

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:

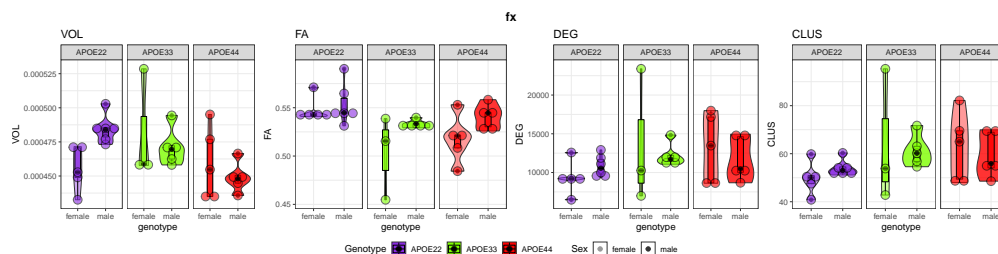
Morris Water Maze - testing spatial navigation memory Segmentation: regional volumes Microstructural properties: FA Tractography Based Connectivity: Degree, and Clustering Coefficient

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

Plots for fx

We embed plots for day d8 probe trials:

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



```
print('fx')
```

```
## [1] "fx"
```

```
lm_fx_VOL <- lm(fx ~ Genotype*Sex, geno_combined_VOL)
summary(lm_fx_VOL)
```

```
##
## Call:
## lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -2.438e-05 -1.136e-05 -1.772e-06  1.536e-05  4.687e-05
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)    4.553e-04  8.835e-06  51.537  <2e-16 ***
## GenotypeAPOE33    2.637e-05  1.443e-05   1.828  0.0806 .
## GenotypeAPOE44    4.014e-06  1.249e-05   0.321  0.7509
## Sexmale          2.918e-05  1.196e-05   2.439  0.0229 *
## GenotypeAPOE33:Sexmale -3.952e-05  1.874e-05  -2.109  0.0461 *
## GenotypeAPOE44:Sexmale -3.942e-05  1.730e-05  -2.279  0.0323 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.976e-05 on 23 degrees of freedom
## Multiple R-squared:  0.3645, Adjusted R-squared:  0.2264
## F-statistic: 2.639 on 5 and 23 DF,  p-value: 0.05007

lm_fx_VOL_f <- lm(fx ~ Genotype, combo_f_FA)
#summary(lm_fx_VOL_f)
lm_fx_VOL_m <- lm(fx ~ Genotype, combo_m_FA)
#summary(lm_fx_VOL_f)

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

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

## Analysis of Variance Table
##
## Response: fx
##           Df      Sum Sq    Mean Sq F value    Pr(>F)
## Genotype    2 2.3648e-09  1.1824e-09   3.0297  0.06793 .
## Sex         1 1.6820e-10  1.6823e-10   0.4311  0.51798
## Genotype:Sex  2 2.6163e-09  1.3082e-09   3.3520  0.05278 .
## Residuals   23 8.9762e-09  3.9027e-10
## ---
## 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 = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -2.637e-05  1.443e-05  -1.828    0.182
## APOE22 - APOE44 == 0 -4.014e-06  1.249e-05  -0.321    0.945
## APOE33 - APOE44 == 0  2.235e-05  1.443e-05   1.549    0.286
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  1.315e-05  1.196e-05   1.100   0.5238
## APOE22 - APOE44 == 0  3.541e-05  1.196e-05   2.960   0.0185 *
## APOE33 - APOE44 == 0  2.225e-05  1.249e-05   1.781   0.1980
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
summary(gllt(mydata.lm, emm(pairwise ~ Sex| Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -2.918e-05  1.196e-05  -2.439   0.0229 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0  1.034e-05  1.443e-05   0.717   0.481
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##

```

```

## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##             Estimate Std. Error t value Pr(>|t|)
## female - male == 0 1.024e-05  1.249e-05    0.82   0.421
## (Adjusted p values reported -- single-step method)

sink()
#3333

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

## [1] "omnibus testing"

joint_tests(ref_grid(lm_fx_VOL))

## model term    df1 df2 F.ratio p.value
## Genotype      2  23   3.055  0.0666
## Sex            1  23   0.145  0.7065
## Genotype:Sex   2  23   3.352  0.0528

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

## Sex = female:
## model term df1 df2 F.ratio p.value
## Genotype   2  23   1.806  0.1868
##
## Sex = male:
## model term df1 df2 F.ratio p.value
## Genotype   2  23   4.418  0.0238

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

## Genotype = APOE22:
## model term df1 df2 F.ratio p.value
## Sex        1  23   5.949  0.0229
##
## Genotype = APOE33:
## model term df1 df2 F.ratio p.value
## Sex        1  23   0.514  0.4806
##
## Genotype = APOE44:
## model term df1 df2 F.ratio p.value
## Sex        1  23   0.672  0.4207

'anova'

## [1] "anova"

anova(lm_fx_VOL)

## Analysis of Variance Table
##
## Response: fx
##           Df      Sum Sq    Mean Sq F value  Pr(>F)
## Genotype   2 2.3648e-09 1.1824e-09  3.0297 0.06793 .

```

```
## Sex          1 1.6820e-10 1.6823e-10 0.4311 0.51798
## Genotype:Sex 2 2.6163e-09 1.3082e-09 3.3520 0.05278 .
## Residuals    23 8.9762e-09 3.9027e-10
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

#anova(lm_fx_VOL_f)
#anova(lm_fx_VOL_m)

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

## contrast          estimate          SE df t.ratio p.value
## APOE22 female effect -1.16e-05 8.13e-06 23 -1.421 0.2529
## APOE33 female effect  1.48e-05 1.00e-05 23  1.475 0.2529
## APOE44 female effect -7.54e-06 8.13e-06 23 -0.928 0.4358
## APOE22 male effect    1.76e-05 7.58e-06 23  2.324 0.1174
## APOE33 male effect    4.46e-06 8.13e-06 23  0.549 0.5884
## APOE44 male effect   -1.78e-05 8.13e-06 23 -2.187 0.1174
##
## P value adjustment: fdr method for 6 tests
contrast(fx_VOL.emm, simple = list("Genotype", "Sex"))

## $`simple contrasts for Genotype`
## Sex = female:
## contrast          estimate          SE df t.ratio p.value
## APOE22 effect -1.01e-05 7.60e-06 23 -1.332 0.2939
## APOE33 effect  1.62e-05 8.67e-06 23  1.873 0.2214
## APOE44 effect -6.11e-06 7.60e-06 23 -0.804 0.4297
##
## Sex = male:
## contrast          estimate          SE df t.ratio p.value
## APOE22 effect  1.62e-05 6.80e-06 23  2.380 0.0390
## APOE33 effect  3.03e-06 7.11e-06 23  0.426 0.6738
## APOE44 effect -1.92e-05 7.11e-06 23 -2.702 0.0382
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
## contrast          estimate          SE df t.ratio p.value
## female effect -1.46e-05 5.98e-06 23 -2.439 0.0229
## male effect    1.46e-05 5.98e-06 23  2.439 0.0229
##
## Genotype = APOE33:
## contrast          estimate          SE df t.ratio p.value
## female effect  5.17e-06 7.21e-06 23  0.717 0.4806
## male effect   -5.17e-06 7.21e-06 23 -0.717 0.4806
##
## Genotype = APOE44:
## contrast          estimate          SE df t.ratio p.value
## female effect  5.12e-06 6.25e-06 23  0.820 0.4207
## male effect   -5.12e-06 6.25e-06 23 -0.820 0.4207
```

