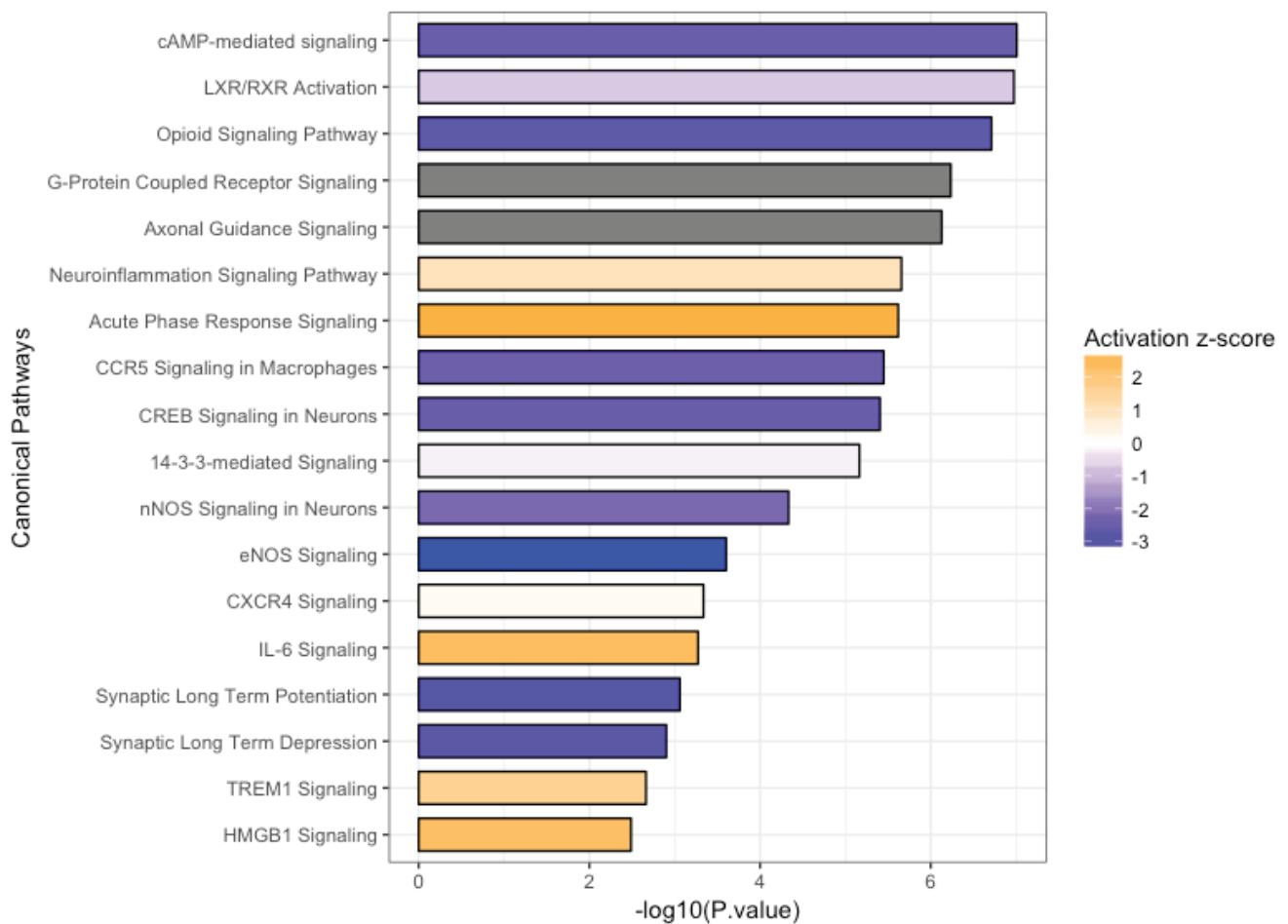


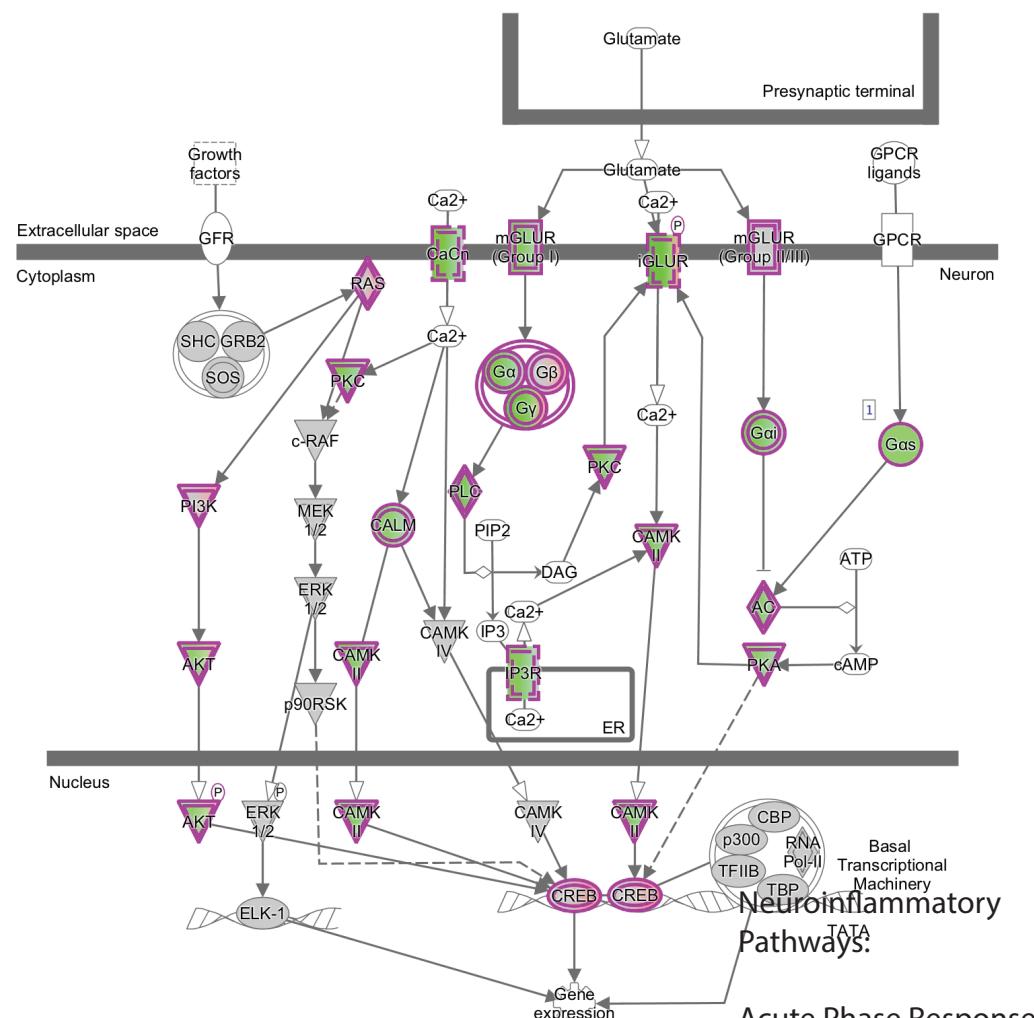
Fig1a Selected Canonical Pathways involved in CONC (WT mice)



