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Supplement to Partitioning Phenotypic Variance due to Parent-of-Origin Effects using Genomic Relatedness Matrices

Contents

Sample Description

ALSPAC is a geographically limited birth cohort based on women in Avon (southwestern England) who were pregnant with due-dates between April and December 1991, inclusive (Boyd *et al.*, 2012; Fraser *et al.*, 2013) . The initial sample size was 15247 pregnancies, from which 14701 children survived to age 1. Over the next three decades, this set of parents (including mothers' partners) and children has completed an extensive set of questionnaires, clinical studies, and biological samples. Parental consent and child's assent (and child's consent, upon majority) were obtained for each measurement occasion. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

The ALSPAC children and mothers were genotyped separately. ALSPAC children were genotyped on Illumina HumanHap550 quad-chip platforms by the Wellcome Trust Sanger Institute (Cambridge, UK) and by the Laboratory Corporation of America (Burlington, USA). ALSPAC mothers were genotyped on Illumina HumanHap660W quad-chip platform by Centre National de Génotypage (Évry, FR). Individuals were QC-filtered for: genotype missingness, X-chromosome mismatch, extreme autosomal heterozygosity, and cryptic relatedness (defined as IBD > 0.125). SNPs were QC-filtered for: excessive missingness, a significant ($p < 1 \times 10^{-6}$) test of Hardy-Weinberg disequilibrium, and minor allele frequency under 1%.

The 465740 SNPs in common to mothers and children were used for phasing. Phasing was done with ShapeIt v2.r727 (Delaneau, Coulonges, and Zagury, 2008), based on a phased version of the 1000 genomes reference panel (Phase 1, Version 3), which we took from the Impute2 reference data repository (haplotype release date December 2013).

Using ancestry-informative principal components, we retained 5564 duos of European ancestry, which was reduced to 5558 duos giving consent to all measures. Across the 38 phenotypes which we analyzed, the numbers of duos with complete data differed slightly; the smallest subsample was 2136 duos (age at menarche), while the largest was 4753 duos (gestational age).

We used a *Perl* script to resolve the parent-of-origin of children's SNPs. The script requires mothers' and children's phased genotypes in *IMPUTE2* format (Marchini *et al.*, 2007). When parental origin is ambiguous (the child is heterozygous at a locus and the locus's membership in the two haplotypes are unclear), the alleles at the locus are assigned to the closest resolved haplotypes. The script outputs the phased genotypes with parent-of-origin assigned to *MACH*-formatted text files.

Phenotyping Methods

PERINATAL MEASURES

Length of gestation was based on last menstrual period date, ultrasound assessment or other clinical indicators. Where there was conflict between the maternal report and ultrasound assessment, an experienced obstetrician reviewed the clinical records and made a best estimate. Birthweight was derived from obstetric data and from central birth notification data: where values disagreed by <100g then the lowest value was accepted; if

the values disagreed by >100g then the value was coded as missing. Crown-heel length and head circumference of newborns were measured by trained staff a few days after birth. Ponderal index was calculated as birthweight (g) x 100 / (crown heel length (cm)^3).

ANTHROPOMETRIC MEASURES (7 year old clinic)

Height was measured to the nearest 0.1 cm using a Harpenden stadiometer (Holtain Ltd., Crymych, UK) and weight was measured to the nearest 50 g using Tanita weighing scales (Tanita UK Ltd, Uxbridge). Sitting Height was measured using the Harpenden sitting height table anthropometer to the last complete mm. The child was positioned on the table with back straight and thighs horizontal. Feet were supported on the footrest so that the knees were at right angles. Waist circumference was measured to the nearest mm at the minimum circumference of the abdomen between the iliac crests and the lowest ribs, the tape was kept perpendicular to the long axis of the body, touching the skin but not compressing the tissue. Hip circumference was measured to the nearest mm at the point of maximum circumference around the child's hips/buttocks, again with the tape kept perpendicular to the long axis of the body segment. The measurement was done over the child's pants. Body mass index was calculated as weight (in kg) divided by height (in m) squared. Waist hip ratio was calculated as waist circumference (in cm) divided by hip circumference (in cm).

BLOOD PRESSURE AND PULSE RATE (7 year old clinic)

Both blood pressure and pulse rates were measured using a Dinamap 9301 Vital Signs monitor. Two readings of systolic and diastolic blood pressure and pulse rates were recorded and averages taken.

HEMOGLOBIN (7 year old clinic)

Blood was sampled using an EDTA tube and hemoglobin levels were measured using the Haemocue system.

INTELLIGENCE (8 year old clinic)

The WISC-III UK was used to assess cognitive function. A short form of the measure was employed where alternate items (always starting with item number 1 in the standard form) were used for all subtests, with the exception of the coding subtest which was administered in its full form. Hence the length of the session was reduced and children were less likely to tire. All tests were administered by members of the psychology team. The ten WISC subtests comprised five verbal subtests:

1. Information (assessing the child's knowledge);
2. Similarities (where similarities between things, e.g., in what way are red and blue alike? must be explained);
3. Arithmetic (comprising mental arithmetic questions);
4. Vocabulary (ascertaining the child's understanding of the meaning of different words)
5. Comprehension (where the child is asked questions about different situations, e.g. why are names in the telephone book in alphabetical order?),

and five performance subtests:

1. Picture completion (where the child must point out what is missing from each of a series of pictures);
2. Coding (where shapes corresponding to different numbers must be copied as quickly as possible within a specified time limit);
3. Picture arrangement (where pictures must be ordered to make a meaningful sequence);
4. Block design (where pictures of specific patterns of blocks are copied with real blocks)
5. Object assembly (which involves putting together puzzles).

LUNG FUNCTION MEASURES (8 year old clinic)

American Thoracic Society (1995) criteria were used as the basis to select lung function measurements that were acceptable for analysis. Spirometers were calibrated at the beginning of each half-day session according to the manufacturer's instructions using a 1L calibration syringe. Pneumotachograph screens were dried with warm air between subjects and cleaned at the end of each day's testing, being allowed to dry overnight. Measurements were made in the sitting position without nose-clips. Children were instructed to fill their lungs completely and blow as hard and fast as possible until there was 'no air' left in their lungs. An on-screen incentive was used to encourage maximal expiratory effort (this comprised a visual of a fairground bell-and-hammer' game – the object being to ring the bell). 'Start of test' criteria were automated within the Spirotrac

programme and manoeuvres failing to meet these were rejected. Each subject was instructed to blow at least three times to produce a maximal expiratory manoeuvre. Repeatability criteria were set to three manoeuvres within 200ml FVC. Most children could not sustain forced expiration for the recommended 6s period. Curves were accepted if they reached a clear plateau of flow and the expiration had continued for >1 second and was judged by the tester to be a maximal effort. The best of three curves was selected for analysis (on the basis of an acceptable curve with the highest FVC measurement). All flow-volume curves were inspected post-hoc by a respiratory paediatrician (John Henderson) to ensure that satisfactory reproducibility criteria had been met and the optimal curve was selected for analysis.

Standard deviation scores adjusted for height, age and gender were calculated for FVC (the volume change of the lung between a full inspiration to total lung capacity and a maximal expiration to residual volume) and FEV1 (the volume exhaled during the first second of a forced expiratory manoeuvre started from the level of total lung capacity). The ratio of FEV1:FVC was calculated on the unadjusted values.

DXA DERIVED MEASURES (9 year old clinic)

Total body DXA scans were performed on all participants using a Lunar Prodigy scanner (Lunar Radiation Corp, Madison, WI) with paediatric scanning software (GE Healthcare Bio-Sciences Corp., Piscataway, NJ). DXA measures of BMD and bone area were derived for total body (less head). All DXA scans were subsequently reviewed by a trained researcher, and re-analysed as necessary, to ensure that borders between adjacent ROI's were placed correctly by the automated software. The coefficient of variation for Total Body Less Head BMD measures was 0.8%, based on the analysis of 122 children who had

two scans performed on the same day. Data on lean mass and fat mass (total body) were also obtained from the same scans.

BLOOD MEASURES (9 year old clinic)

Non-fasting blood samples were taken using standard procedures, with samples spun immediately and frozen at -80C. The measurements were assayed in 2008 after a median of 7.5 years in storage with no previous freeze-thaw cycles during this period Total plasma adiponectin concentrations were determined using ELISA (R&D Systems, Abingdon, UK), with the interassay coefficient of variation (CV) being 7%. Plasma lipids (i.e., total cholesterol, triglycerides, and high-density lipoprotein cholesterol) measured by a modification of the standard Lipid Research Clinics Protocol using enzymatic reagents for lipid determinations, leptin measured by an in-house ELISA validated against commercial methods, high-sensitivity interleukin 6 (IL-6) measured by ELISA (R&D Systems, Abingdon, UK), and C-reactive protein (CRP) measured by automated particle-enhanced immune-turbidimetric assay (Roche UK). All assay coefficients of variation were less than 5 % (Sayers et al. 2010).