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

##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -2.637e-05 1.443e-05 -1.828 0.467
## APOE22 female - APOE44 female == 0 -4.014e-06 1.249e-05 -0.321 0.999
## APOE22 female - APOE22 male == 0 -2.918e-05 1.196e-05 -2.439 0.183
## APOE22 female - APOE33 male == 0 -1.602e-05 1.249e-05 -1.282 0.790
## APOE22 female - APOE44 male == 0 6.229e-06 1.249e-05 0.499 0.996
## APOE33 female - APOE44 female == 0 2.235e-05 1.443e-05 1.549 0.636
## APOE33 female - APOE22 male == 0 -2.809e-06 1.397e-05 -0.201 1.000
## APOE33 female - APOE33 male == 0 1.035e-05 1.443e-05 0.717 0.978
## APOE33 female - APOE44 male == 0 3.260e-05 1.443e-05 2.259 0.249
## APOE44 female - APOE22 male == 0 -2.516e-05 1.196e-05 -2.103 0.319
## APOE44 female - APOE33 male == 0 -1.201e-05 1.249e-05 -0.961 0.925
## APOE44 female - APOE44 male == 0 1.024e-05 1.249e-05 0.820 0.960
## APOE22 male - APOE33 male == 0 1.315e-05 1.196e-05 1.100 0.876
## APOE22 male - APOE44 male == 0 3.540e-05 1.196e-05 2.960 0.067
## APOE33 male - APOE44 male == 0 2.225e-05 1.249e-05 1.781 0.494
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
res<-summary(glht(lm_fx_VOL, emm(pairwise ~ Genotype*Sex))) #consider save to file
#summary(as.glht(pairs(lm_fx_VOL.emm), by = NULL))

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

## $`Sex = female`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -2.637e-05 1.443e-05 -1.828 0.182
## APOE22 - APOE44 == 0 -4.014e-06 1.249e-05 -0.321 0.945
## APOE33 - APOE44 == 0 2.235e-05 1.443e-05 1.549 0.286
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
```

```
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 1.315e-05 1.196e-05 1.100 0.5238
## APOE22 - APOE44 == 0 3.541e-05 1.196e-05 2.960 0.0186 *
## APOE33 - APOE44 == 0 2.225e-05 1.249e-05 1.781 0.1982
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
summary(glht(lm_fx_VOL, emm(pairwise ~ Sex | Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -2.918e-05 1.196e-05 -2.439 0.0229 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0 1.034e-05 1.443e-05 0.717 0.481
## (Adjusted p values reported -- single-step method)
##
## $`Genotype = APOE44`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_VOL)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0 1.024e-05 1.249e-05 0.82 0.421
## (Adjusted p values reported -- single-step method)
mypairs<-pairs(fx_VOL.emm) #_consider save to file
pairs(fx_VOL.emm, by="Genotype")

## Genotype = APOE22:
## contrast estimate SE df t.ratio p.value
```

```
## female - male -2.92e-05 1.20e-05 23 -2.439 0.0229
##
```

```
## Genotype = APOE33:
```

```
## contrast      estimate      SE df t.ratio p.value
## female - male 1.03e-05 1.44e-05 23  0.717 0.4806
##
```

```
## Genotype = APOE44:
```

```
## contrast      estimate      SE df t.ratio p.value
## female - male 1.02e-05 1.25e-05 23  0.820 0.4207
```

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

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

```
## contrast      estimate      SE df t.ratio p.value
## APOE22 - APOE33 -2.64e-05 1.44e-05 23 -1.828 0.1830
## APOE22 - APOE44 -4.01e-06 1.25e-05 23 -0.321 0.9448
## APOE33 - APOE44 2.24e-05 1.44e-05 23  1.549 0.2874
##
```

```
## Sex = male:
```

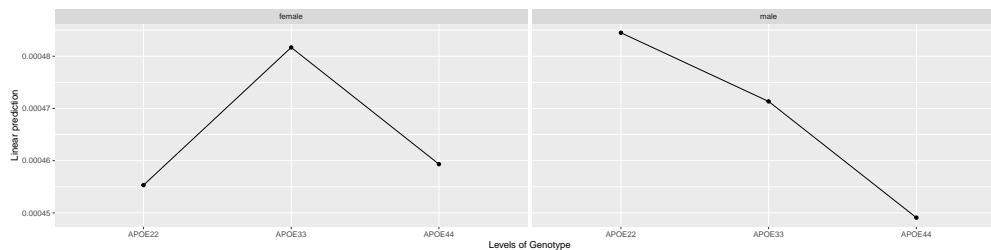
```
## contrast      estimate      SE df t.ratio p.value
## APOE22 - APOE33 1.32e-05 1.20e-05 23  1.100 0.5239
## APOE22 - APOE44 3.54e-05 1.20e-05 23  2.960 0.0185
## APOE33 - APOE44 2.23e-05 1.25e-05 23  1.781 0.1982
##
```

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

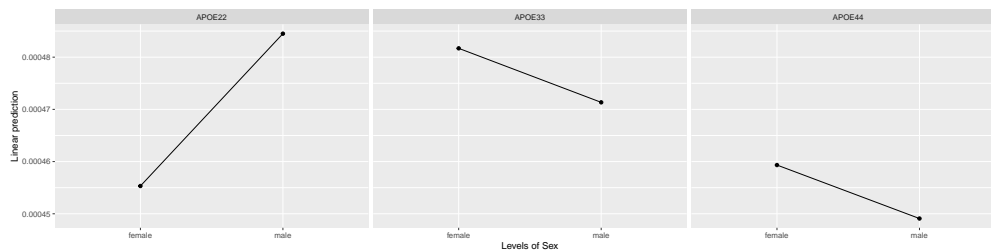
```
print('fx VOL')
```

