# Analyzing Disease Mutations in Proteins Involved in Liquid-Liquid Phase Separation


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## INTRODUCTION

- Liquid-liquid phase separation (LLPS) is the natural process where a liquid separates into two distinct phases which forms membrane-less organelles in cells.
- Condensates can form from high expression, intrinsically disordered regions, multiple folded domains, and other physical properties of proteins.

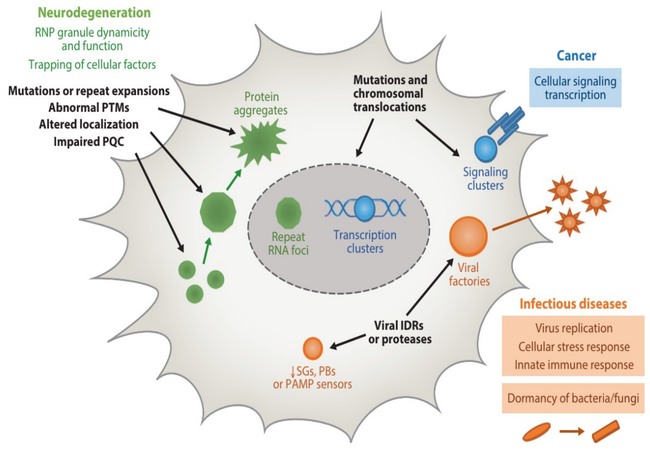
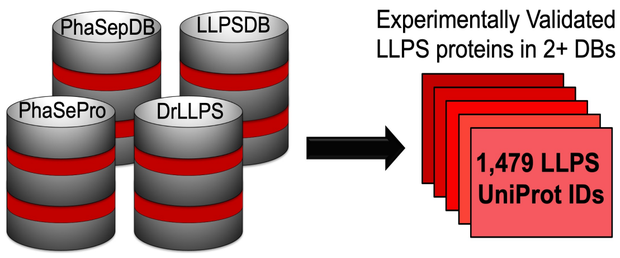



Fig 1. The different LLPS mechanisms in diseases like cancer and neurodegeneration, as displayed by Alberti *et al.* (2019)

## METHODS

ClinVar presents data on human variation and phenotype and the Human Gene Mutation Database (HGMD) presents mutations associated with human disease.

LLPS Protein Databases (DB)




1. **Generate LLPS Gene List**
   - Using the LLPS UniProt IDs, generate a list of gene names
2. **Filtering of ClinVar & HGMD**
   - Pathogenic clinical significance
   - Single nucleotide variants
   - LLPS Vs. Non-LLPS
3. **Systematic Analyses**
   - Edgotype Distribution
   - Significantly Enriched Diseases
   - GOF/LOF

## SYSTEMATIC ANALYSES RESULTS

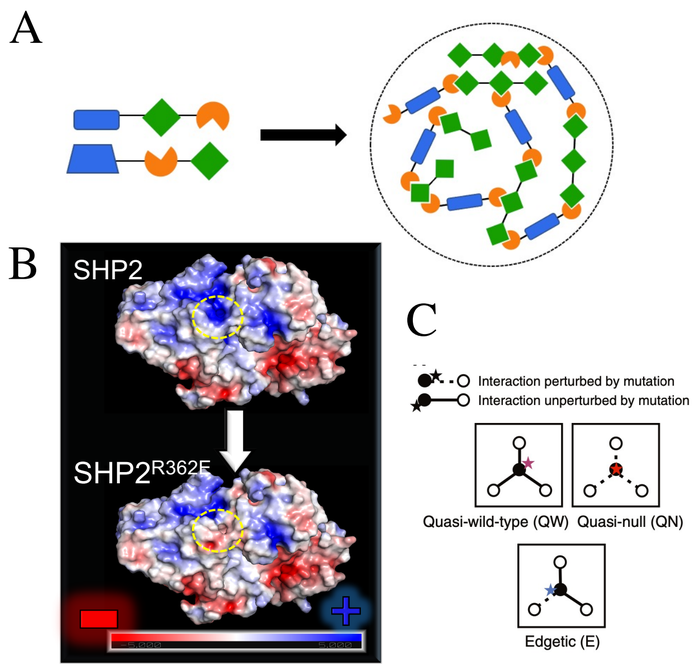
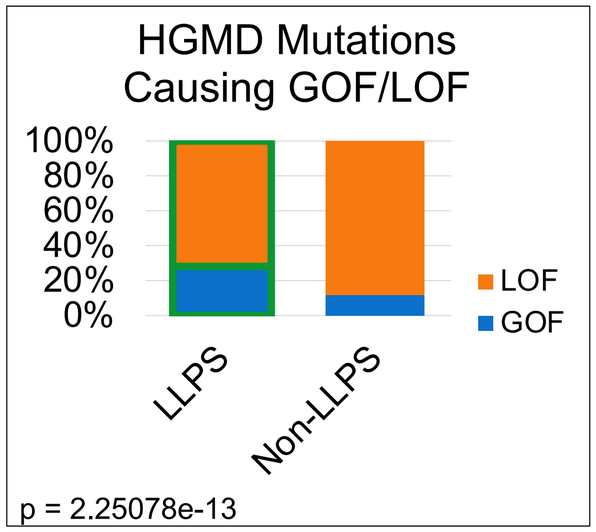



Fig 2.
A) Depiction of protein interactions
B). When the SHP2/PTPN11 protein is mutated (R362E), there is a change of charge in the area of mutation. PDB: 4DGP Provided by Sueda Cetinkaya
C) Three classes of PPI profiles (edgotypes) for mutations as displayed by Sahni *et al.* (2015)




