

A.3_pathway_reference_human_signaling_model.pdf

Sheet1

Pathway
pathway ABL_signaling

Reference (pubmed ID)

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18768933

pathway Met_Receptor

20822955
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Sheet1

pathway Death_Receptor

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pathway Cell_Cycle

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pathway JAK_STAT

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pathway TEK_signaling

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pathway DYRK_signaling

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pathway KIT

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pathway GP130

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A.4_miRNA_validation_reference_human_signaling_model.pdf

Sheet1

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A.5_Feedback_loops.pdf

Loop Type	Simplified Loop-Path	Participating Pathways
Negative Feedback	IL10 → → JAK1:TYK2 → → STAT3 → → SOCS1 ⊣ JAK1:TYK2	JAK_STAT
Negative Feedback	IL10 → → JAK1:TYK2 → → IRS1 → → ERK → → EST2 → → SOCS1 ⊣ JAK1:TYK2	JAK_STAT, MAPK_signaling
Negative Feedback	PRL → → JAK2 → → STAT3 → → SOCS1 ⊣ JAK2	Prolactin_Receptor
Negative Feedback	PRL → → JAK2 → → IRS1 → → ERK → → EST2 → → SOCS1 ⊣ JAK2	Prolactin_Receptor
Negative Feedback	PRL → → JAK2 → → ERK → → SP3 → → SOCS3 ⊣ JAK2	Prolactin_receptor, MAPK_signaling
Negative Feedback	IL9 → → JAK1:JAK3 → → ERK → → MYB → → SOCS3 ⊣ JAK1:JAK3	JAK_STAT, MAPK_signaling
Negative Feedback	CNTF → → JAK1:JAK2 → → IRS1 → → MYB → → SOCS3 ⊣ JAK1:JAK2	GP130, InsulinR_signaling
Negative Feedback	GH2 → → JAK2 → → IRS1 → → MYB → → SOCS3 ⊣ JAK2	Growth_Hormone, InsulinR_signaling
Negative Feedback	IFNG → → JAK1:JAK2 → → IRS1 → → MYB → → SOCS3 ⊣ JAK1:JAK2	JAK_STAT, InsulinR_signaling
Negative Feedback	IL6 → → JAK1:TYK2 → → IRS1 → → MYB → → SOCS3 ⊣ JAK1:TYK2	GP130, InsulinR_signaling
Negative Feedback	CSF2 → → JAK2 → → SHC → → ERK → → SP3 → → SOCS3 ⊣ JAK2	BETA_chain, InsulinR_signaling
Negative Feedback	IL11 → → JAK1:JAK2 → → SHC → → ERK → → SP3 → → SOCS3 ⊣ JAK1:JAK2	GP130, InsulinR_signaling
Negative Feedback	CTF1 → → JAK1:JAK2 → → SHC → → ERK → → SP3 → → SOCS3 ⊣ JAK1:JAK2	GP130, InsulinR_signaling
Negative Feedback	OSM → → JAK1:JAK2 → → SHC → → ERK → → SP3 → → SOCS3 ⊣ JAK1:JAK2	GP130, InsulinR_signaling
Negative Feedback	EGFR:EREG → → SRC → → STAT5 → → CISH ⊣ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	EGFR:EGF → → SRC → → STAT5 → → CISH ⊣ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	CNTF → → JAK1:JAK2 → → SRC → → STAT5 → → CISH ⊣ STAT5	GP130
Negative Feedback	IL5 → → JAK2 → → SRC → → STAT5 → → CISH ⊣ STAT5	JAK_STAT
Negative Feedback	CSF → → JAK2 → → STAT5 → → CISH ⊣ STAT5	BETA_chain

Negative Feedback	IL11 → → JAK1:TYK2 → → STAT5 → → CISH ⊥ STAT5	GP130
Negative Feedback	EGFR:BTC → → SRC → → STAT5 → → CISH ⊥ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	ERBB4:NRG → → STAT5 → → CISH ⊥ STAT5	ERBB_signaling, JAK_STAT
Negative Feedback	IL9 → → JAK1:TYK2 → → STAT5 → → CISH ⊥ STAT5	GAMMA_chain
Negative Feedback	CSF3 → → JAK1:TYK2 → → STAT5 → → CISH ⊥ STAT5	GP130
Negative Feedback	EGFR:AREG → → SRC → → STAT5 → → CISH ⊥ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	IL15 → → JAK1:JAK3 → → STAT5 → → CISH ⊥ STAT5	GAMMA_chain
Negative Feedback	IFNB → → JAK1:TYK2 → → STAT5 → → CISH ⊥ STAT5	JAK_STAT
Negative Feedback	IFNB → → JAK1:TYK2 → → STAT3 → → CISH ⊥ STAT3	JAK_STAT
Negative Feedback	LIF → → JAK1:TYK2 → → STAT5 → → CISH ⊥ STAT5	GP130
Negative Feedback	EGFR:TGFA → → SRC → → STAT5 → → CISH ⊥ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	IFNG → → JAK1:JAK2 → → STAT5 → → CISH ⊥ STAT5	JAK_STAT
Negative Feedback	IL10 → → JAK1:TYK2 → → STAT3 → → CISH ⊥ STAT3	JAK_STAT
Negative Feedback	HBEGF:ERBB4 → → STAT5 → → CISH ⊥ STAT5	ERBB_signaling, JAK_STAT
Negative Feedback	EGFR:EGF → → SRC → → STAT5 → → CISH ⊥ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	OSM → → JAK1:TYK2 → → STAT5 → → CISH ⊥ STAT5	GP130
Negative Feedback	IL6 → → JAK1:TYK2 → → STAT3 → → CISH ⊥ STAT3	GP130
Negative Feedback	EGFR:HBEGF → → SRC → → STAT5 → → CISH ⊥ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	IL6 → → JAK1:TYK2 → → STAT5 → → CISH ⊥ STAT5	GP130
Negative Feedback	OSM → → JAK1:JAK2 → → STAT5 → →	GP130

	CISH ⊣ STAT5	
Negative Feedback	TSLP → → JAK1:JAK3 → → STAT5 → → CISH ⊣ STAT5	GAMMA_chain
Negative Feedback	TSLP → → JAK1:JAK3 → → STAT3 → → CISH ⊣ STAT3	GAMMA_chain
Negative Feedback	CTF → → JAK1:JAK2 → → STAT3 → → CISH ⊣ STAT3	GP130
Negative Feedback	ERBB4:EREG → → STAT5 → → CISH ⊣ STAT5	ERBB_signaling, JAK_STAT
Negative Feedback	ERBB4:NRG → → STAT5 → → CISH ⊣ STAT5	ERBB_signaling, JAK_STAT
Negative Feedback	CNTF → → JAK1:TYK2 → → STAT5 → → CISH ⊣ STAT5	GP130
Negative Feedback	ERBB4:BTC → → STAT5 → → CISH ⊣ STAT5	ERBB_signaling, JAK_STAT
Negative Feedback	EGFR:BTC → → SRC → → STAT5 → → CISH ⊣ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	IL3 → → JAK2 → → STAT5 → → CISH ⊣ STAT5	BETA_chain
Negative Feedback	EGFR:EREG → → SRC → → STAT5 → → CISH ⊣ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	EGFR:HBEGF → → SRC → → STAT5 → → CISH ⊣ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	IFNA → → JAK1:TYK2 → → STAT3 → → CISH ⊣ STAT3	JAK_STAT
Negative Feedback	IFNA → → JAK1:TYK2 → → STAT5 → → CISH ⊣ STAT5	JAK_STAT
Negative Feedback	IL7 → → JAK1:JAK2 → → STAT5 → → CISH ⊣ STAT5	GAMMA_chain
Negative Feedback	EGFR:AREG → → SRC → → STAT5 → → CISH ⊣ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	LIF → → JAK1:TYK2 → → STAT5 → → CISH ⊣ STAT5	GP130
Negative Feedback	EGFR:TGFA → → SRC → → STAT5 → → CISH ⊣ STAT5	EGFR_signaling, JAK_STAT
Negative Feedback	CSF3 → → JAK1:JAK2 → → STAT5 → → CISH ⊣ STAT5	GP130
Negative Feedback	IL11 → → JAK1:JAK2 → → STAT3 → → CISH ⊣ STAT3	GP130
Negative Feedback	IL11 → → JAK1:JAK2 → → STAT5 → →	GP130

	CISH - STAT5	
Negative Feedback	PRL → → JAK2 → → STAT5 → → CISH - STAT5	Prolactin_Receptor, JAK_STAT
Negative Feedback	GH1 → → JAK2 → → STAT5 → → CISH - STAT5	Prolactin_Receptor, JAK_STAT
Negative Feedback	IL2 → → JAK1:JAK3 → → STAT5 → → CISH - STAT5	GAMMA_chain
Negative Feedback	IL6 → → JAK1:JAK2 → → STAT5 → → CISH - STAT5	GP130
Negative Feedback	IL6 → → JAK1:JAK2 → → STAT3 → → CISH - STAT3	GP130
Negative Feedback	MYC:MAX → → CCND1/2/3:CDK4/6 → → RBL1 → → E2F4/5 - MYC	Cell_Cycle
Negative Feedback	CCND1:CDK4/6 → → E2F4/5:RBL1 - MYC → → VEGFA:KDR → → RAS → → ERK → → CCND1	Cell_Cycle, MAPK_signaling
Negative Feedback	CCND1:CDK4/6 → → E2F4/5:RBL1 - MYC → → VEGFA:KDR → → RAS → → SP1 → → CCND1	Cell_Cycle, MAPK_signaling
Negative Feedback	CCND1:CDK4/6 → → E2F4/5:RBL1 - MYC → → VEGFA:KDR → → RAS → → SP1 → → CCND1	Cell_Cycle, MAPK_signaling
Negative Feedback	CCND1:CDK4/6 → → E2F4/5:RBL1 - MYC → → ERBB2 → → ERK → → CCND1	Cell_Cycle, ERBB_signaling
Negative Feedback	CCND1:CDK4/6 → → E2F4/5:RBL1 - MYC → → ERBB2 → → RAS → → SP1 → → CCND1	Cell_Cycle, ERBB_signaling
Negative Feedback	LIF → → JAK1:JAK2 → → STAT3 → → SOCS1 - JAK1:JAK2	GP130
Negative Feedback	LIF → → JAK1:JAK2 → → IRS1 → → ERK → → ETS2 → → SOCS1 - JAK1:JAK2	GP130
Negative Feedback	IL11 → → JAK1:TYK2 → → STAT3 → → SOCS1 - JAK1:TYK2	GP130
Negative Feedback	IL11 → → JAK1:TYK2 → → SHC1 → → KRAS → → ETS2 → → SOCS1 - JAK1:TYK2	GP130
Negative Feedback	IL6 → → JAK1:TYK2 → → STAT3 → → SOCS1 - JAK1:TYK2	GP130
Negative Feedback	IL6 → → JAK1:TYK2 → → SHC1 → → KRAS → → ETS2 → → SOCS1 - JAK1:TYK2	GP130

Negative Feedback	IL4 → → JAK1:JAK3 → → STAT6 → → SOCS1 ⊣ JAK1:JAK3	GP130
Negative Feedback	IL4 → → JAK1:JAK3 → → IRS1 → → RAS → → ETS2 → → SOCS1 ⊣ JAK1:JAK3	GP130, InsulinR_signaling
Negative Feedback	IL13 → → JAK2:TYK2 → → STAT6 → → SOCS1 ⊣ JAK2:TYK2	GAMMA_chain
Negative Feedback	IL13 → → JAK2:TYK2 → → IRS1 → → RAS → → EST2 → → SOCS1 ⊣ JAK2:TYK2	GAMMA_chain, InsulinR_signaling
Negative Feedback	IL13 → → JAK1:JAK2 → → STAT6 → → SOCS1 ⊣ JAK2:JAK2	GAMMA_chain, InsulinR_signaling
Negative Feedback	IL13 → → JAK2:JAK2 → → IRS1 → → RAS → → EST2 → → SOCS1 ⊣ JAK2:JAK2	GAMMA_chain
Negative Feedback	GH1 → → JAK2 → → STAT3 → → SOCS1 ⊣ JAK2	Prolactin_Receptor
Negative Feedback	GH1 → → JAK2 → → IRS1 → → ERK → → EST2 → → SOCS1 ⊣ JAK2	Prolactin_Receptor, InsulinR_signaling
Negative Feedback	GH2 → → JAK2 → → STAT3 → → SOCS1 ⊣ JAK2	Growth_Hormone
Negative Feedback	GH2 → → JAK2 → → IRS1 → → ERK → → EST2 → → SOCS1 ⊣ JAK2	Growth_Hormone, InsulinR_signaling
Negative Feedback	IL6 → → JAK1:JAK2 → → STAT3 → → SOCS1 ⊣ JAK2	GP130
Negative Feedback	IL6 → → JAK1:JAK2 → → IRS1 → → ERK → → EST2 → → SOCS1 ⊣ JAK1:JAK2	GP130, InsulinR_signaling
Negative Feedback	IFNA → → JAK1:TYK2 → → STAT3 → → SOCS1 ⊣ JAK1:TYK2	JAK_STAT
Negative Feedback	IFNA → → JAK1:TYK2 → → IRS → → ERK → → EST2 → → SOCS1 ⊣ JAK1:TYK2	JAK_STAT, InsulinR_signaling
Negative Feedback	IFNB → → JAK1:TYK2 → → STAT3 → → SOCS1 ⊣ JAK1:TYK2	JAK_STAT
Negative Feedback	IFNB → → JAK1:TYK2 → → IRS → → ERK → → EST2 → → SOCS1 ⊣ JAK1:TYK2	JAK_STAT, InsulinR_signaling
Negative Feedback	LIF → → JAK1:TYK2 → → STAT3 → → SOCS1 ⊣ JAK1:TYK2	GP130
Negative Feedback	LIF → → JAK1:TYK2 → → IRS → → ERK → → EST2 → → SOCS1 ⊣ JAK1:TYK2	GP130, InsulinR_signaling
Negative Feedback	TSLP → → JAK1:JAK3 → → STAT3 → → SOCS1 ⊣ JAK1:JAK3	GAMMA_chain

Positive Feedback	VEGFA → → GRB2:SOS1 → → KRAS → → ERK → → SP1 → → VEGFA;	VEGF_signaling, MAPK_signaling
Positive Feedback	VEGFB → → GRB2:SOS1 → → KRAS → → ERK → → SP1 → → VEGFB;	VEGF_signaling, MAPK_signaling
Positive Feedback	FLT1 → → GRB2:SOS1 → → KRAS → → ERK → → SP1 → → FLT1;	VEGF_signaling, MAPK_signaling
Positive Feedback	IL10 → → JAK1:TYK2 → → STAT3 → → IL10;	JAK_STAT
Positive Feedback	ERBB2:ERBB4:BTC → → STAT5 → → MYC:MAX → → ERBB2	ERBB_signaling, JAK_STAT
Positive Feedback	ERBB2:ERBB3:NRG → → STAT1 → → MYC:MAX → → ERBB2	ERBB_signaling, JAK_STAT
Positive Feedback	ERBB2:ERBB4:NRG → → STAT5 → → MYC:MAX → → ERBB2	ERBB_signaling, JAK_STAT
Positive Feedback	ERBB2:ERBB4:EREG → → STAT5 → → MYC:MAX → → ERBB2	ERBB_signaling, JAK_STAT
Positive Feedback	ERBB2:ERBB4:HBEGF → → STAT5 → → MYC:MAX → → ERBB2	ERBB_signaling, JAK_STAT
Positive Feedback	E2F1:DP1/2:HDAC → → E2F1	Cell_Cycle
Positive Feedback	MYC:MAX → → MAX	Cell_Cycle
Positive Feedback	IL2 → → JAK1:JAK3 → → STAT4/6 → → IRF1 → → IL2	JAK_STAT, Prolactin_Receptor
Positive Feedback	FOS:ATF4 → → TP53 → → HRAS → → ERK → → ELK1/4 → → FOS	ATF_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:ATF4 → → TP53 → → TGFA → → EGFR → → STAT1 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS:ATF4 → → TP53 → → HRAS → → ERK → → CREB3 → → FOS	TP53_signaling, MAPK_signaling
Positive Feedback	FOS:ATF4 → → TP53 → → TGFA → → EGFR → → ERK → → CREB3 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS:ATF4 → → TP53 → → HRAS → → ERK → → SP1 → → FOS	ATF_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:ATF4 → → TP53 → → TGFA → → EGFR → → ERK → → SP1 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS:ATF4 → → TP53 → → EPHA2 → → ERK → → ELK1/4 → → FOS	Ephrin_Eph_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:AFT4 → → TP53 → → EGFR → → ERK → → ELK1/4 → → FOS	EGFR_signaling, TP53_signaling, MAPK_signaling

Positive Feedback	FOS:ATF4 → → TP53 → → EPHA2 → → JNKs → → FOS	Ephrin_Eph_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:ATF4 → → TP53 → → TGFA → → JUN → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS:ATF4 → → TP53 → → HRAS → → ERK → → ATF2 → → FOS	ATF_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:ATF4 → → TP53 → → EPHA2 → → ERK → → ATF2 → → FOS	Ephrin_Eph_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:AFT4 → → TP53 → → EGFR → → ERK → → ATF2 → → FOS	EGFR_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:ATF4 → → TP53 → → TGFA → → JAK1:JAK2 → → STAT3 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS:ATF4 → → TP53 → → TGFA → → EGFR:ERBB2 → → STAT3 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	IFNA → → JAK1:TYK2 → → STAT1 → → IRF7 → → IFNA	TLR_signaling, JAK_STAT,
Positive Feedback	IFNA → → EIF2AK2 → → TP53 → → IRF7 → → IFNA	TLR_signaling, TP53_signaling
Positive Feedback	IFNA → → DAPK1 → → TP53 → → IRF7 → → IFNA	Death_Receptor, TP53_signaling
Positive Feedback	IFNG → → JAK1:JAK2 → → STAT1 → → IFNG	JAK_STAT
Positive Feedback	IL2RA → → JAK1:JAK3 → → STAT1/3/5 → → IL2RA	GAMMA_chain
Positive Feedback	CCND1:ESR1 → → MYC → → VEGFA:KDR → → GRB2:SOS1 → → RAS → → ERK → → CCND1	Cell_Cycle, MAPK_signaling
Positive Feedback	CCND1:ESR1 → → MYC → → VEGFA:KDR → → GRB2:SOS1 → → RAS → → SP1 → → CCND1	Cell_Cycle, MAPK_signaling
Positive Feedback	CCND1:ESR1 → → MYC → → VEGFA:KDR → → GRB2:SOS1 → → RAS → → SP1 → → CCND1	Cell_Cycle, MAPK_signaling
Positive Feedback	CCND1:ESR1 → → MYC → → ERBB2 → → RAS → → ERK → → CCND1	Cell_Cycle, ERBB_signaling
Positive Feedback	CCND1:ESR1 → → MYC → → ERBB2 → → RAS → → SP1 → → CCND1	Cell_Cycle, ERBB_signaling
Positive Feedback	CCND1:ESR1 → → CCND1	Cell_Cycle

Positive Feedback	TLR → → MYD88 → → IRF7 → → IFNA → → STAT1 → → MYD88	TLR_signaling, JAK_STAT
Positive Feedback	TLR → → MYD88 → → IRF7 → → IFNB → → STAT1 → → MYD88	TLR_signaling, JAK_STAT
Positive Feedback	OSM:IL6ST → → JAK1:TYK2 → → STAT1/3 → → IL6ST	GP130
Positive Feedback	LEP:IL6ST → → JAK2 → → STAT3 → → IL6ST	GP130
Positive Feedback	CSF3:IL6ST → → JAK1:TYK2 → → STAT1/3 → → IL6ST	GP130
Positive Feedback	CTF1:IL6ST → → JAK1:TYK2 → → STAT1/3 → → IL6ST	GP130
Positive Feedback	IL6:IL6ST → → JAK1:TYK2 → → STAT1/3 → → IL6ST	GP130
Positive Feedback	CNTF:IL6ST → → JAK1:TYK2 → → STAT1/3 → → IL6ST	GP130
Positive Feedback	CNTF:IL6ST → → JAK1:JAK2 → → STAT1/3 → → IL6ST	GP130
Positive Feedback	LIF1:IL6ST → → JAK1:JAK2 → → STAT1/3 → → IL6ST	GP130
Positive Feedback	LIF1:IL6ST → → JAK1:TYK2 → → STAT1/3 → → IL6ST	GP130
Positive Feedback	IL11:IL6ST → → JAK1:TYK2 → → STAT1/3 → → IL6ST	GP130
Positive Feedback	IL2 → → JAK1:JAK3 → → STAT4 → → IRF1 → → IL2	GAMMA_chain
Positive Feedback	ERK → → AR_dimer → → AR	MAPK_signaling, PI3K_AKT
Positive Feedback	TNK2 → → AR_dimer → → AR	InsulinR_signaling, PI3K_AKT
Positive Feedback	AKT → → AR_dimer → → AR	PI3K_AKT
Positive Feedback	TGFB2 → → SMAD2/3 → → TGFB2	TGF_beta
Positive Feedback	TGFB2 → → ERK → → TGFB2	TGF_beta
Positive Feedback	TGFB2 → → JNKs → → JUN → → TGFB2	TGF_beta
Positive Feedback	BDNF:NTRK2 → → PIP3 → → AKT → → CREB → → BDNF	BDNF_signaling
Positive Feedback	JUN → → TP53 → → ERK → → SP1 → → MYB → → JUN	P53_signaling, ATM_signaling
Positive Feedback	JUN → → ATF2 → → CTNNB → → JUN	ATF_signaling, WNT_signaling
Positive Feedback	JUN → → FOS → → SMAD2/3 → → JUN	ATF_signaling, TGF_beta
Positive Feedback	ATM → → TP53 → → VEGFA → → ERK	ATM_signaling, TP53_signaling,

	→ → SP1 → → ATF1 → → ATM	MAPK_signaling, VEGF_signaling
Positive Feedback	ARNT2 → → HIF1A → → VEGFA/B → → ERK → → SP1 → → ATF1 → → ARNT2	HIF1A_signaling, VEGF_signaling, MAPK_signaling
Positive Feedback	ATF3:JUN → → TP53 → → ATF3	HIF1A_signaling
Positive Feedback	ATF3:JUN → → TP53 → → TGFA → → ERK → → JUN → → ATF3	TP53_signaling, MAPK_signaling
Positive Feedback	EGR1 → → TP53 → → TGFA → → ERK → → ELK1/4 → → EGR1	MAPK_signaling, TP53_signaling
Positive Feedback	EGR1 → → TP53 → → EGFR → → ERK → → ELK1/4 → → EGR1	MAPK_signaling, TP53_signaling
Positive Feedback	EGR1 → → TP53 → → VEGFC → → ERK → → ELK1/4 → → EGR1	MAPK_signaling, TP53_signaling
Positive Feedback	EGR1 → → TP53 → → EGFR → → ERK → → CREB → → EGR1	MAPK_signaling, TP53_signaling
Positive Feedback	EGR1 → → TP53 → → TGFA → → ERK → → CREB → → EGR1	MAPK_signaling, TP53_signaling
Positive Feedback	EGR1 → → TP53 → → VEGFA → → ERK → → CREB → → EGR1	MAPK_signaling, TP53_signaling
Positive Feedback	EGR1 → → MYB → → JUN → → ATF1 → → EGR1	ATM_signaling
Positive Feedback	EGR1 → → MYB → → MYC → → ERBB2 → → ERK → → ELK1/4 → → EGR1	ERBB_signaling, MAPK_signaling
Positive Feedback	EGR1 → → MYB → → MYC → → ERBB2 → → ERK → → CREB → → EGR1	ERBB_signaling, MAPK_signaling
Positive Feedback	EGR1 → → MYB → → MYC → → VEGFA → → ERK → → CREB → → EGR1	VEGF_signaling, MAPK_signaling
Positive Feedback	ESR1 → → RET → → CRK → → MKK4/7 → → JUN → → ESR1	P38MAPK , RET_signaling
Positive Feedback	ESR1 → → RET → → NCK1 → → JNK → → ATF1 → → ESR1	RET_signaling, p38MAPK
Positive Feedback	TEAD1 → → YAP1 → → TGFA → → ERK → → SP1 → → TEAD1	SWH_signaling, MAPK_signaling
Positive Feedback	TEAD1 → → YAP1 → → EPHA2 → → ERK → → SP1 → → TEAD1	SWH_signaling, Ephrin_Eph_signaling, MAPK_signaling
Positive Feedback	TGFB2 → → ERK → → JUN:FOS → → TGFB2	TGF_beta, MAPK_signaling
Positive Feedback	TGFB2 → → SMAD2/3 → → JUN → → TGFB2	TGF_beta

Positive Feedback	FN1 → → ITGA4:ITGB7 → → RAC:GTP → → RAF → → ERK → → JUN:FOS → → FN1	Integrin_signaling, MAPK_signaling
Positive Feedback	FN1 → → ITGA4:ITGB7 → → RAC:GTP → → RAF → → ERK → → CREB → → FN1	Integrin_signaling, MAPK_signaling
Positive Feedback	FN1 → → ITGA4:ITGB7 → → RHOA:GTP → → IRS1 → → ERK → → CREB → → FN1	Integrin_signaling, InsulinR_signaling, MAPK_signaling
Positive Feedback	FN1 → → ITGA4:ITGB7 → → RHOA:GTP → → IRS1 → → ERK → → JUN:FOS → → FN1	Integrin_signaling, InsulinR_signaling, MAPK_signaling
Positive Feedback	FN1 → → ITGA4:ITGB7 → → ILK → → CTNNB → → MYC → → JUN:FOS → → FN1	Integrin_signaling, InsulinR_signaling, MAPK_signaling
Positive Feedback	FN1 → → ITGA5:ITGB1 → → ILK → → CTNNB → → MYC → → JUN:FOS → → FN1	Integrin_signaling, InsulinR_signaling, MAPK_signaling
Positive Feedback	FN1 → → ITGA5:ITGB1 → → RHOA:GTP → → IRS1 → → ERK → → CREB → → FN1	Integrin_signaling, InsulinR_signaling, MAPK_signaling
Positive Feedback	FN1 → → ITGA5:ITGB1 → → RHOA:GTP → → IRS1 → → ERK → → JUN:FOS → → FN1	Integrin_signaling, InsulinR_signaling, MAPK_signaling
Positive Feedback	FN1 → → ITGA5:ITGB1 → → RAC:GTP → → RAF → → ERK → → JUN:FOS → → FN1	Integrin_signaling, MAPK_signaling
Positive Feedback	FN1 → → ITGA5:ITGB1 → → RAC:GTP → → RAF → → ERK → → CREB → → FN1	Integrin_signaling, MAPK_signaling
Positive Feedback	FOS:JUN → → TP53 → → HRAS → → ERK → → CREB → → FOS	ATF_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:JUN → → TP53 → → HRAS → → ERK → → SP1 → → FOS	ATF_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:JUN → → TP53 → → HRAS → → ERK → → ELK1/3 → → FOS	ATF_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS:JUN → → TP53 → → TGFA → → EGFR → → STAT1 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS:JUN → → TP53 → → TGFA → → EGFR → → ERK → → CREB3 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS:JUN → → TP53 → → TGFA → → EGFR → → ERK → → SP1 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS:JUN → → TP53 → → EPHA2 → → ERK → → ELK1/4 → → FOS	Ephrin_Eph_signaling, TP53_signaling,

		MAPK_signaling
Positive Feedback	FOS:JUN → → TP53 → → EGFR → → ERK → → ELK1/4 → → FOS	EGFR_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS: JUN → → TP53 → → EPHA2 → → JNKs → → FOS	Ephrin_Eph_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS: JUN → → TP53 → → TGFA → → JUN → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS: JUN → → TP53 → → HRAS → → ERK → → ATF2 → → FOS	ATF_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS: JUN → → TP53 → → EPHA2 → → ERK → → ATF2 → → FOS	Ephrin_Eph_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS: JUN → → TP53 → → EGFR → → ERK → → ATF2 → → FOS	EGFR_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS: JUN → → TP53 → → TGFA → → JAK1:JAK2 → → STAT3 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS: JUN → → TP53 → → TGFA → → EGFR:ERBB2 → → STAT3 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS: JUN → → TP53 → → HRAS → → ERK → → ELK1/4 → → FOS	ATF_signaling, TP53_signaling, MAPK_signaling
Positive Feedback	FOS: JUN → → TP53 → → TGFA → → EGFR → → STAT1 → → FOS	EGFR_signaling, TP53_signaling, JAK_STAT
Positive Feedback	FOS: JUN → → TP53 → → HRAS → → ERK → → CREB3 → → FOS	TP53_signaling, MAPK_signaling
Positive Feedback	IFNB1 → → DAYK → → TP53 → → HRAS → → ERK → → JUN:ATF2 → → IFNB1	JAK_STAT, MAPK_signaling
Positive Feedback	IFNB1 → → DAYK → → TP53 → → EGFR → → ERK → → JUN:ATF2 → → IFNB1	EGFR_signaling, JAK_STAT TP53_signaling, MAPK_signaling
Positive Feedback	IL5 → → JAK2 → → SHC → → ERK → → JUN:FOSL2 → → IL5	JAK_STAT, MAPK_signaling
Positive Feedback	IL5 → → LYN → → MAP3K1 → → ESR1 → → MYC → → IL5	JAK_STAT, MAPK_signaling
Positive Feedback	CSF → → LYN → → MKK4/7 → → JNKs → → MAP3K7 → → NfκB → → CSF	JAK_STAT, NFκB_signaling
Positive Feedback	IGF2 → → SHC:GRB2:SOS1 → → ERK → → HIF1A → → IGF2	InsulingR_signaling, HIF1A_signaling, MAPK_signaling

Positive Feedback	TNF → → TNF:TNFRSF1B:TRADD:TRAF2 → → JNK → → JUN → → JUN:ATF2 → → TNF	NfκB_signaling, TLR_signaling
Positive Feedback	TNF → → IL13:IL13RA:TNF → → FOSL2 → → JUN:FOSL2 → → FOSL2	GAMMA_chain, TLR_signaling
Positive Feedback	TNF → → IL4:IL13RA:IL4R:TNF → → FOSL 2 → → JUN:FOSL2 → → FOSL2	GAMMA_chain, TLR_signaling
Positive Feedback	TNF → → TNF:TNFRSF21 → → NFKB:RELA → → TNF	TLR_signaling, Death_Receptor, NfκB_signaling
Positive Feedback	IL6 → → JAK1:JAK2 → → IRS1 → → PI3K → → PKC → → NfκB1:RELA → → IL6	NfκB_signaling, GP130
Positive Feedback	IL6 → → JAK1:JAK2 → → IRS1 → → PI3K → → PKC → → NfκB2:RELB → → IL6	NfκB_signaling, GP130
Positive Feedback	IL6 → → JAK1:TYK2 → → PI3K → → PKC → → NfκB1:RELA → → IL6	NfκB_signaling, GP130
Positive Feedback	IFNB1 → → EIF2AK2 → → TP53 → → HRAS → → ERK → → JUN:ATF2 → → IFNB1	JAK_STAT, MAPK_signaling
Positive Feedback	IFNB1 → → EIF2AK2 → → TP53 → → EGFR → → ERK → → JUN:ATF2 → → IFNB1	EGFR_signaling, JAK_STAT TP53_signaling, MAPK_signaling
Positive Feedback	IFNB1 → → JAK1:TYK2 → → IRS1 → → PI3K → → PKC → → NfκB1:RELA → → IFNB1	JAK_STAT, NfκB_signaling
Positive Feedback	IFNB1 → → JAK1:TYK2 → → IRS1 → → PI3K → → PKC → → NfκB2:RELA → → IFNB1	JAK_STAT, NfκB_signaling
Positive Feedback	IFNB1 → → JAK1:TYK2 → → IRS1 → → PI3K → → AKT → → PRKCG → → NfκB2:RELA → → IFNB1	JAK_STAT, NfκB_signaling
Positive Feedback	IL8 → → CXCR1:IL8 → → PTK2 → → PLCG → → PKC → → NfκB1:RELA → → IL8	JAK_STAT, NfκB_signaling
Positive Feedback	IL8 → → CXCR1:IL8 → → PTK2 → → PLCG → → PRKCG → → NfκB1:RELA → → IL8	JAK_STAT, NfκB_signaling
Positive Feedback	IL8 → → CXCR1:IL8 → → PTK2 → → PLCG → → PRKCB → → NfκB1:RELA → → IL8	JAK_STAT, NfκB_signaling
Positive Feedback	IL8 → → CXCR1:IL8 → → PTK2 → → PLCG → → PRKCA → → NfκB1:RELA → → IL8	JAK_STAT, NfκB_signaling
Positive Feedback	IL8 → → CXCR1:IL8 → → PTK2 → → PLCG → → PRKCB → → NfκB2:RELB → → IL8	JAK_STAT, NfκB_signaling
Positive Feedback	TLR → → MYD88 → → IRF7 → → IFNA → → J AK1:TYK2 → → STAT1 → → IRF7	JAK_STAT, TLR_signaling
Positive Feedback	TLR → → MYD88 → → IRF7 → → IFNA → → J AK1:TYK2 → → STAT2 → → IRF7	JAK_STAT, TLR_signaling

The detail information related to pathways is recorded in the Supplementary Table 2, 3 and 4.

A.9_HMMA_miRNA_reference.pdf

Sheet1

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	ENSG00000115758	20432256
	ENSG00000131386	19844573
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	ENSG00000131459	20353610
	ENSG00000105398	20484008
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mir-376c(MI0000776)	ENSG00000196839	17322061
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ENSG00000078747	2.278037	6857300
ENSG00000166333	142.076475	78186000
ENSG00000156709	9.618208	32168000
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ENSG00000117450	4033.953444	2279200000
ENSG00000100387	34.311283	5432200
ENSG00000168036	161.798733	45035000
ENSG00000133818	7.260683	40435000
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ENSG00000151247	7.628195	59651000

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ENSG00000141510	5.866428	1239800
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ENSG00000103319	1.257597	367430
ENSG00000166913	115.3521	833790000
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ENSG00000117450	138.2554	2279200000
ENSG00000109320	9.614555	1867100
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ENSG00000174775	8.927459	8148400
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ENSG00000142627	26.05005	79408000
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ENSG00000141510	9.380247	1239800
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ENSG00000158402	5.407933	463240
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ENSG00000137693	15.70347	10365000
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ENSG00000123836	6.344897	3735000
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Sheet1

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Sheet1

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ENSG00000169398	14.207314	8494500
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ENSG00000085733	5785.4875	104870000
ENSG00000181222	3.552498	9835200
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ENSG00000136238	3254.55255	150760000
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ENSG00000115317	5.951429	1109000
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ENSG00000177889	66.477025	95412000
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ENSG00000121691	23.73	4488300
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ENSG00000085832	17.5296	5669100
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ENSG00000153707	0.238693	330450
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ENSG00000117632	59.00044	108380000
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ENSG00000140464	5.289945	17840000
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ENSG00000086758	14.49013	39289000
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ENSG00000121022	6.323611	9630500
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ENSG00000114978	21.92439	33041000
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ENSG00000173039	9.743961	6529100
ENSG00000164951	18.72143	335920
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ENSG00000071051	16.13726	2057000
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Sheet1

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ENSG00000165119	499.80742	1170000000
ENSG00000169398	15.415513	6589900
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ENSG00000164733	674.042837	111610000
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ENSG00000100324	3.568514	250970
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ENSG00000111057	22.49785	6890000000
ENSG00000080839	0.187229	64541
ENSG00000117394	303.7855	50587000
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ENSG00000102871	14.73977	1388600

B.10_cancer_cell_IDs.pdf

Sheet1

Appendix B.9: The ID of three cancer cell lines:

The applied 60 cancer cell lines from three cancer types (breast, colon, and lung) are provided from cancer research organization of The Cancer Genome Atlas and the data can be downloaded from its link (<https://tcga-data.nci.nih.gov>).

ID of 20 breast cancer cell lines:

unc.edu__AgilentG4502A_07_3__TCGA-E2-A15J-01A-11R-A12P-07
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unc.edu__AgilentG4502A_07_3__TCGA-E2-A15L-01A-11R-A12D-07
unc.edu__AgilentG4502A_07_3__TCGA-E2-A15M-01A-11R-A12D-07
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unc.edu__AgilentG4502A_07_3__TCGA-E2-A1B6-01A-31R-A12P-07
unc.edu__AgilentG4502A_07_3__TCGA-E2-A1BC-01A-11R-A12P-07
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unc.edu__AgilentG4502A_07_3__TCGA-E2-A1BD-01A-11R-A12P-07

ID of 20 colon cancer cell lines:

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Sheet1

unc.edu__AgilentG4502A_07_3__TCGA-AA-A02W-01A-01R-A00A-07
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ID of 20 lung cancer cell lines:

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C.2_pathway_keyComponent.pdf

Pathway	Description	Mechanism
MAPK_signaling	A mitogen-activated protein kinase (MAPK) cascade, which composes of diverse protein phosphorylation cascades that function to control different cellular processes related to proliferation, angiogenesis, apoptosis and other.	The activation of this pathway triggers the phosphorylation of protein kinase RAS and its cousin that in turn phosphorylate MEK1/2. Afterwards, ERK1/2 is phosphorylated by MEK1/2 and activates diverse down-stream targets (such as RPS6KA2, TSC2, AR, ESR1, SMAD2/3, EIF4EBP1)
p38MAPK	Functions in a similar way as MAPK_signaling, possesses protein phosphorylation cascades based on protein kinase MAPK14 (p38) and control different cellular processes. This pathway has intensive crosstalk with signaling pathways such as Activin_signaling, TGF_beta.	The phosphorylation of the protein kinase MAPK14 can be triggered by the different activated cellular components (such as MKK3/6, MKK4/7, ACVR:MSTN, ACVR:ACTIVIN, ACVR:GDF11). This activated protein kinase can in turn phosphorylate many target proteins (such as ELK1, ATF2, TP53).
NFkB_signaling	Includes relevant transcriptional regulations of NF-kappa-Bs and has a multitude of functions (initiating inflammatory response and invading pathogens as a part of an innate immune response).	The activation of diverse signaling pathways leads to phosphorylation of I-kappa-B kinases (IKBKA, IKBKB, IKBKE, IKBKG) that phosphorylate the inhibitors of NF-kappa-Bs to free and activate them. The activated NF-kappa-Bs transcriptional regulate many genes (such as IL2, IL2RA, IL13RA2, IL9, IL13, IL15, CSF2, CSF3, VEGFC)
JAK_STAT	The Janus kinases (JAKs) phosphorylate the signal transducers and activators of transcription (STATs) that convey the message from cell-surface into the nucleus.	Diverse ligands (such as IL2, IL4, IL5, IL9, CSF, CSF3, CTF1, IL12A, IL12B, IL6, LIF, OSM and other) bind to their corresponding receptors and phosphorylate different JAKs or combination of them. After the activation of STATs, the activated STATs can be translocated into nucleus to carry the signal information into nucleus by transactivating many target genes (such as SOCS3, CISH, MCL1, PIM1,MYC,TIMP1,IRF1,CD40,FOS ,FCGR1A,GBP1,IL21,ISG15,CCL19

		,IRF7,PRF1,IFNG,IL2RA,IRF4,S100P,CDKN1A,BCL2L1,BCL2,MVP and others).
GP130	Includes a number of interaction related to functional receptor complexes of pathway JAK_STAT that share a common signal transducing receptor component (IL6ST) belonging to the GP130 family.	The ligand-receptor binding (CNTF:CNTR:IL6ST, LIF:LIFR:IL6ST, IL11:IL11RA:IL6ST, IL6:IL6R:IL6ST, CTF1:IL6ST, OSM:OSMR:IL6ST, LEPR:LEP:IL6ST, CSF3:CSF3R:IL6ST, IL12A:IL12B:IL12RB1:IL12RB2:IL6ST) enables the activation of different JAKs or combination of them (JAK1:JAK2, JAK1:TYK2, JAK2:TYK2, JAK2) that in turn activates STATs (STAT1/3/4/5). The activated STATs translocate into nucleus and activate the corresponding target genes (including IRF1, IFNG, MYC, IL21, PIM1, IRF4, VIP, CDKN1A, FOS, CD40).
BETA_chain	Includes diverse reactions related to functional receptor complexes of pathway JAK_STAT that share a common signal transducing receptor component (CSF2RB) belonging to the Beta chain family.	The ligand-receptor binding (CSF2:CSF2RA:CSF2RB, IL5:IL5RA:CSF2RB, IL3:IL3RA:CSF2RB) enables the activation of JAK2 that in turn activates STAT5. The activated STAT5 translocate into nucleus and activate the corresponding target genes (including CCND1, MYC, BCL2L1, CISH).
GAMMA_chain	Includes diverse reactions related to functional receptor complexes of pathway JAK_STAT that share a common signal transducing receptor component (IL2RG) belonging to the Gamma chain family.	The ligand-receptor binding (IL2:IL2RA:IL2RB:IL2RG, IL7:IL7R:IL2RG, IL4:IL4R:IL2RG, IL9:IL9R:IL2RG, IL15:IL15RA:IL2RG) leads to the different combination of JAKs (JAK1:JAK3, JAK1:JAK2, JAK1:TYK2), which in turn activate different STATs (STAT1/3/4/5/6). The activated STATs migrate into nucleus and regulate their target

		genes (including IL21, MMP2, CCND1, IL6ST, HMOX1, FAAH1, REG1A, SOCS1, VEGFA).
TGF_beta	Includes the actions of the transforming growth factor-beta family, which controls the activity of Smad transcription factors.	The ligand-receptor binding (TGFB:TGFBR) activates the SMAD2/3 and other protein kinase (such as MAP3K7, MAPK14, ERK). The activated SMAD2/3 can then translocate into nucleus with the help of SMAD4 to conduct the transcription regulation.
BMP_signaling	This pathway is involved in broad spectra of biological activities in different tissues such as bone, blood vessels, heart, kidney and others. BMPs are members of the transforming growth factor-beta (TGF-beta) family, therefore this pathway has a similar signal transduction structure as TGF_beta.	The ligand-receptor binding (BMP:BMPR1:BMPR2) enables the activation of SMAD1/5/8 and subsequent translocation into nucleus with the help of SMAD4. In nucleus, the SMAD1/5/8 transactivate diverse target genes (such as MSX1/2, IGHA, RUNX2, TCF7, BAMBI, CREB3L2).
Activin_signaling	This pathway has a similar function to the previous described pathway TGF_beta.	The ligand-receptor binding (ACTIVIN:ACVR, GDF11:ACVR, MSTN:ACVR) activates the SMAD1/2/3/5/8 and other protein kinases (such as ERK, MAPK14, JNK).
WNT_signaling	Involves a large number of molecular reactions regulating the production of WNT signaling molecules, interactions with receptors and activation of the downstream molecules. It includes the canonical Wnt pathway and non-canonical Wnt pathway.	Canonical WNT pathway: the ligand-receptor binding (WNT:FZD:LRP5/6) leads to the activation of DVL, which in turn inhibits the CTNNB degradation complex. This inhibition of degradation enables the CTNNB freely translocate into the nucleus where this transcription activator regulate many genes transcription (including MYC, CCND1, WISP, JUN, PITX2). Non-Canonical WNT pathway: the ligand-receptor binding (WNT_CA:FZD_CA:LRP5/6) activates the LPCB, which leads to production of IP3 and DAG. Both key compounds can then activate the corresponding downstream cellular

		components (including CAMK11, ATF2, MAP3K7, NLK)
Hedgehog signaling	Functions in a very similar way as the WNT signaling pathway. It controls the cell proliferation and development begins with the interaction between ligand Hedgehog and transcription factor GLI.	The ligand-receptor binding (PTCH:HH) enables the SMO, SUFU become active, which leads to the activation of GLI. The active GLI migrates into the nucleus and activates a number of target genes (including WNT, CCND, PTCH, FOXs)
SWH signaling	Possesses a core protein kinase cascade in that a series of serine/threonine protein kinases function to regulate diverse cellular processes such as proliferation, apoptosis and other.	The complex formation of FAT:DCHS leads to the subsequent activation of NF2 and MST, which then enables the complex formation of MOBKL1B:SAV1. This complex activates the LATS, which helps YAP to enter into nucleus to activate many target genes (including JUN, TP73, TGFA, IFITM3, GH1).
Notch signaling	This is a highly conserved signaling pathway that is involved in the proper development of organs (such as brain, immune system, pancreas, heart, blood vessels). This pathway is also a communication channel in which cells decide to overtake different fate of differentiation.	Via the ligand binding (DLL:NOTCH, JAG:NOTCH, CNTN1:NOTCH), the receptor Notch is cleaved away by the complex (PSEN:APH1A:NCSTN:PSENEN) from the cell surface. The internal portion of the Notch receptor is set free and migrates into the nucleus to transcriptional regulate many target genes (including IL12RA, CDKN1A, PTCRA, DTX1, HEYL).
ABL signaling	The Abelson non-receptor tyrosine kinase (Abl) signaling pathway is involved in a broad range of biological processes such as oncogenesis, cell growth, adhesion, migration, neurite extension. The pathway PDGF signaling has considerable influence on this pathway.	The key protein kinase ABL1/2 can be phosphorylated by cellular components (such as PDGFA:PDGFB:SRC, PDGFB:PDGFB:SRC). This activated kinase can phosphorylate in turn its downstream target proteins (such as MDM2, DOK1, CTTN, RAC1, CRK, PXN, POLR2A).
AMPK signaling	Functions as a sensor of cellular energy status such as regulates food intake and energy expenditure, mediate the effects of	Upon the ligand-receptor binding (ADIPOR:ADIPOQ, LEPR:LEP ??) or the cellular ATP:ADP ratio falls,

	hormones and cytokines such as leptin, adiponectin. Therefore, this pathway controls the different cellular processes such as proliferation.	the kinase AMP-activated kinase protein (AMPK) is activated, which in turn activates diverse downstream cellular components (including TP53, PFKFB2, SREBF1, ELAVL1, EEF2K, MEF2, CRTC2) and negatively regulate the activity of mTor signaling pathway.
ATF_signaling	Including a number of transcriptional regulation based on the functions of activating transcription factor ATF1/2/3/4.	Different members of this transcription factor family exert their corresponding functions to regulate target genes (including JUN, CCL5, TNF, FOS1, RB1, VIP, TP53).
ATM_signaling	Including a number of reactions related to the key regulator ATM (Ataxia Telangiectasia Mutated Protein), which respond to DNA damage processes.	ATM functions as a 'caretaker' and suppresses tumorigenesis in different cellular processes. After activation by DNA damage or auto-phosphorylation, this tumor suppressor regulates many targets including CHK1/2, TP53, RAD51, BRCA, NF-kB.
BDNF_signaling	BDNF and its receptors are broadly expressed in mammalian brains. And the corresponding simulated intracellular signaling is critical for neuronal survival, morphogenesis, and plasticity.	The ligand-receptor binding (BDNF:NTRK2) invokes various intracellular signaling pathways including MAPK_signaling, PI3K_AKT. The ligand-receptor binding (BDNF:NGFR) triggers the activation of CASP proteins.
BRCA_signaling	The genes BRCA1/2 hold the major responsibility for developing breast or ovarian cancer, which are the leading cause of cancer-related deaths all over the world. The pathway including many relevant molecular interactions related to the BRCA1/2.	The BRCA1 forms a complex with BARD1 with help of the activated H2AFX. Within this complex, BARD1 helps BRCA1 to exert its biological function, e.g., regulating target genes (including CDKN1B, DDB2, XPC) and response to the DNA damage signal to halt the cell cycle. The BRCA2 forms a complex with RAD51 helps to halt the cell cycle by receiving DNA damage signal.
Cell_Cycle	A series of cellular events (G0, G1, S, G2 and M) that leads to cell division and duplication for proliferation.	G0: the resting phase where the cell has accomplished a cycle and stopped dividing. G1: the begin phase where G1

		<p>checkpoint mechanism (CCND1/2/3 + CDK4/6) ensures the cellular readiness for DNA synthesis.</p> <p>S: the DNA replicative phase. The complex CCNE1/2 + CDK2 and CCNA1/2 + CDK2 organize and inspect the DNA replication process.</p> <p>G2: the second gap phase where G2 checkpoint mechanism (CCNA1/2 + CDC2) ensures the cellular readiness for enter mitosis phase and divide.</p> <p>M: the mitosis phase where cell growth stops and the metaphase checkpoint (CCNB1 + CDC2) ensures the cellular readiness for cell division completion.</p>
DYRK_signaling	<p>Dual specificity tyrosine-regulated kinase (DYRKs) play key roles on the cellular processes such as proliferation and apoptosis and is one of major sensors to a variety of cellular stress conditions including DNA damage, cell cycle arrest. This pathway including many relevant molecular interactions based on functions of DYRKs.</p>	<p>DRYK1A phosphorylates its target protein such as EIF2B5, CCNL2, JNK, CREB, CASP9, FOXO1 and other. DYRK2 can be activated by the phosphorylated ATM and then phosphorylate TP53. DRYK4 can activate protein including MAPT, STAT3 and EIF2B5.</p>
Death_Receptor	<p>Includes the extrinsic and intrinsic apoptosis pathways that are defined as a common property of multicellular organisms.</p>	<p>Upon the ligand-receptor binding (FAS:FASLG, TNFSF10:DR4/5, TNF:TNFRSF1A), different caspase proteins (CASP8/10) can be activated to trigger the apoptosis.</p> <p>In response to signals resulting from DNA damage, loss of cell-survive factors or other, pro-apoptotic proteins (including BCL2, BCL2L11, PMAIP, BBC3, BAX, BAK) can promote the mitochondrian release of other pro-apoptotic factors including CYCS, AIFM, EndoG, SMAC.</p>
EGFR_signaling	<p>Epidermal Growth Factor (EGF) signaling pathway is one of the most well studied Receptor Tyrosine Kinases (RTKs) pathway. This pathway regulates activities of a wide range downstream targets and plays key roles in diverse cellular processes including cell growth, proliferation. The</p>	<p>Binding of ligands (AREG, BTC, EGF, EREG, TGFA) to the dimer receptor (EGFR:EGFR, EGFR:ERBB2) enables the auto phosphorylation of the ligand-receptor complex, which in turn invokes signaling cascades, in which</p>

	mutations occurring in different pathway-components such as EGFR, SRC are highly cancer-related.	diverse cellular proteins (including SRC, GRB2, SOS1, PLCG, CBL, JAK1/2) take part in.
EPO_signaling	Including relevant reactions related to erythropoiesis in which a pluripotent hematopoietic stem cell can give rise to mature and stage cells. Erythropoietin (Epo) is therefore usually required for survival, proliferation and differentiation of erythroid progenitor cells.	The ligand-receptor binding (EPO:EPOR) enables the activation of diverse cellular components (including LYN, SYK, JAK2, MAP4K1), which in turn activates their corresponding downstream targets (such as MKK3/6, MAPK14, MYC, CCND, PRKCA, CAMK).
ERK5_signaling	A pathway member of mitogen-activated protein kinase (MAPK) cascades family, which is highly conserved module that is involved in various cellular processes, including cell grow, proliferation, differentiation and migration.	The key component ERK5 can be activated by diverse upstream components such as RAS, MEKK2/3, MEK5, SRC and MAP3K8. The activated ERK5 can then activate the downstream components including CREB, MYC, FOS, SAP1 and SGK.
Ephrin_Eph_signaling	Eph receptors and ephrins form the largest receptor-ligand complexes in the receptor tyrosine kinase family. The signaling pathway influence the cell-cell interaction and migration. The deregulation of this pathway is highly related to the tumor growth, survival, angiogenesis and metastasis.	Upon the ligand-receptor binding (including EFNA:EPHA, EFNB:EPHB) a bi-directional signaling is taking place to transform the signal into downstream targets including ERK, RASA, ACP1, NCK, CTNND, FYN, PTK2.
ERBB_signaling	Including reactions based on receptors (ErbB2/3/4) that regulate signals of cell differentiation, proliferation, migration and survival. This pathway has a very similar structure as the EGFR_signaling.	The ligand-receptor binding (including ERBB4:BTC:ERBB2, ERBB4:NRG3/4:ERBB2, ERBB3:NRG1/2:ERBB2, ERBB4:REG:ERBB2, ERBB4:HBEFG:ERBB2) enable the activation of diverse cellular components such as KRAS, HRAS, RAF, STAT5, PI3K, PKC, S6K, PICTOR.
Estrogen_signaling	This pathway maintains functions of a wide range of mammalian tissues and plays important roles in cellular processes related to growth, development and reproduction. This pathway including signaling transduction process starting from ligand binding of receptor (including ESR1/2,	The ligand-receptor binding (including Estradiol:ESR1, Estradiol:GPER) enables complex formation with SRC, GRB2:SOS1 or the production of cAMP, which in turn leads to activation of RAC1:GTP, CDC42:GTP,

