Supplementary Information: "A Comparison Study of Multivariate Fixed Models and Gene Association with Multiple Traits (GAMuT)"

Appendix A Results of European Lipid Studies

A.1 Information Of the Eight European Cohorts

We analyzed lipid traits from eight European cohorts, where five are from Finland [Finland United States Investigation of NIDDM Genetics (FUSION Stage 2) [Scott et al., 2007], FIN-D2D 2007 (D2d-2007) [Kotronen et al., 2010], The Finnish Diabetes Prevention Study (DPS) [Tuomilehto et al., 2001], METabolic Syndrome in Men (METSIM) [Stancakova et al., 2009], and The Dose Responses to Exercise Training Study (DRs EXTRA) [Kouki et al., 2012], two are from Norway [Nord-Trondelag Health Study 2 and Tromso 4 (HUNT and Tromso) [Holmen et al., 2003; Jacobsen et al., 2012], and one from Germany [The DIAbetes GENetic Study (DIAGEN)] [Schwarz et al., 2006]. The two Norwegian cohorts were combined into one study for a joint analysis. The genotype data were from Metabochip genotyping, which was designed to fine map regions that have been associated with metabolic traits [Altshuler et al., 2010]. For each cohort, 54,741 genetic variants were genotyped, located in 97 genetic regions across the 22 autosomes. For our analysis, we utilized the existing literature as a reference for gene selection and found that 22 gene regions were fine mapped [Li et al., 2014; Liu et al., 2014; Morris et al., 2012; Scott et al., 2012; Voight et al., 2010; Zeggini et al., 2008]. We used Builder Mar. 2006 (NCBI36/hg18) to determine gene positions and 5kb was used to extend the gene region on each side of a gene. The summary of 22 genes and the number of genetic variants in each gene region are given in Table S.1.

Four lipid traits were analyzed: high-density lipoprotein (HDL) levels, low-density lipoprotein (LDL) levels, triglycerides (TG), and total cholesterol (CHOL). The sample sizes for each combination of seven studies and four trait are provided in Table S.2.

A.2 Lipid Traits in Eight European Cohorts

For each trait, inverse normal rank transformation was performed to ensure that the normality assumption was valid. For all studies except for METSIM, age, sex, and type 2 diabetes status were used as covariates. For METSIM, age and type 2 diabetes status were used as covariates since no women were included in the study. A significance threshold of $P < 3.1 \times 10^{-6}$ was taken from Liu et al. [2014] (corresponding to 0.05/16,153 based on the number of genes tested therein).

Table S.3 reports the results of association analysis of 5 European studies for the combinations in Table 1 by

using rare variants (MAF ≤ 0.03). Using common variants (MAF > 0.03), Table S.4 reports the results of association analysis of 5 European studies. The results in Tables S.3 and S.4 show that the gene regions contain both rare and common variants and the association signals are mainly from common variants.

In Table S.4, the F-approximation tests of MFLM and MANOVA are more sensitive than GAMuT. GAMuT based on matrix two tentative association signals [$p = 9.07 \times 10^{-5}$ and $p = 2.99 \times 10^{-5}$] and GAMuT based on linear kernel detected one tentative association signal [$p = 9.07 \times 10^{-5}$] at gene *LPL* in the FUSION study. In comparison, the F-approximation tests of MFLM and MANOVA detected much more association signals.

Appendix B Results of The Trinity Students Study

We performed a pleiotropy analysis of 36 SNP variants in one enzyme gene region on three biochemical traits (denoted by A, B, and C) in a sample of 2232 individuals from the Trinity Students Study. Since the raw traits were not normally distributed, we transformed the three traits by inverse normal rank transformation. We adjusted for three factors: gender, another chemical compound known to affect these biochemical traits as a continuous covariate, and a dichotomous covariate to indicate if supplements containing these biochemical factors was used. In this report, we analyzed four combinations of the three traits: three bivariate combinations (A, B), (A, C), (B, C), and one tri-variate combination (A, B, C). We tested the association between the transformed individual traits and the 36 SNPs by approximate F-test statistics of bivariate and tri-variate linear models and GAMuT. Table 1 presents the p-values of the F-approximation tests based on the Pillai-Bartlett trace and GAMuT for the SNP data of the enzyme gene of the Trinity Students Study [Table 2 of Wang et al., 2015]. We present the results of four combinations of the three traits on the bottom of the Table 1: (A, B), (A, C), (B, C), and (A, B, C). The F-approximation tests provided much stronger results than those of GAMuT since the p-values of the approximate F-distributed tests in the bottom four columns of Table 1 were much smaller than those of GAMuT.

