Exploring Genetic and Phenotypic Approaches to Aggregating Disease Variants

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Genetic Variants Database

- 80,686 unique human genetic disease variants
- Curated from four different source databases
  - HGMD, OMIM, ClinVar, and UniProt

HGMD®
The Human Gene Mutation Database
Cardiff

OMIM®
Online Mendelian Inheritance in Man®

ClinVar

UniProt

- Largest compilation of human disease variant data

	Gene	Mutation	Disease	Source
Variant 1	ATP7B	p.THR1031ILE	Wilson disease (WD)	UniProt

Normalizing Disease Terminology

- Diseases may have different names in different source databases
- We need to first normalize diseases to concepts from the Unified Medical Language System (UMLS)

	Gene	**Mutation**	**Disease**	**Source**	**UMLS**
Variant 1	ATP7B	p.THR1031ILE	Wilson disease (WD)	UniProt	Hepatolenticular Degeneration
Variant 2	ATP7B	p.GLY1111ALA	Hepatocerebral degeneration	HGMD	Hepatolenticular Degeneration

Overarching Goal: leverage known disease-associated human variants to make new disease connections and better understand underlying molecular links

Methods Outline

1. Normalize variants to UMLS concepts
2. Genotypic aggregation
3. Phenotypic aggregation
4. Network construction

1. Normalize variants to UMLS concepts

- Exact & normalized string matching functions through UMLS Terminology Server (UTS) Application Program Interface (API)
  - **Input:** phenotype string (i.e. "Cystic fibrosis")
  - **Output:** CUI (i.e. C0010674)
- Enhanced normalization of input strings → re-run through UTS API

Normalization Type	Original input	Enhanced input	Normalized output
Splitting terms	3MC syndrome type 2 (3MC2)	3MC2	Carnevale syndrome
Expanding stop words	Adrenal disease, association with	Adrenal disease	Adrenal Gland Diseases
Roman numeral substitution	Distal arthrogryposis type I	Distal arthrogryposis type 1	Arthrogryposis, Distal, Type 1

2. Genotypic aggregation

- Variants were aggregated at the gene level

ATP7B

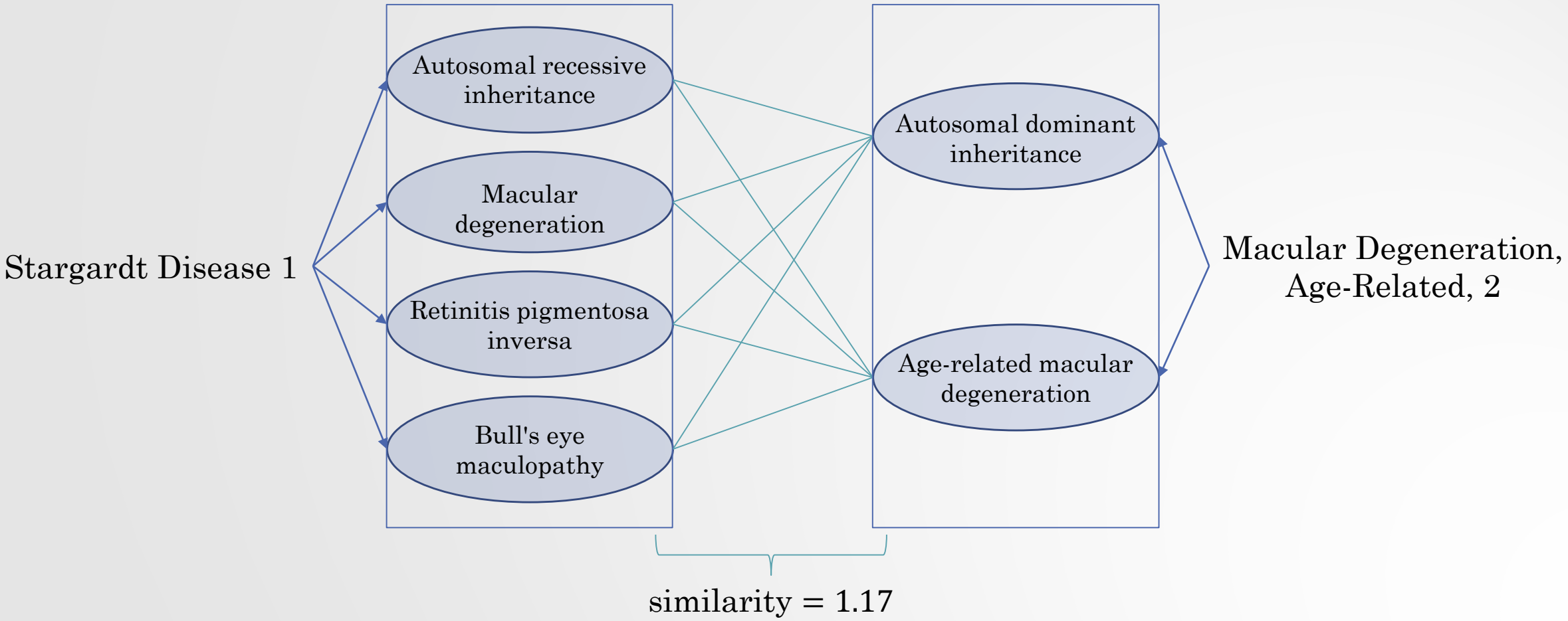
- p.THR1031ILE — Wilson Disease (WD)
- p.GLY1111ALA — Hepatocerebral degeneration
- p.ARG952LYS — Alzheimer disease, association with

