

Appendix A

Supplementary Tables

Table A.1: Sites with Random Allelic Bias.

chrM	asSNP_pos	explanation	conconrdSNP_pos	score	pval	nhets
3	195380708	linked to putative rSNP	195343986	0.413746355	0.012	10
13	24473876	linked to putative rSNP	24429097	0.342206506	0.001	19
2	79226788	linked to putative rSNP	79234011	0.303255216	0.001	8
6	11656064	linked to putative rSNP	11641470	0.388698152	0.001	13
7	22893706	linked to putative rSNP	22892011	0.1773247	0.001	17
6	46378261	unexplained	46372838	0.131808112	0.298	23
12	562651	linked to putative rSNP	553733	0.313721634	0.001	13
12	562580	unexplained	536056	0.353706121	0.052	16
9	104211370	unexplained	104211370	0.056373159	0.904	9
10	52420020	unexplained	52463140	0.368795666	0.07	8
15	51166142	linked to putative rSNP	51127650	0.341124891	0.001	14
12	562661	linked to putative rSNP	573870	0.386307382	0.033	10
10	57391147	unexplained	57424504	0.438082956	0.056	11
14	106598644	unexplained, IgH	106619371	0.172644288	0.172	8
14	106627178	unexplained, IgH	106625322	0.241054365	0.16	10
5	171889524	linked to putative rSNP	171903769	0.475113379	0.028	9
8	80979777	linked to putative rSNP	80977521	0.165461923	0.026	20
7	141437957	linked to putative rSNP	141429029	0.360188346	0.001	11
5	110867634	linked to putative rSNP	110839262	0.172184058	0.001	8
10	32125803	unexplained	32164980	0.241839254	0.518	9
12	8086062	linked to putative rSNP	8086083	0.244866078	0.001	13
8	16870536	linked to putative rSNP	16845136	0.382392542	0.024	9
11	2554149	within imprinted gene KCNQ1	2552450	0.17695326	0.608	8
18	43303114	unexplained	43302764	0.278125778	0.098	8
3	34021986	linked to putative rSNP	34014691	0.321042367	0.046	9

Table A.1: Sites with Random Allelic Bias.

14	106626958	unexplained, IgH	106625322	0.251414942	0.144	9
18	61009609	linked to putative rSNP	61019692	0.424321072	0.002	9
21	39084764	unexplained	39113085	0.438694795	0.097	8
11	362099	linked to putative rSNP	344035	0.43792284	0.001	8
10	71168561	linked to putative rSNP	71119208	0.318892421	0.001	11
6	14397660	linked to putative rSNP	14357172	0.294558813	0.001	12
13	112092991	unexplained	112092991	0.288589199	0.054	12
1	40138507	linked to putative rSNP	40151426	0.296879492	0.003	11
16	75498793	unexplained	75524371	0.312558616	0.154	10
9	114360287	linked to putative rSNP	114357659	0.138953631	0.001	9
12	84220073	linked to putative rSNP	84262595	0.392129301	0.012	10
3	46484283	unexplained	46484283	0.353244439	0.163	7
10	102295658	unexplained	102298664	0.089200481	0.066	12
19	38042814	unexplained	38070460	0.375844732	0.129	9
7	142420355	linked to putative rSNP	142379936	0.14320426	0.002	17
10	134717856	unexplained	134671822	0.29972073	0.091	8
10	11800229	linked to putative rSNP	11801353	0.474904024	0.009	8
12	67835821	linked to putative rSNP	67803505	0.29289579	0.027	12
2	231807181	linked to putative rSNP	231769231	0.269179103	0.001	8
6	100270972	unexplained	100249423	0.31902441	0.188	9
10	835055	linked to putative rSNP	859270	0.361235687	0.028	15
19	19453560	unexplained	19445856	0.4082047	0.132	9
1	171220925	unexplained	171262373	0.410678075	0.147	9
1	248100467	linked to putative rSNP	248059456	0.216975022	0.026	17
12	108279247	unexplained	108263228	0.290672468	0.052	17

KEGG ID	Pathway	P value	Number of genes	Proportion of genes
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Table A.2: List of all pathways significantly associated with age, together with the number and proportion of significantly associated genes ($P < 0.05$, corrected using Bonferroni for the total number of genes in the pathway).

