

# SimpleViolins

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## 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:

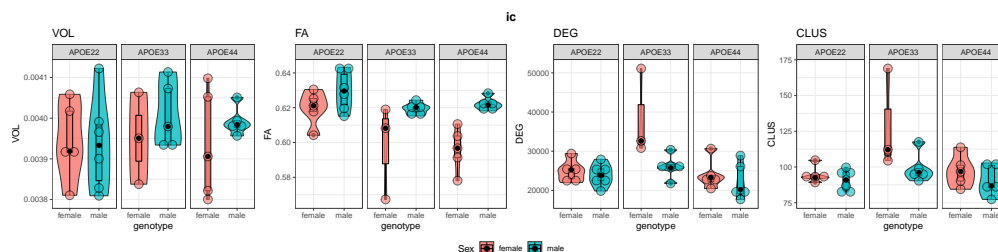
Morris Water Maze - testing spatial navigation memory Segmentation: regional volumes Microstructural properties: FA Tractography Based Connectivity: Degree, and Clustering Coefficient

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

## Plots for ic

We embed plots for day d8 probe trials:

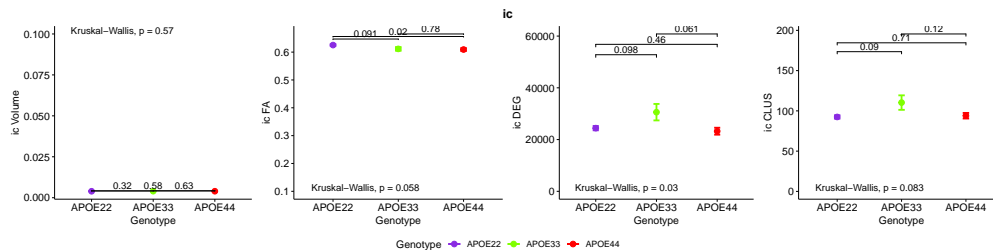
```
## Bin width defaults to 1/30 of the range of the data. Pick better value with `binwidth`.
## Bin width defaults to 1/30 of the range of the data. Pick better value with `binwidth`.
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```



```
## geom_path: Each group consists of only one observation. Do you need to adjust
## the group aesthetic?
```

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```

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## the group aesthetic?
```



```
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
```

```
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)
```

```
#plot significance for group comparisons
```

```
#my_comparisons <- list( c("APOE22", "APOE33"), c("APOE22", "APOE44"), c("APOE33", "APOE44") )
```

```
pic_Volume<-ggline(geno_combined_VOL, x = "Genotype", y = "ic",
  color = "Genotype", fill = "Genotype", error.plot='errorbar', add='mean_se', palette = c('blue', 'red', 'green'),
  point.size = 1.5, ylab='ic Volume')+
  theme_minimal()
```

```

stat_compare_means(comparisons = my_comparisons, method="t.test") ## # Add pairwise comparisons p-values
# stat_compare_means(label.y = 0.01) # Add global p-value
#xlab='', ylab='Percent SW Distance', legend='top', facet.by='Sex')

#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

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)
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, contr="sidak")))

```

```

## NOTE: Results may be misleading due to involvement in interactions
##
## 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 -3.858e-05  4.795e-05 -0.805    0.704
## APOE22 - APOE44 == 0 -2.392e-05  4.425e-05 -0.541    0.852
## APOE33 - APOE44 == 0  1.465e-05  4.883e-05  0.300    0.952
## (Adjusted p values reported -- single-step method)
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
```

