# Integrative interactome analysis for mechanistic discovery and drug repurposing in rare diseases: GPX4-related rare skeletal dysplasia

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Rare diseases pose a major challenge for mechanistic and therapeutic discovery because of limited molecular data and small patient populations. Building on our previously developed interactome-based methods, we present an integrative network analysis workflow for constructing disease-specific functional landscapes by combining protein-protein interactions (PPIs), disease-gene associations, phenotypes, tissue expression, gene perturbation data, and drug-target relationships. We applied it to Spondylometaphyseal dysplasia, Sedaghatian type (SMDS), an ultra-rare lethal skeletal dysplasia caused by GPX4 mutations. Disease-centric and gene-centric networks connected GPX4 with genes implicated in SMDS and related skeletal dysplasias, and with regulators of GPX4 expression, and were enriched for SMDS-relevant phenotypes, fetal-stage functional modules, and brain/testis-enriched genes. Seven high-confidence computationally predicted GPX4 interactors (APBA3, EGR4, FUT5, GAMT, GTF2F1, MATK, and ZNF197) were supported by convergent network, phenotype, and expression evidence. Integrative transcriptomic and network analyses prioritized eleven candidate repurposable drugs, with resveratrol additionally highlighted by network proximity. Nearly 75% of rare diseases are associated with single genes, many understudied with limited experimental data. This study demonstrates an approach to studying a rare disease in the context of its protein interactome to generate mechanistic and therapeutic hypotheses.

*Keywords:* rare disease; protein interactome; protein-protein interaction prediction; GPX4; Sedaghatian-type spondylometaphyseal dysplasia; drug repurposing

## 1. Introduction

There are over 10,000 rare diseases which, though rare individually, affect 10% of the population collectively; nearly half of the patients are children [1]. 75% of the rare diseases are associated with a single gene each though they may present multiple phenotypes (source: our analysis of Orphanet data https://www.orpha.net accessed July 2026 [2]). For example, many rare diseases are pediatric neurodevelopmental disorders, such as Malan syndrome, Tatton-Brown-Rahman syndrome, Sotos syndrome, Weaver syndrome, etc., and each associated with a different gene, NFIX, DNMT3A, NSD1, and EZH2, respectively. Unfortunately, hundreds of genes associated with rare diseases are also understudied biologically, presenting an impediment to inferring molecular mechanisms for a given rare disease, such as pathways or biological processes associated. Characterizing these genes

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in terms of their protein function, structure, and interactions can therefore provide a foundation for data-driven hypothesis-generation in rare disease research.

One critical avenue for discovering mechanisms of diseases and identifying therapeutic targets lies in elucidating protein-protein interactions (PPIs) involving disease-associated genes [3-5]. PPIs drive cellular processes by facilitating signal transduction, formation of cellular structures, and enzymatic reactions. Disease-associated variants are enriched in protein cores and interaction interfaces, and often alter binding affinity or establish novel interactions [6, 7]. As a result, the genetic perturbations can propagate through PPI network (the 'interactome') influencing multiple biological processes, contributing to disease pathogenesis, and presenting multiple phenotypes despite their origin in a single gene [8]. Several studies, led by our group and others, have demonstrated that shared genetic architecture and overlapping phenotypes across distinct disorders can be traced to convergent perturbations in PPI networks [9-14]. Interactomes provide a unifying data structure for integrating heterogeneous molecular, phenotypic, and functional annotations in a disease-centric manner.

Here, we present an interactome-based study of Spondylometaphyseal dysplasia, Sedaghatian type (SMDS), an ultra-rare developmental disorder caused by pathogenic variants in a single gene, GPX4. SMDS is a lethal autosomal-recessive skeletal dysplasia with metaphyseal, vertebral, cardiac, respiratory, and neurodevelopmental manifestations [15-22]. Cardiac-respiratory distress is the primary cause of death in infancy and living patients with severe hypotonia and intractable seizures have been reported [21, 23]. Studies on SMDS have described its clinical presentation [15-20, 22], and linked it to GPX4 mutations [21, 24]. This includes a detailed analysis of the homozygous GPX4 R152H mutation that disrupts enzyme stability and function, and is partially rescued by selenium supplementation or selective antioxidant therapies [25]. No approved therapies exist for SMDS; management has been limited to antioxidant supplementation in a few patients, with anecdotal benefit [24]. Nevertheless, the etiology of this severe lethal dysplasia remains largely unexplored. Hence, novel approaches are needed to understand the fundamental biological mechanisms underlying this disorder. Motivated by the efforts of affected families (www.curegpx4.org) and growing calls from the rare disease community to accelerate mechanistic understanding, we applied our previously established interactome-analysis approach to construct a GPX4-centered interactome and systematically integrated functional annotations to generate testable biological hypotheses. This study illustrates how PPI networks and their functional annotation can support mechanism discovery in single-gene rare diseases for which conventional omics-based analyses are not feasible.

## 2. Methods

*Detailed Methods, including data sources, parameter settings and statistical tests for each analysis, are provided in the Supplementary Information (Section 5); a summary is given here.* Disease associated gene sets were compiled from the DisGeNET database [26], and from Warman et al. [27]. Genes whose knockout, knockdown, mutation, or overexpression changed GPX4 expression were collected from Knockdown Atlas [28]. PPIs involving these genes which have been reported in the literature ('known PPIs') were obtained from HPRD (Human Protein Reference Database,

