CNV_report

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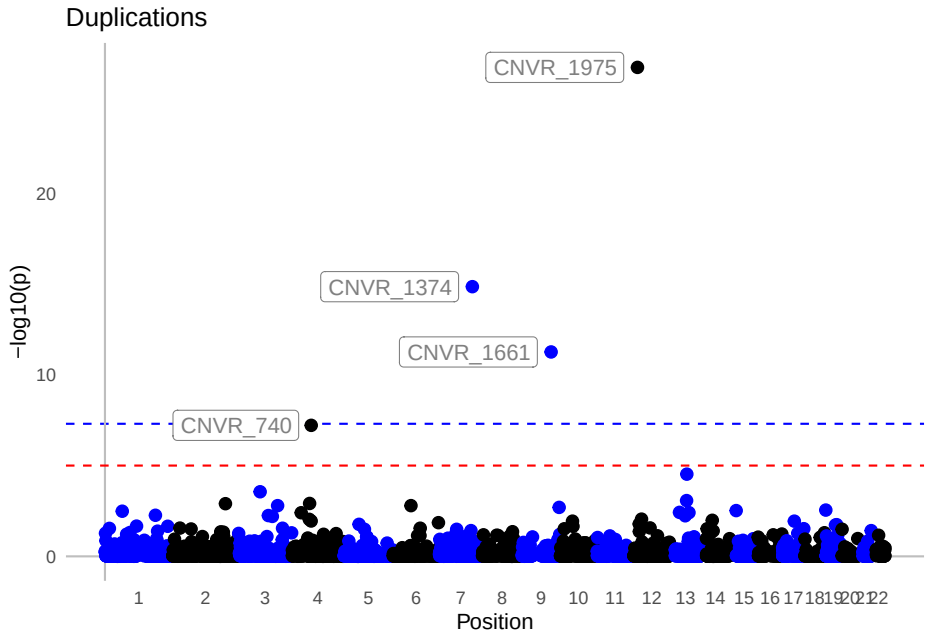
10/4/2022

CNVWAS



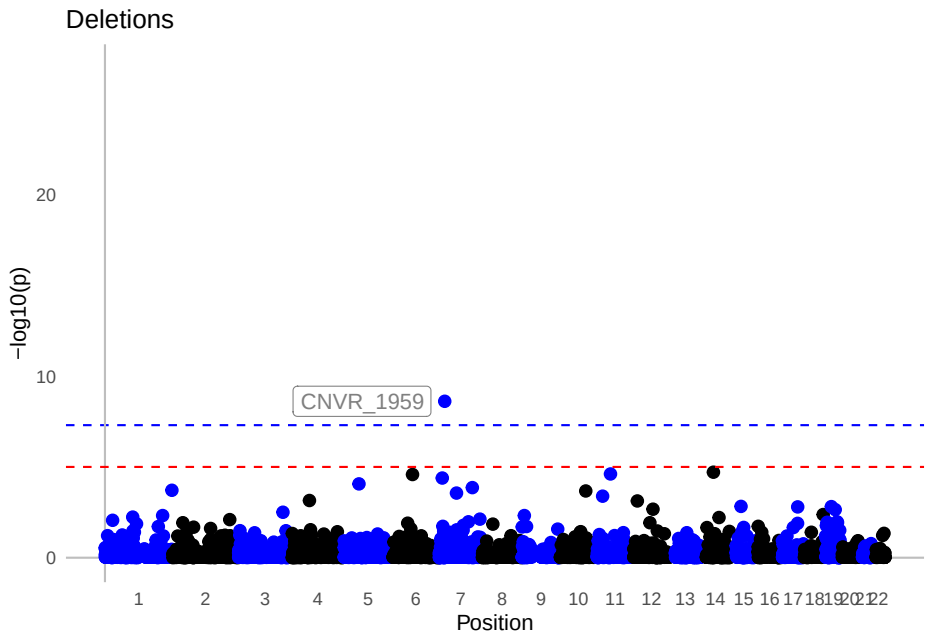


Table 1: Significant CNVRs

CNVR_ID	Chr	Start	End	Type	Coef.	p-value
CNVR_1374	7	122375615	122986940	Gain	0.85 (0.11)	1.4028e-15
CNVR_1661	9	107516115	107545274	Gain	0.82 (0.12)	5.5318e-12
CNVR_1975	12	14522641	14593902	Gain	0.97 (0.09)	1.1750e-27
CNVR_740	4	70783348	70934328	Gain	0.55 (0.1)	6.0865e-08
CNVR_1959	7	20703948	20706901	Loss	1.9 (0.32)	2.4227e-09

CNVRs significant at p < 1e-05. The table includes location and size of CNVR, gain or deletion, and mean and standard deviation of estimated effect.

