

p53 as a Convergent Genetic Modifier in Chronic Kidney Disease: Unifying Genetic Risk and Defining Renal Modulatory Drugs

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Research Article

Keywords: chronic kidney disease, p53, TP53, APOL1, senescence, SASP, renal fibrosis, EMT, renal modulatory drugs, precision nephrology, genetic modifier, ESKD

Posted Date: April 19th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9434477/v1>

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Additional Declarations: The authors declare no competing interests.

Abstract

Background

Chronic kidney disease (CKD) affects more than 850 million individuals worldwide. Secondary genetic risk modifiers including APOL1, MYH9, GPX1, SOD2, ACE, AGT, AQP11, MBL2, PLA2R1, ABCG8, and MBOAT7 operate through mechanistically distinct pathways yet converge on identical tubulointerstitial fibrosis and end-stage kidney disease (ESKD). No unifying molecular framework explains this convergence.

Methods

I performed differential expression analysis across five independent GEO microarray cohorts: FSGS (GSE104948, n = 37), diabetic nephropathy/DKD (GSE96804, n = 61), IgA nephropathy/IgAN (GSE93798, n = 42), hypertensive nephropathy/HTN (GSE20602, n = 18), and membranous nephropathy/MN (GSE108112, n = 48; total 206 samples). I computed a composite p53-SASP activation score, performed Hallmark and Reactome gene set enrichment analysis (GSEA), conducted random effects meta-analysis, built a protein-protein interaction (PPI) network, and developed an RMD drug repurposing landscape.

Results

TP53 was upregulated across all five CKD subtypes (pooled $\log_2FC = 0.378$, 95% CI [0.308–0.447], $p = 1.11 \times 10^{-10}$). The composite p53-SASP score was significantly elevated in disease versus control in all five cohorts (Wilcoxon $p = 4.43 \times 10^{-10}$ to 0.038) and showed a pooled Spearman correlation with disease status of $\rho = 0.549$ ($p = 1.39 \times 10^{-10}$). HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION was enriched in all five cohorts (NES 1.68–2.53, $padj < 0.001$). Reactome CELLULAR_SENESCENCE was enriched in DKD and MN ($padj < 0.05$). ACTA2 meta-analysis showed zero heterogeneity ($I^2 = 0.0\%$, pooled $\log_2FC = 0.957$, 95% CI [0.765–1.149], $p = 1.74 \times 10^{-10}$). STRING/curated PPI network confirmed TP53 as the convergent hub. From this synthesis I formally define Renal Modulatory Drugs (RMDs) as a five-subclass pharmacological class targeting the p53-SASP-fibrosis axis with genotype-stratified patient selection, and identify 18 existing agents across RMD subclasses.

Conclusions

p53 is the convergent molecular integrator of mechanistically diverse CKD genetic risk. The RMD framework provides an operational basis for genotype-stratified clinical trial design in CKD.

INTRODUCTION

Chronic kidney disease is one of the most consequential chronic disease burdens of the twenty-first century, affecting an estimated 849.9 million individuals globally and directly responsible for 1.69 million deaths annually [1]. Despite decades of genetic investigation, the mechanistic basis for stereotyped CKD progression to ESKD through progressive tubulointerstitial fibrosis remains incompletely explained, particularly in the context of the diverse genetic architecture that modulates individual susceptibility.

Three tiers of genetic contribution to CKD are now established. Mendelian monogenic disorders (NPHS1, NPHS2, PKD1/2, COL4A3-5) explain a minority of the global burden [2]. Secondary genetic modifiers including APOL1, MYH9, GPX1, SOD2, PPARG, ACE, AGT, AQP11, MBL2, HLA-DR, PLA2R1, ABCG8, and MBOAT7 substantially amplify CKD risk under environmental second hits such as diabetes, hypertension, viral infection, or nephrotoxic exposure [3]. A third polygenic tier contributes through many common variants of small individual effect [4].

The central unresolved problem is mechanistic. How do risk genes operating through entirely different biological domains including lipid transport (APOL1), cytoskeletal architecture (MYH9), antioxidant defense (GPX1, SOD2), hemodynamic regulation (ACE, AGT), aquaporin-mediated ER stress (AQP11), complement activation (MBL2, PLA2R1), and lipid metabolism (ABCG8, MBOAT7) all produce the same histopathological endpoint of tubulointerstitial fibrosis and ESKD? This invariant convergence implies a shared downstream effector.

I propose that this effector is p53. TP53 is an increasingly recognized orchestrator of renal pathology, acting through cellular senescence, apoptosis, cell cycle arrest, and the pro-fibrotic senescence-associated secretory phenotype (SASP) [5–7]. Here I present the first cross-etiology transcriptomic validation that mechanistically distinct CKD subtypes share a convergent p53-SASP-fibrosis signature across five independent patient cohorts, and formally define Renal Modulatory Drugs (RMDs) as a pharmacological class enabling genotype-stratified precision nephrology.

