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IN-SILICO ANALYSIS OF PULMONARY ARTERIAL HYPERTENSION (PAH) DISEASE-ASSOCIATED GENES USING WEB-BASED BIOINFORMATICS TOOLS

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Abstract:

Pulmonary arterial hypertension (PAH) is a chronic progressive vasculopathy associated with increased pulmonary vascular resistance and vessel lumen narrowing resulting in pathological remodeling, right-sided heart failure, and lesions resembling those seen in atherosclerosis. Existing treatments focus on vasoconstriction but do not address the structural remodeling; therefore, new mechanism-based interventions are critically necessary. In the present work, an integrative bioinformatics analysis was performed to provide insights into the molecular mechanisms of PAH. A complete list of 30 PAH-related genes was compiled from the DisGeNET database and analyzed for GO, KEGG, Reactome, and STRING. Major enriched biological processes were positive regulation of BMP signaling, SMAD phosphorylation, and cartilage/heart development; whereas significant molecular functions included TGF-β/BMP receptor activity and SMAD binding. Pathway analysis also suggested the involvement of fluid shear stress pathways associated with atherosclerosis. Module analysis revealed a central "Signaling by BMP" cluster, and topological analysis identified SMAD4 and BMPR2 to be key hubs of the network. These results further support the importance of impaired BMP signaling in PAH etiology and indicate receptor complexes and SMAD-dependent transcription as top biological targets for therapeutic intervention. This work illustrates the power of integrated bioinformatics in unravelling complex disease mechanisms and expediting the development of targeted therapies.

Keywords: *Pulmonary Arterial Hypertension, Bioinformatics, BMP/TGF-β Signaling, SMAD Proteins, Network Pharmacology, Drug Target Discovery.*

Introduction

Pulmonary arterial hypertension (PAH) is a devastating pulmonary vascular disease characterized by a mean pulmonary arterial pressure (mPAP) ≥20 mmHg at rest, pathological vascular remodeling, rise in pulmonary vascular resistance, and progressive right ventricular (RV) failure (1). Despite the advancement in comprehension of the pathophysiological mechanisms underlying the PAH condition, no curing method has been discovered to date. The five-year survival rate with current combination therapy is roughly 60%. Endothelin receptor antagonists such as bosentan and macitentan, phosphodiesterase-5 inhibitors such as sildenafil and tadalafil, soluble guanylate cyclase stimulators (riociguat), and prostacyclin analogs are FDA-approved for PAH treatment and mainly act in a vasodilating manner; however, they do not effectively prevent occlusion of pulmonary vessels and plexiform lesion formation (2). Therefore, finding the molecular mechanisms driving PAH vascular pathology is essential for targeted therapeutic interventions. Bioinformatics has become an essential tool in biomedical research for deciphering the mechanisms underlying human disease through the integration of multi-omics data (3). Bioinformatics has provided an avenue for conducting functional enrichment analysis, establishing protein-protein interaction networks, and building pathway maps to find dysregulated processes as well as druggable targets.

Methodology

The study was aimed to study the genes involved in pulmonary arterial hypertension though bioinformatics analysis. Even though BMP and TGF-β are the known key regulators of PAH, other potential therapeutic targets was discovered using the methodology that included: (i) identifying the core PAH genes from the DisGeNET database; (ii) conducting functional enrichment analysis (FEA) of the core PAH genes in multiple databases; (iii) constructing and visualising the protein-protein interaction networks between core PAH genes; and (iv) integrating the results of these analyses to develop a comprehensive biological model of PAH.

Bioinformatics pipeline and rationale for database selection:

Bioinformatics uses a combination of techniques to analyse data on genes, their genetic makeup, and the associated diseases using several databases, each one selected according to the type of analysis being performed, with the intent to develop a comprehensive pipeline to follow the entire methodology from the identification of gene-disease associations, all the way to the elucidation of mechanistic pathways. DisGeNET was chosen as the primary database for evidence-based curation of genes due to its extensive collection of known gene-disease associations from curated sources. STRING was selected for the analysis of PPI networks because it encompasses both experimentally derived and predicted interactions, as well as associations from numerous organisms. GeneMANIA was selected to develop functional networks because it identifies the relationships between genes based on many types of genomic data. NetworkAnalyst was chosen as the primary analysis platform for conducting topological analysis and multi-omics enrichment analysis because it provides a user-friendly interface, options, and sophisticated statistical and visualization tools for the user. Reactome was selected to create a conduit from the pathway analysis to the mechanistic map of the biological process, while the remaining databases were used to supplement this effort in providing a complete understanding of the mechanisms of PAH pathophysiology across all levels of available analyses.

Gene curation and dataset preparation

A high-confidence set of genes associated with PAH was curated from DisGeNET (v7.0) is a knowledge platform integrating gene-disease associations from curated repositories, GWAS catalogues, and animal models (4). For this search, the UMLS CUIs associated with the Disease "Pulmonary Arterial Hypertension (PAH)" were used as keywords, and then a filter was applied to include only genes with proven evidence scores greater than 0.1. The final gene set created is as follows: *BMPR2, GDF2, KCNK3, SOX17, TBX4, ENG, ACVRL1, CAV1, ABCC8, NOTCH3, BMP10, SMAD1, ATP13A3, SMAD4, EIF2AK4, BMPR1A, SMAD9, BMPR1B, KCNA5, NOTCH1, KDR, AQP1, TET2, KLF2, PDGFD, GGCX, FBLN2, AHR, TOPBP1, and KLK1.*

Protein-Protein Interaction (PPI) network and cluster analysis

Gene/protein interaction networks were created for the selected 30 genes (PAH) using the STRING (STRING - Search Tool for Retrieval of Interacting Gene/Proteins) database. The STRING database integrates current experimental, curated, predicted, co-expressed, and text-mining data. The 30 PAH associated genes were used as input into STRING using Homo sapiens as a reference species, and using the high confidence interaction score cut-off to include, to the maximum extent possible, statistically relevant Molecular interactions. The analysis looked at the interactions and connections between direct (physical) and indirect (functional) connectivities. The map showed high levels of interaction among those components involved in the BMP/TGF-beta signalling pathway and SMAD proteins.