Table 2: Genes overlapping CNVRs

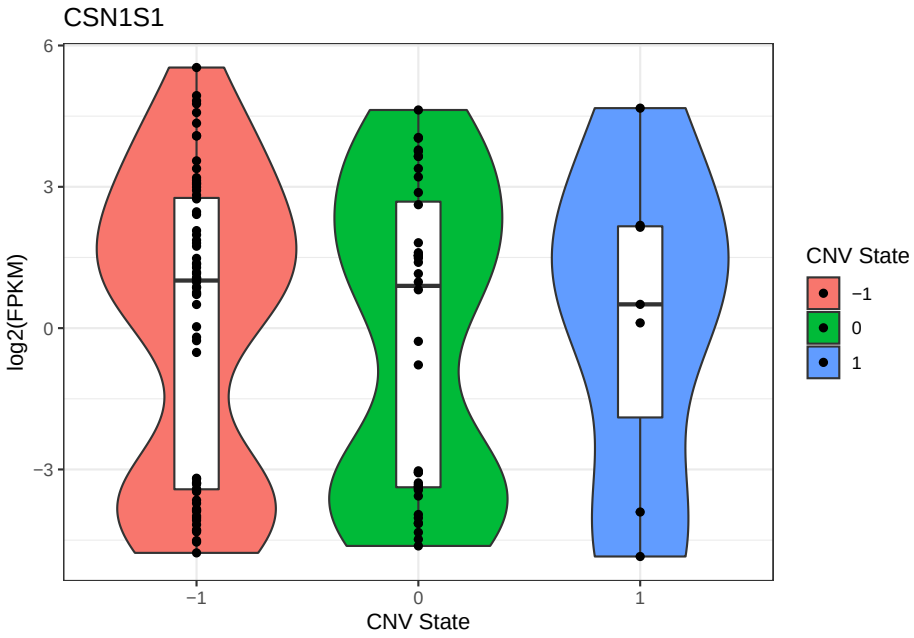
CNVR	Genes
CNVR_1959	CACNA1C, CACNA1C-AS4, CACNA1C-IT3, CACNA1C-AS2, CACNA1C-AS1, ITFG2-AS1, FKBP4, ITFG2, NRIP2, TEX52, FOXM1, RHNO1, TULP3, TEAD4, TSPAN9, LOC100128253, LINC02417, PRMT8
CNVR_1374	CADPS2, TAS2R16, SLC13A1
CNVR_1661	NIPSNAP3A, NIPSNAP3B, ABCA1
CNVR_1975	ATF7IP
CNVR_740	CSN1S1, CSN2, STATH, HTN3, HTN1, CSN1S2AP

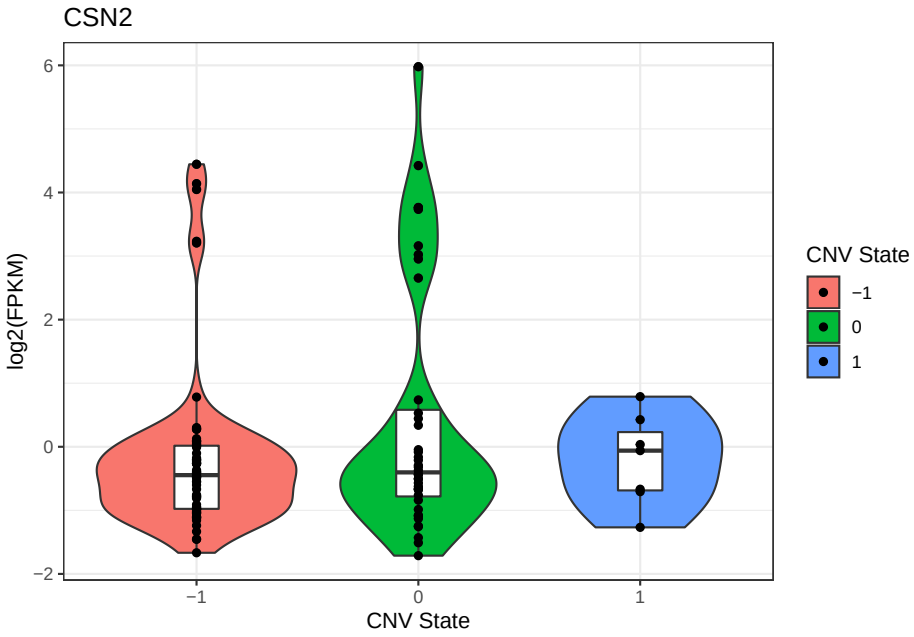
All genes that partially or complete overlap significant CNVRs.

