An atlas of the human kinome reveals the mutational landscape underlying dysregulated phosphorylation cascades in cancer

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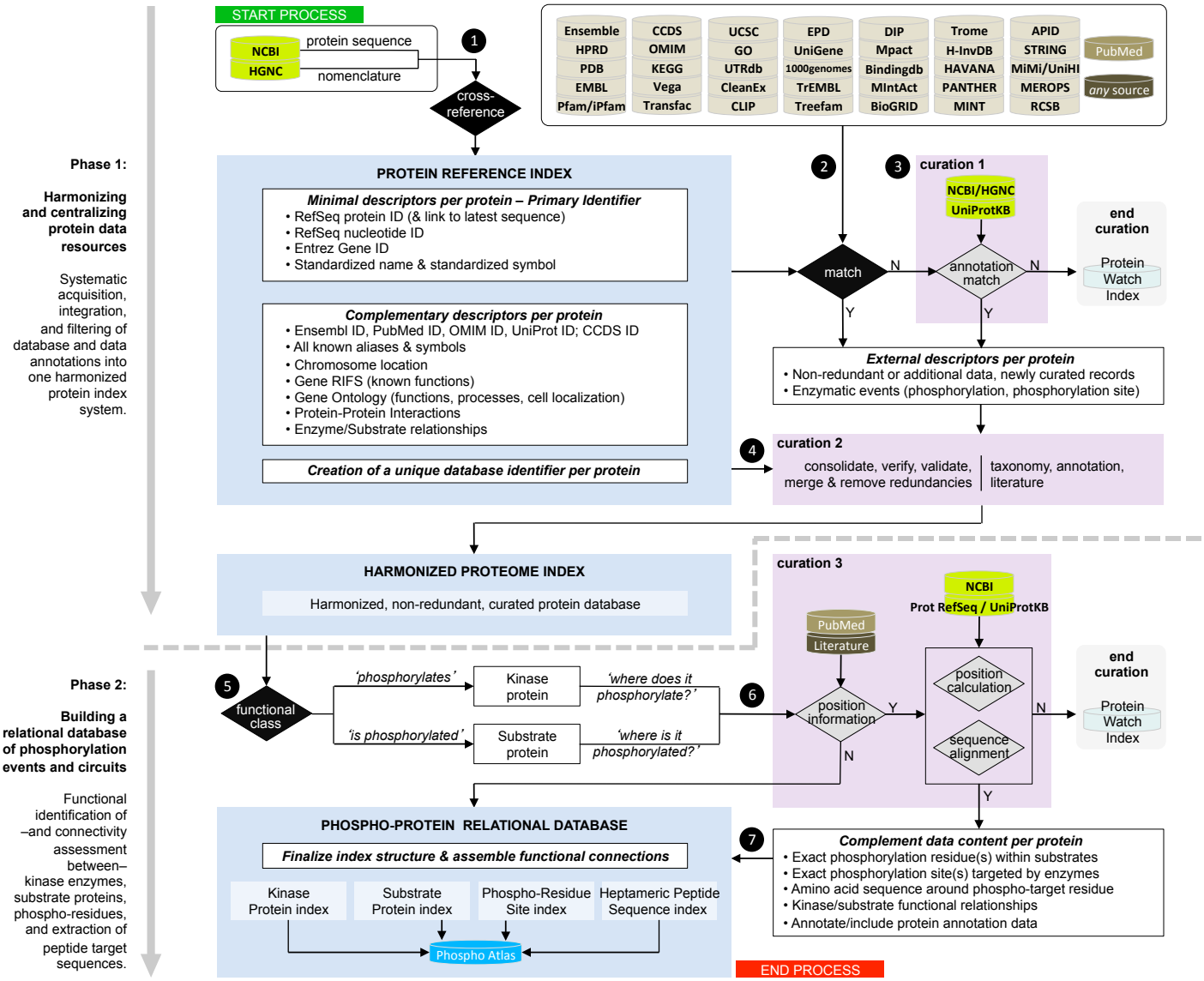
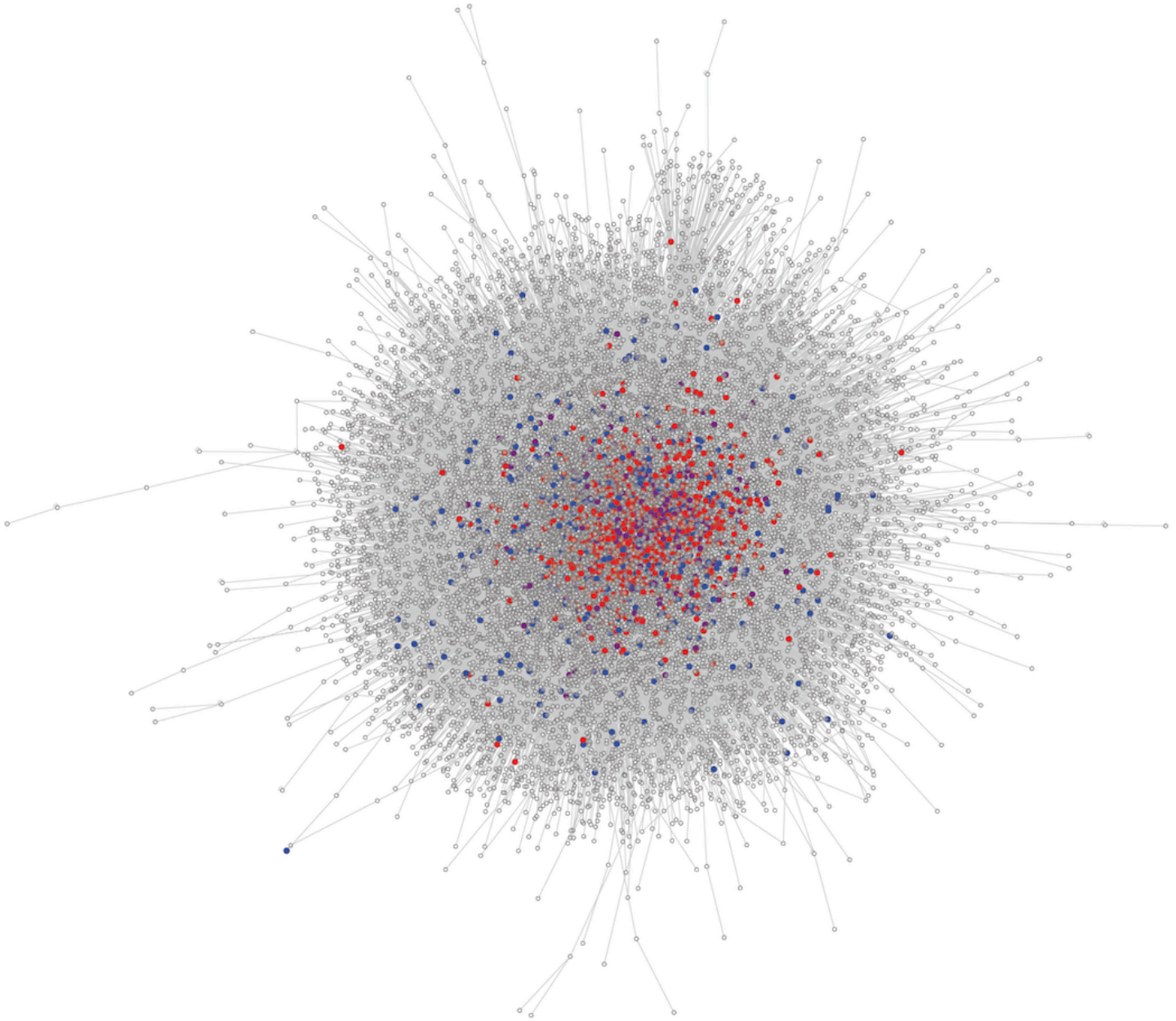
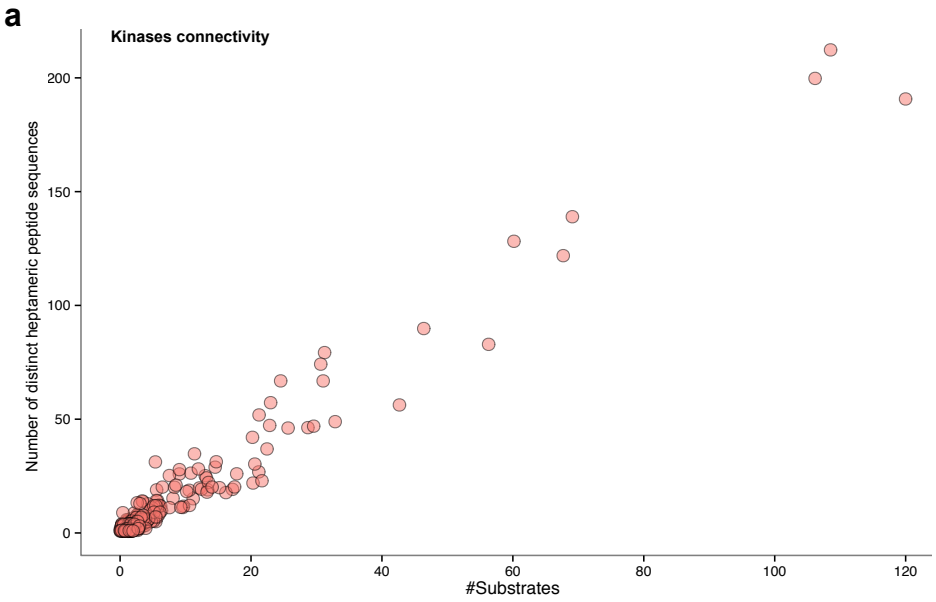
SUPPLEMENTARY FIGURES
S1 to S17