version 9 [29]) and BioGRID (Biological General Repository for Interaction Datasets, version 3.4.159 [30]). To systematically expand the molecular context of GPX4 and SMDS-associated genes, high-confidence computationally predicted PPIs were incorporated using the HiPPIP model (a random forest classifier), which we previously developed and validated for high precision through computational evaluations and experimental validations [11, 31-33]. Following the original HiPPIP publication [11], in which all pairs scoring above 0.5 were deemed high-confidence predictions without distinction between their individual scores, we likewise regard all pairs above this threshold as equally high-confidence predictions; accordingly, individual scores are not used to rank interactors and are not tabulated here. Protein pairs not previously reported but predicted as interacting by HiPPIP were treated as novel (predicted) PPIs. The PPI networks, consisting of direct interactors of input genes as well as shortest paths connecting them, were created using LENS web application [34]. While the public web-application provides only known PPIs, an in-house version of LENS under development, provides networks including HiPPIP-predicted PPIs. Shortest paths were computed using Dijkstra's algorithm, with path length measured as the number of edges and no cap on length, so the closest neighbor of a gene may be one, two, or more edges away. For each gene in the input set, all its closest neighbors in the set, and all shortest paths to them, were included in the network along with the intermediate proteins and interactions. Shortest paths were used to assemble the network neighborhood of the genes of interest and not as a statistical measure of biological relatedness: in scale-free interactomes, path length largely reflects the degree distribution rather than functional relatedness [35], so no inference is drawn from path lengths themselves. The networks were downloaded as SIF files, and visualized in Cytoscape [36]. LENS also provided pathways, diseases, drugs and genome-wide association study (GWAS) annotations significantly enriched among the network genes (P-values from Fisher's exact test).

Global and fetal-context functional modules, containing minimum eight nodes, were identified using shared k-nearest-neighbor graphs and Louvain clustering with HumanBase toolkit [37, 38]. Gene Ontology enrichment was evaluated by Fisher's exact test with Benjamini-Hochberg correction. Genes associated with twelve major SMDS-associated pathophenotypes were compiled from the MONARCH database [39]. Enrichment of these phenotypes within the interactomes was evaluated against a background of 15,451 genes with phenotype annotations, using Fisher's exact test (phenotype gene sets ranged in size from 4 to 355 genes); nominal (uncorrected) P-values and odds ratios are reported. Median expression across 53 postnatal tissues was obtained from GTEx [40]. Logarithmic transcripts per million (TPM) values were standardized by gene. PCA used SVD with iterative imputation in ClustVis [41]; hierarchical clustering used Pearson distance and average linkage in Heatmapper [42].

Repurposable drug candidates were identified by two independent signals: negative score reported in BaseSpace Correlation Engine [43] based on drug-induced and dysplasia-associated transcriptional profiles, and proximity between drug targets from DrugBank [44] and the GPX4/SMDS interactome. The BaseSpace Correlation Engine (formerly NextBio) computes a correlation score from the strength of overlap between two expression profiles, applies statistical criteria including correction for multiple hypothesis testing, ranks correlated profiles by statistical significance, and normalizes scores to 100 for the top-ranked result. Convergence between signals

was treated as stronger evidence; all candidate drugs are computational hypotheses, requiring experimental and clinical validations.

## 3. Results[†]

### 3.1. *GPX4 interactome construction and expansion*

We assembled literature-supported PPIs, and 'novel' PPIs of GPX4 computationally predicted by HiPPIP, a model whose claim for high-confidence prediction was previously validated computationally and experimentally [11, 31-33]. GPX4 is found to have 7 novel interactors; see Fig.

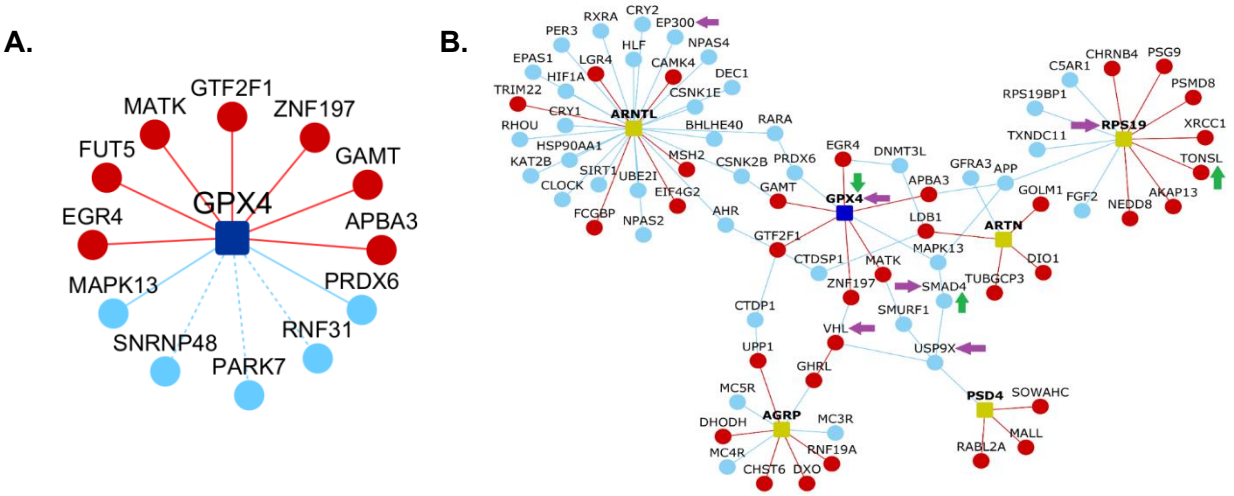



**Figure 1: A. Known and Novel PPIs of GPX4.** Subsequent to carrying out the analysis presented in this study, three additional PPIs have been reported in literature, which are shown in dashed lines. **B. Interactions of GPX4 with other genes speculated to be associated with Sedaghatian type spondylometaphyseal dysplasia**. This network diagram shows the shortest paths connecting the genes from the DisGeNET database (dull green colored nodes) identified through text mining to GPX4. Nodes depict proteins and edges depict PPIs. Red and light blue colored nodes denote novel and known interactors respectively. Red and light blue colored edges denote novel and known PPIs respectively. Purple colored arrows indicate genes associated with cardiac defects, whereas green colored arrows indicate those associated with skeletal defects.

1A and **Table 1**. Among the seven predicted interactors, GAMT presents phenotype-level connection: Human Phenotype Ontology annotations report both GPX4 and GAMT to be associated with hypotonia phenotype (HP:0001252). We analyzed four complementary network views of GPX4: (i) other genes putatively associated with SMDS in DisGeNET [26], (ii) genes associated with other skeletal dysplasias, (iii) genes associated with disorders phenotypically similar to SMDS and (iv) genes whose perturbation causes significant differential expression of GPX4. For each network, we identified enriched functional modules and tested enrichment for SMDS-relevant pathophenotypes.

