SimpleViolins

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Contents

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 ic

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`.
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## 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`.
```
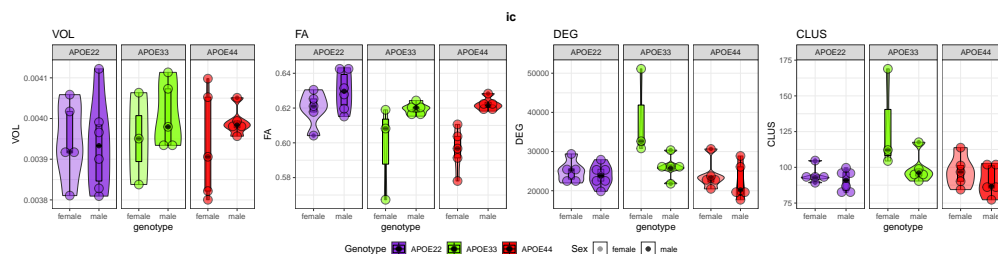


```
print('ic')
```

```
## [1] "ic"
```

```
lm_ic_VOL <- lm(ic ~ Genotype*Sex, geno_combined_VOL)
summary(lm_ic_VOL)
```

```
## 
## Call:
## lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
## 
## Residuals:
##        Min         1Q     Median         3Q        Max
## -1.354e-04 -7.228e-05 -1.526e-05  6.608e-05  1.859e-04
## 
## Coefficients:
##                         Estimate Std. Error t value Pr(>|t|)
## (Intercept)            3.944e-03  4.520e-05  87.252   <2e-16 ***
## GenotypeAPOE33         6.441e-06  7.382e-05   0.087    0.931
## GenotypeAPOE44        -8.506e-06  6.393e-05  -0.133    0.895
## Sexmale               -7.991e-06  6.121e-05  -0.131    0.897
## GenotypeAPOE33:Sexmale 6.427e-05  9.589e-05   0.670    0.509
## GenotypeAPOE44:Sexmale 6.486e-05  8.851e-05   0.733    0.471
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## 
## Residual standard error: 0.0001011 on 23 degrees of freedom
## Multiple R-squared:  0.09319,    Adjusted R-squared:  -0.1039
## F-statistic: 0.4727 on 5 and 23 DF,  p-value: 0.7927
```

```r
lm_ic_VOL_f <- lm(ic ~ Genotype, combo_f_FA)
#summary(lm_ic_VOL_f)
lm_ic_VOL_m <- lm(ic ~ Genotype, combo_m_FA)
#summary(lm_ic_VOL_f)


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

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

```
## Analysis of Variance Table
## 
## Response: ic
##             Df    Sum Sq    Mean Sq F value Pr(>F)
## Genotype     2 9.950e-09 4.9748e-09  0.4869 0.6207
## Sex          1 7.186e-09 7.1859e-09  0.7033 0.4103
## Genotype:Sex 2 7.013e-09 3.5067e-09  0.3432 0.7131
## Residuals   23 2.350e-07 1.0217e-08
```

```r
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 = ic ~ Genotype * Sex, data = geno_combined_VOL)
## 
```

```
## Linear Hypotheses:
##                      Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -6.441e-06  7.382e-05  -0.087    0.996
## APOE22 - APOE44 == 0  8.506e-06  6.393e-05   0.133    0.990
## APOE33 - APOE44 == 0  1.495e-05  7.382e-05   0.202    0.978
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                      Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -7.071e-05  6.121e-05  -1.155    0.491
## APOE22 - APOE44 == 0 -5.635e-05  6.121e-05  -0.921    0.633
## APOE33 - APOE44 == 0  1.436e-05  6.393e-05   0.225    0.973
## (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 = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0 7.991e-06  6.121e-05   0.131    0.897
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                     Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -5.628e-05  7.382e-05  -0.762    0.454
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                     Estimate Std. Error t value Pr(>|t|)
```

```
## female - male == 0 -5.687e-05  6.393e-05   -0.89     0.383
## (Adjusted p values reported -- single-step method)
```

```
sink()
#3333

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

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

```
joint_tests(ref_grid(lm_ic_VOL))
```

```
##  model term   df1 df2 F.ratio  p.value
##  Genotype       2  23   0.345  0.7118
##  Sex            1  23   0.833  0.3710
##  Genotype:Sex   2  23   0.343  0.7131
```

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

```
## Sex = female:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   0.022  0.9785
##
## Sex = male:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   0.766  0.4764
```

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

```
## Genotype = APOE22:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.017  0.8973
##
## Genotype = APOE33:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.581  0.4535
##
## Genotype = APOE44:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.791  0.3829
```

```
'anova'
```

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

```
anova(lm_ic_VOL)
```

```
## Analysis of Variance Table
##
## Response: ic
##              Df    Sum Sq    Mean Sq F value Pr(>F)
## Genotype      2 9.950e-09 4.9748e-09  0.4869 0.6207
## Sex           1 7.186e-09 7.1859e-09  0.7033 0.4103
## Genotype:Sex  2 7.013e-09 3.5067e-09  0.3432 0.7131
## Residuals    23 2.350e-07 1.0217e-08
```

```
#anova(lm_ic_VOL_f)
#anova(lm_ic_VOL_m)
```

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

```
##  contrast              estimate       SE df t.ratio p.value
##  APOE22 female effect -1.68e-05 4.16e-05 23  -0.405  0.8273
##  APOE33 female effect -1.04e-05 5.14e-05 23  -0.202  0.8414
##  APOE44 female effect -2.53e-05 4.16e-05 23  -0.609  0.8226
##  APOE22 male effect   -2.48e-05 3.88e-05 23  -0.640  0.8226
##  APOE33 male effect    4.59e-05 4.16e-05 23   1.103  0.8226
##  APOE44 male effect    3.15e-05 4.16e-05 23   0.758  0.8226
##
## P value adjustment: fdr method for 6 tests
```

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

```
## $`simple contrasts for Genotype`
## Sex = female:
##  contrast       estimate       SE df t.ratio p.value
##  APOE22 effect  6.88e-07 3.89e-05 23   0.018  0.9860
##  APOE33 effect  7.13e-06 4.44e-05 23   0.161  0.9860
##  APOE44 effect -7.82e-06 3.89e-05 23  -0.201  0.9860
##
## Sex = male:
##  contrast       estimate       SE df t.ratio p.value
##  APOE22 effect -4.24e-05 3.48e-05 23  -1.217  0.6657
##  APOE33 effect  2.84e-05 3.64e-05 23   0.779  0.6657
##  APOE44 effect  1.40e-05 3.64e-05 23   0.385  0.7040
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
##  contrast      estimate       SE df t.ratio p.value
##  female effect  4.00e-06 3.06e-05 23   0.131  0.8973
##  male effect   -4.00e-06 3.06e-05 23  -0.131  0.8973
##
## Genotype = APOE33:
##  contrast      estimate       SE df t.ratio p.value
##  female effect -2.81e-05 3.69e-05 23  -0.762  0.4535
##  male effect    2.81e-05 3.69e-05 23   0.762  0.4535
##
## Genotype = APOE44:
##  contrast      estimate       SE df t.ratio p.value
##  female effect -2.84e-05 3.20e-05 23  -0.890  0.3829
##  male effect    2.84e-05 3.20e-05 23   0.890  0.3829
##
## P value adjustment: fdr method for 2 tests
```

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