	GPER) to the activation of downstream targets.	KRAS:GTP, HRAS:GTP, PRKACA, RAP1:GTP, RAPGEF:cAMP and other.
FGF_signaling	Fibroblast Growth Factor (FGF) is one of the well studied Receptor Tyrosine Kinases (RTKs) pathway. The FGF binding can lead to activation of a plethora of signaling pathways involved with cell growth, proliferation and contribute to important functions for normal development, tissue maintenance.	The ligand-receptor binding (FGFR:FGF) enables auto.phosphorylation and the subsequent complex formation with FRS, GRB2, GRB14, GAB1, PI3K, which in turn activates PRKCG, PRKCB, KRAS, HRAS, AKT, ERK, MAP3K7, RASGRP1/2/3/4, CAMK, CREB.
FOXO_signaling	FOXOs belong to a sub family of transcription factor FOXs family which plays important roles in regulating expression of genes that are involved in different cellular processes such as cell growth, proliferation, differentiation and longevity. This pathway including relevant transcription regulations based on the FOXOs function.	The transcription factors FOXOs regulate the expression of their target genes (including CCND, PDK4, CEBPB, IGF1R, PPARG, TGFB2, G6PC, IRS2, ESR1, NOS2, AR). However, their functional activities can be negatively regulated by different protein kinases (such as AKT, DYRK, SGK, JNK).
Growth_Hormone	The effects of growth hormone (GH) can directly influence the cell growth, proliferation and metabolism. This pathway includes major signal transduction processes starting by the GH receptor and mediated by multiple signaling pathways.	The ligand-receptor binding (GHR:GH1, GHR:GH2) enables the complex formation with JAK2, which leads to auto.phosphorylation of JAK2 within the complex. The activated complex GHR:GH1/2:JAK2 can activate diverse downstream components including ERK, AKT, MAP3K7, RASGRP1/2/3/4, CAMK, MAP2K4, MAP2K6, STAT1/3/5.
HIF1_signaling	Directly influenced by the mTor_signaling and MAPK_signaling. Includes a large number of transcriptional regulations based on the function of HIF1.	The activation of HIF1A by ERK or MTOR:MLST8:RPTOR enables the complex formation of ARNT:HIF1A and ARNT2:HIF1A, which then transcriptional regulate many target genes (including ABCB1, IGF2, END1, ADM, VEGFA, HK1, HK2, TGFA, MET).
IGF1R_signaling	This signaling pathway influences the cellular processes including proliferation, cell motility, adhesion and contributes to the apoptosis protection and hypoxia	The ligand-receptor binding (IGF1R:IGF2, IGF1R:IGF1) leads to the recruitment of IRS and SHC and subsequent activation of

	<p>signaling. This pathway is often deregulated in different types of cancer and therefore the receptor IGF1R becomes a putative therapeutic target.</p>	<p>corresponding complexes that in turn regulate the downstream components such as RAF, ERK, PKC, ATF2, MAP3K7, PRKCB, PRKCA, CAMK, SMAD4.</p>
InsulinR_signaling	<p>Insulin is the major hormone controlling energy metabolisms and plays important roles by triggering different signaling pathways.</p>	<p>Insulin (INS) binds to its receptor (INSR), which leads to the tyrosine phosphorylation of IRS. This activation of IRS enables the activation of PI3K and subsequent the PDK, which activates AKT. The activated AKT can regulate a number of its downstream components (including GSK3B, MDM2, PAK1/2, AR, MAP3K8, CASP9). On the other hand, GRB2 and SOS1 are recruited to the activated IRS to trigger the signal cascade MAPK_signaling from RAS, RAF to ERK.</p>
Integrin_signaling	<p>Plays vital roles in cellular processes including cell survival, growth, differentiation, migration, inflammatory responses. This pathway includes relevant interactions related to different integrins, collagens and laminins.</p>	<p>The interactions between integrins and collagen (such as ITGA1:ITGB1:COLLAGEN, ITGA2:ITGB1:COLLAGEN) leads to the phosphorylation of SYK, ILK, MAP3K1 and the subsequent phosphorylation of downstream components (such as GSK3B, MDM2, AKT1S1, PAK). The interaction between integrins and laminin (such as ITGA6:ITGB4:LAMA:LAMB:LAM C, ITGA6:ITGB1:LAMA:LAMB:LAM C) leads to the activation of RAF and RHOA:GTP, which in turn activates the downstream components including ERK, ROCK, MYLK, ETV5, LIML.</p>
KIT_signaling	<p>This pathway helps progenitor cells differentiate into blood and/or vascular endothelial cells and plays important roles in amplification/mobilization processes.</p>	<p>The ligand-receptor binding (KITLG:KIT) enables the recruitment of SRC, GRB10, FYN and subsequent the activation of corresponding complexes that in turn activate MAP3K7, RASGRP1/2/3/4,</p>

		CAMK, MAP2K4, MAP2K6, ATF2, ERK.
MET_Receptor	Induce mitogenic, motogenic, and morphogenic cellular responses and the activation of this pathway is required for normal cellular development.	The ligand-receptor binding (HGF:MET) recruits GRB2, SOS1, SHC1, GAB1, which in turns activates the downstream components such as CRKL, STAT, RAS, ERK. On the other hand, the ligand-receptor complex can phosphorylate PKC, PRKCA, PRKCB, CAMK, MAP3K7 via the activation of PLCG.
NGF_signaling	This pathway contributes the cellular maintenance between survival and death and has a similar structure as BDNF_signaling.	Followed by the ligand-receptor binding (NGF:NTRK1), the auto.phosphoyrlation of this complex takes place, which leads to the activation of downstream components (including IRS, RAS, ERK, PKC, PRKCA, PRKCB, CAMK, MAP3K7). On the other hand, the ligand-receptor binding (NGF:NGFR) leads to the recruitment of NGFRAP1 and MAGED1, which leads to activation of CASP2/3 to trigger the apoptosis.
Neurotrophin_signaling	Including relevant interactions related to the two members (NTF3, NTF4) of neurotrophin family. This pathway has a similar structure as BDNF_signaling and NGF_signaling.	The ligand-receptor bindings (NTF3:NGFR, NTF3:NTRK3, NTF4:NGFR) enable the activation of downstream components (including IRS, RAS, ERK, PKC, PRKCA, CASP2/3).
TP53_signaling	Receive signals from diverse pathways (such as AMPK_signaling, Death_Receptor, p38MAPK and PI3K_AKT) and transform these information into the transcriptional regulation level. Includes diverse transcriptional regulations based on function of TP53, TP63 and TP73.	The activation of TP53 by different cellular components such as MAPK14, DAPK, AMPK, JNK, HIPK2, CHEK, disables the functional restriction of MDM2 and enables the migration of TP53 into the nucleus to transactivate target genes (including CDKN1A, DUSP1, TGFA, EPHA2, TNFRSF10B, APC).
PAK_signaling	The p21-activated kinases (PAKs) are evolutionally conserved and widely expressed in diverse tissues (including	PAKs (including PAK1-7) can be phosphorylated by different protein kinases such as AKT, CDC42:GTP,

	heart, kidney, lung and other). This pathway includes relevant reactions related to the functions of PAK family members and plays important roles in cellular processes such as mitosis, transcription, translation, cell survival.	AR). The activated PAKs can phosphorylate downstream targets such as MYLK, STMN, LIMK, AURKA, ESR, JNKs, RHOA, RAF, to exert their biological functions.
PDGF_signaling	This pathway plays key roles in different cellular processes such as angiogenesis, proliferation, migration and is highly implicated in tissue remodelling, patterning and morphogenesis.	The different combination bindings between ligands (such as PDGFA, PDGFB, PDGFC, and PDGFD) and receptors (such as PDGFRA and PDGFRB) transduce the signal and convey it to the downstream components. For instance, the activated receptors interact with SRC, PI3K, SHP2, SHC, and PLCG, to transfer the signal further via MAPK14, JNKs, ERK.
PI3K_AKT	Includes relevant reactions starting from PI3K, transfers signal via the activation of AKT into the downstream target components. This pathway has key roles in regulation of cellular processes such as cell growth, proliferation, cell cycle and metabolism.	The PI3Kcomplex (PIK3CA:PIK3R) can be activated by diverse components including different receptor tyrosine kinases (such as EGFR:EGF, KDR:VEGFA, FLT1:PGF), JAKs, EPHA:EFNA and other. The activated PI3KCA can catalyze the production of PIP3 to activate PDK, which in turn activates the AKT. The powerful protein kinase can regulate many downstream proteins including GSK3beta, RHEB, TP53, JNK, FOXO, mTor, CDKN1A, RPS6KB1 and other.
Prolactin_Receptor	Contributes to the mammary development processes by regulating many important genes expression level.	The ligand-receptor binding (PRLR:PRL, PRLR:GH1) lead to the activation of protein kinases such as JAK2, NEK3, TEC, FYN and recruit SRC, GRB2, SOS1, which in turn activate downstream components such as RAC1:GTP, CDC42:GTP, RAS, ERK, STAT1/3/5, IRF, CDH, PRKCA, PRKCB, PKC.
RAR_signaling	Contributes the regulation of different cellular processes and developments via binding of several heterodimeric nuclear receptors. This pathway including relevant	The receptor complex formation (RARA:RXR, RARB:RXR, RARG:RXR) regulate the expression level of many target genes

	reactions related to transcriptional regulation of those nuclear receptor complexes.	including THBD, MAOB, GRNH2, RARG, RARB, PLCG, SFTPB, APOA1.
RET_signaling	RET proto-oncogene encodes a receptor tyrosine kinase, which can invoke a signaling cascade by binding to corresponding ligands. The signaling cascade plays essential roles in diverse cellular processes. The loss/gain of function of RET gene are associated with various types of human cancer.	The ligand-receptor bindings (GDNF:RET, NRTN:RET, PSPN:RET, ARTN:RET) invoke the activation of NCK, CRK, PLCG. These activated components transfer signal further by activating corresponding downstream targets including PRKCA, PRKCG, CAMK, MAP3K7, RASGRP1/2/3/4, MAP4K5. On the other hand, the ligand-receptor complex can recruit GRB2:SOS1 to activate the downstream target such as RAS, ERK.
TEK_signaling	TEK is non-receptor tyrosine kinase, which is expressed in diverse types of cells including hematopoietic cell, T-cell, liver cell and other. The signaling pathway invoked by this kinase exert considerable effect on the regulation of distinct cellular processes such as angiogenesis, proliferation.	The ligand-receptor bindings (ANGPT1:TEK, ANGPTL1:TEK) leads to the auto.phosphorylation of TEK kinase, which in turn recruits and activates various components such as GRB2/7/14, DOK2, PI3K and other. The signal is transferred further via those activations resulted in phosphorylation of MAP4K5, MAP4K1, AKT, PXN and CDH.
TLR_signaling	This pathway plays a crucial role in inflammatory responses and is highly involved also in many other cellular processes such as apoptosis.	After ligand binding, TLRs undergo the conformational changes required for recruitment of downstream signaling components including MyD88, IRAKs, TAK1, TAB2 and other, which in turn activates the downstream components including IRFs, IFN-beta, AP-1, NF-kB, JNKs and other.
VEGF_signaling	Plays key roles in cellular processes related to blood vessels such as angiogenesis, vasculogenesis.	The ligand-receptor bindings (VEGFA:KDR, VEGFA:FLT1, VEGFB:FLT1, VEGFC:KDR, VEGFC:FLT4) enables the auto.phosphorylation of corresponding ligand-receptor complex, which recruits the components such as GRB2, SOS1,

		SHC, PLCG. These recruitments lead to the subsequent activation of diverse downstream targets including CALM, PRKCA, ATF2, PTK2B, RASGRP1, MAP3K7, MAP3K.
mTor_signaling	Function as an important sensor to coordinate different cellular processes with the nutrient level and cellular growth factors. This pathway including the signal transduction processes started from mTor complex 1 (mTORC1) and mTor complex 2 (mTORC2).	After activation by RHEB:GTP, the mTORC1 (MTOR:MLST8:RPTOR) is created, which in turn activates diverse downstream components including PPARGC1, HIF1A, EIF4BP1, EIF4G1, RPS6, PPARG, RPS6KB1, PDCD4. The mTORC2 (MTOR:MAPKAP1:MLST8:PRR5:PICTOR) enables the activation of components including SGK1, PRKCG, PRKCA, NEDD4L, IKBK, RAF.

C.5_Inhibitor_MEK_AKT.pdf

Sheet1

	MEK_inhib	AKT_inhib	Both_inhib
RAF	0.976344	1.00009	0.988892
MEK	4.28965e-06	1.00002	4.28951e-06
ERK	0.0458747	1	0.0469964
ESR	0.885902	6.90277	6.70521
DAPK1	0.878547	0.999997	0.864229
TSC2	0.933519	0.794645	0.093839
HIF1A	0.746605	20.8283	6.97832
RICTOR	0.962039	0.989325	0.668635
PPARG	0.886096	7.07657	7.07657
PI3K	1	1	1
PIP3	1.00438	0.999995	1.00439
AKT	1	1	1
CDKN1A	1.53369	1.73498e-07	2.08968e-07
RPS6KB1	0.63666	0.88609	0.0956084
PDCD4	0.962135	0.989473	0.667106
BAD	0.76929	0.916793	0.39552
EIF4G1	0.928956	0.934588	0.821233
EIF4B	0.961879	0.989335	0.667172

C.8.A_prediction_vs_experiment.pdf

Sheet1

uniProt	Predicted Data	Experimental Data
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P18031	12.595825	57.578159
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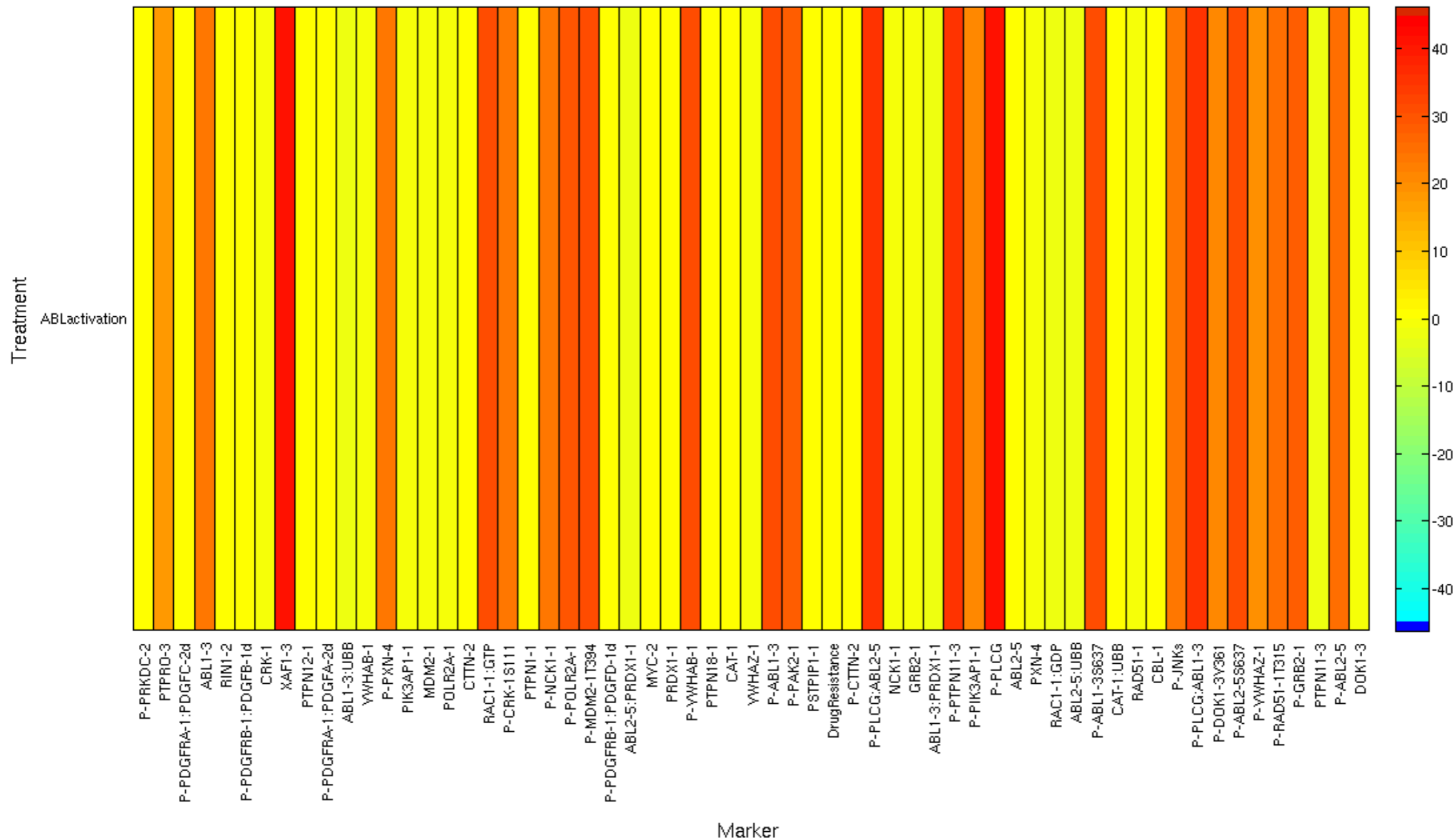
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ENSG00000186298:95.500000	P36873:175.737694
ENSG00000097007:63.290000	P00519:2.158232
ENSG00000121022:37.300000	Q92905:585.587042
ENSG00000101773:13.440000	Q99708:1.023698
ENSG00000197555:15.790000	O43166:2.195302
ENSG00000074696:46.200000	Q9P035:278.065309
ENSG00000078900:2.530000	O15350:0.001884
ENSG00000086758:88.940000	Q7Z6Z7:10.582142
ENSG00000101849:14.340000	O60907:8.822025
ENSG00000172936:12.490000	Q99836:16.667081
ENSG00000123124:5.720000	Q9H0M0:0.329123
ENSG00000080815:17.090000	P49768:10.476899
ENSG00000117335:43.020000	P15529:2.031844
ENSG00000105974:73.110000	Q03135:253.824912
ENSG00000213281:14.650000	P01111:144.391311
ENSG00000133703:14.650000	P01116:144.391311
ENSG00000132646:82.300000	P12004:2755.445811
ENSG00000010810:15.350000	P06241:1.466564
ENSG00000164305:4.910000	P42574:53.223445

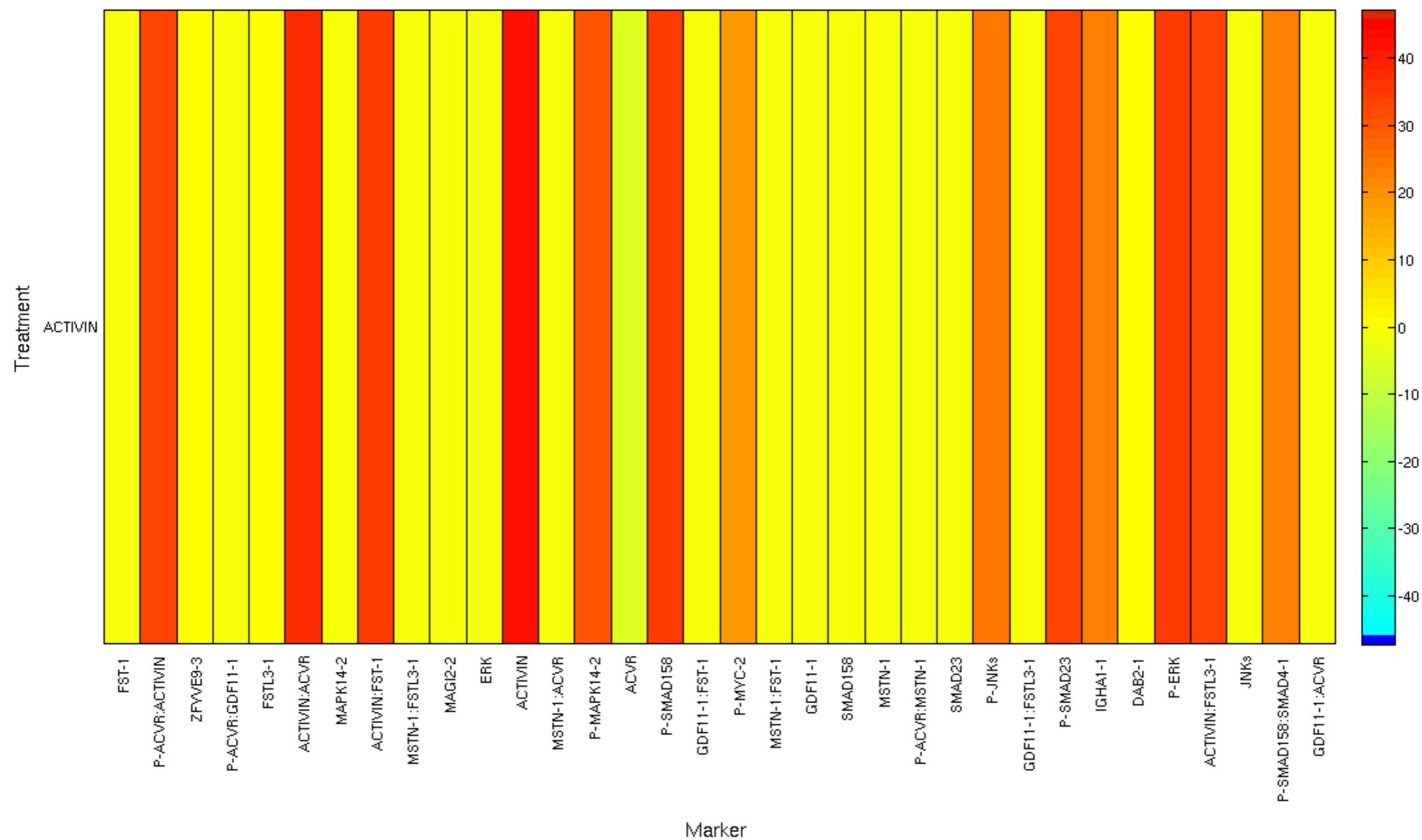
ENSG00000106144:23.220000 P42575:14.787433

Heatmaps (Simulation Results)

Marker Ratios (Log2 Of Geo Mean) bysummary_readout_ABL.tsv



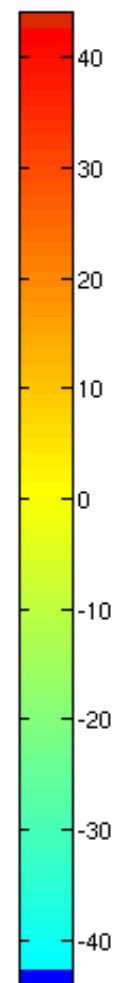
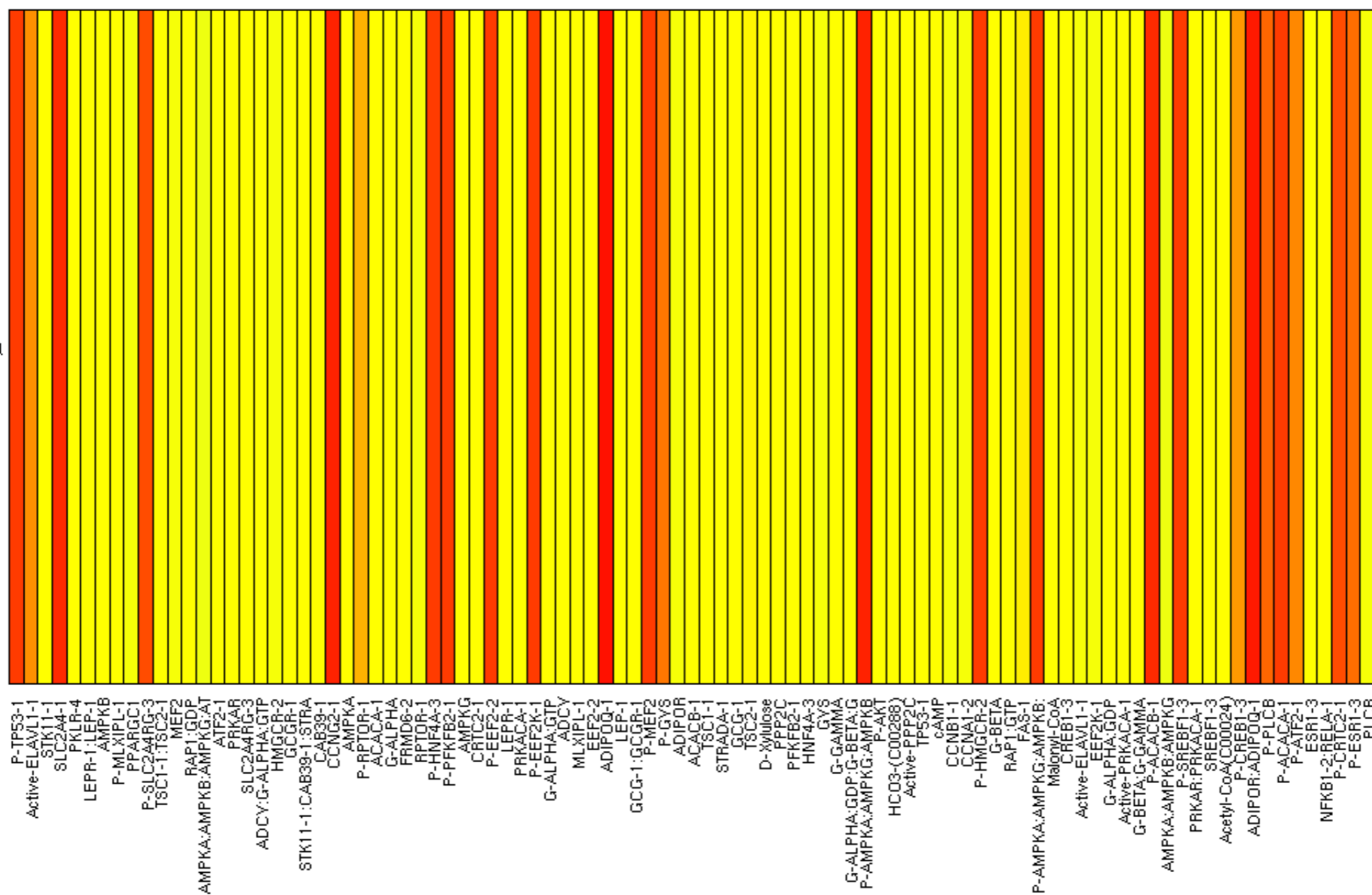
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_ACTIVIN.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_A DIPOQ.tsv

Treatment

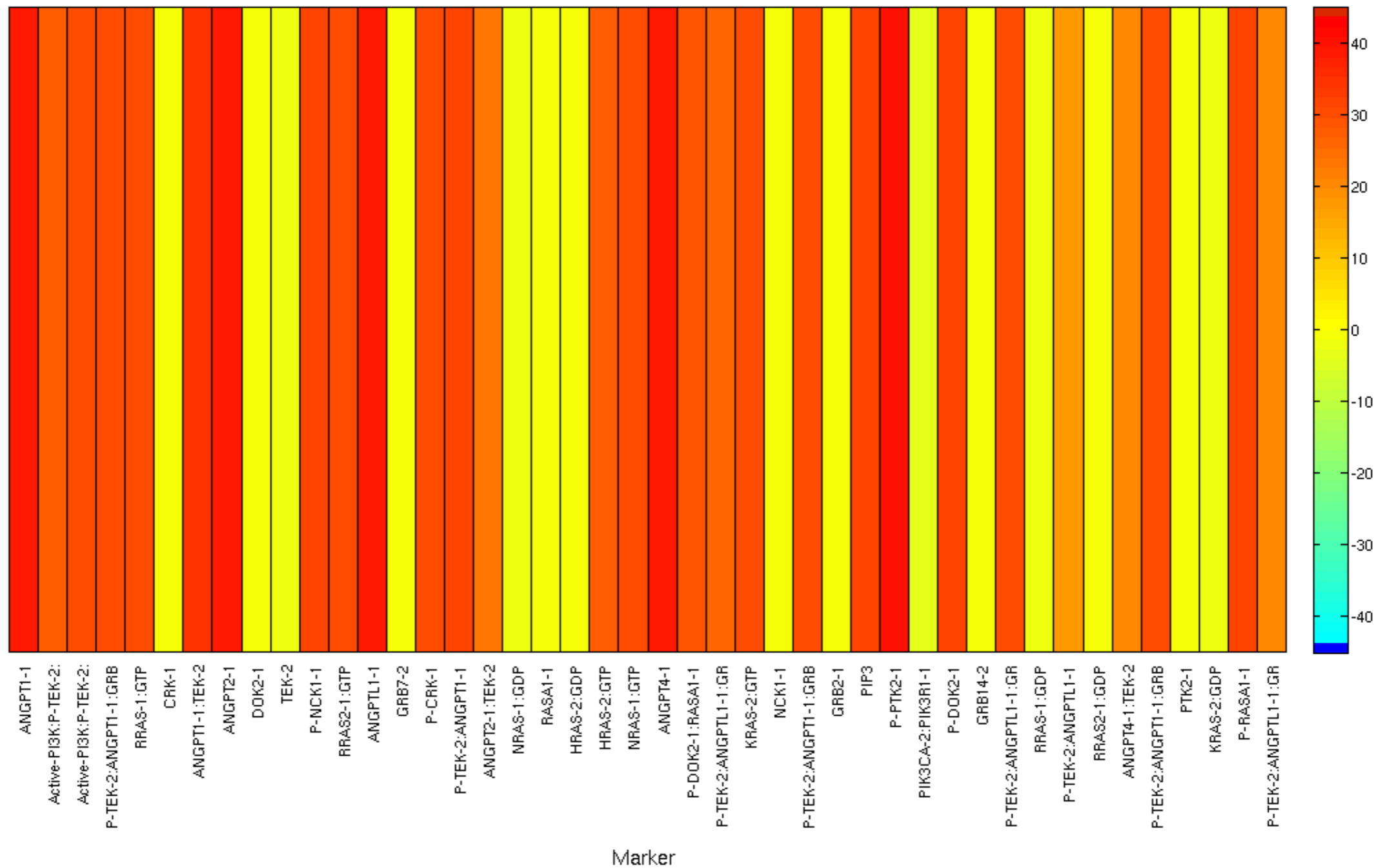
ADIPOQ



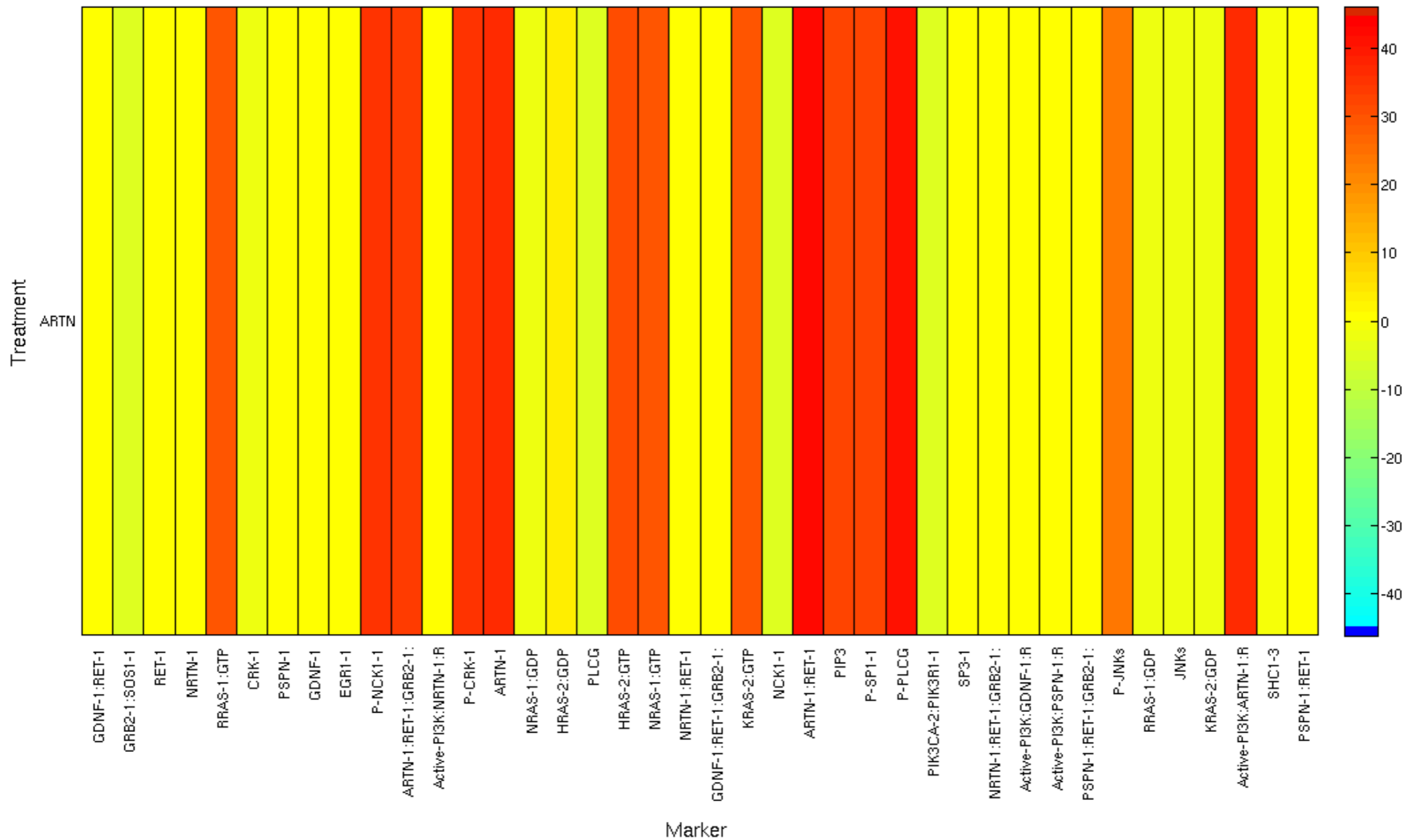
Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_readout_A NGPT.tsv

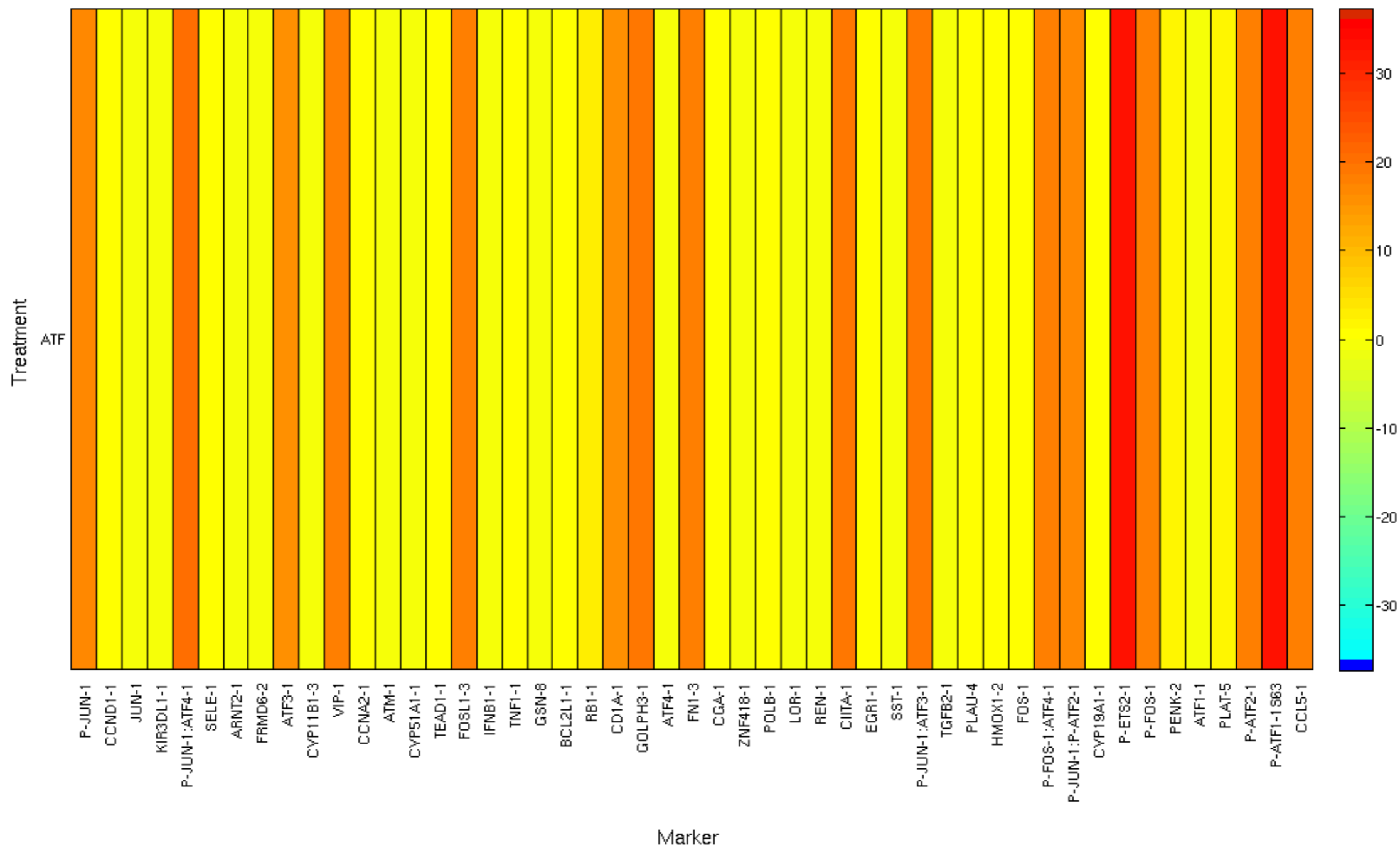
Treatment
ANGPT1



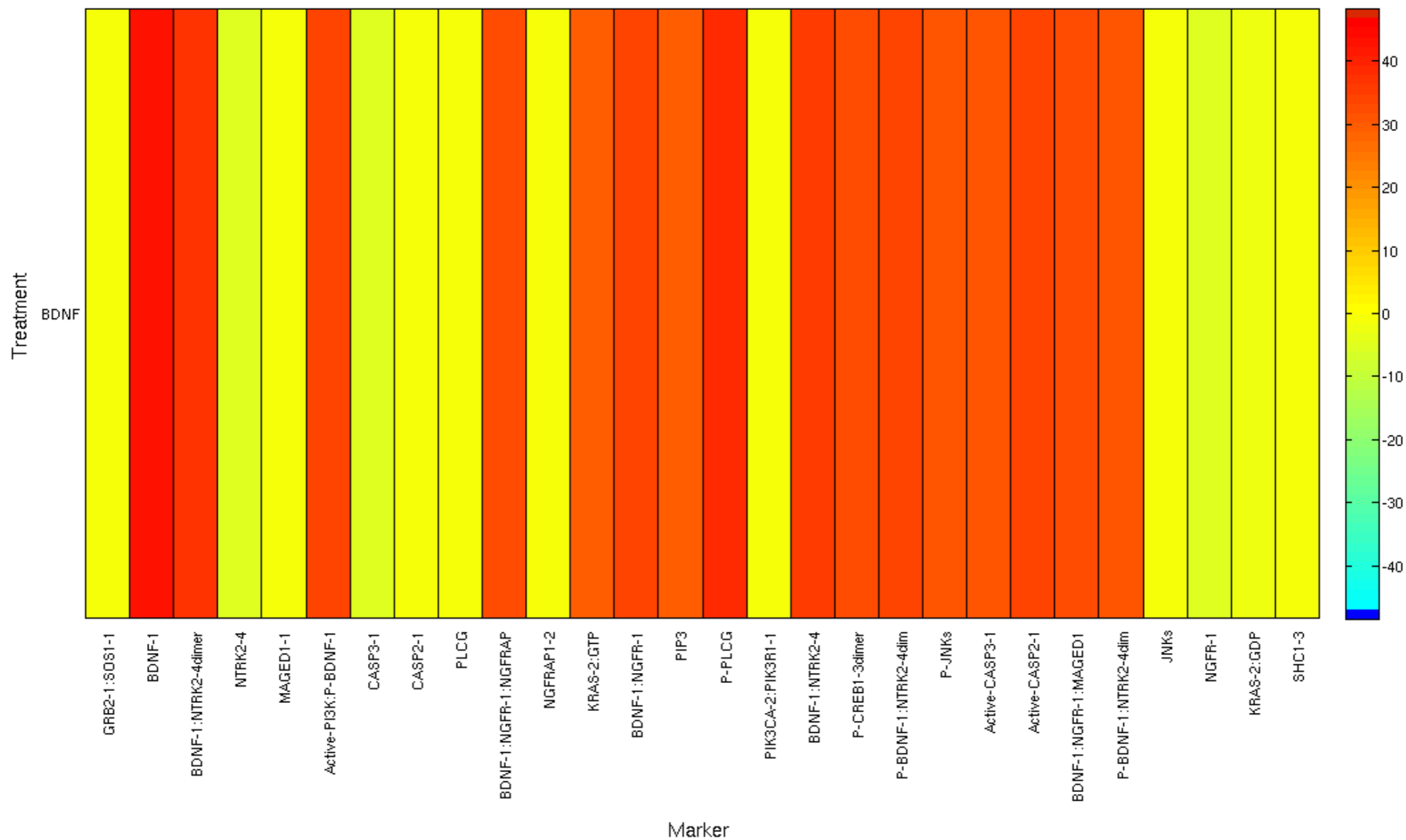
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_A RTN.tsv



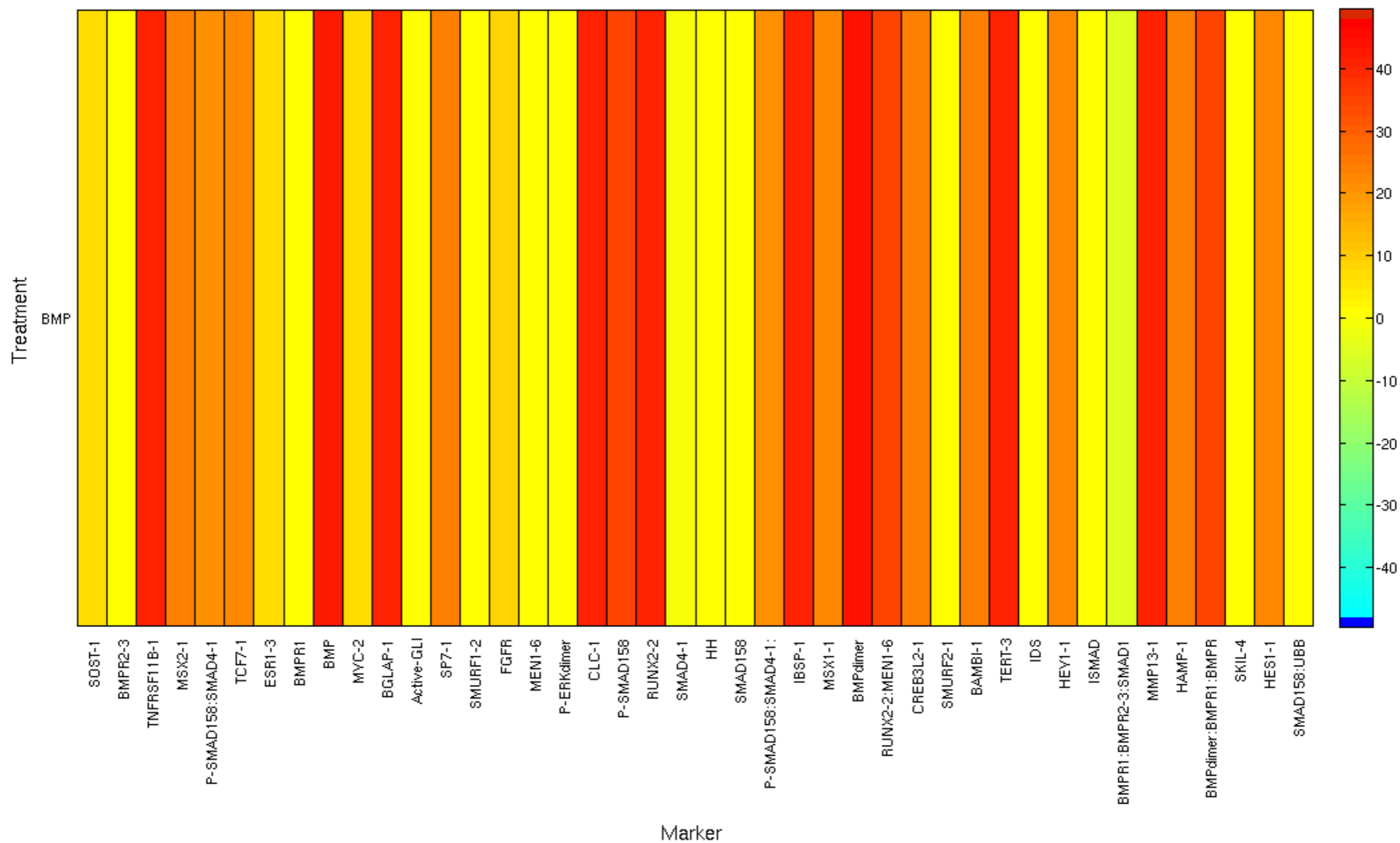
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_A TF.tsv



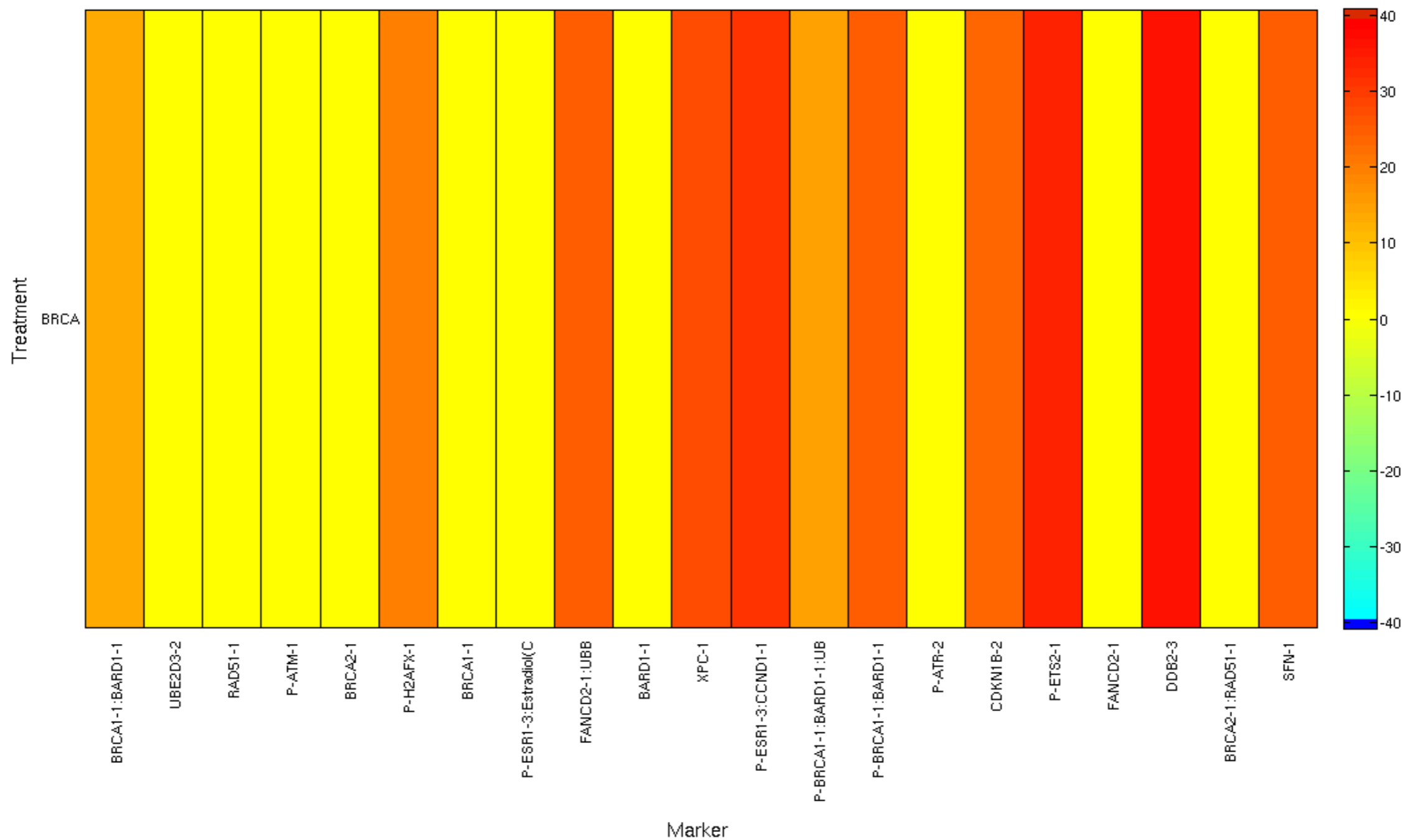
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_BDNF.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_MP.tsv



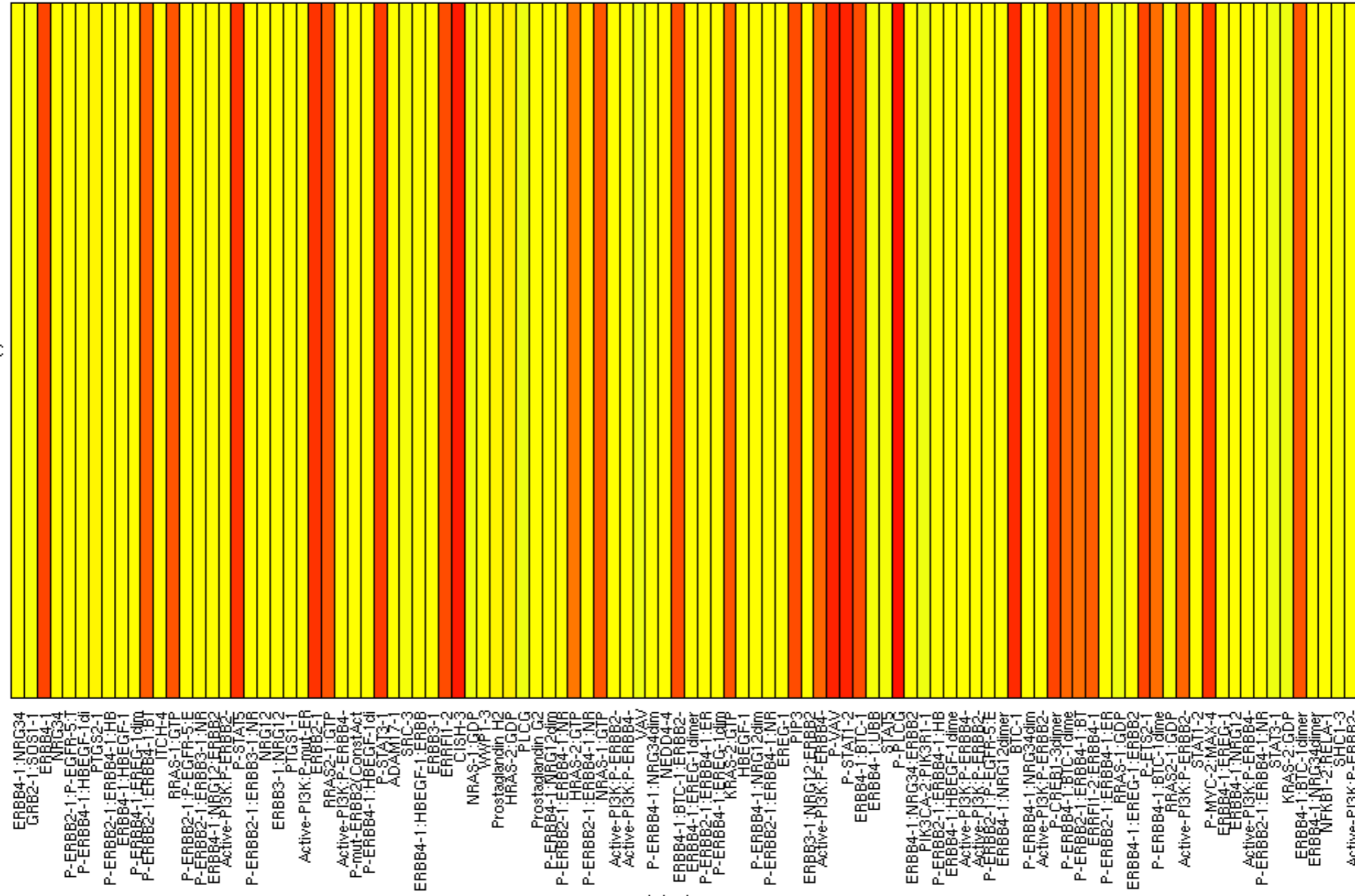
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_B_RCA.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_BTC.tsv