a txt file containing all the significant canonical pathways are provided in the supplemental file1...

Fig 1b CREB Signaling in Neurons

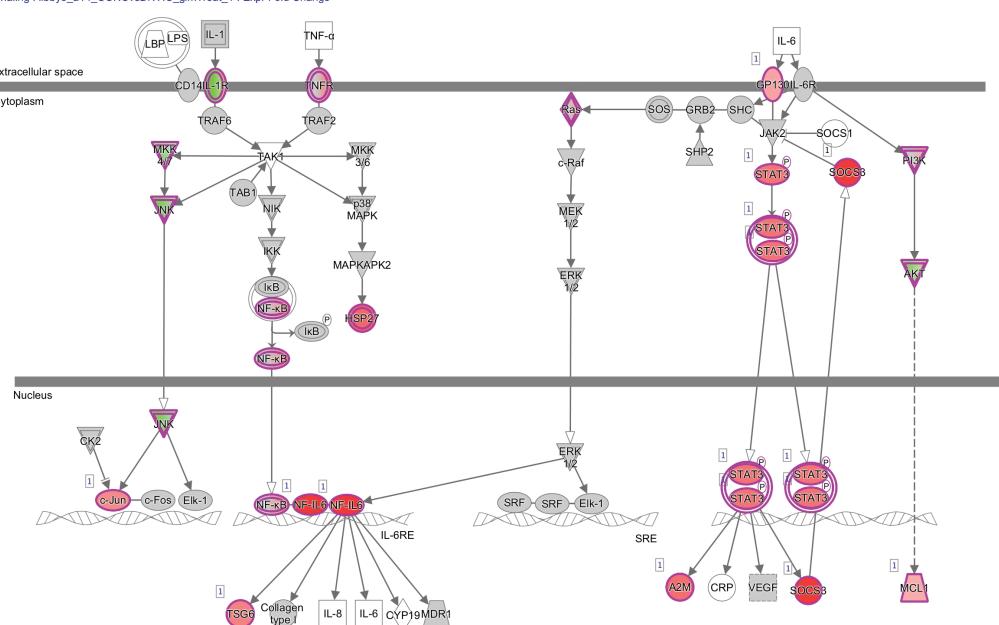
CREB Signaling in Neurons : libby3_a14_CONCvsDNT.C_glmTreat_1 : Expr Fold Change



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Fig 1c IL6 signaling

IL-6 Signaling : libby3_a14_CONCvsDNT.C_glmTreat_1 : Expr Fold Change



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Table 1. Selected Upstream regulator

Upstream Regulator	Expr Fold Change	Predicted Activation State	Activation z-score	p-value of overlap
BDNF	1.152	Inhibited	-2.948	5.71E-15
DDIT3	1.893	Activated	3.2	8.37E-06
JUN	1.645	Activated	2.135	4.66E-12
TGFB1	1.467	Activated	4.47	1.00E-17
TGFBR2	1.155	Activated	2.726	1.03E-04
TNF		Activated	4.734	4.16E-18

A full list of upstream regulator is provided in Supplemental file 2

BDNF: consistent with neuronal process decline

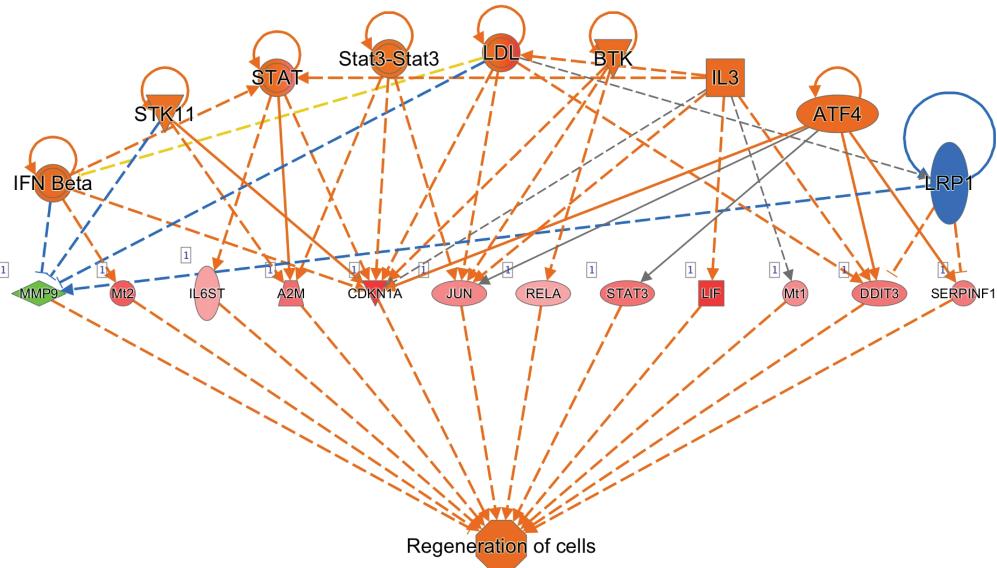
TNF: consistent with increased neuroinflammatory pathway