```
##
##   Simultaneous Tests for General Linear Hypotheses
##
```

```
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                                    Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -6.441e-06  7.382e-05  -0.087    1.000
## APOE22 female - APOE44 female == 0  8.506e-06  6.393e-05   0.133    1.000
## APOE22 female - APOE22 male == 0    7.991e-06  6.121e-05   0.131    1.000
## APOE22 female - APOE33 male == 0   -6.272e-05  6.393e-05  -0.981    0.919
## APOE22 female - APOE44 male == 0   -4.836e-05  6.393e-05  -0.757    0.972
## APOE33 female - APOE44 female == 0  1.495e-05  7.382e-05   0.202    1.000
## APOE33 female - APOE22 male == 0    1.443e-05  7.148e-05   0.202    1.000
## APOE33 female - APOE33 male == 0   -5.628e-05  7.382e-05  -0.762    0.971
## APOE33 female - APOE44 male == 0   -4.192e-05  7.382e-05  -0.568    0.992
## APOE44 female - APOE22 male == 0   -5.153e-07  6.121e-05  -0.008    1.000
## APOE44 female - APOE33 male == 0   -7.123e-05  6.393e-05  -1.114    0.870
## APOE44 female - APOE44 male == 0   -5.687e-05  6.393e-05  -0.890    0.945
## APOE22 male - APOE33 male == 0     -7.071e-05  6.121e-05  -1.155    0.852
## APOE22 male - APOE44 male == 0     -5.635e-05  6.121e-05  -0.921    0.937
## APOE33 male - APOE44 male == 0      1.436e-05  6.393e-05   0.225    1.000
## (Adjusted p values reported -- single-step method)
```

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

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

```
## $`Sex = female`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -6.441e-06  7.382e-05  -0.087    0.996
## APOE22 - APOE44 == 0  8.506e-06  6.393e-05   0.133    0.990
## APOE33 - APOE44 == 0  1.495e-05  7.382e-05   0.202    0.978
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -7.071e-05  6.121e-05  -1.155    0.491
## APOE22 - APOE44 == 0 -5.635e-05  6.121e-05  -0.921    0.633
## APOE33 - APOE44 == 0  1.436e-05  6.393e-05   0.225    0.973
## (Adjusted p values reported -- single-step method)
```

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

```
## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0 7.991e-06  6.121e-05   0.131    0.897
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -5.628e-05  7.382e-05  -0.762    0.454
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -5.687e-05  6.393e-05   -0.89    0.383
## (Adjusted p values reported -- single-step method)
```

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

```
## Genotype = APOE22:
##  contrast        estimate       SE df t.ratio p.value
##  female - male  7.99e-06 6.12e-05 23   0.131  0.8973
##
## Genotype = APOE33:
##  contrast        estimate       SE df t.ratio p.value
##  female - male -5.63e-05 7.38e-05 23  -0.762  0.4535
##
## Genotype = APOE44:
##  contrast        estimate       SE df t.ratio p.value
##  female - male -5.69e-05 6.39e-05 23  -0.890  0.3829
```

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

```
## Sex = female:
```

```
##  contrast          estimate         SE df t.ratio p.value
##  APOE22 - APOE33 -6.44e-06 7.38e-05 23  -0.087  0.9958
##  APOE22 - APOE44  8.51e-06 6.39e-05 23   0.133  0.9903
##  APOE33 - APOE44  1.49e-05 7.38e-05 23   0.202  0.9777
##
## Sex = male:
##  contrast          estimate         SE df t.ratio p.value
##  APOE22 - APOE33 -7.07e-05 6.12e-05 23  -1.155  0.4910
##  APOE22 - APOE44 -5.64e-05 6.12e-05 23  -0.921  0.6330
##  APOE33 - APOE44  1.44e-05 6.39e-05 23   0.225  0.9726
##
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```
print('ic VOL')
```
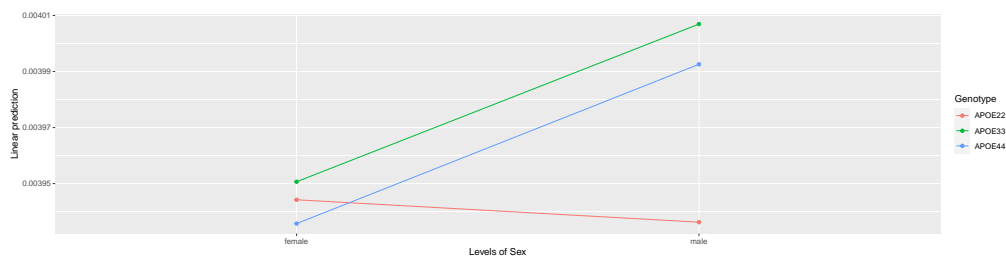
```
## [1] "ic VOL"
```

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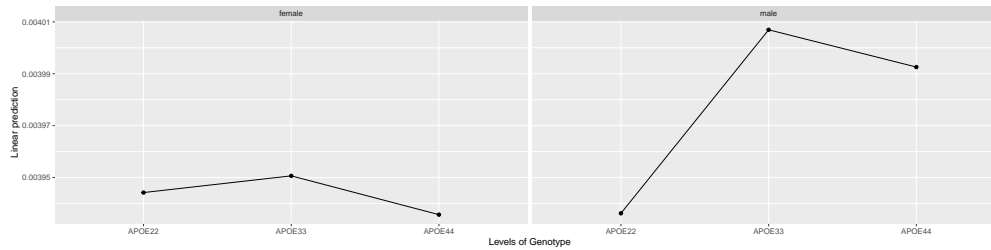


