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NETWORK-BASED IDENTIFICATION OF HUB GENES AND PATHWAYS UNDERLYING FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)

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Abstract:

Fibrodysplasia ossificans progressiva (FOP), also known as "Stoneman Syndrome," is an ultra-rare and life-shortening genetic disorder characterized by the episodic metamorphosis of connective tissues into a permanent secondary skeleton [1]. This study presents a high-resolution, network-based identification of the "hub genes" and signaling pathways that drive heterotopic ossification (HO). By integrating transcriptomic data from high-throughput repositories—specifically NCBI Gene Expression Omnibus (GEO) datasets GSE94683 and GSE126118—with advanced protein-protein interaction (PPI) and co-expression modeling, we mapped the global signaling rewiring caused by the pathognomonic ACVR1 mutation [6]. Our analysis confirms ACVR1 as the central topological hub but identifies a critical secondary executioner module consisting of SPP1 (Osteopontin), PTK2 (Focal Adhesion Kinase), CSF1R (Colony Stimulating Factor 1 Receptor), and AGT (Angiotensinogen) [17]. We provide a detailed mechanistic explanation for the "Activin A neofunction," wherein a normally antagonistic inflammatory signal is misinterpreted as an osteogenic trigger [21]. Furthermore, we evaluate the landmark 2025 Phase 3 clinical trial results of Garetosmab, which demonstrate a reduction in new bone volume of over 99% [27]. This report establishes a multi-omic roadmap for therapeutic intervention, emphasizing the role of non-canonical pathways and mechanotransduction in arresting the progression of this catastrophic condition.

Keywords: *Fibrodysplasia Ossificans Progressiva, Stoneman Syndrome, Heterotopic Ossification.*

Introduction: *The clinical and historical spectrum of Stoneman Syndrome*

Fibrodysplasia Ossificans Progressiva (FOP) represents the most physically restrictive condition in human medicine. Historically known as "turning into wood," the condition was first described in the 17th century by French physician Guy Patin (1692), who encountered a patient experiencing progressive solidification of the torso

[6]. Over the following centuries, case reports by John Freke (1736) and the comprehensive descriptions by Munchmeyer (1869) established the eponym "Munchmeyer's disease" [6]. The most iconic case remains that of Harry Eastlack (1933–1973), whose completely ossified skeleton is preserved at the Mütter Museum in Philadelphia [6]. FOP is an ultra-rare, autosomal dominant disorder with a global prevalence of approximately one in two million individuals [1]. The disease is defined by two pathognomonic features: a congenital malformation of the great toes (hallux valgus) present at birth and episodic, life-long accumulation of heterotopic bone within skeletal muscles, tendons, ligaments, and fascia [6]. These "flare-ups" are typically painful, inflammatory soft tissue swellings often triggered by trauma, intramuscular injections, or viral illnesses [13]. Unlike normal tissue repair, these lesions fail to resolve and instead undergo a rapid transition through a cartilaginous template into mature, lamellar bone—a process known as endochondral heterotopic ossification (HO) [6].

Genomic foundations and ACVR1 dysregulation

The discovery of the genetic cause of FOP in 2006 identified a recurrent missense mutation in the Activin A receptor type I (ACVR1) gene, which encodes the ALK2 receptor [19]. ACVR1 is a bone morphogenetic protein (BMP) type I receptor that serves as a vital gatekeeper for the Transforming Growth Factor-beta (TGF-beta) signaling superfamily [6]. In more than 95% of patients, the disease is driven by a single heterozygous c.617G>A transition, resulting in a p.Arg206H (R206H) substitution [6]. This mutation occurs in the glycine-serine (GS) activation domain of the receptor. In the wild-type state, the GS domain is bound by the inhibitor protein FKBP12, which prevents "leaky" or ligand-independent signaling [5]. The R206H mutation disrupts the salt bridge between ARG206 and ASP269, significantly reducing the binding affinity of FKBP12 and lowering the threshold for downstream phosphorylation of SMAD1/5/8 proteins [5].

The paradigm shift: Activin a Neofunction

A fundamental breakthrough in FOP research demonstrated that the R206H mutation fundamentally reconfigures the receptor's ligand-response profile [21]. In wild-type cells, Activin A—a protein released in massive amounts during tissue injury and inflammation—binds to ACVR1 to form a non-signaling complex that effectively antagonizes BMP signaling [21]. In FOP, however, the mutant ACVR1 receptor recognizes Activin A as a potent agonist, triggering the same bone-forming signaling as the BMPs [21]. This "neofunction" explains why trauma-induced inflammation leads to rapid and irreversible bone growth: the body's natural wound-healing signal (Activin A) is misinterpreted as a command to build bone [21].