TGFB: increase during axonal injury, consistant with literature

Upregulation of Ddit3 and Jun as well as their related downstream gene network. Then transition to Figure 2 on Ddit3 and Jun KO

Fig 1d Cell regeneration signaling is activated in CONC (neuronal)

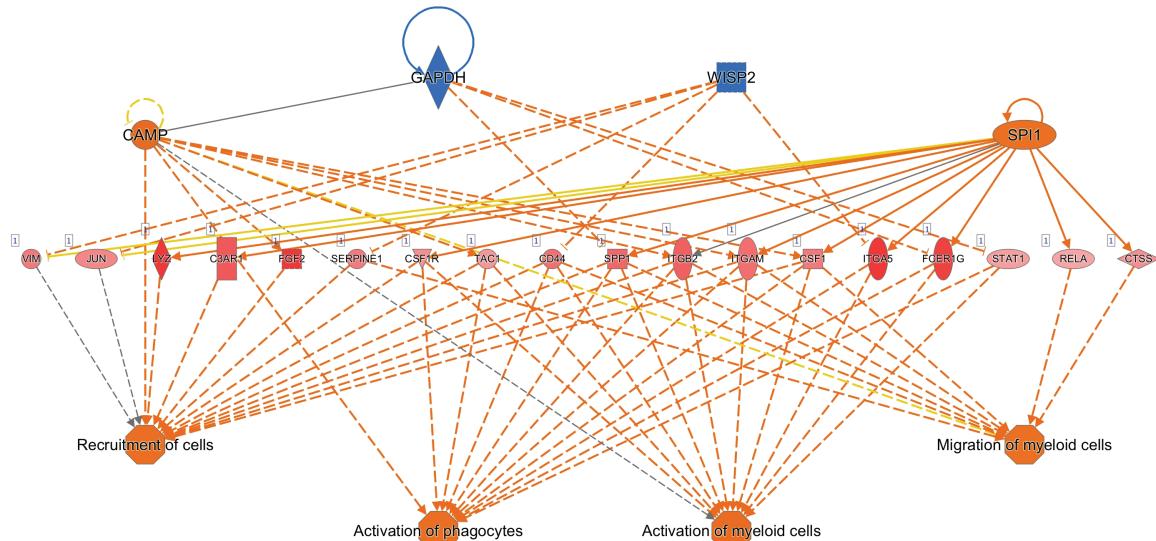
14 11



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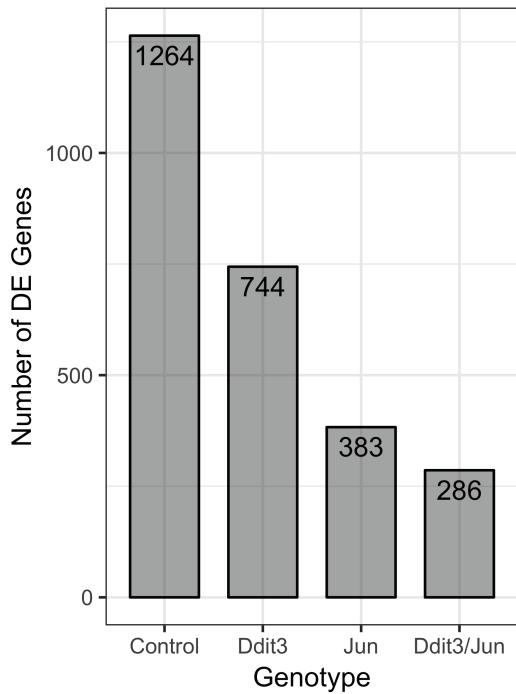
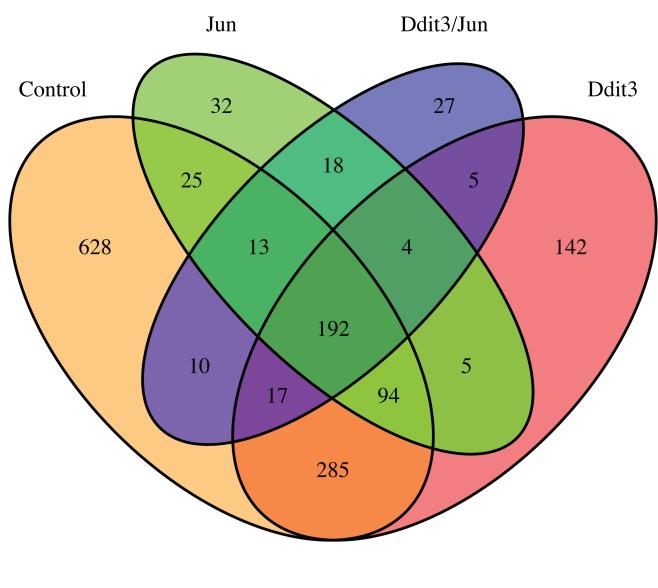
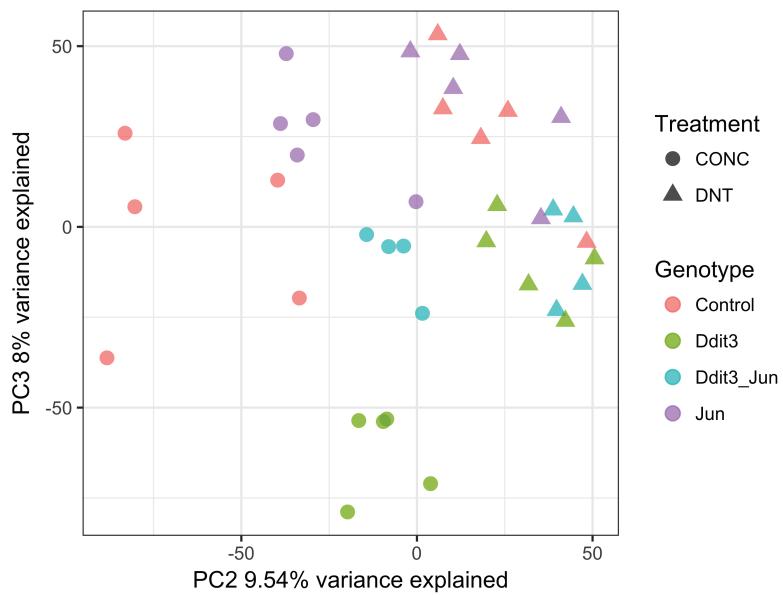
Fig 1e myeloid cell signaling is activated in CONC