```
## [1] "fx VOL"
```

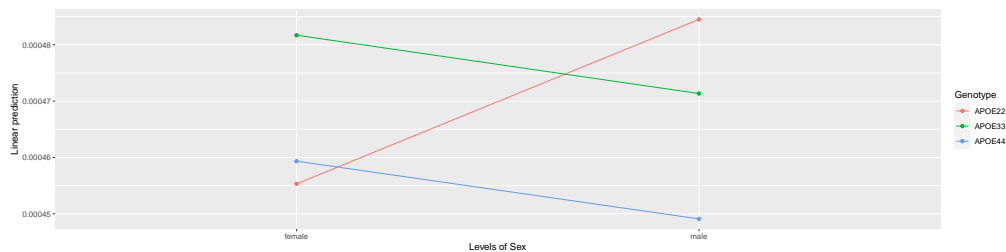
```
emmip(lm_fx_VOL, ~ Genotype | Sex )
```



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

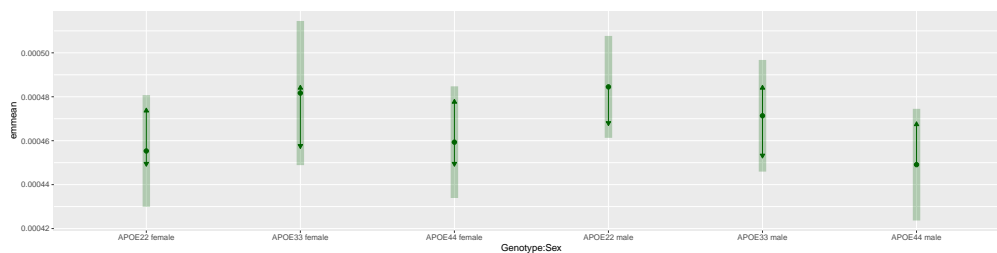


```
emmip(lm_fx_VOL, Genotype~ Sex )
```

```
sink()
```

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



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

```
'simple stats'
```

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

```
print('fx')
```

```
## [1] "fx"
```

```
lm_fx_FA <- lm(fx ~ Genotype*Sex, geno_combined_FA)
summary(lm_fx_FA)
```

```
##
```

```
## Call:
```

```
## lm(formula = fx ~ Genotype * Sex, data = geno_combined_FA)
```

```
##
```

```
## Residuals:
```

```
##      Min       1Q   Median       3Q      Max
## -0.048213 -0.008483 -0.003539  0.006695  0.036991
```

```
##
```

```
## Coefficients:
```

```
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)      0.548151   0.009258  59.211 < 2e-16 ***
## GenotypeAPOE33    -0.045172   0.015118  -2.988  0.00657 **
## GenotypeAPOE44    -0.030483   0.013092  -2.328  0.02905 *
## Sexmale           0.005117   0.012535   0.408  0.68688
## GenotypeAPOE33:Sexmale 0.024983   0.019638   1.272  0.21602
## GenotypeAPOE44:Sexmale 0.018041   0.018125   0.995  0.32993
```

```
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
```

```
## Residual standard error: 0.0207 on 23 degrees of freedom
```

```
## Multiple R-squared:  0.4363, Adjusted R-squared:  0.3138
## F-statistic:  3.56 on 5 and 23 DF,  p-value: 0.01572

lm_fx_FA_f <- lm(fx ~ Genotype, combo_f_FA)
#summary(lm_fx_FA_f)
lm_fx_FA_m <- lm(fx ~ Genotype, combo_m_FA)
#summary(lm_fx_FA_m)

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

## Analysis of Variance Table
##
## Response: fx
##              Df      Sum Sq    Mean Sq F value    Pr(>F)
## Genotype      2 0.0045172 0.00225862   5.2709 0.01305 *
## Sex           1 0.0023173 0.00231728   5.4078 0.02923 *
## Genotype:Sex  2 0.0007937 0.00039683   0.9261 0.41038
## Residuals    23 0.0098557 0.00042851
## ---
## 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 = fx ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.04517    0.01512   2.988  0.0174 *
## APOE22 - APOE44 == 0  0.03048    0.01309   2.328  0.0714 .
## APOE33 - APOE44 == 0 -0.01469    0.01512  -0.972  0.6007
## ---
## 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 = fx ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.020189   0.012535   1.611  0.261
## APOE22 - APOE44 == 0  0.012442   0.012535   0.993  0.589
## APOE33 - APOE44 == 0 -0.007747   0.013092  -0.592  0.826
## (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 = fx ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##             Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.005117   0.012535  -0.408   0.687
## (Adjusted p values reported -- single-step method)
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##             Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.03010    0.01512  -1.991   0.0585 .
## ---
## 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 = fx ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##             Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.02316    0.01309  -1.769   0.0902 .
## ---
## 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, "fx_FA_SimpleStats.txt", sep=''))
'omnibus testing'

## [1] "omnibus testing"
joint_tests(ref_grid(lm_fx_FA))

##   model term    df1 df2 F.ratio p.value

```

```
## Genotype      2  23   6.041  0.0078
## Sex           1  23   6.117  0.0212
## Genotype:Sex  2  23   0.926  0.4104

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

## Sex = female:
## model term df1 df2 F.ratio p.value
## Genotype    2  23   5.123  0.0145
##
## Sex = male:
## model term df1 df2 F.ratio p.value
## Genotype    2  23   1.340  0.2816

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

## Genotype = APOE22:
## model term df1 df2 F.ratio p.value
## Sex        1  23   0.167  0.6869
##
## Genotype = APOE33:
## model term df1 df2 F.ratio p.value
## Sex        1  23   3.964  0.0585
##
## Genotype = APOE44:
## model term df1 df2 F.ratio p.value
## Sex        1  23   3.129  0.0902

'anova'

## [1] "anova"

anova(lm_fx_FA)

## Analysis of Variance Table
##
## Response: fx
##           Df    Sum Sq   Mean Sq F value    Pr(>F)
## Genotype    2  0.0045172  0.00225862   5.2709  0.01305 *
## Sex         1  0.0023173  0.00231728   5.4078  0.02923 *
## Genotype:Sex  2  0.0007937  0.00039683   0.9261  0.41038
## Residuals   23  0.0098557  0.00042851
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

#anova(lm_fx_FA_f)
#anova(lm_fx_FA_m)

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

## contrast           estimate      SE df t.ratio p.value
## APOE22 female effect  0.015489  0.00852  23   1.818  0.1377
## APOE33 female effect -0.029683  0.01052  23  -2.821  0.0486
## APOE44 female effect -0.014994  0.00852  23  -1.760  0.1377
## APOE22 male effect    0.020606  0.00794  23   2.594  0.0486
## APOE33 male effect    0.000417  0.00852  23   0.049  0.9614
```

```
## APOE44 male effect      0.008164 0.00852 23    0.958  0.4176
```

```
##
```

```
## P value adjustment: fdr method for 6 tests
```

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

```
## $`simple contrasts for Genotype`
```

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

```
## contrast      estimate      SE df t.ratio p.value
```

```
## APOE22 effect  0.02522 0.00797 23    3.165  0.0130
```

```
## APOE33 effect -0.01995 0.00908 23   -2.196  0.0576
```

```
## APOE44 effect -0.00526 0.00797 23   -0.661  0.5153
```

```
##
```

```
## Sex = male:
```

```
## contrast      estimate      SE df t.ratio p.value
```

```
## APOE22 effect  0.01088 0.00713 23    1.526  0.3361
```

```
## APOE33 effect -0.00931 0.00745 23   -1.249  0.3361
```

```
## APOE44 effect -0.00157 0.00745 23   -0.210  0.8355
```

```
##
```

```
## P value adjustment: fdr method for 3 tests
```

```
##
```

```
## $`simple contrasts for Sex`
```

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

