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 fi

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`.
```
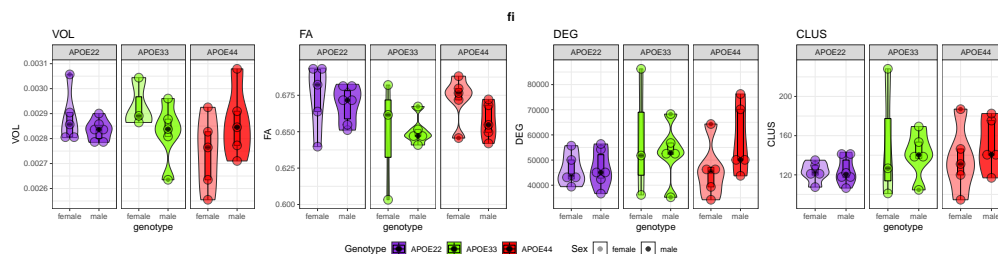


```
print('fi')
```

```
## [1] "fi"
```

```
lm_fi_VOL <- lm(fi ~ Genotype*Sex, geno_combined_VOL)
summary(lm_fi_VOL)
```

```
##
## Call:
## lm(formula = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Residuals:
##        Min         1Q     Median         3Q        Max
## -1.889e-04 -6.864e-05  3.110e-07  5.381e-05  2.159e-04
##
## Coefficients:
##                        Estimate Std. Error t value Pr(>|t|)
## (Intercept)           2.886e-03  5.090e-05  56.701   <2e-16 ***
## GenotypeAPOE33        4.727e-05  8.311e-05   0.569   0.5750
## GenotypeAPOE44       -1.444e-04  7.198e-05  -2.007   0.0567 .
## Sexmale              -5.189e-05  6.891e-05  -0.753   0.4591
## GenotypeAPOE33:Sexmale -5.738e-05 1.080e-04  -0.531   0.6002
## GenotypeAPOE44:Sexmale  1.740e-04 9.965e-05   1.746   0.0942 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.0001138 on 23 degrees of freedom
## Multiple R-squared:  0.2308, Adjusted R-squared:  0.06359
## F-statistic:  1.38 on 5 and 23 DF,  p-value: 0.2682
```

```r
lm_fi_VOL_f <- lm(fi ~ Genotype, combo_f_FA)
#summary(lm_fi_VOL_f)
lm_fi_VOL_m <- lm(fi ~ Genotype, combo_m_FA)
#summary(lm_fi_VOL_f)


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

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

```
## Analysis of Variance Table
##
## Response: fi
##              Df     Sum Sq    Mean Sq F value  Pr(>F)
## Genotype      2 2.2405e-08 1.1202e-08  0.8649 0.43433
## Sex           1 2.3900e-10 2.3900e-10  0.0184 0.89315
## Genotype:Sex  2 6.6743e-08 3.3371e-08  2.5766 0.09779 .
## Residuals    23 2.9789e-07 1.2952e-08
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```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 = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                       Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -4.727e-05  8.311e-05  -0.569   0.8373
## APOE22 - APOE44 == 0  1.444e-04  7.198e-05   2.007   0.1327
## APOE33 - APOE44 == 0  1.917e-04  8.311e-05   2.307   0.0744 .
## ---
## 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 = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                       Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  1.010e-05  6.891e-05   0.147    0.988
## APOE22 - APOE44 == 0 -2.953e-05  6.891e-05  -0.429    0.904
## APOE33 - APOE44 == 0 -3.964e-05  7.198e-05  -0.551    0.847
## (Adjusted p values reported -- single-step method)
```

```r
summary(glht(mydata.lm, emm(pairwise ~ Sex| Genotype)))
```

```
## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0 5.189e-05  6.891e-05   0.753    0.459
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0 1.093e-04  8.311e-05   1.315    0.202
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
```

```
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                       Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -1.221e-04  7.198e-05  -1.696    0.103
## (Adjusted p values reported -- single-step method)
```

```
sink()
#3333
```

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

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

```
joint_tests(ref_grid(lm_fi_VOL))
```

```
##  model term    df1 df2 F.ratio p.value
##  Genotype        2  23   1.117  0.3444
##  Sex             1  23   0.091  0.7660
##  Genotype:Sex    2  23   2.577  0.0978
```

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

```
## Sex = female:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   3.285  0.0556
##
## Sex = male:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   0.165  0.8486
```

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

```
## Genotype = APOE22:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.567  0.4591
##
## Genotype = APOE33:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   1.728  0.2016
##
## Genotype = APOE44:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   2.876  0.1034
```

```
'anova'
```

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

```
anova(lm_fi_VOL)
```

```
## Analysis of Variance Table
##
## Response: fi
##              Df     Sum Sq    Mean Sq F value  Pr(>F)
## Genotype      2 2.2405e-08 1.1202e-08  0.8649 0.43433
## Sex           1 2.3900e-10 2.3900e-10  0.0184 0.89315
## Genotype:Sex  2 6.6743e-08 3.3371e-08  2.5766 0.09779 .
```

```
## Residuals     23 2.9789e-07 1.2952e-08
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
#anova(lm_fi_VOL_f)
#anova(lm_fi_VOL_m)

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

```
##  contrast              estimate       SE df t.ratio p.value
##  APOE22 female effect  3.89e-05 4.68e-05 23   0.830  0.7688
##  APOE33 female effect  8.62e-05 5.78e-05 23   1.490  0.4497
##  APOE44 female effect -1.06e-04 4.68e-05 23  -2.253  0.2047
##  APOE22 male effect   -1.30e-05 4.37e-05 23  -0.297  0.7688
##  APOE33 male effect   -2.31e-05 4.68e-05 23  -0.493  0.7688
##  APOE44 male effect    1.65e-05 4.68e-05 23   0.353  0.7688
##
## P value adjustment: fdr method for 6 tests
```

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

```
## $`simple contrasts for Genotype`
## Sex = female:
##  contrast       estimate       SE df t.ratio p.value
##  APOE22 effect  3.24e-05 4.38e-05 23   0.739  0.4672
##  APOE33 effect  7.97e-05 4.99e-05 23   1.595  0.1866
##  APOE44 effect -1.12e-04 4.38e-05 23  -2.558  0.0528
##
## Sex = male:
##  contrast       estimate       SE df t.ratio p.value
##  APOE22 effect -6.48e-06 3.92e-05 23  -0.165  0.8701
##  APOE33 effect -1.66e-05 4.10e-05 23  -0.405  0.8701
##  APOE44 effect  2.31e-05 4.10e-05 23   0.563  0.8701
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
##  contrast       estimate       SE df t.ratio p.value
##  female effect  2.59e-05 3.45e-05 23   0.753  0.4591
##  male effect   -2.59e-05 3.45e-05 23  -0.753  0.4591
##
## Genotype = APOE33:
##  contrast       estimate       SE df t.ratio p.value
##  female effect  5.46e-05 4.16e-05 23   1.315  0.2016
##  male effect   -5.46e-05 4.16e-05 23  -1.315  0.2016
##
## Genotype = APOE44:
##  contrast       estimate       SE df t.ratio p.value
##  female effect -6.10e-05 3.60e-05 23  -1.696  0.1034
##  male effect    6.10e-05 3.60e-05 23   1.696  0.1034
##
## P value adjustment: fdr method for 2 tests
```

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