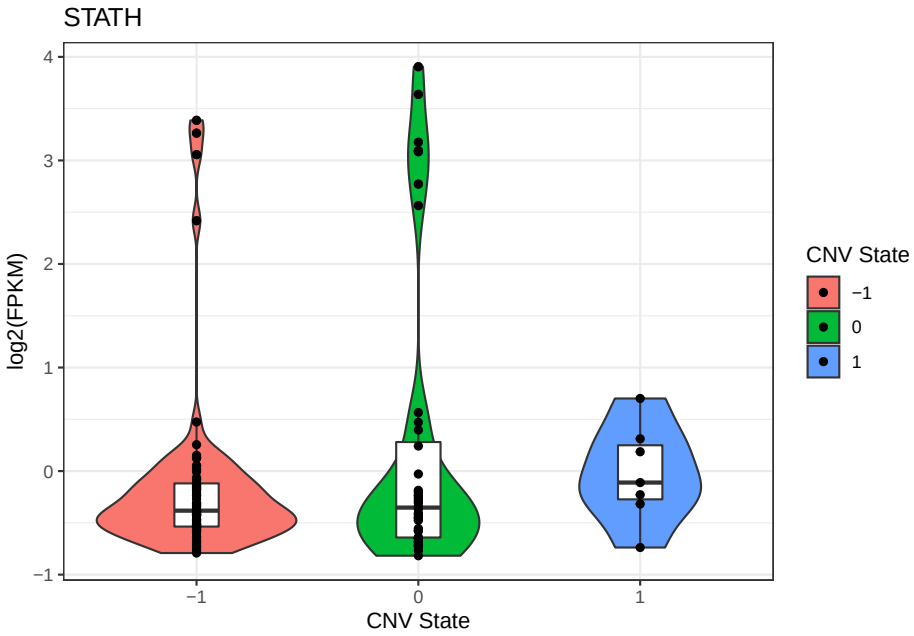
Expression

We examined the association of copy number state and expression (log2(FPKM)). Expression was adjusted to account for the effect of cPg-methylation by taking the residuals from a linear model. Copy number is

assumed to be additive. Expression is measured for all genes that overlap with a CNVR, except for TAS2R16, which did not have enough observations to model.






STATH
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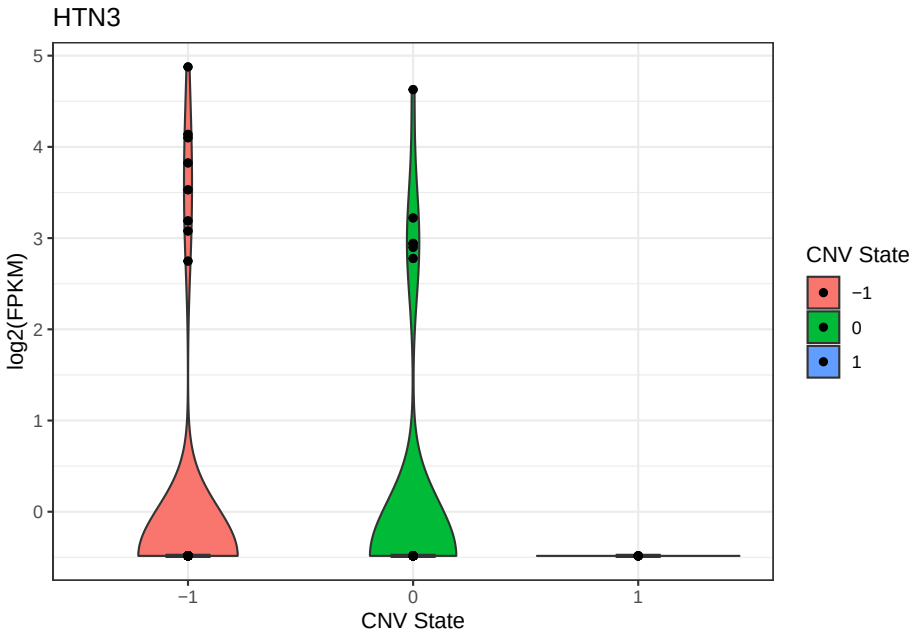
3
2
1
0
−1
−1
0
1
CNV State
CNV State
−1
0
1


HTN3
log2(FPKM)
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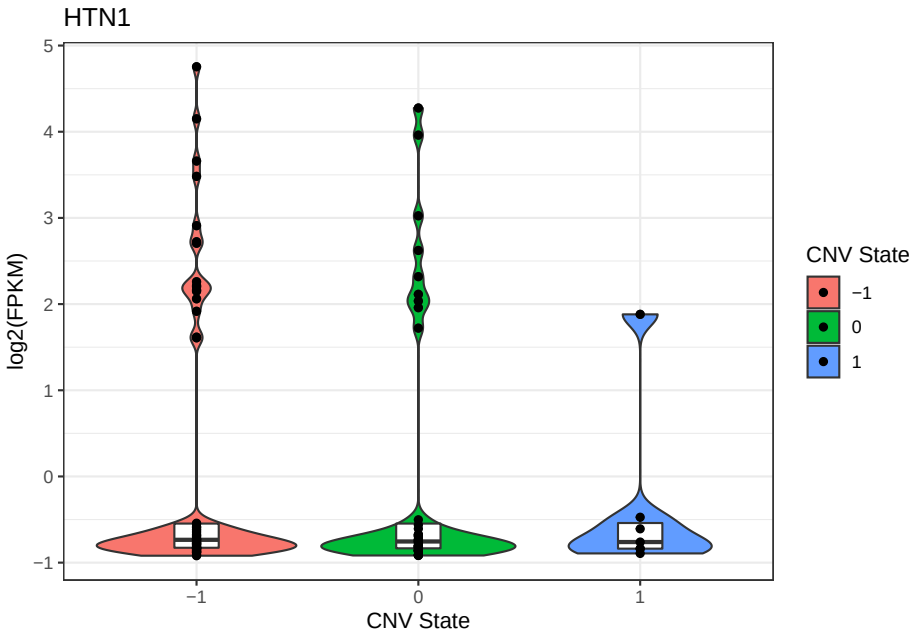
4
3
2
1
0
−1
0
1
CNV State
CNV State
−1
0
1


