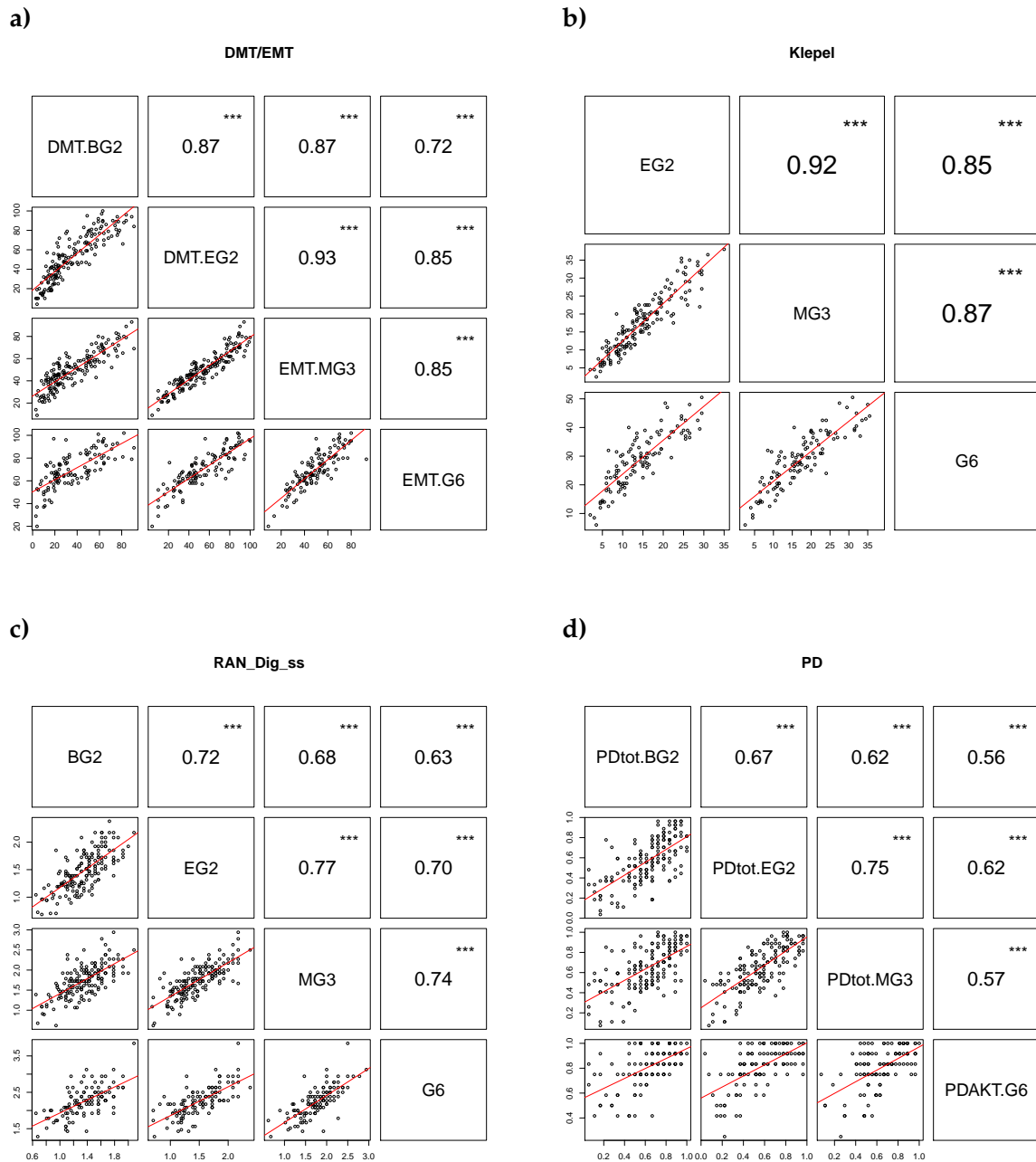
