Investigating the molecular cause of hypermobile Ehlers-Danlos syndrome

MSB 1014 - Network Biology

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1 Introduction

1.1 Background

- Ehlers-Danlos syndromes are a group of heritable connective tissue disorders that can be classified into multiple subtypes
- current classification describes 13 subtypes [1]
- most common form: hypermobile EDS (hEDS) - only subtype with unknown molecular cause
- diagnosis based on clinical presentation
- identify molecular cause for: diagnosis, understanding, potential treatment [2]
- current state: ongoing study with aim to do this by analysing genes of 1000 affected individuals, results not expected before 2025 [3]
- many studies investigated genes but no clear molecular cause with connection to connective tissue established yet [4]
- until then use data known
- problem with existing data: criteria change in 2017, earlier diagnosed people might not classify anymore [5] + there is a unclear overlap with Hypermobility Spectrum Disorder (HSD) and terms often used interchangeable and diagnoses often grouped together (unclear whether there is a difference) [5, 6]
- we know the clinical representation and how other eds types work (kind of)

1.2 Aim

- aim: investigate moleculare cause of hypermobile EDS
- studying differentially expressed genes in hEDS patients
- which biological processes and pathways are affected
- similarities to pathways/processes/function affected by other EDS genes
- TODO: what do we want to do in the big picture: find candidate genes? is this to ambitious?

2 Methods

2.1 Analysis of Differentially Expressed Genes and Network Creation

- data accessible at NCBI GEO database with the accession number GSE218012 [2]
- analysis with DeSeq2 in R based on the analysis exported from GEO2R [7] to identily up-regulated and down-regulated genes
- $|\log2FoldChange| > 0.5$, $pValue < 0.05$, pValue adjusted with Benjamini and Hochberg False Discovery Rate
- query differentially expressed genes from string db [8] (confidence cut off 0.4)
- query eds genes related to other eds types additionally: 21 genes retrieved from Disease Ontology with Disease Ontology ID 13359 [9], queried from string
- load data about differential expression, for EDS genes and differentially expressed genes

2.2 Enrichment analysis and clustering

- exploratory enrichment analysis on whole network
- large network, thus cluster before to get better insights for specific parts
- two different cluster methods used with different resulting cluster structure

2.2.1 MCODE

- MCODE finds "densely connected regions in large protein-protein interaction networks that may represent molecular complexes" [10]
- results in smaller clusters
- suited to analyse molecular function
- do we see clusters with other molecular functions than expected
- are genes clustered together with other eds genes
- are clusters generelly mostly upregulated or downregulated

2.2.2 Community Clustering

- small cluster not helpful for biological processes and pathways
- therefore use second clustering method
- community clustering with GLay, "more suitable for functional interpretation" [11]

3 Results

3.1 Differentially Expressed Genes and Network creation

- 908 differentially expressed genes with chosen thresholds section 2.1
- String was able to query 828 of them [TODO: provide table of not queried in supplementary material or at least github?]
- after querying additional genes that are known to be related to other eds types: resulting network with 847 nodes and 6129 edges

4 Discussion

References

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