2D:4D RATIO (11 year old clinic)

Participants' hands were photocopied during the eleven year old clinic visit, and measurements of the second and fourth fingers were taken from the photocopies with the use of digital calipers (accurate to 0.1 mm). The 2D:4D was calculated as the length of the second digit divided by the length of the fourth digit.

AGE AT MENARCHE

Age at menarche was derived from a series of nine postal questionnaires pertaining to pubertal development, sent approximately yearly from age 8 to 17 years. The questionnaires asked 'Has your daughter started her menstrual periods yet?' and, if yes: 'How old was your daughter when she had her first period?' Answers were given in years and months. These data were supplemented by questionnaires administered to girls at two research clinics attended at 12 years 10 months and 13 years 10 months asking 'Have you started your periods yet?' and, if yes: 'When did you have your first period?' The first-reported age at onset was used, as these results are least likely to be affected by recall bias (Sequeira et al. 2017).

TRANSFORMATIONS

The following variables were highly skewed and so subjected to inverse normal transformations before analysis: waist hip ratio, hip circumference, waist circumference, BMI, ponderal index, FEV1/FVC ratio, bone area, fat mass, lean mass, triglycerides, VLDL, LDL, HDL, IL6, CRP, Leptin and adiponectin.

Supplementary Tables

Table SI: Diagonal elements of ALSPAC GRMs

Summary statistics of the diagonal elements of GRMs of individuals in the ALSPAC data, for the additive (A_{ii}), dominance (Δ_{ii}), and parent-of-origin effects (Γ_{ii}), respectively. The expected value for each is 1 in the absence of inbreeding.

GRM	N	mean	sd	median	trimmed	mad	Min	max	range	skew	kurtosis
A_{ii}	4753	1.0	0.01	1	1.0	0.01	0.98	1.03	0.05	0.24	0.41
Δ_{ii}	4753	1.0	0.03	1	1.0	0.02	0.93	1.18	0.25	0.65	1.25
Γ_{ii}	4753	0.98	0.01	0.98	0.98	0.01	0.96	1.02	0.06	0.19	0.45

Table SII: Descriptive Statistics of 36 ALSPAC Phenotypes

Phenotype	Units	N	Mean	SD	Min	Max	Mean Age(Months)	Age SD	Min Age	Mx Age
2D:4D (Left hand)	-	3847	0.966	0.032	0.844	1.087	140.781	2.721	127	163
Adiponectin	ng/ml	2972	13193.417	5490.027	90.368	43064.130	-	-	-	-
Age at first tooth	months	4262	6.989	2.364	1.000	16.000	-	-	-	-
Age at Menarche	Years	2136	12.673	1.145	8.417	16.667	-	-	-	-
Birth Weight	G	4689	3487.250	469.701	1752.000	5140.000	-	-	-	-
Body Mass Index	-	4065	16.187	2.001	10.848	29.686	89.997	3.133	82	113
Bone Area	cm^2	3858	1136.374	161.243	679.381	1820.254	118.213	3.602	105	138
Bone Mineral Density	g/cm^2	3858	0.777	0.053	0.603	0.982	118.213	3.602	105	138
C-reactive Protein	mg/L	2974	0.735	2.442	0.010	67.440	-	-	-	-
Crown Heel Length	cm	3848	50.910	2.145	42.000	59.000	-	-	-	-
Diastolic Blood Pressure	mmHg	4013	56.202	6.440	37.000	82.500	90.000	3.149	82	113
Fat Mass	G	3858	8489.803	4955.289	1268.194	34205.771	118.213	3.602	105	138
FEV1	Z score	3624	0.021	0.979	-3.768	3.782	103.467	3.331	89	124
FEV1/FVC	-	3625	0.885	0.066	0.501	1.000	103.467	3.330	89	124
FVC	Z score	3675	0.009	0.975	-3.205	3.994	103.470	3.319	89	124
Gestational Age	weeks	4753	39.807	1.284	37.000	44.000	-	-	-	-
HDL	mmol/L	2974	1.400	0.307	0.440	2.680	-	-	-	-
Head Circumference	cm	3894	34.937	1.273	30.500	40.000	-	-	-	-
Height	cm	4069	125.861	5.546	104.400	148.200	89.992	3.116	82	113
Hemoglobin	g/L	3217	124.549	7.588	95.000	156.000	90.040	3.237	82	113
Hip Circumference	cm	4064	65.431	5.176	51.400	95.200	89.995	3.130	82	113

Interleukin-6	pg/ml	2966	1.271	1.572	0.007	20.051	-	-	-	-
LDL	mmol/L	2974	2.353	0.595	0.563	9.184	-	-	-	-
Lean Mass	g	3858	24498.312	3172.135	15847.163	42012.328	118.213	3.602	105	138
Leptin	ng/mL	2973	8.253	8.109	0.900	92.000	-	-	-	-
Number of teeth (15 months)	-	4376	9.591	3.326	0.000	20.000	-	-	-	-
Performance IQ	-	3847	100.549	16.826	46.000	145.000	103.475	3.410	89	125
Ponderal Index	$gx100/cm^3$	3795	2.632	0.242	1.566	4.025	-	-	-	-
Pulse Rate	Bpm	4013	82.920	10.610	42.000	126.000	90.000	3.149	82	113
Sitting Height	cm	4068	67.990	2.773	59.200	78.800	89.998	3.132	82	113
Systolic Blood Pressure	mmHg	4016	98.640	9.067	66.500	135.000	89.998	3.147	82	113
Total IQ	-	3836	105.454	16.265	45.000	149.000	103.475	3.414	89	125
Triglycerides	mmol/L	2974	1.141	0.584	0.180	8.910	-	-	-	-
Verbal IQ	-	3850	108.536	16.638	50.000	155.000	103.477	3.423	89	125
Waist-Hip Ratio	-	4062	0.861	0.041	0.685	1.030	89.992	3.123	82	113
Waist Circumference	cm	4065	56.348	5.057	46.200	90.000	89.997	3.132	82	113

N: Number of

SD: Standard deviation

Min: Minimum

Max: Maximum

Table SIII: GCTA Estimates of *G-REMLadp* models in ALSPAC

Variance component estimates of 36 standardized phenotypes in ALSPAC, estimates and standard errors generated using GCTA-GREML to estimate multiple components simultaneously. VarA: proportion of phenotypic variance attributable to additive genetic effects; SEvarA: standard error of proportion of phenotypic variance attributable to additive genetic effects. VarD: proportion of phenotypic variance attributable to dominance effects; SEvarD: standard error of proportion of phenotypic variance attributable to dominance effects. VarP: proportion of phenotypic variance attributable to parent-of-origin effects; SEvarP: standard error of proportion of phenotypic variance attributable to parent-of-origin effects. Compare Table SIV for estimates fit using GCTA-GREML to fit single variance components and Table SVII for estimates based on unstandardized phenotypes.

Phenotype	VarA	SEvarA	VarD	SEvarD	VarP	SEvarP
2D:4D (Left hand)	0.301	0.090	-0.019	0.133	-0.025	0.091
Adiponectin	0.140	0.117	-0.123	0.169	-0.039	0.118
Age at first tooth	0.425	0.083	0.114	0.121	0.156	0.082
Age at Menarche	0.337	0.162	0.195	0.246	0.179	0.162
Birth Weight	0.317	0.075	-0.118	0.110	0.021	0.074
Body Mass Index	0.399	0.087	-0.010	0.128	0.086	0.087
Bone Area	0.455	0.091	-0.065	0.133	0.086	0.090
Bone Mineral Density	0.454	0.091	-0.075	0.133	0.084	0.090
C-reactive Protein	0.165	0.115	0.119	0.172	0.068	0.119
Crown Heel Length	0.292	0.090	-0.138	0.132	0.038	0.091
Diastolic Blood Pressure	0.193	0.088	-0.076	0.132	0.114	0.088
Fat Mass	0.502	0.090	0.339	0.134	0.016	0.088
FEV1	0.300	0.098	-0.040	0.140	0.073	0.100
FEV1/FVC	0.376	0.097	0.060	0.143	0.018	0.096
FVC	0.370	0.097	0.017	0.136	0.159	0.097
Gestational Age	0.175	0.074	0.132	0.112	-0.055	0.072
HDL	0.114	0.114	-0.201	0.171	-0.024	0.117
Head Circumference	0.433	0.089	0.042	0.134	-0.095	0.088
Height	0.468	0.088	0.029	0.128	-0.146	0.082
Hemoglobin	0.423	0.107	0.274	0.159	0.038	0.108
Hip Circumference	0.507	0.088	-0.026	0.129	0.060	0.086
Interleukin-6	0.115	0.119	0.255	0.174	0.092	0.118
LDL	0.124	0.117	-0.184	0.173	0.072	0.118
Lean Mass	0.356	0.091	0.133	0.138	0.009	0.091
Leptin	0.416	0.117	0.018	0.170	0.041	0.115
Number of teeth (15 months)	0.325	0.082	-0.011	0.117	0.019	0.079
Performance IQ	0.209	0.090	0.230	0.135	-0.029	0.091
Ponderal Index	0.237	0.094	0.005	0.137	-0.018	0.090