```
emmip(lm_ic_VOL, ~ Sex | Genotype )
```
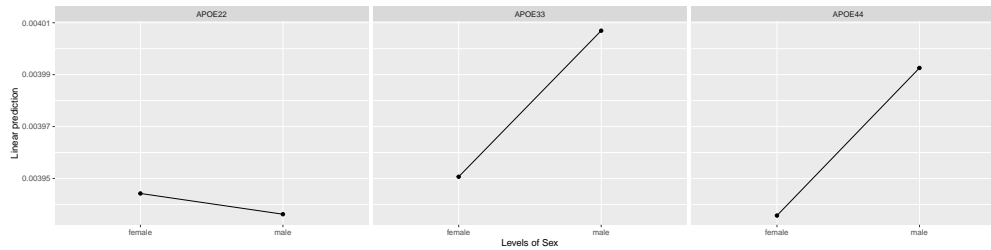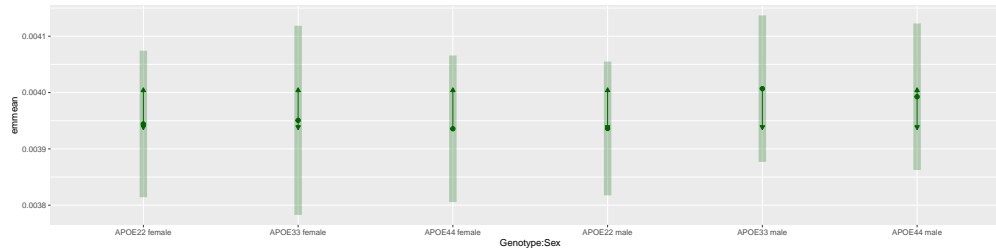


```
emmip(lm_ic_VOL, Genotype~ Sex  )
```



```
sink()
```

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

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

```
'simple stats'
```

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

```
print('ic')
```

```
## [1] "ic"
```

```
lm_ic_FA <- lm(ic ~ Genotype*Sex, geno_combined_FA)
summary(lm_ic_FA)
```

```
##
## Call:
## lm(formula = ic ~ Genotype * Sex, data = geno_combined_FA)
##
## Residuals:
##        Min         1Q     Median         3Q        Max
## -0.0308930 -0.0041263  0.0006374  0.0059384  0.0208270
##
## Coefficients:
##                        Estimate Std. Error t value Pr(>|t|)
## (Intercept)            0.619760   0.005320 116.495  < 2e-16 ***
## GenotypeAPOE33        -0.021588   0.008688  -2.485  0.02067 *
## GenotypeAPOE44        -0.023672   0.007524  -3.146  0.00452 **
## Sexmale                0.010103   0.007203   1.403  0.17412
## GenotypeAPOE33:Sexmale 0.011325   0.011286   1.004  0.32604
## GenotypeAPOE44:Sexmale 0.016188   0.010416   1.554  0.13380
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.0119 on 23 degrees of freedom
## Multiple R-squared:  0.5763, Adjusted R-squared:  0.4842
## F-statistic: 6.258 on 5 and 23 DF,  p-value: 0.000839
```

```
lm_ic_FA_f <- lm(ic ~ Genotype, combo_f_FA)
#summary(lm_ic_FA_f)
lm_ic_FA_m <- lm(ic ~ Genotype, combo_m_FA)
#summary(lm_ic_FA_f)


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

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

```
## 
## Response: ic
##             Df   Sum Sq    Mean Sq F value    Pr(>F)
## Genotype     2 0.0015605 0.00078027  5.5137 0.0110621 *
## Sex          1 0.0025078 0.00250781 17.7213 0.0003339 ***
## Genotype:Sex 2 0.0003595 0.00017977  1.2703 0.2997152
## Residuals   23 0.0032548 0.00014151
## ---
## 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 = ic ~ Genotype * Sex, data = geno_combined_FA)
## 
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 0.021588   0.008688   2.485   0.0519 .
## APOE22 - APOE44 == 0 0.023672   0.007524   3.146   0.0121 *
## APOE33 - APOE44 == 0 0.002084   0.008688   0.240   0.9687
## ---
## 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 = ic ~ Genotype * Sex, data = geno_combined_FA)
## 
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.010262   0.007203   1.425    0.345
## APOE22 - APOE44 == 0  0.007484   0.007203   1.039    0.560
## APOE33 - APOE44 == 0 -0.002779   0.007524  -0.369    0.928
## (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 = ic ~ Genotype * Sex, data = geno_combined_FA)
## 
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.010103   0.007203  -1.403    0.174
## (Adjusted p values reported -- single-step method)
## 
## 
```

```
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.021428   0.008688  -2.467   0.0215 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.026291   0.007524  -3.494  0.00195 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
```

```r
sink()
#3333

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

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

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

```r
joint_tests(ref_grid(lm_ic_FA))
```

```
##  model term    df1 df2 F.ratio p.value
##  Genotype        2  23   5.874  0.0087
##  Sex             1  23  18.174  0.0003
##  Genotype:Sex    2  23   1.270  0.2997
```

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

```
## Sex = female:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   5.725  0.0096
##
## Sex = male:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   1.111  0.3462
```

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

```
## Genotype = APOE22:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   1.967  0.1741
##
## Genotype = APOE33:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   6.084  0.0215
##
## Genotype = APOE44:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23  12.211  0.0020
```

```
'anova'
```

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

```
anova(lm_ic_FA)
```

```
## Analysis of Variance Table
##
## Response: ic
##             Df    Sum Sq    Mean Sq F value    Pr(>F)
## Genotype     2 0.0015605 0.00078027  5.5137 0.0110621 *
## Sex          1 0.0025078 0.00250781 17.7213 0.0003339 ***
## Genotype:Sex 2 0.0003595 0.00017977  1.2703 0.2997152
## Residuals   23 0.0032548 0.00014151
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
#anova(lm_ic_FA_f)
#anova(lm_ic_FA_m)

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

```
##  contrast           estimate      SE df t.ratio p.value
##  APOE22 female effect  0.00545 0.00490 23   1.113  0.2912
##  APOE33 female effect -0.01614 0.00605 23  -2.669  0.0274
##  APOE44 female effect -0.01822 0.00490 23  -3.721  0.0067
##  APOE22 male effect    0.01555 0.00456 23   3.407  0.0072
##  APOE33 male effect    0.00529 0.00490 23   1.080  0.2912
##  APOE44 male effect    0.00807 0.00490 23   1.648  0.1695
##
## P value adjustment: fdr method for 6 tests
```