00900	Terpenoid Backbone Biosynthesis	6.23E-13	chrM	asSNP_pos
00980	Metabolism of Xenobiotics By Cytochrome P450	6.47E-13	3	195380708
01040	Biosynthesis of Unsaturated Fatty Acids	1.11E-12	13	24473876
00100	Steroid Biosynthesis	1.33E-12	2	79226788

KEGG ID	Pathway	P value	Number of genes	Proportion of genes
00650	Butanoate Metabolism	1.51E-12	6	11656064
04146	Peroxisome	1.56E-12	7	22893706
00830	Retinol Metabolism	1.93E-12	6	46378261
00010	Glycolysis Gluconeogenesis	3.59E-12	12	562651
00051	Fructose and Mannose Metabolism	3.99E-12	12	562580
00290	Valine Leucine and Isoleucine Biosynthesis	1.15E-11	9	104211370
00561	Glycerolipid Metabolism	2.63E-11	10	52420020
00620	Pyruvate Metabolism	4.20E-11	15	51166142
00770	Pantothenate and COA Biosynthesis	4.76E-11	12	562661
00280	Valine Leucine and Isoleucine Degradation	5.79E-11	10	57391147
00020	Citrate Cycle TCA Cycle	1.12E-10	14	106598644
04916	Melanogenesis	3.34E-10	14	106627178
04910	Insulin Signalling Pathway	3.70E-10	5	171889524
00565	Ether Lipid Metabolism	5.89E-10	8	80979777
00350	Tyrosine Metabolism	9.44E-10	7	141437957
00640	Propanoate Metabolism	1.03E-09	5	110867634
04530	Tight Junction	1.12E-09	10	32125803
00030	Pentose Phosphate Pathway	1.74E-09	12	8086062
03320	PPAR Signalling Pathway	1.83E-09	8	16870536
00630	Glyoxylate and Dicarboxylate Metabolism	2.22E-09	11	2554149

KEGG ID	Pathway	P value	Number of genes	Proportion of genes
00982	Drug Metabolism Cytochrome P450	2.93E-09	18	43303114
00260	Glycine Serine and Threonine Metabolism	7.02E-09	3	34021986
00140	Steroid Hormone Biosynthesis	7.49E-09	14	106626958
00380	Tryptophan Metabolism	1.17E-08	18	61009609
04930	Type II Diabetes Mellitus	1.98E-08	21	39084764
05412	Arrhythmogenic Right Ventricular Cardiomyopathy Arvc	7.44E-08	11	362099
00052	Galactose Metabolism	9.27E-08	10	71168561
04340	Hedgehog Signaling Pathway	1.12E-07	6	14397660
00480	Glutathione Metabolism	1.45E-07	13	112092991
00532	Glycosaminoglycan Biosynthesis Chondroitin Sulfate	1.53E-07	1	40138507
04920	Adipocytokine Signaling Pathway	2.87E-07	16	75498793
05214	Glioma	4.26E-07	9	114360287
05322	Systemic Lupus Erythematosus	4.56E-07	12	84220073
05414	Dilated Cardiomyopathy	5.64E-07	3	46484283
00410	Beta Alanine Metabolism	1.11E-06	10	102295658
00330	Arginine and Proline Metabolism	1.39E-06	19	38042814
04510	Focal Adhesion	1.47E-06	7	142420355
00340	Histidine Metabolism	1.53E-06	10	134717856