Functional association and gene prediction using GeneMANIA

The GeneMANIA website is a sophisticated resource for predicting the function of genes and determining the functional relationships between genes using various data sources, including co-expression, interaction, genetic interaction, and other methods. entered a list of PAH-associated genes into GeneMANIA with the default weighting parameters. By doing this, GeneMANIA produced an expanded functional association network by adding more genes that are also functionally related to the original gene list. The many similarities seen in the functional associations, such as angiogenesis, endothelial cell differentiation, vascular development, and signal transduction.

Network topology and hub gene identification using NetworkAnalyst

NetworkAnalyst is a web application that helps you analyse complex networks to help visualise and analyse the topology of your network. The main purpose is to use network centrality to help you identify the main regulatory nodes (hubs). The protein interaction (PPI) network generated in STRING was uploaded to NetworkAnalyst for further analysis, where the topological parameters degree centrality and betweenness centrality were computed, finding the gene's connectivity, and their regulatory impact on the network. Five hub genes, which are influential in connecting with many other genes, include BMPR2, SMAD4, ENG, ACVRL1, and KDR. The sub-networks provide a more concentrated view of the highly interconnected modules within the network.

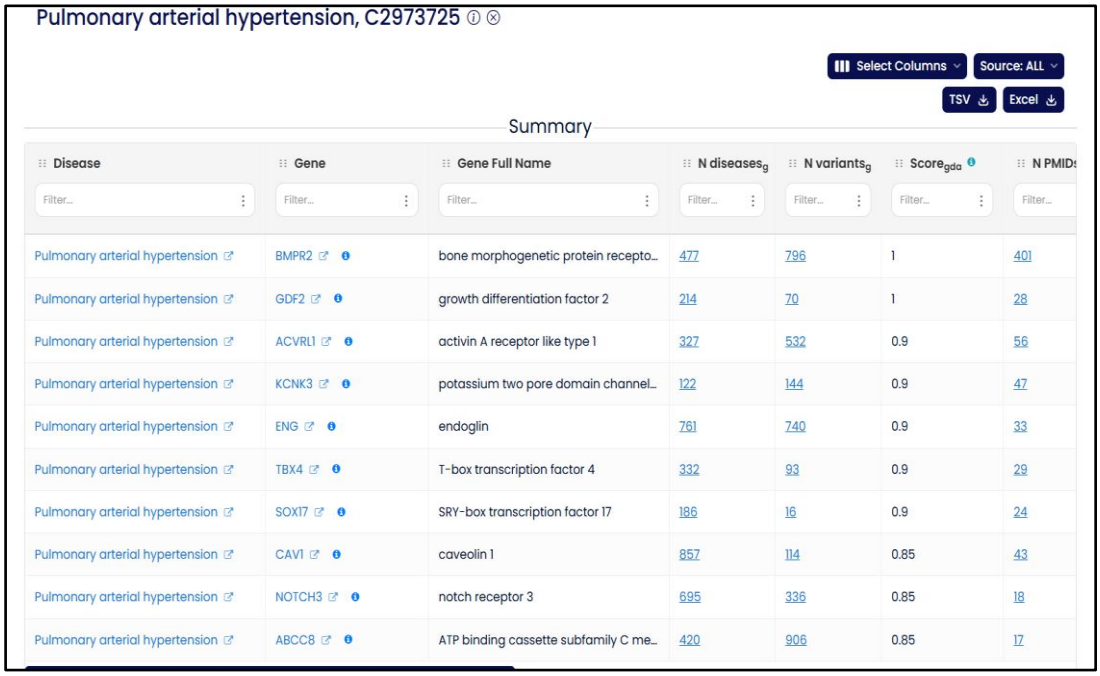
Pathway enrichment analysis using Reactome

To obtain a more thorough understanding of the underlying mechanism(s) through which the 30 seed genes influence disease, Reactome pathway analysis was performed. It was identified that Reactome pathways were significantly overrepresented (FDR < 0.05) based on this data set, relative to the rest of the Homo sapiens genome, and illustrated the pathways of the top-enriched Reactome Pathways in the Reactome Pathway Browser. In addition, each gene's role within the pathway (e.g., ligand, receptor, transducer) in event-based descriptions of the Reactome Pathways was displayed (5).

Results

Core gene set associated with PAH

30 high-confidence PAH-related genes were identified from the DisGeNET query (Piñero et 2020).



