

Dissection of prodromal Alzheimer's disease

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1. ABSTRACT

Pathophysiological changes of Alzheimer's Disease (AD) begin decades before clinical symptoms become apparent, providing an important window for early diagnosis and intervention. Prodromal stage of AD, a great opportunity for effective treatment and postponing the disease onset, has drawn extensive attention. The application of different biomarkers including neuroimaging, biochemical substances and genes makes AD-related pathology detectable *in vivo* and exploring novel biomarkers with relatively non-invasive and low cost has intrigued a wide range of interests. To identify individuals with high risk of

conversion to AD and apply the research concept of prodromal AD into clinical practice, the utility of various biomarkers for distinguishing prodromal AD is evaluated in this review. Additionally, clinical management focusing on the stage of prodromal AD is summarized in this review for dementia prevention.

2. INTRODUCTION

Alzheimer's Disease (AD), characterized by progressive and irreversible cognitive decline, is considered as the most common form of

neurodegenerative disorders leading to dementia. AD approximately accounts for 50% of dementia (1) and results in globally heavy healthcare burden with an estimated cost of \$1 trillion by 2050 (2). Previous studies have demonstrated that pathophysiological features of AD begin decades before clinical symptoms become apparent (3). Due to the extensive neuronal loss at the stage of dementia, therapeutic intervention for AD at this stage is too late. The prodromal stage of AD and even the stage prior to the clinical symptom onset but with AD pathophysiological changes, i.e. preclinical AD shall be targeted.

Prodromal AD is a symptomatic pre-dementia stage and amnesic mild cognitive impairment (aMCI) is a transitional state between healthy elderly and AD dementia (4). aMCI has been initially considered as the prodromal AD due to its high likelihood of conversion to AD. The annual progression rates from aMCI to AD is approximately 10% to 15% (5). Previous studies suggested that early identification of patients with aMCI was of great benefits for improving the disease intervention outcomes and monitoring the progression of AD.

Alzheimer's pathologies include senile plaques made of amyloid- β (A β) accumulation and neurofibrillary tangles (NFTs) formation in multiple cortices (6). Currently, the application of multiple biomarkers derived from cerebrospinal fluid (CSF), positron emission tomography (PET), etc, has made AD-related pathologies detectable *in vivo*, providing possibilities for the diagnosis of AD at the prodromal stage and increasing the predictive power of aMCI conversion to AD (7-10). Additionally, topographical biomarkers, such as structural alterations, hypometabolism or hypoperfusion in several specific brain regions can indicate AD dementia, and risk genes can predispose to AD dementia. However, the utility of most biomarkers has some limitations because of their relative invasiveness, radioactivity and costliness. Therefore, more attention has been increasingly paid to various novel body fluid biomarkers, such as blood- and urine-based markers due to their accessibility and relatively low cost (11, 12).

Neuroimaging and biochemical markers provide essential and complementary information from different perspectives to enhance our understanding of AD. Most previous studies focused on revealing the anatomical, functional and biochemical differences between patients and healthy elderly at group level (13). Machine learning and pattern recognition techniques for early identifying patients with prodromal AD may potentially be of significance in clinical practice (13-16).

Here, we introduce the evolution of prodromal AD diagnostic criteria overtime. Then, we elucidate

characteristic neuroimaging markers and CSF biomarkers in prodromal AD, and AD susceptibility genes. Meanwhile, we describe the diagnostic and prognostic values of these biomarkers with the application of machine learning methods, e.g. support vector machine (SVM). At the end, we summarize the development of pharmacologic and non-pharmacologic management in prodromal AD.

3. THE DEFINITION OF PRODROMAL AD

Different recommendations for prodromal AD have been proposed over the past decades. Initially, prodromal AD was defined as the symptomatic pre-dementia stage of AD, mainly referring to MCI (17). Patients with MCI are diagnosed primarily based on the criteria proposed by Petersen *et al.* in 2001, which are: memory loss complaint preferably confirmed by an informant; objective cognitive impairment in single or multiple domains, adjusted for age and education; preservation of independence in functional abilities and failure to meet the criteria for dementia, such as the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (5). However, due to the broad range and the absence of specific biomarkers, the identification of prodromal AD has relatively great heterogeneity.

Recently, with the advances of distinctive and reliable biomarkers supportive of AD pathology, it is more likely to achieve the accurate diagnosis of prodromal AD *in vivo*. Two diagnostic systems have been proposed. According to the international working group (IWG) in 2007, the definition of prodromal AD requires the clinical symptoms and the presence of at least one biomarker reflecting Alzheimer's pathology (4, 18). It is generally considered that typically episodic memory loss, together with the biomarker evidence from CSF or imaging (e.g., CSF A β 42 or PET amyloid), will recognize AD with higher accuracy at the prodromal stage. Therefore, the renewed proposal of prodromal AD is a substantial improvement over the previously clinical definition (19). However, the revised diagnostic criteria neglect the classification of these supportive biomarkers. In 2014, Dubois and colleagues further classified the biomarkers as diagnostic markers (pathophysiological markers) and progression markers (topographical or downstream markers), indicating that the diagnosis of prodromal AD *in vivo* requires the presence of clinical signs and at least one pathophysiological biomarker (the coexistence of decreased A β 42 and increased total-tau/phosphorylated-tau in CSF or retention on amyloid PET or an autosomal dominant monogenic AD mutation) (19). Currently, studies have showed that it was not sufficient for individuals with isolated brain amyloidopathy or tauopathy to develop clinical AD and the combination of biomarkers involving amyloid and tau pathologies may substantially increase the

diagnostic specificity of AD. Thus, according to the latest criteria proposed by Dubois in 2016, individuals with the co-occurrence of amyloid and tau pathologies have the highest risk for developing AD, regardless of the stage (prodromal stage or even at asymptomatic preclinical stage) (20). The novel definition of prodromal AD includes the occurrence of the clinical phenotype of AD (either typical or atypical) with positive biomarkers of both amyloidopathy (A+) and tauopathy (T+).

