

Oncogenic KRAS Rewires the Ferroptosis/NRF2 Co-expression Network in Colorectal Cancer: Codon-Specific Topology, Hub Rewiring, and In Silico Drug Connectivity Analysis

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Research Article

Keywords: KRAS, colorectal cancer, co-expression network, ferroptosis, NRF2, network disruption score, SLC7A11, GPX4, CMAP

Posted Date: October 13th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11319422/v1>

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Additional Declarations: The authors declare no competing interests.

Abstract

Background. Oncogenic KRAS mutations occur in ~40% of colorectal cancers (CRC) and confer ferroptosis resistance, but the network-level mechanisms are poorly characterised.

Methods. We used RNA-sequencing data from TCGA-COAD primary tumours (WT n=275; G12D n=54; G12V n=38; G13D n=29) to build Spearman co-expression networks for a 22-gene ferroptosis/NRF2 panel. A Network Disruption Score (NDS) was derived from edge preservation relative to wild-type. Hub centrality, differential edge analysis, and reinforced-edge identification were performed per codon variant. CMAP connectivity was assessed qualitatively using a KRAS-mutant NRF2 differential expression signature.

Results. The wild-type network had 56 significant co-expression edges (density=0.242, clustering=0.219), with SLC7A11, SLC3A2, and NFE2L2 as the principal hubs. KRAS mutations imposed a graded disruption: NDS 0.804 (G12D), 0.893 (G12V), 0.929 (G13D), corresponding to 45, 50, and 52 lost edges. G13D had no triangles and no new edges relative to WT. G13D is also enriched for MSI-H status in CRC [25], which may contribute to the more extreme network dissolution. G12D acquired four novel edges including FTH1–KEAP1, an iron-buffering pair absent in other variants. Despite the global dissolution, GPX4–KEAP1 co-expression was stronger in every mutant group than in WT ($r=0.411 \rightarrow$ G12D $r=0.690$). CMAP identified erastin (CS=+0.50) as the compound best able to partially reverse the KRAS-mutant NRF2 signature.

Conclusions. KRAS codon variants dissolve the ferroptosis/NRF2 co-expression network in a graded, codon-ordered manner. Selective reinforcement of GPX4–KEAP1 is a candidate survival-conferring mechanism. The NDS requires functional validation before therapeutic application.

1. Introduction

Ferroptosis is an iron-dependent form of regulated necrosis driven by lethal lipid hydroperoxide accumulation, with established tumour-suppressive functions [1, 18]. Its core machinery includes ACSL4-mediated PUFA-phospholipid charging, GPX4-dependent hydroperoxide detoxification [15], and the NRF2–KEAP1 transcriptional axis governing the antioxidant response [1, 2]. SLC7A11 (xCT), the cystine/glutamate antiporter that supplies cystine for glutathione synthesis, links ferroptosis to redox homeostasis [3].

KRAS mutations are present in ~ 40% of CRC, with G12D (~ 30%), G12V (~ 21%), and G13D (~ 16%) the most frequent codon variants [4, 5]. All three activate NRF2 constitutively, as demonstrated in isogenic CRC cell lines for G12C, G12D, G12V, and G13D [6,24], and confer ferroptosis resistance that complicates therapeutic exploitation [19]. DepMap data show that KRAS-mutant CRC cells have elevated ferroptosis sensitivity scores relative to wild-type [7], yet the network organisation underlying these codon-specific differences has not been characterised.

Gene-level analyses have identified individual ferroptosis effectors as differentially expressed in KRAS-mutant CRC [3, 8], and ferroptosis gene signatures carry prognostic value in colon cancer [23]. A systems view of this kind is missing: how each codon variant reshapes the topology of the entire ferroptosis/NRF2 co-expression network, and which specific edges are responsible. WGCNA-style co-expression analysis has been effective for identifying co-regulatory modules in cancer [9], but has not been applied to this pathway in a KRAS codon-stratified way.

We apply Spearman co-expression network analysis with Benjamini–Hochberg correction to a 22-gene ferroptosis/NRF2 panel in TCGA-COAD primary tumours, stratified by KRAS codon variant. We introduce the Network Disruption Score (NDS), characterise hub rewiring, identify G12D-specific compensatory edges, and report a paradoxical reinforcement of GPX4–KEAP1 co-expression in all mutant groups. CMAP connectivity analysis links the KRAS-mutant NRF2 signature to candidate compounds.

