NGV Hunters

(c3-la-team-b)

Day 2: Team Progress Update

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Main Purpose

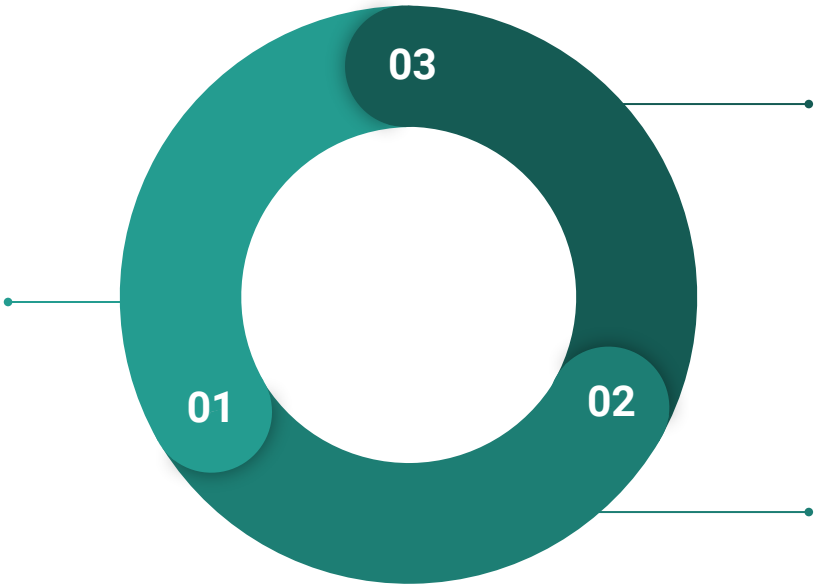
The NGV hunters recognize the genetic complexity of Motor Neuron Disease and the multimodality of translating insight from motor neuron disease to effective drugs both for the (1) prevention of disease and for the (2) treatment of disease.

Aim 1: Exploring Genetic Variation

To explore the genetic variations that exist within different sub variations of the disease

A. Slow progression vs Fast Progression

B. Differences Across Biological Sex



Aim 3: Drug Discovery Based on Genetic Targets

A. Drugs that are already FDA/EMA approved

B. Drugs currently studied in pre-clinical research

C. New drug research from labs conducting research on chemicals with physical characteristics similar to what we predicted would work with our target genes

Aim 2: Mendelian Randomization for Drug Target Discovery

To explore genetic drug targets which may differ from causal genetic finds

Aim 1: Exploring Genetic Variations

01 Data Set Involved

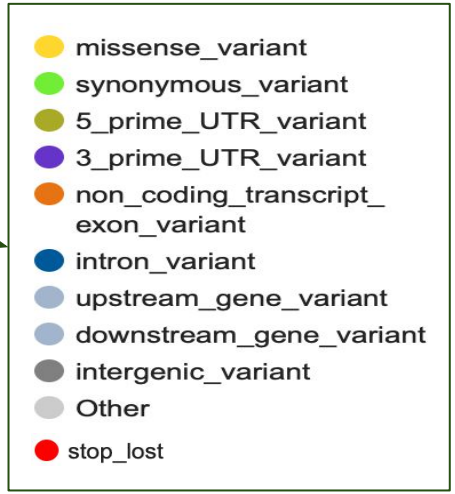
- Whole Genome Sequencing from ALS patients
- Working on a panel of genes associated with ALS disease

02 Methods to Explore

- Workflow development starting from Fastq to VCF, annotating VCF with ACMG classification
- Looking for pathogenic or high impact variants from the categories listed

03 Problems to Tackle

- Access to controls samples
- Access to real ALS samples (WGS)
- Access to other omics datasets like BulkRNAseq, CHiPseq, ATACseq, Single Cell RNAseq



Aim 2: Mendelian Randomization for Drug Target Discovery

01	Data Set Involved	• ALS GWAS Summary Statistics • eQTL data from PsychENCODE (brain) and eQTLGen (blood) • Druggable genome data from Finan et al
02	Methods to Explore	• Filter eQTLs that are 5kb up and downstream of druggable genes • 2 Sample MR to infer causal effect of expression on ALS outcome • Take any significant genes and see if they encode targets of already approved or clinical phase drugs
03	Problems to Tackle	• Lots of data prep • MR tricky and requires post analysis QC
04	Future Steps	• Include expression data from other tissue (muscle - skeletal from GTEx) • Include pQTLs • Colocalization

Aim 3: Drug Discovery Based on Genetic Targets

01	Data Set Involved	• Part A: DrugBank - (Canada Operated) Database of FDA approved drugs • Part B: PubMed • Part C: UK BioBank
02	Methods to Explore	• Part A: Database Management (SQL) for connecting and exploring data, R for biostatistical analysis • Part B: Text mining and text annotation with PubTator and Litvar • Part C: GraphNN for Edge-Level Link Predictions for Novel ALS Gene Targets with Mapped Drugs
03	Problems to Tackle	• DrugBank: Takes a few days to get full approval ○ Alternatives exist like: chembl, pharmacodb • Lots of disparate data that must be organized and connected
04	Future Steps	• Exploring multiple databases • Connected drugs found from the databases to the lit review of current research • Connecting to previously failed drug trials to determine what went wrong

Thank you and Questions!

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