Project proposal: Investigating the molecular cause of hypermobile Ehlers-Danlos syndrome

1 Background

Ehlers-Danlos syndrome is a group of heritable connective tissue disorders that can be classified into multiple subtypes. The current classification proposed in 2017 describes 13 subtypes [1]. The most common form is hypermobile EDS (hEDS), the only subtype with unknown molecular cause. A diagnosis is, therefore, only done by clinical presentation. Identifying the molecular cause is necessary to simplify the diagnosis process and understand the pathways affected by the mutations to find potential treatment options [2].

While an ongoing study aims to find the genetic cause of hEDS by analysing the genes of around 1000 affected individuals, results are not expected before 2025 [3]. Until then, it is essential to utilise the already collected data to understand more about hEDS. Performing research based on already collected data is complicated because the diagnosis criteria changed with the new subtype classification in 2017, causing individuals diagnosed with hEDS before this change to not fulfilling the criteria anymore and being diagnosed with Hypermobility Spectrum Disorder (HSD) [4]. However, the clinical representation of those two diagnoses overlaps, and the terms are often used interchangeably. Both diagnoses are also often grouped as hEDS/HSD because it is currently not clear whether they are different to each other or not [5, 4].

Although many studies investigated several genes, no clear molecular cause with a connection to connective tissue has been established yet [6].

2 Aim

This project aims to investigate the molecular cause of hypermobile EDS by studying the influence of differentially expressed genes in hEDS patients. It particularly tries to find which biological processes and corresponding pathways are affected by the found genes. Eventually, the goal is to create a network based on the found genes and to find hubs of relevant genes more likely to be part of the molecular cause of hEDS.

3 Approach

To answer the research question, the following structured approach will be pursued:

Analysis of Differentially Expressed Genes A dataset of gene expression profiles from dermal fibroblasts from patients with hEDS and healthy controls is used. It is available on the Gene Expression Omnibus (GEO) database with the accession number GSE218012 [5]. This data will then be analysed with GEO2R to identify up-regulated and down-regulated genes.

Enrichment and Pathway Analyses To determine biological processes and molecular functions associated with the identified genes, clusterProfiler [7] will be used for further analysis. Pathways related to the differentially expressed genes will be identified as well.

Network creation The differentially expressed genes and further relevant genes identified in the earlier steps will be used to create a network in Cytoscape [8]. This will be done by querying the STRING database [9]. To include knowledge of other EDS subtypes, the related disease network will be included in the query. Depending on the amount of knowledge gained by the Enrichment and Pathway Analyses, additional interactors might be included by extending the network using STRING.

Network propagation Network propagation will be applied to spread the influence of differentially expressed genes. Heat diffusion in Cytoscape offers a simple implementation of network propagation. The goal is to find interactions between and hubs of affected genes, find affected pathways and eventually identify genes that are more likely to cause the clinical representation of hypermobile EDS.

4 Context within the course

Exploring the influence of differentially expressed genes using a network is ultimately related to network biology. The use of a propagation method to find affected belongs to the field of network algorithms, while the creation of the network itself relates to the field of network data.

References

[1] Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, et al. The 2017 international classification of the Ehlers–Danlos syndromes. American Journal of Medical Genetics Part C: Seminars in Medical Genetics. 2017 3;175:8-26.

[2] Ritelli M, Colombi M. Molecular Genetics and Pathogenesis of Ehlers-Danlos Syndrome and Related Connective Tissue Disorders. Genes. 2020 5;11.

[3] HEDGE (Hypermobile Ehlers-Danlos Genetic Evaluation) Study - The Ehlers Danlos Society;. Available from: `https://www.ehlers-danlos.com/hedge/`.

[4] Gensemer C, Burks R, Kautz S, Judge DP, Lavallee M, Norris RA. Hypermobile Ehlers-Danlos syndromes: Complex phenotypes, challenging diagnoses, and poorly understood causes. Developmental dynamics : an official publication of the American Association of Anatomists. 2021 3;250:318.

[5] Ritelli M, Chiarelli N, Cinquina V, Zoppi N, Bertini V, Venturini M, et al. RNA-Seq of Dermal Fibroblasts from Patients with Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders Supports Their Categorization as a Single Entity with Involvement of Extracellular Matrix Degrading and Proinflammatory Pathomechanisms. Cells. 2022 12;11.

[6] Caliogna L, Guerrieri V, Annunziata S, Bina V, Brancato AM, Castelli A, et al. Biomarkers for Ehlers-Danlos Syndromes: There Is a Role? International Journal of Molecular Sciences 2021, Vol 22, Page 10149. 2021 9;22:10149.

[7] Wu T, Hu E, Xu S, Chen M, Guo P, Dai Z, et al. clusterProfiler 4.0: A universal enrichment tool for interpreting omics data. Innovation. 2021 8;2.

[8] Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome research. 2003 11;13:2498-504.

[9] Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic acids research. 2023 1;51:D638-46.