HTN1
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4
3
2
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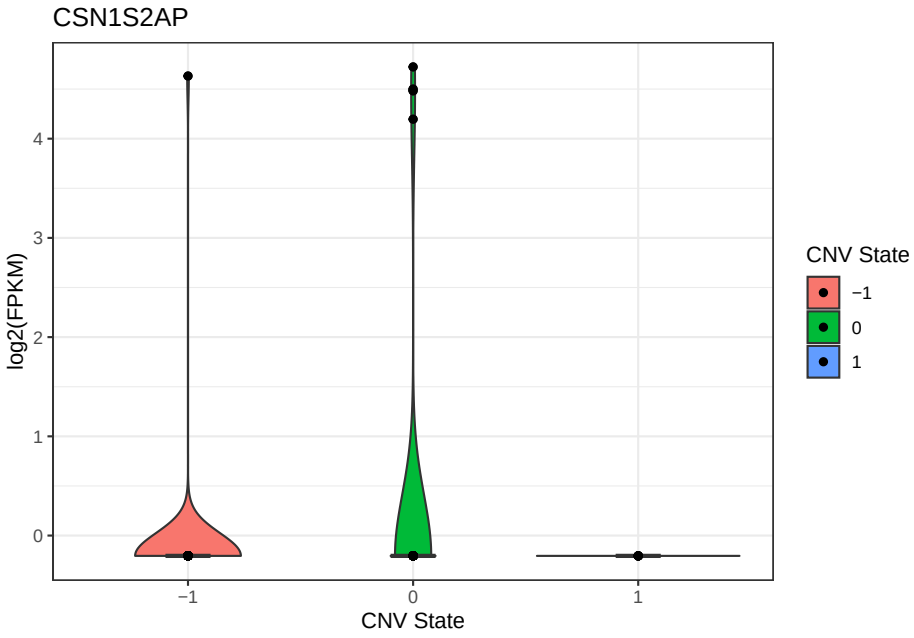
0
−1
−1
0
1
CNV State
CNV State
−1
0
1


CSN1S2AP
log2(FPKM)
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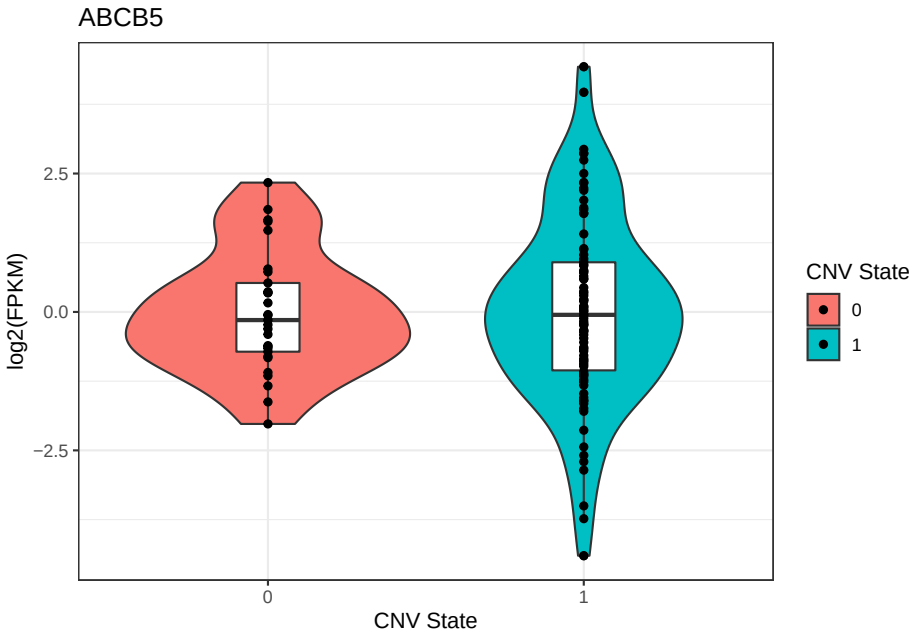
2
1
0
−1
0
1
CNV State
CNV State
−1
0
1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0
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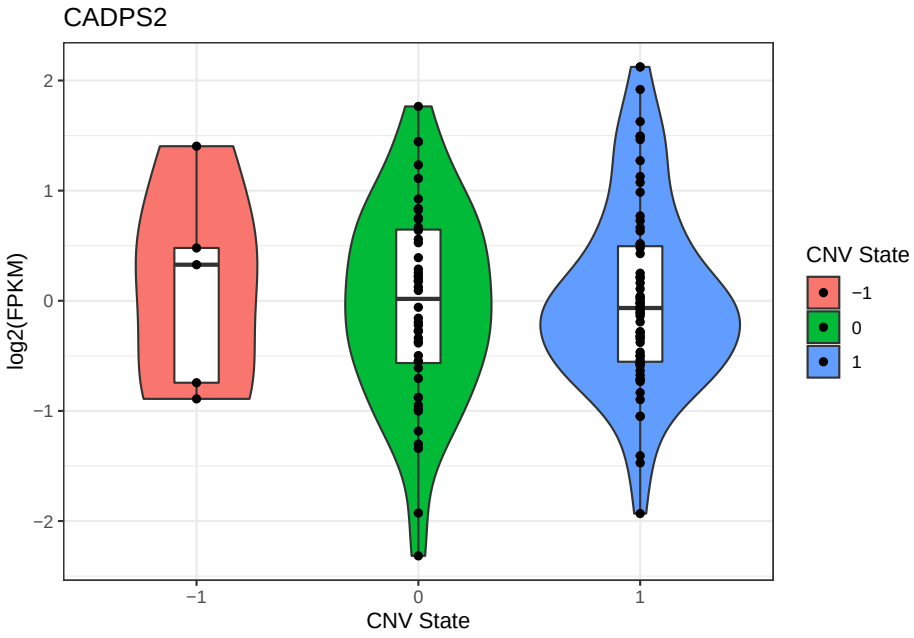
CNV State
CNV State
0
1


