Supporting Information for Hilvo et al. (2015)

May 14, 2015

Contents

1 Libraries and functions

The R scripts provided in this vignette fully reproduces the TCGA survival analyses of Hilvo et al (2015). The following R packages may be required:

- `survival`

We use a local library for some low level functions. This will be loaded from `http://www.markowetzlab.org/supplements/` if not present on the local machine.

2 External Data Sources

The package Hilvo2015-supplement-data.Rdata contains the publicly available data described in the following subsections. This will be loaded from `http://www.markowetzlab.org/supplements/` if not present on the local machine.

```
## load data file from local copy or from URL
if (file.exists("Hilvo2015-supplementary-data.Rdata")){
    load("Hilvo2015-supplementary-data.Rdata")
    cat("Hilvo2015-supplementary-data.Rdata loaded from local copy")
} else {
    #load(url("https://github.com/InesdeSantiago/survivalTCGAOC/blob/master/Hilvo2015-su
    #cat("Hilvo2015-supplementary-data.Rdata loaded from URL")
    cat("please download file from github repository: https://github.com/InesdeSantiago/s
}

## Hilvo2015-supplementary-data.Rdata loaded from local copy
```

2.1 TCGA data

Data from 489 high-grade serous ovarian cancers reported by The Cancer Genome Atlas Research Network (Nature, 2011, 609-615) were obtained from `https://tcga-data.nci.nih.gov/docs/publications/ov_2011/`. The `exp.TCGAOC` object contains the gene expression matrix obtained from `https://tcga-data.nci.nih.gov/docs/publications/ov_2011/`:

```
dim(exp.TCGAOC)

## [1] 11864   489
```

The `clinical.TCGAOC` object contains the clinical annotations for all samples obtained from: `https://tcga-data.nci.nih.gov/docs/dictionary/TCGA_BCR_DataDictionary.xml`

```r
dim(clinical.TCGAOC)
```

```
## [1] 488  12
```

```r
colnames(clinical.TCGAOC)
```

```
##  [1] "AgeAtDiagnosis..yrs."           "VITALSTATUS"
##  [3] "TUMORSTAGE"                     "TUMORGRADE"
##  [5] "TUMORRESIDUALDISEASE"           "PRIMARYTHERAPYOUTCOMESUCCESS"
##  [7] "PERSONNEOPLASMCANCERSTATUS"     "OverallSurvival.mos."
##  [9] "ProgressionFreeStatus"          "ProgressionFreeSurvival..mos.."
## [11] "PlatinumFreeInterval..mos.."    "PlatinumStatus"
```

2.2 Copy Number Alterations (CNA)

The CNA data was downloaded from cBioPortal (`http://cbioportal.org`) using the TCGA set of 489 high-grade serous ovarian cancers. Only 316 tumours have CNA data available:

```r
dim(CNAtable)
```

```
## [1] 316  69
```

3 Survival analysis for the TCGA cohort

To validate the metabolomics findings with gene expression data, survival analyses were performed for The Cancer Genome Atlas (TCGA) data. Survival analysis based on gene expression and copy number was performed for genes of those selected KEGG pathways that showed most interesting metabolomics results: fatty acid import and beta oxidation, omega oxidation, ketone body production, pentose phosphate pathway reactions related to 3-erythritol accumulation, leucine degradation reactions related to 3-hydroxyisovaleric acid accumulation, peroxisomal biogenesis factors related to Zellweger syndrome as well as ALDH5A1 gene encoding for SSADH enzyme.

```
colnames(CNAtable)
```

```
##  [1] "ACAA1"   "ACAA2"   "ACADL"   "ACADM"   "ACADS"   "ACADSB"  "ACADVL"
##  [8] "ACAT1"   "ACOX1"   "ACSBG1"  "ACSBG2"  "ACSL1"   "ACSL3"   "ACSL5"
## [15] "ACSL6"   "ADH1A"   "ADH1B"   "ADH1C"   "ADH5"    "ADH6"    "ADH7"
## [22] "ALDH1B1" "ALDH2"   "ALDH3A2" "ALDH5A1" "ALDH7A1" "ALDH9A1" "AUH"
## [29] "BDH1"    "BDH2"    "BTD"     "CPT1A"   "CPT1B"   "CPT2"    "CYP4A11"
## [36] "CYP4B1"  "CYP4F11" "DLD"     "ECHS1"   "ECI1"    "ECI2"    "EHHADH"
## [43] "FABP4"   "HADH"    "HADHA"   "HADHB"   "HLCS"    "HMGCL"   "HMGCS1"
## [50] "HMGCS2"  "MCCC1"   "MCCC2"   "OXCT1"   "OXCT2"   "PEX1"    "PEX10"
## [57] "PEX12"   "PEX13"   "PEX14"   "PEX16"   "PEX19"   "PEX3"    "PEX5"
## [64] "PEX6"    "PEX7"    "RPIA"    "SHPK"    "TALDO1"  "TKT"
```

For each gene of interest, we subdivided the TCGA Ovarian Cancer cohort according to:

- Four quartiles of gene expression
- Different copy number alterations: Loss, wt and gain

First, we simplified the Gistic scores obtained from the downloaded table as "loss","wt","gain":

```
CNAallgenes <- CNAtable
CNAallgenes[CNAallgenes==-2] <- "loss" #hom del
CNAallgenes[CNAallgenes==-1] <- "loss" #het loss
CNAallgenes[CNAallgenes==0] <- "wt"
CNAallgenes[CNAallgenes==1] <- "gain" #gain
CNAallgenes[CNAallgenes==2] <- "gain" #amp
CNAallgenes <- t(CNAallgenes)
```

```
# Survival wrapper function
survwrapp <- function(gene, plot = TRUE) {
```

```
    # par(mfrow=c(1,2),mar=c(20,4,5,4))

    # by quartiles
    group <- cut(as.numeric(exp.TCGAOC[gene, ]), quantile(as.numeric(exp.TCGAOC[gene,
        ]), probs = c(0, 0.25, 0.5, 0.75, 1)))
    names(group) <- names(exp.TCGAOC[gene, ])
    survmat <- cbind(groups = group[rownames(clinical.TCGAOC)], clinical.TCGAOC)
    pvalue1 <- plotsurv(survmat, colors = c("blue", "lightblue", "gray", "red"),
        maint = "", plot = plot)
    if (plot) {
        title(main = paste(gene, "\nBy expression quartile"))
    }

    # by mutation type
    group <- factor(CNAallgenes[gene, ], levels = c("loss", "wt", "gain"))
    survmat <- cbind(groups = group[rownames(clinical.TCGAOC)], clinical.TCGAOC)
    pvalue2 <- plotsurv(survmat, colors = c("turquoise4", "darkgray", "orangered"),
        maint = "", plot = plot)

    if (plot) {
        title(main = paste(gene, "\nBy CNA type"))
    }

    # this function returns the chisq p-values obtained in both cases
    # 'by_ExpQuartiles' and 'by_CNA'
    return(c(by_ExpQuartiles = pvalue1, by_CNA = pvalue2))
}

plotsurv <- function(survmat, colors, maint, timecol = "OverallSurvival.mos.",
    eventcol = "VITALSTATUS", plot = TRUE) {
    library(survival)

    # fix survmat
    if (eventcol == "VITALSTATUS") {
        survmat$VITALSTATUS <- as.character(survmat$VITALSTATUS)
        survmat$VITALSTATUS[survmat$VITALSTATUS == "LIVING"] <- 0
        survmat$VITALSTATUS[survmat$VITALSTATUS == "DECEASED"] <- 1
        survmat$VITALSTATUS <- as.numeric(survmat$VITALSTATUS)
    }
    if (eventcol == "ProgressionFreeStatus") {
        survmat$ProgressionFreeStatus <- as.character(survmat$ProgressionFreeStatus)
        survmat$ProgressionFreeStatus[survmat$ProgressionFreeStatus == "DiseaseFree"] <-
        survmat$ProgressionFreeStatus[survmat$ProgressionFreeStatus == "Recurred/Progres
```

```
        survmat$ProgressionFreeStatus <- as.numeric(survmat$ProgressionFreeStatus)
    }
    survmat <- subset(survmat, select = c("groups", timecol, eventcol))
    survmat <- na.omit(survmat)

    # plot
    ss <- Surv(as.numeric(survmat[, timecol]), survmat[, eventcol])
    if (plot) {
        plot(survfit(ss ~ survmat$groups), col = colors, xlab = paste(timecol,
            "[months]"), ylab = "Survival Probability", lwd = 3, las = 1, main = maint)
        legendtext = paste(levels(survmat$group), ": n=", table(survmat$group),
            sep = "")
        legend("topright", col = colors, legend = legendtext, lty = 1)
    }

    # Pvalue and HR
    res <- survdiff(ss ~ survmat$group)

    p <- 1 - pchisq(res$chisq, 1)
    if (p < 0.001) {
        p <- format(p, scientific = TRUE, nsmall = 3)
    } else {
        p <- round(p, 3)
    }

    if (plot) {
        text(100, 0.6, paste("p-value=", p))
        options(scipen = 10)
    }

    return(p)
}
```

3.1 Supplementary Table S7: survival analyses using TCGA data

Survival analysis was performed for the following genes:

```
genes <- c('ALDH5A1','DLD','PEX6','HMGCL','ACSL3','ADH1B','HLCS','AUH','ALDH7A1',
'MCCC2','PEX12','OXCT1','ALDH1B1','EHHADH','HMGCS1','FABP4','ECI1','HADHA','CPT1B')
```

For each one of the selected genes, we investigated if low expression and loss in copy numbers of the gene were associated with worse overall survival. The following code reproduces the p-values in supplementary table 7.

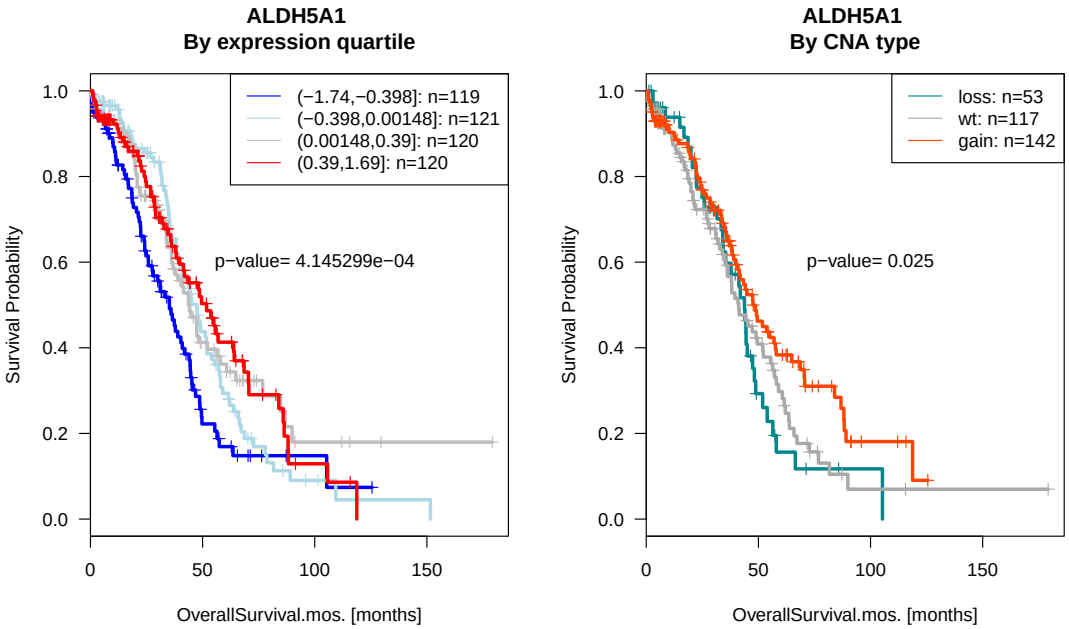
```
library(knitr)
pvalues <- t(sapply(genes, survwrapp, plot=FALSE))
kable(pvalues)
```

	by_ExpQuartiles	by_CNA
ALDH5A1	4.145299e-04	0.025
DLD	4.627128e-04	0.12
PEX6	8.578187e-04	0.235
HMGCL	0.004	0.56
ACSL3	0.009	0.137
ADH1B	0.027	0.641
HLCS	0.029	0.388
AUH	0.033	0.093
ALDH7A1	0.029	0.022
MCCC2	0.887	1.702884e-04
PEX12	0.427	0.003
OXCT1	0.178	0.004
ALDH1B1	0.217	0.005
EHHADH	0.063	0.01
HMGCS1	0.082	0.012
FABP4	0.059	0.018
ECI1	0.355	0.025
HADHA	0.043	0.031
CPT1B	0.088	0.04

3.2 Figure 2E and Figure S5: Low gene expression and loss of ALDH5A1 copy number were both associated to poor overall survival

Intriguingly, the most significant findings were obtained for the ALDH5A1 gene, as in the TCGA data set both low expression and loss in copy numbers of the gene were associated with worse overall survival of the patients.

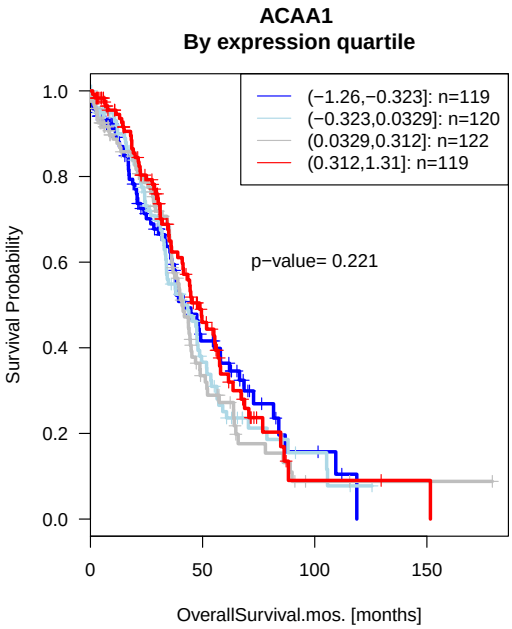
```
par(mfrow=c(1,2))
survwrapp("ALDH5A1")
```

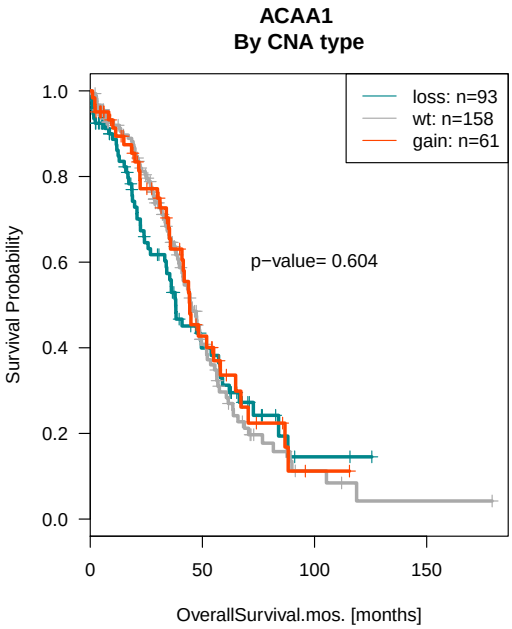


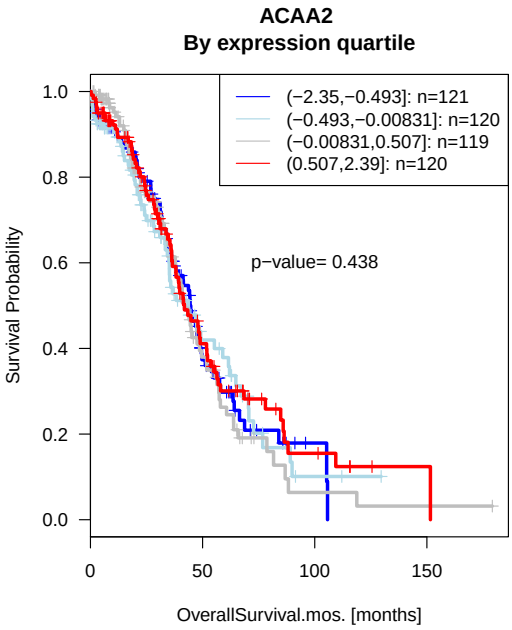

```
## by_ExpQuartiles          by_CNA
##  "4.145299e-04"         "0.025"
```

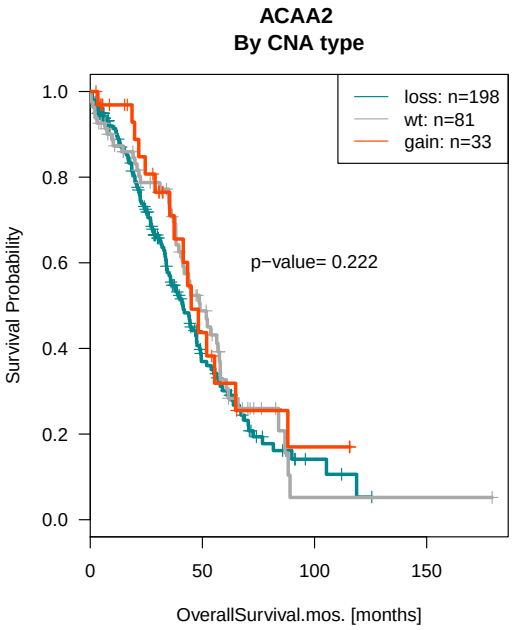
The survival plots for all analysed genes can be inspected with the following code:

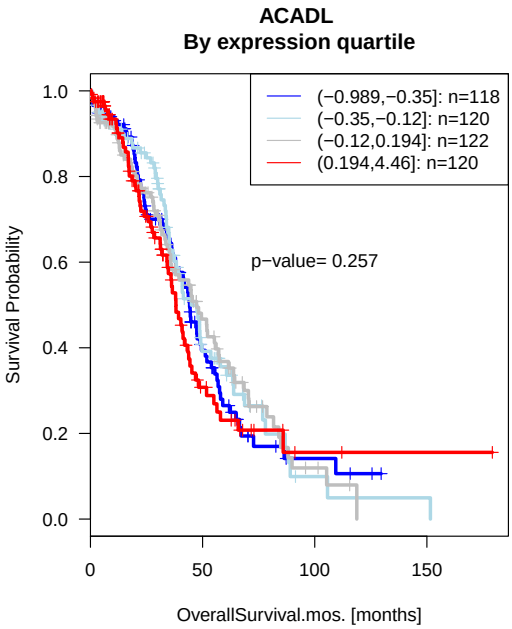
```
par(mfrow=c(1,2))
pvalues <- sapply(colnames(CNAtable), survwrapp, plot=TRUE)
```

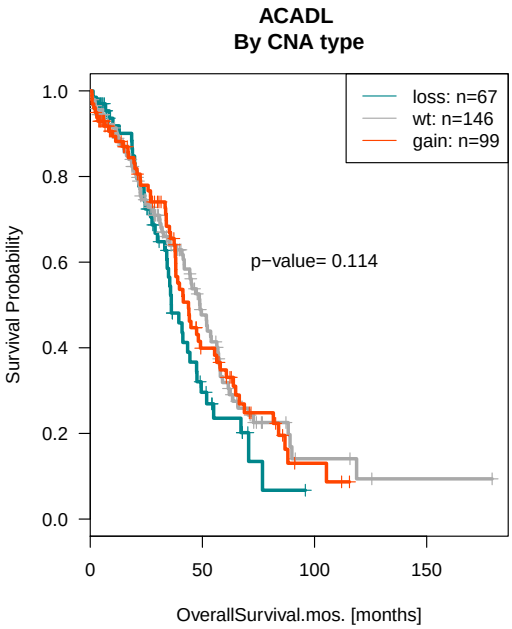

ACAA1
By expression quartile
(−1.26,−0.323]: n=119
(−0.323,0.0329]: n=120
(0.0329,0.312]: n=122
(0.312,1.31]: n=119
p−value= 0.221
Survival Probability
OverallSurvival.mos. [months]

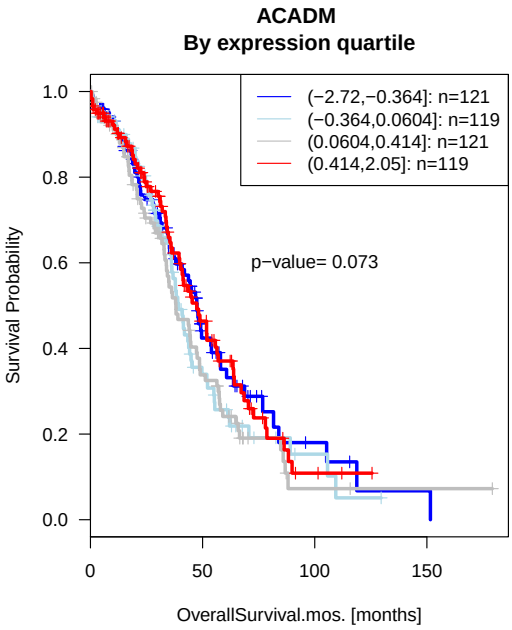

ACAA1
By CNA type
loss: n=93
wt: n=158
gain: n=61
p−value= 0.604
Survival Probability
OverallSurvival.mos. [months]

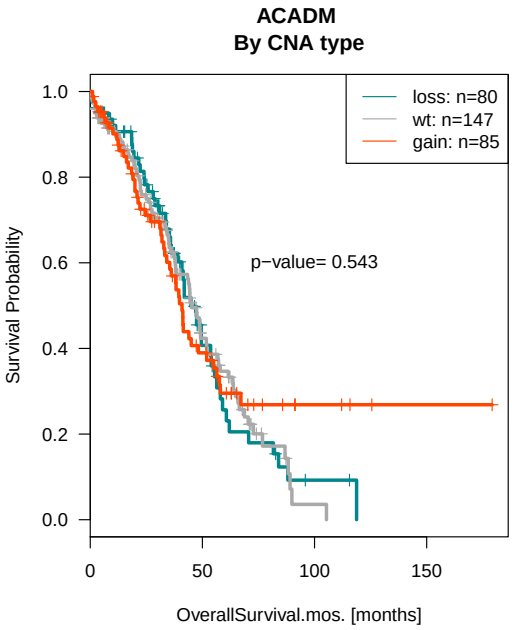

ACAA2
By expression quartile
(−2.35,−0.493]: n=121
(−0.493,−0.00831]: n=120
(−0.00831,0.507]: n=119
(0.507,2.39]: n=120
p−value= 0.438
Survival Probability
OverallSurvival.mos. [months]

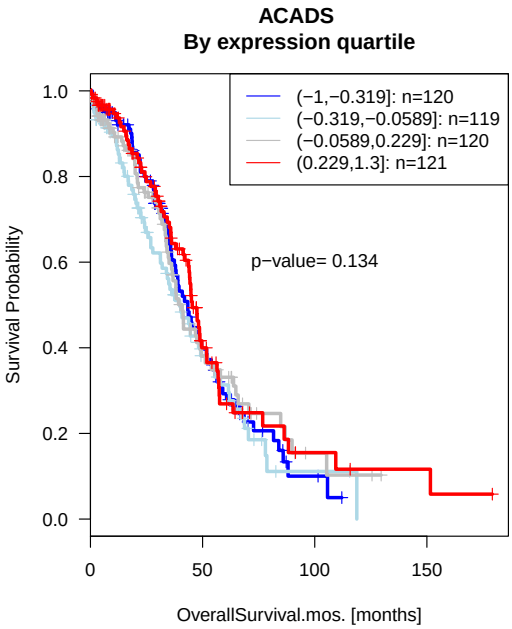

ACAA2
By CNA type
loss: n=198
wt: n=81
gain: n=33
p−value= 0.222
Survival Probability
OverallSurvival.mos. [months]