Pulmonary arterial hypertension, C2973725

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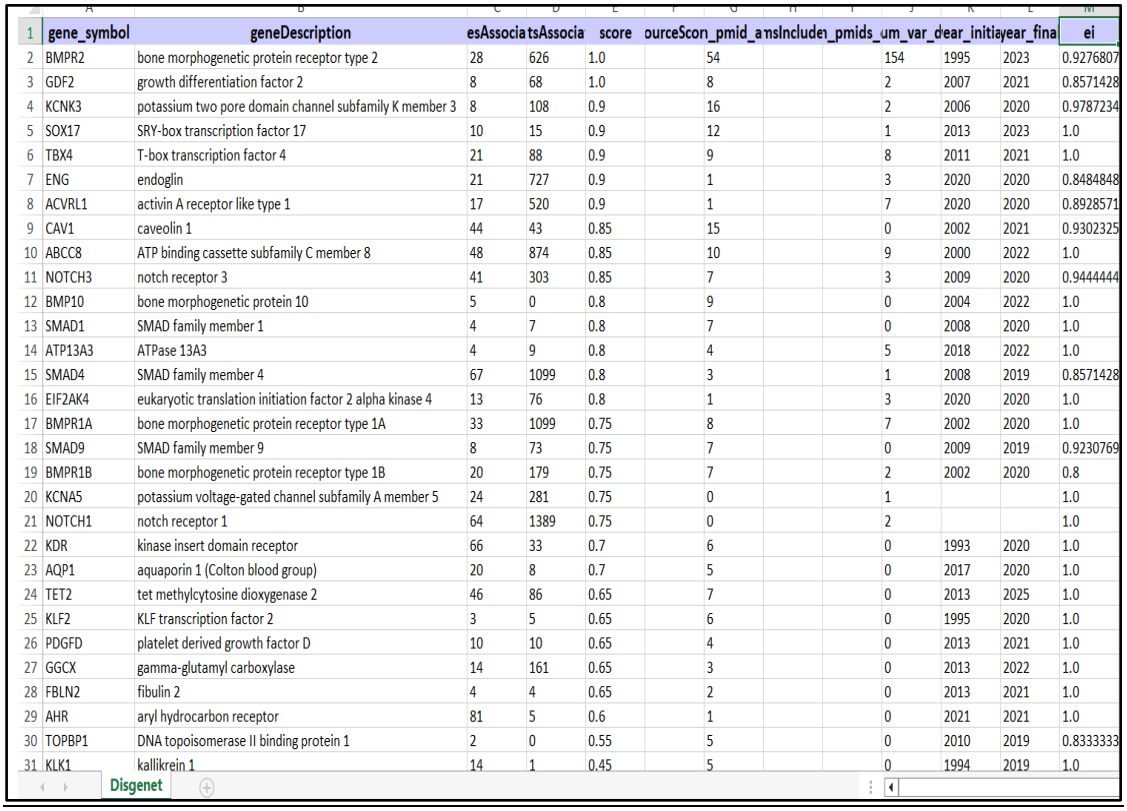
Summary

Disease	Gene	Gene Full Name	N diseases$_g$	N variants$_g$	Score$_{gda}$	N PMIDs
Pulmonary arterial hypertension	BMPR2	bone morphogenetic protein recepto...	477	796	1	401
Pulmonary arterial hypertension	GDF2	growth differentiation factor 2	214	70	1	28
Pulmonary arterial hypertension	ACVRL1	activin A receptor like type 1	327	532	0.9	56
Pulmonary arterial hypertension	KCNK3	potassium two pore domain channel...	122	144	0.9	47
Pulmonary arterial hypertension	ENG	endoglin	761	740	0.9	33
Pulmonary arterial hypertension	TBX4	T-box transcription factor 4	332	93	0.9	29
Pulmonary arterial hypertension	SOX17	SRY-box transcription factor 17	186	16	0.9	24
Pulmonary arterial hypertension	CAV1	caveolin 1	857	114	0.85	43
Pulmonary arterial hypertension	NOTCH3	notch receptor 3	695	336	0.85	18
Pulmonary arterial hypertension	ABCC8	ATP binding cassette subfamily C me...	420	906	0.85	17