Treatment

BTC

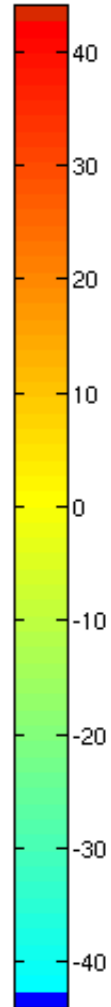
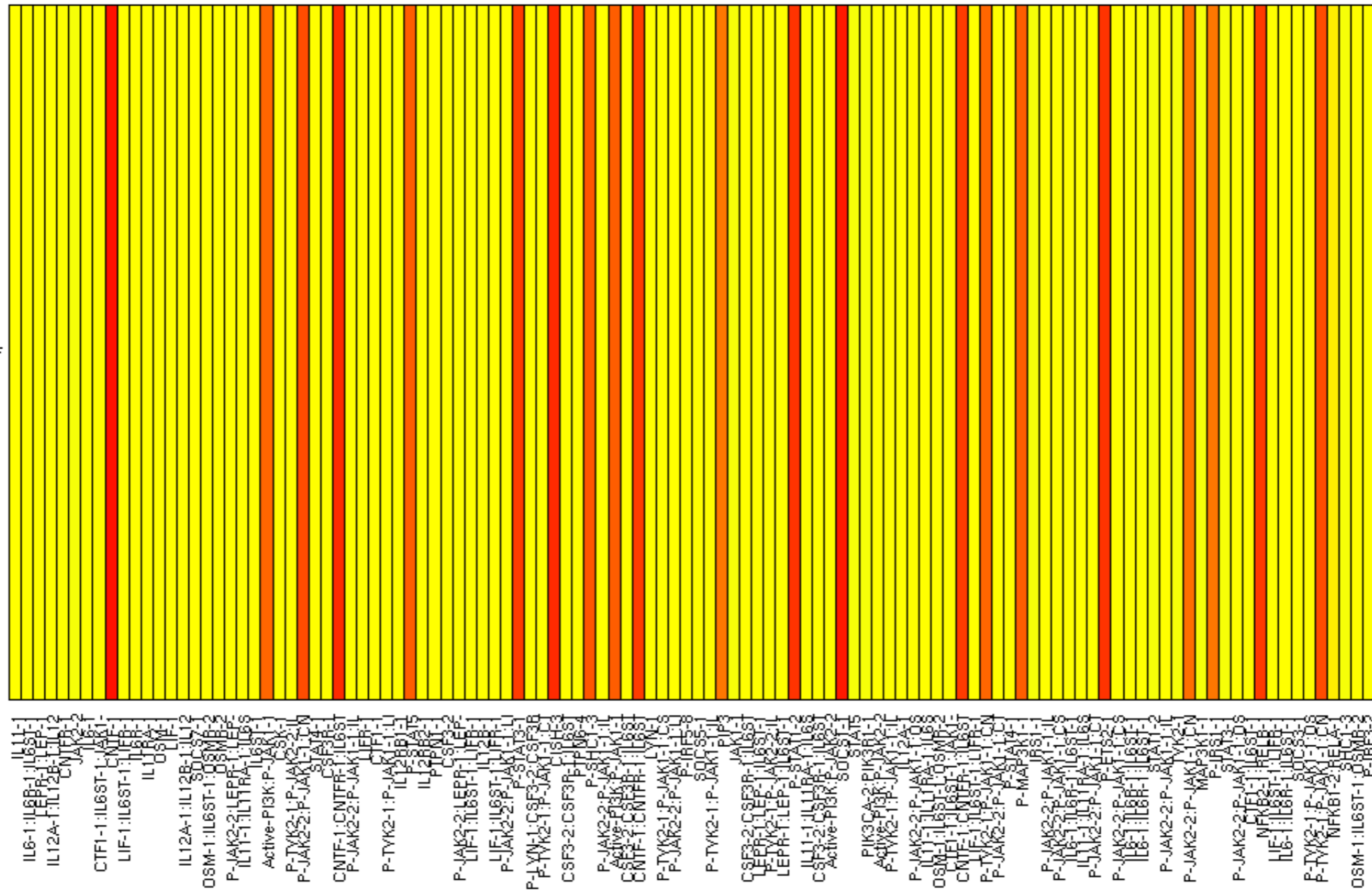


Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_readout_CNTF.tsv

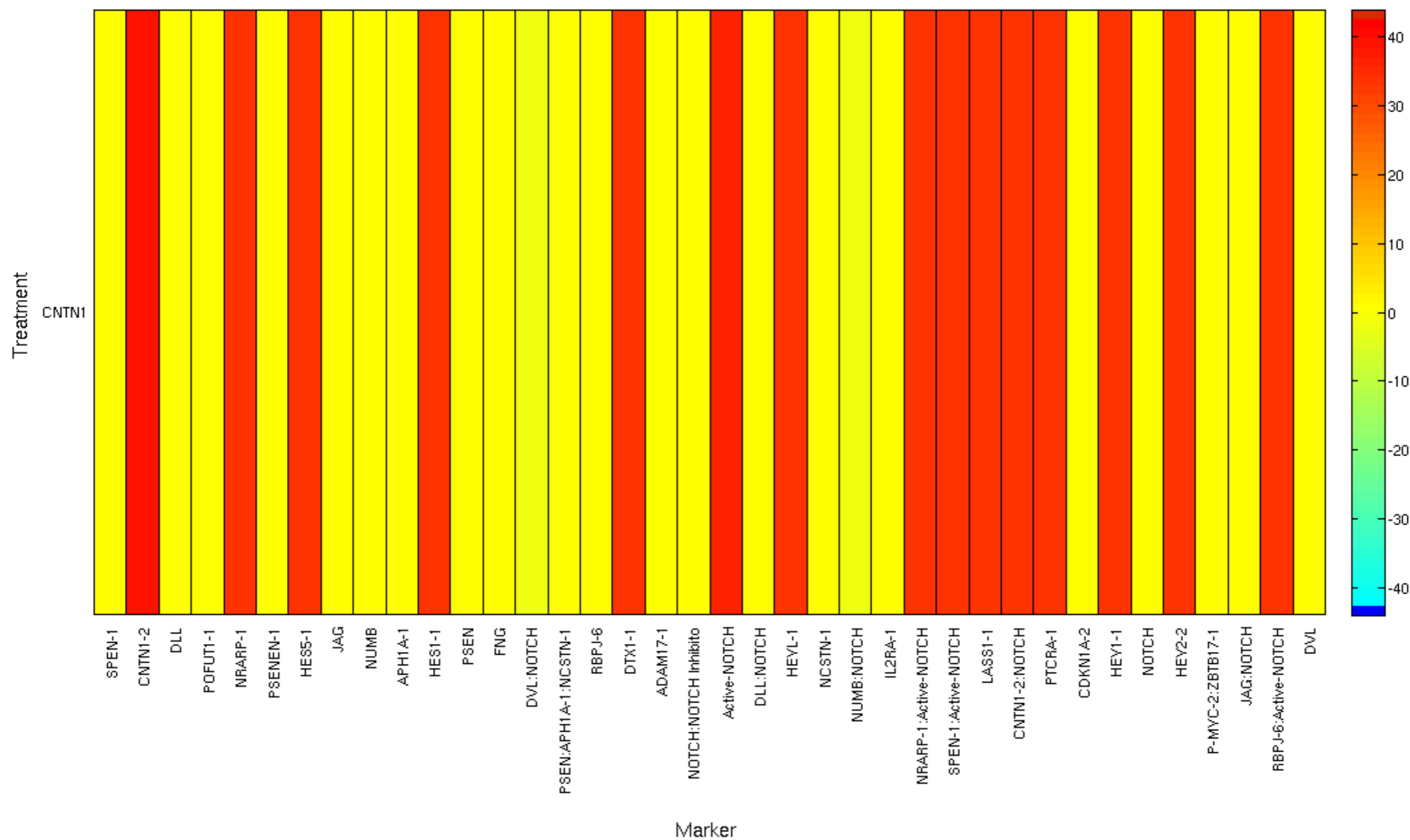
Treatment

CNTF

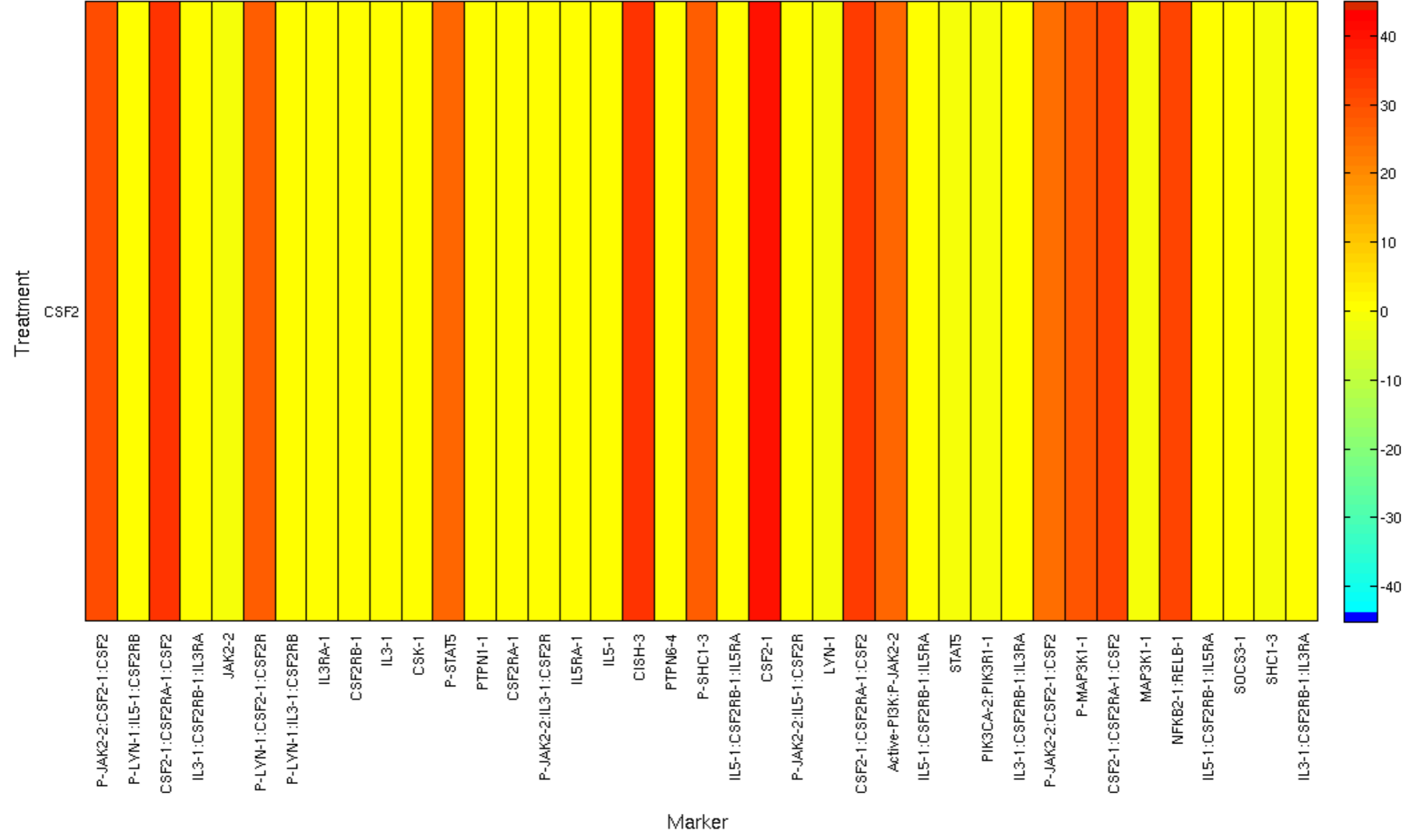


Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_readout_CNTN1.tsv



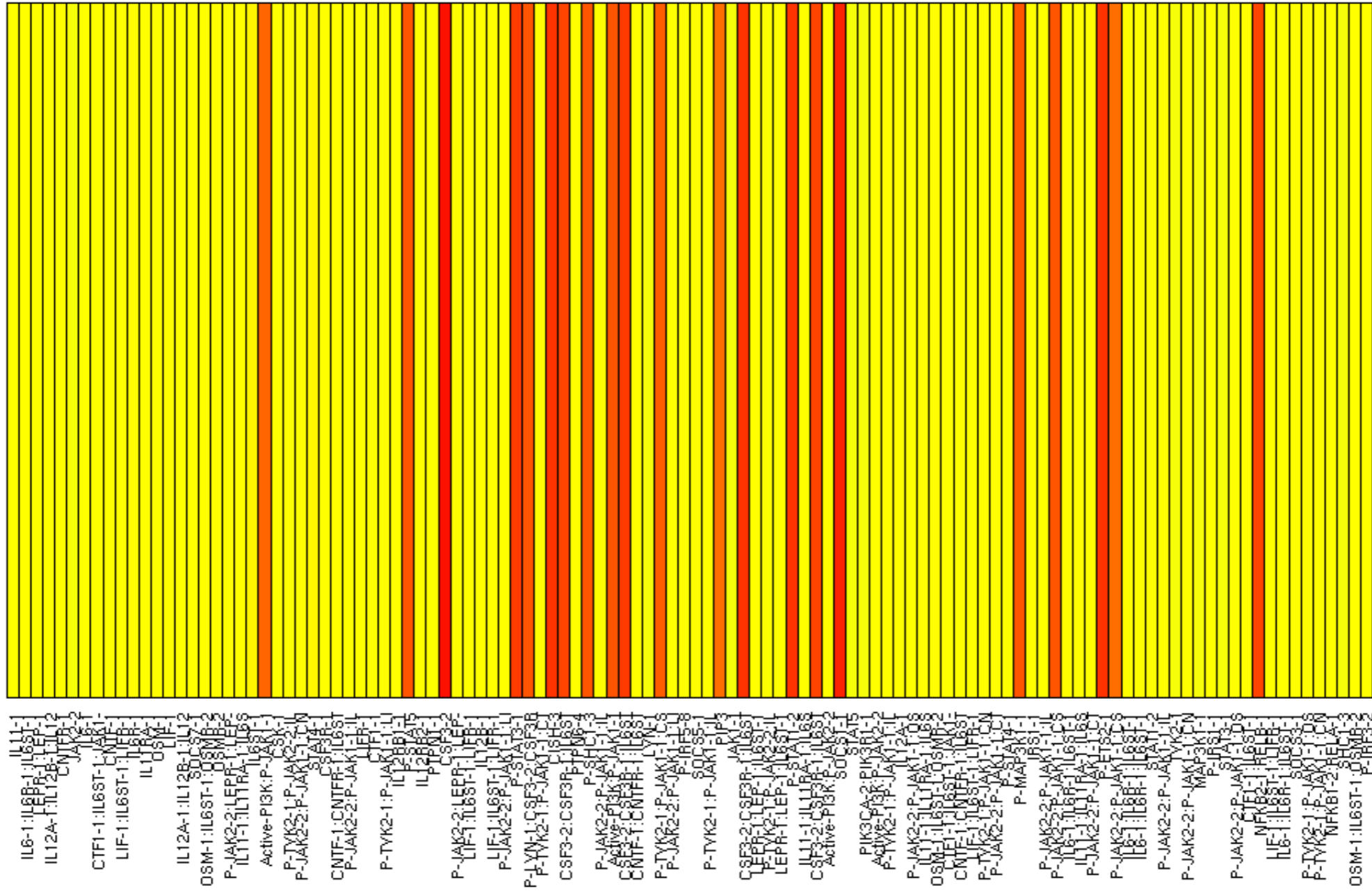
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_CSF2.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_SF3.tsv

Treatment

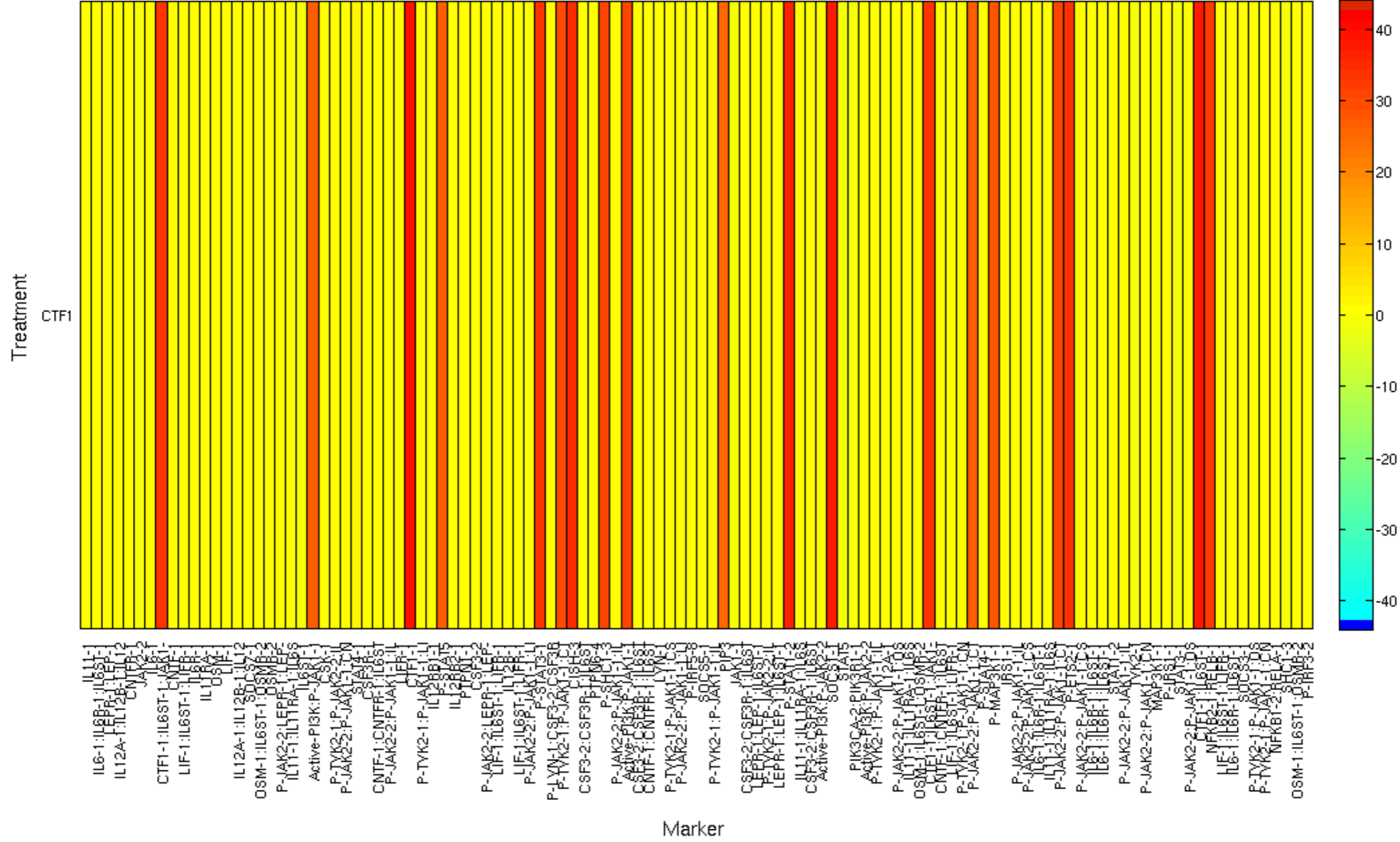
CSF3



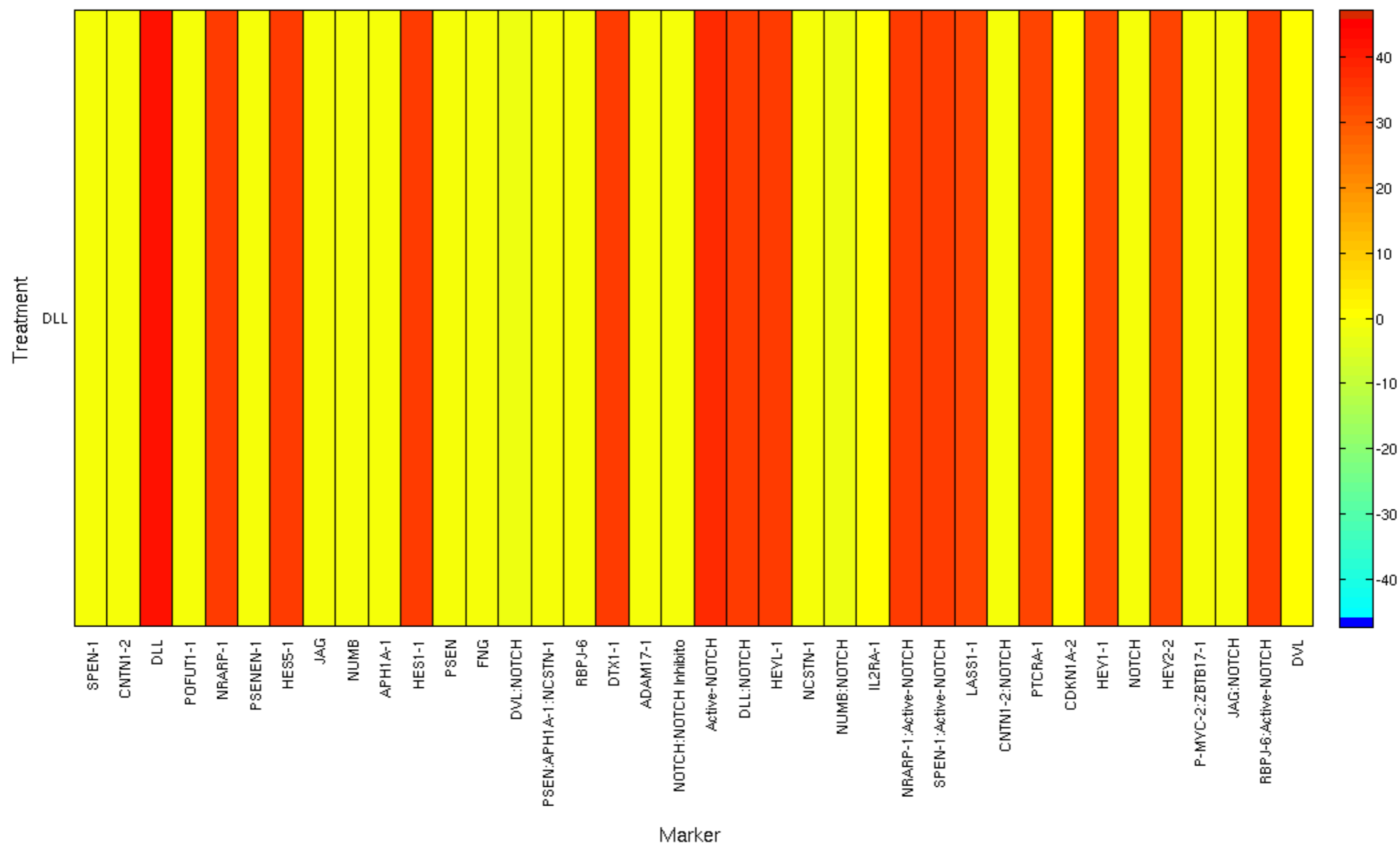
Marker



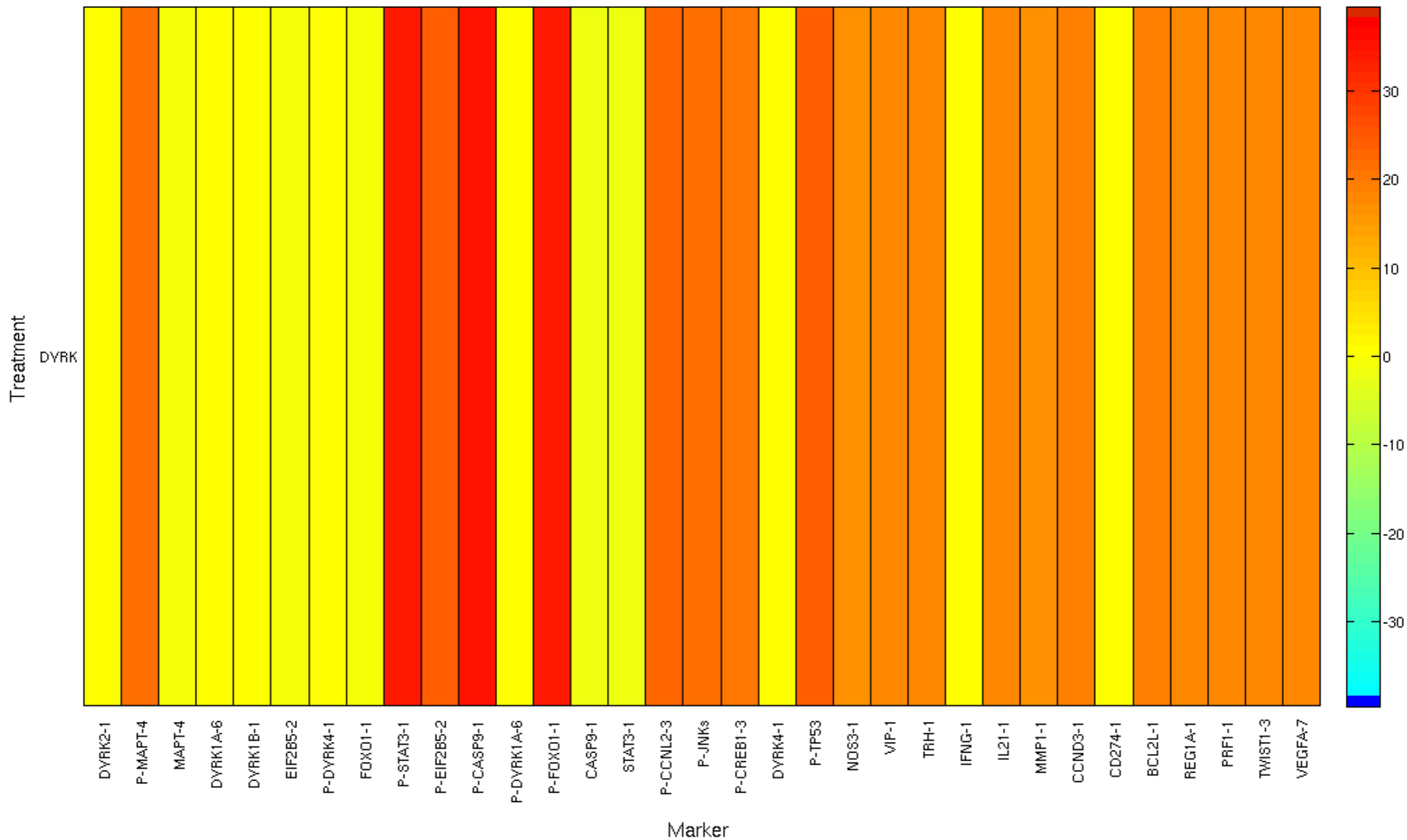
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_C TF1.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_DLL.tsv



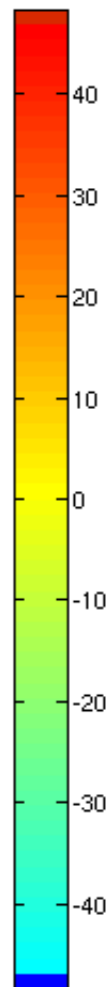
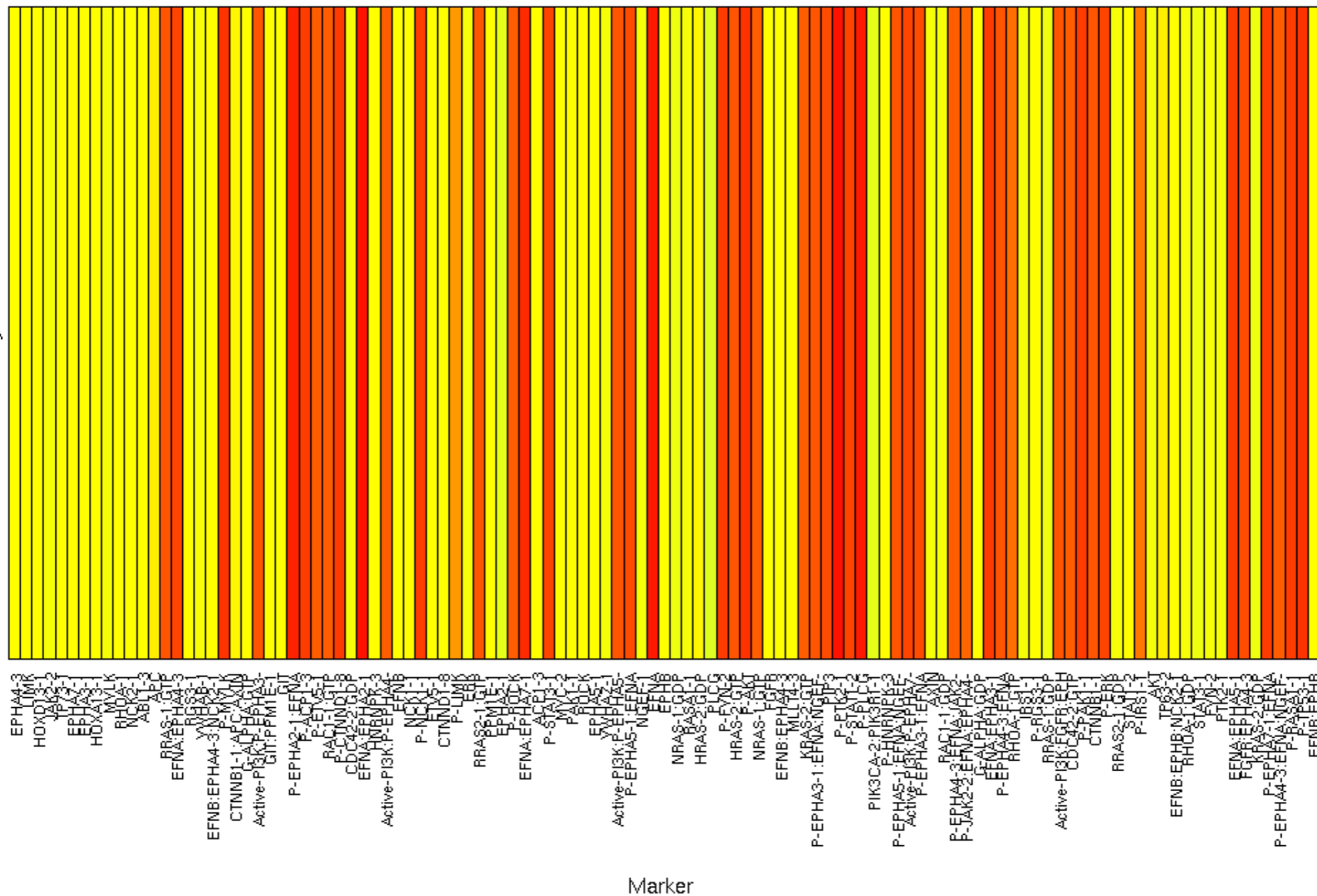
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_D_YRK.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_EFNA.tsv

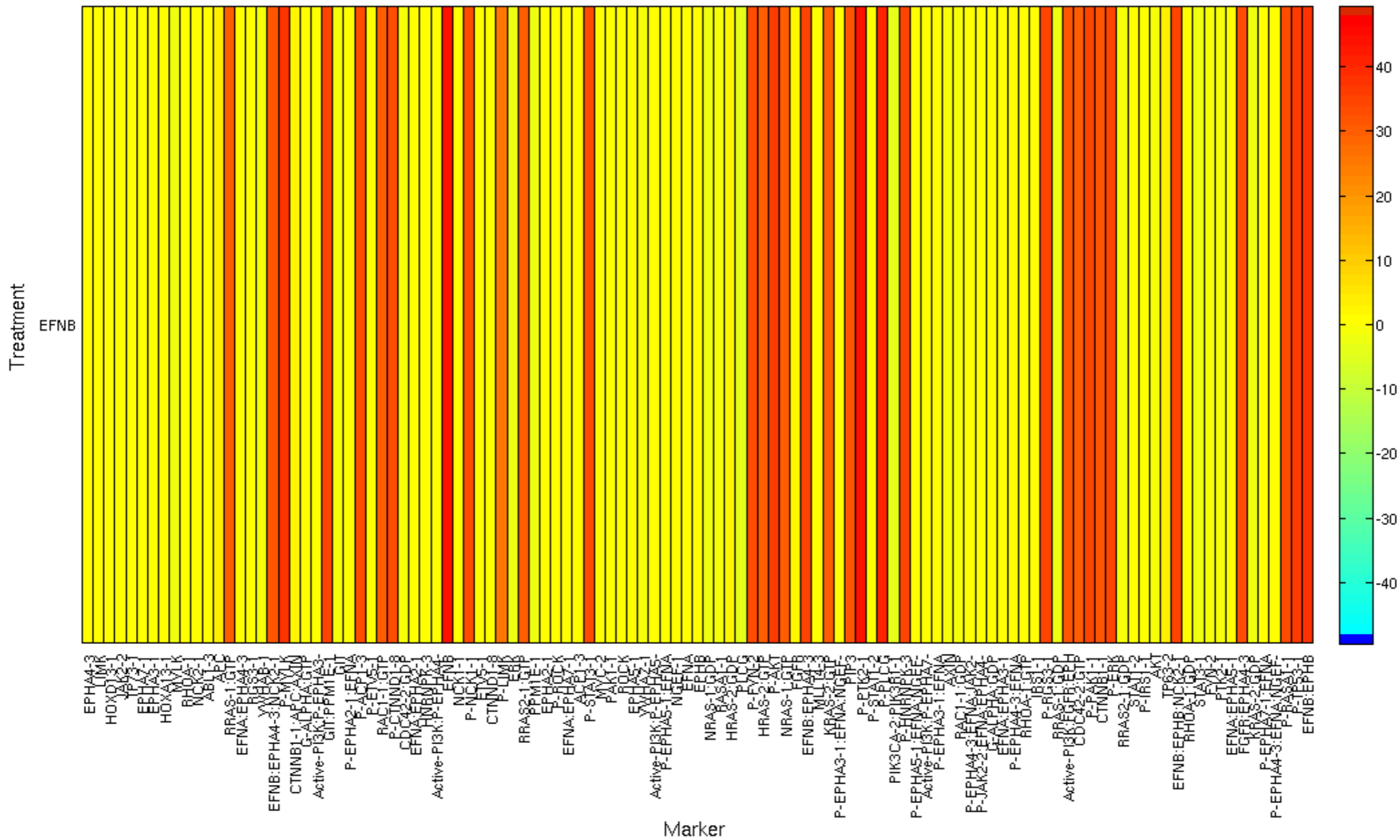
Treatment

EFNA



Marker

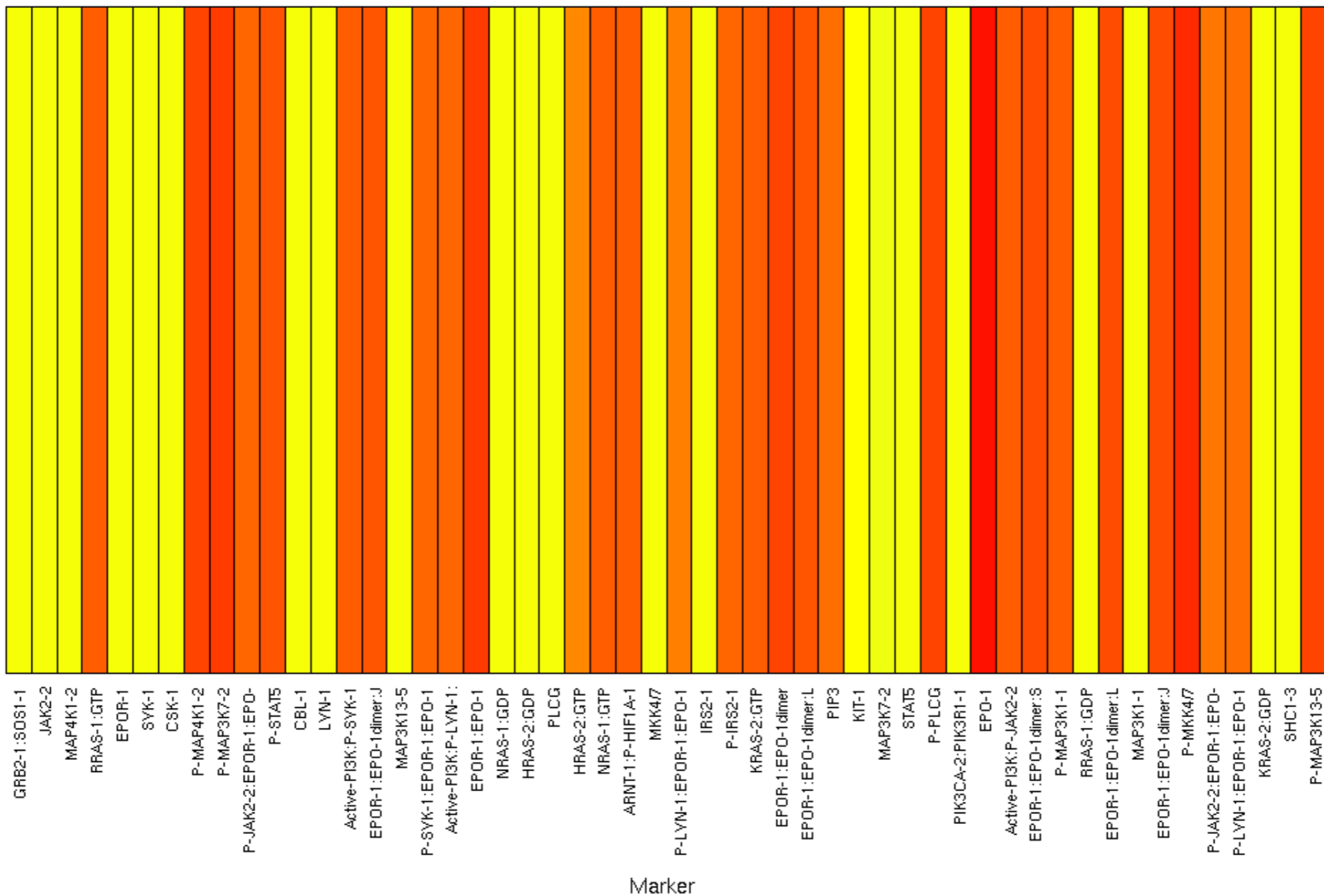
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_EFNB.tsv



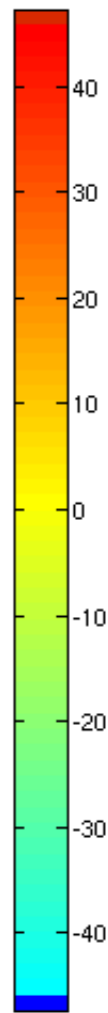
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_EPO.tsv

Treatment

EPO



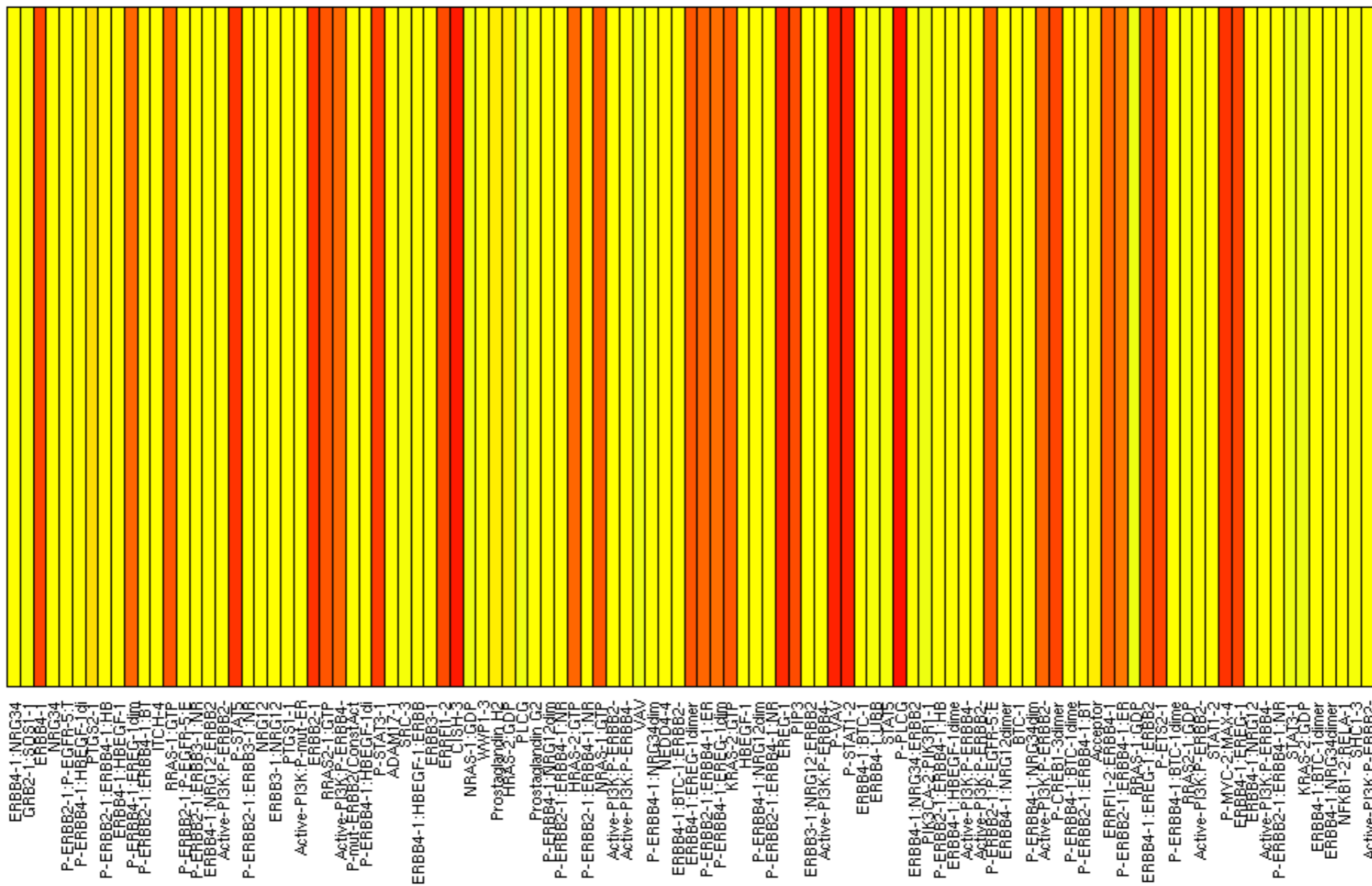
Marker



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_REG.tsv

Treatment

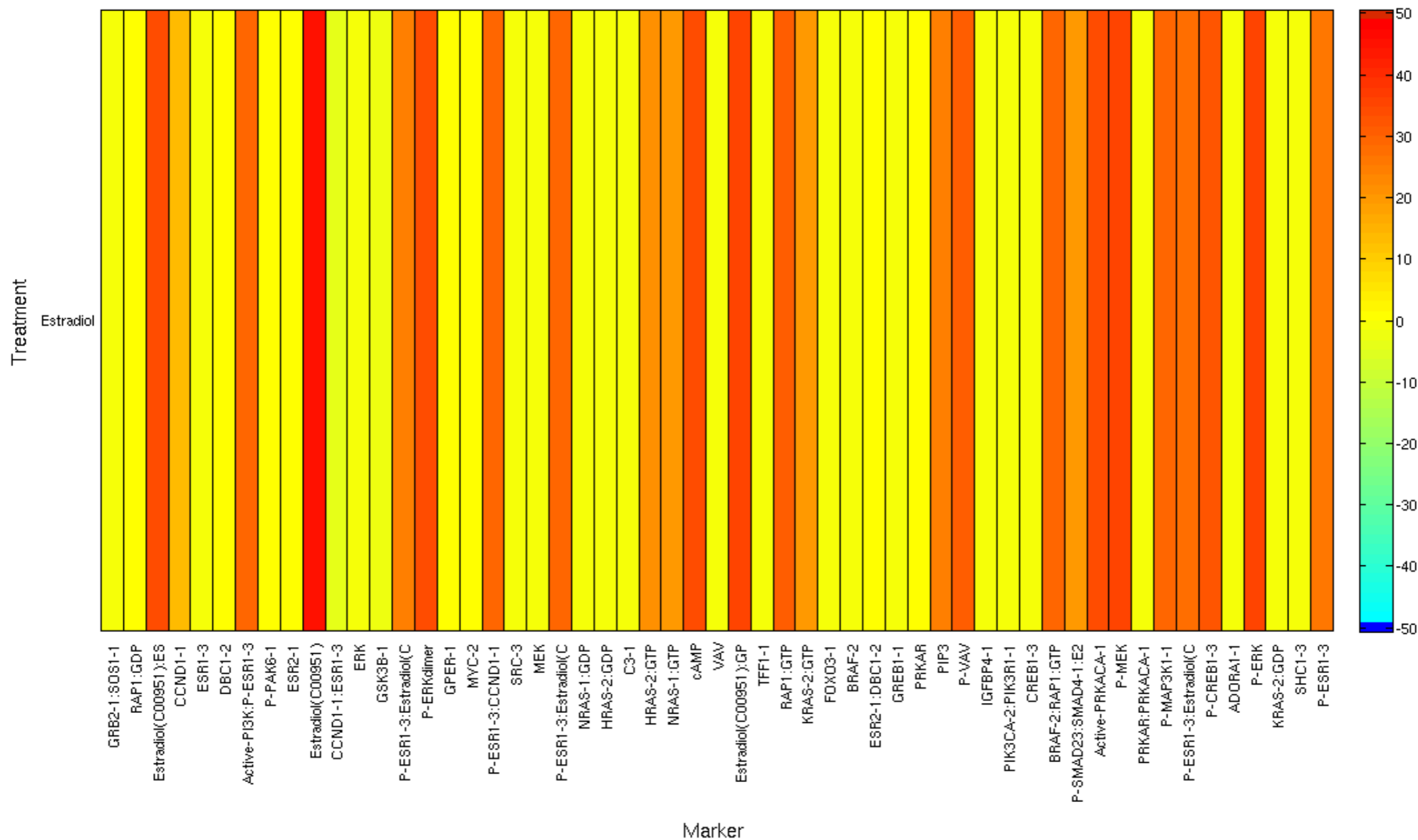
EREG



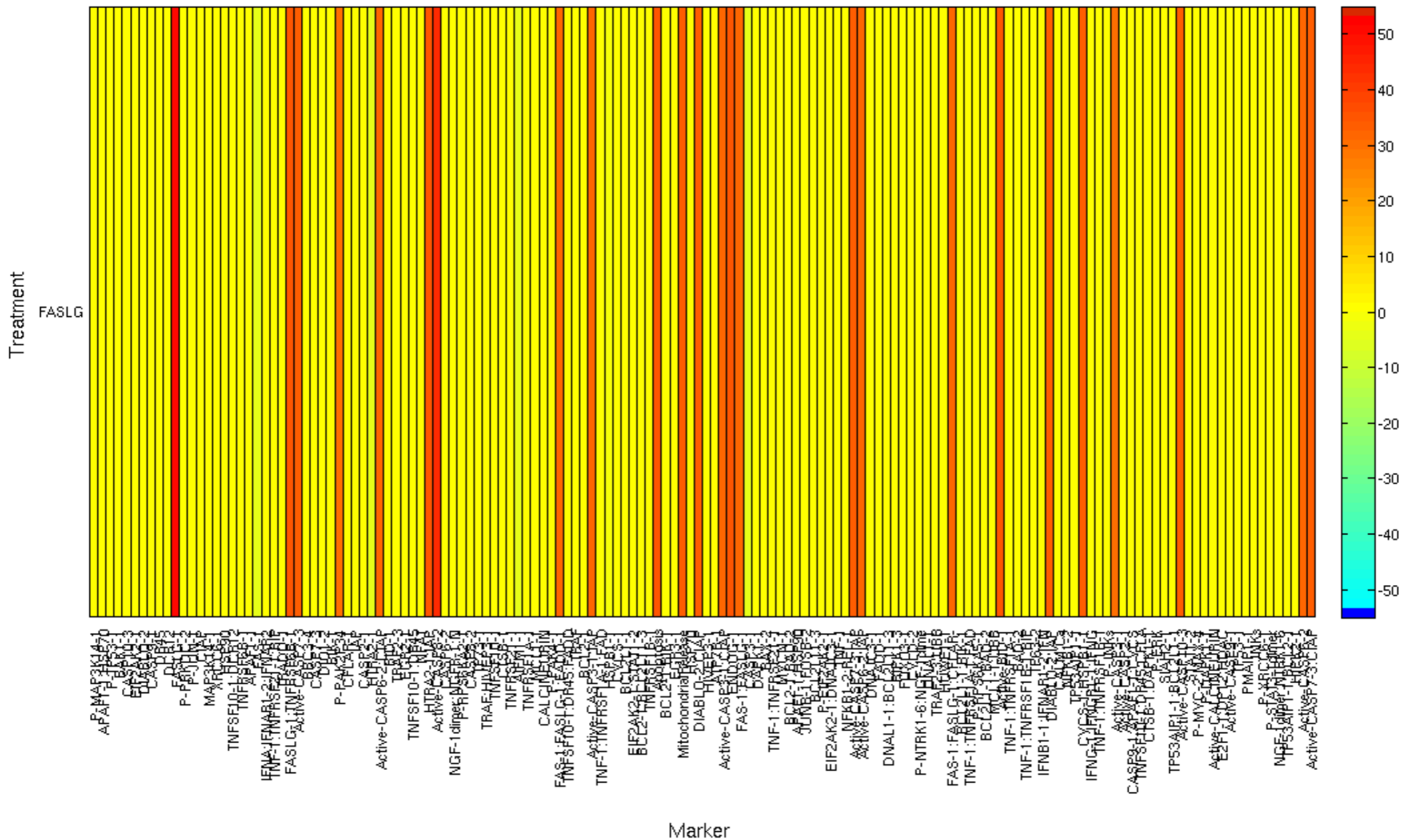
Marker

ERBB4-1:NRG34
 GRB2-1:SOX1-1
 ERBB4-1:NRG34
 NRG34
 P-ERBB2-1:P-EGFR-S-T
 P-ERBB4-1:HBEGF-1
 P-ERBB4-1:HBEGF-1
 P-ERBB2-1:ERBB4-1:HB
 ERBB4-1:HBEGF-1
 P-ERBB2-1:ERBB4-1:BT
 ERBB4-1:HBEGF-1:STAT1-2
 ERBB4-1:HBEGF-1:STAT1-3
 ERBB4-1:HBEGF-1:STAT1-4
 RRAS-1:GTP
 P-ERBB2-1:P-EGFR-S-E
 P-ERBB2-1:ERBB3-1:NR
 ERBB4-1:NRG12:ERBB2
 Active-PI3K:P-ERBB2
 P-ERBB2-1:ERBB3-1:NR
 ERBB3-1:NRG12
 NRG12
 ERBB3-1:PTGS1-1
 Active-PI3K:P-myl-EA
 ERBB2-1
 ERBB2-1
 RRAS2-1:GTP
 Active-PI3K:P-ERBB4
 P-mut-ERBB2(Cons)Act
 P-ERBB4-1:HBEGF-1:Id1
 P-STAT1-1
 P-STAT1-2
 P-STAT1-3
 ADAM17-1
 SRC-3
 ERBB3-1
 ERBB3-1
 ERBB3-1
 ERBB3-1
 NRAS-1:GDP
 WWP1-3
 Prostaglandin_H2
 HRAS-2:GDP
 HRAS-2:PLCC
 Prostaglandin_G2
 P-ERBB4-1:NRG12:Id1
 P-ERBB2-1:ERBB4-1:NR
 HRAS-2:GTP
 P-ERBB2-1:ERBB4-1:NR
 ERBB4-1:GTP
 Active-PI3K:P-ERBB2
 Active-PI3K:P-ERBB4
 VAV
 P-ERBB4-1:NRG34:Id1
 NRG34
 ERBB4-1:BTC-1:ERBB2
 ERBB4-1:EREG-1dimer
 P-ERBB2-1:ERBB4-1:ER
 P-ERBB4-1:EREG-1dimer
 KRAS-2:GTP
 KRAS-2:GTP
 HBEGF-1
 P-ERBB4-1:NRG12:Id1
 P-ERBB2-1:ERBB4-1:NR
 ERREG-1
 PIP3
 ERBB3-1:NRG12:ERBB2
 Active-PI3K:P-ERBB4
 P-VAV
 P-STAT1-2
 ERBB4-1:BTC-1
 ERBB4-1:BTC-1
 ERBB4-1:STAT1-2
 ERBB4-1:STAT1-3
 ERBB4-1:STAT1-4
 P-PLCG
 ERBB4-1:NRG34:ERBB2
 PIK3CA-2:PIK3R1-1
 P-ERBB2-1:ERBB4-1:HB
 ERBB4-1:HBEGF-1dimer
 Active-PI3K:P-ERBB4
 Active-PI3K:P-ERBB2
 P-ERBB2-1:P-EGFR-S:E
 ERBB4-1:NRG12dimer
 BTC-1
 P-ERBB4-1:NRG34:Id1
 Active-PI3K:P-ERBB2
 P-CREB1-3dimer
 P-ERBB4-1:BTC-1dimer
 P-ERBB2-1:ERBB4-1:BT
 Acceptor
 ERBB1-2:ERBB4-1
 P-ERBB2-1:ERBB4-1:ER
 RRAS-1:GDP
 ERBB4-1:EREG-1:ERBB2
 P-ETS2-1
 P-ERBB4-1:BTC-1dimer
 ERBB2-1:Id1
 Active-PI3K:P-ERBB2
 STAT1-2
 P-MYC-2:MAX-4
 ERBB4-1:EREG-1
 ERBB4-1:NRG12
 Active-PI3K:P-ERBB4
 P-ERBB2-1:ERBB4-1:NR
 STAT1-1
 KRAS-2:GDP
 ERBB4-1:BTC-1dimer
 ERBB4-1:NRG34dimer
 NFKB1-2:RELA-1
 SHC1-3
 Active-PI3K:P-ERBB2