Pulse Rate	0.112	0.087	-0.044	0.128	-0.051	0.084
Sitting Height	0.450	0.087	0.085	0.127	-0.111	0.083
Systolic Blood Pressure	0.313	0.088	-0.147	0.130	0.145	0.088
Total IQ	0.357	0.089	0.260	0.134	-0.142	0.088
Triglycerides	0.013	0.115	-0.063	0.171	-0.057	0.120
Verbal IQ	0.440	0.089	0.295	0.133	-0.098	0.089
Waist-Hip Ratio	0.100	0.085	-0.242	0.124	-0.022	0.085
Waist Circumference	0.450	0.088	-0.091	0.127	-0.019	0.085

Table SIV: Single-component GCTA Estimates of *G-REMLadp* models in ALSPAC

Standardized variance component estimates of 36 phenotypes in ALSPAC generated using three runs of GCTA-GREML, fitting single components each time. VarA: proportion of phenotypic variance attributable to additive genetic effects; SEvarA: standard error of proportion of phenotypic variance attributable to additive genetic effects. VarD: proportion of phenotypic variance attributable to dominance effects; SEvarD: standard error of proportion of phenotypic variance attributable to dominance effects. VarP: proportion of phenotypic variance attributable to parent-of-origin effects; SEvarP: standard error of proportion of phenotypic variance attributable to parent-of-origin effects. Compare Table SIII for estimates fit using GCTA-GREML to fit multiple variance components.

Phenotype	VarA	SEvarA	VarD	SEvarD	VarP	SEvarP
2D:4D (Left hand)	0.302	0.090	-0.036	0.134	-0.032	0.092
Adiponectin	0.142	0.117	-0.128	0.169	-0.040	0.118
Age at first tooth	0.415	0.084	0.097	0.123	0.138	0.083
Age at Menarche	0.334	0.162	0.198	0.248	0.170	0.163
Birth Weight	0.312	0.075	-0.092	0.111	0.008	0.074
Body Mass Index	0.396	0.088	-0.029	0.130	0.068	0.088
Bone Area	0.449	0.092	-0.036	0.136	0.059	0.091
Bone Mineral Density	0.448	0.092	-0.048	0.135	0.057	0.091
C-reactive Protein	0.169	0.115	0.120	0.172	0.077	0.119
Crown Heel Length	0.293	0.090	-0.141	0.133	0.030	0.092
Diastolic Blood Pressure	0.191	0.088	-0.045	0.132	0.116	0.088
Fat Mass	0.502	0.090	0.339	0.136	0.025	0.090
FEV1	0.299	0.099	-0.040	0.141	0.070	0.100
FEV1/FVC	0.376	0.098	0.052	0.144	0.028	0.097
FVC	0.371	0.097	0.038	0.138	0.164	0.098
Gestational Age	0.174	0.074	0.127	0.113	-0.056	0.072
HDL	0.112	0.114	-0.199	0.171	-0.038	0.117
Head Circumference	0.436	0.089	0.036	0.136	-0.109	0.088
Height	0.474	0.088	0.036	0.129	-0.163	0.083
Hemoglobin	0.437	0.107	0.330	0.161	0.055	0.109
Hip Circumference	0.505	0.088	-0.024	0.131	0.041	0.087
Interleukin-6	0.116	0.120	0.264	0.174	0.094	0.118
LDL	0.119	0.117	-0.176	0.173	0.080	0.119
Lean Mass	0.359	0.091	0.152	0.139	-0.019	0.091
Leptin	0.417	0.117	0.061	0.171	0.039	0.116

Number of teeth (15 months)	0.326	0.082	-0.028	0.117	0.021	0.079
Performance IQ	0.218	0.090	0.246	0.135	-0.031	0.092
Ponderal Index	0.238	0.094	0.029	0.138	-0.025	0.090
Pulse Rate	0.110	0.087	-0.044	0.128	-0.051	0.084
Sitting Height	0.453	0.087	0.066	0.128	-0.129	0.083
Systolic Blood Pressure	0.303	0.088	-0.085	0.131	0.150	0.089
Total IQ	0.364	0.089	0.281	0.135	-0.158	0.089
Triglycerides	0.013	0.115	-0.066	0.171	-0.059	0.120
Verbal IQ	0.441	0.089	0.296	0.134	-0.122	0.089
Waist-Hip Ratio	0.097	0.086	-0.239	0.124	-0.021	0.086
Waist Circumference	0.450	0.088	-0.080	0.130	-0.029	0.086

Table SV: HE Regression Estimates of G-REMLadp models in ALSPAC

Variance component estimates of 36 standardized phenotypes in ALSPAC, estimates and standard errors generated with single-components HE regression. VarA: proportion of phenotypic variance attributable to additive genetic effects; SEvarA: standard error of proportion of phenotypic variance attributable to additive genetic effects. VarD: proportion of phenotypic variance attributable to dominance effects; SEvarD: standard error of proportion of phenotypic variance attributable to dominance effects. VarP: proportion of phenotypic variance attributable to parent-of-origin effects; SEvarP: standard error of proportion of phenotypic variance attributable to parent-of-origin effects. Compare Table SIII for estimates fit using GCTA-GREML to estimate variance components.

Phenotype	VarA	SEvarA	VarD	SEvarD	VarP	SEvarP
2D:4D (Left hand)	0.298	0.136	-0.010	0.191	-0.039	0.124
Adiponectin	0.135	0.165	-0.089	0.251	-0.067	0.167
Age at first tooth	0.402	0.115	0.099	0.175	0.134	0.118
Age at Menarche	0.321	0.228	0.112	0.332	0.169	0.236
Birth Weight	0.294	0.104	-0.104	0.152	-0.008	0.108
Body Mass Index	0.383	0.121	-0.018	0.180	0.070	0.121
Bone Area	0.475	0.129	-0.006	0.186	0.049	0.126
Bone Mineral Density	0.475	0.129	-0.016	0.186	0.046	0.126
C-reactive Protein	0.132	0.160	0.206	0.248	0.073	0.165
Crown Heel Length	0.291	0.133	-0.106	0.187	-0.004	0.127
Diastolic Blood Pressure	0.178	0.118	-0.012	0.183	0.117	0.125
Fat Mass	**0.483**	**0.089**	**0.384**	**0.135**	**0.013**	**0.091**
FEV1	0.274	0.138	-0.064	0.201	0.058	0.136
FEV1/FVC	0.372	0.135	0.032	0.198	0.010	0.138
FVC	0.341	0.134	0.020	0.207	0.154	0.135
Gestational Age	0.180	0.102	0.130	0.149	-0.063	0.107
HDL	0.118	0.171	-0.189	0.244	-0.050	0.164
Head Circumference	0.430	0.134	-0.181	0.133	-0.097	0.128
Height	0.448	0.121	-0.015	0.177	-0.176	0.123
Hemoglobin	0.473	0.156	0.317	0.237	0.066	0.160
Hip Circumference	0.425	0.120	-0.030	0.174	0.048	0.124
Interleukin-6	0.071	0.161	0.258	0.250	0.091	0.170
LDL	0.118	0.157	-0.139	0.246	0.025	0.163
Lean Mass	0.388	0.128	0.135	0.189	-0.014	0.129
Leptin	0.362	0.168	0.151	0.256	0.013	0.168
Number of teeth (15 months)	0.301	0.110	-0.043	0.171	0.011	0.113
Performance IQ	0.221	0.130	0.244	0.192	-0.032	0.124
Ponderal Index	0.216	0.126	0.013	0.197	-0.027	0.135
Pulse Rate	0.105	0.123	-0.032	0.183	-0.057	0.126

Sitting Height	0.435	0.121	0.052	0.180	-0.146	0.125
Systolic Blood Pressure	0.300	0.124	-0.051	0.179	0.147	0.121
Total IQ	0.400	0.136	0.261	0.192	-0.162	0.128
Triglycerides	0.022	0.167	-0.059	0.248	-0.047	0.165
Verbal IQ	0.484	0.138	0.286	0.196	-0.128	0.129
Waist-Hip Ratio	0.021	0.118	-0.233	0.174	-0.005	0.122
Waist Circumference	0.425	0.120	-0.070	0.180	-0.037	0.124

Table SVI: Accuracy of χ^2 approximations across all simulations

Accuracy of χ^2 approximations to noncentral F, measured as percent relative difference ("%Diff") between the average test statistic observed in the simulations and the expected value. This has been computed over all simulation replicates performed for this study. N: Number of simulated phased genotypes; Parent Corr: average correlation of simulated parental genotypes; MAF Diff: average difference in simulated parental MAFs; #Reps: number of simulated replications; POE Wald %Diff: percent relative difference between the observed 1-df Wald test statistic for HE regression of parent-of-origin variance components and the expected value, averaged across simulated replications; HE F %Diff is 3-df F test is the percent relative difference between the 3-df Wald test of additive, dominance, and parent-of-origin variance components in Haseman-Elston regression and the expected value, averaged across simulated replications; REML LRT %Diff: the percent relative difference between the 3-df χ^2 test of additive, dominance, and parent-of-origin variance components from REML fitting using GCTA and the expected value, averaged across simulated replications.