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

```
## $`simple contrasts for Genotype`
## Sex = female:
##  contrast       estimate      SE df t.ratio p.value
##  APOE22 effect  0.01509 0.00458 23   3.295  0.0095
##  APOE33 effect -0.00650 0.00522 23  -1.245  0.2256
##  APOE44 effect -0.00859 0.00458 23  -1.875  0.1103
##
```

```
## Sex = male:
##  contrast      estimate      SE df t.ratio p.value
##  APOE22 effect  0.00592 0.00410 23   1.444  0.4811
##  APOE33 effect -0.00435 0.00428 23  -1.015  0.4811
##  APOE44 effect -0.00157 0.00428 23  -0.366  0.7176
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
##  contrast      estimate      SE df t.ratio p.value
##  female effect -0.00505 0.00360 23  -1.403  0.1741
##  male effect    0.00505 0.00360 23   1.403  0.1741
##
## Genotype = APOE33:
##  contrast      estimate      SE df t.ratio p.value
##  female effect -0.01071 0.00434 23  -2.467  0.0215
##  male effect    0.01071 0.00434 23   2.467  0.0215
##
## Genotype = APOE44:
##  contrast      estimate      SE df t.ratio p.value
##  female effect -0.01315 0.00376 23  -3.494  0.0020
##  male effect    0.01315 0.00376 23   3.494  0.0020
##
## P value adjustment: fdr method for 2 tests
```

```r
#post hoc tests
summary(glht(lm_ic_FA, emm(pairwise ~ Genotype*Sex, contr="sidak"))) #consider save to file
```

```
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                                 Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0  0.0215877  0.0086876   2.485   0.1687
## APOE22 female - APOE44 female == 0  0.0236719  0.0075237   3.146   0.0451 *
## APOE22 female - APOE22 male == 0   -0.0101028  0.0072034  -1.403   0.7236
## APOE22 female - APOE33 male == 0    0.0001594  0.0075237   0.021   1.0000
## APOE22 female - APOE44 male == 0   -0.0026191  0.0075237  -0.348   0.9992
## APOE33 female - APOE44 female == 0  0.0020842  0.0086876   0.240   0.9999
## APOE33 female - APOE22 male == 0   -0.0316905  0.0084117  -3.767   0.0112 *
## APOE33 female - APOE33 male == 0   -0.0214283  0.0086876  -2.467   0.1743
## APOE33 female - APOE44 male == 0   -0.0242068  0.0086876  -2.786   0.0952 .
## APOE44 female - APOE22 male == 0   -0.0337747  0.0072034  -4.689   0.0012 **
## APOE44 female - APOE33 male == 0   -0.0235125  0.0075237  -3.125   0.0472 *
## APOE44 female - APOE44 male == 0   -0.0262910  0.0075237  -3.494   0.0210 *
## APOE22 male - APOE33 male == 0      0.0102622  0.0072034   1.425   0.7108
## APOE22 male - APOE44 male == 0      0.0074837  0.0072034   1.039   0.8990
## APOE33 male - APOE44 male == 0     -0.0027785  0.0075237  -0.369   0.9990
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
```

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

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

```
## $`Sex = female`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                     Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 0.021588   0.008688   2.485   0.0518 .
## APOE22 - APOE44 == 0 0.023672   0.007524   3.146   0.0119 *
## APOE33 - APOE44 == 0 0.002084   0.008688   0.240   0.9687
## ---
## 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 = ic ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                     Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.010262   0.007203   1.425    0.345
## APOE22 - APOE44 == 0  0.007484   0.007203   1.039    0.560
## APOE33 - APOE44 == 0 -0.002779   0.007524  -0.369    0.928
## (Adjusted p values reported -- single-step method)
```

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

```
## $`Genotype = APOE22`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.010103   0.007203  -1.403    0.174
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_FA)
##
```

```
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.021428   0.008688  -2.467   0.0215 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.026291   0.007524  -3.494  0.00195 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
```
```
mypairs<-pairs(ic_FA.emm) #_consider save to file
pairs(ic_FA.emm, by="Genotype")
```
```
Genotype = APOE22:
contrast   estimate   SE df t.ratio p.value
female - male -0.0101 0.00720 23 -1.403 0.1741
##
Genotype = APOE33:
contrast   estimate   SE df t.ratio p.value
female - male -0.0214 0.00869 23 -2.467 0.0215
##
Genotype = APOE44:
contrast   estimate   SE df t.ratio p.value
female - male -0.0263 0.00752 23 -3.494 0.0020
```
```
pairs(ic_FA.emm, by="Sex")
```
```
Sex = female:
contrast   estimate   SE df t.ratio p.value
APOE22 - APOE33   0.02159 0.00869 23   2.485 0.0521
APOE22 - APOE44   0.02367 0.00752 23   3.146 0.0121
APOE33 - APOE44   0.00208 0.00869 23   0.240 0.9688
##
Sex = male:
contrast   estimate   SE df t.ratio p.value
APOE22 - APOE33   0.01026 0.00720 23   1.425 0.3452
APOE22 - APOE44   0.00748 0.00720 23   1.039 0.5605
APOE33 - APOE44 -0.00278 0.00752 23 -0.369 0.9278
##
P value adjustment: tukey method for comparing a family of 3 estimates
```
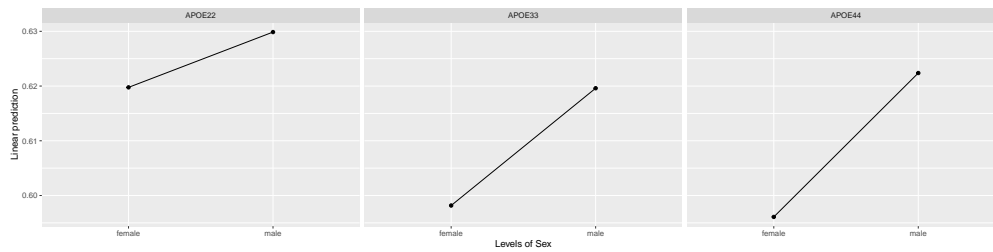```
print('ic FA')
```
```
## [1] "ic FA"
```
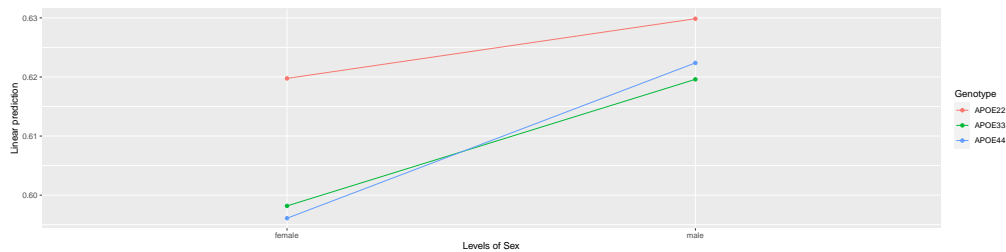
```
emmip(lm_ic_FA, ~ Genotype | Sex )
```
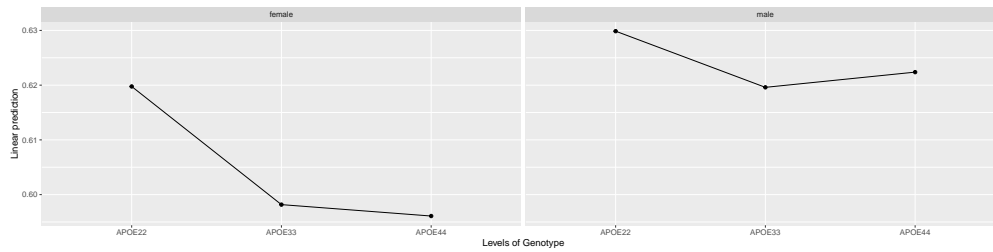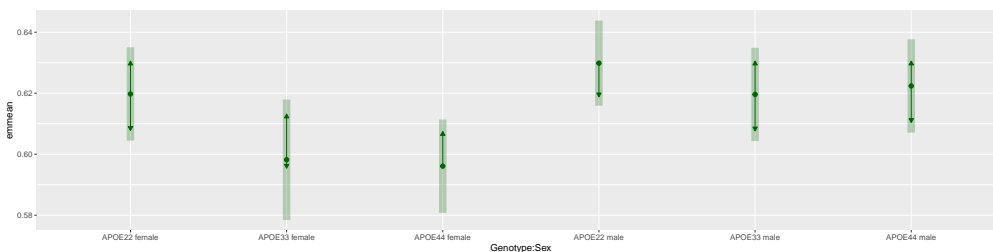