Figure 1: IMG: Gene Curation from DisGeNET



	A	B	C	D	E	F	G	H	I	J	K	L	M
1	gene_symbol	geneDescription	esAssocia	tsAssocia	score	ourceScor	n_pmid_a	nsIncluder	_pmids_	um_var_d	ear_initia	year_fina	ei
2	BMPR2	bone morphogenetic protein receptor type 2	28	626	1.0		54			154	1995	2023	0.9276807
3	GDF2	growth differentiation factor 2	8	68	1.0		8			2	2007	2021	0.8571428
4	KCNK3	potassium two pore domain channel subfamily K member 3	8	108	0.9		16			2	2006	2020	0.9787234
5	SOX17	SRY-box transcription factor 17	10	15	0.9		12			1	2013	2023	1.0
6	TBX4	T-box transcription factor 4	21	88	0.9		9			8	2011	2021	1.0
7	ENG	endoglin	21	727	0.9		1			3	2020	2020	0.8484848
8	ACVRL1	activin A receptor like type 1	17	520	0.9		1			7	2020	2020	0.8928571
9	CAV1	caveolin 1	44	43	0.85		15			0	2002	2021	0.9302325
10	ABCC8	ATP binding cassette subfamily C member 8	48	874	0.85		10			9	2000	2022	1.0
11	NOTCH3	notch receptor 3	41	303	0.85		7			3	2009	2020	0.9444444
12	BMP10	bone morphogenetic protein 10	5	0	0.8		9			0	2004	2022	1.0
13	SMAD1	SMAD family member 1	4	7	0.8		7			0	2008	2020	1.0
14	ATP13A3	ATPase 13A3	4	9	0.8		4			5	2018	2022	1.0
15	SMAD4	SMAD family member 4	67	1099	0.8		3			1	2008	2019	0.8571428
16	EIF2AK4	eukaryotic translation initiation factor 2 alpha kinase 4	13	76	0.8		1			3	2020	2020	1.0
17	BMPR1A	bone morphogenetic protein receptor type 1A	33	1099	0.75		8			7	2002	2020	1.0
18	SMAD9	SMAD family member 9	8	73	0.75		7			0	2009	2019	0.9230769
19	BMPR1B	bone morphogenetic protein receptor type 1B	20	179	0.75		7			2	2002	2020	0.8
20	KCNA5	potassium voltage-gated channel subfamily A member 5	24	281	0.75		0			1			1.0
21	NOTCH1	notch receptor 1	64	1389	0.75		0			2			1.0
22	KDR	kinase insert domain receptor	66	33	0.7		6			0	1993	2020	1.0
23	AQP1	aquaporin 1 (Colton blood group)	20	8	0.7		5			0	2017	2020	1.0
24	TET2	tet methylcytosine dioxygenase 2	46	86	0.65		7			0	2013	2025	1.0
25	KLF2	KLF transcription factor 2	3	5	0.65		6			0	1995	2020	1.0
26	PDGFD	platelet derived growth factor D	10	10	0.65		4			0	2013	2021	1.0
27	GGCX	gamma-glutamyl carboxylase	14	161	0.65		3			0	2013	2022	1.0
28	FBLN2	fibulin 2	4	4	0.65		2			0	2013	2021	1.0
29	AHR	aryl hydrocarbon receptor	81	5	0.6		1			0	2021	2021	1.0
30	TOPBP1	DNA topoisomerase II binding protein 1	2	0	0.55		5			0	2010	2019	0.8333333
31	KLK1	kallikrein 1	14	1	0.45		5			0	1994	2019	1.0

Disgenet

Figure 2: LIST OF 30 GENES

Using STRING analysis with this seed set of 30 high-confidence PAH-related genes produced a statistically significant PPI network (PPI enrichment p-value < 1.0e-16) consisting of 28 nodes and 78 predicted high-confidence edges (interaction score ≥0.700) (6). MCL clustering of this gene set produced three discrete clusters of genes that contain functions related to PAH pathogenesis. Cluster 1, which was the largest and most interrelated cluster, was the BMP/SMAD signaling cluster consisting of 10 genes: BMPR2, ACVRL1, ENG, GDF2, BMP10, BMPR1A, BMPR1B, SMAD1, SMAD4, and SMAD9. Cluster 2 consisted of genes that regulate vascular tone (KCNK3, KCNA5, KDR, and CAV1). Cluster 3 contained genes that act as transcriptional regulators (SOX17, TBX4, NOTCH1, NOTCH3, and TET2).

Analysis of gene enrichment reveals dominance of BMP and TGF beta signaling pathways

In Multiomics enrichment analysis performed using the NetworkAnalyst tool (7) the results for GO Biological Process were significant (FDR= 2.14e-14), with "BMP Signaling Pathway" (GO: 0030509) having the highest enrichment score. The most enriched Molecular function was "Transforming Growth Factor Beta Receptor Activity" (GO: 0005024), followed by SMAD Binding (GO: 0046332). From KEGG analysis, the TGF-Beta Signaling Pathway (hsa 04350) was the most enriched (FDR=3.89e-08), and from WikiPathways (WP1425; FDR= 1.05e-09), the Bone Morphogenetic Protein (BMP) Signaling and Regulation (8).

