Computational Simulation of Progranulin for Blood-Based Detection of Parkinson's Disease up to 7 Years Before Symptom Onset

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Parkinson's disease (PD) is a neurological degenerative disease that affects signal pathways in the brain, leading to motor control issues, as well as various other conditions. Detecting PD is challenging because its symptoms develop slowly and are initially subtle. PD's symptoms overlap with different neurological disorders, allowing it to be easily confused with disorders like Essential Tremor or Multiple System Atrophy (MSA). However, there may be a way to detect it years before it worsens. Recently, the granulin protein has been linked to the onset of PD, suggesting it could serve as a biomarker. Our research aims to identify granulin precursor proteins that are cleaved into granulin proteins. "Antibody" is a general term used to classify proteins that bind to various structures, allowing the body to identify and/or destroy them. We hypothesize that antibodies binding to the protein's surface could be used to detect and diagnose PD. We will use HDOCK to find binding sites between the granulin precursor and a specific antibody. We will use Prodigy for binding energy. We will use P2Rank to predict the best binding sites on the granulin precursor. Based on the visual inspection and binding energy, we have selected antibody 1IGT as the most appropriate candidate for granulin protein detection. By finding the antibody that best binds to the granulin precursor, we can modify it to help us locate it. This would allow doctors to diagnose PD much earlier and provide faster, more effective treatment.

1. INTRODUCTION

PD was first published around 1817, when Dr. James Parkinson published his paper "An Essay on the Shaking Palsy." [1] In 1912, Dr. Frederick Lewy discovered abnormal protein deposits (now called Lewy bodies) in the brains of PD patients. In 1967, Levodopa (L-DOPA) was introduced as a potential drug therapy for PD patients. [2] In 1997, it was discovered that a mutation in the alpha-synuclein gene was linked to PD. Finally, in 2024, Dr. Jenny Hällkvist and her team linked PGRN overexpression to PD. [2]

PD is a genetic disease that is more common in people above the age of 50 [3]. It is caused by various factors that lead to the breakdown of nerve cells in the brain. Some early-onset PD symptoms are tremors, stiffness, and bradykinesia. [3] However, as the disease progresses, one gradually loses control of certain motor functions, leading to rigid movements and balance problems. The main cause of symptoms for PD is a loss of neurons in the brain, specifically the cells that produce dopamine (a hormone that helps regulate motor control). Management for the symptoms includes clinical drugs such as levodopa (also known as L-DOPA), dopamine agonists, physical therapy, exercise, anti-depressants, hospital/personal care, etc [4].

PD symptoms typically begin around 20 years before the clinical onset. 20 years before the onset, patients may have symptoms such as hyposmia (loss or impairment of sense of smell), constipation, or bladder disorder. [3] 10 years before the onset of the disease, patients may develop a sleep disorder, obesity, or depression. At or around the clinical onset, patients may experience symptoms such as a unilateral tremor. As the disease progresses, patients may have bilateral disease, poor balance, falling, and cognitive decline. At 20 years post clinical onset, patients are often chair/bed bound and experience dementia [3].

PD isn't diagnosed through a single test like other conditions [3]. Instead, doctors use medical history, brain scans, and specific physical tests to see if your symptoms line up with PD or if it is just a similar disease [5]. Usually, medical history allows for an insight into your family and your present conditions to see if there is any history of conditions that may predispose you to PD. Brain scans can locate any degeneration in clusters of nerve cells within the brain, which, if present, are often caused by neurodegenerative diseases such as PD [5]. Because PD af-

fects the patient's motor abilities, checking whether they can perform tasks to locate any symptoms of PD, such as muscle stiffness, loss of posture/balance, or tremors, can help identify what the condition truly is [5].