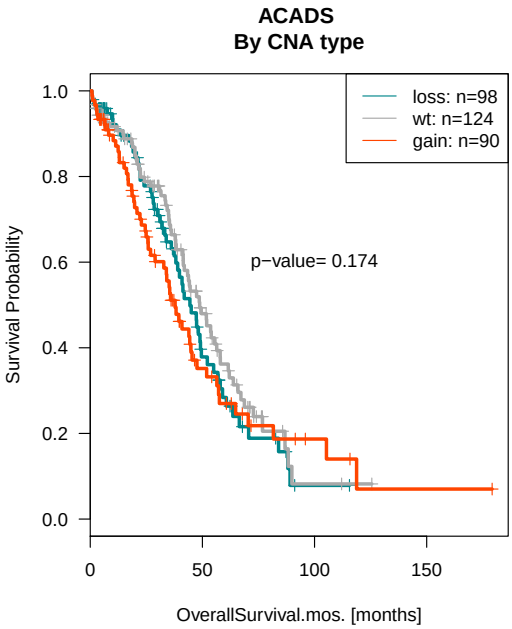

ACADL
By expression quartile
(−0.989,−0.35]: n=118
(−0.35,−0.12]: n=120
(−0.12,0.194]: n=122
(0.194,4.46]: n=120
p−value= 0.257
Survival Probability
OverallSurvival.mos. [months]

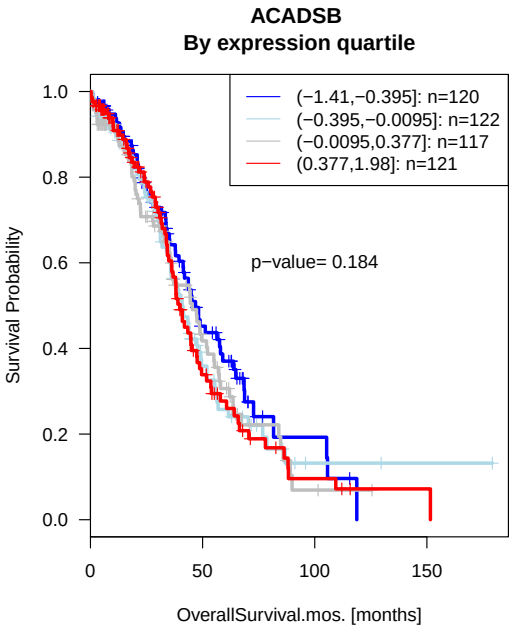

ACADL
By CNA type
loss: n=67
wt: n=146
gain: n=99
p−value= 0.114
Survival Probability
OverallSurvival.mos. [months]

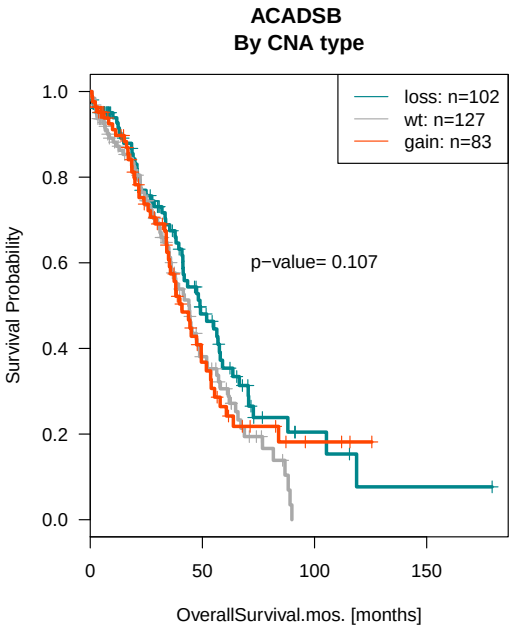

ACADM
By expression quartile
(−2.72,−0.364]: n=121
(−0.364,0.0604]: n=119
(0.0604,0.414]: n=121
(0.414,2.05]: n=119
p−value= 0.073
Survival Probability
OverallSurvival.mos. [months]

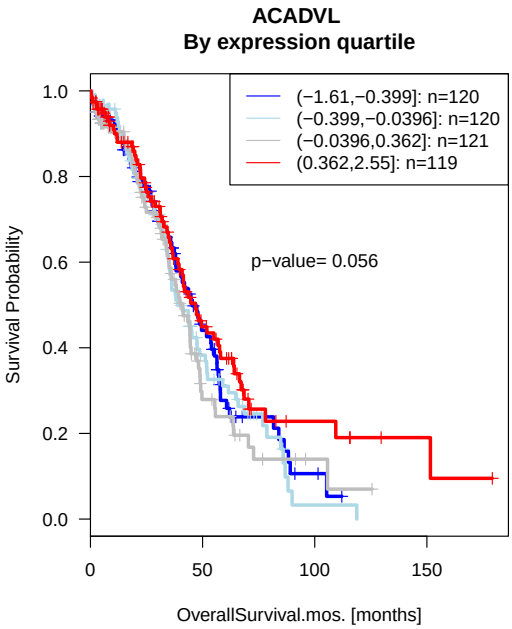

ACADM
By CNA type
loss: n=80
wt: n=147
gain: n=85
p−value= 0.543
Survival Probability
OverallSurvival.mos. [months]

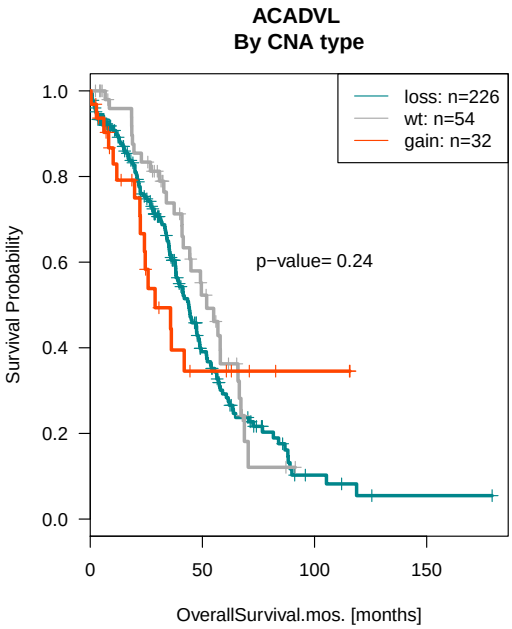

ACADS
By expression quartile
(−1,−0.319]: n=120
(−0.319,−0.0589]: n=119
(−0.0589,0.229]: n=120
(0.229,1.3]: n=121
p−value= 0.134
Survival Probability
OverallSurvival.mos. [months]

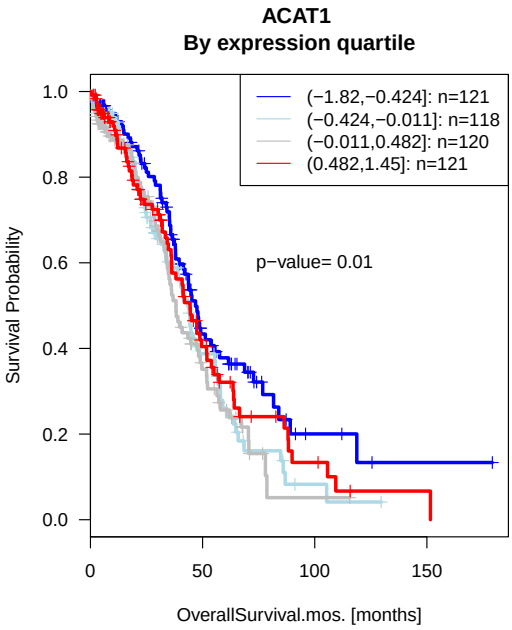

ACADS
By CNA type
loss: n=98
wt: n=124
gain: n=90
p−value= 0.174
Survival Probability
OverallSurvival.mos. [months]

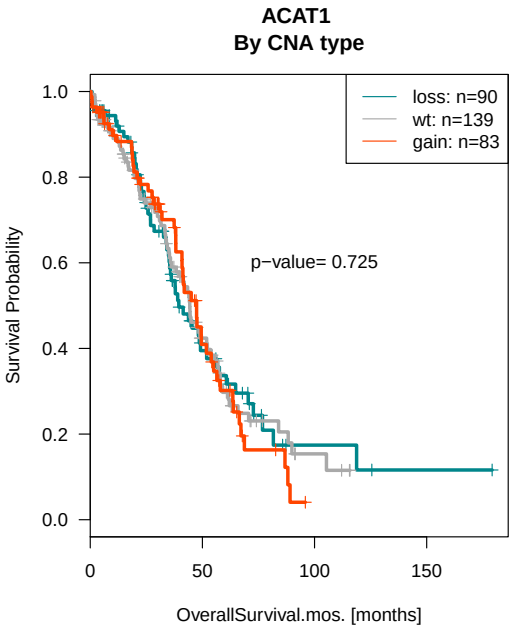

ACADSB
By expression quartile
(−1.41,−0.395]: n=120
(−0.395,−0.0095]: n=122
(−0.0095,0.377]: n=117
(0.377,1.98]: n=121
p−value= 0.184
Survival Probability
OverallSurvival.mos. [months]

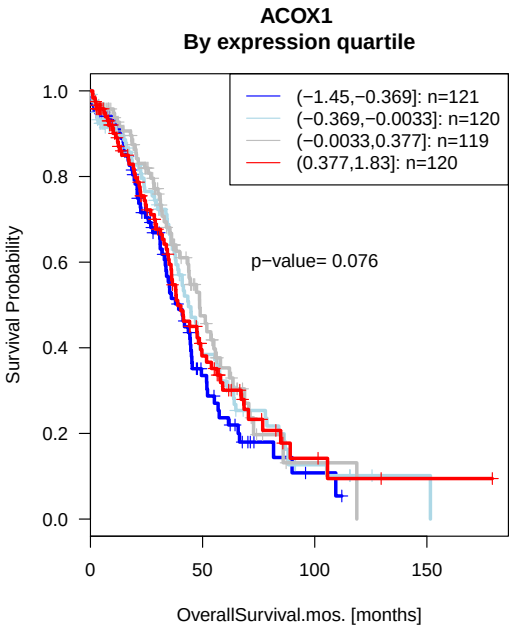

ACADSB
By CNA type
loss: n=102
wt: n=127
gain: n=83
p−value= 0.107
Survival Probability
OverallSurvival.mos. [months]

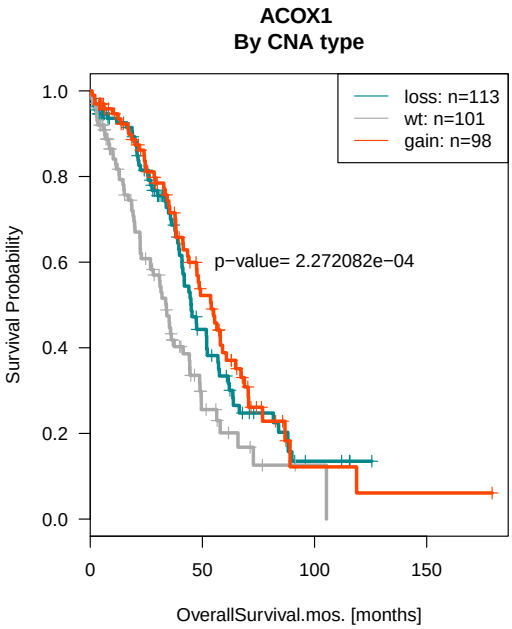

ACADVL
By expression quartile
(−1.61,−0.399]: n=120
(−0.399,−0.0396]: n=120
(−0.0396,0.362]: n=121
(0.362,2.55]: n=119
p−value= 0.056
Survival Probability
OverallSurvival.mos. [months]

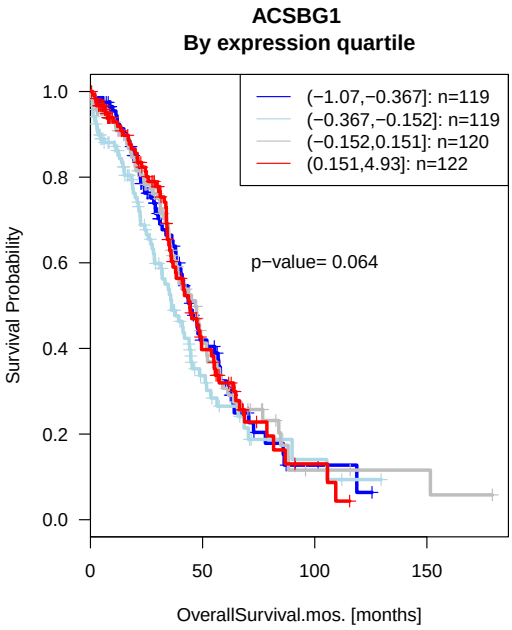

ACADVL
By CNA type
loss: n=226
wt: n=54
gain: n=32
p−value= 0.24
Survival Probability
OverallSurvival.mos. [months]

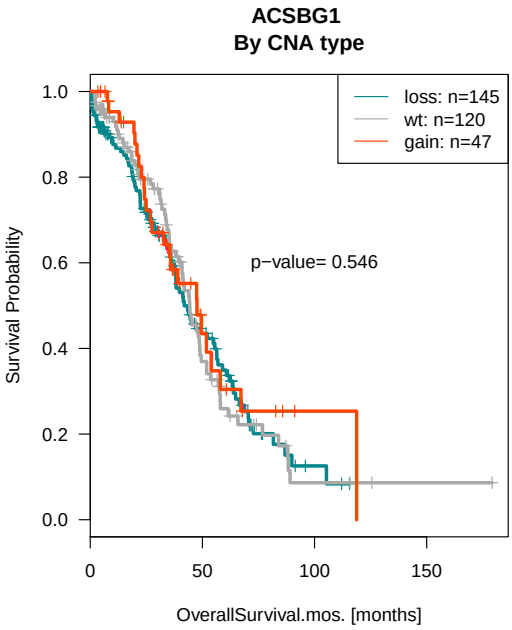

ACAT1
By expression quartile
(−1.82,−0.424]: n=121
(−0.424,−0.011]: n=118
(−0.011,0.482]: n=120
(0.482,1.45]: n=121
p−value= 0.01
Survival Probability
OverallSurvival.mos. [months]

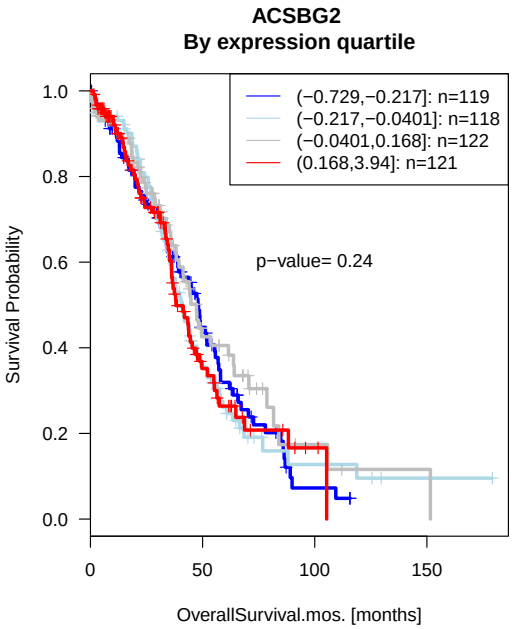

ACAT1
By CNA type
loss: n=90
wt: n=139
gain: n=83
p−value= 0.725
Survival Probability
OverallSurvival.mos. [months]

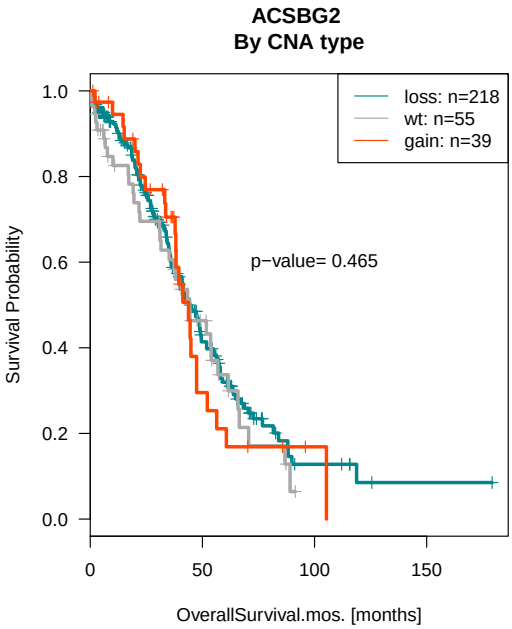

ACOX1
By expression quartile
(−1.45,−0.369]: n=121
(−0.369,−0.0033]: n=120
(−0.0033,0.377]: n=119
(0.377,1.83]: n=120
p−value= 0.076
Survival Probability
OverallSurvival.mos. [months]

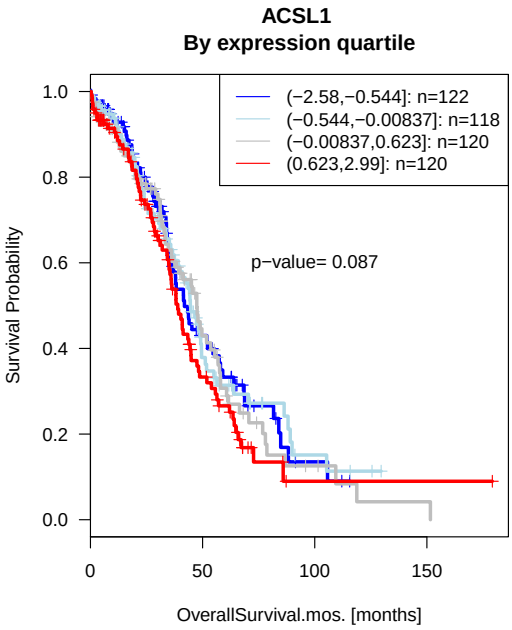

ACOX1
By CNA type
loss: n=113
wt: n=101
gain: n=98
p−value= 2.272082e−04
Survival Probability
OverallSurvival.mos. [months]

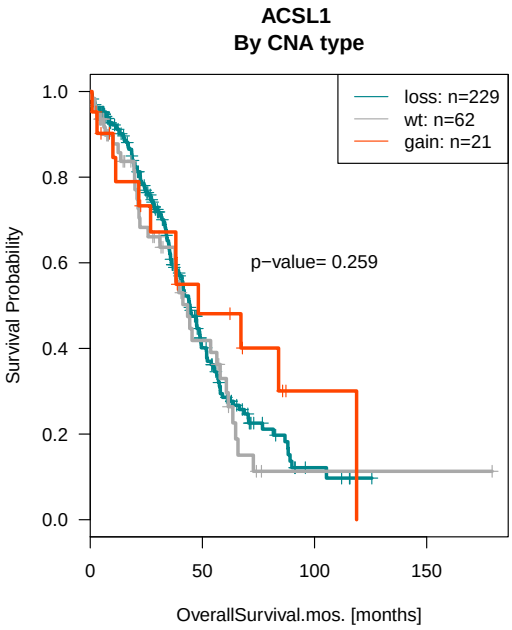

ACSBG1
By expression quartile
(−1.07,−0.367]: n=119
(−0.367,−0.152]: n=119
(−0.152,0.151]: n=120
(0.151,4.93]: n=122
p−value= 0.064
Survival Probability
OverallSurvival.mos. [months]

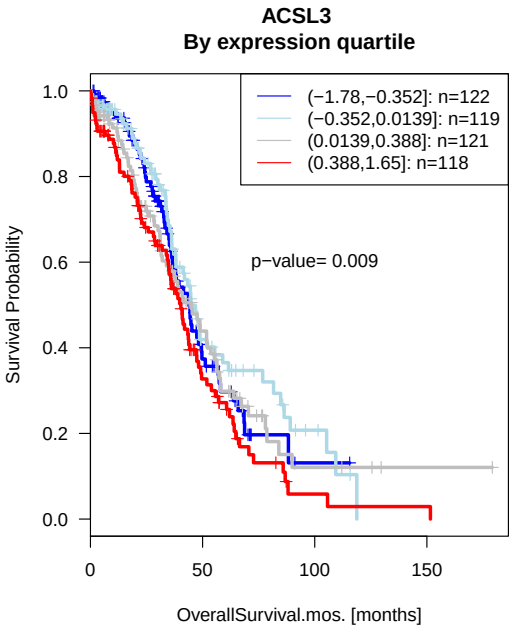

ACSBG1
By CNA type
loss: n=145
wt: n=120
gain: n=47
p−value= 0.546
Survival Probability
OverallSurvival.mos. [months]

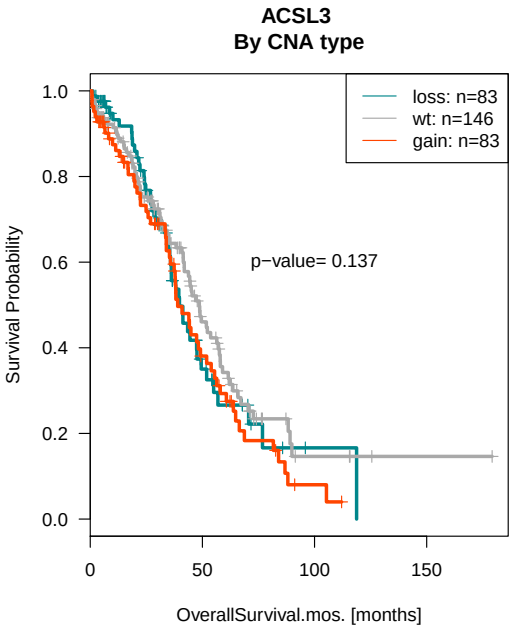

ACSBG2
By expression quartile
(−0.729,−0.217]: n=119
(−0.217,−0.0401]: n=118
(−0.0401,0.168]: n=122
(0.168,3.94]: n=121
p−value= 0.24
Survival Probability
OverallSurvival.mos. [months]

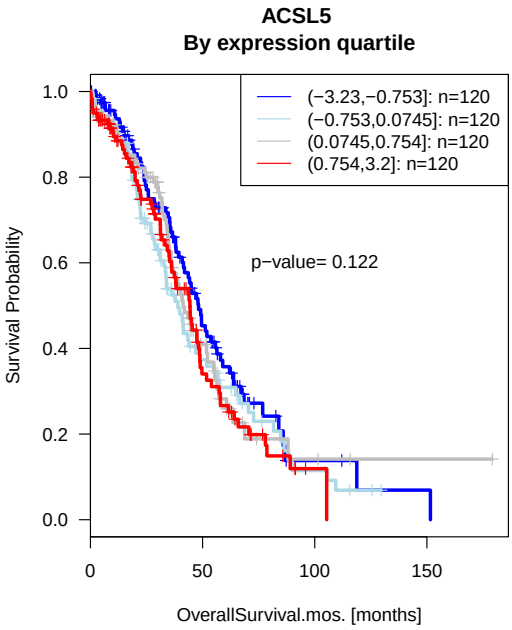

ACSBG2
By CNA type
loss: n=218
wt: n=55
gain: n=39
p−value= 0.465
Survival Probability
OverallSurvival.mos. [months]

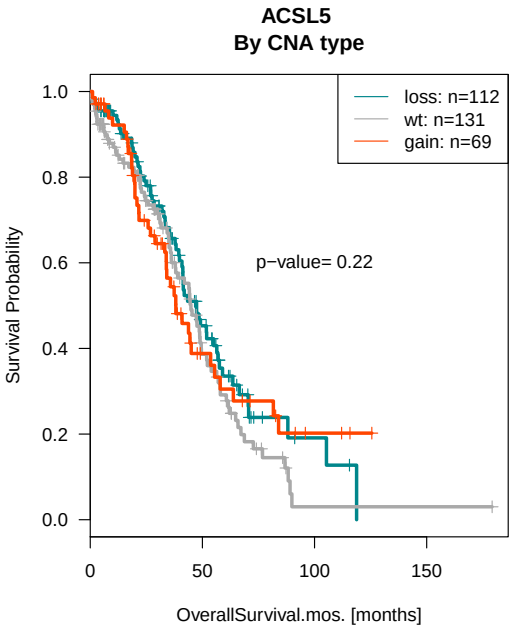

ACSL1
By expression quartile
(−2.58,−0.544]: n=122
(−0.544,−0.00837]: n=118
(−0.00837,0.623]: n=120
(0.623,2.99]: n=120
p−value= 0.087
Survival Probability
OverallSurvival.mos. [months]

