Supplementary Information

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

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Supplementary Table 1: Biological relevance of novel interactors of GPX4. The table lists different pieces of evidence gathered from our study that support the biological validity of the computationally predicted novel interactors of GPX4 to SMDS or GPX4 itself. Note that in the table, "phenotypic similarity" refers to "phenotypic similarity with SMDS" (unless specified otherwise). SMDS: SpondyloMetaphyseal Dysplasia, Sedaghatian type, SD: Spondylometaphyseal Dysplasia.

Gene	Potential biological relevance to GPX4/SMDS
APBA3	An intermediate interactor of GPX4 and IARS2, an arrhythmia-and X-linked spondyloepimetaphyseal dysplasia-associated gene (the latter is a bone dysplasia phenotypically similar to SMDS) A known interactor of BCR1, mutations in which leads to underexpression of KIAA0586, a gene associated with Joubert syndrome (which shares several phenotypes with SMDS) An intermediate interactor of GPX4 and APP, which is targeted by resveratrol, a drug currently in clinical trials for skeletal dysplasias Co-occurred with GPX4 and its other novel interactors (GAMT and GTF2F1), and with potential SMDS-associated genes (RPS19) and/or their novel interactors (NEDD8, PSMD8, XRCC1 and DXO) in a cellular oxidant detoxification module Co-occurred along with novel interactors of GPX4 (GTF2F1) and novel interactors of SD-associated genes (RXRB, SLC48A1 and SF3A2) in an epithelial morphogenesis and fetus-specific protein catabolic process Co-occurred with other novel interactors of GPX4 (GTF2F1) and novel interactors of genes associated with phenotypically similar bone dysplasias (DNASE1L1) in a toxic substance response module
EGR4	A transcription factor that regulates hind brain development in *Xenopus* Connected via DNMT3L to a novel interactor of the (potentially) SMDS-associated ARTN called LDB1, mutations in which lead to patterning defects Showed expression-based clustering with GPX4 due to elevated expression in brain tissues EGR4 mice mutants shared 6 phenotypes with GPX4 mice mutants: male infertility, oligozoospermia, small testis, abnormal sperm head morphology, decreased testis weight and kinked sperm flagellum Co-occurred in an adenylate cyclase-activating GPCR signaling module along with other novel interactors of GPX4 (MATK and ZNF197) and with potential SMDS-associated genes (ARTN and AGRP) and/or their novel interactors (CHRNB4, PSG9, TONSL, CAMK4, FCGBP, DIO1 and DHODH) Co-occurred in extracellular organization/cartilage development modules with other novel interactors of GPX4 (FUT5 and ZNF197) and with SD-associated genes (COL2A1 and TRPV4) and novel interactors of SD-associated genes (SPDYA, MST1, DRD2, KMT2D, GP5, LY6H, SERPINA4, CLSPN, IKZF2 and TM6SF2) Co-occurred in autophosphorylation and neurogenesis modules with other novel interactors of GPX4 (FUT5 and ZNF197) and genes whose perturbation leads to differential expression of GPX4 (NTRK1 and DNMT3L)
FUT5	Showed expression-based clustering with GPX4 due to elevated expression in the testis Co-occurred in extracellular organization/cartilage development modules with other novel interactors of GPX4 (EGR4 and ZNF197) and with SD-associated genes (COL2A1 and TRPV4) and novel interactors of SD-associated genes (SPDYA, MST1, DRD2, KMT2D, GP5, LY6H, SERPINA4, CLSPN, IKZF2 and TM6SF2) Co-occurred in autophosphorylation and neurogenesis modules with other novel interactors of GPX4 (EGR4 and ZNF197) and genes whose perturbation leads to differential expression of GPX4 (NTRK1 and DNMT3L)
GAMT	An intermediate interactor connecting GPX4 with the ciliary protein TERF1 GAMT mice mutants shared 4 phenotypes with GPX4 mice mutants decreased body weight: decreased body weight, oligozoospermia, reduced male fertility and postnatal lethality