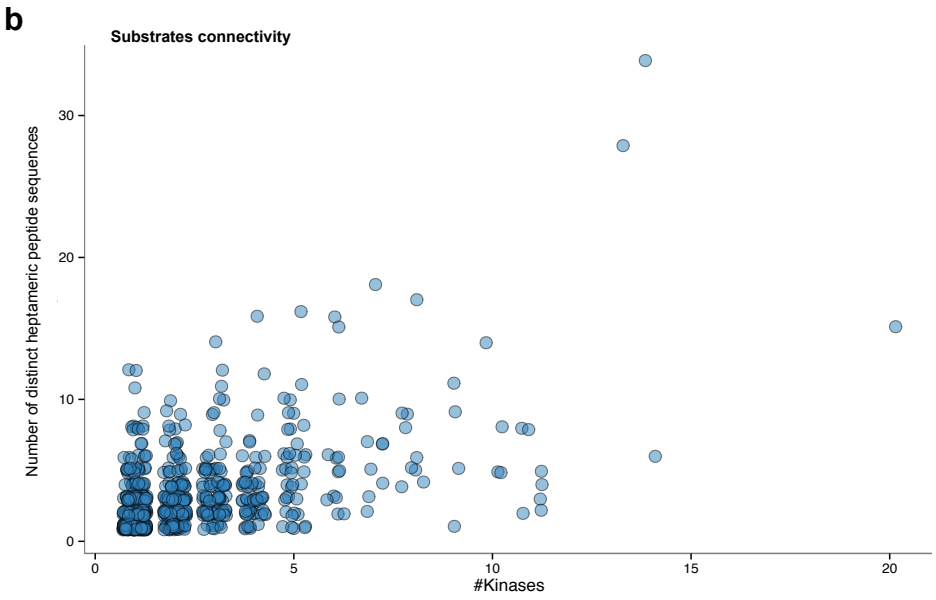


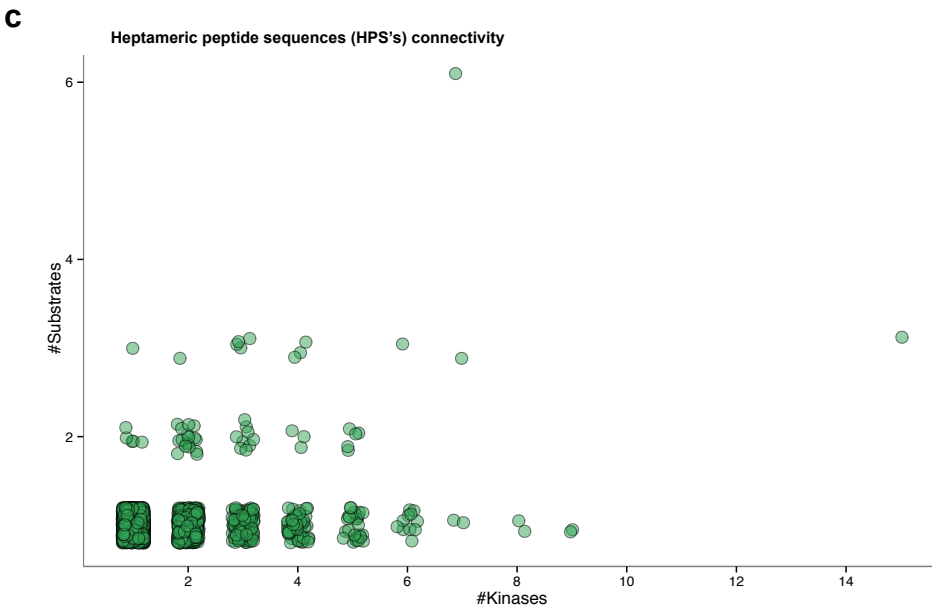
Supplement Figure S1

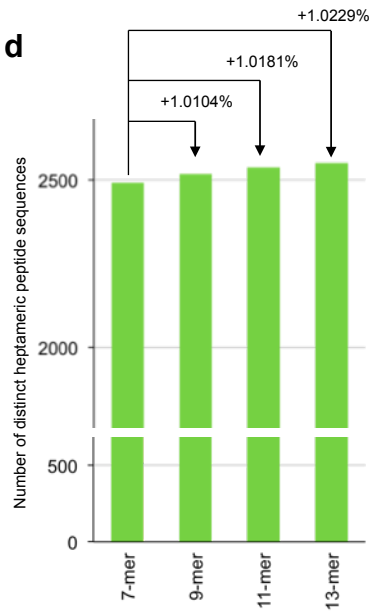


Supplement Figure S2

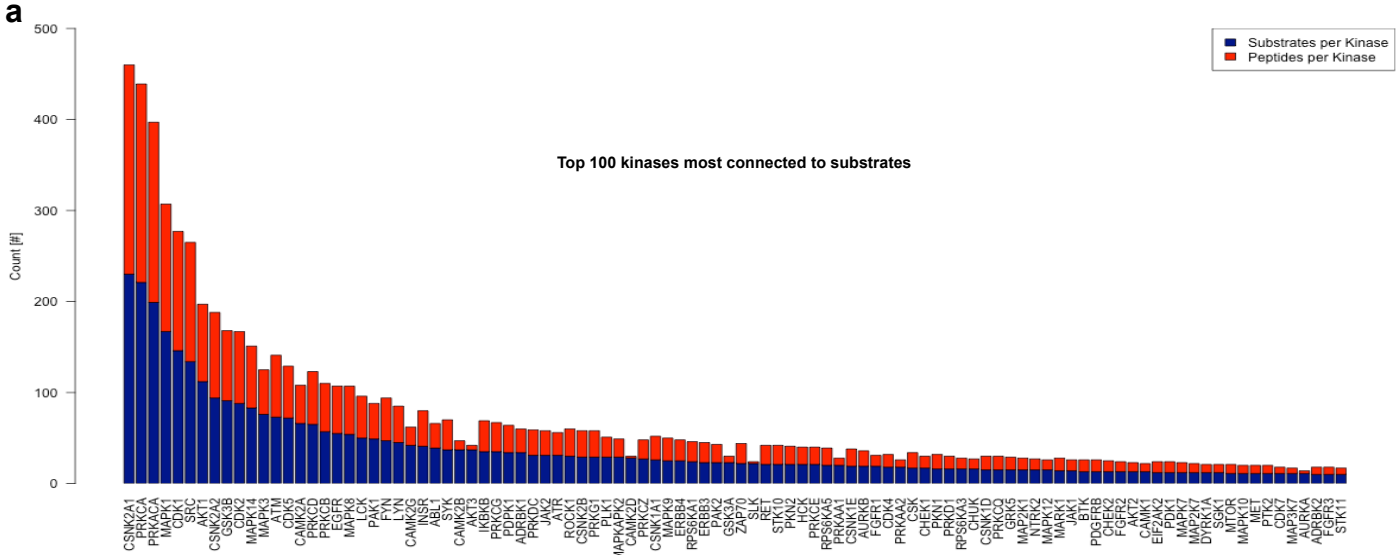


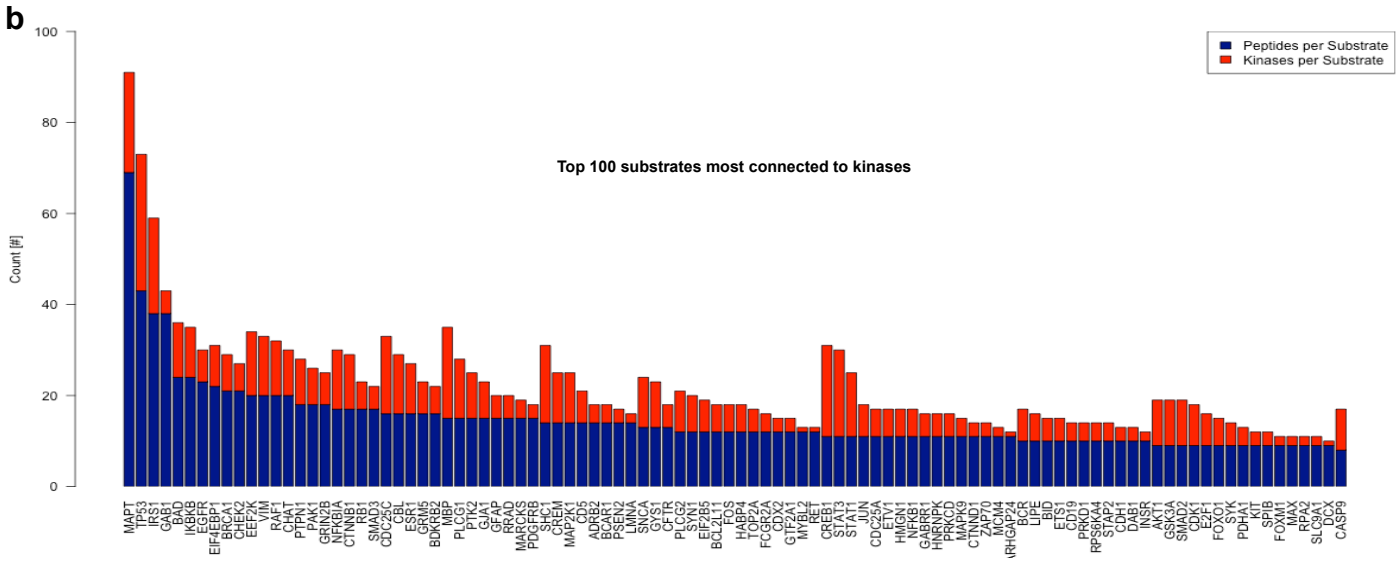


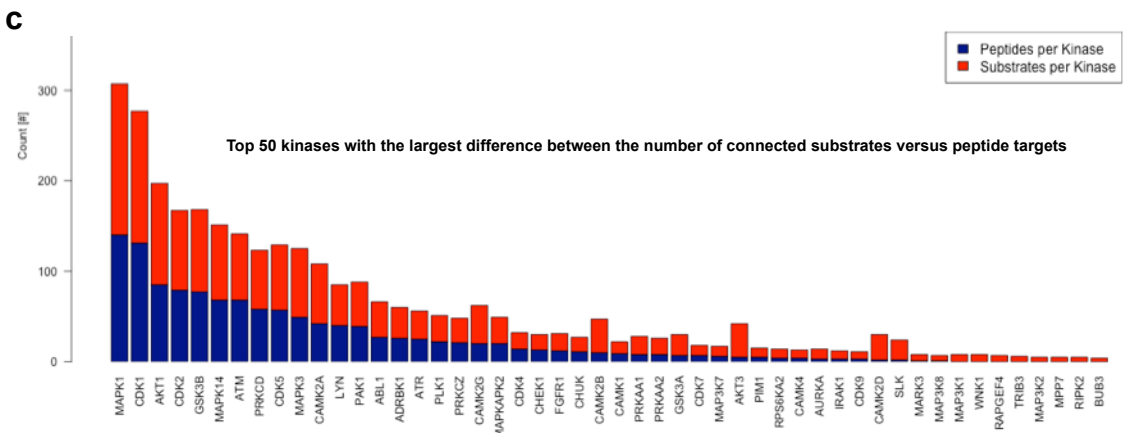




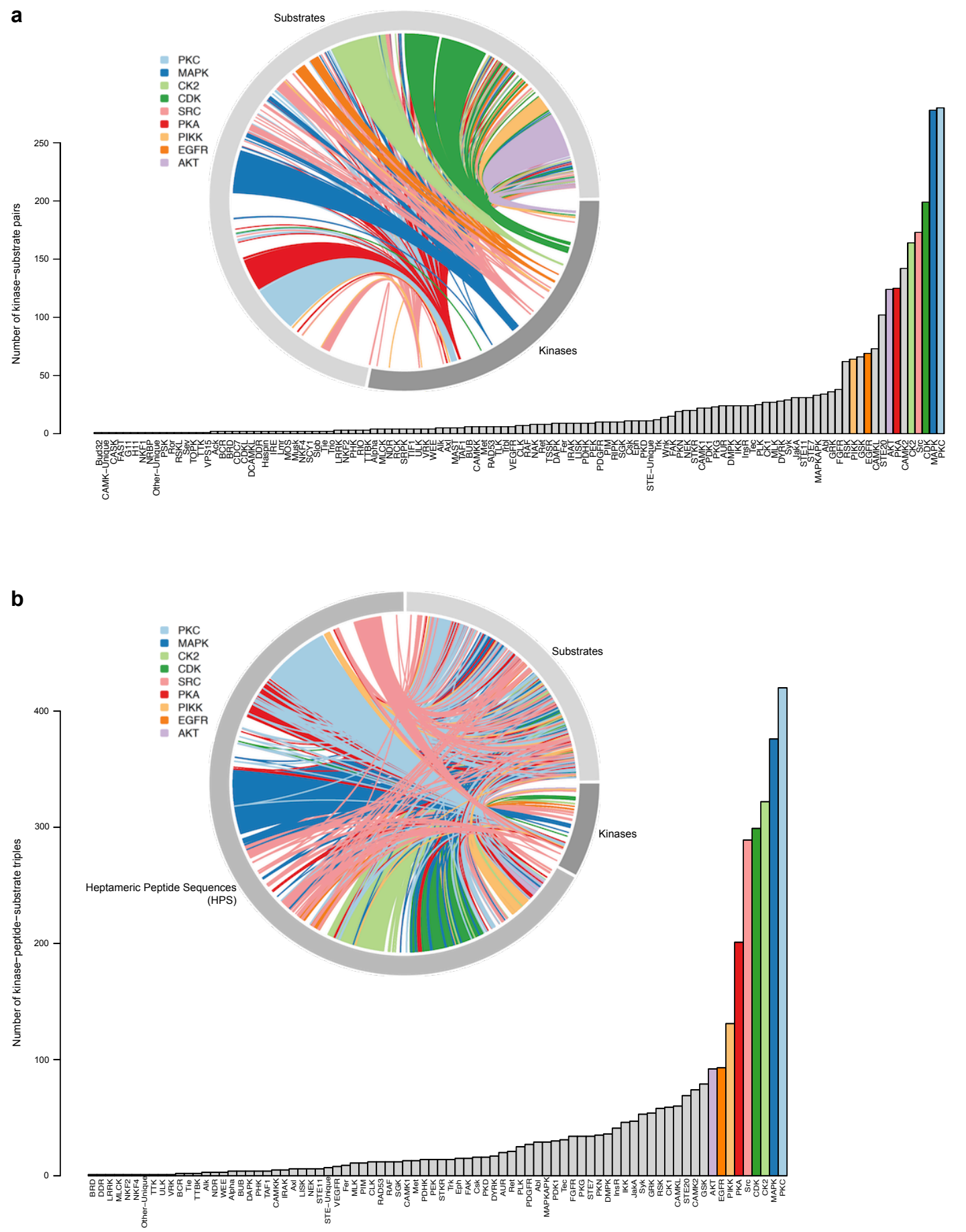
Supplement Figure S3







Supplement Figure S4

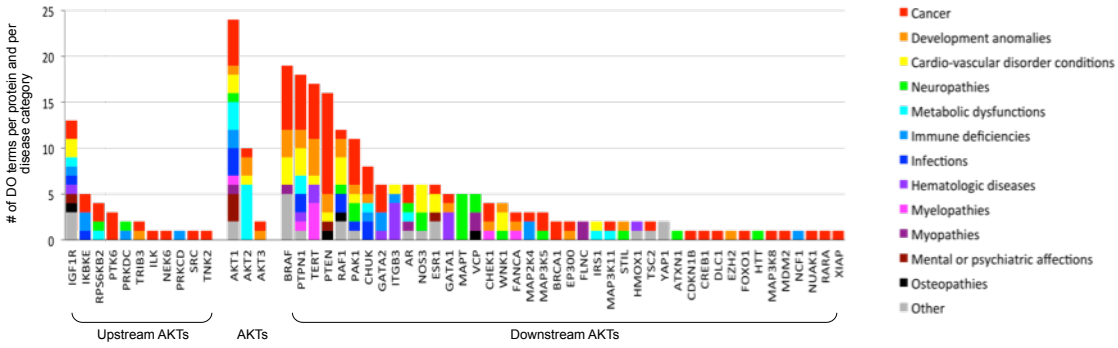


Supplement Figure S5

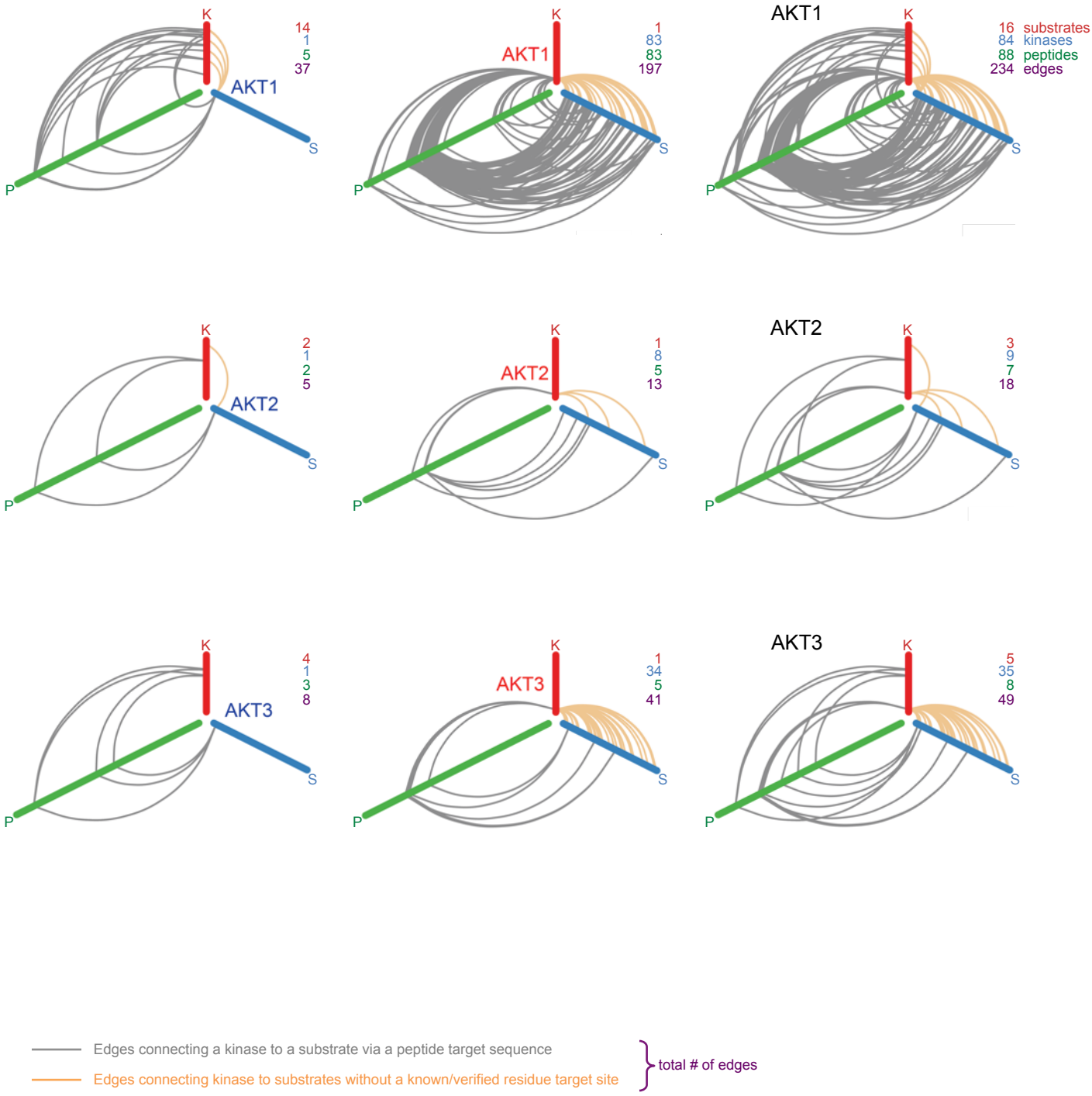
a

Disease category (Disease Onotology-terms were classified under 13 categories)	# of different DO terms per category	# of associated proteins per category	ontology details
Cancer	63	40	including malignant cancers, neoplasms, or hamartomas, across all tissue or cell types
Development anomalies	26	18	including congenital disorders, multisystem diseases, growth defects, mental retardation, intellectual disability
Cardio-vascular disorder conditions	23	14	including atherosclerosis, coronary artery disease, hypertension, cardiopathies
Neuropathies	18	14	including neurodegenerative disorders
Metabolic dysfunctions	11	9	including diabetes, obesity, insulin and glycemic dysregulation
Immune deficiencies	12	10	including auto-immune disorders
Infections	9	8	both viral & bacterial
Hematologic diseases	13	7	including anemic and bleeding disorders
Myelopathies	8	5	including bone marrow disorders
Myopathies	7	5	including muscular degenerative diseases
Mental or psychiatric affections	6	4	-
Osteopathies	4	4	-
Other	23	13	including disorders of eye, kidney, lung, skin, thyroid, digestive and reproductive system