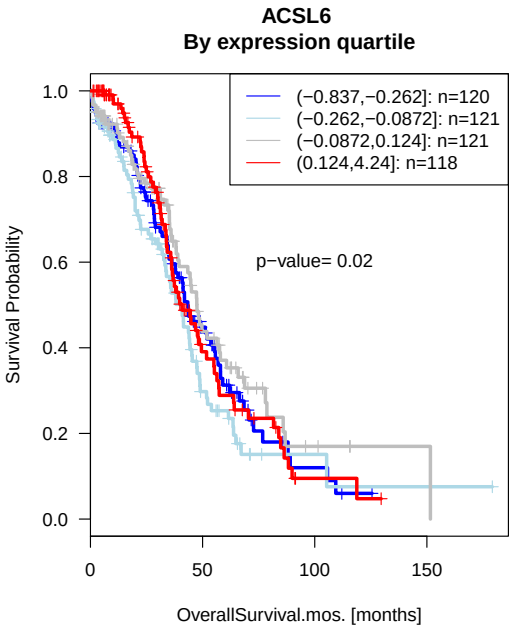

ACSL1
By CNA type
loss: n=229
wt: n=62
gain: n=21
p−value= 0.259
Survival Probability
OverallSurvival.mos. [months]

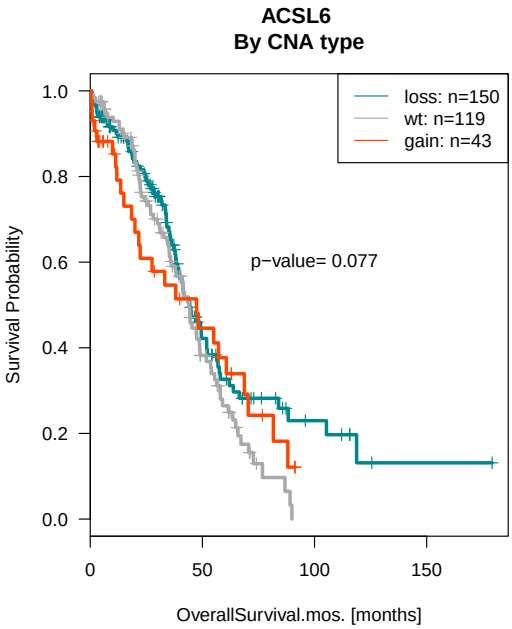

ACSL3
By expression quartile
(−1.78,−0.352]: n=122
(−0.352,0.0139]: n=119
(0.0139,0.388]: n=121
(0.388,1.65]: n=118
p−value= 0.009
Survival Probability
OverallSurvival.mos. [months]

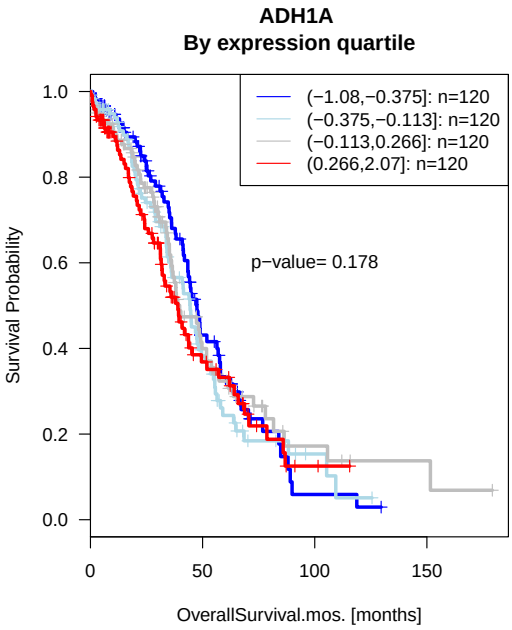

ACSL3
By CNA type
loss: n=83
wt: n=146
gain: n=83
p−value= 0.137
Survival Probability
OverallSurvival.mos. [months]

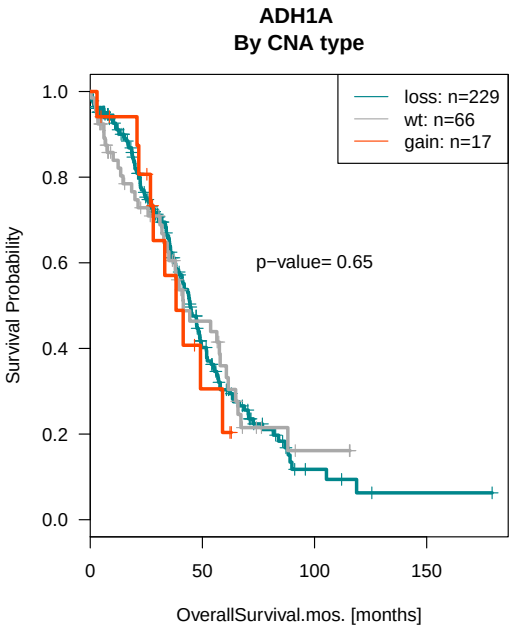

ACSL5
By expression quartile
(−3.23,−0.753]: n=120
(−0.753,0.0745]: n=120
(0.0745,0.754]: n=120
(0.754,3.2]: n=120
p−value= 0.122
Survival Probability
OverallSurvival.mos. [months]

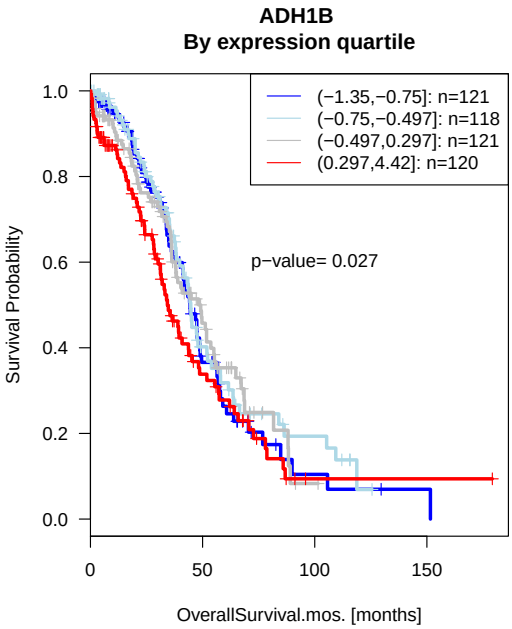

ACSL5
By CNA type
loss: n=112
wt: n=131
gain: n=69
p−value= 0.22
Survival Probability
OverallSurvival.mos. [months]

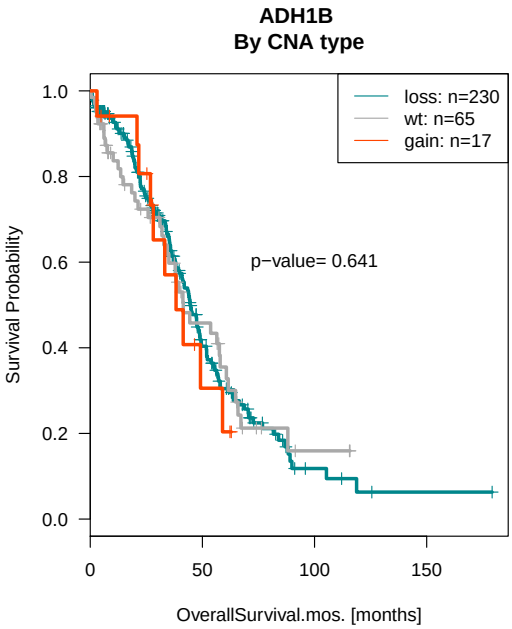

ACSL6
By expression quartile
(−0.837,−0.262]: n=120
(−0.262,−0.0872]: n=121
(−0.0872,0.124]: n=121
(0.124,4.24]: n=118
p−value= 0.02
Survival Probability
OverallSurvival.mos. [months]

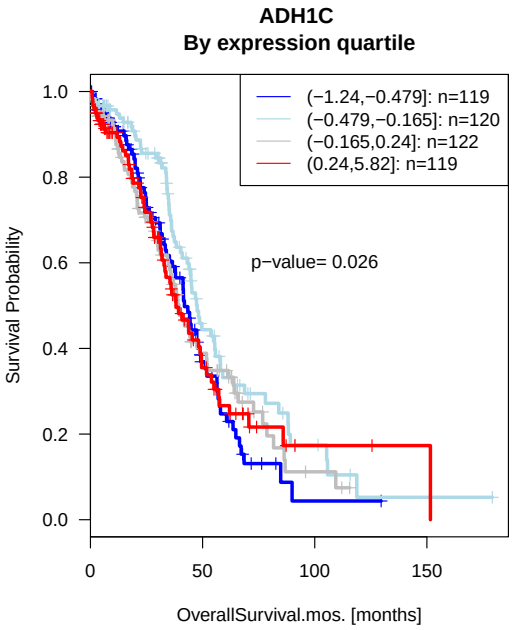

ACSL6
By CNA type
loss: n=150
wt: n=119
gain: n=43
p−value= 0.077
Survival Probability
OverallSurvival.mos. [months]

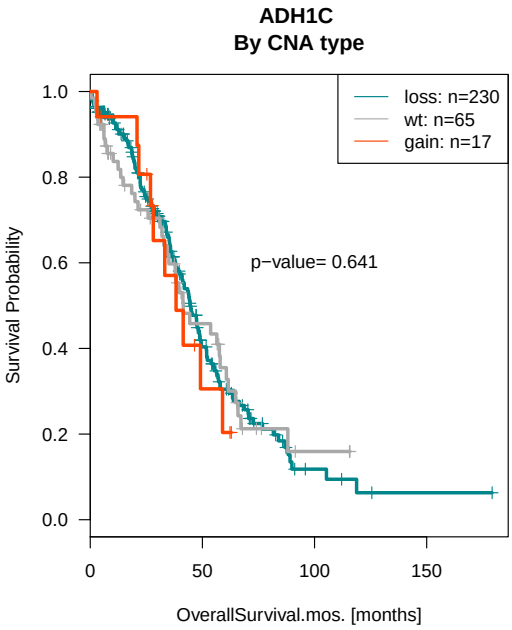

ADH1A
By expression quartile
(−1.08,−0.375]: n=120
(−0.375,−0.113]: n=120
(−0.113,0.266]: n=120
(0.266,2.07]: n=120
p−value= 0.178
Survival Probability
OverallSurvival.mos. [months]

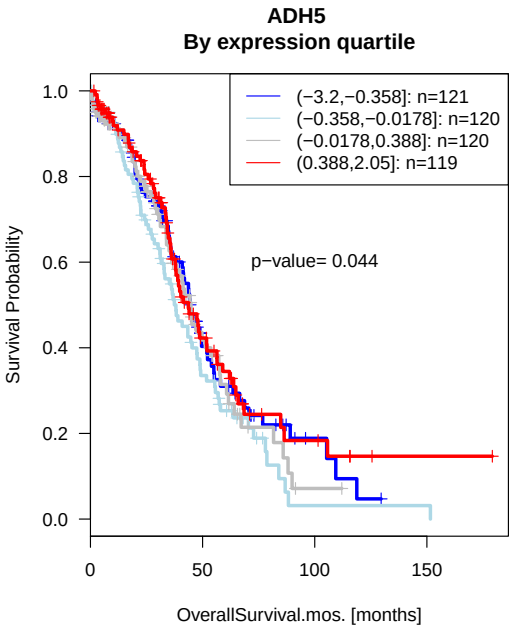

ADH1A
By CNA type
loss: n=229
wt: n=66
gain: n=17
p−value= 0.65
Survival Probability
OverallSurvival.mos. [months]

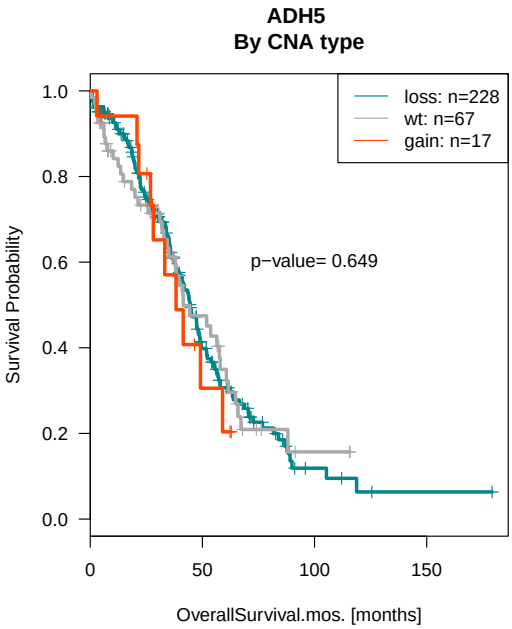

ADH1B
By expression quartile
(−1.35,−0.75]: n=121
(−0.75,−0.497]: n=118
(−0.497,0.297]: n=121
(0.297,4.42]: n=120
p−value= 0.027
Survival Probability
OverallSurvival.mos. [months]

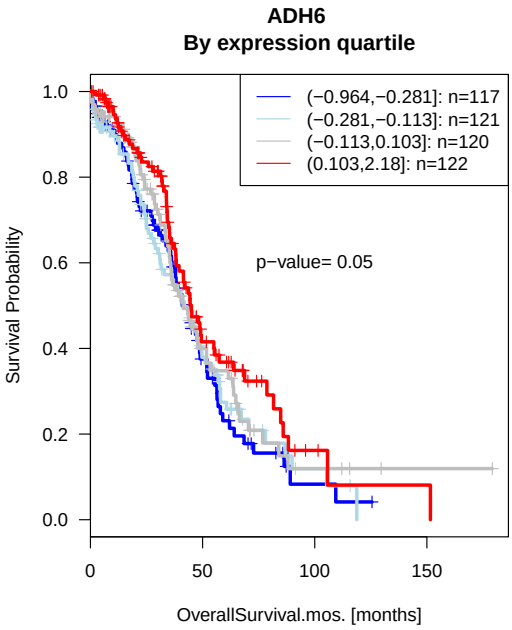

ADH1B
By CNA type
loss: n=230
wt: n=65
gain: n=17
p−value= 0.641
Survival Probability
OverallSurvival.mos. [months]

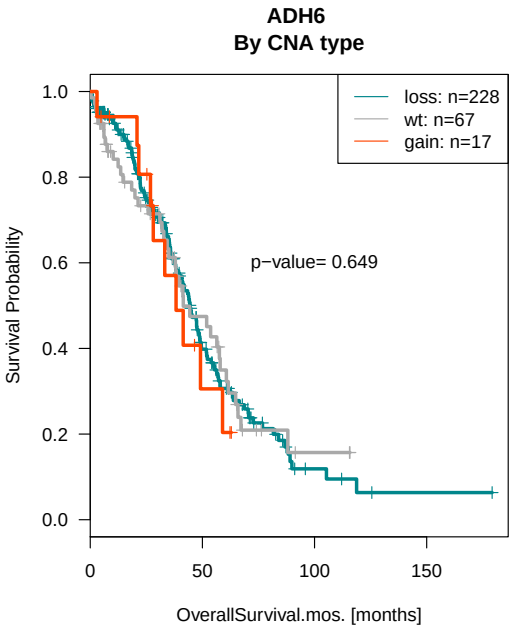

ADH1C
By expression quartile
(−1.24,−0.479]: n=119
(−0.479,−0.165]: n=120
(−0.165,0.24]: n=122
(0.24,5.82]: n=119
p−value= 0.026
Survival Probability
OverallSurvival.mos. [months]

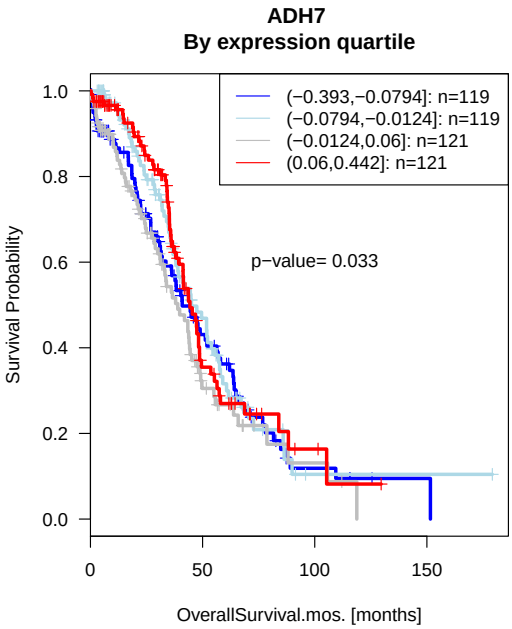

ADH1C
By CNA type
loss: n=230
wt: n=65
gain: n=17
p−value= 0.641
Survival Probability
OverallSurvival.mos. [months]

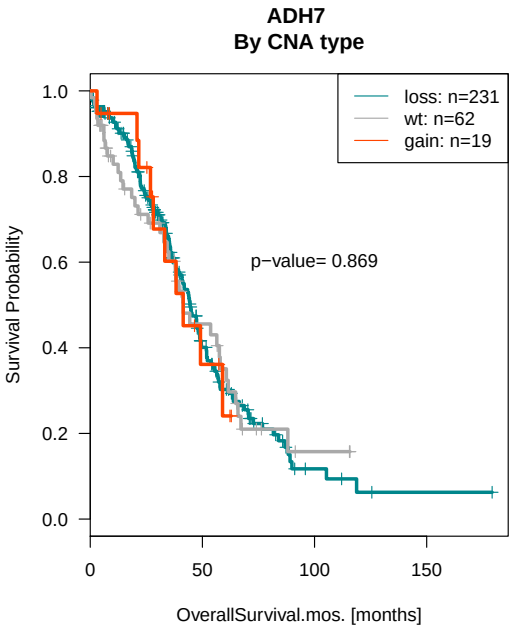

ADH5
By expression quartile
(−3.2,−0.358]: n=121
(−0.358,−0.0178]: n=120
(−0.0178,0.388]: n=120
(0.388,2.05]: n=119
p−value= 0.044
Survival Probability
OverallSurvival.mos. [months]

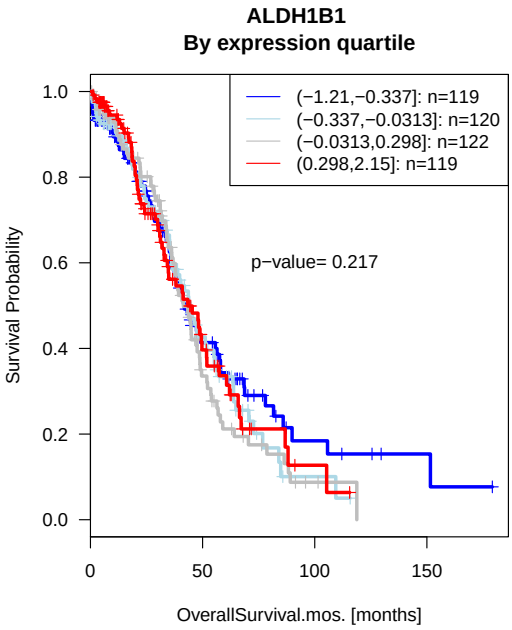

ADH5
By CNA type
loss: n=228
wt: n=67
gain: n=17
p−value= 0.649
Survival Probability
OverallSurvival.mos. [months]

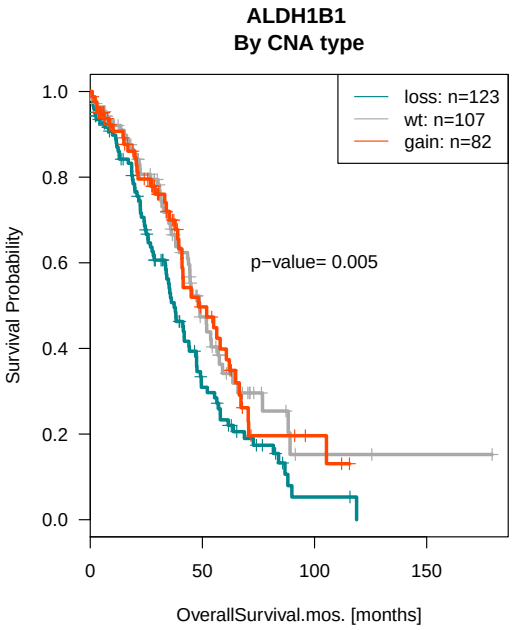

ADH6
By expression quartile
(−0.964,−0.281]: n=117
(−0.281,−0.113]: n=121
(−0.113,0.103]: n=120
(0.103,2.18]: n=122
p−value= 0.05
Survival Probability
OverallSurvival.mos. [months]

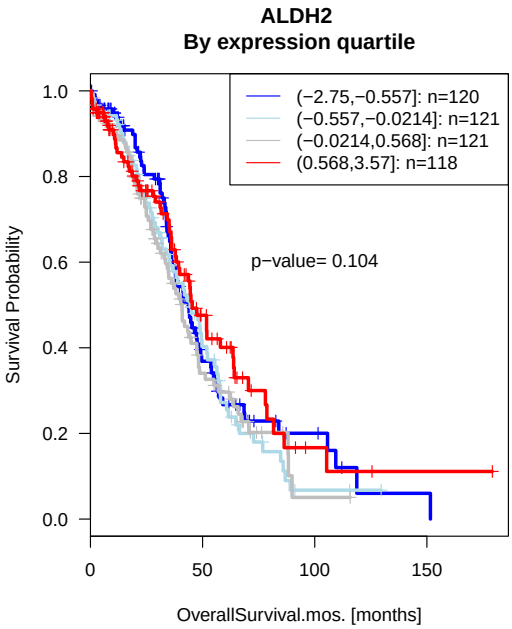

ADH6
By CNA type
loss: n=228
wt: n=67
gain: n=17
p−value= 0.649
Survival Probability
OverallSurvival.mos. [months]

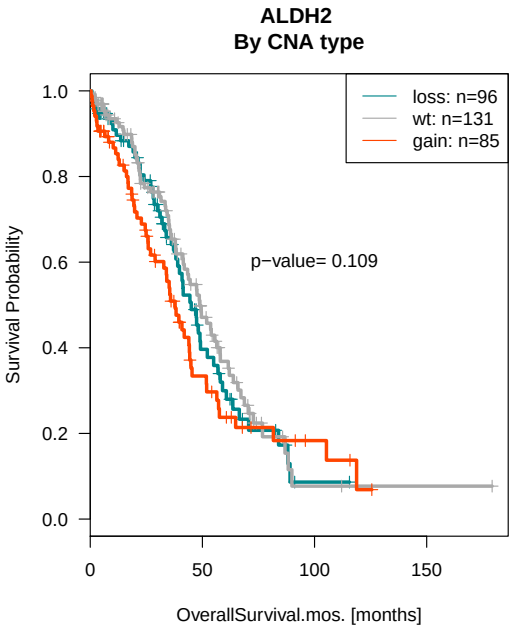

ADH7
By expression quartile
(−0.393,−0.0794]: n=119
(−0.0794,−0.0124]: n=119
(−0.0124,0.06]: n=121
(0.06,0.442]: n=121
p−value= 0.033
Survival Probability
OverallSurvival.mos. [months]