```
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                                    Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -4.727e-05  8.311e-05  -0.569    0.992
## APOE22 female - APOE44 female == 0  1.444e-04  7.198e-05   2.007    0.367
## APOE22 female - APOE22 male == 0    5.189e-05  6.891e-05   0.753    0.972
## APOE22 female - APOE33 male == 0    6.199e-05  7.198e-05   0.861    0.952
## APOE22 female - APOE44 male == 0    2.235e-05  7.198e-05   0.311    1.000
## APOE33 female - APOE44 female == 0  1.917e-04  8.311e-05   2.307    0.230
## APOE33 female - APOE22 male == 0    9.916e-05  8.047e-05   1.232    0.816
## APOE33 female - APOE33 male == 0    1.093e-04  8.311e-05   1.315    0.773
## APOE33 female - APOE44 male == 0    6.963e-05  8.311e-05   0.838    0.957
## APOE44 female - APOE22 male == 0   -9.254e-05  6.891e-05  -1.343    0.757
## APOE44 female - APOE33 male == 0   -8.244e-05  7.198e-05  -1.145    0.856
## APOE44 female - APOE44 male == 0   -1.221e-04  7.198e-05  -1.696    0.546
## APOE22 male - APOE33 male == 0      1.010e-05  6.891e-05   0.147    1.000
## APOE22 male - APOE44 male == 0     -2.953e-05  6.891e-05  -0.429    0.998
## APOE33 male - APOE44 male == 0     -3.964e-05  7.198e-05  -0.551    0.993
## (Adjusted p values reported -- single-step method)
```

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

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

```
## $`Sex = female`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -4.727e-05  8.311e-05  -0.569   0.8373
## APOE22 - APOE44 == 0  1.444e-04  7.198e-05   2.007   0.1325
## APOE33 - APOE44 == 0  1.917e-04  8.311e-05   2.307   0.0745 .
## ---
## 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 = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
```

```
## Linear Hypotheses:
##                     Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  1.010e-05  6.891e-05    0.147    0.988
## APOE22 - APOE44 == 0 -2.953e-05  6.891e-05   -0.429    0.904
## APOE33 - APOE44 == 0 -3.964e-05  7.198e-05   -0.551    0.847
## (Adjusted p values reported -- single-step method)
summary(glht(lm_fi_VOL, emm(pairwise ~ Sex | Genotype)))

## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                      Estimate Std. Error t value Pr(>|t|)
## female - male == 0 5.189e-05  6.891e-05    0.753    0.459
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                      Estimate Std. Error t value Pr(>|t|)
## female - male == 0 1.093e-04  8.311e-05    1.315    0.202
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##                       Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -1.221e-04  7.198e-05   -1.696    0.103
## (Adjusted p values reported -- single-step method)
mypairs<-pairs(fi_VOL.emm) #_consider save to file
pairs(fi_VOL.emm, by="Genotype")

## Genotype = APOE22:
##  contrast      estimate       SE df t.ratio p.value
##  female - male 5.19e-05 6.89e-05 23   0.753  0.4591
##
## Genotype = APOE33:
##  contrast      estimate       SE df t.ratio p.value
##  female - male 1.09e-04 8.31e-05 23   1.315  0.2016
##
```

```
## Genotype = APOE44:
##  contrast        estimate       SE df t.ratio p.value
##  female - male -1.22e-04 7.20e-05 23  -1.696  0.1034
```

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

```
## Sex = female:
##  contrast          estimate       SE df t.ratio p.value
##  APOE22 - APOE33 -4.73e-05 8.31e-05 23  -0.569  0.8379
##  APOE22 - APOE44  1.44e-04 7.20e-05 23   2.007  0.1332
##  APOE33 - APOE44  1.92e-04 8.31e-05 23   2.307  0.0749
##
## Sex = male:
##  contrast          estimate       SE df t.ratio p.value
##  APOE22 - APOE33  1.01e-05 6.89e-05 23   0.147  0.9882
##  APOE22 - APOE44 -2.95e-05 6.89e-05 23  -0.429  0.9041
##  APOE33 - APOE44 -3.96e-05 7.20e-05 23  -0.551  0.8472
##
## P value adjustment: tukey method for comparing a family of 3 estimates
```
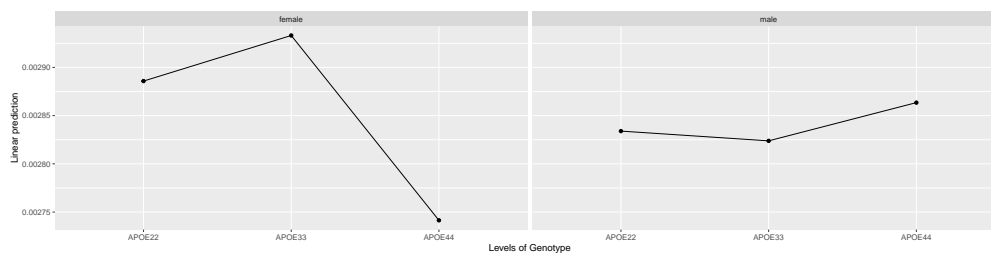
```r
print('fi VOL')
```
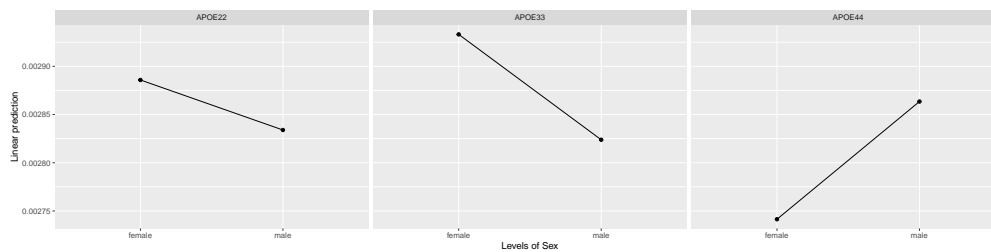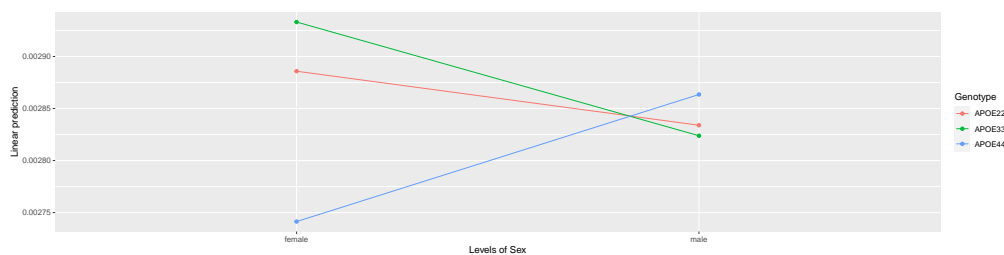
```
## [1] "fi VOL"
```