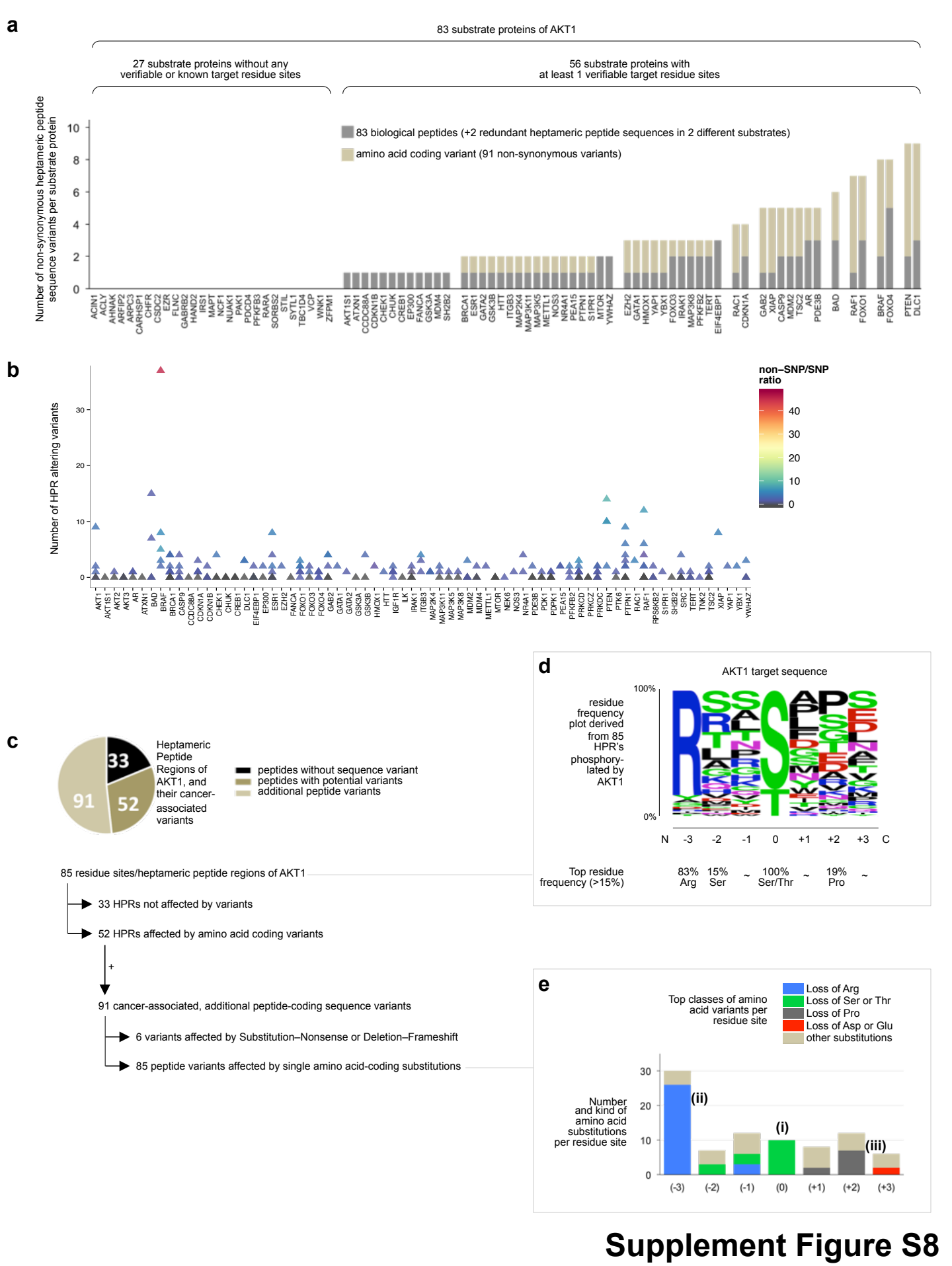
b



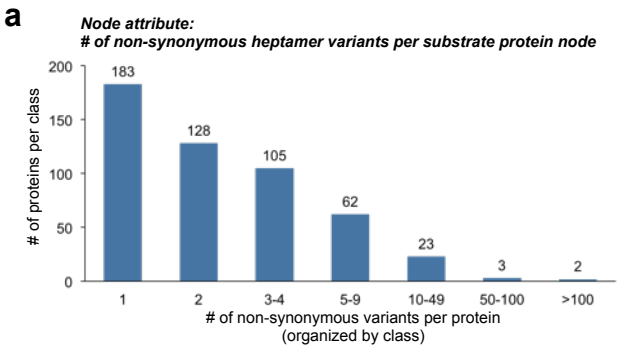
Supplement Figure S6

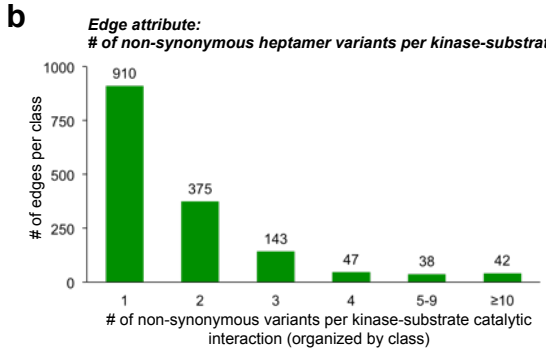


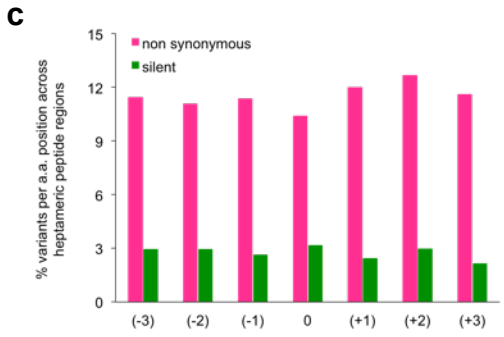
Supplement Figure S7

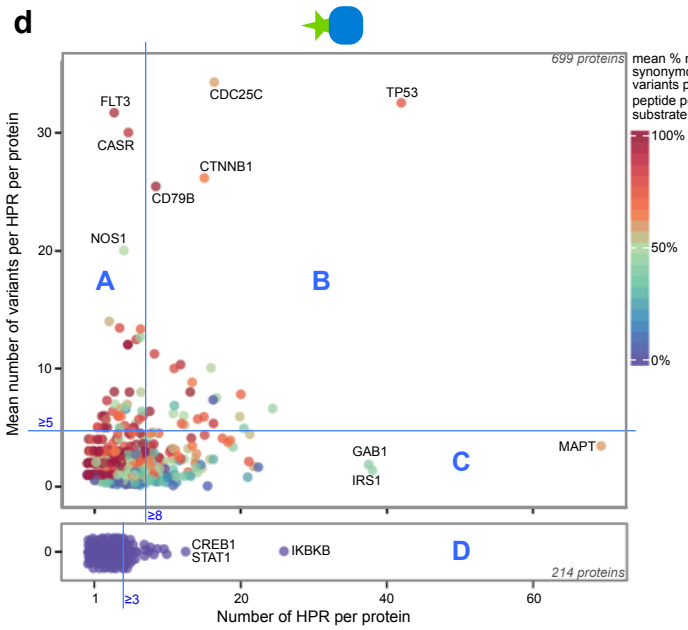


Supplement Figure S8









e

A

Protein name	# of peptides (per protein)	Avergae # of variants per peptide (per protein)	% of non-synonymous variants
	(x-axis)	(y-axis)	(color-code)
FLT3	4	31.8	95.7
CASR	3	30.0	90.0
NOS1	5	20.0	50.0
APC	3	14.0	57.0
WT1	2	13.5	83.3
MYC	5	13.4	75.0
ELK1	6	12.7	44.4
BRAF	6	12.5	87.9
DAPP1	4	12.0	100.0
SPP1	4	12.0	100.0
BCL2	6	8.0	52.9
PPP1R14A	4	8.0	100.0
XIAP	2	8.0	100.0
NEFH	3	7.3	89.6
ACP1	4	7.0	58.3
CDK5	4	7.0	50.0
PLA2G4A	4	6.8	50.0
KRT8	5	6.6	60.0
MAP4K1	5	6.6	20.0
GSK3B	5	6.4	40.0
CAV1	3	6.3	83.3
CTDP1	6	6.0	83.3
GRIA1	4	6.0	82.5
MAPK8	4	6.0	66.7
CYTH2	3	6.0	100.0
DAB2	3	6.0	100.0
SREBF1	2	6.0	66.7
STK11	6	5.7	83.3
PTPRR	3	5.7	86.7
MSN	3	5.7	50.0
AMPH	6	5.3	50.0
CDH1	5	5.2	85.0

B

Protein name	# of peptides (per protein)	Avergae # of variants per peptide (per protein)	% of non-synonymous variants
	(x-axis)	(y-axis)	(color-code)
CTNNB1	17	34.4	59.6
TP53	43	32.5	80.7
CDC25C	15	26.2	66.4
CD79B	7	25.4	100.0
PTEN	7	11.3	86.9
ETV1	11	10.4	90.9
BDKRB2	16	10.1	52.1
KIT	9	10.0	81.4
GFAP	15	8.8	65.7
FCGR2A	12	8.0	100.0
EEF2K	19	7.8	73.7
AKT1	16	7.6	46.9
PLCG1	15	7.3	3.3
STAT3	11	6.8	30.3
BAD	24	6.6	44.8
GRM5	8	6.4	100.0
PLCG2	12	6.3	50.0
HABP4	12	6.0	50.0
GRIN2B	18	5.9	55.5
SHC1	14	5.9	75.0
SNCA	13	5.8	76.9
HMGN1	11	5.4	72.7
RRAD	15	5.3	90.0
CDX2	12	5.3	58.3