Another diagnostic framework was proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA) in 2011, which adopted the term "MCI due to AD" to refer to the symptomatic predementia phase of AD (21). The workgroup established two sets of criteria, including core clinical criteria and research criteria, the latter of which incorporated biomarkers derived from neuroimaging and CSF. It also proposed that the application of biomarkers contributes to confirm levels of certainty for the diagnosis of MCI due to AD. If individuals with MCI have positive biomarkers for both A β and neuronal injury, they will present the highest level of certainty to develop AD dementia over time, indicating that they are more likely to be "MCI due to AD". Nevertheless, individuals with isolated brain amyloidopathy or a positive biomarker reflecting neuronal injury only have intermediate likelihood of conversion to AD dementia.

Taken together, both two diagnostic frameworks emphasize the significance of conjoint application of biomarkers reflecting amyloid and neurodegeneration in the diagnosis of prodromal AD or MCI due to AD. However, compared with IWG-2 criteria, NIA-AA framework requires the decreased CSF A β 42 while IWG-2 rule emphasizes the coexistence of tau (p- or t-tau) changes in the CSF for corroborating Alzheimer's pathology (20).

4. PATHOPHYSIOLOGICAL BIOMARKERS IN PRODRAMAL AD

4.1. CSF biomarkers

Numerous studies have detected decreased concentrations of A β 42 and increased levels of total and phosphorylated tau in the CSF of patients with AD, yielding relatively high specificity in the disease diagnosis and possibly predicting the progression of MCI into AD (22-24). In MCI patients, subjects with greater memory complaints have increased likelihood of AD-related pathology, which is defined as the presence of low CSF A β 42 together with high CSF tau or phosphorylated tau levels (25). Several studies suggest the application of decreased A β 42/40 ratio for improving diagnostic accuracy due to its better correspondence to amyloid PET than A β 42 alone in patients with AD (26). Additionally, the ratio of phosphorylated tau or total tau to A β 42 also has great accuracy in detecting amyloid positive subjects with

MCI, indicating the role of CSF biomarkers in the early and accurate detection of Alzheimer's pathologies (27). Furthermore, combination of different CSF biomarkers has stronger accuracy in diagnosis of AD. For example, applying three CSF biomarkers, i.e. A β 42, total tau and phosphorylated tau, could advance AD diagnosis accuracy with 93.5.% in sensitivity and 82.7.% in specificity (8).

The above-mentioned CSF biomarkers are likely to predict clinical progression of AD as well. Sierra-Rio *et al.* (7) found that MCI and subjective cognitive decline (SCD) individuals with pathological AD CSF biomarkers profile, such as abnormal A β 42/ phosphorylated tau ratio, had a higher proportion of conversion to the stage of dementia during 5-year follow-up. However, CSF A β levels alone may be not effective for detecting MCI patients with high risk of developing AD (1).

4.2. Amyloid PET biomarkers

Compared with *in vivo* MRI techniques, imaging with amyloid PET could offer more important insight in abnormal neuropathological lesions of AD. Besides the reduced levels of A β 42 in the CSF, A β deposition can be detected in brain by PET imaging with special tracers, such as ¹¹C-Pittsburgh Compound B (PIB), 18F-florbetapir, *etc* (28). Studies have confirmed that abnormal PIB PET scans are associated with longitudinally cognitive decline in prodromal AD and even in cognitively normal elderly (29, 30). For example, amyloid-positive MCI patients are more likely to progress to AD dementia than those without A β deposition after two-year follow-up (31). Hatashita also found that amyloid positive patients with MCI have a greater increased annual rate in PIB standardized uptake value ratio (SUVR) than amyloid-negative MCI patients and are likely to develop AD dementia within a shorter period. Interestingly, although A β deposition is considered to initiate the AD pathological cascade, its load severity is not directly related to the clinical symptoms and the risk profile may reach a plateau as A β load is increasing (31).

4.3. Tau PET biomarkers

Selective tau ligands, including (18F) THK5117, (18F)THK5351, (18F)AV1451 (T807) and (11C)PBB3, can mirror the distribution of tau protein in several neurodegenerative disorders, such as AD, frontotemporal dementia, progressive supranuclear palsy, *et al* (32, 33). Although A β may be the initial accelerator for the onset of AD, the pathological aggregation of tau has been suggested to have a closely direct correlation with patterns of neurodegeneration and cognitive impairment than A β . For example, there was a significantly negative association between (18F)AV1451 and 18F-FDG uptake in AD (34). Contrary to A β imaging, (18F)

AV1451 retention in key brain regions that were related to memory, visuospatial function and language presented a strong link to neuropsychological scores. Moreover, there are significant associations between (18F)AV1451 deposition and CSF biomarkers, notably for total tau and phosphorylated tau,¹⁸¹ possibly suggesting the consistency of CSF and PET in measuring tau protein (9).