[†] *Additional details are provided in Supplementary Information referred to in Section 5.*

Table 1: Biological relevance of novel interactors of GPX4. See Supplementary Material for additional details.

| Gene | Potential relevance to GPX4/SMDS |
|---|---|
| **APBA3** | Connects GPX4 to skeletal dysplasia genes (IARS2), resveratrol target APP, and oxidative stress pathways. |
| **EGR4** | Brain developmental TF; co-expressed with GPX4; six shared GPX4 mouse phenotypes; implicated in cartilage/neurogenesis modules. |
| **FUT5** | Testis-enriched; co-expressed with GPX4; implicated in cartilage development and neurogenesis. |
| **GAMT** | Links GPX4 to TERF1; 4 mouse phenotypes and 1 human phenotype shared with GPX4; oxidative stress module. |
| **GTF2F1** | Connects GPX4 with PAM16 (Megarbane SMD) and resveratrol targets; participates in oxidative stress and epithelial morphogenesis modules. |
| **MATK** | Brain-enriched; participates in GPCR signaling and cartilage development modules. |
| **ZNF197** | Links GPX4 to VHL/HIF1A signaling and skeletal dysplasia genes; shared mouse phenotype; implicated in VEGFA regulation, cartilage development, ROS metabolism, and neurogenesis. |

## 3.2. *Interactome of GPX4 and other genes putatively associated with SMDS*

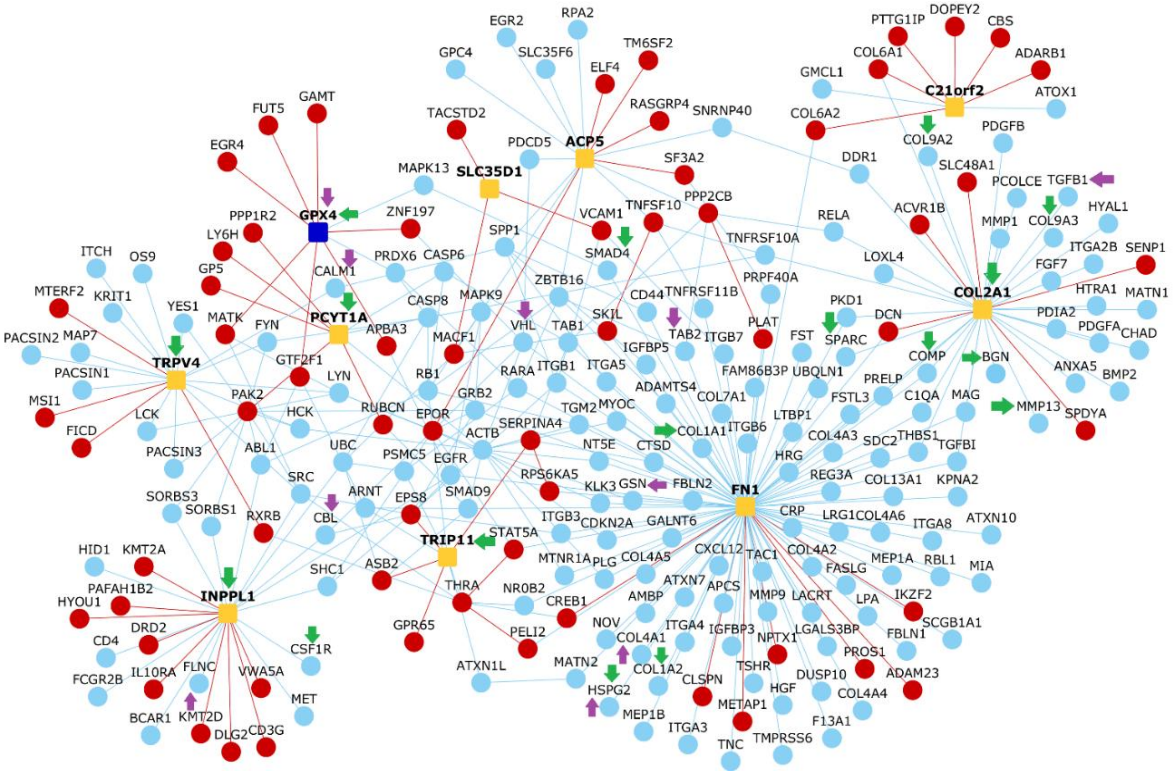



**Figure 2: GPX4 interaction network linking GPX4 to genes associated with other spondylometaphyseal dysplasias and related skeletal dysplasias**. Shown are the shortest paths connecting GPX4 to disease-associated genes (orange). Nodes represent proteins and edges represent PPIs; red/light blue indicate novel/known interactors and PPIs, respectively. Purple and green arrows denote genes associated with cardiac and skeletal defects.

DisGeNET lists six genes – AGRP, ARNTL, ARTN, LOH19CR1, PSD4, and RPS19 – as potentially associated with SMDS based on a prior study [45]. That study identified an SMDS-associated variant within a sperm RNA element mapping to GPX4; sperm RNA elements are short exon-sized sequences corresponding to unique coding and non-coding transcripts [45]. Their disease

association scores in DisGeNET are very low (0.01), indicating some, but minimal supporting evidence, whereas GPX4 has a higher score of 0.72. These genes were tagged as potentially linked to SMDS in DisGeNET based on co-mention of gene and disease names in literature. Given the scarcity of information on SMDS, these co-mentions may provide testable insights. We included these genes in our network analysis to assess whether they exhibited biologically meaningful connectivity to GPX4 and the broader SMDS molecular landscape.

