

SimpleViolins

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Contents

Data sources	1
Plots for CPu	1

Data sources

We evaluate genotype and sex differences in mouse models of Alzheimer's disease risk, based on APOE alleles: APOE2 is protective, APOE3 is control, and APOE4 represents genetic risk for AD. One allele increases risk by 3 times, and two APOE4 alleles increase risk by 10 times (ref) in relation to APOE3 . We use multiple data sources:

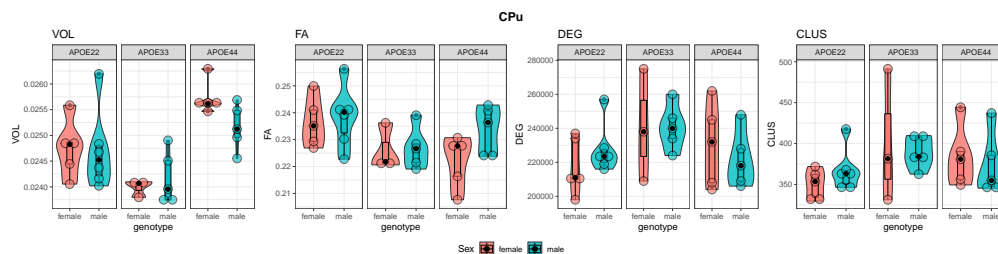
Morris Water Maze - testing spatial navigation memory Segmentation: regional volumes Microstructural properties: FA Tractography Based Connectivity: Degree, and Clustering Coefficient

We read the data and normalize volumes to the whole brain.

Plots for CPu

We embed plots for day d8 probe trials:

```
## Bin width defaults to 1/30 of the range of the data. Pick better value with `binwidth`.
## Bin width defaults to 1/30 of the range of the data. Pick better value with `binwidth`.
## Bin width defaults to 1/30 of the range of the data. Pick better value with `binwidth`.
## Bin width defaults to 1/30 of the range of the data. Pick better value with `binwidth`.
## Bin width defaults to 1/30 of the range of the data. Pick better value with `binwidth`.
```



```
print('CPu')
```

```
## [1] "CPu"
```

```
lm_CPu_VOL <- lm(CPu ~ Genotype*Sex, geno_combined_VOL)
summary(lm_CPu_VOL)
```

```
##
## Call:
## lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -7.026e-04 -3.106e-04 -6.856e-05  1.250e-04  1.486e-03
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)    2.476e-02  2.420e-04 102.283 < 2e-16 ***
## GenotypeAPOE33  -7.692e-04  3.952e-04  -1.946  0.06395 .
## GenotypeAPOE44   9.720e-04  3.423e-04   2.840  0.00928 **
## Sexmale         -4.568e-05  3.277e-04  -0.139  0.89036
## GenotypeAPOE33:Sexmale 2.317e-04  5.134e-04   0.451  0.65601
## GenotypeAPOE44:Sexmale -5.205e-04  4.739e-04  -1.098  0.28336
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.0005412 on 23 degrees of freedom
## Multiple R-squared:  0.5711, Adjusted R-squared:  0.4778
## F-statistic: 6.124 on 5 and 23 DF,  p-value: 0.0009559

lm_CPu_VOL_f <- lm(CPu ~ Genotype, combo_f_FA)
#summary(lm_CPu_VOL_f)
lm_CPu_VOL_m <- lm(CPu ~ Genotype, combo_m_FA)
#summary(lm_CPu_VOL_f)

#omnibus testing
#https://cran.r-project.org/web/packages/emmeans/vignettes/confidence-intervals.html#adjust

#33333
sink(paste(outpath, "CPu_VOL_SimpleModels.txt"))
mydata.lm <- lm(CPu ~ Genotype*Sex, data = geno_combined_VOL)
anova(mydata.lm)

## Analysis of Variance Table
##
## Response: CPu
##           Df      Sum Sq    Mean Sq F value    Pr(>F)
## Genotype    2 8.0970e-06 4.0485e-06 13.8218 0.0001142 ***
## Sex          1 1.9980e-07 1.9980e-07  0.6822 0.4173028
## Genotype:Sex  2 6.7230e-07 3.3610e-07  1.1476 0.3349205
## Residuals   23 6.7368e-06 2.9290e-07
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

summary(glht(mydata.lm, emm(pairwise ~ Genotype|Sex, adjust="sidak")))
```

#consider save to file

```
## $`Sex = female`
##
## Simultaneous Tests for General Linear Hypotheses
##
```

```

## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.0007692  0.0003952   1.946   0.1479
## APOE22 - APOE44 == 0 -0.0009720  0.0003423  -2.840   0.0242 *
## APOE33 - APOE44 == 0 -0.0017413  0.0003952  -4.406   <0.001 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.0005375  0.0003277   1.640   0.2494
## APOE22 - APOE44 == 0 -0.0004515  0.0003277  -1.378   0.3685
## APOE33 - APOE44 == 0 -0.0009890  0.0003423  -2.889   0.0218 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
summary(glht(mydata.lm, emm(pairwise ~ Sex| Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## female - male == 0  4.568e-05  3.277e-04   0.139   0.89
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.0001860  0.0003952  -0.471   0.642
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##