The granulin precursor protein, also known as Progranulin (PRGN), is a precursor to granulin and is linked to neurodegenerative diseases, including PD. Parkinson's. [6] Additionally, PGRN is a glycoprotein that helps maintain the brain. [6] It controls neural function, inhibits neuroinflammation, and plays a role in neuronal lysosomal function. In the body, PGRN is a part of the PPN, a network of three proteins that work together in the lysosomal environment. PGRN is related to Parkinson's as an excess of PGRN in the plasma is linked to the disease. [6] Recently, it has been shown that the protein can be used to detect PD up to 7 years before symptom onset. [7] The schematic of the granulin detection is displayed in Figure 1. Molecular docking simulations are computer-generated simulations used to predict or visualize the binding between two separate molecules. [8] These simulations are monumentally crucial in drug discovery because of their ability to show how a molecule of medicine may interact with a pathogen's active site (although the target does not have to be a pathogen). [9] Molecular docking simulations involve looking at all possible candidates and ranking them to find the best suitors. By predicting the best binding orientations and the best affinities, researchers can view vast amounts of compounds in short periods, making it much easier and faster to find potential finalists for testing. [9]

In the human body, a group of specialized proteins are used to identify and destroy potential pathogens such as bacteria, viruses, and toxins; these proteins are known as antibodies. The immune system makes each antibody in your body, and every one of them has a unique structure. These structures are like a lock and key, and their specific shape allows for quick and easy binding to their target (referred to as an antigen). Recently, Hallqvist et al. identified granulin as a biomarker for PD. [7] Based on this finding, progranulin-targeting antibodies can be used for detection, potentially identifying PD up to 7 years before symptom onset. In our research, we have developed an antibody that specifically binds to the granulin precursor. Depending on how the antibody was designed, it can have varying functions. In current research, we have used antibodies to detect granulin protein. These antibody-based methods can be used for the early detection of PD.

2. METHOD

UniProt is a database compiled by scientists worldwide that contains data on many proteins [10]. We used UniProt to find the amino acid sequences of the granulin precursor and the antibodies that we tested. AlphaFold 3 is an AI-powered tool that predicts a protein's 3D structure from its amino acid sequence. We used AlphaFold 3 to make models of the granulin precursor and antibodies. [11] After this, we downloaded the PDB files of each antibody for the molecular docking simulations from the Protein Data Bank. [12] The next step was to observe how each antibody interacts with PRGN, the target protein. HDOCK is a computational tool for finding potential binding sites between two specific molecules. [13] We used HDOCK to identify potential binding sites between the granulin precursor and various antibodies. ChimeraX is software for visualizing proteins and their properties (such as electrostatic charge) [14]. We used this software to visualize the granulin precursor, allowing us to provide images or view specific sections.

P2Rank is a machine learning-based method that identifies the optimal binding sites on a protein and ranks them by their binding strength. [15] We used it to determine which sites would allow the most potent binding to the PRGN, compared with the binding predictions from HDOCK. Binding energy is the minimum energy required to dissociate a complex into its constituent parts. Finally, we used the PRODIGY software to calculate the binding energy between the granulin precursor and each antibody upon binding. [16]

3. RESULTS

For blood-based detection up to seven years before symptoms manifest, the study employed computer simulations to determine the optimal antibody that binds to PRGN, a protein associated with early-stage PD. In addition, we have assessed the binding energies of ten antibodies and modeled interactions using programs such as AlphaFold 3, HDOCK, P2Rank, ChimeraX, and PRODIGY. The most promising candidate for early PD detection was determined to be antibody 1IGT based on binding site proximity and energy data.

Surface properties of Granulin protein: ESP, or electrostatic surface potential, is a way to describe the charge of specific locations on the surface of a molecule, as well as the intensity of said charges. The ESP of a molecule can be useful in finding the ways the antibodies can bind to the surface of the protein. "ChimeraX" (as well as the protein's amino acid data) was used to visualize the ESP of the protein. Figure 2A shows the results. A binding site is a location on a molecule that is optimal for another molecule to connect and bind itself. P2RANK webserver is a machining learning-based method and was used to predict these sites. Figure 2b represents the sites predicted by P2RANK. Both the ESP and the binding sites were useful in finding ideal binding locations on PRGN.

