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Are Blood-Based Protein Biomarkers for Alzheimer's Disease also Involved in Other Brain Disorders? A Systematic Review

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Abstract.
Background: Alzheimer's disease (AD) biomarkers are urgently needed for both early and accurate diagnosis and prediction of disease progression. Past research has studied blood-based proteins as potential AD biomarkers, revealing many candidate proteins. To date only limited effort has been made to investigate the disease specificity of AD candidate proteins and whether these proteins are also involved in other neurodegenerative or psychiatric conditions.
Objective: This review seeks to determine if blood-based AD candidate protein biomarkers are disease specific.
Methods: A two-stage systematic literature search was conducted. Firstly, the most consistently identified AD protein biomarkers in blood were determined from a list of published discovery or panel-based (>100 proteins) blood proteomics studies in AD. Secondly, an online database search was conducted using the 10 most consistently identified proteins to determine if they were involved in other brain disorders, namely frontotemporal lobe dementia, vascular dementia, Lewy body disease, Parkinson's disease, schizophrenia, depression, and autism.
Results: Among the reviewed candidate proteins, plasma protease C1 inhibitor, pancreatic prohormone, and fibrinogen γ chain were found to have the least evidence for non-specificity to AD. All other candidates were found to be affected by other brain disorders.
Conclusion: Since we found evidence that the majority of AD candidate proteins might also be involved in other brain disorders, more research into the disease specificity of AD protein biomarkers is required.

Keywords: Alzheimer's disease biomarker, autism, blood, cross-disorder comparison, depression, other types of dementia, Parkinson's disease, proteins, schizophrenia

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia affecting up to 6% of the population over the age of 65. It is clinically manifested by progressive cognitive decline such as memory loss and executive dysfunction, as well as psychiatric symptoms and behavioral disturbances [1].

The pathophysiology of AD remains poorly understood. However, it is characterized by neuronal degeneration and brain shrinkage, particularly in the hippocampus and mesial temporal lobe structures [2]. At the microscopic level, two main pathological features predominate. The deposition of amyloid-β and

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hyperphosphorylated tau proteins leads to the formation of amyloid plaques and neurofibrillary tangles in brain tissue [3].

Though several methods have been developed to alleviate the symptoms of AD, no therapies have been developed that can modify the course of the disease [4]. This stems not only from a lack of a detailed understanding of the pathophysiological processes underpinning the disease, but also an inability to diagnose patients both accurately and early. It has been estimated that about two-thirds of dementia patients go undiagnosed [5], and that by the time of diagnosis AD pathology has been developing for ∼20 years [6]. Thus biomarkers that can diagnose AD accurately and early are urgently needed.

Presently, a definitive diagnosis of AD can only be made postmortem. Clinical diagnosis of AD remains difficult especially to non-specialists. Current methods for diagnosing AD involve a detailed history and neuropsychological testing to establish the presence of dementia. Other investigations must then be conducted to distinguish AD from other forms of dementias such as vascular dementia (VaD), frontotemporal lobe dementia (FTD), and Lewy body disease (LBD) [1, 7].

Protein biomarkers in the cerebrospinal fluid (CSF) such as a reduced amyloid-β or an elevated tau concentration have been used with a fair degree of accuracy to diagnose early AD [8]. Yet a lumbar puncture remains a relatively invasive procedure and may not be practical for conducting large-scale studies on AD. Neuroimaging methods such as positron emission tomography (PET) to measure amyloid in the brain or magnetic resonance imaging (MRI) to measure atrophy of medial temporal structures have also proved useful [9, 10]. However, PET is expensive and not readily available in many places, while brain atrophy, as measured by MRI, requires specialized facilities and is less specific to AD. The use of blood-based biomarkers is therefore an attractive alternative given the accessibility of blood [11].

The search for blood-based biomarkers for AD has thus far yielded promising results. Recently, Kiddle et al. [11] conducted a review summarizing the most frequently reported AD biomarkers in blood. Kiddle et al. [11] showed that 163 blood protein markers of AD have been found from 21 literature studies, of which only 33% of proteins have been seen in independent studies. Despite this, four proteins were found to be associated with AD in 5 independent cohorts. However, thus far no attempt has been made to determine whether these proteins identified are also involved in other dementia types or mental illnesses. It is thus vital to determine whether the protein biomarkers identified in literature are AD specific or simply indicative of a general brain disorder.