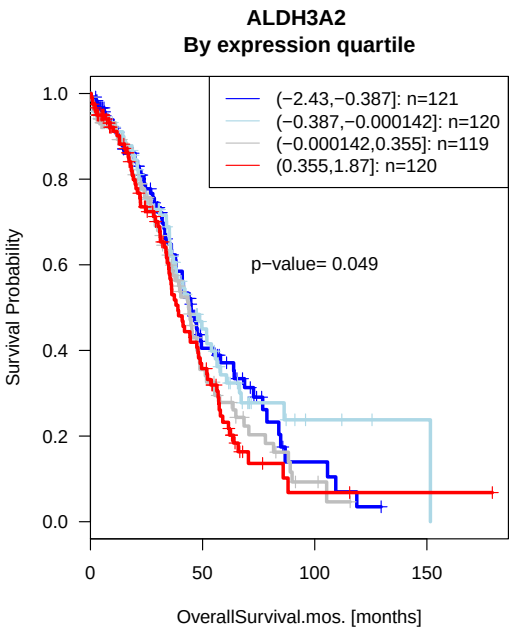

ADH7
By CNA type
loss: n=231
wt: n=62
gain: n=19
p−value= 0.869
Survival Probability
OverallSurvival.mos. [months]

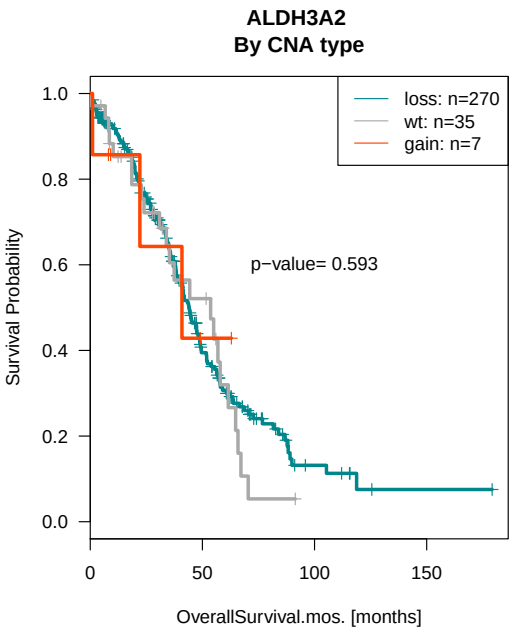

ALDH1B1
By expression quartile
(−1.21,−0.337]: n=119
(−0.337,−0.0313]: n=120
(−0.0313,0.298]: n=122
(0.298,2.15]: n=119
p−value= 0.217
Survival Probability
OverallSurvival.mos. [months]

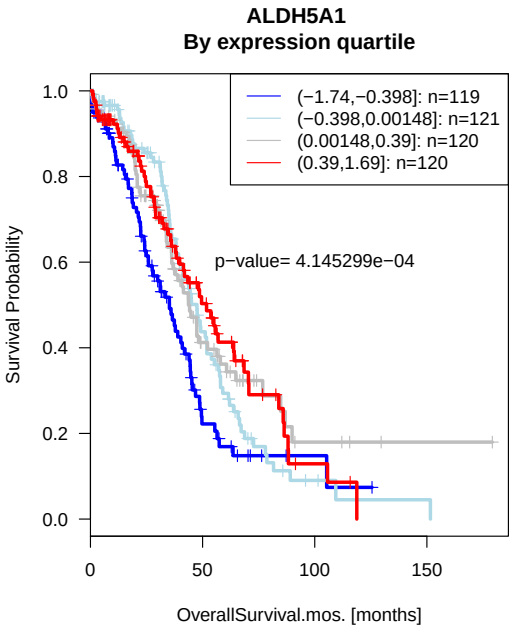

ALDH1B1
By CNA type
loss: n=123
wt: n=107
gain: n=82
p−value= 0.005
Survival Probability
OverallSurvival.mos. [months]

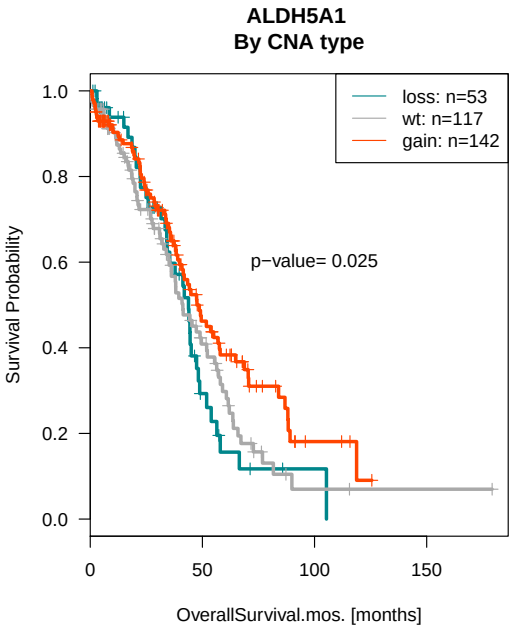

ALDH2
By expression quartile
(−2.75,−0.557]: n=120
(−0.557,−0.0214]: n=121
(−0.0214,0.568]: n=121
(0.568,3.57]: n=118
p−value= 0.104
Survival Probability
OverallSurvival.mos. [months]

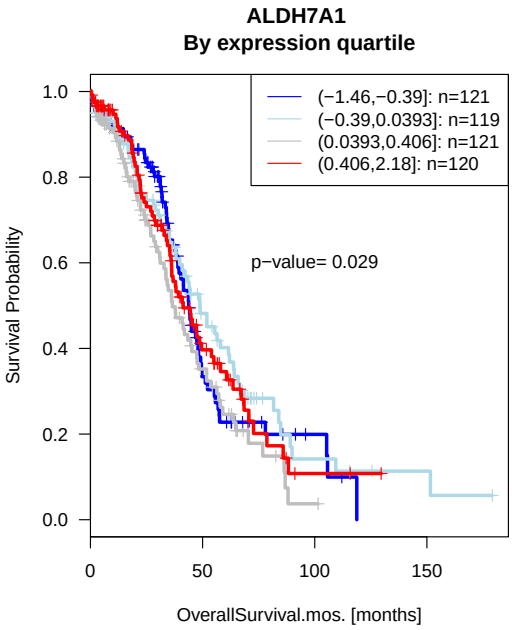

ALDH2
By CNA type
loss: n=96
wt: n=131
gain: n=85
p−value= 0.109
Survival Probability
OverallSurvival.mos. [months]

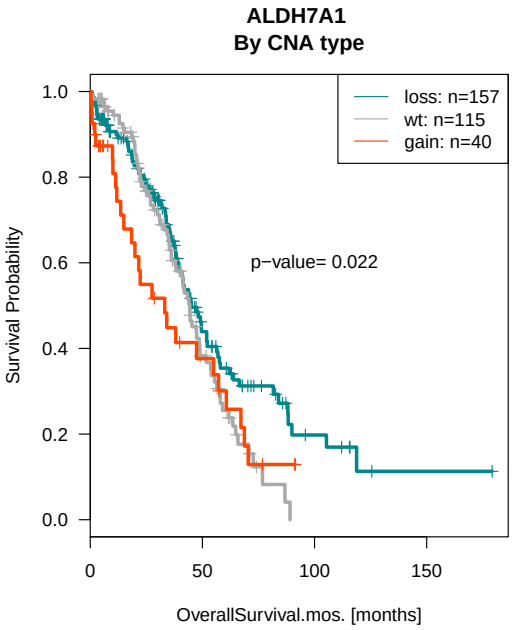

ALDH3A2
By expression quartile
(−2.43,−0.387]: n=121
(−0.387,−0.000142]: n=120
(−0.000142,0.355]: n=119
(0.355,1.87]: n=120
p−value= 0.049
Survival Probability
OverallSurvival.mos. [months]

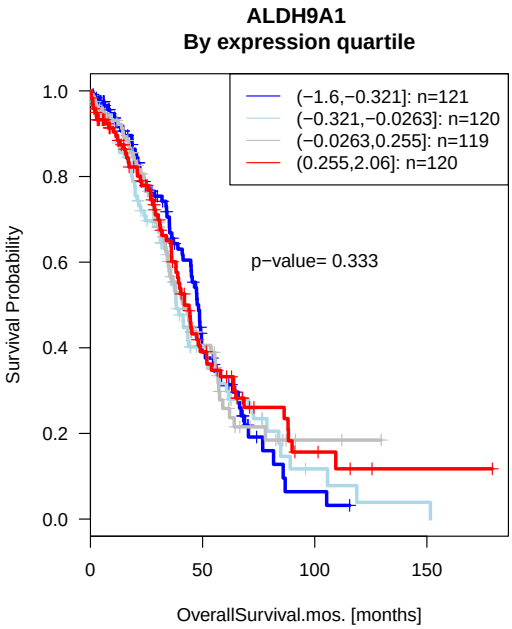

ALDH3A2
By CNA type
loss: n=270
wt: n=35
gain: n=7
p−value= 0.593
Survival Probability
OverallSurvival.mos. [months]

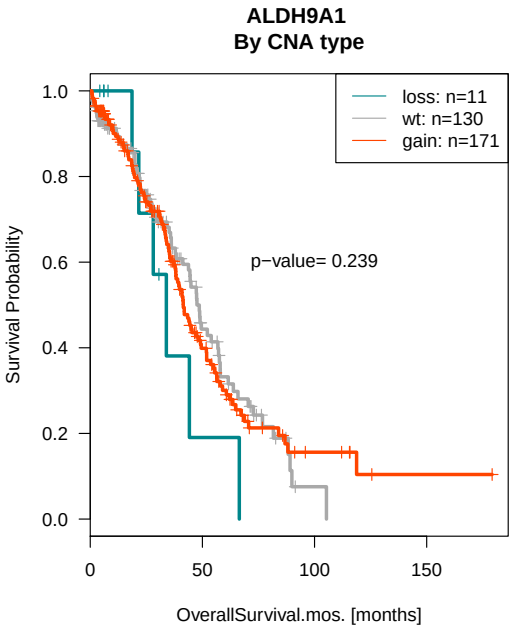

ALDH5A1
By expression quartile
(−1.74,−0.398]: n=119
(−0.398,0.00148]: n=121
(0.00148,0.39]: n=120
(0.39,1.69]: n=120
p−value= 4.145299e−04
Survival Probability
OverallSurvival.mos. [months]

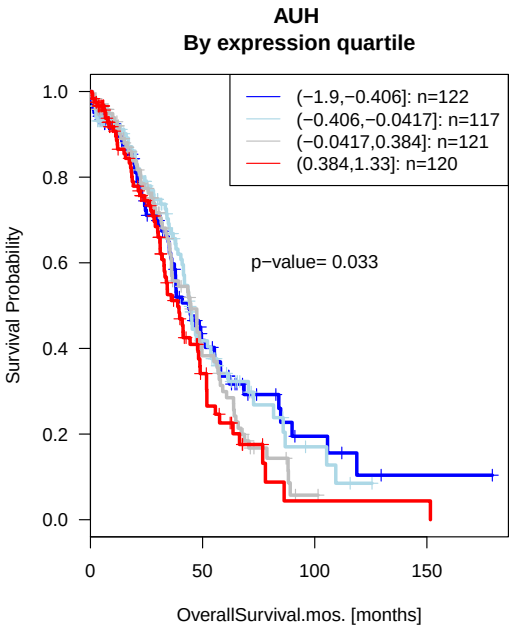

ALDH5A1
By CNA type
loss: n=53
wt: n=117
gain: n=142
p−value= 0.025
Survival Probability
OverallSurvival.mos. [months]

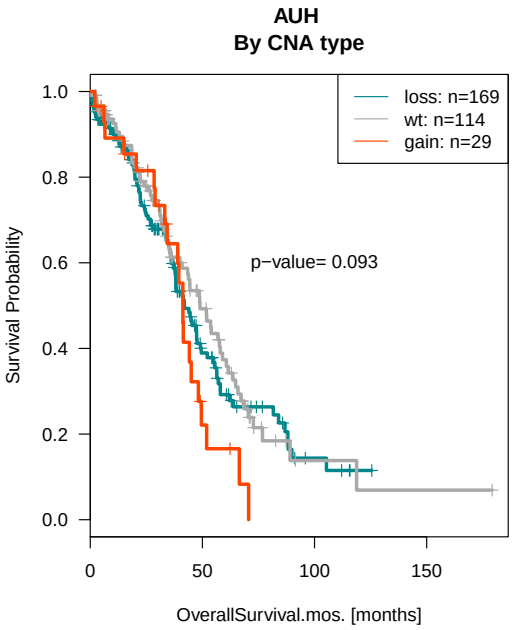

ALDH7A1
By expression quartile
(−1.46,−0.39]: n=121
(−0.39,0.0393]: n=119
(0.0393,0.406]: n=121
(0.406,2.18]: n=120
p−value= 0.029
Survival Probability
OverallSurvival.mos. [months]

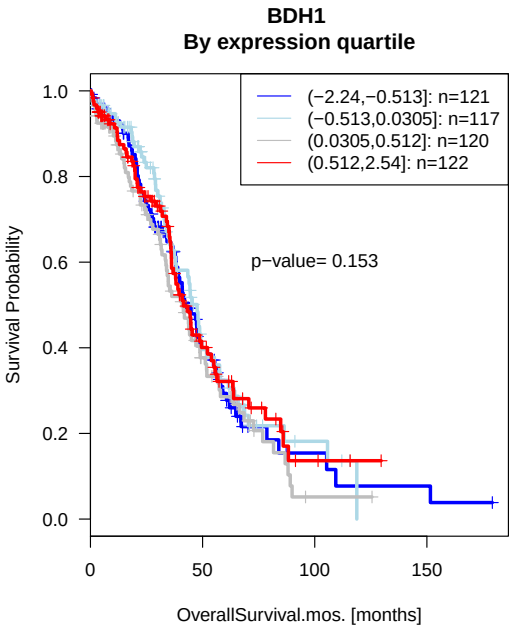

ALDH7A1
By CNA type
loss: n=157
wt: n=115
gain: n=40
p−value= 0.022
Survival Probability
OverallSurvival.mos. [months]

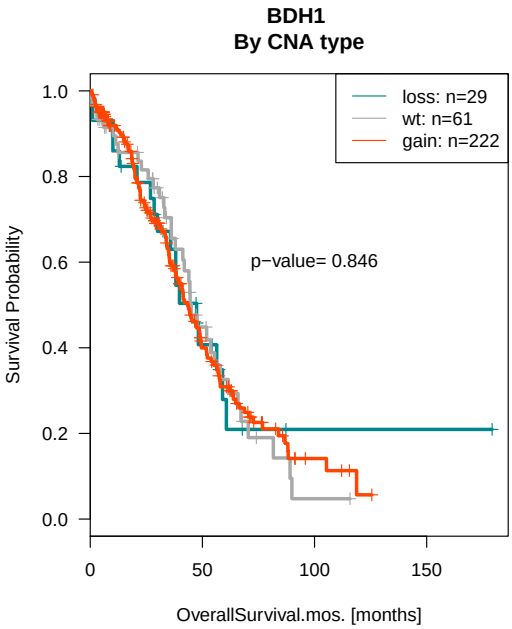

ALDH9A1
By expression quartile
(−1.6,−0.321]: n=121
(−0.321,−0.0263]: n=120
(−0.0263,0.255]: n=119
(0.255,2.06]: n=120
p−value= 0.333
Survival Probability
OverallSurvival.mos. [months]

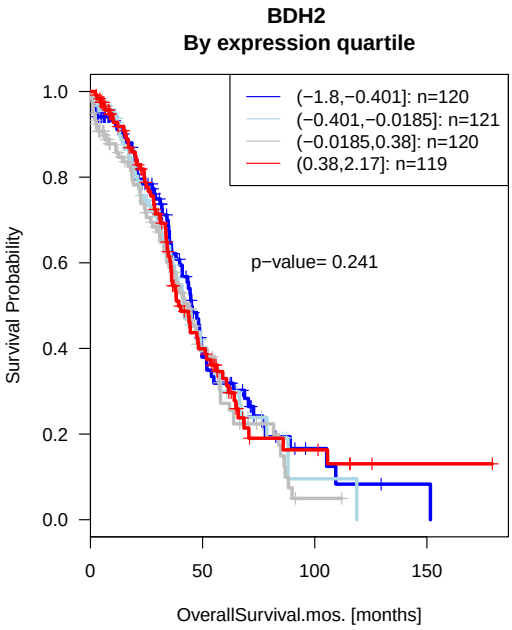

ALDH9A1
By CNA type
loss: n=11
wt: n=130
gain: n=171
p−value= 0.239
Survival Probability
OverallSurvival.mos. [months]

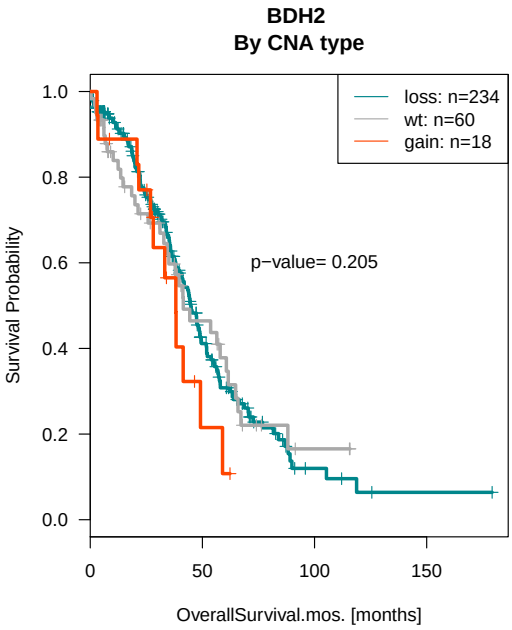

AUH
By expression quartile
(−1.9,−0.406]: n=122
(−0.406,−0.0417]: n=117
(−0.0417,0.384]: n=121
(0.384,1.33]: n=120
p−value= 0.033
Survival Probability
OverallSurvival.mos. [months]

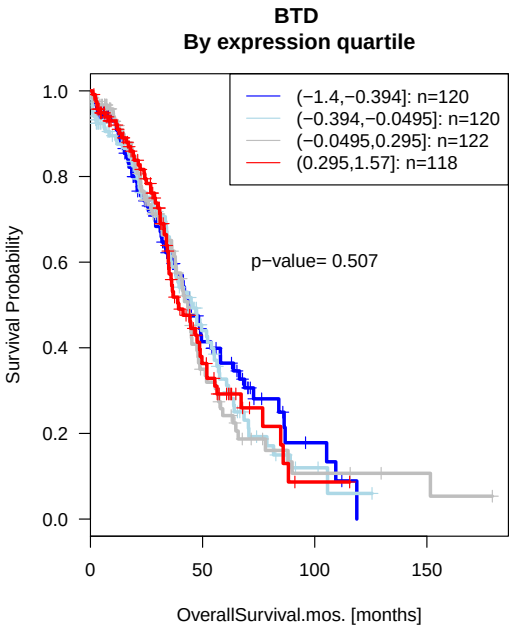

AUH
By CNA type
loss: n=169
wt: n=114
gain: n=29
p−value= 0.093
Survival Probability
OverallSurvival.mos. [months]

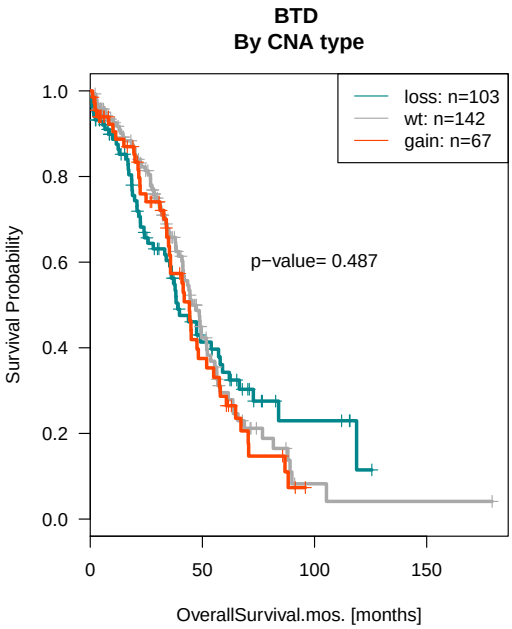

BDH1
By expression quartile
(−2.24,−0.513]: n=121
(−0.513,0.0305]: n=117
(0.0305,0.512]: n=120
(0.512,2.54]: n=122
p−value= 0.153
Survival Probability
OverallSurvival.mos. [months]

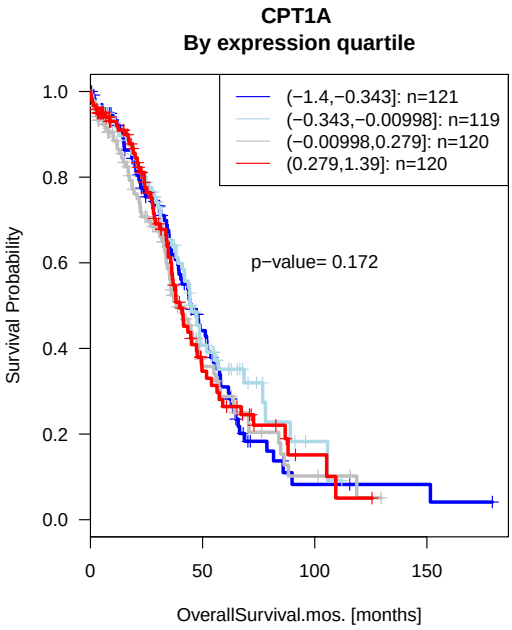

BDH1
By CNA type
loss: n=29
wt: n=61
gain: n=222
p−value= 0.846
Survival Probability
OverallSurvival.mos. [months]

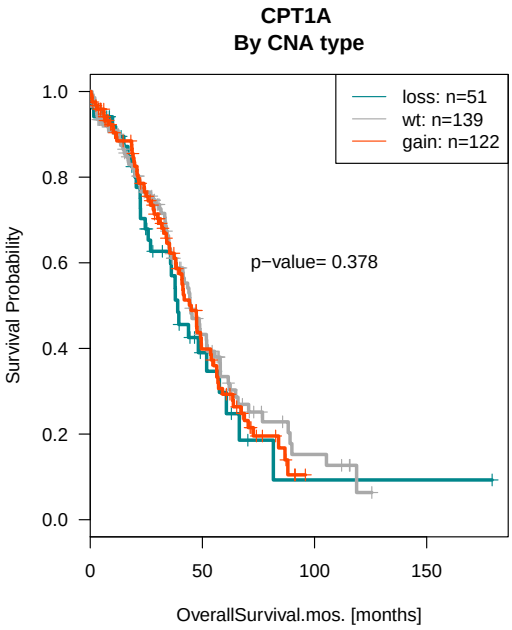

BDH2
By expression quartile
(−1.8,−0.401]: n=120
(−0.401,−0.0185]: n=121
(−0.0185,0.38]: n=120
(0.38,2.17]: n=119
p−value= 0.241
Survival Probability
OverallSurvival.mos. [months]

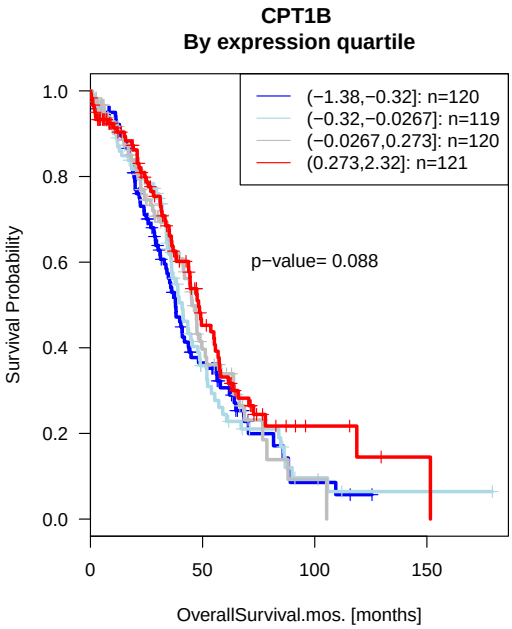

BDH2
By CNA type
loss: n=234
wt: n=60
gain: n=18
p−value= 0.205
Survival Probability
OverallSurvival.mos. [months]