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Table S.1: **Summary of 22 Genes and the Number of Genetic Variants in Each Gene Region by Mar. 2006 (NCBI36/hg18).** The number of variants is the number of genetic variants in a region of **Start (-5Kb) - End (+5Kb) Positions**. * The gene region of *PCSK9* is (55277737, 55303114), and (55271537, 55286109) is the region in the database. # The length is the length of the region in bp.

Gene	Chromosome Region	Gene Positions (bp)	Start (-5Kb) - End (+5Kb) Positions (Length#)	Number of Variants
*PCSK9**	1	55277737 - 55303114	55271537 - 55286109 (14572)	74
APOB	2	21077806 - 21120450	21072806 - 21125450 (52644)	223
IGF2BP2	3	186844221 - 187025521	186839221 - 187030521 (191300)	231
CDKAL1	6	20642667 - 21340613	20637667 - 21345613 (707946)	560
JAZF1	7	27836718 - 28186962	27831718 - 28191962 (360244)	384
LPL	8	19840862 - 19869050	19835862 - 19874050 (38188)	212
CDKN2B	9	21992902 - 21999312	21987902 - 22004312 (16410)	64
CDC123	10	12277971 - 12332593	12272971 - 12337593 (64622)	265
IDE	10	94201421 - 94323832	94196421 - 94328832 (132411)	327
KIF11	10	94342805 - 94405132	94337805 - 94410132 (72327)	216
HHEX	10	94439661 - 94445388	94434661 - 94450388 (15727)	30
TCF7L2	10	114699999 - 114917426	114694999 - 114922426 (227427)	258
KCNQ1	11	2422797 - 2826916	2417797 - 2831916 (414119)	660
MTNR1B	11	92342437 - 92355596	92337437 - 92360596 (23159)	106
HMGA2	12	64504507 - 64646338	64499507 - 64651338 (151831)	214
TSPAN8	12	69805144 - 69838046	69800144 - 69843046 (42902)	54
HNF1A	12	119900932 - 119924697	119895932 - 119929697 (33765)	71
OASL	12	119942478 - 119961428	119937478 - 119966428 (28950)	108
FTO	16	52295376 - 52705882	52290376 - 52710882 (420506)	191
LDLR	19	11061038 - 11105505	11056038 - 11110505 (54467)	43
APOE	19	50100879 - 50104490	50095879 - 50109490 (13611)	35
GIPR	19	50863342 - 50877557	50858342 - 50882557 (24215)	37

Table S.2: **Sample Sizes of the Four Lipid Traits for Each of the Seven Studies.**

Study	HDL	LDL	TG	CHOL
D2d-2007	2075	2074	2075	2075
DIAGEN	1470	1454	1470	1471
DPS	412	410	412	412
DRs EXTRA	1157	1157	1157	1157
FUSION Stage 2	2496	1892	2062	2500
METSIM	1346	1345	1346	1346
Norway	2484	2320	2487	2476

Table S.3: **Association analysis of four lipid traits in five European cohorts using rare variants (MAF≤0.03).** The associations that attain a threshold significance of p-value $< 3.1 \times 10^{-6}$ are marked by red. The results of "Basis of both GVF and $\beta_\ell(t)$" were based on smoothing both GVF and genetic effect functions $\beta_\ell(t)$ of model (5), and the results of "Basis of β-smooth only" were based on smoothing $\beta_\ell(t)$ only approach of model (7). Abbreviation: GVF = genetic variant function.

