A Supplementary figures
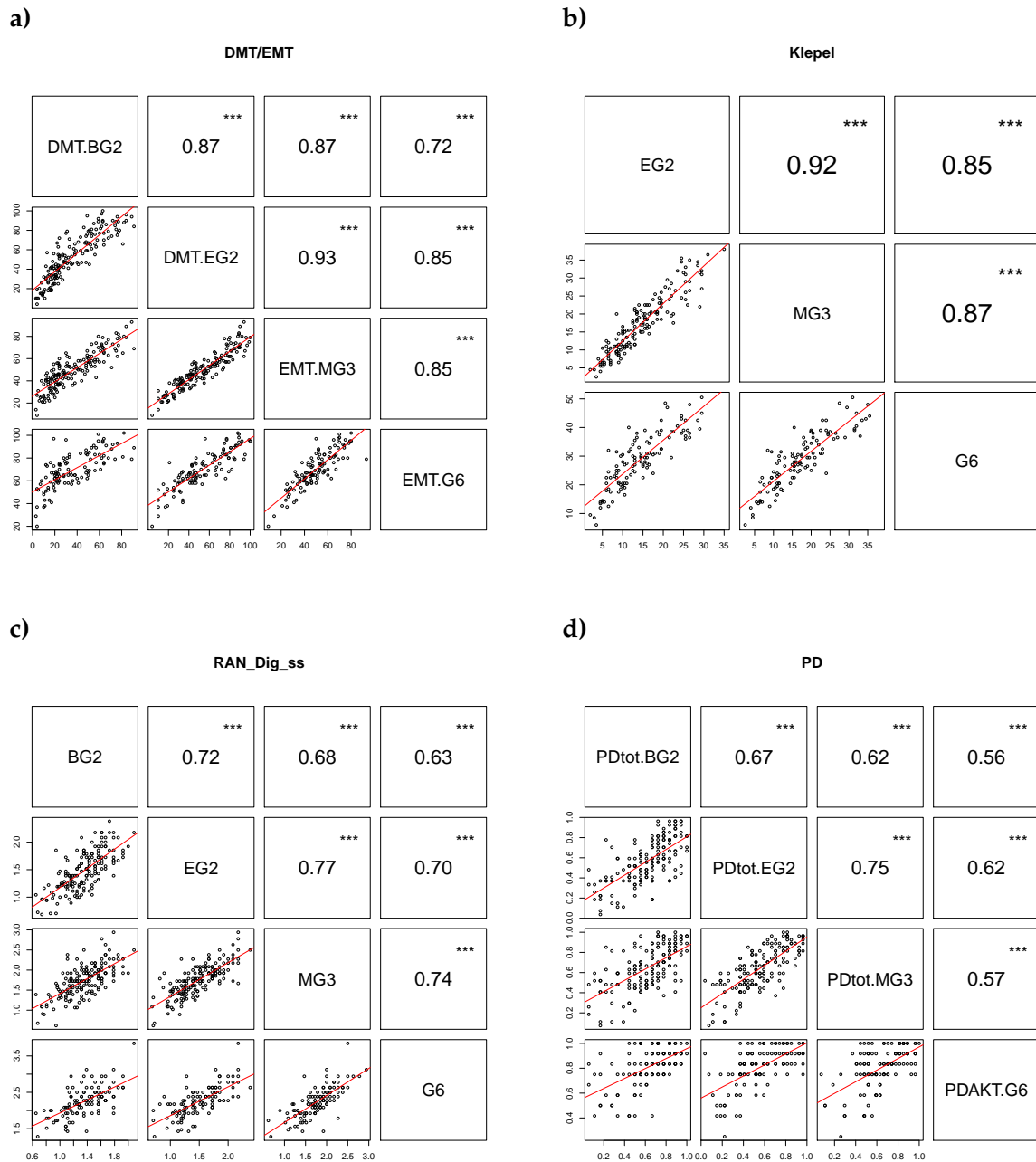
a)

b)

c)

d)