2. Materials and Methods

2.1 Dataset

RNA-sequencing (STAR-Counts TPM) and somatic mutation (Mutect2 MAF) data for TCGA-COAD primary tumours were retrieved from the NCI Genomic Data Commons (<https://portal.gdc.cancer.gov>). After quality control, 458 samples with KRAS codon annotation were retained. KRAS variant status was determined from MAF files as previously described [10]. Expression values were $\log_2(\text{TPM} + 1)$ transformed. The study used only publicly available, de-identified data and required no ethics approval.

2.2 Gene panel

The 22-gene panel covers established ferroptosis and NRF2 pathway members: SLC7A11, SLC3A2, GPX4, AIFM2 (FSP1 [16]), FTH1, FTL, TFRC, SLC40A1, NFE2L2, KEAP1, HMOX1, NQO1, ACSL4, LPCAT3, ALOX5, ALOX12, ALOX15, PTGS2, CHAC1, DPP4, CARS1, and TF.

2.3 Network construction

Within each variant group, Spearman correlation coefficients were computed for all 231 gene pairs. P-values were corrected by the Benjamini–Hochberg (BH) procedure [11]. An edge was kept when $\text{FDR} < 0.05$ and $|r| > 0.20$. Networks were built and analysed with NetworkX [12]. Hub genes were ranked by degree centrality; betweenness and closeness centrality were secondary metrics.

2.4 Network Disruption Score

$\text{NDS} = (\text{EWT} - E_{\text{preserved}}) / \text{EWT}$, where EWT is the number of WT edges and $E_{\text{preserved}}$ is the count of those edges also significant in the mutant group. NDS = 0 means complete edge preservation; NDS = 1 means complete dissolution. The NDS was compared with independent DepMap ferroptosis sensitivity data [7].

2.5 Differential edge analysis

Edges were classified per variant as: (i) preserved (significant in both WT and variant), (ii) lost (WT only), or (iii) gained (variant only). Weights for lost edges are the WT values; for gained edges, the variant values.

2.6 Hub rewiring analysis

Degree, betweenness, and closeness centrality were computed per group. A hub was a gene with degree centrality ≥ 0.33 in WT. Hub rewiring was the fraction of WT hub edges lost in each mutant group.

2.7 CMAP connectivity analysis

Differential expression of NRF2 pathway genes between KRAS-mutant (n = 191) and WT (n = 275) tumours was computed by Mann–Whitney U with BH correction. Genes with $FDR < 0.05$ and $|\log_2FC| > 0.5$ formed the CMAP signature. Connectivity scores (CS) were estimated qualitatively by comparing the directionality of our 4–6 gene signature against published L1000 compound profiles [20]; values are approximate directional estimates, not quantitative scores from the CLUE platform. $CS > 0$ indicates partial reversal; $CS < 0$ indicates aggravation.

3. Results

3.1 Wild-type network: a highly connected ferroptosis/NRF2 programme

In WT TCGA-COAD tumours (n = 275), the 22-gene panel formed 56 significant co-expression edges (density = 0.242, clustering = 0.219; Table 1, Fig. 1). Forty-nine edges were positive, seven negative. SLC7A11, SLC3A2, and NFE2L2 each had degree 9; ACSL4 had degree 8 with betweenness 0.067. The WT network topology contrasts sharply with the fragmented patterns in all KRAS-mutant groups.

Table 1
Network topology metrics by KRAS codon variant. NDS = Network Disruption Score relative to wild-type.