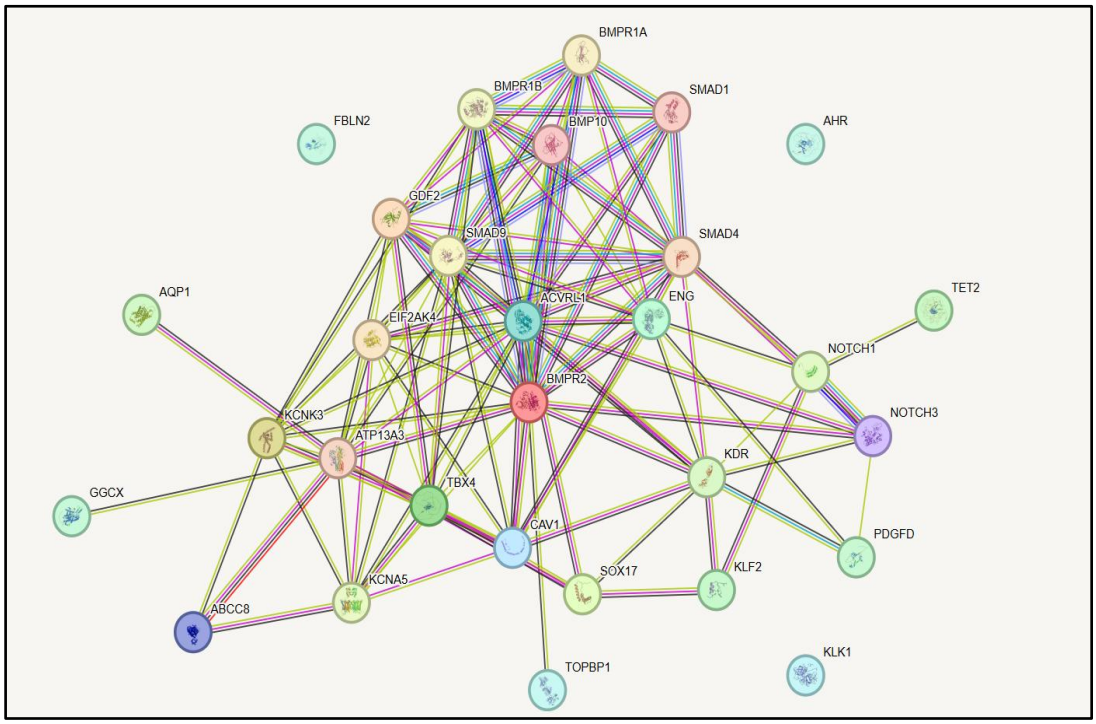


Figure 3: STRING-generated PPI network image

Table 1: Summary of significantly enriched GO terms and signaling pathways identified from network-based functional analysis of pulmonary arterial hypertension–associated genes

Theme	Representative GO terms / Pathways
BMP / TGF-β Signaling Pathway	BMP signaling pathway (GO:0030509), TGF-β signaling pathway (KEGG hsa04350), Signaling by BMP (Reactome HSA-201451), Transforming growth factor beta receptor activity
SMAD-mediated Signal Transduction	SMAD binding (GO:0046332), Pathway-restricted SMAD protein phosphorylation, Heteromeric SMAD protein complex, I-SMAD binding
Growth Factor Receptor & Kinase Activity	BMP receptor activity, TGF-β receptor activity type I, Transmembrane receptor protein serine/threonine kinase activity, Activin receptor domains
Developmental Differentiation & Cell Fate	Bone morphogenetic protein signaling and regulation, Osteoblast differentiation, Cartilage development, Heart development

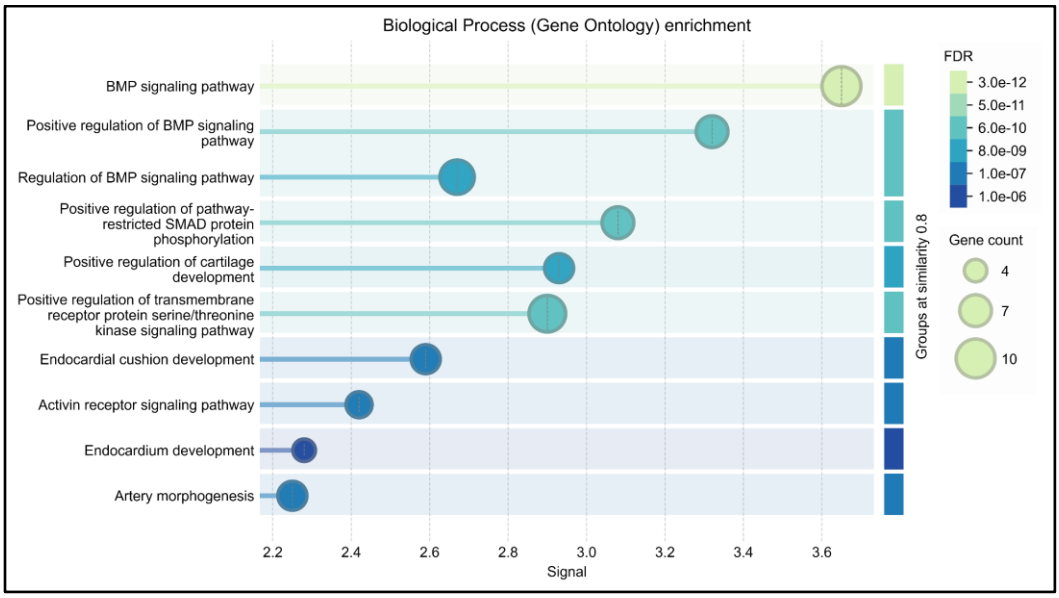


Figure 4: Enriched Gene Ontology biological processes associated with BMP/TGF-β signaling and vascular development in pulmonary arterial hypertension

Functional network expansion and hub gene identification

GeneMANIA was used to expand the Network by incorporating twenty functionally related Genes (ex, *SMAD5, ID1, TGFBR2, BMP6*) with a co-expression rate of forty-five percent (45%) and pathway sharing rate of thirty percent (30%) as the major association types (9). The Topological analysis of the thirty-two Gene Network by NetworkAnalyst showed that twelve of these Genes were Hub Genes (high betweenness centrality). The Top Five Hub Genes were SMAD4 (betweenness centrality: 0.312), BMPR2 (0.287), ACVRL1 (0.265), ENG (0.241), and TGFBR2 (0.228).