Study	Gene	Number of Rare Variants (MAF ≤ 0.03)	Combinations of Traits	P-values of the F-approximation Based on Pillai-Bartlett Trace					P-values of GAMuT	
				Basis of both GVF and $\beta_\ell(t)$		Basis of beta-Smooth Only		MANOVA	Projection	Linear
				B-sp Basis	Fourier Basis	B-sp Basis	Fourier Basis	Model (S.1)	Matrix	Kernel
D2d-2007	**APOE**	21	**LDL,TG**	9.55×10^{-1}	9.67×10^{-1}	9.55×10^{-1}	9.67×10^{-1}	9.55×10^{-1}	9.69×10^{-1}	9.69×10^{-1}
			LDL,CHOL	7.02×10^{-1}	8.85×10^{-1}	7.02×10^{-1}	8.85×10^{-1}	7.02×10^{-1}	9.22×10^{-1}	9.22×10^{-1}
			TG,CHOL	9.98×10^{-1}	9.95×10^{-1}	9.98×10^{-1}	9.95×10^{-1}	9.98×10^{-1}	9.99×10^{-1}	9.99×10^{-1}
			LDL,TG,CHOL	9.00×10^{-1}	9.59×10^{-1}	9.00×10^{-1}	9.59×10^{-1}	9.00×10^{-1}	8.51×10^{-1}	9.90×10^{-1}
	LPL	136	**LDL,TG**	6.62×10^{-1}	5.80×10^{-1}	6.39×10^{-1}	5.80×10^{-1}	6.39×10^{-1}	5.08×10^{-1}	5.08×10^{-1}
FUSION	**APOE**	21	**LDL,TG**	3.47×10^{-2}	2.10×10^{-2}	3.47×10^{-2}	2.10×10^{-2}	3.47×10^{-2}	8.93×10^{-2}	8.93×10^{-2}
			LDL,CHOL	1.36×10^{-2}	1.32×10^{-2}	1.36×10^{-2}	1.32×10^{-2}	1.36×10^{-2}	2.54×10^{-2}	2.54×10^{-2}
			TG,CHOL	3.37×10^{-2}	2.05×10^{-2}	3.37×10^{-2}	2.05×10^{-2}	3.37×10^{-2}	1.34×10^{-1}	1.34×10^{-1}
			LDL,TG,CHOL	3.93×10^{-2}	2.79×10^{-2}	3.93×10^{-2}	2.79×10^{-2}	3.93×10^{-2}	7.49×10^{-2}	4.81×10^{-2}
	LPL	133	**LDL,TG**	8.27×10^{-2}	5.12×10^{-2}	8.29×10^{-2}	5.12×10^{-2}	8.29×10^{-2}	1.63×10^{-1}	1.63×10^{-1}
			LDL,TG,CHOL	2.03×10^{-1}	1.65×10^{-1}	2.03×10^{-1}	1.65×10^{-1}	2.03×10^{-1}	3.02×10^{-1}	2.05×10^{-1}
Norway	**APOE**	20	**LDL,TG**	8.83×10^{-1}	7.48×10^{-1}	8.83×10^{-1}	7.48×10^{-1}	8.83×10^{-1}	7.45×10^{-1}	7.45×10^{-1}
			LDL,CHOL	9.74×10^{-1}	9.17×10^{-1}	9.74×10^{-1}	9.17×10^{-1}	9.74×10^{-1}	7.85×10^{-1}	6.85×10^{-1}
			TG,CHOL	8.62×10^{-1}	7.79×10^{-1}	8.62×10^{-1}	7.79×10^{-1}	8.62×10^{-1}	7.81×10^{-1}	7.81×10^{-1}
			LDL,TG,CHOL	9.80×10^{-1}	9.10×10^{-1}	9.80×10^{-1}	9.10×10^{-1}	9.80×10^{-1}	9.49×10^{-1}	7.78×10^{-1}
DIAGEN	**APOE**	20	**LDL,TG**	9.68×10^{-1}	8.80×10^{-1}	9.68×10^{-1}	8.80×10^{-1}	9.68×10^{-1}	8.54×10^{-1}	8.54×10^{-1}
			LDL,CHOL	8.06×10^{-1}	6.55×10^{-1}	8.06×10^{-1}	6.55×10^{-1}	8.06×10^{-1}	9.51×10^{-1}	9.51×10^{-1}
			TG,CHOL	8.87×10^{-1}	7.42×10^{-1}	8.87×10^{-1}	7.42×10^{-1}	8.87×10^{-1}	8.34×10^{-1}	8.34×10^{-1}
			LDL,TG,CHOL	7.31×10^{-1}	5.58×10^{-1}	7.31×10^{-1}	5.58×10^{-1}	7.31×10^{-1}	4.66×10^{-1}	8.91×10^{-1}
METSIM	**APOE**	21	**LDL,TG**	7.89×10^{-1}	6.41×10^{-1}	7.89×10^{-1}	6.41×10^{-1}	7.89×10^{-1}	8.52×10^{-1}	8.52×10^{-1}
			LDL,CHOL	7.98×10^{-1}	8.04×10^{-1}	7.98×10^{-1}	8.04×10^{-1}	7.98×10^{-1}	5.17×10^{-1}	5.17×10^{-1}
			LDL,TG,CHOL	7.15×10^{-1}	6.22×10^{-1}	7.15×10^{-1}	6.22×10^{-1}	7.15×10^{-1}	5.23×10^{-1}	6.74×10^{-1}
	LDLR	29	**LDL,TG**	1.70×10^{-2}	6.50×10^{-2}	1.70×10^{-2}	6.50×10^{-2}	1.70×10^{-2}	1.18×10^{-1}	1.18×10^{-1}
			LDL,CHOL	1.42×10^{-3}	2.31×10^{-1}	1.42×10^{-3}	2.31×10^{-1}	1.42×10^{-3}	1.25×10^{-1}	1.25×10^{-1}
			TG,CHOL	1.53×10^{-2}	1.83×10^{-1}	1.53×10^{-2}	1.83×10^{-1}	1.53×10^{-2}	1.46×10^{-1}	1.46×10^{-1}
			LDL,TG,CHOL	1.06×10^{-3}	1.55×10^{-1}	1.06×10^{-3}	1.55×10^{-1}	1.06×10^{-3}	9.77×10^{-2}	1.18×10^{-1}