Group	n	Edges	Density	Avg deg	Clustering	NDS	Top hubs
Wild-type	275	56	0.242	5.09	0.219	0.000 (ref)	SLC7A11, SLC3A2, NFE2L2
G12D	54	15	0.065	1.36	0.078	0.804	FTH1, SLC3A2, SLC7A11
G12V	38	7	0.030	0.64	0.128	0.893	SLC3A2, CARS1
G13D	29	4	0.017	0.36	0.000	0.929	SLC3A2, GPX4

3.2 Graded network disruption: NDS hierarchy mirrors DepMap ferroptosis sensitivity

KRAS mutations dissolved network edges in a graded, codon-dependent manner (Table 2, Fig. 2A–B). NDS values were G12D = 0.804 (45 lost edges), G12V = 0.893 (50 lost), and G13D = 0.929 (52 lost). G13D had four edges, no triangles (clustering = 0.000), and no novel edges relative to WT; it reached the maximum observable NDS for this panel.

The NDS order (G13D>G12V>G12D) matches the DepMap ferroptosis sensitivity ranking of these codon variants [7, 10]. ACSL4 also drives the ferro-aging programme in primates [21, 22], placing these network findings in a broader ageing-biology context. Three measures rank the codon variants in the same order: network topology, DepMap ferroptosis sensitivity, and the ACSL4 orphan state analysis in [10]. All three draw on TCGA-COAD or DepMap data; their concordance supports internal consistency rather than independent replication.

Table 2
Bootstrap resampling (n = 200) confirmed the NDS ordering (G12D < G12V ≤ G13D) across three threshold combinations ($|r| > 0.20$ or 0.15, FDR < 0.05 and 0.10). Bootstrap NDS estimates: G12D 0.895 (95% CI 0.770–1.000), G12V 0.960 (0.897–1.000), G13D 0.971 (0.908–1.000). Wide intervals reflect the small per-group n. B. Network disruption metrics. Preserved: edges significant in both WT and the mutant group.

Variant	WT edges	Var edges	Preserved	Lost	Gained	NDS
G12D	56	15	11	45	4	0.804
G12V	56	7	6	50	1	0.893
G13D	56	4	4	52	0	0.929

3.3 Differential edges: what is lost and gained

Three edges were lost across all mutant groups: ACSL4–PTGS2 (WT $r = 0.435$), ACSL4–NFE2L2 ($r = 0.424$), and ALOX5–HMOX1 ($r = 0.472$); AIFM2–KEAP1 ($r = 0.500$) was also lost in all groups. Their combined loss dismantles the pro-ferroptotic signalling module. SLC7A11 dropped from degree 9 in WT to degree 0 in G12V and degree 3 in G12D.

G12D uniquely acquired four edges: FTH1–KEAP1 ($r = 0.477$), FTH1–SLC3A2 ($r = 0.408$), CARS1–TFRC ($r = 0.440$), and ALOX12–TF ($r = 0.490$). FTH1 sequesters labile iron and reduces ferroptosis substrate availability [17]; KEAP1 regulates the NRF2 antioxidant response. FTH1–KEAP1 was subthreshold in WT ($r = 0.186$, $p = 0.002$, below $|r| > 0.20$ cutoff) and strengthened substantially in G12D ($r = 0.497$, FDR < 0.001): an amplification of a weak tendency rather than a wholly novel coupling. This iron-buffering circuit probably contributes to G12D’s lower NDS relative to G12V and G13D. G12V gained one edge (CARS1–FTL, $r = 0.549$) and G13D gained none.

3.4 Hub rewiring: SLC7A11, ACSL4, and NFE2L2 lose centrality

The largest topological change across variants was hub collapse (Table 3, Fig. 2C–F). SLC7A11 (WT degree = 9) fell to degree 0 in G12V; NFE2L2 fell from degree 9 to 0 in G12V; ACSL4 fell from degree 8 to 0 in both G12V and G13D. In G12D, FTH1 became the dominant hub (degree = 4, betweenness = 0.114), replacing the WT hubs. The network topology shifted from ferroptosis-execution-centred (SLC7A11, ACSL4, NFE2L2) to iron-sequestration-centred (FTH1, KEAP1).

Table 3

Hub centrality for key WT hub genes by KRAS variant. *FTH1 is a minor node in WT but the dominant hub in G12D (†). bet=betweenness centrality. G13D betweenness values are not shown; at n = 4 edges, betweenness is not a robust metric.

