

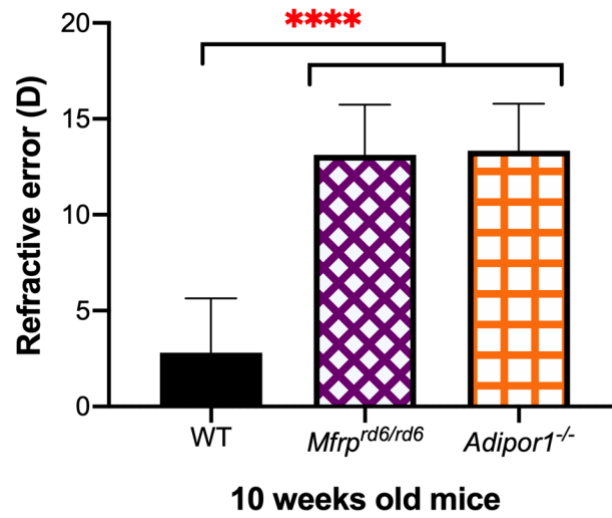


Figure S1: Significant changes in refractive error (Diopter) observed in *Adipor1*<sup>-/-</sup> and *Mfrp*<sup>rd6</sup> mice, by 10 weeks of age.

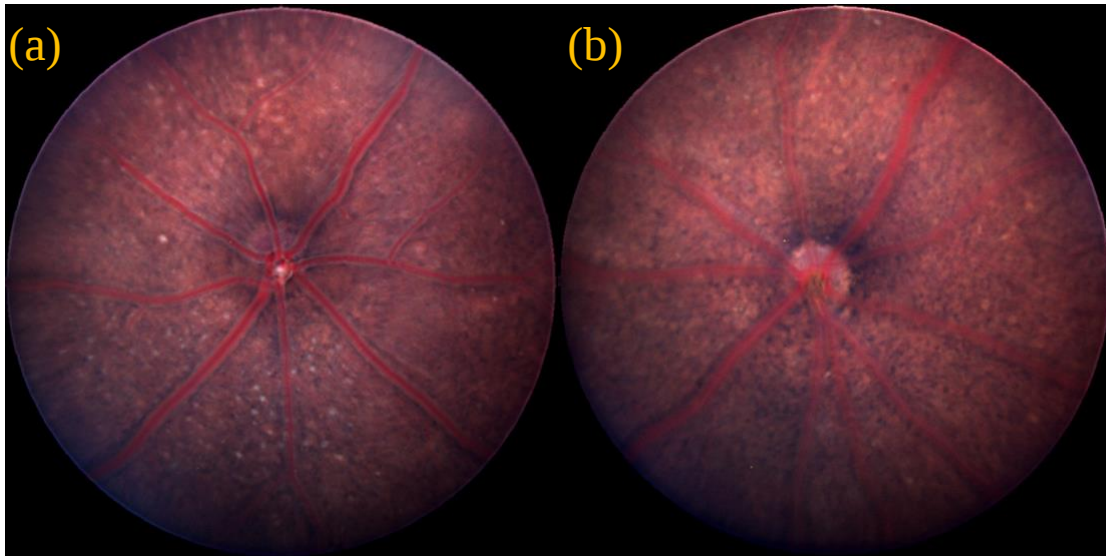


Figure S2: Spots observed by fundus photodocumentation in 10-week-old (a) double heterozygous (*Adipor1*<sup>+/-</sup>/*Mfrp*<sup>+/-rd6</sup>) and (b) single heterozygous *Adipor1*<sup>+/-</sup> mice. N= 5.