We extracted the interactors of these six genes and the shortest paths connecting them to GPX4 in the PPI network and found that each gene was connected to GPX4 by fewer than three intermediate interactions. Notably, these paths traversed six of the seven novel interactors of GPX4 (Fig. 1B). This interactome was enriched in genes associated with myocarditis, atrial septal defect, and platyspondyly (P = 5.33E-04, 0.016 and 0.018; odds ratio = 55.8, 3.37 and 5.38, respectively). From this, we identified fetus-specific and tissue-naive (or 'global') modules. Fetus-specific modules may provide insights into the congenital underpinnings of SMDS. Cellular oxidant detoxification pathway was identified in both global (M4: *Q*-value = 2.15E-03) and fetus-specific (M3: *Q*-value = 2.77E-03) contexts. G-protein coupled receptor signaling pathway was detected both as a global (M3: *Q*-value = 4.25E-04) and fetus-specific (M2: *Q*-value = 3.4E-04) module. *Cell growth* (M1: *Q*-value = 2.38E-04) and *response to redox state* (M2: *Q*-value = 2.38E-04) were detected only as global modules.

### 3.3. *Interactome of GPX4 and genes associated with other skeletal dysplasias*

Nine genes representing twelve related skeletal dysplasias were curated from Warman et al. [27]. Their network consisting of direct interactors and shortest paths to GPX4 contained 93 intermediate proteins and 26 novel interactions (Fig. 2). This interactome was enriched in genes associated with arrhythmia (P-value = 0.041, odds ratio = 1.88), cardiorespiratory arrest (P-value = 9.25E-03, odds ratio = 13.38), myocarditis (*P*-value = 4.64E-03, odds ratio = 19.11), metaphyseal cupping (P-value = 1.9E-07, odds ratio = 22.5), platyspondyly (*P*-value = 4.98E-13, odds ratio = 10.43) and abnormal ribs (*P*-value = 8.9E-03, odds ratio = 3.93). Paired global/fetal modules implicated extracellular-matrix and cartilage development, vascular development/cell migration, and apoptosis. Additional fetal modules involved cytoskeletal organization, cellular maintenance, and protein catabolism, indicating convergence of GPX4-associated networks with clinically relevant skeletal and cardiovascular phenotypes.

### 3.4. *Interactome of GPX4 and genes associated with disorders phenotypically like SMDS*

We used Phenogrid from MONARCH to identify the diseases that were phenotypically most similar to SMDS. Seven skeletal dysplasias shared 70% phenotypic similarity with SMDS: X-linked spondyloepimetaphyseal dysplasia, acrocapitofemoral dysplasia, A4 type SMD, Dyggve-Melchior-Clausen disease, autosomal recessive Megarbane type SMD, metaphyseal acroscyphodysplasia and X-linked Dyggve-Melchior-Clausen disease. Four of them had genetic associations reported in DisGeNET: X-linked spondyloepimetaphyseal dysplasia (BGN and IARS2), acrocapitofemoral dysplasia (IHH), Dyggve-Melchior-Clausen disease (DYM), and autosomal recessive Megarbane type SMD (PAM16). GPX4 was connected to these five genes through 13 intermediate interactors

including three novel interactors of GPX4 (APBA3, GTF2F1 and ZNF197) (Fig. 3). This interactome was enriched in genes associated with arrhythmia, cardiorespiratory arrest, cerebellar hypoplasia, agenesis of corpus callosum, metaphyseal cupping, platyspondyly and abnormal ribs (P = 0.042, 5.9E-04, 8.63E-03, 1.88E-03, 3.73E-05, 5.9E-09 and 3.8E-03; odds ratio = 3.05, 54.2, 4.95, 5.65, 45.18, 19.9 and 9.57, respectively, in that order), mirroring key SMDS clinical features. Five modules were detected in both global and fetus-specific contexts: skeletal system development/embryo development/gastrulation, lipid storage/reactive oxygen species biosynthetic process, humoral response, cellular response to toxic substance and membrane organization. A fetus-specific module enriched for neurogenesis was also identified, consistent with neurodevelopmental manifestations of SMDS.

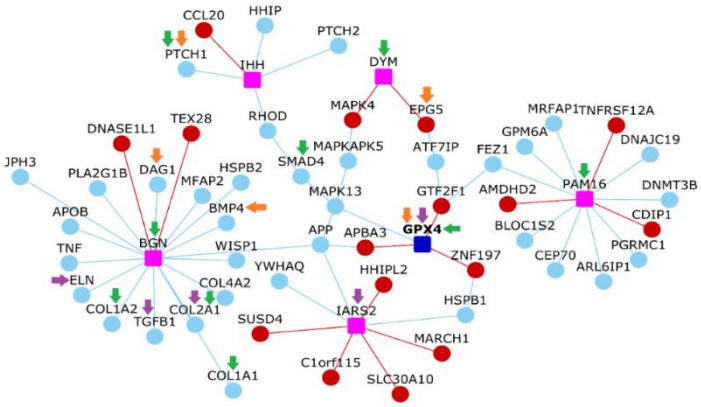



**Figure 3: Interactions of GPX4 with genes associated with bone dysplasias sharing phenotypic similarity with Sedaghatian type spondylometaphyseal dysplasia.** This network diagram shows the shortest paths connecting GPX4 with the genes associated with X-linked spondyloepimetaphyseal dysplasia, acrocapitofemoral dysplasia, Dyggve-Melchior-Clausen disease and autosomal recessive Megarbane type SMD (pink colored nodes). Nodes depict proteins and edges depict PPIs. Red and light blue colored nodes denote novel and known interactors respectively. Red and light blue colored edges denote novel and known PPIs respectively. Purple, green and orange arrows indicate genes associated with cardiac, skeletal and brain defects respectively.