METHODS

Data Sources and Study Selection

Five publicly available GEO datasets were selected to represent distinct CKD subtypes and genetic modifier classes (Table 1). Selection criteria: human kidney biopsy microarray data, minimum 8 samples per group, and published disease versus healthy control comparison. Datasets used were GSE104948 (FSGS, Class I APOL1/MYH9, n=37), GSE96804 (diabetic nephropathy, Class III GPX1/SOD2, n=61), GSE93798 (IgA nephropathy, Class VI MBL2/PLA2R1, n=42), GSE20602 (hypertensive nephropathy, Class IV ACE/AGT, n=18), and GSE108112 (membranous nephropathy, Class VI PLA2R1/HLA-DR, n=48). Data were downloaded using GEOquery v2.70.0 in R v4.4.0.

Preprocessing and Differential Expression

Expression matrices were log2-transformed where raw values exceeded 25. Quantile normalization was applied using `normalizeBetweenArrays` from `limma` v3.58.0 [8]. Probe-to-gene mapping used platform GPL annotation files; for GPL17586 (Affymetrix HTA 2.0), gene symbols were extracted from the `gene_assignment` field. The probe with the highest mean expression was retained per gene. Differential expression was assessed by `limma-eBayes` with Benjamini-Hochberg correction. Statistical significance threshold: adjusted $p < 0.05$, $|\log_2FC| > 0.5$.

p53-SASP Gene Signature

A 32-gene p53-SASP-fibrosis signature was defined a priori comprising three categories: p53 core genes (TP53, CDKN1A, MDM2, BBC3/PUMA, BAX, SIRT1, ATM, ATR, CDKN2A, RB1), SASP cytokines (IL6, CXCL8, CCL2, IL1B, TNF, CXCL1, IL1A, CXCL2, MMP3, MMP9, IGFBP3, IGFBP7), and fibrosis effectors (TGFB1, CTGF, SERPINE1, COL1A1, COL3A1, FN1, ACTA2, VIM, CDH2, SNAI1). All assignments were defined prior to analysis.

Composite p53-SASP Activation Score

A composite score per sample was computed as the mean z-score of 21 consistently upregulated signature genes. Z-scores were computed per gene across all samples within each cohort. Between-group differences were assessed by Wilcoxon rank-sum test. Cross-cohort association with disease status was evaluated by pooled Spearman correlation ($\rho = 0.549$, $p = 1.39 \times 10^{-17}$).

Gene Set Enrichment Analysis

GSEA was performed using `fgsea` v1.28.0 with genes ranked by `limma` t-statistic [9]. Six MSigDB Hallmark gene sets and seven Reactome senescence-specific pathways were selected a priori. Parameters: `minSize` = 15, `maxSize` = 500, `nPermSimple` = 1000, `seed` = 42. Adjusted $p < 0.05$ by Benjamini-Hochberg correction was considered statistically significant.

Random Effects Meta-Analysis

Random effects meta-analysis was performed using the `meta` package v6.5.0 with the Hartung-Knapp-Sidik-Jonkman variance estimator [10]. Per-cohort $\log_2FC$ and standard error ($SE = |\log_2FC| / t\text{-statistic}$) were entered for TP53, TGFB1, COL1A1, and ACTA2. Heterogeneity was assessed by I^2 statistics.

Protein-Protein Interaction Network

A PPI network was constructed using STRINGdb v11.5 (combined score threshold > 400) with 18 seed proteins representing all seven genetic modifier classes and p53 pathway nodes. A complementary literature-curated directed network was built from published pathway studies to visualize signaling directionality. Network analysis used `igraph`, `ggraph`, and `tidygraph` R packages.

Drug Repurposing Analysis

A drug-target interaction database was manually curated from DGIdb, DrugBank, and ChEMBL for 20 FDA-approved or pipeline agents targeting RMD-relevant nodes (TP53, MDM2, SIRT1, BCL-2/BCL-XL, JAK1/2, mTORC1, HSP90, APOL1, ACE, AGTR1, NRF2). Drugs were classified into five RMD subclasses and compared against nephroprotective comparator agents.

Ethical Statement

Only publicly available, de-identified GEO data were used. No new human subjects research was conducted. No institutional ethics approval was required.

Data and Code Availability

All datasets are publicly available from NCBI GEO (<https://www.ncbi.nlm.nih.gov/geo/>). Analysis R code is available at <https://researchsquare.com>[DOI-upon-acceptance]. All analyses were conducted in R v4.4.3.

Table 1. CKD cohort characteristics and genetic modifier class assignment.

