Using NetraAI Hypothesis-Generation for Patient Stratification and Target Discovery in ALS

Joseph Geraci[1,2,3,4], Ravi Bhargava[5,6], Bessi Qorri[1], Paul Leonchyk[1], Douglas Cook[1,7], Moses Cook[8], Fanny Sie[6], Luca Pani[1,9,10,11]

[1]NetraMark Corp, [2]Department of Pathology and Molecular Medicine, Queen's University, [3]Centre for Biotechnology and Genomic Medicine, Medical College of Georgia, Augusta University, [4]Arthur C. Clarke Center for Human Imagination, School of Physical Sciences, University of California San Diego, [5]Department of Biomedical and Molecular Sciences, Queen's University, [6]Science and Research, Roche Integrated Informatics, F. Hoffmann La-Roche, [7]Department of Surgery, Queen's University, [8]Department of Medical Biophysics, University of Toronto, [9]Department of Psychiatry and Behavioral Sciences, Leonard M. Miller School of Medicine, University of Miami, [10]Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, [11]VeraSci

BACKGROUND

Amyotrophic lateral sclerosis (ALS) is a devastating progressive neurodegenerative and neuromuscular disease with no known cure and treatment is focused on symptom management.

CHALLENGES:

- ALS is a complex genetic disease with cellular damage accumulating due to genetic factors and exposure to environmental risks.
- Disease heterogeneity contributes to the variable diagnosis, progression, and prognosis of each individual.

NEED:

- Understanding of ALS manifestations and progression.
- Identification of therapeutic targets to halt or slow ALS progression.

OBJECTIVES

Use a machine learning (ML) systems-level approach to analyze ALS patient data to identify covariates and clusters of factors that provide a classification of disease and potential therapeutic targets

METHODOLOGY & WORKFLOW

Dataset:

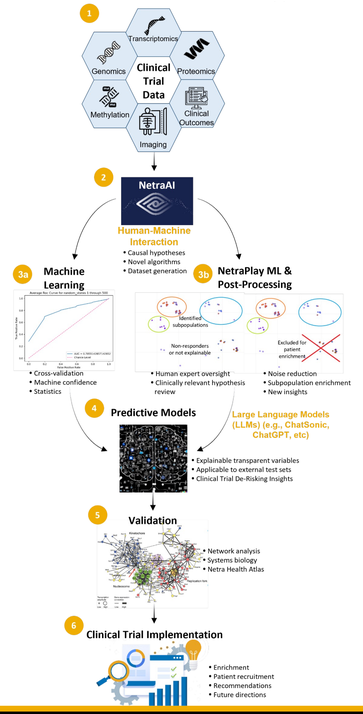
Publicly available dataset provided by patient advocacy groups AnswerALS and EverythingALS.

- 800 ALS patients and 100 healthy controls from 8 neuromuscular clinics in the US.
- iPSC lines generated from patients' peripheral blood mononuclear cells.
- Consortium generated multi-omics data, focusing on transcriptomics.

Perspective Analytics & Hypothesis-Generation:

Using NetraAI to discover unknown subpopulations that are defined by multiple genes and provide explanations for underlying driving mechanisms behind each subpopulation.

NetraMark Workflow
Generative Clinical Trial Decision Support



RESULTS

NetraAI replicated previously identified ALS drug targets.

Using NetraAI, we:

- Verified several of the same gene targets that have been recently reported in ALS (***Table 1***)
- Identified several genes that belong to the same gene family as those previously reported (***Table 2***).

Table 1. NetraAI-replicated ALS drug targets.

Drug Target	Function
DNM3TA	DNA methylation
ERN1	Sensor for endoplasmic reticulum unfolded protein response (UPR)
HSPD1	Innate immune response
PPIA	Survival and growth pathways; mediator of inflammation
VCP	Protein segregation and degradation; DNA repair and replication; cell cycle regulation
PPP3CB	Calmodulin & protein phosphatase 2B-binding activity; NFAT signaling; apoptosis; cell degradation

Table 2. NetraAI-identified drug targets structurally similar to previously reported targets.

