REVEALING POTENTIAL MECHANISMS FOR EHLERS-DANLOS SYNDROME USING KNOWLEDGE GRAPHS

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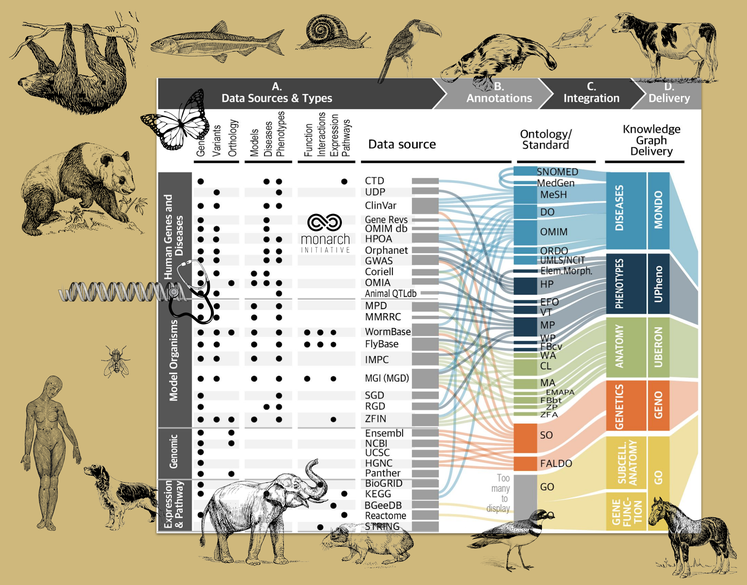
BACKGROUND

Ehlers-Danlos Syndrome (EDS) is a heritable connective tissue disorder. Here, we focus on 1 of 14 subtypes: **hypermobile** (hEDS)

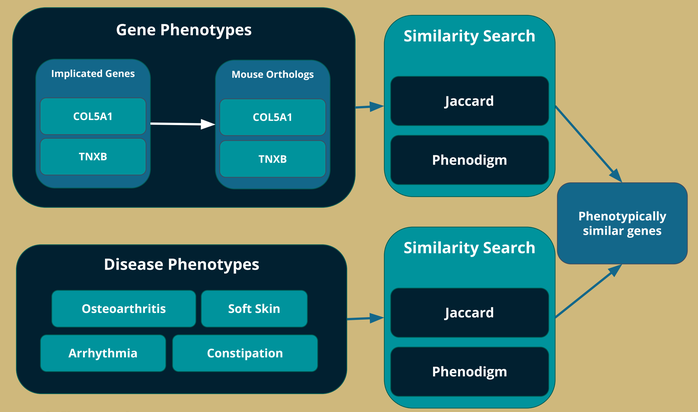
- There are no know underlying genes or mechanisms for **hEDS**
- Diagnosis is difficult: symptoms and associated genes vary

Knowledge Graphs (KGs):

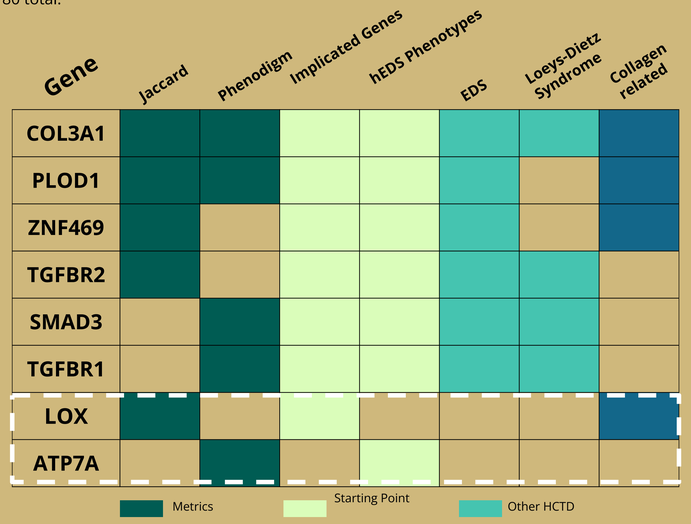
- Combine heterogeneous data to reveal potential relationships of interest
- Incorporate environmental factors to look beyond genetics
- Represent data in a human and computer readable manner, allowing both to ask questions



The Monarch KG connects data types from different sources, representing relationships between phenotypes and genotypes, and between disease and phenotypes as well as orthologous genes across species. A key theme is computable phenotyping and interoperability within and across species to ultimately enable hypotheses and applications.