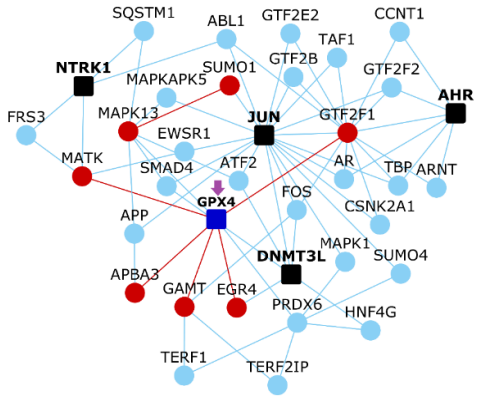



**Figure 4: Four genes whose perturbation affects GPX4 expression, which are closely connected to GPX4 in the network.** Nodes represent proteins and edges represent PPIs; red/light blue denote novel/known interactors and PPIs, respectively. Black nodes are the 4 genes mentioned and purple arrows indicate genes associated with heart defects.

### 3.5. *Interactome of GPX4 and genes that affect GPX4 expression when perturbed*

From the Knockdown Atlas (BaseSpace Correlation Engine [28]), we compiled 136 genes whose knockout, knockdown, mutation or overexpression significantly affects GPX4 expression. The connecting network included all the seven novel interactors of GPX4. Among the 136, four were closely connected to GPX4, namely, AHR, DNMT3L, JUN and NTRK1 (Fig. 4). Mutations in JUN lead to GPX4 underexpression, whereas DNMT3L knockdown, AHR knockout, and NTRK1 overexpression lead to GPX4 overexpression. This interactome was enriched in genes associated

with cardiorespiratory arrest and myocarditis (P = 3.2E-03 and 1.52E-03; odds ratio = 23.06 and 32.9, respectively), suggesting regulatory network effects relevant to SMDS-associated cardiac phenotypes.

Telomere maintenance/organization and positive regulation of neurogenesis were detected both as global and fetus-specific modules. Six additional global modules were identified: cellular response to retinoic acid, detoxification, peptidyl-threonine phosphorylation, regulation of cellular protein localization, DNA replication and protein autophosphorylation. Three additional fetal modules were detected: negative regulation of myeloid cell differentiation, TGF-β receptor signaling pathway and positive regulation of endopeptidase activity.

### 3.6. *Tissue-elevated gene clusters in the integrated GPX4 landscape.*

We merged the interactomes described in the previous sections to construct an integrated GPX4 functional landscape containing 342 genes and 461 PPIs. We then clustered its genes hierarchically by GTEx tissue expression [40]. GPX4 and 59 genes clustering with it showed high expression in

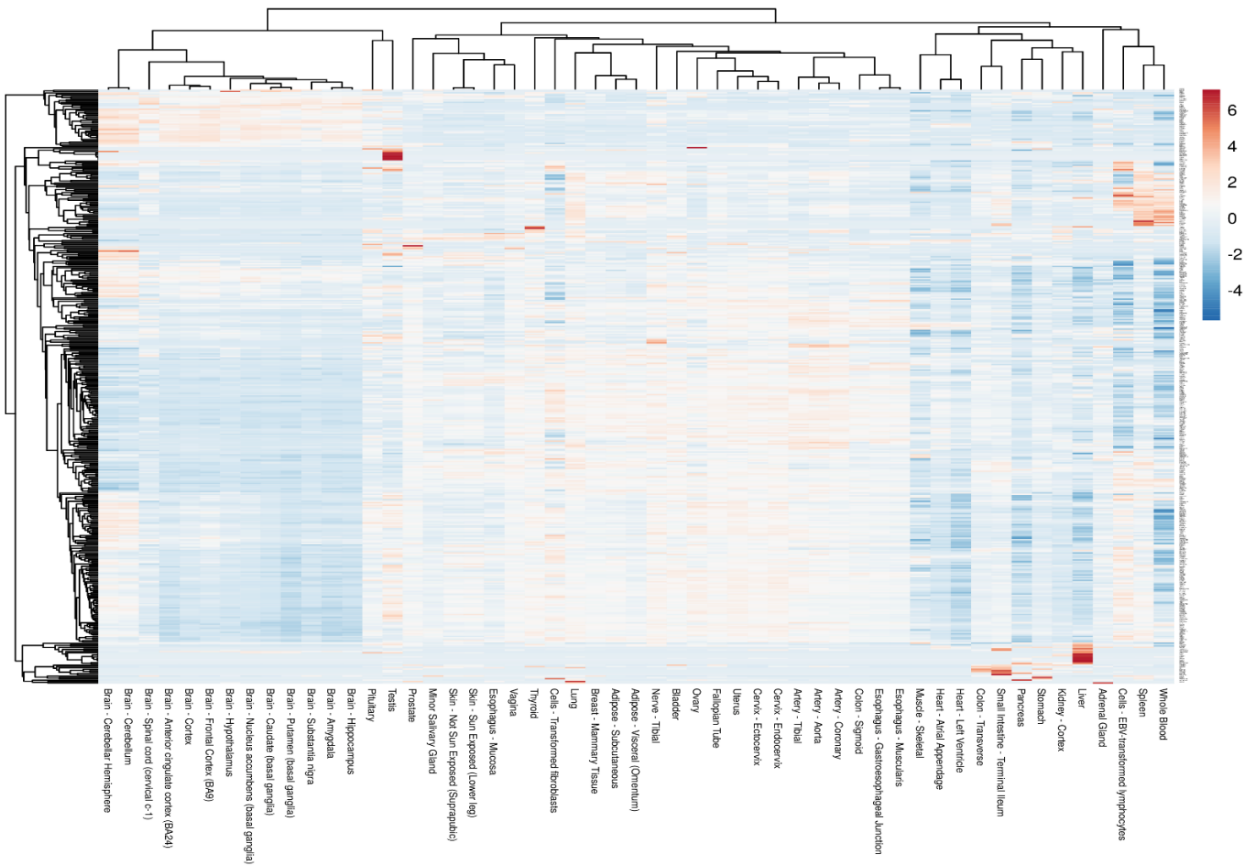



**Figure 5: Clustering analysis of genes in the integrated GPX4 interactome.** Tissue expression patterns of genes in the integrated **GPX4** interactome across 53 human tissues. The interactome comprises GPX4 and the shortest paths connecting it to genes associated with SMDS, other spondylometaphyseal dysplasias, and phenotypically similar skeletal dysplasias. Heatmap values represent normalized Z-scores of log-transformed TPM expression levels. Hierarchical clustering identified four major gene clusters with elevated expression in (i) brain/testis, (ii) whole blood/spleen, (iii) liver, and (iv) small intestine.

brain tissues or testis, with or without elevated expression in EBV-transformed lymphocytes and spleen (Fig. 5). This cluster included novel interactors of GPX4, namely, EGR4, MATK, and FUT5.