```
## contrast      estimate      SE df t.ratio p.value
```

```
## female effect -0.00256 0.00627 23   -0.408  0.6869
```

```
## male effect    0.00256 0.00627 23    0.408  0.6869
```

```
##
```

```
## Genotype = APOE33:
```

```
## contrast      estimate      SE df t.ratio p.value
```

```
## female effect -0.01505 0.00756 23   -1.991  0.0585
```

```
## male effect    0.01505 0.00756 23    1.991  0.0585
```

```
##
```

```
## Genotype = APOE44:
```

```
## contrast      estimate      SE df t.ratio p.value
```

```
## female effect -0.01158 0.00655 23   -1.769  0.0902
```

```
## male effect    0.01158 0.00655 23    1.769  0.0902
```

```
##
```

```
## P value adjustment: fdr method for 2 tests
```

```
#post hoc tests
```

```
summary(glht(lm_fx_FA, emm(pairwise ~ Genotype*Sex, contr="sidak")))
```

```
##
```

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

```
##
```

```
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_FA)
```

```
##
```

```
## Linear Hypotheses:
```

```
##
```

```
## APOE22 female - APOE33 female == 0  0.045172  0.015118  2.988  0.0633 .
```

```
## APOE22 female - APOE44 female == 0  0.030483  0.013092  2.328  0.2219
```

```
## APOE22 female - APOE22 male == 0   -0.005117  0.012535  -0.408  0.9983
```

```
## APOE22 female - APOE33 male == 0    0.015072  0.013092  1.151  0.8536
```

```
## APOE22 female - APOE44 male == 0    0.007325  0.013092  0.559  0.9926
```

```
## APOE33 female - APOE44 female == 0 -0.014689  0.015118  -0.972  0.9217
```

```

## APOE33 female - APOE22 male == 0    -0.050289    0.014637   -3.436    0.0238 *
## APOE33 female - APOE33 male == 0    -0.030100    0.015118   -1.991    0.3755
## APOE33 female - APOE44 male == 0    -0.037847    0.015118   -2.504    0.1631
## APOE44 female - APOE22 male == 0    -0.035600    0.012535   -2.840    0.0855 .
## APOE44 female - APOE33 male == 0    -0.015411    0.013092   -1.177    0.8420
## APOE44 female - APOE44 male == 0    -0.023158    0.013092   -1.769    0.5017
## APOE22 male - APOE33 male == 0       0.020189    0.012535    1.611    0.5984
## APOE22 male - APOE44 male == 0       0.012442    0.012535    0.993    0.9150
## APOE33 male - APOE44 male == 0      -0.007747    0.013092   -0.592    0.9905
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)

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

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

## $`Sex = female`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.04517    0.01512   2.988   0.0173 *
## APOE22 - APOE44 == 0  0.03048    0.01309   2.328   0.0713 .
## APOE33 - APOE44 == 0 -0.01469    0.01512  -0.972   0.6006
## ---
## 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 = fx ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  0.020189    0.012535    1.611    0.261
## APOE22 - APOE44 == 0  0.012442    0.012535    0.993    0.589
## APOE33 - APOE44 == 0 -0.007747    0.013092   -0.592    0.826
## (Adjusted p values reported -- single-step method)

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

## $`Genotype = APOE22`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_FA)
##

```

```

## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.005117   0.012535  -0.408   0.687
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
##   Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.03010    0.01512  -1.991   0.0585 .
## ---
## 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 = fx ~ Genotype * Sex, data = geno_combined_FA)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0 -0.02316    0.01309  -1.769   0.0902 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## (Adjusted p values reported -- single-step method)

```

```

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

```

```

## Genotype = APOE22:
## contrast      estimate      SE df t.ratio p.value
## female - male -0.00512 0.0125 23  -0.408  0.6869
##
## Genotype = APOE33:
## contrast      estimate      SE df t.ratio p.value
## female - male -0.03010 0.0151 23  -1.991  0.0585
##
## Genotype = APOE44:
## contrast      estimate      SE df t.ratio p.value
## female - male -0.02316 0.0131 23  -1.769  0.0902

```

```

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

```

```

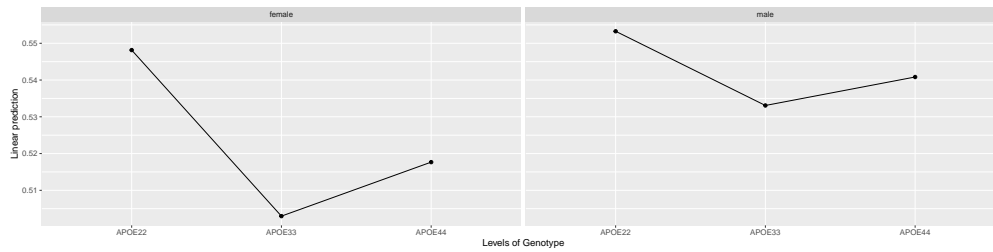
## Sex = female:
## contrast      estimate      SE df t.ratio p.value
## APOE22 - APOE33 0.04517 0.0151 23   2.988  0.0174
## APOE22 - APOE44 0.03048 0.0131 23   2.328  0.0717
## APOE33 - APOE44 -0.01469 0.0151 23  -0.972  0.6017

```

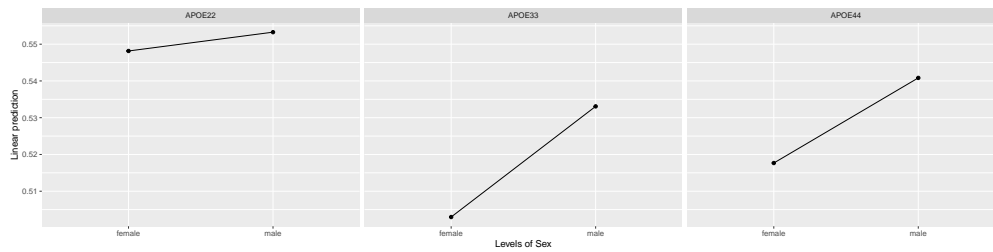
```
##
## Sex = male:
## contrast      estimate      SE df t.ratio p.value
## APOE22 - APOE33  0.02019  0.0125  23   1.611  0.2614
## APOE22 - APOE44  0.01244  0.0125  23   0.993  0.5888
## APOE33 - APOE44 -0.00775  0.0131  23  -0.592  0.8259
##
## P value adjustment: tukey method for comparing a family of 3 estimates
print('fx FA')
```