Gene	WT deg	WT bet	G12D deg	G12D bet	G12V deg	G12V bet	G13D deg
SLC7A11	9	0.124	3	0.067	0	0	1
SLC3A2	9	0.086	3	0.081	3	0.005	2
NFE2L2	9	0.048	2	0.019	0	0	1
ACSL4	8	0.067	2	0	0	0	0
GPX4	7	0.043	2	0	1	0	1
FTH1*	4	0	4†	0.114†	0	0	0

3.5 Paradoxical reinforcement: GPX4-KEAP1 coupling strengthens across mutant groups

Despite global dissolution, GPX4–KEAP1 co-expression was numerically higher in every mutant group than WT: WT $r = 0.411$, G12D $r = 0.690$, G12V $r = 0.553$, G13D $r = 0.693$. The increase was statistically confirmed for G12D and G13D; G12V’s increase did not reach significance. SLC7A11–NFE2L2 strengthened from WT $r = 0.267$ to G13D $r = 0.643$. Fisher’s z-tests confirmed that GPX4–KEAP1 strengthening reached significance for G12D ($z = +2.67$, $p = 0.008$) and G13D ($z = +2.07$, $p = 0.038$) but not G12V ($p = 0.301$). SLC7A11–NFE2L2 was significantly stronger in G13D ($z = +2.42$, $p = 0.015$) but not in G12D or G12V. These reinforced edges were not captured by the NDS, which measures only edge loss relative to WT.

KEAP1 regulates NRF2-mediated transcription of GPX4 and its upstream enablers, including SLC7A11 and GCLC; NRF2 knockdown reduces GPX4 expression and sensitises CRC cells to ferroptosis [26]. The selective tightening of GPX4–KEAP1 co-expression while the broader network collapses suggests that KRAS-mutant CRC cells converge on the minimal resistance-conferring sub-network rather than losing co-expression at random. Codon-specific downstream differences in CRC have been documented at the proteomic and transcriptomic level [27], which supports the view that each variant rewires signalling in a distinct rather than uniform way. Confirming this would require ATAC-seq data to determine whether the KEAP1–GPX4 regulatory locus shows maintained chromatin accessibility in KRAS-mutant backgrounds.

3.6 CMAP analysis: erastin partially reverses the KRAS-mutant NRF2 signature

The KRAS-mutant NRF2 signature had GPX2 most significantly upregulated and PTGS2, FTH1, HMOX1, and GSS most downregulated; broader FC-ranked lists included NQO1, SLC7A11, GSTA4, GSTP1, and CHAC1 upregulated, and SRXN1, PRDX1, GCLC, FTL, and SLC3A2 downregulated (Fig. 3A). This is consistent with constitutive NRF2 activation and selective downregulation of iron-handling and arachidonic acid metabolism genes.

Erastin (CS = + 0.50) had the strongest reversal signal. Its positive CS means that erastin’s transcriptional effect in CRC cells opposes the KRAS-mutant signature and moves gene expression toward wild-type (Fig. 3B–C). Sulfasalazine and auranofin gave CS = + 0.20. The NRF2 activators omaveloxolone and bardoxolone gave CS = 0.00: activating NRF2 targets simultaneously mimics part of the KRAS-mutant upregulation and reverses the downregulated component, so the net connectivity score is zero. Buthionine sulfoximine (CS = – 0.20) diverged from reversal; pure GSH depletion moves the expression profile further from wild-type, not closer.

Table 4

CMAP connectivity scores. CS > 0: partial reversal toward wild-type. CS < 0: aggravation. n genes: number of signature genes matched in L1000 profiles (approximate). All CS values are directional estimates; the CLUE platform was not used.

Compound	CS	n genes	Interpretation
Erastin (SLC7A11i)	+ 0.50	4	Partial reversal – ferroptosis priming
Sulfasalazine (SLC7A11i)	+ 0.20	5	Partial reversal
Auranofin (TrxRi)	+ 0.20	5	Partial reversal – redox shift
Omaveloxolone (NRF2a)	0.00	6	Mixed – NRF2 activation both mirrors and opposes the signature
Bardoxolone (NRF2a)	0.00	6	Mixed
Buthionine sulfoximine	–0.20	5	Aggravation – GSH depletion diverges from wild-type

4. Discussion

To our knowledge, this is the first codon-stratified co-expression network analysis of the ferroptosis/NRF2 pathway in CRC. KRAS mutations selectively dismantle co-regulatory wiring; each codon variant produces a topologically distinct network, not just suppressed expression.