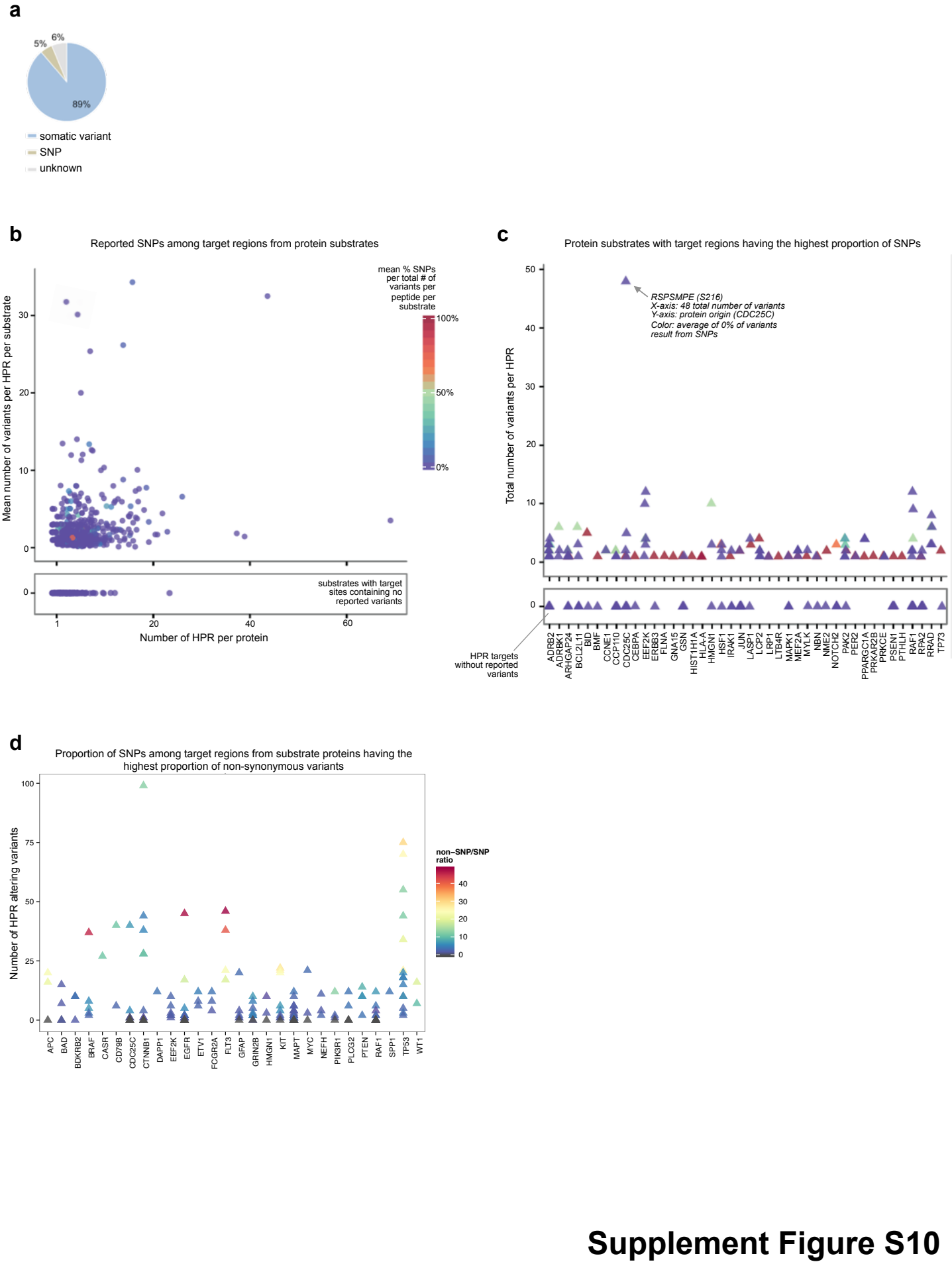
C

Protein name	# of peptides (per protein)	Avergae # of variants per peptide (per protein)	% of non-synonymous variants
	(x-axis)	(y-axis)	(color-code)
MAPT	69	3.5	60.6
GAB1	38	1.8	40.8
IRS1	38	1.4	43.9
EGFR	23	4.4	55.0
EIF4EBP1	22	1.7	9.1
CHEK2	21	2.1	78.6
BRCA1	21	1.7	58.7
CHAT	20	4.9	40.0
VIM	20	0.8	25.0
RAF1	19	3.4	42.1
PTPN1	18	3.9	68.1
NFKBIA	17	4.4	87.3
RB1	17	3.7	68.1
SMAD3	17	2.4	29.4
CBL	16	4.1	75.0
GJA1	15	3.5	66.7
PDGFRB	15	2.3	53.9
MBP	15	0.9	26.7
PTK2	15	0.1	6.7
CD5	14	4.1	95.2
ESR1	14	3.2	54.8
CREM	14	2.4	50.0
PSEN2	14	1.9	14.3
ADRB2	14	1.6	53.6
BCAR1	14	1.2	46.4
MAP2K1	13	2.2	26.9
CFTR	13	1.0	34.6
GYS1	13	0.4	20.5
FOS	12	2.8	62.5
BCL2L11	12	2.3	45.8
GTF2A1	12	2.3	50.0
MYBL2	12	2.0	66.0
RET	12	1.7	40.3
EIF2B5	12	1.4	33.3
TOP2A	12	0.9	33.3
GABRR1	11	3.1	65.2
ZAP70	11	2.5	67.6
NFKB1	11	2.4	86.4
HNRNPK	11	2.0	59.5
CDC25A	11	1.3	72.7
PRKCD	11	1.3	43.3
ARHGAP24	11	1.0	81.8
CTNND1	11	0.9	54.5
MCM4	11	0.9	27.3
PAK1	11	0.8	45.5
SYN1	11	0.1	9.1
DAB1	10	3.1	100.0
BID	10	2.5	50.0
CD19	10	2.4	70.0
PRKD1	10	2.1	50.0
INSR	10	1.3	33.3
BCR	10	0.8	25.0
RPS6KA4	10	0.8	20.0
LIPE	10	0.8	10.0
ETS1	10	0.4	20.0
SPIB	9	3.2	55.6
DCX	9	2.9	84.8
PDHA1	9	2.9	27.8
SYK	9	1.8	63.9
SMAD2	9	1.6	51.9
SLC9A1	9	1.1	77.8
MAX	9	1.0	29.6
E2F1	9	1.0	27.8
FOXM1	9	0.8	38.9
RPA2	9	0.4	33.3
BMX	8	4.5	75.0
SLC4A1	8	4.5	68.8
ITGB2	8	3.6	25.0
GTF2A1L	8	3.5	75.0
LCK	8	3.4	68.8
CASP9	8	2.5	75.0
GAB2	8	2.5	54.2
JAK2	8	2.4	75.0
PAK2	8	2.1	62.5
PPP1R8	8	1.6	81.3
CSNK1E	8	1.0	75.0
EIF2AK2	8	0.9	75.0
CCP110	8	0.8	37.5
DCLRE1C	8	0.6	37.5
FPR1	8	0.6	20.8
MAPK8IP1	8	0.6	15.6
PKN1	8	0.4	25.0
EPOR	8	0.4	12.5
GRIN2A	7	4.6	45.2
STMN1	7	3.6	92.9
YWHAZ	7	2.7	14.3
CRTC2	7	2.6	42.9
MAP2	7	2.4	95.2
FOXO1	7	2.4	56.0
LCP2	7	2.3	78.6
MEF2C	7	2.1	71.4
BTK	7	2.0	26.2
ITPR1	7	1.9	81.0
CDKN1A	7	1.9	78.6
MEF2A	7	1.7	85.7
PTPN7	7	1.6	57.1
ABL1	7	1.4	67.9
PTPN6	7	1.3	42.9
XRCC1	7	1.3	14.3
HSPB1	7	1.1	57.1
CDKN1B	7	1.1	28.6
PRKDC	7	1.0	57.1
RACGAP1	7	0.9	42.9
IRAK1	7	0.7	42.9
LMNA	7	0.7	28.6
ERBB2	7	0.6	57.1
TSC2	7	0.6	42.9
MAPK9	7	0.6	28.6
NFATC3	7	0.4	28.6
CDC25B	7	0.3	28.6
SRF	7	0.3	14.3

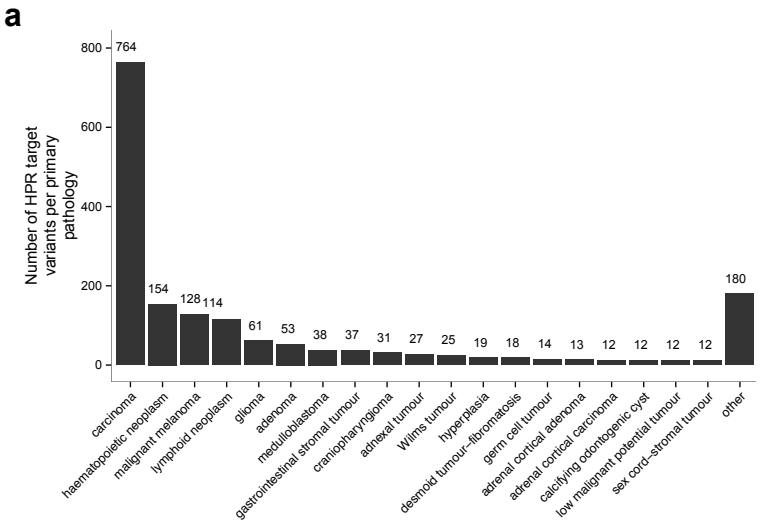
D

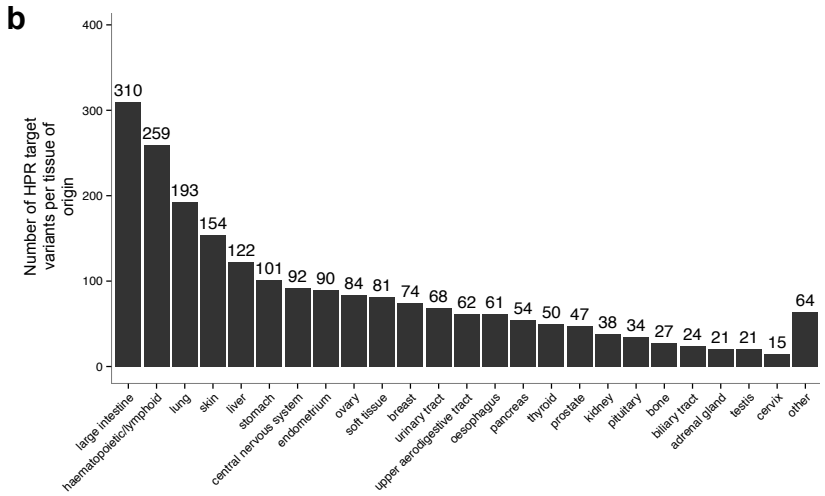
Protein name	# of peptides (per protein)	Avergae # of variants per peptide (per protein)	% of non-synonymous variants
	(x-axis)	(y-axis)	(color-code)
IKBKB	24	0.0	0.0
CREB1	11	0.0	0.0
STAT1	11	0.0	0.0
CDK1	9	0.0	0.0
GSK3A	9	0.0	0.0
HMGA1	8	0.0	0.0
PPP1R2	8	0.0	0.0
ATF1	6	0.0	0.0
CHUK	6	0.0	0.0
MTOR	6	0.0	0.0
TCF7L2	6	0.0	0.0
ADRA1B	5	0.0	0.0
ADRA2A	5	0.0	0.0
CDK6	5	0.0	0.0
CFL1	5	0.0	0.0
DNM1	5	0.0	0.0
EIF2S1	5	0.0	0.0
PEBP1	5	0.0	0.0
RGS19	5	0.0	0.0
ADD2	4	0.0	0.0
CLTB	4	0.0	0.0
CRK	4	0.0	0.0
EEF1B2	4	0.0	0.0
HDAC1	4	0.0	0.0
HDAC5	4	0.0	0.0
JUNB	4	0.0	0.0
MAPK10	4	0.0	0.0
MAPK14	4	0.0	0.0
MAPK15	4	0.0	0.0
MYCN	4	0.0	0.0
NDE1	4	0.0	0.0
NFKBIB	4	0.0	0.0
RAD17	4	0.0	0.0
RASA1	4	0.0	0.0
STAT5A	4	0.0	0.0
CDC6	3	0.0	0.0
CEBPB	3	0.0	0.0
EEF2	3	0.0	0.0
GRK1	3	0.0	0.0
INCENP	3	0.0	0.0
LIMK1	3	0.0	0.0
MAFA	3	0.0	0.0
NRGN	3	0.0	0.0
PPP1R9B	3	0.0	0.0
RXRA	3	0.0	0.0
SH3BP2	3	0.0	0.0
SLC12A2	3	0.0	0.0
SYNGAP1	3	0.0	0.0
TOB1	3	0.0	0.0