N	Parent Corr	MAF Diff	#Reps	POE Wald %Diff	HE F Diff	REML LRT Diff
1000	0.00	0.00	2727	4.629	-11.660	-10.550
1000	0.00	0.05	900	1.371	-40.240	-41.590
1000	0.25	0.00	876	-17.770	58.080	-32.670
1000	0.25	0.05	504	-16.660	-23.200	-37.190
2000	0.00	0.00	2775	-0.058	-19.010	-16.100
2000	0.00	0.05	900	1.292	-55.990	-60.040
2000	0.25	0.00	900	-32.830	60.010	-48.060
2000	0.25	0.05	876	-30.460	-29.630	-48.330
4000	0.00	0.00	2675	2.240	-21.770	-22.980
4000	0.00	0.05	888	-2.641	-63.860	-66.920
4000	0.25	0.00	600	-45.610	51.890	-57.480
4000	0.25	0.05	600	-43.710	-35.000	-56.030
5000	0.00	0.00	280	2.702	1.745	1.752
5000	0.00	0.05	280	-2.181	-1.452	-5.536
7500	0.00	0.00	250	-10.930	-4.248	0.628
7500	0.00	0.05	240	6.520	6.118	12.700

Table SVII: GCTA Estimates of *G-REMLadp* models of unstandardized phenotypes in ALSPAC

Variance component estimates of 36 unstandardized phenotypes in ALSPAC, estimates and standard errors generated using GCTA-GREML to estimate multiple components simultaneously. VarA: proportion of phenotypic variance attributable to additive genetic effects; SEvarA: standard error of proportion of phenotypic variance attributable to additive genetic effects. VarD: proportion of phenotypic variance attributable to dominance effects; SEvarD: standard error of proportion of phenotypic variance attributable to dominance effects. VarP: proportion of phenotypic variance attributable to parent-of-origin effects; SEvarP: standard error of proportion of phenotypic variance attributable to parent-of-origin effects. VarE: estimate of phenotypic error variance; SEvarE: standard error of estimate of phenotypic error variance. PhVar: Estimate of phenotypic variance. PhSE: Standard error of phenotypic variance estimate. Compare Table SIV for estimates based on standardized phenotypes. See Table SIII for descriptive statistics for each phenotype.

Phenotype	VarA	SEvarA	VarD	SEvarD	VarP	SEvarP	VarE	SEvarE	PhVar	PhSE
2D:4D (Left hand)	3.0×10^{-4}	9.2×10^{-5}	-2.0×10^{-5}	1.4×10^{-5}	-2.5×10^{-5}	9.2×10^{-5}	7.5×10^{-4}	1.9×10^{-4}	1.0×10^{-3}	2.3×10^{-5}
Adiponectin	0.136	0.114	-0.120	0.166	-0.038	0.115	0.998	0.234	0.976	0.025
Age at first tooth	2.376	0.474	0.636	0.678	0.873	0.459	1.700	0.938	5.585	0.122
Age at Menarche	0.443	0.214	0.257	0.324	0.236	0.214	0.380	0.440	1.316	0.041
Birth Weight	68668.472	16478.140	-25620.92	23774.703	4548.509	15960.585	169126.413	32808.301	216722.430	4506.383
Body Mass Index	0.382	0.085	-0.009	0.123	0.082	0.083	0.504	0.172	0.959	0.021
Bone Area	0.430	0.088	-0.062	0.126	0.082	0.085	0.495	0.175	0.945	0.022
Bone Mineral Density	1.3×10^{-3}	2.6×10^{-4}	-2.1×10^{-4}	3.7×10^{-4}	2.4×10^{-4}	2.5×10^{-4}	1.5×10^{-3}	5.2×10^{-4}	2.8×10^{-3}	6.5×10^{-5}
C-reactive Protein	0.153	0.107	0.111	0.160	0.064	0.111	0.603	0.219	0.931	0.024
Crown Heel Length	1.298	0.404	-0.612	0.586	0.168	0.407	3.588	0.819	4.443	0.102

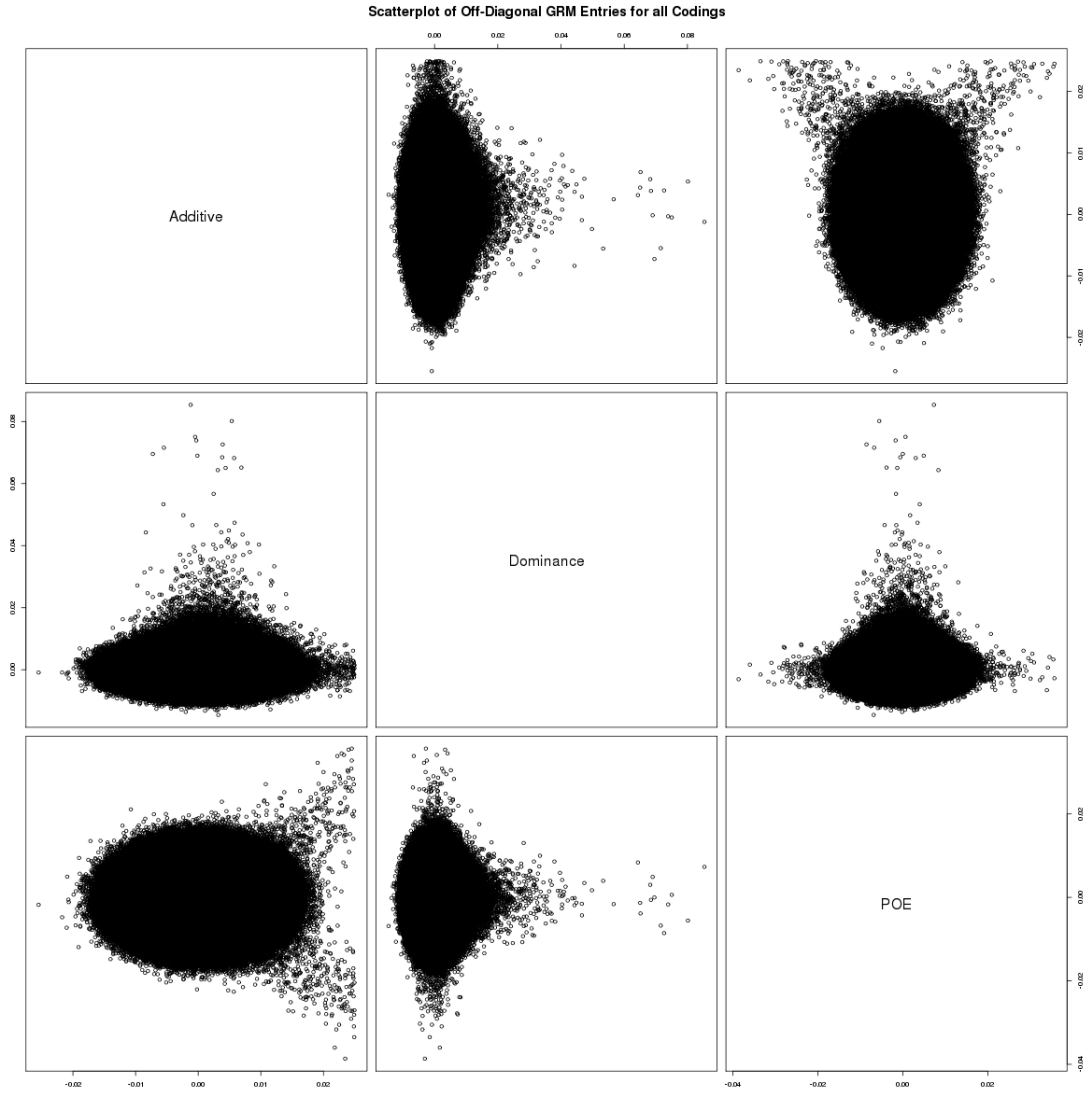
Diastolic BP	7.978	3.654	-3.131	5.461	4.704	3.649	31.842	7.346	41.394	0.930
Fat Mass	0.441	0.081	0.297	0.118	0.014	0.077	0.126	0.159	0.878	0.020
FEV1	0.288	0.095	-0.039	0.135	0.070	0.096	0.642	0.190	0.961	0.023
FEV1/FVC	0.371	0.098	0.059	0.141	0.018	0.095	0.540	0.195	0.988	0.023
FVC	0.353	0.094	0.016	0.130	0.152	0.093	0.434	0.180	0.954	0.022
Gest. Age	0.289	0.122	0.217	0.185	-0.090	0.118	1.229	0.251	1.644	0.034
HDL	0.110	0.110	-0.194	0.166	-0.024	0.113	1.073	0.226	0.965	0.025
Head Circumference	0.650	0.136	0.063	0.201	-0.143	0.131	0.931	0.275	1.501	0.034
Height	14.298	2.736	0.899	3.895	-4.448	2.507	19.772	5.357	30.520	0.682
Hemoglobin	24.284	6.254	15.722	9.131	2.203	6.181	15.242	12.208	57.451	1.444
Hip Circumference	0.472	0.084	-0.024	0.120	0.056	0.080	0.427	0.166	0.931	0.021
Interleukin-6	0.115	0.119	0.253	0.173	0.091	0.117	0.533	0.237	0.992	0.026
LDL	0.119	0.113	-0.177	0.166	0.069	0.114	0.949	0.228	0.960	0.025
Lean Mass	0.310	0.080	0.116	0.121	0.008	0.079	0.437	0.165	0.870	0.020
Leptin	0.359	0.102	0.015	0.147	0.035	0.099	0.453	0.200	0.862	0.023
Number of teeth (15 months)	3.597	0.919	-0.120	1.292	0.211	0.869	7.368	1.808	11.056	0.238
Perform. IQ	59.208	25.498	64.957	38.142	-8.068	25.794	166.771	51.841	282.867	6.474
Ponderal Index	$1.4x10^{-2}$	$5.5x10^{-3}$	$3.0x10^{-4}$	$8.0x10^{-3}$	$-1.1x10^{-3}$	$5.2x10^{-3}$	$4.5x10^{-2}$	$1.1x10^{-2}$	0.059	$1.4x10^{-3}$
Pulse Rate	12.366	9.662	-4.904	14.185	-5.660	9.340	108.920	19.315	110.723	2.477
Sitting Height	3.408	0.675	0.641	0.960	-0.844	0.627	4.373	1.331	7.578	0.169
Systolic BP	25.804	7.294	-12.141	10.707	11.940	7.307	56.874	14.479	82.477	1.858
Total IQ	94.213	23.878	68.501	35.524	-37.494	23.310	138.613	48.441	263.833	6.056
Triglycerides	0.013	0.114	-0.062	0.169	-0.056	0.119	1.098	0.236	0.993	0.026
Verbal IQ	121.119	25.017	81.285	36.742	-26.993	24.417	100.077	50.481	275.488	6.328