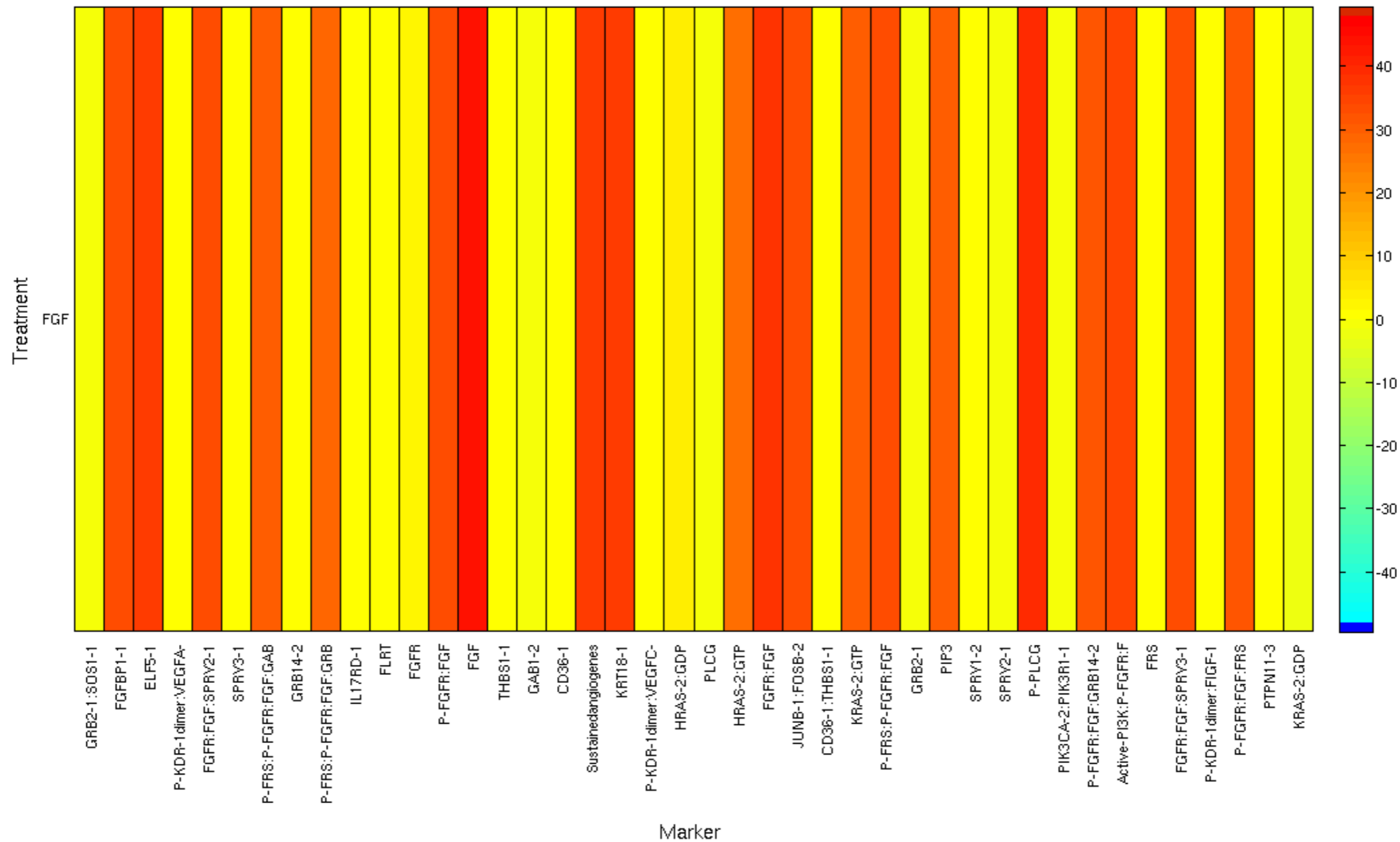
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_Estradiol_C00951_tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_FASLG.tsv



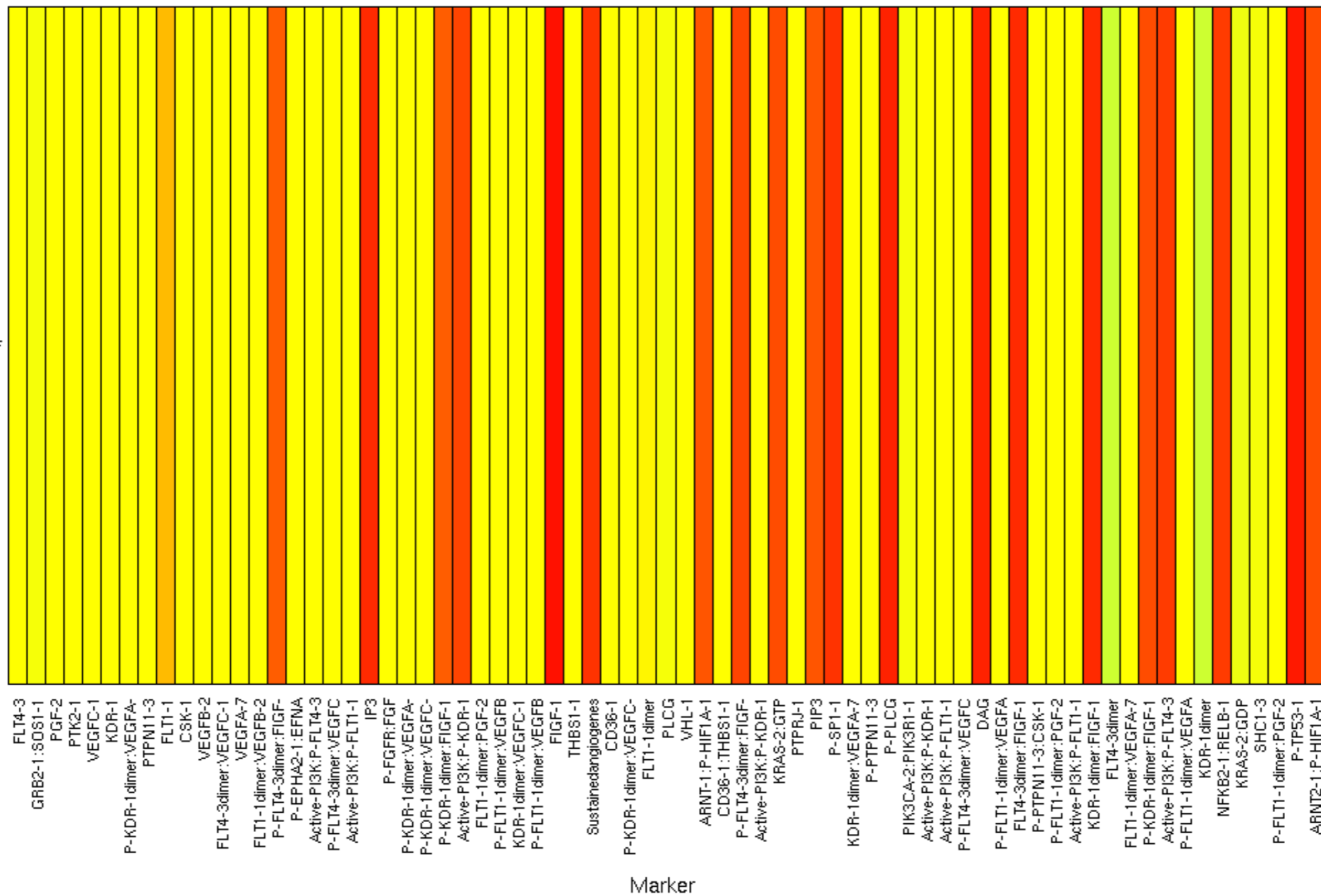
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_FGF.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_FIGF.tsv

Treatment

FIGF

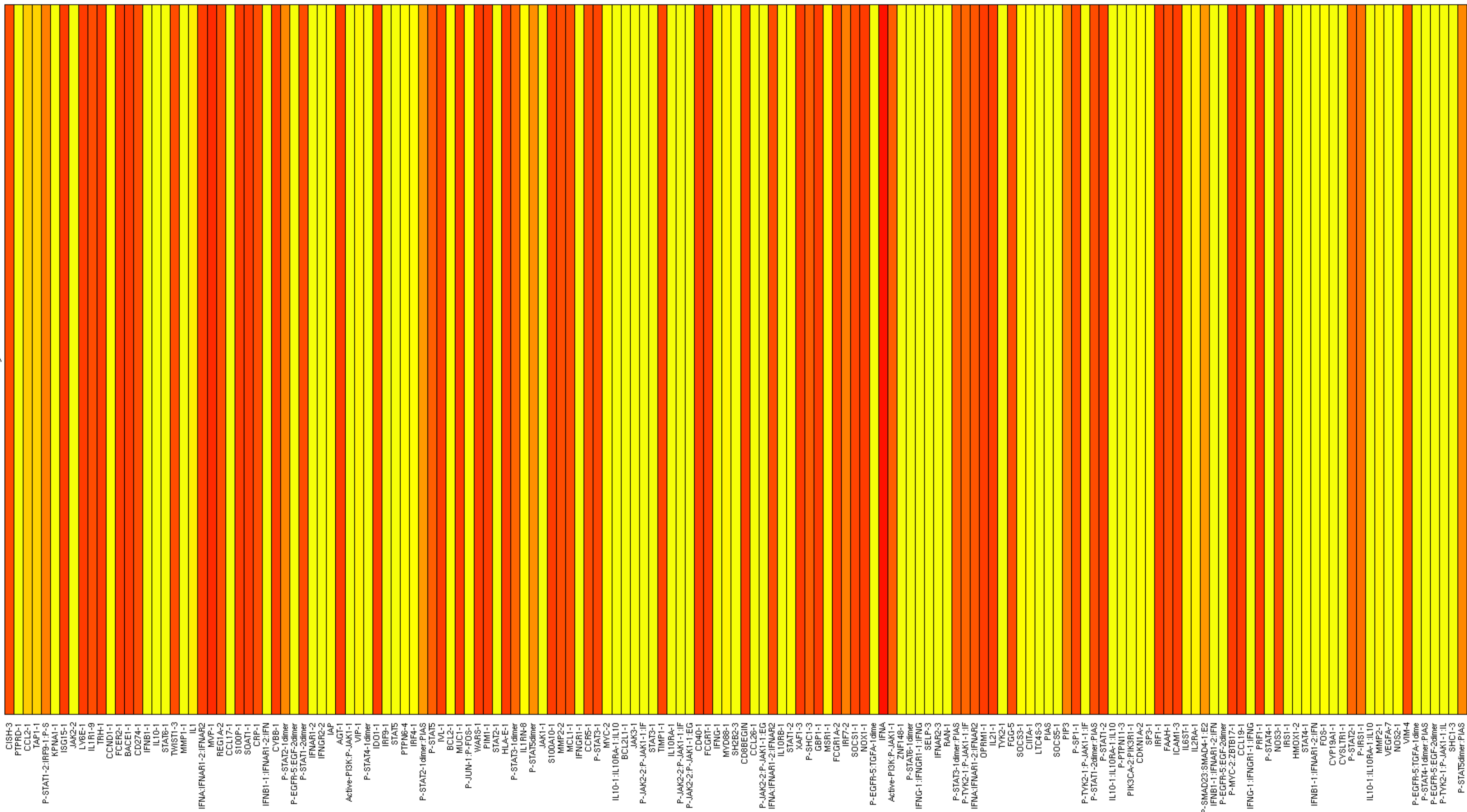


Marker



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_FNA.tsv

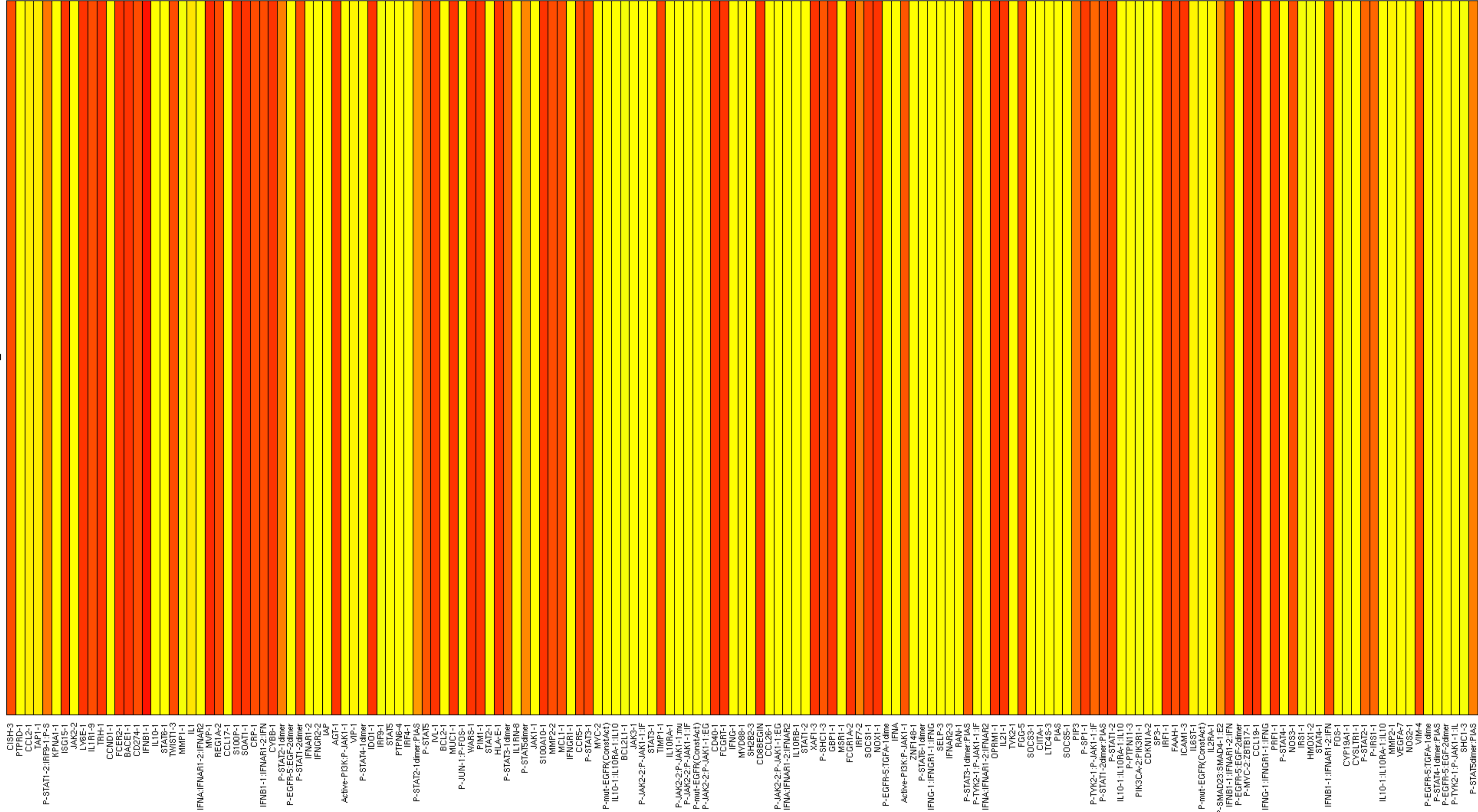
Treatment
IFNA



Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_eadout_FNB1.tsv

Treatment
IFNB1



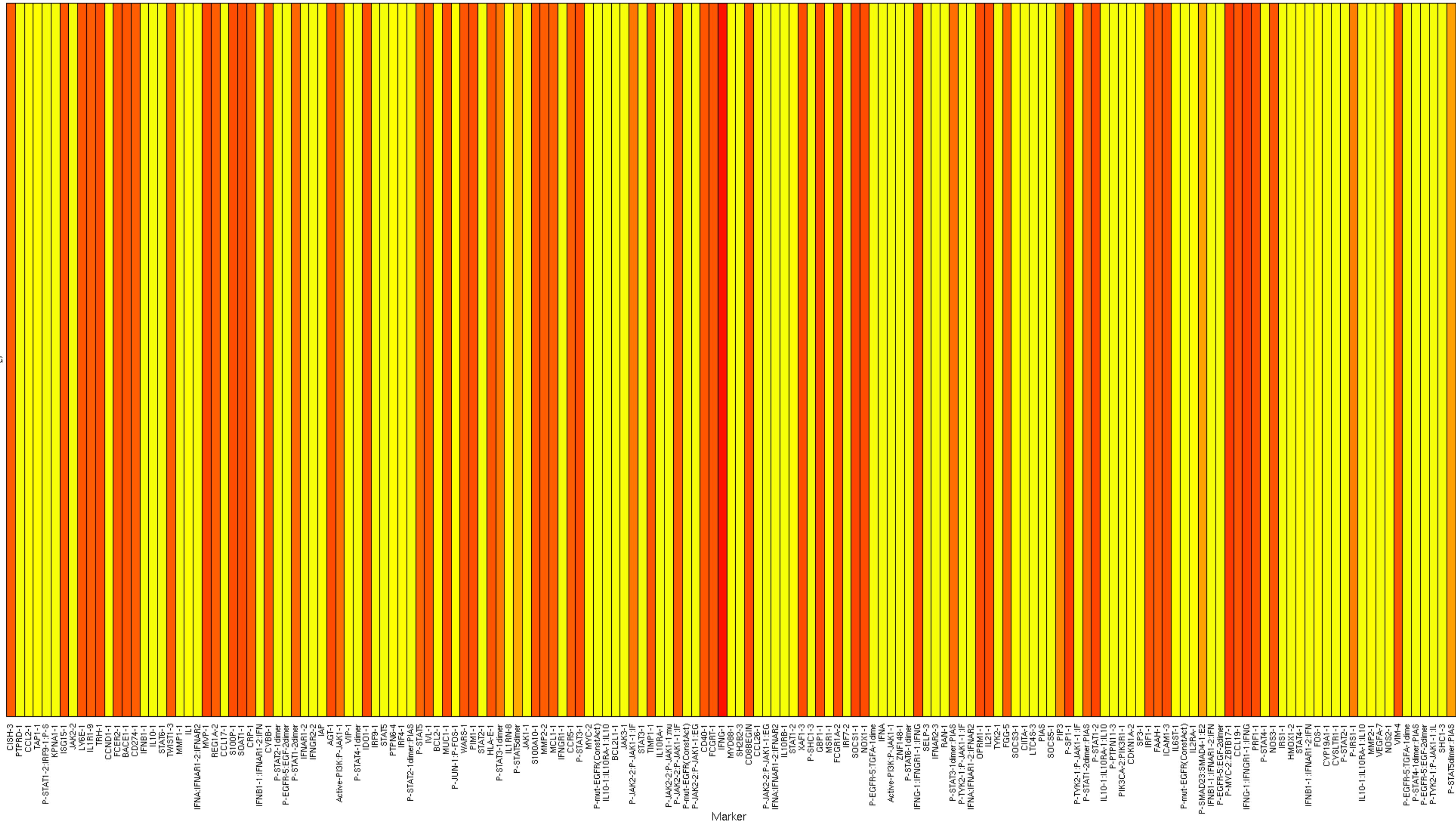
Marker

- CISH-3
- PTPRD-1
- CCL2-1
- XAF1-1
- P-STAT1-2:IRF9-1:IF-5
- KPNAL1-1
- JAK2-2
- ISG15-1
- LY8E-1
- IL1RI-3
- TRH-1
- CCND1-1
- FCER2-1
- BACE1-1
- CD274-1
- IFNB1-1
- IL10-1
- STAT6-1
- TWIST1-3
- MMP1-1
- ILI
- IFNA:IFNAR1-2:IFNAR2
- MVP-1
- REG1A-2
- CCL17-1
- S100P-1
- SOAT1-1
- CRP-1
- IFNB1-1:IFNAR1-2:IFN
- CYBB-1
- P-STAT2-1:dimer
- P-EGFR-5:EGF-2:dimer
- P-STAT1-2:dimer
- IFNAR1-2
- IFNGR2-2
- IAP
- AGT-1
- Active-PI3K:P-JAK1-1
- VIP-1
- P-STAT4-1:dimer
- IDO1-1
- IRF9-1
- STAT5
- PTPN6-4
- IRF4-1
- P-STAT2-1:dimer:PIAS
- P-STAT5
- IVL-1
- BCL2-1
- MUC1-1
- P-JUN-1:P-FOS-1
- WARS-1
- PIM1-1
- STAT2-1
- HLA-E-1
- P-STAT3-1:dimer
- IL1RN-8
- P-STAT3:dimer
- JAK1-1
- S100A10-1
- MMP2-2
- MCL1-1
- IFNGR1-1
- CCRS-1
- P-STAT3-1
- MYC-2
- P-mut-EGFR(ConstAct)
- IL10-1:IL10RA-1:IL10
- BCL2L1-1
- JAK3-1
- P-JAK2-2:P-JAK1-1:IF
- STAT3-1
- TIMP1-1
- IL10RA-1
- P-JAK2-2:P-JAK1-1:IF
- P-JAK2-2:P-JAK1-1:IF
- P-mut-EGFR(ConstAct)
- P-mut-EGFR(ConstAct)
- P-JAK2-2:P-JAK1-1:IF
- CD4-1
- FCGR1-1
- IFNG-1
- MYO8-1
- SH2B2-3
- COBEBGIN
- CCL28-1
- P-JAK2-2:P-JAK1-1:IF
- IFNA:IFNAR1-2:IFNAR2
- IL10RB-1
- STAT1-2
- XAF1-3
- P-SH2-1-3
- GBPI-1
- MSR1-1
- FCGR1A-2
- IRF7-2
- SOC3-1
- NDX1-1
- P-EGFR-5:TGFA-1:dime
- IFNA
- Active-PI3K:P-JAK1-1
- ZNF148-1
- P-STAT6-1:dimer
- IFNG-1:IFNGR1-1:IFNG
- SELP-3
- IFNAR2-3
- RAN-1
- P-STAT3-1:dimer:PIAS
- P-TYK2-1:P-JAK1-1:IF
- IFNA:IFNAR1-2:IFNAR2
- OPRM1-1
- IL21-1
- TYK2-1
- FGG-5
- SOC3-1
- CIITA-1
- LTC4S-3
- PIAS
- SOC35-1
- PIP3
- P-SPT1-1
- P-TYK2-1:P-JAK1-1:IF
- P-STAT1-2:dimer:PIAS
- P-STAT1-2
- IL10-1:IL10RA-1:IL10
- P-PTPN11-3
- PIK3CA-2:PIK3R1-1
- CDKN1A-2
- SP3-1
- IRF1-1
- FAAH-1
- ICAM1-3
- IL6ST-1
- IL2RA-1
- P-mut-EGFR(ConstAct)
- P-SMAD3:SMAD4-1:E2
- IFNB1-1:IFNAR1-2:IFN
- P-EGFR-5:EGF-2:dimer
- P-MYC-2:ZBTB7-1
- CCL19-1
- IFNG-1:IFNGR1-1:IFNG
- PREF1-1
- P-STAT4-1
- NOS3-1
- IRSI-1
- HMOX1-2
- STAT4-1
- IFNB1-1:IFNAR1-2:IFN
- FOS-1
- CYP19A1-1
- CYSLTR1-1
- P-STAT2-1
- P-IRSI-1
- IL10-1:IL10RA-1:IL10
- MMP2-1
- VEGFA-7
- NOS2-1
- VIM-4
- P-EGFR-5:TGFA-1:dime
- P-STAT6-1:dimer:PIAS
- P-EGFR-5:EGF-2:dimer
- P-TYK2-1:P-JAK1-1:IF
- SHC1-3
- P-STAT3:dimer:PIAS

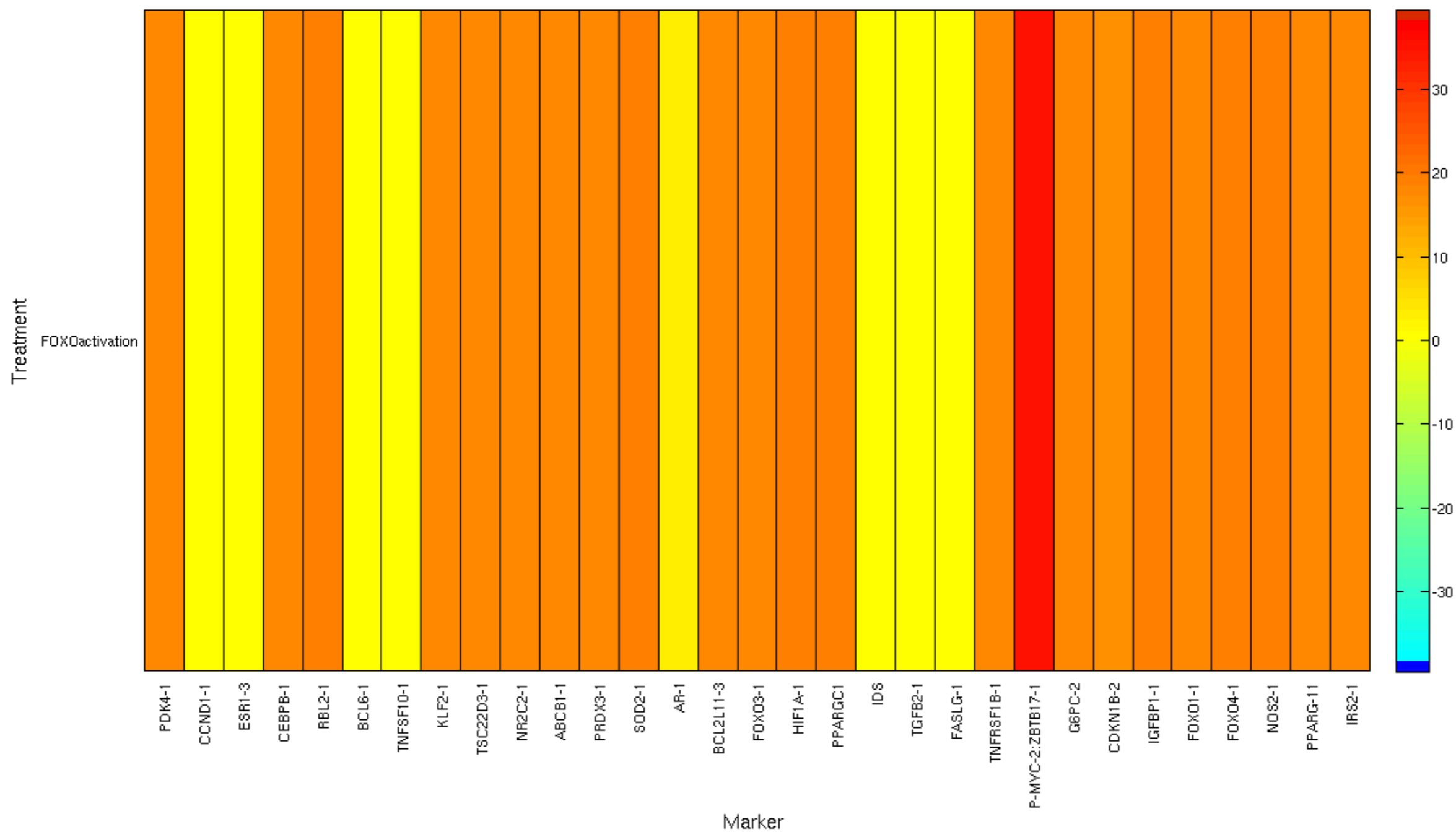


Marker Ratios (Log2 Of Geo Mean) bysummary_readout_FNG.tsv

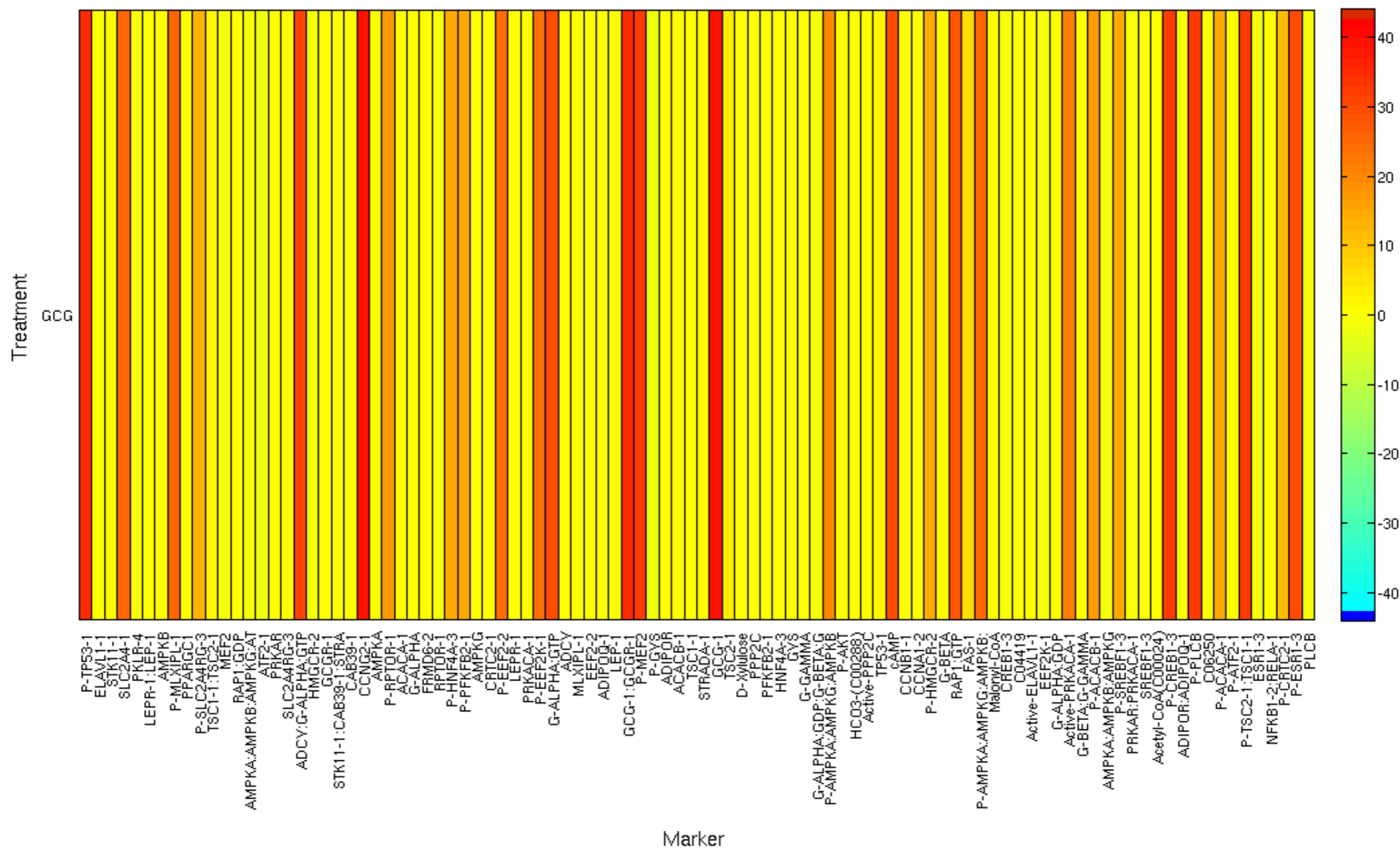
Treatment
IFNG



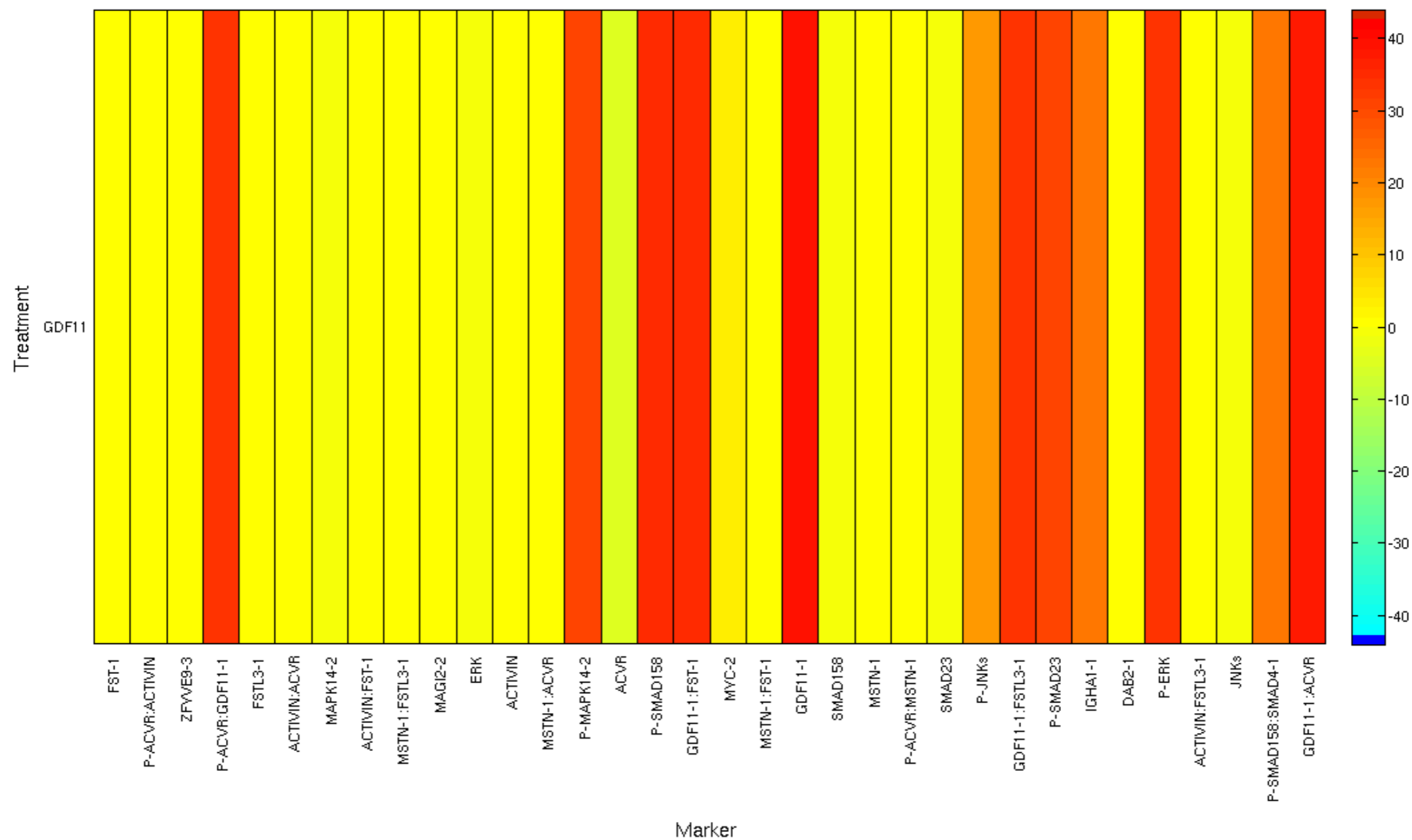
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_FOXO.tsv



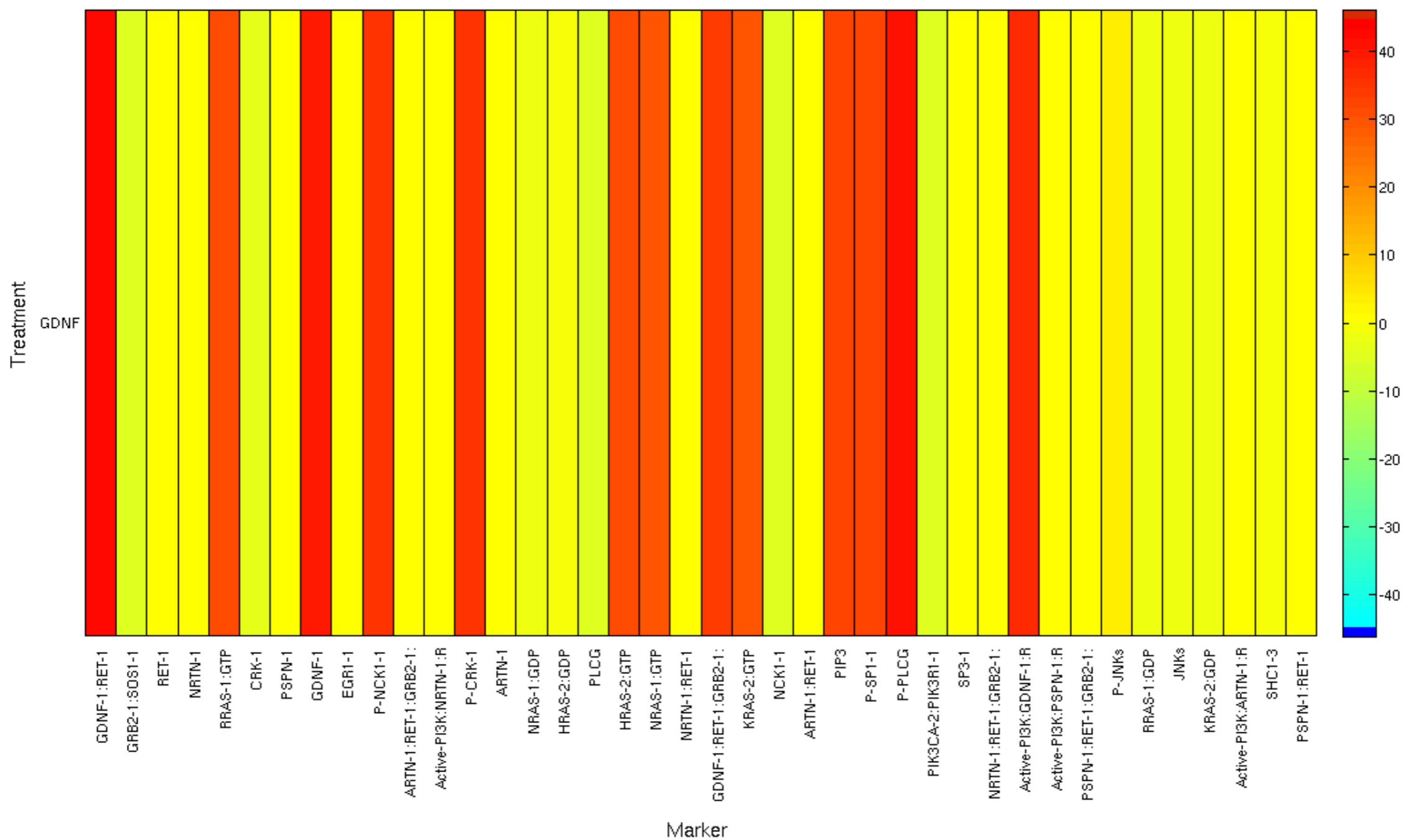
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_G.CG.tsv



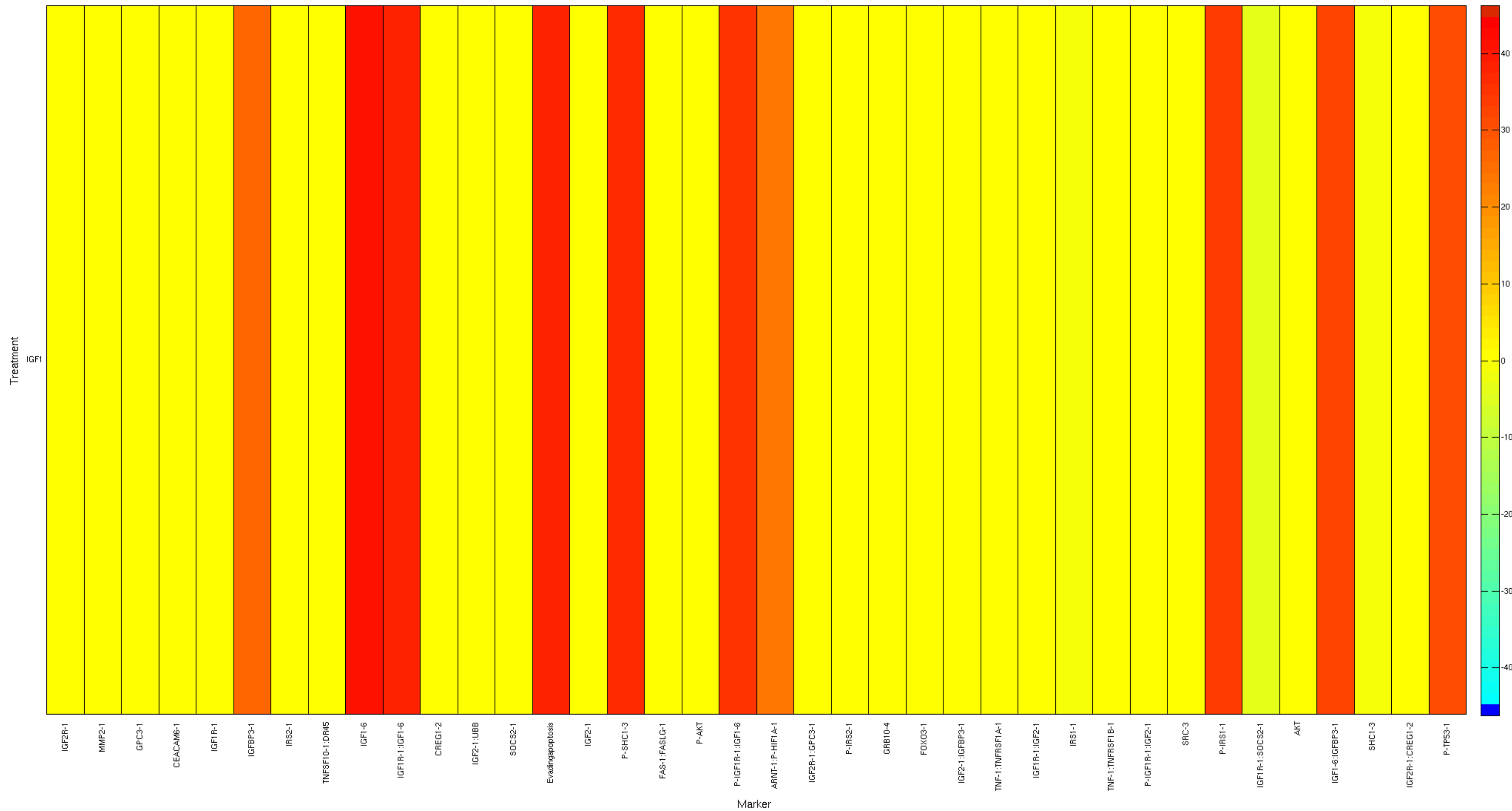
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_GDF11.tsv



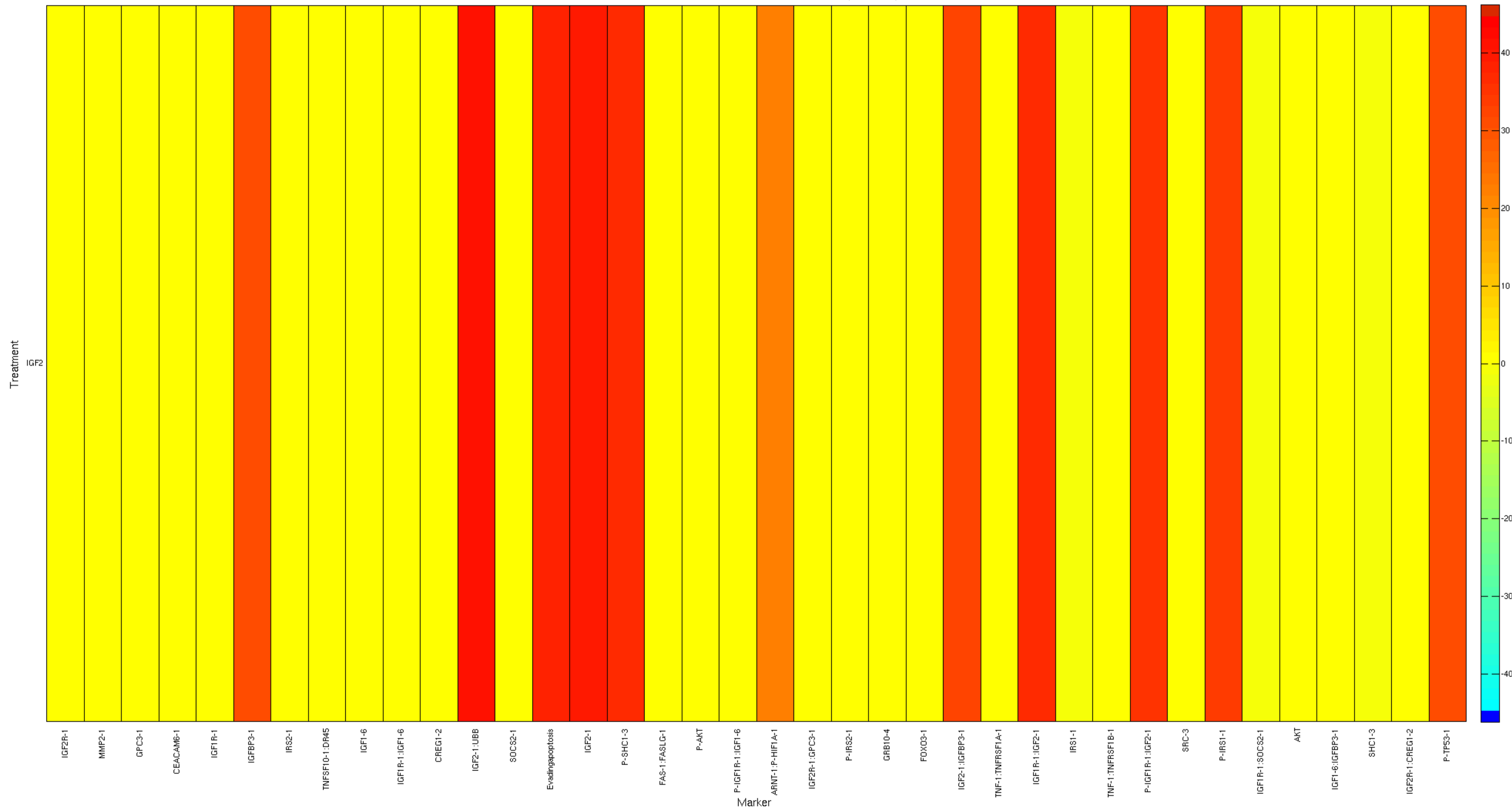
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_GDNF.tsv



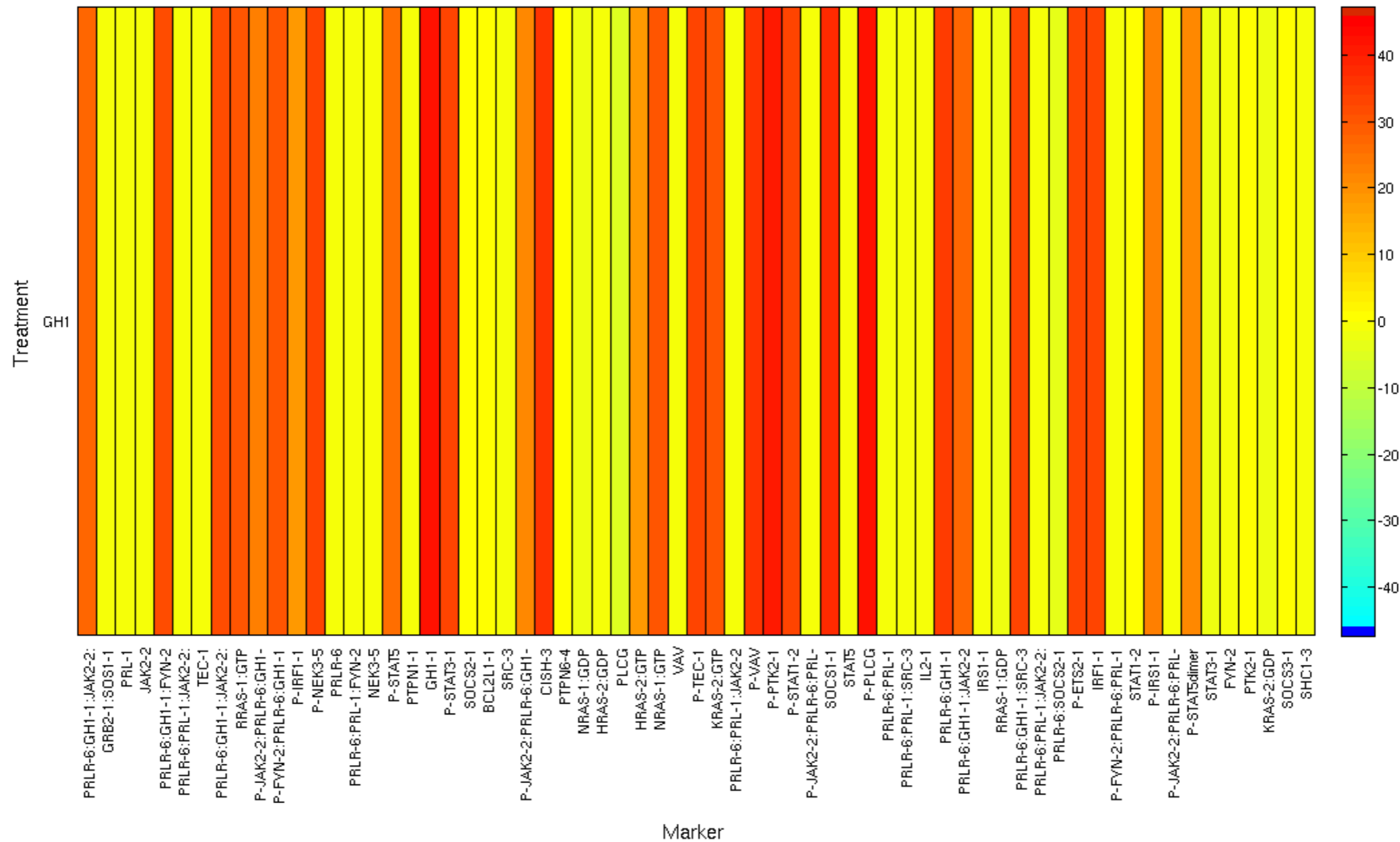
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_IGF1.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_IGF2.tsv



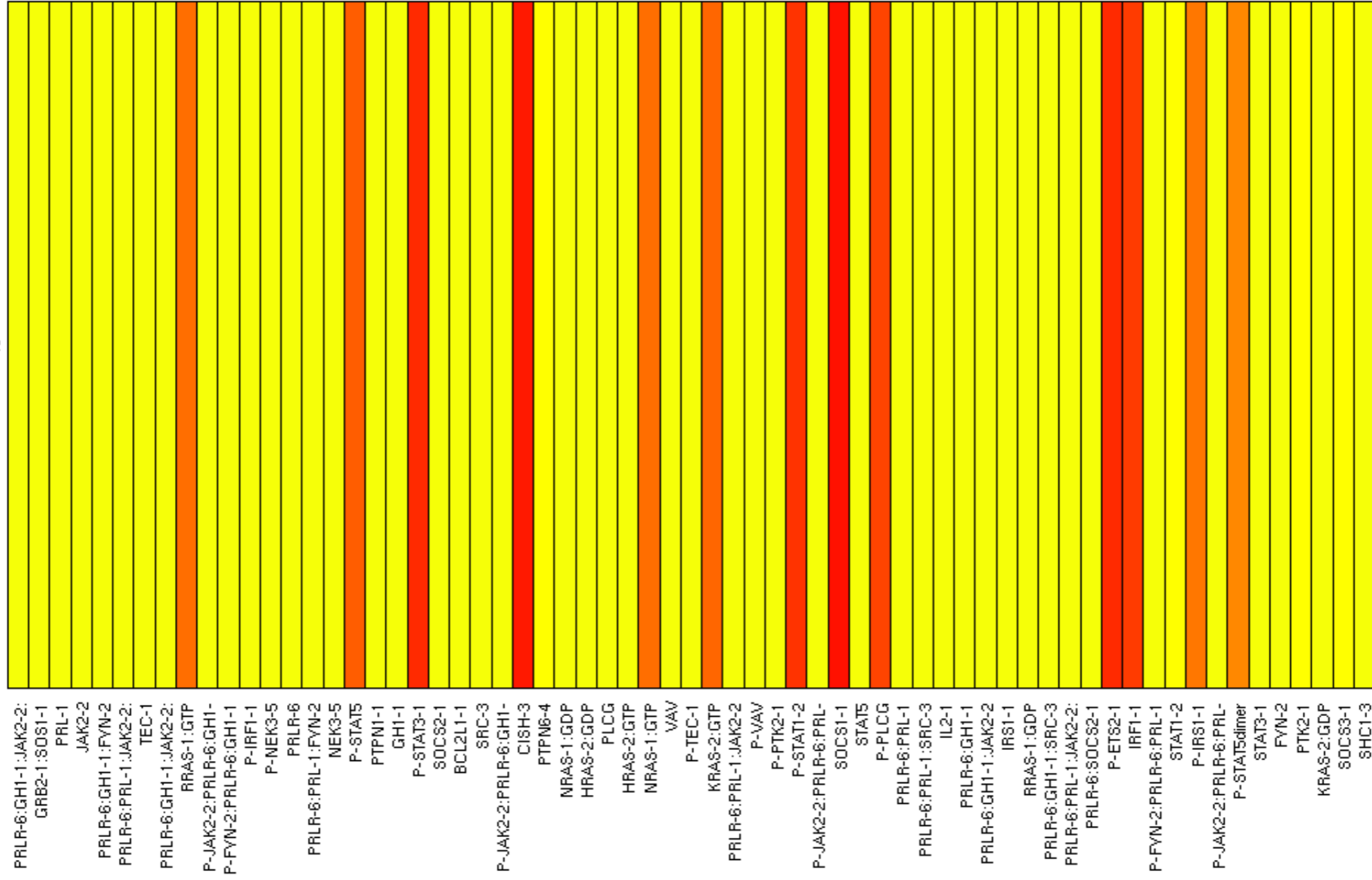
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_GH1.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_GH2.tsv