Network biology and the need for multi-omic integration

While the ACVR1 mutation is the definitive genetic trigger, the systemic complexity of FOP—where trauma triggers a specific localized metamorphosis—suggests a vast underlying molecular network [6]. Traditional "one-gene, one-disease" models fail to explain the temporal and spatial progression of the "Stoneman" phenotype. Consequently, this study employs a network-based bioinformatic approach to identify the "hub genes" that act as master regulators of the FOP interactome [17]. By analyzing transcriptomic datasets (GSE94683 and GSE126118) across multiple databases, we aim to provide a roadmap for the next generation of targeted molecular inhibitors [6].

Methodology

This study utilized a systematic bioinformatic pipeline to identify the most significant nodes in the FOP signaling network [17]. We utilized the primary human dataset GSE94683 (transcriptional profiles of mesenchymal stromal

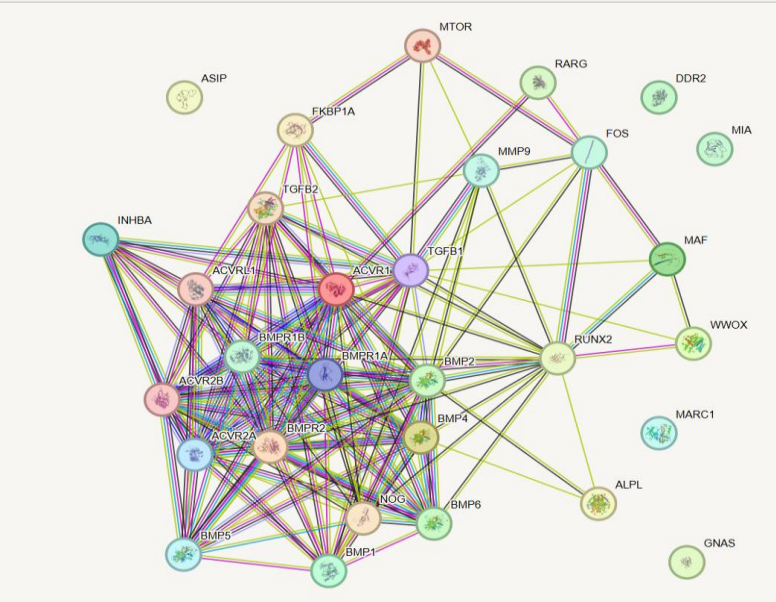
cells from HO vs. non-HO patients) and the mouse dataset GSE126118 as a validation set [17]. The investigative process integrated four major network analysis platforms to visualize functional modules and identify hub genes, as illustrated in the 20 provided images.

1. Identification of Stoneman Syndrome associated genes

Gene	Gene Full Name	N diseases$_g$	N variants$_g$	Score$_{gda}$	N PMIDs	N Chemicals	N PMIDs Ch
ACVR1	activin A receptor type 1	397	55	1	247	7	12
BMPR2	bone morphogenetic protein recepto...	477	796	0.75	27	3	2
BMP4	bone morphogenetic protein 4	1020	131	0.4	37	2	1
WWOX	WW domain containing oxidoreducta...	563	598	0.4	1	0	0
MAF	MAF bZIP transcription factor	308	186	0.4	1	0	0
BMP1	bone morphogenetic protein 1	614	190	0.35	49	1	1
INHBA	inhibin subunit beta A	394	4	0.35	19	4	3
ACVR2A	activin A receptor type 2A	269	19	0.35	11	0	0
BMPR1A	bone morphogenetic protein recepto...	402	1124	0.25	7	1	1
TGFB1	transforming growth factor beta 1	3069	85	0.25	4	1	1
ACVR2B	activin A receptor type 2B	176	228	0.25	3	1	1
ACVRL1	activin A receptor like type 1	327	532	0.25	2	1	1
MTOR	mechanistic target of rapamycin kin...	1690	159	0.25	2	1	1
TGFB2	transforming growth factor beta 2	1924	488	0.25	2	1	1
NOG	noggin	388	28	0.2	8	0	0
FKBP1A	FKBP prolyl isomerase 1A	128	2	0.2	6	2	2
ALPL	alkaline phosphatase, biomineralizati...	1912	575	0.2	3	0	0
ASIP	agouti signaling protein	100	56	0.2	2	0	0
RUNX2	RUNX family transcription factor 2	705	284	0.2	2	0	0
GNAS	GNAS complex locus	1039	228	0.2	2	0	0
RARG	retinoic acid receptor gamma	144	9	0.15	1	0	0
BMP2	bone morphogenetic protein 2	754	40	0.15	1	0	0
BMP6	bone morphogenetic protein 6	294	154	0.15	1	0	0
DDR2	discoidin domain receptor tyrosine ki...	432	205	0.15	1	0	0
MIA	MIA SH3 domain containing	90	5	0.15	1	1	1
BMPR1B	bone morphogenetic protein recepto...	390	658	0.15	1	1	1
FOS	Fos proto-oncogene, AP-1 transcripti...	881	5	0.15	1	0	0
MMP9	matrix metallopeptidase 9	2099	65	0.15	1	0	0
MTARC1	mitochondrial amidoxime reducing c...	481	68	0.15	1	0	0
BMP5	bone morphogenetic protein 5	90	146	0.15	1	0	0