3 10

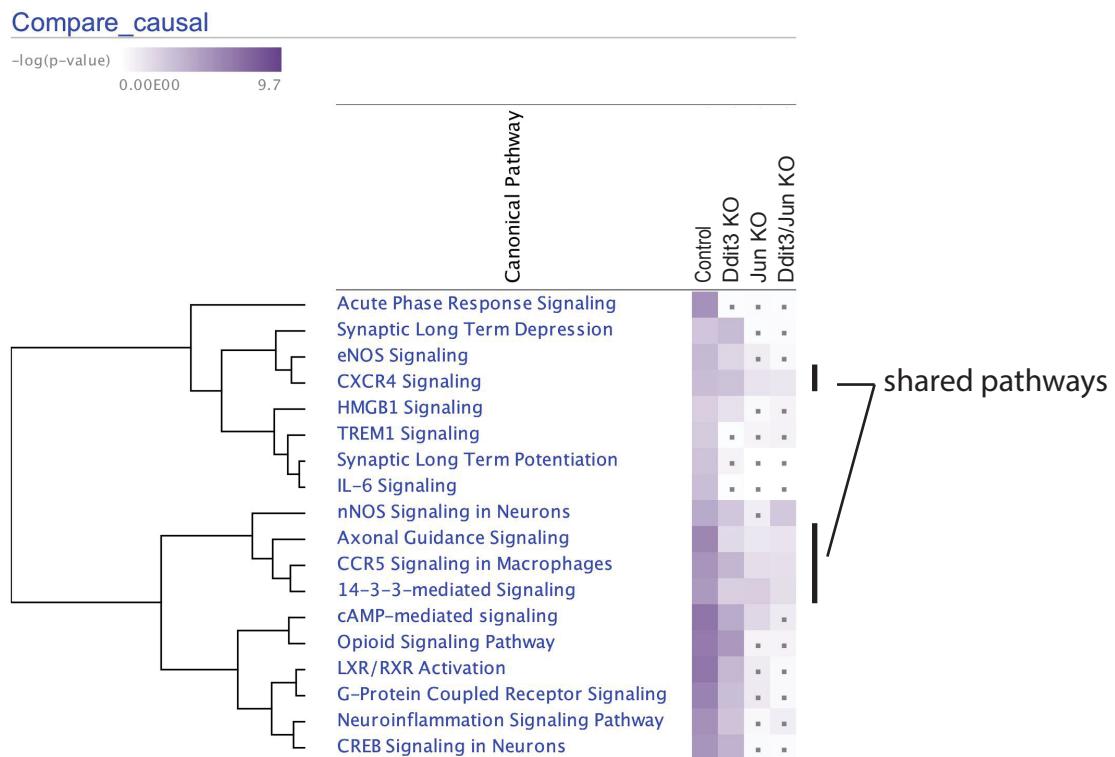


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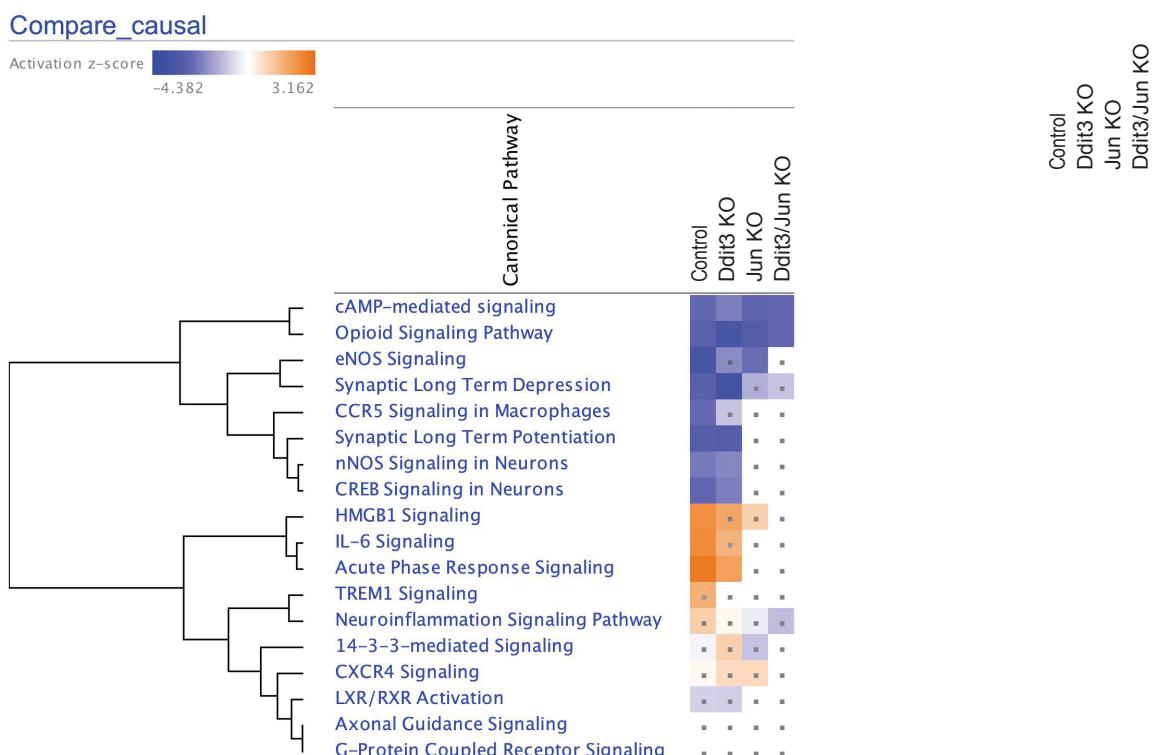
Fig2. Jun KO is more protective than Ddit3 KO in CONC