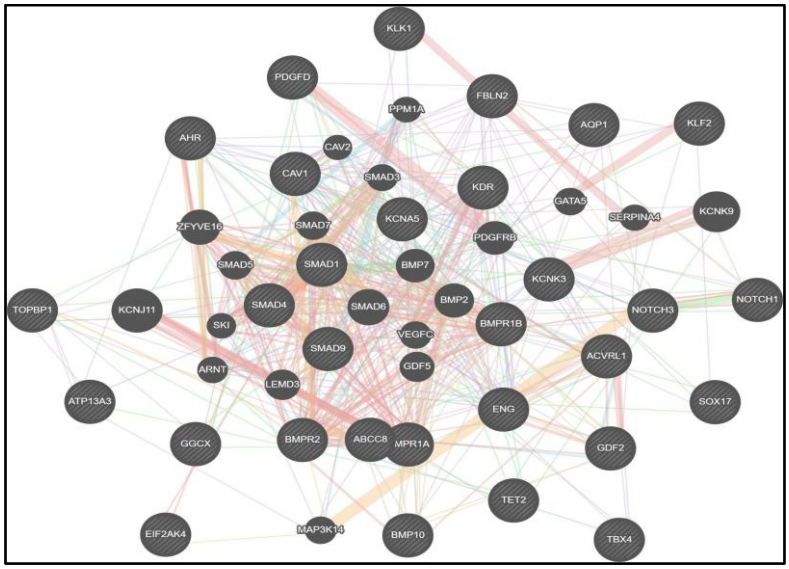


Figure 5: GeneMANIA functional association network visualization

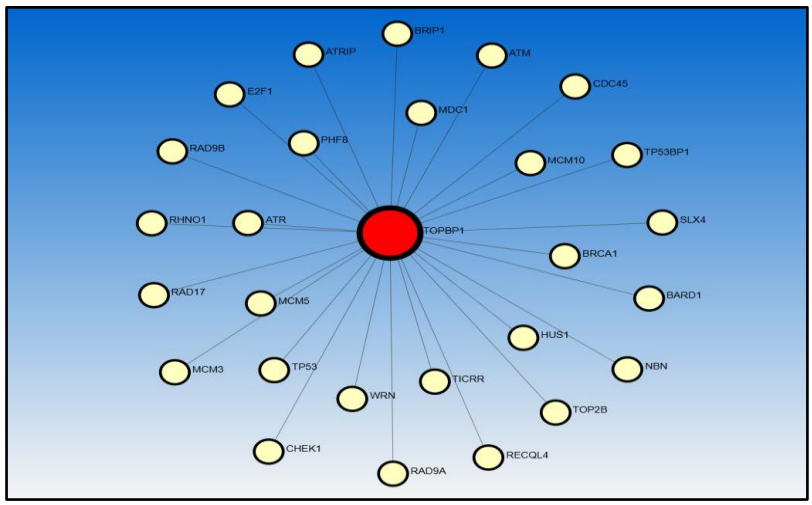


Figure 6: NetworkAnalyst hub gene and subnetwork visualization

Mechanistic pathway dissection with reactome

The seed gene overrepresentation analysis using Reactome has provided additional validation of the overarching theme of "Signaling by BMP," which had both a large false-discovery rate of 2.41e-15 and a considerable strength of 2.34, as it contains 9 out of the 13 seed Genes (5). Utilizing the Reactome Browser to search through the 9 seed gene table, it was determined that *BMPR2* and *ACVRL1* are receptors, *SMAD1* and *SMAD9* are considered R-SMADs, *SMAD4* is a co-SMAD and *GDF2* and *BMP10* are ligands. In addition to this finding, the second most significantly enriched pathway was "Pre-Notch Processing in the Endoplasmic Reticulum" (R-HSA-1912399; FDR=0.0284). This pathway involves NOTCH1, NOTCH3 and ENG.

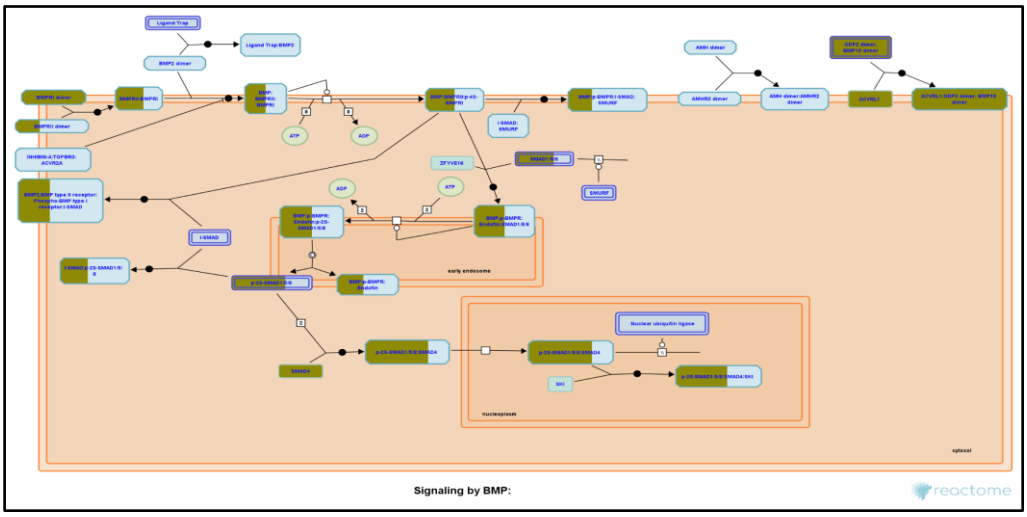


Figure 7: Mechanistic mapping of PAH genes within the Reactome "Signaling by BMP" pathway, integrated with PPI data