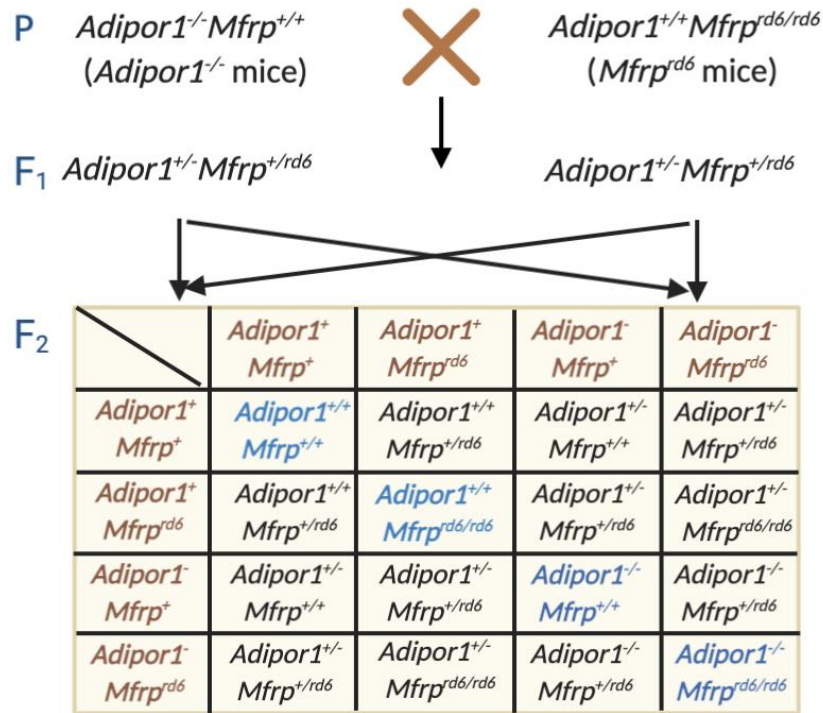


Figure S3: Generation of (*Adipor1*<sup>tm1Dgen</sup> × *Mfrp*<sup>rd6</sup>) F2 intercross progeny. Single gene *Adipor1*<sup>-/-</sup> and *Mfrp*<sup>rd6</sup> mutant mice were crossed to produce *Adipor1*/*Mfrp* double heterozygous mice (F1). The double heterozygous mice were intercrossed to produce F2 mice with nine possible genotypic combinations as shown in the 16 Punnett square.

| Source       | Nparm | DF | Sum of Squares | F Ratio | Prob>F |
|--------------|-------|----|----------------|---------|--------|
| Adipor1      | 2     | 2  | 1.7333333      | 18.5589 | <.0001 |
| Mfrp         | 2     | 2  | 2.6027778      | 27.8681 | <.0001 |
| Adipor1*Mfrp | 4     | 4  | 1.8930577      | 10.1346 | <.0001 |

Table S1: Effect tests obtained from fit model analysis of fundal spots, with the Prob>F = <0.0001 for both individual gene and gene interaction effects, confirming significant effect due to individual mutations as well as due to gene interaction.

| Term                   | Estimate  | Std Error | T Ratio | Prob> t       |
|------------------------|-----------|-----------|---------|---------------|
| Intercept              | 0.2       | 0.096642  | 2.07    | <b>0.0434</b> |
| Adipor1[1-0]           | 0.6       | 0.136672  | 4.39    | <.0001        |
| Adipor1[2-1]           | 0.2       | 0.136672  | 1.46    | 0.1493        |
| Mfrp[1-0]              | -0.075    | 0.123195  | -0.61   | 0.5453        |
| Mfrp[2-1]              | 0.875     | 0.123195  | 7.10    | <.0001        |
| Adipor1[1-0]*Mfrp[1-0] | 0.275     | 0.17084   | 1.61    | 0.1134        |
| Adipor1[1-0]*Mfrp[2-0] | -0.875    | 0.166222  | -5.26   | <.0001        |
| Adipor1[2-1]*Mfrp[1-0] | -0.2      | 0.166222  | -1.18   | 0.2417        |
| Adipor1[2-1]*Mfrp[2-1] | -1.37e-15 | 0.151097  | -0.00   | 1.0000        |

