., 2018).

In many respects, the SAMP8 mouse exhibits important AD-associated pathologies including shortened lifespan, reviewed by Griñán-Ferré et al. (2018). To further go into details, age-dependent deposition of Aβ in the hippocampus is observed, but it does not culminate in Aβ plaques (Akiguchi et al., 2017). Similarly, there is an age-related increase in phosphorylated tau, yet neurofibrillary tangles in the brain do not seem to form (Akiguchi et al., 2017). To a limited extent, neurodegeneration in the aged SAMP8 mouse has been reported. In the basal forebrain, there seems to be a 20% reduction in the density of cholinergic neurons (Tooyama et al., 1997). The authors relate this to the memory deficits observed in these mice. Such cognitive phenotypes, based on the Morris Water Maze and Novel Object Recognition for example, are reported as early as 2 months (Akiguchi et al., 2017). As for chromatin modifications, an emphasis of the current review, there still remains much to be explored in the SAMP8 model. Firstly, in the hippocampus, SAMP8 mice show significant downregulation of HDAC3 and SIRT1, in addition to an upregulation of miRNAs that have been found to be dysregulated in the hippocampus of AD patients; these miRNAs are speculated to antagonize senescence-controlling genes (Cosín-Tomás et al., 2014). Nonetheless, reliable quantifications of important histone modifications (e.g. $H3K9^{me3}$, $H3K27^{me3}$, $H4K20^{me3}$) remain largely absent. In an investigation of oxidative damage, SAMP8 mice exhibit notable nucleic acid oxidation, especially in brain tissue (Gan et al., 2012). This is evidenced by 8-oxo-2′-deoxyguanosine, a product of oxidative damage. Thus, further investigation of the DNA damage response (DDR) pathway (e.g. γH2AX, p-ATM, and p-ATR) is warranted to better characterize levels of DNA damage and response. Although the SAMP8 mouse model is promising in terms of many AD-associated pathologies, it has not been shown that its epigenetic signatures mirror human cases of SLOAD. As we will lay out, particular epigenetic anomalies seem to characterize SLOAD, thus a model lacking these features may not be adequate to explore early SLOAD pathogenic mechanisms or effective therapeutics.

### Bmi1$^{+/-}$ mouse model of SLOAD

Recently, two reports using both *in vitro* and *in vivo* models of BMI1 deficiency revealed that they display notable SLOAD-associated phenotypes (Flamier et al., 2018; El Hajjar et al., 2019). BMI1 is an integral part of the Polycomb Repressive Complex 1 (PRC1), which maintains transcriptional repression at developmental and senescence-associated genes mainly through mono-ubiquitination of histone H2A at lysine 119 (Bhattacharya et al., 2015). The BMI1 protein exhibits a well-conserved sequence homology between mouse and man (Bhattacharya et al., 2015; Abdouh et al., 2016). Notably, the protein is also abundantly found at the repeat DNA sequence-rich heterochromatin, and BMI1 inactivation in primary human cells or in mice results in loss of heterochromatin, as shown using the H3K9$^{me3}$, HP1, ATRx and DEK1 heterochromatin markers (Abdouh et al. 2016).

While *Bmi1*-deficient mice (*Bmi1*$^{-/-}$) exhibit severe developmental growth defects, premature ageing features, cerebellar, cortical and retinal degeneration and die prematurely (van der Lugt et al., 1994; Chatoo et al., 2009; Barabino et al., 2016), *Bmi1* hemi-deficient mice (*Bmi1*$^{+/-}$) develop normally, retain fertility and best recapitulate SLOAD (El Hajjar et al., 2019) (**Table 1**). This begs the question, what advantages and disadvantages does this new model of SLOAD have over previously established models? Firstly, *Bmi1*$^{+/-}$ mice exhibit an approximate 50% reduction in Bmi1 protein in cortical tissue (El Hajjar et al., 2019). This mirrors the ~50% reduction in *BMI1* expression that is reported in the human frontal cortex and hippocampus in SLOAD samples (Flamier et al., 2018). Notably, BMI1 reduction is not present in FEOAD or other neurodegenerative conditions (Flamier et al., 2018). What is striking is that reduced *BMI1* expression is also observed in induced pluripotent stem cell (iPSC)-derived neurons from SLOAD patients (Flamier et al., 2018), suggesting an underlying mechanism that persists despite reprogramming from fibroblast to iPSC to neuron.

