

MAPPING DISEASE PATHWAYS IN INTERSTITIAL LUNG DISEASE DUE TO ABCA3 DEFICIENCY

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01 Introduction

Interstitial lung disease (ILD) due to ABCA3 deficiency is a rare genetic respiratory disease caused by a variety of mutations on the ABCA3 gene. ABCA3 encodes for an ATP-binding cassette transporter that facilitates the translocation of phospholipids into lamellar bodies and further the pulmonary surfactant metabolism (1, 2). The clinical outcomes of the disease vary from fatal respiratory distress syndrome in the neonatal phase to chronic ILD developing during infancy or childhood with impaired breathing and recurrent pulmonary infections. Although, some patients have shown improvements in respiratory functions after prednisolone, azithromycin or hydroxychloroquine treatement (3-5), there are currently no guidelines for therapeutic care of ILD patients with ABCA3 deficiency and lung transplantation may be the only curative procedure available (6). To find optimal treatment, which may vary greatly between genotypic/phenotypic subgroups, remains a challenge.

Using Mavatar Discovery, which enables disease modeling at the systems level through analysis of thousands of transcriptomics datasets, we aimed to identify context-specific gene networks for ILD due to ABCA3 deficiency (4).

02 Challenge

Current case-reports find variable treatment response in ILD patients with different ABCA3 variants. To connect the genotypic/phenotypic patient groups with alternative treatment plans remains a challenge. This is further complicated by the low number of cases and quick disease progression.

03 Solution

We used Mavatar Discovery comprehensive lung disease data resource, to create a gene co-expression network around ABCA3. This resource was built from a diverse set of lung conditions, including chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and cystic fibrosis. Network was constructed using the following parameters: search gene: ABCA3, tissue: Lung, context: General v.1.0, distance = 3, neighbors = 4, and gene type filter: protein coding genes. Further investigation of the network identifies pathways, known drug targets, and closely

ILD-associated disease functions, which can help researchers identify alternative therapeutic strategies and potential marker genes for phenotypic association.

04 Results

The network constructed around ABCA3 gene showed enrichment of biological processes such as respiratory gaseous exchange by respiratory system (including SFTPB, SFTPD, SFTPA2, and SFTPA1) and surfactant homeostasis (including SFTPD, NAPSA, LPCAT1, and ABCA3). In addition to ABCA3, several of these genes (SFTPB, SFTPA2, and SFTPA1) have also been associated with rare diseases causing respiratory distress. Moreover, SFTPB, SFTPD, SFTPA2, SFTPA1, and ABCA3 are further known common sites for mutations in patients with congenital surfactants deficiency.

By querying a network on all genes mentioned above, with parameters; distance = 3, neighbors = 3 (**Fig1.**), the graph was explored for potential drug target and biomarker identification. Seven known drug targets were identified, six of which have been previously used or tested for variable forms of lung cancer and respiratory diseases.