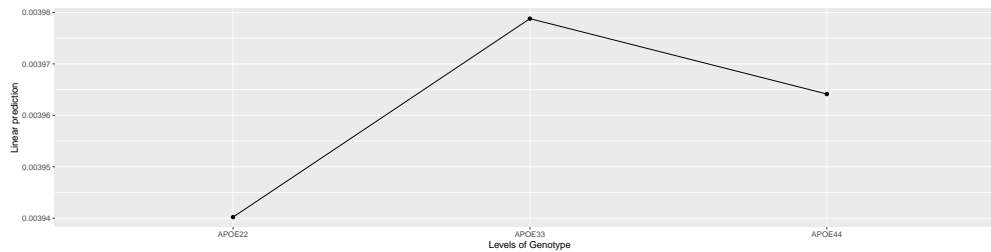


```
print('ic VOL')
```

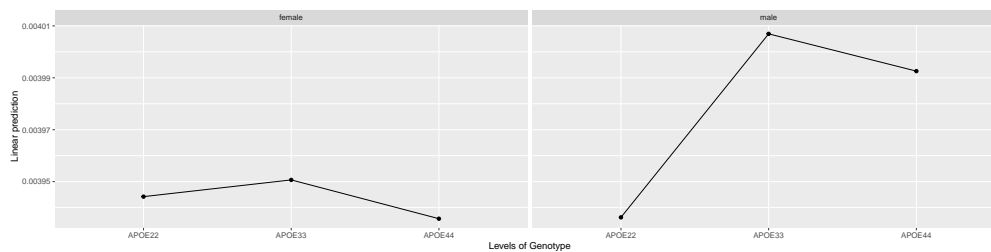
```
## [1] "ic VOL"
```

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

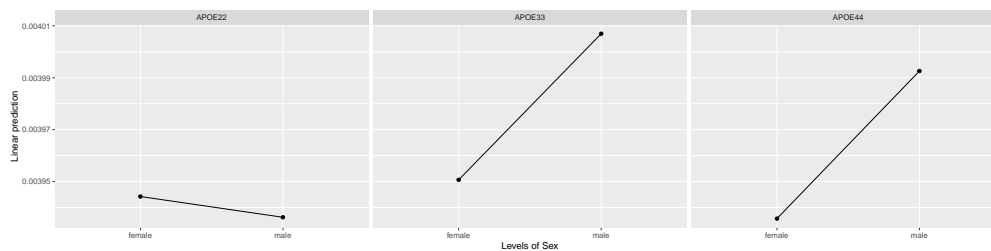
```
## NOTE: Results may be misleading due to involvement in interactions
```



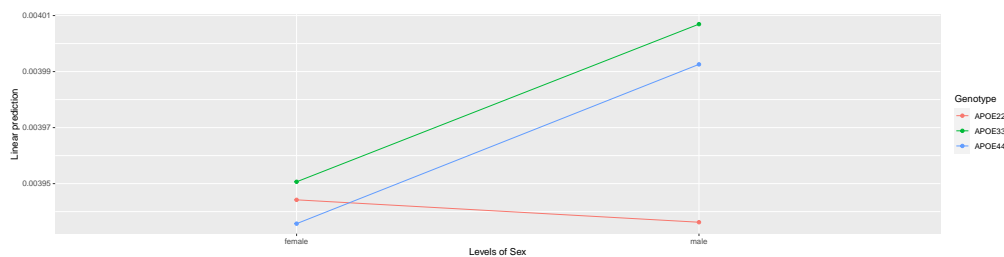
```
emmip(lm_ic_VOL, ~ Genotype | Sex )
```



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

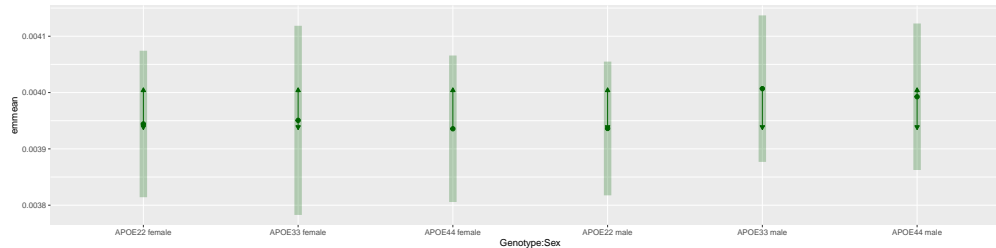


```
emmip(lm_ic_VOL, Genotype~ Sex )
```



```
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   0.0517 .
## 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(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)

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"

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

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
#post hoc tests
#post hoc tests
summary(glht(lm_ic_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 = ic ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.0159249  0.0056428   2.822  0.0253 *
## APOE22 - APOE44 == 0  0.0155778  0.0052080   2.991  0.0172 *
## APOE33 - APOE44 == 0 -0.0003472  0.0057463  -0.060  0.9980
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
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  0.16866