This literature review seeks to build on the work of Kiddle et al. [11] by attempting to establish if identified potential blood-based protein biomarkers for AD are involved in other neurodegenerative or psychiatric disorders.

METHODS

This systematic review was split into two tasks: (1) compilation of an up to date list of potential blood-based protein biomarkers of AD; and (2) compilation of literature evidence for non-specificity of the most promising markers. For the second task, the biomarkers most consistently associated with AD were identified and a literature search was conducted to determine if these proteins were identified as potential biomarkers in other brain disorders.

AD candidate proteins

For this study, the review criteria of Kiddle et al. [11] were repeated to bring it up to date. This consisted of identifying studies of blood protein biomarkers of AD-related phenotypes, including studies of plasma, serum, and leucocyte proteins. The requirements for inclusion as a biomarker were that a protein had to have been identified in a discovery study, rather than a candidate based study. Exceptions were made for panel-based studies that included more than 100 candidate proteins as these were considered to be broad enough to exclude bias.

As in Kiddle et al. [11], studies were identified from two recent reviews on AD-related blood protein biomarkers by Lista et al. [12] and Zurbig and Jahn [13]. In addition, studies that used the Myriad Rules Based Medicine Human Discovery Multi-Analyte Profile (MAP), several of which were published after the two reviews, were also included. Finally the PubMed search term 'Alzheimer blood protein discovery' was used to identify additional studies. The proteins were then ranked according to the extent in which they had been replicated in independent research cohorts.

AD candidate proteins in other brain disorders

The top 10 AD-related proteins were identified from the compiled list and a systematic literature

search was conducted to determine if these protein biomarkers were also involved in other brain disorders, namely: FTD, VaD, LBD, Parkinson's disease (PD), schizophrenia (SCZ), depression (DEP), and autism (AUT).

An Ovid search strategy was devised using MEDLINE, PsychInfo, and Embase. The search strategy utilized a combination of Medical Subject Heading (MeSH) terms, key words, and Boolean operators. The 10 identified proteins were mapped to the appropriate MeSH terms on each of the databases with keywords used when necessary. The selected terms were then combined with the appropriate MeSH terms for the respective brain disorders using the Boolean operator 'And'.

The papers obtained during the search were then screened through additional eligibility criteria. Since this was an exploratory study, fairly broad criteria were used to determine the suitability of papers. Papers deemed suitable had to be blood-based studies examining the association of a difference in quantity of any of the searched proteins with any of the searched diseases. A protein was deemed a potential biomarker if this was explicitly stated in the paper, or if the reviewed study found any statistically significant difference in the quantity of the blood-based protein for the respective diseases. Papers explicitly showing that there was no statistically significant difference in protein quantity were also included for comparison. Only papers written in English and published after 1990 were included. Papers investigating genotypes that could potentially affect protein levels, as well as studies that investigated changes in the characteristics of the proteins such as glycosylation were excluded.

RESULTS

AD candidate proteins

In addition to the 21 papers identified by Kiddle et al. [11], two recent studies by Burnham et al. [14] and Sattlecker et al. [15] were added, bringing the total number of discovery or panel-based proteomics studies to 23 in total [14–36]. These 23 papers, utilizing 18 independent research cohorts, identified a total of 179 potential blood-based protein biomarkers (Supplementary Table 1). The proteins were ranked in order of the number of independent cohorts that they had been associated with, and the top 10 proteins identified for comparison with other brain disorders (Table 1). These proteins included all markers associated with an AD-related phenotype in at least four independent cohorts.

Of the 10 proteins, five proteins—pancreatic prohormone, apolipoprotein E, alpha-2-macroglobulin, complement C3, and alpha-1-antitrypsin—were found to be associated with AD phenotypes in five independent cohorts. The other five proteins—complement factor H, plasma protease C1 inhibitor, serum amyloid P component, fibrinogen γ chain, and serum albumin—were found to be associated with AD phenotypes in four independent cohorts. All the proteins were identified in at least four separate papers with pancreatic prohormone being identified in the most papers at seven.