```r
emmip(lm_fi_VOL, ~ Genotype | Sex )
```



```r
emmip(lm_fi_VOL, ~ Sex | Genotype )
```
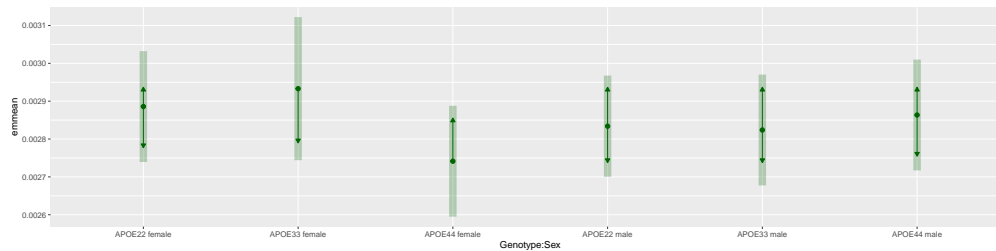


```r
emmip(lm_fi_VOL, Genotype~ Sex  )
```



```r
sink()
```

8

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



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

```
'simple stats'
```

[1] "simple stats"

```
print('fi')
```

[1] "fi"

```
lm_fi_FA <- lm(fi ~ Genotype*Sex, geno_combined_FA)
summary(lm_fi_FA)
```

```
##
## Call:
## lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Residuals:
##       Min        1Q    Median        3Q       Max
## -0.045696 -0.009889  0.002339  0.012594  0.033102
##
## Coefficients:
##                       Estimate Std. Error t value Pr(>|t|)
## (Intercept)           0.674432   0.008517  79.184   <2e-16 ***
## GenotypeAPOE33       -0.025466   0.013909  -1.831   0.0801 .
## GenotypeAPOE44       -0.002072   0.012045  -0.172   0.8649
## Sexmale              -0.005803   0.011532  -0.503   0.6196
## GenotypeAPOE33:Sexmale  0.007586   0.018068   0.420   0.6785
## GenotypeAPOE44:Sexmale -0.009255   0.016676  -0.555   0.5843
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.01905 on 23 degrees of freedom
## Multiple R-squared:  0.2502, Adjusted R-squared:  0.08722
## F-statistic: 1.535 on 5 and 23 DF,  p-value: 0.2181
```

```
lm_fi_FA_f <- lm(fi ~ Genotype, combo_f_FA)
#summary(lm_fi_FA_f)
lm_fi_FA_m <- lm(fi ~ Genotype, combo_m_FA)
#summary(lm_fi_FA_f)


#33333
```

```
sink(paste(outpath, "fi_FA_SimpleModels.txt"))
mydata.lm <- lm(fi ~ Genotype*Sex, data = geno_combined_FA)
anova(mydata.lm)
```

```
## Analysis of Variance Table
##
## Response: fi
##              Df    Sum Sq    Mean Sq F value  Pr(>F)
## Genotype      2 0.0021195 0.00105977  2.9217 0.07402 .
## Sex           1 0.0003538 0.00035376  0.9753 0.33364
## Genotype:Sex  2 0.0003108 0.00015541  0.4285 0.65660
## Residuals    23 0.0083426 0.00036272
## ---
## 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 = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.025466   0.013909   1.831    0.181
## APOE22 - APOE44 == 0  0.002072   0.012045   0.172    0.984
## APOE33 - APOE44 == 0 -0.023394   0.013909  -1.682    0.232
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.017881   0.011532   1.550    0.287
## APOE22 - APOE44 == 0  0.011327   0.011532   0.982    0.595
## APOE33 - APOE44 == 0 -0.006554   0.012045  -0.544    0.850
## (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 = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                Estimate Std. Error t value Pr(>|t|)
## female - male == 0 0.005803   0.011532   0.503     0.62
```

```
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                     Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.001783   0.013909  -0.128    0.899
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0  0.01506    0.01205    1.25    0.224
## (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, "fi_FA_SimpleStats.txt",sep=''))
'omnibus testing'
```

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

```
joint_tests(ref_grid(lm_fi_FA))
```

```
##  model term    df1 df2 F.ratio  p.value
##  Genotype        2  23   2.918   0.0742
##  Sex             1  23   0.772   0.3888
##  Genotype:Sex    2  23   0.428   0.6566
```

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

```
## Sex = female:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   1.913  0.1703
##
## Sex = male:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   1.250  0.3051
```

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

```
## Genotype = APOE22:
```

```
##  model term df1 df2 F.ratio p.value
##  Sex           1  23   0.253  0.6196
##
## Genotype = APOE33:
##  model term df1 df2 F.ratio p.value
##  Sex           1  23   0.016  0.8991
##
## Genotype = APOE44:
##  model term df1 df2 F.ratio p.value
##  Sex           1  23   1.563  0.2238
```

```
'anova'
```

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

```
anova(lm_fi_FA)
```

```
## Analysis of Variance Table
##
## Response: fi
##               Df    Sum Sq    Mean Sq F value  Pr(>F)
## Genotype       2 0.0021195 0.00105977  2.9217 0.07402 .
## Sex            1 0.0003538 0.00035376  0.9753 0.33364
## Genotype:Sex   2 0.0003108 0.00015541  0.4285 0.65660
## Residuals     23 0.0083426 0.00036272
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
#anova(lm_fi_FA_f)
#anova(lm_fi_FA_m)

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

```
##  contrast              estimate      SE df t.ratio p.value
##  APOE22 female effect  0.01236 0.00784 23   1.576  0.3036
##  APOE33 female effect -0.01311 0.00968 23  -1.354  0.3036
##  APOE44 female effect  0.01029 0.00784 23   1.312  0.3036
##  APOE22 male effect    0.00656 0.00731 23   0.897  0.4547
##  APOE33 male effect   -0.01132 0.00784 23  -1.444  0.3036
##  APOE44 male effect   -0.00477 0.00784 23  -0.608  0.5488
##
## P value adjustment: fdr method for 6 tests
```