3. Phenotypic aggregation

- Semantic similarity for OMIM diseases
  - Each disease associated to Human Phenotype Ontology (HPO) manifestations
  - HPOSim R package used to calculate pairwise similarities between manifestations of two diseases

- Semantic similarity for non-OMIM diseases
  - Leverage terminologies to calculate similarity based on hierarchies

3. Phenotypic aggregation



3. Phenotypic aggregation

- Semantic similarity cutoff: 0.63 (75th percentile)

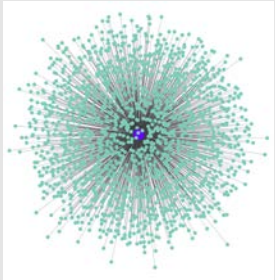
Disease 1	**Disease 2**	**Semantic similarity**
Stargardt Disease 1	Macular Degeneration, Age-Related, 2	1.17
Asperger Syndrome, X-linked, Susceptibility To, 1	Mental Retardation, Autosomal Dominant 6	0.70
Macrocephaly/Autism Syndrome	Retinitis Pigmentosa 18	0

4. Network construction

- A bipartite graph was constructed, linking human genetic variants to diseases
  - Looking for disease hubs, where one disease is linked to many variants

- A disease-disease connection graph was constructed, with links between diseases that have similar manifestations and/or are mapped to the same gene
  - Looking for connections that differ between approaches

A



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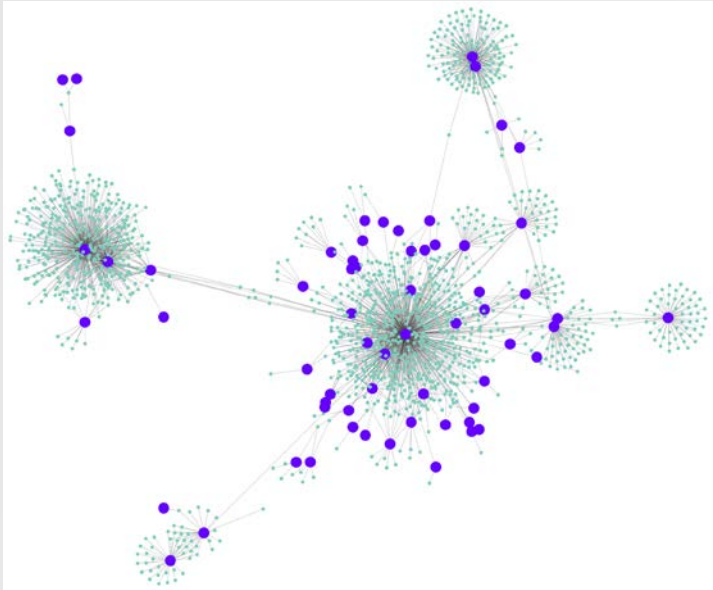