Table S.4: **Association analysis of four lipid traits in five European cohorts using common variants (MAF>0.03).** The associations that attain a threshold significance of p-value $< 3.1 \times 10^{-6}$ are marked by red. The results of "Basis of both GVF and $\beta_\ell(t)$" were based on smoothing both GVF and genetic effect functions $\beta_\ell(t)$ of model (5), and the results of "Basis of β-smooth only" were based on smoothing $\beta_\ell(t)$ only approach of model (7). Abbreviation: GVF = genetic variant function.

Study	Gene	Number of Common Variants (MAF > 0.03)	Combinations of Traits	P-values of the F-approximation Based on Pillai-Bartlett Trace					P-values of GAMuT	
				Basis of both GVF and $\beta_\ell(t)$		Basis of beta-Smooth Only		MANOVA	Projection	Linear
				B-sp Basis	Fourier Basis	B-sp Basis	Fourier Basis	Model (S.1)	Matrix	Kernel
D2d-2007	**APOE**	14	**LDL,TG**	7.84×10^{-25}	1.45×10^{-25}	7.84×10^{-25}	1.45×10^{-25}	7.84×10^{-25}	1.58×10^{-1}	1.58×10^{-1}
			LDL,CHOL	9.00×10^{-21}	1.49×10^{-21}	9.00×10^{-21}	1.49×10^{-21}	9.00×10^{-21}	8.60×10^{-2}	8.60×10^{-2}
			TG,CHOL	2.14×10^{-20}	4.52×10^{-21}	2.14×10^{-20}	4.52×10^{-21}	2.14×10^{-20}	4.70×10^{-1}	4.70×10^{-1}
			LDL,TG,CHOL	2.69×10^{-21}	3.16×10^{-22}	2.69×10^{-21}	3.16×10^{-22}	2.69×10^{-21}	3.10×10^{-1}	1.30×10^{-1}
	LPL	76	**LDL,TG**	2.54×10^{-2}	2.24×10^{-2}	2.54×10^{-2}	2.24×10^{-2}	3.72×10^{-1}	3.84×10^{-2}	3.84×10^{-3}
FUSION	**APOE**	14	**LDL,TG**	2.41×10^{-7}	9.54×10^{-8}	2.41×10^{-7}	9.54×10^{-8}	2.41×10^{-7}	9.39×10^{-3}	9.39×10^{-3}
			LDL,CHOL	3.77×10^{-7}	1.47×10^{-7}	3.77×10^{-7}	1.47×10^{-7}	3.77×10^{-7}	8.09×10^{-3}	8.09×10^{-3}
			TG,CHOL	1.61×10^{-4}	6.93×10^{-5}	1.61×10^{-4}	6.93×10^{-5}	1.61×10^{-4}	7.78×10^{-1}	7.78×10^{-1}
			LDL,TG,CHOL	8.83×10^{-6}	2.90×10^{-6}	8.83×10^{-6}	2.90×10^{-6}	8.83×10^{-6}	4.97×10^{-2}	7.49×10^{-3}
	LPL	79	**LDL,TG**	1.10×10^{-3}	1.85×10^{-3}	1.10×10^{-3}	1.85×10^{-3}	2.82×10^{-2}	9.07×10^{-5}	9.07×10^{-5}
