Maastricht University

Faculty of Health, Medicine and Life Sciences

EUROPEAN JOINT PROGRAMME RARE DISEASES

BiGCaT bioinformatics

Identifying Genetic Interactions Between Pathways
- A 22q11.2 Deletion Syndrome Study -

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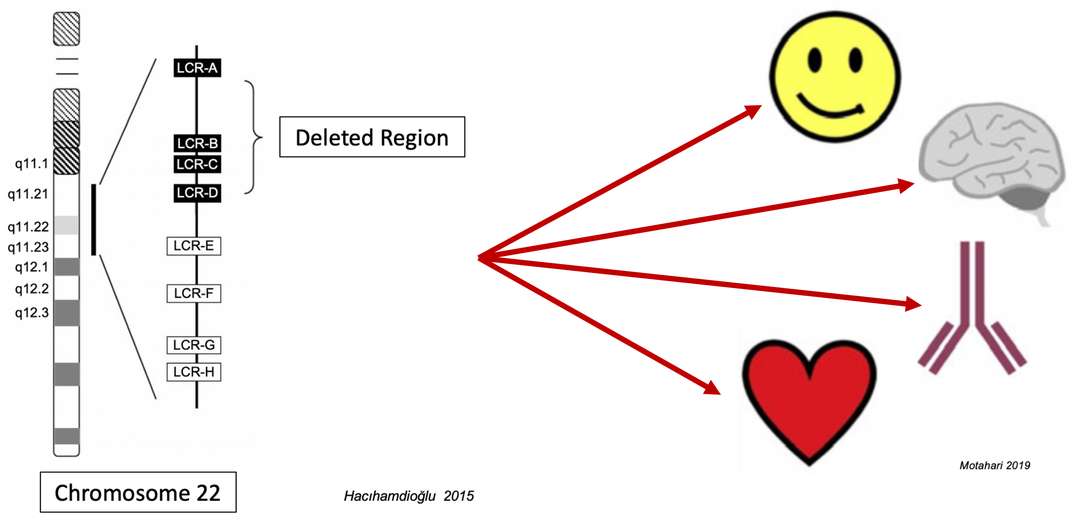
Background

22q11.2 Deletion Syndrome (**22q11DS**), also known as DiGeorge or Velocardiofacial Syndrome, is a rare genetic disorder caused by a deletion of multiple genes within the q11.2 region from one copy of chromosome 22. Researchers have identified various clinical characteristics associated with 22q11DS, including craniofacial anomalies, neuropsychiatric disorders, immunodeficiency, and heart defects. Despite our increased knowledge about this disease at the clinical level, its underlying biology, mainly the complex interaction mechanisms between the deleted genes and each of the varying phenotypes, have not yet been fully understood.



Data & Methods

We collected data from:

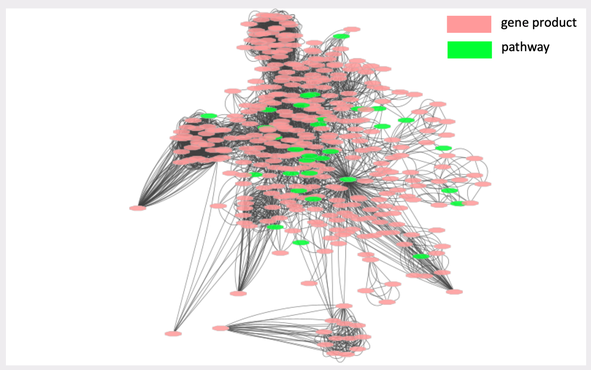
1. Gene-pathway network derived from WikiPathways repository
2. Protein-protein interaction from STRING
3. Microarray gene expression data (Jalbrzikowski et al. [2015])

First, a gene-pathway network was created and extended by the protein-protein interactions from the STRING database. The edges of the network were weighted by the transformed T-statistic, using the microarray gene expression data.

STRING Database (protein-protein interaction)

Wikipathways (gene-pathway network)

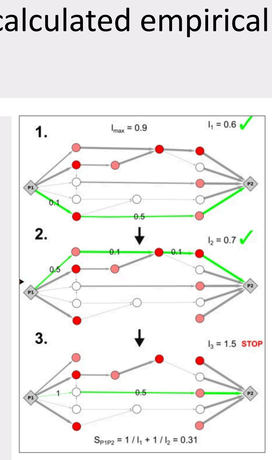
Whole-blood microarray (22q11DS patients & controls)



Next, we applied the pathway interaction method, proposed by Kelder et al. (2011), which identifies the network paths between the 22q11.2 Deletion Syndrome pathway (WP4657) and other pathways. A path between a pair of pathways is 'accepted' if the weighted length sum is less than 0.9. Once all paths between each pathway pair were collected, we generated 1,000 same-sized random gene-sets and calculated empirical p-values.

