Team 7: CMT4J

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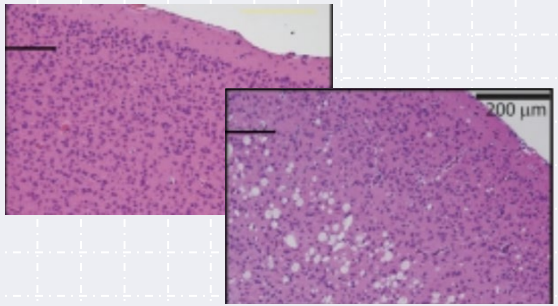
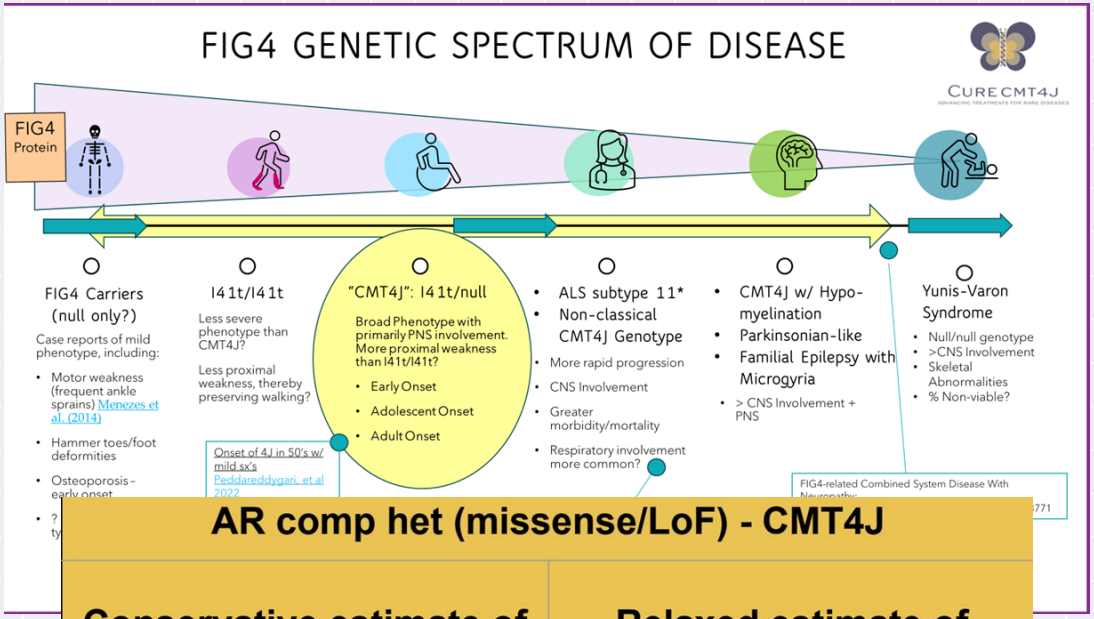
Background on CMT4J

- CMT4J is an ultra-rare form of hereditary neuropathy (1/1,000,000).
- Caused by a mutation in the FIG4 gene:
  - Autosomal recessive inheritance, commonly I41T/null (60/100).
  - Mutation reduces binding affinity but can be rescued.
- Clinically presents itself with high variability, often misdiagnosed e.g. CIDP.
- AAV gene therapy recruiting for clinical trial.



Vacuolation => spongiform encephalopathy (Lenk 2011)

FIG4 Variants Are Difficult to Categorize



AR comp het (missense/LoF) - CMT4J	
Conservative estimate of affected individuals	**Relaxed estimate of affected individuals**
6,714	10,866

- Lack of data for non-classical genotypes, affects **clinical trial eligibility**.
- FIG4 disease severity varies significantly. Why?
- Broad Institute frequency analysis says there should be more 4J cases

Goal: Characterize FIG4 Variants Using *in silico* Methods and Case Studies To Compensate For Low Sample Sizes

Data

ClinVar, gnomAD variants of FIG4

AlphaMissense predictions for AA mutation pathogenicity

Case Studies of 4J, ALS-11, YV, etc.

Fig4 + Vac14 structure

Methods

Correlate Pathogenicity with *in silico* Binding Affinity Data

Easy-to-compute, general across diseases, relevant for AAV trial

Score FIG4 Variants in Literature Across The Spectrum

Many Variants of Unknown Significance (VUS), in-silico scoring is cheap preliminary look.