AD candidate proteins in other brain disorders

The initial literature search yielded a total of 3,223 papers across all three databases. Sixty-two papers were then identified through manually searching the abstracts for papers that conducted blood proteomic studies in the relevant conditions. This was eventually narrowed down to 29 papers after closer review and exclusion of duplicate papers from the different databases [37–65] (Fig. 1).

Of the 29 papers, 12 of them studied DEP, nine studied SCZ, eight studied PD, and a single paper studied AUT. One paper, Domenici et al. [60], studied both SCZ and DEP. No papers could be found on any of the dementia types such as VaD, FTD, and LBD (Table 2).

Serum albumin was identified in 14 papers followed by complement C3 in nine papers and alpha-2-macroglobulin in seven papers. Conversely, plasma protease C1 inhibitor was not identified in any papers, while pancreatic prohormone and fibrinogen γ chain were each only identified in a single paper.

When we consider the relationship between the proteins and other conditions, it can be seen that two proteins (plasma protease C1 inhibitor and fibrinogen γ chain) have not been found to associate with any of the other diseases. By contrast, the other eight blood protein markers of AD have been related to at least one other brain disorder. Pancreatic prohormone and complement factor H were found to be associated with PD. Apolipoprotein E and serum amyloid P were associated with both PD and SCZ. Alpha-2-macroglobulin, complement C3, and serum albumin were found to be associated with PD, SCZ and DEP. Finally, alpha-1-antitrypsin was associated with PD, SCZ, DEP, and AUT (Table 1).

Table 1
The top 10 Alzheimer's disease (AD)-related blood-based proteins with details of the number of cohorts and studies they were identified in as well as their association with the various brain disorders. Papers were found on Parkinson's disease (PD), Schizophrenia (SCZ), Depression (DEP), and Autism (AUT). No papers were found on frontotemporal lobe dementia (FTD), vascular dementia (VaD), or Lewy Body disease (LBD). (+), protein increased in condition; (−), protein decreased in condition; (=), no significant difference in protein levels; (?), significant difference but direction not specified

Protein	Cohorts	Studies	AD	PD	SCZ	DEP	AUT
Pancreatic prohormone	5	7	With AD: (+) O'Bryant et al. [16] (+) Doecke et al. [17] (+) Soares et al. [18] (+) Hu et al. [19] (+) Sattlecker et al. [15] With Brain Amyloid: (+) Kiddle et al. [20] (+) Burnham et al. [14]	(+) Unger et al. [47]			
Apolipoprotein E	5	6	With AD: (−) Soares et al. [18] (−) Doecke et al. [17] (−) Hu et al. [19] (−) Zhang et al. [21] With Brain Amyloid: (−) Kiddle et al. [20] (+) Thambisetty et al. [27] With treatment response: (+) Akuffo et al. [23]	(−) Alberio et al. [52] (−) Goldknopf et al. [56] (+) Ikeda et al. [65]	(−) Dean et al. [51]		
Alpha-2-macroglobulin	5	6	With Treatment Efficacy: (+) Akuffo et al. [23] With AD: (+) Hye et al. [24] (+) Thambisetty et al. 2008 [25] (+) O'Bryant et al. [16] (+) Zhang et al. [21] (−) Ijsselstijn et al. [26]	(=) Dufek et al. [55] (−) Domenici et al. [60] (−) Alberio et al. [52]	(+) Schwarz et al. [58]	(+) Fujita et al. [49] (+) Tsiouris et al. [50] (−)Domenici et al. [60]	
Complement C3	5	5	With AD: (+) Zhang et al. [21] (+) Ijsselstijn et al. [26] (?) Thambisetty et al. [22] With AD Rate of Decline: (+) Sattlecker et al. [15] With Brain Amyloid: (−) Kiddle et al. [20] (?) Thambisetty et al. 2010 [27]	(−) Alberio et al. [52] (=) Dufek et al. [55] (+) Domenici et al. [60]	(+) Boyaiyan et al. [48]	(=) Nunes et al. [44] (+) Song [61] (+) Al-Hakeim [63] (=) Berk et al. [64] (+) Domenici et al. [60]	
Alpha-1-antitrypsin	5	5	With AD: (+) Choi et al. [28]	(=) Dufek et al. [55] (+) Domenici et al. [60]	(+) Yang et al. [59] (+) Schwarz et al. [58]	(+) Song [61]	(−) Russo et al. [62]