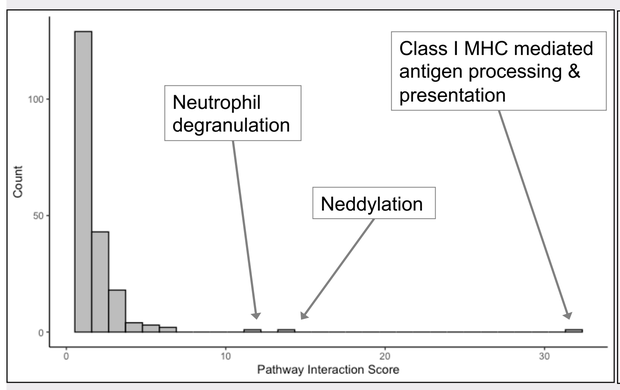
Workflow for Finding Pathway Interactions (Kelder 2011)

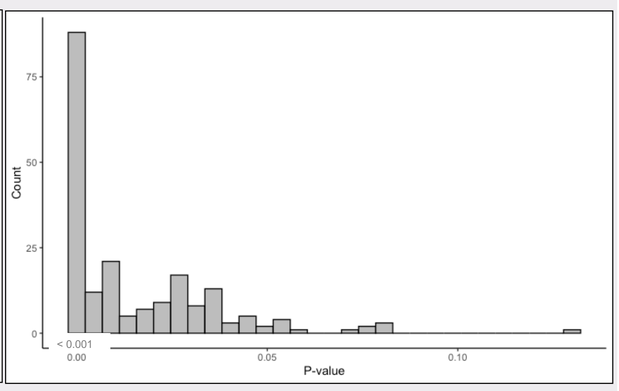
1. Find the weighted shortest path between the 22q11.2 Deletion Syndrome pathway and another candidate pathway
2. If the sum of weighted length is less than the given threshold (0.9), remove the edges and find the next shortest path
3. Stop if the weighted length sum exceeds the threshold



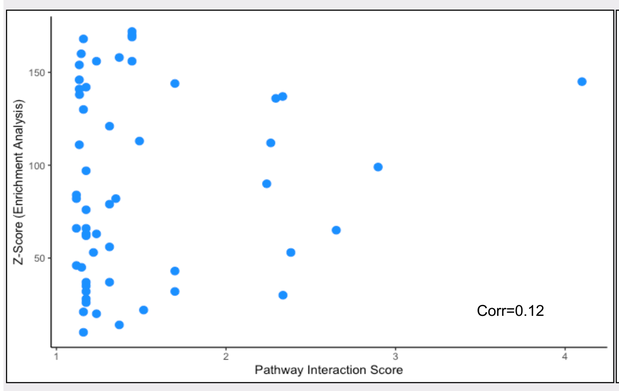
Results

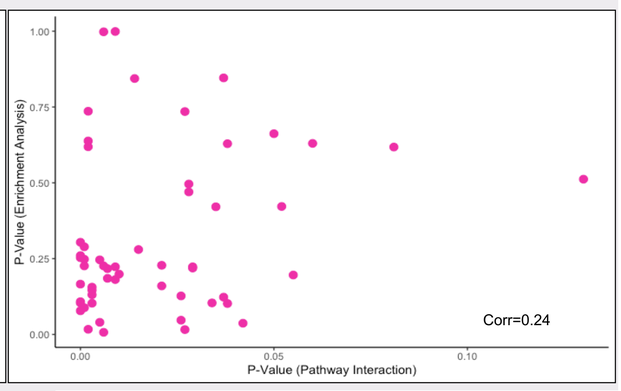
Out of total 1,066 candidate pathways, our initial analysis identified 202 pathways contained at least one prominent path to the 22q11.2 pathway. The score ranged from 1.118 to 31.897. For the collected pathways, empirical p-value ranged from <0.001 to 0.13.





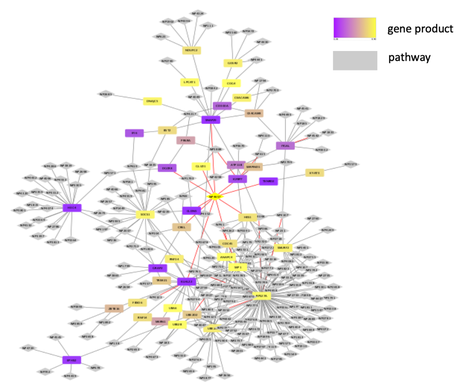
Initial comparison between pathway interaction and pathway enrichment scores did not associate well with each other. This might indicate the pathway interaction method can reveal additional information that a simple enrichment analysis cannot.





Finally, we created a network of the accepted paths between WP4657 and 202 candidate pathways and visualized the results.

The current networks is comprised of 203 pathways and 44 genes, centred around the WP4657 node. Most genes closer to WP4657 tend to have higher weights, and we could identify several clusters around certain genes.



Conclusion & Discussion

- The pathway interaction method collectively treats significantly differentially expressed genes and constructs plausible molecular paths from one group to another, revealing information not readily visible by gene enrichment analyses
- We are trying to give convincing biological explanations regarding the molecular mechanisms between the gene deletion and the respective disease phenotypes and generalize our findings with additional datasets.
- Our increased understanding of the molecular mechanisms of 22q11DS will help us develop better screening techniques and improved treatment schemes for the disease, for example, by identifying biomarkers that can be used as effective drug targets.

Acknowledgements

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References

1. Jalbrzikowski, M et al. Transcriptome Profiling of Peripheral Blood in 22q11.2 Deletion Syndrome Reveals Functional Pathways Related to Psychosis and Autism Spectrum Disorder. PLoS ONE 10(7): e0132542 (2015)
2. Kelder, T. et al. Exploring pathway interactions in insulin resistant mouse liver. BMC Syst Biol 5, 127 (2011)
3. Morrow. B et al. "Molecular genetics of 22q11.2 deletion syndrome." American journal of medical genetics. Part A vol. 176,10 : 2070-2081. (2018)