# ICAM1 Associations

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```
suppressPackageStartupMessages({
  library(dplyr)
  library(data.table)
  library(ggplot2)
  library(ggpubr)
})
geno = fread("genotype_master.csv")
pheno = fread("cdp_phenotyping_master.csv")

icam1 = select(geno, id, ICAM1_rs1799969G)

icam1 = left_join(pheno, icam1, by = "id") |>
  filter(genotype_exclude == 0)
```

*From the merged dataset, we select key variables for modeling:* ***SBP (`sbp_mean`)****, the ICAM1 genotype (`ICAM1_rs1799969G`, coded additively as 0/1/2 for A/G alleles),* ***sex****, and* ***BMI****.*

```
icam1 = icam1 |>
  select(sbp_mean, ICAM1_rs1799969G, sex, bmi)
```

### *Linear Regression: Additive Model (without BMI)*

*We first assess the additive effect of the G allele on SBP, adjusting only for sex.*

```
lm(data = icam1, formula = sbp_mean ~ ICAM1_rs1799969G + sex) |>
  summary()
```

```

Call:
lm(formula = sbp_mean ~ ICAM1_rs1799969G + sex, data = icam1)
```

```
Residuals:
    Min      1Q  Median      3Q     Max
-47.532  -9.086  -0.083   6.458  63.917

Coefficients:
                 Estimate Std. Error t value Pr(>|t|)
(Intercept)       105.532      3.097  34.079   <2e-16 ***
ICAM1_rs1799969G    4.010      1.769   2.267   0.0249 *
sexM                2.541      2.828   0.898   0.3704
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 14.6 on 149 degrees of freedom
  (43 observations deleted due to missingness)
Multiple R-squared:  0.04139,   Adjusted R-squared:  0.02853
F-statistic: 3.217 on 2 and 149 DF,  p-value: 0.04288
```

### *Linear Regression: Additive Model (with BMI)*

*Next, we adjust for potential confounding by body mass index (BMI).*

```r
lm(data = icam1, formula = sbp_mean ~ ICAM1_rs1799969G + sex + bmi) |>
  summary()
```

```
Call:
lm(formula = sbp_mean ~ ICAM1_rs1799969G + sex + bmi, data = icam1)

Residuals:
    Min      1Q  Median      3Q     Max
-53.774  -8.699  -0.674   6.997  63.433

Coefficients:
                 Estimate Std. Error t value Pr(>|t|)
(Intercept)       83.0563     9.8115   8.465 3.23e-14 ***
ICAM1_rs1799969G   3.9401     1.8211   2.164   0.0322 *
sexM               5.1972     3.1453   1.652   0.1007
bmi                0.7609     0.3262   2.333   0.0211 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Residual standard error: 14.71 on 139 degrees of freedom
  (52 observations deleted due to missingness)
Multiple R-squared:  0.08178,   Adjusted R-squared:  0.06196
F-statistic: 4.127 on 3 and 139 DF,  p-value: 0.007729
```

*In both models above, the **G allele of rs1799969** is significantly associated with **higher systolic blood pressure**, suggesting a potential functional role of this variant in regulating vascular physiology.*

### *Linear Regression: Genotype as Categorical (without BMI)*

*We now treat genotype as a categorical variable to allow for potential non-linear effects.*

```
lm(data = icam1, formula = sbp_mean ~ as.factor(ICAM1_rs1799969G) + sex) |>
  summary()
```

```
Call:
lm(formula = sbp_mean ~ as.factor(ICAM1_rs1799969G) + sex, data = icam1)

Residuals:
    Min      1Q  Median      3Q     Max
-44.326  -8.800  -0.069   7.109  62.078

Coefficients:
                             Estimate Std. Error t value Pr(>|t|)
(Intercept)                   102.326      3.677  27.830  < 2e-16 ***
as.factor(ICAM1_rs1799969G)1    8.743      3.447   2.537  0.01223 *
as.factor(ICAM1_rs1799969G)2    9.621      3.660   2.629  0.00948 **
sexM                            2.852      2.820   1.011  0.31349
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 14.53 on 148 degrees of freedom
  (43 observations deleted due to missingness)
Multiple R-squared:  0.05763,   Adjusted R-squared:  0.03853
F-statistic: 3.017 on 3 and 148 DF,  p-value: 0.03185
```

### *Linear Regression: Genotype as Categorical (with BMI)*

*We repeat this model, now adjusting for BMI.*

```
lm(data = icam1, formula = sbp_mean ~ as.factor(ICAM1_rs1799969G) + sex + bmi) |>
  summary()
```

```
Call:
lm(formula = sbp_mean ~ as.factor(ICAM1_rs1799969G) + sex + bmi,
    data = icam1)

Residuals:
    Min      1Q  Median      3Q     Max
-50.229  -9.104  -1.643   7.562  61.183