			(+) Yu et al. [29] (+) Liao et al. [30] (+) Doecke et al. [17] With Brain Amyloid: (−) Kiddle et al. [20]			
Complement factor H	4	5	With Treatment Response (−) Akuffo et al. [23] With AD: (+) Hye et al. [24] (+) Thambisetty et al. [25] (+) Henkel et al. [36] (+) Zhang et al. [21]	(+) Alberio et al. [52] (+) Goldknopf et al. [56]		
Plasma protease C1 inhibitor	4	4	With AD: (−) Cutler et al. [31] (−) Henkel et al. [36] (+) Ijsselstijn et al. [26]			
Serum amyloid P component	4	4	With AD: (?) Thambisetty et al. [22] (+) Hye et al. [24] (−) Hu et al. [19] With Brain Amyloid: (−) Kiddle et al. [20]	(+) Chen et al. [46] (=) Alberio et al. [52] (+) Domenici et al. [60]	(+) Schwarz et al. a [57]	
Fibrinogen γ chain	4	4	With AD: (?) Thambisetty et al. [22] (?) Hu et al. [19] (+) Choi et al. [28] With Brain Amyloid: (−) Kiddle et al. [20] (?) Thambisetty et al. [27]	(=) Alberio et al. [52]		
Serum albumin	4	4	With AD: (?) Thambisetty et al. [22] (−) Doecke et al. [17] (+) Hye et al. [24] (+) Thambisetty et al. 2008 [25]	(=) Jimenez-Jimenez et al. [37] (−) Usha et al. [53] (−) Goldknopf et al. [56] (+) Alberio et al. [52]	(−) Pae et al. [38] (−) Huang [39] (−) Reddy et al. [54]	(−) Swartz [40] (−) Park et al. [41] (−) Hung et al. [42] (−) Kalender et al. [43] (−) Nunes et al. [44] (−) Maes et al. [45] (−) Song [61]

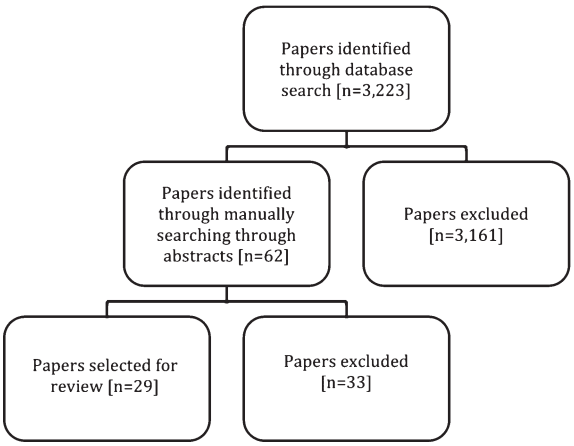

Fig. 1. Search tree detailing the process of selecting papers for review.

DISCUSSION

The results from our systematic literature review suggest that a majority of these candidate proteins are also involved in other brain disorders. However, three candidate proteins, plasma protease C1 inhibitor, fibrinogen γ chain, and pancreatic prohormone, might be AD specific biomarkers as their association with AD is relatively well replicated and there appears to be very little evidence of association between their level in blood and other brain disorders. No studies were found on protease C1 inhibitor while the only study that tested for fibrinogen γ chain found no significant difference in quantity for PD [52].

Raised levels of pancreatic prohormone were found to be present in patients with PD. However, this was only shown in a single paper that studied the post-prandial (i.e., after meal) secretion of pancreatic prohormone and not a generalized increase in blood levels of the protein [47]. In contrast it was standard practice for subjects to undergo overnight fasting before blood sampling for the AD studies reviewed. Given this and the fact that blood pancreatic prohormone levels have been found to be associated with AD in the most studies, its feasibility as a potential biomarker of AD remains relatively strong.