```

```
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0 0.0005662 0.0003423  1.654    0.112
## (Adjusted p values reported -- single-step method)
```

```
sink()
#3333

sink(paste(outpath, "CPu_VOL_SimpleStats.txt", sep=''))
'omnibus testing'
```

```
## [1] "omnibus testing"
```

```
joint_tests(ref_grid(lm_CPu_VOL))
```

```
## model term    df1 df2 F.ratio p.value
## Genotype      2  23  13.818 0.0001
## Sex           1  23   0.476 0.4970
## Genotype:Sex   2  23   1.148 0.3349
```

```
joint_tests(ref_grid(lm_CPu_VOL), by = "Sex", adjust = "sidak")
```

```
## Sex = female:
## model term df1 df2 F.ratio p.value
## Genotype   2  23  10.239 0.0007
##
## Sex = male:
## model term df1 df2 F.ratio p.value
## Genotype   2  23   4.186 0.0282
```

```
joint_tests(ref_grid(lm_CPu_VOL), by = "Genotype", adjust = "sidak" )
```

```
## Genotype = APOE22:
## model term df1 df2 F.ratio p.value
## Sex        1  23   0.019 0.8904
##
## Genotype = APOE33:
## model term df1 df2 F.ratio p.value
## Sex        1  23   0.222 0.6423
##
## Genotype = APOE44:
## model term df1 df2 F.ratio p.value
## Sex        1  23   2.736 0.1117
```

```
'anova'
```

```
## [1] "anova"
```

```
anova(lm_CPu_VOL)
```

```
## Analysis of Variance Table
```

```
##
```

```
## Response: CPu
```

```
##           Df      Sum Sq    Mean Sq F value    Pr(>F)
## Genotype   2 8.0970e-06 4.0485e-06 13.8218 0.0001142 ***
```

```
## Sex          1 1.9980e-07 1.9980e-07 0.6822 0.4173028
## Genotype:Sex 2 6.7230e-07 3.3610e-07 1.1476 0.3349205
## Residuals    23 6.7368e-06 2.9290e-07
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

#anova(lm_CPu_VOL_f)
#anova(lm_CPu_VOL_m)

#post hoc comparison
CPu_VOL.emm <- emmeans(lm_CPu_VOL , ~ Genotype | Sex, adjust = "sidak")
contrast(CPu_VOL.emm, simple = c("Genotype", "Sex")) #FDR

## contrast          estimate          SE df t.ratio p.value
## APOE22 female effect  3.37e-06 0.000223 23   0.015 0.9881
## APOE33 female effect -7.66e-04 0.000275 23  -2.784 0.0316
## APOE44 female effect  9.75e-04 0.000223 23   4.378 0.0013
## APOE22 male effect   -4.23e-05 0.000208 23  -0.204 0.9881
## APOE33 male effect   -5.80e-04 0.000223 23  -2.603 0.0318
## APOE44 male effect    4.09e-04 0.000223 23   1.837 0.1188
##
## P value adjustment: fdr method for 6 tests
contrast(CPu_VOL.emm, simple = list("Genotype", "Sex"))

## $`simple contrasts for Genotype`
## Sex = female:
## contrast          estimate          SE df t.ratio p.value
## APOE22 effect -6.76e-05 0.000208 23  -0.325 0.7484
## APOE33 effect -8.37e-04 0.000238 23  -3.523 0.0027
## APOE44 effect  9.04e-04 0.000208 23   4.342 0.0007
##
## Sex = male:
## contrast          estimate          SE df t.ratio p.value
## APOE22 effect  2.87e-05 0.000186 23   0.154 0.8791
## APOE33 effect -5.09e-04 0.000195 23  -2.611 0.0324
## APOE44 effect  4.80e-04 0.000195 23   2.464 0.0324
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
## contrast          estimate          SE df t.ratio p.value
## female effect  2.28e-05 0.000164 23   0.139 0.8904
## male effect   -2.28e-05 0.000164 23  -0.139 0.8904
##
## Genotype = APOE33:
## contrast          estimate          SE df t.ratio p.value
## female effect -9.30e-05 0.000198 23  -0.471 0.6423
## male effect   9.30e-05 0.000198 23   0.471 0.6423
##
## Genotype = APOE44:
## contrast          estimate          SE df t.ratio p.value
## female effect  2.83e-04 0.000171 23   1.654 0.1117
## male effect   -2.83e-04 0.000171 23  -1.654 0.1117
```

```
##
## P value adjustment: fdr method for 2 tests
#post hoc tests
summary(glht(lm_CPu_VOL, emm(pairwise ~ Genotype*Sex, contr="sidak"))) #consider save to file

##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 7.692e-04 3.952e-04 1.946 0.39948
## APOE22 female - APOE44 female == 0 -9.720e-04 3.423e-04 -2.840 0.08558 .
## APOE22 female - APOE22 male == 0 4.568e-05 3.277e-04 0.139 0.99999
## APOE22 female - APOE33 male == 0 5.832e-04 3.423e-04 1.704 0.54125
## APOE22 female - APOE44 male == 0 -4.058e-04 3.423e-04 -1.186 0.83800
## APOE33 female - APOE44 female == 0 -1.741e-03 3.952e-04 -4.406 0.00243 **
## APOE33 female - APOE22 male == 0 -7.235e-04 3.827e-04 -1.891 0.43051
## APOE33 female - APOE33 male == 0 -1.860e-04 3.952e-04 -0.471 0.99671
## APOE33 female - APOE44 male == 0 -1.175e-03 3.952e-04 -2.973 0.06514 .
## APOE44 female - APOE22 male == 0 1.018e-03 3.277e-04 3.105 0.04923 *
## APOE44 female - APOE33 male == 0 1.555e-03 3.423e-04 4.544 0.00180 **
## APOE44 female - APOE44 male == 0 5.662e-04 3.423e-04 1.654 0.57154
## APOE22 male - APOE33 male == 0 5.375e-04 3.277e-04 1.640 0.58012
## APOE22 male - APOE44 male == 0 -4.515e-04 3.277e-04 -1.378 0.73789
## APOE33 male - APOE44 male == 0 -9.890e-04 3.423e-04 -2.889 0.07740 .
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
res<-summary(glht(lm_CPu_VOL, emm(pairwise ~ Genotype*Sex))) #consider save to file
#summary(as.glht(pairs(lm_CPu_VOL.emm), by = NULL))
summary(glht(lm_CPu_VOL, emm(pairwise ~ Genotype, contr="sidak")))

## NOTE: Results may be misleading due to involvement in interactions
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 0.0006534 0.0002567 2.545 0.0459 *
## APOE22 - APOE44 == 0 -0.0007118 0.0002369 -3.004 0.0168 *
## APOE33 - APOE44 == 0 -0.0013651 0.0002614 -5.222 <0.001 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
summary(glht(lm_CPu_VOL, emm(pairwise ~ Genotype | Sex)))

## $`Sex = female`
##
## Simultaneous Tests for General Linear Hypotheses
```

```
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.0007692  0.0003952   1.946   0.1477
## APOE22 - APOE44 == 0 -0.0009720  0.0003423  -2.840   0.0242 *
## APOE33 - APOE44 == 0 -0.0017413  0.0003952  -4.406  <0.001 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.0005375  0.0003277   1.640   0.2494
## APOE22 - APOE44 == 0 -0.0004515  0.0003277  -1.378   0.3686
## APOE33 - APOE44 == 0 -0.0009890  0.0003423  -2.889   0.0217 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
summary(glht(lm_CPu_VOL, emm(pairwise ~ Sex | Genotype)))

## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0 4.568e-05 3.277e-04  0.139   0.89
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.0001860  0.0003952  -0.471   0.642
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
```

```
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0 0.0005662  0.0003423   1.654   0.112
## (Adjusted p values reported -- single-step method)

mypairs<-pairs(CPu_VOL.emm) #_consider save to file
pairs(CPu_VOL.emm, by="Genotype")

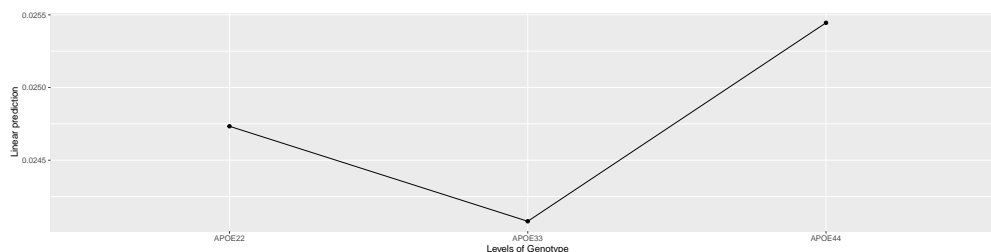
## Genotype = APOE22:
## contrast      estimate      SE df t.ratio p.value
## female - male  4.57e-05 0.000328 23   0.139  0.8904
##
## Genotype = APOE33:
## contrast      estimate      SE df t.ratio p.value
## female - male -1.86e-04 0.000395 23  -0.471  0.6423
##
## Genotype = APOE44:
## contrast      estimate      SE df t.ratio p.value
## female - male  5.66e-04 0.000342 23   1.654  0.1117

pairs(CPu_VOL.emm, by="Sex")

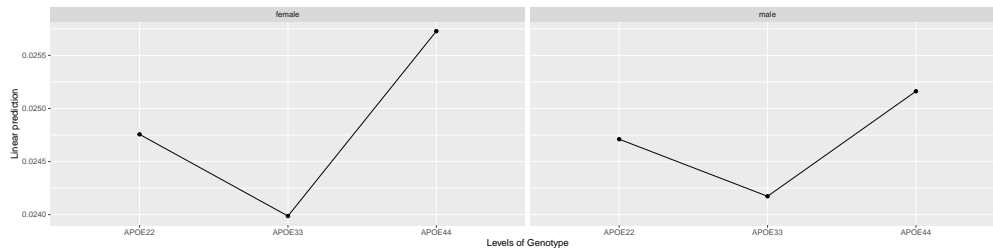
## Sex = female:
## contrast      estimate      SE df t.ratio p.value
## APOE22 - APOE33  0.000769 0.000395 23   1.946  0.1486
## APOE22 - APOE44 -0.000972 0.000342 23  -2.840  0.0242
## APOE33 - APOE44 -0.001741 0.000395 23  -4.406  0.0006
##
## Sex = male:
## contrast      estimate      SE df t.ratio p.value
## APOE22 - APOE33  0.000538 0.000328 23   1.640  0.2496
## APOE22 - APOE44 -0.000451 0.000328 23  -1.378  0.3687
## APOE33 - APOE44 -0.000989 0.000342 23  -2.889  0.0217
##
## P value adjustment: tukey method for comparing a family of 3 estimates
print('CPu VOL')

## [1] "CPu VOL"
emmip(lm_CPu_VOL, ~ Genotype)

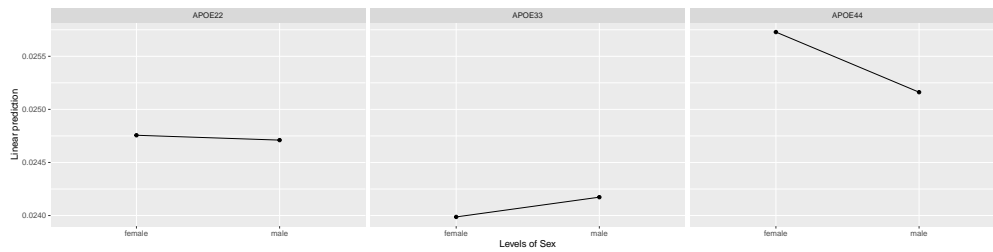
## NOTE: Results may be misleading due to involvement in interactions
```