KEGG ID	Pathway	P value	Number of genes	Proportion of genes
04360	Axon Guidance	1.66E-06	10	11800229
04060	ECM Receptor Interaction	1.77E-06	12	67835821
04150	MTOR Signaling Pathway	2.02E-06	2	231807181
04270	Vascular Smooth Muscle Contraction	3.31E-06	6	100270972
00071	Fatty Acid Metabolism	3.84E-06	10	835055
04142	Lysosome	4.43E-06	19	19453560
00983	Drug Metabolism Other Enzymes	5.71E-06	1	171220925
00040	Pentose and Glucuronate Interconversions	6.49E-06	1	248100467
05416	Viral Myocarditis	1.16E-05	12	108279247
1000	Amino Sugar and Nucleotide Sugar Metabolism	1.70E-05	7	0.179
05217	Basal Cell Carcinoma	1.80E-05	10	0.192
00510	N-Glycan Biosynthesis	1.82E-05	7	0.175
04260	Cardiac Muscle Contraction	1.83E-05	5	0.0847
05216	Thyroid Cancer	1.99E-05	8	0.364
05120	Epithelial Cell Signaling In Helicobacter Pylori Infection	4.85E-05	11	0.186

Table A.3: List of the seven pathways which were significantly associated with age, discovered by looking for enrichment of single gene age associations.

KEGG ID	Pathway	P value
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650	Butanoate Metabolism	8.86E+06
4060	ECM Receptor Interaction	3.64E+05
4146	Peroxisome	2.61E+07
620	Pyruvate Metabolism	5.49E+05
100	Steroid Biosynthesis	2.39E+11
900	Terpenoid Backbone Biosynthesis Valine Leucine and Isoleucine	2.13E+05
290	Degradation	5.58E+06

Table A.4: Key showing which pathways correspond to which nodes in Figure 3.2, and the maximum Spearman correlation of that phenotype with any of the others representing pathways.

Node	Pathway	Maximum rho with other phenotype
1	Glycolysis Gluconeogenesis	0.91
2	Citrate Cycle TCA Cycle	0.90
3	Pentose Phosphate Pathway	0.84
4	Fructose and Mannose Metabolism	0.84
5	Beta Alanine Metabolism	0.85
6	Glutathione Metabolism	0.85
7	Pyruvate Metabolism	0.81
8	Butanoate Metabolism	0.94
9	Drug Metabolism Cytochrome P450	0.84
10	Biosynthesis of Unsaturated Fatty Acids	0.92
11	Fatty Acid Metabolism	0.87
12	Glyoxylate and Dicarboxylate Metabolism	0.80
13	Glycerolipid Metabolism	0.90
14	Terpenoid Backbone Biosynthesis	0.90
15	Valine Leucine and Isoleucine Biosynthesis	0.84
16	Pantothenate and COA Biosynthesis	0.85
17	Tryptophan Metabolism	0.82
18	Peroxisome	0.92
19	Insulin Signaling Pathway	0.84
20	Propanoate Metabolism	0.92
21	Valine Leucine and Isoleucine Degradation	0.94
22	Retinol Metabolism	0.90
23	Steroid Hormone Biosynthesis	0.84
24	Steroid Biosynthesis	0.90

KEGG ID	Pathway	Heritability	Proportion
00900	Terpenoid Backbone Biosynthesis	1.53E-11	0.0898
00980	Metabolism of Xenobiotics By Cytochrome P450	0.0904	0.0986
01040	Biosynthesis of Unsaturated Fatty Acids	0.253	0.11
00100	Steroid Biosynthesis	0.406	0.143
00650	Butanoate Metabolism	0.39	0.137
04146	Peroxisome	0.453	0.152
00830	Retinol Metabolism	0.449	0.149
00010	Glycolysis Gluconeogenesis	0.417	0.14
00051	Fructose and Mannose Metabolism	0.316	0.109
00290	Valine Leucine and Isoleucine Biosynthesis	2.61E-12	0.0771
00561	Glycerolipid Metabolism	0.337	0.113
00620	Pyruvate Metabolism	0.368	0.117
00770	Pantothenate and COA Biosynthesis	0.477	0.136
00280	Valine Leucine and Isoleucine Degradation	0.51	0.147
00020	Citrate Cycle TCA Cycle	0.436	0.126
04916	Melanogenesis	2.23E-16	0.0708
04910	Insulin Signaling Pathway	0.453	0.121
00565	Ether Lipid Metabolism	1.13E-15	0.064