```
emmip(lm_ic_FA, ~ Sex | Genotype )
```



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



```
sink()

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



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

```
'simple stats'
```

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

```
print('ic')
```

```
## [1] "ic"
```

```
lm_ic_DEG <- lm(ic ~ Genotype*Sex, geno_combined_DEG)
summary(lm_ic_DEG)
```

16

```
##
## Call:
## lm(formula = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -7382.7 -3038.0  -364.2  1734.8 12936.3
##
## Coefficients:
##                         Estimate Std. Error t value Pr(>|t|)
## (Intercept)              25034.0     2121.7  11.799 3.09e-11 ***
## GenotypeAPOE33           13151.7     3464.7   3.796 0.000933 ***
## GenotypeAPOE44            -952.8     3000.5  -0.318 0.753693
## Sexmale                  -1127.8     2872.8  -0.393 0.698232
## GenotypeAPOE33:Sexmale  -11030.6     4500.7  -2.451 0.022274 *
## GenotypeAPOE44:Sexmale    -566.4     4154.0  -0.136 0.892737
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 4744 on 23 degrees of freedom
## Multiple R-squared:  0.5186, Adjusted R-squared:  0.414
## F-statistic: 4.956 on 5 and 23 DF,  p-value: 0.003181
```

```
lm_ic_DEG_f <- lm(ic ~ Genotype, combo_f_FA)
#summary(lm_ic_DEG_f)
lm_ic_DEG_m <- lm(ic ~ Genotype, combo_m_FA)
#summary(lm_ic_DEG_f)

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

```
## Analysis of Variance Table
##
## Response: ic
##              Df    Sum Sq   Mean Sq F value   Pr(>F)
## Genotype      2 269891145 134945572  5.9956 0.008023 **
## Sex           1 127638555 127638555  5.6710 0.025910 *
## Genotype:Sex  2 160184427  80092213  3.5585 0.045034 *
## Residuals    23 517669221  22507357
## ---
## 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 = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -13151.7     3464.7  -3.796  0.00261 **
```

```
## APOE22 - APOE44 == 0     952.8     3000.5   0.318  0.94587
## APOE33 - APOE44 == 0   14104.5     3464.7   4.071  0.00128 **
## ---
## 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 = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                     Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0    -2121       2873  -0.738    0.743
## APOE22 - APOE44 == 0     1519       2873   0.529    0.858
## APOE33 - APOE44 == 0     3640       3000   1.213    0.457
## (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 = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0     1128       2873   0.393    0.698
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0    12158       3465   3.509  0.00188 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
```

```
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0      1694       3000   0.565    0.578
## (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, "ic_DEG_SimpleStats.txt",sep=''))
'omnibus testing'
```

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

```
joint_tests(ref_grid(lm_ic_DEG))
```

```
##  model term    df1 df2 F.ratio  p.value
##  Genotype        2  23   8.478   0.0017
##  Sex             1  23   7.670   0.0109
##  Genotype:Sex    2  23   3.558   0.0450
```

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

```
## Sex = female:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   9.572  0.0009
##
## Sex = male:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   0.743  0.4865
```

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

```
## Genotype = APOE22:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.154  0.6982
##
## Genotype = APOE33:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23  12.315  0.0019
##
## Genotype = APOE44:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.319  0.5778
```

```
'anova'
```

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

```
anova(lm_ic_DEG)
```

```
## Analysis of Variance Table
##
## Response: ic
##              Df    Sum Sq   Mean Sq F value    Pr(>F)
## Genotype      2 269891145 134945572  5.9956  0.008023 **
## Sex           1 127638555 127638555  5.6710  0.025910 *
## Genotype:Sex  2 160184427  80092213  3.5585  0.045034 *
```

```
## Residuals     23 517669221   22507357
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
#anova(lm_ic_DEG_f)
#anova(lm_ic_DEG_m)

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

```
##  contrast            estimate   SE df t.ratio p.value
##  APOE22 female effect    -1570 1953 23  -0.804  0.5158
##  APOE33 female effect    11582 2411 23   4.803  0.0005
##  APOE44 female effect    -2522 1953 23  -1.292  0.3140
##  APOE22 male effect      -2697 1820 23  -1.482  0.3039
##  APOE33 male effect       -576 1953 23  -0.295  0.7705
##  APOE44 male effect      -4217 1953 23  -2.159  0.1245
##
## P value adjustment: fdr method for 6 tests
```

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

```
## $`simple contrasts for Genotype`
## Sex = female:
##  contrast       estimate   SE df t.ratio p.value
##  APOE22 effect    -4066 1826 23  -2.227  0.0360
##  APOE33 effect     9085 2082 23   4.364  0.0007
##  APOE44 effect    -5019 1826 23  -2.749  0.0172
##
## Sex = male:
##  contrast       estimate   SE df t.ratio p.value
##  APOE22 effect     -201 1633 23  -0.123  0.9033
##  APOE33 effect     1920 1708 23   1.124  0.4867
##  APOE44 effect    -1720 1708 23  -1.007  0.4867
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
##  contrast       estimate   SE df t.ratio p.value
##  female effect      564 1436 23   0.393  0.6982
##  male effect       -564 1436 23  -0.393  0.6982
##
## Genotype = APOE33:
##  contrast       estimate   SE df t.ratio p.value
##  female effect     6079 1732 23   3.509  0.0019
##  male effect      -6079 1732 23  -3.509  0.0019
##
## Genotype = APOE44:
##  contrast       estimate   SE df t.ratio p.value
##  female effect      847 1500 23   0.565  0.5778
##  male effect       -847 1500 23  -0.565  0.5778
##
## P value adjustment: fdr method for 2 tests
```