```

```

## APOE22 female - APOE44 female == 0 0.0236719 0.0075237 3.146 0.04518 *
## APOE22 female - APOE22 male == 0 -0.0101028 0.0072034 -1.403 0.72367
## APOE22 female - APOE33 male == 0 0.0001594 0.0075237 0.021 1.00000
## APOE22 female - APOE44 male == 0 -0.0026191 0.0075237 -0.348 0.99922
## APOE33 female - APOE44 female == 0 0.0020842 0.0086876 0.240 0.99987
## APOE33 female - APOE22 male == 0 -0.0316905 0.0084117 -3.767 0.01122 *
## APOE33 female - APOE33 male == 0 -0.0214283 0.0086876 -2.467 0.17434
## APOE33 female - APOE44 male == 0 -0.0242068 0.0086876 -2.786 0.09494 .
## APOE44 female - APOE22 male == 0 -0.0337747 0.0072034 -4.689 0.00131 **
## APOE44 female - APOE33 male == 0 -0.0235125 0.0075237 -3.125 0.04730 *
## APOE44 female - APOE44 male == 0 -0.0262910 0.0075237 -3.494 0.02095 *
## APOE22 male - APOE33 male == 0 0.0102622 0.0072034 1.425 0.71082
## APOE22 male - APOE44 male == 0 0.0074837 0.0072034 1.039 0.89897
## APOE33 male - APOE44 male == 0 -0.0027785 0.0075237 -0.369 0.99897
## ---
## 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

```



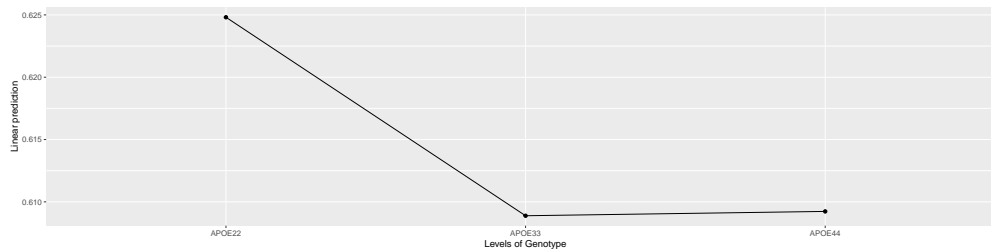
```
pairs(ic_FA.emm, by="Sex")
```

```
## 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')
```