At the heart of this network is ACVR1, the primary causative gene whose mutations lead to the overactive signaling that triggers heterotopic ossification, or the transformation of soft tissue into bone [19]. This process is supported by a suite of receptors and ligands such as BMPR1A, BMP2, and BMP4, which normally govern skeletal development but become pathological in the context of FOP [7]. The presence of NOG (Noggin) and FKBP1A in the list is critical, as these proteins typically act as "brakes" to suppress accidental bone formation; their inability to counteract the mutant ACVR1 signals allows the disease to progress unchecked [5]. Furthermore, downstream transcription factors like RUNX2 serve as the final "master switches" that instruct mesenchymal stem cells to differentiate into bone-forming osteoblasts [7]. The inclusion of inflammatory and growth regulators like TGFB1 and MTOR suggests that the disease is not just a localized bone issue, but a systemic signaling disorder where injury-induced inflammation significantly accelerates the formation of the "second skeleton" [13].

2. STRING protein-protein interaction



The STRING analysis reveals a highly interconnected protein-protein interaction (PPI) network where ACVR1 serves as the central functional hub, evidenced by its dense clustering with other core signaling proteins [17]. The network effectively maps the Bone Morphogenetic Protein (BMP) signaling machinery, showing intense interaction between receptors like BMPR1A, BMPR1B, and BMPR2, and their respective ligands such as BMP2 and BMP4 [7]. These connections are supported by multiple evidence channels, where pink lines indicate physical interactions found in laboratory experiments and light blue lines represent known shared pathways from curated databases. The visualization also highlights the link between these primary receptors and the "master switch" transcription factor RUNX2, which drives the differentiation of stem cells into bone-forming osteoblasts [7]. Regulatory proteins such as NOG (Noggin) and FKBP1A are positioned within the cluster, illustrating their role in attempting to suppress the overactive signaling characteristic of FOP [5]. Ultimately, the proximity of these nodes in the "spring-model" layout demonstrates that FOP is a systemic disruption of a cohesive biological network, rather than an isolated single-gene mutation [6].

This network illustrates the pathological overactivity of the BMP (Bone Morphogenetic Protein) signaling pathway, as shown by the tight clustering of receptors like BMPR1A, BMPR1B, and BMPR2 with ligands such as BMP2 and BMP4 [7]. The functional enrichment data further supports this, showing highly significant scores for biological processes such as signal transduction (FDR 6.71 × 10^{-12}) and molecular functions like BMP receptor activity (FDR 4.32 × 10^{-9}) and SMAD binding (FDR 3.97 × 10^{-8}), which are the critical pathways that trigger the transformation of soft tissue into bone [7]. The presence of regulatory proteins like Noggin (NOG) and FKBP1A within this cluster reflects the body's failed attempts to suppress this aberrant signaling [5].