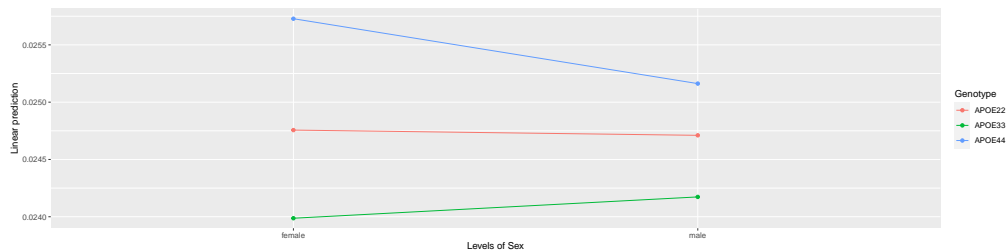

```
emmip(lm_CPu_VOL, ~ Genotype | Sex )
```



```
emmip(lm_CPu_VOL, ~ Sex | Genotype )
```

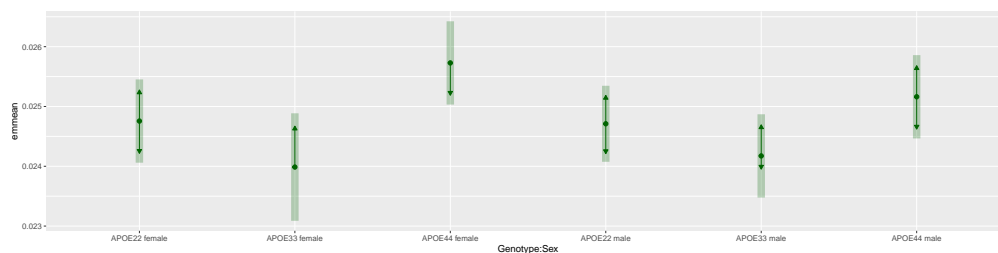


```
emmip(lm_CPu_VOL, Genotype~ Sex )
```



```
sink()
```

```
plot(CPu_VOL.emm, by = NULL, comparisons = TRUE, adjust = "mvt",  
horizontal = FALSE, colors = "darkgreen", main = "CPu VOL")
```



```
ggsave(paste(outpath, 'CPu_VOL_emmeans.pdf', sep=''), plot = last_plot(), device='pdf', scale=1, width=16)
```

```
'simple stats'
```

```
## [1] "simple stats"
```

```
print('CPu')
```

```
## [1] "CPu"
```

```

lm_CPu_FA <- lm(CPu ~ Genotype*Sex, geno_combined_FA)
summary(lm_CPu_FA)

##
## Call:
## lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -0.0157390 -0.0071250  0.0007236  0.0057157  0.0178542
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)      0.236449   0.004266  55.423  <2e-16 ***
## GenotypeAPOE33    -0.010244   0.006967  -1.470   0.1550
## GenotypeAPOE44    -0.014434   0.006033  -2.392   0.0253 *
## Sexmale           0.002017   0.005777   0.349   0.7302
## GenotypeAPOE33:Sexmale -0.001301  0.009050  -0.144   0.8869
## GenotypeAPOE44:Sexmale  0.009600  0.008353   1.149   0.2623
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.00954 on 23 degrees of freedom
## Multiple R-squared:  0.3388, Adjusted R-squared:  0.195
## F-statistic: 2.357 on 5 and 23 DF,  p-value: 0.07251

lm_CPu_FA_f <- lm(CPu ~ Genotype, combo_f_FA)
#summary(lm_CPu_FA_f)
lm_CPu_FA_m <- lm(CPu ~ Genotype, combo_m_FA)
#summary(lm_CPu_FA_f)

#33333
sink(paste(outpath, "CPu_FA_SimpleModels.txt"))
mydata.lm <- lm(CPu ~ Genotype*Sex, data = geno_combined_FA)
anova(mydata.lm)

## Analysis of Variance Table
##
## Response: CPu
##      Df      Sum Sq    Mean Sq F value    Pr(>F)
## Genotype    2 0.00072293 0.00036146   3.9719 0.03298 *
## Sex          1 0.00018127 0.00018127   1.9919 0.17153
## Genotype:Sex  2 0.00016811 0.00008405   0.9236 0.41131
## Residuals   23 0.00209312 0.00009101
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
summary(glht(mydata.lm, emm(pairwise ~ Genotype|Sex, adjust="sidak")))) #consider save to file

## $`Sex = female`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)

```

```

##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 0.010244  0.006967  1.470  0.3220
## APOE22 - APOE44 == 0 0.014434  0.006033  2.392  0.0627 .
## APOE33 - APOE44 == 0 0.004190  0.006967  0.601  0.8202
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.011545  0.005777  1.999  0.135
## APOE22 - APOE44 == 0  0.004835  0.005777  0.837  0.684
## APOE33 - APOE44 == 0 -0.006711  0.006033 -1.112  0.516
## (Adjusted p values reported -- single-step method)
summary(glht(mydata.lm, emm(pairwise ~ Sex| Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.002017  0.005777 -0.349  0.73
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.0007154  0.0069668 -0.103  0.919
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)

```

```

##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.011616  0.006033  -1.925  0.0666 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)

sink()
#3333

#omnibus testing
#https://cran.r-project.org/web/packages/emmeans/vignettes/confidence-intervals.html#adjust

sink(paste(outpath, "CPu_FA_SimpleStats.txt", sep=''))
'omnibus testing'

## [1] "omnibus testing"

joint_tests(ref_grid(lm_CPu_FA))

##   model term    df1 df2 F.ratio p.value
##   Genotype      2  23   3.860  0.0359
##   Sex            1  23   1.740  0.2001
##   Genotype:Sex    2  23   0.924  0.4113

joint_tests(ref_grid(lm_CPu_FA), by = "Sex", adjust = "sidak")

## Sex = female:
##   model term df1 df2 F.ratio p.value
##   Genotype    2  23   2.978  0.0708
##
## Sex = male:
##   model term df1 df2 F.ratio p.value
##   Genotype    2  23   2.001  0.1581

joint_tests(ref_grid(lm_CPu_FA), by = "Genotype", adjust = "sidak" )

## Genotype = APOE22:
##   model term df1 df2 F.ratio p.value
##   Sex        1  23   0.122  0.7302
##
## Genotype = APOE33:
##   model term df1 df2 F.ratio p.value
##   Sex        1  23   0.011  0.9191
##
## Genotype = APOE44:
##   model term df1 df2 F.ratio p.value
##   Sex        1  23   3.707  0.0666

'anova'

## [1] "anova"

anova(lm_CPu_FA)

## Analysis of Variance Table
##
## Response: CPu