5. TOPOGRAPHICAL BIOMARKERS IN PRODROMAL AD

5.1. Structural MRI biomarkers

Currently, the relationship between the pathological cascade of AD and the emergence of clinical symptoms has been elucidated in numerous studies, most of which confirm clinical symptoms closely in parallels with progressive worsening of neurodegeneration, such as the formation of phosphorylated tau, neural dysfunction and brain atrophy, rather than A β accumulation (3). The distribution of neurofibrillary pathology initially appears in the medial temporal regions (11, 35, 36), subsequently leading to significant gray matter atrophy and further disrupting the processing of episodic memory. Using structural MRI, researchers have reported a significant volume reduction of the medial temporal cortices in AD patients, which is strongly correlated with memory loss (11, 37, 38). Additionally, a similar spatially distribution patterns of brain atrophy, primarily on medial temporal regions (e.g., hippocampal and entorhinal cortex), have also been demonstrated in patients with aMCI (39, 40). Furthermore, for individuals with positive PIB PET scans, hippocampal atrophy can predict shorter time-to-progression from MCI to AD (31). In summary, there is a general consistency of the brain structural changes in individuals with AD or aMCI, and structural MRI is a promising tool to assist in the detection of prodromal AD.

5.2. FDG-PET biomarkers

Previous studies based on (18F) fluorodeoxyglucose PET (FDG-PET) have confirmed hypometabolism in multiple brain regions in patients with MCI, such as posterior cingulate, inferior parietal lobe and medial temporal cortices, which are identical to the abnormal metabolic mechanism occurred in AD (41-43). As mentioned in prior studies, the progressive accumulation of A β , detected by decreased CSF A β levels or positive amyloid PET, is not capable of tracking progression to AD dementia. In contrast, tau-related neurodegeneration may be useful for this prediction. Higher baseline concentrations of tau protein in the CSF are more predictive of decline in cerebral glucose metabolism, further leading to subsequent cognitive impairment (44). Thus, FDG-PET has been recommended as a strong predictor of progression from MCI to AD. Using FDG-PET, posterior precuneus

and cingulate are thought to be the brain regions with potential value for predicting AD progression from MCI (45, 46). Additionally, hypometabolism in posterior cingulate, combined with Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) Total Mod and Mini-Mental State Exam (MMSE) scores could improve the progressive prediction from MCI to AD with a sensitivity of 96.4.% and a specificity of 81.2.% (45). In conclusion, special metabolic changes in FDG-PET probably increase with progression to AD dementia and determine the risk of progression.

5.3. Functional MRI biomarkers

The advance of functional MRI, indirectly mirroring neuronal activities, provides a promising technique that allows to non-invasively investigating intrinsic brain functional characteristics in AD. The presence of abnormal focal brain activity and disrupted functional connectivity within default mode network (DMN) has been shown in both AD and MCI patients (47-49). However, most of previous studies have not recruited prodromal individuals with biomarkers of AD pathologies.

Recently, the association between amyloidogenesis and neuronal dysfunction has been investigated. Zhou *et al.* found that there was significant correlation between amyloid load and fractional amplitude of low frequency fluctuation (fALFF) (50). It is also reported that amyloid-positive patients with MCI exhibit increased hippocampal activation during an associative face-name memory encoding task both at baseline and over 36-month follow-up, which may reflect the employment of compensatory strategies in the early stage of AD and/or amyloid induced excitotoxicity (51). Early MCI (EMCI) patients with positive amyloid might present more widespread disruption of functional connectivity within DMN than those without amyloid deposition (52), while other studies revealed no association between the DMN connectivity and amyloid deposition (53). Therefore, further studies are needed to confirm whether amyloid deposition contributes to aberrant functional connectivity. Moreover, the alterations of functional connectivity in aMCI, such as the enhanced functional connectivity between parahippocampus and middle frontal gyrus, have the potentially predictive value for future episodic memory decline, which is independent of amyloid deposition (54). Consequently, functional MRI has the potential to elucidate the characteristics of prodromal AD and A β pathology may be linked to changes of brain functional activity.

6. OTHER BIOMARKERS IN PRODROMAL AD

6.1. DTI biomarkers

White matter tract alterations have been consistently described in AD. It has been confirmed

that white matter (WM) degeneration is concomitant with gray matter loss, further influencing the information communication between distributed brain regions (55). Diffusion tensor imaging (DTI) is sensitive to WM ultrastructural damage and has been used in studying neurodegenerative disorders. For aMCI patients, studies have confirmed the reduced fractional anisotropy (FA) and increased mean diffusivity (MD) in several fiber bundles, such as the cingulum bundles, the parahippocampal cingulum and long-distance association fascicles. Reduction of white matter FA in the uncinate fasciculus was in parallel with hippocampal atrophy and might specifically contribute to early impairment in episodic memory (56). Given that high-level cognitive processes depend on interaction among distributed brain regions, DTI equipped with graph theoretical approach can further elucidate the topological properties from a systematic perspective. The decreased global efficiency and weakened small-worldness of WM structural networks have been found in aMCI patients (57-59).

White matter lesion load (WMLL) strongly correlates with amyloid load (50). In MCI and SCD cohorts, the axial diffusivity (DA), radial diffusivity (DR), and MD in WM hyperintensities (WMHs) are significantly higher for A β + individuals compared with A β - individuals, suggesting that amyloid deposition may be associated with disrupted structural integrity (60). Additionally, WMHs had a negative effect on hippocampal volume in individuals with abnormal CSF A β 42 levels (61). Furthermore, reduction in white matter integrity is greater in MCI patients with higher level of CSF total tau (62). In short, DTI parameters provide the information of white matter lesions in prodromal AD, which may reflect the underlying AD-related pathologies.