Treatment

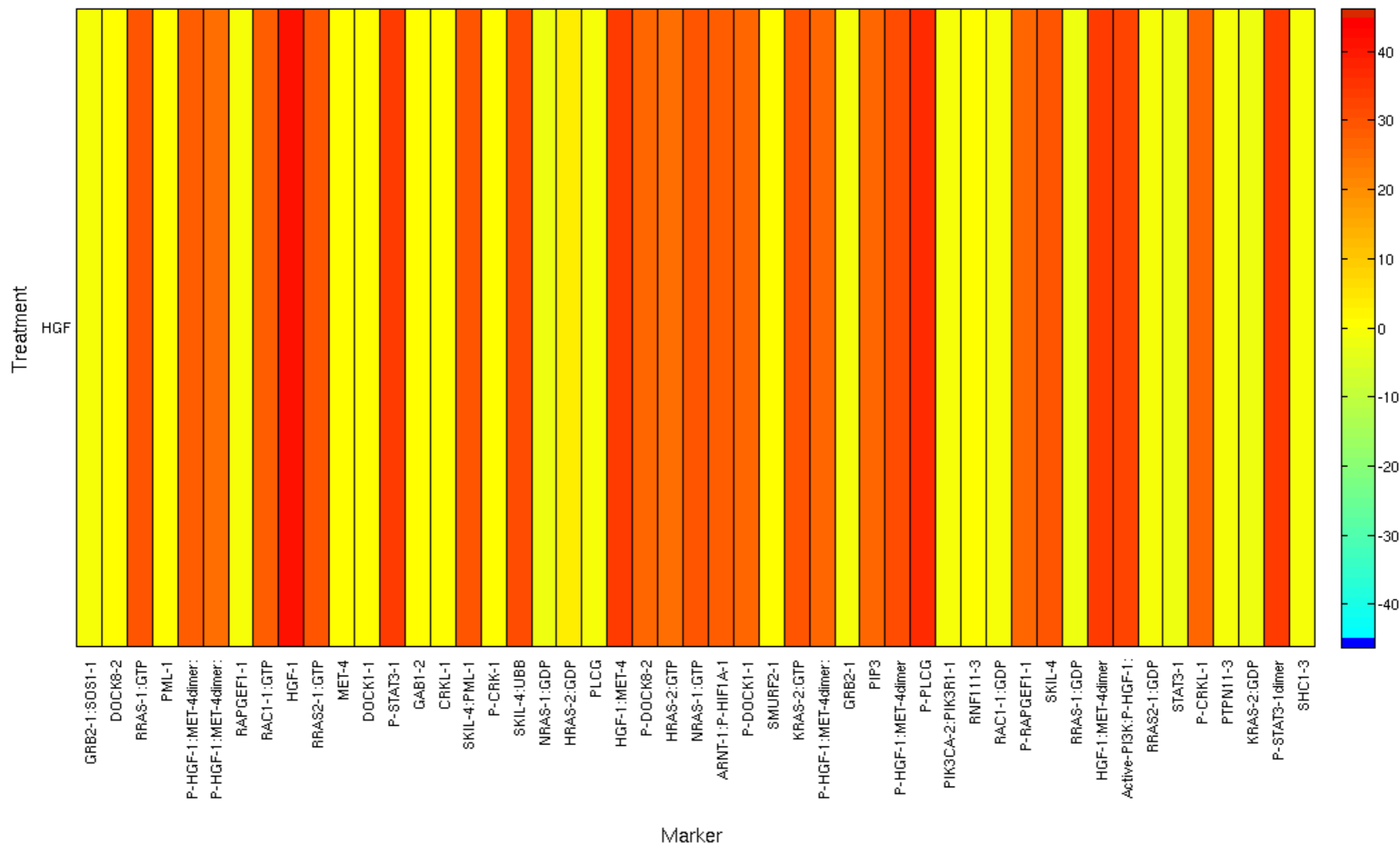
GH2



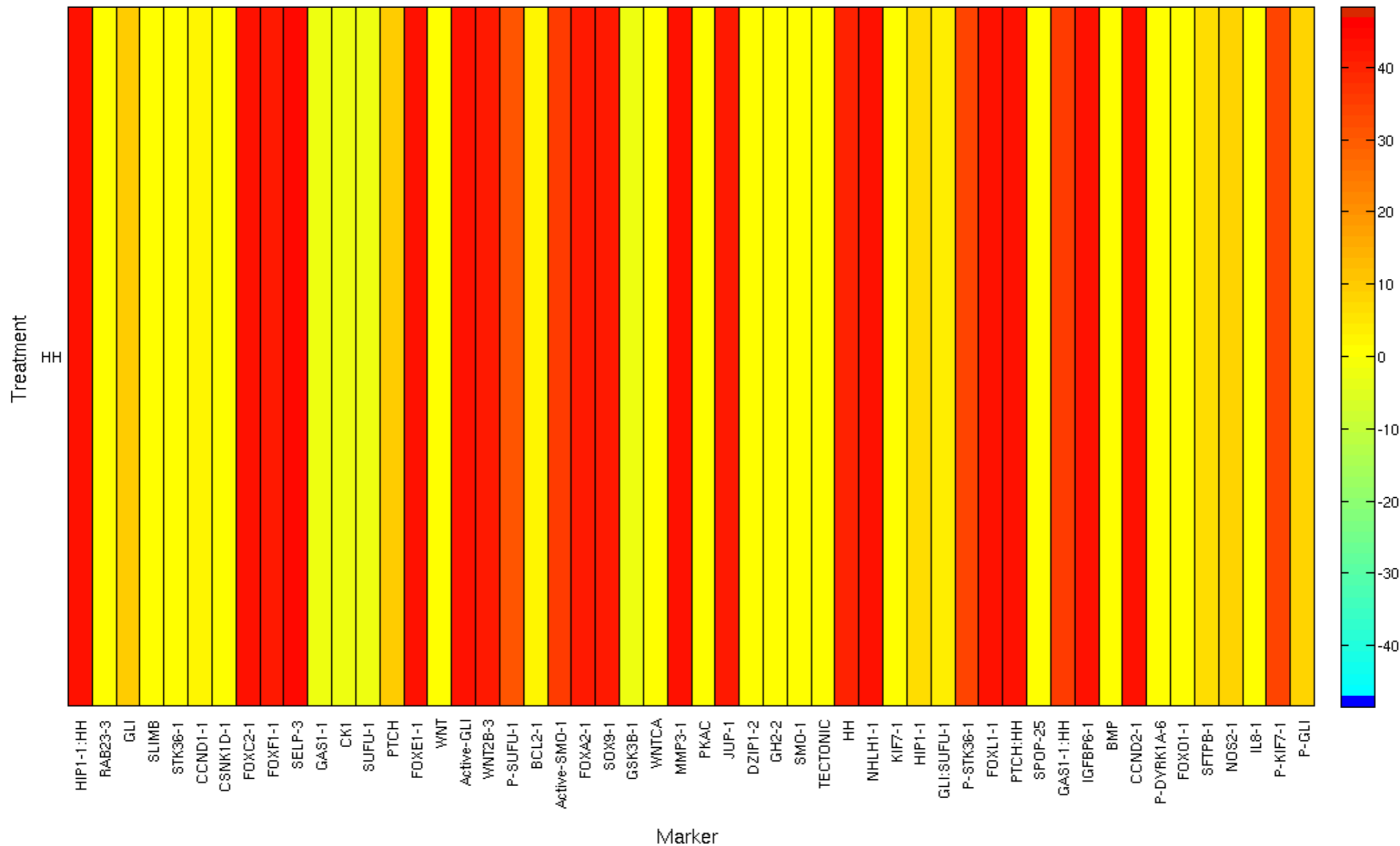
Marker



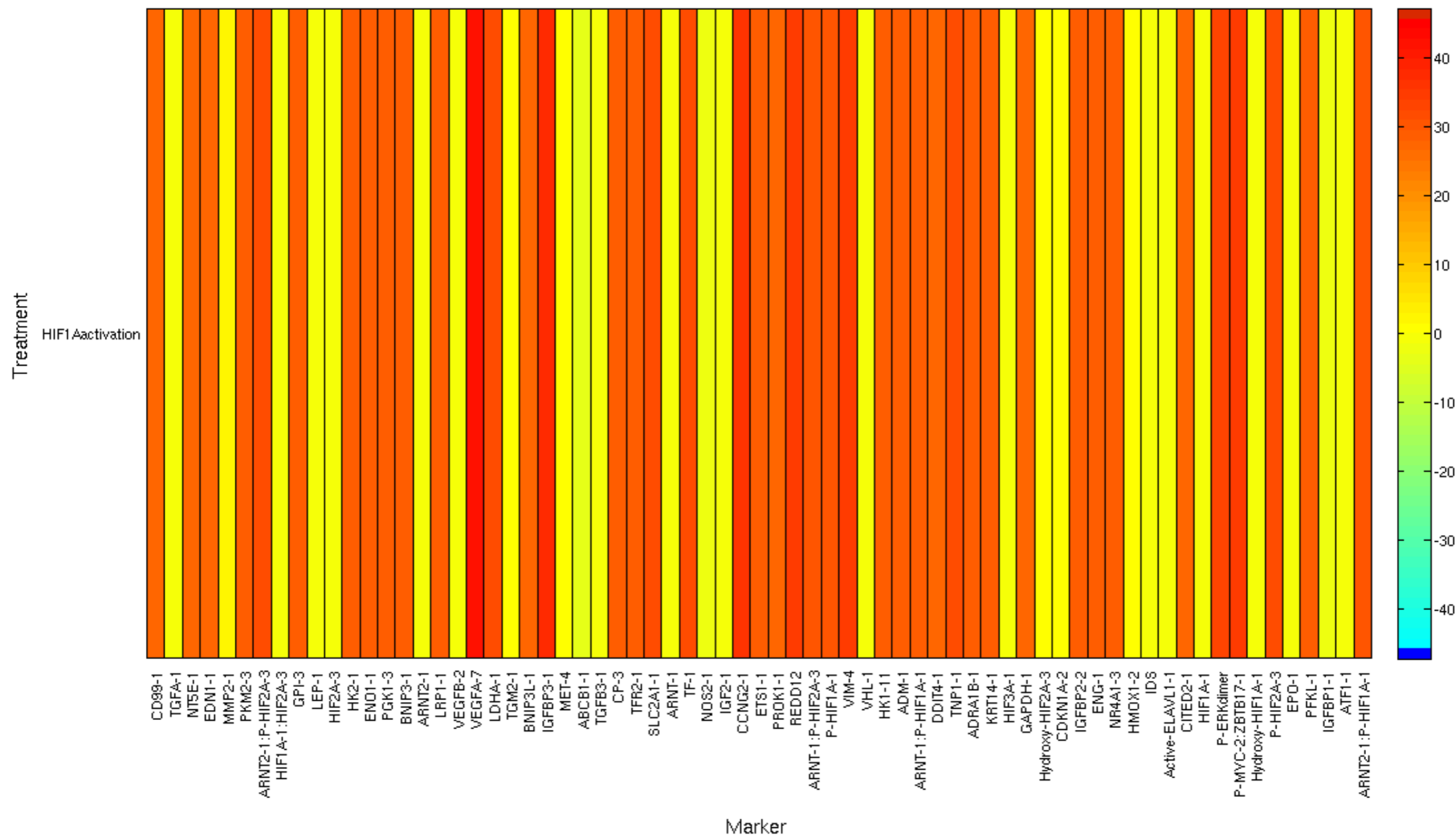
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_HGF.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_H.H.tsv

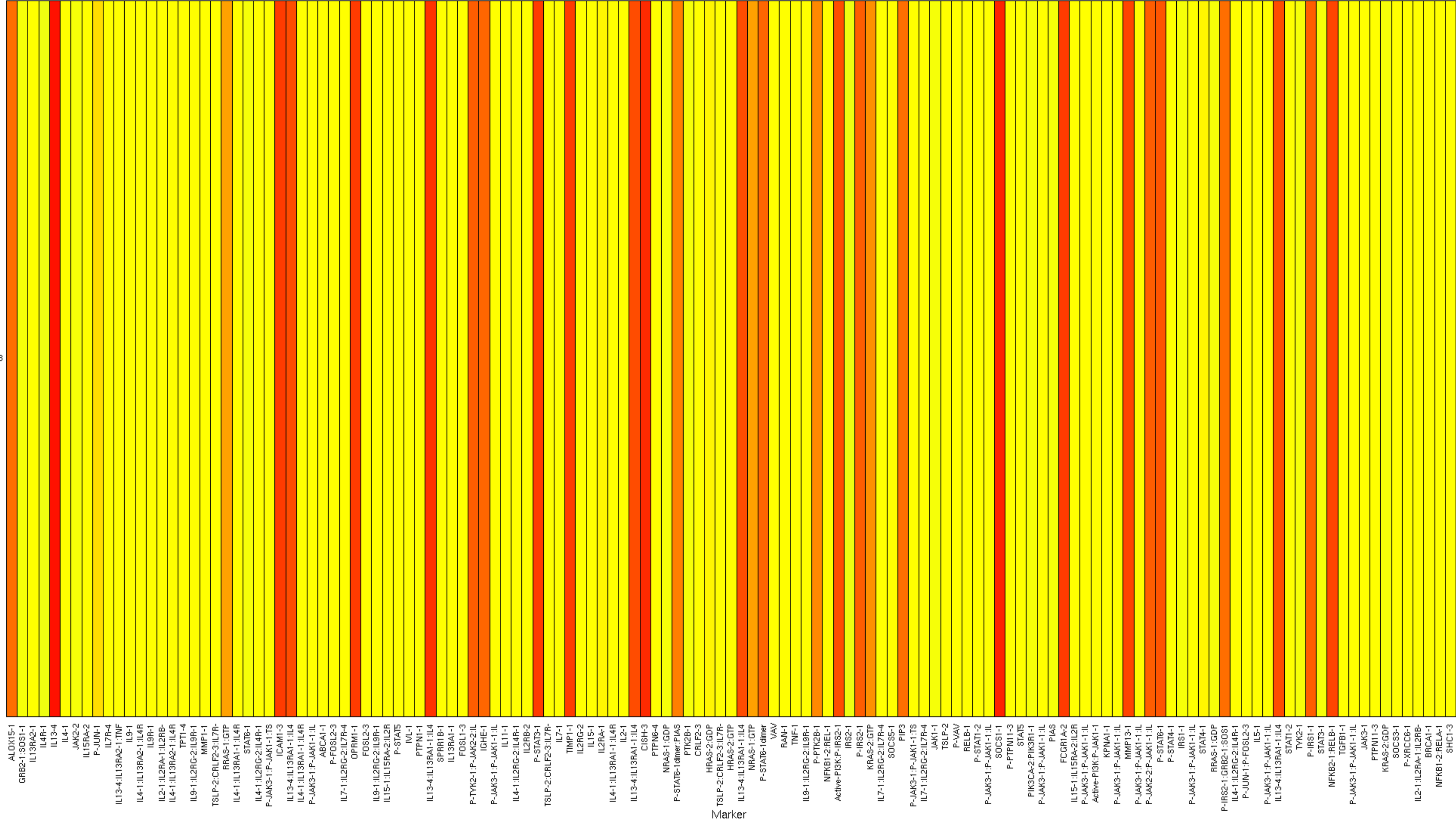


Marker Ratios (Log2 Of Geo Mean) bysummary_readout_HIF1.tsv



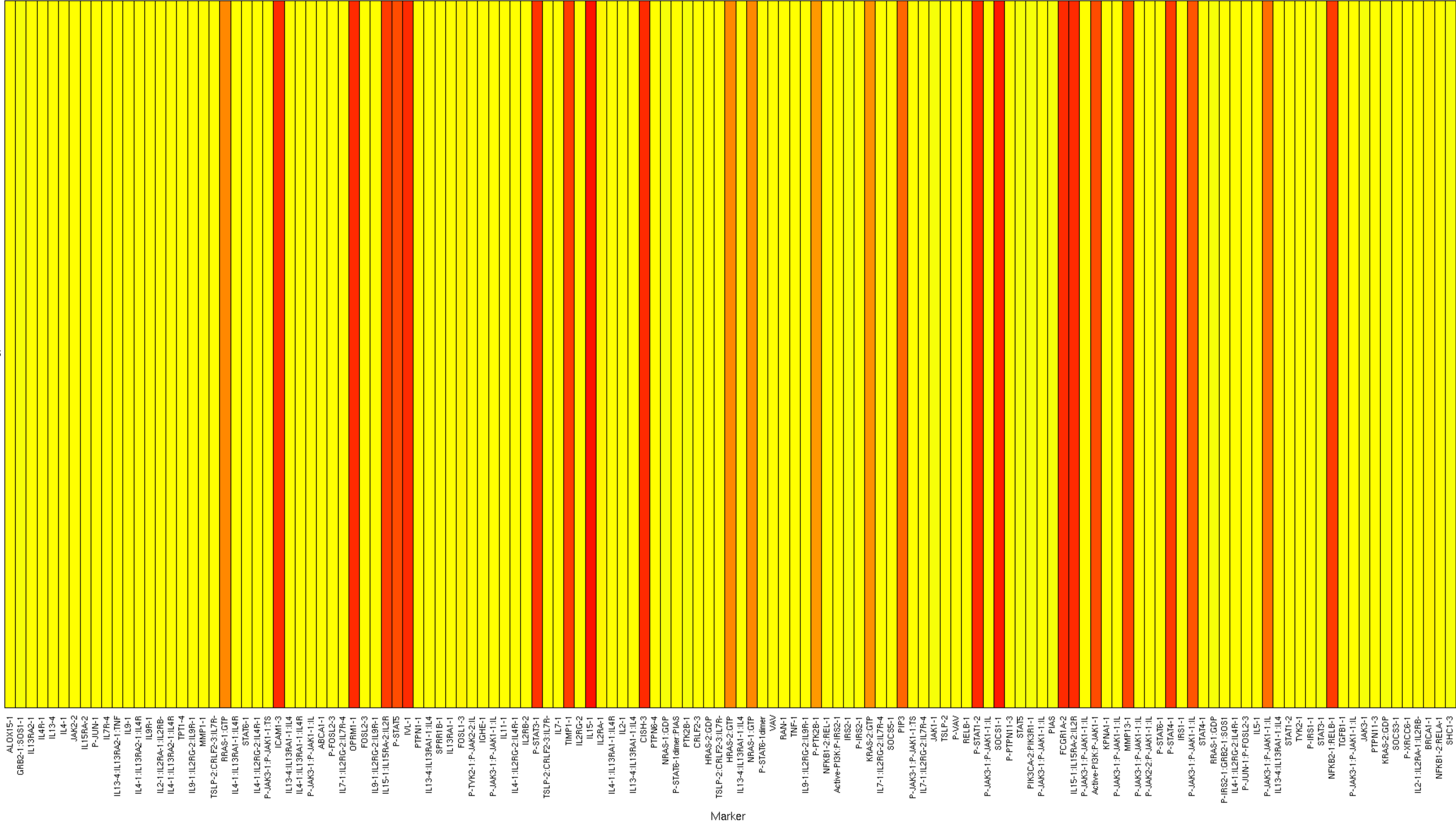
Marker Ratios (Log2 Of Geo Mean) bysummary_eadout_L13.tsv

Treatment
IL13



Marker Ratios (Log2 Of Geo Mean) bysummary_eadout_L15.tsv

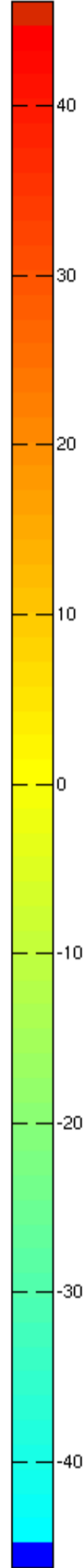
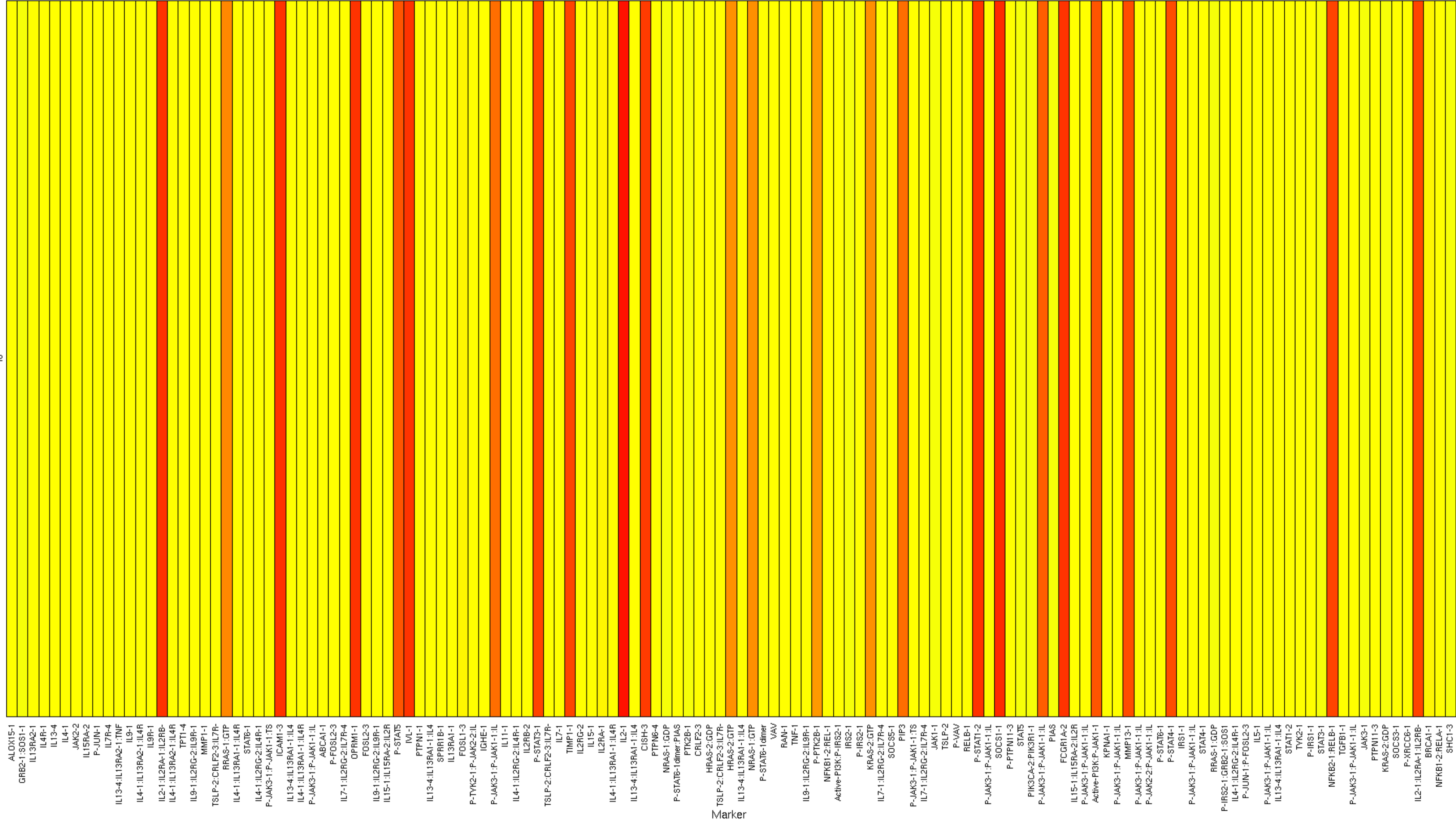
Treatment
IL15



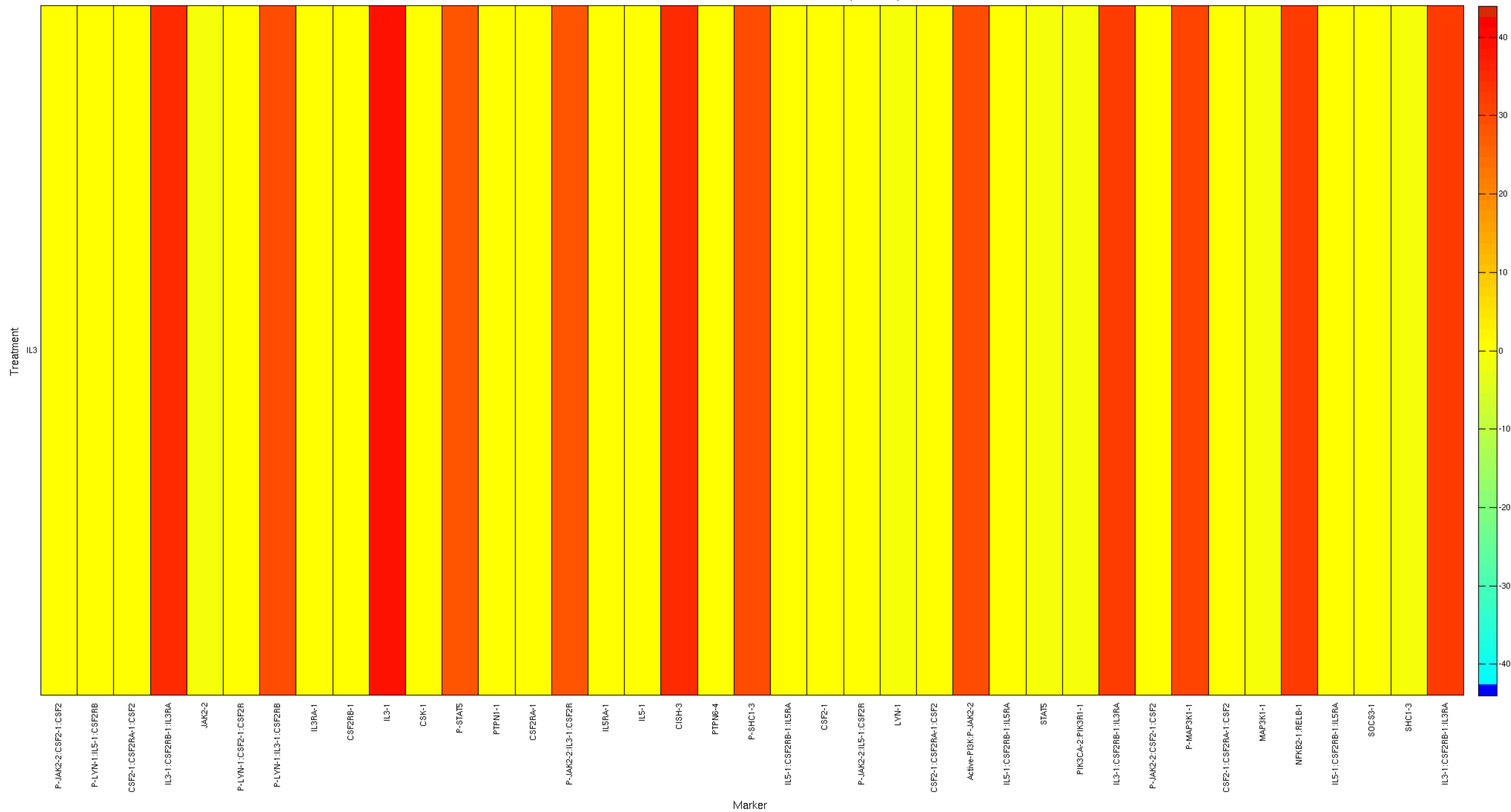
Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_readout_L2.tsv

Treatment
E

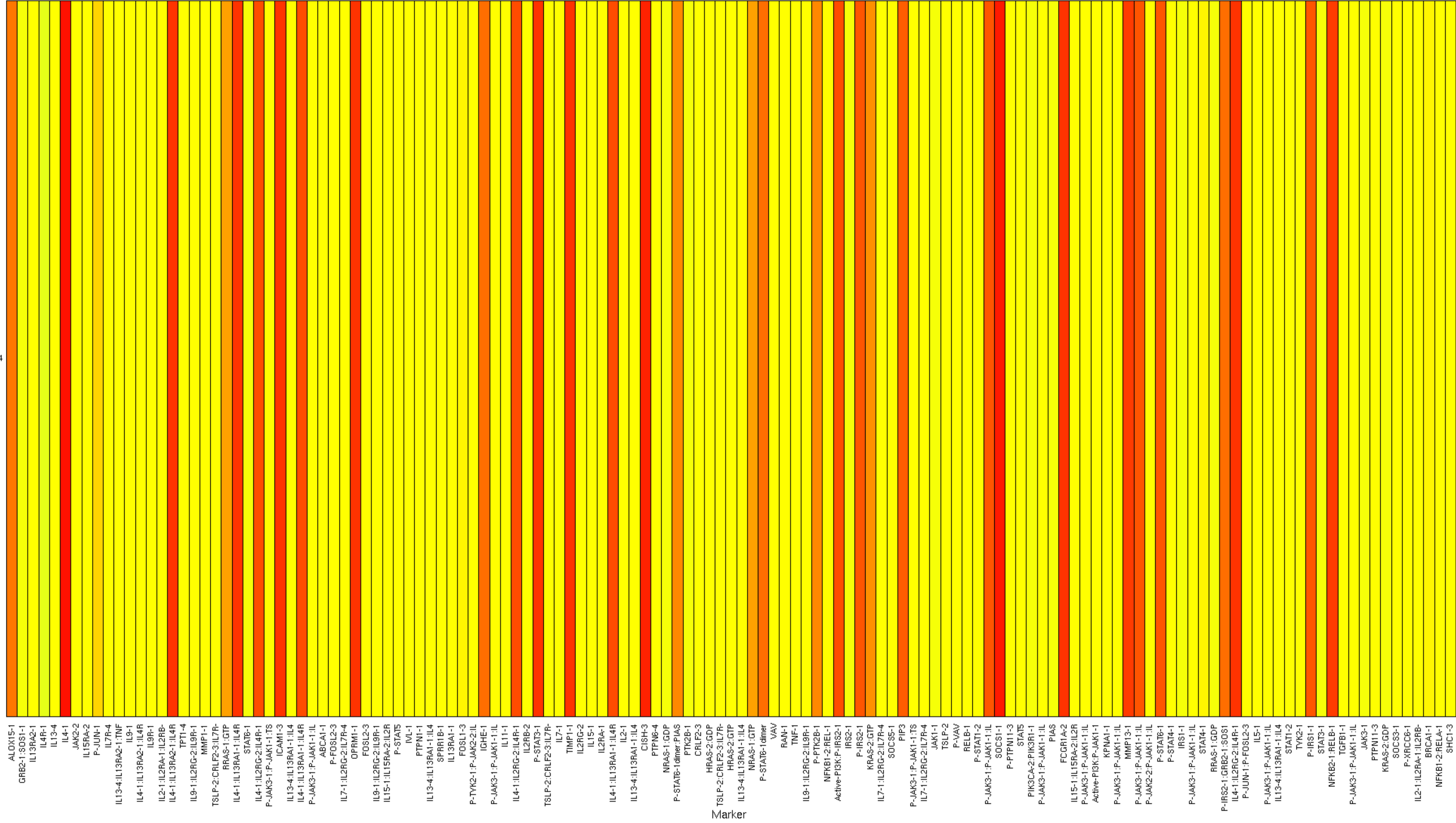


Marker Ratios (Log2 Of Geo Mean) bysummary_readout_L3.tsv

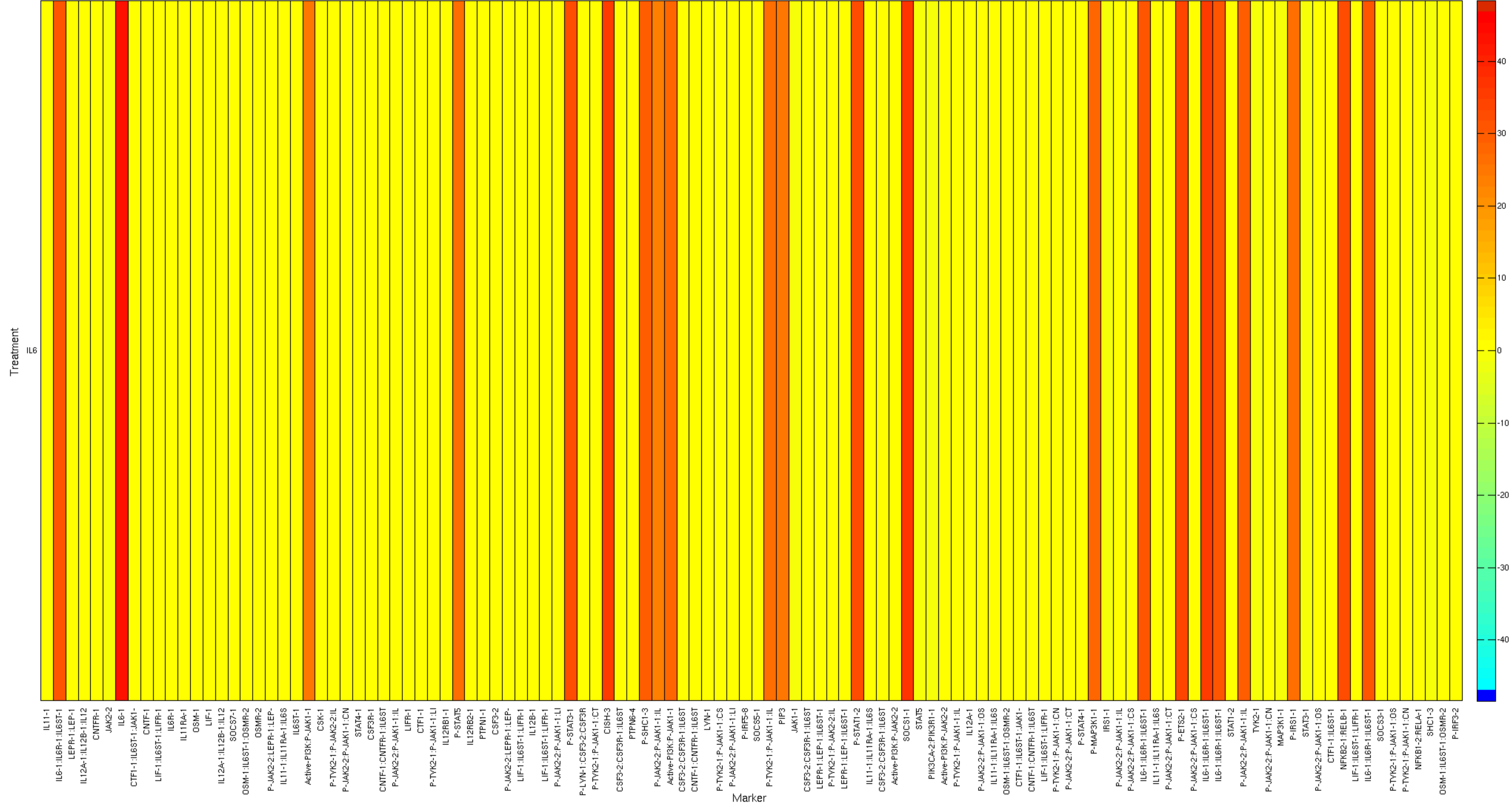


Marker Ratios (Log2 Of Geo Mean) bysummary_readout_L4.tsv

Treatment
IL4

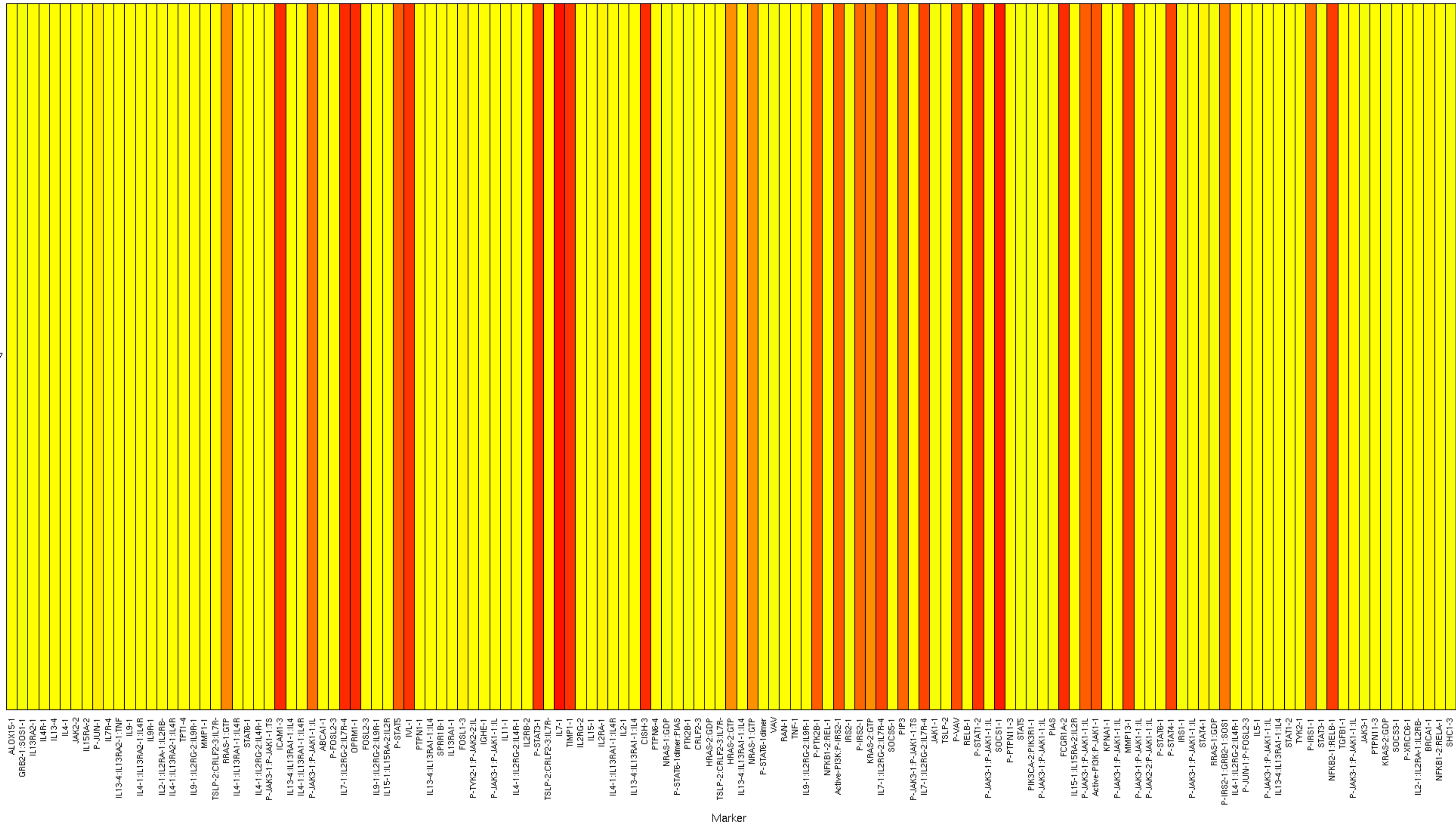


Marker Ratios (Log2 Of Geo Mean) bysummary_readout_L6.tsv



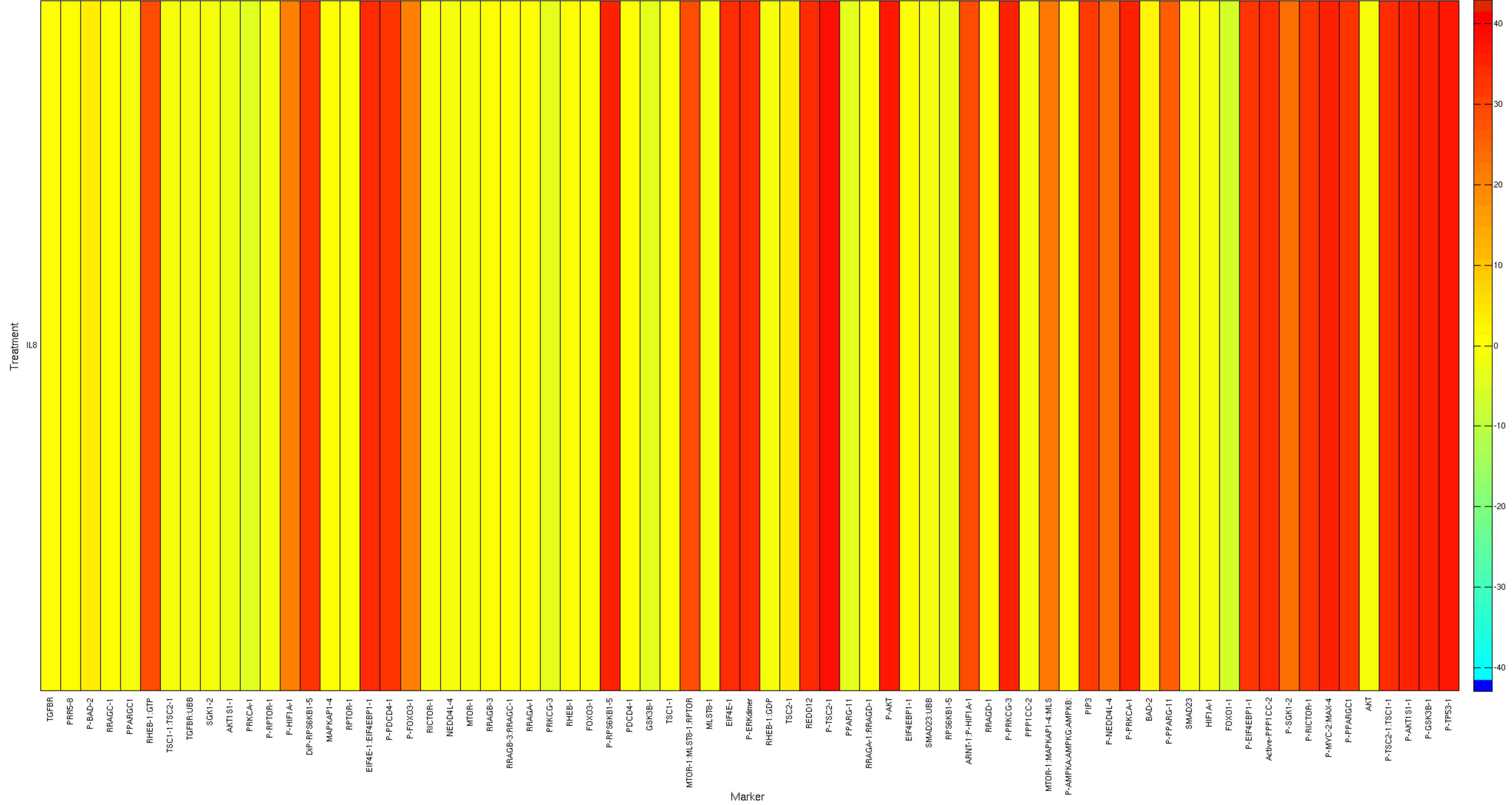
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_L7.tsv

Treatment
IL7

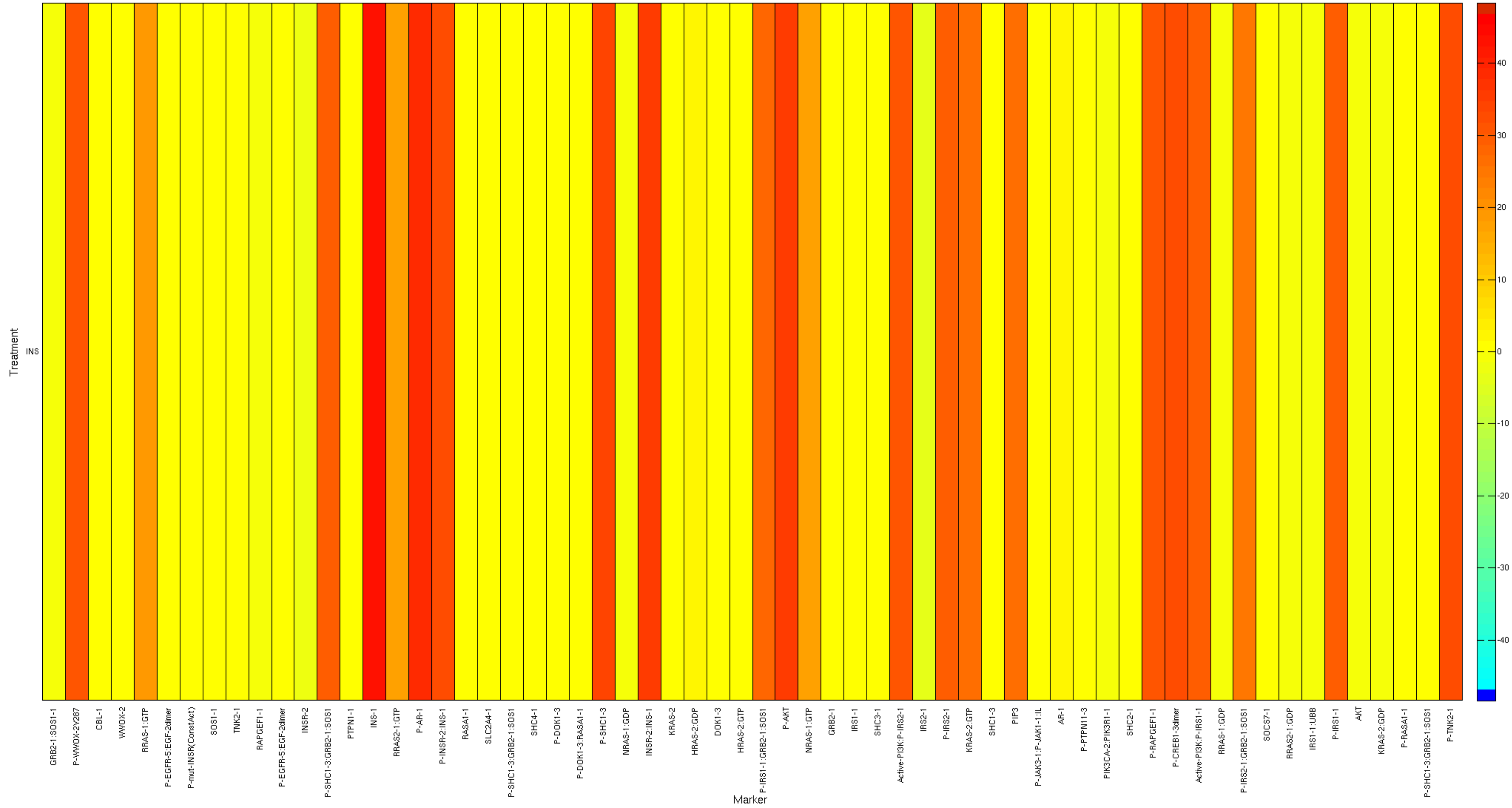


Marker

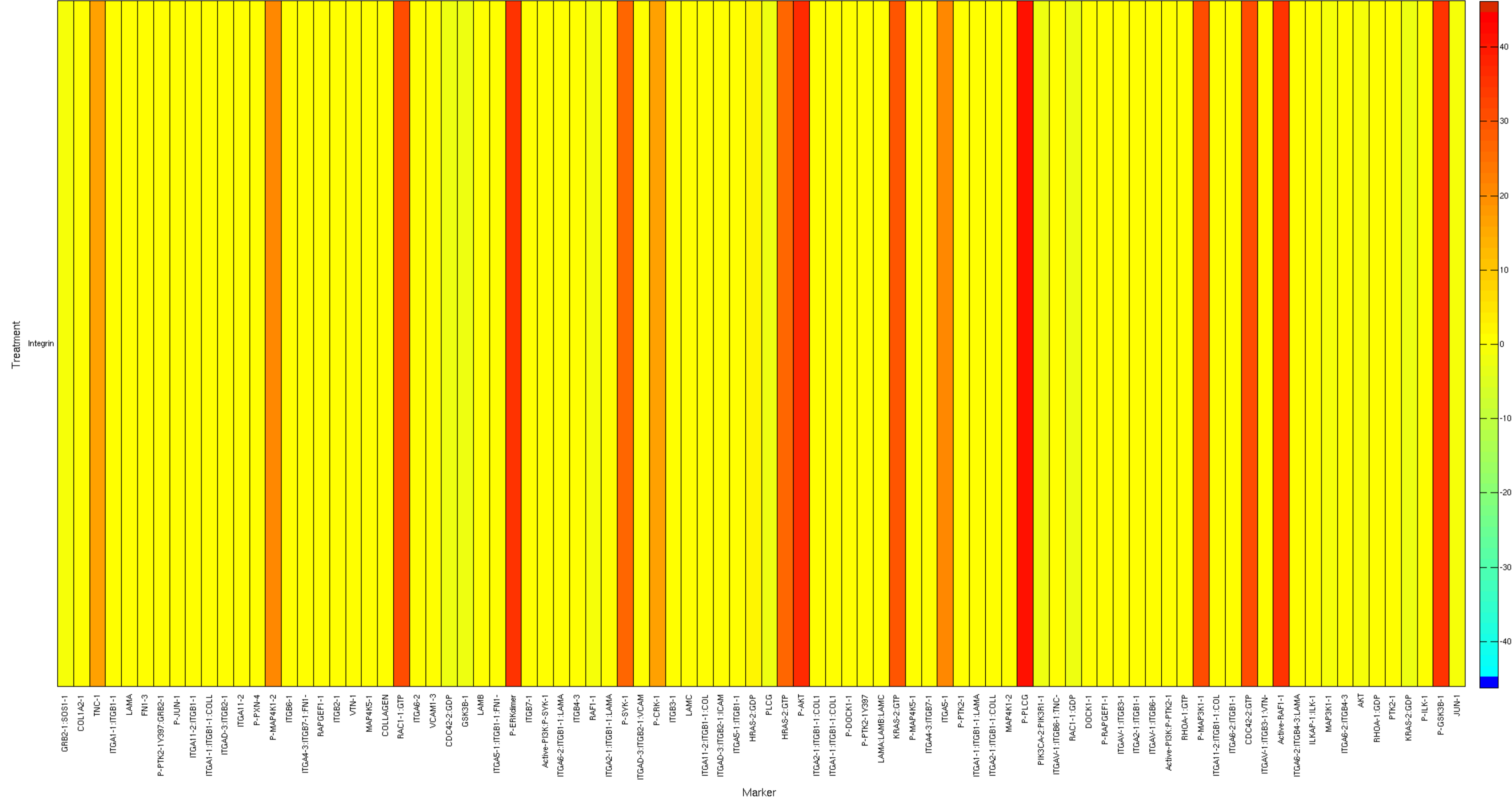
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_L8.tsv



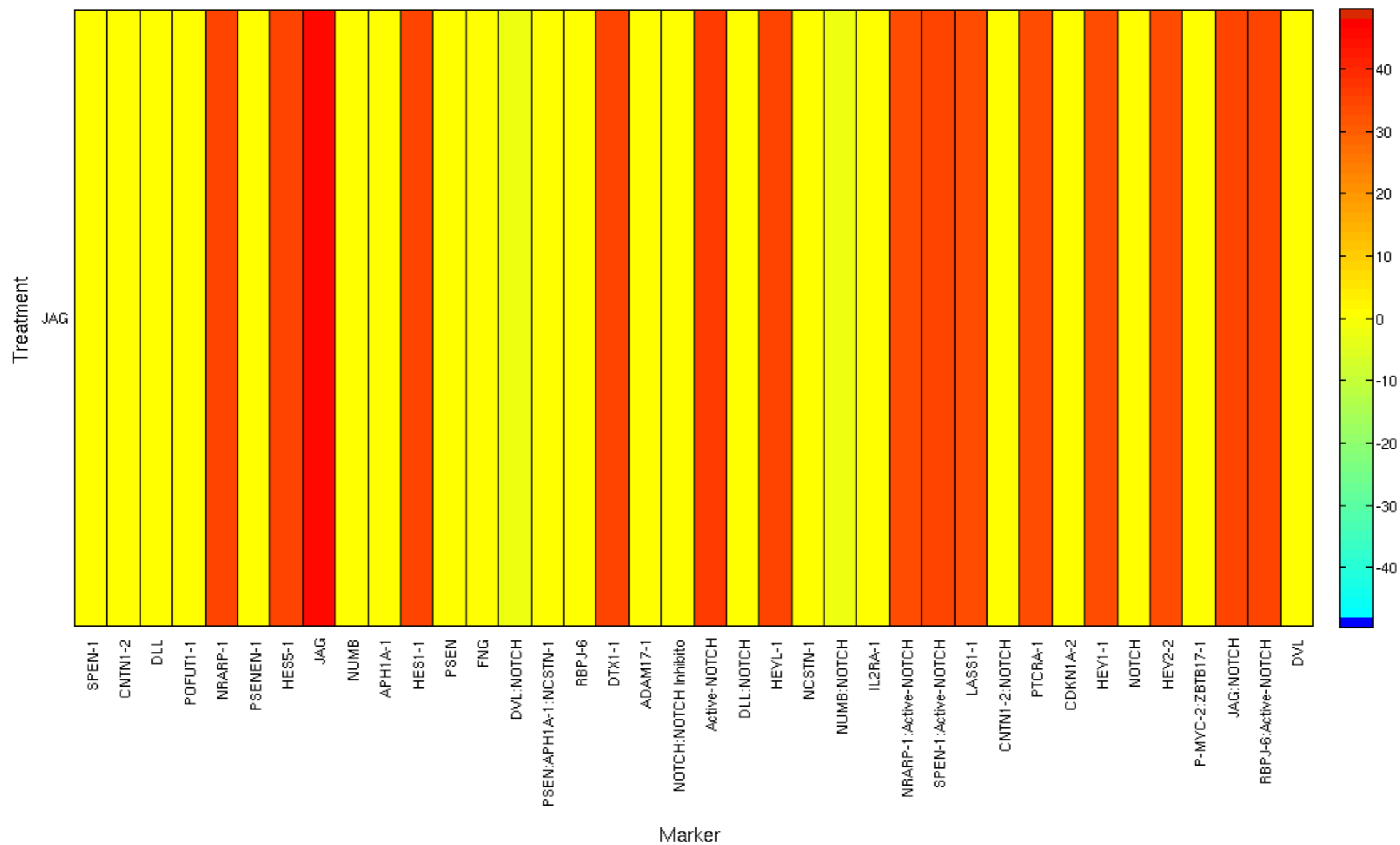
Marker Ratios (Log2 Of Geo Mean) bysummary_eadout_NS.tsv