```

```
##           Df      Sum Sq    Mean Sq F value  Pr(>F)
## Genotype      2 0.00072293 0.00036146   3.9719 0.03298 *
## Sex           1 0.00018127 0.00018127   1.9919 0.17153
## Genotype:Sex  2 0.00016811 0.00008405   0.9236 0.41131
## Residuals    23 0.00209312 0.00009101
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

#anova(lm_CPu_FA_f)
#anova(lm_CPu_FA_m)

#post hoc comparison
CPu_FA.emm <- emmeans(lm_CPu_FA , ~ Genotype | Sex, adjust = "sidak")
contrast(CPu_FA.emm, simple = c("Genotype", "Sex")) #FDR

## contrast            estimate      SE df t.ratio p.value
## APOE22 female effect  0.00583 0.00393 23   1.486  0.3018
## APOE33 female effect -0.00441 0.00485 23  -0.909  0.4471
## APOE44 female effect -0.00860 0.00393 23  -2.190  0.1282
## APOE22 male effect    0.00785 0.00366 23   2.145  0.1282
## APOE33 male effect    -0.00369 0.00393 23  -0.941  0.4471
## APOE44 male effect    0.00302 0.00393 23   0.768  0.4502
##
## P value adjustment: fdr method for 6 tests

contrast(CPu_FA.emm, simple = list("Genotype", "Sex"))

## $`simple contrasts for Genotype`
## Sex = female:
## contrast            estimate      SE df t.ratio p.value
## APOE22 effect      0.008226 0.00367 23   2.240  0.1051
## APOE33 effect     -0.002018 0.00419 23  -0.482  0.6343
## APOE44 effect     -0.006208 0.00367 23  -1.691  0.1566
##
## Sex = male:
## contrast            estimate      SE df t.ratio p.value
## APOE22 effect      0.005460 0.00328 23   1.663  0.1650
## APOE33 effect     -0.006085 0.00343 23  -1.772  0.1650
## APOE44 effect      0.000625 0.00343 23   0.182  0.8571
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
## contrast            estimate      SE df t.ratio p.value
## female effect     -0.001008 0.00289 23  -0.349  0.7302
## male effect       0.001008 0.00289 23   0.349  0.7302
##
## Genotype = APOE33:
## contrast            estimate      SE df t.ratio p.value
## female effect     -0.000358 0.00348 23  -0.103  0.9191
## male effect       0.000358 0.00348 23   0.103  0.9191
##
## Genotype = APOE44:
## contrast            estimate      SE df t.ratio p.value
```

```

## female effect -0.005808 0.00302 23 -1.925 0.0666
## male effect 0.005808 0.00302 23 1.925 0.0666
##
## P value adjustment: fdr method for 2 tests
#post hoc tests
#post hoc tests
summary(glht(lm_CPu_FA, emm(pairwise ~ Genotype, contr="sidak")))

## NOTE: Results may be misleading due to involvement in interactions

##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 0.010895 0.004525 2.408 0.0608 .
## APOE22 - APOE44 == 0 0.009634 0.004176 2.307 0.0750 .
## APOE33 - APOE44 == 0 -0.001261 0.004608 -0.274 0.9596
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
summary(glht(lm_CPu_FA, emm(pairwise ~ Genotype*Sex, contr="sidak"))) #consider save to file

##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 0.0102443 0.0069668 1.470 0.6837
## APOE22 female - APOE44 female == 0 0.0144341 0.0060334 2.392 0.1989
## APOE22 female - APOE22 male == 0 -0.0020165 0.0057766 -0.349 0.9992
## APOE22 female - APOE33 male == 0 0.0095289 0.0060334 1.579 0.6175
## APOE22 female - APOE44 male == 0 0.0028180 0.0060334 0.467 0.9968
## APOE33 female - APOE44 female == 0 0.0041898 0.0069668 0.601 0.9898
## APOE33 female - APOE22 male == 0 -0.0122608 0.0067456 -1.818 0.4726
## APOE33 female - APOE33 male == 0 -0.0007154 0.0069668 -0.103 1.0000
## APOE33 female - APOE44 male == 0 -0.0074263 0.0069668 -1.066 0.8889
## APOE44 female - APOE22 male == 0 -0.0164506 0.0057766 -2.848 0.0842 .
## APOE44 female - APOE33 male == 0 -0.0049051 0.0060334 -0.813 0.9618
## APOE44 female - APOE44 male == 0 -0.0116161 0.0060334 -1.925 0.4111
## APOE22 male - APOE33 male == 0 0.0115455 0.0057766 1.999 0.3713
## APOE22 male - APOE44 male == 0 0.0048346 0.0057766 0.837 0.9569
## APOE33 male - APOE44 male == 0 -0.0067109 0.0060334 -1.112 0.8704
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
res<-summary(glht(lm_CPu_FA, emm(pairwise ~ Genotype*Sex))) #consider save to file
#summary(as.glht(pairs(lm_CPu_FA.emm), by = NULL))

```

```
summary(glht(lm_CPu_FA, emm(pairwise ~ Genotype | Sex)))

## $`Sex = female`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 0.010244  0.006967   1.470   0.3222
## APOE22 - APOE44 == 0 0.014434  0.006033   2.392   0.0627 .
## APOE33 - APOE44 == 0 0.004190  0.006967   0.601   0.8202
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 0.011545  0.005777   1.999   0.135
## APOE22 - APOE44 == 0 0.004835  0.005777   0.837   0.684
## APOE33 - APOE44 == 0 -0.006711  0.006033  -1.112   0.516
## (Adjusted p values reported -- single-step method)
summary(glht(lm_CPu_FA, emm(pairwise ~ Sex | Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.002017  0.005777  -0.349   0.73
## (Adjusted p values reported -- single-step method)
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.0007154  0.0069668  -0.103   0.919
```

```

## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.011616  0.006033  -1.925  0.0666 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
mypairs<-pairs(CPu_FA.emm) #_consider save to file
pairs(CPu_FA.emm, by="Genotype")

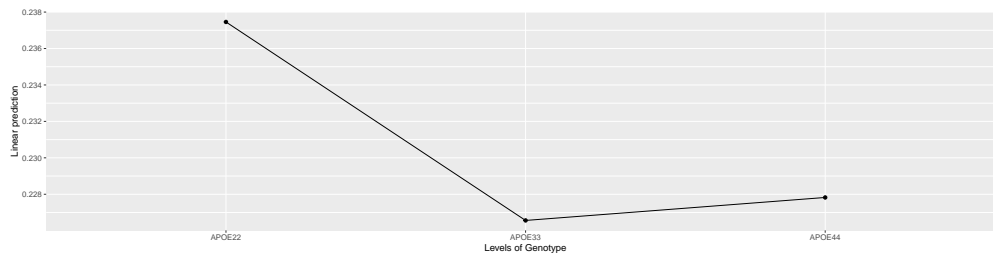
## Genotype = APOE22:
## contrast      estimate      SE df t.ratio p.value
## female - male -0.002017 0.00578 23  -0.349  0.7302
##
## Genotype = APOE33:
## contrast      estimate      SE df t.ratio p.value
## female - male -0.000715 0.00697 23  -0.103  0.9191
##
## Genotype = APOE44:
## contrast      estimate      SE df t.ratio p.value
## female - male -0.011616 0.00603 23  -1.925  0.0666
pairs(CPu_FA.emm, by="Sex")

## Sex = female:
## contrast      estimate      SE df t.ratio p.value
## APOE22 - APOE33 0.01024 0.00697 23   1.470  0.3232
## APOE22 - APOE44 0.01443 0.00603 23   2.392  0.0630
## APOE33 - APOE44 0.00419 0.00697 23   0.601  0.8208
##
## Sex = male:
## contrast      estimate      SE df t.ratio p.value
## APOE22 - APOE33 0.01155 0.00578 23   1.999  0.1351
## APOE22 - APOE44 0.00483 0.00578 23   0.837  0.6844
## APOE33 - APOE44 -0.00671 0.00603 23  -1.112  0.5164
##
## P value adjustment: tukey method for comparing a family of 3 estimates
print('CPu FA')

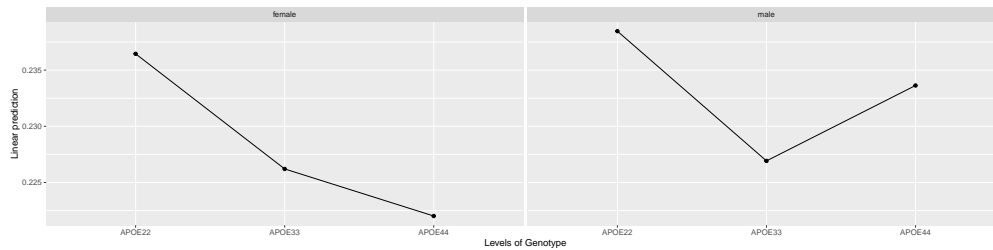
## [1] "CPu FA"
emmip(lm_CPu_FA, ~ Genotype)

## NOTE: Results may be misleading due to involvement in interactions

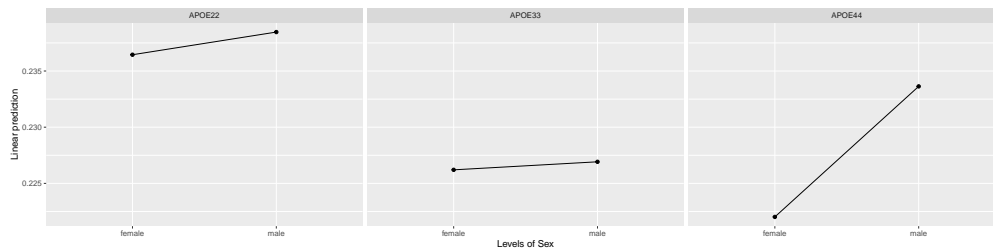
```

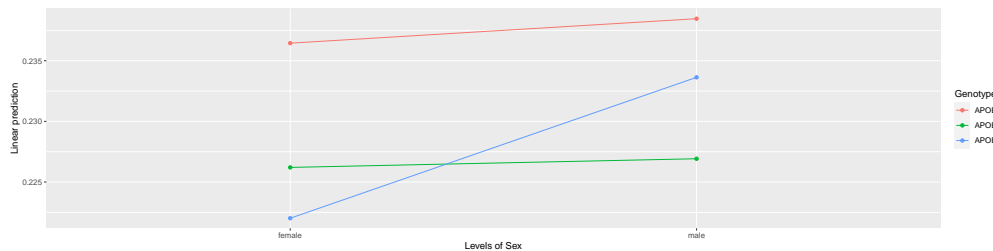
```
emmip(lm_CPu_FA, ~ Genotype | Sex )
```



```
emmip(lm_CPu_FA, ~ Sex | Genotype )
```