6.2. Blood-based biomarkers

Compared to PET and CSF biomarkers, the utilization of blood-based biomarkers is relatively non-invasive and economical in assisting the disease diagnosis and prognosis (12). Among numerous candidate biomarkers in blood, plasma clusterin has been proposed as a potentially peripheral biomarker of AD. Clusterin is found overexpressed in the brain of AD patients (63, 64). MCI patients have higher plasma clusterin levels compared to controls, which is confirmed as a strong risk factor for conversion to AD dementia (65). The potential mechanisms may be that clusterin levels in plasma is associated with the longitudinally structural atrophy for patients with MCI (66).

Plasma tau is another candidate for the early diagnosis of AD. High plasma tau was associated with low CSF A β 42, accelerated worsening of cognitive impairment, brain atrophy, and cortical hypometabolism

(67). However, Mattsson *et al.* thought that plasma tau was not sufficient to be an AD biomarker because it just partly reflected the AD-related pathology (67). Moreover, plasma A β 42 and plasma A β 42/A β 40 ratio have the possibility for identifying AD dementia with a sensitivity of 86%, further suggesting their potential to be the diagnostic biomarkers (1).

Besides, a number of studies have shown numerous other blood-based biomarkers, such as the plasma APLP1-derived A β -like peptides 28 (APL1 β 28), hyperhomocysteinemia levels, leptin, *et al.* (12, 68, 69). To date, blood-based biomarkers present a limited value for the diagnosis and prognosis of AD mainly due to lack of thorough study and methodological issues (20). Further studies are needed to investigate their use for screening prodromal AD.

6.3. Urine biomarkers

Alzheimer-associated neuronal thread protein (AD7c-NTP) is found overexpressed in brains with AD (70). Studies *in vitro* have investigated that overexpression of AD7c-NTP in transfected neuronal cells promotes neuritic sprouting and apoptotic cell death, which are two primary abnormalities associated with AD-related neurodegeneration (70). Besides elevated AD7c-NTP levels in cortex and brain tissues during the early stages of AD, its levels in CSF have been shown relatively high and increased AD7c-NTP was positively correlated with CSF tau within the AD group (71, 72). It is also widely considered that the level of AD7c-NTP is correlated with the severity of dementia (72). Therefore, researchers speculate that AD7c-NTP has the potential to be a biomarker of AD. Subsequently, Ghanbari *et al.* detected and measured AD7c-NTP in urine, which had the same molecular weight as AD7c-NTP in brain tissue and CSF and was found significantly higher in the AD group than the non-AD group (73). Besides patients with AD, Ma L *et al.* (74) further confirmed that the urinary levels of AD7c-NTP in the MCI group were significantly higher than those of healthy controls, suggesting that AD7c-NTP in urine has the potential to be a promising biomarker for identifying the individuals with high risk factor at prodromal stage of AD.

6.4. Microbiota biomarkers

A large body of studies suggested that chronic bacterial infections might contribute to the pathogenesis of AD. Variant secretory molecules from microbes, such as amyloids, rhamnolipids (RL), lipopolysaccharides, *et al.*, have been reported to be closely correlated with AD pathologies. Andreadou and colleagues found elevated RL levels in sera and CSF of patients with AD and MCI compared with healthy controls, which were also related to the severity of the disease (75). Additionally, emerging evidences

Table 1. Summary of biomarkers for prodromal AD

Classification	Parameters/Measures	Features	References
Pathophysiological biomarkers			
CSF ¹	A β 42, total tau, p- tau, A β 42/40 ratio, A β 42/p-tau ratio, <i>etc</i>	(1) There are decreased concentrations of A β 42 and elevated levels of tau in prodromal AD; (2) The combination of different biomarkers in the CSF will advance the diagnostic accuracy; (3) Prodromal individuals with pathological AD CSF biomarkers have higher risk of conversion to dementia.	(7, 8, 23, 27)
Amyloid PET	¹¹ C-Pittsburgh Compound B (PIB), ¹⁸ F-flutemetamol, ¹⁸ F-florbetaben, ¹⁸ F-florbetapir, <i>etc</i>	(1) Amyloid PET can detect A β deposition <i>in vivo</i> before the appearance of typical AD symptoms; (2) A β deposition is associated with longitudinally cognitive decline but without relation to A β load severity.	(10, 30)
Tau PET	(18F)THK5117, (18F) THK5351, (18F) AV1451(T807), (11C) PBB3, <i>etc</i>	(1) The distribution of tau has a closely direct correlation with patterns of neurodegeneration and cognitive impairment than A β ; (2) There are associations between tau deposition and CSF biomarkers.	(9,33)
Topographical biomarkers			
Structural MRI	Volume, cortical thickness, sulcal depth, metric distortion, mean curvature, <i>etc</i>	(1) Similar spatially patterns of brain atrophy have been presented in aMCI ² and AD patients; (2) Longitudinally, for individuals with A β +, atrophy in medial temporal regions can predict shorter time-to-progression from MCI to AD.	(40,102)
FDG-PET ³	Fluorodeoxyglucose metabolism	(1) Hypometabolism of multiple brain regions in MCI (e.g., posterior cingulate, medial temporal cortices) is nearly identical to the abnormally metabolic manifestations occurred in AD; (2) FDG-PET is a strong predictor of progression from MCI to AD.	(42, 46, 47)
Functional MRI	Amplitude of low frequency fluctuation (ALFF), fractional ALFF (fALFF), regional homogeneity (ReHo), functional connectivity strength, <i>etc</i>	(1) MCI has abnormal local brain activity and disrupted functional connectivity in multiple brain regions similar to AD; (2) A β pathology may be associated with aberrant functional activity.	(48, 51, 52)
Other biomarkers			
DTI ⁴	Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), efficiency, betweenness centrality, <i>etc</i> .	(1) MCI has similar white matter alterations of AD, which are associated with cognitive dysfunction; (2) There are correlations between white matter lesion load (WMLL) and AD-related pathology.	(57, 58, 61, 63)
Blood	Plasma clusterin, tau, A β 42/A β 40 ratio, A β 42, APL1 β 28 ⁵ , leptin, <i>etc</i>	(1) Plasma clusterin levels are higher in MCI and have association with cognitive performances; (2) Plasma tau just partly reflected the AD-related pathology, while plasma A β 42 and A β 42/A β 40 ratio may be the potentially diagnostic biomarkers.	(1, 66, 68)
Urine	AD7c-NTP ⁶	(1) AD7c-NTP is associated with AD-related neurodegeneration; (2) The urinary levels of AD7c-NTP in MCI may be a potential biomarker.	(71, 75)
Microbiota	Secretory products (e.g. amyloids, rhamnolipids, lipopolysaccharides), gut microbiota (e.g. bacteria, fungi and viruses)	Elevated RL levels in sera and CSF of patients with AD and MCI.	(76)