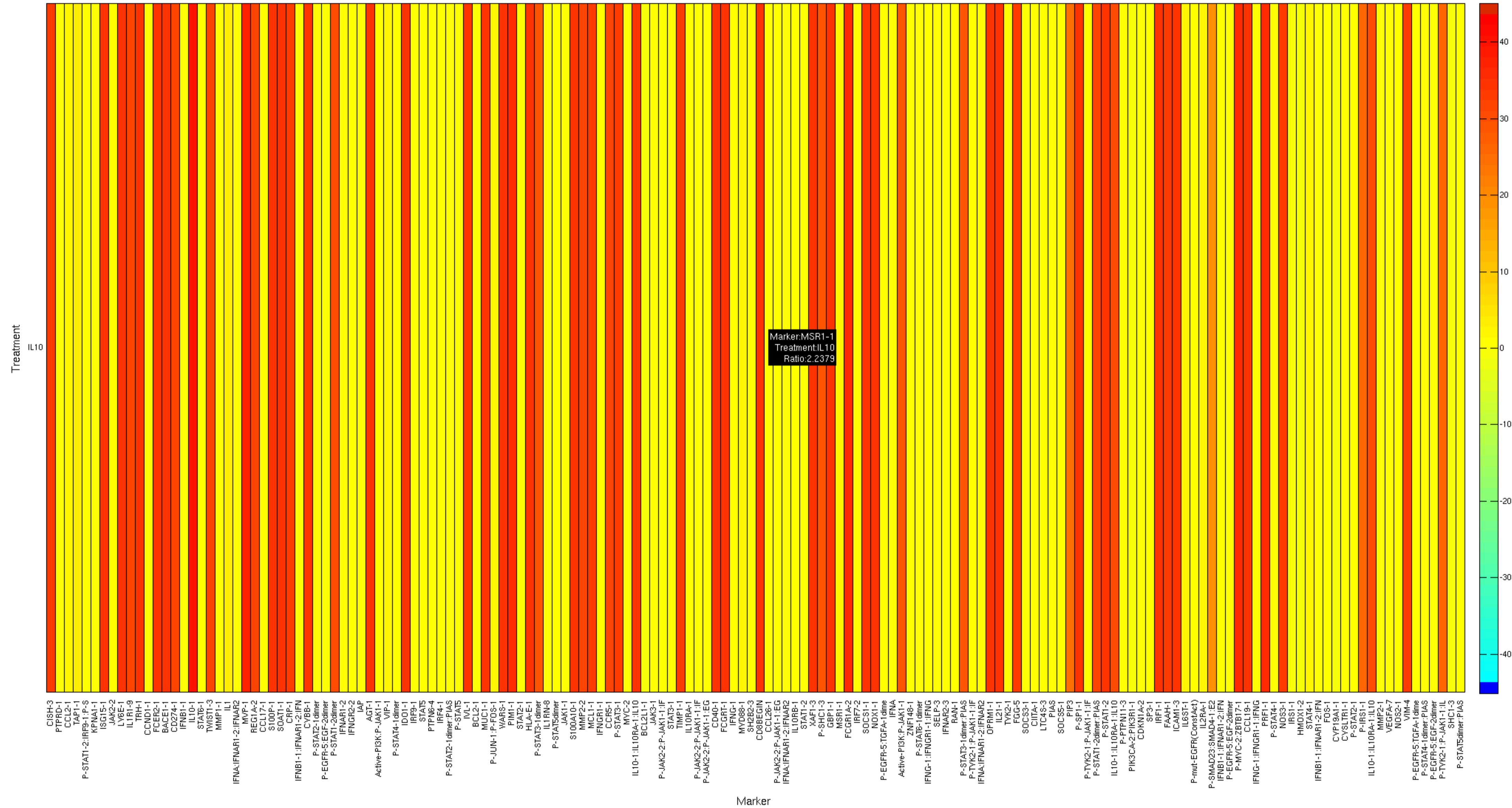
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_integrin.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_JAG.tsv

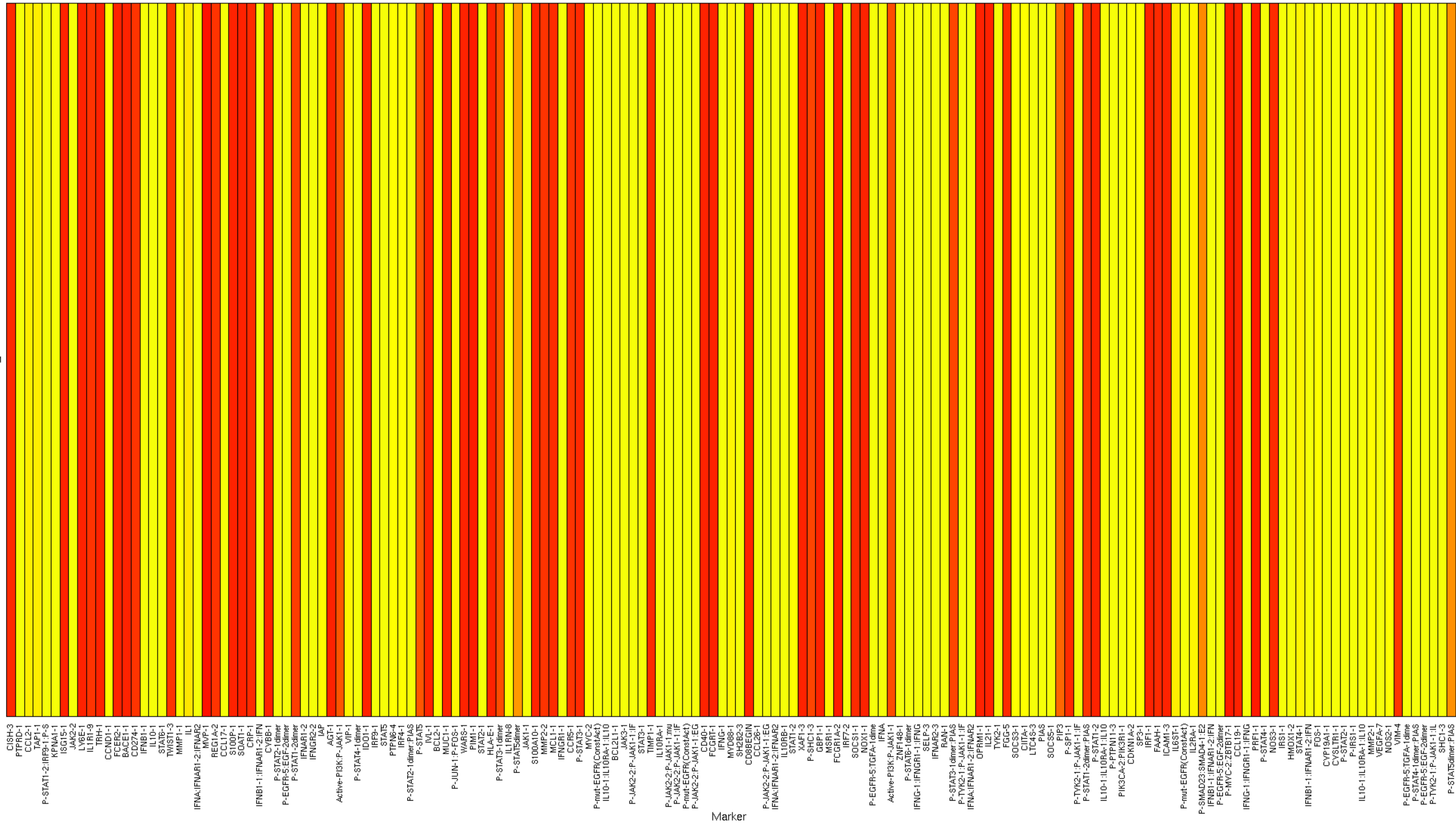


Marker Ratios (Log2 Of Geo Mean) bysummary_eadout_L10.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_eadout_L11.tsv

Treatment
IL11

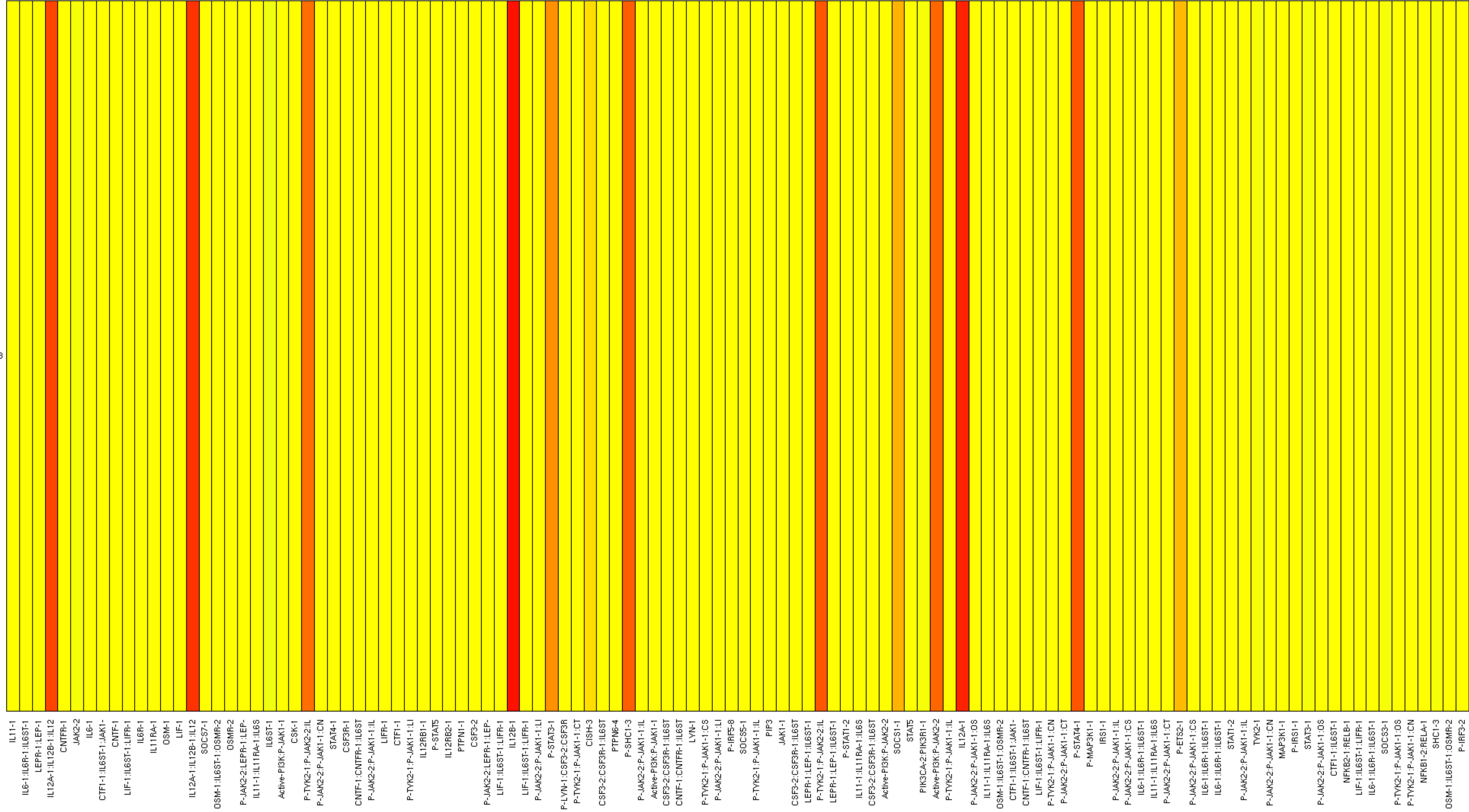


Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_readout_L12A.tsv

Treatment

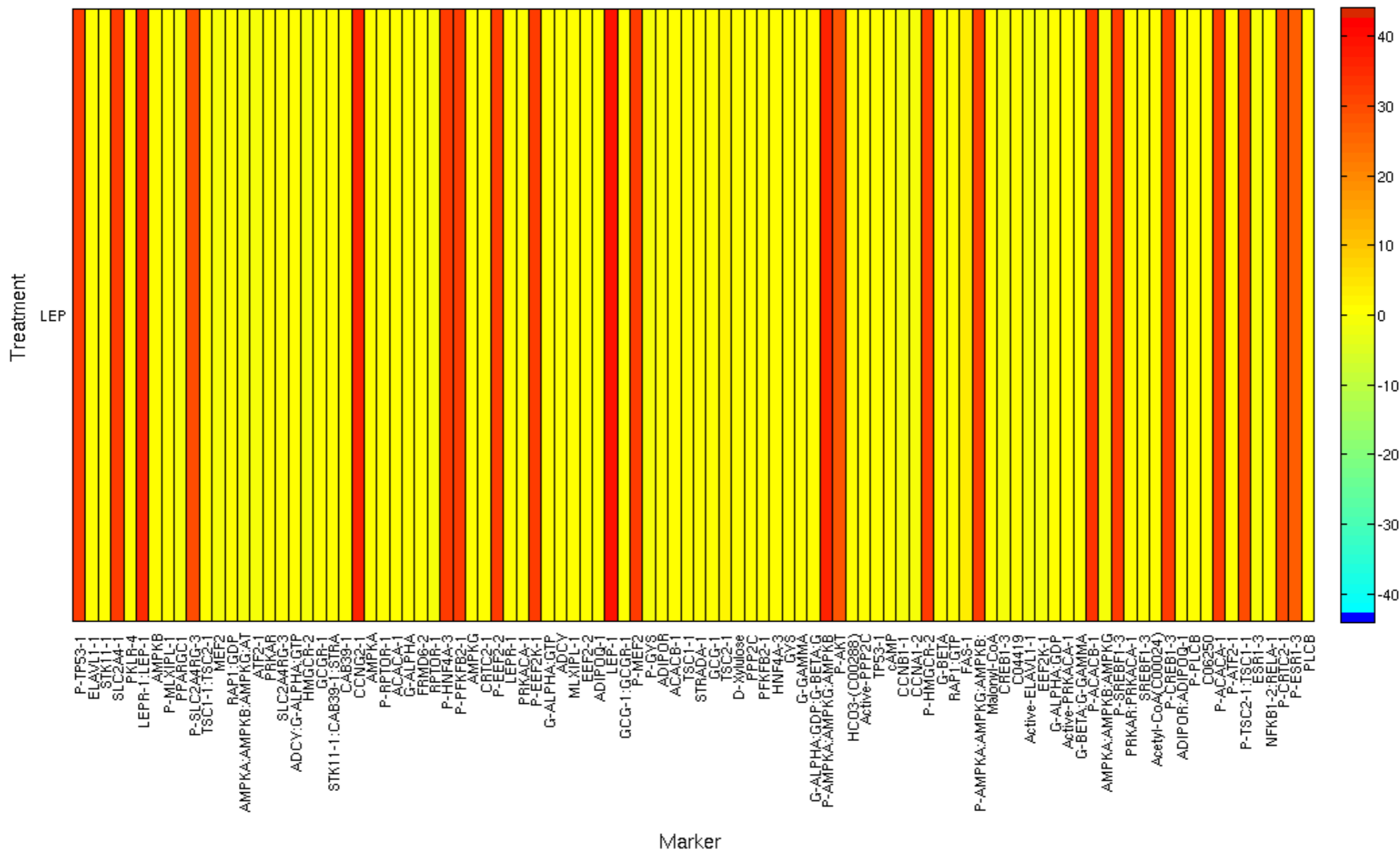
IL12A:IL12B



Marker



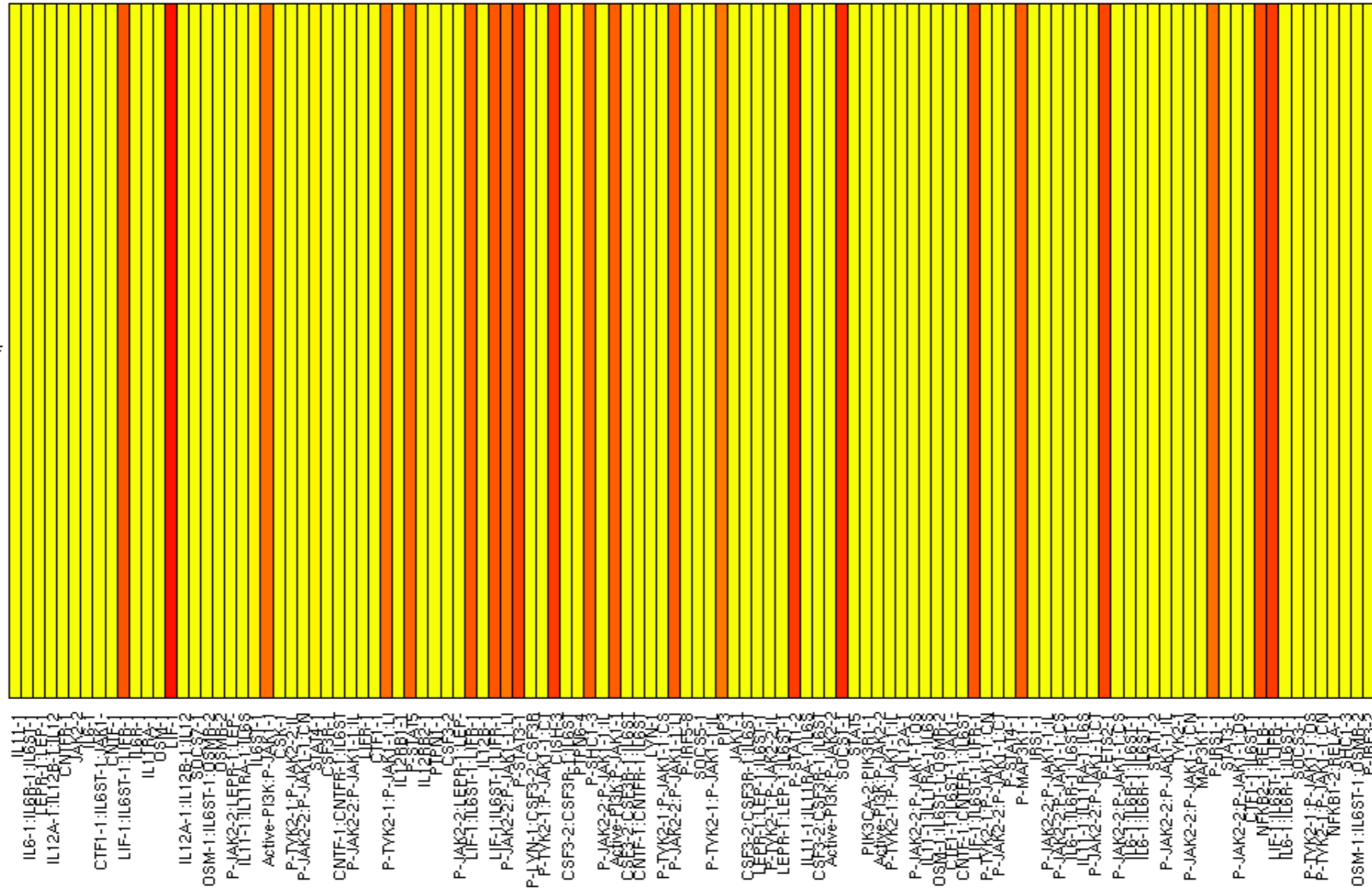
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_EP.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_LIF.tsv

Treatment

LIF



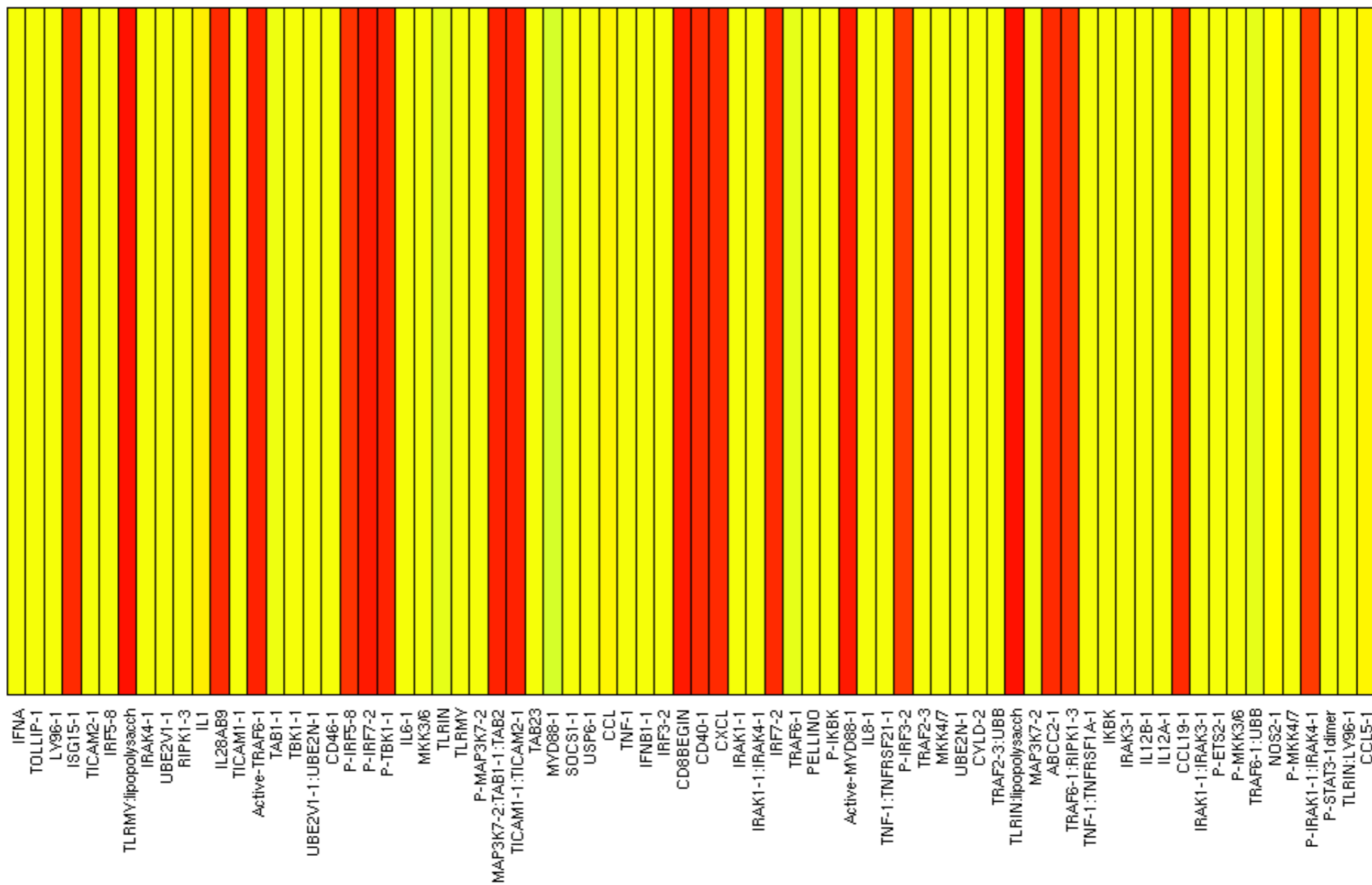
Marker



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_lipoplysaccharide.tsv

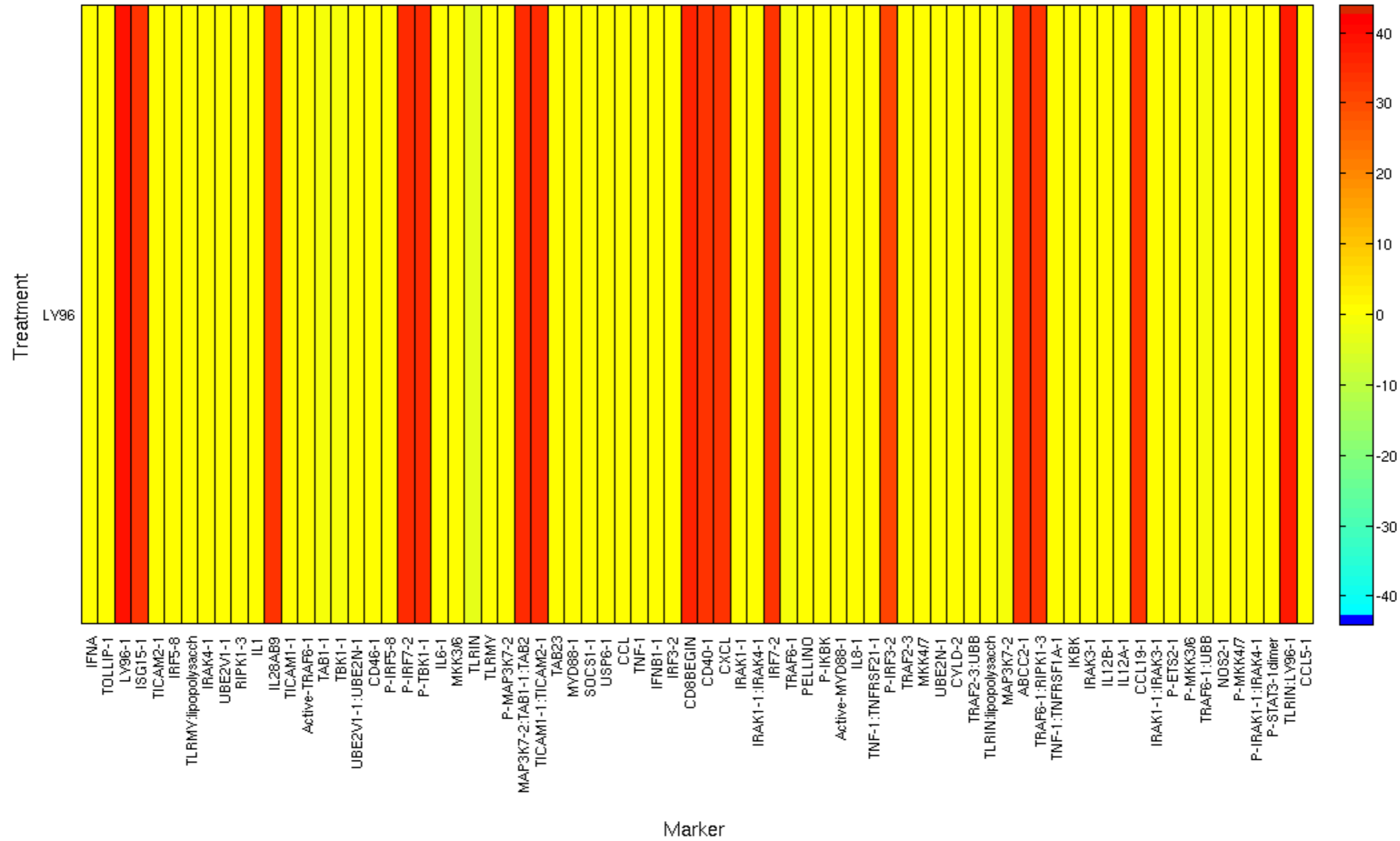
Treatment

lipopolysaccharide



Marker

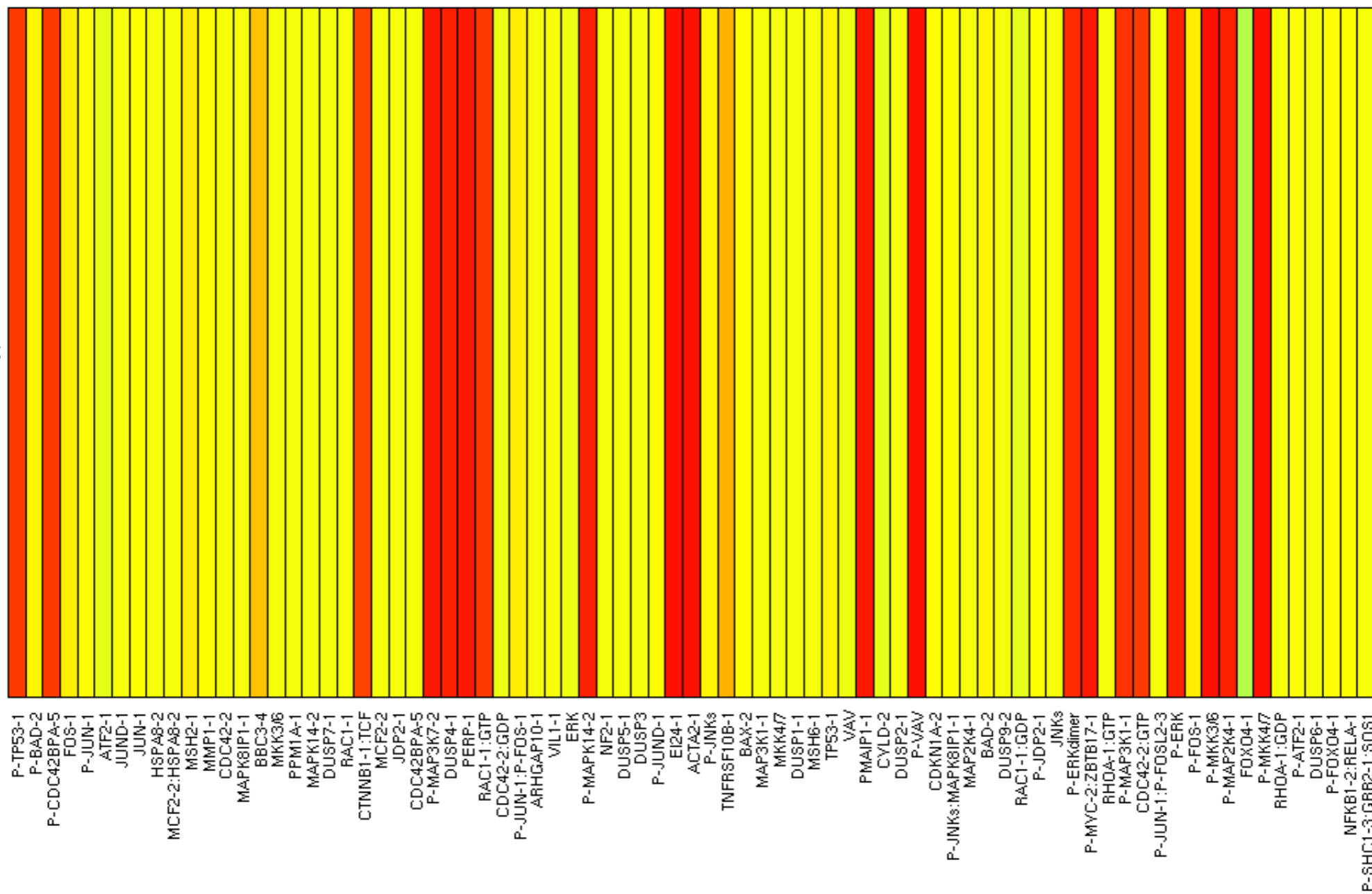
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_Y96.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_p38MAPK.tsv

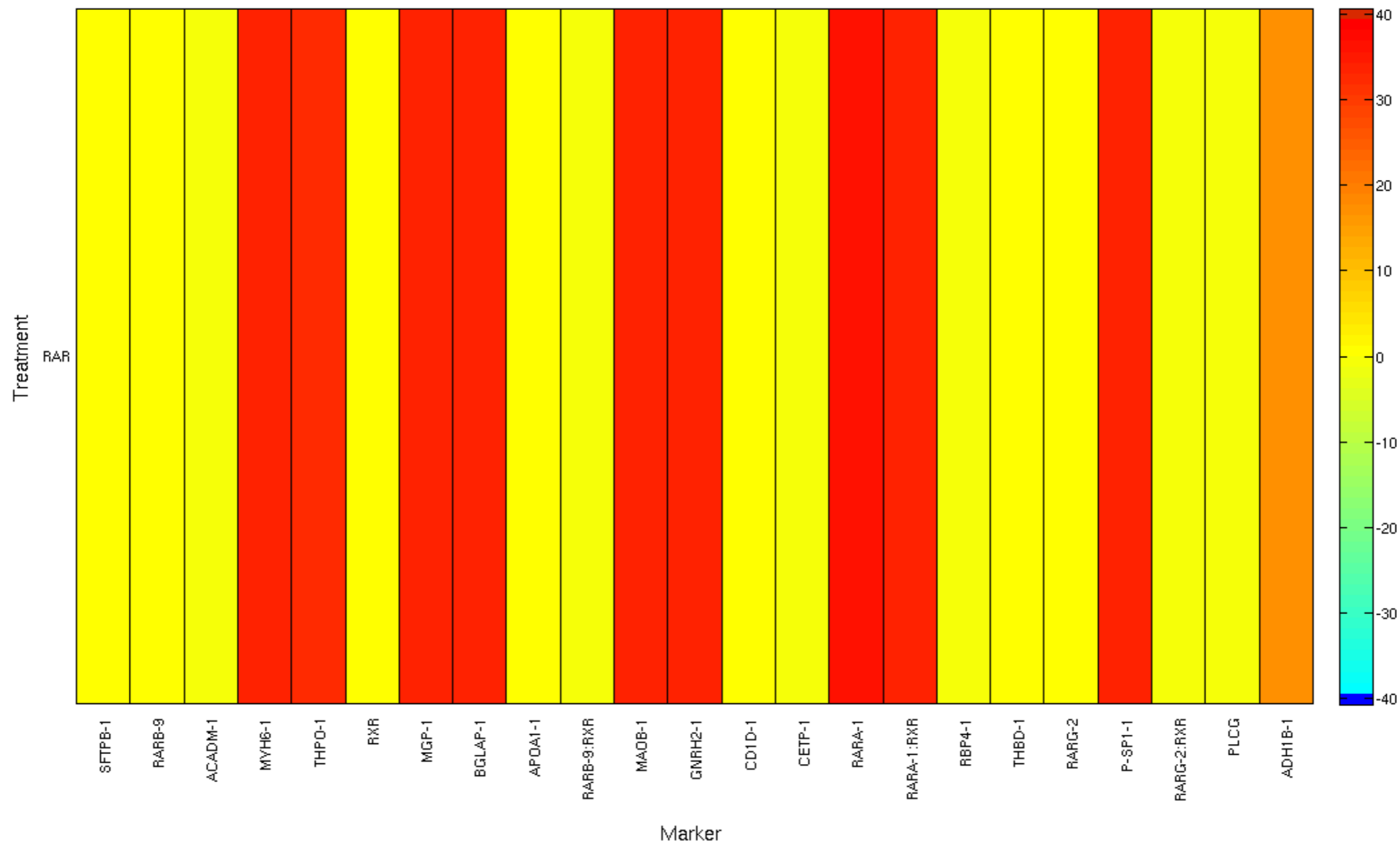
Treatment

p38MAPK

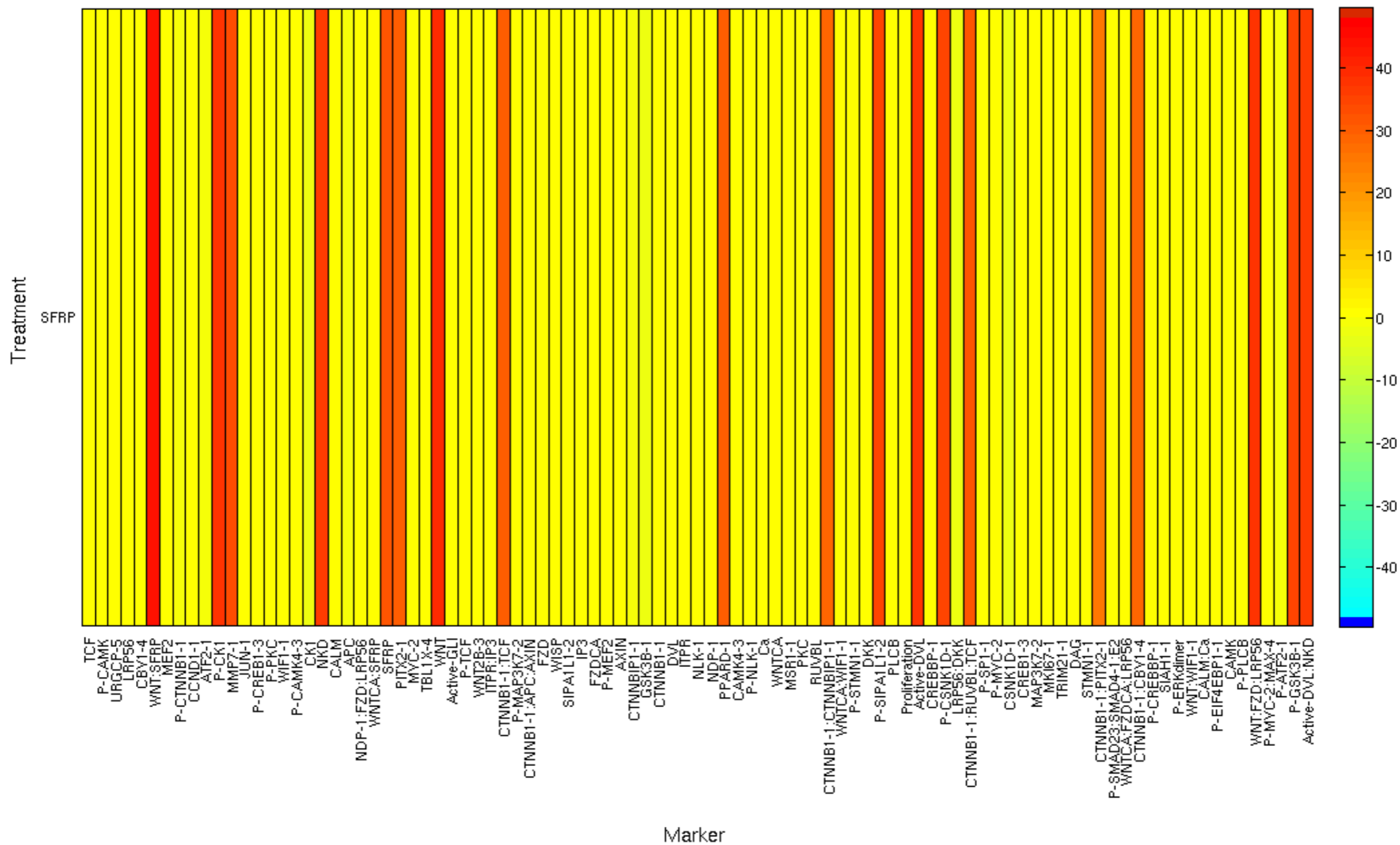


Marker

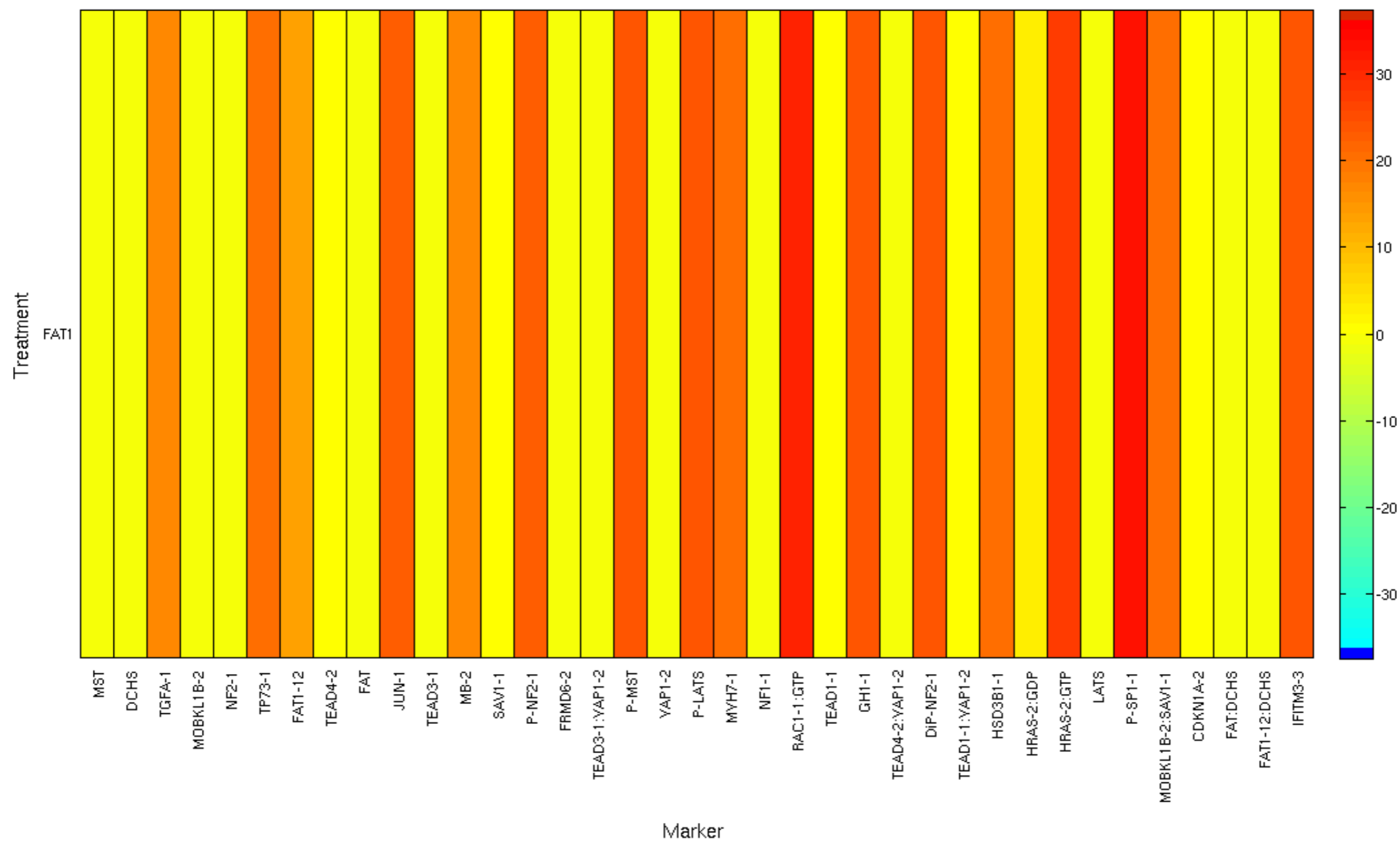
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_RAR.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_SFRP.tsv



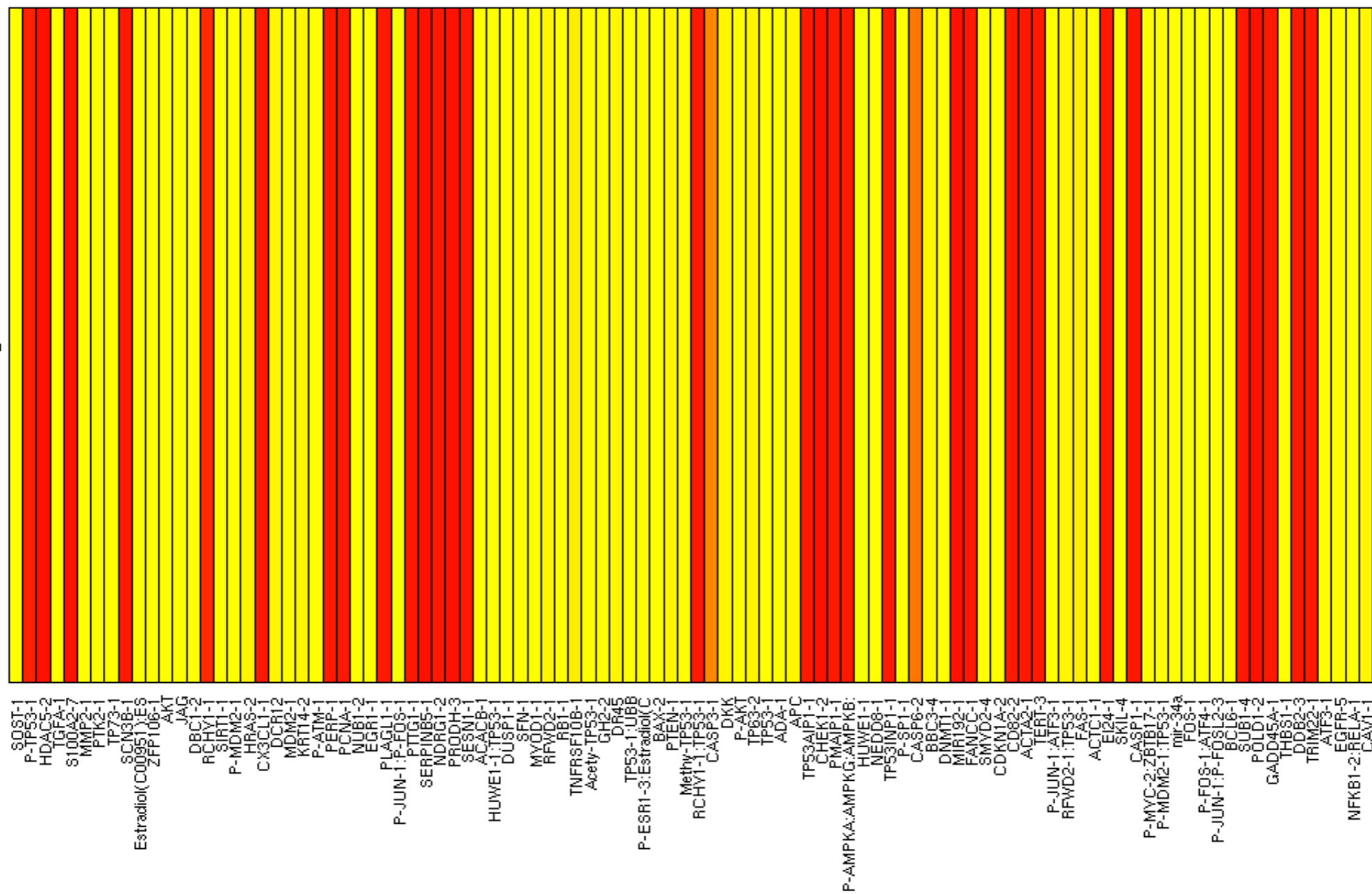
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_S.WH.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_p53.tsv

Treatment

TP53activation

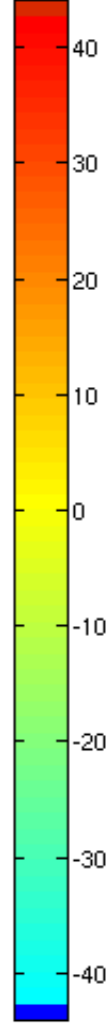
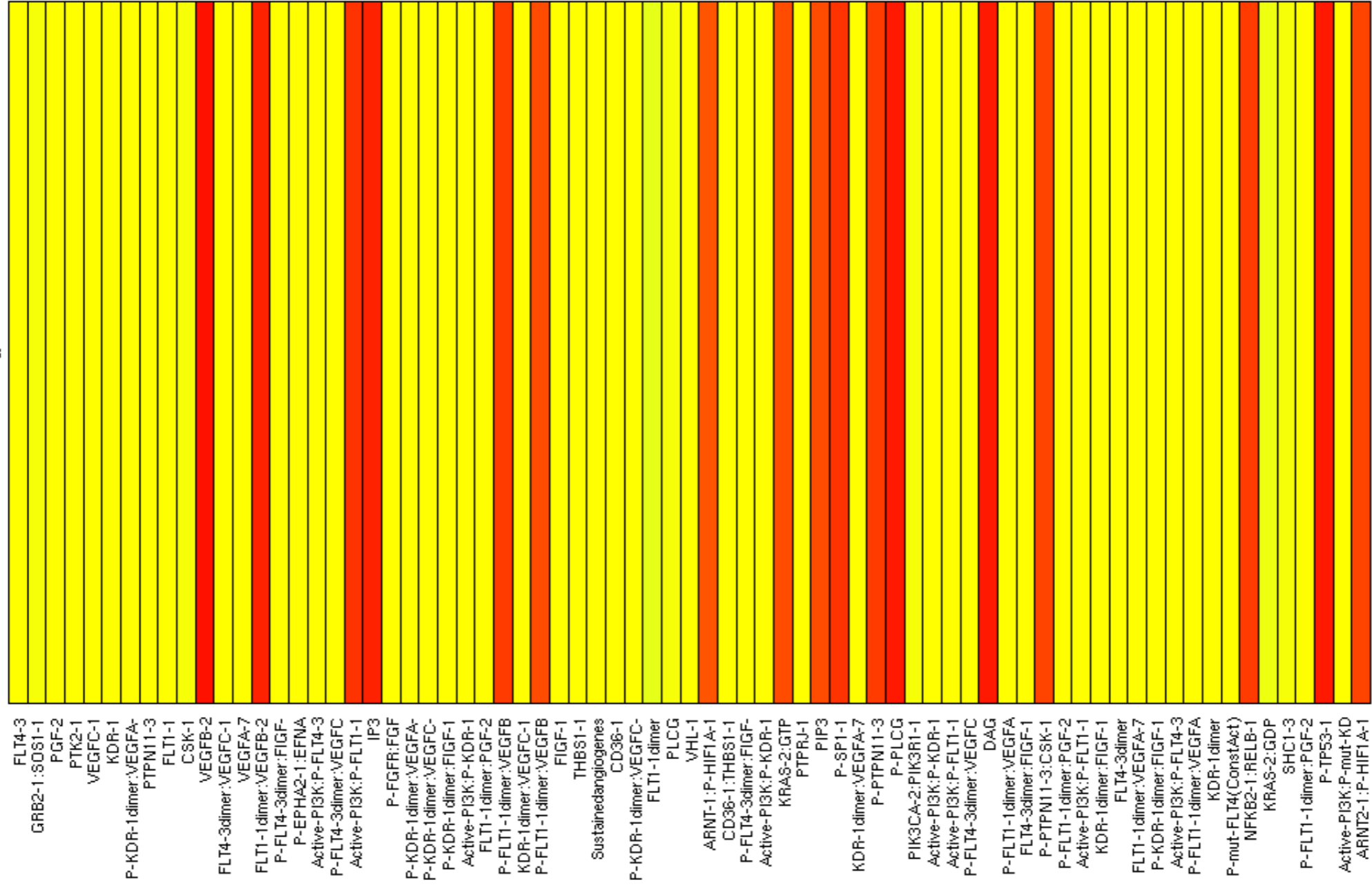


Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_readout_VEGFB.tsv

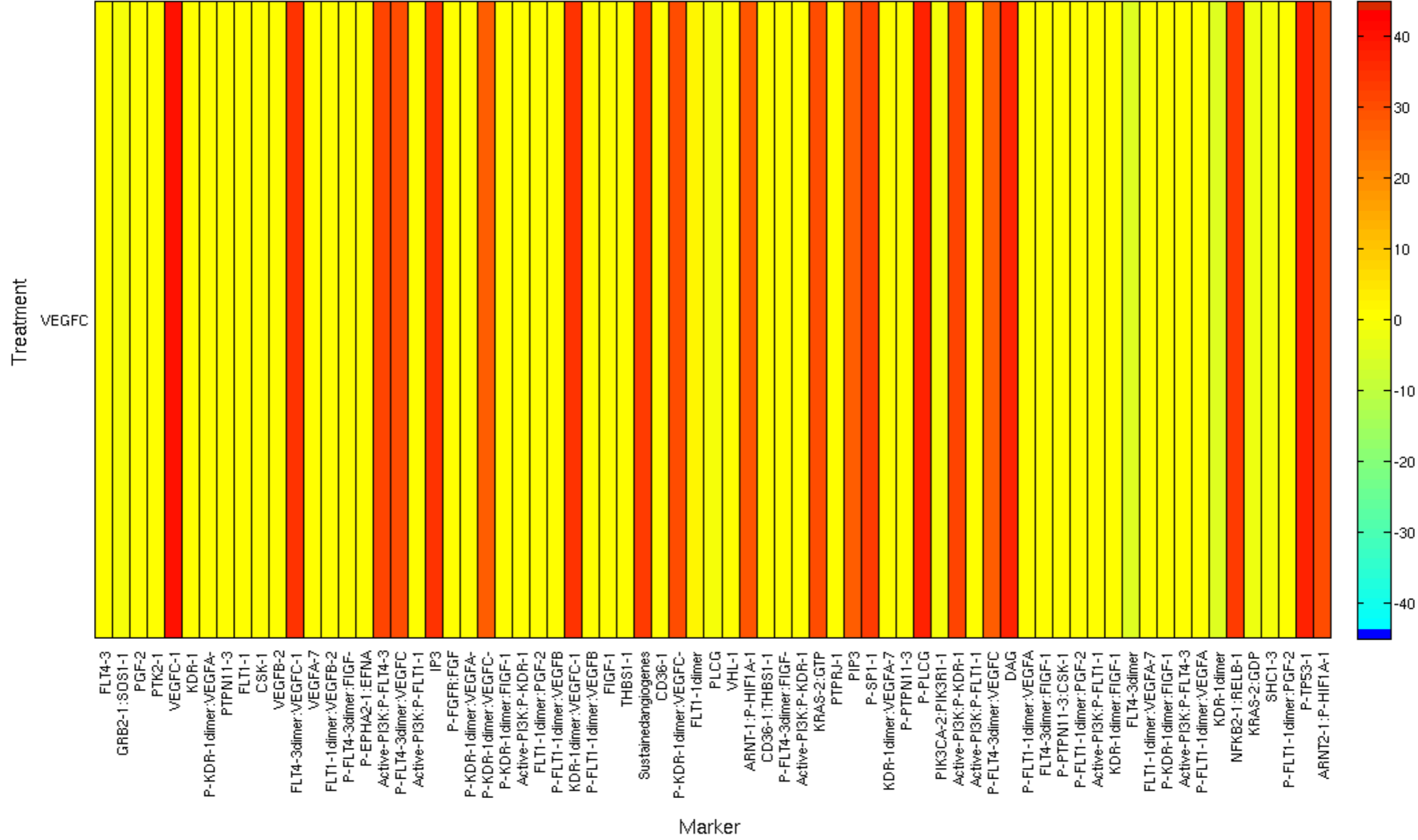
Treatment

VEGFB



Marker

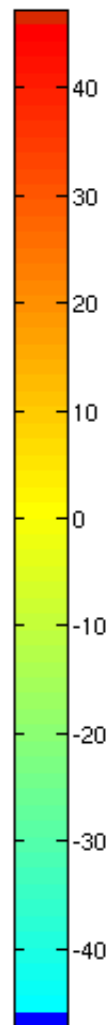
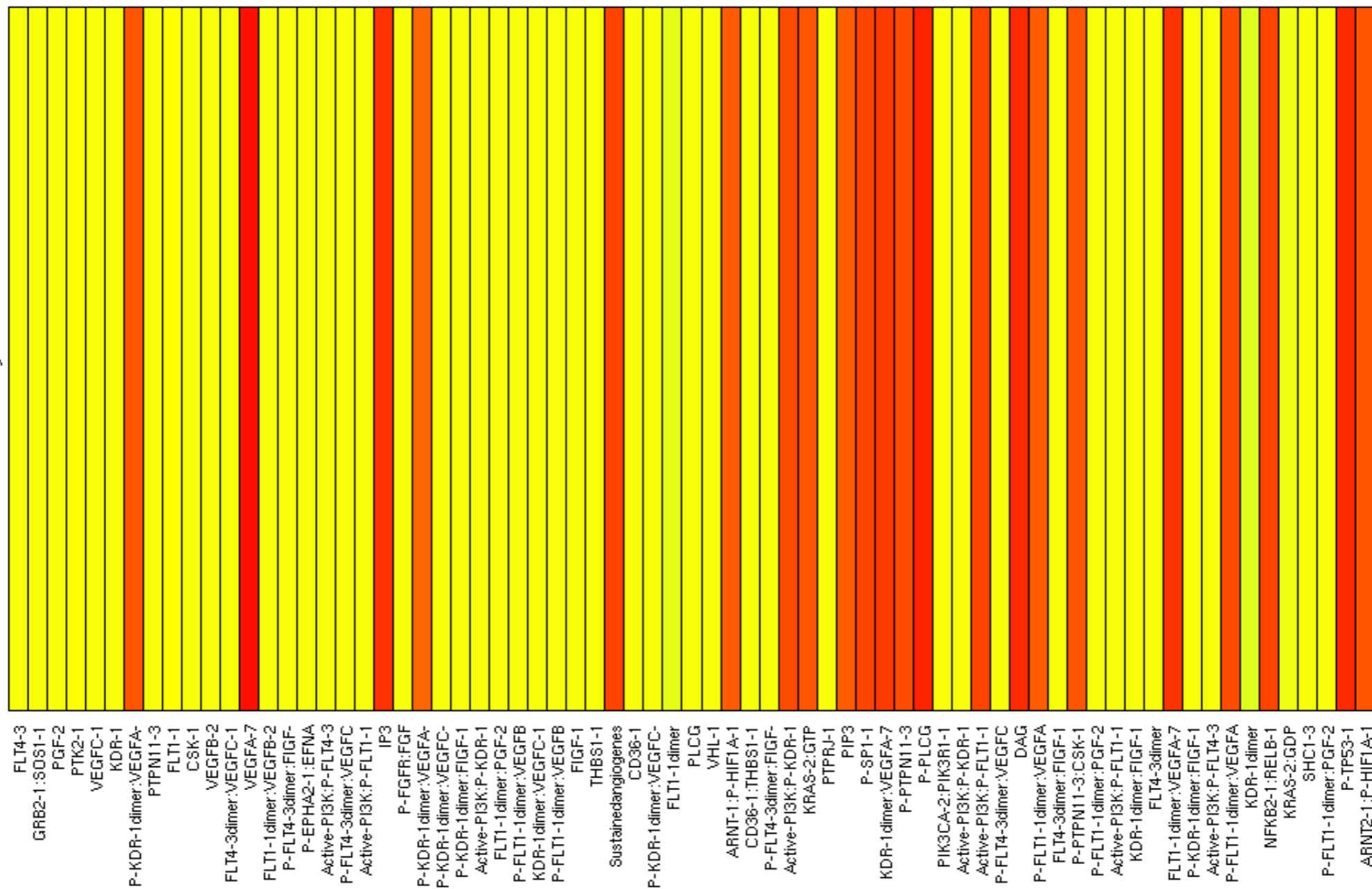
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_VEGFC.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_VEGFA.tsv

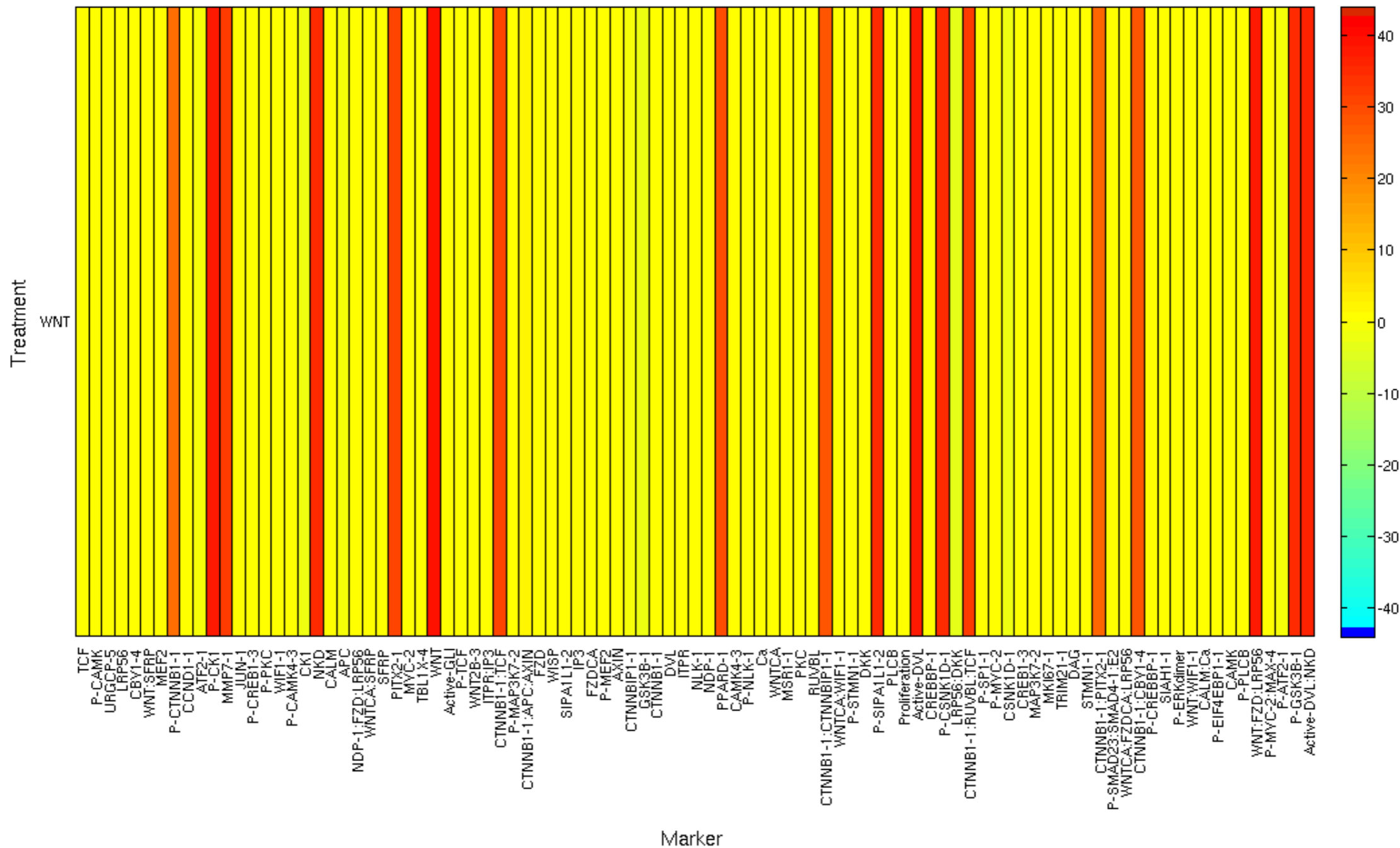
Treatment

VEGFA



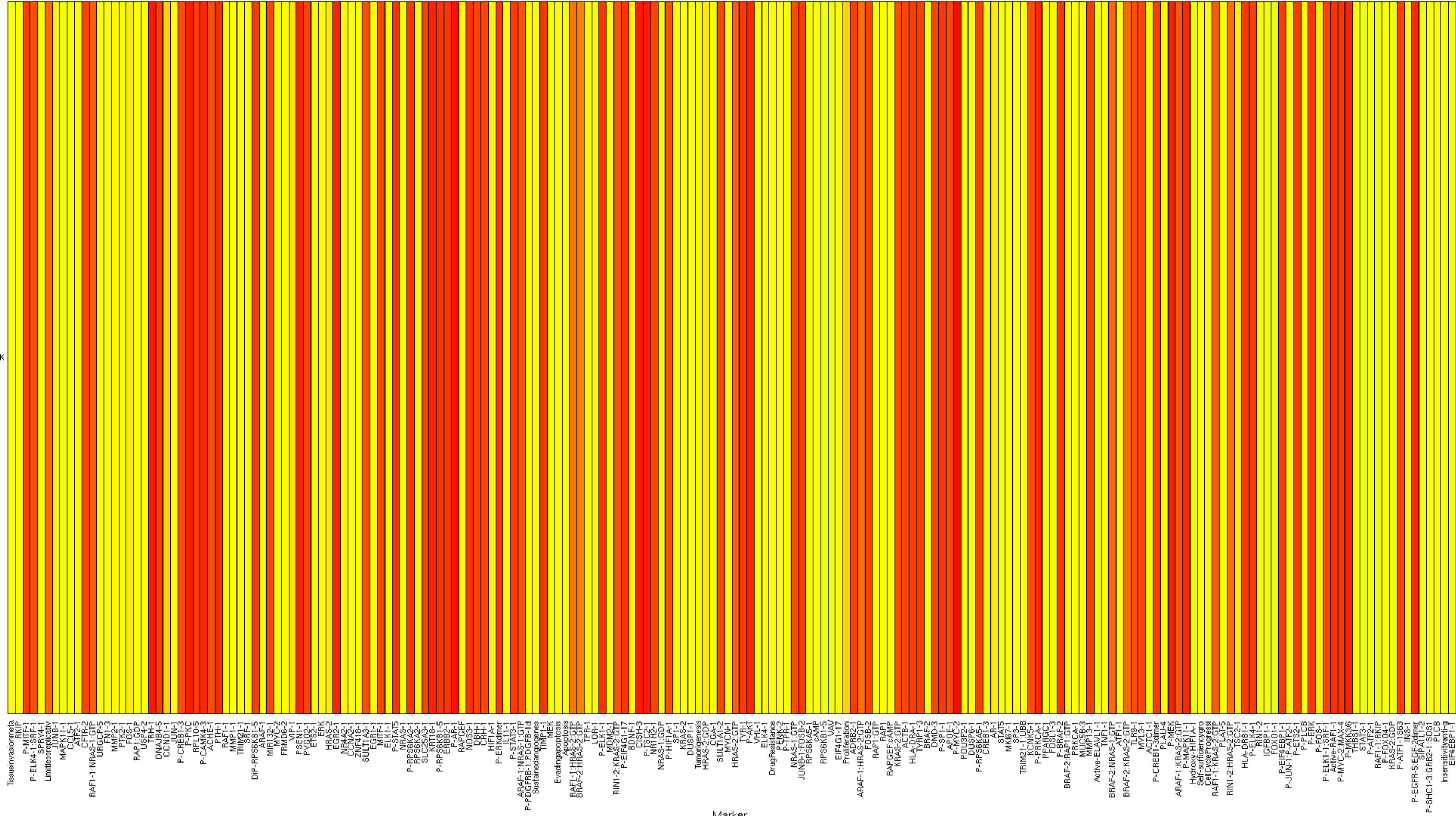
Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_readout_WNT.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_M_APK.tsv

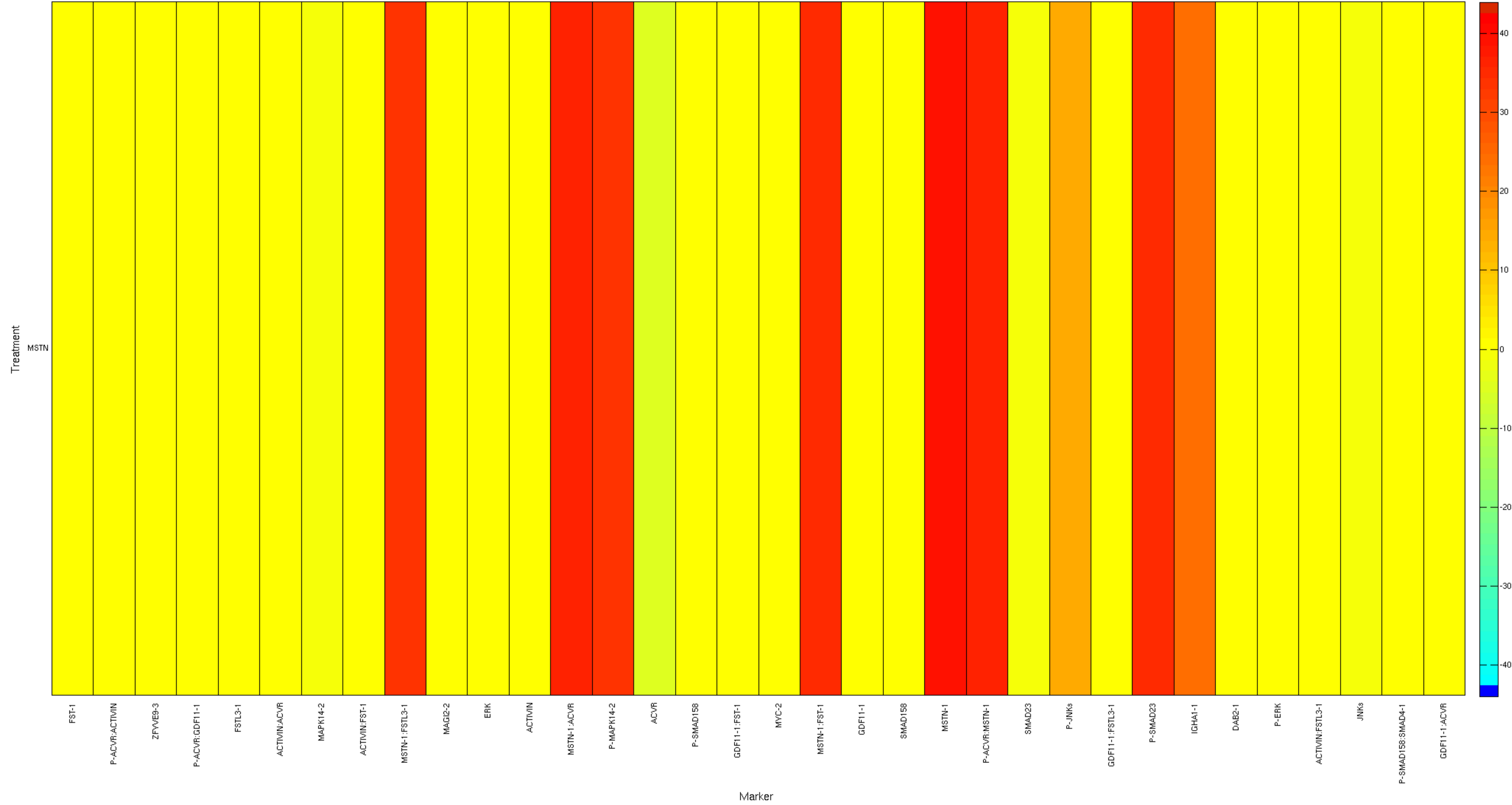
Treatment
MAPK



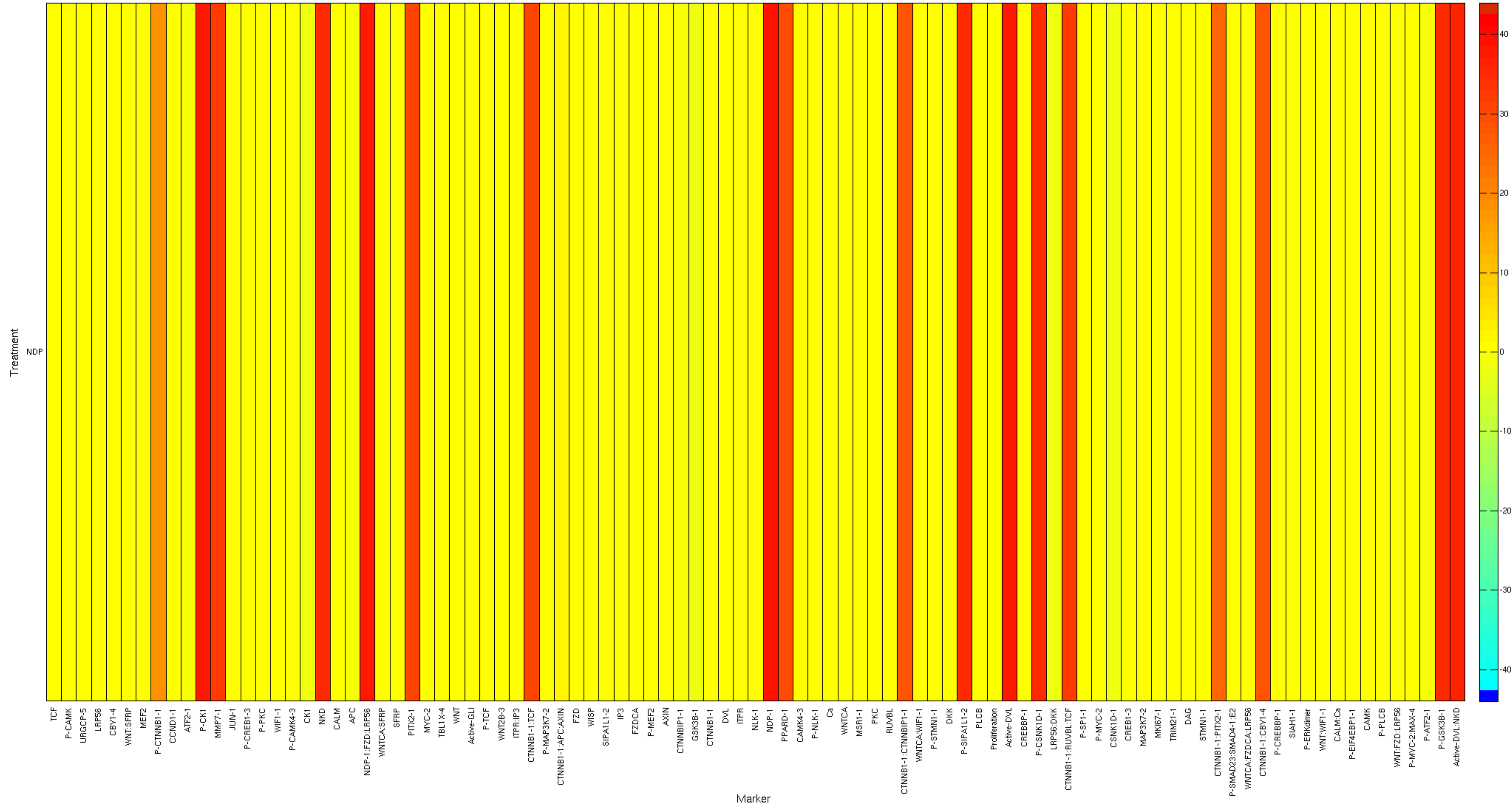
Tissue/invivo/mets
P-MITF-1
P-ELK4-1-SRF-1
SPRY4-1
Limitless/replicativity
MUC1-1
MUC2-1
ATF2-1
CFTR-2
RAF1-1:NRAS-1-GTP
URCP-5
MMP-3
MMP-13
PTK2-1
FOS-1
RAP1-GDP
USP4-2
DNMT3A-1
CCND1-1
JUN-1
P-CREB1-3
P-PKC
RPL10-5
P-CAMK2-1
ACEH1
PTH-1
RAFI-1
MMP1-1
TRIM21-1
MMP2-1
DIP-RP86KB1-5
ARAF-1
MIR132-1
MYC-2
FRMD6-2
PSEMI-1
PSEMI-1
PVGD2-1
ETS2-1
ERK
HRAS-2
MEG2-1
CCNA3-1
CCNA3-1
ZNF418-1
SULT1A3-1
EGRI-1
MMP-1
EML1-1
P-STAT5
NRAS-1
P-RP86KA2-1
RP86KA2-1
SLC25A3-1
P-RP86KB1-5
ERRBB2-1
P-AR-1
RAGEF
NOS3-1
ORH1
ORH1
HIF1A-1
P-ERKdimer
LL11-1
P-STAT3-1
ARAF-1:NRAS-GTP
P-P-GRB2-1
P-GRB2-1
Substrate/Target
TIMP1-1
MEK
Evading/apoptosis
Apoptosis
BAF1-1:HRAS-3-GTP
BRAEF-2:HRAS-3-GTP
TPR-1
LOR-1
P-ELK1-1
MDM2-1
P-EIF4G1-17
BDMF-1
CISH-3
P-TSC2-1
NTRH2-1
MPAS-1-GDP
P-HIF1-1
SP1-1
KRAS-2
DUSP1-1
Tumorigenesis
HRAS-2-GDP
SULT1A1-2
MYCN-1
HRAS-2-GTP
TVR1-1
P-AKT
ELK4-1
ELK4-1
DrugResistance
P-ENK-2
P-TFR1
NRAS-1-GTP
JUNB-1-DSE2
RP86KAMP
RP86KB1-5
VAV
EIF4G1-17
PROM1-1
PROM1-1
ARAF-1:HRAS-2-GTP
FOSB-2
RAF1-GTP
RAF1-GTP
RAGEF-CAMP
KRAS-1-GTP
ACTB-1
HLA-DRA-1
TYRPT-3
BRAF-2
DMD-3
FAPD-1
FAPD-1
P-MYC-2
P-POU3F2-1
DUSP8-1
P-RP86KA5-1
CREB3
STAT5
STAT5
MKI67-1
SP3-1
TRIM21-1-JUBB
P-PCWS-1
P-PCWS-1
PEAR1-1
FOSL1-3
P-BRAF-2
P-BRAF-2
PRKCA-1
MMP13-1
MMP13-1
MMP13-1
TNF1-1
Active-ELAV1-1
BRAF-2:NRAS-1-GTP
A1TF1-1
BRAF-2:KRAS-1-GTP
MVL3-1
MVL3-1
P-CREB1-3dimer
ACTC1-1
PLAU4
P-MMP6
ARAF-1:KRAS-2-GTP
P-MAPK11-1
Hydroxy-HIF1A-1
Self-sufficiency/cygro
CellCycleProgression
RAF1-1:KRAS-2-GTP
RINI-2:HRAS-2-GTP
TSC2-1
HLA-DRB1-1
P-ELK4-1
RINI-2
IGFBP1-1
EDVD1-1
P-EIF4EBP1-1
P-JUN1:P-ATF2-1
P-ETS2-1
P-PLCB
P-PLCB
P-PLCB
P-PLCB
P-ELK1-1-SRF-1
Active-RAF1-1
P-MYC-2:MAX-4
P-MKK3/6
P-MKK3/6
P-ATF2-1
P-ATF2-1
RAF1-1:RKIP
P-FOXO4-1
KRAS-2-GDP
P-A1F1-1S63
P-EGFR-5:EGF-2N3
SIPAT11-2
P-SH1-3:GRB2-1:SOS1
PLCB
Insensitivity/anti-g
EIF4EBP1-1

Marker

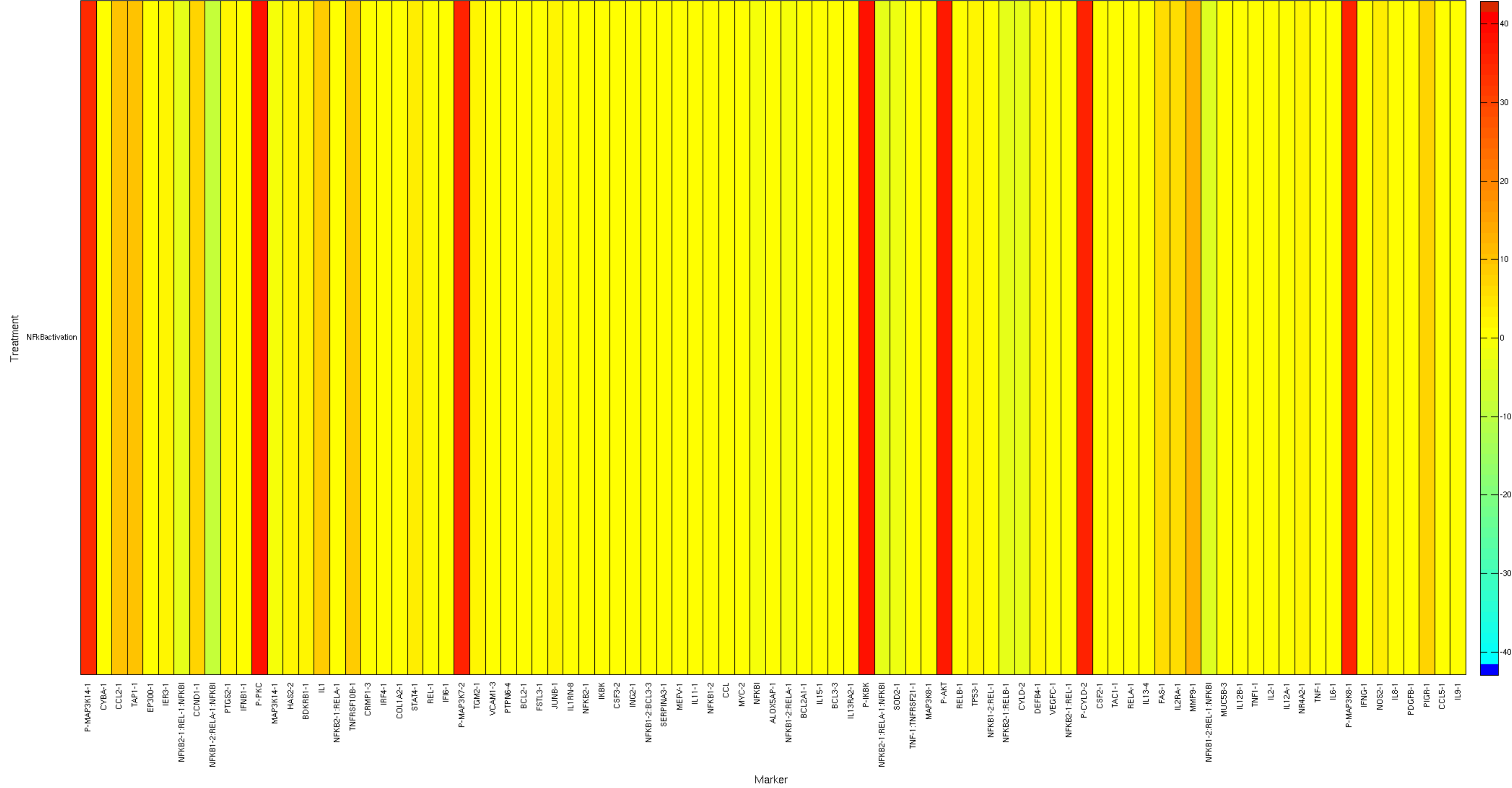
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_MSTN.tsv



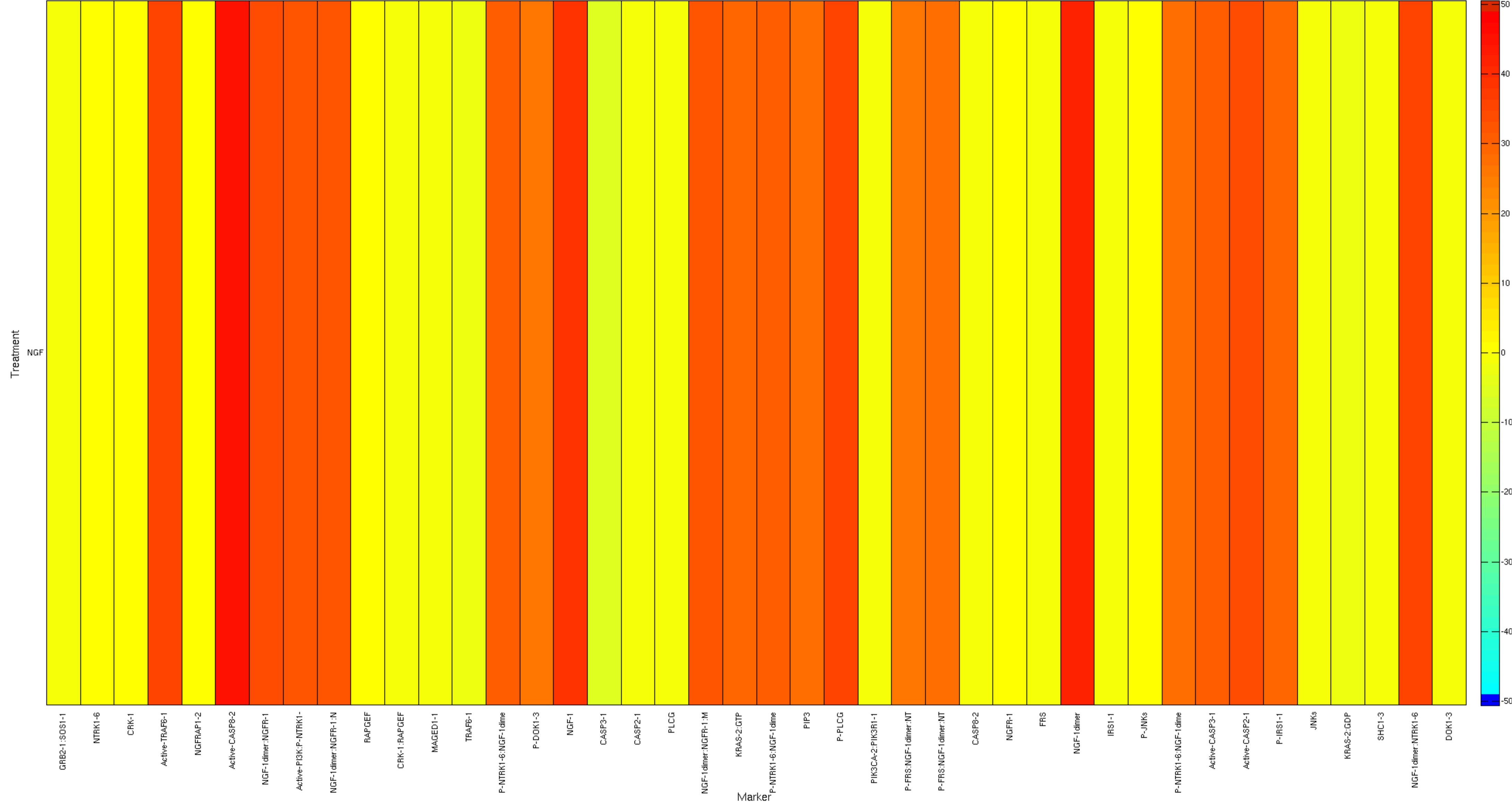
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_N_DP.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_N_FkB.tsv



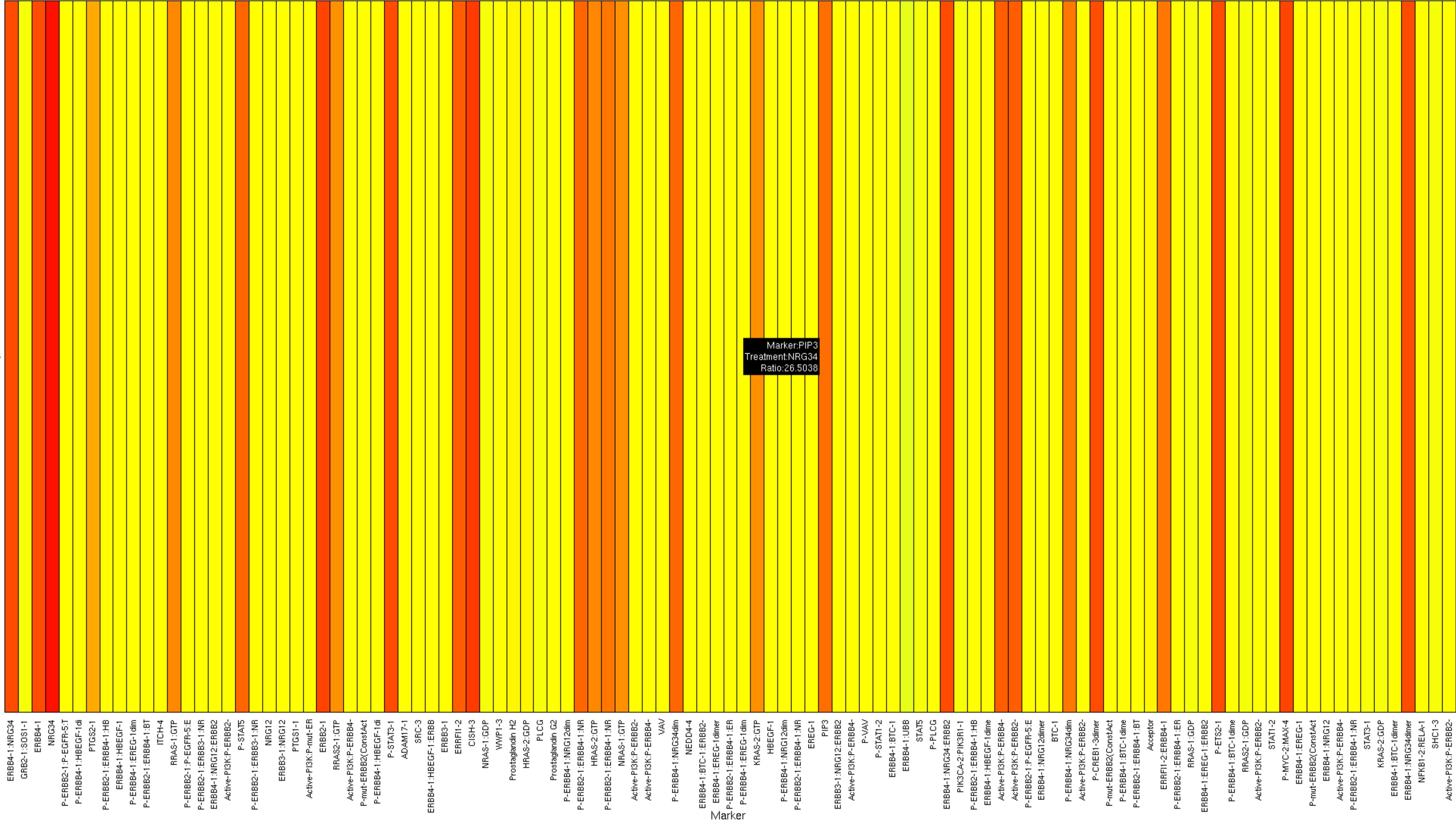
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_N_GF.tsv



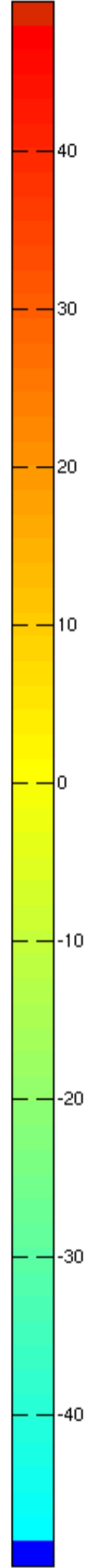
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_N_RG3_4.tsv

Treatment

NRG34



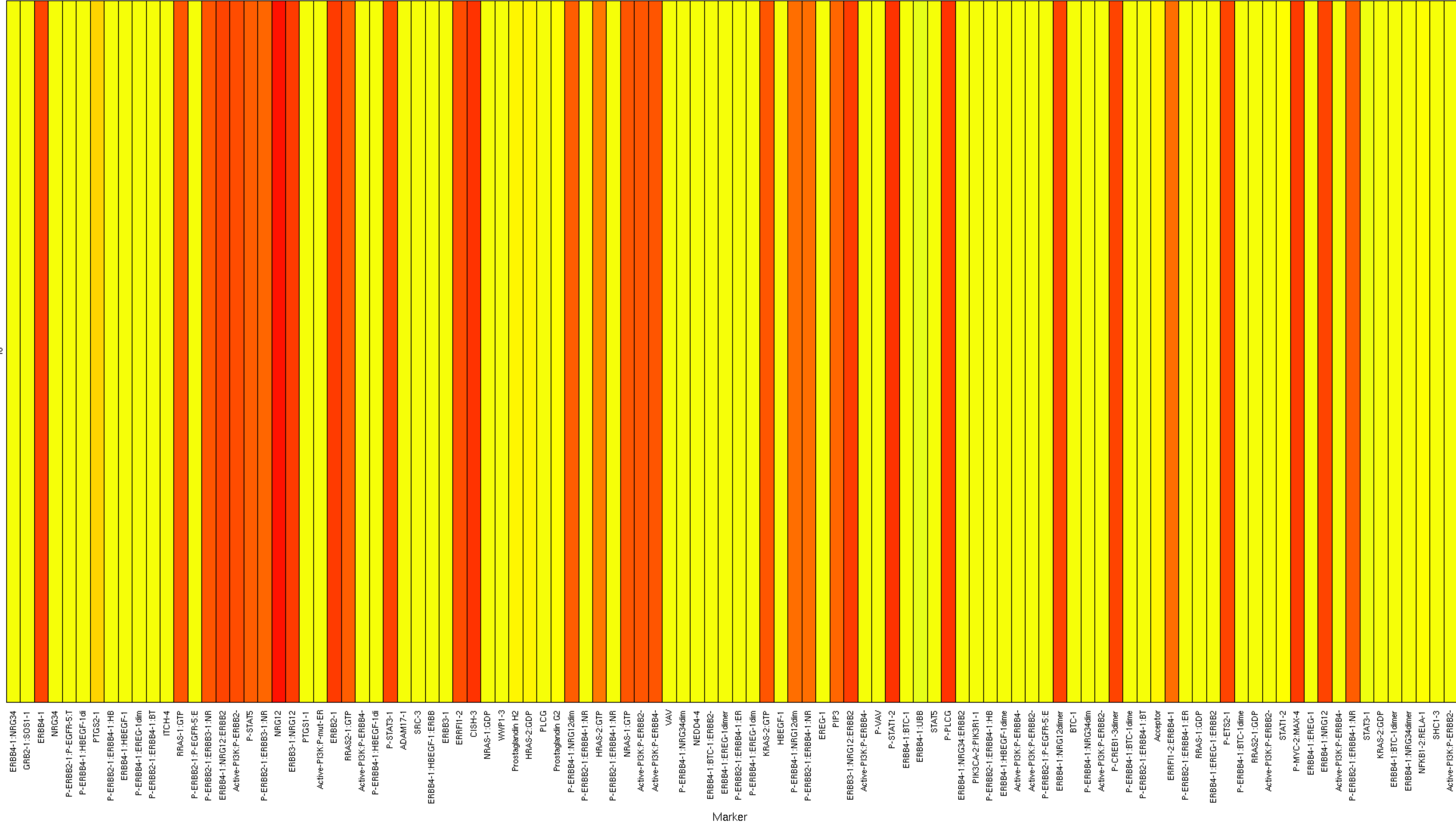
Marker:PI3K
Treatment:NRG34
Ratio:26.5038



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_N_RG1_2_tsv

Treatment

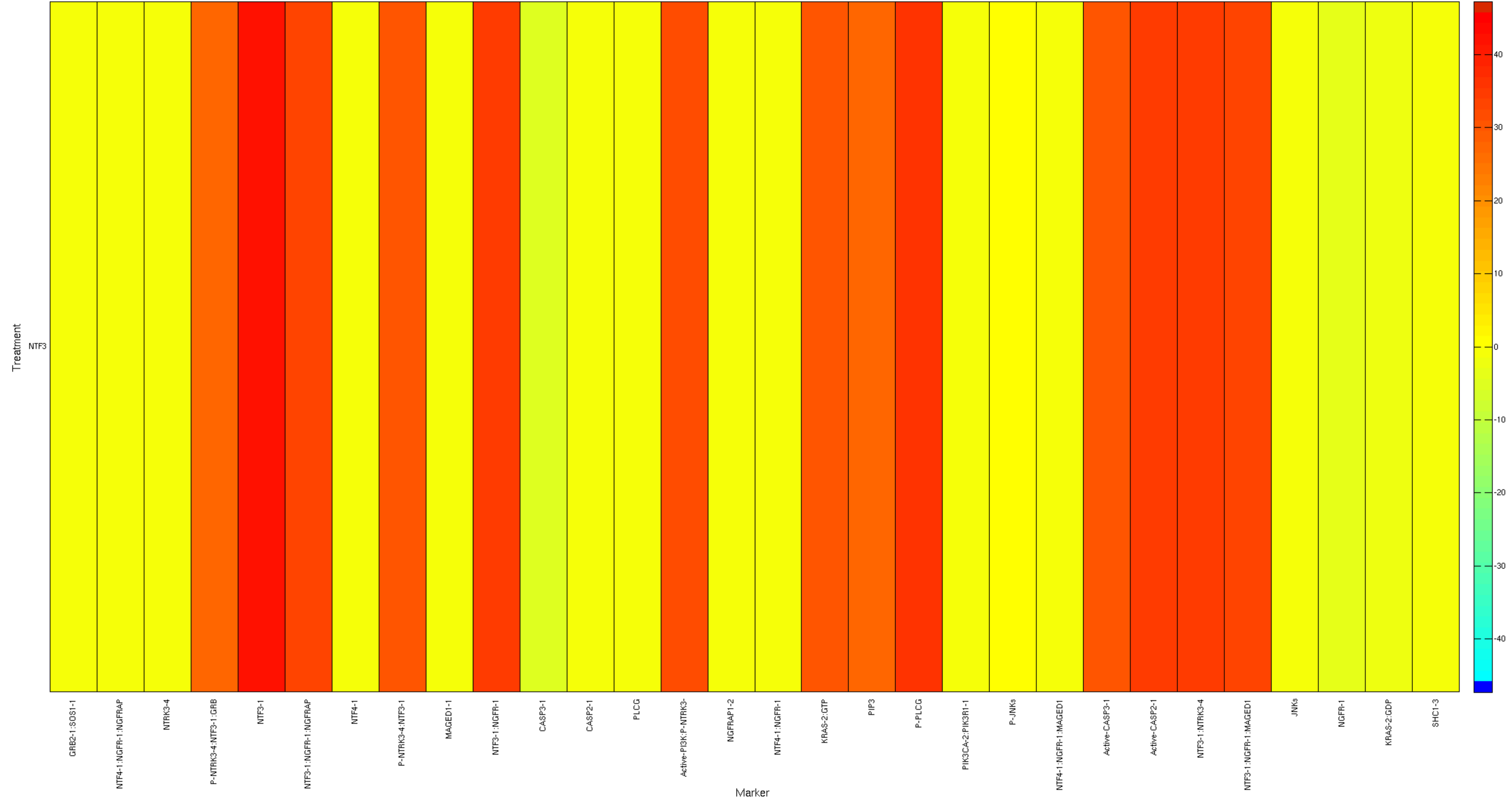
NRG12



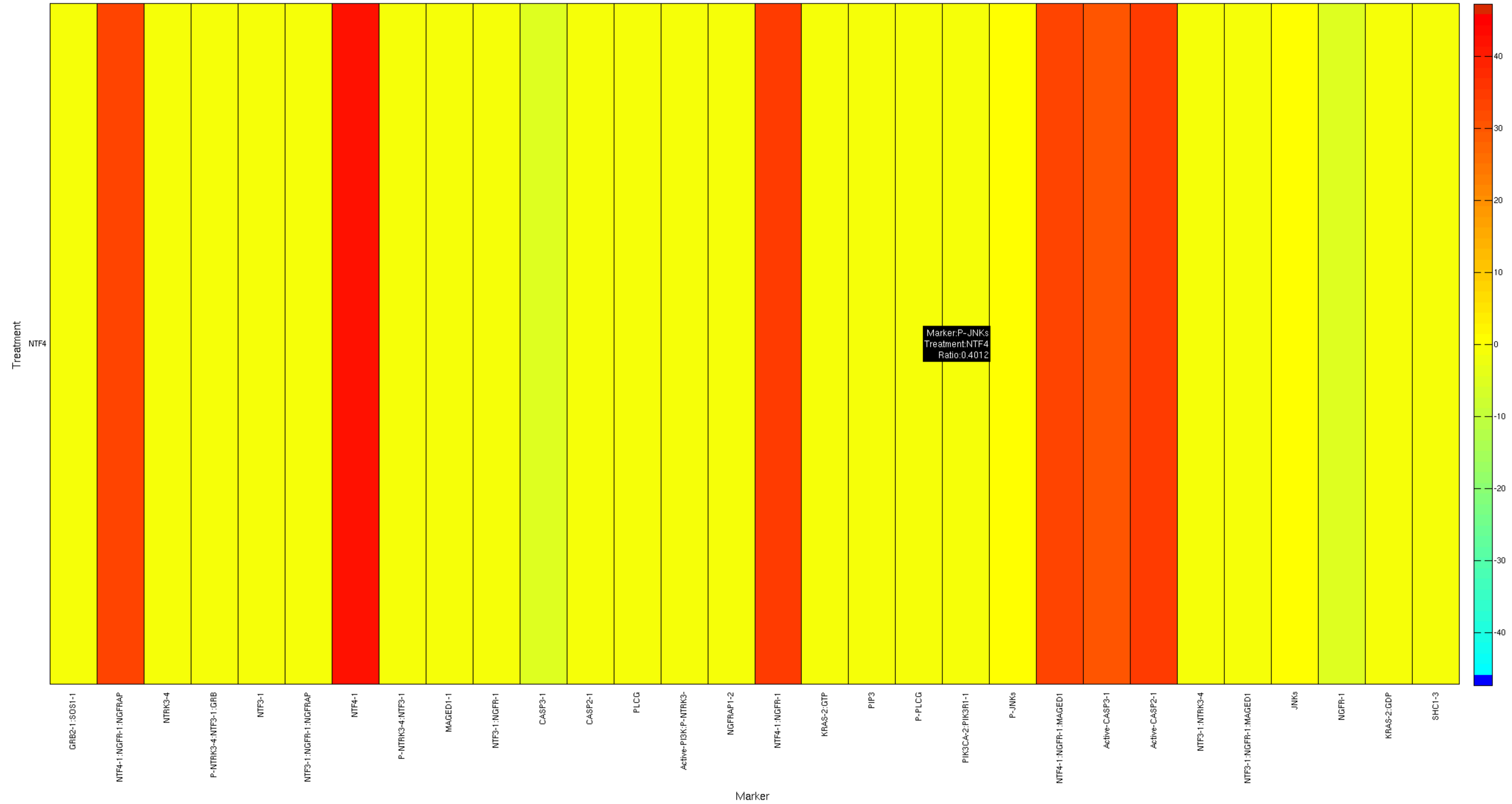
Marker



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_NTF3.tsv



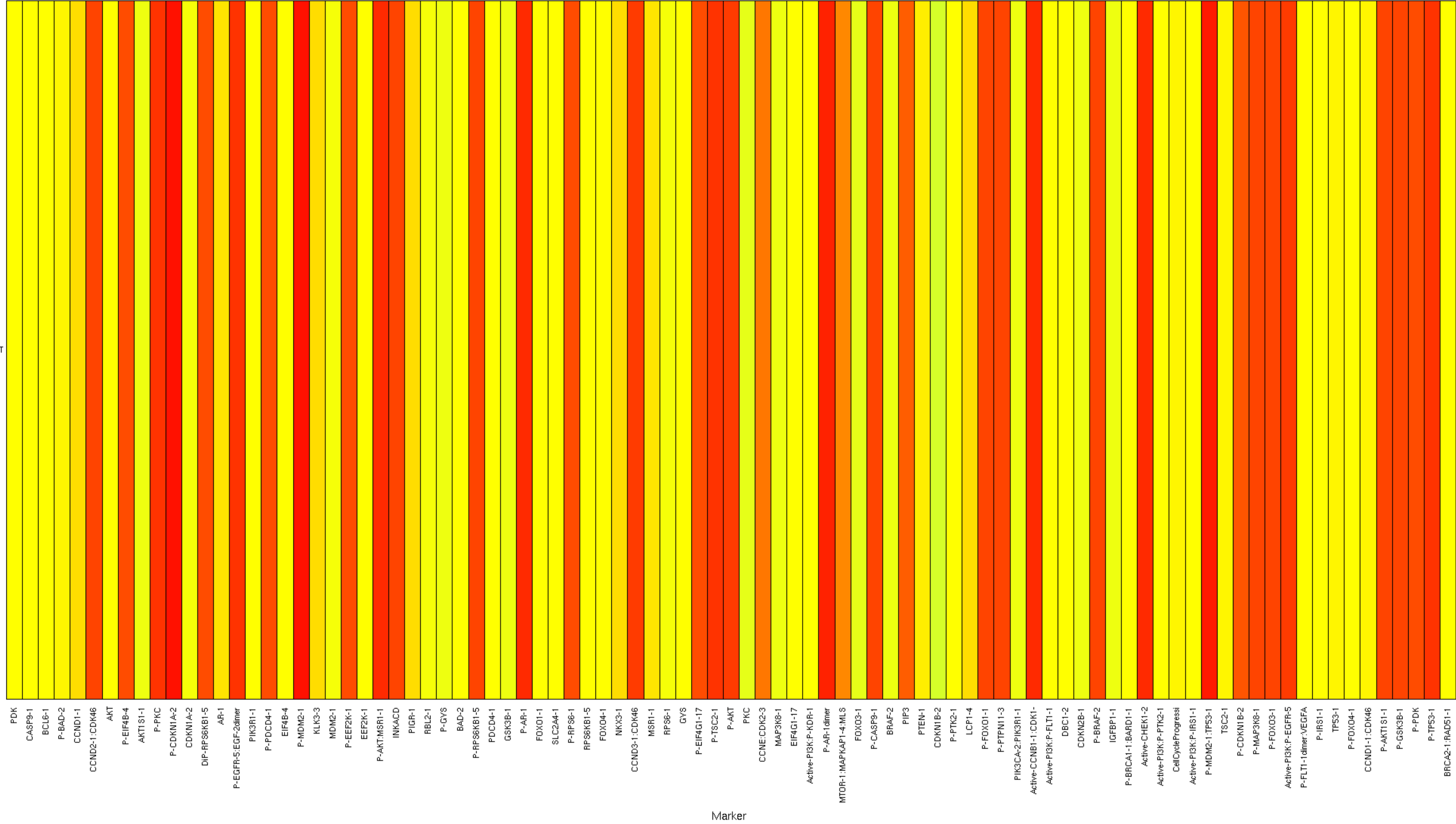
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_N_TF4.tsv



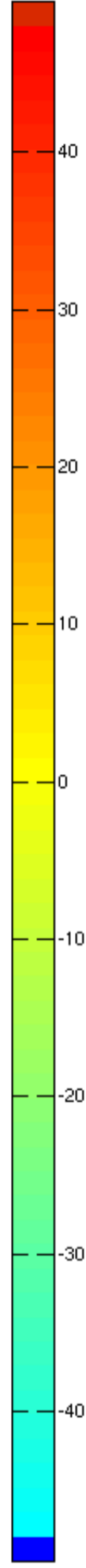
Marker Ratios (Log2 Of Geo Mean) bysummary_r_eadout_p_l3K_A_KT.tsv