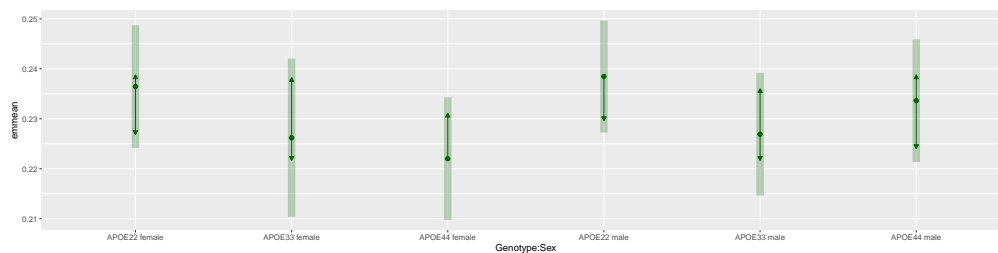


```
emmip(lm_CPu_FA, Genotype~ Sex )
```



```
sink()
```

```
plot(CPu_FA.emm, by = NULL, comparisons = TRUE, adjust = "mvt",  
horizontal = FALSE, colors = "darkgreen", main ="CPu FA")
```



```
ggsave(paste(outpath, 'CPu_FA_emmeans.pdf', sep=''), plot = last_plot(), device='pdf', scale=1, width=16,
```

```

'simple stats'

## [1] "simple stats"
print('CPu')

## [1] "CPu"
lm_CPu_DEG <- lm(CPu ~ Genotype*Sex, geno_combined_DEG)
summary(lm_CPu_DEG)

##
## Call:
## lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -31667 -11917  -3800   14800   34333
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)      218000      8706  25.040  <2e-16 ***
## GenotypeAPOE33      22667     14217   1.594   0.125
## GenotypeAPOE44      12200     12312   0.991   0.332
## Sexmale           9917      11788   0.841   0.409
## GenotypeAPOE33:Sexmale  -9783     18468  -0.530   0.601
## GenotypeAPOE44:Sexmale -18317     17045  -1.075   0.294
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 19470 on 23 degrees of freedom
## Multiple R-squared:  0.1853, Adjusted R-squared:  0.008217
## F-statistic: 1.046 on 5 and 23 DF,  p-value: 0.4148

lm_CPu_DEG_f <- lm(CPu ~ Genotype, combo_f_FA)
#summary(lm_CPu_DEG_f)
lm_CPu_DEG_m <- lm(CPu ~ Genotype, combo_m_FA)
#summary(lm_CPu_DEG_f)

#33333
sink(paste(outpath, "CPu_DEG_SimpleModels.txt"))
mydata.lm <- lm(CPu ~ Genotype*Sex, data = geno_combined_DEG)
anova(mydata.lm)

## Analysis of Variance Table
##
## Response: CPu
##           Df      Sum Sq   Mean Sq F value Pr(>F)
## Genotype    2 1538125392 769062696  2.0294 0.1543
## Sex          1   5580291    5580291  0.0147 0.9045
## Genotype:Sex  2  439053800 219526900  0.5793 0.5683
## Residuals   23  8716275000 378968478

summary(glht(mydata.lm, emm(pairwise ~ Genotype|Sex, adjust="sidak")))
```

#consider save to file

```

## $`Sex = female`
##

```

```

## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -22667     14217  -1.594    0.267
## APOE22 - APOE44 == 0   -12200     12312  -0.991    0.589
## APOE33 - APOE44 == 0    10467     14217   0.736    0.744
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -12883     11788  -1.093    0.528
## APOE22 - APOE44 == 0     6117     11788   0.519    0.863
## APOE33 - APOE44 == 0    19000     12312   1.543    0.290
## (Adjusted p values reported -- single-step method)
summary(glht(mydata.lm, emm(pairwise ~ Sex| Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -9917     11788  -0.841    0.409
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -133.3    14216.8  -0.009    0.993
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
## Simultaneous Tests for General Linear Hypotheses
##

```

```

## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0      8400      12312   0.682   0.502
## (Adjusted p values reported -- single-step method)

sink()
#3333

#omnibus testing
#https://cran.r-project.org/web/packages/emmeans/vignettes/confidence-intervals.html#adjust

sink(paste(outpath, "CPu_DEG_SimpleStats.txt", sep=''))
'omnibus testing'

## [1] "omnibus testing"

joint_tests(ref_grid(lm_CPu_DEG))

##   model term    df1 df2 F.ratio p.value
##   Genotype      2  23   2.004  0.1577
##   Sex           1  23   0.006  0.9414
##   Genotype:Sex   2  23   0.579  0.5683

joint_tests(ref_grid(lm_CPu_DEG), by = "Sex", adjust = "sidak")

## Sex = female:
##   model term df1 df2 F.ratio p.value
##   Genotype   2  23   1.327  0.2849
##
## Sex = male:
##   model term df1 df2 F.ratio p.value
##   Genotype   2  23   1.247  0.3060

joint_tests(ref_grid(lm_CPu_DEG), by = "Genotype", adjust = "sidak" )

## Genotype = APOE22:
##   model term df1 df2 F.ratio p.value
##   Sex        1  23   0.708  0.4089
##
## Genotype = APOE33:
##   model term df1 df2 F.ratio p.value
##   Sex        1  23   0.000  0.9926
##
## Genotype = APOE44:
##   model term df1 df2 F.ratio p.value
##   Sex        1  23   0.465  0.5019

'anova'

## [1] "anova"

anova(lm_CPu_DEG)

## Analysis of Variance Table
##
## Response: CPu
##           Df      Sum Sq   Mean Sq F value Pr(>F)

```

```
## Genotype      2 1538125392 769062696 2.0294 0.1543
## Sex           1   5580291   5580291 0.0147 0.9045
## Genotype:Sex  2  439053800 219526900 0.5793 0.5683
## Residuals    23 8716275000 378968478

#anova(lm_Cpu_DEG_f)
#anova(lm_Cpu_DEG_m)

#post hoc comparison
Cpu_DEG.emm <- emmeans(lm_Cpu_DEG , ~ Genotype | Sex, adjust = "sidak")
contrast(Cpu_DEG.emm, simple = c("Genotype", "Sex")) #FDR

## contrast            estimate    SE df t.ratio p.value
## APOE22 female effect  -11897 8013 23  -1.485  0.4842
## APOE33 female effect   10769 9894 23   1.088  0.4842
## APOE44 female effect    303 8013 23   0.038  0.9702
## APOE22 male effect    -1981 7469 23  -0.265  0.9519
## APOE33 male effect    10903 8013 23   1.361  0.4842
## APOE44 male effect    -8097 8013 23  -1.010  0.4842
##
## P value adjustment: fdr method for 6 tests
contrast(Cpu_DEG.emm, simple = list("Genotype", "Sex"))

## $`simple contrasts for Genotype`
## Sex = female:
## contrast            estimate    SE df t.ratio p.value
## APOE22 effect      -11622 7493 23  -1.551  0.3134
## APOE33 effect       11044 8543 23   1.293  0.3134
## APOE44 effect        578 7493 23   0.077  0.9392
##
## Sex = male:
## contrast            estimate    SE df t.ratio p.value
## APOE22 effect      -2256 6702 23  -0.337  0.7395
## APOE33 effect       10628 7009 23   1.516  0.3667
## APOE44 effect      -8372 7009 23  -1.195  0.3667
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
## contrast            estimate    SE df t.ratio p.value
## female effect     -4958.3 5894 23  -0.841  0.4089
## male effect       4958.3 5894 23   0.841  0.4089
##
## Genotype = APOE33:
## contrast            estimate    SE df t.ratio p.value
## female effect      -66.7 7108 23  -0.009  0.9926
## male effect        66.7 7108 23   0.009  0.9926
##
## Genotype = APOE44:
## contrast            estimate    SE df t.ratio p.value
## female effect     4200.0 6156 23   0.682  0.5019
## male effect     -4200.0 6156 23  -0.682  0.5019
##
```

```
## P value adjustment: fdr method for 2 tests
#post hoc tests
summary(glht(lm_CPu_DEG, emm(pairwise ~ Genotype*Sex, contr="sidak"))) #consider save to file

##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -22666.7 14216.8 -1.594 0.608
## APOE22 female - APOE44 female == 0 -12200.0 12312.1 -0.991 0.916
## APOE22 female - APOE22 male == 0 -9916.7 11787.9 -0.841 0.956
## APOE22 female - APOE33 male == 0 -22800.0 12312.1 -1.852 0.453
## APOE22 female - APOE44 male == 0 -3800.0 12312.1 -0.309 1.000
## APOE33 female - APOE44 female == 0 10466.7 14216.8 0.736 0.975
## APOE33 female - APOE22 male == 0 12750.0 13765.3 0.926 0.935
## APOE33 female - APOE33 male == 0 -133.3 14216.8 -0.009 1.000
## APOE33 female - APOE44 male == 0 18866.7 14216.8 1.327 0.766
## APOE44 female - APOE22 male == 0 2283.3 11787.9 0.194 1.000
## APOE44 female - APOE33 male == 0 -10600.0 12312.1 -0.861 0.952
## APOE44 female - APOE44 male == 0 8400.0 12312.1 0.682 0.982
## APOE22 male - APOE33 male == 0 -12883.3 11787.9 -1.093 0.878
## APOE22 male - APOE44 male == 0 6116.7 11787.9 0.519 0.995
## APOE33 male - APOE44 male == 0 19000.0 12312.1 1.543 0.640
## (Adjusted p values reported -- single-step method)

res<-summary(glht(lm_CPu_DEG, emm(pairwise ~ Genotype*Sex))) #consider save to file
#summary(as.glht(pairs(lm_CPu_DEG.emm), by = NULL))

summary(glht(lm_CPu_DEG, emm(pairwise ~ Genotype )))

## NOTE: Results may be misleading due to involvement in interactions
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -17775 9234 -1.925 0.154
## APOE22 - APOE44 == 0 -3042 8523 -0.357 0.932
## APOE33 - APOE44 == 0 14733 9404 1.567 0.279
## (Adjusted p values reported -- single-step method)

summary(glht(lm_CPu_DEG, emm(pairwise ~ Genotype | Sex)))

## $`Sex = female`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
```

```

##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -22667      14217  -1.594    0.267
## APOE22 - APOE44 == 0   -12200      12312  -0.991    0.589
## APOE33 - APOE44 == 0    10467      14217   0.736    0.744
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -12883      11788  -1.093    0.528
## APOE22 - APOE44 == 0    6117      11788   0.519    0.863
## APOE33 - APOE44 == 0   19000      12312   1.543    0.290
## (Adjusted p values reported -- single-step method)
summary(glht(lm_CPu_DEG, emm(pairwise ~ Sex | Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -9917      11788  -0.841    0.409
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -133.3    14216.8  -0.009    0.993
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0    8400      12312   0.682    0.502