			LDL,TG,CHOL	2.06×10^{-3}	7.51×10^{-3}	2.06×10^{-3}	7.51×10^{-3}	4.60×10^{-2}	2.99×10^{-5}	6.99×10^{-4}
Norway	**APOE**	15	**LDL,TG**	1.36×10^{-26}	5.10×10^{-26}	9.02×10^{-26}	5.10×10^{-26}	9.02×10^{-26}	1.39×10^{-1}	1.39×10^{-1}
			LDL,CHOL	9.64×10^{-30}	1.09×10^{-29}	6.02×10^{-29}	1.09×10^{-29}	6.02×10^{-29}	5.97×10^{-2}	5.97×10^{-2}
			TG,CHOL	6.04×10^{-21}	7.01×10^{-21}	2.32×10^{-20}	7.01×10^{-21}	2.32×10^{-20}	1.03×10^{-1}	1.03×10^{-1}
			LDL,TG,CHOL	7.60×10^{-26}	2.84×10^{-25}	7.59×10^{-25}	2.84×10^{-25}	7.59×10^{-25}	1.97×10^{-1}	9.89×10^{-2}
DIAGEN	**APOE**	15	**LDL,TG**	1.35×10^{-8}	1.51×10^{-8}	2.44×10^{-8}	1.51×10^{-8}	2.44×10^{-8}	6.89×10^{-3}	6.89×10^{-3}
			LDL,CHOL	7.68×10^{-10}	6.78×10^{-10}	2.41×10^{-9}	6.78×10^{-10}	2.41×10^{-9}	3.23×10^{-2}	3.23×10^{-2}
			TG,CHOL	3.57×10^{-6}	3.51×10^{-6}	4.80×10^{-6}	3.51×10^{-6}	4.80×10^{-6}	8.20×10^{-2}	8.20×10^{-2}
			LDL,TG,CHOL	2.35×10^{-10}	2.23×10^{-10}	5.70×10^{-10}	2.23×10^{-10}	5.70×10^{-10}	8.71×10^{-4}	9.90×10^{-3}
METSIM	**APOE**	14	**LDL,TG**	6.46×10^{-8}	5.16×10^{-7}	2.97×10^{-8}	5.16×10^{-7}	2.97×10^{-8}	8.99×10^{-2}	8.99×10^{-2}
			LDL,CHOL	1.91×10^{-5}	3.64×10^{-6}	7.24×10^{-6}	3.64×10^{-6}	7.24×10^{-6}	1.74×10^{-2}	1.74×10^{-2}
			LDL,TG,CHOL	5.09×10^{-7}	2.25×10^{-6}	1.81×10^{-7}	2.25×10^{-6}	1.81×10^{-7}	1.03×10^{-2}	3.23×10^{-2}
	LDLR	14	**LDL,TG**	1.61×10^{-4}	2.09×10^{-4}	1.63×10^{-4}	2.09×10^{-4}	1.97×10^{-4}	2.35×10^{-3}	2.35×10^{-3}
			LDL,CHOL	7.81×10^{-5}	1.89×10^{-5}	1.60×10^{-5}	1.89×10^{-5}	3.35×10^{-5}	1.72×10^{-4}	1.72×10^{-4}
			TG,CHOL	1.88×10^{-4}	1.58×10^{-4}	9.49×10^{-5}	1.58×10^{-4}	1.44×10^{-4}	1.14×10^{-2}	1.14×10^{-2}
			LDL,TG,CHOL	1.07×10^{-4}	1.08×10^{-4}	8.35×10^{-5}	1.08×10^{-4}	1.42×10^{-4}	9.33×10^{-4}	3.31×10^{-4}

Appendix C Power Comparison of Six Traits When the Correlations are Low and High

In Figures S.1 and S.2, the empirical power levels are plotted when the residual correlations are low. In Figures S.3 and S.4, the empirical power levels are plotted when the residual correlations are high.