```
## [1] "fx FA"
```

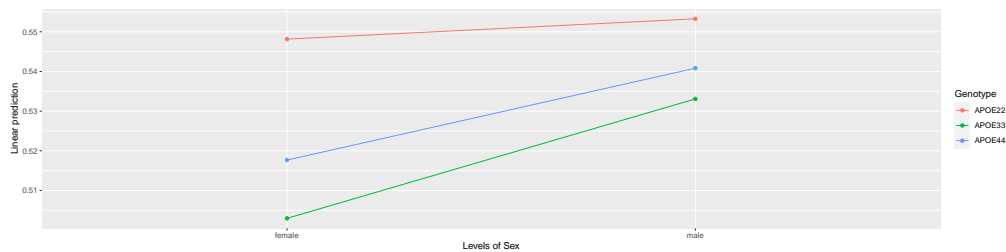
```
emmip(lm_fx_FA, ~ Genotype | Sex )
```



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

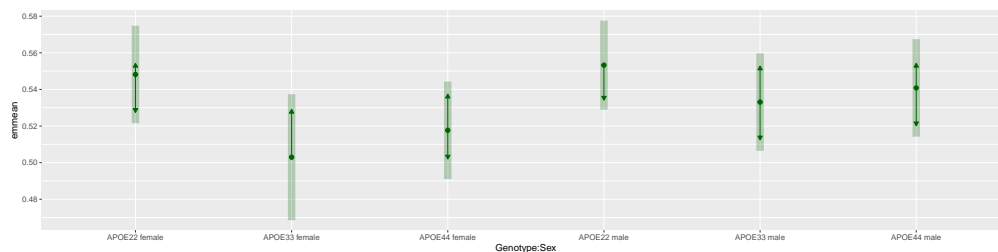


```
emmip(lm_fx_FA, Genotype~ Sex )
```



```
sink()
```

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




```

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

'simple stats'

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

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

##
## Call:
## lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -6556.3 -1442.3  -249.8   2080.7   9842.7
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)         9330       1617   5.768 7.09e-06 ***
## GenotypeAPOE33         4214       2641   1.595   0.124
## GenotypeAPOE44         3852       2287   1.684   0.106
## Sexmale              1508       2190   0.689   0.498
## GenotypeAPOE33:Sexmale -2790       3431  -0.813   0.424
## GenotypeAPOE44:Sexmale -2943       3167  -0.929   0.362
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 3617 on 23 degrees of freedom
## Multiple R-squared:  0.1552, Adjusted R-squared:  -0.02843
## F-statistic: 0.8452 on 5 and 23 DF,  p-value: 0.5318

lm_fx_DEG_f <- lm(fx ~ Genotype, combo_f_FA)
#summary(lm_fx_DEG_f)
lm_fx_DEG_m <- lm(fx ~ Genotype, combo_m_FA)
#summary(lm_fx_DEG_f)

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

## Analysis of Variance Table
##
## Response: fx
##              Df    Sum Sq Mean Sq F value Pr(>F)
## Genotype      2  40847168 20423584  1.5615 0.2313
## Sex           1   494574    494574  0.0378 0.8475
## Genotype:Sex  2  13933495  6966747  0.5326 0.5941
## Residuals    23 300830010 13079566
##
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 = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -4213.5      2641.2  -1.595    0.267
## APOE22 - APOE44 == 0  -3852.4      2287.3  -1.684    0.232
## APOE33 - APOE44 == 0   361.1       2641.2   0.137    0.990
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -1423.5      2189.9  -0.650    0.794
## APOE22 - APOE44 == 0   -909.7      2189.9  -0.415    0.910
## APOE33 - APOE44 == 0   513.8       2287.3   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 = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -1508        2190  -0.689    0.498
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##              Estimate Std. Error t value Pr(>|t|)
## female - male == 0    1282        2641   0.485    0.632
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##

```

```

## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##             Estimate Std. Error t value Pr(>|t|)
## female - male == 0      1434      2287   0.627   0.537
## (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, "fx_DEG_SimpleStats.txt", sep=''))
'omnibus testing'

## [1] "omnibus testing"
joint_tests(ref_grid(lm_fx_DEG))

## model term    df1 df2 F.ratio p.value
## Genotype      2  23   1.726  0.2002
## Sex           1  23   0.086  0.7723
## Genotype:Sex   2  23   0.533  0.5941

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

## Sex = female:
## model term df1 df2 F.ratio p.value
## Genotype   2  23   1.880  0.1753
##
## Sex = male:
## model term df1 df2 F.ratio p.value
## Genotype   2  23   0.220  0.8039

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

## Genotype = APOE22:
## model term df1 df2 F.ratio p.value
## Sex       1  23   0.475  0.4978
##
## Genotype = APOE33:
## model term df1 df2 F.ratio p.value
## Sex       1  23   0.235  0.6321
##
## Genotype = APOE44:
## model term df1 df2 F.ratio p.value
## Sex       1  23   0.393  0.5368

'anova'

## [1] "anova"
anova(lm_fx_DEG)

## Analysis of Variance Table
##

```

```
## Response: fx
##           Df      Sum Sq Mean Sq F value Pr(>F)
## Genotype    2  40847168 20423584  1.5615 0.2313
## Sex          1   494574   494574  0.0378 0.8475
## Genotype:Sex  2  13933495  6966747  0.5326 0.5941
## Residuals   23 300830010 13079566

#anova(lm_fx_DEG_f)
#anova(lm_fx_DEG_m)

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

## contrast            estimate    SE df t.ratio p.value
## APOE22 female effect -2487.4 1489 23  -1.671  0.6498
## APOE33 female effect  1726.1 1838 23   0.939  0.7314
## APOE44 female effect  1365.0 1489 23   0.917  0.7314
## APOE22 male effect   -978.9 1388 23  -0.705  0.7314
## APOE33 male effect    444.6 1489 23   0.299  0.9215
## APOE44 male effect   -69.2 1489 23  -0.047  0.9633
##
## P value adjustment: fdr method for 6 tests

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

## $`simple contrasts for Genotype`
## Sex = female:
## contrast      estimate    SE df t.ratio p.value
## APOE22 effect  -2689 1392 23  -1.931  0.1975
## APOE33 effect   1525 1587 23   0.961  0.4117
## APOE44 effect   1164 1392 23   0.836  0.4117
##
## Sex = male:
## contrast      estimate    SE df t.ratio p.value
## APOE22 effect   -778 1245 23  -0.625  0.9202
## APOE33 effect    646 1302 23   0.496  0.9202
## APOE44 effect    132 1302 23   0.101  0.9202
##
## P value adjustment: fdr method for 3 tests
##
## $`simple contrasts for Sex`
## Genotype = APOE22:
## contrast      estimate    SE df t.ratio p.value
## female effect  -754 1095 23  -0.689  0.4978
## male effect     754 1095 23   0.689  0.4978
##
## Genotype = APOE33:
## contrast      estimate    SE df t.ratio p.value
## female effect   641 1321 23   0.485  0.6321
## male effect   -641 1321 23  -0.485  0.6321
##
## Genotype = APOE44:
## contrast      estimate    SE df t.ratio p.value
## female effect   717 1144 23   0.627  0.5368
```