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

```
## $`simple contrasts for Genotype`
## Sex = female:
##  contrast       estimate      SE df t.ratio p.value
##  APOE22 effect   0.00918 0.00733 23   1.252  0.3346
##  APOE33 effect  -0.01629 0.00836 23  -1.949  0.1909
##  APOE44 effect   0.00711 0.00733 23   0.970  0.3423
##
## Sex = male:
##  contrast       estimate      SE df t.ratio p.value
##  APOE22 effect   0.00974 0.00656 23   1.485  0.3705
```

```
##  APOE33 effect -0.00814 0.00686 23  -1.188  0.3705
##  APOE44 effect -0.00159 0.00686 23  -0.232  0.8186
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
##  contrast         estimate      SE df t.ratio p.value
##  female effect  0.002901 0.00577 23   0.503  0.6196
##  male effect   -0.002901 0.00577 23  -0.503  0.6196
##
## Genotype = APOE33:
##  contrast         estimate      SE df t.ratio p.value
##  female effect -0.000892 0.00695 23  -0.128  0.8991
##  male effect    0.000892 0.00695 23   0.128  0.8991
##
## Genotype = APOE44:
##  contrast         estimate      SE df t.ratio p.value
##  female effect  0.007529 0.00602 23   1.250  0.2238
##  male effect   -0.007529 0.00602 23  -1.250  0.2238
##
## P value adjustment: fdr method for 2 tests
```

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

```
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                                 Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0  0.025466   0.013909   1.831    0.465
## APOE22 female - APOE44 female == 0  0.002072   0.012045   0.172    1.000
## APOE22 female - APOE22 male == 0    0.005803   0.011532   0.503    0.996
## APOE22 female - APOE33 male == 0    0.023683   0.012045   1.966    0.389
## APOE22 female - APOE44 male == 0    0.017129   0.012045   1.422    0.712
## APOE33 female - APOE44 female == 0 -0.023394   0.013909  -1.682    0.554
## APOE33 female - APOE22 male == 0   -0.019664   0.013467  -1.460    0.690
## APOE33 female - APOE33 male == 0   -0.001783   0.013909  -0.128    1.000
## APOE33 female - APOE44 male == 0   -0.008337   0.013909  -0.599    0.990
## APOE44 female - APOE22 male == 0    0.003731   0.011532   0.323    0.999
## APOE44 female - APOE33 male == 0    0.021611   0.012045   1.794    0.487
## APOE44 female - APOE44 male == 0    0.015057   0.012045   1.250    0.807
## APOE22 male - APOE33 male == 0      0.017881   0.011532   1.550    0.635
## APOE22 male - APOE44 male == 0      0.011327   0.011532   0.982    0.918
## APOE33 male - APOE44 male == 0     -0.006554   0.012045  -0.544    0.994
## (Adjusted p values reported -- single-step method)
```

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

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

```
## $`Sex = female`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.025466   0.013909   1.831    0.181
## APOE22 - APOE44 == 0  0.002072   0.012045   0.172    0.984
## APOE33 - APOE44 == 0 -0.023394   0.013909  -1.682    0.232
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.017881   0.011532   1.550    0.287
## APOE22 - APOE44 == 0  0.011327   0.011532   0.982    0.595
## APOE33 - APOE44 == 0 -0.006554   0.012045  -0.544    0.850
## (Adjusted p values reported -- single-step method)
```

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

```
## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                 Estimate Std. Error t value Pr(>|t|)
## female - male == 0 0.005803   0.011532   0.503    0.62
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.001783   0.013909  -0.128    0.899
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
```

```
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0  0.01506    0.01205    1.25    0.224
## (Adjusted p values reported -- single-step method)
```

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

```
## Genotype = APOE22:
##  contrast        estimate      SE df t.ratio p.value
##  female - male   0.00580 0.0115 23   0.503  0.6196
##
## Genotype = APOE33:
##  contrast        estimate      SE df t.ratio p.value
##  female - male  -0.00178 0.0139 23  -0.128  0.8991
##
## Genotype = APOE44:
##  contrast        estimate      SE df t.ratio p.value
##  female - male   0.01506 0.0120 23   1.250  0.2238
```

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

```
## Sex = female:
##  contrast        estimate      SE df t.ratio p.value
##  APOE22 - APOE33  0.02547 0.0139 23   1.831  0.1820
##  APOE22 - APOE44  0.00207 0.0120 23   0.172  0.9838
##  APOE33 - APOE44 -0.02339 0.0139 23  -1.682  0.2334
##
## Sex = male:
##  contrast        estimate      SE df t.ratio p.value
##  APOE22 - APOE33  0.01788 0.0115 23   1.550  0.2869
##  APOE22 - APOE44  0.01133 0.0115 23   0.982  0.5952
##  APOE33 - APOE44 -0.00655 0.0120 23  -0.544  0.8505
##
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```r
print('fi FA')
```

```
## [1] "fi FA"
```
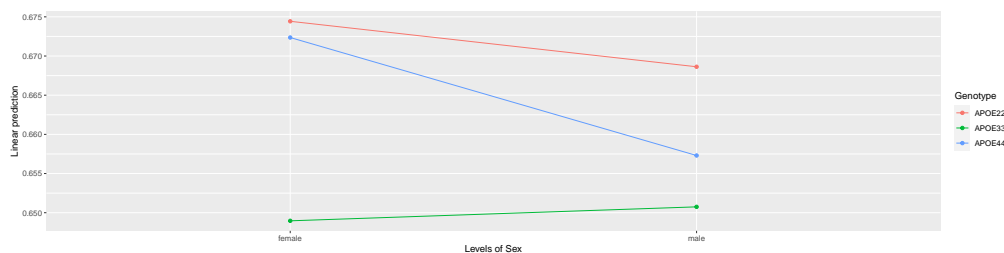
```r
emmip(lm_fi_FA, ~ Genotype | Sex )
```
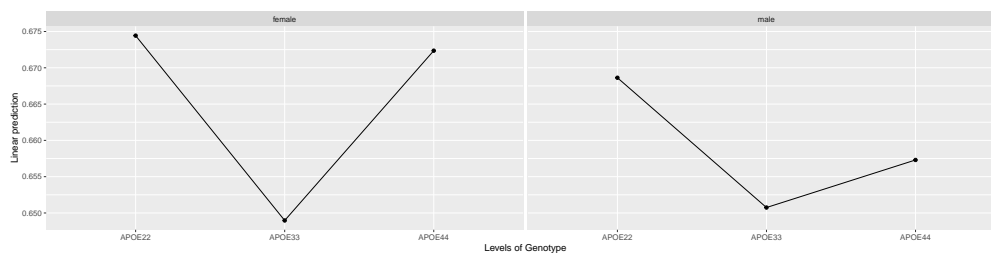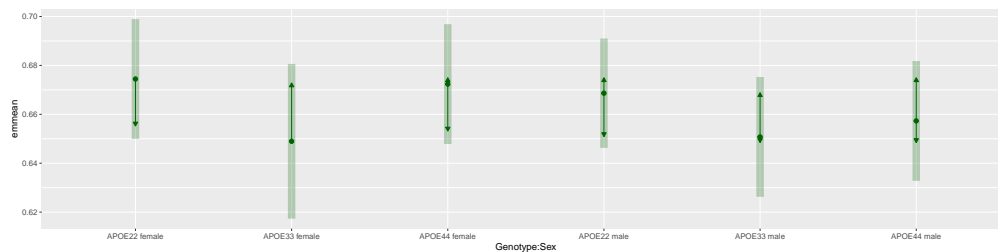


```r
emmip(lm_fi_FA, ~ Sex | Genotype )
```
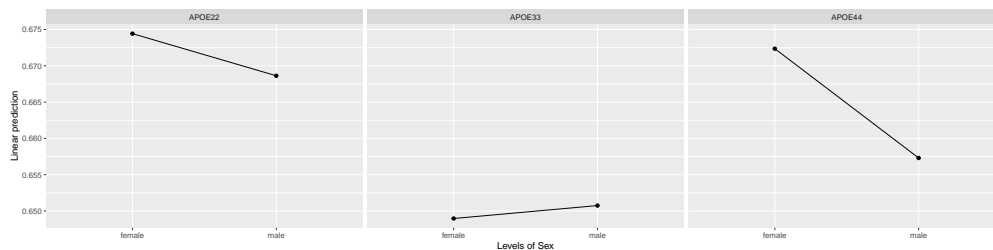
```
emmip(lm_fi_FA, Genotype~ Sex  )
```



```
sink()
```