Thoroughly described in El Hajjar et al. (2019), *Bmi1* hemi-deficient mice exhibit many of the important AD-associated phenotypes regarding both behavior and histopathology. Just as it is the case in human AD, the disease onset in *Bmi1*$^{+/-}$ mice is age-dependent, including extracellular amyloid accumulations (although rare), tauopathy, neurodegeneration and cognitive decline (El Hajjar et al., 2019). In this study, amyloid pathology was evidenced by immunoblotting for the C99 fragment, a product of pathogenic APP cleavage by β-secretase. In parallel with the accumulation of the amyloidogenic peptide, Bace1 levels are significantly increased. Although amyloid plaques were not observed upon cortical sectioning, amyloid reactivity was increased in the neuronal soma (El Hajjar et al., 2019). Yet, this can be expected given murine App is much less prone to aggregate into plaques than the human isoform (Bharadwaj, 2019). However, when *Bmi1*$^{+/-}$ mice were crossed with human *APP* transgenic mice, the resulting progeny displayed an even more advanced disease-related phenotypes, indicative of possible interaction between these two pathways (El Hajjar et al., 2019). Tauopathy in the *Bmi1*$^{+/-}$ mouse included p-Tau accumulation and large p-Tau deposits in the cortex, whereas p-Tau tangles were not observed. Neurodegeneration is evidenced by an approximate 20% reduction in NeuN-positive cortical neurons supported by an approximate 2-fold increase in apoptotic neurons in old *Bmi1*$^{+/-}$ mice compared to WT littermates (El Hajjar et al., 2019). In the hippocampus there is a marked reduction of neuronal density coupled with an increase in apoptosis. Finally, cognitive decline is characterized behaviorally by the Morris water maze probe test and at the cellular level by diminished LTP in the hippocampal CA1 region.

For the purposes of this review, the epigenetic profile of this model sets it apart from others. At an early age, 2–3 months-old *in vivo* and embryonic day 18.5 *in vitro*, *Bmi1*$^{+/-}$ neurons already exhibit loss of heterochromatin, and this before any indication that DNA damage is present (El Hajjar et al., 2019). In the aged *Bmi1*$^{+/-}$ mouse (15 months old), neuronal heterochromatin depletion persists, repetitive genomic elements are de-repressed and chromocenters appear smaller and more numerous (El Hajjar et al., 2019). Importantly, DDR proteins such as p-ATM, p-ATR and γH2AX accumulated preferentially at repetitive elements in cerebral cortex extracts, as shown using chromatin immuno-precipitation (ChIP) analysis, indicative of heterochromatic genome instability (El Hajjar et al., 2019).

## Chromatin Signatures May Distinguish FEOAD from SLOAD

As we attempt to discern differences between FEOAD and SLOAD, there is mounting evidence that chromatin signatures may be a distinguishing factor. Already, global but modest heterochromatin reduction is a well-characterized phenomenon associated with normal cellular aging, reviewed in Kane (2019). However, severe heterochromatin depletion is observed in SLOAD frontal cortex sections compared to non-demented age-matched controls, which correlates with reduced *BMI1* expression (El Hajjar et al., 2019). Hence, it is striking to note that despite severe brain neurodegeneration, brain samples from patients with FEOAD do not present reduced *BMI1* expression or depletion of heterochromatin (Flamier et al., 2018; El Hajjar et al., 2019). Although, given the small sample size, independent confirmation of these results is essential, it seems that the aforementioned modest aging-related heterochromatin reduction cannot explain the marked difference observed between FEOAD and SLOAD cases.

Specifically, heterochromatin loss in SLOAD frontal cortical sections consists of significantly less H3K9$^{me3}$ nuclear staining, in conjunction with smaller and more numerous chromocenters (El Hajjar et al., 2019). ChIP analysis revealed that in age-matched controls, BMI1 and H3K9$^{me3}$ enrichment occurs at repetitive elements such as McBOX, SATIII and SATA, which is depleted in the context of SLOAD (El Hajjar et al., 2019). Interestingly, there is an accumulation of DDR proteins

**Table 1** | **Comparative analysis of *BMI1* expression and chromatin state between SLOAD and FEOAD**

| Disease/model | Genetics | Age of onset | BMI1 expression | Heterochromatin | DDR | Sources |
|---|---|---|---|---|---|---|
| SLOAD | Polygenic | +++ | Reduced | Affected | +++ | Flamier et al. (2018); El Hajjar et al. (2019) |
| *Bmi1*$^{+/-}$ mice | Bmi1 deficiency | +++ | Reduced | Affected | +++ | Flamier et al. (2018); El Hajjar et al. (2019) |
| SAMP8 mice | Unknown, derived from AKR/J background | + | Unknown | Unknown | +++ | Gan et al. (2012); Akiguchi et al. (2017); Griñán-Ferré et al. (2018) |
| FEOAD | *APP*, *PSEN1* or *PSEN2* mutations | + | Normal | Normal | + | Flamier et al. (2018) |
| 3xTg-AD mice | PS1$^{m146V}$, tau$^{P301L}$, APP$^{Swe}$ | + | Normal | Unknown | Unknown | Walker et al. (2013); Flamier et al. (2018) |

SLOAD excludes SEOAD and FLOAD cases homozygous for APOE4. FEOAD designates cases with known pathogenic mutations. DDR: DNA damage response; FEOAD: familial early-onset Alzheimer's disease; FLOAD: familial late-onset Alzheimer's disease; SEOAD: sporadic early-onset Alzheimer's disease; SLOAD: sporadic late-onset Alzheimer's disease.