Abbreviations: ¹ cerebrospinal fluid; ² amnesic mild cognitive impairment; ³ fluorodeoxyglucose positron emission tomography; ⁴ diffusion tensor imaging; ⁵ APLP1-derived A β -like peptides 28; ⁶ Alzheimer-associated neuronal thread protein.

indicated that gut microbiota plays an important role in modulating brain plasticity and cognitive function in ageing (76). The pathway of information communication between brain and gut might exist, further modulated by plenty of microbiota, like bacteria, fungi and viruses. The dysfunction of “microbiota-gut-brain axis” might be associated with AD-related pathogenesis (77). Previous studies have shown

that the initial inflammation caused by the microbial infection may drive amyloidosis and the deposition of A β in the brain may serve as a protective response to microbial affection (78-80). Currently, however, there are few studies involving the characteristics of gut microbiota and the relationship between gut microbiota and cognition in patients with prodromal AD. Summary of biomarkers for prodromal AD is listed in Table 1.

7. GENETIC CONTRIBUTIONS TO PRODRAMAL AD

Currently, AD is divided into early-onset AD (EOAD), who presents typically AD symptoms before 65 years, and late-onset AD (LOAD). It is generally recognized that AD is strongly associated with genetic mutations. EOAD is caused by mutations of autosomal dominant inheritance involving amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2), while LOAD or sporadic AD, has a strong genetic and environmental influence, such as educational years, cognitive reserve, diet, diabetes, etc (81).

The specific Alzheimer's pathologies are likely to be present before clinical symptoms become apparent in autosomal dominant Alzheimer disease mutation carriers (82, 83). For example, in a cross-sectional study, cognitively unimpaired PSEN1 E280A mutation carriers had significantly decreased hippocampal volume, hypometabolism in precuneus, lower A β 1-42 and higher total tau /phosphorylated tau181 in CSF compared with noncarriers (82). However, there are few studies involving the effect of these genes (APP, PSEN1, PSEN2) on prodromal AD. One study enrolled fourteen mutation carriers (presenilin-1 and amyloid beta precursor protein) and fifty healthy controls. It showed that compared with noncarriers, asymptomatic and MCI subjects with mutation had decreased cerebral perfusion, which were also associated with increasing cerebral amyloid deposition and declined cognitive function (84). Therefore, we propose that in individuals with autosomal dominant Alzheimer disease, characteristically structural, functional and pathological changes would be present at the stage of preclinical and prodromal AD.

The possession of the apolipoprotein E (APOE) ϵ 4 allele is generally thought to be a high risk factor for developing late-onset AD and its presence is related to increased levels of A β senile plaques, the critical component of Alzheimer's pathology (85-87). For patients with AD, APOE ϵ 4 carriers, especially those with two ϵ 4 alleles have significantly more neuritic plaques and neurofibrillary tangles (NFTs) in cerebral cortices than those with either one or no ϵ 4 alleles (85). Individuals with MCI ϵ 4+ also displayed lower levels of CSF A β 42 than those with MCI ϵ 4- (88). The link between APOE ϵ 4 allele and episodic memory loss has some inconsistencies. Several studies suggested that APOE ϵ 4 allele was only associated with memory decline in subjects with cognitive impairment, but not in cognitively normal controls (89, 90). However, in a longitudinal study for cognitively intact elderly, APOE ϵ 4 allele carriers had a higher rate of cognitive decline and slower information processing speeds after 6 years (91). To date, although several genes associated with AD have been found, APOE ϵ 4 is still the core

genetic risk factor of progression to LOAD (20, 92-94). Common genes associated with AD in Chinese and in Caucasian population are summarized below (Table 2) (81, 82, 93-95), and those genes encoded protein products are related to several molecular pathways leading to AD (Figure 1) (81, 92).