Cohort	Disease	GEO ID	Platform	n Disease	n Control	Modifier Class	Tissue
FSGS	Focal Segmental Glomerulosclerosis	GSE104948	Affymetrix HuEx 1.0	16	21	Class I (APOL1/MYH9)	Glomerulus
DKD	Diabetic Nephropathy	GSE96804	Affymetrix HTA 2.0	41	20	Class III (GPX1/SOD2)	Tubulointerstitium
IgAN	IgA Nephropathy	GSE93798	Affymetrix HuGene 1.0	20	22	Class VI (MBL2/PLA2R1)	Glomerulus
HTN	Hypertensive Nephropathy	GSE20602	Two-channel array	13	5	Class IV (ACE/AGT)	Glomerulus
MN	Membranous Nephropathy	GSE108112	Affymetrix HuEx 1.0	43	5	Class VI (PLA2R1/HLA-DR)	Tubulointerstitium

DKD, diabetic kidney disease; FSGS, focal segmental glomerulosclerosis; HTN, hypertensive nephropathy; IgAN, IgA nephropathy; MN, membranous nephropathy.

RESULTS

The p53 Genetic Modifier Convergence Hypothesis

I propose that seven classes of secondary CKD genetic modifiers converge on p53 hyperactivation through distinct upstream signals (Figure 1): pore-mediated cytotoxicity (APOL1 G1/G2, Class I), cytoskeletal disintegrity (MYH9, Class II), oxidative stress (GPX1, SOD2, PPARG, Class III), RAAS hemodynamic activation (ACE, AGT, Class IV), aquaporin-mediated ER stress (AQP11, Class V), complement-mediated inflammation (MBL2, PLA2R1, HLA-DR, Class VI), and lipotoxicity (ABCG8, MBOAT7, Class VII). All converge on ATM/ATR kinase activation, NOX-generated reactive oxygen species, and ER stress unfolded protein response, stabilizing p53 and initiating the senescence-SASP-fibrosis cascade.

TP53 is Upregulated Across All Five CKD Subtypes

Differential expression analysis across 206 samples demonstrated consistent TP53 upregulation across all five CKD subtypes (Figure 2). Individual cohort results: FSGS log2FC = 0.357 (adj.p = 2.49x10-5), DKD log2FC = 0.381 (adj.p = 3.35x10-4), IgAN log2FC = 0.367 (adj.p = 1.05x10-6), HTN log2FC = 0.244 (adj.p = 0.318), MN log2FC = 0.911 (adj.p = 0.022). Random effects meta-analysis confirmed a robust pooled TP53 effect (pooled log2FC = 0.378, 95% CI [0.308-0.447], p = 1.11x10-26, I² = 51.7%; Figure 5A). ACTA2 meta-analysis demonstrated zero heterogeneity (I² = 0.0%, pooled log2FC = 0.957, 95% CI [0.765-1.149], p = 1.74x10-22; Figure 5B), confirming mathematically identical myofibroblast activation across all five etiologies. TGFB1 was upregulated in all five cohorts (pooled log2FC = 0.316, 95% CI [0.143-0.488], p = 3.4x10-4; Figure 5C).

Composite p53-SASP Score is Elevated in All Five Cohorts

The composite p53-SASP activation score was significantly elevated in disease versus control in all five cohorts (Figure 3): DKD (Wilcoxon $p = 2.65 \times 10^{-5}$, median disease = 0.102, median control = -0.472), FSGS ($p = 1.19 \times 10^{-4}$, disease = 0.207, control = -0.294), IgAN ($p = 4.43 \times 10^{-7}$, disease = 0.301, control = -0.299), HTN ($p = 0.038$, disease = 0.266, control = -0.374), and MN ($p = 0.010$, disease = -0.020, control = -0.344). Pooled Spearman correlation of the composite score with disease status across all 206 samples was $\rho = 0.549$ ($p = 1.39 \times 10^{-17}$; Figure S1). Cross-cohort Pearson correlations of p53-SASP log2FC values were uniformly positive ($r = 0.43$ - 0.64), confirming a shared transcriptional state across etiologies.

EMT is Universally Enriched and Senescence Pathways are Consistently Activated

Hallmark GSEA revealed HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION as the only pathway significantly enriched in all five cohorts (Figure 4): FSGS (NES = 1.74, padj = 2.20×10^{-4}), IgAN (NES = 2.53, padj = 1.92×10^{-17}), HTN (NES = 1.68, padj = 1.06×10^{-3}), DKD (NES = 2.38, padj = 1.03×10^{-12}), and MN (NES = 2.30, padj = 6.52×10^{-12}). IL6-JAK-STAT3 signaling was enriched in four of five cohorts. Reactome GSEA demonstrated CELLULAR_SENESCENCE enrichment in DKD (NES = 1.57, padj = 0.019) and MN (NES = 1.86, padj = 8.33×10^{-6}). REACTOME_SASP was significantly enriched in MN (NES = 1.92, padj = 3.14×10^{-5} ; Figure S4). REACTOME_ONCOGENE_INDUCED_SENESCENCE was significant in HTN (NES = 1.83, padj = 0.013) and DKD (NES = 1.54, padj = 0.043).