CADPS2
log2(FPKM)
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1
0
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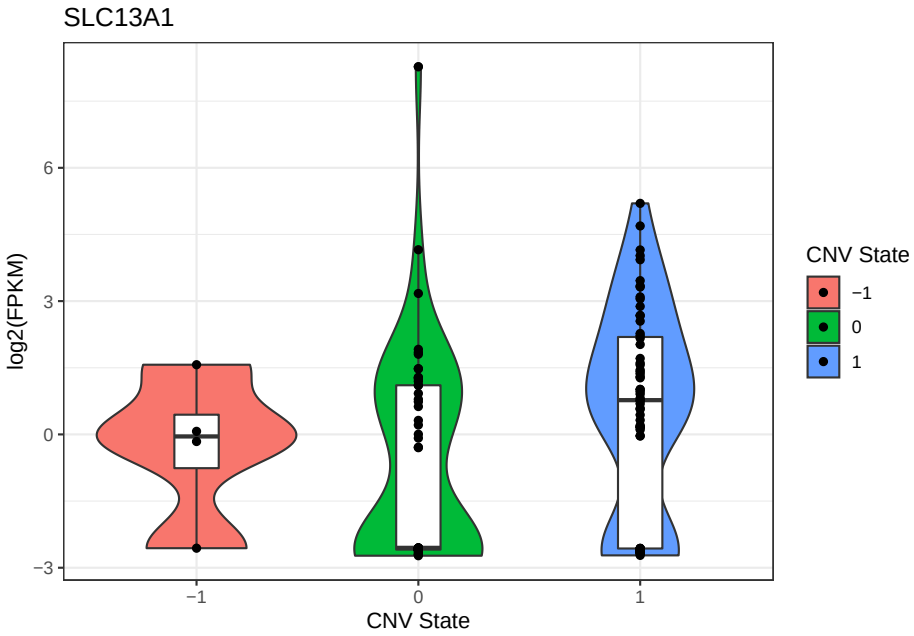
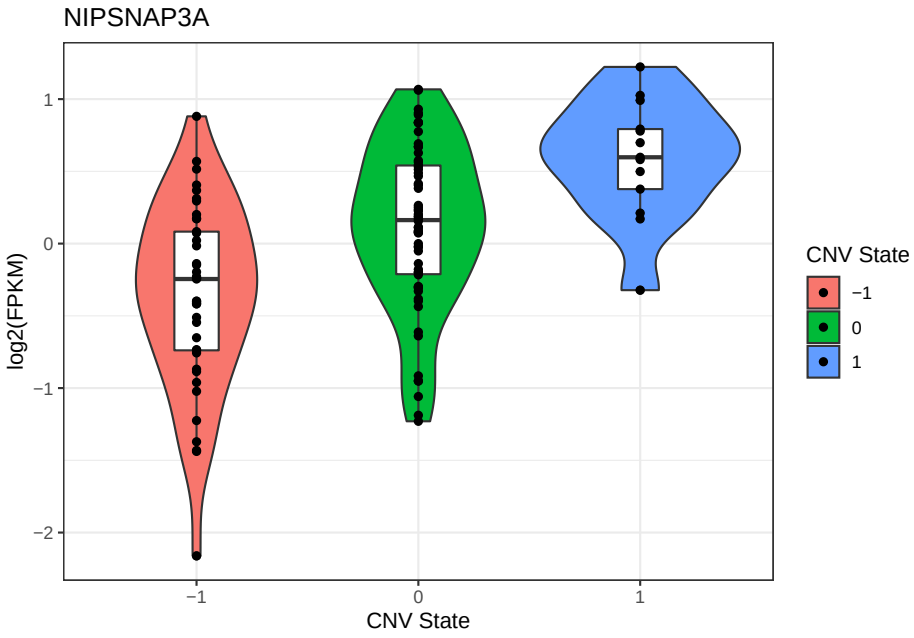
−2
−1
0
1
CNV State
CNV State
−1
0
1