Treatment

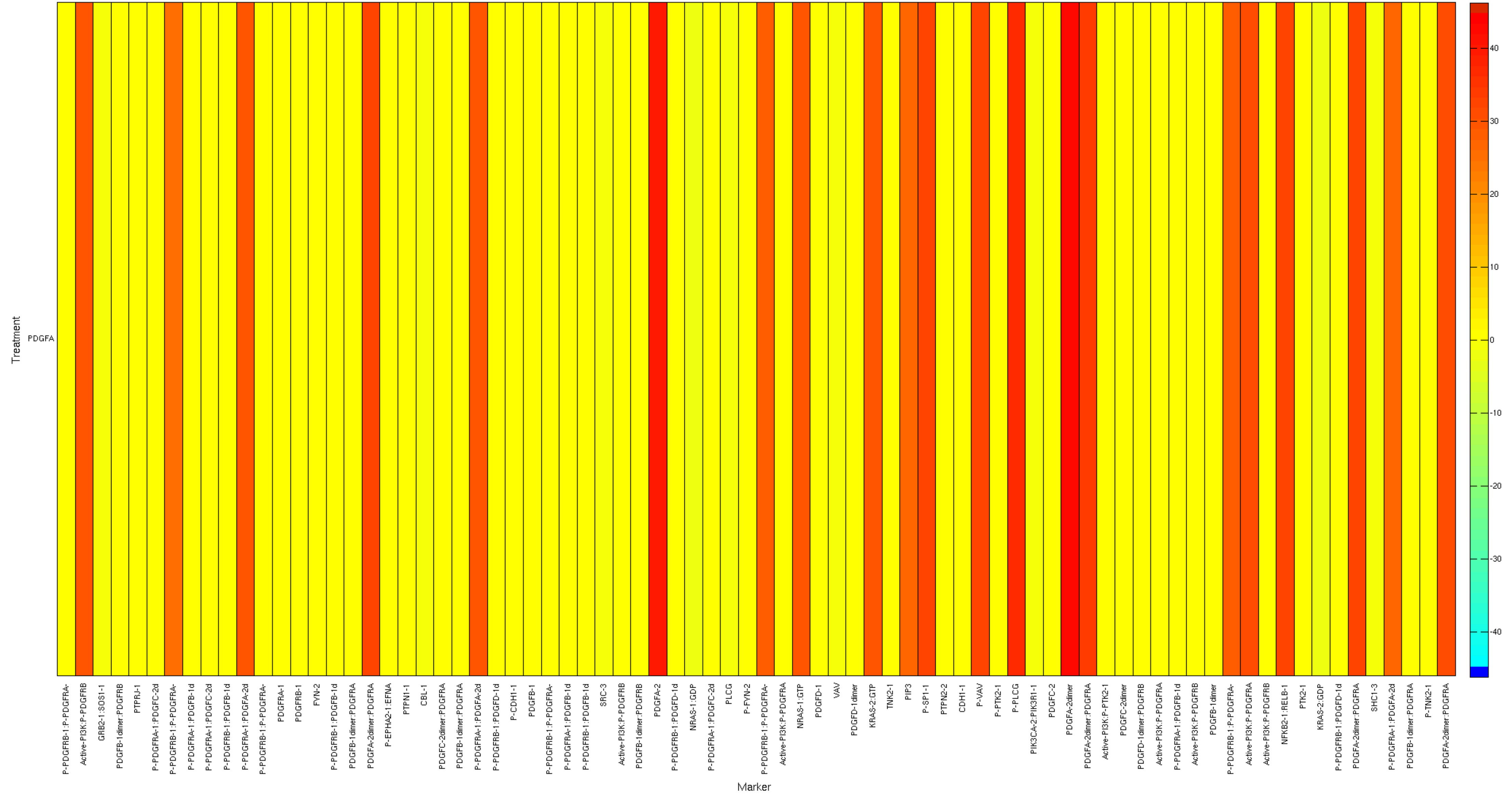
PI3KAKT



Marker

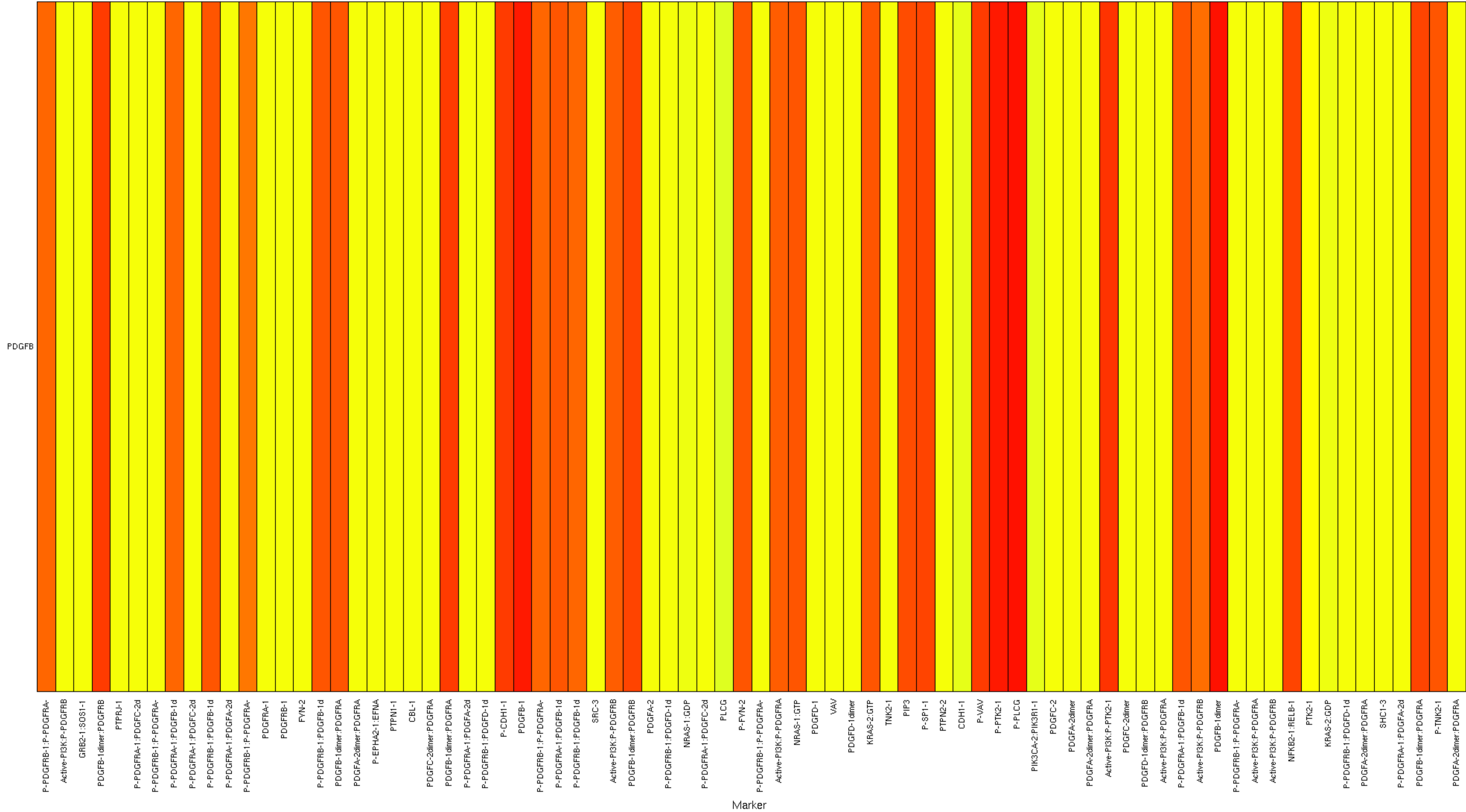


Marker Ratios (Log2 Of Geo Mean) bysummary_readout_pDGFA.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_pDGFB.tsv

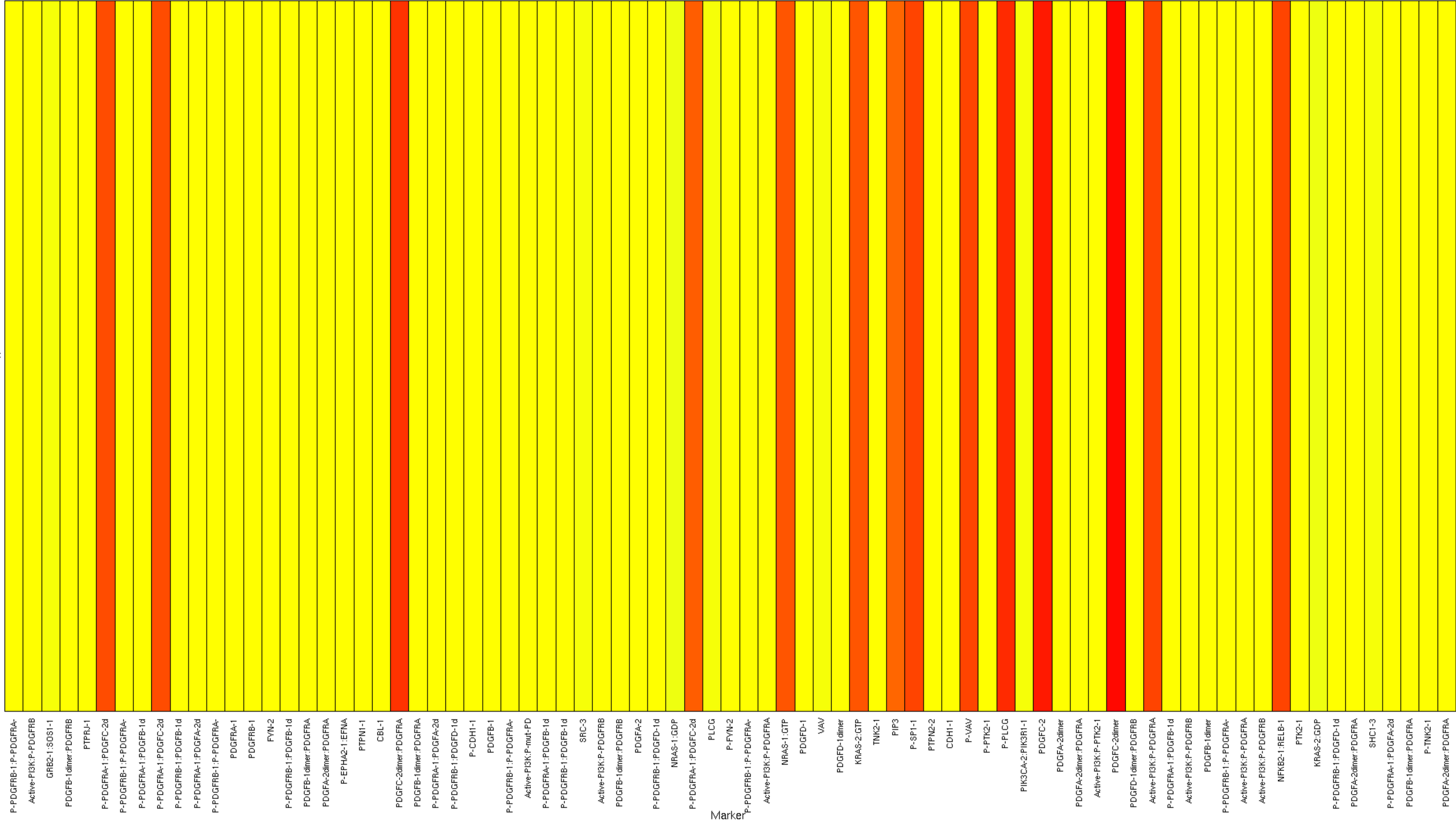
Treatment



Marker

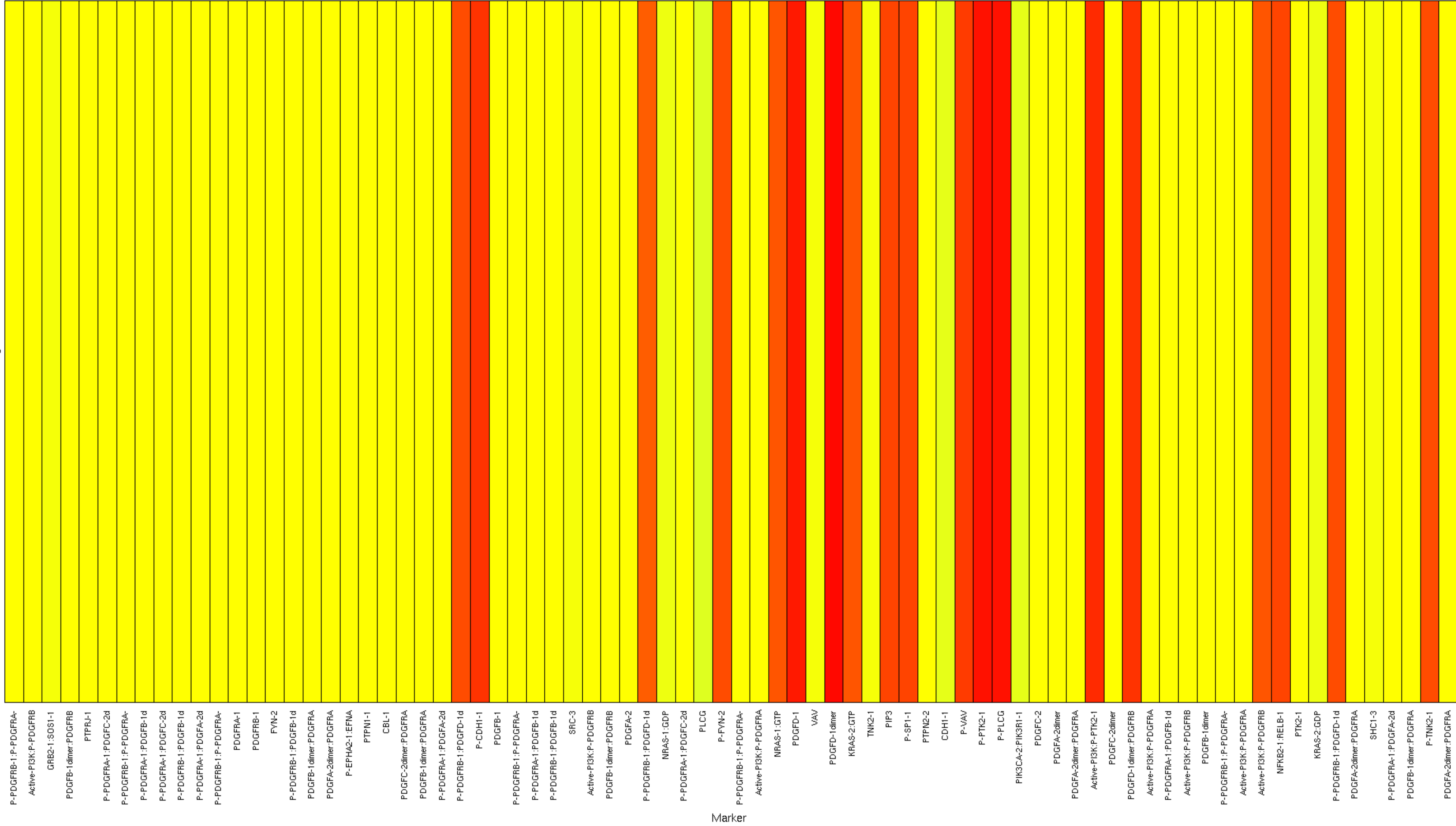
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_pDGFC.tsv

Treatment
PDGFC



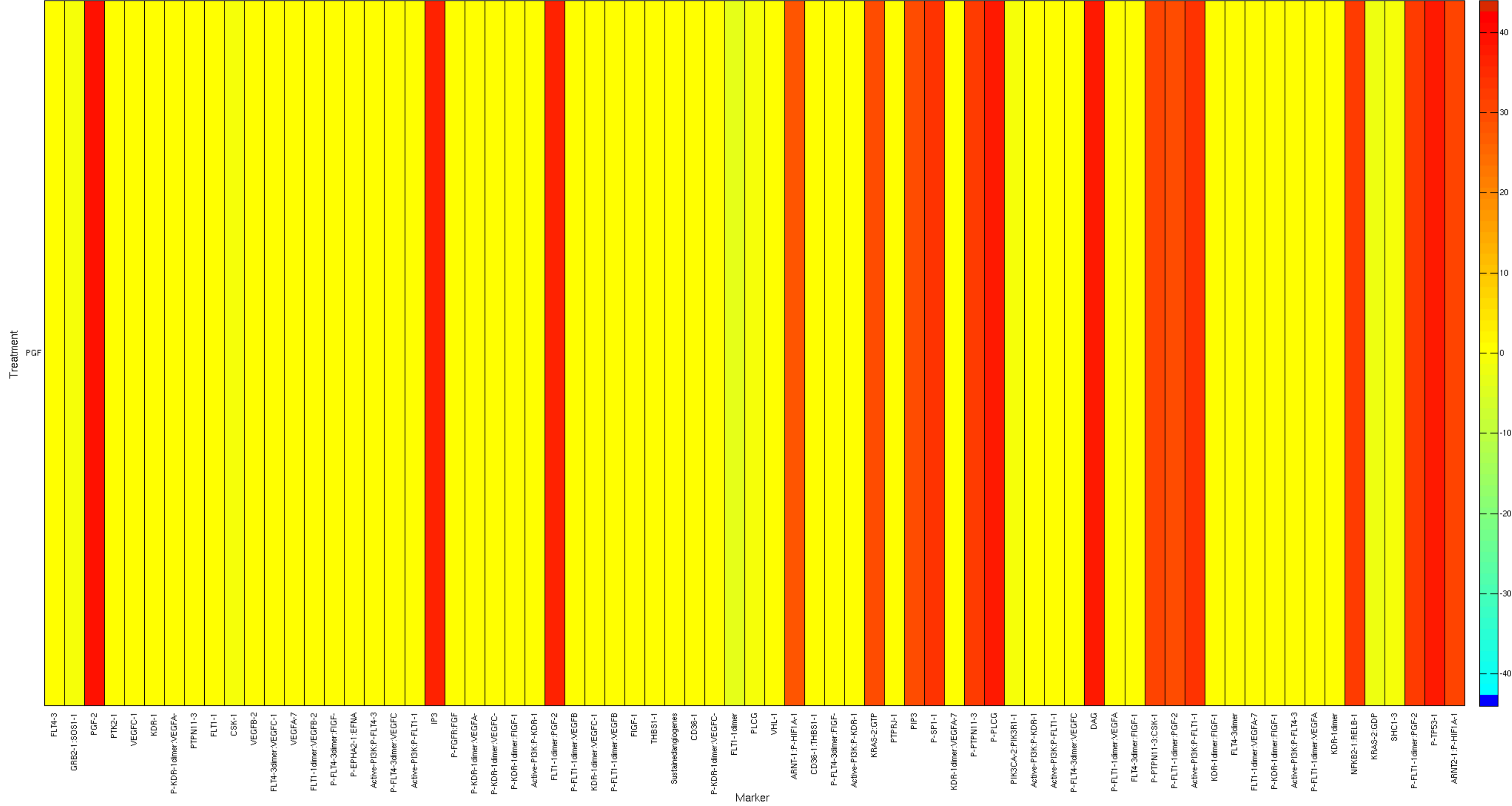
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_pDGFD.tsv

Treatment
PDGFD

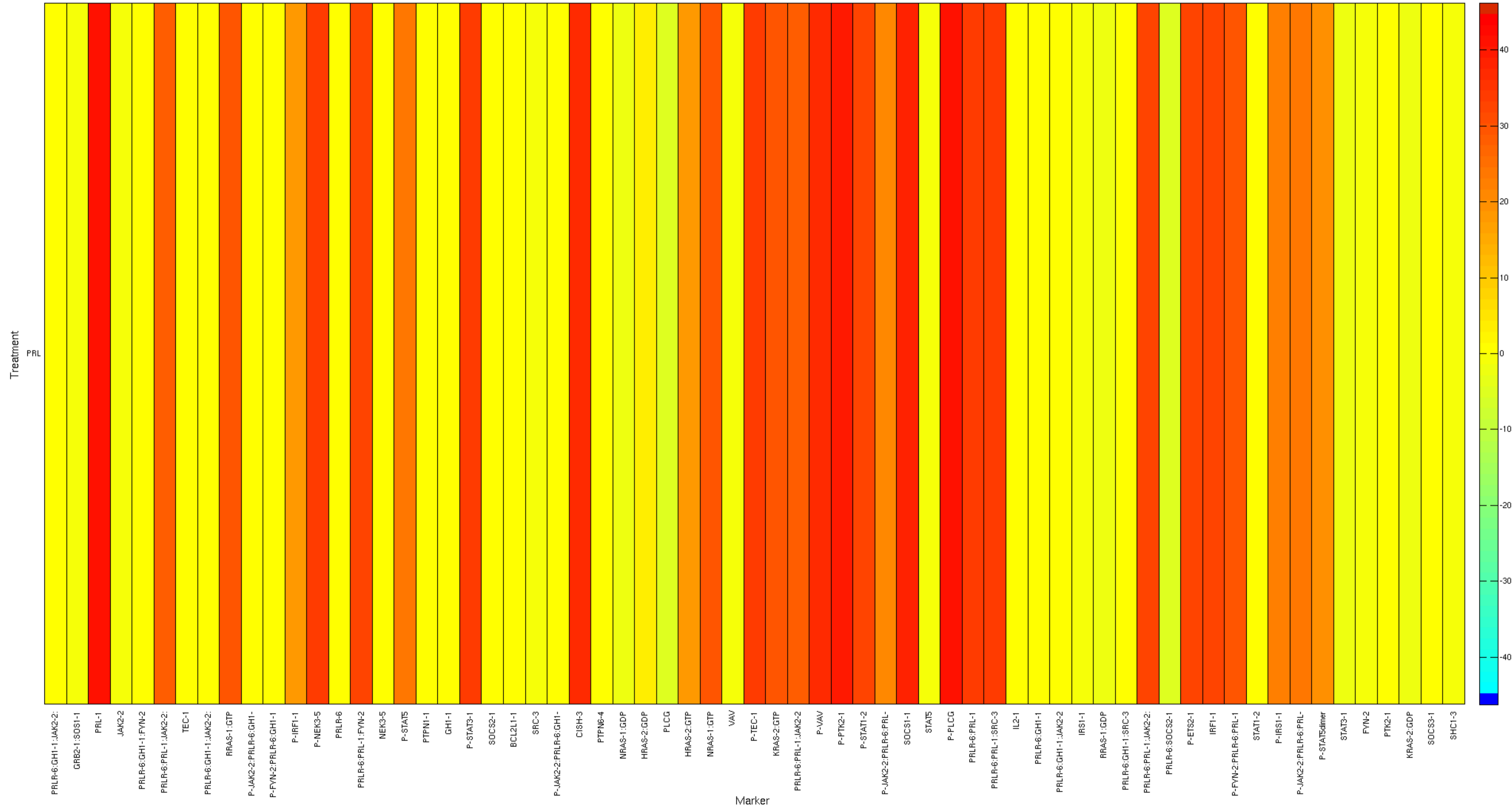


Marker

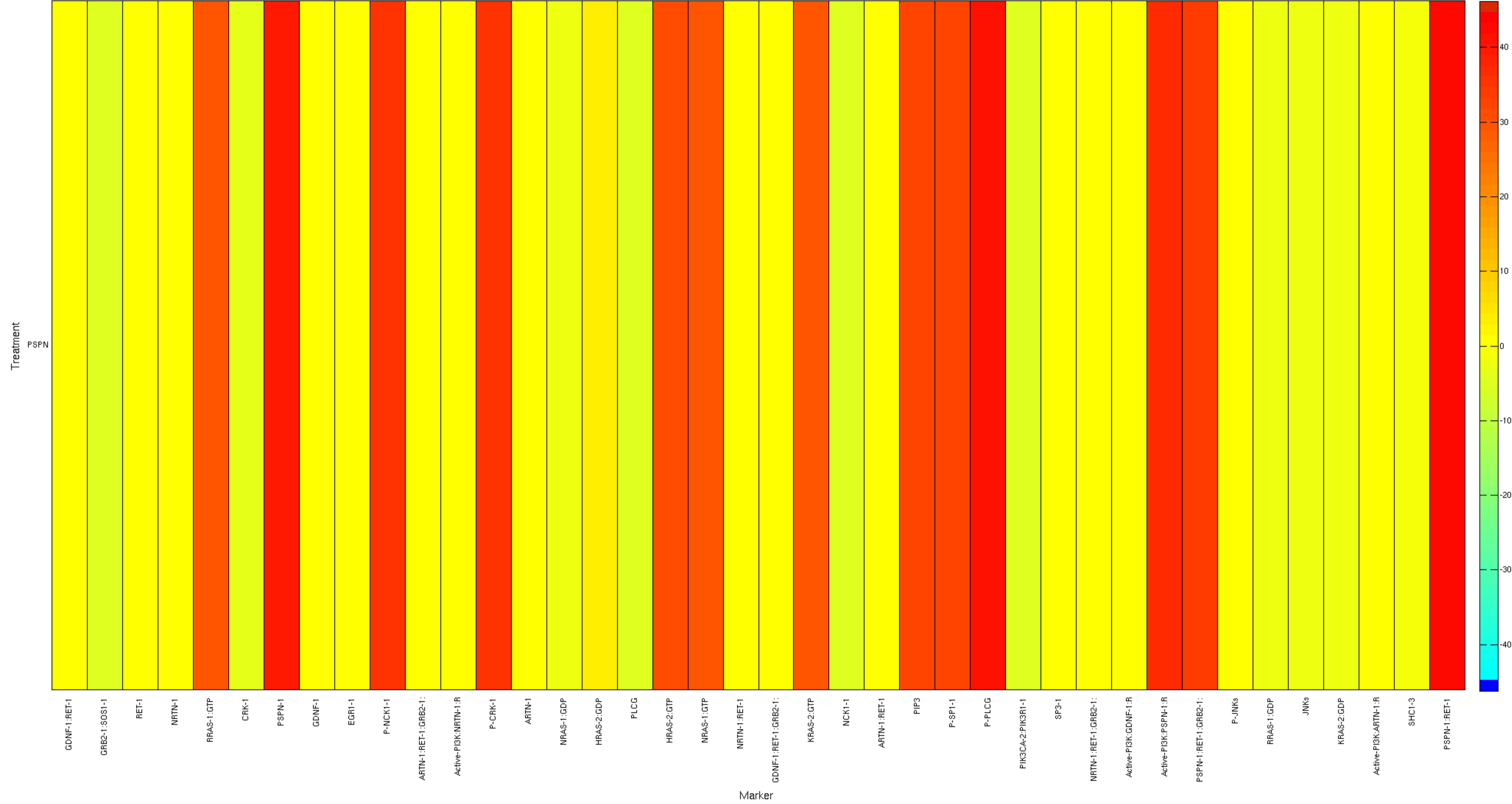
Marker Ratios (Log2 Of Geo Mean) bysummary_readout_p_GF.tsv



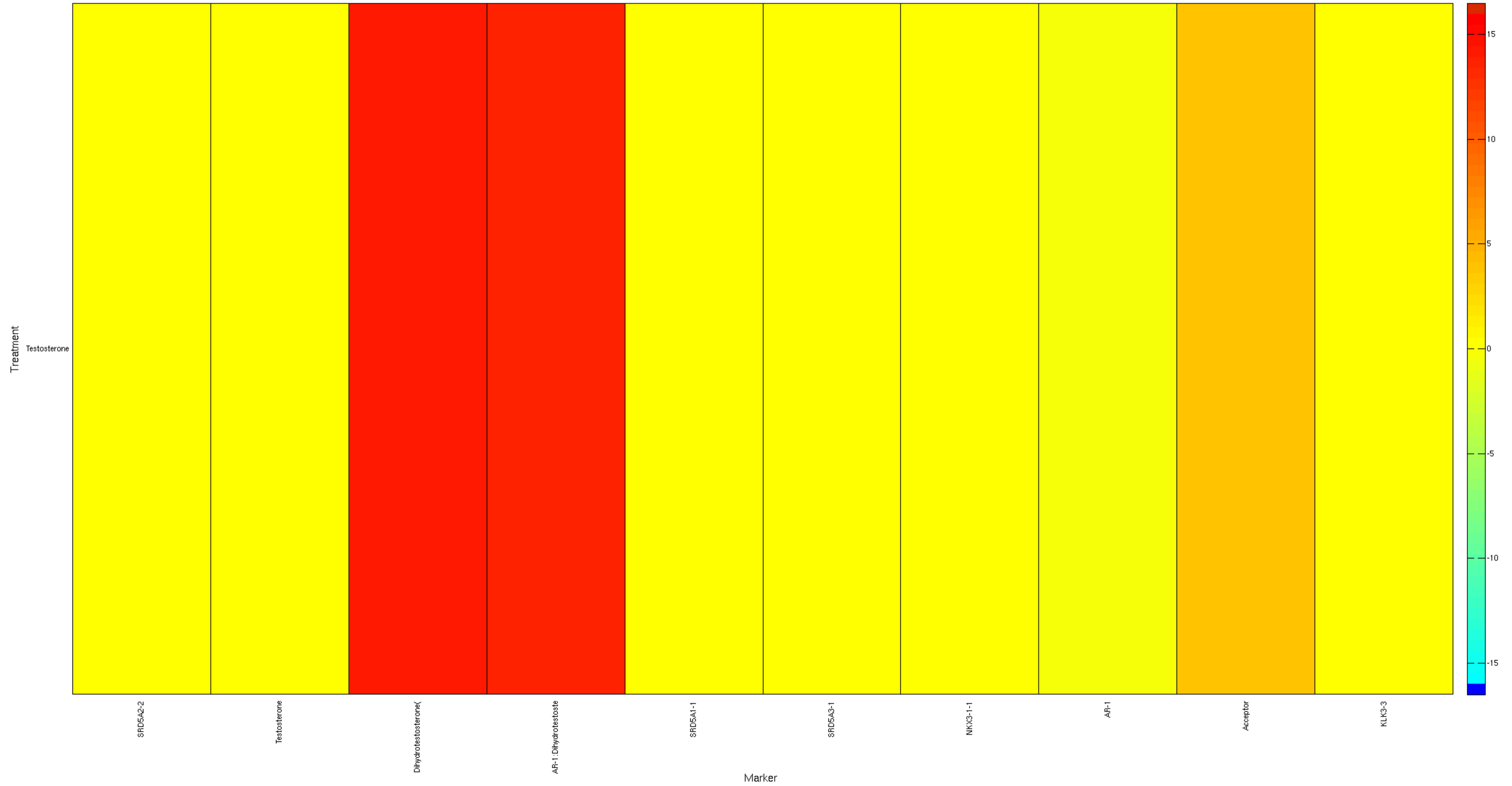
Marker Ratios (Log2 Of Geo Mean) bysummary_eadout_pRL.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_pSPN.tsv

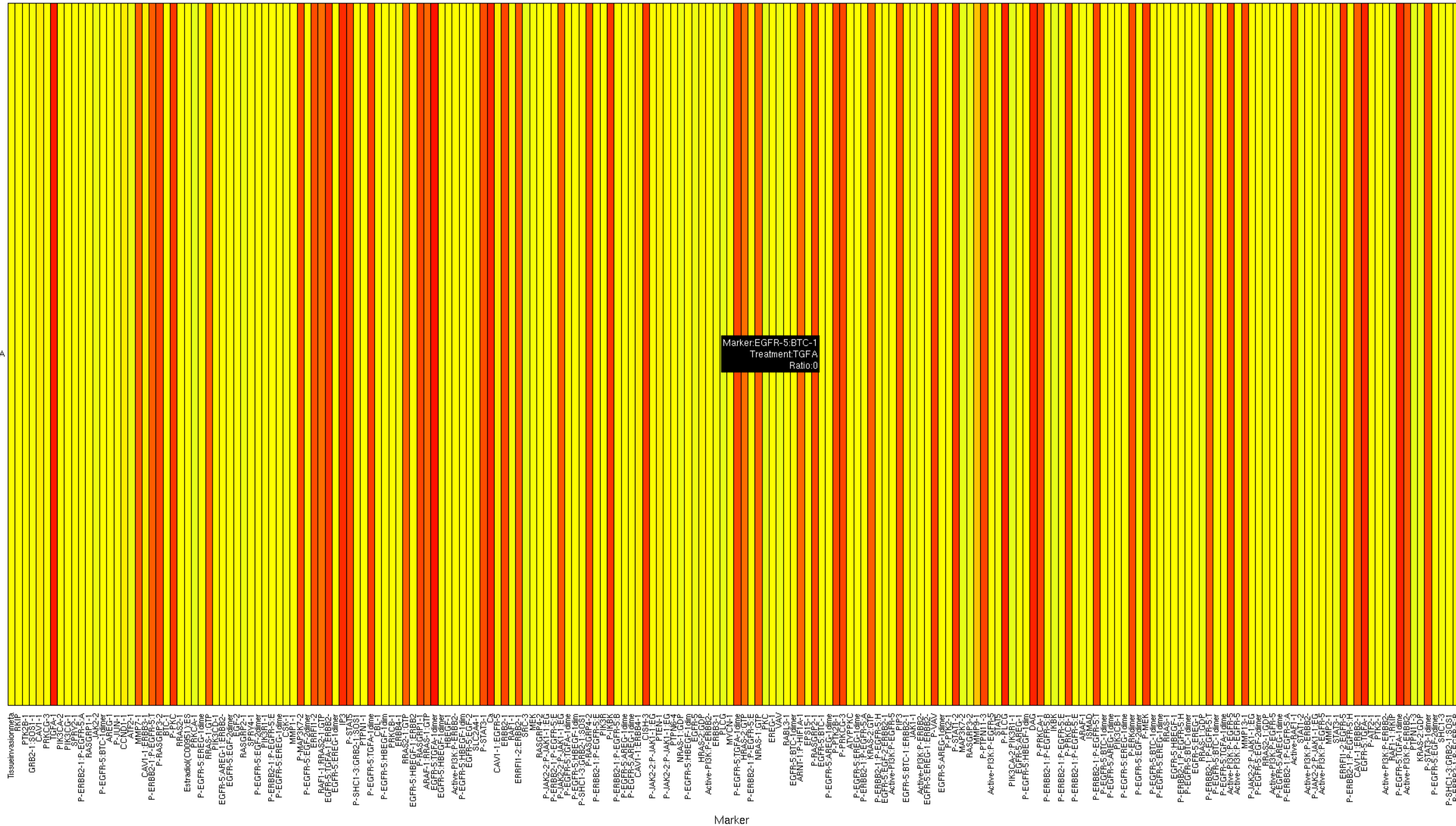


Marker Ratios (Log2 Of Geo Mean) bysummary_readout_estosterone.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_TGFA.tsv

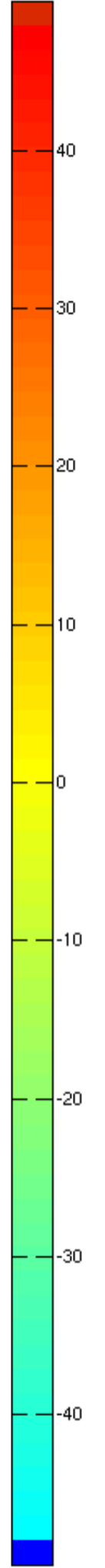
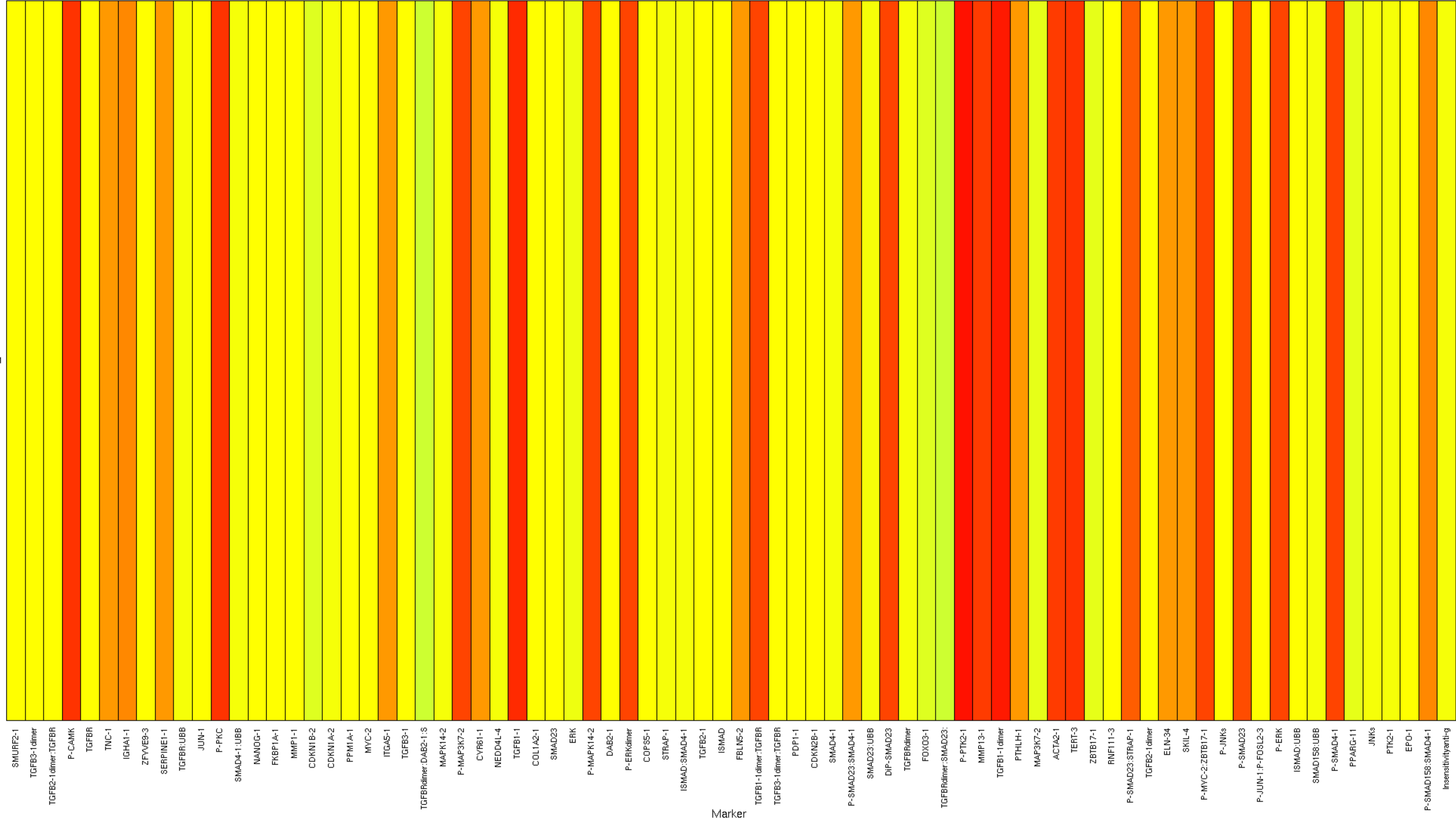
Treatment
TGFA



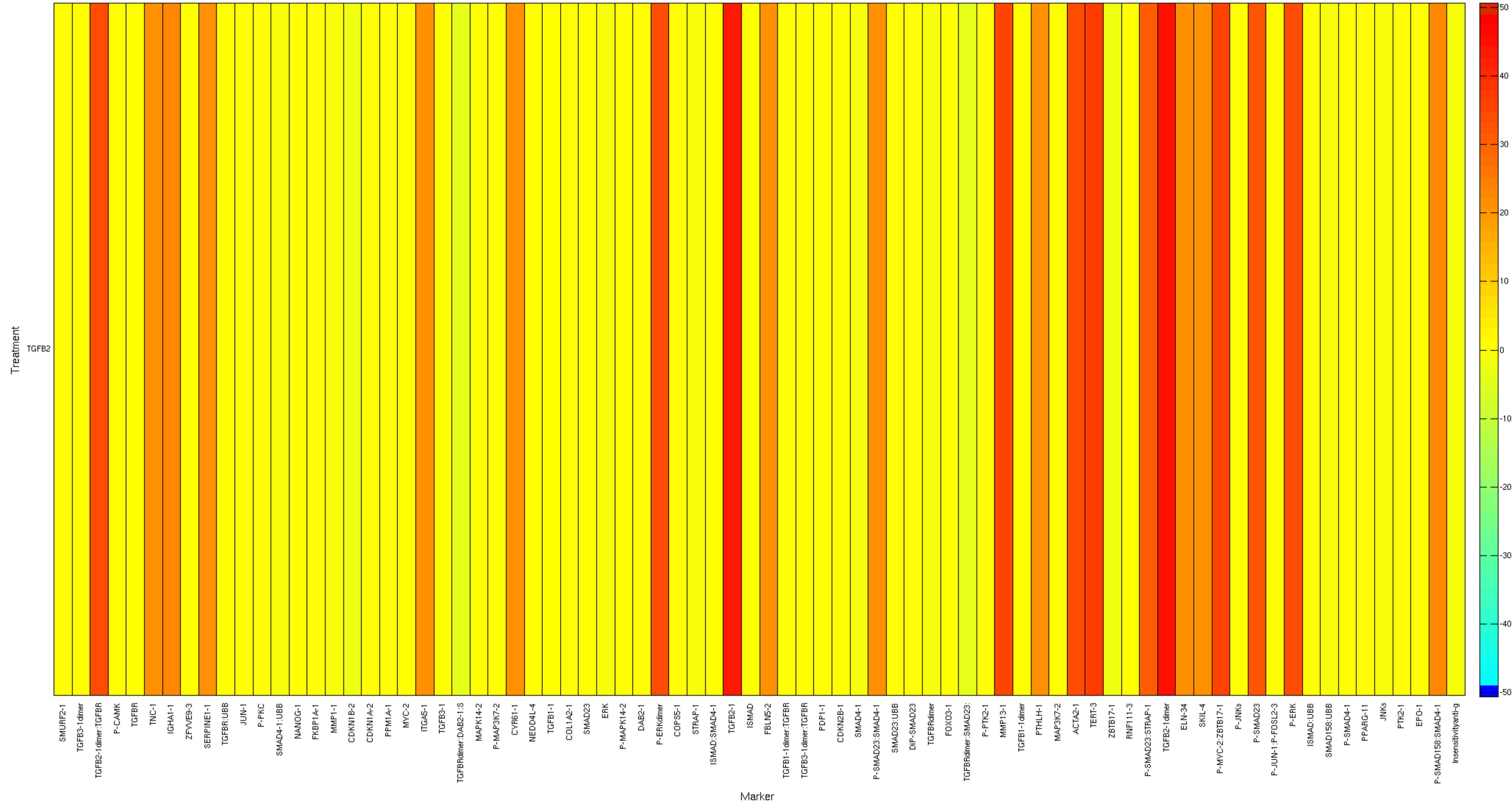
Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_readout_TGFB1.tsv

Treatment
TGFB1



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_TGFB2.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_TGFB3.tsv

Treatment

TGFB3

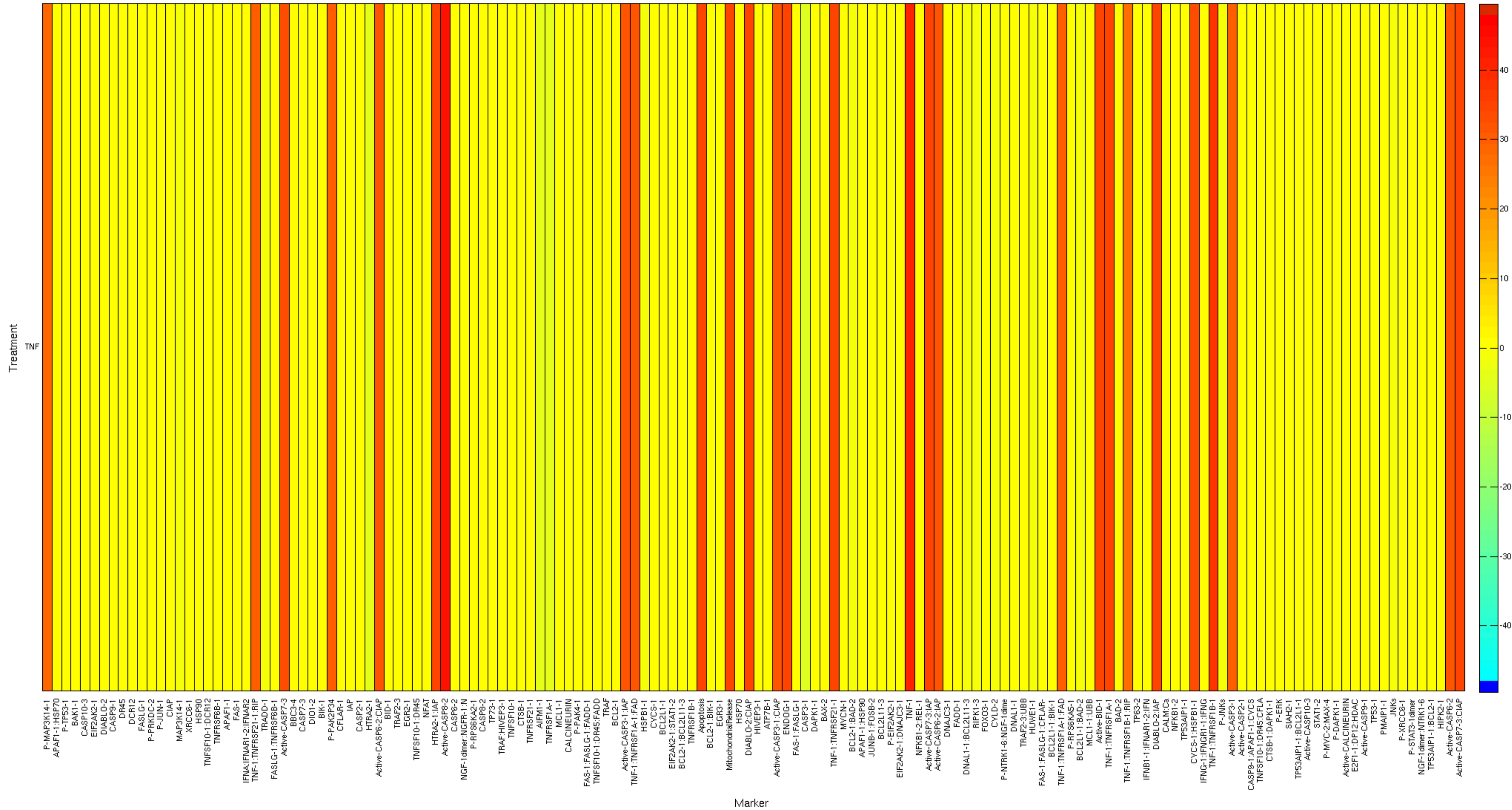


Marker:CDKN2B-1
Treatment:TGFB3
Ratio:0.00079326

Marker

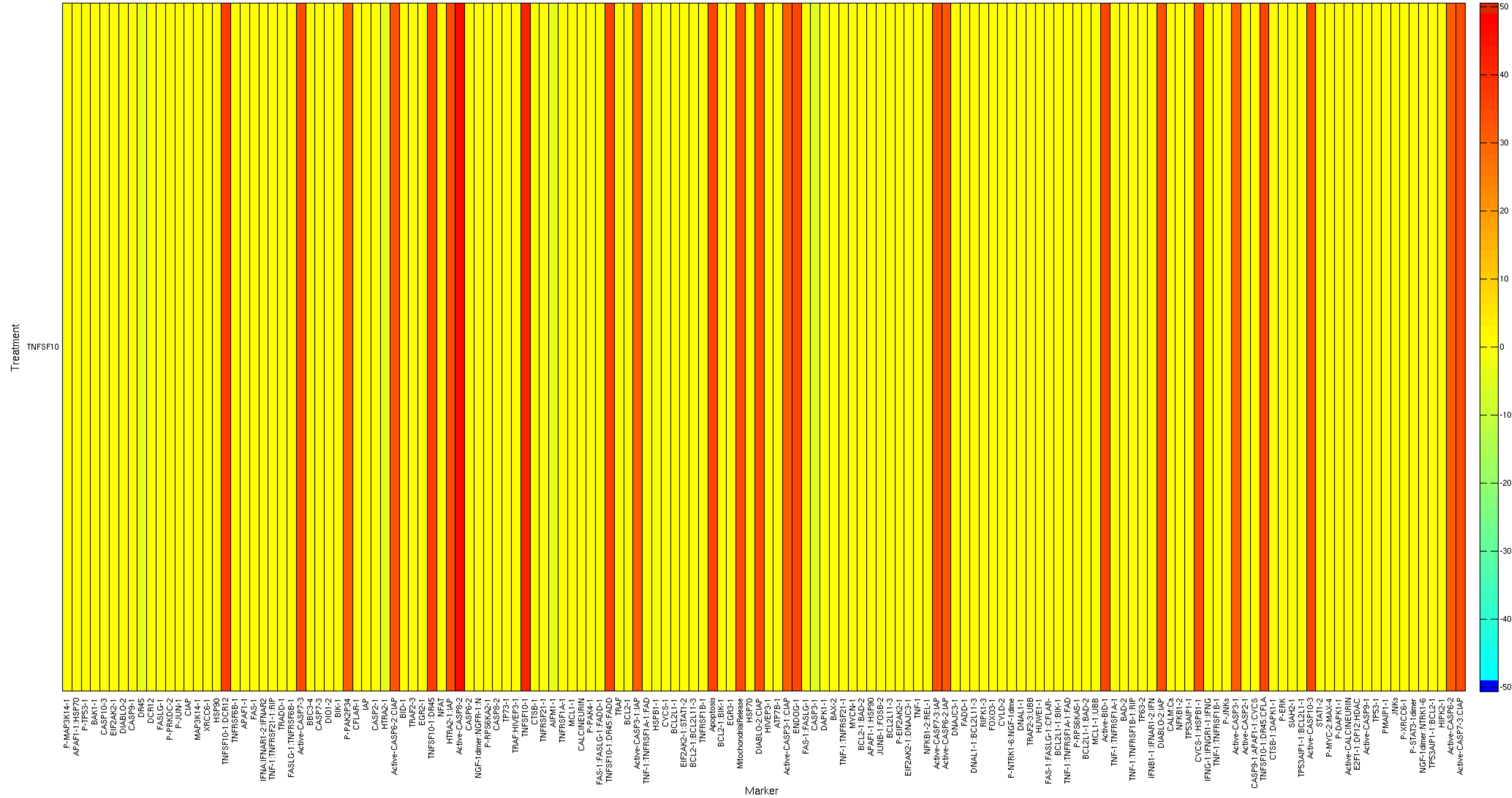


Marker Ratios (Log2 Of Geo Mean) bysummary_readout_TNF.tsv



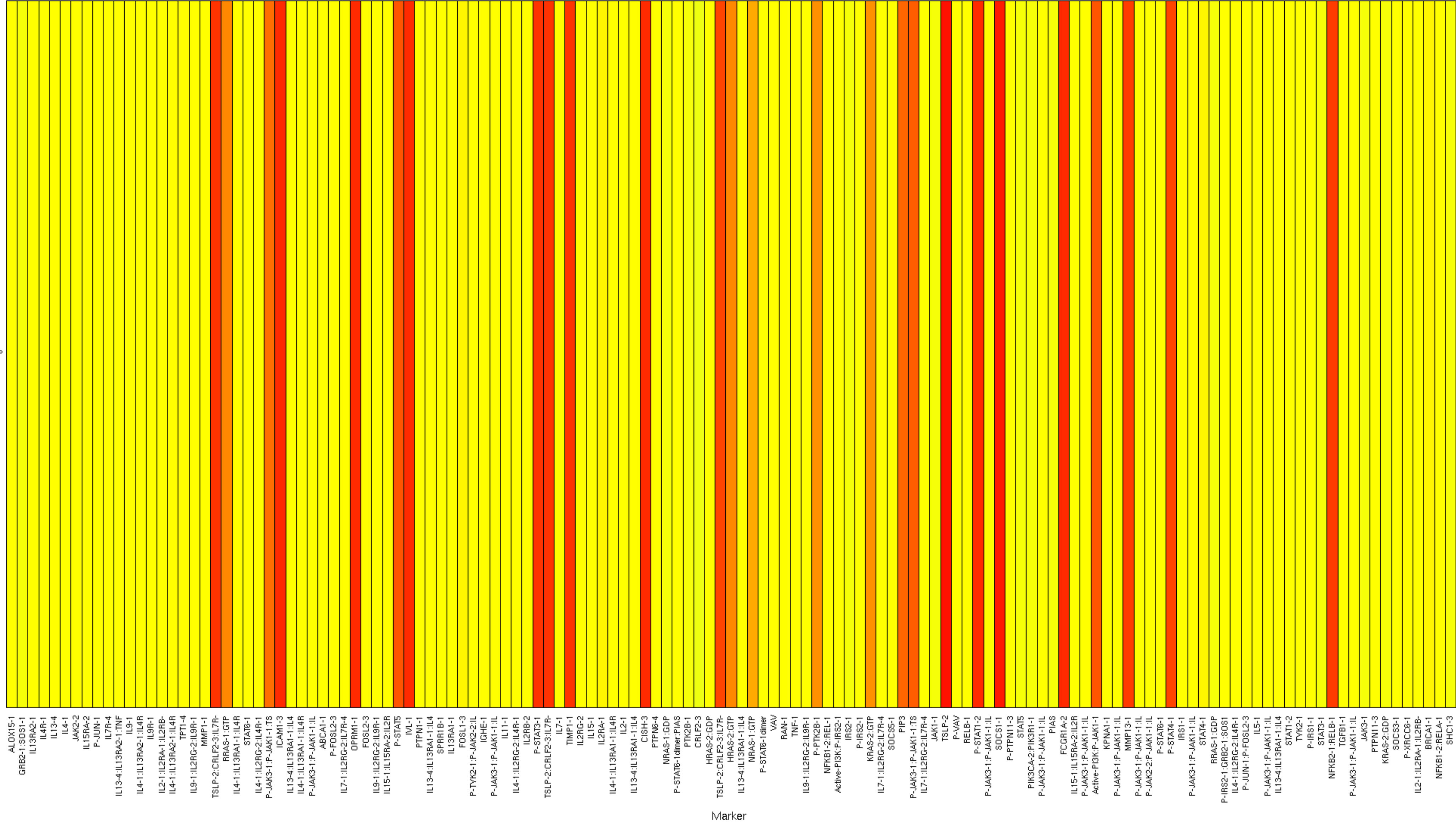
Marker

Marker Ratios (Log2 Of Geo Mean) bysummary_eadout_TNFSF10.tsv



Marker Ratios (Log2 Of Geo Mean) bysummary_readout_TSLP.tsv

Treatment
TSLP



Marker