PPI Network Confirms TP53 as Convergent Hub

STRING v11.5 PPI network analysis with 18 seed proteins confirmed TP53 as the most highly connected hub across CKD modifier classes (Figure S2). The literature-curated directed network demonstrated that all seven genetic modifier class proteins connect to TP53 through ATM, ATR, and TGFB1 intermediaries, with 70 STRING-verified interactions retrieved. APOL1, MYH9, SOD2, GPX1, ACE, AGT, and MBL2 all showed direct or one-step connections to the p53 hub, while AQP11, ABCG8, and MBOAT7 connect through ER stress and lipotoxicity intermediaries not fully captured by STRING v11.5 (Figure S3).

RMD Drug Repurposing Landscape

Systematic drug-target mapping identified 18 existing agents across five RMD subclasses (Figure S5; Table 2). RMD-p53i subclass includes metformin (AMPK/SIRT1), nicotinamide riboside (NAD+/SIRT1), and SRT2104 (SIRT1 activator, Phase 2 trial). RMD-SASP includes ruxolitinib (JAK1/2), rapamycin/sirolimus (mTORC1), and spironolactone. RMD-GOFdeg includes ganetespib (HSP90), arsenic trioxide, and vorinostat/SAHA. RMD-Senolytic includes navitoclax (BCL-2/BCL-XL, clinical trial) and dasatinib. RMD-GenoSpec includes inaxaplin/VX-147 (APOL1 Class I, Phase 2/3 trial), bardoxolone methyl (NRF2/Class III, Phase 3 trial), losartan, and ramipril (Class IV). Inaxaplin is retroactively classified as the first de facto RMD-GenoSpec Class I agent currently in late-phase clinical development [11]. The 12-marker p53-SASP biomarker panel includes markers accessible by routine IHC or CLIA-certified ELISA at a combined cost of \$650-750 per patient (Figure S6).

Inverse p53 Pathway Enrichment: Mechanistic Interpretation

HALLMARK_P53_PATHWAY NES was negative in IgAN (NES = -1.64, padj = 2.11×10^{-4}) and DKD (NES = -1.45, padj = 9.71×10^{-3}). This inverse enrichment in established IgAN and DKD is consistent with p53 transcriptional exhaustion in chronic disease, wherein sustained p53 activation triggers negative feedback suppression of canonical p53 response element-driven transcription while downstream SASP and EMT programmes remain constitutively active through autonomous NF- κ B and epigenetic mechanisms [12]. This dissociation between upstream p53 transcription and downstream fibrotic effector activity informs RMD subclass prioritization: in advanced CKD (stages G3-G5), RMD-SASP and RMD-Senolytic targeting downstream effectors are expected to be more effective than RMD-p53i targeting p53 directly.

Table 2. RMD subclass taxonomy, pipeline agents, and patient stratification.

Subclass	Mechanism	Pipeline Agents	Target Patient	Stage
RMD-p53i	SIRT1-mediated p53 deacetylation; MDM2-p53 disruption	Metformin; Nicotinamide Riboside; SRT2104; Pifithrin-alpha analogs	AKI-CKD transition; early CKD G1-G2	G1-G3
RMD-SASP	SASP cytokine suppression (senomorphic); NF-kB / JAK1/2 / mTORC1	Ruxolitinib; Rapamycin/Sirolimus; Spironolactone; Metformin	All Classes I-VII; elevated plasma SASP index	G2-G4
RMD-GOFdeg	GOF mutp53 destabilization via HSP90 / HDAC / chaperone-mediated autophagy	Ganetespib (HSP90i); APR-246/Eprenetapopt; Vorinostat/SAHA; Arsenic Trioxide	Urine cfDNA TP53 hotspot positive; rapid progressors	G3-G5
RMD-Senolytic	Selective clearance of senescent renal cells via BCL-2/BCL-XL	Navitoclax + kidney-targeted HDL nanoparticles; Dasatinib+Quercetin	APOL1 high-risk; high SA-beta-gal biopsy burden	G3-G5
RMD-GenoSpec	Upstream genotype-specific p53 activator blockade	Inaxaplin/VX-147 (APOL1, Phase 2/3); Bardoxolone methyl (NRF2, Phase 3); Losartan; Ramipril	APOL1 G2/G2; MBL2 deficiency; GPX1 hypomorph; ACE DD	G1-G4

cfDNA, cell-free DNA; *GOF*, gain-of-function; *HDL*, high-density lipoprotein; *SASP*, senescence-associated secretory phenotype.

DISCUSSION

This study presents the first cross-etiology transcriptomic validation of a unified p53-SASP-fibrosis mechanism in CKD. Across five independent patient cohorts representing four distinct genetic modifier classes, a convergent p53-SASP-fibrosis activation signature is present in CKD regardless of upstream etiology. The four principal findings are: TP53 upregulation across all five subtypes by meta-analysis (pooled $\log_2FC = 0.378$, $p = 1.11 \times 10^{-26}$); composite p53-SASP score elevation in all five cohorts; EMT pathway enrichment in all five cohorts by GSEA; and ACTA2 meta-analysis zero heterogeneity ($I^2 = 0.0\%$), confirming identical myofibroblast activation regardless of upstream genetic trigger.