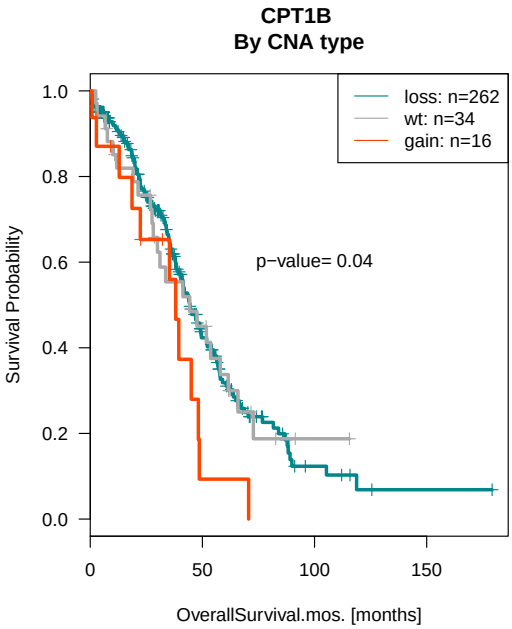

BTD
By expression quartile
(−1.4,−0.394]: n=120
(−0.394,−0.0495]: n=120
(−0.0495,0.295]: n=122
(0.295,1.57]: n=118
p−value= 0.507
Survival Probability
OverallSurvival.mos. [months]

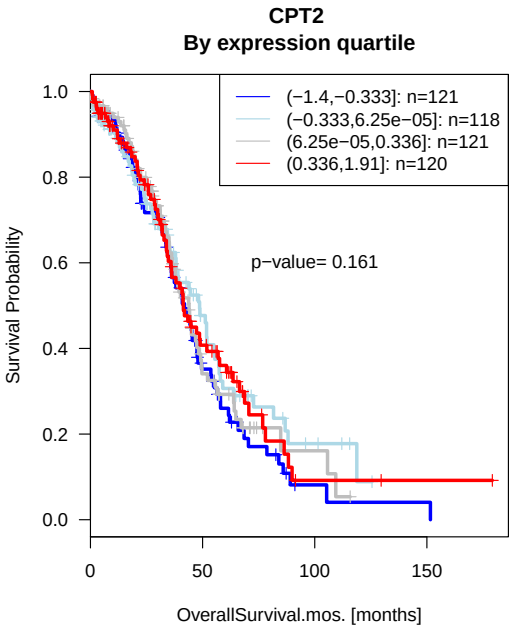

BTD
By CNA type
loss: n=103
wt: n=142
gain: n=67
p−value= 0.487
Survival Probability
OverallSurvival.mos. [months]

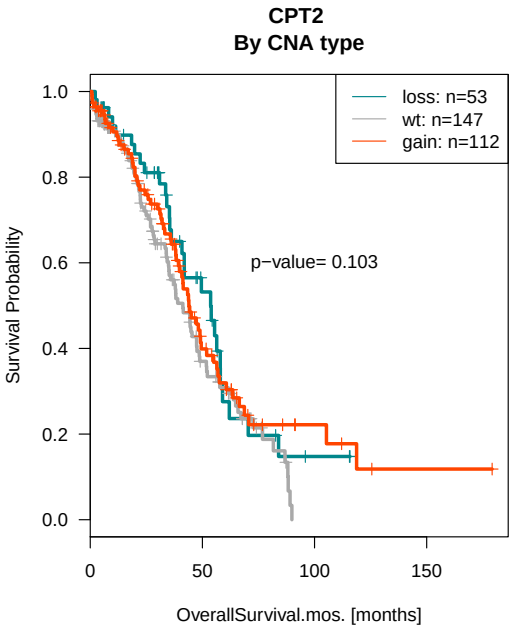

CPT1A
By expression quartile
(−1.4,−0.343]: n=121
(−0.343,−0.00998]: n=119
(−0.00998,0.279]: n=120
(0.279,1.39]: n=120
p−value= 0.172
Survival Probability
OverallSurvival.mos. [months]

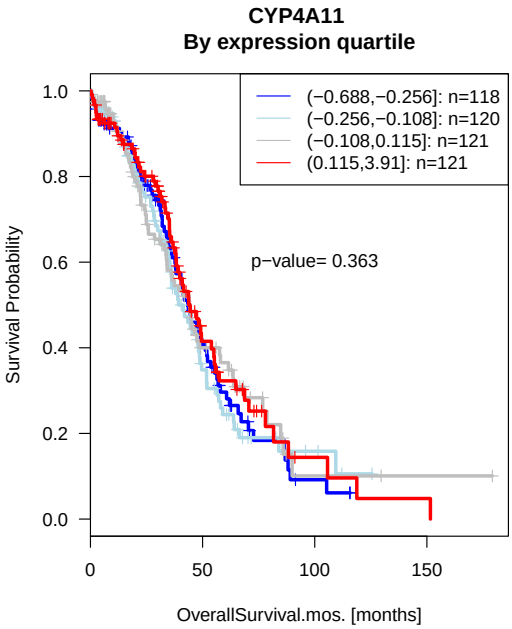

CPT1A
By CNA type
loss: n=51
wt: n=139
gain: n=122
p−value= 0.378
Survival Probability
OverallSurvival.mos. [months]

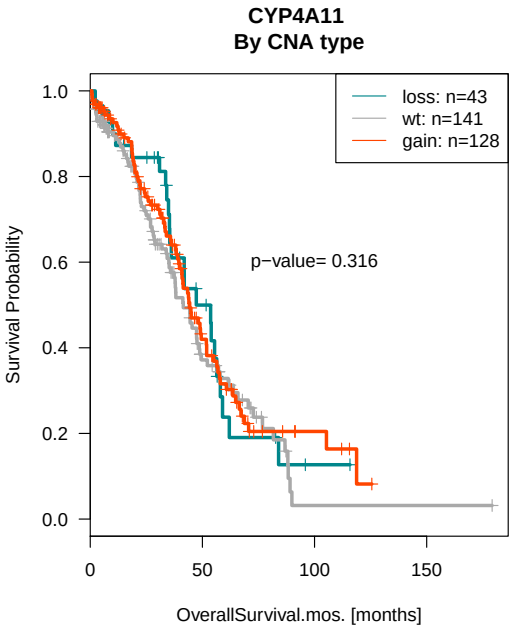

CPT1B
By expression quartile
(−1.38,−0.32]: n=120
(−0.32,−0.0267]: n=119
(−0.0267,0.273]: n=120
(0.273,2.32]: n=121
p−value= 0.088
Survival Probability
OverallSurvival.mos. [months]

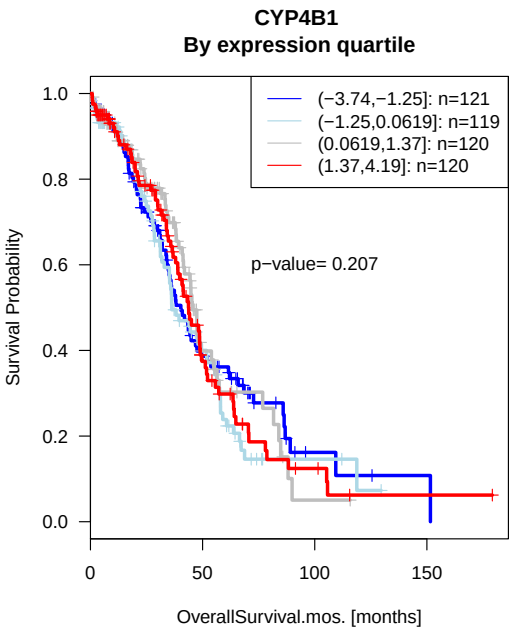

CPT1B
By CNA type
loss: n=262
wt: n=34
gain: n=16
p−value= 0.04
Survival Probability
OverallSurvival.mos. [months]

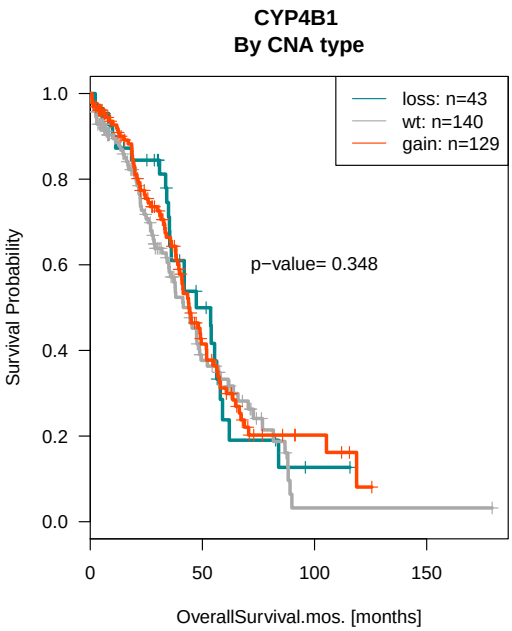

CPT2
By expression quartile
(−1.4,−0.333]: n=121
(−0.333,6.25e−05]: n=118
(6.25e−05,0.336]: n=121
(0.336,1.91]: n=120
p−value= 0.161
Survival Probability
OverallSurvival.mos. [months]

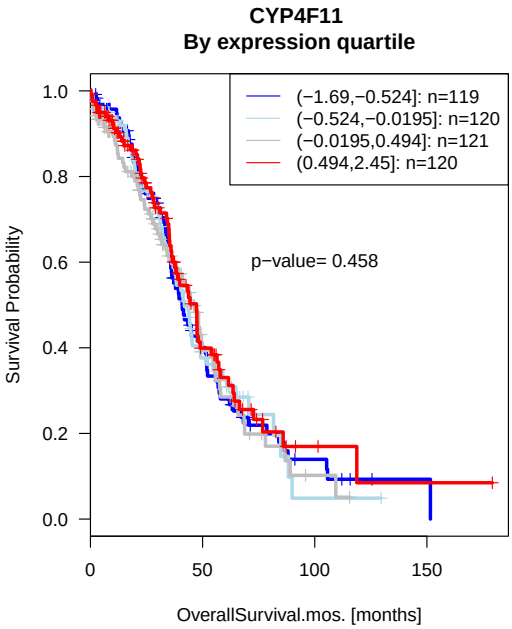

CPT2
By CNA type
loss: n=53
wt: n=147
gain: n=112
p−value= 0.103
Survival Probability
OverallSurvival.mos. [months]

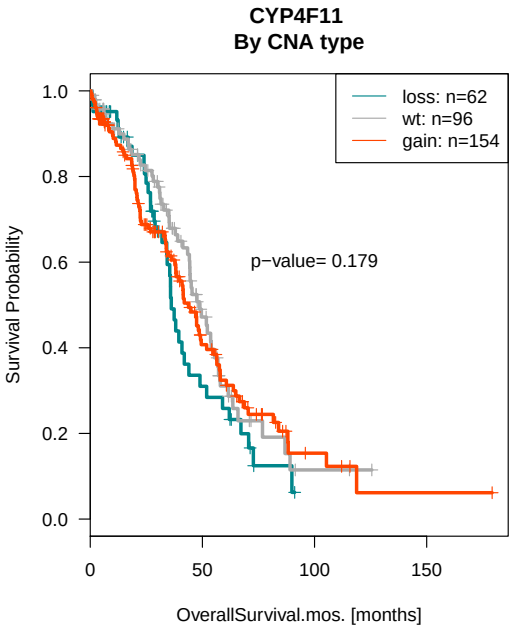

CYP4A11
By expression quartile
(−0.688,−0.256]: n=118
(−0.256,−0.108]: n=120
(−0.108,0.115]: n=121
(0.115,3.91]: n=121
p−value= 0.363
Survival Probability
OverallSurvival.mos. [months]

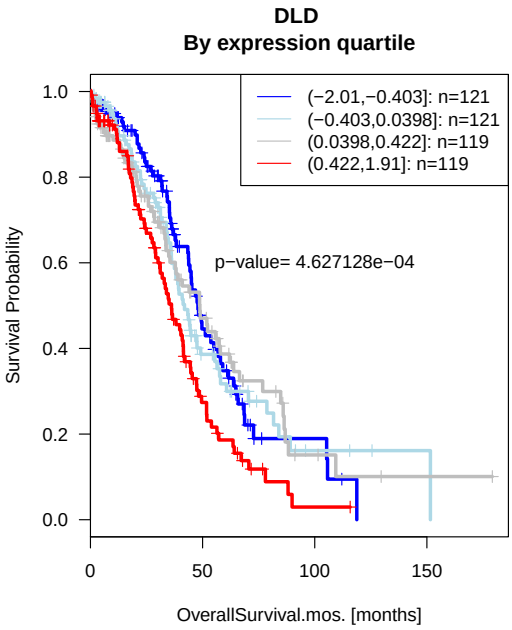

CYP4A11
By CNA type
loss: n=43
wt: n=141
gain: n=128
p−value= 0.316
Survival Probability
OverallSurvival.mos. [months]

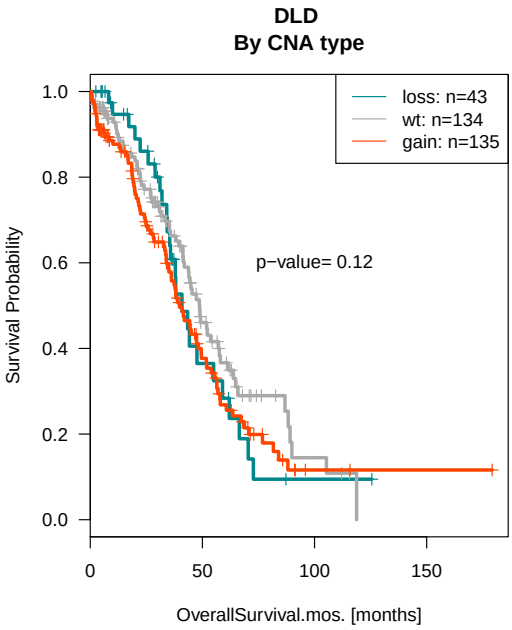

CYP4B1
By expression quartile
(−3.74,−1.25]: n=121
(−1.25,0.0619]: n=119
(0.0619,1.37]: n=120
(1.37,4.19]: n=120
p−value= 0.207
Survival Probability
OverallSurvival.mos. [months]

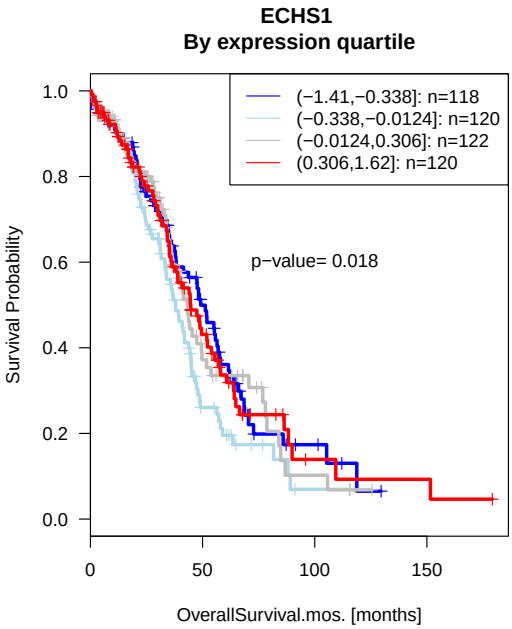

CYP4B1
By CNA type
loss: n=43
wt: n=140
gain: n=129
p−value= 0.348
Survival Probability
OverallSurvival.mos. [months]

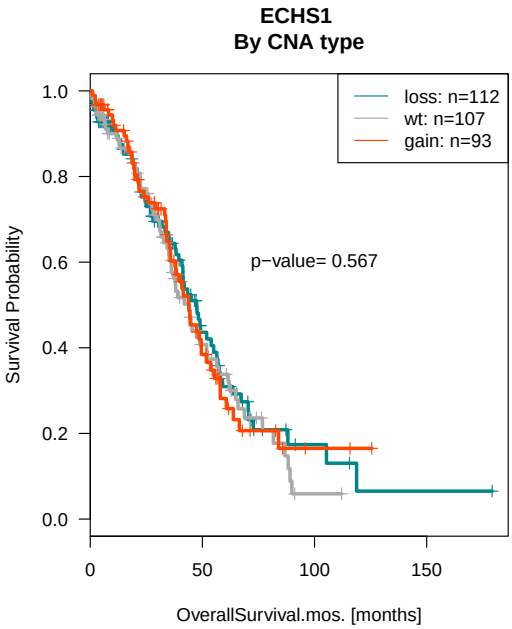

CYP4F11
By expression quartile
(−1.69,−0.524]: n=119
(−0.524,−0.0195]: n=120
(−0.0195,0.494]: n=121
(0.494,2.45]: n=120
p−value= 0.458
Survival Probability
OverallSurvival.mos. [months]

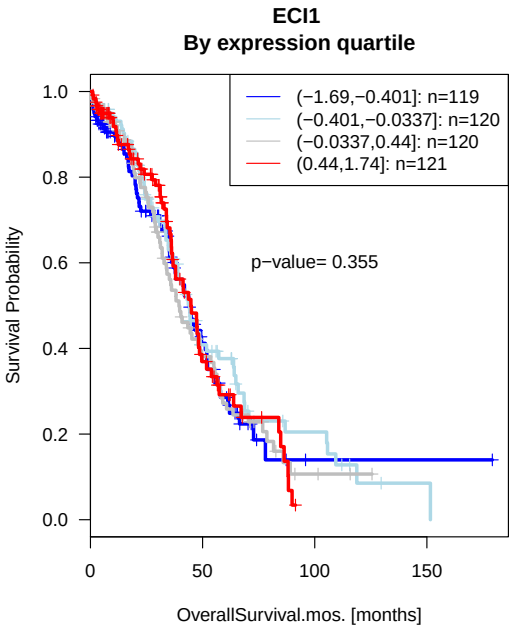

CYP4F11
By CNA type
loss: n=62
wt: n=96
gain: n=154
p−value= 0.179
Survival Probability
OverallSurvival.mos. [months]

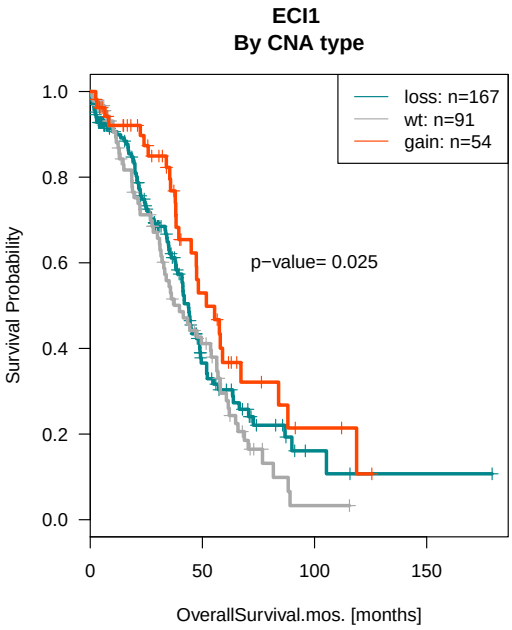

DLD
By expression quartile
(−2.01,−0.403]: n=121
(−0.403,0.0398]: n=121
(0.0398,0.422]: n=119
(0.422,1.91]: n=119
p−value= 4.627128e−04
Survival Probability
OverallSurvival.mos. [months]

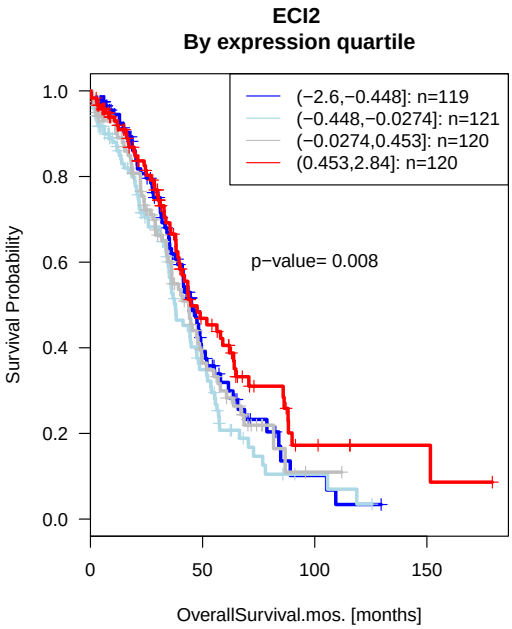

DLD
By CNA type
loss: n=43
wt: n=134
gain: n=135
p−value= 0.12
Survival Probability
OverallSurvival.mos. [months]

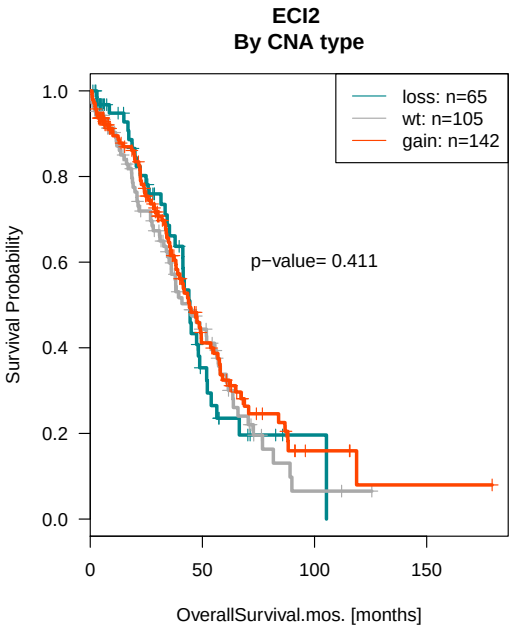

ECHS1
By expression quartile
(−1.41,−0.338]: n=118
(−0.338,−0.0124]: n=120
(−0.0124,0.306]: n=122
(0.306,1.62]: n=120
p−value= 0.018
Survival Probability
OverallSurvival.mos. [months]

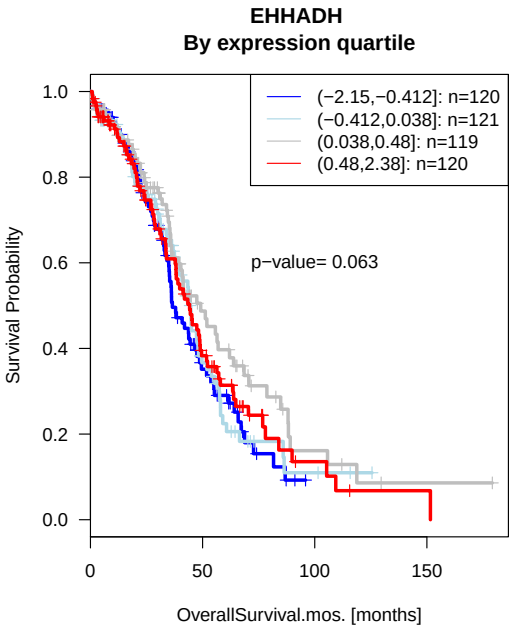

ECHS1
By CNA type
loss: n=112
wt: n=107
gain: n=93
p−value= 0.567
Survival Probability
OverallSurvival.mos. [months]