Comparison of Canonical Pathways across all genotypes



dot means the pathways are not significantly involved based on the DE genes (p value > 0.05)



dot means the pathway is not predicted upregulated or downregulated
(activation z-score is between -2 and 2)

Fig 3. "shared pathways"

Neuronal pathways:

Axonal Guidance Signaling : injury response (independent of Jun and Ddit3)

14-3-3 mediated signaling: upstream of Jun

Inflammatory pathways:

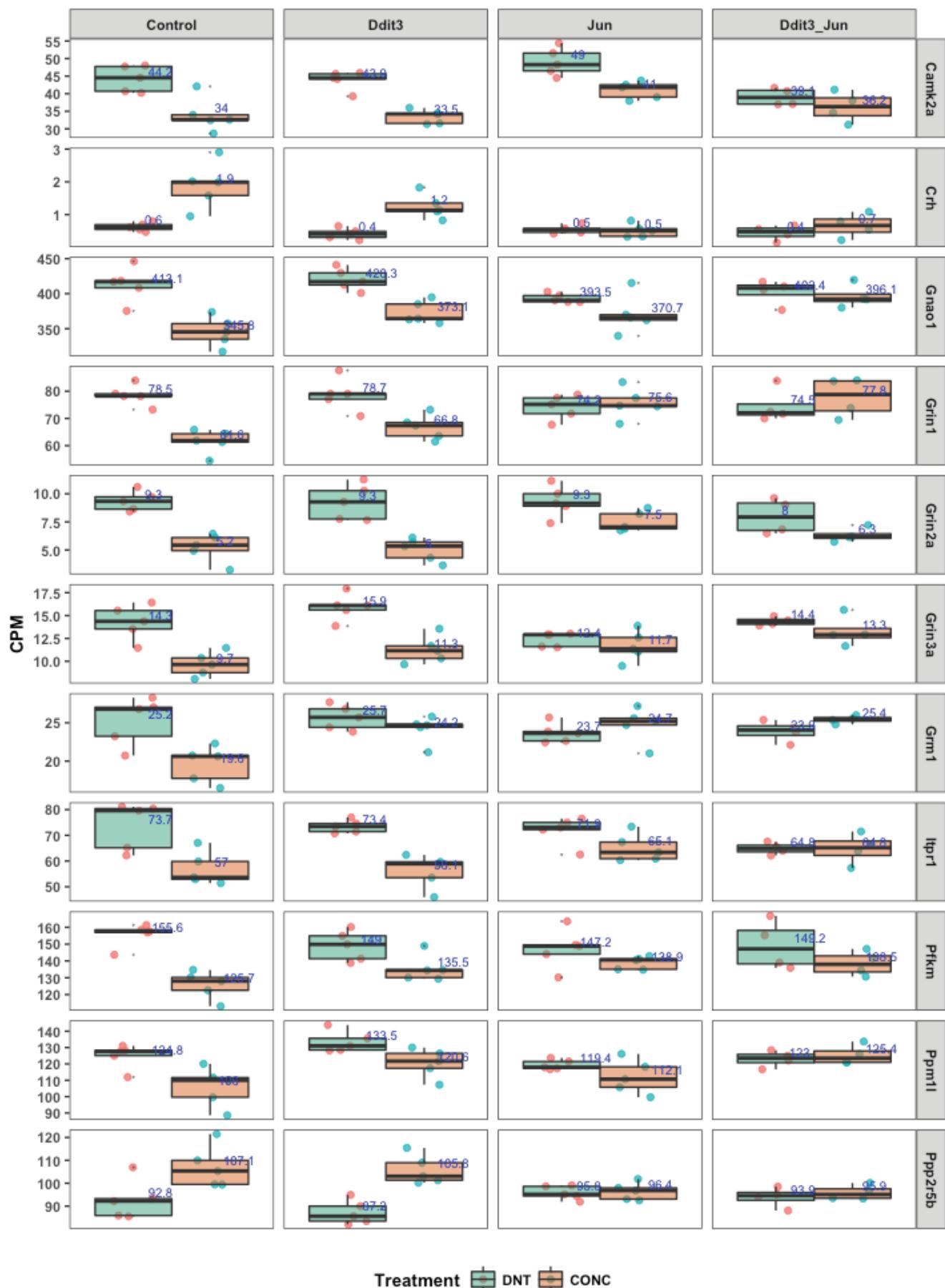
CCR5 Signaling in Macrophages (decrease after CONC), upstream of jun