SLC13A1
log2(FPKM)
6
3
0
−3
−1
0
1
CNV State
CNV State
−1
0
1


NIPSNAP3A
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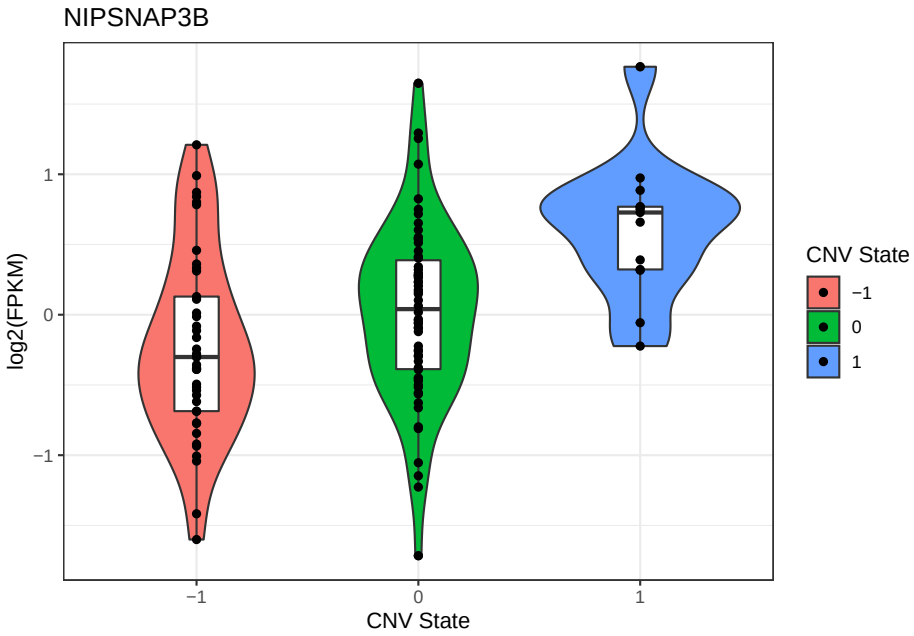
−2
−1
0
1
CNV State
CNV State
−1
0
1


NIPSNAP3B
log2(FPKM)
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CNV State
CNV State
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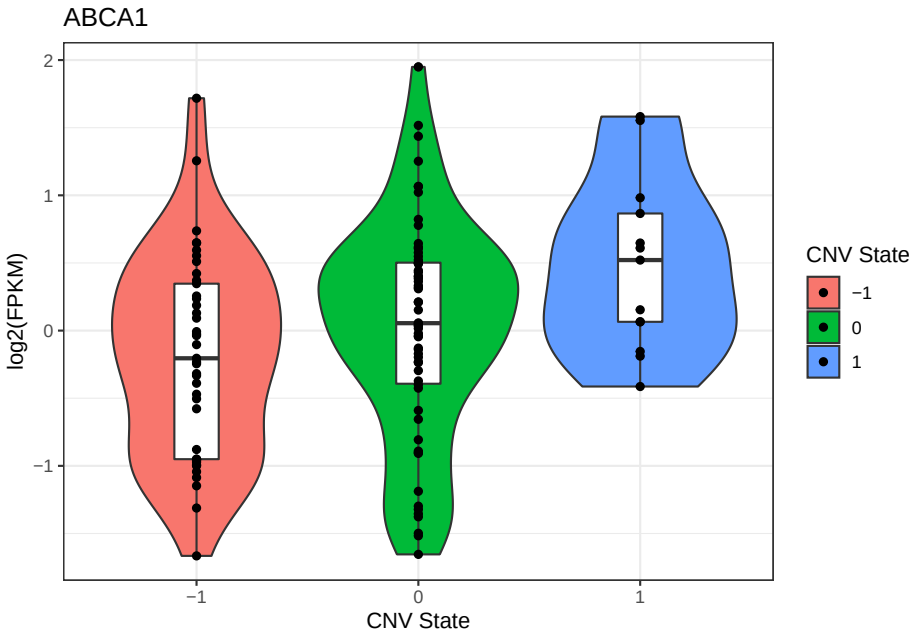
0
1


ABCA1
log2(FPKM)
2
1
0
−1
−1
0
1
CNV State
CNV State
−1
0
1

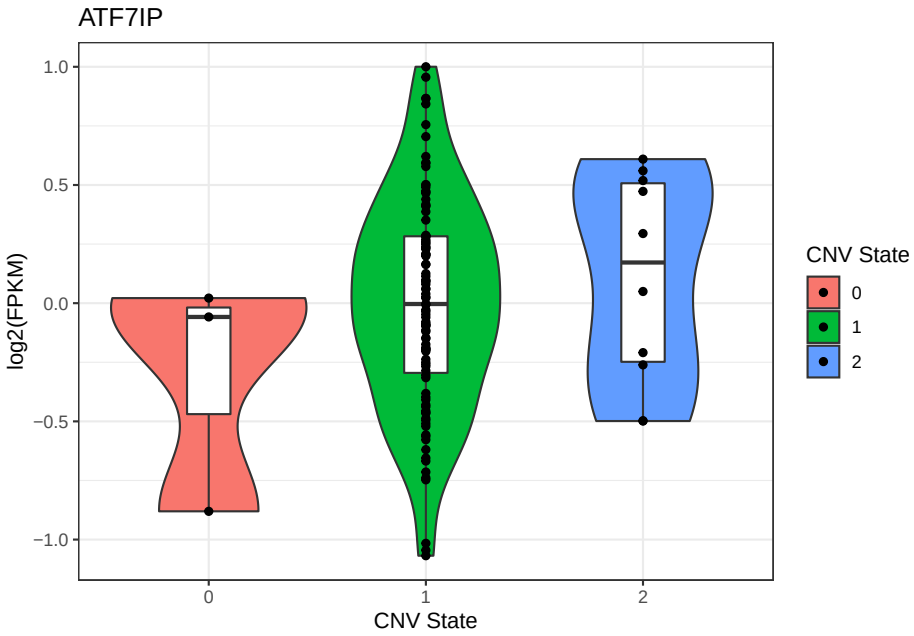


Table 3: Correlation of Copy Number and Expression

Gene	r	p-value
CSN1S1	-0.04	0.6834
CSN2	0.12	0.1938
STATH	0.13	0.1802
HTN3	-0.04	0.6606
HTN1	-0.05	0.5923
CSN1S2AP	0.11	0.2635
ABCB5	0.01	0.9506
CADPS2	0.01	0.9196
SLC13A1	0.21	0.0222
NIPSNAP3A	0.47	1.3041e-07
NIPSNAP3B	0.35	0.0001
ABCA1	0.24	0.0087
ATF7IP	0.11	0.2206