KEGG ID	Pathway	Heritability	Proportion
00350	Tyrosine Metabolism	0.342	0.0975
00640	Propanoate Metabolism	0.591	0.157
04530	Tight Junction	0.103	0.0751
00030	Pentose Phosphate Pathway	0.291	0.0831
03320	PPAR Signaling Pathway	0.235	0.0777
00630	Glyoxylate and Dicarboxylate Metabolism	0.275	0.0836
00982	Drug Metabolism Cytochrome P450	0.248	0.0811
00260	Glycine Serine and Threonine Metabolism	0.599	0.141
00140	Steroid Hormone Biosynthesis	0.655	0.167
00380	Tryptophan Metabolism	0	0.0491
04930	Type II Diabetes Mellitus	0.594	0.13
05412	Arrhythmogenic Right Ventricular Cardiomyopathy Arvc	0.241	0.0674
00052	Galactose Metabolism	3.40E-11	0.0504
04340	Hedgehog Signaling Pathway	0.375	0.08
00480	Glutathione Metabolism	0.415	0.0804
00532	Glycosaminoglycan Biosynthesis Chondroitin Sulfate	0.273	0.0682
04920	Adipocytokine Signaling Pathway	1.30E-20	0.0475
05214	Glioma	0.102	0.0466

KEGG ID	Pathway	Heritability	Proportion
05322	Systemic Lupus Erythematosus	8.17E-17	0.045
05414	Dilated Cardiomyopathy	0.532	0.0867
00410	Beta Alanine Metabolism	0.709	0.14
00330	Arginine and Proline Metabolism	1.70E-16	0.0402
04510	Focal Adhesion	0.397	0.0669
00340	Histidine Metabolism	0.519	0.0874
04360	Axon Guidance	0.606	0.0995
04060	ECM Receptor Interaction	0.792	0.196
04150	MTOR Signaling Pathway	0.219	0.0511
04270	Vascular Smooth Muscle Contraction	0.27	0.0542
00071	Fatty Acid Metabolism	0.823	0.204
04142	Lysosome	0.566	0.0804
00983	Drug Metabolism Other Enzymes	0	0.0322
00040	Pentose and Glucuronate Interconversions	0.562	0.0792
05416	Viral Myocarditis	0.569	0.0815
00520	Amino Sugar and Nucleotide Sugar Metabolism	0.453	0.0577
05217	Basal Cell Carcinoma	0.593	0.0799
00510	N Glycan Biosynthesis	5.87E-16	0.0313
04260	Cardiac Muscle Contraction	8.30E-13	0.0312
05216	Thyroid Cancer	2.56E-09	0.0332

KEGG ID	Pathway	Heritability	Proportion
05120	Epithelial Cell Signaling In Helicobacter Pylori Infection	0.652	0.0859
04060	Cytokine Cytokine Receptor Interaction	3.51E-17	0.0276
00120	Primary Bile Acid Biosynthesis	1.69E-16	0.0265
00190	Oxidative Phosphorylation	1.41E-11	0.0268
00760	Nicotinate and Nicotinamide Metabolism	0.401	0.0433
00360	Phenylalanine Metabolism	0.711	0.088
00512	O Glycan Biosynthesis	1.78E-18	0.0253
05213	Endometrial Cancer	0.428	0.0408
00250	Alanine Aspartate and Glutamate Metabolism	0.526	0.0507
00564	Glycerophospholipid Metabolism	0	0.0231
04012	ERBB Signaling Pathway	0.121	0.0253
05211	Renal Cell Carcinoma	3.64E-11	0.0237
02010	ABC Transporters	0.506	0.0454
04710	Circadian Rhythm Mammal	0.0407	0.0292
05222	Small Cell Lung Cancer	1.03E-17	0.024
04062	Chemokine Signaling Pathway	0.124	0.0277
00590	Arachidonic Acid Metabolism	0.141	0.027
04610	Complement and Coagulation Cascades	0.504	0.0453