CXCR4 Signaling

22 DE genes from all these shared pathways are all belong to 192 DE genes shared across all genotypes

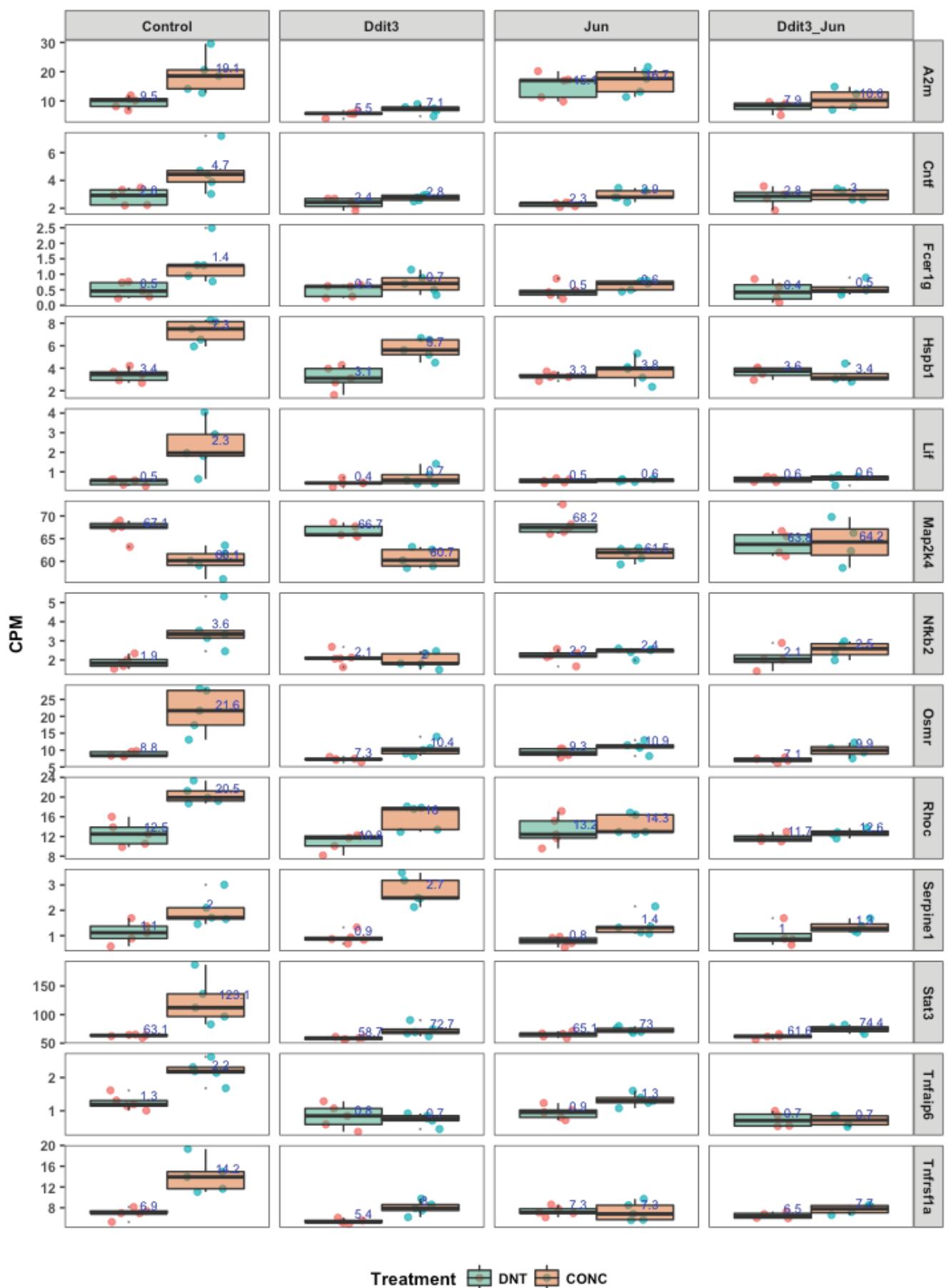
"Ablim2" "Arhgef3" "Cacnb3" "Cacng5" "Cdkn1a" "Ecel1" "Elmo1" "Fgf1"
"Fgf12" "Gnal" "Gng4" "Itga5" "Limk1" "Mapk10" "Mmp12" "Mmp15"
"Ppp2r2c" "Rhoq" "Tuba4a" "Tubb2a" "Tubb3" "Tubb4a"

Fig 4. Jun but not Ddit3 protects against neuronal decline during ONC



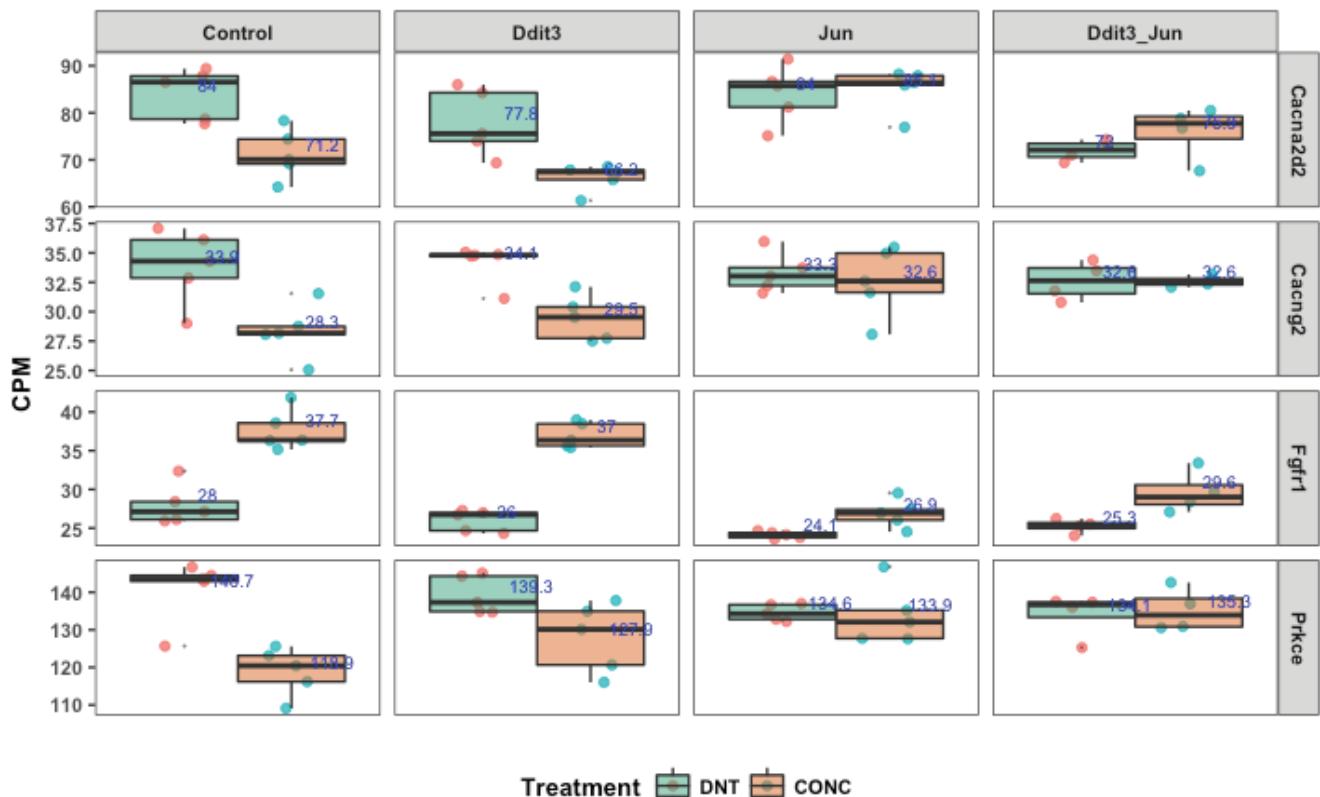
Selected DE genes involved in: Synaptic long term potentiation, Synaptic long term depression
 CREB Signaling in Neurons, CDK5 Signaling, nNOS Signaling in Neurons

