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Proteomic Data Advances Targeted Drug Development for Neurodegenerative Diseases

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Neurodegenerative diseases, including Alzheimer's disease, Frontotemporal dementia, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and multiple sclerosis, are a group of diseases known for loss of neurons, leading to loss of function. While these diseases are onerous for both the individual and the family, there is still a severe lack of therapeutic drugs available for treatment, necessitating a push to develop novel drugs. Unfortunately, drug development continues to face a high failure rate, as seen with current Alzheimer's drugs. Researchers continue to press forward to investigate new avenues of drug development for neurodegenerative disease.

In Ge *et al.* (1), included in this issue, authors explore proteomic data from both the brain and blood to search for new insight into therapeutic options. Ge *et al*. highlight that proteins are critical to some of the functions lost in these diseases and are often targeted in successful drugs. The brain's proteome can account for pathology, such as neuron loss, and blood proteins are able to cross the blood-brain barrier to reach targets. Ge *et al.* curated a list of 22 proteins that they believe to be relevant to neurodegenerative diseases, such as ACE, MAP1S, GRN, and GPNMB; several of these are being looked at independently for drug development with the Accelerating Medicines Partnership Program for Alzheimer' Disease (AMP-AD) through the National Institute on Aging.

Using a Mendelian randomization (MR) analysis, Ge *et al.* (1), made inferences about genetic variations and their potential causality in diseases. Mendelian randomization attempts to create a natural experiment by creating a set of assumptions about the relevance, independence, and impact on the outcome of the instruments, which often refers to genetic variants (2). For example, people with a variation in the ALDH1 gene often have an adverse reaction to alcohol. Using these people as a single group against those without the genetic variation can confirm with fewer confounding variables that those who drink less alcohol often have lower blood pressure, rather than looking at a randomized group of drinkers and non-drinkers (2). Ge *et al.* selected this method in an attempt to remove confounding variables. Even in populations of those with or without neurodegenerative disease (Alzheimer's vs non-Alzheimer's), there may be differences in behaviors between them; MR groups by genetic code to remove this problem. There are positives to this method, such as removing outside variables, but also negatives. As Ge *et al.* pointed out, the results are only correlational; further evidence would be needed to prove causation which may be desirable for drug development. Ge *et al.* also mention that the results of these groupings would not necessarily translate to individual prognosis or treatment. This is an important factor to consider in the discovery of drug targets from proteomic data. This data is pooled from groups of people but targeted therapies could be even more relevant if personalized to proteomic data from an individual. Unfortunately, the cost of this would likely make it prohibitive but further exploration into this idea would be a big advantage in personalized medicine.

By performing an assessment of drug safety, linkage and druggability at this stage, a large number of targets could be narrowed down into a few optimal targets, reducing costs and workload later down the line. *Ge et al*. (1) utilized the GOT-IT framework (3) to evaluate the different relevant proteins they found in terms of safety, druggability and any legal issues. The creation of this framework is in an effort to allow for overlap between academia and industry in

drug testing. As noted by Ge *et al.*, performing some of the drug discovery in house will be able to reduce costs and increase efficiency of which targets to continue to put forward for further research phases.

Ge *et al.* (1) observed that the protein GRN, which encodes for progranulin, as a possible target for Alzheimer's disease. Studies such as Rhinn *et al.* (4) and Petkau and Leavitt (5), have also begun to investigate progranulin as a target for neurodegenerative disease, even concluding that reduction of progranulin is known to be causative of frontotemporal dementia (4). Benefits of injected progranulin included reduced plaques and increased amyloid phagocytosis. Although there has been movement forward with progranulin based therapies, there is not a lot of information about the mechanisms behind their actions. This could lead to possible risk of psychiatric side effects. Studies have begun to look into the pharmacological regulators involved with circulating progranulin. Since they are linked in some way with CSF and the brain, there is some risk that adding further progranulin could have further reaching effects than originally intended (6). Further research would be critical here to improve understanding before introducing additional variables. The recent expansion in research on progranulin is encouraging as a plausible target for proteomic-based therapies.