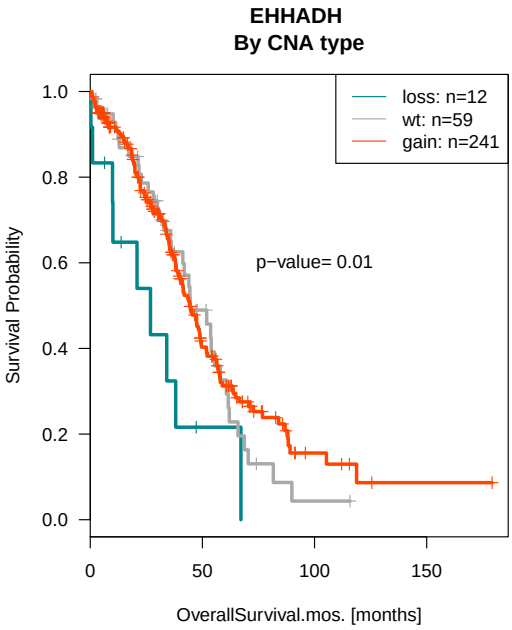

ECI1
By expression quartile
(−1.69,−0.401]: n=119
(−0.401,−0.0337]: n=120
(−0.0337,0.44]: n=120
(0.44,1.74]: n=121
p−value= 0.355
Survival Probability
OverallSurvival.mos. [months]

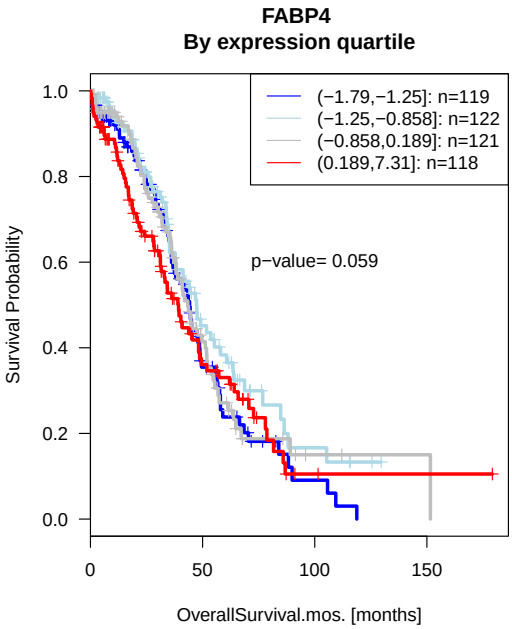

ECI1
By CNA type
loss: n=167
wt: n=91
gain: n=54
p−value= 0.025
Survival Probability
OverallSurvival.mos. [months]

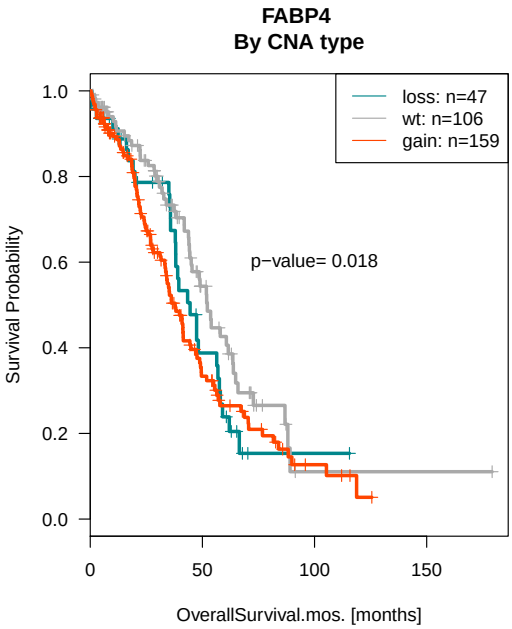

ECI2
By expression quartile
(−2.6,−0.448]: n=119
(−0.448,−0.0274]: n=121
(−0.0274,0.453]: n=120
(0.453,2.84]: n=120
p−value= 0.008
Survival Probability
OverallSurvival.mos. [months]

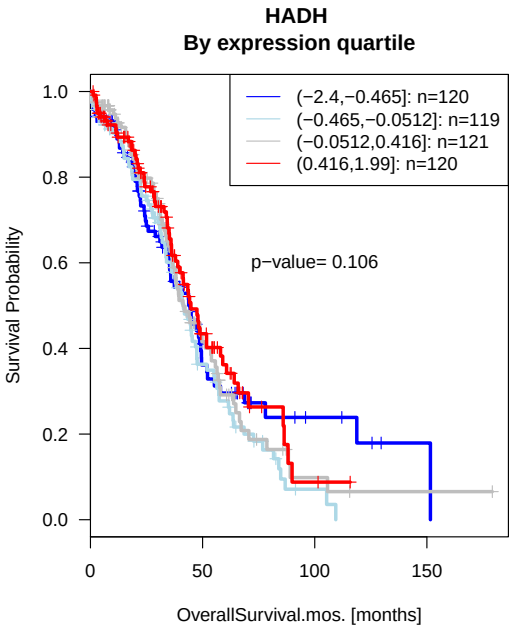

ECI2
By CNA type
loss: n=65
wt: n=105
gain: n=142
p−value= 0.411
Survival Probability
OverallSurvival.mos. [months]

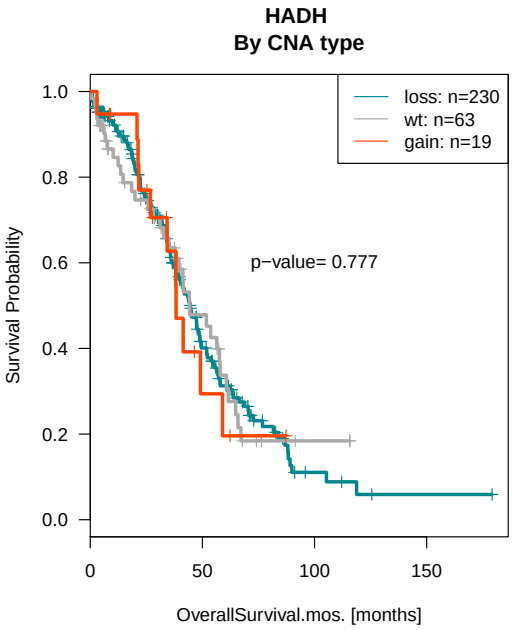

EHHADH
By expression quartile
(−2.15,−0.412]: n=120
(−0.412,0.038]: n=121
(0.038,0.48]: n=119
(0.48,2.38]: n=120
p−value= 0.063
Survival Probability
OverallSurvival.mos. [months]

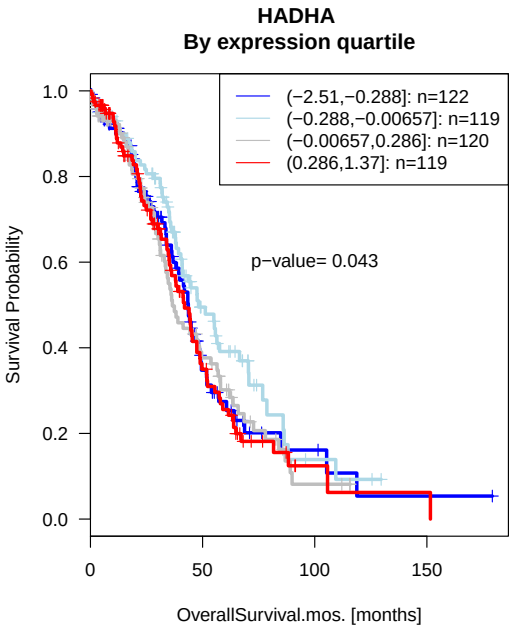

EHHADH
By CNA type
loss: n=12
wt: n=59
gain: n=241
p−value= 0.01
Survival Probability
OverallSurvival.mos. [months]

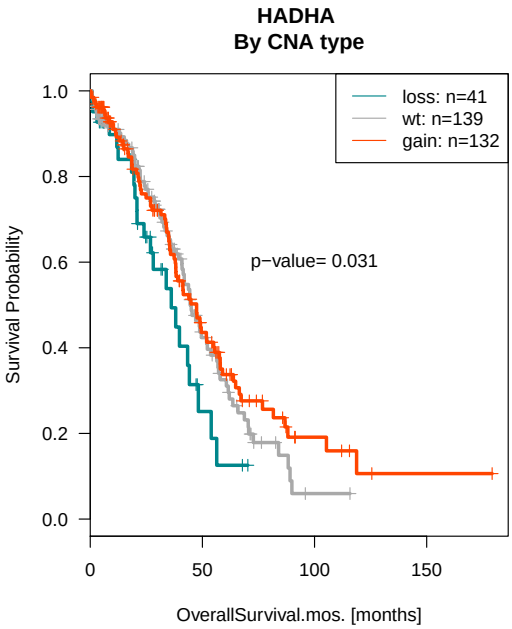

FABP4
By expression quartile
(−1.79,−1.25]: n=119
(−1.25,−0.858]: n=122
(−0.858,0.189]: n=121
(0.189,7.31]: n=118
p−value= 0.059
Survival Probability
OverallSurvival.mos. [months]

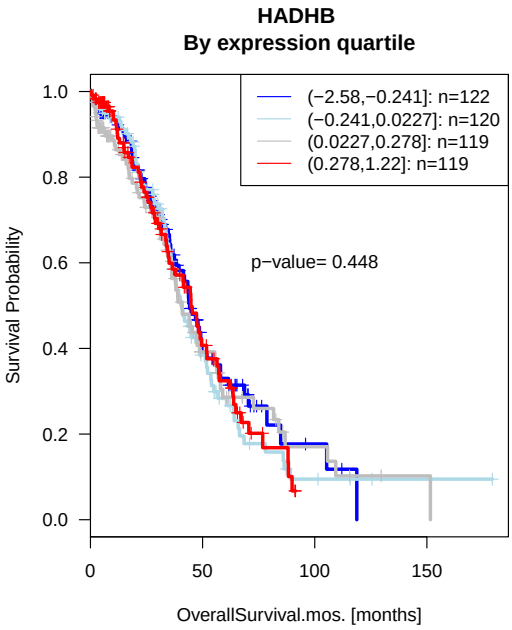

FABP4
By CNA type
loss: n=47
wt: n=106
gain: n=159
p−value= 0.018
Survival Probability
OverallSurvival.mos. [months]

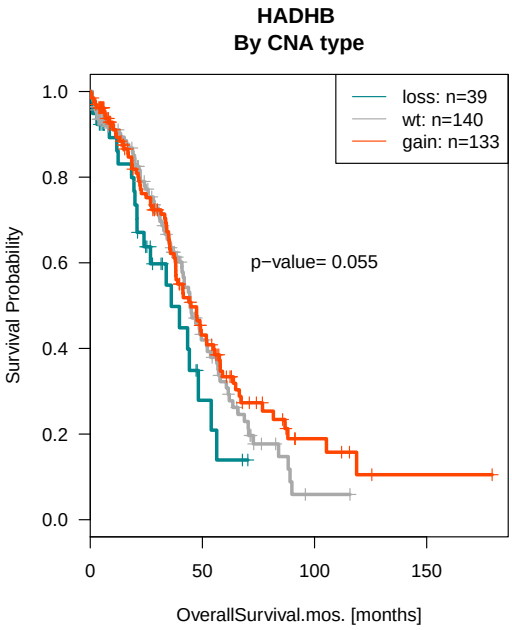

HADH
By expression quartile
(−2.4,−0.465]: n=120
(−0.465,−0.0512]: n=119
(−0.0512,0.416]: n=121
(0.416,1.99]: n=120
p−value= 0.106
Survival Probability
OverallSurvival.mos. [months]

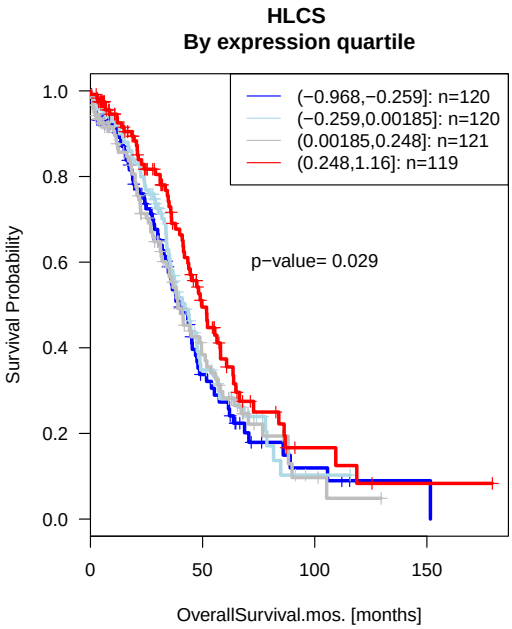

HADH
By CNA type
loss: n=230
wt: n=63
gain: n=19
p−value= 0.777
Survival Probability
OverallSurvival.mos. [months]

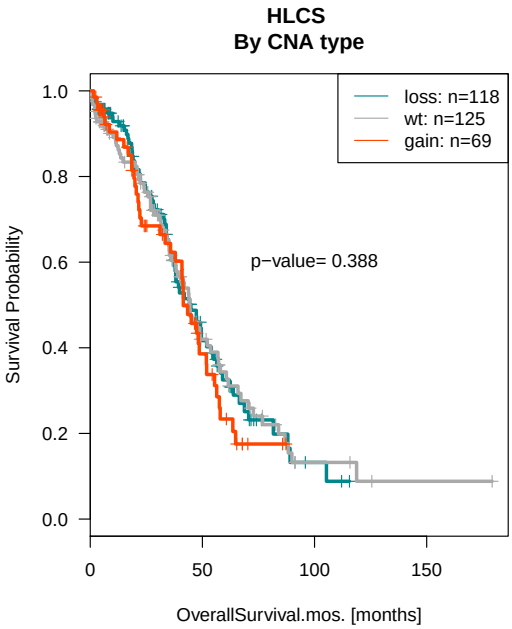

HADHA
By expression quartile
(−2.51,−0.288]: n=122
(−0.288,−0.00657]: n=119
(−0.00657,0.286]: n=120
(0.286,1.37]: n=119
p−value= 0.043
Survival Probability
OverallSurvival.mos. [months]

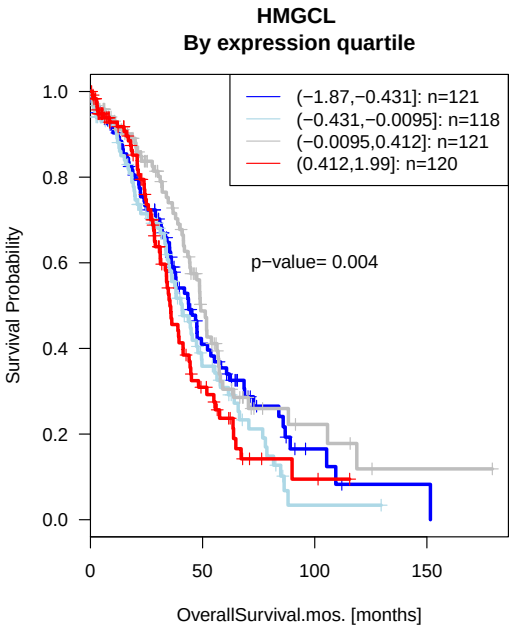

HADHA
By CNA type
loss: n=41
wt: n=139
gain: n=132
p−value= 0.031
Survival Probability
OverallSurvival.mos. [months]

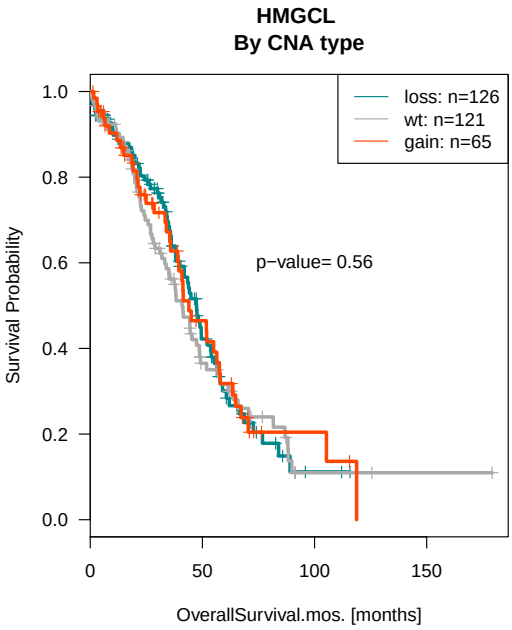

HADHB
By expression quartile
(−2.58,−0.241]: n=122
(−0.241,0.0227]: n=120
(0.0227,0.278]: n=119
(0.278,1.22]: n=119
p−value= 0.448
Survival Probability
OverallSurvival.mos. [months]

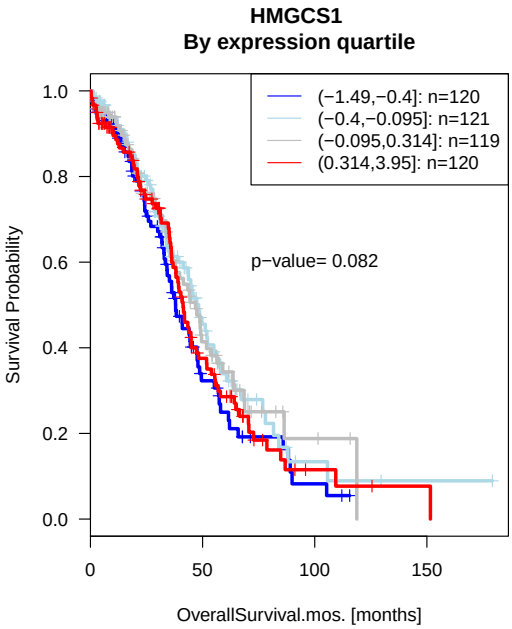

HADHB
By CNA type
loss: n=39
wt: n=140
gain: n=133
p−value= 0.055
Survival Probability
OverallSurvival.mos. [months]

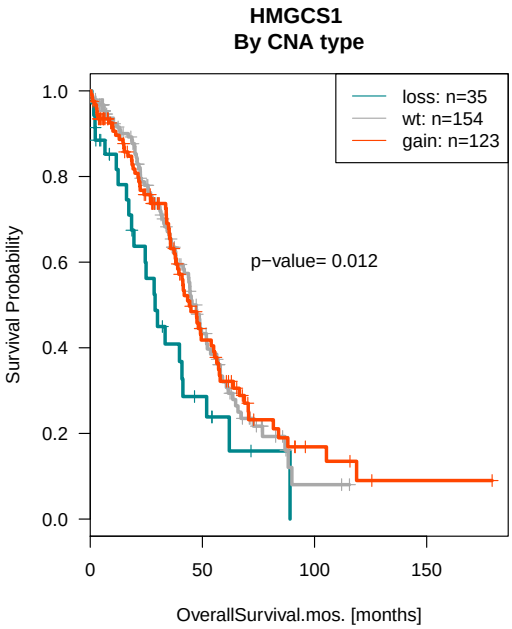

HLCS
By expression quartile
(−0.968,−0.259]: n=120
(−0.259,0.00185]: n=120
(0.00185,0.248]: n=121
(0.248,1.16]: n=119
p−value= 0.029
Survival Probability
OverallSurvival.mos. [months]

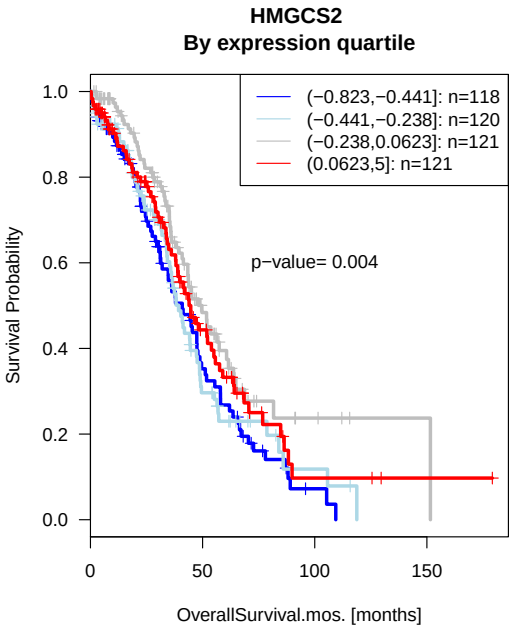

HLCS
By CNA type
loss: n=118
wt: n=125
gain: n=69
p−value= 0.388
Survival Probability
OverallSurvival.mos. [months]

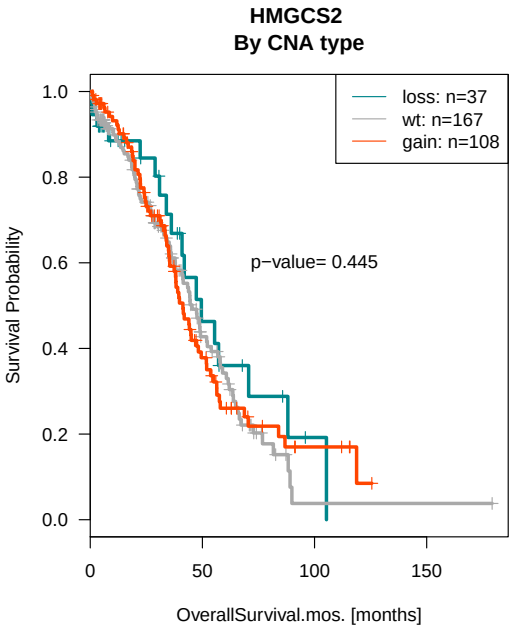

HMGCL
By expression quartile
(−1.87,−0.431]: n=121
(−0.431,−0.0095]: n=118
(−0.0095,0.412]: n=121
(0.412,1.99]: n=120
p−value= 0.004
Survival Probability
OverallSurvival.mos. [months]

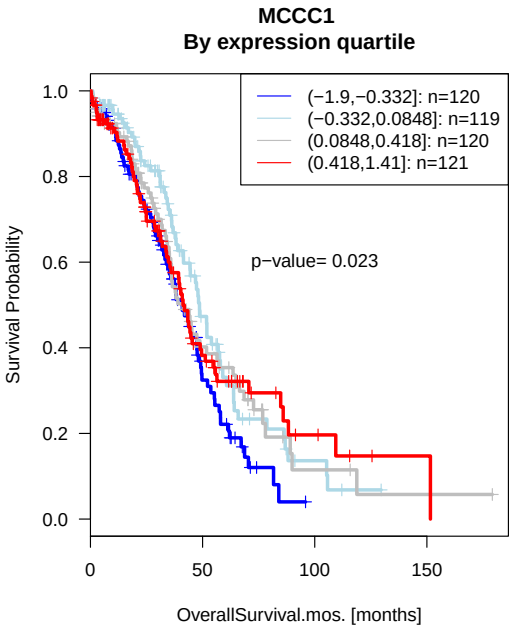

HMGCL
By CNA type
loss: n=126
wt: n=121
gain: n=65
p−value= 0.56
Survival Probability
OverallSurvival.mos. [months]

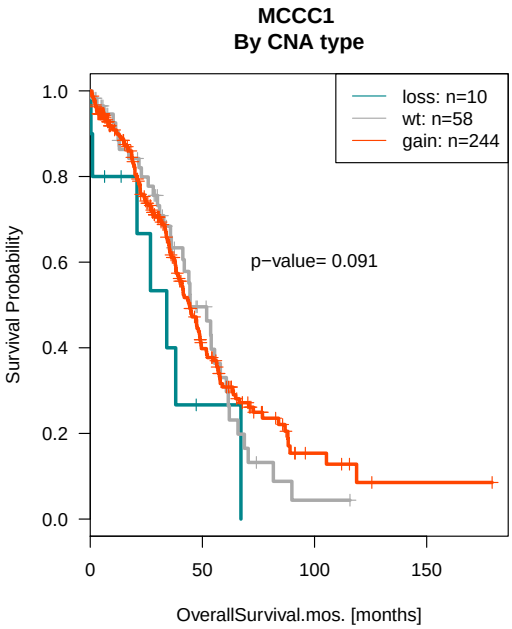

HMGCS1
By expression quartile
(−1.49,−0.4]: n=120
(−0.4,−0.095]: n=121
(−0.095,0.314]: n=119
(0.314,3.95]: n=120
p−value= 0.082
Survival Probability
OverallSurvival.mos. [months]