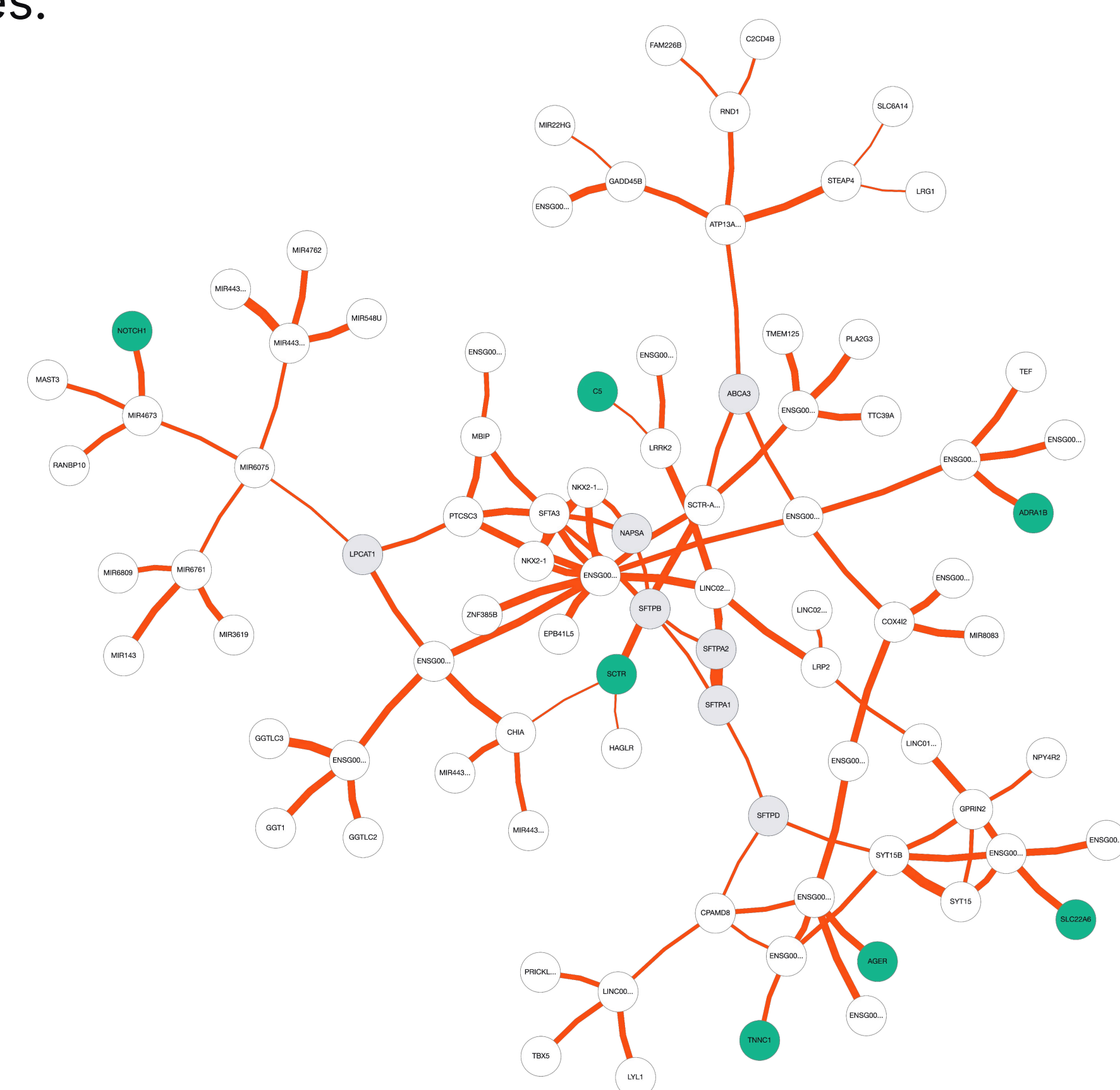


Figure 1. Lung General (v.1.0) gene co-expression network created with Mavatar Discovery 1.6.1 around selected genes. Nodes represent genes, edges represent co-expression. Green nodes show known drug targets

05 Conclusion

Our system-level approach successfully identified gene networks associated with relevant biological functions across respiratory diseases, including interstitial lung disease (ILD). The flexible adjustment of input parameters allows analyses to be focused narrowly on genes in close proximity to selected targets or expanded to provide a broader network-level perspective. In this study, this flexibility enabled the identification of drug targets previously indicated for lung diseases that, based on their proximity to ILD-related mechanisms and relevance to other pulmonary conditions, may represent putative drug-repurposing candidates for ILD.

OUR FINDINGS HIGHLIGHT

- These results demonstrate the potential of Mavatar Discovery as a powerful tool for uncovering complex functional mechanisms of understudied and rare diseases.
- Our system-level approach identified gene networks linked to key biological mechanisms across respiratory diseases, including ILD.
- These findings highlight Mavatar Discovery's potential to uncover repurposing opportunities and mechanistic insights in rare and understudied diseases.

06 References

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