Brain-elevated genes were enriched for axon development, regulation of trans-synaptic signaling, regulation of ion transmembrane transport, protein localization to mitochondrion and neural nucleus development; testis-elevated genes for DNA recombination, aging, regulation of cyclin-dependent protein kinase activity, regulation of DNA metabolic process, mitotic cell cycle phase transition and extrinsic apoptotic signaling pathway; and small intestine-elevated genes for cell fate commitment, in utero embryonic development, epithelial cell proliferation, mRNA transcription, toxin transport and mesenchymal cell proliferation. None of these remained significant after multiple-testing correction, whereas the enrichments of liver-elevated genes (platelet degranulation and regulation of response to wounding) and of lymphocyte-, whole blood- and spleen-elevated genes (including leukocyte differentiation, leukocyte migration and adaptive immune response) did. We separately examined the interactome containing the intermediate interactors connecting the 4 genes (AHR, DNMT3L, JUN and NTRK1) whose perturbation affects GPX4 expression to GPX4, together with the known and novel interactors of these genes. We identified a group of nine testis-elevated genes that clustered with GPX4: FUT5, MX1, PDE6G, NCR1, MAGEC1, SUMO4, NTRK1, MSX2 and FKBP4.

### 3.7. *Interconnections of GPX4 and genes associated with Joubert syndrome*

Joubert syndrome with Jeune asphyxiating thoracic dystrophy (JATD) exhibited 64% phenotypic similarity with SMDS, sharing neurodevelopmental, skeletal, cardiac, and respiratory features. To investigate potential molecular links, we examined shortest paths connecting GPX4 to Joubert syndrome-associated genes (IFT140, KIAA0586, and CSPP1). The resulting network contained multiple novel GPX4 interactors and perturbation-associated genes, suggesting shared molecular pathways between these disorders (Fig. 6a). Extending this analysis to ciliary proteins identified TERF1 as the closest ciliary protein connected to GPX4, which may point to a potential role for

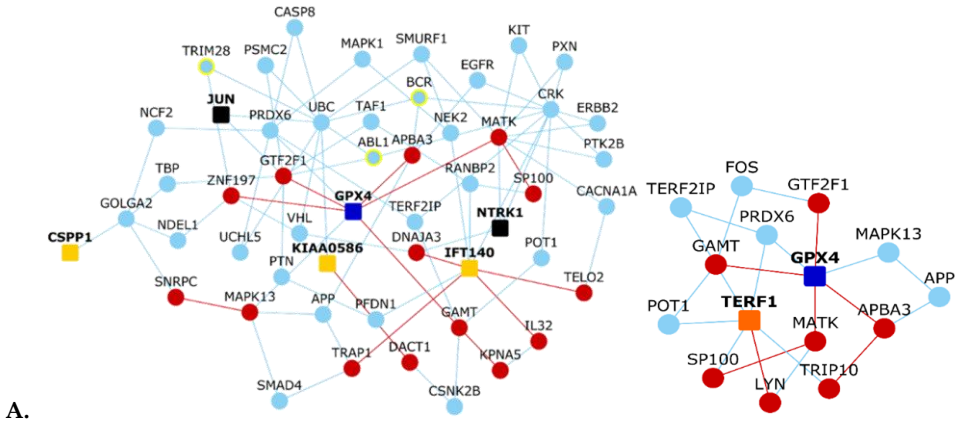



**Figure 6:** GPX4 interactions with ciliary proteins and Joubert syndrome-associated genes. (A) Shortest paths connecting GPX4 to three Joubert syndrome/Jeune asphyxiating thoracic dystrophy genes, together with genes whose perturbation affects GPX4, IFT140, or KIAA0586 expression. (B) Network of shortest paths connecting the ciliary protein TERF1 to GPX4. Nodes represent proteins and edges represent PPIs; red/light blue indicate novel/known interactors and PPIs.

ciliary biology in SMDS (Fig. 6b). Functional module analysis highlighted detoxification as both a global and fetus-specific module, together with enrichment of developmental, cell cycle, JAK–STAT signaling, proteostasis, and organelle-related processes.

### 3.8. *Repurposable drugs for SMDS*

We adopted two complementary strategies to identify repurposable drugs for SMDS using the integrated interactome of SMDS-associated genes. First, we applied a transcriptome-based drug repurposing approach that identifies compounds whose gene expression signatures are inversely correlated with disease-associated expression profiles, using the BaseSpace Correlation Engine [28, 43, 46]. An SMDS drug-protein interactome was then constructed, representing drugs that target one or more proteins within the SMDS interactome. Thirty-six drugs targeted 16 proteins in this network, including 5 novel interactors (PSMD8, XRCC1, DHODH, GHRL and VHL) (Fig. 7a). Four dysplasia-related gene expression datasets were selected, comprising two datasets corresponding to chondrodysplasia and two corresponding to immuno-osseous dysplasia (tibial growth plate hypertrophic zone of Cog and Schmid mice versus wild-type littermates, GSE30628 [47]; skin fibroblasts of Schimke immuno-osseous dysplasia cell lines SD60 and SD8 versus healthy controls, GSE35551 [48]). No SMDS expression datasets are available, so these dysplasias serve as proxies and may differ etiologically from SMDS. We then compiled a list of chemical compounds whose differential gene expression profiles (drug versus no drug) were negatively correlated with at least one of the four dysplasia-associated expression datasets (disease versus control). Using this approach, eleven candidate drugs were identified that may be evaluated for therapeutic value in SMDS (Fig. 7a): seven with expression profiles negatively correlated with chondrodysplasia and