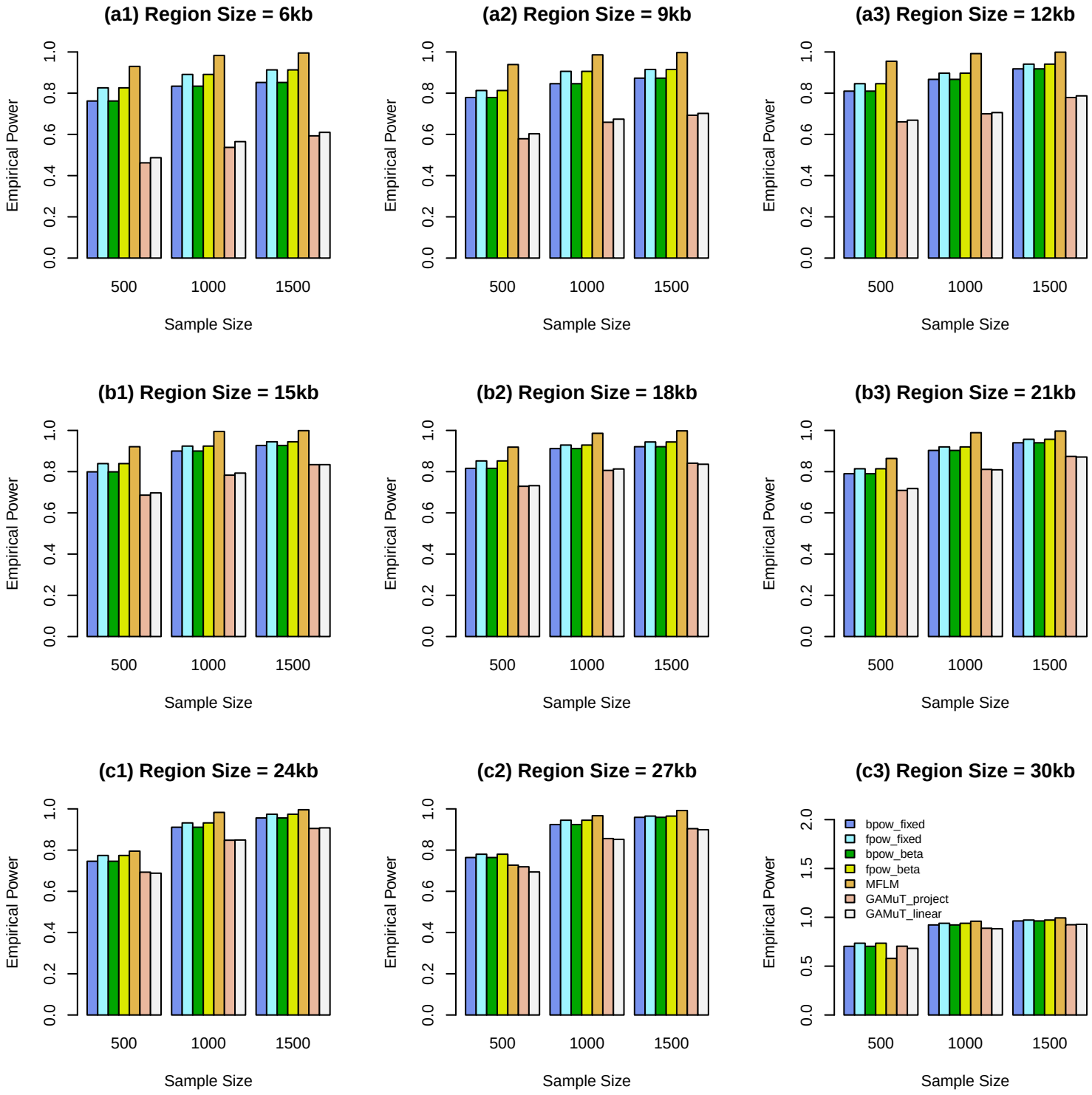

Figure S.1: **The empirical power of the approximate F-distributed tests of the additive models of MANOVA (1) and MFLM (5) and (7) based on Pillai-Bartlett trace and GAMuT at $\alpha = 2.5 \times 10^{-6}$ for six traits and low correlation, when some causal variants are rare and some are common, 20%/80% causal variants have negative/positive effects for each of six traits, and 5% variants are causal.** The order of B-spline basis was 4, the number of B-spline basis functions was $K = K_\beta = 15$, and the number of Fourier basis functions was $K = K_\beta = 21$.