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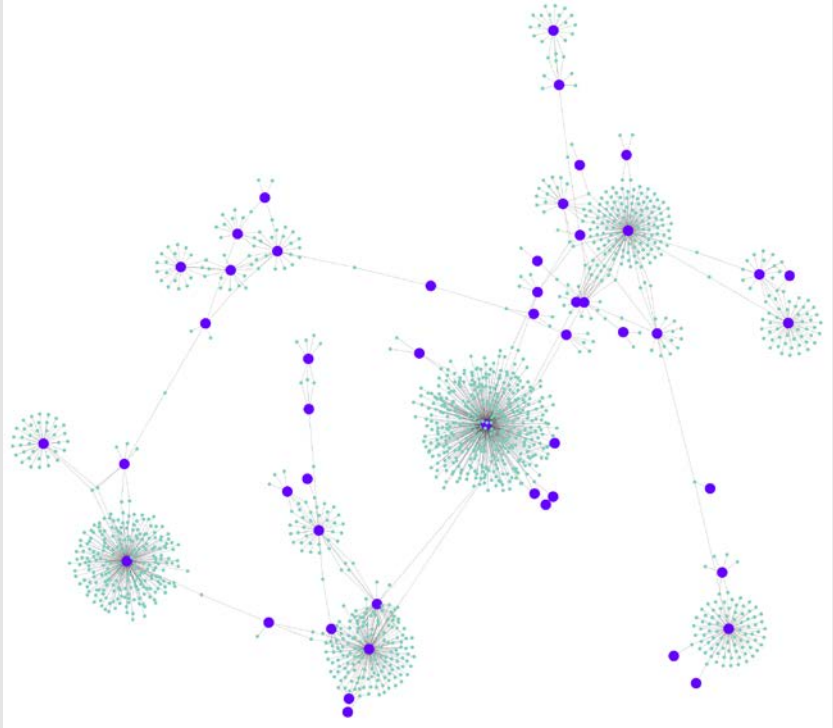
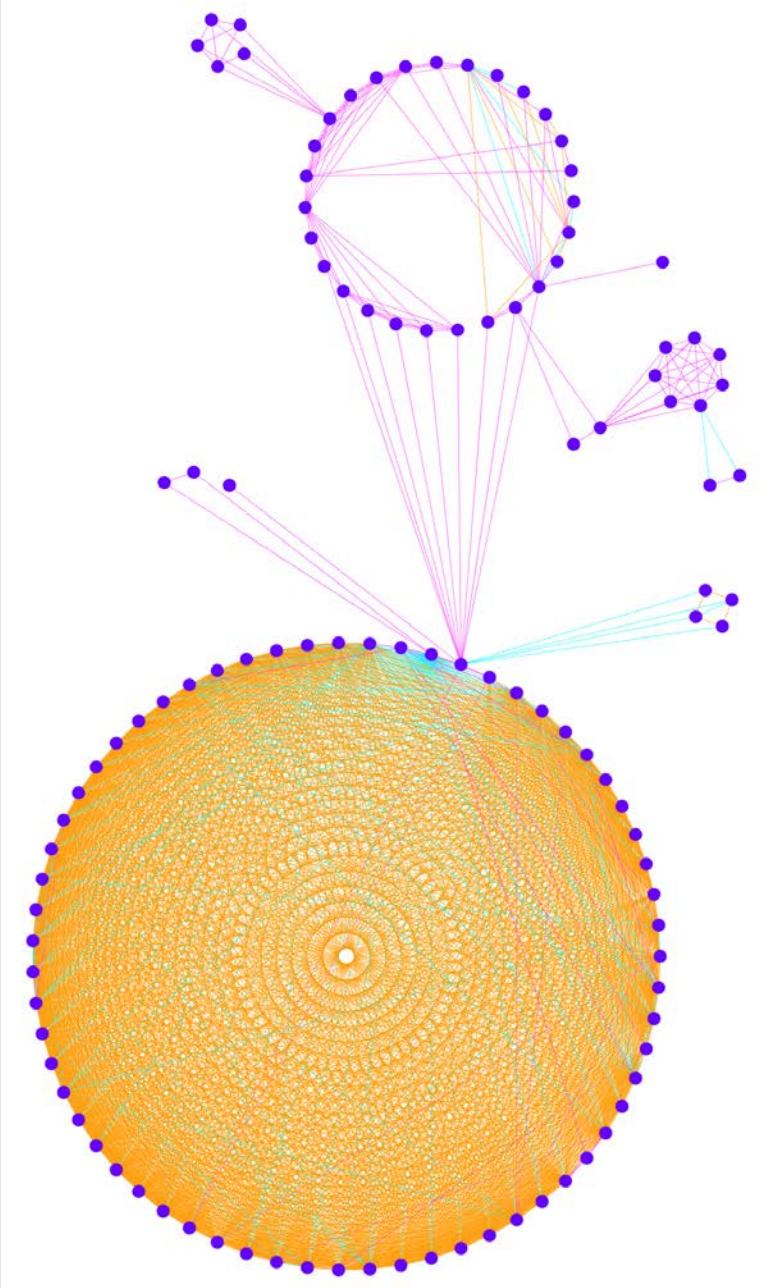


Results: Bipartite graph

- The three largest connected components (A, B, C, in order of size) of the bipartite graph linking diseases (purple) to variants (green)

- **Component A**: Hemophilia A
- **Component B**: consists mainly of eye-related diseases
- **Component C**: contains many congenital/ developmental diseases



Results: Disease-disease graph

- Subset of diseases from top three connected components were linked if they shared the same gene or similar manifestations (similarity >= 0.63)

Edge	Gene	Manifestations
Pink	✓	
Orange		✓
Blue	✓	✓

Results: Disease-association examples

Disease 1	Disease 2	Gene	Manifestations
Retinitis Pigmentosa 64	Cone-rod Dystrophy 16	Yes	No
Mental Retardation, Autosomal Dominant 6	Autism, X-Linked, Susceptibility To, 1 (Finding)	No	Yes
Branched-chain Keto Acid Dehydrogenase Kinase Deficiency	Autistic Disorder	Yes	Yes

Conclusions

- Variants were aggregated by gene, and diseases were aggregated by similar manifestations
- Disease-disease associations through both genotypic and phenotypic approaches were analyzed

- Future Work:
  - Aggregate hierarchical (non-OMIM) diseases
  - Continue exploring ways to aggregate variants genotypically (e.g., protein domain, metabolic pathway)
  - Incorporate drug associations to create a tripartite relationship

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