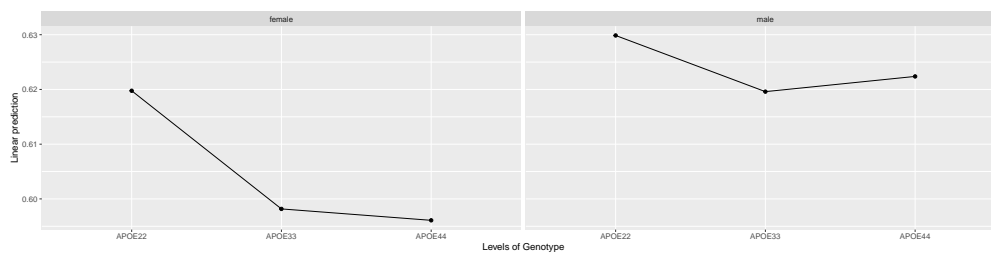
```
## [1] "ic FA"
```

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

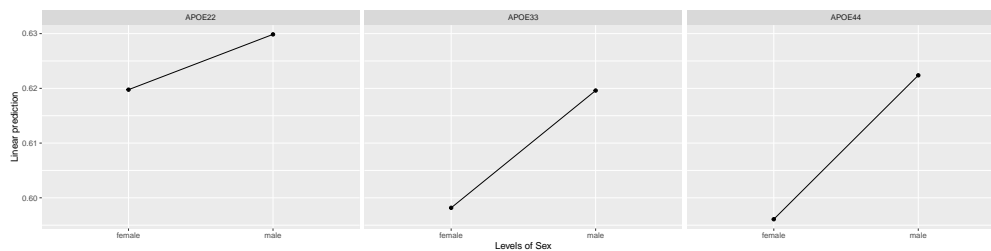
```
## NOTE: Results may be misleading due to involvement in interactions
```



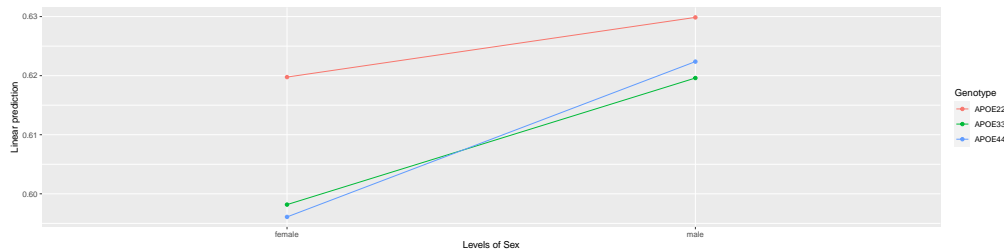
```
emmip(lm_ic_FA, ~ Genotype | Sex )
```



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

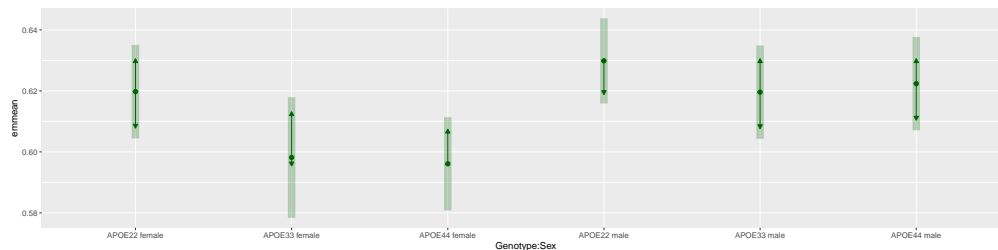


```
emmip(lm_ic_FA, Genotype~ Sex )
```



```
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, height=10)
```

```
'simple stats'
```