Additionally, Ge *et al.* (1) also highlighted their interest in GPNMB protein, a transmembrane glycoprotein nonmetastatic melanoma protein B, as an inviting target for Parkinson's disease treatment. High levels of GPNMB can be indicative of Parkinson's risk and this paper's research found it to be a druggable target. Other papers have also looked into GPNMB seemingly having a very high probability of Parkinson's risk and those with high plasma levels to be at even higher risk of severity (7). Diaz-Ortiz *et al.* (7) took data from lab-manipulated patient samples, increasing their clinical relevance and application. As both papers mention, GPNMB is also a desirable drug target due to its expression in both the brain and blood. Additionally, the protein's location at the cell surface improves its availability as a drug target (7).

Overall, this paper presents evidence for 22 potential proteomic targets for therapies aimed at neurodegenerative diseases. More work is needed to confirm causation, reproducibility, and expand the study into different groups. Trials into safety and efficacy of these drug targets will undoubtedly be necessary before introducing any discoveries into an aging population. It would also be interesting to see this study repeated using eQTLs to see if there was any overlap in the results. Although eQTLs do not always correlate exactly with pQTLs due to the difference in correlation of mRNA and protein expression (8), overlap would confirm using broader data sets that these are viable targets.

Although only correlational at this time, this paper displays that there can be links between pathology and proteomics. This paper is relevant in that it emphasizes the translational aspect of research in directly examining the genetic code in relation to therapies. It highlights a large group of possible targets, using a method that can reduce costs and overlap the collaboration between academia and the pharmaceutical industry. With the increasing life expectancy and the aging baby boomer generation, developing many possible avenues in drug development for neurodegenerative diseases is becoming even more important.

Acknowledgements and Disclosures

Figure 1. Blood and brain proteomic data was taken from databases and put through mendelian randomization. After further statistical testing (for example, colocalization), possible targets were analyzed for safety, druggability and causation using various metrics, in hopes of creating a pipeline to reduce costs and time of sorting through large data sets. This resulted in 22 possible drug targets for further research.

References:

(1). Ge Y, Ou Y, Deng Y, Wu B, Yang L, Zhang Y, *et al.* (2022): Prioritization of drug targets for neurodegenerative diseases by integrating genetic and proteomic data from brain and blood. *Biol Psychiatry*.

(2). Davies NM, Holmes MV, Smith GD (2018): Reading Mendelian randomisation studies: A guide, glossary, and checklist for clinicians. *BMJ*, 362.

(3). Emmerich CH, Gamboa LM, Hofmann MCJ, Bonin-Andresen M, Arbach O, Schendel P, *et al.* (2021): Improving target assessment in biomedical research: the GOT-IT recommendations. *Nat Rev Drug Discov* 20: 64–81.

(4). Rhinn H, Tatton N, McCaughey S, Kurnellas M, Rosenthal A (2022): Progranulin as a therapeutic target in neurodegenerative diseases. *Trends in Pharmacological Sciences* 43;8: 641–652.

(5). Petkau TL, Leavitt BR (2014): Progranulin in neurodegenerative disease. *Trends in Neurosciences* 37;7: 388–398.

(6). Ghidoni R, Stoppani E, Rossi G, Piccoli E, Albertini V, Paterlini A, *et al.* (2012): Optimal plasma progranulin cutoff value for predicting null progranulin mutations in neurodegenerative diseases: A multicenter Italian study. *Neurodegenerative Diseases* 9;3: 121–127.

(7). Diaz-Ortiz ME, Seo Y, Posavi M, Cordon MC, Clark E, Jain N, *et al.* (2022): GPNMB confers risk for Parkinson's disease through interaction with α-Synuclein. *Science* 377;6608.

(8). Battle A, Khan Z, Wang SH, Mitrano A, Ford MJ, Pritchard JK, *et al.* (2015): Impact of regulatory variation from RNA to protein. *Science* 347;6222: 664–667.

Blood & brain
proteomic data

Mendelian Randomization
Replication
Colocalization

15
brain-based
proteins

1
brain and
blood-based
protein

6
blood-based
proteins

22
possible drug targets for
neurodegenerative disease

Tier 1 (Approval drugs/
clinical trials)

Tier 2 (Similar action to
approved drugs)

Tier 3 (ECM/Major drug
targets)

Finan's
Criteria
(Druggability)

Rule of
Five

Causality

Safety

Good Binding
Site

High to Low

Exploration of safety,
druggability, and causality