Drug Target	Function
MAP3K5	Mediator of apoptosis signaling
MAPK1	
NOS1	Multifunctional signaling molecule and neurotransmitter; SOD1 upregulation
PTK2	Cell adhesion, migration, and survival; ubiquitous proteasome system and protein degradation
PTPRC	Transmembrane receptor protein phosphatase activity; immune cell function
RARA	Autophagy
NR3C2	Aldosterone signaling pathway
KCNB1	Regulator of cortex and hippocampus neuronal firing
P2Y12	Neuroinflammation; platelet aggregation
SCYL3	Neuronal function, survival; cell migration, adhesion
SLC25	Mitochondrial function; neuron energy production; apoptosis; L-glutamate and aspartate transmembrane transport; malate-aspartate shuttle
RPS6KA1	Mediator of cell survival; cell growth, motility, survival, and proliferation
RPS6KA2	
KCNV2	Neurotransmitter release regulation; neuronal excitability

Identification of 8 novel ALS target classes using NetraAI.

45 targets were uncovered that may shed light into ALS pathophysiology and treatment efforts. These individual targets were grouped into a collection called "target classes" that align to a unique ALS characteristic.

- The 8 target classes are not exhaustive, representing key areas that have the potential to play a role in ALS that warrant further investigation.
- These target classes suggest that the simultaneous targeting of several key hallmarks of ALS with combination targeted therapy may have the potential to slow progression, with an enhanced possibility of maintaining and sustaining an improved quality of life (QoL) for certain ALS patients. (***Figure 1***).

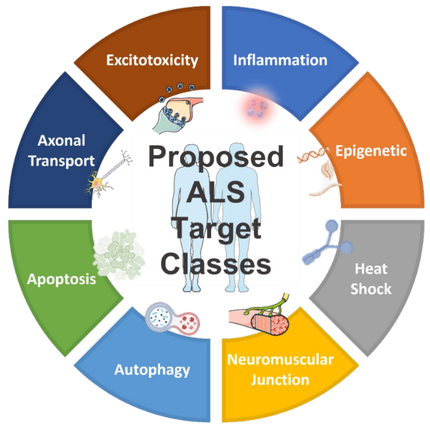


Figure 2. Proposed target classes for ALS uncovered by NetraAI. Novel genes associated with ALS characteristics can be grouped into these 8 target classes.

CONCLUSIONS & SIGNIFICANCE

SUMMARY OF KEY FINDINGS

Using NetraAI, an augmented intelligence approach, we were able to:

- Report on 6 genes that have been previously reported to be implicated in ALS. (Table 1)
- Report on 14 genes that belong to the same gene family as those previously reported to be implicated in ALS. (Table 2)
- Identify 45 targets that are grouped into 8 target classes that correspond to key characteristics of ALS: inflammation, epigenetic, heat shock, neuromuscular junction, autophagy, apoptosis, axonal transport, and excitotoxicity. (Figure 1)

SIGNIFICANCE OF METHODOLOGY AND FINDINGS

1. Validating of genes previously implicated in ALS and corroborate the results obtained using NetraAI.

- NetraAI generates a mosaic of etiological hypotheses that are easily understood allows for the quick exploration and consideration of potential targets.
- 8 target classes highlight genetic drivers that are associated with subgroups of patients that can be useful in matching patients to therapy and for drug discovery in ALS.
- Clinical trials can benefit by understanding which patient subpopulations are best aligned with the mechanism of action of their drug to improve drug response signal.

2. 8 target classes represent broad ALS characteristics that may be targeted.

- The target classes are not novel on their own, but the combination of genes driving each target class are novel.
- Some target classes include genetic drivers related to other target classes (e.g., heat shock target class has dynactin and axonal transport target class has 2 HDAC genes) highlighting the claim that ALS is a multisystem disorder.

FUTURE USE AND APPLICATION

Use of statistics to assign a level of confidence to hypotheses.

Having a system capable of generating hypotheses that are dually scrutinized through:

- Statistical significance testing
- Biological plausibility

Hypotheses that survive can be pushed forward for more research.

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