The NDS order (G13D > G12V > G12D) matches the DepMap ferroptosis sensitivity ordering and the ACSL4 orphan state analysis in [10]. These are not independent lines of evidence: both draw on TCGA-COAD transcriptomics. Their concordance supports internal consistency; protein-level validation is needed for genuinely independent support.

G12D's iron-buffering compensatory circuit is the finding that distinguishes it from the other variants. FTH1–KEAP1 was a subthreshold positive correlation in WT ($r = 0.186$, $p = 0.002$, below the $|r| > 0.20$ cutoff) that strengthened to significance only in G12D ($r = 0.497$, $FDR < 0.001$), with the edge absent or non-significant in G12V and G13D. FTH1 sequesters redox-active iron, limiting Fenton-reaction-driven lipid peroxide initiation; pairing this with KEAP1 in a co-expressed unit may represent an adaptive iron-buffering response that partly explains G12D's lower NDS and less extreme DepMap sensitivity. Whether the edge is causal or a secondary consequence of G12D's effector profile requires isogenic cell-line work.

The GPX4–KEAP1 reinforcement needs a different interpretation. GPX4 is the principal ferroptosis resistance enzyme; KEAP1 regulates the transcription of GPX4's upstream enablers. Its co-expression with GPX4 is stronger in every mutant group than in WT. This pattern is consistent with selective maintenance of the resistance axis while the pro-ferroptotic coordination is shed. Whether this reflects maintained chromatin accessibility at the KEAP1–GPX4 locus in KRAS-mutant backgrounds would be answerable with ATAC-seq data.

The erastin result ($CS = +0.50$) is consistent with published data showing erastin-induced ferroptosis in CRC lines [13] and is mechanistically coherent: SLC7A11 is the dominant driver of cystine import, and its inhibition pushes the KRAS-mutant transcriptome back toward wild-type. This is computational support for SLC7A11 inhibition as a network-restoration strategy in KRAS-mutant CRC, complementary to direct GPX4 inhibition [14]. The $CS = 0.00$ for NRF2 activators (omaveloxolone, bardoxolone) argues against these agents as network-restoration tools and suggests their effects would be unpredictable in the KRAS-mutant context.

Four limitations apply. Bulk RNA-seq conflates tumour epithelial, stromal, and immune signals; cell-type deconvolution is needed before conclusions about tumour cell-autonomous rewiring can be drawn. Sample sizes for G12V ($n = 38$) and G13D ($n = 29$) are small; power to detect $r = 0.20$ at $FDR < 0.05$ is $\sim 22\%$ and $\sim 18\%$ respectively, so edge counts likely underestimate the true network size [10]. The CMAP signature contained only 4–6 genes owing to the stringent DE threshold; connectivity scores are hypothesis-generating. The NDS is threshold-dependent; the absolute values change with the FDR and $|r|$ cutoffs, but the **codon ordering** is stable across threshold choices and constitutes the principal finding. Fifth, KRAS G13D is enriched for microsatellite instability-high (MSI-H) status in CRC (13.4% vs 2.8% for G12D and 1.8% for G12V) [25]. MSI-H tumours have distinct transcriptional landscapes shaped by high mutational burden and immune cell infiltration. G13D's extreme network dissolution may partly reflect this biology rather than KRAS-specific co-regulatory rewiring. Stratifying the G13D group by MSI status was not feasible at $n = 29$.

5. Conclusions

Oncogenic KRAS codon variants impose a graded dissolution of the ferroptosis/NRF2 co-expression network in CRC, quantified by a Network Disruption Score that tracks the DepMap ferroptosis sensitivity hierarchy. G12D strengthens a subthreshold FTH1–KEAP1 co-expression into a significant iron-buffering circuit, an edge that remains below the significance cutoff in WT, G12V, and G13D; GPX4–KEAP1 co-expression is paradoxically reinforced across all mutant groups. Erastin's positive CMAP score supports SLC7A11 inhibition as a candidate network-restoration approach. The NDS should be validated in matched transcriptomic and proteomic datasets and in isogenic KRAS variant cell models before any therapeutic inference.