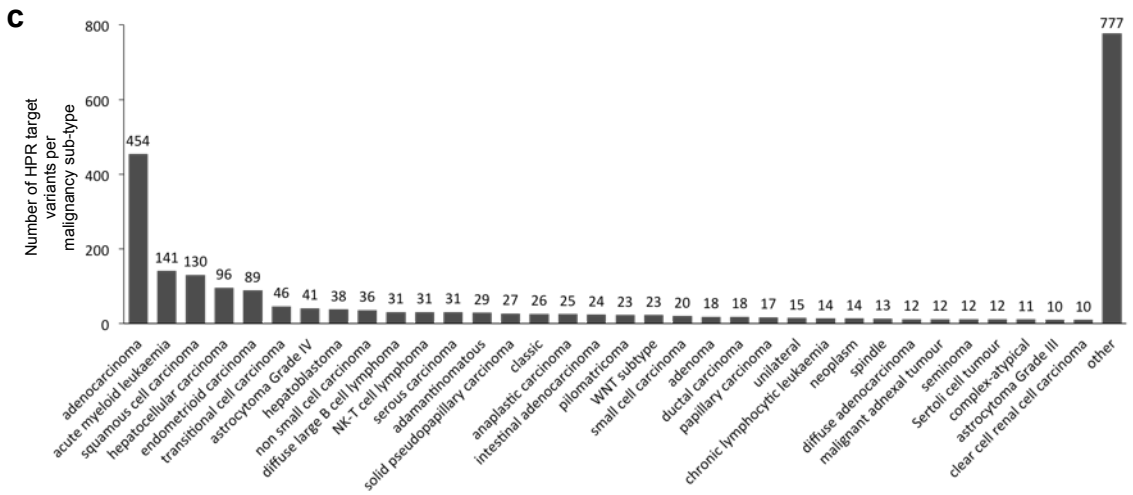
Supplement Figure S9



Supplement Figure S10

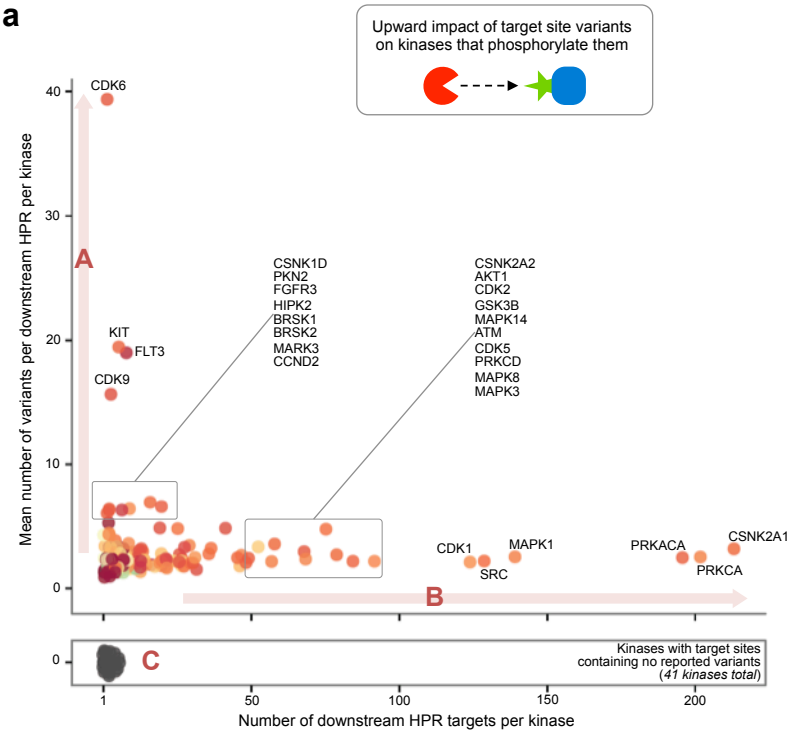






Supplement Figure S11

a



b

Kinases with the highest average of non-synonymous HPR variants per targeted HPR

Kinase name	# of distinct heptameric peptide regions phosphory-lated by the listed kinase	mean # of variants per HPR target per kinase	mean % non-synonymous variants per HPR target per kinase (% nsHPRv)
CHUK	11	1.7	100.0
TEC	7	2.0	100.0
GSK3A	7	1.8	100.0
GRK1	6	3.0	100.0
MAP3K7	6	2.8	100.0
PTK6	6	1.5	100.0
BUB1	6	1.0	100.0
PAK3	5	2.3	100.0
MAP3K5	5	1.8	100.0
BMPR1B	5	1.0	100.0
ERBB2	5	1.0	100.0
OXSR1	4	3.0	100.0
BLK	4	2.0	100.0
RPS6KA2	4	1.5	100.0
TAF1	4	1.5	100.0
FER	4	1.3	100.0
STK4	4	1.3	100.0
ABL2	4	1.0	100.0
MAPKAPK3	4	1.0	100.0
CAMKK1	3	2.0	100.0
RPS6KA4	3	2.0	100.0
SIK1	3	2.0	100.0
SIK3	3	2.0	100.0
FGR	3	1.5	100.0
AURKA	3	1.0	100.0
AXL	3	1.0	100.0
CLK2	3	1.0	100.0
FGFR4	3	1.0	100.0
IRAK1	3	1.0	100.0
PRKAR1A	3	1.0	100.0
TYK2	3	1.0	100.0
EPHB1	2	2.0	100.0
PKM	2	2.0	100.0
RPS6KB1	2	2.0	100.0
SIK2	2	2.0	100.0
TGFBR1	2	2.0	100.0
WEE1	2	2.0	100.0
DAPK1	2	1.5	100.0
DYRK1B	2	1.5	100.0
BCR	2	1.0	100.0
CAMK2D	2	1.0	100.0
CDK3	2	1.0	100.0
CDK8	2	1.0	100.0
EPHB2	2	1.0	100.0
FRK	2	1.0	100.0
IRAK4	2	1.0	100.0
MAP2K3	2	1.0	100.0
NME1-NME2	2	1.0	100.0
NME2	2	1.0	100.0
RAD17	2	1.0	100.0
CCND2	1	5.0	100.0
NEK8	1	3.0	100.0
ACVR1B	1	2.0	100.0
CSF1R	1	2.0	100.0
MAP4K1	1	2.0	100.0
MATK	1	2.0	100.0
NUAK1	1	2.0	100.0
PKD1	1	2.0	100.0
PTPN11	1	2.0	100.0
STK3	1	2.0	100.0
BCAT2	1	1.0	100.0
CCNE1	1	1.0	100.0
CSNK1G1	1	1.0	100.0
DAPK3	1	1.0	100.0
DMPK	1	1.0	100.0
HIPK3	1	1.0	100.0
NEK2	1	1.0	100.0
PRKCI	1	1.0	100.0
PRKY	1	1.0	100.0
TAOK1	1	1.0	100.0
TTK	1	1.0	100.0
TTN	1	1.0	100.0
ZRANB2	1	1.0	100.0

c

A

Kinases with the highest average # of variants per targeted HPR (y-axis extremes)

Kinase name	# of distinct heptameric peptide regions phosphory-lated by the listed kinase (x-axis)	mean # of variants per HPR target per kinase (y-axis)	mean % non-synonymous variants per HPR target per kinase (% nsHPRv) (color-code)
CDK6	1	39.0	84.6
KIT	5	19.0	82.5
FLT3	7	18.7	95.4
CDK9	3	15.3	87.0
CSNK1D	15	6.6	81.1
PKN2	19	6.3	84.1
FGFR3	8	6.0	75.0
HIPK2	5	6.0	91.7
BRSK1	2	6.0	83.3
BRSK2	2	6.0	83.3
MARK3	1	6.0	83.3
CCND2	1	5.0	100.0
CSNK1E	19	4.5	87.0
CAMK2A	42	4.5	87.2
GSK3B	75	4.5	79.4
CSNK1A1	25	4.4	79.0
PLK3	3	4.0	75.0
FCGR3A	1	4.0	75.0
TAOK2	1	4.0	50.0
VRK1	1	4.0	75.0
KDR	4	3.5	78.6
SGK1	9	3.2	75.0
CDK5	57	3.2	81.0
CSNK2B	29	3.2	75.9
GRK1	6	3.0	100.0
AKT3	5	3.0	66.7
OXSR1	4	3.0	100.0
PHKA1	4	3.0	66.7
EPHB4	3	3.0	66.7
STK38	3	3.0	66.7
NEK8	1	3.0	100.0
SHC1	1	3.0	66.7

B

Kinases with the highest # of targeted HPRs (x-axis extremes)

Kinase name	# of distinct heptameric peptide regions phosphory-lated by the listed kinase (x-axis)	mean # of variants per HPR target per kinase (y-axis)	mean % non-synonymous variants per HPR target per kinase (% nsHPRv) (color-code)
CSNK2A1	213	2.8	81.3
PRKCA	201	2.2	76.6
PRKACA	195	2.1	83.1
MAPK1	140	2.1	76.9
SRC	128	1.9	80.3
CDK1	124	1.7	74.8
CSNK2A2	91	1.9	75.7
AKT1	85	1.8	82.1
CDK2	79	2.4	80.8
GSK3B	75	4.5	79.4
MAPK14	68	1.9	76.3
ATM	67	2.6	84.8
CDK5	57	3.2	81.0
PRKCD	56	1.8	77.1
MAPK8	53	2.9	63.4
MAPK3	49	2.0	83.8
PRKCB	48	1.8	83.1
FYN	47	2.3	76.1
EGFR	47	1.4	67.6
LCK	46	2.1	81.3
CAMK2A	42	4.5	87.2
LYN	37	2.6	79.7
INSR	35	2.5	79.6
SYK	31	1.9	73.8
IKBKB	31	1.2	87.5
ROCK1	30	1.7	83.9
PRKCG	30	1.7	79.5
CSNK2B	29	3.2	75.9
PRKDC	28	2.9	88.0
PDPK1	28	1.3	80.0
ABL1	27	1.5	61.9
ADRBK1	26	2.1	82.6
JAK2	26	1.9	63.0
PRKG1	26	1.8	85.7
CSNK1A1	25	4.4	79.0
ATR	25	2.4	85.4
MAPK9	25	1.8	71.4
ERBB4	23	1.8	60.0
ERBB3	22	2.0	66.7
RPS6KA1	22	2.0	87.5
PLK1	22	1.5	84.2
STK10	21	2.1	87.9
RET	21	2.0	54.2
ZAP70	21	1.3	75.0