Overall, there were a greater number of papers linking the AD candidate proteins to PD and SCZ, relative to the other disorders reviewed. It is noteworthy that AD and PD are both old age psychiatric disorders, and that psychotic symptoms occur in both AD and SCZ [66]. A further similarity between AD and SCZ is atrophy of the medial temporal lobe [66]. Given the findings of this review, it is plausible that some of the candidate markers of AD are indicative of general medial temporal lobe atrophy.

It should be noted that alpha-2-macroglobulin, complement C3, alpha-1-antitrypsin, complement factor H, serum amyloid P, and serum albumin can be considered as acute-phase proteins. These are a class of protein that characteristically increase or decrease in plasma concentrations as part of an inflammatory response. Indeed many of the studies found were investigations into the response of acute-phase proteins in the various neurodegenerative and psychiatric conditions [50, 55, 59, 61, 64]. Thus the change in concentration of these proteins found in the various conditions could be a reflection of underlying inflammatory processes that are associated with the conditions. Therefore, acute-phase proteins are less likely to be AD specific.

Serum albumin is the protein that by far produced the most search results This is unsurprising as it is the most abundant protein in blood and so is highly studied. Studies have found serum albumin to be lowered in both SCZ [38, 39, 54] and DEP [40–45, 61]. In PD, Goldknopf et al. [56] and Usha et al. [53] showed serum albumin to be decreased. However, Jimenez-Jimenez et al. [37] found no difference in serum albumin concentration while Alberio et al. [52] showed an increase in concentration of serum albumin in PD. Serum albumin, in addition to being an acute-phase protein, is also generally used as a nutritional marker [43]. Thus, the decrease in serum albumin levels, which is found in most of the studies, might be attributed to malnutrition due to a lack of self-care found in patients with neurodegenerative or psychiatric conditions. For this reason serum albumin is unlikely to be a marker specific to AD.

A number of proteins did not show clear directions in their associations with the various conditions with the results of different studies contradicting each other. For example, apolipoprotein E was found to be elevated in PD by Ikeda et al. [65], but lowered in Alberio et al. [52] and Goldknopf et al. [56]. This could be due to small sample sizes, cohort heterogeneity and differences in proteomic approaches, and will need further validation. However, there are some proteins that show consistent associations in certain conditions. Serum albumin, as mentioned above, has been found by all papers reviewed to be consistently lowered in SCZ [38, 39, 54] and DEP [40–45, 61]. Pancreatic prohormone has also been shown in papers to be consistently raised in AD [15–20]. This inconsistency in results among the majority of proteins, as well as their association with other conditions, creates a rather unclear picture and lowers their potential to be used as biomarkers of AD.

Table 2
List of papers selected with details of the conditions studied, sample size, and proteomic method used