Waist-Hip Ratio	$1.5x10^{-4}$	$1.3x10^{-4}$	$-3.5x10^{-4}$	$1.8x10^{-4}$	$-3.2x10^{-5}$	$1.2x10^{-4}$	$1.7x10^{-3}$	$2.6x10^{-4}$	$1.5x10^{-3}$	$3.2x10^{-5}$
Waist Circumference	0.423	0.084	-0.086	0.120	-0.018	0.080	0.620	0.166	0.939	0.021

Supplementary Figures

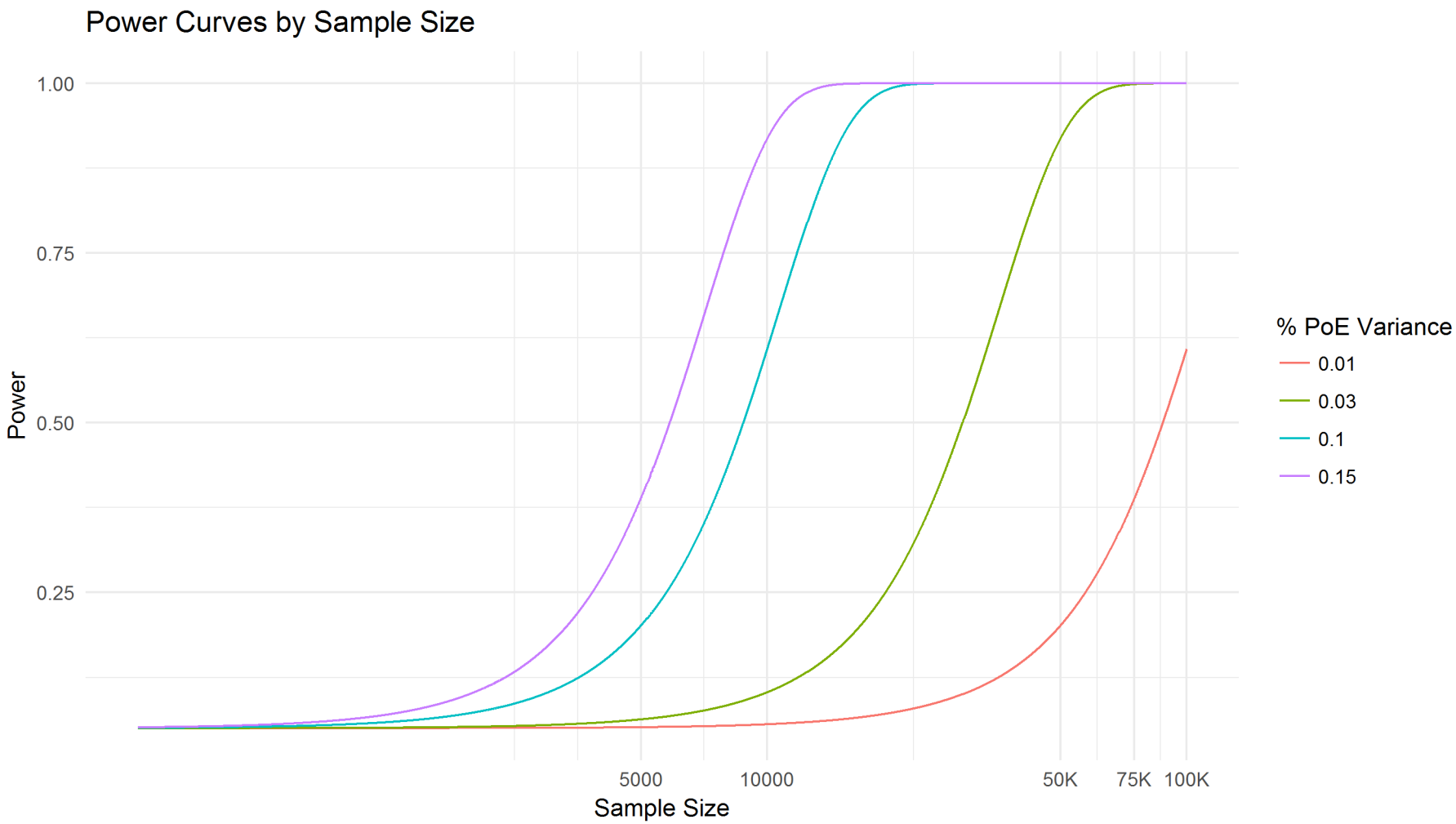
S1: *Scatterplot matrix of off diagonal elements of ALSPAC GRMs*

Scatterplot matrix of off diagonal elements of genetic relationship matrices for additive, dominance, and parent-of-origin effects, taken from the analysis of gestational age in ALSPAC. See Tables SII, SIII, and SVII for descriptive statistics and G-REMLadp model results from this analysis.