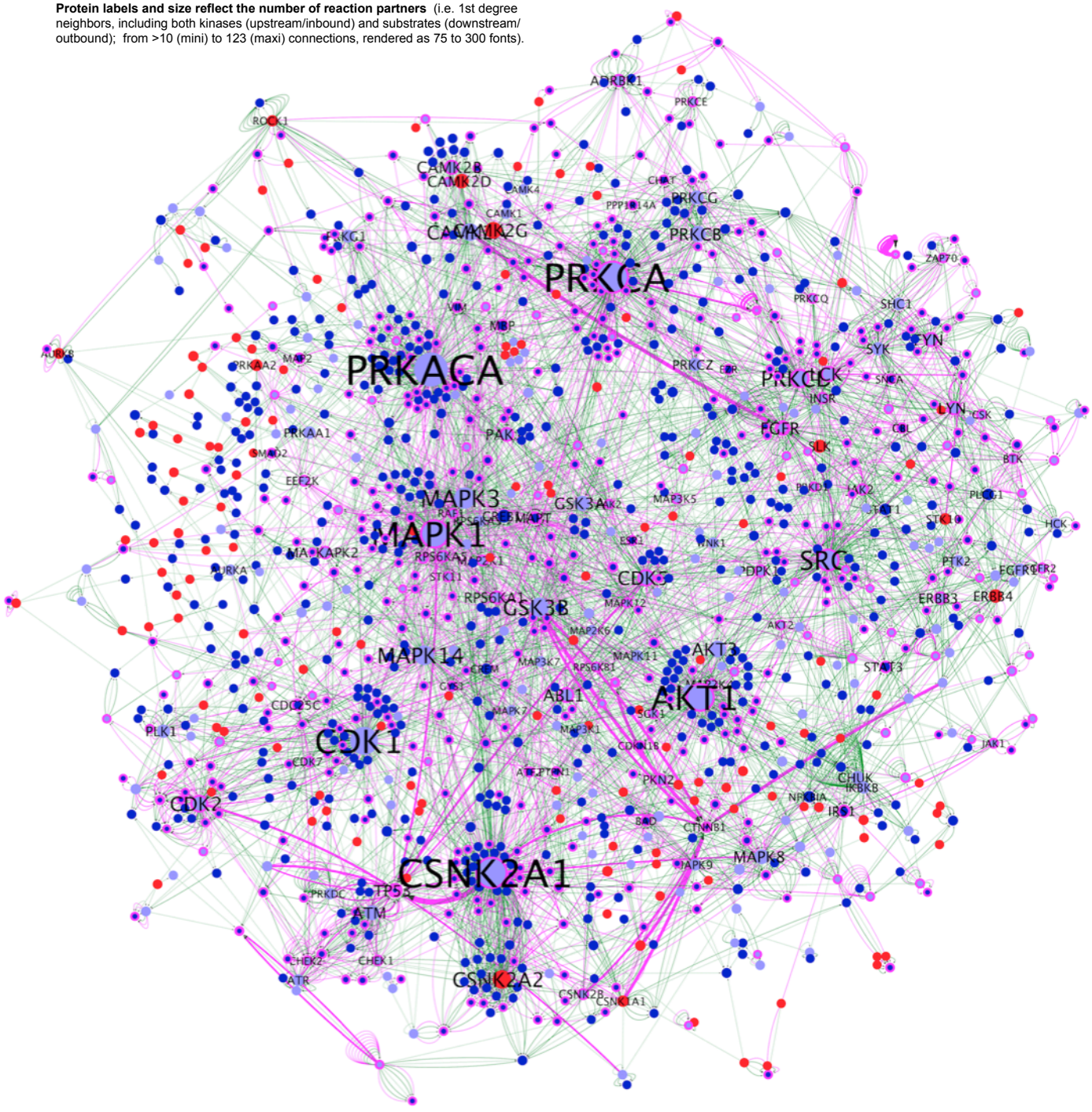
C

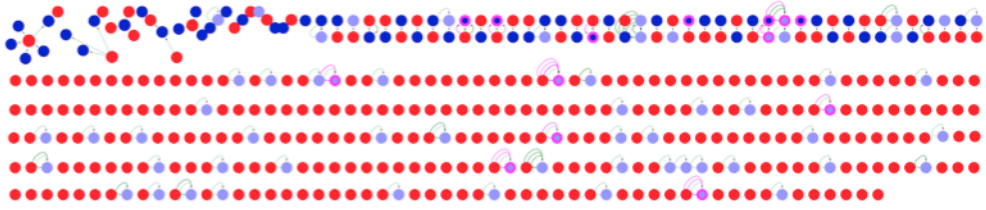
Kinases with the lowest # of variants per targeted HPR

Kinase name	# of distinct heptameric peptide regions phosphory-lated by the listed kinase (x-axis)	mean # of variants per HPR target per kinase (y-axis)	mean % non-synonymous variants per HPR target per kinase (% nsHPRv) (color-code)
MAP3K14	6	0.0	0.0
PRKACG	4	0.0	0.0
EEF2K	3	0.0	0.0
MNAT1	3	0.0	0.0
IGF1R	2	0.0	0.0
MAPK15	2	0.0	0.0
NLK	2	0.0	0.0
PKMYT1	2	0.0	0.0
TESK1	2	0.0	0.0
TESK2	2	0.0	0.0
ACVR1	1	0.0	0.0
BRD4	1	0.0	0.0
CAD	1	0.0	0.0
CCNA2	1	0.0	0.0
CDK16	1	0.0	0.0
CDK19	1	0.0	0.0
CDK20	1	0.0	0.0
CLK4	1	0.0	0.0
CRK	1	0.0	0.0
DAPK2	1	0.0	0.0
DDR1	1	0.0	0.0
EIF2AK1	1	0.0	0.0
EIF2AK3	1	0.0	0.0
LIMK2	1	0.0	0.0
MAP3K10	1	0.0	0.0
MAP3K11	1	0.0	0.0
MAP3K3	1	0.0	0.0
MAP3K9	1	0.0	0.0
MAPK4	1	0.0	0.0
MAPK6	1	0.0	0.0
MELK	1	0.0	0.0
MYT1	1	0.0	0.0
NRK	1	0.0	0.0
PEG3	1	0.0	0.0
PINK1	1	0.0	0.0
PRKAR2A	1	0.0	0.0
PRKD3	1	0.0	0.0
PRKRIR	1	0.0	0.0
TRPM7	1	0.0	0.0
UHMK1	1	0.0	0.0
WEE2	1	0.0	0.0

Supplement Figure S12

Protein labels and size reflect the number of reaction partners (i.e. 1st degree neighbors, including both kinases (upstream/inbound) and substrates (downstream/outbound); from >10 (mini) to 123 (maxi) connections, rendered as 75 to 300 fonts).





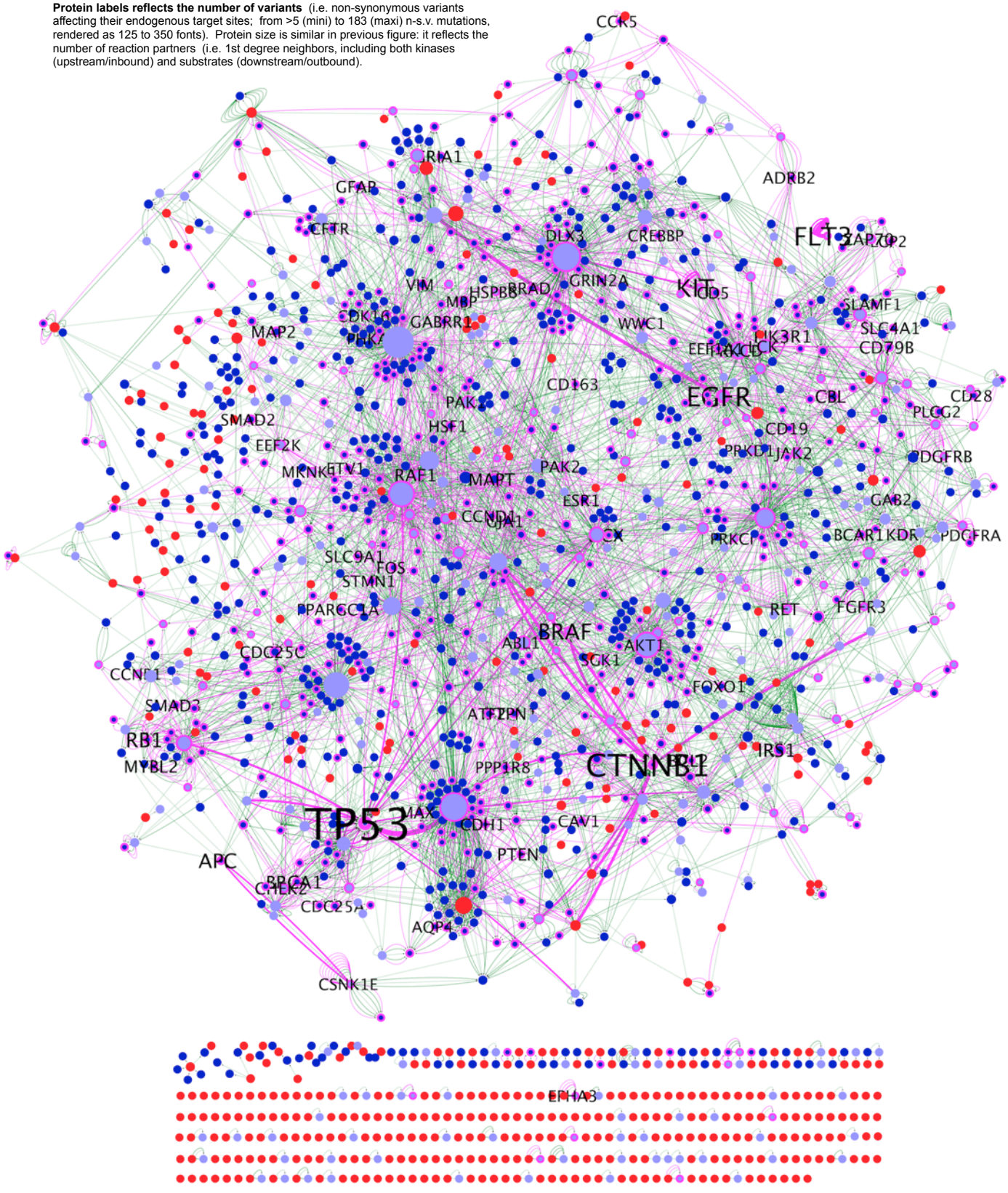
419 proteins not interconnected to the main network

(158 edges)

- Protein that functions as a kinase only; the diameter increases proportionally with the number of substrates it phosphorylates.
- Protein that functions both as a kinase and a substrate; the diameter increases proportionally to the sum of all of kinases phosphorylating it and all substrates it phosphorylates.
- Protein that functions as a substrate only; the diameter increases proportionally with the number of kinases phosphorylating it
- phosphorylation with unknown target site
- individual phosphorylation on a known target site (with no known non-synonymous mutation within the immediate target site range); residue target sites are annotated in the middle of each connector
- individual phosphorylation on a known target site with one or more known non-synonymous mutation(s) within the immediate target site range; the line width increases with the number of mutations
- margin increases proportionally with the number of known non-synonymous mutations within the immediate range of any target site