Pearson correlation and p-value of copy number and expression, corrected for cPg methylation. NIPSNAP3A, NIPSNAP3B, and ABCA1 show a statistically significant and positive correlation. SLC13A1 and ATF7IP show a similar relationship but is effected by outliers.

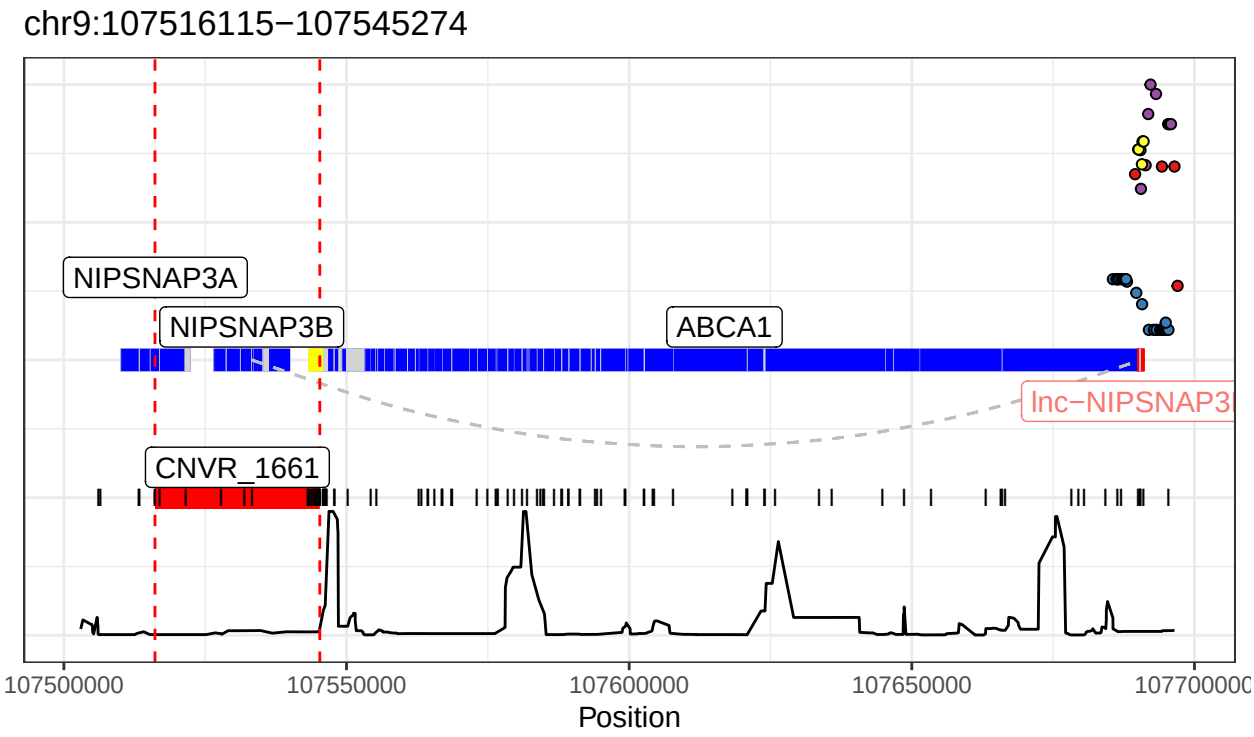


Figure 1: CNVR1661 overlaps with NIPSNAP3A, fully contains NIPSNAP3B, and overlaps with the promoter region (yellow) or ABCA1. All eQTLs point to lnc-NIPSNAP3B. Exons are denoted in gray among the genes, while probes are in black along the CNVR. Recombination rate is plotted at the bottom. SNPs are colored according to LD (r2 >= 0.6).