KEGG ID	Pathway	Heritability	Proportion
03022	Basal Transcription Factors	0.537	0.0424
00600	Sphingolipid Metabolism	8.68E-19	0.0219
05410	Hypertrophic Cardiomyopathy Hcm	3.30E-13	0.0147
04912	GNRH Signaling Pathway	3.11E-16	0.0187
04720	Long Term Potentiation	0	0.0183
03050	Proteasome	0.425	0.0314
04620	JAK Stat Signaling Pathway	0.503	0.0382
05330	Allograft Rejection	0	0.016
03450	Non Homologous End Joining	0.132	0.0199
05320	Autoimmune Thyroid Disease	0	0.0156
03060	Protein Export	0.235	0.0197
03420	Nucleotide Excision Repair	3.19E-14	0.0178
00660	Alpha Linolenic Acid Metabolism	0.458	0.0311
04144	Endocytosis	0.0714	0.0181
05010	Alzheimers Disease	0.0757	0.0172
00591	Linoleic Acid Metabolism	3.00E-11	0.0159
00240	Pyrimidine Metabolism	6.42E-13	0.0152
00270	Cysteine and Methionine Metabolism	0.00281	0.0162
03410	Base Excision Repair	0.377	0.0219
04722	Neurotrophin Signaling Pathway	4.88E-18	0.0152

KEGG ID	Pathway	Heritability	Proportion
04070	Phosphatidylinositol Signaling System	0.312	0.0207
04960	Aldosterone Regulated Sodium Reabsorption	3.36E-15	0.0142
05130	Pathogenic Escherichia Coli Infection	0.158	0.0158
04310	WNT Signaling Pathway	0.176	0.0174
00562	Inositol Phosphate Metabolism	3.24E-16	0.0138
05221	Acute Myeloid Leukemia	0.472	0.0268
00071	Selenoamino Acid Metabolism	3.71E-10	0.0137
04742	Taste Transduction	0.149	0.0174
00531	Glycosaminoglycan Degradation	2.23E-19	0.0135
05340	Primary Immunodeficiency	0	0.0133
04640	Hematopoietic Cell Lineage	2.35E-16	0.0132
05310	Asthma	0.331	0.0183
04620	TGF Beta Signaling Pathway	1.72E-18	0.0131
00860	Porphyrin and Chlorophyll Metabolism	9.84E-16	0.0124
04612	Antigen Processing and Presentation	2.03E-11	0.0129
05010	Parkinsons Disease	4.25E-09	0.012
00790	Folate Biosynthesis	1.07E-11	0.0119
00500	Starch and Sucrose Metabolism	0.429	0.0111
05223	Non Small Cell Lung Cancer	0	0.0115

KEGG ID	Pathway	Heritability	Proportion
03030	DNA Replication	0	0.0116
04622	RIG I Like Receptor Signaling Pathway	0	0.0117
04666	FC Gamma R Mediated Phagocytosis	0.747	0.0415
04514	Cell Adhesion Molecules CAMS	0.278	0.016
03430	Mismatch Repair	7.18E-17	0.011
03010	Ribosome	8.63E-19	0.0108
05220	Chronic Myeloid Leukemia	0.333	0.0164
00910	Nitrogen Metabolism	0	0.0106
04330	Notch Signaling Pathway	0.585	0.0251
04520	Adherens Junction	1.15E-09	0.0107
05210	Colorectal Cancer	0.289	0.0141
03018	RNA Degradation	1.03E-13	0.00998
03440	Homologous Recombination	0	0.0093
00920	Sulfur Metabolism	0.121	0.011
00310	Lysine Degradation	0.446	0.0166
04662	B Cell Receptor Signaling Pathway	0.494	0.0183
00430	Taurine and Hypotaurine Metabolism	8.53E-13	0.00891
04964	Proximal Tubule Bicarbonate Reclamation	0.456	0.0163
04614	Renin Angiotensin System	0.556	0.0183
00970	Aminoacyl tRNA Biosynthesis	0.107	0.0102