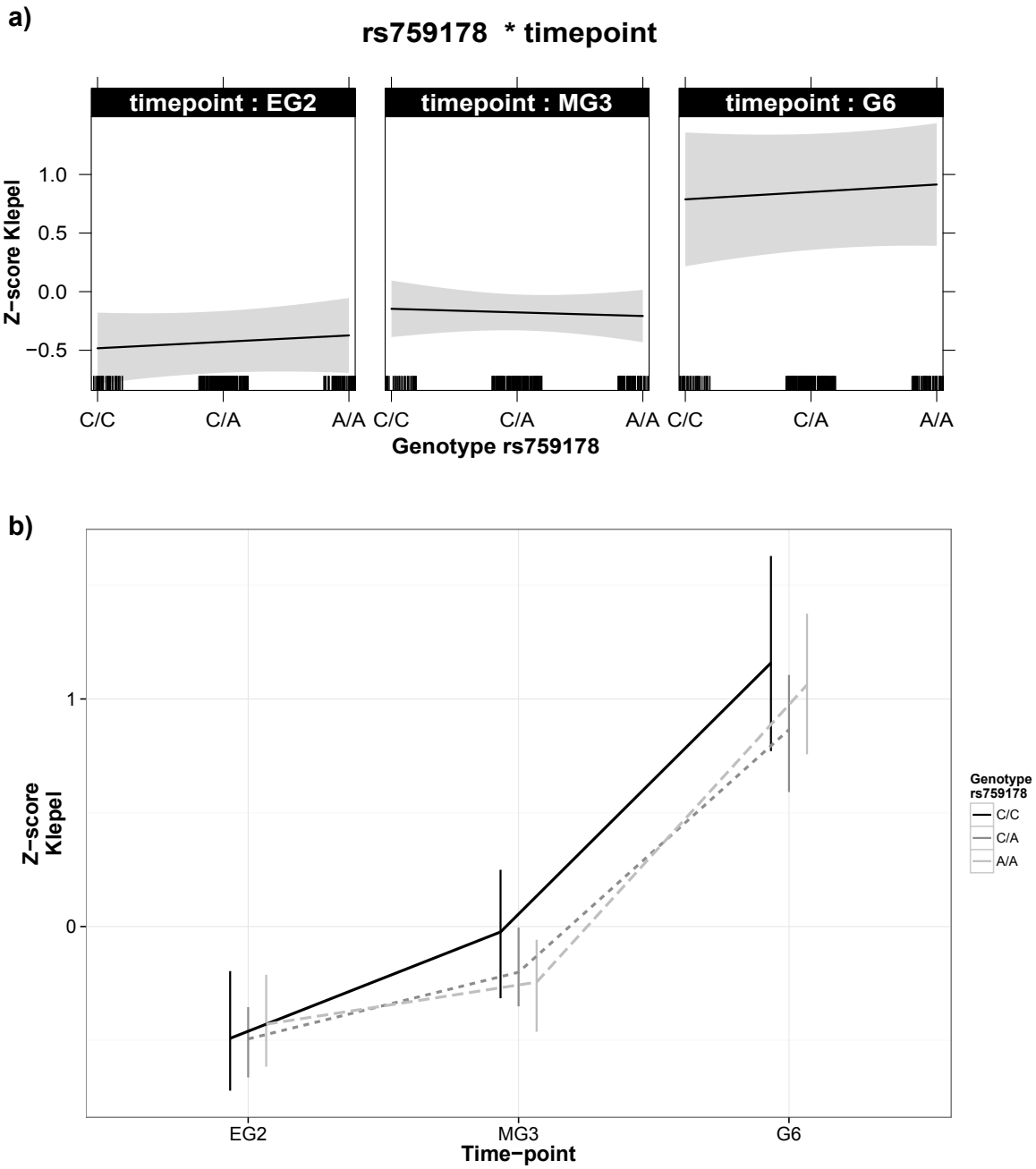