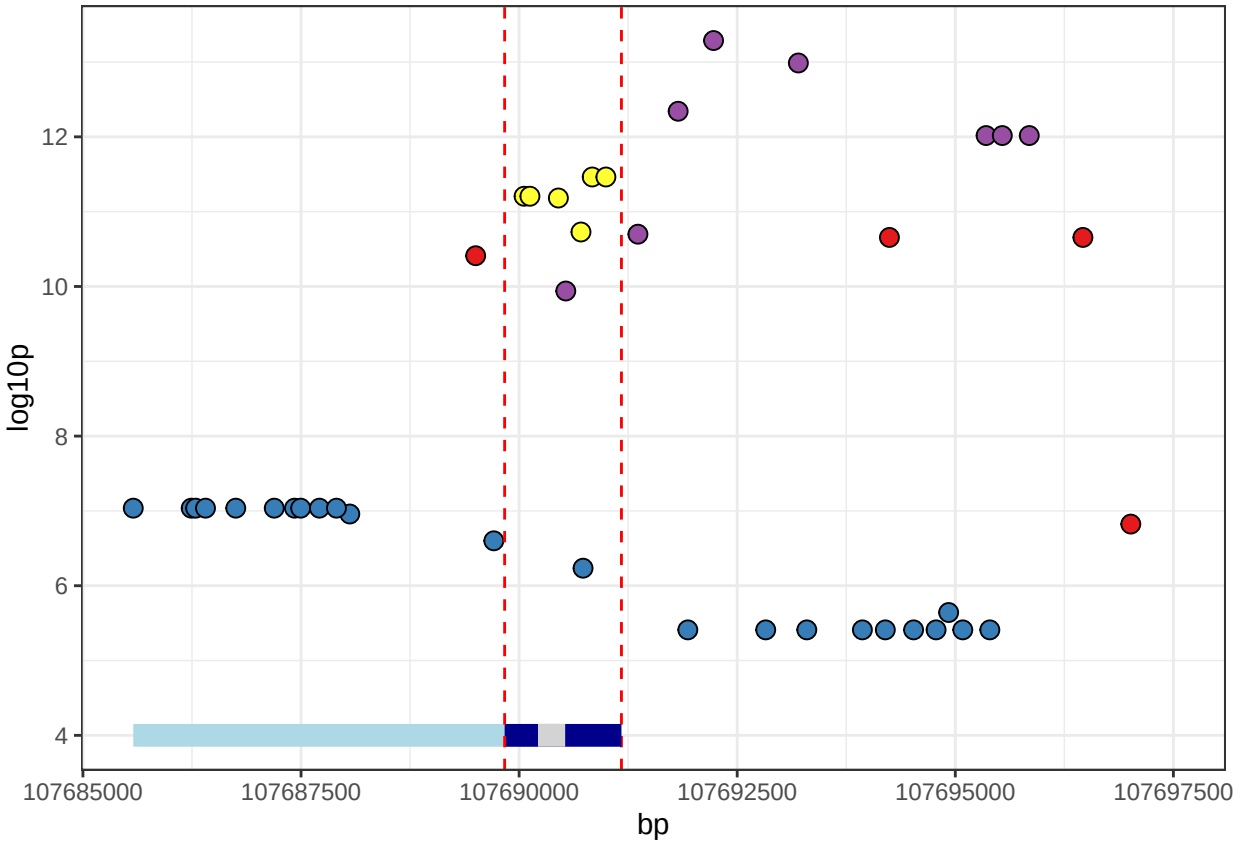


Figure 2: Zoomed in view of lnc-NIPSNAP3B.

Annotation

Interpretation

ABCA1 mediates the transfer of cellular cholesterol across the plasma membrane to apolipoprotein A-I. The efflux function of ABCA1 has anti-cancer activity that is compromised following inhibition of expression by oncogenic or loss-of-function mutations. ABCA1 deficiency permits increased mitochondrial cholesterol and inhibits the release of mitochondrial cell death-promoting molecules, facilitating cancer cell survival (Smith & Land, 2012). ABCA1 Mutations in ABCA1 yield diminish its tumor suppressor functions in patients with chronic myelomonocytic leukemia (Viaud et al., 2020). Low expression of ABCA1 has been linked to worse outcomes in several cancer types including prostate, glioblastoma, pancreatic, breast, lung, and ovarian (Wu et al., 2022).

NIPSNAP3A (NIPSNAP4) and NIPSNAP3B (NIPSNAP3) are homoglous genes with putative roles in vesicular trafficking. ABCA1 is also a regulator of vesicular trafficking, and the close proximity of the genes may indicate a functional relationship. (Buechler et al., 2004). The NIPSNAP family interacts with a variety of mitochondrial and cytoplasmic proteins, and have been implicated in multiple cellular processes associated with different physiologic and pathologic conditions including cancer. (Fathi et al., 2021). NIPSNAP1 and NIPSNAP2 are active in the regulation of mitophagy (Abudu et al., 2019).

Next Steps

Determine pathogenicity of CNVs? https://github.com/Genotek/ClassifyCNV

(Han et al., 2020) annotated CNVRs with transcription start sites, open chromatin, TAD domains, and CTCF binding sites as a proxy for TAD boundaries. Also PFC enhancer annotations, generated by overlapping cross-tissue DNase-seq and ATAC-seq assay information with H3K27ac CHIP-seq peaks. Regions overlapping H3K4me3 peaks and within 2kb of a TSS were exlucded from the set of enhancers. Promoters are gene specific, genes predicted to be the targets of enhancers from Hi-C were most useful.

References

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Buechler C, Bodzioch M, Bared SM, Sigruener A, Boettcher A, Lapicka-Bodzioch K, Aslanidis C, Duong CQ, Grandl M, Langmann T, Dembinska-Kiec A, Schmitz G. Expression pattern and raft association of NIPSNAP3 and NIPSNAP4, highly homologous proteins encoded by genes in close proximity to the ATP-binding cassette transporter A1. Genomics. 2004 Jun;83(6):1116-24. doi: 10.1016/j.ygeno.2003.12.011. PMID: 15177564.

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