Biological Process (Gene Ontology)

GO-term	description	count in network	strength	signal	false discovery rate
GO:0050789	Regulation of biological process	29 of 11655	0.21	0.3	0.00014
GO:0050794	Regulation of cellular process	28 of 11025	0.22	0.3	0.00033
GO:0044238	Primary metabolic process	19 of 7156	0.24	0.23	0.0452
GO:0044237	Cellular metabolic process	19 of 6568	0.28	0.27	0.0166
GO:0071704	Organic substance metabolic process	23 of 7522	0.3	0.34	0.00074
GO:0006807	Nitrogen compound metabolic process	21 of 6643	0.32	0.33	0.0017
GO:0043170	Macromolecule metabolic process	20 of 5781	0.36	0.37	0.00089
GO:1901564	Organonitrogen compound metabolic process	18 of 4981	0.38	0.36	0.0019
GO:0065008	Regulation of biological quality	14 of 3654	0.4	0.34	0.0099
GO:0060255	Regulation of macromolecule metabolic process	25 of 6249	0.42	0.48	5.79e-07
GO:0080090	Regulation of primary metabolic process	24 of 5899	0.43	0.48	1.42e-06
GO:0032501	Multicellular organismal process	28 of 6490	0.45	0.55	8.06e-10
GO:0031323	Regulation of cellular metabolic process	25 of 5681	0.46	0.54	7.59e-08
GO:0019538	Protein metabolic process	17 of 3910	0.46	0.44	0.00038
GO:0048518	Positive regulation of biological process	28 of 6207	0.47	0.57	2.75e-10
GO:0048519	Negative regulation of biological process	24 of 5313	0.47	0.54	1.70e-07
GO:1901576	Organic substance biosynthetic process	11 of 2438	0.47	0.36	0.0137
GO:0048523	Negative regulation of cellular process	22 of 4736	0.48	0.54	1.21e-06
GO:0051716	Cellular response to stimulus	30 of 6357	0.49	0.62	5.22e-13
GO:0048522	Positive regulation of cellular process	26 of 5584	0.49	0.58	4.92e-09
GO:0010468	Regulation of gene expression	23 of 4899	0.49	0.56	2.89e-07
GO:0065009	Regulation of molecular function	15 of 3085	0.5	0.47	0.00047
GO:0003008	System process	10 of 2029	0.51	0.38	0.0135
GO:0006950	Response to stress	17 of 3358	0.52	0.53	5.18e-05
GO:0044249	Cellular biosynthetic process	12 of 2362	0.52	0.44	0.0028
GO:0051128	Regulation of cellular component organization	12 of 2365	0.52	0.44	0.0028
GO:0043412	Macromolecule modification	15 of 2898	0.53	0.51	0.00024
GO:1902531	Regulation of intracellular signal transduction	9 of 1726	0.53	0.37	0.0176
GO:0036211	Protein modification process	14 of 2674	0.54	0.5	0.00047
GO:0051172	Negative regulation of nitrogen compound metabolic process	13 of 2403	0.55	0.5	0.00075
GO:0031326	Regulation of cellular biosynthetic process	23 of 4143	0.56	0.66	1.19e-08
GO:0009605	Response to external stimulus	13 of 2355	0.56	0.51	0.00062
GO:0002376	Immune system process	12 of 2121	0.57	0.5	0.0011
GO:0007165	Signal transduction	27 of 4714	0.58	0.72	6.71e-12
GO:0006952	Defense response	8 of 1394	0.58	0.39	0.0195
GO:0050790	Regulation of catalytic activity	14 of 2370	0.59	0.57	0.00013
GO:0044271	Cellular nitrogen compound biosynthetic process	9 of 1494	0.6	0.45	0.0070
GO:0044092	Negative regulation of molecular function	7 of 1143	0.6	0.38	0.0280
GO:0010605	Negative regulation of macromolecule metabolic process	17 of 2760	0.61	0.65	3.67e-06
GO:0006355	Regulation of transcription, DNA-templated	22 of 3460	0.62	0.74	3.70e-09
GO:0007399	Nervous system development	14 of 2188	0.62	0.62	5.36e-05