Fig 5. Jun but not Ddit3 protects attenuates activation of neuroinflammation during ONC



Selected DE genes involved in: Acute phase response signaling, IL6 signaling, Ccr5 signaling in macrophages, HMGB1 signaling

Fig 6



Selected DE genes involved in both neuronal process as well as neuroinflammation

Fig 2 x

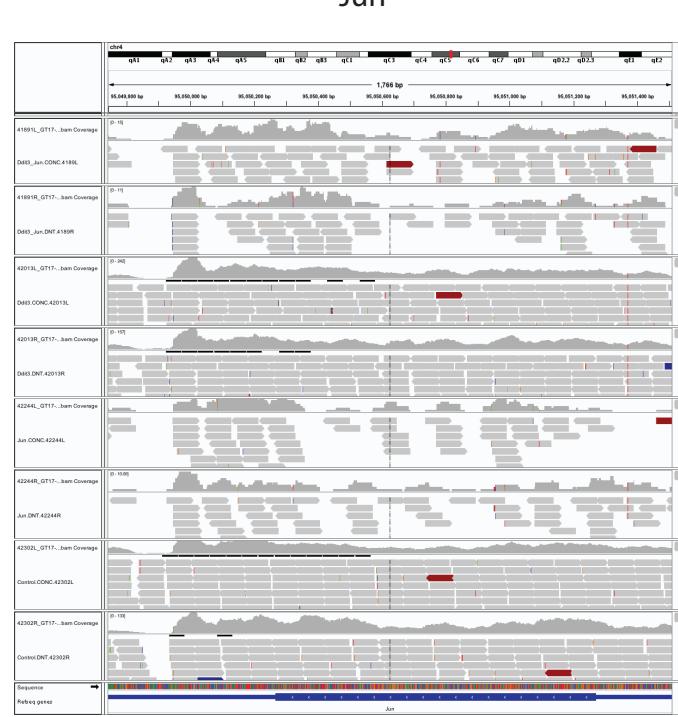
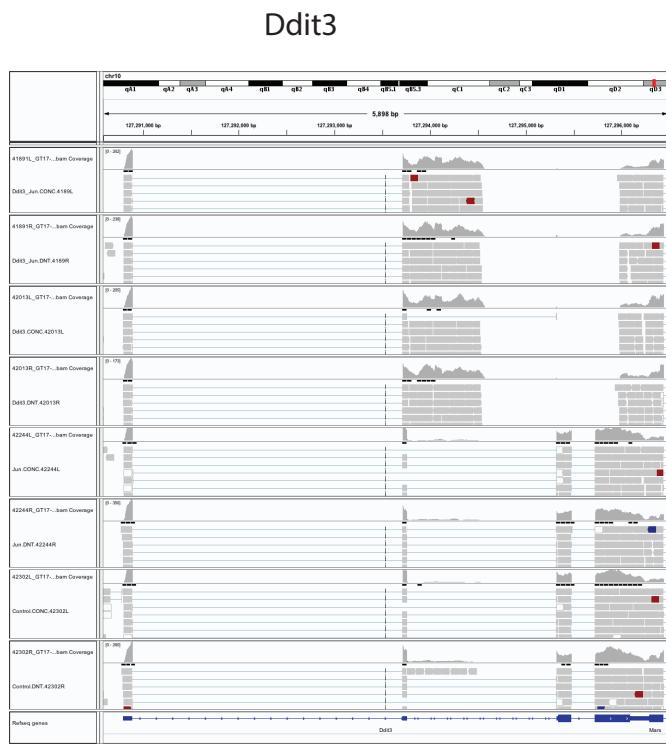
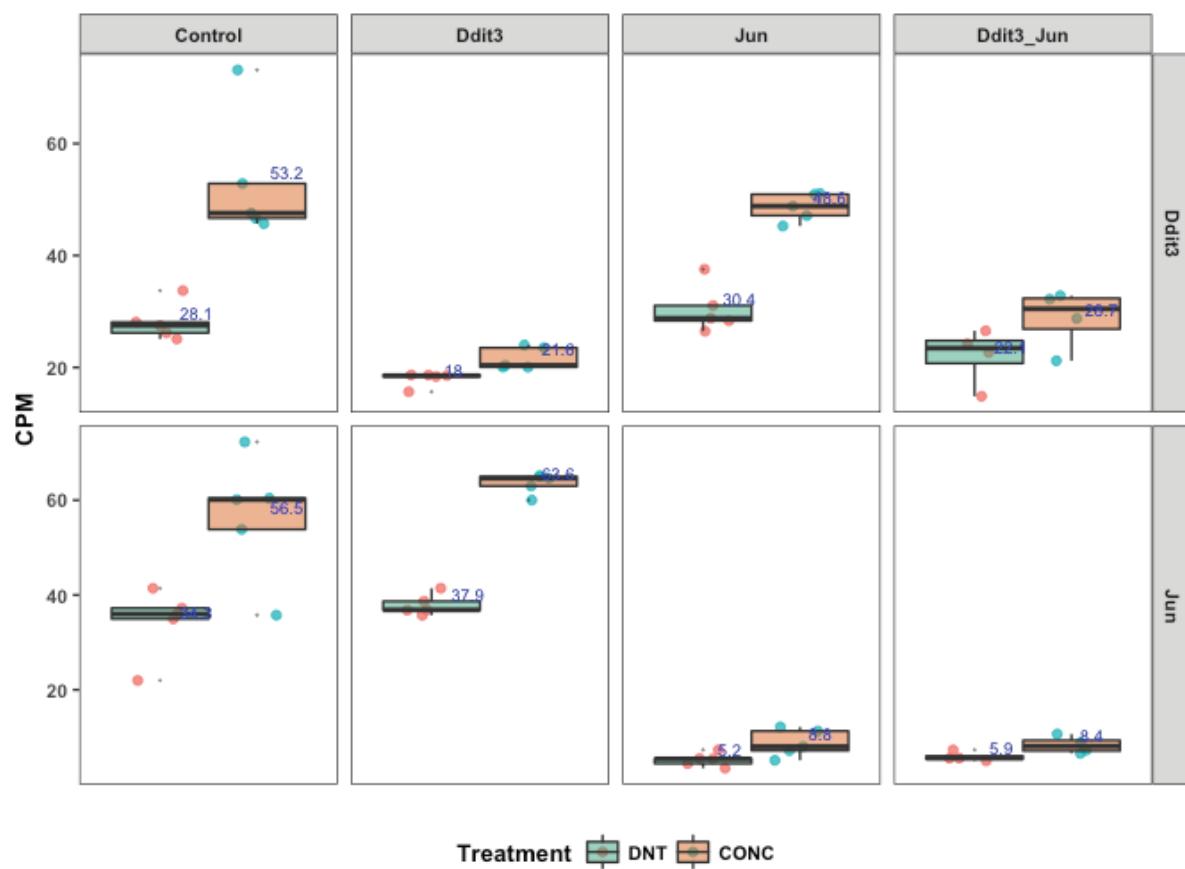