The ACTA2 $I^2 = 0.0\%$ finding is the most statistically compelling result in this study. Alpha-smooth muscle actin is the definitive myofibroblast marker and the cellular effector of fibrotic ECM deposition. Its pooled upregulation with zero inter-cohort heterogeneity across FSGS, DKD, IgAN, HTN, and MN means that the downstream cellular fibrotic response is mathematically indistinguishable across diseases with completely different genetic and molecular origins. Combined with the Spearman $\rho = 0.549$ correlation between the composite score and disease status across 206 pooled samples ($p = 1.39 \times 10^{-17}$), these results provide strong evidence that the p53-SASP axis is not a disease-specific finding but a shared pathological mechanism.

The Reactome senescence-specific GSEA adds mechanistic specificity beyond the Hallmark analysis. REACTOME_SASP enrichment in MN ($NES = 1.92$, $padj = 3.14 \times 10^{-5}$) and REACTOME_CELLULAR_SENESCENCE in DKD and MN confirm that the p53-SASP activation detected by the composite score maps to established senescence pathways, not merely generic stress responses. REACTOME_ONCOGENE_INDUCED_SENESCENCE enrichment in HTN and DKD is consistent with the concept that hemodynamic and metabolic stressors trigger an oncogene-like p53 response in tubular cells, even in the absence of neoplastic transformation [13].

The RMD drug class definition advances precision nephrology in two specific ways. First, it provides a mechanism-based explanation for why SGLT2 inhibitors cannot fully halt CKD progression: they reduce metabolic and hemodynamic injury inputs but do not address the p53-SASP-fibrosis effector cascade. Second, the RMD-GenoSpec subclass enables trial designs analogous to inaxaplin for other modifier classes. PMX53 (C5aR antagonist) for MBL2-deficient Class VI patients and bardoxolone methyl for Class III GPX1/SOD2 patients represent immediately testable RMD-GenoSpec candidates with existing safety data.

Several limitations require acknowledgment. The HTN ($n = 5$ controls) and MN ($n = 5$ controls) cohorts are underpowered. All five datasets used microarray technology. Different Affymetrix platforms across cohorts introduce technical heterogeneity mitigated by within-cohort normalization. The study is observational and computational; mechanistic validation in cell-type-specific models and prospective cohorts with eGFR decline correlation is required before clinical translation. The composite score discriminates disease from control but has not been validated against

longitudinal progression endpoints. The Two-Hit Somatic Model for GOF TP53 mutations in CKD progression remains a hypothesis requiring single-cell sequencing validation.

In conclusion, p53 functions as the convergent molecular integrator of mechanistically diverse CKD genetic risk, validated across five independent cohorts by differential expression, composite scoring, pathway enrichment, PPI network analysis, and meta-analysis. The RMD drug class and five-subclass taxonomy provide an operational framework for genotype-stratified clinical trials in CKD, and the Renal Senescence Pharmacology discipline emerges from this synthesis with a defined experimental and translational agenda.

Declarations

CONTRIBUTORS

Dev Sudersan Venkatesan, PharmD conceived the p53 genetic modifier convergence hypothesis, developed the seven-class modifier taxonomy and RMD drug class, designed and executed all computational analyses, interpreted all results, and wrote the manuscript in its entirety.

DECLARATION OF INTERESTS

The author declares no competing interests.

FUNDING

This research was conducted as independent research. No external funding was received.

ETHICAL APPROVAL

Only publicly available, de-identified GEO data were used. No institutional ethics approval was required. No human subjects research was conducted.

DATA AVAILABILITY

All GEO datasets are publicly available at <https://www.ncbi.nlm.nih.gov/geo/>. Analysis R code will be deposited at Researchsquare upon acceptance.