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



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

```
'simple stats'
```

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

```
print('fi')
```

```
## [1] "fi"
```

```
lm_fi_DEG <- lm(fi ~ Genotype*Sex, geno_combined_DEG)
summary(lm_fi_DEG)
```

```
##
## Call:
## lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -21929.3  -6854.2   -855.8   7591.3  28195.7
##
## Coefficients:
##                    Estimate Std. Error t value Pr(>|t|)
## (Intercept)          46291.2     5639.7   8.208 2.75e-08 ***
## GenotypeAPOE33       11781.1     9209.5   1.279    0.214
```

```
## GenotypeAPOE44          -198.8      7975.7  -0.025     0.980
## Sexmale                  340.5      7636.1   0.045     0.965
## GenotypeAPOE33:Sexmale  -5351.0    11963.5  -0.447     0.659
## GenotypeAPOE44:Sexmale  11634.5    11041.8   1.054     0.303
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 12610 on 23 degrees of freedom
## Multiple R-squared:  0.173,  Adjusted R-squared:  -0.006832
## F-statistic: 0.962 on 5 and 23 DF,  p-value: 0.4612
```

```
lm_fi_DEG_f <- lm(fi ~ Genotype, combo_f_FA)
#summary(lm_fi_DEG_f)
lm_fi_DEG_m <- lm(fi ~ Genotype, combo_m_FA)
#summary(lm_fi_DEG_f)

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

```
## Analysis of Variance Table
##
## Response: fi
##             Df     Sum Sq    Mean Sq F value Pr(>F)
## Genotype     2  359036685  179518342  1.1288 0.3407
## Sex          1   64911127   64911127  0.4082 0.5292
## Genotype:Sex 2  340979282  170489641  1.0721 0.3588
## Residuals   23 3657650816  159028296
```

```
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 = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -11781.1     9209.5  -1.279    0.420
## APOE22 - APOE44 == 0    198.8     7975.7   0.025    1.000
## APOE33 - APOE44 == 0  11979.9     9209.5   1.301    0.408
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0    -6430       7636  -0.842    0.681
```

```
## APOE22 - APOE44 == 0   -11436       7636  -1.498     0.310
## APOE33 - APOE44 == 0    -5006       7976  -0.628     0.807
## (Adjusted p values reported -- single-step method)
```

```r
summary(glht(mydata.lm, emm(pairwise ~ Sex| Genotype)))
```

```
## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -340.5     7636.1  -0.045    0.965
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0     5010       9210   0.544    0.592
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -11975       7976  -1.501    0.147
## (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, "fi_DEG_SimpleStats.txt",sep=''))
'omnibus testing'
```

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

```r
joint_tests(ref_grid(lm_fi_DEG))
```

```
##  model term   df1 df2 F.ratio p.value
##  Genotype       2  23   1.233  0.3100
```

```
## Sex           1  23   0.258  0.6163
## Genotype:Sex  2  23   1.072  0.3588
```

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

```
## Sex = female:
##  model term df1 df2 F.ratio p.value
##  Genotype    2  23   1.024  0.3748
##
## Sex = male:
##  model term df1 df2 F.ratio p.value
##  Genotype    2  23   1.138  0.3379
```

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

```
## Genotype = APOE22:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.002  0.9648
##
## Genotype = APOE33:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.296  0.5916
##
## Genotype = APOE44:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   2.254  0.1468
```

```
'anova'
```

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

```
anova(lm_fi_DEG)
```

```
## Analysis of Variance Table
##
## Response: fi
##             Df     Sum Sq   Mean Sq F value Pr(>F)
## Genotype     2  359036685 179518342  1.1288 0.3407
## Sex          1   64911127  64911127  0.4082 0.5292
## Genotype:Sex 2  340979282 170489641  1.0721 0.3588
## Residuals   23 3657650816 159028296
```

```
#anova(lm_fi_DEG_f)
#anova(lm_fi_DEG_m)

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

```
##  contrast              estimate   SE df t.ratio p.value
##  APOE22 female effect     -5078 5191 23  -0.978  0.4057
##  APOE33 female effect      6703 6410 23   1.046  0.4057
##  APOE44 female effect     -5277 5191 23  -1.017  0.4057
##  APOE22 male effect       -4738 4839 23  -0.979  0.4057
##  APOE33 male effect        1692 5191 23   0.326  0.7474
##  APOE44 male effect        6698 5191 23   1.290  0.4057
##
## P value adjustment: fdr method for 6 tests
```

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

```
## $`simple contrasts for Genotype`
## Sex = female:
##  contrast       estimate    SE df t.ratio p.value
##  APOE22 effect     -3861  4854 23  -0.795  0.4345
##  APOE33 effect      7920  5534 23   1.431  0.4345
##  APOE44 effect     -4060  4854 23  -0.836  0.4345
##
## Sex = male:
##  contrast       estimate    SE df t.ratio p.value
##  APOE22 effect     -5955  4341 23  -1.372  0.3595
##  APOE33 effect       475  4540 23   0.105  0.9176
##  APOE44 effect      5480  4540 23   1.207  0.3595
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
##  contrast       estimate    SE df t.ratio p.value
##  female effect      -170  3818 23  -0.045  0.9648
##  male effect         170  3818 23   0.045  0.9648
##
## Genotype = APOE33:
##  contrast       estimate    SE df t.ratio p.value
##  female effect      2505  4605 23   0.544  0.5916
##  male effect       -2505  4605 23  -0.544  0.5916
##
## Genotype = APOE44:
##  contrast       estimate    SE df t.ratio p.value
##  female effect     -5988  3988 23  -1.501  0.1468
##  male effect        5988  3988 23   1.501  0.1468
##
## P value adjustment: fdr method for 2 tests
```