```

```
## (Adjusted p values reported -- single-step method)
```

```
mypairs<-pairs(CPu_DEG.emm) #_consider save to file  
pairs(CPu_DEG.emm, by="Genotype")
```

```
## Genotype = APOE22:  
## contrast      estimate      SE df t.ratio p.value  
## female - male   -9917 11788 23  -0.841  0.4089  
##
```

```
## Genotype = APOE33:  
## contrast      estimate      SE df t.ratio p.value  
## female - male   -133 14217 23  -0.009  0.9926  
##
```

```
## Genotype = APOE44:  
## contrast      estimate      SE df t.ratio p.value  
## female - male   8400 12312 23   0.682  0.5019
```

```
pairs(CPu_DEG.emm, by="Sex")
```

```
## Sex = female:  
## contrast      estimate      SE df t.ratio p.value  
## APOE22 - APOE33  -22667 14217 23  -1.594  0.2682  
## APOE22 - APOE44  -12200 12312 23  -0.991  0.5899  
## APOE33 - APOE44   10467 14217 23   0.736  0.7448  
##
```

```
## Sex = male:  
## contrast      estimate      SE df t.ratio p.value  
## APOE22 - APOE33  -12883 11788 23  -1.093  0.5279  
## APOE22 - APOE44   6117 11788 23   0.519  0.8629  
## APOE33 - APOE44   19000 12312 23   1.543  0.2901  
##
```

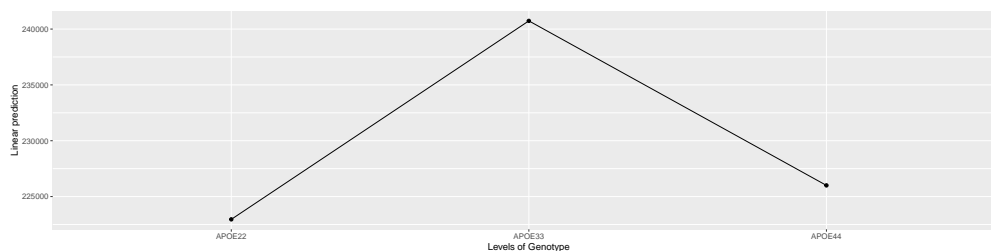
```
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```
print('CPu DEG')
```

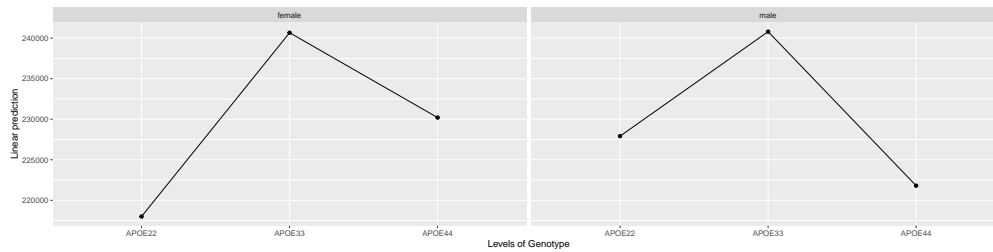
```
## [1] "CPu DEG"
```

```
emmip(lm_CPu_DEG, ~ Genotype)
```

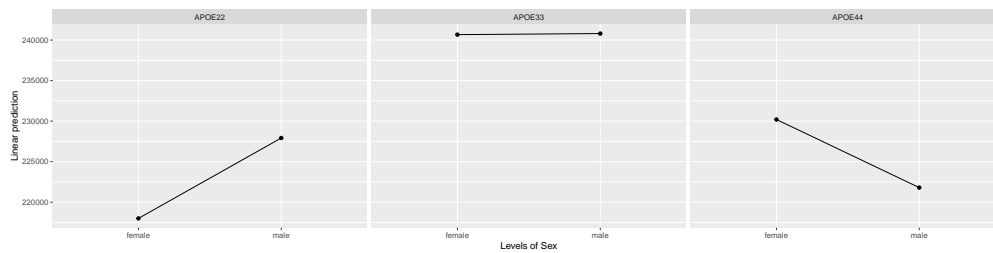
```
## NOTE: Results may be misleading due to involvement in interactions
```



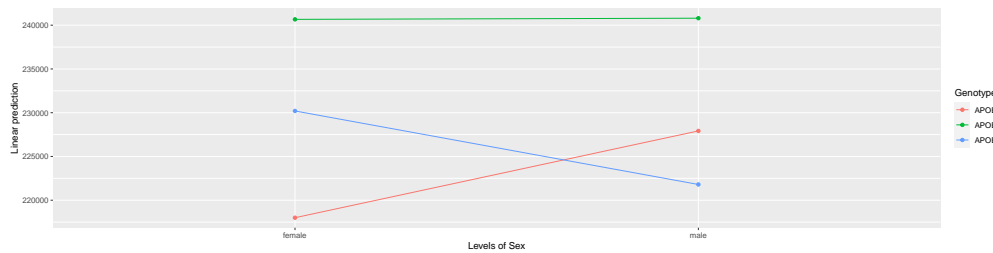
```
emmip(lm_CPu_DEG, ~ Genotype | Sex )
```

```
emmip(lm_CPu_DEG, ~ Sex | Genotype )
```