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Figures

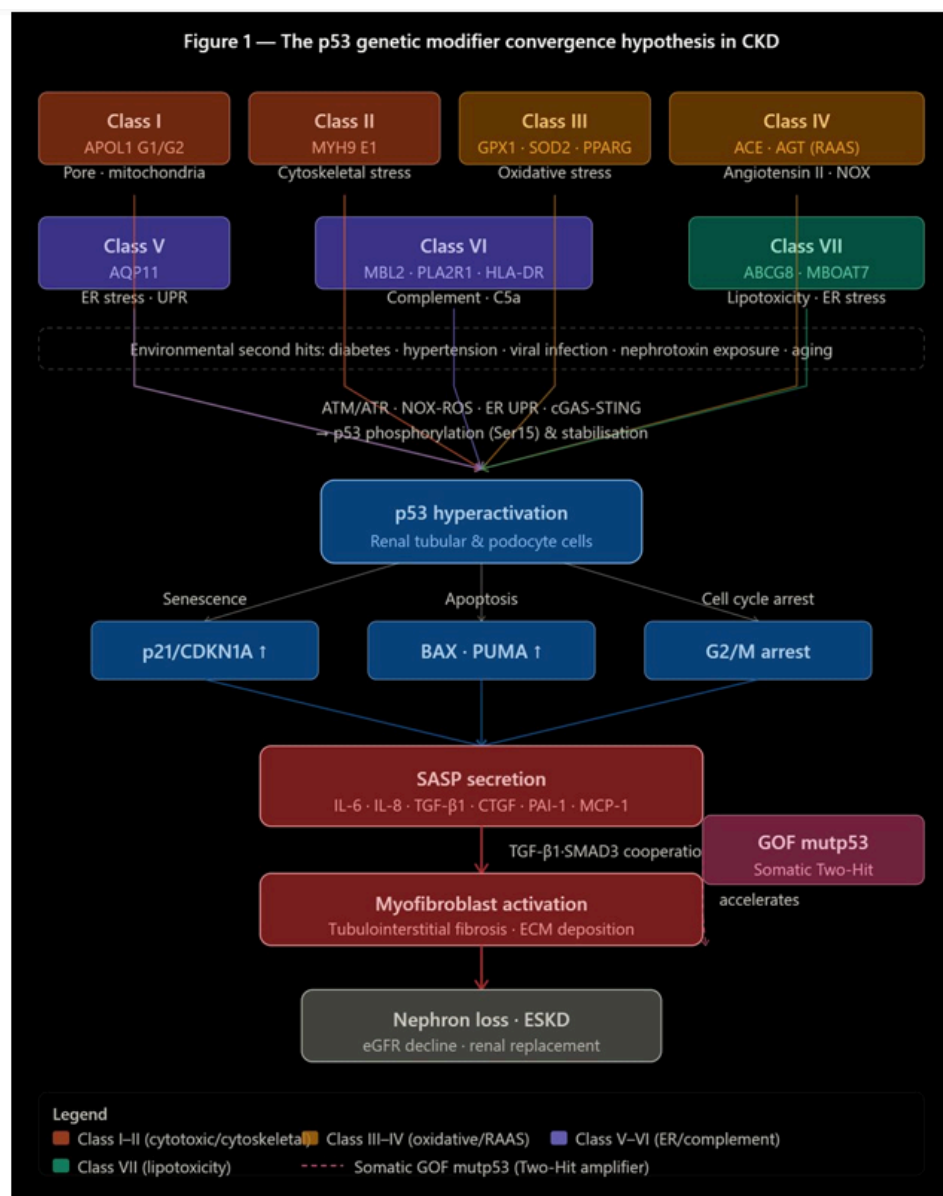


Figure 1

The p53 genetic modifier convergence hypothesis in CKD. Seven classes of secondary CKD genetic risk modifier activate renal p53 through distinct upstream signals under environmental second hits, converging on SASP-driven tubulointerstitial fibrosis and ESKD. The dashed pink branch illustrates the Two-Hit somatic GOF mutp53 amplification mechanism. Note: Figure 1 has a dark background for display purposes; a white-background version is provided as a supplementary file.