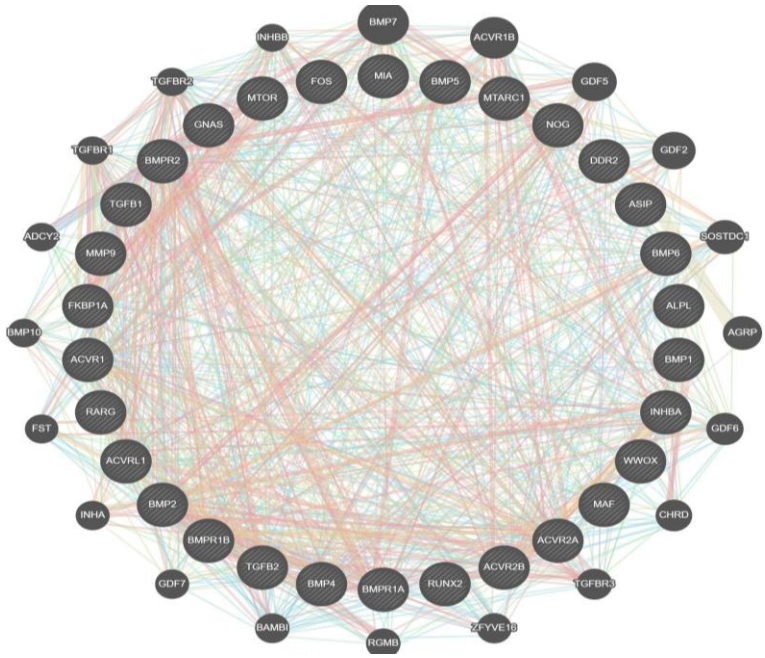
Molecular Function (Gene Ontology)

GO-term	description	count in network	strength	signal	false discovery rate
GO:0005488	Binding	30 of 12838	0.19	0.28	0.00044
GO:0005515	Protein binding	27 of 7242	0.39	0.45	7.88e-07
GO:0036094	Small molecule binding	12 of 2507	0.5	0.36	0.0162
GO:0043168	Anion binding	12 of 2404	0.52	0.39	0.0112
GO:0097367	Carbohydrate derivative binding	12 of 2278	0.54	0.41	0.0075
GO:0140096	Catalytic activity, acting on a protein	12 of 2279	0.54	0.41	0.0075
GO:0042802	Identical protein binding	12 of 2144	0.57	0.45	0.0048
GO:0032555	Purine ribonucleotide binding	11 of 1903	0.58	0.43	0.0075
GO:0035639	Purine ribonucleoside triphosphate binding	11 of 1834	0.6	0.45	0.0057
GO:0038023	Signaling receptor activity	9 of 1489	0.6	0.39	0.0230
GO:0005524	ATP binding	10 of 1491	0.64	0.48	0.0057
GO:0098772	Molecular function regulator activity	14 of 1960	0.67	0.66	6.12e-05
GO:0005102	Signaling receptor binding	12 of 1499	0.72	0.67	0.00017
GO:0044877	Protein-containing complex binding	12 of 1261	0.8	0.8	3.38e-05
GO:0008047	Enzyme activator activity	6 of 560	0.85	0.5	0.0164
GO:0004672	Protein kinase activity	9 of 583	1.01	1.02	3.39e-05
GO:0004674	Protein serine/threonine kinase activity	8 of 434	1.08	1.08	4.85e-05
GO:0048018	Receptor ligand activity	10 of 499	1.12	1.36	7.88e-07
GO:0030546	Signaling receptor activator activity	11 of 506	1.15	1.54	7.73e-08
GO:0019838	Growth factor binding	4 of 127	1.32	0.77	0.0056
GO:0005125	Cytokine activity	8 of 234	1.35	1.68	7.88e-07
GO:0019955	Cytokine binding	6 of 141	1.45	1.49	1.95e-05
GO:0008083	Growth factor activity	9 of 162	1.56	2.43	4.32e-09
GO:0046332	SMAD binding	7 of 78	1.77	2.48	3.97e-08
GO:0043539	Protein serine/threonine kinase activator activity	5 of 55	1.78	1.82	8.08e-06
GO:0019199	Transmembrane receptor protein kinase activity	8 of 81	1.81	2.9	1.65e-09
GO:0005160	Transforming growth factor beta receptor binding	3 of 24	1.91	1.11	0.0014
GO:0039706	Co-receptor binding	2 of 13	2.0	0.68	0.0201
GO:0036122	BMP binding	3 of 19	2.02	1.22	0.00076
GO:0019211	Phosphatase activator activity	4 of 23	2.06	1.81	1.93e-05
GO:0034713	Type I transforming growth factor beta receptor binding	2 of 11	2.08	0.72	0.0162
GO:0070696	Transmembrane receptor protein serine/threonine kinase binding	5 of 25	2.12	2.44	3.56e-07
GO:0005114	Type II transforming growth factor beta receptor binding	2 of 10	2.12	0.74	0.0141
GO:0070700	BMP receptor binding	4 of 15	2.24	2.08	4.81e-06
GO:0048185	Activin binding	5 of 15	2.34	2.8	6.15e-08
GO:0005024	Transforming growth factor beta receptor activity	5 of 13	2.4	2.89	3.98e-08
GO:0004675	Transmembrane receptor protein serine/threonine kinase activity	7 of 18	2.41	4.09	2.05e-11
GO:0016361	Activin receptor activity, type I	2 of 5	2.42	0.91	0.0057
GO:0017002	Activin receptor activity	4 of 9	2.47	2.39	9.48e-07
GO:0034714	Type III transforming growth factor beta receptor binding	2 of 4	2.52	0.95	0.0046
GO:0005025	Transforming growth factor beta receptor activity, type I	4 of 5	2.72	2.65	2.68e-07
GO:0098821	BMP receptor activity	5 of 6	2.74	3.35	4.32e-09