	Co-occurred with GPX4 and its other novel interactors (APBA3 and GTF2F1), and with potential SMDS-associated genes (RPS19) and/or their novel interactors (NEDD8, PSMD8, XRCC1 and DXO) in a cellular oxidant detoxification module
GTF2F1	An intermediate interactor of GPX4 and PAM16, a Megarbane type SMD gene associated with metaphyseal cupping and platyspondyly A known interactor of ABL1, mutations in which leads to underexpression of KIAA0586, a gene associated with Joubert syndrome (which shares several phenotypes with SMDS) An intermediate interactor of GPX4 and two targets (AHR and CSNK2A1) of resveratrol, a drug currently in clinical trials for skeletal dysplasias Connected via CTDSP1 to a novel interactor of the (potentially) SMDS-associated ARTN called LDB1, mutations in which lead to patterning defects Co-occurred with GPX4 and its other novel interactors (APBA3 and GAMT), and with potential SMDS-associated genes (RPS19) and/or their novel interactors (NEDD8, PSMD8, XRCC1 and DXO) in a cellular oxidant detoxification module Co-occurred along with other novel interactors of GPX4 (GTF2F1) and novel interactors of SD-associated genes (RXRB, SLC48A1 and SF3A2) in an epithelial morphogenesis module Co-occurred with other novel interactors of GPX4 (APBA3) and novel interactors of genes associated with phenotypically similar bone dysplasias (DNASE1L1) in a toxic substance response module
MATK	Showed expression-based clustering with GPX4 due to elevated expression in brain tissues Co-occurred in an adenylate cyclase-activating GPCR signaling module along with other novel interactors of GPX4 (EGR4 and ZNF197) and with potential SMDS-associated genes (ARTN and AGRP) and/or their novel interactors (CHRNB4, PSG9, TONSL, CAMK4, FCGBP, DIO1 and DHODH) Co-occurred in a fetus-specific extracellular organization/cartilage development modules with other novel interactors of GPX4 (FUT5 and ZNF197) and with SD-associated genes (COL2A1 and TRPV4) and novel interactors of SD-associated genes (SPDYA, MST1, DRD2, KMT2D, GP5, LY6H, SERPINA4, CLSPN, IKZF2, TM6SF2, CD3G, FICD, NPTX1 and RASGRP4)
ZNF197	An intermediate interactor of GPX4 and the myocarditis-associated VHL An intermediate interactor of GPX4 and IARS2, an arrhythmia-and X-linked spondyloepimetaphyseal dysplasia-associated gene (the latter is a bone dysplasia phenotypically similar to SMDS) A known interactor of TRIM28, mutations in which leads to underexpression of IFT140, a gene associated with Joubert syndrome (which shares several phenotypes with SMDS) ZNF197 mice mutants shared the phenotype, reduced male fertility, with GPX4 mice mutants Recruited by VHL to inhibit HIF1A transcriptional activity. Speculation: GPX4 exerts its inhibitory activity on VEGFA, a critical component of the VEGF signaling pathway that is known to play a role in bone development, via its direct interaction with the ZNF197-VHL complex. Perturbed GPX4 activity in SMDS may remove this inhibitory effect and promote abnormal VEFGA protein expression and bone development Co-occurred in an adenylate cyclase-activating GPCR signaling module along with other novel interactors of GPX4 (MATK and EGR4) and with potential SMDS-associated genes (ARTN and AGRP) and/or their novel interactors (CHRNB4, PSG9, TONSL, CAMK4, FCGBP, DIO1 and DHODH) Co-occurred in extracellular organization/cartilage development modules with other novel interactors of GPX4 (EGR4 and ZNF197) and with SD-associated genes (COL2A1 and TRPV4) and novel interactors of SD-associated genes (SPDYA, MST1, DRD2, KMT2D, GP5, LY6H, SERPINA4, CLSPN, IKZF2 and TM6SF2) Co-occurred in a humoral immune response module along genes associated with bone dysplasia that are phenotypically similar to SMDS (IHH) and novel interactors of bone dysplasia genes (TEX28, HHIPL2, SUSD4 and SLC30A10) Co-occurred in a fetus-specific lipid storage/reactive oxygen species biosynthetic process module with novel interactors of bone dysplasia genes (CCL20, AMDHD2, HHIPL2 and SLC30A10) Co-occurred in autophosphorylation and neurogenesis modules with other novel interactors of GPX4 (EGR4 and FUT5) and genes whose perturbation leads to differential expression of GPX4 (NTRK1 and DNMT3L)