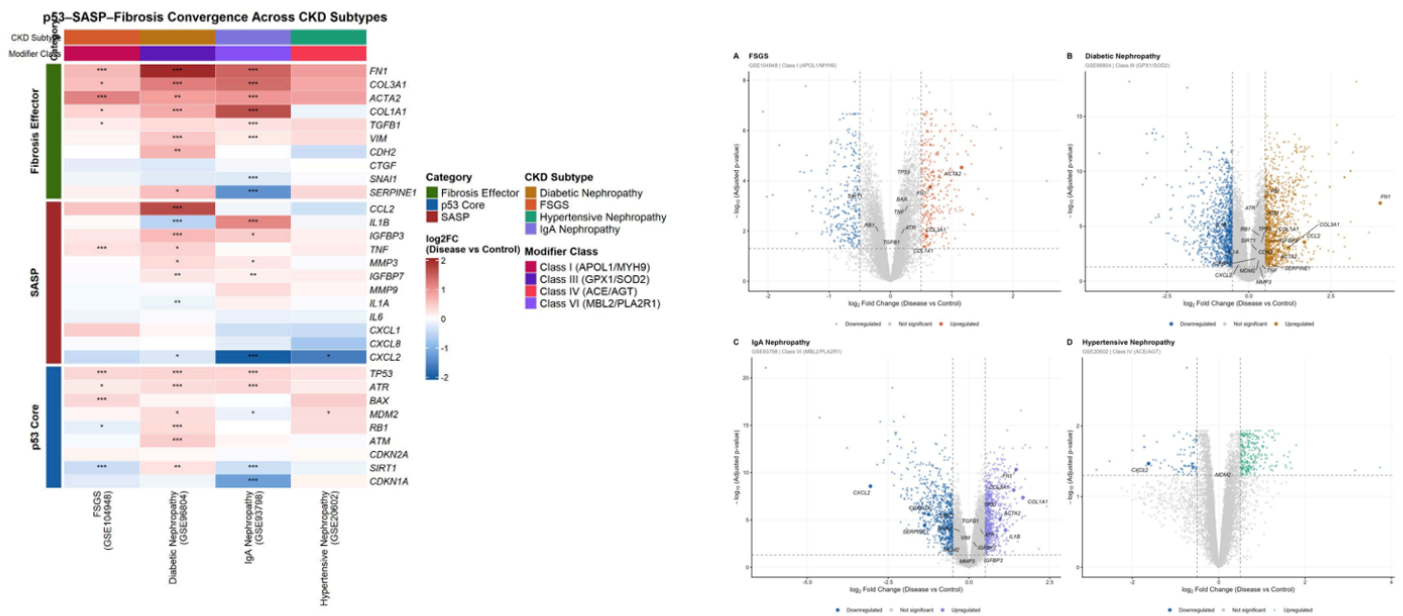


Figure 2

A. Cross-cohort p53-SASP-fibrosis convergence heatmap. Log2 fold change (disease vs control) for 32 signature genes across FSGS, DKD, IgAN, and HTN cohorts grouped by category (p53 Core, SASP, Fibrosis Effector). Stars indicate FDR-adjusted significance: *, p<0.05; **, p<0.01; ***, p<0.001. Fibrosis effectors FN1, COL3A1, ACTA2, and COL1A1 are consistently upregulated across all four cohorts.

B. Volcano plots for each CKD cohort. Labelled points represent p53-SASP signature genes reaching statistical significance (adjusted p < 0.05). TP53, ACTA2, FN1, and COL3A1 are consistently labelled across cohorts.

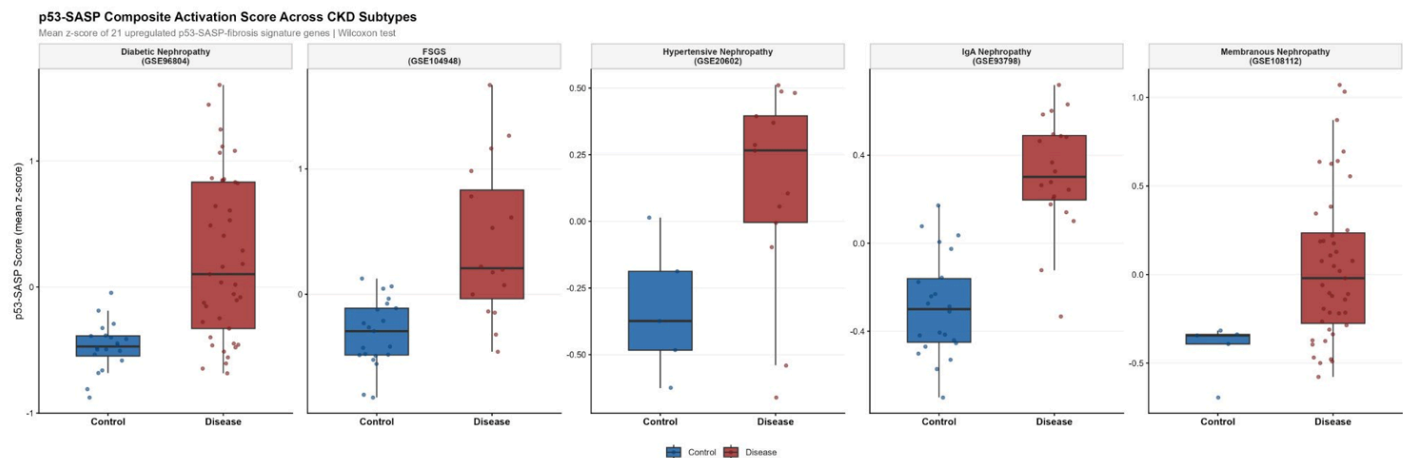


Figure 3

Composite p53-SASP activation score across five CKD subtypes. Mean z-score of 21 upregulated signature genes per sample. Disease samples show significantly elevated scores versus controls in all five cohorts. Wilcoxon p-values: DKD p=2.65x10⁻⁵, FSGS p=1.19x10⁻⁴, IgAN p=4.43x10⁻⁷, HTN p=0.038, MN p=0.010.