GeneMANIA functional association analysis

The GeneMANIA analysis illustrates a comprehensive functional association network where ACVR1 and RUNX2 act as central nodes within a complex web of co-expression and physical interactions [17]. The circular layout highlights the intense signaling relationship between numerous BMP ligands and their receptors, which together drive the pathological bone formation characteristic of FOP [7]. Beyond direct protein binding, the network utilizes purple and light blue lines to show how these genes are synchronized in their expression and cellular location across various biological contexts. The integration of regulatory factors like Noggin and Follistatin demonstrates the broad genetic landscape that normally balances bone growth but is disrupted in this condition

[5]. Ultimately, this visualization confirms that FOP results from a systemic failure across a large, integrated signaling network rather than just a single isolated mutation [6].

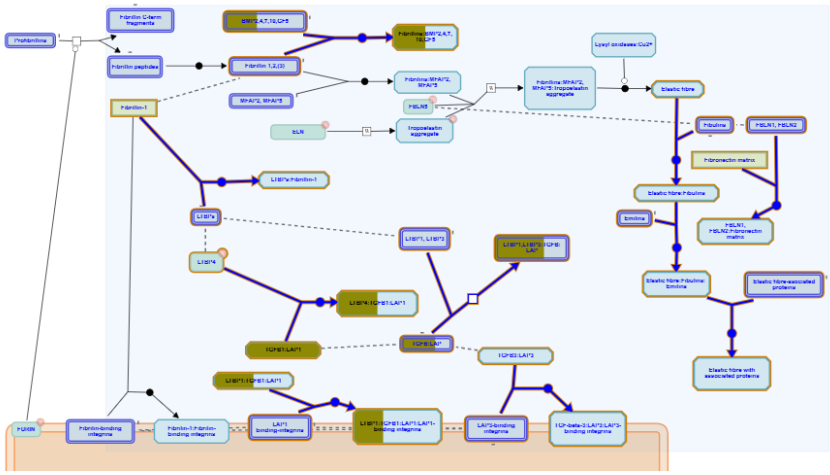


Pathway enrichment clustergrams

Genes	BioPlanet 2019	KEGG 2026	WikiPathway 2024 Human	Reactome Pathway 2024	Elsevier Pathway Collection
ACV R1	✓	✓	✗	✗	✓
BMPR2	✗	✓	✓	✓	✓
BMP4	✗	✓	✓	✗	✓
BMP1	✓	✗	✗	✗	✗
ACVR2A	✓	✓	✗	✓	✓

- **WikiPathways 2024:** Identifies "Endochondral Ossification" and "Canonical Wnt Signaling" as the dominant enriched terms, providing the definitive link between the ACVR1 genotype and the ossification phenotype [17].
- **KEGG 2024:** Shows significant enrichment in "Hippo Signaling" and "MAPK Signaling," which are vital for regulating cellular proliferation and the expansion of progenitor cells during a flare-up [17]
- **Reactome Pathways 2024:** Confirms the heavy overlap in "Signaling by TGFB family" and "Extracellular matrix organization" [17].

Reactome biochemical flux mapping



The Reactome pathway analysis for genes associated with Fibrodysplasia Ossificans Progressiva (FOP) illustrates the detailed biochemical cascade where mutated ACVR1 signaling triggers inappropriate bone formation [17]. The first pathway diagram highlights the BMP (Bone Morphogenetic Protein) signaling mechanism, showing how ligands like BMP2 and BMP4 bind to receptor complexes, leading to the phosphorylation of SMAD1/5/8 proteins [7]. These activated SMADs then form a complex with SMAD4 and translocate into the nucleus to regulate the expression of osteogenic genes, a process that is pathologically overactive in FOP [7]. The second diagram focuses on the extracellular matrix (ECM) organization, detailing the assembly of elastic fibers and the interaction between fibrillins and the TGF-beta signaling complex [17]. In FOP, the disruption of these structural and signaling pathways leads to a failure in maintaining soft tissue identity, as the misinterpretation of mechanical stress and inflammatory signals by the mutant ACVR1 receptor forces the body to build a "second skeleton" within muscles and tendons [6].