Results

Binding complex visualization enriched with predicted pathogenicity

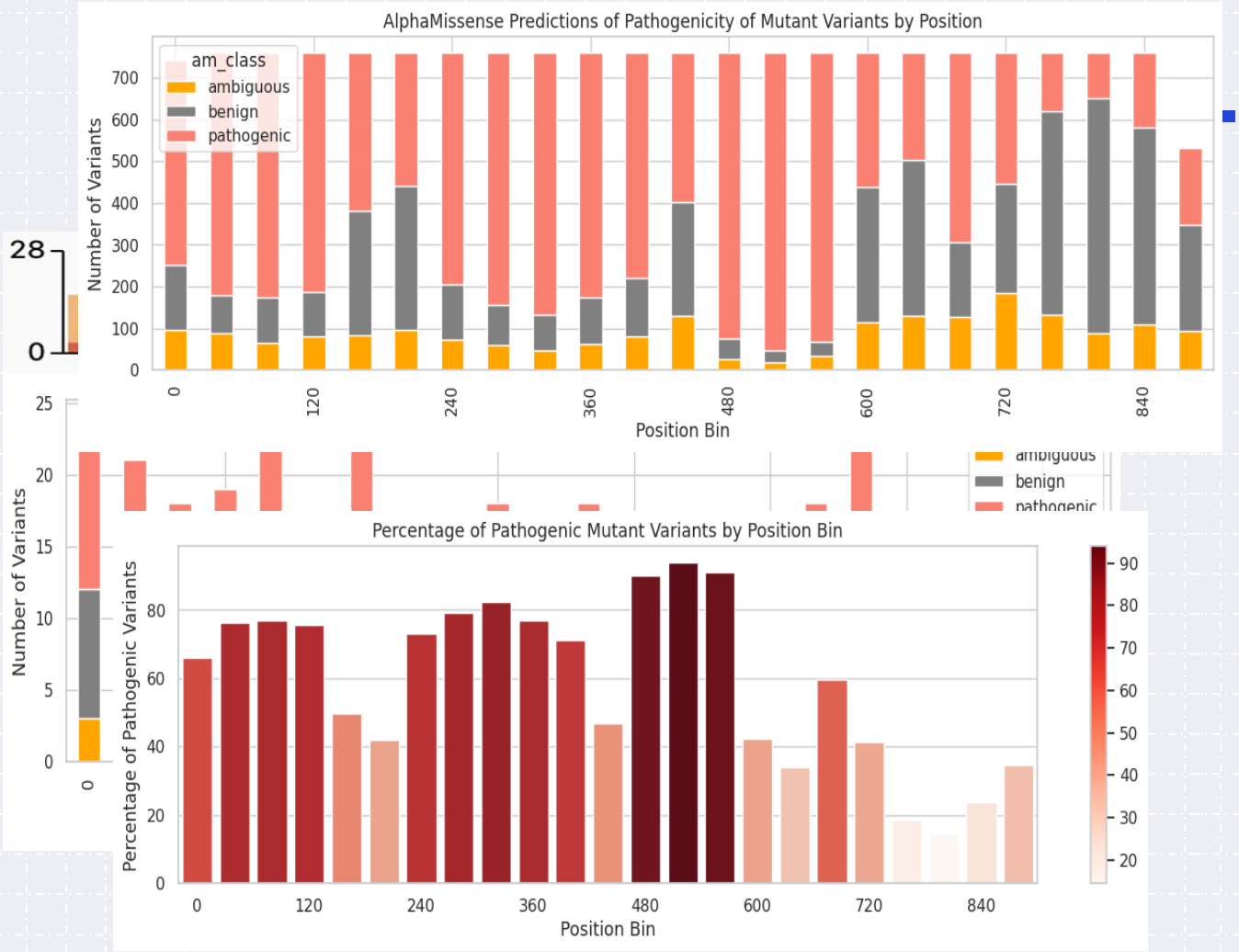
- Predicted binding complex of Vac14 and Fig4 generated using MegaDock
- Residues colored according to average predicted pathogenicity
- **High pathogenicity at binding interface and active site**

- I41T has very high predicted pathogenicity (0.97)
- Near binding interface of Vac14
- Loop residues all >0.95 predicted pathogenicity

Results

ClinVar annotations for AlphaMissense landscape (many uncertain VUS)

AlphaMissense predictions of all possible missense mutations show high pathogenicity from residue 480 - 550



Discussion + Future Directions

Discussion

- Characterized 438 protein missense variants of FIG4 using AlphaMissense
- Binding complex structure enrichment with predicted pathogenicity is validated by clinically relevant mutations

Future Directions

- Use AI for protein optimization → novel AAV therapeutics with longer lasting + higher affinity FIG4
- Investigate sphingosine 1-phosphate as immunogenic biomarker. Fingolimod could be therapeutic as in MS.