Table S2: Parameter estimates (the change in the response associated with a one-unit change of the predictor, all other predictors being held constant) obtained from fit test analysis for fundal spots, showing which variables/predictor have significant influence on the response. The genotypes were considered ordinal variables with 0 – Wild type; 1- heterozygous and 2- homozygous.

| Source       | Nparm | DF | Sum of Squares | F Ratio  | Prob>F           |
|--------------|-------|----|----------------|----------|------------------|
| Adipor1      | 2     | 2  | 15.308814      | 216.9900 | <b>0.0074</b>    |
| Mfrp         | 2     | 2  | 14.799119      | 209.7655 | <b>&lt;.0001</b> |
| Adipor1*Mfrp | 4     | 4  | 5.946472       | 42.1432  | 0.5715           |

Table S3: Effect tests obtained from fit model analysis for axial length, with the Prob>F = <0.05 for both the individual gene contributions. Gene interaction effect is non-significant, confirming the absence of interaction between *Adipor1* and *Mfrp* for determining axial length.

| Term                   | Estimate  | Std Error | T Ratio | Prob> t          |
|------------------------|-----------|-----------|---------|------------------|
| Intercept              | 3.2392857 | 0.012345  | 262.40  | <b>&lt;.0001</b> |
| Adipor1[1-0]           | -0.00458  | 0.01667   | -0.27   | 0.7839           |
| Adipor1[2-1]           | -0.055956 | 0.019804  | -2.83   | <b>0.0053</b>    |
| Mfrp[1-0]              | -0.005649 | 0.015791  | -0.36   | 0.7210           |
| Mfrp[2-1]              | -0.107922 | 0.014092  | -7.66   | <b>&lt;.0001</b> |
| Adipor1[1-0]*Mfrp[1-0] | -0.000857 | 0.020434  | -0.04   | 0.9666           |
| Adipor1[1-0]*Mfrp[2-0] | 0.0177221 | 0.018653  | 0.95    | 0.3434           |
| Adipor1[2-1]*Mfrp[1-0] | 0.0110892 | 0.024023  | 0.46    | 0.6449           |
| Adipor1[2-1]*Mfrp[2-1] | 0.0111524 | 0.021071  | 0.53    | 0.5973           |

Table S4: Parameter estimates (the change in the response associated with a one-unit change of the predictor, all other predictors being held constant) obtained from fit test analysis for axial length, showing which variables/predictor have significant influence on the response. The genotypes were considered ordinal variables with 0 – Wild type; 1- heterozygous and 2- homozygous.

| Source              | Nparm | DF | Sum of Squares | F Ratio  | Prob>F           |
|---------------------|-------|----|----------------|----------|------------------|
| <i>Adipor1</i>      | 2     | 2  | 15.308814      | 216.9900 | <b>&lt;.0001</b> |
| <i>Mfrp</i>         | 2     | 2  | 14.799119      | 209.7655 | <b>&lt;.0001</b> |
| <i>Adipor1*Mfrp</i> | 4     | 4  | 5.946472       | 42.1432  | <b>&lt;.0001</b> |

Table S5: Effect Tests obtained from fit model analysis for PR degeneration, with the Prob>F = <0.0001 for both individual gene and gene interaction effects, confirming significant effect due to individual mutations as well as due to gene interaction.