Molecular docking simulations: In the next step, we performed molecular docking simulations to observe which antibodies bind closest to the optimal sites in Figure 2b. Molecular docking is the process by which specific binding molecules, such as antibodies, bind (or "dock") to particular targets. The HDOCK program was used to find the optimal binding sites on the granulin protein. In Figure 3, the software ChimeraX was used to represent the data gathered visually. Pink/black represents the antibody, while purple represents the PGRN.

Antibody selection criteria: The most appropriate antibody was be selected based on the following criteria in the next step. When the predicted binding site for an antibody was modeled using HDOCK, it should have appeared close to the top 2 binding sites predicted by P2Rank (see Figure 2). Based on these criteria, antibodies 1A5F, 2VXS, 3HFM, 1IGT, and 3D85 were selected for the subsequent evaluation. The PRODIGY software compared the binding energy (amount of energy needed to separate two distinct structures at the molecular level) for each construct of a given antibody and the PRGN with others. This data was used to determine which construct has the strongest binding affinity. By cross-referencing both selection criteria, we determined that the antibody best suited for binding to granulin is 1IGT. The binding energy of the PRGN-antibody complex is shown in Table 1.

Binding Energy Data

The binding energy of each antibody with PGRN computed using the PRODIGY software. The unit is in kcal/mol.

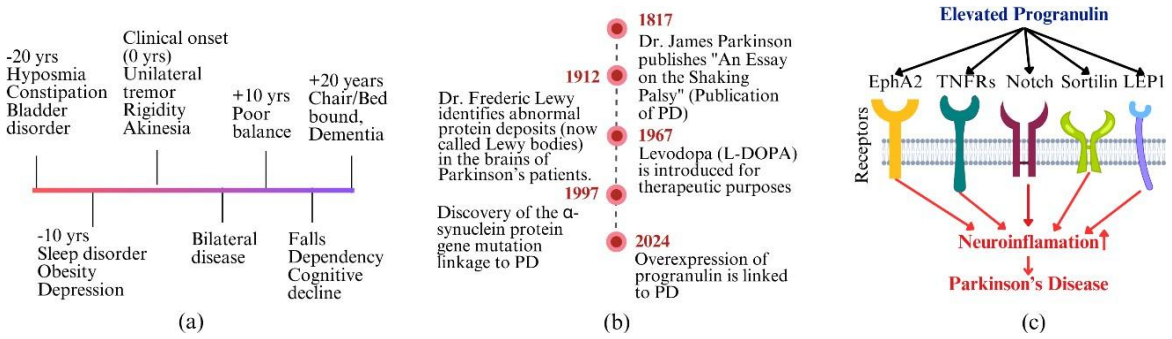

Fig. 1. (a) Timeline of PD symptom progression relative to clinical onset (generated by a student using Canva). **(b)** Timeline of information relating to the history of PD. **(c)** Schematic representation of progranulin-mediated neuroinflammation and PD formation (figure was generated by a student using Canva)

Table 1. The binding energy of each antibody with PGRN was computed using the PRODIGY software. The unit is in kcal/mol.

Property	1A5F	1igt	1lk3	2vxs	2xqb	3D85	3GD6	3HFM	4a6y	5XRQ
Binding Energy (kcal/mol)	-14.0	-14.8	-10.8	-14.2	-13.8	-13.4	-17.6	-11.5	-15.0	-15.7

4. DISCUSSION

Application: By identifying the most appropriate antibody binding to the PRGN protein, a novel PD detection-based method can be developed. Because PRGN is linked to PD, detecting PRGN with these antibodies will allow early PD detection. Due to these antibodies being able to locate PRGN much earlier than the onset of PD, doctors can provide treatment before any severe symptoms occur (in the same way surgeons can cut off benign tumors before they turn cancerous). This research will help in developing a diagnostic method for PD. Since these antibodies can detect PRGN before the onset of significant symptoms, they provide an opportunity for early intervention. Figure 4 shows that the PRGN protein is present outside the cell surface and that its blood/CSF concentration suggests it could be useful for detection.