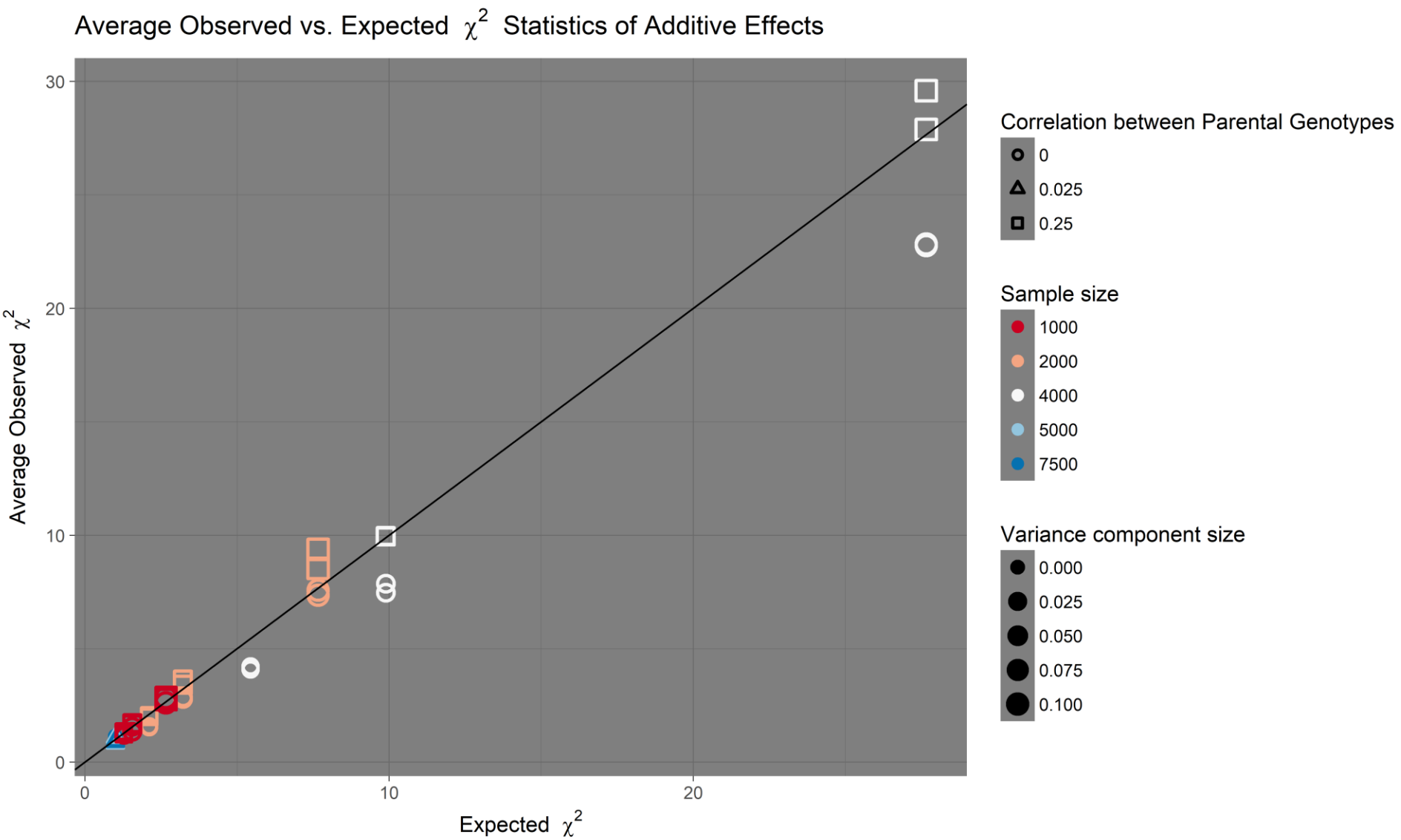
S2: Expected power to detect parent-of-origin effects tagged by $m = 10000$ loci

Expected power to detect parent-of-origin effects tagged by $m = 10000$ loci, by sample size: Curves generated using Haseman-Elston regression approximation to the Wald test of nonzero effect. %PoE: proportion of phenotypic variance attributable to parent-of-origin effects; Sample size: number of unrelated individuals with phased genotypes in the sample that would be used to estimate POEs; Power: proportion of test statistics generated under a non-null distribution with noncentrality parameter as given in Equation 4 that would exceed a 95% critical value in the Wald test of a null variance component.


Power Curves by Sample Size
1.00
0.75
0.50
0.25
Power
5000
10000
50K
75K
100K
Sample Size
% PoE Variance
0.01
0.03
0.1
0.15

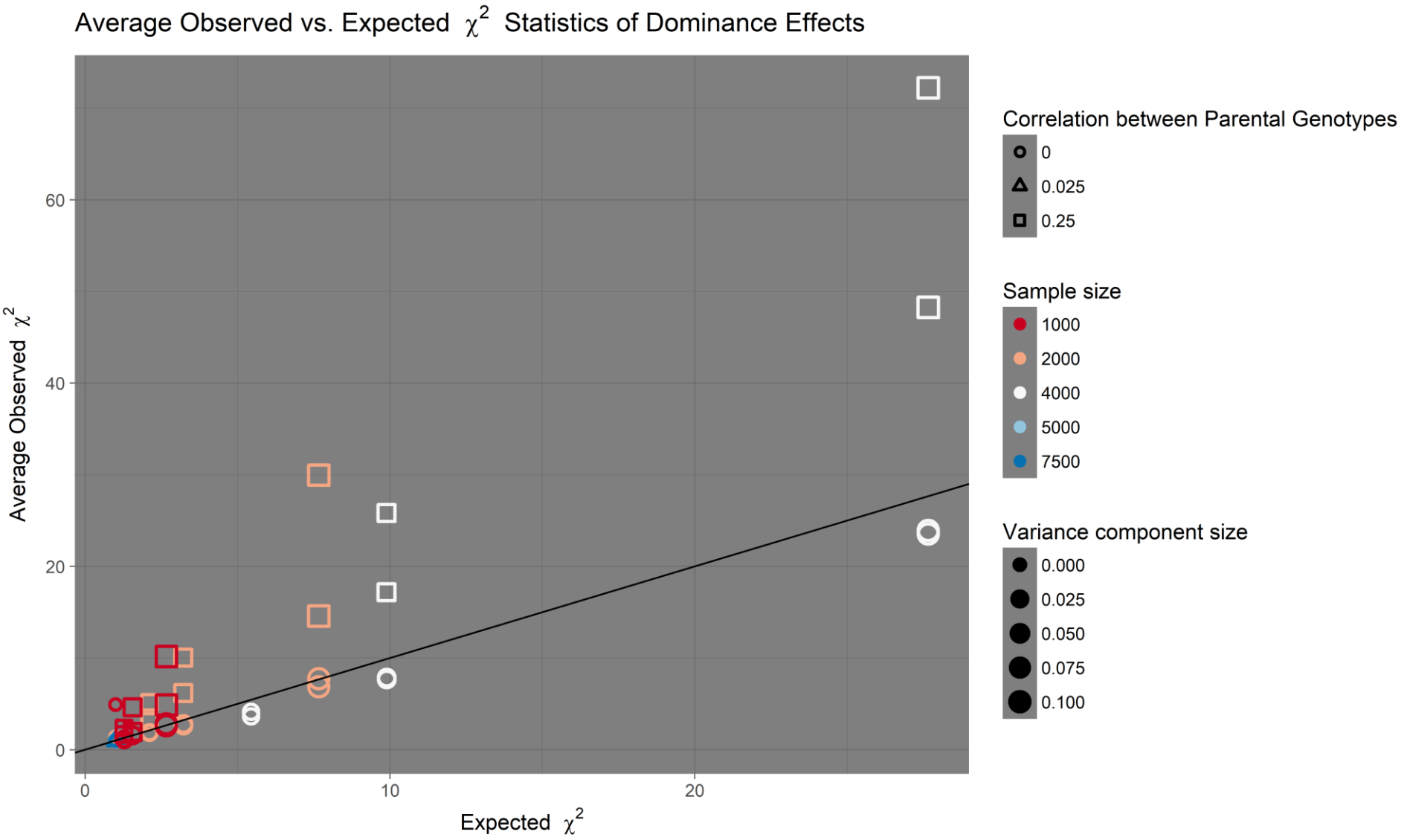
S3: *Wald test statistics for simulated additive effects*

Observed Wald test statistics for simulated additive effects, averaged over replications, versus their expected values. Averaged observed χ^2 is the mean Wald test statistic over replications, within a particular simulated condition; Expected χ^2 is the expected Wald test statistic for that effect size; Correlation between parental genotypes: the average correlation between maternal and paternal transmitted genotypes, circles being no correlation, triangles low correlation, $r = 0.025$, and squares high correlation, $r = 0.25$; Sample size, coded by point colour is the number of simulated children with phased, parent-of-origin determined genotypes; Variance component size, coded by point size, is the population value of the proportion of phenotypic variance explained by the simulated additive effects. The black line is the line of equality.