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

```
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                                 Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -13151.7     3464.7  -3.796  0.01043 *
## APOE22 female - APOE44 female == 0     952.8     3000.5   0.318  0.99950
## APOE22 female - APOE22 male == 0      1127.8     2872.8   0.393  0.99861
## APOE22 female - APOE33 male == 0       -993.2     3000.5  -0.331  0.99939
## APOE22 female - APOE44 male == 0       2647.0     3000.5   0.882  0.94658
## APOE33 female - APOE44 female == 0   14104.5     3464.7   4.071  0.00543 **
## APOE33 female - APOE22 male == 0     14279.5     3354.7   4.257  0.00356 **
## APOE33 female - APOE33 male == 0     12158.5     3464.7   3.509  0.02018 *
## APOE33 female - APOE44 male == 0     15798.7     3464.7   4.560  0.00175 **
## APOE44 female - APOE22 male == 0       175.0     2872.8   0.061  1.00000
## APOE44 female - APOE33 male == 0     -1946.0     3000.5  -0.649  0.98565
## APOE44 female - APOE44 male == 0      1694.2     3000.5   0.565  0.99233
## APOE22 male - APOE33 male == 0       -2121.0     2872.8  -0.738  0.97464
## APOE22 male - APOE44 male == 0        1519.2     2872.8   0.529  0.99433
## APOE33 male - APOE44 male == 0        3640.2     3000.5   1.213  0.82484
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
```
```
res<-summary(glht(lm_ic_DEG, emm(pairwise ~ Genotype*Sex))) #consider save to file
#summary(as.glht(pairs(lm_ic_DEG.emm), by = NULL))

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

```
## $`Sex = female`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                 Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -13151.7     3464.7  -3.796  0.00250 **
## APOE22 - APOE44 == 0     952.8     3000.5   0.318  0.94588
## APOE33 - APOE44 == 0   14104.5     3464.7   4.071  0.00127 **
## ---
## 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 = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                     Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0    -2121       2873  -0.738    0.743
## APOE22 - APOE44 == 0     1519       2873   0.529    0.858
## APOE33 - APOE44 == 0     3640       3000   1.213    0.457
## (Adjusted p values reported -- single-step method)
```

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

```
## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0    1128       2873   0.393    0.698
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0   12158       3465   3.509  0.00188 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0    1694       3000   0.565    0.578
## (Adjusted p values reported -- single-step method)
```

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

```
## Genotype = APOE22:
##  contrast       estimate   SE df t.ratio p.value
##  female - male      1128 2873 23   0.393  0.6982
##
```

```
## Genotype = APOE33:
##  contrast       estimate   SE df t.ratio p.value
##  female - male    12158 3465 23   3.509  0.0019
##
## Genotype = APOE44:
##  contrast       estimate   SE df t.ratio p.value
##  female - male     1694 3000 23   0.565  0.5778
```

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

```
## Sex = female:
##  contrast          estimate   SE df t.ratio p.value
##  APOE22 - APOE33    -13152 3465 23  -3.796  0.0026
##  APOE22 - APOE44       953 3000 23   0.318  0.9461
##  APOE33 - APOE44     14104 3465 23   4.071  0.0013
##
## Sex = male:
##  contrast          estimate   SE df t.ratio p.value
##  APOE22 - APOE33     -2121 2873 23  -0.738  0.7435
##  APOE22 - APOE44      1519 2873 23   0.529  0.8581
##  APOE33 - APOE44      3640 3000 23   1.213  0.4576
##
## P value adjustment: tukey method for comparing a family of 3 estimates
```
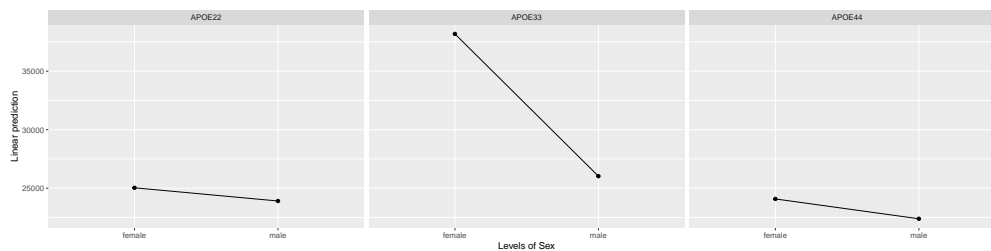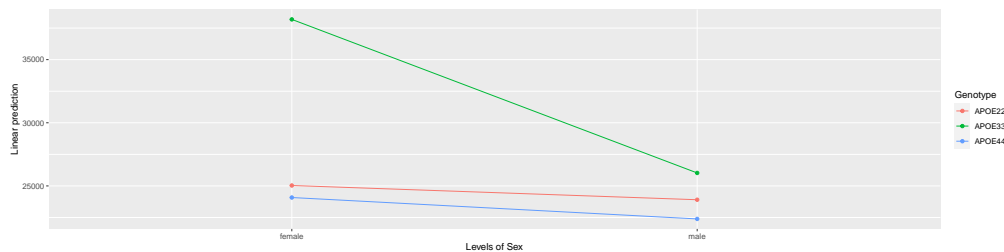
```
print('ic DEG')
```

```
## [1] "ic DEG"
```

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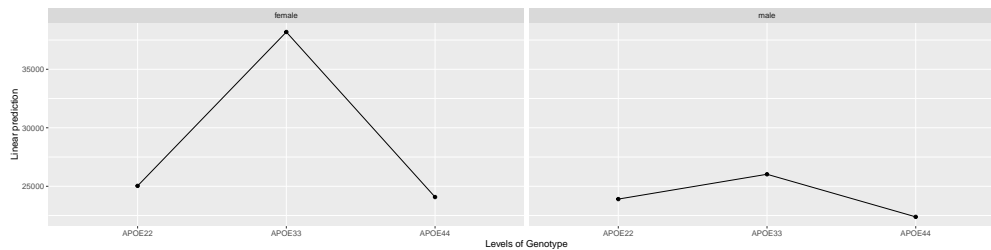

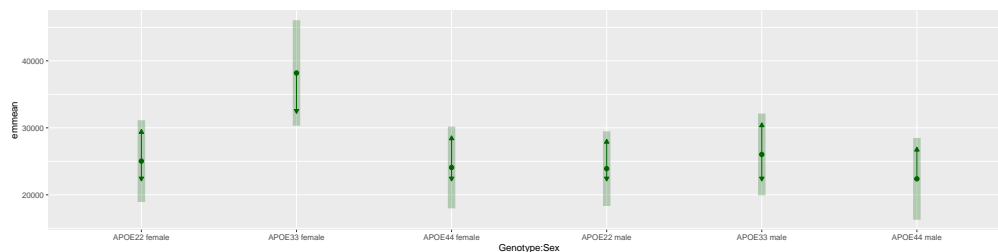```
emmip(lm_ic_DEG, ~ Sex | Genotype)
```