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

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

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

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

```
##
## 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  0.00256 **
## APOE22 - APOE44 == 0   952.8    3000.5   0.318  0.94587
## APOE33 - APOE44 == 0  14104.5    3464.7   4.071  0.00132 **
## ---
## 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  0.458
## (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 0.01052 *
## 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 0.00546 **
## APOE33 female - APOE22 male == 0 14279.5 3354.7 4.257 0.00349 **
## APOE33 female - APOE33 male == 0 12158.5 3464.7 3.509 0.02017 *
## APOE33 female - APOE44 male == 0 15798.7 3464.7 4.560 0.00171 **
```

```

## 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  0.82491
## ---
## 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 )))

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

##
## 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    -7636      2250  -3.393  0.00680 **
## APOE22 - APOE44 == 0     1236      2077   0.595  0.82385
## APOE33 - APOE44 == 0     8872      2292   3.872  0.00221 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)

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  0.00254 **
## APOE22 - APOE44 == 0   952.8     3000.5   0.318  0.94587
## APOE33 - APOE44 == 0 14104.5     3464.7   4.071  0.00122 **
## ---
## 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(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)
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")

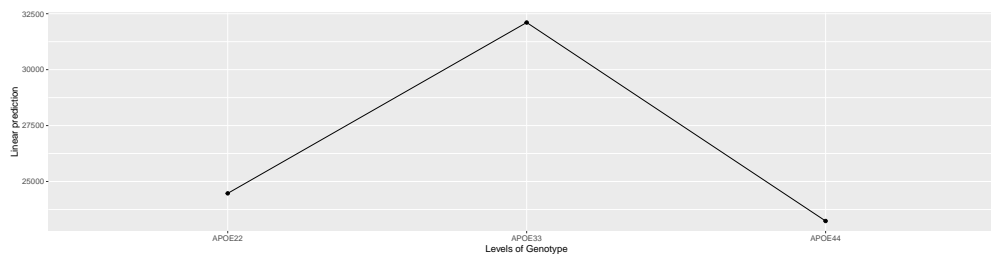
## Sex = female:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - APOE33  -13152 3465 23  -3.796  0.0026
## APOE22 - APOE44    953 3000 23   0.318  0.9461
## APOE33 - APOE44   14104 3465 23   4.071  0.0013
##
## Sex = male:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - 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')

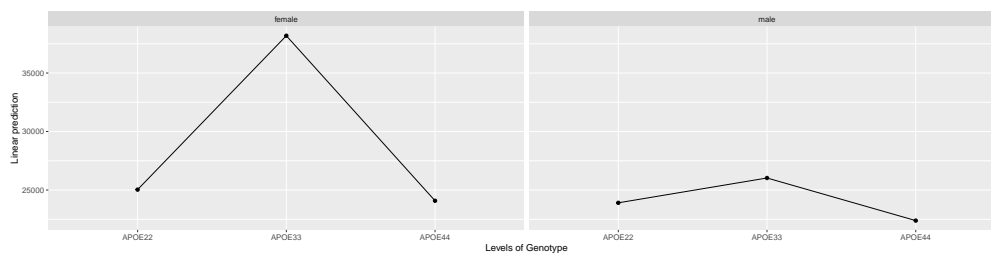
## [1] "ic DEG"

emmip(lm_ic_DEG, ~ Genotype)
```

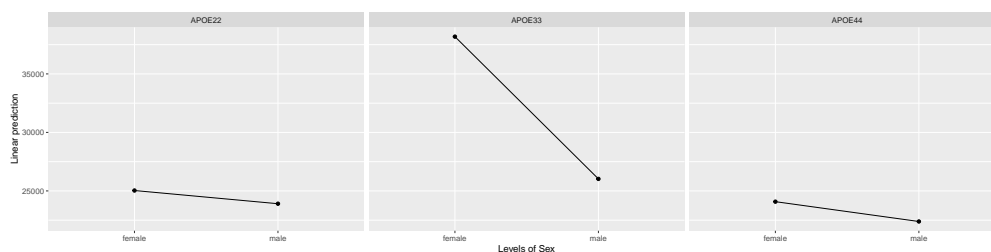
## NOTE: Results may be misleading due to involvement in interactions



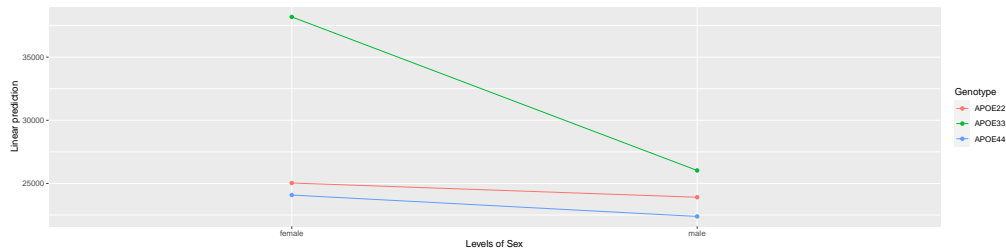
```
emmip(lm_ic_DEG, ~ Genotype | Sex )
```