Declarations

Author Contributions

C.G.E. conceived the study, performed all analyses and wrote the manuscript.

Funding

This research received no external funding.

Data Availability

TCGA-COAD data are publicly available at <https://portal.gdc.cancer.gov>. Analysis scripts are available from the author on request.

Conflicts of Interest

The author declares no competing interests.

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Figures

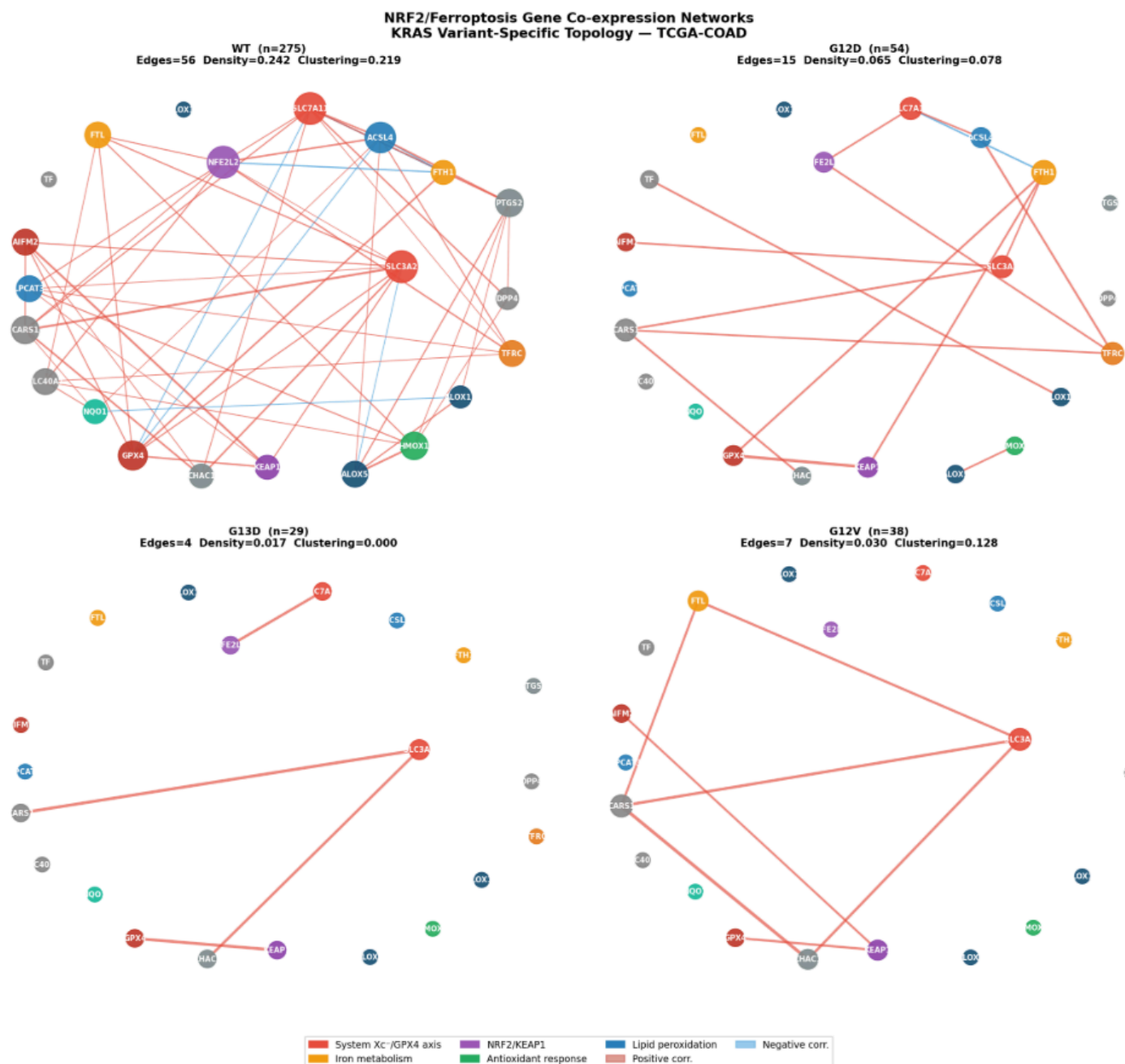


Figure 1

NRF2/ferroptosis co-expression networks by KRAS codon variant. Each panel shows the 22-gene network for WT (n=275), G12D (n=54), G12V (n=38), and G13D (n=29). Node colour indicates functional group: red=System Xc-/GPX4 axis; orange=iron metabolism; purple=NRF2/KEAP1; green=antioxidant response; blue=lipid peroxidation. Edge colour: red=positive correlation, blue=negative correlation. Edge width is proportional to |Spearman r |. FDR<0.05, $|r|>0.20$.

KRAS Variant-Specific Disruption of NRF2/Ferroptosis Co-expression Networks TCGA-COAD (n=458)