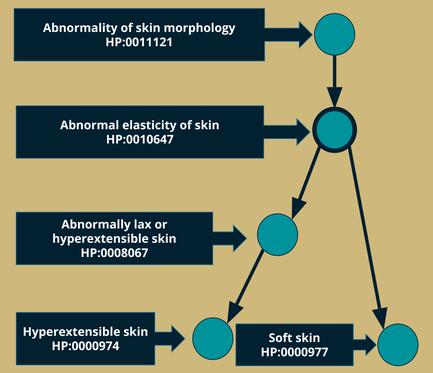


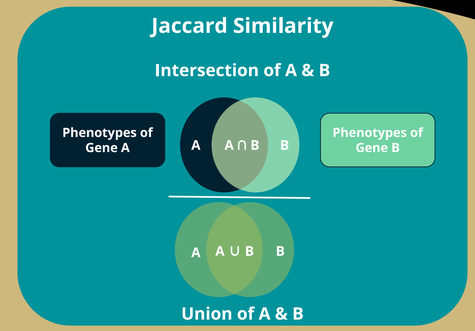
Workflow Diagram from input, disease phenotypes and implicated genes, to output, set of phenotypically similar genes. Phenotypes of genes presumably implicated, i.e., TNXB, MYLK, COL5A1, MYH11, COL12A1, COL1A1, COL1A2, were expanded using mouse orthologs. hEDS-associated genes and phenotypes were used as input to semantic similarity algorithms (Jaccard and Phenodigm). *Semantic similarity* measures the similarity between sets of terms based on their meaning. Twenty (20) genes were selected from each method using each input, 80 total.



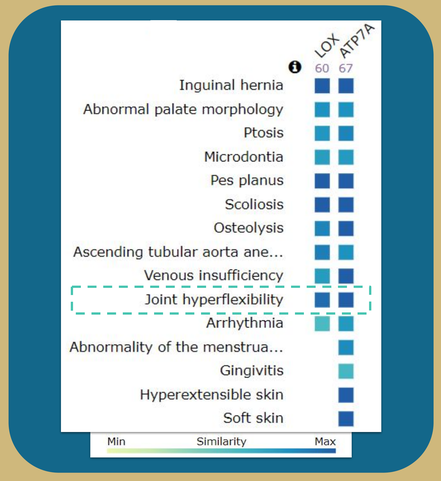
Notable Genes. Columns show how genes were selected, which diseases they are implicated in and if their function is collagen related. Many have been previously implicated in EDS or Loeys-Dietz Syndrome (another heritable connective tissue disorder). LOX and ATP7A (white line), were not implicated in EDS or Loeys- Dietz Syndrome and both have functions involving copper, which is of particular interest.

Phenodigm Similarity measure that looks at phylogenetic relatedness using ontologies and their topology.





hEDS Phenotype Similarity
Comparison of LOX and ATP7A phenotypes and their similarities to hEDS phenotypes. The results generated using the Monarch KG are visualized into a grid (Phenogrid). The number above each column and box colors represent how similar the gene phenotypes are to hEDS. *Joint hyperflexibility* is a symptom commonly seen in hEDS patients, which makes it of great significance to be related to both the LOX and ATP7A genes.



Conclusions & Future Directions

Clinical geneticists have found LOX mutations in hEDS patients. LOX and ATP7A mutations result in many overlapping phenotypes with those known for hEDS, making them good candidates for future study. While copper pathways have been suggested to play a role in hEDS, these genes have not yet been linked.

Ongoing work includes incorporating potential drugs, therapeutics, and patient surveys into the KG, as well as further exploration of other pathways, such as protein interactions. Future methodological work includes machine learning embedding of the graph and edge predictions.

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