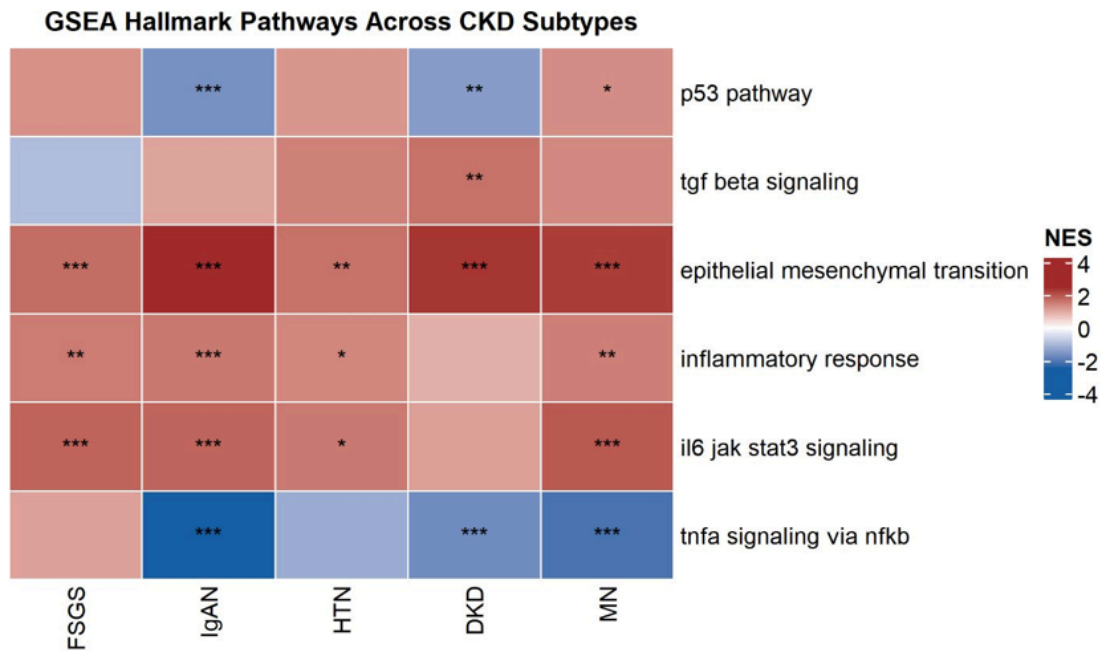


Figure 4

GSEA Hallmark pathway enrichment across five CKD subtypes.

HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION is the only pathway significantly enriched in all five cohorts (NES 1.68-2.53, padj < 0.001). Stars: *, padj<0.05; **, padj<0.01; ***, padj<0.001. Negative NES for p53 pathway in IgAN and DKD reflects p53 transcriptional exhaustion in established CKD.

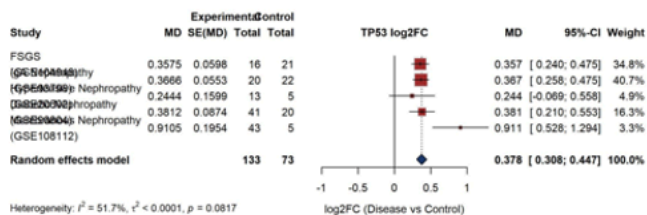


Figure 5A. TP53 forest plot.

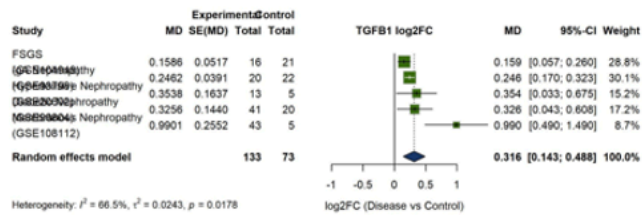


Figure 5C. TGFB1 forest plot.

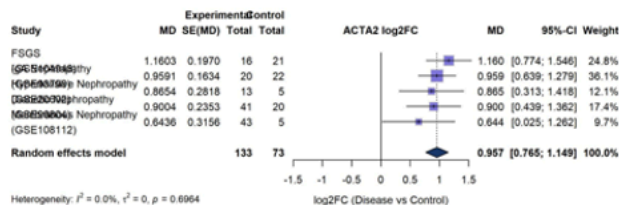


Figure 5B. ACTA2 forest plot.

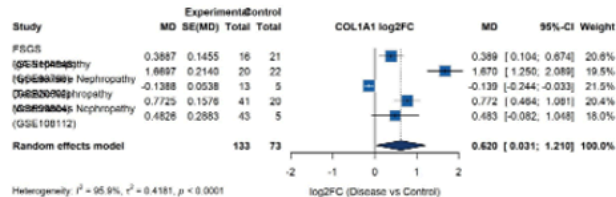


Figure 5D. COL1A1 forest plot.

Figure 5

Random effects meta-analysis forest plots.

(A) TP53: pooled log2FC = 0.378 [0.308-0.447], $p = 1.11 \times 10^{-26}$, $I^2 = 51.7\%$. (B) ACTA2: pooled log2FC = 0.957 [0.765-1.149], $p = 1.74 \times 10^{-22}$, $I^2 = 0.0\%$ (zero heterogeneity across five CKD subtypes). (C) TGFB1: pooled log2FC = 0.316 [0.143-0.488], $p = 3.4 \times 10^{-4}$. (D) COL1A1: pooled log2FC = 0.620 [0.031-1.210], $I^2 = 95.9\%$ (high heterogeneity attributed to tissue compartment differences).

Supplementary Files

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- [SUPPLEMENTARYFIGURES.docx](#)