Coefficients:
                             Estimate Std. Error t value Pr(>|t|)
(Intercept)                   78.6536    10.0066   7.860 9.83e-13 ***
as.factor(ICAM1_rs1799969G)1   9.6549     3.5529   2.717  0.00742 **
as.factor(ICAM1_rs1799969G)2   9.8019     3.7539   2.611  0.01002 *
sexM                           5.5273     3.1225   1.770  0.07891 .
bmi                            0.7836     0.3235   2.422  0.01672 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 14.58 on 138 degrees of freedom
  (52 observations deleted due to missingness)
Multiple R-squared:  0.1044,    Adjusted R-squared:  0.07845
F-statistic: 4.022 on 4 and 138 DF,  p-value: 0.00407
```

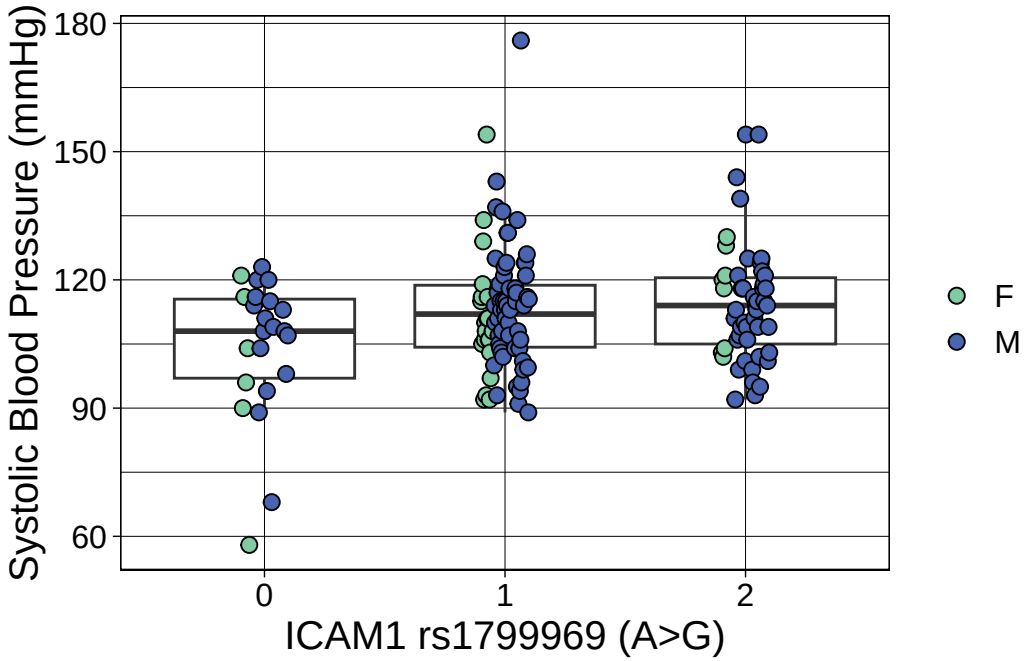
*These models reinforce our previous findings. Individuals carrying the* ***G allele*** *tend to have* ***higher SBP****, even when accounting for sex and BMI. This effect is consistent whether the genotype is treated as a continuous dosage or as a factor.*

### *Visualization*

*To visualize the relationship between genotype and SBP, we create a boxplot stratified by genotype and colored by sex.*

```r
plt = ggplot(data = icam1, aes(x = as.factor(ICAM1_rs1799969G), y = sbp_mean)) +
  geom_boxplot(outlier.shape = NA) +
  geom_point(aes(fill = sex), size = 2.5, color = "black", shape = 21, position = position_d
  scale_fill_manual(values = c("#80cba4", "#4965b0")) +
  xlab("ICAM1 rs1799969 (A>G)") +
  ylab("Systolic Blood Pressure (mmHg)") +
  labs(fill = "") +
  theme_linedraw() +
  theme(text = element_text(size = 15))

suppressWarnings(print(plt))
```




***Interpretation***

*These results indicate that* ***rs1799969 in the ICAM1 gene is significantly associated with systolic blood pressure levels****, where* ***carriers of the G allele tend to exhibit higher SBP****.*

*This association suggests a* ***protective role of the A allele****, which may contribute to lower vascular pressure through mechanisms involving endothelial adhesion or immune signaling, given ICAM1's known biological functions.*

*Interestingly, population genetic data show that the **A allele is substantially more common in Andean populations** compared to other global populations. This observation, combined with our association analysis, suggests that the **Andean-enriched A allele is associated with lower blood pressure**, potentially representing an adaptive cardiovascular trait in high-altitude environments.*

*Further studies are warranted to investigate the functional mechanisms underlying this association and to explore whether similar effects are observed in other cohorts and ancestries.*