Limitation: The data shown in this paper were collected from existing datasets and generated via AI-powered computer simulations. This means that the data provided may not be experimentally valid, especially considering that the data wasn't applied in a lab setting. In this research, we only tested 10 antibodies. Therefore, the data provided samples only a smaller fraction of the possible antibodies, some of which may be much better at binding to PRGN. Due to the nature of computer simulations and the fact that humans programmed them, there is a chance that errors were present within our data. As such, experiments may be necessary to validate our data.

Future work: It has been observed that, in patients with neurodegenerative diseases like PD, PRGN levels are elevated in peripheral blood. The brain also has increased levels of PRGN. If antibodies are used for therapeutic purposes, animal testing may be necessary to ensure they do not cause adverse side effects. Any testing must account for the possibility that some people may have slightly more or slightly less PRGN present, possibly due to genetics or environmental factors. Due to the experimental nature of this test and the fact that these antibodies may be expensive to produce, work must be done to make it more accessible price-wise. PGRN levels are increased in other neurodegenerative diseases, so the test may be able to detect

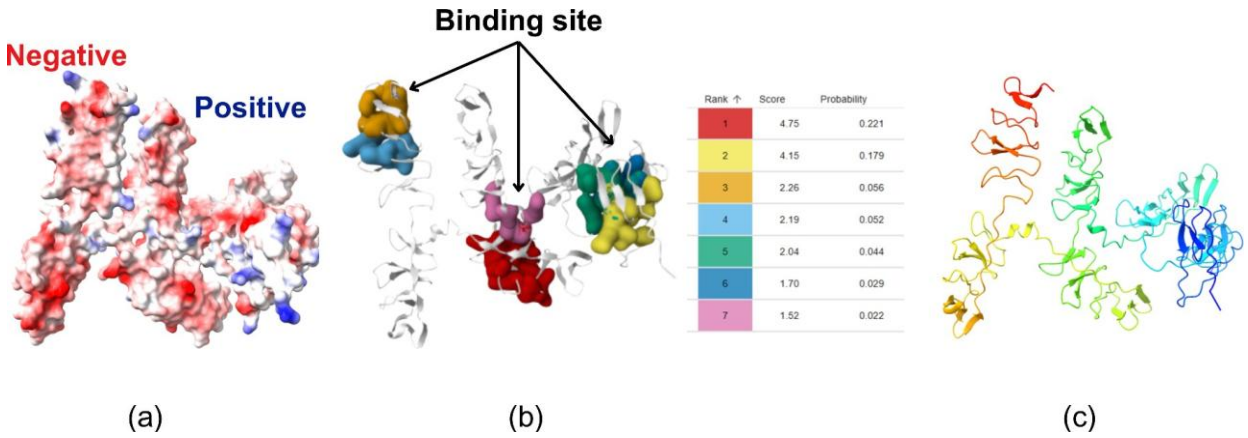

Fig. 2. (a) Electrostatic surface potential (ESP) is a property of a molecule that describes the distribution of charges across its (the molecule's own surface; a specific location/region on a molecule where another molecule can bind with non-covalent interactions; and (c) granulin protein ribbon structure for reference (generated using ChimeraX).