# A Supplementary figures



**Figure S1:** Correlation panel of phenotypes of interest per phenotype. **a)** Word reading fluency: DMT test in time-point BG2 and EG2, EMT test in time-point MG3 and G6; **c)** Rapid Naming Digits; **b)** Nonword reading fluency; **d)** Phoneme deletion tests: PD1, PD2 and PDakt.



**Figure S2:** Z-standardised performance on nonword reading fluency (Klepel test) per educational time-point and genotypic groups of rs759178. a) Interaction plot of time-point x rs759178. b) Fitted residuals to the mixed linear model including the rs759178 and timepoint x rs759178 as variables; the points and error bars are the mean and standard deviation of the mean per time-point.

## B Longitudinal models

### B.0.1 NRT and $PD_{AKT}$ : 1 time-point

$$\text{Phenotype} = \beta_0 + \beta_1 \text{age.c} + \beta_2(1|\text{fam}) + \beta_3 \text{timepoint} + \beta_4 \text{sex} + \beta_5 \text{cohort} + \beta_6 \text{group} \quad (\text{S1})$$

$$\text{Phenotype} = \beta_0 + \beta_1 \text{age.c} + \beta_2(1|\text{fam}) + \beta_3 \text{timepoint} + \beta_4 \text{sex} + \beta_5 \text{cohort} + \beta_6 \text{group} + \beta_7 \text{SNP}_i \quad (\text{S2})$$

### B.0.2 DMT and EMT: 2 time-points

$$\text{Phenotype} = \beta_0 + \beta_1 \text{age.c} + \beta_2(1|\text{fam}) + \beta_3(1|\text{id}) + \beta_4 \text{timepoint} + \beta_5 \text{sex} + \beta_6 \text{cohort} + \beta_7 \text{group} \quad (\text{S3})$$

$$\text{Phenotype} = \beta_0 + \beta_1 \text{age.c} + \beta_2(1|\text{fam}) + \beta_3(1|\text{id}) + \beta_4 \text{timepoint} + \beta_5 \text{sex} + \beta_6 \text{cohort} + \beta_7 \text{group} + \beta_8 \text{SNP}_i \quad (\text{S4})$$

$$\omega \text{ Phenotype} = \beta_0 + \beta_1 \text{age.c} + \beta_2(1|\text{fam}) + \beta_3(1|\text{id}) + \beta_4 \text{timepoint} + \beta_5 \text{sex} + \beta_6 \text{cohort} + \beta_7 \text{group} + \beta_8 \text{SNP}_i + \beta_9 \text{timepoint} * \text{SNP}_i \quad (\text{S5})$$

### B.0.3 Klepel, $RAN_{Dig}$ and $PD_{tot}$ : >3 time-points

$$\text{Phenotype} = \beta_0 + \beta_1 \text{age.c} + \beta_2(1|\text{fam}) + \beta_3(1 + \text{age.c}|\text{id}) + \beta_4 \text{timepoint} + \beta_5 \text{sex} + \beta_6 \text{cohort} + \beta_7 \text{group} \quad (\text{S6})$$

$$\text{Phenotype} = \beta_0 + \beta_1 \text{age.c} + \beta_2(1|\text{fam}) + \beta_3(1 + \text{age.c}|\text{id}) + \beta_4 \text{timepoint} + \beta_5 \text{sex} + \beta_6 \text{cohort} + \beta_7 \text{group} + \beta_8 \text{SNP}_i \quad (\text{S7})$$

$$\text{Phenotype} = \beta_0 + \beta_1 \text{age.c} + \beta_2(1|\text{fam}) + \beta_3(1 + \text{age.c}|\text{id}) + \beta_4 \text{timepoint} + \beta_5 \text{sex} + \beta_6 \text{cohort} + \beta_7 \text{group} + \beta_8 \text{SNP}_i + \beta_9 \text{timepoint} * \text{SNP}_i \quad (\text{S8})$$

## C Supplementary tables

### C.1 Covariates

| Covariate | Levels                           |
|-----------|----------------------------------|
| Age       | Continuous                       |
| Sex       | Male, female                     |
| Cohort    | Groningen, Nijmegen, Amsterdam   |
| Group     | Familial Risk, Non-familial risk |

**Table S1:** List of covariates that have been regressed out from the raw scores per time-point, and that have been included into the linear regression models.

### C.2 Mixed effect models, null models

| Time-points | Fixed terms |     |        |       | Random terms |               | Phenotype   | Measure                             |
|-------------|-------------|-----|--------|-------|--------------|---------------|---|-------------------------------------|
| 1           | age.c       | sex | cohort | group | family       |               | Nonword Repetition<br>Phoneme Deletion                                | NWR<br>$PD_{AKT}$                   |
| 2           | age.c       | sex | cohort | group | family       | subject       | Word Reading Fluency<br>Word Reading Fluency                          | DMT<br>EMT                          |
| >3          | age.c       | sex | cohort | group | family       | age.c subject | Nonword Reading Fluency<br>Rapid Naming of Digits<br>Phoneme Deletion | Klepel<br>$RAN_{dig}$<br>$PD_{tot}$ |

**Table S2:** Null models for each measurement, specifying the fixed effect and random terms for each trait, depending on the number of available measures per subject.