(i.e. p-ATM, p-ATR and p-CHK1) in SLOAD brains (frontal cortex) that is absent even in FEOAD samples (El Hajjar et al., 2019). Lastly, ChIP revealed that p-ATR and γH2AX were enriched at genomic repeats in AD brains (El Hajjar et al., 2019). Seemingly, de-repressed repetitive elements are more susceptible to DNA damage accumulation, an observation also shown in a stem cell model of aging (Zhang et al., 2015). As a consequence of accumulated DNA damage, the constitutively activated DDR pathway seems to enhance amyloid and tau pathologies in cortical neurons of *Bmi1*$^{-/-}$ mice (El Hajjar et al., 2019).

Heterochromatin loss following BMI1 deficiency may be attributable not only to BMI1's direct chromatin maintenance functions, but additionally to its protective functions against oxidative damage. In post-mitotic neurons specifically, BMI1 represses the pro-oxidant activity of p53, namely p53's repressive control over the transcription of antioxidant defense genes (Chatoo et al., 2009). BMI1 may also directly repress the expression of pro-oxidant genes (Liu et al., 2009). The resulting increase of pro-oxidant conditions following BMI1 deficiency may thus also drive heterochromatin loss, although this remains to be tested. As shown in the case of tauopathy in *Drosophilia*, heterochromatin loss can be driven by oxidative damage, culminating in neuronal apoptosis (Frost et al., 2014). The aberrant gene expression, which results from heterochromatin loss, is cited as a likely underlying mechanism of cell death. Ago3, a regulator of retrotransposon activity and a homolog of human PIWIL1, is one such gene that becomes deregulated following heterochromatin loss (Frost et al., 2014). In human AD brains, specifically hippocampal neurons that stained positively for phosphorylated tau, both chromatin relaxation (using the H3K9$^{me2}$ antibody) and a corresponding dysregulated gene expression profile were observed (Frost et al., 2014). Going forward, it is important to bolster the data showing oxidative damage induces heterochromatin loss. For example, can ROS scavengers mitigate heterochromatin loss in BMI1-deficient neurons? Moreover, the identity of such de-repressed loci is paramount. Is oxidative damage-induced heterochromatin de-repression random, or are there particular features that render some loci more vulnerable?

Decreased H3K9$^{me3}$ levels are not only an important indicator of de-repressed constitutive heterochromatin, they may also be implicated in diminished DNA damage repair capacity. H3K9$^{me3}$ at double-strand DNA breaks (DSBs) is essential to activate TIP60 which goes on to activate ATM as part of the DDR pathway (Sun et al., 2009). However, a recent study in cancer cells showed that hypermethylation of H3K9 surrounding DSBs masked the H3K9$^{me3}$ signal that is essential for homologous DNA repair. Mechanistically, H3K9 hypermethylation impaired the recruitment of TIP60 and ATM at DNA breaks (Sulkowski et al., 2020). Cited above, DNA damage accrues preferentially at de-repressed repetitive elements in SLOAD models, which may be indicative of increased susceptibility to DNA damage or of diminished DNA repair capacity. Of course, these two phenomena may be present simultaneously. In the context of SLOAD, it is possible that depletion of H3K9$^{me3}$ at such loci results in an analogous disruption of the DDR pathway; however this is not yet shown. In summary, the *Bmi1*$^{+/-}$ mouse model appears to recapitulate *new cardinal features* of SLOAD that are not found in FEOAD brains or mouse models.

## Future Directions

Going forward, it is important to gather more robust data supporting BMI1 deficiency and chromatin anomalies as a differentiating factor between FEOAD and SLOAD. These phenotypes have been highlighted here, albeit in studies of very small sample sizes. These observations have been revelatory because these pathologies precede other AD-associated phenotypes in the *Bmi1*$^{+/-}$ mouse model. Perhaps there are other chromatin or gene-expression anomalies that develop before amyloid and Tau pathologies in SLOAD. Moreover, it remains to be shown whether BMI1 deficiency is present or not in FEOAD iPSC-derived neurons, as is the case with SLOAD iPSC-derived neurons. Nonetheless, considering the current AD mouse models, the *Bmi1*$^{+/-}$ model has notable advantages. It presents chromatin anomalies from a very early age whereas more severe AD-associated pathologies develop much later (e.g. $A\beta_{42}$ accumulation, tauopathy and neuronal loss among others), and it does not rely on overexpressed FEOAD-associated human genes which are suspected to induce many nonspecific anomalies. Delineating FEOAD and SLOAD from one another, if it is in fact the case, is thus essential for continued research and drug development. If we are indeed dealing with two, etiologically distinct disorders, they are likely to require two distinct treatments.

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