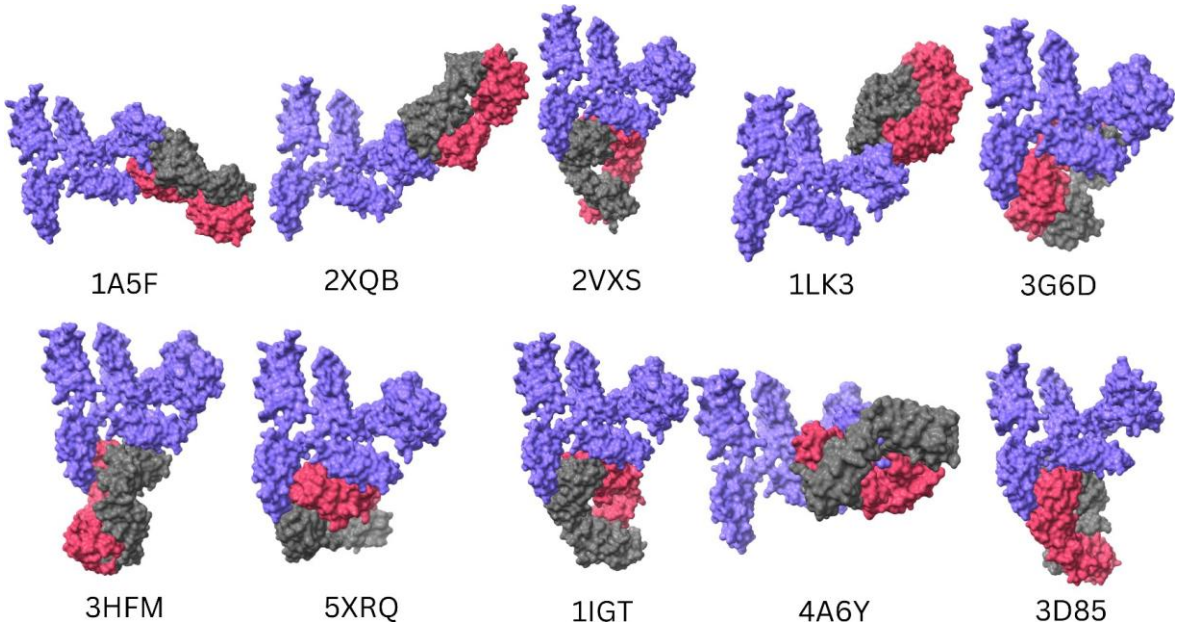

Fig. 3. The images show all antibodies tested and their locations when binding to the PRGN protein. Pink/black represents the antibody, purple represents the PRGN.

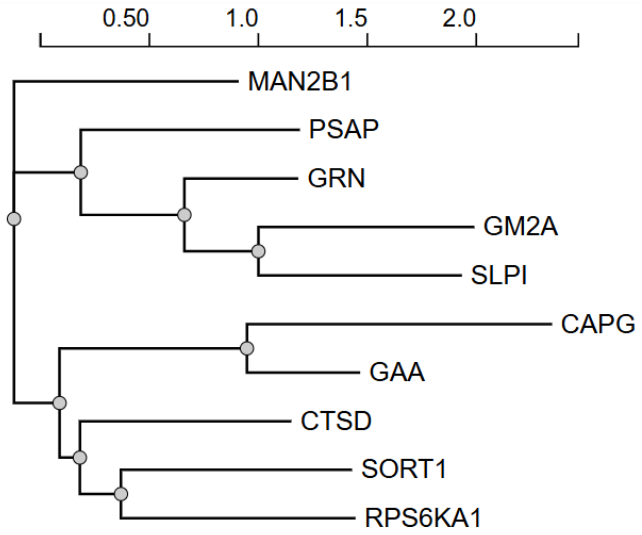

Fig. 4. Hierarchical clustering dendrogram showing the similarity among lysosomal or associated proteins. Distances reflect expression or sequence-based relationships. Close clustering of proteins such as GM2A and SLPI indicates substantial similarity, whereas SORT1 and RPS6KA1 are more distantly related.