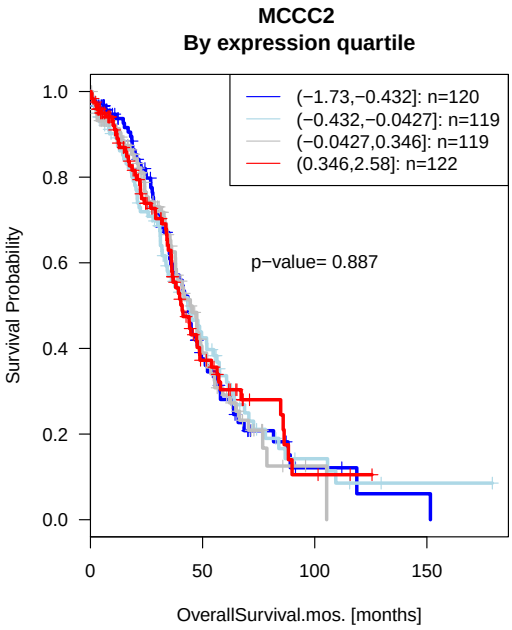

HMGCS1
By CNA type
loss: n=35
wt: n=154
gain: n=123
p−value= 0.012
Survival Probability
OverallSurvival.mos. [months]

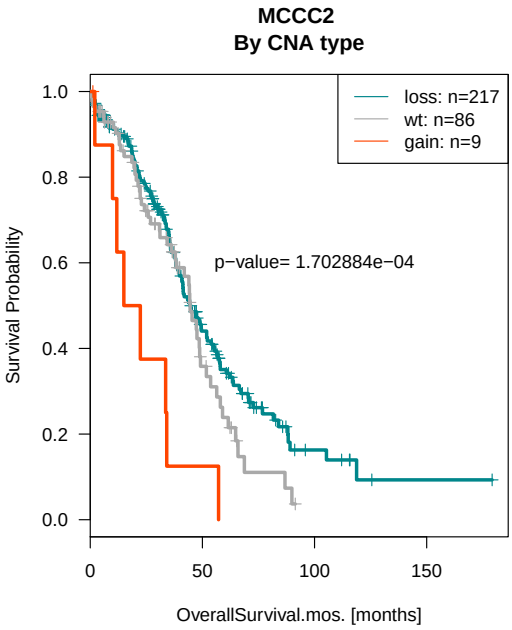

HMGCS2
By expression quartile
(−0.823,−0.441]: n=118
(−0.441,−0.238]: n=120
(−0.238,0.0623]: n=121
(0.0623,5]: n=121
p−value= 0.004
Survival Probability
OverallSurvival.mos. [months]

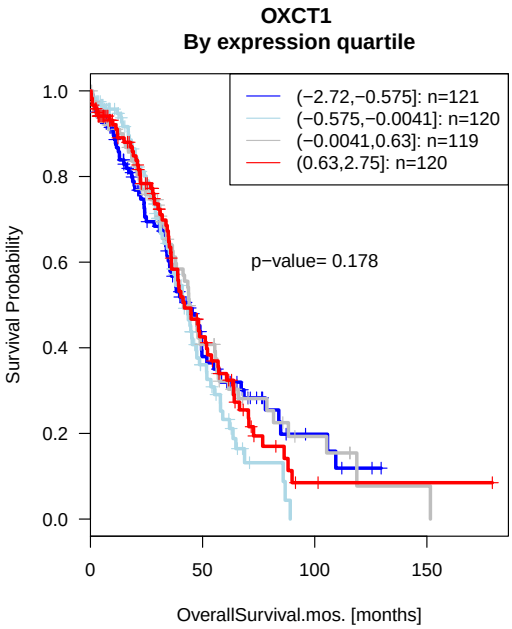

HMGCS2
By CNA type
loss: n=37
wt: n=167
gain: n=108
p−value= 0.445
Survival Probability
OverallSurvival.mos. [months]

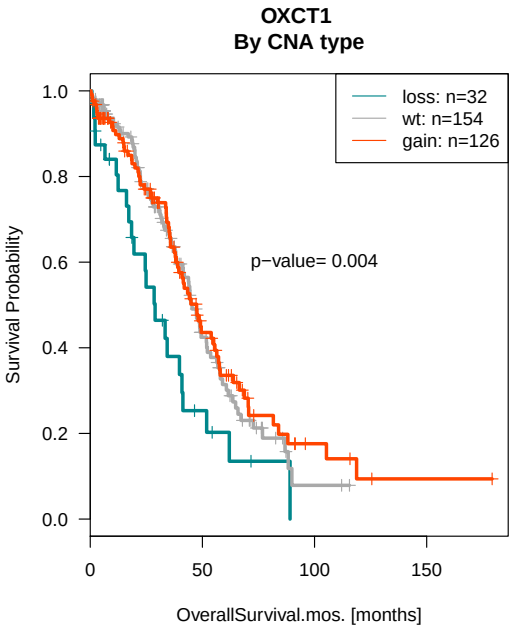

MCCC1
By expression quartile
(−1.9,−0.332]: n=120
(−0.332,0.0848]: n=119
(0.0848,0.418]: n=120
(0.418,1.41]: n=121
p−value= 0.023
Survival Probability
OverallSurvival.mos. [months]

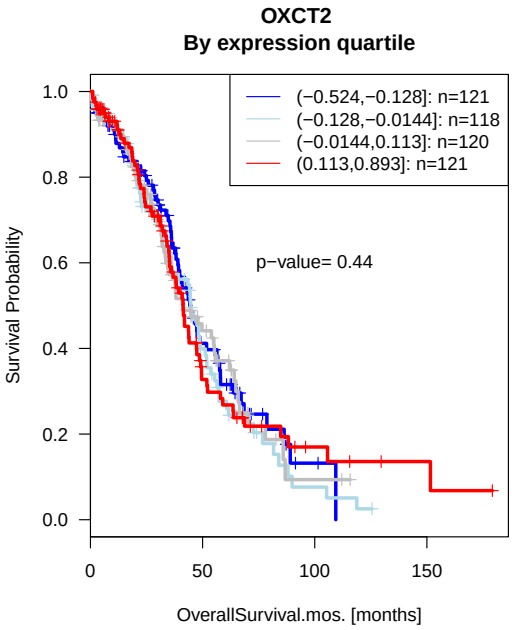

MCCC1
By CNA type
loss: n=10
wt: n=58
gain: n=244
p−value= 0.091
Survival Probability
OverallSurvival.mos. [months]

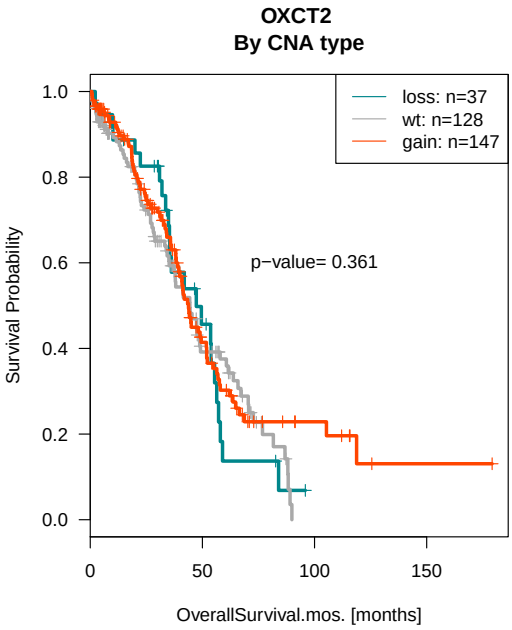

MCCC2
By expression quartile
(−1.73,−0.432]: n=120
(−0.432,−0.0427]: n=119
(−0.0427,0.346]: n=119
(0.346,2.58]: n=122
p−value= 0.887
Survival Probability
OverallSurvival.mos. [months]

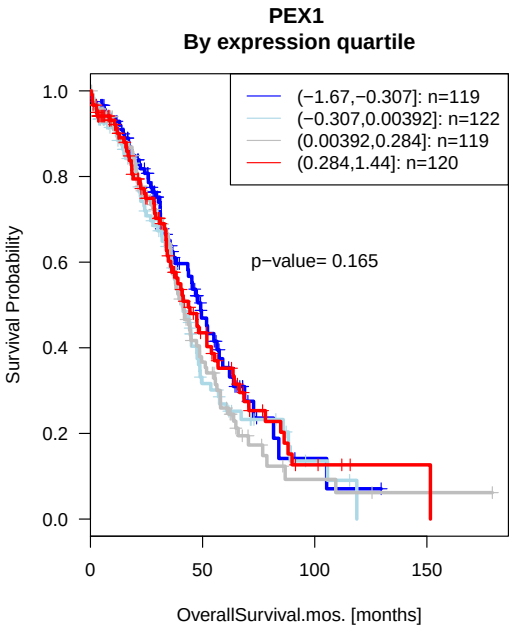

MCCC2
By CNA type
loss: n=217
wt: n=86
gain: n=9
p−value= 1.702884e−04
Survival Probability
OverallSurvival.mos. [months]

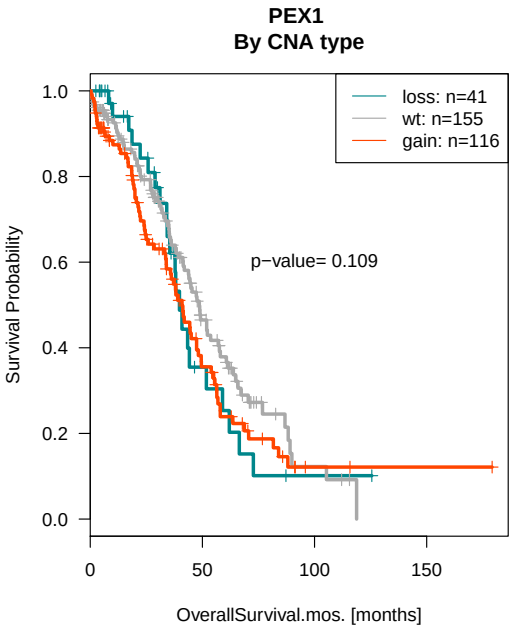

OXCT1
By expression quartile
(−2.72,−0.575]: n=121
(−0.575,−0.0041]: n=120
(−0.0041,0.63]: n=119
(0.63,2.75]: n=120
p−value= 0.178
Survival Probability
OverallSurvival.mos. [months]

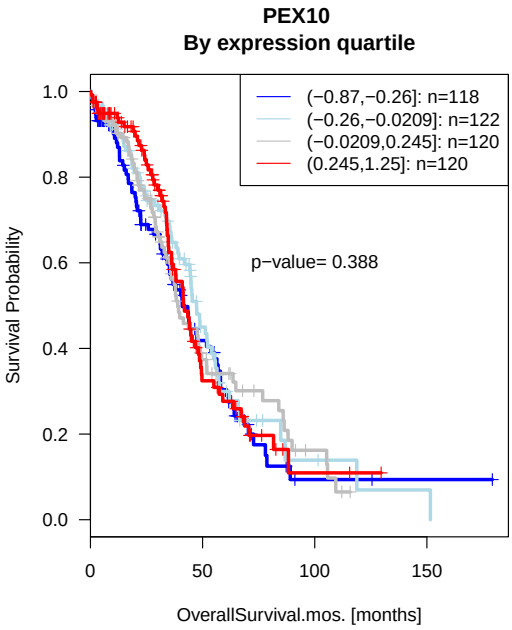

OXCT1
By CNA type
loss: n=32
wt: n=154
gain: n=126
p−value= 0.004
Survival Probability
OverallSurvival.mos. [months]

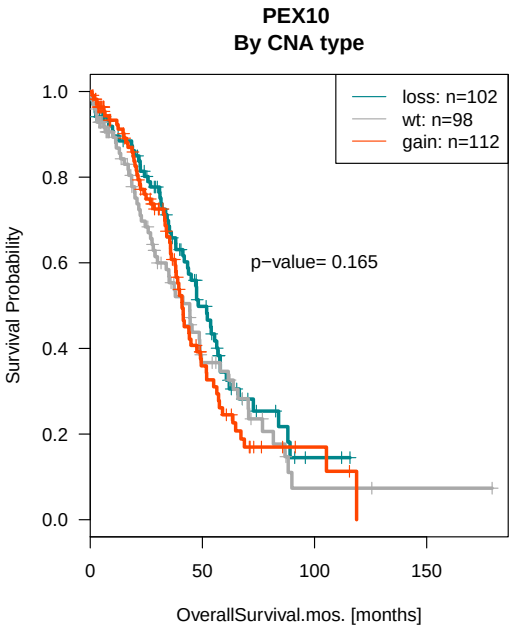

OXCT2
By expression quartile
(−0.524,−0.128]: n=121
(−0.128,−0.0144]: n=118
(−0.0144,0.113]: n=120
(0.113,0.893]: n=121
p−value= 0.44
Survival Probability
OverallSurvival.mos. [months]

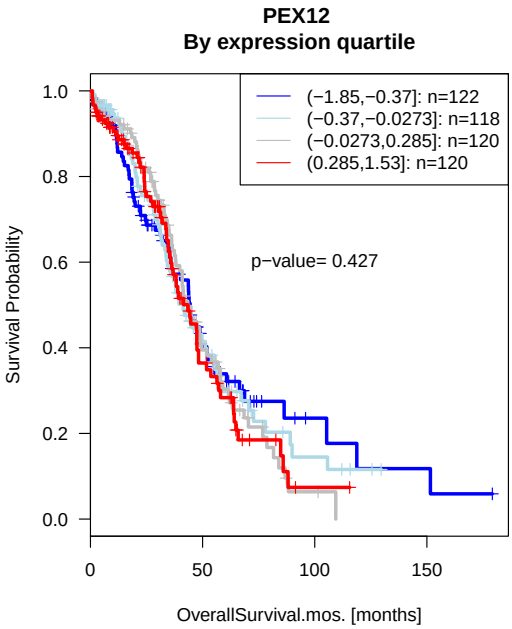

OXCT2
By CNA type
loss: n=37
wt: n=128
gain: n=147
p−value= 0.361
Survival Probability
OverallSurvival.mos. [months]

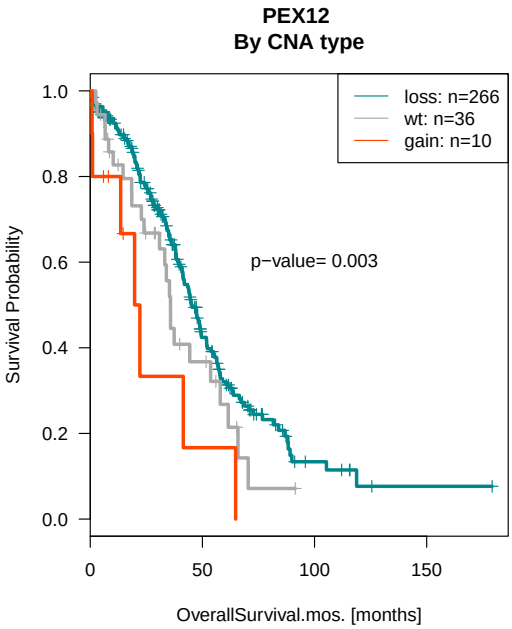

PEX1
By expression quartile
(−1.67,−0.307]: n=119
(−0.307,0.00392]: n=122
(0.00392,0.284]: n=119
(0.284,1.44]: n=120
p−value= 0.165
Survival Probability
OverallSurvival.mos. [months]

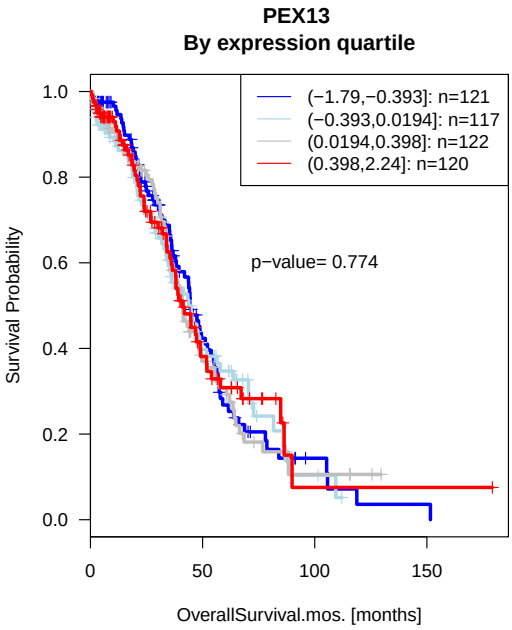

PEX1
By CNA type
loss: n=41
wt: n=155
gain: n=116
p−value= 0.109
Survival Probability
OverallSurvival.mos. [months]

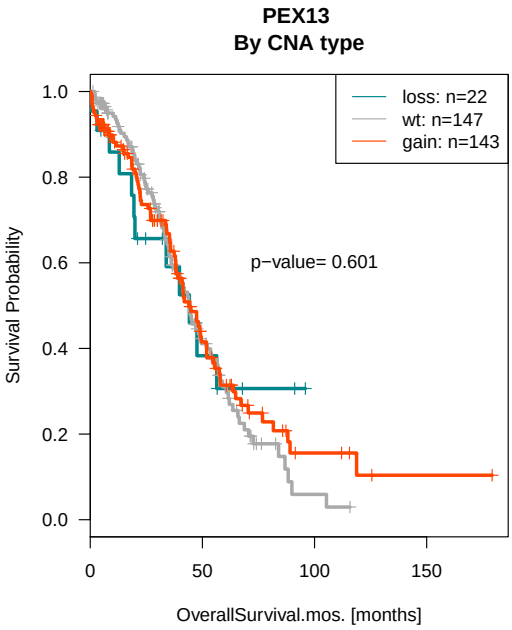

PEX10
By expression quartile
(−0.87,−0.26]: n=118
(−0.26,−0.0209]: n=122
(−0.0209,0.245]: n=120
(0.245,1.25]: n=120
p−value= 0.388
Survival Probability
OverallSurvival.mos. [months]

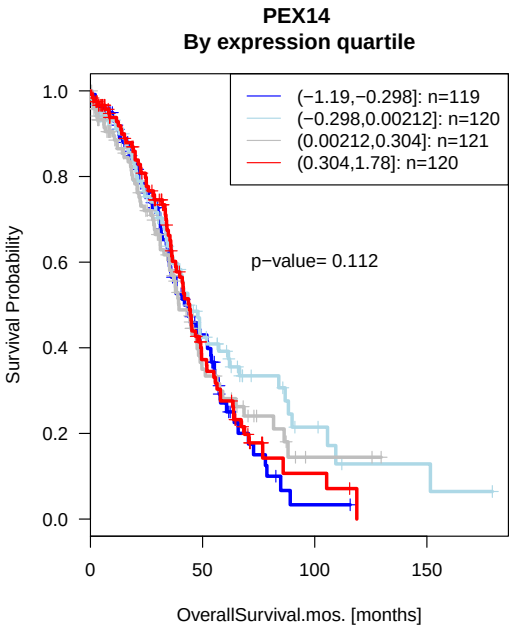

PEX10
By CNA type
loss: n=102
wt: n=98
gain: n=112
p−value= 0.165
Survival Probability
OverallSurvival.mos. [months]

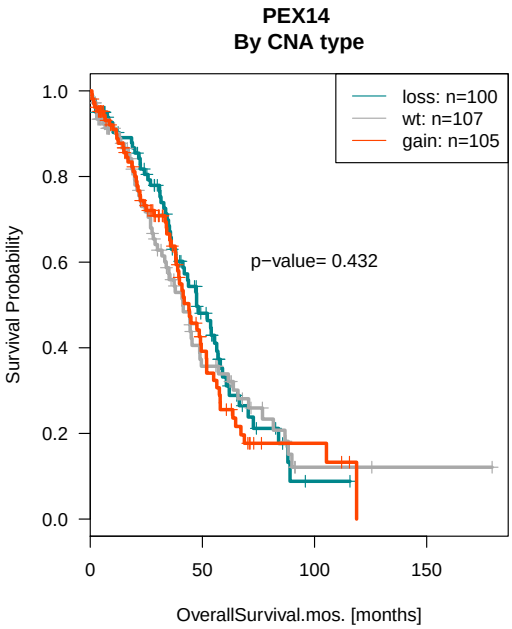

PEX12
By expression quartile
(−1.85,−0.37]: n=122
(−0.37,−0.0273]: n=118
(−0.0273,0.285]: n=120
(0.285,1.53]: n=120
p−value= 0.427
Survival Probability
OverallSurvival.mos. [months]

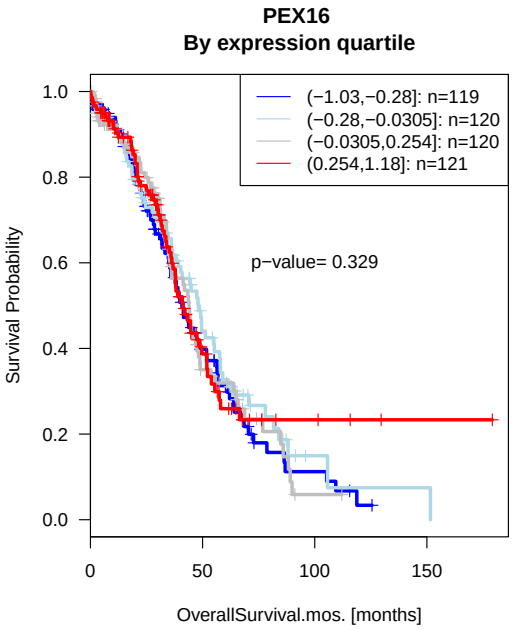

PEX12
By CNA type
loss: n=266
wt: n=36
gain: n=10
p−value= 0.003
Survival Probability
OverallSurvival.mos. [months]

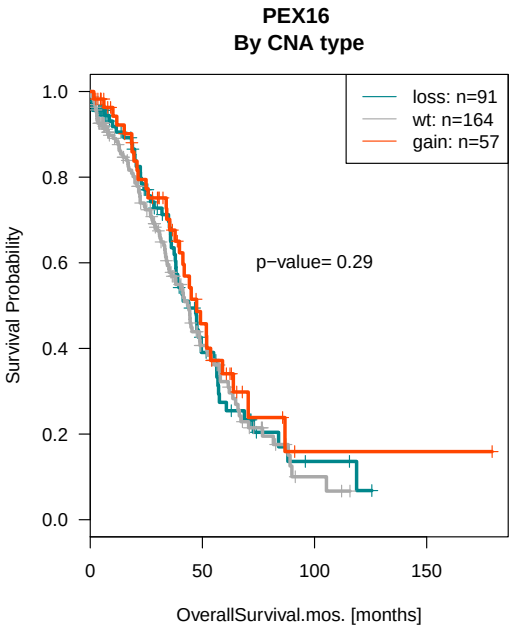

PEX13
By expression quartile
(−1.79,−0.393]: n=121
(−0.393,0.0194]: n=117
(0.0194,0.398]: n=122
(0.398,2.24]: n=120
p−value= 0.774
Survival Probability
OverallSurvival.mos. [months]