8. DISCRIMINATIVE ANALYSIS FOR IDENTIFYING PRODRAMAL AD

Although special biomarkers derived from neuroimaging techniques and biochemical methods have provided important information for accurate diagnosis and disease monitoring, most of these findings focus on revealing the group differences and have limited clinical translation (13). To improve the identification of prodromal AD, thus, several studies increasingly highlight the machine learning and pattern recognition techniques, such as support vector machine (SVM), which is a specifically supervised machine learning method mainly for classifying between groups (95-97). Through these approaches, structural, functional and biochemical features can be employed to discriminate prodromal AD from healthy controls (96, 98-100).

Structural MRI has been considered to have relatively high validity for assisting clinicians in detecting AD due to the specific atrophy patterns in multiple brain regions, such as hippocampus. The volume of hippocampus is an effective biomarker for identifying AD from healthy controls with high accuracy, but a relatively lower discriminative power between MCI patients and controls. Given CA1 field, one subfield of hippocampus, has more apparent atrophy than the whole volume of hippocampus, structural changes in CA1 field have higher accuracy for identifying patients with MCI (100). Based on hippocampal shape features extracted from 23 aMCI and 25 healthy controls, Emilie *et al.* found that the classification rate for aMCI and controls was 83%, with about 83% sensitivity and 84% specificity, respectively (100). The region with the most significantly discriminative power approximately corresponded to CA1 subfield. Moreover, previous studies have presented that patients with aMCI also have characteristically cortical morphological changes. Li *et al.* selected 24 aMCI and 26 controls, then extracted six cortical features for each aMCI subject and further identified abnormally spatial patterns via multivariate pattern classification. This study showed that different surface features had various contributions in discriminating patients with aMCI, predominately distributed in the medial temporal lobe and parietal regions (101).

Studies also demonstrate the potential classification value based on resting-state functional MRI (99, 102). In a longitudinal resting-state study, 26 aMCI patients were enrolled and Bai *et al.* found

Table 2. AD causative and susceptibility genes

Gene	Location	Encoded protein	Function	Mechanism	Onset of AD
APP	21q21.3.	amyloid precursor protein	Neuronal growth, Synaptic formation and repair, A β production	Proteolysis of APP in the amyloidogenic pathway	EOAD ¹ /Familial AD
PSEN1	14q24.3.	PSEN1 transmembrane protein	Regulate γ -secretase activity and A β production	Proteolysis of APP in the amyloidogenic pathway	EOAD/Familial AD
PSEN2	1q31-q42	PSEN2 transmembrane protein	Regulate γ -secretase activity and A β production	Proteolysis of APP in the amyloidogenic pathway	EOAD/Familial AD
APOE ϵ 4	19q13.2.	APOE protein	Promote neuroinflammation, inhibit A β clearance, be involved in cholesterol metabolism, synaptic function	Cholesterol metabolism	LOAD ²
SORL1	11q23.2.-q24.2.	Sortilin Related Receptor 1/ Neuronal APOE Receptor	Mediate APP processing and A β production	Cholesterol metabolism	LOAD
Clusterin (CLU)	8p21-p12	Clusterin/apolipoprotein J (APOJ)	A β deposition, lipid transport, apoptosis, immunoregulation,	Cholesterol and immune metabolism	LOAD
ABCA7	19p13.3.	ATP-binding cassette subfamily A member 7	Cholesterol homeostasis, immunoregulation, A β accumulation, phagocytosis,	Cholesterol and immune metabolism	LOAD
CR1	1q32	C3b/C4b receptor	Immunoregulation, neuroprotective effect, A β clearance	Immune metabolism	LOAD
CD33	19q13.3.	Transmembrane receptor	Clathrin-independent endocytosis, cell growth regulation	Immune metabolism	LOAD
BIN1	2q14.3.	Myc box-dependent-interacting protein 1	Clathrin-independent endocytosis, modulate tau-related pathology, immunoregulation	Endocytosis metabolism	LOAD
CD2AP	6p12	CD2-associated protein	Cytoskeleton regulation, receptor-mediated endocytosis	Endocytosis metabolism	LOAD
PICALM	11q14	Phosphatidylinositol binding clathrin assembly protein	Clathrin-mediated endocytosis	Endocytosis metabolism	LOAD
IL-8 ³ gene -251T>A	4q13-21	a CXC chemokine	Neurons damage, A β -induced proinflammatory responses	Inflammatory response	LOAD
PSEN1 (K311R)	Hydrophilic loop (HL) domain of the C-terminal cytoplasmic loop	PSEN1 transmembrane protein	Affect A β production and tau phosphorylation	APP processing and tau phosphorylation	Familial LOAD
TOMM40	19q13.3.2	Translocase of outer mitochondrial membrane 40 (TOMM40)	Import protein precursors into mitochondria	Protein transport	LOAD

Abbreviations: ¹ early-onset AD; ² late-onset AD; ³ Interleukin-8

that a high recognition accuracy of aMCI converters from non-converters was obtained by investigating the longitudinal changes of hippocampal sub-region functional networks (both the sensitivity and specificity were 83.3.%) (99). Another study further integrated multiple network topological and connectivity properties and reported significant classification improvement with an accuracy of 91.9.% (102). However, the number of aMCI patients involved in this study was only twelve.