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

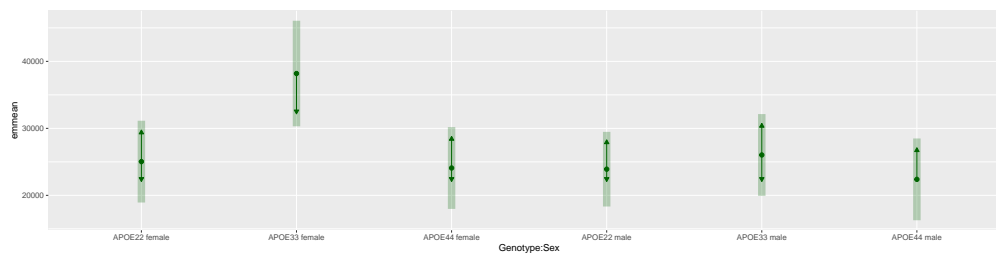


```
emmip(lm_ic_DEG, Genotype~ Sex )
```



```
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

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 0.00694 **
## APOE22 - APOE44 == 0   -2.640       8.684   -0.304 0.95027
## APOE33 - APOE44 == 0   31.215     10.028    3.113 0.01303 *
## ---
## 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)

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"

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
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  0.02728 *
## 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  0.99721
## APOE33 female - APOE44 female == 0  31.21513  10.02761   3.113  0.04847 *
## APOE33 female - APOE22 male == 0   37.87358   9.70919   3.901  0.00825 **
## APOE33 female - APOE33 male == 0   29.13373  10.02761   2.905  0.07502 .
```

```

## APOE33 female - APOE44 male == 0    37.80373    10.02761    3.770    0.01112 *
## APOE44 female - APOE22 male == 0     6.65845     8.31445     0.801    0.96416
## APOE44 female - APOE33 male == 0    -2.08140     8.68416    -0.240    0.99987
## APOE44 female - APOE44 male == 0     6.58860     8.68416     0.759    0.97149
## APOE22 male - APOE33 male == 0     -8.73985     8.31445    -1.051    0.89448
## 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 )))

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

##
##   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  -21.297      6.513  -3.270  0.00893 **
## APOE22 - APOE44 == 0   -1.355      6.011  -0.225  0.97238
## APOE33 - APOE44 == 0   19.943      6.633   3.007  0.01650 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)

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  0.00692 **
## APOE22 - APOE44 == 0   -2.640      8.684  -0.304  0.95028
## APOE33 - APOE44 == 0   31.215     10.028   3.113  0.01323 *
## ---
## 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)
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

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

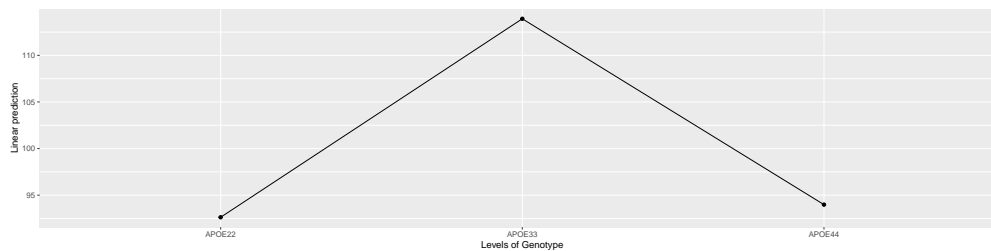
## Sex = female:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - APOE33 -33.8551 10.03 23  -3.376  0.0071
## APOE22 - APOE44  -2.6400  8.68 23  -0.304  0.9504
## APOE33 - APOE44  31.2151 10.03 23   3.113  0.0131
##
## Sex = male:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - 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')

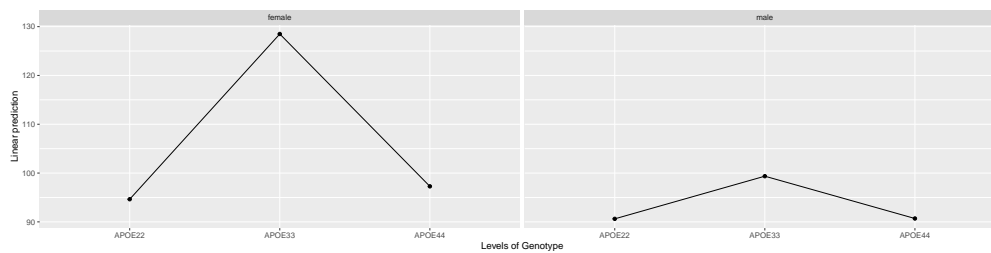
## [1] "ic CLUS"

emmip(lm_ic_CLUS, ~ Genotype)
```