| Term                   | Estimate  | Std Error | T Ratio | Prob> t          |
|------------------------|-----------|-----------|---------|------------------|
| Intercept              | 2.5097667 | 0.062606  | 40.09   | <b>&lt;.0001</b> |
| Adipor1[1-0]           | -0.239121 | 0.081443  | -2.94   | <b>0.0041</b>    |
| Adipor1[2-1]           | -1.434896 | 0.081443  | -17.62  | <b>&lt;.0001</b> |
| Mfrp[1-0]              | 0.0041458 | 0.08282   | 0.05    | 0.9602           |
| Mfrp[2-1]              | -1.278356 | 0.071724  | -17.82  | <b>&lt;.0001</b> |
| Adipor1[1-0]*Mfrp[1-0] | -0.20185  | 0.110843  | -1.82   | 0.0714           |
| Adipor1[1-0]*Mfrp[2-0] | 0.1241006 | 0.101042  | 1.23    | 0.2221           |
| Adipor1[2-1]*Mfrp[1-0] | 0.1884038 | 0.108932  | 1.73    | 0.0866           |
| Adipor1[2-1]*Mfrp[2-1] | 0.9040249 | 0.101481  | 8.91    | <b>&lt;.0001</b> |

Table S6: Parameter Estimates (the change in the response associated with a one-unit change of the predictor, all other predictors being held constant) obtained from fit test analysis for PR degeneration, showing which variables/predictor have significant influence on the response. The near-zero coefficients indicate the variables with very little influence on the response. The variables with Prob>|t|= <0.05 are considered to have significant influence on response (PR degeneration in this case). The genotypes were considered ordinal variables with 0 – Wild type; 1- heterozygous and 2- homozygous.

| Adipor1 | Mfrp | Spots |
|---------|------|-------|
| 0       | 0    | 0     |
| 0       | 0    | 0     |
| 0       | 0    | 0     |
| 0       | 0    | 1     |
| 0       | 0    | 0     |
| 0       | 1    | 0     |
| 0       | 1    | 0     |
| 0       | 1    | 1     |
| 0       | 1    | 0     |
| 0       | 1    | 0     |
| 0       | 1    | 0     |
| 0       | 1    | 0     |
| 0       | 1    | 0     |
| 0       | 1    | 0     |
| 1       | 0    | 1     |
| 1       | 0    | 0     |
| 1       | 0    | 1     |
| 1       | 0    | 1     |
| 1       | 0    | 1     |
| 1       | 1    | 1     |
| 1       | 1    | 1     |
| 1       | 1    | 1     |

[illegible]

|   |   |   |
|---|---|---|
| 2 | 2 | 1 |
| 2 | 2 | 1 |

Supplementary S7: Data from fundus spot analysis: Nine genotypic combinations of *Adipor1/Mfrp* double mutants used as independent variables, and data from fundus spot used as a response variable for factorial ANOVA. The genotypes were given variables with 0 – Wild type; 1- heterozygous and 2- homozygous.

| Adipor1 | Mfrp | Axial length |
|---------|------|--------------|
| 0       | 0    | 3.27         |
| 0       | 0    | 3.27         |
| 0       | 0    | 3.18         |
| 0       | 0    | 3.26         |
| 0       | 0    | 3.25         |
| 0       | 0    | 3.27         |
| 0       | 0    | 3.24         |
| 0       | 0    | 3.2          |
| 0       | 0    | 3.2          |
| 0       | 0    | 3.25         |
| 0       | 0    | 3.27         |
| 0       | 0    | 3.23         |
| 0       | 0    | 3.23         |
| 0       | 0    | 3.23         |
| 0       | 1    | 3.27         |
| 0       | 1    | 3.22         |
| 0       | 1    | 3.14         |
| 0       | 1    | 3.15         |
| 0       | 1    | 3.2          |
| 0       | 1    | 3.27         |
| 0       | 1    | 3.25         |
| 0       | 1    | 3.26         |
| 0       | 1    | 3.23         |
| 0       | 1    | 3.29         |
| 0       | 1    | 3.32         |
| 0       | 1    | 3.28         |
| 0       | 1    | 3.26         |
| 0       | 1    | 3.24         |
| 0       | 1    | 3.26         |

