Integration of proteomic data and clinical annotations reveals ciliopathy mechanisms

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Motivation

Understanding the molecular and cellular mechanisms of diseases is vital for dissecting pathogenesis, identifying appropriate therapeutic targets and designing effective treatments. Recent advances in DNA sequencing technology have provided a torrent of genetic data that can now be used to elucidate the genetic basis of human diseases. A consensus has emerged among biologists that to fully exploit the available data, they have to be correlated with additional type of data. This is especially important for rare-disease genetics, mainly because of the small number of available patients.

Data

Tandem Affinity Purification experiments: 453 experiments using 202 baits.

Proteomic Data

Gene phenotype associations from HPO

DNA Sequencing

Phenotype relations from HPO

Clinical Data

Methodology

Algorithm

Input : Proteomic (TAP) data, Clinical data
(*i.e* set *S* of genes associated with a phenotype)

1 : Create *M* random permutations of TAP data.
2 : Use a scoring system to create weighted graphs from the TAP data (experimental and permuted).
3 : Calculate enrichment scores (*ES*) for the experimental data
4 : Estimate the statistical significance of an observed *ES* by comparing it with a set of enrichment scores ES_{null} computed by the permuted data.
5 : Construct a disease/phenotype network from the known and predicted disease/phenotype associated genes.

Computational Methods

Enrichment score computation

Input : Weighted graph $G=(V,E,w)$, set $S \subseteq V$
1 : for $\boldsymbol{p} \in V$ do
2 : $W = \langle w_{(\boldsymbol{p},p')} : (\boldsymbol{p},p') \in E \rangle$ (decreasing order)
3 : for $i \in \left[1, |W|\right]$ do
4 : $L_i = \left\{ p' \in V : (\boldsymbol{p},p') \in E, w_{(\boldsymbol{p},p')} \geq w_i \right\}$
5 : $F(S,i) = \sum_{p' \in L_i \cap S} \frac{w_{(\boldsymbol{p},p')}}{\sum_{g \in S} w_{(\boldsymbol{p},g)}} - \sum_{p' \in L_i \setminus S} \frac{1}{|L| - |S|}$
7 : end
6 : $ES(G,S,\boldsymbol{p}) = \max\left(\max_i F(S,i), 0\right)$
8 : end

ES Null distribution

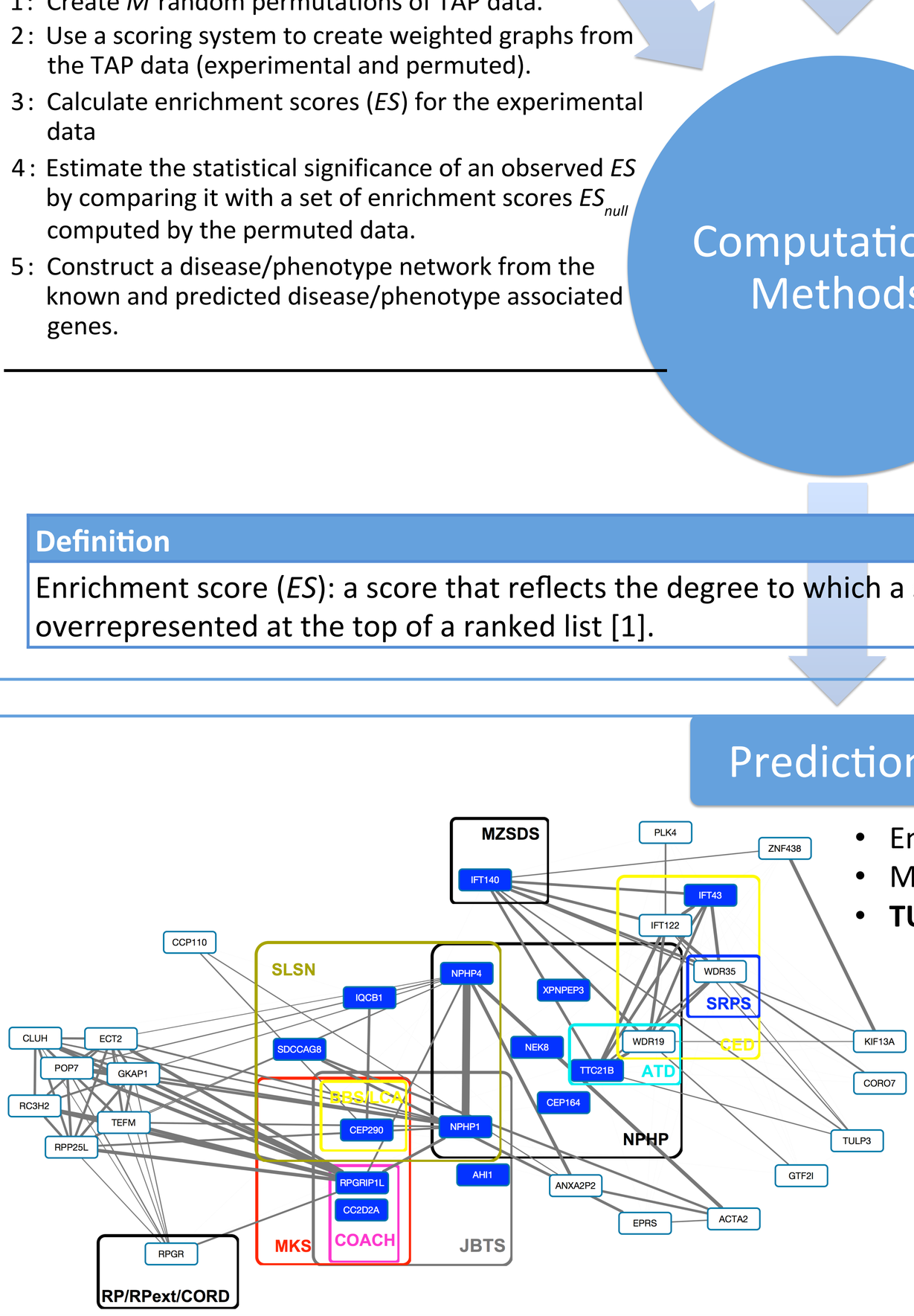
Input : Set of weighted graphs $\boldsymbol{G} = \{G_1,\ldots,G_N\}$ with $G_i = (V,E_i,w_i)$, set $S \subseteq V$
1 : $ES_{null} = \{\ \}$
2 : for $G_i \in \boldsymbol{G}$ do
3 : Compute Enrichment Score
4 : $ES_{null} = ES_{null} \cup \{ES(G_i,S,p)\ \forall\ p \in V\}$
5 : end

Definition

Enrichment score (*ES*): a score that reflects the degree to which a set *S* is overrepresented at the top of a ranked list [1].

Results - Conclusions

Predictions



- End-stage renal failure for a patient with **IFT122** mutation [2]
- Mutations in **WDR19** are associated with NPHP [3]
- **TULP3:**
  - Required for ciliary GPCR localization [4,5].
  - Gpr161 mutations phenocopy Tulp3 and IFT-A mutants, and cause increased Shh signalling [5].
  - Abnormal Hh signaling has been linked to NPHP [6,7]
  - NPHP proteins have been implied to ciliary GPCR localization [8].

➢ **Abnormal Hh signaling may be the cause of NPHP**
➢ **GPCR mislocalization is a possible way by which cilia defects affect Hh signaling.**

References:

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