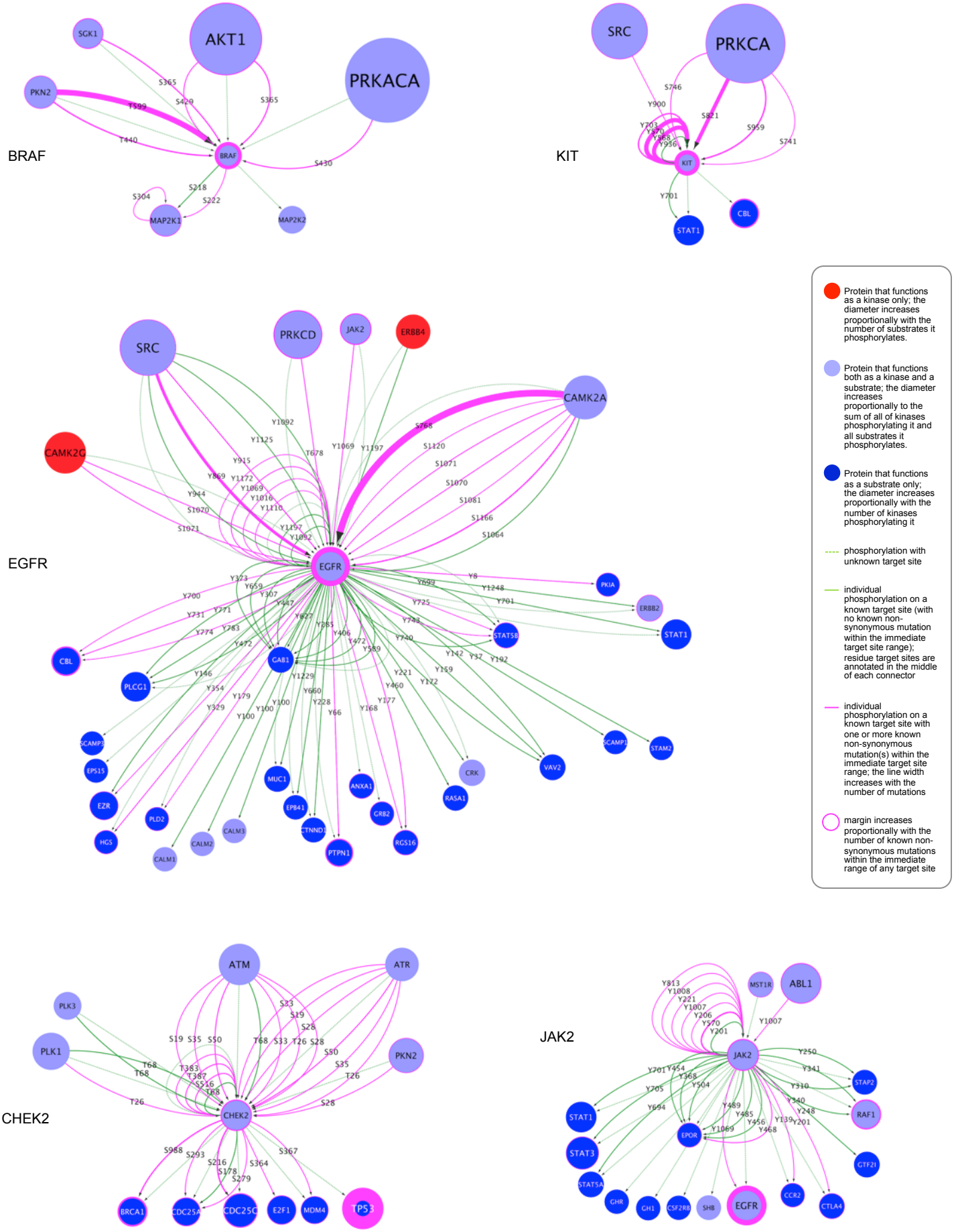
Supplement Figure S13

Protein labels reflects the number of variants (i.e. non-synonymous variants affecting their endogenous target sites; from >5 (mini) to 183 (maxi) n-s.v. mutations, rendered as 125 to 350 fonts). Protein size is similar in previous figure: it reflects the number of reaction partners (i.e. 1st degree neighbors, including both kinases (upstream/inbound) and substrates (downstream/outbound).

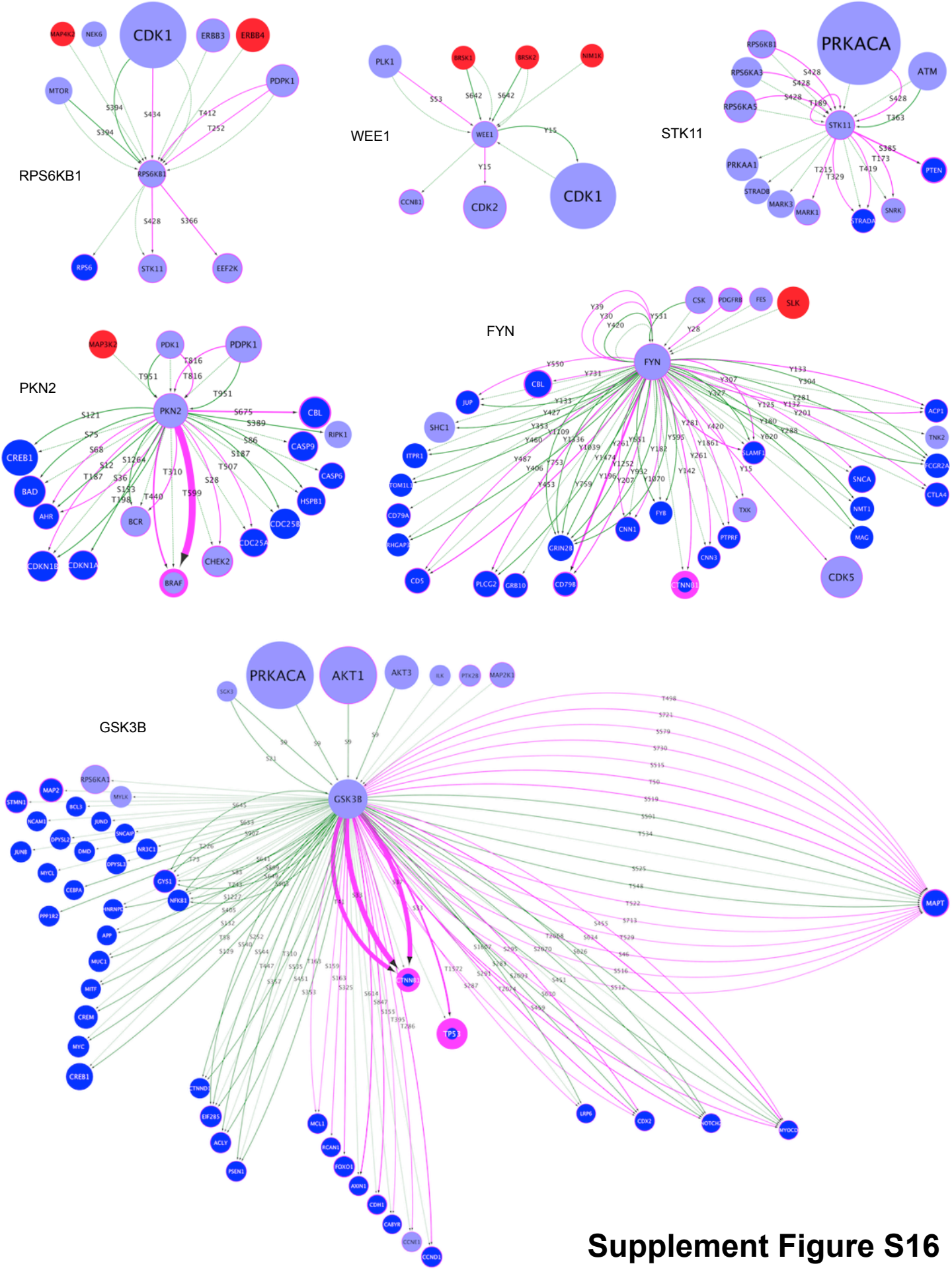


- Protein that functions as a kinase only; the diameter increases proportionally with the number of substrates it phosphorylates.
- Protein that functions both as a kinase and a substrate; the diameter increases proportionally to the sum of all of kinases phosphorylating it and all substrates it phosphorylates.
- Protein that functions as a substrate only; the diameter increases proportionally with the number of kinases phosphorylating it
- phosphorylation with unknown target site
- individual phosphorylation on a known target site (with no known non-synonymous mutation within the immediate target site range); residue target sites are annotated in the middle of each connector
- individual phosphorylation on a known target site with one or more known non-synonymous mutation(s) within the immediate target site range; the line width increases with the number of mutations
- margin increases proportionally with the number of known non-synonymous mutations within the immediate range of any target site

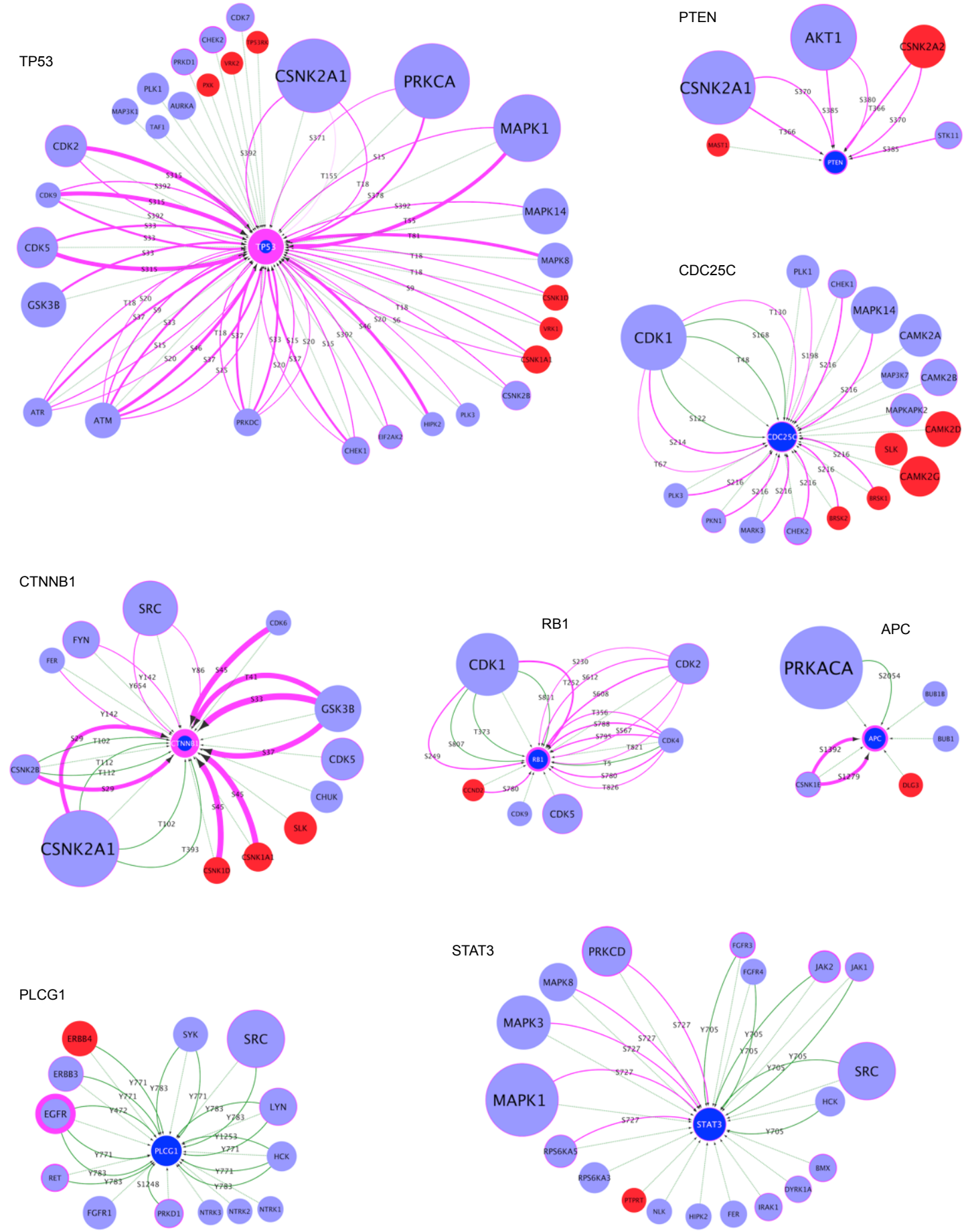
Supplement Figure S14



Supplement Figure S15



Supplement Figure S16



Supplement Figure S17