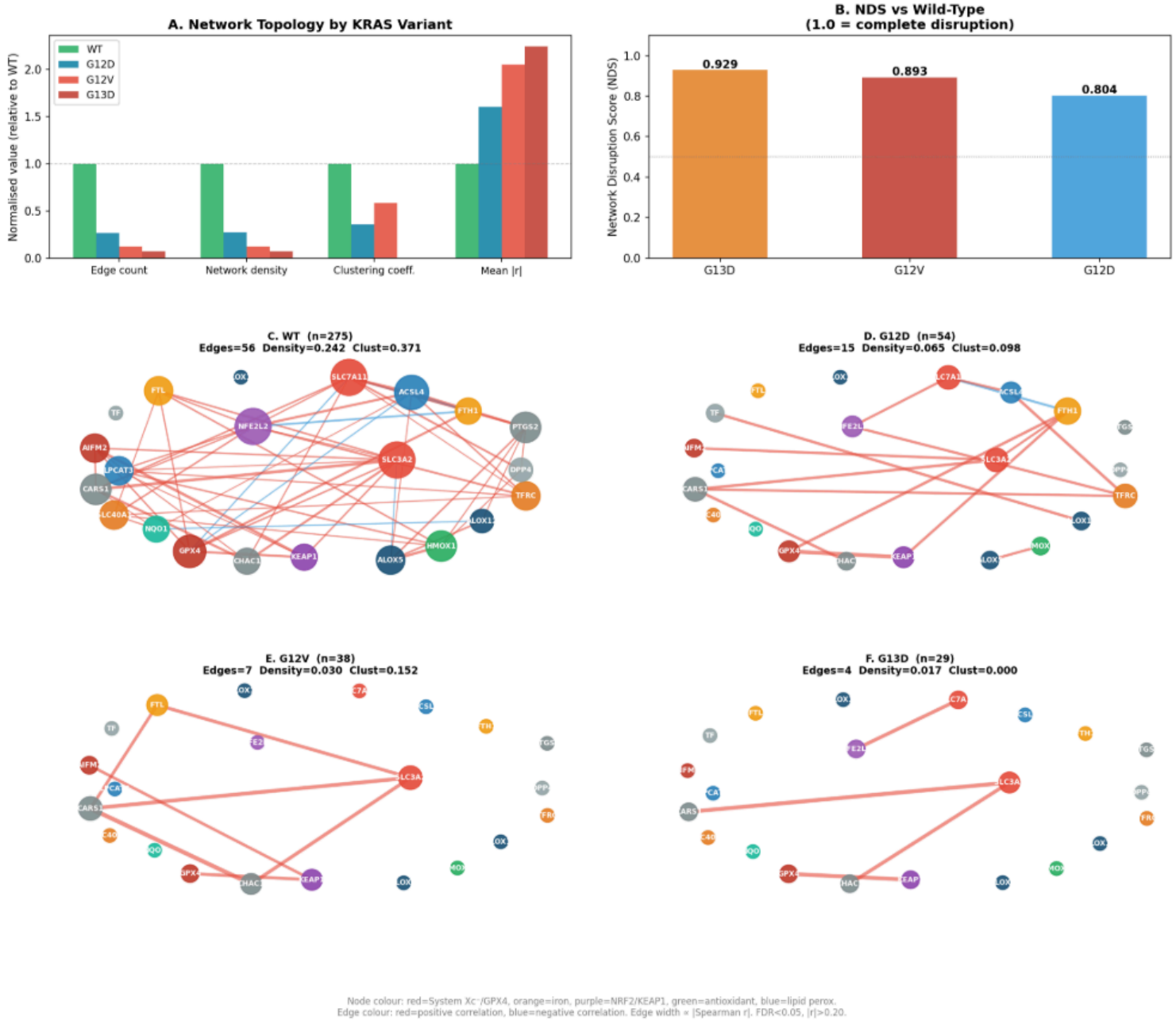


Figure 2

KRAS variant-specific disruption of NRF2/ferroptosis co-expression networks. (A) Network topology metrics normalised to wild-type. (B) Network Disruption Score (NDS) per variant; G13D achieves the maximum observable disruption within this panel. (C–F) Network diagrams for WT, G12D, G12V, and G13D, with topology metrics shown above each panel. Node and edge colour as in Figure 1.