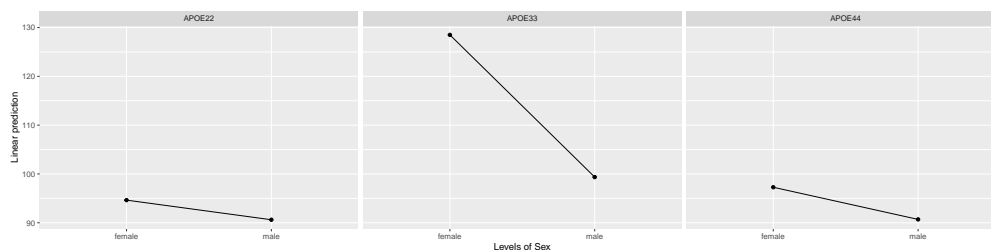
## NOTE: Results may be misleading due to involvement in interactions



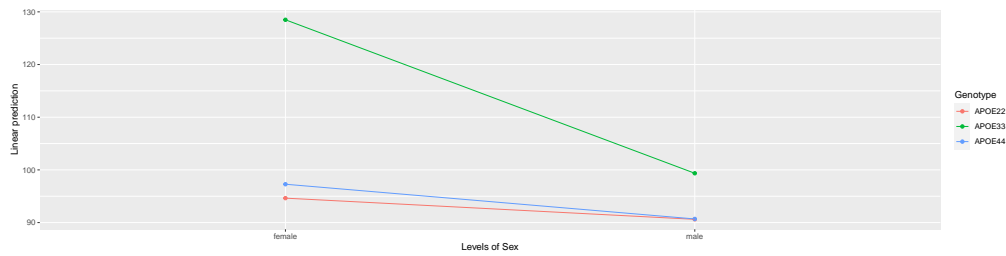
```
emmip(lm_ic_CLUS, ~ Genotype | Sex )
```



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

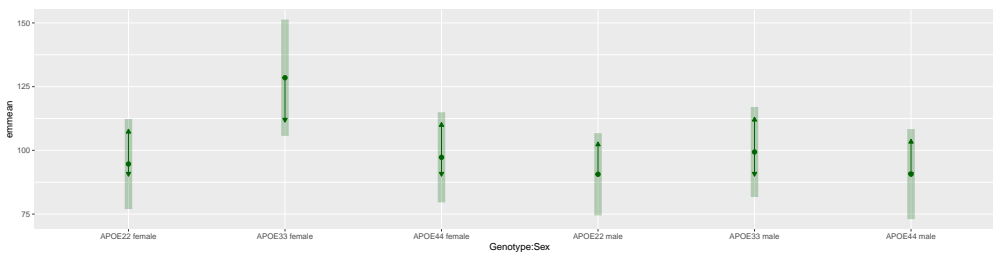


```
emmip(lm_ic_CLUS, Genotype~ Sex )
```



```
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)
```