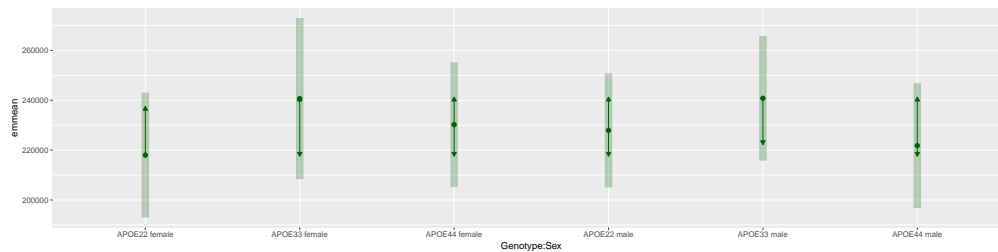


```
emmip(lm_CPu_DEG, Genotype~ Sex )
```



```
sink()
```

```
plot(CPu_DEG.emm, by = NULL, comparisons = TRUE, adjust = "mvt",
horizontal = FALSE, colors = "darkgreen", main ="CPu DEG")
```



```
ggsave(paste(outpath,'CPu_DEG_emmeans.pdf',sep=''), plot = last_plot(), device='pdf', scale=1, width=16
```

```
'simple stats'
```

```
## [1] "simple stats"
```

```
print('CPu')
```

```
## [1] "CPu"
```

```
lm_CPu_CLUS <- lm(CPu ~ Genotype*Sex, geno_combined_CLUS)
summary(lm_CPu_CLUS)
```

```
##
```

```
## Call:
```

```

## lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -70.017 -20.873  -5.233  11.696  89.933
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)      350.33      16.50  21.229  <2e-16 ***
## GenotypeAPOE33      50.99      26.95   1.892   0.0711 .
## GenotypeAPOE44      33.83      23.34   1.449   0.1607
## Sexmale           17.17      22.34   0.768   0.4501
## GenotypeAPOE33:Sexmale -29.15      35.01  -0.833   0.4135
## GenotypeAPOE44:Sexmale -27.20      32.31  -0.842   0.4086
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 36.9 on 23 degrees of freedom
## Multiple R-squared:  0.1803, Adjusted R-squared:  0.002162
## F-statistic: 1.012 on 5 and 23 DF,  p-value: 0.4332

lm_CPu_CLUS_f <- lm(CPu ~ Genotype, combo_f_FA)
#summary(lm_CPu_CLUS_f)
lm_CPu_CLUS_m <- lm(CPu ~ Genotype, combo_m_FA)
#summary(lm_CPu_CLUS_f)

#33333
sink(paste(outpath, "CPu_CLUS_SimpleModels.txt"))
mydata.lm <- lm(CPu ~ Genotype*Sex, data = geno_combined_CLUS)
anova(mydata.lm)

## Analysis of Variance Table
##
## Response: CPu
##           Df Sum Sq Mean Sq F value Pr(>F)
## Genotype    2  5566.0  2783.01   2.0439 0.1524
## Sex          1    0.1    0.07  0.0001 0.9943
## Genotype:Sex  2  1324.6   662.30   0.4864 0.6210
## Residuals   23 31317.3  1361.62

summary(glht(mydata.lm, emm(pairwise ~ Genotype|Sex, adjust="sidak")))
```

#consider save to file

```

## `$Sex = female`
##
##      Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -50.99      26.95  -1.892   0.163
## APOE22 - APOE44 == 0   -33.83      23.34  -1.449   0.332
## APOE33 - APOE44 == 0    17.17      26.95   0.637   0.801
## (Adjusted p values reported -- single-step method)
##

```

```
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -21.839    22.344  -0.977    0.598
## APOE22 - APOE44 == 0   -6.629    22.344  -0.297    0.953
## APOE33 - APOE44 == 0   15.210    23.338   0.652    0.793
## (Adjusted p values reported -- single-step method)
summary(glht(mydata.lm, emm(pairwise ~ Sex| Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0  -17.17     22.34  -0.768    0.45
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0   11.98     26.95   0.445    0.661
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0   10.03     23.34   0.43    0.671
## (Adjusted p values reported -- single-step method)

sink()
#3333

#omnibus testing
```

```
#https://cran.r-project.org/web/packages/emmeans/vignettes/confidence-intervals.html#adjust
```

```
sink(paste(outpath, "CPu_CLUS_SimpleStats.txt", sep=''))  
'omnibus testing'
```

```
## [1] "omnibus testing"
```

```
joint_tests(ref_grid(lm_CPu_CLUS))
```

```
## model term    df1 df2 F.ratio p.value  
## Genotype      2  23   2.233  0.1299  
## Sex           1  23   0.013  0.9094  
## Genotype:Sex  2  23   0.486  0.6210
```

```
joint_tests(ref_grid(lm_CPu_CLUS), by = "Sex", adjust = "sidak")
```

```
## Sex = female:  
## model term df1 df2 F.ratio p.value  
## Genotype    2  23   2.035  0.1536  
##  
## Sex = male:  
## model term df1 df2 F.ratio p.value  
## Genotype    2  23   0.491  0.6181
```

```
joint_tests(ref_grid(lm_CPu_CLUS), by = "Genotype", adjust = "sidak" )
```

```
## Genotype = APOE22:  
## model term df1 df2 F.ratio p.value  
## Sex        1  23   0.590  0.4501  
##  
## Genotype = APOE33:  
## model term df1 df2 F.ratio p.value  
## Sex        1  23   0.198  0.6607  
##  
## Genotype = APOE44:  
## model term df1 df2 F.ratio p.value  
## Sex        1  23   0.185  0.6714
```

```
'anova'
```

```
## [1] "anova"
```

```
anova(lm_CPu_CLUS)
```

```
## Analysis of Variance Table
```

```
##
```

```
## Response: CPu
```

```
##           Df  Sum Sq Mean Sq F value Pr(>F)  
## Genotype    2   5566.0  2783.01   2.0439 0.1524  
## Sex         1     0.1    0.07   0.0001 0.9943  
## Genotype:Sex 2   1324.6   662.30   0.4864 0.6210  
## Residuals   23  31317.3  1361.62
```

```
#anova(lm_CPu_CLUS_f)
```

```
#anova(lm_CPu_CLUS_m)
```

```
#post hoc comparison
```

```
CPu_CLUS.emm <- emmeans(lm_CPu_CLUS , ~ Genotype | Sex, adjust = "sidak")
```

```
contrast(CPu_CLUS.emm, simple = c("Genotype", "Sex")) #FDR
```

```
## contrast      estimate    SE df t.ratio p.value
## APOE22 female effect -27.47 15.2 23  -1.808  0.5020
## APOE33 female effect  23.53 18.8 23   1.254  0.6668
## APOE44 female effect   6.36 15.2 23   0.419  0.8113
## APOE22 male effect  -10.30 14.2 23  -0.727  0.7116
## APOE33 male effect   11.54 15.2 23   0.760  0.7116
## APOE44 male effect   -3.67 15.2 23  -0.241  0.8113
##
## P value adjustment: fdr method for 6 tests
```

```
contrast(CPu_CLUS.emm, simple = list("Genotype", "Sex"))
```

```
## $`simple contrasts for Genotype`
## Sex = female:
## contrast      estimate    SE df t.ratio p.value
## APOE22 effect -28.27 14.2 23  -1.991  0.1756
## APOE33 effect  22.72 16.2 23   1.403  0.2610
## APOE44 effect   5.55 14.2 23   0.391  0.6994
##
## Sex = male:
## contrast      estimate    SE df t.ratio p.value
## APOE22 effect  -9.49 12.7 23  -0.747  0.6940
## APOE33 effect  12.35 13.3 23   0.930  0.6940
## APOE44 effect  -2.86 13.3 23  -0.215  0.8314
##
## P value adjustment: fdr method for 3 tests
```

```
## $`simple contrasts for Sex`
## Genotype = APOE22:
## contrast      estimate    SE df t.ratio p.value
## female effect  -8.58 11.2 23  -0.768  0.4501
## male effect     8.58 11.2 23   0.768  0.4501
##
## Genotype = APOE33:
## contrast      estimate    SE df t.ratio p.value
## female effect   5.99 13.5 23   0.445  0.6607
## male effect    -5.99 13.5 23  -0.445  0.6607
##
## Genotype = APOE44:
## contrast      estimate    SE df t.ratio p.value
## female effect   5.01 11.7 23   0.430  0.6714
## male effect    -5.01 11.7 23  -0.430  0.6714
##
## P value adjustment: fdr method for 2 tests
```

```
#post hoc tests
```

```
summary(glht(lm_CPu_CLUS, emm(pairwise ~ Genotype*Sex, contr="sidak"))) #consider save to file
```

```
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
```

```
## Linear Hypotheses:
##
##      Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -50.993    26.948  -1.892    0.430
## APOE22 female - APOE44 female == 0 -33.826    23.338  -1.449    0.696
## APOE22 female - APOE22 male == 0  -17.169    22.344  -0.768    0.970
## APOE22 female - APOE33 male == 0  -39.008    23.338  -1.671    0.561
## APOE22 female - APOE44 male == 0  -23.798    23.338  -1.020    0.906
## APOE33 female - APOE44 female == 0   17.167    26.948   0.637    0.987
## APOE33 female - APOE22 male == 0   33.823    26.092   1.296    0.783
## APOE33 female - APOE33 male == 0    11.985    26.948   0.445    0.997
## APOE33 female - APOE44 male == 0    27.195    26.948   1.009    0.909
## APOE44 female - APOE22 male == 0    16.657    22.344   0.745    0.974
## APOE44 female - APOE33 male == 0    -5.182    23.338  -0.222    1.000
## APOE44 female - APOE44 male == 0    10.028    23.338   0.430    0.998
## APOE22 male - APOE33 male == 0   -21.839    22.344  -0.977    0.920
## APOE22 male - APOE44 male == 0    -6.629    22.344  -0.297    1.000
## APOE33 male - APOE44 male == 0     15.210    23.338   0.652    0.985
## (Adjusted p values reported -- single-step method)

res<-summary(glht(lm_CPu_CLUS, emm(pairwise ~ Genotype*Sex))) #consider save to file
#summary(as.glht(pairs(lm_CPu_CLUS.emm), by = NULL))
summary(glht(lm_CPu_CLUS, emm(pairwise ~ Genotype )))

## NOTE: Results may be misleading due to involvement in interactions

##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##      Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -36.42    17.50  -2.081    0.116
## APOE22 - APOE44 == 0  -20.23    16.15  -1.252    0.435
## APOE33 - APOE44 == 0   16.19    17.82   0.908    0.640
## (Adjusted p values reported -- single-step method)

summary(glht(lm_CPu_CLUS, emm(pairwise ~ Genotype | Sex)))

## $`Sex = female`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##      Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -50.99    26.95  -1.892    0.163
## APOE22 - APOE44 == 0  -33.83    23.34  -1.449    0.332
## APOE33 - APOE44 == 0   17.17    26.95   0.637    0.801
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
```

```
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -21.839    22.344  -0.977   0.598
## APOE22 - APOE44 == 0   -6.629    22.344  -0.297   0.953
## APOE33 - APOE44 == 0   15.210    23.338   0.652   0.793
## (Adjusted p values reported -- single-step method)
summary(glht(lm_CPu_CLUS, emm(pairwise ~ Sex | Genotype)))

## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0  -17.17     22.34  -0.768   0.45
## (Adjusted p values reported -- single-step method)
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0   11.98     26.95   0.445   0.661
## (Adjusted p values reported -- single-step method)
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = CPu ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0   10.03     23.34   0.43   0.671
## (Adjusted p values reported -- single-step method)
mypairs<-pairs(CPu_CLUS.emm) #_consider save to file
pairs(CPu_CLUS.emm, by="Genotype")

## Genotype = APOE22:
##   contrast      estimate    SE df t.ratio p.value
## female - male  -17.2 22.3 23  -0.768  0.4501
##
## Genotype = APOE33:
```

```
## contrast      estimate    SE df t.ratio p.value
## female - male      12.0 26.9 23   0.445  0.6607
##
## Genotype = APOE44:
## contrast      estimate    SE df t.ratio p.value
## female - male      10.0 23.3 23   0.430  0.6714
```

```
pairs(CPu_CLUS.emm, by="Sex")
```

```
## Sex = female:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - APOE33  -50.99 26.9 23  -1.892  0.1636
## APOE22 - APOE44  -33.83 23.3 23  -1.449  0.3332
## APOE33 - APOE44   17.17 26.9 23   0.637  0.8014
##
```

```
## Sex = male:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - APOE33  -21.84 22.3 23  -0.977  0.5981
## APOE22 - APOE44   -6.63 22.3 23  -0.297  0.9527
## APOE33 - APOE44   15.21 23.3 23   0.652  0.7933
##
```