### C.3 Likelihood ratio tests

| Formula   | Df | AIC     | BIC     | logLik  | deviance | $\chi^2$ | $\chi^2_{df}$ | Pr( $\chi^2$ ) |
|---|----|---------|---------|---------|----------|----------|---------------|----------------|
| H <sub>0</sub> Z EMT ~ age.c + (1 fam) + (1 id) + timep + sex + cohort + group  | 10 | 537.15  | 573.02  | -258.57 | 517.15   |          |               |                |
| H <sub>1</sub> Z EMT ~ age.c + (1 fam) + (1 id) + timep + sex + cohort + group + rs6935076                            | 11 | 534.29  | 573.75  | -256.14 | 512.29   | 4.86     | 1             | 0.028          |
| H <sub>0</sub> Z Klepel ~ age.c + (1 fam) + (1 + age.c id) + timep + sex + cohort + group + rs759178                  | 14 | 576.43  | 633.29  | -274.21 | 548.43   |          |               |                |
| H <sub>1</sub> Z Klepel ~ age.c + (1 fam) + (1 + age.c id) + timep + sex + cohort + group + rs759178 + timep*rs759178 | 16 | 573.30  | 638.28  | -270.65 | 541.30   | 7.13     | 2             | 0.028          |
| H <sub>0</sub> Z RAN <sub>dig</sub> ~ age.c + (1 fam) + (1 + age.c id) + timep + sex + cohort + group                 | 14 | 1009.63 | 1071.14 | -490.81 | 981.63   |          |               |                |
| H <sub>1</sub> Z RAN <sub>dig</sub> ~ age.c + (1 fam) + (1 + age.c id) + timep + sex + cohort + group + rs2038137     | 15 | 1005.13 | 1071.04 | -487.57 | 975.13   | 6.50     | 1             | 0.011          |
| H <sub>0</sub> Z RAN <sub>dig</sub> ~ age.c + (1 fam) + (1 + age.c id) + timep + sex + cohort + group                 | 14 | 997.56  | 1058.91 | -484.78 | 969.56   |          |               |                |
| H <sub>1</sub> Z RAN <sub>dig</sub> ~ age.c + (1 fam) + (1 + age.c id) + timep + sex + cohort + group + rs761100      | 15 | 992.63  | 1058.36 | -481.32 | 962.63   | 6.93     | 1             | 0.009          |
| H <sub>0</sub> Z NWR ~ age.c + (1 fam) + sex + cohort + group   | 8  | 443.44  | 467.99  | -213.72 | 427.44   |          |               |                |
| H <sub>1</sub> Z NWR ~ age.c + (1 fam) + sex + cohort + group + rs17236239  | 9  | 439.06  | 466.68  | -210.53 | 421.06   | 6.38     | 1             | 0.01           |

**Table S3:** Likelihood ratio test (LRT) between nested mixed models for the SNPs and timepoint\*SNP terms that are nominally significant. For each LRT, the  $\chi^2$  statistic and associated P value is shown

## C.4 Haplotype analyses

| Time-points<br>Haplotype | BG2 |         |                |       | EG2      |         |                |          | MG3   |         |                |          | G6       |         |                |          |       |
|--------------------------|-----|---------|----------------|-------|----------|---------|----------------|----------|-------|---------|----------------|----------|----------|---------|----------------|----------|-------|
|                          | N   | $\beta$ | R <sup>2</sup> | P     | N        | $\beta$ | R <sup>2</sup> | P        | N     | $\beta$ | R <sup>2</sup> | P        | N        | $\beta$ | R <sup>2</sup> | P        |       |
| rs2038137 rs761100       | 11  | 146     | 0.387          | 0.075 | 8.47e-04 | 149     | 0.312          | 0.046    | 0.008 | 150     | 0.304          | 0.045    | 9.47e-03 | 108     | 0.255          | 0.031    | 0.068 |
| rs2038137 rs761100       | 12  | 146     | -0.234         | 0.008 | 0.300    | 149     | -0.005         | 3.38e-06 | 0.982 | 150     | 1.76e-03       | 4.16e-07 | 0.994    | 108     | 0.042          | 2.35e-04 | 0.875 |
| rs2038137 rs761100       | 22  | 146     | -0.337         | 0.054 | 0.005    | 149     | -0.325         | 0.048    | 0.007 | 150     | -0.316         | 0.047    | 8.05e-04 | 108     | -0.265         | 0.034    | 0.057 |