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

```
sink()
```

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



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

```
'simple stats'
```

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

```
print('ic')
```

```
## [1] "ic"
```

```
lm_ic_CLUS <- lm(ic ~ Genotype*Sex, geno_combined_CLUS)
summary(lm_ic_CLUS)
```

```
##
## Call:
## lm(formula = ic ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -24.073  -7.060  -2.001   6.264  40.447
##
## Coefficients:
##                     Estimate Std. Error t value Pr(>|t|)
## (Intercept)           94.638      6.141  15.412  1.3e-13 ***
## GenotypeAPOE33        33.855     10.028   3.376   0.0026 **
## GenotypeAPOE44         2.640      8.684   0.304   0.7639
## Sexmale               -4.018      8.314  -0.483   0.6334
## GenotypeAPOE33:Sexmale -25.115    13.026  -1.928   0.0663 .
## GenotypeAPOE44:Sexmale  -2.570    12.023  -0.214   0.8326
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 13.73 on 23 degrees of freedom
## Multiple R-squared:  0.4432, Adjusted R-squared:  0.3222
## F-statistic: 3.661 on 5 and 23 DF,  p-value: 0.01391
```

24

```
lm_ic_CLUS_f <- lm(ic ~ Genotype, combo_f_FA)
#summary(lm_ic_CLUS_f)
lm_ic_CLUS_m <- lm(ic ~ Genotype, combo_m_FA)
#summary(lm_ic_CLUS_f)

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

```
## Analysis of Variance Table
##
## Response: ic
##              Df Sum Sq Mean Sq F value  Pr(>F)
## Genotype      2 1707.6  853.79  4.5285 0.02197 *
## Sex           1  948.0  948.05  5.0285 0.03487 *
## Genotype:Sex  2  796.0  397.98  2.1109 0.14399
## Residuals    23 4336.3  188.54
## ---
## 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 = ic ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -33.855     10.028  -3.376  0.00683 **
## APOE22 - APOE44 == 0    -2.640      8.684  -0.304  0.95025
## APOE33 - APOE44 == 0    31.215     10.028   3.113  0.01290 *
## ---
## 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 = ic ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -8.73985    8.31445  -1.051    0.553
## APOE22 - APOE44 == 0 -0.06985    8.31445  -0.008    1.000
## APOE33 - APOE44 == 0  8.67000    8.68416   0.998    0.585
## (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 = ic ~ Genotype * Sex, data = geno_combined_CLUS)
## 
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0    4.018      8.314   0.483    0.633
## (Adjusted p values reported -- single-step method)
## 
## 
## $`Genotype = APOE33`
## 
##   Simultaneous Tests for General Linear Hypotheses
## 
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_CLUS)
## 
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0    29.13      10.03   2.905  0.00797 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
## 
## 
## $`Genotype = APOE44`
## 
##   Simultaneous Tests for General Linear Hypotheses
## 
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_CLUS)
## 
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0    6.589      8.684   0.759    0.456
## (Adjusted p values reported -- single-step method)
```

```r
sink()
#3333

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

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

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

```r
joint_tests(ref_grid(lm_ic_CLUS))
```

```
##  model term   df1 df2 F.ratio p.value
##  Genotype       2  23   6.268  0.0067
##  Sex            1  23   6.444  0.0184
##  Genotype:Sex   2  23   2.111  0.1440
```

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

```
## Sex = female:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   6.524  0.0057
##
## Sex = male:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   0.691  0.5110
```

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

```
## Genotype = APOE22:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.234  0.6334
##
## Genotype = APOE33:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   8.441  0.0080
##
## Genotype = APOE44:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.576  0.4557
```

```
'anova'
```

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

```
anova(lm_ic_CLUS)
```

```
## Analysis of Variance Table
##
## Response: ic
##             Df Sum Sq Mean Sq F value  Pr(>F)
## Genotype     2 1707.6  853.79  4.5285 0.02197 *
## Sex          1  948.0  948.05  5.0285 0.03487 *
## Genotype:Sex 2  796.0  397.98  2.1109 0.14399
## Residuals   23 4336.3  188.54
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
#anova(lm_ic_CLUS_f)
#anova(lm_ic_CLUS_m)

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

```
##  contrast           estimate   SE df t.ratio p.value
##  APOE22 female effect   -5.54 5.65 23  -0.980  0.5056
##  APOE33 female effect   28.31 6.98 23   4.057  0.0029
##  APOE44 female effect   -2.90 5.65 23  -0.513  0.7351
##  APOE22 male effect     -9.56 5.27 23  -1.815  0.2134
##  APOE33 male effect     -0.82 5.65 23  -0.145  0.8859
##  APOE44 male effect     -9.49 5.65 23  -1.679  0.2134
##
## P value adjustment: fdr method for 6 tests
```

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

```
## $`simple contrasts for Genotype`
## Sex = female:
##  contrast       estimate   SE df  t.ratio p.value
##  APOE22 effect   -12.17 5.29 23   -2.302  0.0461
##  APOE33 effect    21.69 6.03 23    3.600  0.0045
##  APOE44 effect    -9.53 5.29 23   -1.802  0.0846
##
## Sex = male:
##  contrast       estimate   SE df  t.ratio p.value
##  APOE22 effect    -2.94 4.73 23   -0.621  0.5676
##  APOE33 effect     5.80 4.94 23    1.174  0.5676
##  APOE44 effect    -2.87 4.94 23   -0.580  0.5676
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
##  contrast       estimate   SE df  t.ratio p.value
##  female effect     2.01 4.16 23    0.483  0.6334
##  male effect      -2.01 4.16 23   -0.483  0.6334
##
## Genotype = APOE33:
##  contrast       estimate   SE df  t.ratio p.value
##  female effect    14.57 5.01 23    2.905  0.0080
##  male effect     -14.57 5.01 23   -2.905  0.0080
##
## Genotype = APOE44:
##  contrast       estimate   SE df  t.ratio p.value
##  female effect     3.29 4.34 23    0.759  0.4557
##  male effect      -3.29 4.34 23   -0.759  0.4557
##
## P value adjustment: fdr method for 2 tests
```

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