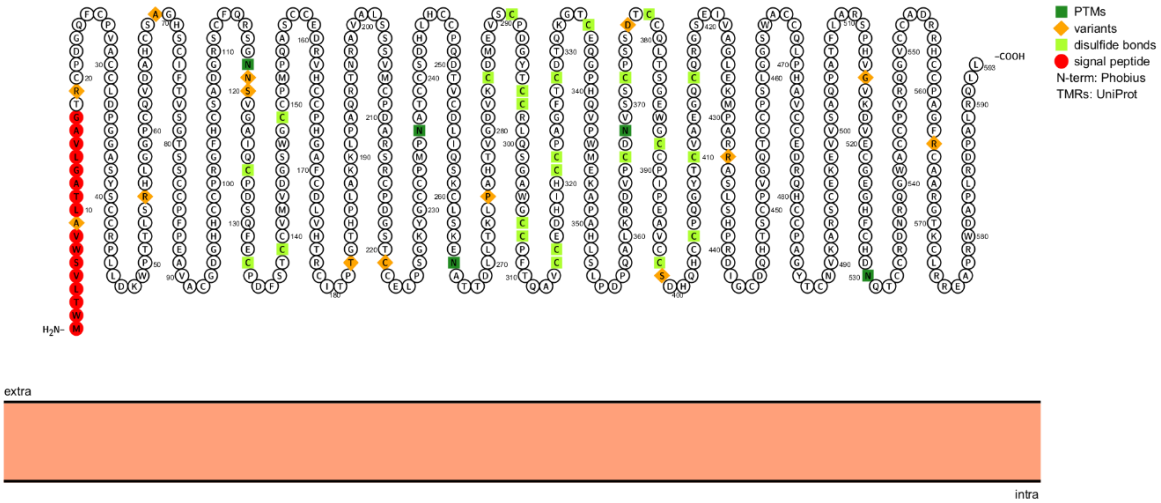

Fig. 5. Schematic of the granulin protein showing the amino acid sequence with mapped mutations. This figure shows that the PRGN is detectable outside the cell and is more likely to be detected in blood.

other diseases, such as Alzheimer's disease or frontotemporal dementia. The detection threshold for PGRN is at least 61.55 ng/mL.

5. CONCLUSION

In this study, we have used computational methods to predict the binding of specific antibodies to the PRGN. By determining the antibodies that can bind, there is a possibility of predicting Parkinson's (and other neurogenerative diseases) 7 years before symptoms appear. By selecting the antibodies that can bind, predicting PD (and other neurogenerative diseases) is possible 7 years before symptoms appear. After testing which antibodies bound closest to the optimal binding site and determining the binding energy (lower is better), we found that the 1igt antibody had the best chance of binding, based on the criteria for binding. If a blood-based detection system or treatment is developed that targets PGRN, 1igt would be the best fit due to its binding site and energy.

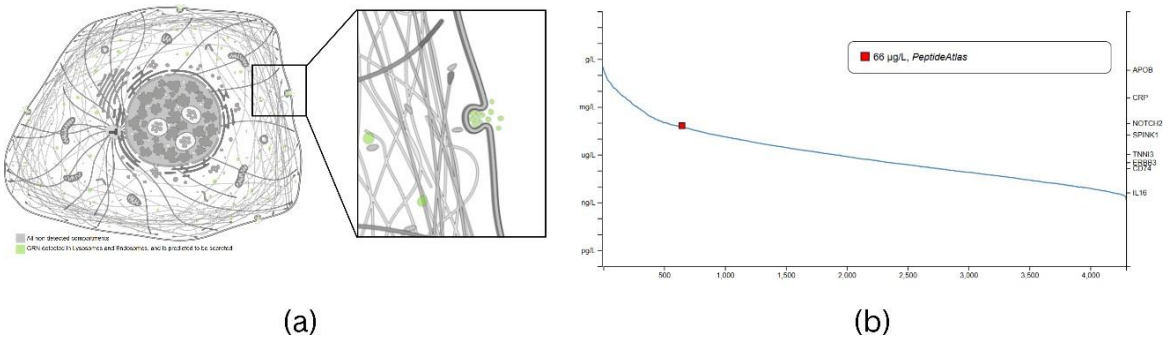

Fig. 6. (a)Subcellular localization of the PRGN protein (in green) shows its presence in lysosomes and endosomes. The zoomed-in video highlights PRGN being secreted via vesicular transport. (b) The concentration of PRGN in human plasma indicates that the threshold is 66 µg/L. Both images are obtained from the Human Protein Atlas website. [17]

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