**Table S4:** Haplotype analyses of rs2038137-rs761100 for Rapid Naming Digits per time-point.

## C.5 Conditional analyses

| SNP <sub>test</sub> | SNP <sub>cov</sub> | BG2 |         |       | EG2 |         |       | MG3 |         |       | G6  |         |       |
|---------------------|--------------------|-----|---------|-------|-----|---------|-------|-----|---------|-------|-----|---------|-------|
|                     |                    | N   | $\beta$ | P     | N   | $\beta$ | P     | N   | $\beta$ | P     | N   | $\beta$ | P     |
| rs2038137           | rs761100           | 159 | -0.134  | 0.531 | 162 | -0.226  | 0.290 | 163 | -0.274  | 0.204 | 111 | -0.186  | 0.489 |
| rs761100            | rs2038137          | 159 | -0.223  | 0.277 | 162 | -0.100  | 0.624 | 163 | -0.053  | 0.796 | 111 | -0.095  | 0.723 |

**Table S5:** Conditional association of RAN digits with rs761100 and rs2038137 from Plink.

## C.6 LME model estimates

### Null model estimates, per phenotype

|              | Estimate | Std. Error | T value |
|--------------|----------|------------|---------|
| (Intercept)  | -0.51    | 0.13       | -3.86   |
| age_years.c  | -0.06    | 0.13       | -0.45   |
| timepointEG2 | 0.71     | 0.10       | 7.22    |
| sex2         | 0.18     | 0.14       | 1.27    |
| cohort2      | -0.21    | 0.15       | -1.41   |
| cohort3      | -0.35    | 0.23       | -1.52   |
| group2       | 0.58     | 0.14       | 4.05    |

**Table S6:** Estimates for the null model of DMT.

|             | Estimate | Std. Error | T value |
|-------------|----------|------------|---------|
| (Intercept) | -0.50    | 0.19       | -2.61   |
| age_years.c | -0.01    | 0.12       | -0.06   |
| timepointG6 | 1.07     | 0.39       | 2.75    |
| sex2        | 0.08     | 0.13       | 0.63    |
| cohort2     | -0.21    | 0.14       | -1.54   |
| cohort3     | -0.31    | 0.22       | -1.41   |
| group2      | 0.45     | 0.13       | 3.37    |

**Table S7:** Estimates for the null model of EMT.

|              | Estimate | Std. Error | T value |
|--------------|----------|------------|---------|
| (Intercept)  | -0.43    | 0.10       | -4.19   |
| age_years.c  | -0.01    | 0.09       | -0.14   |
| timepointMG3 | 0.27     | 0.07       | 3.72    |
| timepointG6  | 1.47     | 0.35       | 4.17    |
| sex2         | 0.00     | 0.11       | 0.02    |
| cohort2      | -0.32    | 0.11       | -2.84   |
| cohort3      | -0.36    | 0.18       | -2.04   |
| group2       | 0.41     | 0.11       | 3.71    |

**Table S8:** Estimates for the null model of Klepel.

|             | Estimate | Std. Error | T value |
|-------------|----------|------------|---------|
| (Intercept) | -0.16    | 0.30       | -0.53   |
| age_years.c | -0.07    | 0.22       | -0.33   |
| sex2        | 0.18     | 0.15       | 1.22    |
| cohort2     | -0.06    | 0.16       | -0.40   |
| cohort3     | -0.05    | 0.23       | -0.22   |
| group2      | 0.58     | 0.16       | 3.63    |

**Table S9:** Estimates for the null model of NWR.

|              | Estimate | Std. Error | T value |
|--------------|----------|------------|---------|
| (Intercept)  | -0.24    | 0.13       | -1.88   |
| age_years.c  | -0.16    | 0.14       | -1.08   |
| timepointEG2 | -0.15    | 0.12       | -1.29   |
| timepointMG3 | 0.34     | 0.22       | 1.55    |
| sex2         | 0.28     | 0.13       | 2.07    |
| cohort2      | -0.17    | 0.14       | -1.22   |
| cohort3      | -0.36    | 0.22       | -1.62   |
| group2       | 0.68     | 0.14       | 4.98    |