Given different biomarkers reflect pathological characteristics of AD from diverse perspectives,

integration of multiple biomarkers appears to achieve more effective diagnosis of prodromal AD. For instance, patients with aMCI could be distinguished from healthy controls with a classification accuracy of 83.5.9% via combining gray matter volume and white matter features, such as FA and MD (103). Long *et al.* adopted multi-level features from 29 aMCI and 33 controls, such as the Hurst exponent (HE), amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo) and gray matter density (GMD), achieving a high classification accuracy of 96.7.7%, with a sensitivity of 93.1.0% and a specificity of 100%

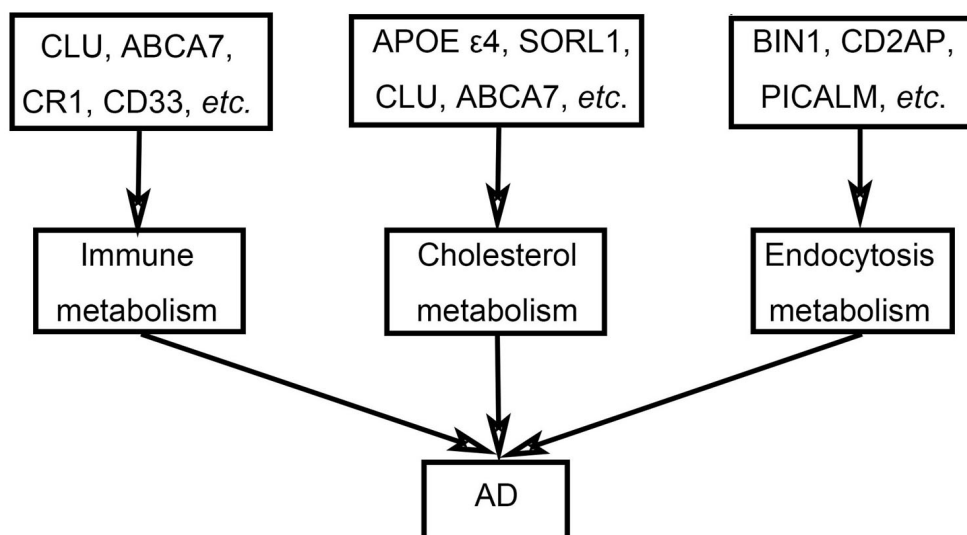


Figure 1. Molecular pathways involved in AD-related genes.

(104). Furthermore, features derived from PET, CSF and *APOE* have also been integrated for improving the discrimination ability (96, 105). However, it is worthwhile to note that employing more biomarkers do not necessarily contribute to the improvement of classification accuracy (96).

At the end, imaging features for classifying prodromal AD from healthy controls are briefly summarized (Table 3) (106, 107). Given that most of studies are based on the small clinical cohorts without brain autopsy confirmation, and the relatively low diagnostic accuracy (about 70%-85%), it is not fully reliable to directly apply these results in the clinical practice currently. The discriminative results derived from big data analysis are likely to have higher reliability and accuracy in assisting in the diagnosis of prodromal AD.

9. CLINICAL INTERVENTION AT PRODROMAL STAGE OF AD

It has been widely accepted that pharmacologic treatment and nonpharmacologic management are the two critical components of AD management. Nowadays, neurotransmitter regulation, based on three cholinesterase inhibitors (i.e. donepezil, rivastigmine and galantamine) and memantine, is mainly used to relieve AD clinical symptoms, but it still has great difficulty to reverse the disease progression (108). Therefore, researches involved in drugs targeting A β or tau protein in the treatment of AD, such as vaccines, antibodies or modulators of γ - and β -secretase, have been generally developed in order to intervene the whole process of AD (109). Recently, however, most of such clinical trials failed. The possible reason may be that the stage selected

for disease-modifying therapies focuses on dementia stage, in which vast majority of neurons have lost. Consequently, effective strategies for the onset of preventing AD dementia should be managed in the prodromal or preclinical AD. We have listed some completely clinical trials targeting A β and tau pathology for MCI or early AD over the years in Table 4 (110-117).

Given that AD has complexly pathophysiological mechanisms and multiple factors, such as nutritional supplement, cognitive training, physical exercise, etc., nonpharmacologic management may be of great significance for AD prevention and intervention. For example, early cognitive training (or cognitive rehabilitation) is thought to be very important for the treatment of patients with MCI and mild dementia (118).

10. FUTURE DIRECTIONS

The application of various biomarkers is valuable and necessary to offer some persuasive evidences for the accurate diagnosis of prodromal AD. Nowadays, evolving researches are focusing on the key stage before the occurrence of the first clinical phenotype, including the stage of preclinical AD and the situation at risk of AD. Current research suggests that not all individuals with A β deposition will develop cognitive symptoms, so the classification for 'asymptomatic at-risk state has been proposed. According to the updated conception, subjects of asymptomatic at risk for AD can be detected in cognitively normal individuals exhibiting an isolated AD pathophysiological biomarker (eg, amyloidopathy or tauopathy) (20). The risk of developing AD is also determined by some established factors, such as age, cognitive reserve, *APOE* genotype, and so forth.