```

## male effect      -717 1144 23  -0.627  0.5368
##
## P value adjustment: fdr method for 2 tests
#post hoc tests
summary(glht(lm_fx_DEG, emm(pairwise ~ Genotype*Sex, contr="sidak"))) #consider save to file

##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -4213.5      2641.2  -1.595    0.608
## APOE22 female - APOE44 female == 0 -3852.4      2287.3  -1.684    0.553
## APOE22 female - APOE22 male == 0  -1508.5      2189.9  -0.689    0.981
## APOE22 female - APOE33 male == 0  -2932.0      2287.3  -1.282    0.790
## APOE22 female - APOE44 male == 0  -2418.2      2287.3  -1.057    0.892
## APOE33 female - APOE44 female == 0   361.1      2641.2   0.137    1.000
## APOE33 female - APOE22 male == 0   2705.0      2557.3   1.058    0.892
## APOE33 female - APOE33 male == 0    1281.5      2641.2   0.485    0.996
## APOE33 female - APOE44 male == 0    1795.3      2641.2   0.680    0.982
## APOE44 female - APOE22 male == 0    2343.9      2189.9   1.070    0.887
## APOE44 female - APOE33 male == 0     920.4      2287.3   0.402    0.998
## APOE44 female - APOE44 male == 0    1434.2      2287.3   0.627    0.988
## APOE22 male - APOE33 male == 0    -1423.5      2189.9  -0.650    0.986
## APOE22 male - APOE44 male == 0    -909.7      2189.9  -0.415    0.998
## APOE33 male - APOE44 male == 0     513.8      2287.3   0.225    1.000
## (Adjusted p values reported -- single-step method)

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

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

## $`Sex = female`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##
## Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0 -4213.5      2641.2  -1.595    0.267
## APOE22 - APOE44 == 0 -3852.4      2287.3  -1.684    0.232
## APOE33 - APOE44 == 0   361.1      2641.2   0.137    0.990
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)

```

```
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -1423.5    2189.9  -0.650    0.794
## APOE22 - APOE44 == 0   -909.7    2189.9  -0.415    0.910
## APOE33 - APOE44 == 0    513.8    2287.3   0.225    0.973
## (Adjusted p values reported -- single-step method)
summary(ghlt(lm_fx_DEG, emm(pairwise ~ Sex | Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -1508    2190  -0.689    0.498
## (Adjusted p values reported -- single-step method)
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0    1282    2641   0.485    0.632
## (Adjusted p values reported -- single-step method)
##
## $`Genotype = APOE44`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_DEG)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0    1434    2287   0.627    0.537
## (Adjusted p values reported -- single-step method)
mypairs<-pairs(fx_DEG.emm) #_consider save to file
pairs(fx_DEG.emm, by="Genotype")

## Genotype = APOE22:
## contrast      estimate    SE df t.ratio p.value
## female - male   -1509 2190 23  -0.689  0.4978
##
## Genotype = APOE33:
## contrast      estimate    SE df t.ratio p.value
## female - male    1282 2641 23   0.485  0.6321
```

```
##
## Genotype = APOE44:
## contrast      estimate    SE df t.ratio p.value
## female - male    1434 2287 23   0.627  0.5368

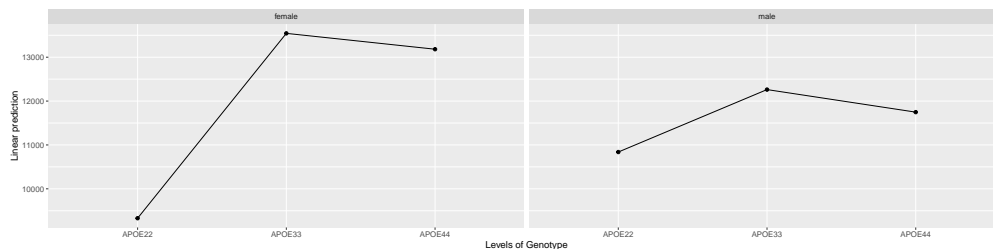
pairs(fx_DEG.emm, by="Sex")

## Sex = female:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - APOE33   -4214 2641 23  -1.595  0.2678
## APOE22 - APOE44   -3852 2287 23  -1.684  0.2325
## APOE33 - APOE44     361 2641 23   0.137  0.9898
##
## Sex = male:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - APOE33   -1423 2190 23  -0.650  0.7942
## APOE22 - APOE44    -910 2190 23  -0.415  0.9096
## APOE33 - APOE44     514 2287 23   0.225  0.9726
##
## P value adjustment: tukey method for comparing a family of 3 estimates

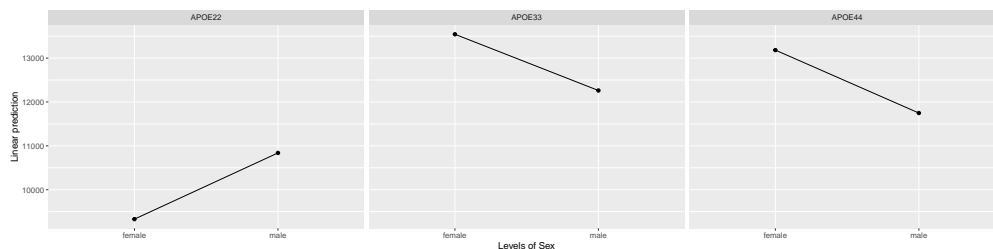
print('fx DEG')

## [1] "fx DEG"

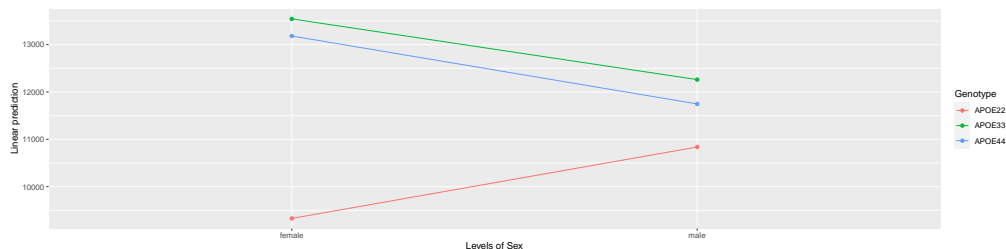
emmip(lm_fx_DEG, ~ Genotype | Sex )
```



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

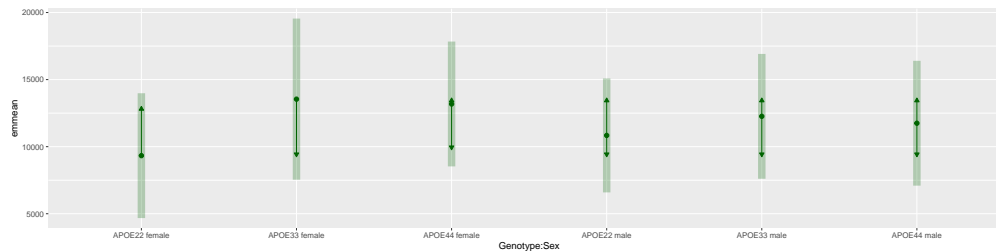