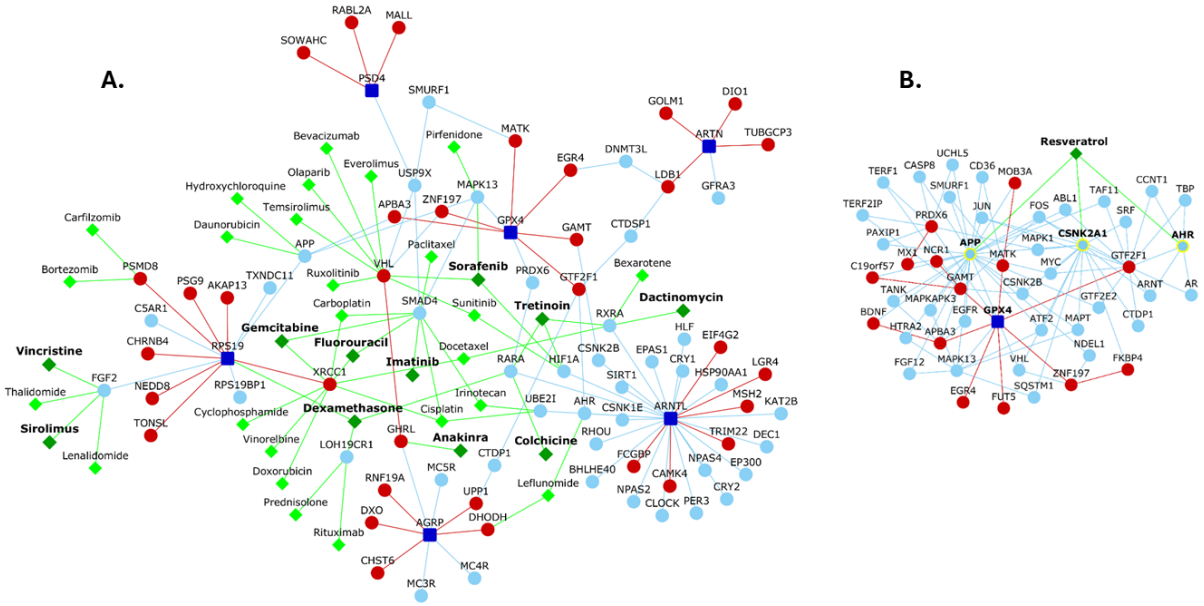



**Figure 7: SMDS associated drug–protein interactome.** (A) Drug–protein interactome linking drugs (green nodes) to proteins in the SMDS interactome; green edges denote drug–protein interactions. Repurposing candidates identified by comparative transcriptomic analysis are shown as dark green nodes with bold labels. (B) Network connecting GPX4 to the three targets of resveratrol (yellow-bordered nodes). Red and light blue nodes denote novel and known interactors, respectively; red and light blue edges denote novel and known PPIs, respectively.

ten with profiles negatively correlated with immuno-osseous dysplasia. Although subsets of genes were differentially expressed in the same direction for both the drug and disorder, the overall transcriptome-level signatures were anticorrelated. These drugs, namely, anakinra, colchicine, dactinomycin, dexamethasone, fluorouracil, gemcitabine, imatinib, sirolimus, sorafenib, tretinoin, and vincristine each target one to three proteins in the interactome.

In our second approach, we compiled a list of drugs that are currently approved for, or are undergoing phase I/II/III clinical trials in, different forms of skeletal dysplasias [49], and identified their protein targets using Drug Bank [44]. This resulted in eight drugs with 56 protein targets in the interactome; the drugs are etidronic acid, risedronic acid, denosumab (osteogenesis imperfecta), resveratrol (pseudoachondroplasia), carbamazepine (Schmid type metaphyseal dysplasia), asfotase alfa (hypophosphatasia), burosumab (X-linked hypophosphatemia), and N-acetylcysteine (diastrophic dysplasia). We examined the shortest paths connecting each of these protein targets to GPX4 and identified those exhibiting the closest network proximity. Three resveratrol targets – AHR, CSNK2A1 and APP – were connected to GPX4 via single intermediate interactors (Fig. 7b). Specifically, both AHR and CSNK2A1 were found to be connected to GPX4 via GTF2F1, a novel interactor of GPX4, whereas APP was connected via known (MAPK13) and novel (APBA3) interactors. Further supporting this network-based observation, resveratrol gene-expression profile was negatively correlated with the expression profile of immuno-osseous dysplasia.

## 4. Discussion

SMDS is an under-characterized skeletal dysplasia caused by GPX4 mutations. To expand the functional landscape of this disorder, we constructed both disease-centric and gene-centric neighborhood networks of GPX4, augmented with novel (hitherto unknown) interactors predicted by the HiPPIP algorithm. These complementary networks linked GPX4 to putative SMDS genes, related skeletal dysplasias, phenotypically similar disorders, and genes whose perturbation alters GPX4 expression. Together, they revealed consistent enrichment for SMDS-associated pathophenotypes, tissue-naïve and fetus-specific functional modules, brain/testis-enriched genes, and identified 11 candidate repurposable drugs.

Several novel interactors detected in this study have been linked to developmental deficits. EGR4 regulates hindbrain development [50], XRCC1 deficiency causes cerebellar abnormalities in mice [51], and LDB1 is required for embryonic patterning, cardiac development, and regulation of the skeletal dysplasia gene LMX1B [52, 53]. These independent observations strengthen the biological plausibility of the predicted GPX4 interaction network. Across all analyses, GPX4 emerged as a central node linking skeletal, neurodevelopmental, cardiovascular, and systemic processes. Enrichment of fetus-specific functional modules suggests developmental roles for GPX4 in cellular maintenance, cytoskeletal organization, apoptosis, and vascular development, consistent with the congenital manifestations of SMDS. The network also connected GPX4 to Joubert syndrome-associated genes and the ciliary protein TERF1, suggesting ciliary biology as a possible contributor to disease mechanisms. Enrichment of detoxification pathways in both global and fetal contexts further reinforces the established role of GPX4 in oxidative stress protection, while links

to telomere maintenance and TGF-β signaling suggest additional mechanisms warranting investigation.