Table 3. Imaging features for classification of prodromal AD

Techniques	Subjects	Parameters/Measures	Discriminative performance	Features	References
Structural MRI					
	23 aMCI ¹ , 25 controls	Spherical harmonics (SPHARM) coefficients	83% accuracy, 83% sensitivity, 84% specificity.	The medial part of the head of the hippocampus, and CA1 subfield.	(101)
	24 aMCI, 26 controls	Cortical thickness, sulcal depth, surface area, gray matter volume, metric distortion, mean curvature	76% accuracy in the left hemisphere and 80% accuracy in the right hemisphere using all six cortical feature.	The left medial temporal lobe, supramarginal and right inferior parietal lobes.	(102)
	122 aMCI, 130 controls 130 AD	Cortical thickness/ Normalized thickness index (NTI)	76% accuracy in predicting the conversion from aMCI to AD according to the baseline NTI.	Right medial temporal, left lateral temporal, right posterior cingulated.	(107)
Functional MRI					
	26 aMCI 18 controls	Functional connectivity	83.3.% sensitivity and 83.3.% specificity in classifying aMCI converters from non-converters.	Hippocampus subregional networks	(100)
	12 MCI, 25 controls	Local connectivity and global topological properties	91.9.% accuracy	Amygdala, parietal gyrus, temporal pole, superior frontal region, and lingual gyrus	(103)
	20 AD, 15 aMCI, 20 controls	Large-scale network (LSN) indexes	95% receiver operating characteristic curve (AUC), 93% sensitivity, 90% specificity	The global LSN connectivity	(108)
Multi-modal MRI					
	79 aMCI, 204 controls	Subcortical volumetrics and Fractional anisotropy (FA)	71.0.9% accuracy, 51.9.6% sensitivity, 78.4.0% specificity.	Right lateral ventricle volume and FA value for the right crus of the fornix.	(96)
	64 aMCI, 64 controls	Gray matter volume (GMV), fractional anisotropy (FA), and mean diffusivity (MD)	83.5.9% accuracy	Medial temporal lobe, precuneus, cingulate gyrus, parietal lobe, and frontal lobe.	(104)
	29 aMCI, 33 controls	Hurst exponent (HE), ALFF, regional homogeneity (ReHo), gray matter density (GMD)	96.7.7% accuracy, 93.1.0% sensitivity, 100% specificity	Default mode regions and subcortical regions such as lentiform nucleus and amygdala	(105_ ENREF_96)

Abbreviations: ¹ amnesic mild cognitive impairment

Among them, years of education is one of the proxies of cognitive reserve, which is found to be associated with the increased functional connectivity in the left frontal cortex (119). Cognitively normal elderly people with two *APOE* $\epsilon 4$ alleles have a very great risk of conversion to AD (20). Additionally, it's worth noting that although SCD is an indicator of subsequent cognitive decline in some studies, it is not a proxy for preclinical AD due to not necessarily imply a progression to clinical symptoms (120). In summary, stratifying high-risk or low-risk individuals would facilitate the selection of a biomarker "threshold" of AD changes that may be beneficial for designing specific studies (20). Currently, combining machine learning techniques with biomarkers stemmed from neuroimaging and biochemical methods contributes to the prediction of conversion into AD from those

with prodromal symptoms. In the future, further computational algorithms are required to advance the precision of identifying the earliest and very subtle abnormalities of the individuals even in the asymptomatic at-risk stage (20). Given the limited distinguishing power in recent studies mainly caused by the absence of big sample, additional researches will be needed to fully resolve this critical issue. Meanwhile, launching longitudinal studies would have greater significance and prospect for elucidating the whole progression of AD.

11. CONCLUSION

Neuroimaging, biochemical and genetic markers play a crucial role in characterizing and identifying prodromal AD. Recently, although several

Table 4. Clinical trials targeting A β and tau pathology for prodromal or early AD

Study	Mechanism	Subjects	Sample	Intervention	Duration	Main results	References
Aβ-targeted studies							
	BACE1 ¹ inhibitor	mild-moderate AD	511	Rosiglitazone	24 weeks	APOE ϵ 4 non-carriers exhibited cognitive and functional improvement in response to rosiglitazone	(111)
	γ -secretase modulator (GSM)	MCI	96	CHF5074	12 weeks	CHF5074 is well tolerated in MCI patients	(112)
	α -secretase activator	mild-moderate AD	159	EHT0202	Over 3 months	Safe and generally well tolerated	(113)
	Inhibition of A β aggregation	mild-moderate AD	353	ELND005	78 weeks	The 250 mg dose demonstrated safety and primary clinical efficacy outcomes were not significant	(114)
	Active immunization against A β 42	mild-moderate AD	372	AN1792	12 months	Subacute meningoencephalitis occurred in a subset of patients treated with AN1792	(115)
	Passive immunization	mild-moderate AD	234	Bapineuzumab	78 weeks	Primary efficacy outcomes were not significant	(116)
Tau-targeted studies							
	GSK-3 ² inhibitor	mild-moderate AD	30	tideglusib	20 weeks	Valuable safety and efficacy for the treatment of AD patients	(117)
	Inhibition of tau aggregation	aMCI ³	144	davunetide	12 weeks	AL-108 was generally safe, well tolerated for the treatment of AD	(118)

Abbreviations: ¹ Beta-site APP-cleaving enzyme 1; ² glycogen synthase kinase 3 beta; ³ amnesic mild cognitive impairment

new body fluid biomarkers have lots of advantages, there are few biomarkers with higher sensitivity and specificity in diagnosing AD, especially in the early stage of the disease. Thus, in the future study, linking multiple biomarkers, combined with novel machine learning techniques, may be an effective approach for accurately screening prodromal AD and further providing opportunities for clinical intervention.

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