Using NetraAI to Discover Parkinson's Disease Subtypes: Generative AI Reveals Transcriptomic Personas Linking Mitochondrial, Microbiome, and Immune Signaling

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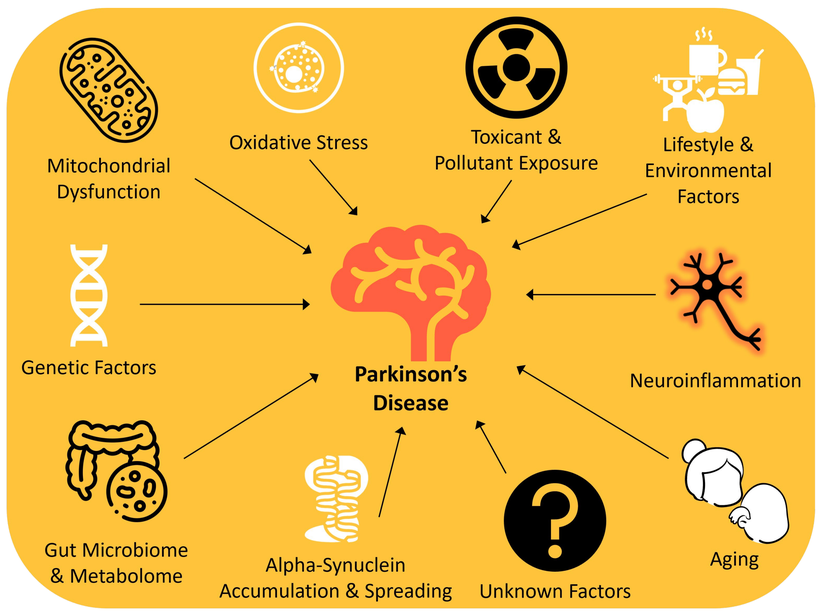
INTRODUCTION

Parkinson's Disease (PD) and Alzheimer's Disease (AD) are two major neurodegenerative disorders characterized by complex and varied symptoms and progression rates. The etiology remains largely unknown, underscoring the heterogeneity of these conditions.



Machine learning (ML) systems offer a powerful tool to address the clinical variability of PD and shed light on its underlying mechanisms, providing valuable insights for improved treatment strategies.

OBJECTIVES

Using a novel ML approach, NetraAI, we aim to identify genetic drivers within self-discovered PD patient subpopulations and uncover pivotal disease pathways, and patient enrichment criteria for future trials.

METHODOLOGY

DATASET:

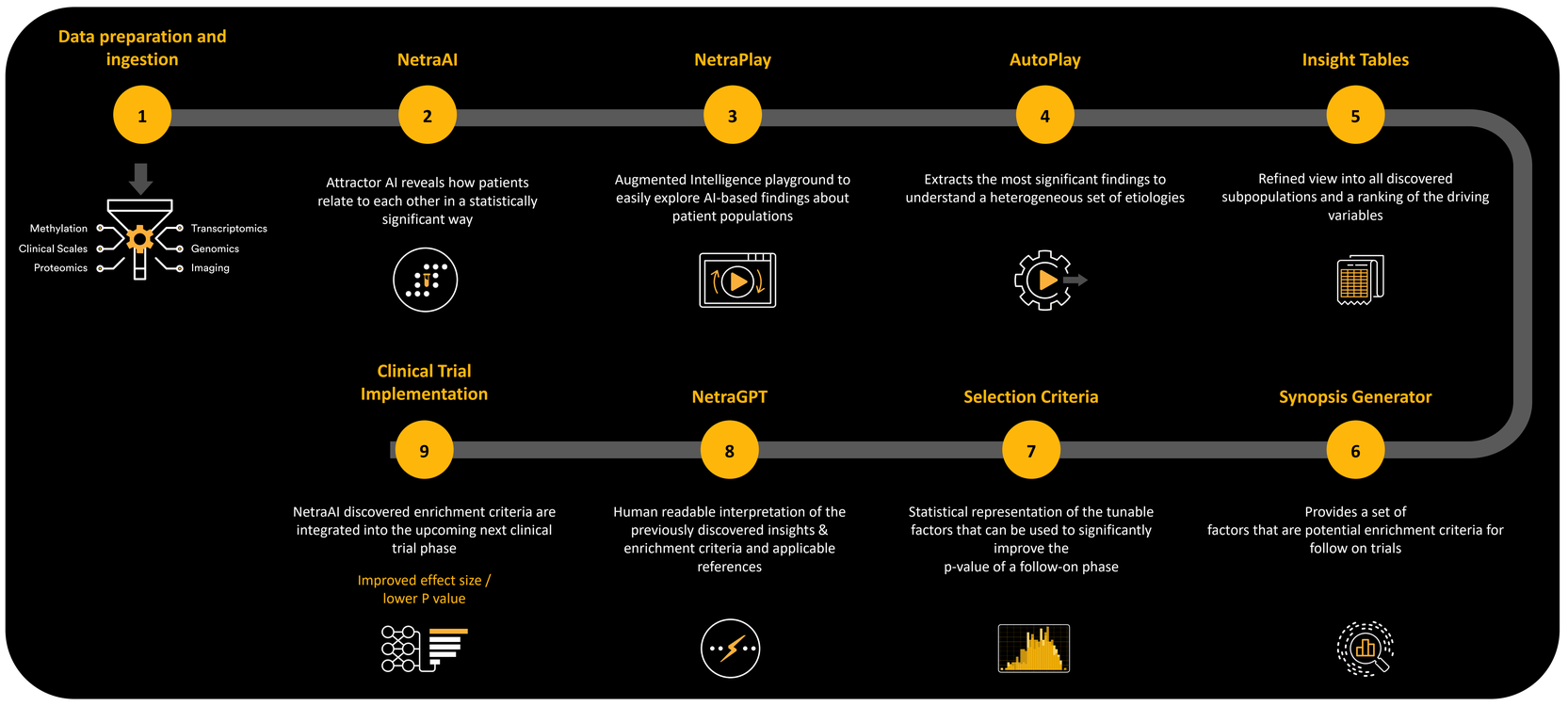
Transcriptomic dataset (n=588) obtained and assembled from the Michael J. Fox Foundation:

- 191 controls
- 397 PD patients

MACHINE LEARNING APPROACH:

NetraAI, powered by its unique Attractor AI algorithms, was used to identify causal clusters of variables called *hypotheses* which attempt to explain specific subpopulations.

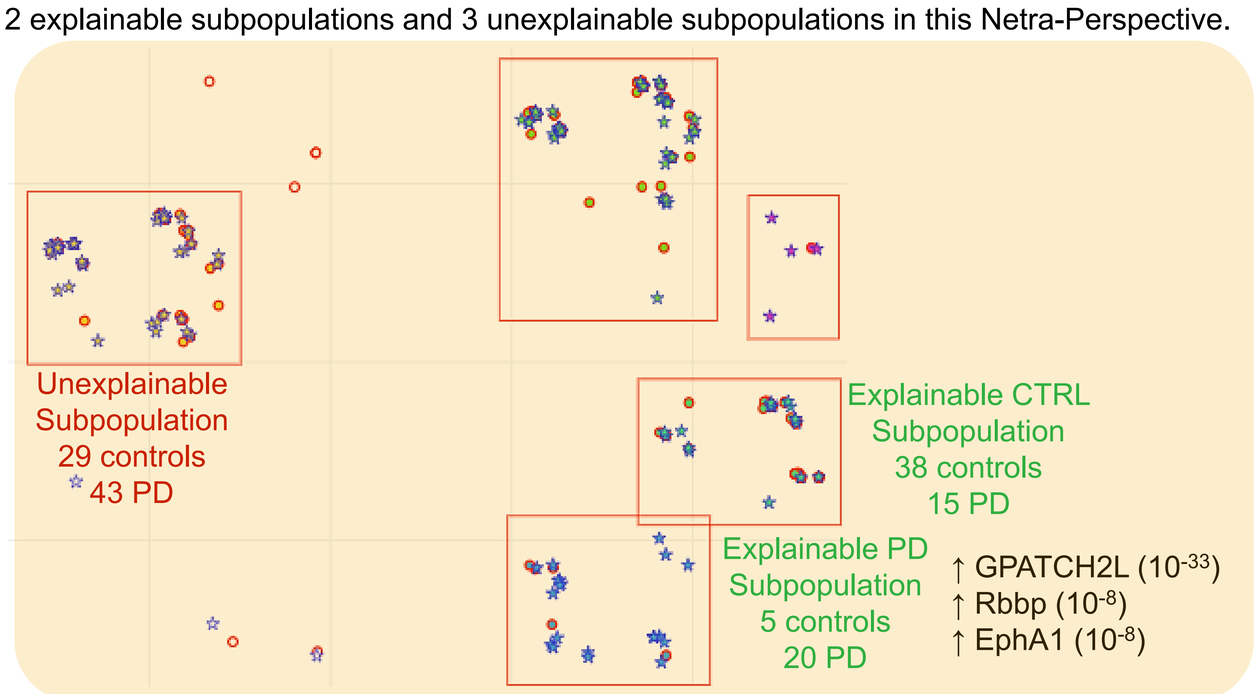
- Netra-Perspectives are self-discovered explainable patient populations that capture different aspects of complex diseases like PD:
  - Each Netra-Perspective fractures the patient population into explainable and unexplainable subsets of patients according to a set of variables.
  - Combining different perspectives provides a holistic view of the patient population.
- Cross-hypothesis integration reveals significant variables and pathways linked to PD.