|   |   |      |
|---|---|------|
| 0 | 1 | 3.29 |
| 0 | 1 | 3.24 |
| 0 | 1 | 3.2  |
| 0 | 1 | 3.17 |
| 0 | 1 | 3.13 |
| 0 | 1 | 3.25 |
| 0 | 1 | 3.22 |
| 1 | 0 | 3.15 |
| 1 | 0 | 3.27 |
| 1 | 0 | 3.29 |
| 1 | 0 | 3.27 |
| 1 | 0 | 3.23 |
| 1 | 0 | 3.26 |
| 1 | 0 | 3.24 |
| 1 | 0 | 3.3  |
| 1 | 0 | 3.29 |
| 1 | 0 | 3.28 |
| 1 | 0 | 3.21 |
| 1 | 0 | 3.19 |
| 1 | 0 | 3.29 |
| 1 | 0 | 3.14 |
| 1 | 0 | 3.22 |
| 1 | 0 | 3.17 |
| 1 | 0 | 3.19 |
| 1 | 1 | 3.23 |
| 1 | 1 | 3.24 |
| 1 | 1 | 3.25 |
| 1 | 1 | 3.2  |
| 1 | 1 | 3.3  |
| 1 | 1 | 3.19 |
| 1 | 1 | 3.25 |
| 1 | 1 | 3.15 |
| 1 | 1 | 3.27 |
| 1 | 1 | 3.15 |
| 1 | 1 | 3.14 |
| 1 | 1 | 3.24 |
| 1 | 1 | 3.21 |
| 1 | 1 | 3.13 |
| 1 | 1 | 3.26 |

|   |   |      |
|---|---|------|
| 1 | 1 | 3.25 |
| 1 | 1 | 3.24 |
| 1 | 1 | 3.2  |
| 1 | 1 | 3.27 |
| 1 | 1 | 3.25 |
| 1 | 1 | 3.22 |
| 1 | 1 | 3.32 |
| 1 | 1 | 3.25 |
| 1 | 1 | 3.32 |
| 1 | 1 | 3.26 |
| 1 | 1 | 3.2  |
| 1 | 1 | 3.26 |
| 1 | 1 | 3.28 |
| 1 | 1 | 3.2  |
| 1 | 1 | 3.26 |
| 1 | 1 | 3.24 |
| 1 | 1 | 3.14 |
| 1 | 1 | 3.25 |
| 1 | 1 | 3.24 |
| 1 | 1 | 3.3  |
| 1 | 1 | 3.23 |
| 1 | 1 | 3.27 |
| 1 | 1 | 3.28 |
| 1 | 1 | 3.17 |
| 1 | 1 | 3.29 |
| 1 | 1 | 3.24 |
| 1 | 1 | 3.15 |
| 1 | 1 | 3.23 |
| 1 | 1 | 3.14 |
| 1 | 1 | 3.16 |
| 1 | 1 | 3.22 |
| 1 | 1 | 3.29 |
| 1 | 1 | 3.24 |
| 1 | 1 | 3.19 |
| 1 | 1 | 3.15 |
| 0 | 2 | 3.1  |
| 0 | 2 | 3.1  |
| 0 | 2 | 3.11 |
| 0 | 2 | 3.15 |

|   |   |      |
|---|---|------|
| 0 | 2 | 3.07 |
| 0 | 2 | 3.07 |
| 0 | 2 | 3.08 |
| 0 | 2 | 3.05 |
| 0 | 2 | 3.19 |
| 0 | 2 | 3.18 |
| 0 | 2 | 3.16 |
| 0 | 2 | 3.17 |
| 0 | 2 | 3.15 |
| 0 | 2 | 3.18 |
| 0 | 2 | 3.08 |
| 0 | 2 | 3.14 |
| 0 | 2 | 3.13 |
| 0 | 2 | 3.16 |
| 0 | 2 | 3.14 |
| 0 | 2 | 3.13 |
| 0 | 2 | 3.1  |
| 1 | 2 | 3.18 |
| 1 | 2 | 3.13 |
| 1 | 2 | 3.12 |
| 1 | 2 | 3.14 |
| 1 | 2 | 3.1  |
| 1 | 2 | 3.12 |
| 1 | 2 | 3.17 |
| 1 | 2 | 3.11 |
| 1 | 2 | 3.18 |
| 1 | 2 | 3.17 |
| 1 | 2 | 3.19 |
| 1 | 2 | 3.14 |
| 1 | 2 | 3.19 |
| 1 | 2 | 3.06 |
| 1 | 2 | 3.1  |
| 1 | 2 | 3.18 |
| 1 | 2 | 3.09 |
| 1 | 2 | 3.13 |
| 1 | 2 | 3.14 |
| 1 | 2 | 3.12 |
| 2 | 0 | 3.14 |
| 2 | 0 | 3.11 |