```
emmip(lm_fx_DEG, Genotype~ Sex )
```



```
sink()
```

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



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

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

```
print('fx')
```

```
## [1] "fx"
```

```
lm_fx_CLUS <- lm(fx ~ Genotype*Sex, geno_combined_CLUS)
summary(lm_fx_CLUS)
```

```
##
## Call:
## lm(formula = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -21.200  -5.411  -1.081   6.294  31.356
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)      49.814      5.227   9.530 1.88e-09 ***
## GenotypeAPOE33      14.173      8.535   1.661  0.1104
## GenotypeAPOE44      13.019      7.392   1.761  0.0915 .
## Sexmale           4.212      7.077   0.595  0.5575
## GenotypeAPOE33:Sexmale -6.930     11.088  -0.625  0.5381
## GenotypeAPOE44:Sexmale -7.567     10.233  -0.739  0.4671
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 11.69 on 23 degrees of freedom
## Multiple R-squared:  0.1861, Adjusted R-squared:  0.009187
## F-statistic: 1.052 on 5 and 23 DF, p-value: 0.4119
```

```
lm_fx_CLUS_f <- lm(fx ~ Genotype, combo_f_FA)
#summary(lm_fx_CLUS_f)
lm_fx_CLUS_m <- lm(fx ~ Genotype, combo_m_FA)
#summary(lm_fx_CLUS_f)
```

```
#33333
```

```
sink(paste(outpath, "fx_CLUS_SimpleModels.txt"))
```



```

mydata.lm <- lm(fx ~ Genotype*Sex, data = geno_combined_CLUS)
anova(mydata.lm)

## Analysis of Variance Table
##
## Response: fx
##           Df Sum Sq Mean Sq F value Pr(>F)
## Genotype    2  628.07  314.035   2.2990 0.1230
## Sex          1    0.56   0.560   0.0041 0.9495
## Genotype:Sex  2   89.81   44.907   0.3288 0.7231
## Residuals   23 3141.70  136.596

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 = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -14.173     8.535  -1.661   0.241
## APOE22 - APOE44 == 0  -13.019     7.392  -1.761   0.204
## APOE33 - APOE44 == 0   1.155     8.535   0.135   0.990
## (Adjusted p values reported -- single-step method)
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -7.243     7.077  -1.023   0.570
## APOE22 - APOE44 == 0   -5.452     7.077  -0.770   0.724
## APOE33 - APOE44 == 0   1.791     7.392   0.242   0.968
## (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 = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##           Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -4.212     7.077  -0.595   0.558
## (Adjusted p values reported -- single-step method)
##
##

```

```

## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##             Estimate Std. Error t value Pr(>|t|)
## female - male == 0    2.718      8.535   0.318   0.753
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##             Estimate Std. Error t value Pr(>|t|)
## female - male == 0    3.354      7.392   0.454   0.654
## (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, "fx_CLUS_SimpleStats.txt", sep=''))
'omnibus testing'

## [1] "omnibus testing"

joint_tests(ref_grid(lm_fx_CLUS))

## model term    df1 df2 F.ratio p.value
## Genotype      2  23   2.429  0.1104
## Sex           1  23   0.019  0.8902
## Genotype:Sex   2  23   0.329  0.7231

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

## Sex = female:
## model term df1 df2 F.ratio p.value
## Genotype   2  23   2.047  0.1520
##
## Sex = male:
## model term df1 df2 F.ratio p.value
## Genotype   2  23   0.582  0.5666

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

## Genotype = APOE22:
## model term df1 df2 F.ratio p.value
## Sex        1  23   0.354  0.5575
##

```

```

## Genotype = APOE33:
## model term df1 df2 F.ratio p.value
## Sex          1  23   0.101  0.7530
##
## Genotype = APOE44:
## model term df1 df2 F.ratio p.value
## Sex          1  23   0.206  0.6542
'anova'

## [1] "anova"
anova(lm_fx_CLUS)

## Analysis of Variance Table
##
## Response: fx
##           Df Sum Sq Mean Sq F value Pr(>F)
## Genotype    2  628.07  314.035   2.2990 0.1230
## Sex          1    0.56   0.560   0.0041 0.9495
## Genotype:Sex  2   89.81  44.907   0.3288 0.7231
## Residuals   23 3141.70  136.596

#anova(lm_fx_CLUS_f)
#anova(lm_fx_CLUS_m)

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

## contrast          estimate    SE df t.ratio p.value
## APOE22 female effect   -8.75  4.81 23  -1.820  0.4912
## APOE33 female effect    5.42  5.94 23   0.912  0.5768
## APOE44 female effect    4.26  4.81 23   0.886  0.5768
## APOE22 male effect    -4.54  4.48 23  -1.013  0.5768
## APOE33 male effect     2.70  4.81 23   0.562  0.6958
## APOE44 male effect     0.91  4.81 23   0.189  0.8516
##
## P value adjustment: fdr method for 6 tests
contrast(fx_CLUS.emm, simple = list("Genotype", "Sex"))

## $`simple contrasts for Genotype`
## Sex = female:
## contrast          estimate    SE df t.ratio p.value
## APOE22 effect    -9.06  4.50 23  -2.015  0.1673
## APOE33 effect     5.11  5.13 23   0.996  0.3884
## APOE44 effect     3.95  4.50 23   0.879  0.3884
##
## Sex = male:
## contrast          estimate    SE df t.ratio p.value
## APOE22 effect    -4.23  4.02 23  -1.052  0.7221
## APOE33 effect     3.01  4.21 23   0.716  0.7221
## APOE44 effect     1.22  4.21 23   0.290  0.7744
##
## P value adjustment: fdr method for 3 tests
##

```

```

## `$simple contrasts for Sex`
## Genotype = APOE22:
## contrast      estimate    SE df t.ratio p.value
## female effect   -2.11 3.54 23  -0.595  0.5575
## male effect     2.11 3.54 23   0.595  0.5575
##
## Genotype = APOE33:
## contrast      estimate    SE df t.ratio p.value
## female effect    1.36 4.27 23   0.318  0.7530
## male effect    -1.36 4.27 23  -0.318  0.7530
##
## Genotype = APOE44:
## contrast      estimate    SE df t.ratio p.value
## female effect    1.68 3.70 23   0.454  0.6542
## male effect    -1.68 3.70 23  -0.454  0.6542
##
## P value adjustment: fdr method for 2 tests
#post hoc tests
summary(glht(lm_fx_CLUS, emm(pairwise ~ Genotype*Sex, contr="sidak"))) #consider save to file