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

```
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                                 Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -11781.133   9209.511  -1.279    0.792
## APOE22 female - APOE44 female == 0    198.800   7975.670   0.025    1.000
## APOE22 female - APOE22 male == 0     -340.467   7636.123  -0.045    1.000
## APOE22 female - APOE33 male == 0    -6770.600   7975.670  -0.849    0.954
## APOE22 female - APOE44 male == 0   -11776.200   7975.670  -1.477    0.680
## APOE33 female - APOE44 female == 0  11979.933   9209.511   1.301    0.780
## APOE33 female - APOE22 male == 0    11440.667   8917.071   1.283    0.790
## APOE33 female - APOE33 male == 0     5010.533   9209.511   0.544    0.994
## APOE33 female - APOE44 male == 0        4.933   9209.511   0.001    1.000
```

```
## APOE44 female - APOE22 male == 0      -539.267    7636.123   -0.071    1.000
## APOE44 female - APOE33 male == 0     -6969.400    7975.670   -0.874    0.949
## APOE44 female - APOE44 male == 0    -11975.000    7975.670   -1.501    0.665
## APOE22 male - APOE33 male == 0       -6430.133    7636.123   -0.842    0.956
## APOE22 male - APOE44 male == 0      -11435.733    7636.123   -1.498    0.667
## APOE33 male - APOE44 male == 0       -5005.600    7975.670   -0.628    0.988
## (Adjusted p values reported -- single-step method)
```

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

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

```
## $`Sex = female`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -11781.1     9209.5  -1.279    0.420
## APOE22 - APOE44 == 0    198.8     7975.7   0.025    1.000
## APOE33 - APOE44 == 0  11979.9     9209.5   1.301    0.408
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                    Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0    -6430       7636  -0.842    0.681
## APOE22 - APOE44 == 0   -11436       7636  -1.498    0.310
## APOE33 - APOE44 == 0    -5006       7976  -0.628    0.807
## (Adjusted p values reported -- single-step method)
```

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

```
## $`Genotype = APOE22`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                 Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -340.5     7636.1  -0.045    0.965
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
```

```
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0     5010       9210   0.544    0.592
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## female - male == 0    -11975       7976  -1.501    0.147
## (Adjusted p values reported -- single-step method)
```

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

```
## Genotype = APOE22:
##  contrast       estimate   SE df t.ratio p.value
##  female - male      -340 7636 23  -0.045  0.9648
##
## Genotype = APOE33:
##  contrast       estimate   SE df t.ratio p.value
##  female - male      5011 9210 23   0.544  0.5916
##
## Genotype = APOE44:
##  contrast       estimate   SE df t.ratio p.value
##  female - male    -11975 7976 23  -1.501  0.1468
```

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

```
## Sex = female:
##  contrast         estimate   SE df t.ratio p.value
##  APOE22 - APOE33   -11781 9210 23  -1.279  0.4207
##  APOE22 - APOE44      199 7976 23   0.025  0.9997
##  APOE33 - APOE44    11980 9210 23   1.301  0.4090
##
## Sex = male:
##  contrast         estimate   SE df t.ratio p.value
##  APOE22 - APOE33    -6430 7636 23  -0.842  0.6812
##  APOE22 - APOE44   -11436 7636 23  -1.498  0.3106
##  APOE33 - APOE44    -5006 7976 23  -0.628  0.8066
##
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```
print('fi DEG')
```
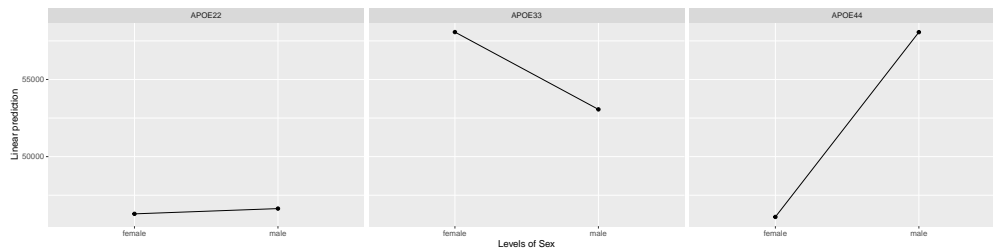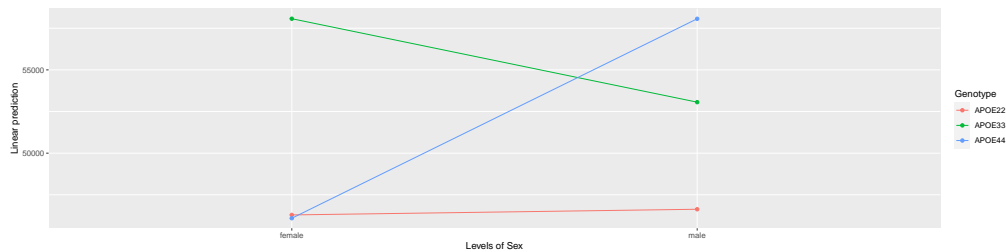
```
## [1] "fi DEG"
```

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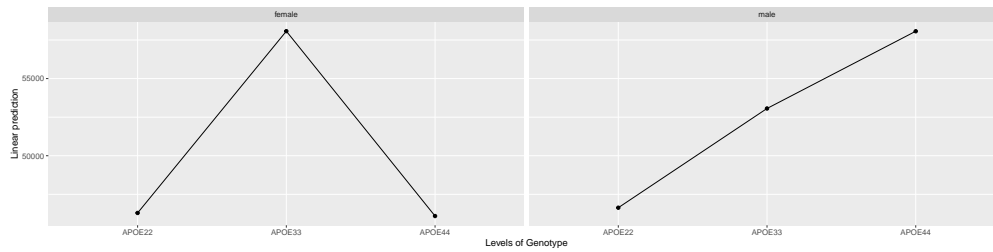


```
emmip(lm_fi_DEG, ~ Sex | Genotype )
```
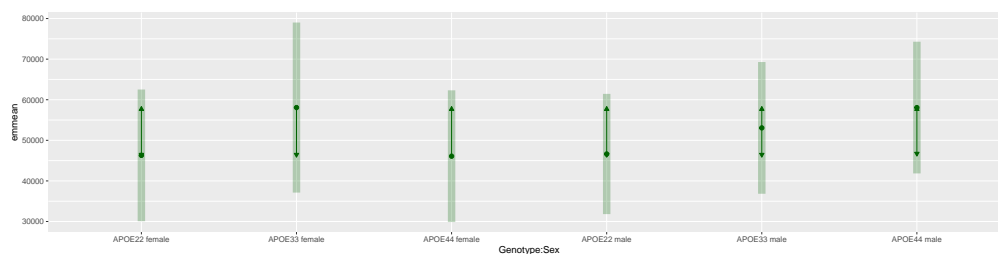


```
emmip(lm_fi_DEG, Genotype~ Sex  )
```



```
sink()
```