```
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                                Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -33.85513   10.02761  -3.376  0.02738 *
## APOE22 female - APOE44 female == 0  -2.64000    8.68416  -0.304  0.99960
## APOE22 female - APOE22 male   == 0   4.01845    8.31445   0.483  0.99628
## APOE22 female - APOE33 male   == 0  -4.72140    8.68416  -0.544  0.99356
## APOE22 female - APOE44 male   == 0   3.94860    8.68416   0.455  0.99720
## APOE33 female - APOE44 female == 0  31.21513   10.02761   3.113  0.04868 *
## APOE33 female - APOE22 male   == 0  37.87358    9.70919   3.901  0.00828 **
## APOE33 female - APOE33 male   == 0  29.13373   10.02761   2.905  0.07494 .
## APOE33 female - APOE44 male   == 0  37.80373   10.02761   3.770  0.01106 *
```

```
## APOE44 female - APOE22 male == 0      6.65845      8.31445    0.801   0.96417
## APOE44 female - APOE33 male == 0     -2.08140      8.68416   -0.240   0.99987
## APOE44 female - APOE44 male == 0      6.58860      8.68416    0.759   0.97150
## APOE22 male - APOE33 male == 0       -8.73985      8.31445   -1.051   0.89451
## APOE22 male - APOE44 male == 0       -0.06985      8.31445   -0.008   1.00000
## APOE33 male - APOE44 male == 0        8.67000      8.68416    0.998   0.91306
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
```

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

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

```
## $`Sex = female`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -33.855     10.028  -3.376  0.00713 **
## APOE22 - APOE44 == 0   -2.640      8.684  -0.304  0.95026
## APOE33 - APOE44 == 0   31.215     10.028   3.113  0.01297 *
## ---
## 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 = ic ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -8.73985    8.31445  -1.051    0.553
## APOE22 - APOE44 == 0 -0.06985    8.31445  -0.008    1.000
## APOE33 - APOE44 == 0  8.67000    8.68416   0.998    0.585
## (Adjusted p values reported -- single-step method)
```

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

```
## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                 Estimate Std. Error t value Pr(>|t|)
## female - male == 0    4.018      8.314   0.483    0.633
```

```
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0    29.13      10.03   2.905  0.00797 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = ic ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0    6.589      8.684   0.759    0.456
## (Adjusted p values reported -- single-step method)
```

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

```
## Genotype = APOE22:
##  contrast       estimate    SE df t.ratio p.value
##  female - male      4.02  8.31 23   0.483  0.6334
##
## Genotype = APOE33:
##  contrast       estimate    SE df t.ratio p.value
##  female - male     29.13 10.03 23   2.905  0.0080
##
## Genotype = APOE44:
##  contrast       estimate    SE df t.ratio p.value
##  female - male      6.59  8.68 23   0.759  0.4557
```

```r
pairs(ic_CLUS.emm, by="Sex")
```

```
## Sex = female:
##  contrast          estimate    SE df t.ratio p.value
##  APOE22 - APOE33  -33.8551 10.03 23  -3.376  0.0071
##  APOE22 - APOE44   -2.6400  8.68 23  -0.304  0.9504
##  APOE33 - APOE44   31.2151 10.03 23   3.113  0.0131
##
## Sex = male:
##  contrast          estimate    SE df t.ratio p.value
##  APOE22 - APOE33   -8.7399  8.31 23  -1.051  0.5531
##  APOE22 - APOE44   -0.0698  8.31 23  -0.008  1.0000
```
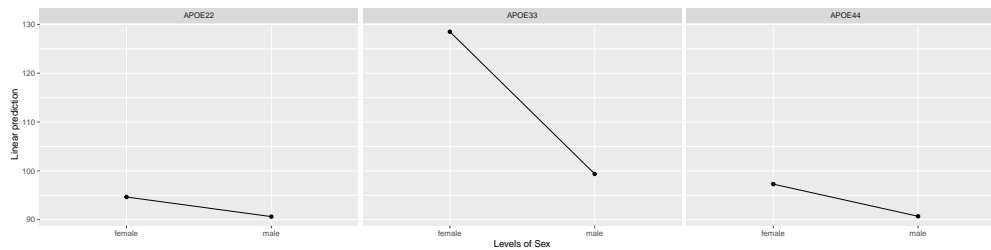
```
## APOE33 - APOE44   8.6700  8.68 23   0.998  0.5853
##
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```
print('ic CLUS')
```
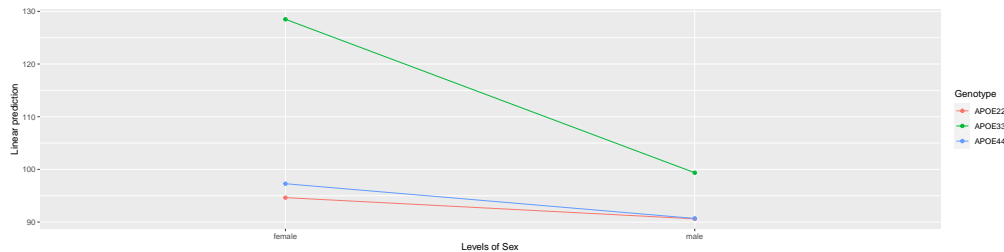
```
## [1] "ic CLUS"
```

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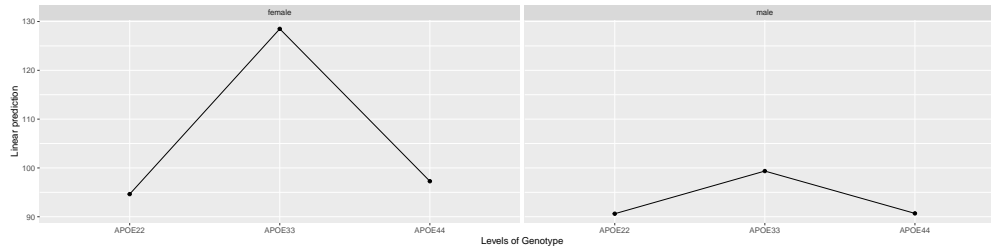


```
emmip(lm_ic_CLUS, ~ Sex | Genotype )
```
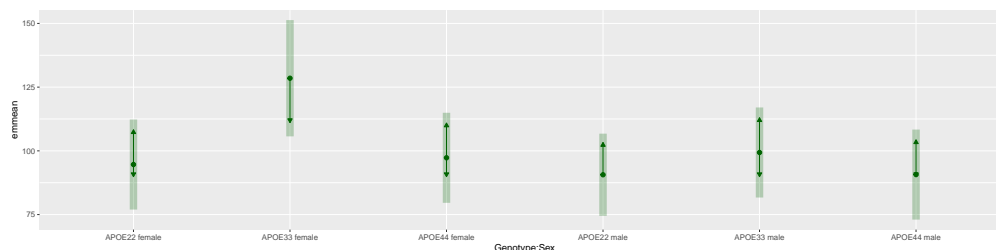


```
emmip(lm_ic_CLUS, Genotype~ Sex  )
```



```
sink()
```

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



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