|   |   |      |
|---|---|------|
| 2 | 0 | 3.17 |
| 2 | 0 | 3.19 |
| 2 | 0 | 3.24 |
| 2 | 0 | 3.13 |
| 2 | 0 | 3.2  |
| 2 | 0 | 3.25 |
| 2 | 1 | 3.14 |
| 2 | 1 | 3.18 |
| 2 | 1 | 3.19 |
| 2 | 1 | 3.22 |
| 2 | 1 | 3.21 |
| 2 | 1 | 3.2  |
| 2 | 1 | 3.18 |
| 2 | 1 | 3.14 |
| 2 | 1 | 3.24 |
| 2 | 1 | 3.11 |
| 2 | 1 | 3.16 |
| 2 | 1 | 3.19 |
| 2 | 1 | 3.23 |
| 2 | 1 | 3.22 |
| 2 | 1 | 3.14 |
| 2 | 2 | 3.06 |
| 2 | 2 | 3.16 |
| 2 | 2 | 3.07 |
| 2 | 2 | 3.04 |
| 2 | 2 | 3.02 |
| 2 | 2 | 3.09 |
| 2 | 2 | 3.11 |
| 2 | 2 | 3.07 |
| 2 | 2 | 3.12 |
| 2 | 2 | 3.11 |
| 2 | 2 | 3.18 |
| 2 | 2 | 3.19 |
| 2 | 2 | 3.11 |
| 2 | 2 | 3.13 |

Supplementary S8: Data for axial length measurement: Nine genotypic combinations of *Adipor1/Mfrp* double mutants used as independent variables, and axial length values used as response variable for factorial ANOVA. The genotypes were given variables with 0 – Wild type; 1- heterozygous and 2- homozygous.

| Adipor1 | Mfrp | Degeneration |
|---------|------|--------------|
| 0       | 0    | 2.42275      |
| 0       | 0    | 2.0892       |
| 0       | 0    | 2.13795      |
| 0       | 0    | 2.5481       |
| 0       | 0    | 2.9754       |
| 0       | 0    | 2.28405      |
| 0       | 0    | 2.72015      |
| 0       | 0    | 2.6268       |
| 0       | 0    | 2.7835       |
| 1       | 0    | 2.0561       |
| 1       | 0    | 2.22615      |
| 1       | 0    | 1.8972       |
| 1       | 0    | 1.91605      |
| 1       | 0    | 2.37375      |
| 1       | 0    | 2.08895      |
| 1       | 0    | 2.64365      |
| 1       | 0    | 2.20335      |
| 1       | 0    | 2.49975      |
| 1       | 0    | 2.40045      |
| 1       | 0    | 2.60085      |
| 1       | 0    | 2.31475      |
| 1       | 0    | 2.2974       |
| 0       | 1    | 2.69445      |
| 0       | 1    | 2.609        |
| 0       | 1    | 2.6468       |
| 0       | 1    | 2.405        |
| 0       | 1    | 2.4836       |
| 0       | 1    | 2.78175      |
| 0       | 1    | 2.5266       |
| 0       | 1    | 2.7052       |
| 0       | 1    | 2.3637       |
| 0       | 1    | 2.4565       |
| 0       | 1    | 2.2522       |
| 0       | 1    | 2.24215      |
| 1       | 1    | 1.7352       |
| 1       | 1    | 2.04475      |
| 1       | 1    | 1.602        |
| 1       | 1    | 2.1799       |