No.	Disease	Sample size	Sample type	Proteomic method	Title
1	PD	52	Plasma	Two-dimensional Gel Electrophoresis (2DGE) and mass spectrometry	Chen et al. [46]
2	PD	66	Serum	Human pancreatic polypeptide radioimmunoassay	Unger et al. [47]
3	PD	90	Plasma	2D-GE and mass spectrometry	Alberio et al. [52]
4	PD	45	Plasma	Bromocresol green	Usha et al. [53]
5	PD	29	Serum	Nephelometry	Dufek et al. [55]
6	PD	140	Serum	2DGE	Goldknopf et al. [56]
7	PD	56	Serum	Automated immunoturbidimetric method	Ikeda et al. [65]
8	PD	78	Serum	Nephelometry	Jimenez-Jimenez et al. [37]
9	SCZ	170	Plasma	Bromocresol green	Pae et al. [38]
10	SCZ	245	Serum	Bromocresol green	Huang [39]
11	SCZ	87	Serum	C3H50 assay	Boyajyan et al. [48]
12	SCZ	59	Plasma	Western blot	Dean et al. [51]
13	SCZ	83	Plasma	Bromocresol green	Reddy et al. [54]
14	SCZ	185	Serum	Human MAP	Schwarz et al. [57]
15	SCZ	42	Plasma	2DGE and mass spectrometry	Yang et al. [59]
16	SCZ	130	Serum	Human MAP	Schwarz et al. [58]
17	DEP	407	Serum	Unspecified	Swartz [40]
18	DEP	105	Serum	Unspecified	Park et al. [41]
19	DEP	146	Serum	AU5000 automated chemistry analyzer	Hung et al. [42]
20	DEP	141	Serum	Bromcresol green	Kalender et al. [43]
21	DEP	74	Serum	Nephelometry	Nunes et al. [44]
22	DEP	67	Serum	TSP- Kodak Ektachem Analyzer SP electrophoresis	Maes et al. [45]
23	DEP	45	Serum	Nephelometry	Fujita et al. [49]
24	DEP	38	Serum	Sandwich enzyme-linked immunosorbent assay (ELISA)	Tsiouris et al. [50]
25	DEP	27	Plasma	Nephelometry Modified electrophoresis system	Song [61]
26	DEP	73	Serum	Immunodiffusion plates	Al-Hakeim [63]
27	DEP	112	Serum	Nephelometry	Berk et al. [64]
28	SCZ DEP	729	Plasma	Human MAP	Domenici et al. [60]
29	AUT	71	Serum	Indirect ELISA with monoclonal IgG to AAT	Russo et al. [62]

The differences in the proteomic methods used to quantify the proteins across the reviewed studies was a complication faced in this review. Methods ranged from staining with bromocresol green dye for serum albumin to more complex methods such as 2-D gel electrophoresis, nephelometry, ELISA, and antibody/aptamer microarray technology. This may mean that some of the candidate protein markers have never been appropriately tested for association with the other brain disorders. While older studies were limited in their protein profiling, restricted to small groups of proteins such as inflammatory markers or antioxidant content, later studies with the new human MAP technology were able to sample a much more comprehensive list of proteins, allowing potential biomarkers to be discovered in a more unbiased fashion.

Surprisingly, no papers were discovered on any of the non-AD dementia types searched, namely FTD, VaD, and LBD. This is possibly due to the relatively low level of blood biomarker research performed for these conditions. However, a greater number of studies in CSF have been performed for these disorders. For example, one of the most replicated blood protein markers of AD is alpha-1-antitrypsin, whose level in CSF has been shown not to be significantly different between AD and LBD subjects [67]. Blood levels of transthyretin have been shown to be associated with AD-related phenotypes in two independent cohorts. Another CSF study has shown that CSF levels of transthyretin differ in both AD and PD subjects relative to controls [68]. Both of these CSF studies demonstrate non-specificity of these markers in a tissue that surrounds the brain, which increases the chances that these proteins will be less specific blood-based marker of AD.

Another reason for the lack of relevant papers found for other dementia types is the proteins we investigated, i.e., some of the less well-replicated blood-based AD

biomarkers have been related to these disorders. For example APOA1 has been shown to predict PD motor disease severity and age at onset [69]. The lack of diagnostic evidence to separate different dementia types might also be a factor for the lack of research done in this area. It is also noteworthy that some papers focused on dementias in general instead of splitting them into the different subtypes and were therefore excluded.

While this review gives an idea of the current literature available with regards to AD blood protein biomarkers in other conditions, there are nonetheless certain limitations. Since the inclusion criteria for the review was kept fairly broad in order to get a comprehensive impression of the amount of literature available for the chosen AD biomarkers, there is a lack of consistency in the methodology used in the different papers reviewed. This makes it difficult to compare papers with each other since there is a difference in criteria used to determine if blood proteins are elevated or lowered.

The heterogeneity in the protocol and methodology of the studies could also potentially contribute to the inconsistency in the results. This can be seen even in the AD biomarkers where contradictory results in the direction of protein associations are seen. Watt et al. [70] have shown that one source of variability in blood-based markers is the differences in pre-analytical methodologies with regard to blood collection, processing and storage.