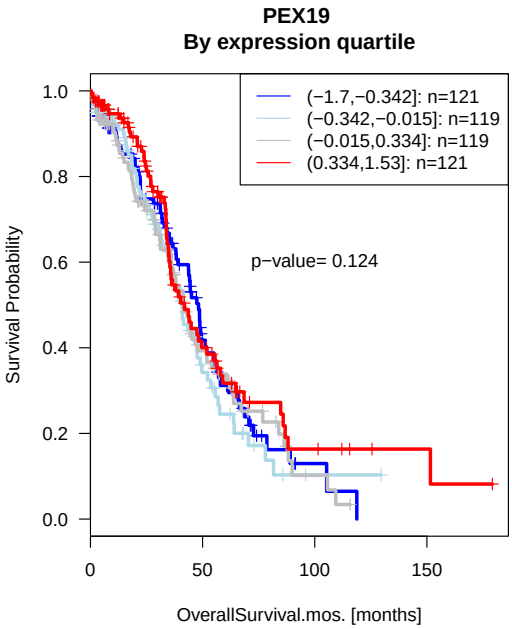

PEX13
By CNA type
loss: n=22
wt: n=147
gain: n=143
p−value= 0.601
Survival Probability
OverallSurvival.mos. [months]

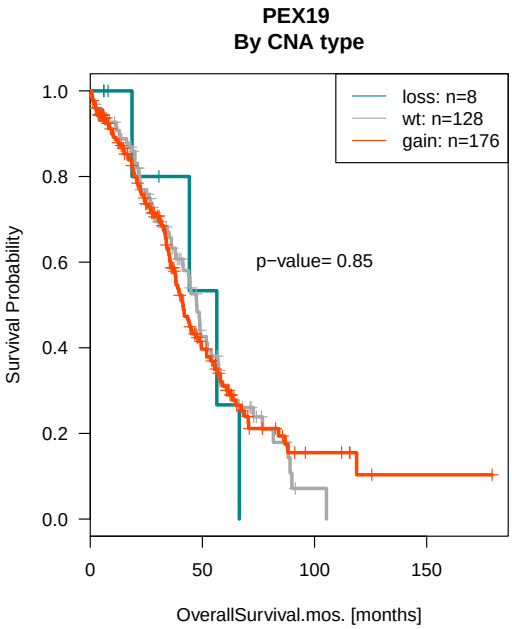

PEX14
By expression quartile
(−1.19,−0.298]: n=119
(−0.298,0.00212]: n=120
(0.00212,0.304]: n=121
(0.304,1.78]: n=120
p−value= 0.112
Survival Probability
OverallSurvival.mos. [months]

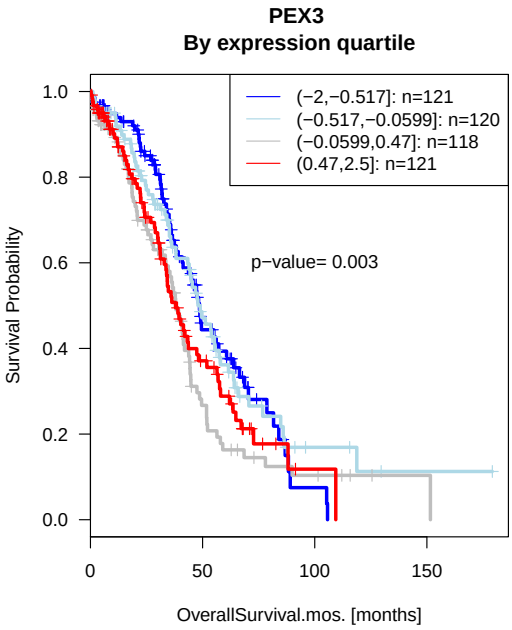

PEX14
By CNA type
loss: n=100
wt: n=107
gain: n=105
p−value= 0.432
Survival Probability
OverallSurvival.mos. [months]

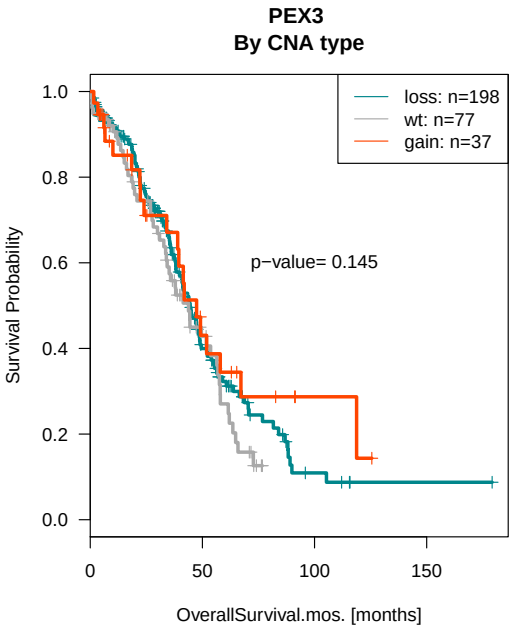

PEX16
By expression quartile
(−1.03,−0.28]: n=119
(−0.28,−0.0305]: n=120
(−0.0305,0.254]: n=120
(0.254,1.18]: n=121
p−value= 0.329
Survival Probability
OverallSurvival.mos. [months]

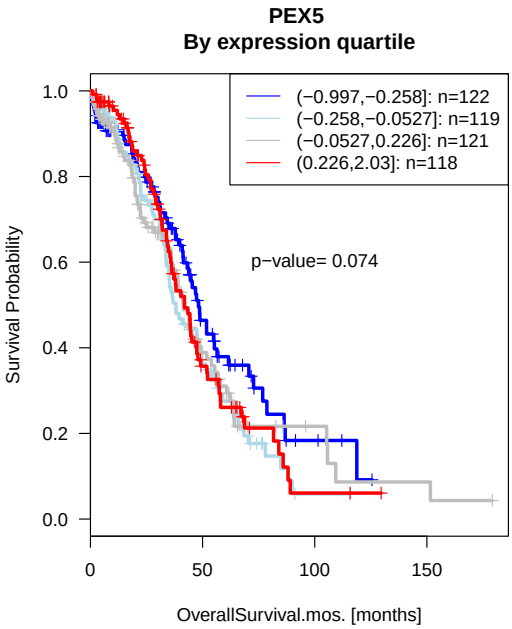

PEX16
By CNA type
loss: n=91
wt: n=164
gain: n=57
p−value= 0.29
Survival Probability
OverallSurvival.mos. [months]

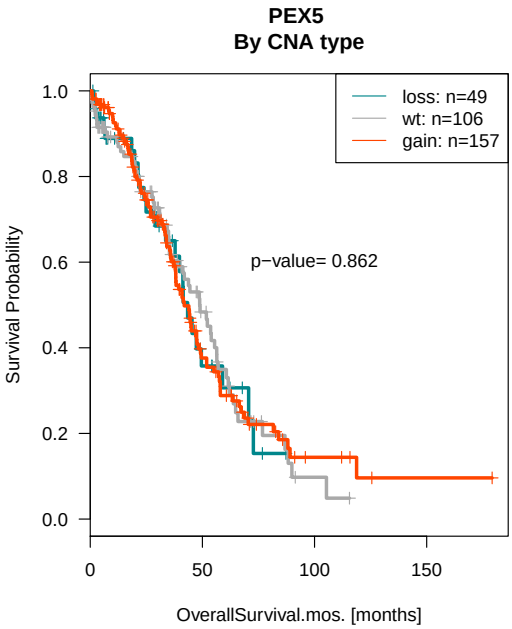

PEX19
By expression quartile
(−1.7,−0.342]: n=121
(−0.342,−0.015]: n=119
(−0.015,0.334]: n=119
(0.334,1.53]: n=121
p−value= 0.124
Survival Probability
OverallSurvival.mos. [months]

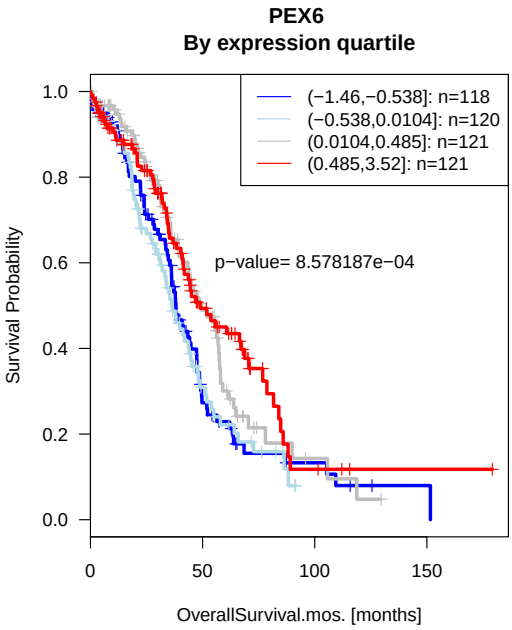

PEX19
By CNA type
loss: n=8
wt: n=128
gain: n=176
p−value= 0.85
Survival Probability
OverallSurvival.mos. [months]

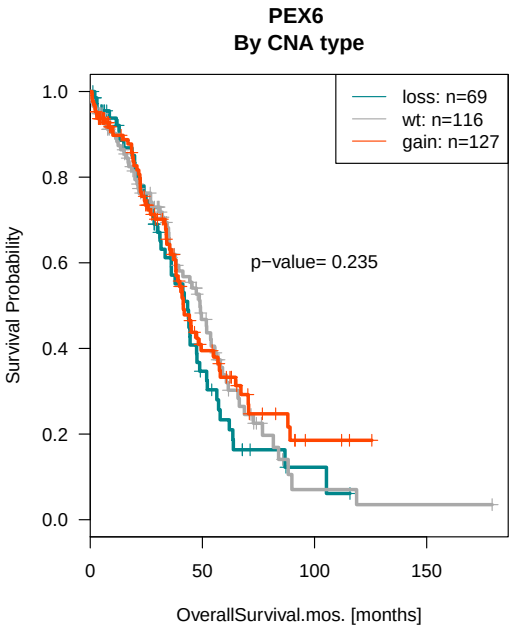

PEX3
By expression quartile
(−2,−0.517]: n=121
(−0.517,−0.0599]: n=120
(−0.0599,0.47]: n=118
(0.47,2.5]: n=121
p−value= 0.003
Survival Probability
OverallSurvival.mos. [months]

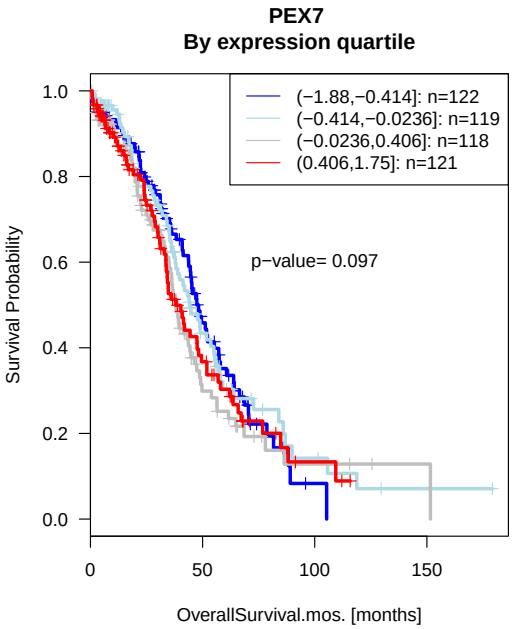

PEX3
By CNA type
loss: n=198
wt: n=77
gain: n=37
p−value= 0.145
Survival Probability
OverallSurvival.mos. [months]

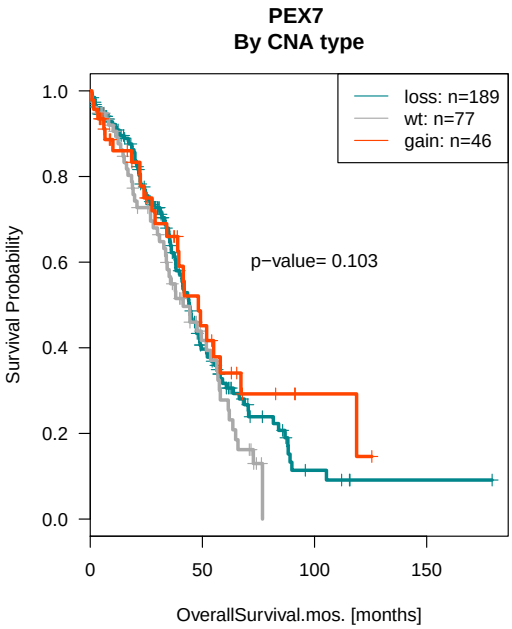

PEX5
By expression quartile
(−0.997,−0.258]: n=122
(−0.258,−0.0527]: n=119
(−0.0527,0.226]: n=121
(0.226,2.03]: n=118
p−value= 0.074
Survival Probability
OverallSurvival.mos. [months]

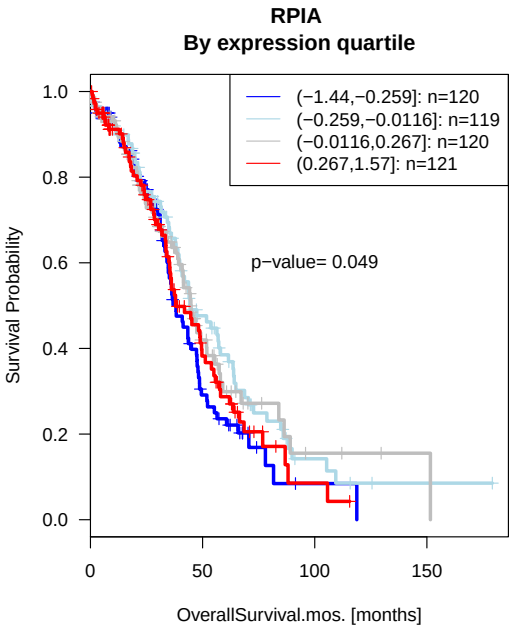

PEX5
By CNA type
loss: n=49
wt: n=106
gain: n=157
p−value= 0.862
Survival Probability
OverallSurvival.mos. [months]

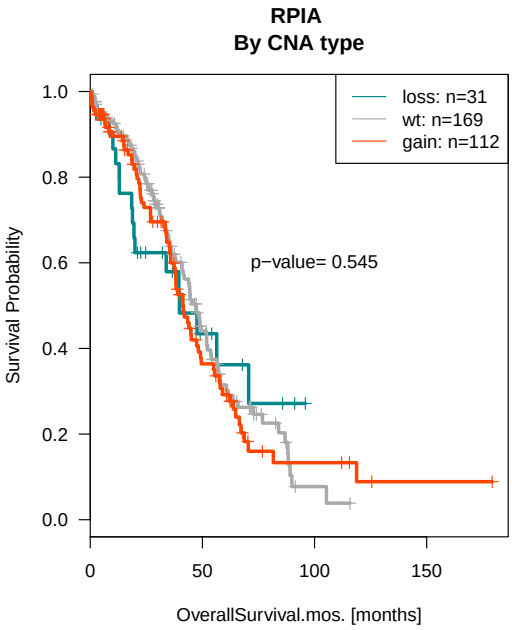

PEX6
By expression quartile
(−1.46,−0.538]: n=118
(−0.538,0.0104]: n=120
(0.0104,0.485]: n=121
(0.485,3.52]: n=121
p−value= 8.578187e−04
Survival Probability
OverallSurvival.mos. [months]

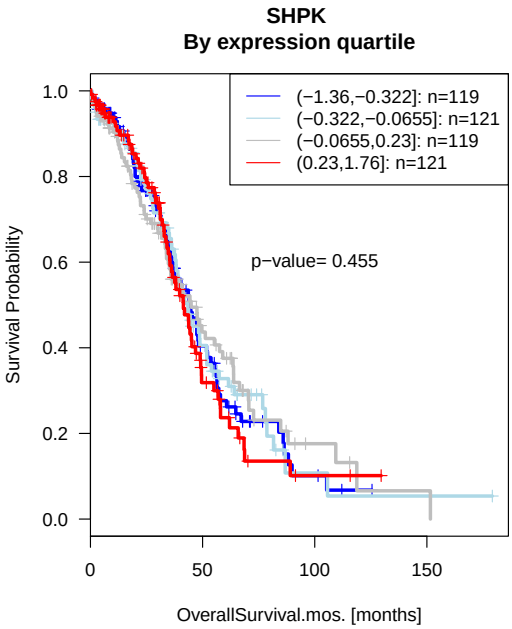

PEX6
By CNA type
loss: n=69
wt: n=116
gain: n=127
p−value= 0.235
Survival Probability
OverallSurvival.mos. [months]

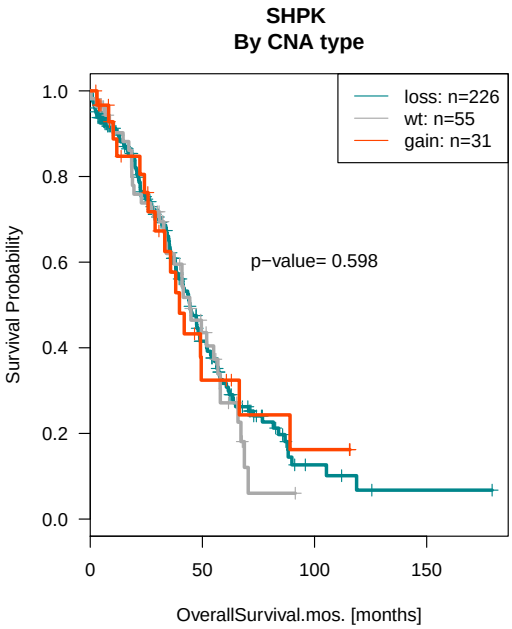

PEX7
By expression quartile
(−1.88,−0.414]: n=122
(−0.414,−0.0236]: n=119
(−0.0236,0.406]: n=118
(0.406,1.75]: n=121
p−value= 0.097
Survival Probability
OverallSurvival.mos. [months]

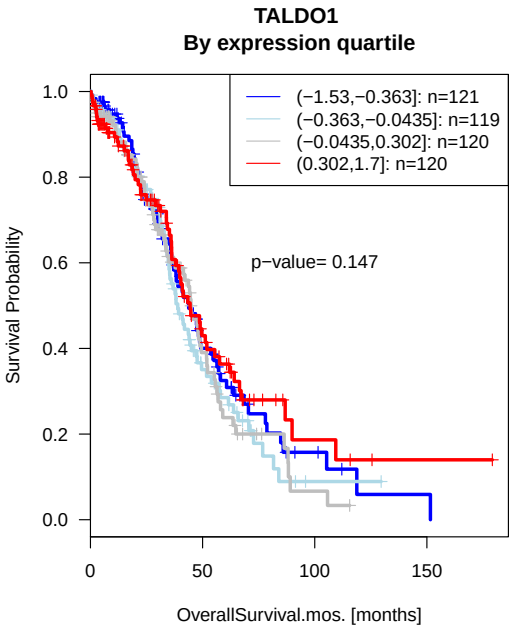

PEX7
By CNA type
loss: n=189
wt: n=77
gain: n=46
p−value= 0.103
Survival Probability
OverallSurvival.mos. [months]

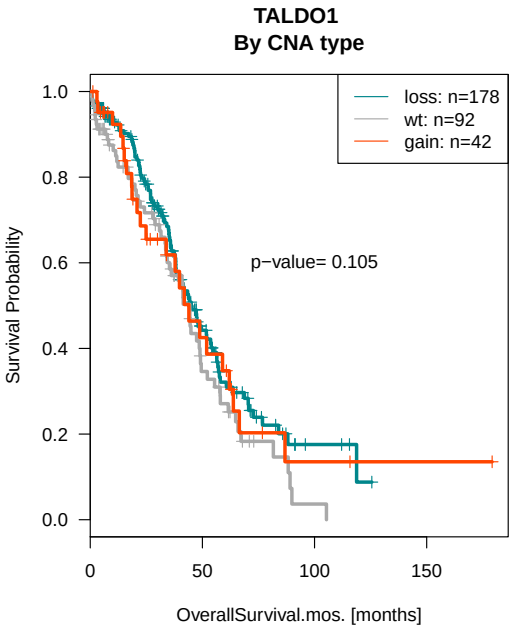

RPIA
By expression quartile
(−1.44,−0.259]: n=120
(−0.259,−0.0116]: n=119
(−0.0116,0.267]: n=120
(0.267,1.57]: n=121
p−value= 0.049
Survival Probability
OverallSurvival.mos. [months]

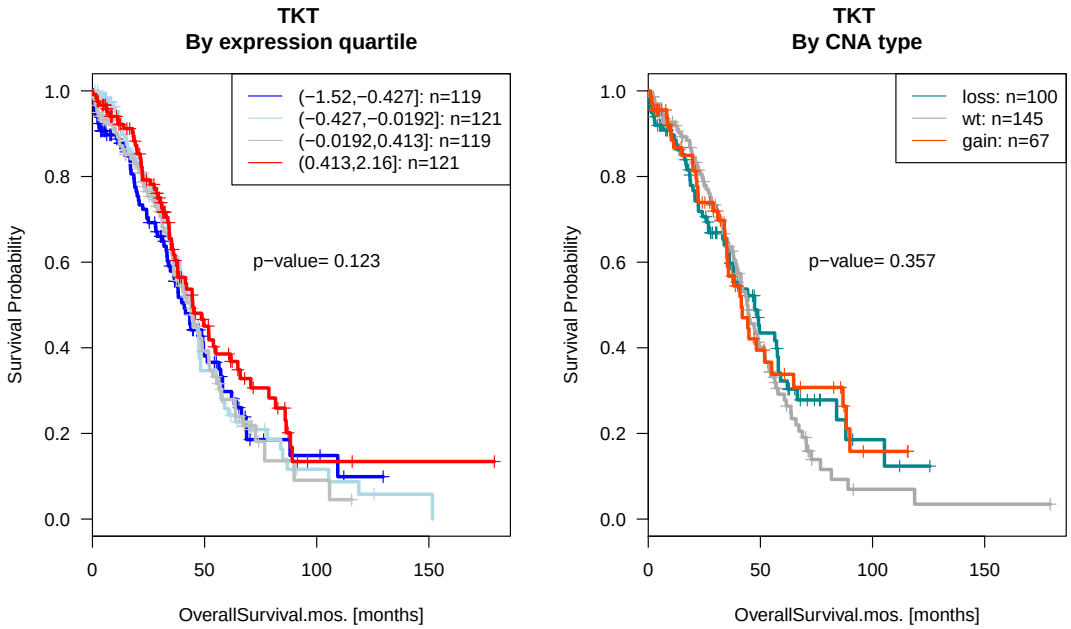

RPIA
By CNA type
loss: n=31
wt: n=169
gain: n=112
p−value= 0.545
Survival Probability
OverallSurvival.mos. [months]


SHPK
By expression quartile
(−1.36,−0.322]: n=119
(−0.322,−0.0655]: n=121
(−0.0655,0.23]: n=119
(0.23,1.76]: n=121
p−value= 0.455
Survival Probability
OverallSurvival.mos. [months]


SHPK
By CNA type
loss: n=226
wt: n=55
gain: n=31
p−value= 0.598
Survival Probability
OverallSurvival.mos. [months]


TALDO1
By expression quartile
(−1.53,−0.363]: n=121
(−0.363,−0.0435]: n=119
(−0.0435,0.302]: n=120
(0.302,1.7]: n=120
p−value= 0.147
Survival Probability
OverallSurvival.mos. [months]


TALDO1
By CNA type
loss: n=178
wt: n=92
gain: n=42
p−value= 0.105
Survival Probability
OverallSurvival.mos. [months]



4 Session info: R-packages and their versions used for this analysis

```
sessionInfo()

## R version 3.1.2 (2014-10-31)
## Platform: x86_64-apple-darwin10.8.0 (64-bit)
##
## locale:
## [1] en_GB.UTF-8/en_GB.UTF-8/en_GB.UTF-8/C/en_GB.UTF-8/en_GB.UTF-8
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
## [1] survival_2.38-1 knitr_1.9
##
## loaded via a namespace (and not attached):
## [1] evaluate_0.6  formatR_1.1   highr_0.4.1   splines_3.1.2 stringr_0.6.2
## [6] tools_3.1.2
```