Average Observed vs. Expected χ^2 Statistics of Additive Effects
Average Observed χ^2
Expected χ^2
0
10
20
30
Correlation between Parental Genotypes
0
0.025
0.25
Sample size
1000
2000
4000
5000
7500
Variance component size
0.000
0.025
0.050
0.075
0.100

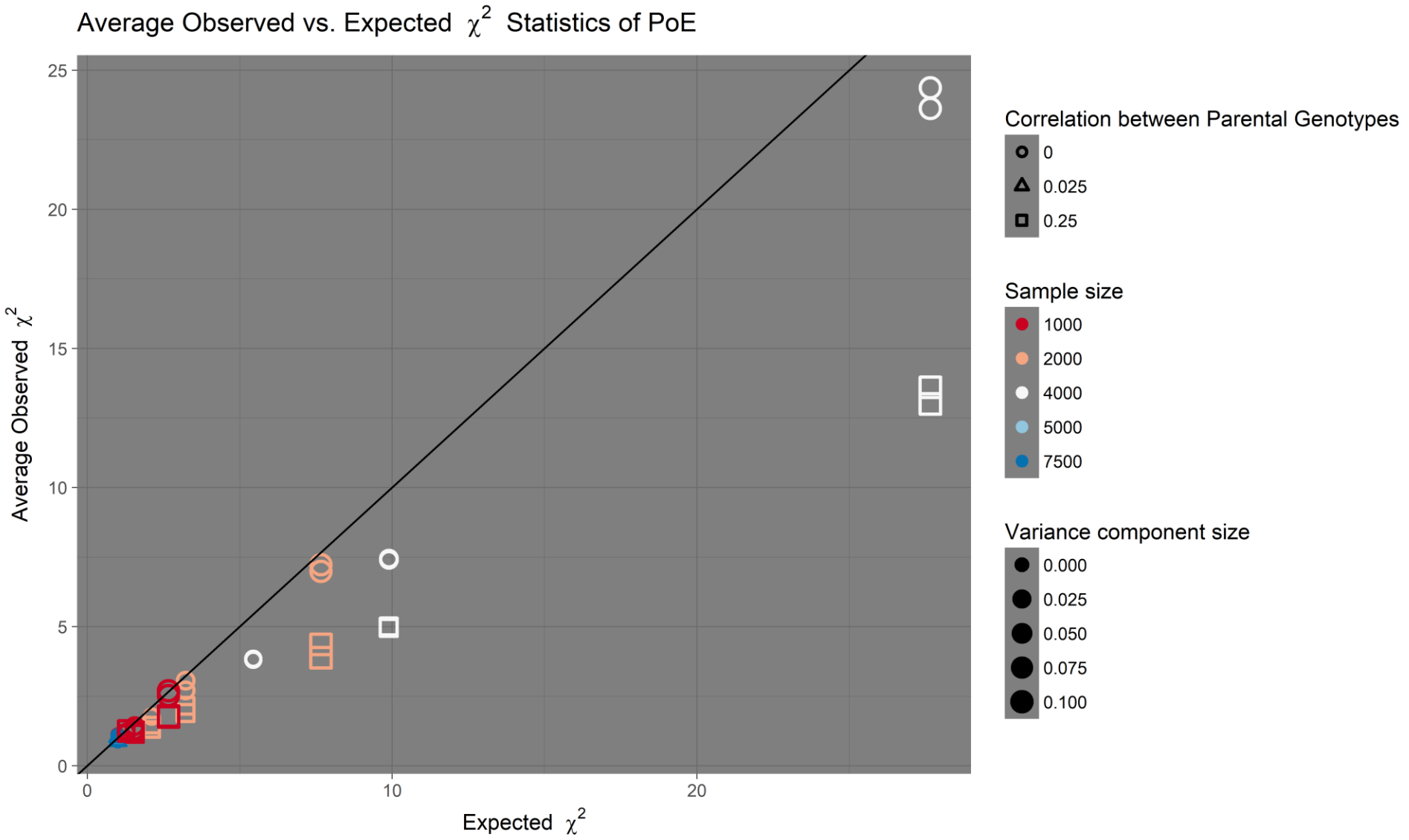
S4: *Wald test statistics for simulated dominance effects*

Observed Wald test statistics for simulated dominance effects, averaged over replications, versus their expected values. Averaged observed χ^2 is the mean Wald test statistic over replications, within a particular simulated condition; Expected χ^2 is the expected Wald test statistic for that effect size; Correlation between parental genotypes: the average correlation between maternal and paternal transmitted genotypes, circles being no correlation, triangles low correlation, $r = 0.025$, and squares high correlation, $r = 0.25$; Sample size, coded by point colour is the number of simulated children with phased, parent-of-origin determined genotypes; Variance component size, coded by point size, is the population value of the proportion of phenotypic variance explained by the simulated additive effects. The black line is the line of equality.


Average Observed vs. Expected χ^2 Statistics of Dominance Effects
Average Observed χ^2
Expected χ^2
0
20
40
60
0
10
20
Correlation between Parental Genotypes
0
0.025
0.25
Sample size
1000
2000
4000
5000
7500
Variance component size
0.000
0.025
0.050
0.075
0.100

S5: *Wald test statistics for simulated parent-of-origin effects*

Observed Wald test statistics for simulated parent-of-origin effects (POE), averaged over replications, versus their expected values. Averaged observed χ^2 is the mean Wald test statistic over replications, within a particular simulated condition; Expected χ^2 is the expected Wald test statistic for that effect size; Correlation between parental genotypes: the average correlation between maternal and paternal transmitted genotypes, circles being no correlation, triangles low correlation, $r = 0.025$, and squares high correlation, $r = 0.25$; Sample size, coded by point colour is the number of simulated children with phased, parent-of-origin determined genotypes; Variance component size, coded by point size, is the population value of the proportion of phenotypic variance explained by the simulated additive effects. The black line is the line of equality.


Average Observed vs. Expected χ^2 Statistics of PoE
Average Observed χ^2
Expected χ^2
0
5
10
15
20
25
0
10
20
Correlation between Parental Genotypes
0
0.025
0.25
Sample size
1000
2000
4000
5000
7500
Variance component size
0.000
0.025
0.050
0.075
0.100

Appendix: Correlations between codings of phased genotypes at two loci

Notation and Parental gametes, considering two linked loci

Consider loci I and II, which are in linkage disequilibrium. Represent the four transmitted alleles at these loci by four random variables: for the first locus, $\tau_{I,Mo}$, $\tau_{I,Fa}$ and $\tau_{II,Mo}$, $\tau_{II,Fa}$ at the second locus, where

$$\tau = \begin{cases} 1 & \text{if minor allele transmitted} \\ 0 & \text{if major allele transmitted} \end{cases}$$

We assume: random mating so that $\tau_{\cdot,Mo}$ are independent of $\tau_{\cdot,Fa}$, and equal allele frequencies across sexes. For simplicity, assume that the minor allele frequencies(MAFs) are equal across loci; the results here can be extended straightforwardly to loci with differing MAFs.

With MAF equal to p and defining $q = 1 - p$:

- $E(\tau_{I,Mo}) = E(\tau_{I,Fa}) = E(\tau_{II,Mo}) = E(\tau_{II,Fa}) = p$
- Because the τ are indicator variables, $E(\tau_{I,Mo}^2) = E(\tau_{I,Fa}^2) = E(\tau_{II,Mo}^2) = E(\tau_{II,Fa}^2) = p$
- $\mathrm{Var}(\tau_{I,Mo}) = \mathrm{Var}(\tau_{I,Fa}) = \mathrm{Var}(\tau_{II,Mo}) = \mathrm{Var}(\tau_{II,Fa}) = p - p^2 = pq$

Then, following standard notation, let D be the covariance between gametes at the two loci. (e.g. Sved, 1968)

The means of cross-products are:

- $E(\tau_{I,Mo}\tau_{II,Mo}) = E(\tau_{I,Fa}\tau_{II,Fa}) = D + p^2$

By the independence of maternal and paternal gametes:

- $E(\tau_{I,Mo}\tau_{II,Fa}) = E(\tau_{I,Fa}\tau_{II,Mo}) = E(\tau)^2 = p^2$
- $E(\tau_{I,Mo}\tau_{I,Fa}\tau_{II,Mo}\tau_{II,Fa}) = E(\tau_{I,Mo}\tau_{II,Mo})E(\tau_{I,Fa}\tau_{II,Fa}) = (D + p^2)^2$
- $E(\tau_{I,Mo}\tau_{I,Fa}\tau_{II,Mo}) = E(\tau_{I,Fa})E(\tau_{I,Mo}\tau_{II,Mo}) = p(D + p^2)$