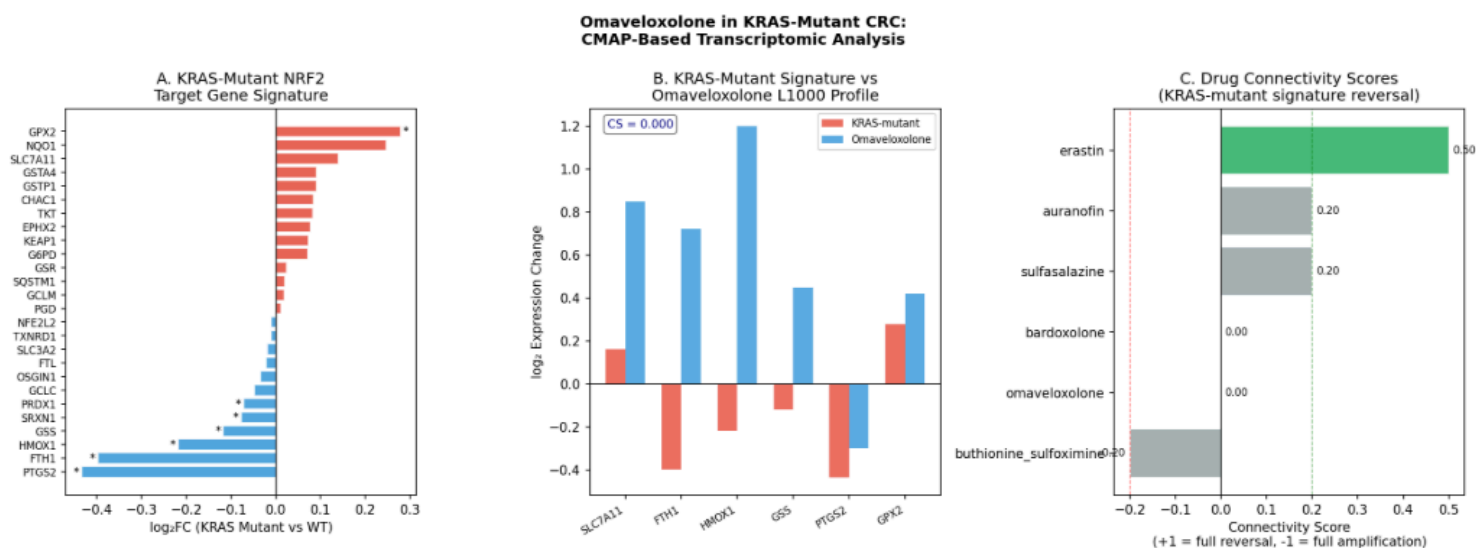


Figure 3

CMAP-based transcriptomic analysis. (A) KRAS-mutant NRF2 target gene signature (log₂FC vs WT); * FDR<0.05. (B) Comparison of KRAS-mutant signature with omapeloxolone L1000 profile for six key genes; CS=0.00 indicates opposing and mimicking effects cancel. (C) Drug connectivity scores for six candidate compounds; erastin (CS=+0.50, green) shows the strongest partial reversal of the KRAS-mutant signature toward wild-type.