Another potential source of heterogeneity is the different disease stages investigated in the different studies. For example, of the 21 AD studies reviewed: 11 were case-control studies [16, 17, 21, 24, 28–33, 36], 2 studied subjects with early to late AD symptoms [18, 19], 2 studied AD drug efficacy [23, 34], 2 studied pre-symptomatic subjects (based on eventual conversion or brain amyloid burden) [26, 27], one studied early versus late stage AD symptoms (MCI vs AD), one studied AD progression [35], and one studied pre/post-symptomatic subjects as well as AD progression [22]. Given the relative lack of replication studies across the disease stages, and the use of different proteomic techniques, disease-stage specific findings should not be over-interpreted at this stage. This would be an interesting area for further study.

The lack of studies found on a particular protein or disease might also not be reflective of a lack of association. Rather it might indicate a lack of research conducted on a specific protein with a specific disease. It is possible that some proteins and diseases are just less researched and therefore would not be expected to yield as much search results. This paper attempted to take this factor into account by also including papers that explicitly mentioned if a particular protein was not found to have altered concentration in the blood. However, with the tendency for papers to only mention proteins with significant results, and for researchers to mostly publish positive results, it is possible that some of these negative findings might have been missed.

This paper considered depression both as a psychiatric illness as well as a symptom. Therefore the trends seen in the various proteins for depression should be seen as indicative of depressive symptoms instead of a defined psychiatric illness such as major depressive disorder or dysthymia. A number of papers studied depression in relation with other comorbidities such as renal disease and therefore might not be indicative of the general population [41–43].

There remain many avenues for future enquiry. Only the top 10 in a list of 179 potential blood-based biomarkers were selected for further study in this review. This choice was made to focus on the most replicated proteins and also to make the review practical given that searches involving these 10 proteins returned 3,223 studies. It might thus be appropriate to determine if any of the other AD-related proteins down the list are associated with other neurodegenerative or psychiatric conditions in future studies. It will also be interesting to see if the AD-related proteins are found in other neurodegenerative disorders not studied in this review, such as Huntington's disease or motor neuron disease.

Of all the 29 papers reviewed, only three papers used human MAP technology, allowing the study of hundreds of proteins at once [57, 58, 60]. When this technology, and other high-throughput proteomics approaches such as SOMAscan [11, 15], are applied more frequently in the study of various neurodegenerative and psychiatric conditions, it is likely that a clearer picture of potential protein biomarkers will be obtainable.

It is also important to consider multi-variate approaches to studying the proteomics of various conditions. This review considered the association of individual proteins with the various conditions. However, due to the multiplicity of factors involved in the pathophysiology of various brain disorders, it is likely to be more helpful to consider patterns in groups of proteins instead of just single proteins in isolation. Employment of high-throughput proteomics approaches, such as MAP, is making this kind of study increasingly possible and it is likely that this will be the norm in the future.

Finally, while this review was able to demonstrate the non-specificity of some protein markers of AD, larger cross-disorder studies using standardized pre-analytical and proteomic approaches need to be performed to confirm and extend the findings of this review. At present cross-disorder studies have low sample size, for example Edvinsson used 80 subjects to show that plasma levels of neuropeptide Y were non-specific between AD and FTD [71]. In fact for the large AD blood biomarker studies subjects are excluded if they have a non-AD dementia diagnosis. Large cross-disorder studies would allow the specificity of AD markers to be assessed independently of literature biases and platform differences. This would enable greater accuracy in determining whether identified protein biomarkers are specific to AD or simply indicative of a generalized neurodegenerative state.

CONCLUSION

From this review it would appear that pancreatic prohormone, plasma protease C1 inhibitor and fibrinogen γ chain are the AD-related blood-based biomarkers that have the least evidence for association with other neurodegenerative and psychiatric conditions. Many of the other proteins, however, were found to be associated with other conditions, especially PD, SCZ, and DEP. The direction of association between proteins was often found to be inconsistent, with contradictory evidence found between different studies.

It is likely that more extensive proteomic studies need to be conducted before the association between blood-based protein biomarkers and various neurodegenerative and psychiatric conditions can be fully elucidated.

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SUPPLEMENTARY MATERIAL

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