Fig 7. upstream regulator analysis revealed Jun and Ddit3 specific targeting genes during CONC

DDIT3,JUN 4

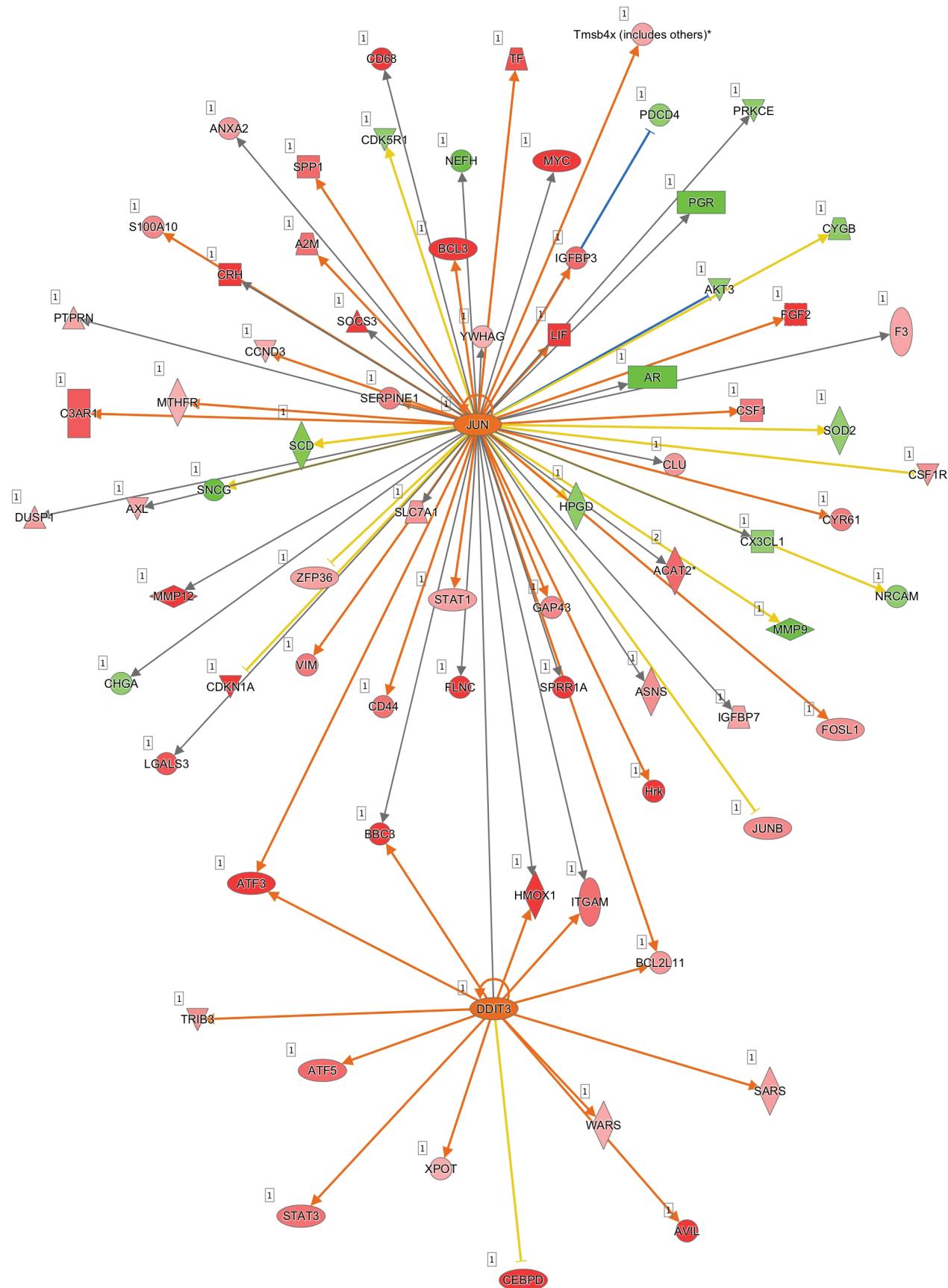


Fig 8. selected Jun and Ddit3 gene targets
 (Avil and Atf5 is a Ddit3 specific gene targets)