RESULTS

One Netra-Perspective of a self-discovered PD population with explainable and unexplainable subpopulations.

2 explainable subpopulations and 3 unexplainable subpopulations in this Netra-Perspective.



NetraAI decides which subpopulations are explainable through a purity criteria in addition to the statistical significance of the driving variables.

- The unexplainable subpopulation (23 CTRL; 43 PD) does not satisfy a definition of an explainable subpopulation due to the lack of purity and statistically significant variables.
- The explainable subpopulations satisfy a purity criteria and the existence of significant driving variables.
- The system also provides explanatory variables for separating the two explainable subpopulations along with significance values.
- GPATCH2L, Rbbp7, and EphA1 are all upregulated in the PD group.

Protein-protein interaction (PPI) network revealing local interactions and co-expression for the Netra-Perspective.

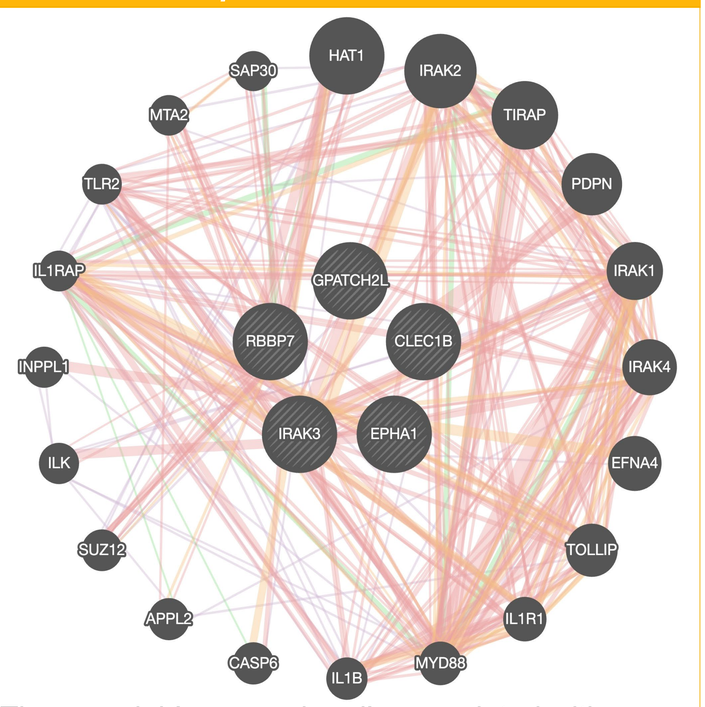
Using the genes characterizing the PD subpopulation, GPATCH2L, Rbbp, EphA1, we also implicated CLEC1B and IRAK3 via GeneMania:

- GPATCH2L is connected to TLR4
- CLEC1B is connected to CD36, TLR2, PDPN, RACK1
- IRAK3 is connected to TLR4

These allowed GeneMania to reveal a network rich with implications for PD. Importantly, these proteins of interest are closely linked to immune-mediated functions.

- GPATCH2L: macromolecule metabolism; mitochondrial quality control
- Rbbp: regulation of transcription and chromatin remodeling
- EphA1: improves inflammatory responses and neuropathological changes of PD model
- CLECB1: regulates cytotoxicity and cytokine secretion; platelet activation
- IRAK3: negative regulatory marker of inflammation; dyskinesias

A different Netra-Perspective strongly implicated the gene BPI (upregulated in PD) which is involved in protecting against gram-negative bacteria.



These variables are primarily associated with immune signaling, particularly the innate immune system's response to microbial pathogens, which may involve interactions with the microbiome.

Note: this is one of several Netra-Perspectives generated, with others highlighting more of a mitochondrial and microbiome role.

Hypothesis: *BPI is overexpressed in some PD patients as a protective immune response to gut microbiome dysbiosis impacting brain health.*

CONCLUSIONS & SIGNFICANCE

- This study highlights the potential of ML to untangle the intricate web of factors contributing to PD, offering insights applicable to other neurodegenerative disorders, including AD.
  - Transcriptomic markers GPATCH2L, Rbbp, BPI, and EphA1 in addition to CLEC1B and IRAK3 underscore the pivotal role of the immune system and response in PD pathogenesis.
  - NetraAI has the ability to uncover key variables in disease pathogenesis through causal clusters. Other Netra-Perspectives highlight different patient subpopulations characterized by different variables, including those heavily implicated in mitochondrial and microbiome signaling such as BPI which warrants additional research and validation efforts.
  - NetraAI results combined with PPI networks reveal additional insights into disease pathogenesis that can assist in identifying biomarkers and treatment approaches.

SIGNFICANCE

- Our approach opens new avenues for the diagnosis and treatment of these debilitating conditions.
- This research not only advances our understanding of the disease but also offers a scientific foundation for future investigations into the role of immune-related factors in neurodegenerative disorders & provides new opportunities for improving clinical trials through patient enrichment.

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