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



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

```
'simple stats'
```

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

```
print('fi')
```

```
## [1] "fi"
```

```
lm_fi_CLUS <- lm(fi ~ Genotype*Sex, geno_combined_CLUS)
summary(lm_fi_CLUS)
```

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```
## 
## Call:
## lm(formula = fi ~ Genotype * Sex, data = geno_combined_CLUS)
## 
## Residuals:
##     Min      1Q  Median      3Q     Max
## -50.937 -15.302  -3.082  12.532  76.223
## 
## Coefficients:
##                       Estimate Std. Error t value Pr(>|t|)
## (Intercept)            122.792     13.335   9.208 3.54e-09 ***
## GenotypeAPOE33          29.185     21.776   1.340    0.193
## GenotypeAPOE44          13.000     18.858   0.689    0.497
## Sexmale                  1.635     18.055   0.091    0.929
## GenotypeAPOE33:Sexmale -12.713     28.287  -0.449    0.657
## GenotypeAPOE44:Sexmale  13.757     26.108   0.527    0.603
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## 
## Residual standard error: 29.82 on 23 degrees of freedom
## Multiple R-squared:  0.1536, Adjusted R-squared:  -0.03045
## F-statistic: 0.8345 on 5 and 23 DF,  p-value: 0.5387
```

```r
lm_fi_CLUS_f <- lm(fi ~ Genotype, combo_f_FA)
#summary(lm_fi_CLUS_f)
lm_fi_CLUS_m <- lm(fi ~ Genotype, combo_m_FA)
#summary(lm_fi_CLUS_f)

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

```
## Analysis of Variance Table
## 
## Response: fi
##              Df  Sum Sq Mean Sq F value Pr(>F)
## Genotype      2  2880.1 1440.06  1.6197 0.2197
## Sex           1    69.2   69.17  0.0778 0.7828
## Genotype:Sex  2   760.5  380.25  0.4277 0.6571
## Residuals    23 20448.9  889.08
```

```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 = fi ~ Genotype * Sex, data = geno_combined_CLUS)
## 
## Linear Hypotheses:
##                   Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -29.18      21.78  -1.340    0.387
## APOE22 - APOE44 == 0  -13.00      18.86  -0.689    0.771
## APOE33 - APOE44 == 0   16.18      21.78   0.743    0.740
```

```
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                     Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -16.47      18.06  -0.912    0.638
## APOE22 - APOE44 == 0   -26.76      18.06  -1.482    0.318
## APOE33 - APOE44 == 0   -10.29      18.86  -0.545    0.850
## (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 = fi ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -1.635     18.055  -0.091    0.929
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0    11.08      21.78   0.509    0.616
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##    Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -15.39      18.86  -0.816    0.423
## (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, "fi_CLUS_SimpleStats.txt",sep=''))
'omnibus testing'
```

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

```
joint_tests(ref_grid(lm_fi_CLUS))
```

```
##  model term    df1 df2 F.ratio  p.value
##  Genotype        2  23   1.710   0.2030
##  Sex             1  23   0.031   0.8627
##  Genotype:Sex    2  23   0.428   0.6571
```

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

```
## Sex = female:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   0.905  0.4183
##
## Sex = male:
##  model term df1 df2 F.ratio p.value
##  Genotype     2  23   1.134  0.3391
```

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

```
## Genotype = APOE22:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.008  0.9286
##
## Genotype = APOE33:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.259  0.6158
##
## Genotype = APOE44:
##  model term df1 df2 F.ratio p.value
##  Sex          1  23   0.666  0.4228
```

```
'anova'
```

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

```
anova(lm_fi_CLUS)
```

```
## Analysis of Variance Table
##
## Response: fi
##              Df  Sum Sq Mean Sq F value Pr(>F)
## Genotype      2  2880.1 1440.06  1.6197 0.2197
## Sex           1    69.2   69.17  0.0778 0.7828
## Genotype:Sex  2   760.5  380.25  0.4277 0.6571
## Residuals    23 20448.9  889.08
```

```
#anova(lm_fi_CLUS_f)
#anova(lm_fi_CLUS_m)

#post hoc comparison
```

```
fi_CLUS.emm <- emmeans(lm_fi_CLUS , ~ Genotype | Sex, adjust = "sidak")
contrast(fi_CLUS.emm, simple = c("Genotype", "Sex")) #FDR
```

```
##  contrast              estimate   SE df t.ratio p.value
##  APOE22 female effect    -15.05 12.3 23  -1.226  0.5412
##  APOE33 female effect     14.13 15.2 23   0.932  0.5412
##  APOE44 female effect     -2.05 12.3 23  -0.167  0.8687
##  APOE22 male effect      -13.42 11.4 23  -1.173  0.5412
##  APOE33 male effect        3.05 12.3 23   0.249  0.8687
##  APOE44 male effect       13.34 12.3 23   1.087  0.5412
##
## P value adjustment: fdr method for 6 tests
```

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

```
## $`simple contrasts for Genotype`
## Sex = female:
##  contrast      estimate   SE df t.ratio p.value
##  APOE22 effect   -14.06 11.5 23  -1.225  0.3895
##  APOE33 effect    15.12 13.1 23   1.156  0.3895
##  APOE44 effect    -1.06 11.5 23  -0.092  0.9271
##
## Sex = male:
##  contrast      estimate   SE df t.ratio p.value
##  APOE22 effect   -14.41 10.3 23  -1.404  0.3928
##  APOE33 effect     2.06 10.7 23   0.192  0.8494
##  APOE44 effect    12.35 10.7 23   1.150  0.3928
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
##  contrast     estimate   SE df t.ratio p.value
##  female effect  -0.817 9.03 23  -0.091  0.9286
##  male effect     0.817 9.03 23   0.091  0.9286
##
## Genotype = APOE33:
##  contrast     estimate    SE df t.ratio p.value
##  female effect   5.539 10.89 23   0.509  0.6158
##  male effect    -5.539 10.89 23  -0.509  0.6158
##
## Genotype = APOE44:
##  contrast     estimate   SE df t.ratio p.value
##  female effect  -7.696 9.43 23  -0.816  0.4228
##  male effect     7.696 9.43 23   0.816  0.4228
##
## P value adjustment: fdr method for 2 tests
```