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.
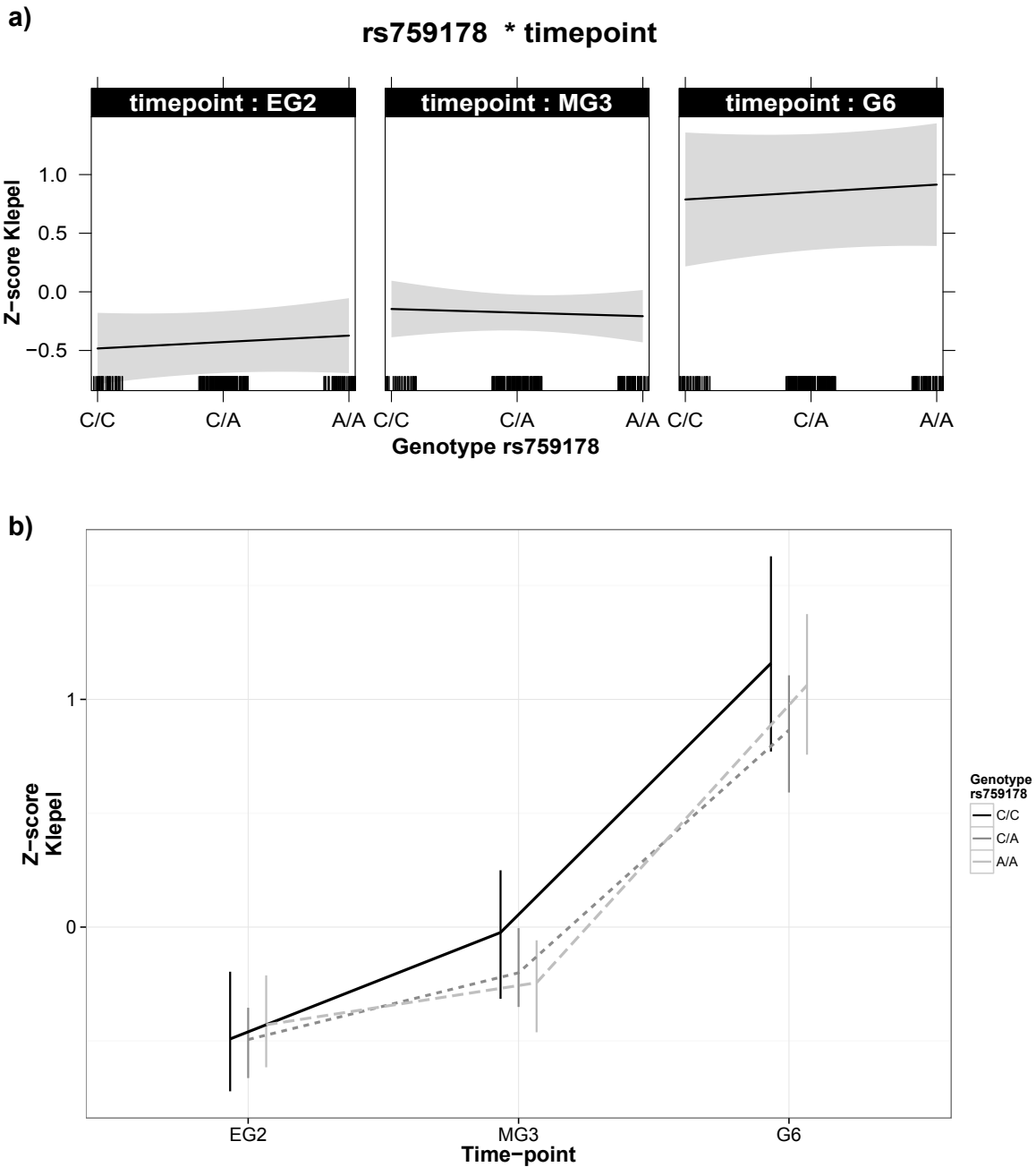
a)

rs759178 * timepoint

b)

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

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

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

B.0.2 DMT and EMT: 2 time-points

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

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

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

B.0.3 Klepel, RAN$_{Dig}$ and PD$_{tot}$: >3 time-points

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

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

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

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	NWR
							Phoneme Deletion	PD_{AKT}
2	age.c	sex	cohort	group	family	subject	Word Reading Fluency	DMT
							Word Reading Fluency	EMT
>3	age.c	sex	cohort	group	family	age.c|subject	Nonword Reading Fluency	Klepel
							Rapid Naming of Digits	RAN_{dig}
							Phoneme Deletion	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	χ^2	χ^2_{df}	$Pr(\chi^2)$
H_0	Z EMT ~ age.c + (1|fam) + (1|id) + timep + sex + cohort + group	10	537.15	573.02	-258.57	517.15			
H_1	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_0	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_1	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_0	Z RAN_{dig} ~ age.c + (1|fam) + (1 + age.c|id) + timep + sex + cohort + group	14	1009.63	1071.14	-490.81	981.63			
H_1	Z RAN_{dig} ~ 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_0	Z RAN_{dig} ~ age.c + (1|fam) + (1 + age.c|id) + timep + sex + cohort + group	14	997.56	1058.91	-484.78	969.56			
H_1	Z RAN_{dig} ~ 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_0	Z NWR ~ age.c +(1|fam) + sex + cohort + group	8	443.44	467.99	-213.72	427.44			
H_1	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 χ^2 statistic and associated P value is shown

C.4 Haplotype analyses

Time-points		BG2				EG2				MG3				G6			
Haplotype		N	β	R^2	P	N	β	R^2	P	N	β	R^2	P	N	β	R^2	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_{test}	SNP_{cov}	BG2			EG2			MG3			G6		
		N	β	P	N	β	P	N	β	P	N	β	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.