The tissue-specific functional landscape of SMDS reveals strong expression of a gene cluster including GPX4 in both the brain and testis. Guo et al. have reported that the human brain and testis exhibit the highest similarity in gene expression patterns among 17 examined tissues [54]. This has been attributed to shared exocytotic processes and receptors, and to the involvement of both tissues in human speciation [55]. Functionally, the brain-elevated genes identified in this cluster were only nominally enriched (not significant after multiple-testing correction) for axon development, synaptic signalling, and mitochondrial protein localization – processes central to neural connectivity and plasticity – and would, if confirmed, be consistent with known roles of GPX4 in protecting neurons from oxidative damage. In contrast, testis-elevated genes were likewise only nominally associated with DNA recombination, cell cycle regulation, and apoptosis, which would be consistent with a role for GPX4 in germ cell maintenance and reproductive fitness. Of note, GTEx does not include bone or cartilage samples, so expression of these genes in skeletal tissue could not be assessed here. The skeletal relevance of the GPX4 interactome therefore rests on the enrichment for skeletal dysplasia phenotypes, the cartilage- and extracellular-matrix-related modules, and the links to known skeletal dysplasia genes described above, rather than on tissue expression; the relevance of the brain and testis signal to the skeletal phenotype of SMDS remains to be established.

We shortlisted 11 drugs for potential prioritization in SMDS. The prominence of anticancer drugs among the candidates likely reflects the involvement of essential cellular pathways common to both oncogenesis and skeletal dysplasia. Identification of fluorouracil, gemcitabine, and imatinib points to shared signaling pathways, including SMAD4 and TGF-β signaling [56], between dysplasia and oncogenic mechanisms. Seven of the eleven candidates (dactinomycin, fluorouracil, gemcitabine, imatinib, sirolimus, sorafenib and vincristine) are cytotoxic or broadly immunosuppressive agents, and SMDS presents in neonates, in whom such drugs carry substantial pediatric and developmental safety risks; the realistic therapeutic window for these compounds is therefore narrow, and we regard them as hypotheses about the pathways implicated here rather than as clinical candidates. The identification of anakinra and dexamethasone – both modulators of immune responses [57] – supports a role for immune dysregulation in SMDS pathophysiology. Network-based analysis further highlighted resveratrol, in our view the most defensible candidate because, unlike the cytotoxic agents above, it has reached a phase II trial in a related skeletal dysplasia (pseudoachondroplasia; NCT03866200; terminated due to recruitment challenges), implicating oxidative and inflammatory pathways [58] as potential intervention points. Finally, the observed network connections between SMDS and other skeletal dysplasias are consistent with the fact that the drugs used for osteogenesis imperfecta, hypophosphatasia, and pseudoachondroplasia target proteins linked to GPX4. Collectively, these findings nominate repurposable therapeutic candidates that warrant experimental validation. Because patient-derived material is not available, a realistic next step is to test the predicted GPX4 interactions and the highest-priority compounds (resveratrol first) in cellular or model-organism systems of GPX4 deficiency, carrying forward only candidates with mechanistic support and an acceptable pediatric safety profile. Since SMDS is typically lethal early in life, the immediate value of findings in this work is likely to lie in clarifying disease mechanism and in identifying pathways that would need to be targeted very early in

development; the same pipeline may be more directly actionable for rare genetic disorders with later onset and longer survival, where small patient populations similarly preclude conventional discovery.

This study has several limitations. First, all networks were assembled from shortest paths through the human interactome, which are biased toward highly connected, well-studied genes; enrichment for common phenotypes or for brain- and testis-elevated expression may therefore partly reflect properties of the interactome and of study bias rather than GPX4-specific biology. We did not perform a degree-preserving randomization (null model) to quantify this, and we did not compare our results against a baseline that uses only the direct interactors of GPX4 without shortest-path expansion. For the same reason, observations of network proximity (for example, of the ciliary protein TERF1 or of the resveratrol targets to GPX4) are reported descriptively and were not tested against degree-matched expectations. Second, the tissue-level functional enrichments did not remain significant after correction for multiple testing, and phenotype-enrichment P-values are nominal (uncorrected); both are presented as hypothesis-generating. Third, because no SMDS expression data exist, the transcriptome-based drug analysis uses chondrodysplasia and immuno-osseous dysplasia datasets as proxies, which assumes that the transcriptional signature of SMDS resembles theirs; this assumption is untested. Fourth, the seven novel GPX4 interactors are computational predictions that (albeit believed to be of high confidence) were not experimentally tested here, and the six DisGeNET-derived genes rest on literature co-mention with minimal supporting evidence.

The methods and tools used here have been applied previously by our group to other disorders, so the contribution of this work is their application to SMDS rather than a new method, and we did not benchmark the approach against alternative rare-disease gene-prioritization methods (such as network propagation or phenotype-driven tools), because no ground truth beyond GPX4 itself is available for SMDS. The novel interactors predicted by HiPPIP substantially expand the molecular landscape of GPX4 and provide experimentally testable hypotheses for elucidating the molecular mechanisms underlying SMDS. Together, our findings position GPX4 as a focal node at the intersection of skeletal dysplasia, neurodevelopmental disorders, and systemic homeostasis, providing a structured framework for prioritizing genes, pathways, and therapeutic hypotheses for this rare disease.

## 5. Supplementary Material

Additional details and vector graphics figures, which can be magnified without loss of resolution and searched by gene name, are available on Zenodo (https://doi.org/10.5281/zenodo.23091097) and at https://severus.dbmi.pitt.edu/gpx4/. All analyses were performed using web-based tools, so no scripts were used.

## 6. Author Contributions

MKG formulated the project idea to put the interactome-based analysis together motivated by the call “Let’s Find a Cure Together” (https://www.curegpx4.org/). KBK carried out the analysis of the interactomes, presenting literature-based evidence, supervised by NB and MKG. Manuscript has been drafted by KBK and edited by MKG.

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