##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 female - APOE33 female == 0 -14.173     8.535  -1.661   0.568
## APOE22 female - APOE44 female == 0 -13.019     7.392  -1.761   0.506
## APOE22 female - APOE22 male == 0   -4.212     7.077  -0.595   0.990
## APOE22 female - APOE33 male == 0  -11.456     7.392  -1.550   0.636
## APOE22 female - APOE44 male == 0   -9.664     7.392  -1.307   0.777
## APOE33 female - APOE44 female == 0   1.155     8.535   0.135   1.000
## APOE33 female - APOE22 male == 0   9.961     8.264   1.205   0.829
## APOE33 female - APOE33 male == 0   2.718     8.535   0.318   0.999
## APOE33 female - APOE44 male == 0   4.509     8.535   0.528   0.994
## APOE44 female - APOE22 male == 0   8.806     7.077   1.244   0.809
## APOE44 female - APOE33 male == 0   1.563     7.392   0.211   1.000
## APOE44 female - APOE44 male == 0   3.354     7.392   0.454   0.997
## APOE22 male - APOE33 male == 0    -7.243     7.077  -1.023   0.905
## APOE22 male - APOE44 male == 0    -5.452     7.077  -0.770   0.970
## APOE33 male - APOE44 male == 0     1.791     7.392   0.242   1.000
## (Adjusted p values reported -- single-step method)

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

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

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

```

```

##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0  -14.173      8.535  -1.661    0.241
## APOE22 - APOE44 == 0  -13.019      7.392  -1.761    0.204
## APOE33 - APOE44 == 0   1.155      8.535   0.135    0.990
## (Adjusted p values reported -- single-step method)
##
##
## $`Sex = male`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## APOE22 - APOE33 == 0   -7.243      7.077  -1.023    0.570
## APOE22 - APOE44 == 0   -5.452      7.077  -0.770    0.724
## APOE33 - APOE44 == 0    1.791      7.392   0.242    0.968
## (Adjusted p values reported -- single-step method)
summary(glht(lm_fx_CLUS, emm(pairwise ~ Sex | Genotype)))

## $`Genotype = APOE22`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0   -4.212      7.077  -0.595    0.558
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE33`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0    2.718      8.535   0.318    0.753
## (Adjusted p values reported -- single-step method)
##
##
## $`Genotype = APOE44`
##
## Simultaneous Tests for General Linear Hypotheses
##
## Fit: lm(formula = fx ~ Genotype * Sex, data = geno_combined_CLUS)
##
## Linear Hypotheses:

```

```
##               Estimate Std. Error t value Pr(>|t|)
## female - male == 0      3.354      7.392   0.454   0.654
## (Adjusted p values reported -- single-step method)
```

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

```
## Genotype = APOE22:
## contrast      estimate    SE df t.ratio p.value
## female - male   -4.21  7.08 23  -0.595  0.5575
##
```

```
## Genotype = APOE33:
## contrast      estimate    SE df t.ratio p.value
## female - male    2.72  8.54 23   0.318  0.7530
##
```

```
## Genotype = APOE44:
## contrast      estimate    SE df t.ratio p.value
## female - male    3.35  7.39 23   0.454  0.6542
```

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

```
## Sex = female:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - APOE33  -14.17  8.54 23  -1.661  0.2416
## APOE22 - APOE44  -13.02  7.39 23  -1.761  0.2048
## APOE33 - APOE44    1.15  8.54 23   0.135  0.9900
##
```

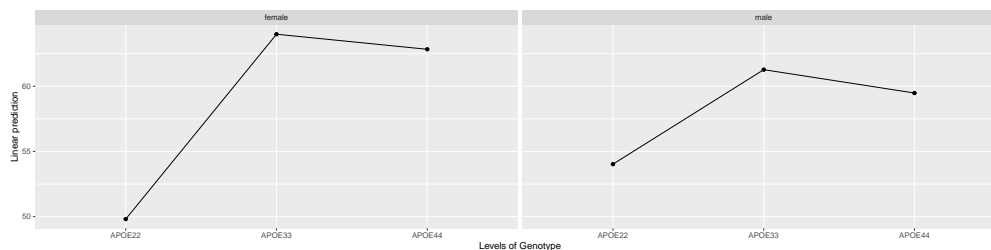
```
## Sex = male:
## contrast      estimate    SE df t.ratio p.value
## APOE22 - APOE33   -7.24  7.08 23  -1.023  0.5699
## APOE22 - APOE44   -5.45  7.08 23  -0.770  0.7246
## APOE33 - APOE44    1.79  7.39 23   0.242  0.9682
##
```

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

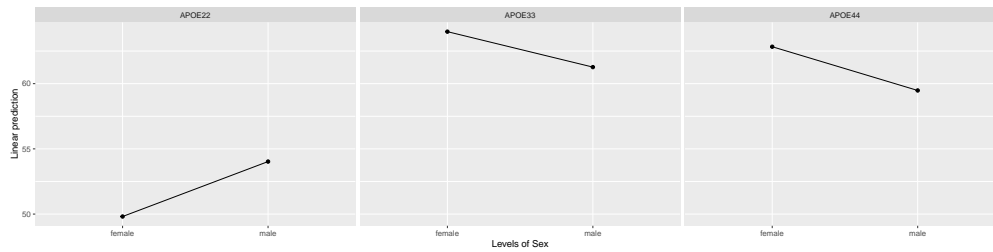
```
print('fx CLUS')
```

```
## [1] "fx CLUS"
```

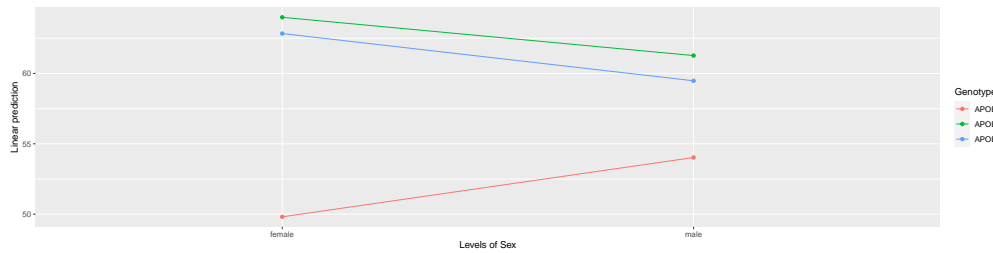
```
emmip(lm_fx_CLUS, ~ Genotype | Sex )
```



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

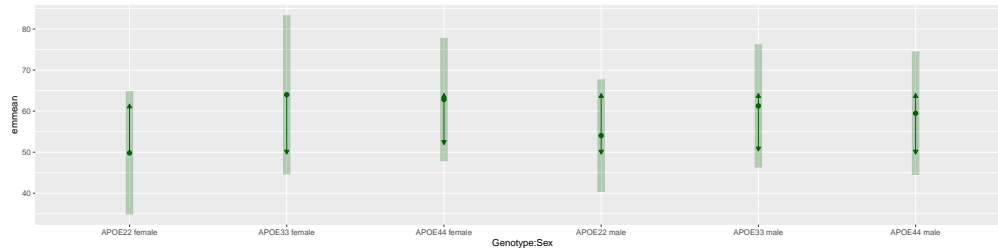


```
emmip(lm_fx_CLUS, Genotype~ Sex )
```



```
sink()
```

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



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