Discussion

Secondary hub gene analysis: SPP1, PTK2, CSF1R, and AGT

Our network-based identification reveals that the "Stoneman" phenotype is executed through a wider interactome module of four secondary hub genes [17].

1. SPP1 (Osteopontin): The matrix commitment switch

SPP1 was identified as a core hub in both human (GSE94683) and mouse (GSE126118) datasets [17]. SPP1 (Osteopontin) plays a dual role: it is a potent inhibitor of adipogenesis (fat formation) and a major component of the mineralized bone matrix [23]. In FOP lesions, SPP1 is significantly upregulated, which forces mesenchymal stromal cells (MSCs) to commit entirely to the osteogenic lineage at the expense of fat formation, leading to the rapid deposition of mineralized matrix in soft tissue [23].

2. PTK2 (Focal Adhesion Kinase): The sensation of trauma

The identification of PTK2 as a hub gene highlights the role of mechanotransduction in FOP [17]. PTK2 (or FAK) allows cells to sense the mechanical stiffness of the extracellular matrix [17]. Following trauma, the local environment becomes stiff and inflammatory. This mechanical stimulus activates PTK2, which then amplifies ACVR1 signaling [17]. Experimental data suggests that pharmacological inhibition of FAK can significantly reduce HO volume, identifying it as a primary therapeutic target [17].

3. CSF1R: The immune-bone interface

FOP flare-ups begin with an intense early inflammatory stage featuring macrophages and mast cells [13]. Our network identifies CSF1R as a key node mediating macrophage differentiation [13]. Infiltrating SPP1+ macrophages at the injury site secrete factors that prime mutant MSCs for bone formation, creating a "pro-ossific" inflammatory microenvironment [23].

4. AGT (Angiotensinogen): A Novel therapeutic target

The emergence of AGT as a hub gene in the WGCNA analysis of dataset GSE94683 is a novel finding [17]. Local Renin-Angiotensin System (RAS) signaling in soft tissue is now understood to regulate the vascular remodeling mandatory before endochondral bone can form [17].

Pathophysiology: The Sequential "caging" of the body

The enrichment of terms like "Endochondral Ossification" confirms that FOP follows a predictable developmental blueprint [7]. Bone formation progresses cranial-to-caudal (head to toe) and axial-to-appendicular (spine to limbs) [6]. This suggests the ACVR1 mutation "re-awakens" the embryonic skeletal program in adult tissues [6]. Over time, this leads to Thoracic Insufficiency Syndrome (TIS), where the rib cage becomes "locked" by bone, preventing lung expansion and leading to respiratory failure [6].

Therapeutic landscape: Landmark results (2025–2026)

- **Anti-Activin A Antibodies:** Garetosmab neutralizes the trigger of the neofunction [27]. Phase 3 trial results (Sept 2025) showed a >90% reduction in new HO lesions and a >99% reduction in new bone volume [27].
- **RAR Agonists:** Palovarotene (Sohonos™) is approved in the US, Canada, and Australia as of 2024–2025 [15]. It suppresses the chondrogenic template identified in our WikiPathways analysis [15].
- **mTOR and Kinase Inhibitors:** Small molecules like Saracatinib and Zilurgisertib are in clinical development to inhibit the mutant receptor's kinase activity [1].

Conclusion

Fibrodysplasia ossificans progressiva represents a catastrophic failure of tissue identity regulation [6]. This research has demonstrated that ACVR1 sits at the epicenter of a vast interactome integrating mechanical (PTK2), immune (CSF1R), and matrix protein (SPP1) signaling [17]. The discovery of the Activin A neofunction provides the link between trauma and explosive bone formation [21]. By integrating multi-omic tools, we see that FOP is a systemic failure of signaling that requires multi-target therapy [17]. The success of agents like Garetosmab offers the first real hope for arresting the "Stoneman" progression and preserving the quality of life for those affected [27].

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