|   |   |         |
|---|---|---------|
| 1 | 1 | 2.25375 |
| 1 | 1 | 2.10175 |
| 1 | 1 | 2.39535 |
| 1 | 1 | 2.3806  |
| 1 | 1 | 2.3753  |
| 1 | 1 | 1.8931  |
| 1 | 1 | 2.21065 |
| 1 | 1 | 1.73435 |
| 1 | 1 | 2.04155 |
| 2 | 1 | 1.0181  |
| 2 | 1 | 0.8398  |
| 2 | 1 | 0.6133  |
| 2 | 1 | 0.8096  |
| 2 | 1 | 0.8088  |
| 2 | 1 | 1.11765 |
| 2 | 1 | 0.8202  |
| 2 | 1 | 0.79155 |
| 2 | 1 | 0.842   |
| 2 | 1 | 0.8644  |
| 2 | 1 | 0.6809  |
| 2 | 1 | 0.8162  |
| 2 | 1 | 0.78275 |
| 2 | 1 | 0.76505 |
| 2 | 0 | 0.7912  |
| 2 | 0 | 0.8514  |
| 2 | 0 | 0.6231  |
| 2 | 0 | 0.83225 |
| 2 | 0 | 0.7795  |
| 2 | 0 | 1.06085 |
| 2 | 0 | 0.7645  |
| 2 | 0 | 0.99525 |
| 2 | 0 | 0.8237  |
| 0 | 2 | 1.69335 |
| 0 | 2 | 0.92985 |
| 0 | 2 | 1.2851  |
| 0 | 2 | 1.2436  |
| 0 | 2 | 1.5099  |
| 0 | 2 | 1.22505 |
| 0 | 2 | 1.2739  |

|   |   |         |
|---|---|---------|
| 0 | 2 | 1.4026  |
| 0 | 2 | 1.2816  |
| 0 | 2 | 1.25285 |
| 0 | 2 | 1.21845 |
| 0 | 2 | 1.1887  |
| 0 | 2 | 1.1814  |
| 0 | 2 | 0.86005 |
| 0 | 2 | 1.09275 |
| 0 | 2 | 1.12975 |
| 1 | 2 | 0.9421  |
| 1 | 2 | 0.98605 |
| 1 | 2 | 0.83615 |
| 1 | 2 | 1.12595 |
| 1 | 2 | 1.1025  |
| 1 | 2 | 0.8048  |
| 1 | 2 | 0.9176  |
| 1 | 2 | 0.8773  |
| 1 | 2 | 0.9759  |
| 1 | 2 | 0.8569  |
| 1 | 2 | 0.9467  |
| 1 | 2 | 0.85795 |
| 1 | 2 | 0.92605 |
| 1 | 2 | 0.8136  |
| 1 | 2 | 0.81075 |
| 2 | 2 | 0.5882  |
| 2 | 2 | 0.5703  |
| 2 | 2 | 0.5695  |
| 2 | 2 | 0.5357  |
| 2 | 2 | 0.6014  |
| 2 | 2 | 0.66885 |
| 2 | 2 | 0.571   |
| 2 | 2 | 0.5088  |
| 2 | 2 | 0.5111  |
| 2 | 2 | 0.68265 |
| 2 | 2 | 0.4601  |
| 2 | 2 | 0.5615  |
| 2 | 2 | 0.66175 |

Supplementary S9: Data for PR degeneration: Nine genotypic combinations of *Adipor1/Mfrp* double mutants used as independent variables, and PR nuclear count values used as response

variable for factorial ANOVA. The genotypes were given variables with 0 – Wild type; 1- heterozygous and 2- homozygous.