KEGG ID	Pathway	Heritability	Proportion
04672	Intestinal Immune Network For IGA Production	0	0.00883
04810	Regulation of Actin Cytoskeleton	0.215	0.0104
05215	Prostate Cancer	1.55E-09	0.00719
00563	Glycosylphosphatidylinositol Gpi Anchor Biosynthesis	0	0.00816
04660	NOD Like Receptor Signaling Pathway	0	0.00828
04540	Gap Junction	0.121	0.0096
00903	Limonene and Pinene Degradation	4.80E-12	0.00822
05200	Pathways In Cancer	0.275	0.0119
04660	Toll Like Receptor Signaling Pathway	8.13E-17	0.00782
04730	Long Term Depression	0.128	0.00885
04020	Calcium Signaling Pathway	0.148	0.00936
04320	Dorso Ventral Axis Formation	0.271	0.00857
05110	Vibrio Cholerae Infection	0.353	0.011
04115	P53 Signaling Pathway	1.07	-0.0975
04962	Vasopressin Regulated Water Reabsorption	0.331	0.0107
04670	Leukocyte Transendothelial Migration	0.248	0.00871
03020	RNA Polymerase	2.52E-16	0.00609
04664	FC Epsilon RI Signaling Pathway	0.35	0.00908
04140	Regulation of Autophagy	0	0.00509

KEGG ID	Pathway	Heritability	Proportion
05010	Huntingtons Disease	0.894	0.0529
00670	One Carbon Pool By Folate	9.11E-13	0.00564
04660	T Cell Receptor Signaling Pathway	0.487	0.0103
00740	Riboflavin Metabolism	0.252	0.00627
00533	Glycosaminoglycan Biosynthesis Keratan Sulfate	0	0.00452
00230	Purine Metabolism	3.84E-18	0.00462
04130	Snare Interactions In Vesicular Transport	1.20E-17	0.00475
05020	Prion Diseases	0.272	0.0059
05219	Bladder Cancer	0.229	0.00531
03040	Spliceosome	0.224	0.00573
04010	Mapk Signaling Pathway	0.221	0.00506
00534	Glycosaminoglycan Biosynthesis Heparan Sulfate	1.40E-18	0.00416
00604	Glycosphingolipid Biosynthesis Ganglio Series	0	0.00372
04940	Type I Diabetes Mellitus	0.446	0.00735
04623	Cytosolic DNA Sensing Pathway	0.431	0.00706
05332	Graft Versus Host Disease	0.432	0.00691
04740	Olfactory Transduction	0	0.0035
04110	Cell Cycle	5.02E-18	0.00369
00511	Other Glycan Degradation	1.07E-24	0.00321
05140	Leishmania Infection	0.136	0.00381

KEGG ID	Pathway	Heritability	Proportion
04914	Progesterone Mediated Oocyte Maturation	1.82E-19	0.00322
04120	Ubiquitin Mediated Proteolysis	2.55E-15	0.00315
00604	Glycosphingolipid Biosynthesis Globo Series	0	0.00271
00601	Glycosphingolipid Biosynthesis Lacto and Neolacto Series	0.213	0.00341
04370	VEGF Signaling Pathway	0.192	0.00362
00053	Ascorbate and Aldarate Metabolism	0	0.00197
04650	Natural Killer Cell Mediated Cytotoxicity	4.16E-19	0.00222
05212	Pancreatic Cancer	5.99E-48	0.00212
04114	Oocyte Meiosis	1.82E-11	0.00201
04210	Apoptosis	0.632	0.00523
05218	Melanoma	0.349	0.00284
04080	Neuroactive Ligand Receptor Interaction	1.76E-17	0.00158
05014	Amyotrophic Lateral Sclerosis ALS	0	0.00102
04950	Maturity Onset Diabetes of The Young	8.21E-12	0.000707