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

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

```
##
## Linear Hypotheses:
##                                Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -29.1847    21.7756  -1.340    0.759
## APOE22 female - APOE44 female == 0 -13.0004    18.8582  -0.689    0.981
## APOE22 female - APOE22 male == 0    -1.6347    18.0554  -0.091    1.000
## APOE22 female - APOE33 male == 0   -18.1060    18.8582  -0.960    0.925
## APOE22 female - APOE44 male == 0   -28.3920    18.8582  -1.506    0.663
## APOE33 female - APOE44 female == 0  16.1843    21.7756   0.743    0.974
## APOE33 female - APOE22 male == 0    27.5500    21.0841   1.307    0.777
## APOE33 female - APOE33 male == 0    11.0787    21.7756   0.509    0.995
## APOE33 female - APOE44 male == 0     0.7927    21.7756   0.036    1.000
## APOE44 female - APOE22 male == 0    11.3657    18.0554   0.629    0.987
## APOE44 female - APOE33 male == 0    -5.1056    18.8582  -0.271    1.000
## APOE44 female - APOE44 male == 0   -15.3916    18.8582  -0.816    0.961
## APOE22 male - APOE33 male == 0     -16.4713    18.0554  -0.912    0.939
## APOE22 male - APOE44 male == 0     -26.7573    18.0554  -1.482    0.677
## APOE33 male - APOE44 male == 0     -10.2860    18.8582  -0.545    0.993
## (Adjusted p values reported -- single-step method)
```

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

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

```
## $`Sex = female`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                 Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -29.18      21.78  -1.340    0.387
## APOE22 - APOE44 == 0   -13.00      18.86  -0.689    0.771
## APOE33 - APOE44 == 0    16.18      21.78   0.743    0.740
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                 Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -16.47      18.06  -0.912    0.638
## APOE22 - APOE44 == 0   -26.76      18.06  -1.482    0.318
## APOE33 - APOE44 == 0   -10.29      18.86  -0.545    0.850
## (Adjusted p values reported -- single-step method)
```

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

```
## $`Genotype = APOE22`
```

```
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -1.635     18.055  -0.091    0.929
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0    11.08      21.78   0.509    0.616
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fi ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##                  Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -15.39      18.86  -0.816    0.423
## (Adjusted p values reported -- single-step method)
```

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

```
## Genotype = APOE22:
##  contrast        estimate   SE df t.ratio p.value
##  female - male     -1.63 18.1 23  -0.091  0.9286
##
## Genotype = APOE33:
##  contrast        estimate   SE df t.ratio p.value
##  female - male     11.08 21.8 23   0.509  0.6158
##
## Genotype = APOE44:
##  contrast        estimate   SE df t.ratio p.value
##  female - male    -15.39 18.9 23  -0.816  0.4228
```

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

```
## Sex = female:
##  contrast          estimate   SE df t.ratio p.value
##  APOE22 - APOE33     -29.2 21.8 23  -1.340  0.3881
##  APOE22 - APOE44     -13.0 18.9 23  -0.689  0.7720
```
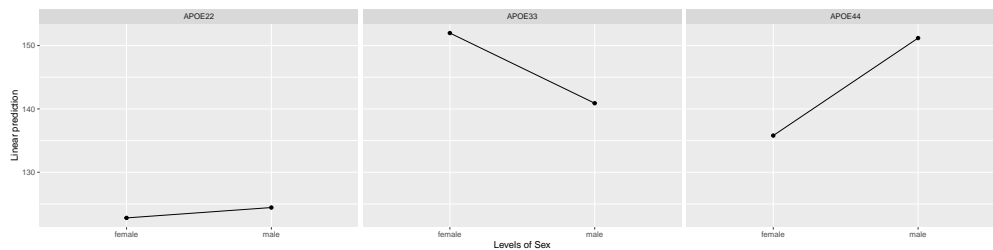
```
##  APOE33 - APOE44     16.2 21.8 23   0.743  0.7407
##
## Sex = male:
##  contrast        estimate   SE df t.ratio p.value
##  APOE22 - APOE33    -16.5 18.1 23  -0.912  0.6382
##  APOE22 - APOE44    -26.8 18.1 23  -1.482  0.3178
##  APOE33 - APOE44    -10.3 18.9 23  -0.545  0.8498
##
## P value adjustment: tukey method for comparing a family of 3 estimates
```

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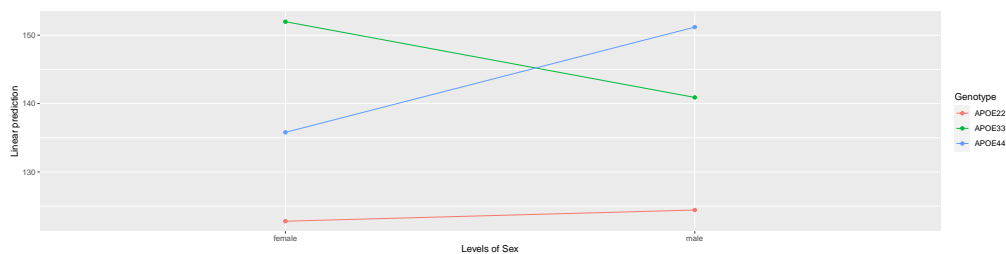
```
## [1] "fi CLUS"
```

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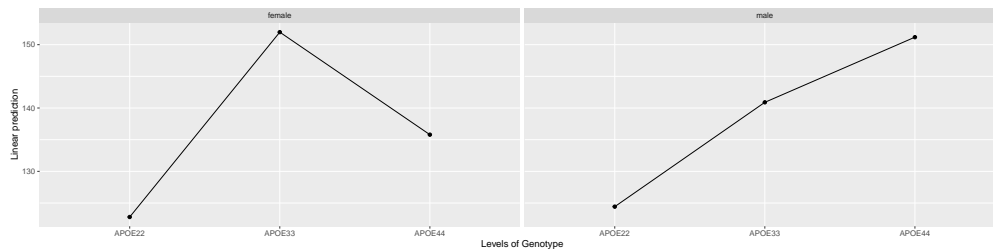


```
emmip(lm_fi_CLUS, ~ Sex | Genotype )
```
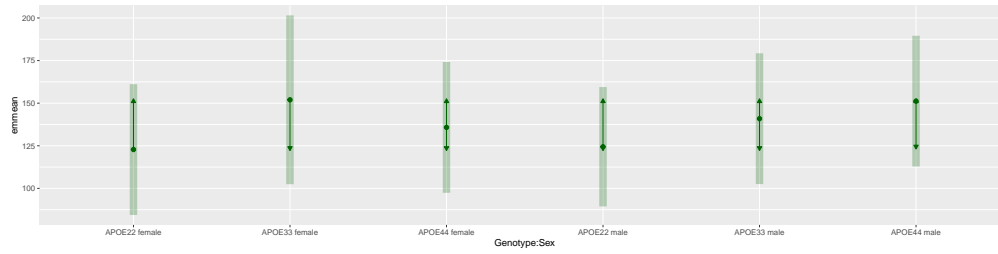


```
emmip(lm_fi_CLUS, Genotype~ Sex  )
```



```
sink()
```

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

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