PTEN, CDKN2A, CREBBP, ATRX, FUS, MAP2K1, SH2B1, LMNA, ATM, …

SOD1, LRRK2, KIT, PTPN11, MAPT, SOS1, ACTB, PRPF31, APOA1

Fig 3. If data was available by Bayrak *et al.* (2021), mutations were labeled as GOF or LOF with regards to gene expression. Provided by Sueda Cetinkaya

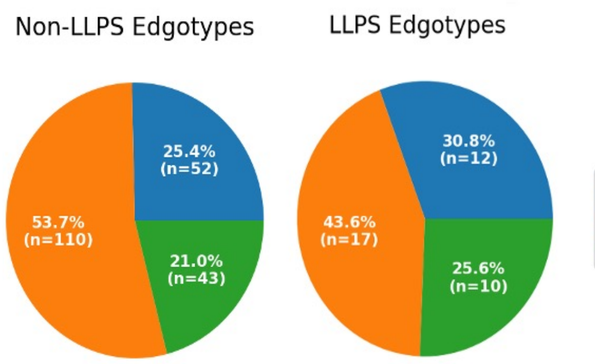



Fig. 4 LLPS & non-LLPS edgotypes

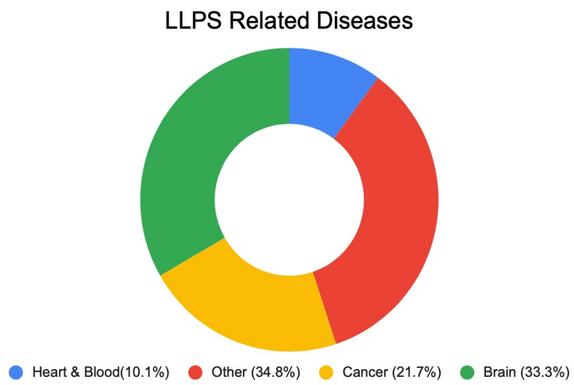



Fig 5. Distribution of LLPS mutation enriched diseases for ClinVar Database

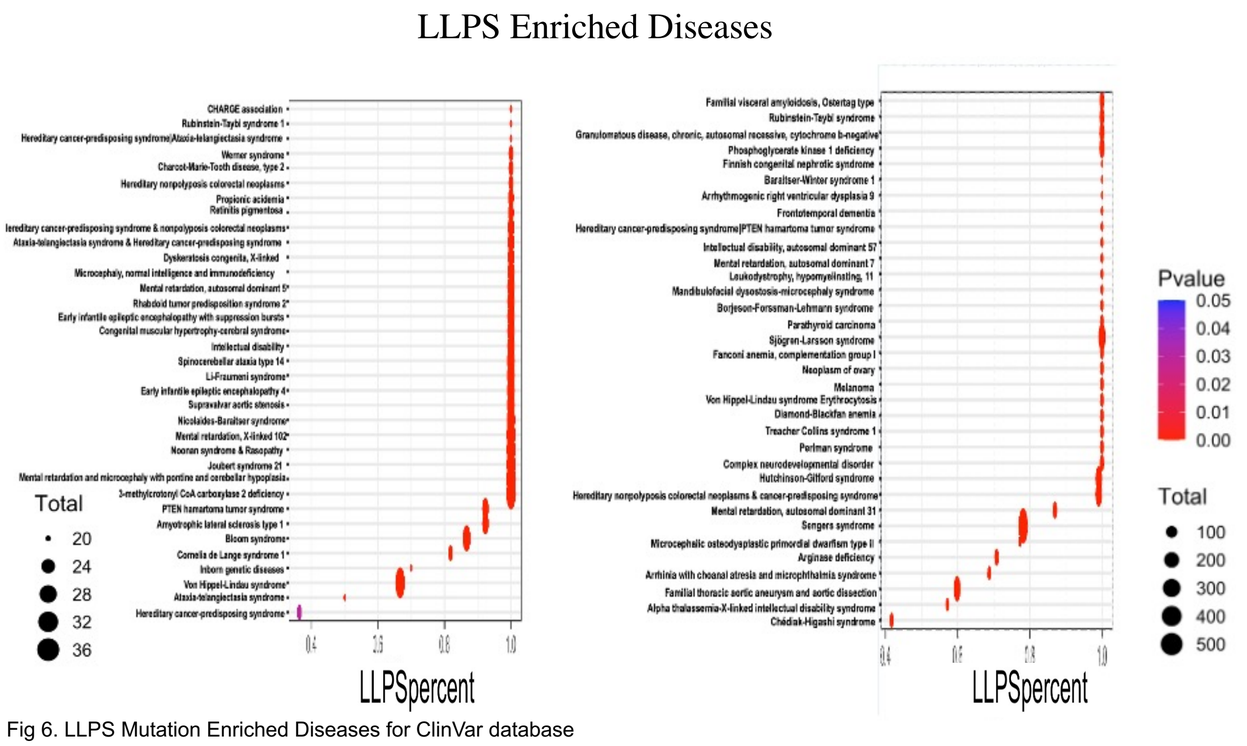



Fig 6. LLPS Mutation Enriched Diseases for ClinVar database

## CONCLUSION

Overall, we observe significant data associating cancer and neurodegenerative diseases with mutations in LLPS genes based on the HGMD and ClinVar databases.

- There are no significant differences between edgotype characterization of LLPS and non-LLPS gene mutations in HGMD.
- Some of the genes enriched for GOF/LOF mutations include tumor suppressor genes and oncogenes like PTEN and CDKN2A.

## FUTURE DIRECTIONS

We acquired promising data in our systematic analyses for further investigating the impact of mutations on protein structure and properties to understand the roles of LLPS in diseases. Joining the structural analyses with our current data and performing the same analyses on cancer mutation databases like The Cancer Genome Atlas will allow us to better understand the roles of mutations in LLPS related diseases.


### Acknowledgements

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