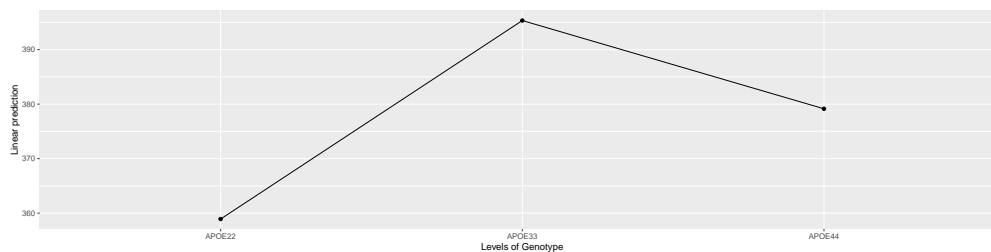
```
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```
print('CPu CLUS')
```

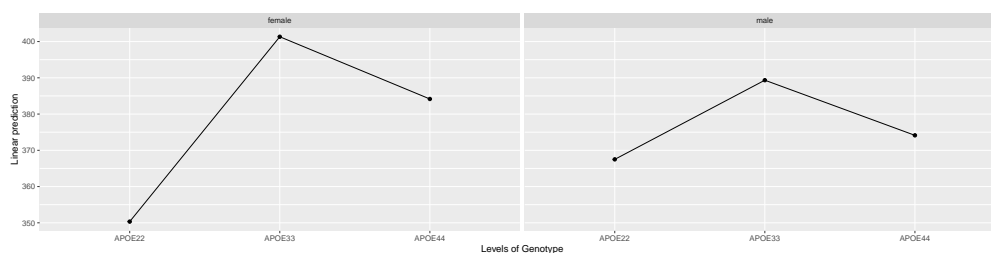
```
## [1] "CPu CLUS"
```

```
emmip(lm_CPu_CLUS, ~ Genotype)
```

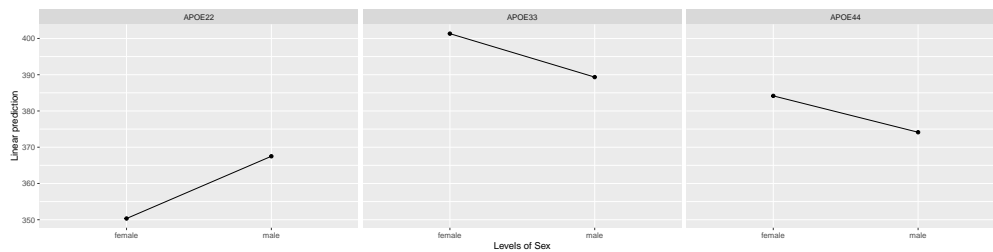
```
## NOTE: Results may be misleading due to involvement in interactions
```



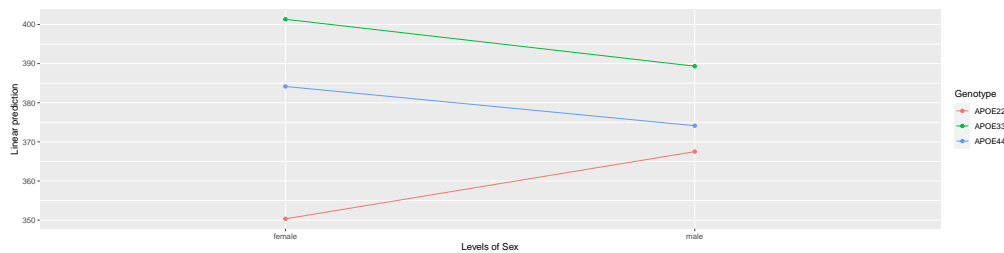
```
emmip(lm_CPu_CLUS, ~ Genotype | Sex )
```



```
emmip(lm_CPu_CLUS, ~ Sex | Genotype )
```

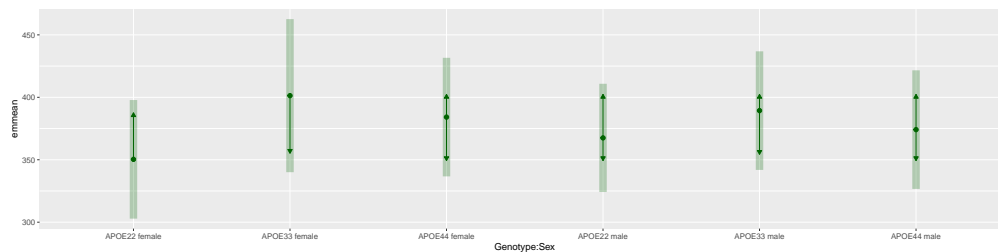



```
emmip(lm_CPu_CLUS, Genotype~ Sex )
```



```
sink()
```

```
plot(CPu_CLUS.emm, by = NULL, comparisons = TRUE, adjust = "mvt",
horizontal = FALSE, colors = "darkgreen", main = "CPu CLUS")
```



```
ggsave(paste(outpath, 'CPu_CLUS_emmeans.pdf', sep=''), plot = last_plot(), device='pdf', scale=1, width=10, height=10)
```