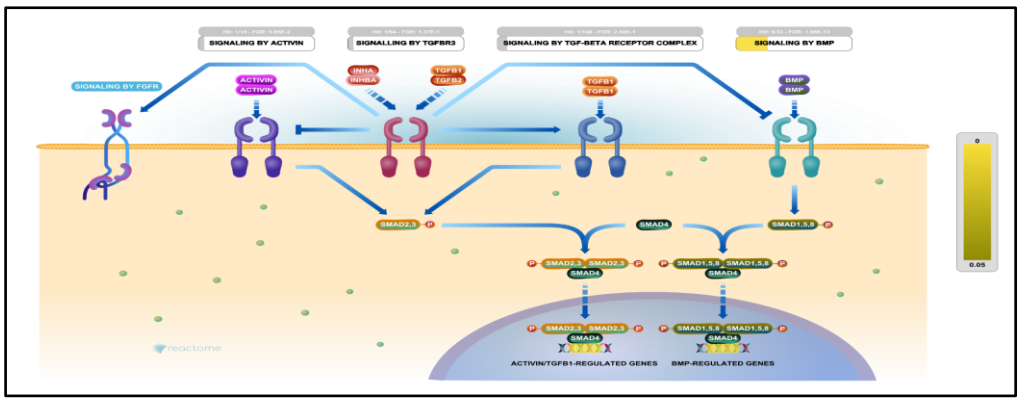


Figure 8: Signaling by TGFB family members. Signaling by TGF-β family members illustrating ligand–receptor interactions, SMAD activation, and downstream transcriptional regulation involved in vascular remodeling and pulmonary arterial hypertension

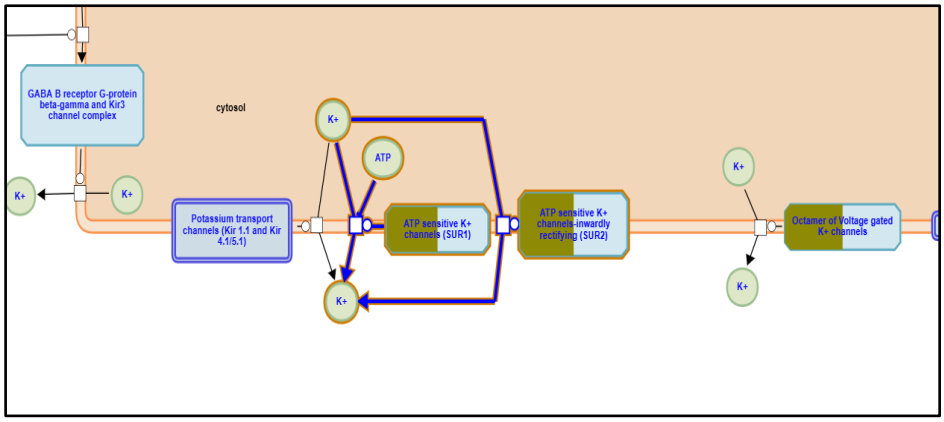


Figure 9: ATP-sensitive potassium (KATP) channel signaling showing the regulation of membrane potential by ATP/ADP levels and its role in pulmonary vascular tone and smooth muscle cell function

Synthesis: An integrated multi-layer molecular model of PAH

The overall synthesis of all the individual analytical components produces one comprehensive model of how PAH is caused. Most importantly, at the center of this model is a fault in BMP/SMAD signaling as described in STRING Cluster 1 and Reactome's "Signaling by BMP" pathway. As seen in the topological view, this is a network governed by a number of key hub genes where SMAD4 and BMPR2 serve as the major bottlenecks. In terms of function, the network's function as defined by enrichment analysis indicates that the BMP/TGF-β signal transduction mechanism is the biological system being disrupted. In terms of the specific mechanisms involved, they are easily defined, and an example is the process of receptor complex formation and, to our surprise, the co-processing of components of the Notch signalling pathway within the endoplasmic reticulum.

Thus, this integrated model moves beyond simply listing genes to create a deeper understanding of the whole system by identifying not only the broken pathways, but also the specific molecules within each of those pathways that have the greatest degree of topological vulnerability and where the individual biochemical steps are most likely to be faulty. Therefore, this refined model can be used as a direct blueprint for the development of therapeutic agents by highlighting hub proteins and convergent mechanisms as the primary targets for pharmacological interventions.

Discussions

The findings from multiple sources confirm the central role of BMP/TGF-β signaling in the pathogenesis of PAH, while also revealing novel features and shared mechanisms within this signaling network. The strong statistical strength of enrichment signals observed in independent datasets supports prioritizing the BMP/TGF-b signalling axis for therapeutic targeting in PAH. Our findings also overlap significantly with previously established studies on the genetic basis of PAH that identified mutations (i.e., BMPR2, ACVRL1, ENG) as primary causes of hereditary PAH (10). The joint enrichment and central placement of SMAD proteins (1/4/9) provide additional computational evidence for the phenotype resulting from BMPR2 haploinsufficiency, where diminished levels of SMAD1/5/9 signal to activate pro-proliferative TGF-β/SMAD2/3 signalling. This study also represents an important advance in the identification of SMAD4 as the top hub gene according to betweenness centrality analysis applied to the topology of SMAD protein interactions. Although BMPR2 mutations account for a significant portion of the genetics of PAH (11), the SMAD proteins serve as a common mediator for nuclear translocation of the BMP- and TGF-β-activated R-SMADs. Thus, SMAD4 will act as an important point of convergence and represent a potential rate limiting step for the signalling pathways involved in BMP and TGF-β signalling.