Correlation between additive codings

- Let the additive coding at locus I be $X_{AI} = \tau_{I,Mo} + \tau_{I,Fa}$ and define X_{AII} analogously for locus II
- Then $E(X_{AI}) = E(X_{AII}) = 2p$ and $\mathrm{Var}(X_{AI}) = \mathrm{Var}(X_{AII}) = 2pq$
- The covariance between loci is

$$\begin{aligned} E(X_{AI}X_{AII}) - E(X_{AI})E(X_{AII}) &= E\left(\tau_{I,Mo}\tau_{II,Mo} + \tau_{I,Mo}\tau_{II,Fa} + \tau_{I,Fa}\tau_{II,Mo} + \tau_{I,Fa}\tau_{II,Fa}\right) - 4p^2 \\ &= (D + p^2) + p^2 + p^2 + (D + p^2) - 4p^2 \\ &= 2D \end{aligned}$$

- This means that the correlation is $r = \frac{2D}{2pq} = \frac{D}{pq}$, which is the typical correlation coefficient used to summarize LD

Correlation between parent-of-origin codings

- Let the parent-of-origin coding at locus I be $X_{\gamma I} = \tau_{I,Mo} - \tau_{I,Fa}$ and define $X_{\gamma II}$ analogously for locus II.
- Then $E\left(X_{\gamma I}\right) = p - p = 0 = E\left(X_{\gamma II}\right)$
- $\mathrm{Var}\left(X_{\gamma I}\right) = E\left(\tau_{I,Mo}^2 - 2\tau_{I,Mo}\tau_{I,Fa} + \tau_{I,Fa}^2\right) = p - 2p^2 + p = 2pq = \mathrm{Var}\left(X_{\gamma II}\right)$, which is also the same variance as in the additive coding.
- The covariance is:

$$\begin{aligned} E\left(X_{\gamma I}X_{\gamma II}\right) - E\left(X_{\gamma I}\right)E\left(X_{\gamma II}\right) &= E\left(\tau_{I,Mo}\tau_{II,Mo} - \tau_{I,Mo}\tau_{II,Fa} - \tau_{I,Fa}\tau_{II,Mo} + \tau_{I,Fa}\tau_{II,Fa}\right) - 0 \\ &= (D + p^2) - p^2 - p^2 + (D + p^2) \\ &= 2D \end{aligned}$$

- This means that the correlation is also $r = \frac{2D}{2pq} = \frac{D}{pq}$

Correlation between dominance codings

- Let the dominance coding at locus I be $X_{\Delta I} = 2pX_{AI} - 2\tau_{I,Mo}\tau_{I,Fa} = 2p\tau_{I,Mo} + 2p\tau_{I,Fa} - 2\tau_{I,Mo}\tau_{I,Fa}$ and define $X_{\Delta II}$ analogously for locus II.
- Then $E(X_{\Delta I}) = 2p^2 + 2p^2 - 2p^2 = 2p^2 = E(X_{\Delta II})$
- The variance is:

$$\begin{aligned}\mathrm{Var}(X_{\Delta I}) &= EX_{\Delta I}^2 - EX_{\Delta I}{}^2 \\ &= E\left(4p^2\tau_{I,Mo}^2 + 4p^2\tau_{I,Fa}^2 + 8p^2\tau_{I,Mo}\tau_{I,Fa} - 8p\tau_{I,Mo}^2\tau_{I,Fa} - 8p\tau_{I,Mo}\tau_{I,Fa}^2 + 4\tau_{I,Mo}^2\tau_{I,Fa}^2\right) - 4p^4 \\ &= 4p^3 + 4p^3 + 8p^4 - 8p^3 - 8p^3 + 4p^2 - 4p^4 \\ &= 4p^4 - 8p^3 + 4p^2 \\ &= 4p^2(p^2 - 2p + 1) \\ &= 4p^2q^2 \\ &= \mathrm{Var}(X_{\Delta II})\end{aligned}$$

– , which is the square of the variance of the additive coding

- The covariance is:

$$\begin{aligned}\mathrm{Cov}(X_{\Delta I}, X_{\Delta II}) &= E(X_{\Delta I}X_{\Delta II}) - E(X_{\Delta I})E(X_{\Delta II}) \\ &= E\left(\left(2p\tau_{I,Mo} + 2p\tau_{I,Fa} - 2\tau_{I,Mo}\tau_{I,Fa}\right)\left(2p\tau_{II,Mo} + 2p\tau_{II,Fa} - 2\tau_{II,Mo}\tau_{II,Fa}\right)\right) - 4p^4 \\ &= E\left(4p^2\tau_{I,Mo}\tau_{II,Mo} + 4p^2\tau_{I,Mo}\tau_{II,Fa} - 4p\tau_{I,Mo}\tau_{II,Mo}\tau_{II,Fa}\right) \\ &\quad + E\left(4p^2\tau_{I,Fa}\tau_{II,Fa} + 4p^2\tau_{I,Fa}\tau_{II,Mo} - 4p\tau_{I,Fa}\tau_{II,Fa}\tau_{II,Mo}\right) \\ &\quad + E\left(-4p\tau_{I,Fa}\tau_{I,Mo}\tau_{II,Mo} - 4p\tau_{I,Fa}\tau_{I,Mo}\tau_{II,Fa} + 4\tau_{I,Mo}\tau_{II,Mo}\tau_{I,Fa}\tau_{II,Fa}\right) - 4p^4 \\ &= 4p^2(D + p^2) + 4p^4 - 4p^2(D + p^2) \\ &\quad + 4p^2(D + p^2) + 4p^4 - 4p^2(D + p^2) \\ &\quad - 4p^2(D + p^2) - 4p^2(D + p^2) + 4(D + p^2)^2 - 4p^4 \\ &= 4p^4 - 8p^2(D + p^2) + 4(D + p^2)^2 \\ &= 4\left(p^2 - (D + p^2)\right)^2 \\ &= 4D^2\end{aligned}$$

- This means that the correlation is $r_\Delta = \frac{4D^2}{4p^2q^2} = \frac{D^2}{p^2q^2}$, which is the square of the LD correlation between locus I and locus II

Cross-locus, cross-coding correlation: additive and parent-of-origin

- This is relatively simple because the two codings have the same variance and the parent-of-origin coding has a mean of 0

$$\begin{aligned}\mathrm{Cov}(X_{AI}, X_{\gamma II}) &= E\left((\tau_{I,Mo} + \tau_{I,Fa})(\tau_{II,Mo} - \tau_{II,Fa})\right) \\ &= E(\tau_{I,Mo}\tau_{II,Mo} - \tau_{I,Mo}\tau_{II,Fa} + \tau_{I,Fa}\tau_{II,Mo} - \tau_{I,Fa}\tau_{II,Fa}) \\ &= (D + p^2) - p^2 + p^2 - (D + p^2) \\ &= 0\end{aligned}$$

- Because the covariance is 0, the correlation is as well

Cross-locus, cross-coding correlation: additive and dominance

$$\begin{aligned}\mathrm{Cov}(X_{AI}, X_{\Delta II}) &= E\left((\tau_{I,Mo} + \tau_{I,Fa})(2p\tau_{II,Mo} + 2p\tau_{II,Fa} - 2\tau_{II,Mo}\tau_{II,Fa})\right) - 4p^3 \\ &= E(2p\tau_{I,Mo}\tau_{II,Mo} + 2p\tau_{I,Mo}\tau_{II,Fa} - 2\tau_{I,Mo}\tau_{II,Mo}\tau_{II,Fa} + 2p\tau_{I,Fa}\tau_{II,Mo} + 2p\tau_{I,Fa}\tau_{II,Fa} - 2\tau_{I,Fa}\tau_{II,Mo}\tau_{II,Fa}) - 4p^3 \\ &= 2p(D + p^2) + 2p^3 - 2p(D + p^2) + 2p^3 + 2p(D + p^2) - 2p(D + p^2) - 4p^3 \\ &= 0\end{aligned}$$

Cross-locus, cross-coding correlation: parent-of-origin and dominance

$$\begin{aligned}\mathrm{Cov}(X_{\gamma I}, X_{\Delta II}) &= E\left((\tau_{I,Mo} - \tau_{I,Fa})(2p\tau_{II,Mo} + 2p\tau_{II,Fa} - 2\tau_{II,Mo}\tau_{II,Fa})\right) \\ &= E(2p\tau_{I,Mo}\tau_{II,Mo} + 2p\tau_{I,Mo}\tau_{II,Fa} - 2\tau_{I,Mo}\tau_{II,Mo}\tau_{II,Fa} - 2p\tau_{I,Fa}\tau_{II,Mo} - 2p\tau_{I,Fa}\tau_{II,Fa} + 2\tau_{I,Fa}\tau_{II,Mo}\tau_{II,Fa}) \\ &= 2p(D + p^2) + 2p^3 - 2p(D + p^2) - 2p^3 - 2p(D + p^2) + 2p(D + p^2) \\ &= 0\end{aligned}$$

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