**Table S10:** Estimates for the null model of  $PD_{tot}$ .

|              | Estimate | Std. Error | T value |
|--------------|----------|------------|---------|
| (Intercept)  | -0.63    | 0.10       | -6.41   |
| age_years.c  | 0.07     | 0.09       | 0.74    |
| timepointEG2 | 0.21     | 0.08       | 2.75    |
| timepointMG3 | 0.71     | 0.14       | 4.98    |
| timepointG6  | 1.49     | 0.44       | 3.43    |
| sex2         | -0.05    | 0.10       | -0.47   |
| cohort2      | -0.10    | 0.11       | -0.96   |
| cohort3      | 0.06     | 0.17       | 0.36    |
| group2       | 0.12     | 0.10       | 1.12    |

**Table S11:** Estimates for the null model of  $RAN_{dig}$



## Full model estimates

|             | Estimate | Std. Error | T value |
|-------------|----------|------------|---------|
| (Intercept) | -0.90    | 0.27       | -3.37   |
| age_years.c | 0.02     | 0.12       | 0.13    |
| timepointG6 | 0.99     | 0.39       | 2.53    |
| sex2        | 0.07     | 0.13       | 0.50    |
| cohort2     | -0.22    | 0.14       | -1.59   |
| cohort3     | -0.28    | 0.22       | -1.24   |
| group2      | 0.46     | 0.14       | 3.40    |
| rs6935076   | 0.22     | 0.10       | 2.18    |

**Table S12:** Estimates for the full model of EMT rs6935076.

|                       | Estimate | Std. Error | T value |
|-----------------------|----------|------------|---------|
| (Intercept)           | -0.55    | 0.22       | -2.45   |
| age_years.c           | 0.00     | 0.09       | 0.01    |
| timepointMG3          | 0.44     | 0.11       | 4.20    |
| timepointG6           | 1.37     | 0.38       | 3.59    |
| sex2                  | 0.00     | 0.11       | 0.02    |
| cohort2               | -0.32    | 0.11       | -2.78   |
| cohort3               | -0.37    | 0.18       | -2.00   |
| group2                | 0.41     | 0.11       | 3.67    |
| rs759178              | 0.05     | 0.08       | 0.60    |
| timepointMG3:rs759178 | -0.08    | 0.04       | -2.23   |
| timepointG6:rs759178  | 0.02     | 0.07       | 0.33    |

**Table S13:** Estimates for the full model of Klepel timepoint\*rs759178 interaction.

|             | Estimate | Std. Error | T value |
|-------------|----------|------------|---------|
| (Intercept) | -0.52    | 0.34       | -1.52   |
| age_years.c | -0.13    | 0.22       | -0.59   |
| sex2        | 0.19     | 0.15       | 1.27    |
| cohort2     | -0.10    | 0.16       | -0.61   |
| cohort3     | -0.19    | 0.23       | -0.82   |
| group2      | 0.53     | 0.16       | 3.25    |
| rs17236239  | 0.29     | 0.12       | 2.49    |

**Table S14:** Estimates for the full model of NWR rs17236239.

|              | Estimate | Std. Error | T value |
|--------------|----------|------------|---------|
| (Intercept)  | -0.28    | 0.17       | -1.68   |
| age_years.c  | 0.10     | 0.09       | 1.05    |
| timepointEG2 | 0.19     | 0.08       | 2.48    |
| timepointMG3 | 0.67     | 0.14       | 4.69    |
| timepointG6  | 1.36     | 0.43       | 3.13    |
| sex2         | -0.03    | 0.10       | -0.30   |
| cohort2      | -0.14    | 0.11       | -1.27   |
| cohort3      | 0.05     | 0.17       | 0.27    |
| group2       | 0.13     | 0.10       | 1.24    |
| rs2038137    | -0.19    | 0.07       | -2.53   |

**Table S15:** Estimates for the full model of  $RAN_{dig}$  rs2038137.

|              | Estimate | Std. Error | T value |
|--------------|----------|------------|---------|
| (Intercept)  | -0.23    | 0.18       | -1.29   |
| age_years.c  | 0.08     | 0.09       | 0.89    |
| timepointEG2 | 0.20     | 0.08       | 2.58    |
| timepointMG3 | 0.69     | 0.14       | 4.75    |
| timepointG6  | 1.42     | 0.44       | 3.24    |
| sex2         | -0.05    | 0.10       | -0.45   |
| cohort2      | -0.14    | 0.11       | -1.30   |
| cohort3      | 0.03     | 0.17       | 0.16    |
| group2       | 0.12     | 0.10       | 1.14    |
| rs761100     | -0.19    | 0.07       | -2.61   |

**Table S16:** Estimates for the full model of  $RAN_{dig}$  rs761100.