The central role of SMAD4 within the TGF-beta pathway makes it clear that modulation of either SMAD4 itself or its interactions with other proteins could rebalance all of the altered output of TGF-beta signalling resulting from PAH. Whilst this is a compelling but complex target for therapeutics. It was also found that multiple levels of dysregulation were identified through our analysis of the pathways involved, showing additional pathogenic relevance. In particular, there is a high degree of enrichment for fluid shear stress and atherosclerosis from KEGG pathways, indicating a computational relationship between genetic susceptibility and hemodynamic overload through the identification of flow-dependent genes such as KLF2 and ENG, both known to mediate the defective mechanotransduction seen with PAH (12). Another strong signal has emerged for Pre-NOTCH Processing in the Endoplasmic Reticulum, suggesting the convergence of pathogenic mechanisms during biosynthesis and trafficking of receptors. ENDOG serves as a structural and functional point of contact between TGF-β/BMP

signalling and NOTCH signalling in this process. As such, this supports an accurate biochemical hypothesis of impaired BMP-NOTCH signalling once again in the pathology of PAH, as reported by (13). The study identified and analyzed the molecular mechanisms leading to the development of pulmonary arterial hypertension. The scope of the study can be improved by overcoming the limitations and focusing on the future research prospects of drug docking and drug delivery.

Therapeutic implications and future directions

On the translational level, this analysis supports the shift from targeting individual mutated genes towards modulating the druggable network modules of the target. Notably, the enriched terms associated with this analysis, 'BMP receptor activity' and 'Heteromeric SMAD protein complex', reflect old, valid lines of investigation for the development of additional targets for the treatment of pulmonary arterial hypertension (PAH). In conjunction with that strategy, three strategies have emerged from our computational approaches to find therapeutic avenues to target these pathways:

- BMP Pathway Potentiation through the use of ligand traps such as BMP9/10 and/or using receptor stabilizers (14), such as FK506 that have previously demonstrated BMP Type II Receptor (BMPR2) activation potential;
- SMAD Modulation by selectively enhancing SMAD1/5/9, and/or inhibiting SMAD2/3
- Targeting Convergent Nodes like the shared Endoplasmic Reticulum (ER) processing machinery. The identified hub genes, particularly SMAD4, are high-value targets necessitating the development of sophisticated intervention strategies, such as protein-protein interaction inhibitors.

Additionally, numerous approaches exist to restore BMPR2 function, as extensive research has demonstrated a significant correlation between BMPR2 mutations and patient survival in pulmonary arterial hypertension (PAH) (15). In addition, the combined utilization of this newly developed network model with existing drug-target databases will allow for the development of in silico drug repurposing screening approaches, as demonstrated in recent bioinformatics studies.

Contemporary genomic studies in comparison

The support for our conclusions comes from the results obtained using data from recent genomic studies that were larger in size than our own experiments. Results from the identification of *BMPR2, ACVRL1, and SMAD4* (the three main components of our network) matched the findings of previous genome-wide association (GWA) studies and meta-analyses conducted at the international level, which found these genes to be significant contributors to PAH risk (16). Additionally, the description of mutations in GDF2 (Glycoprotein Growth Factor 2) and modified levels of BMP9/BMP10 in PAH patients provides a biological source of evidence for many of the ligand/receptor disruptions identified through our Reactome analyses (17). The use of a network-based strategy to combine the various genetic studies will add context for how disparate mutations ultimately lead to a dysfunctional common pathway in individuals with PAH.

Limitations and implications

As bioinformatics is a developing field, the findings of this work are subject to limitations arising from the areas under investigation. For example, the study is based on existing knowledge captured in publicly available databases. Many potential new genes or interactions that do not currently exist may affect PAH development, but the study could not account for them. Functional predictions were made based on correlation but need validation

with mechanistic wet-lab studies. While the identified "topological hubs" identify important genes, the actual role of these genes in PAH development will need to be assessed through functional studies in relevant cell cultures and animal models of PAH. Furthermore, this study did not consider transcriptome or proteomic data from individual subjects. Inflammation and immunity play roles in PAH development (18). Since the gene responsible for this information was not curated, it may be a limitation of the process or indicate a need to use an integrated multi-omic approach. Future research should include gene expression data from patients with pulmonary arterial hypertension (PAH), and provide further insight into dynamically regulated nodes within the overall static interaction field.

Conclusion

The current study employed a multi-step bioinformatics process to evaluate the complex molecular architecture of PAH. A refined model of PAH pathogenesis was developed through the use of gene curation using evidence-based data as well as protein-protein interaction networks, topological analysis, and mapping of mechanistic pathways. The analysis supports the centrality of the *BMP/TGF-β/SMAD signaling pathway,* while providing new information on its interaction with the Notch pathway during receptor processing and identifying *SMAD4* as a critical hub for signaling regulation. These results extend beyond simply providing a list of genes associated with PAH and provide insight into the dysregulated pathway and most vulnerable parts, and biochemical lesions associated with PAH. Importantly, this study illustrates the value of integrating bioinformatics to generate hypotheses and how this approach can change from a static to a dynamic approach to examining genetic information, revealing networks that describe the biological basis of disease and potential therapeutic targets. The identified hub genes and converging pathways provide a prioritized list of high-value candidate genes for future therapeutic development. Ultimately, this detailed new map of vascular remodeling in PAH guides the new generation of therapy development; that is, targeted, disease-modifying therapies that will treat the underlying cause of PAH, rather than just treating its symptoms, thereby making the next generation of therapy more effective than current treatment options (19).

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