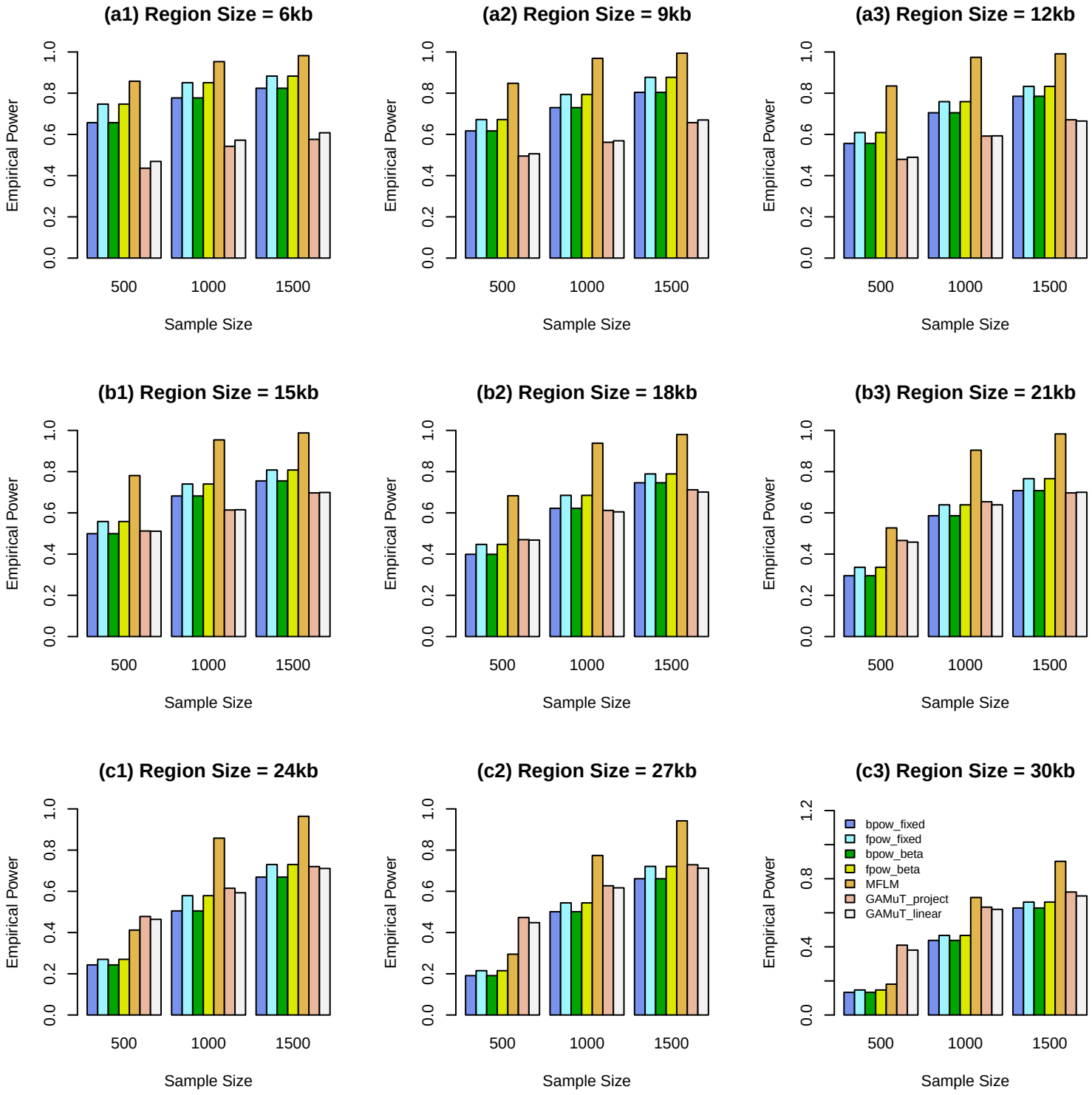

Figure S.2: **The empirical power of the approximate F-distributed tests of the additive models of MANOVA (1) and MFLM (5) and (7) based on Pillai-Bartlett trace and GAMuT at $\alpha = 2.5 \times 10^{-6}$ for six traits and low correlation, when all causal variants are rare, 20%/80% causal variants have negative/positive effects for each of six traits, and 5% variants are causal.** The order of B-spline basis was 4, the number of B-spline basis functions was $K = K_\beta = 15$, and the number of Fourier basis functions was $K = K_\beta = 21$.

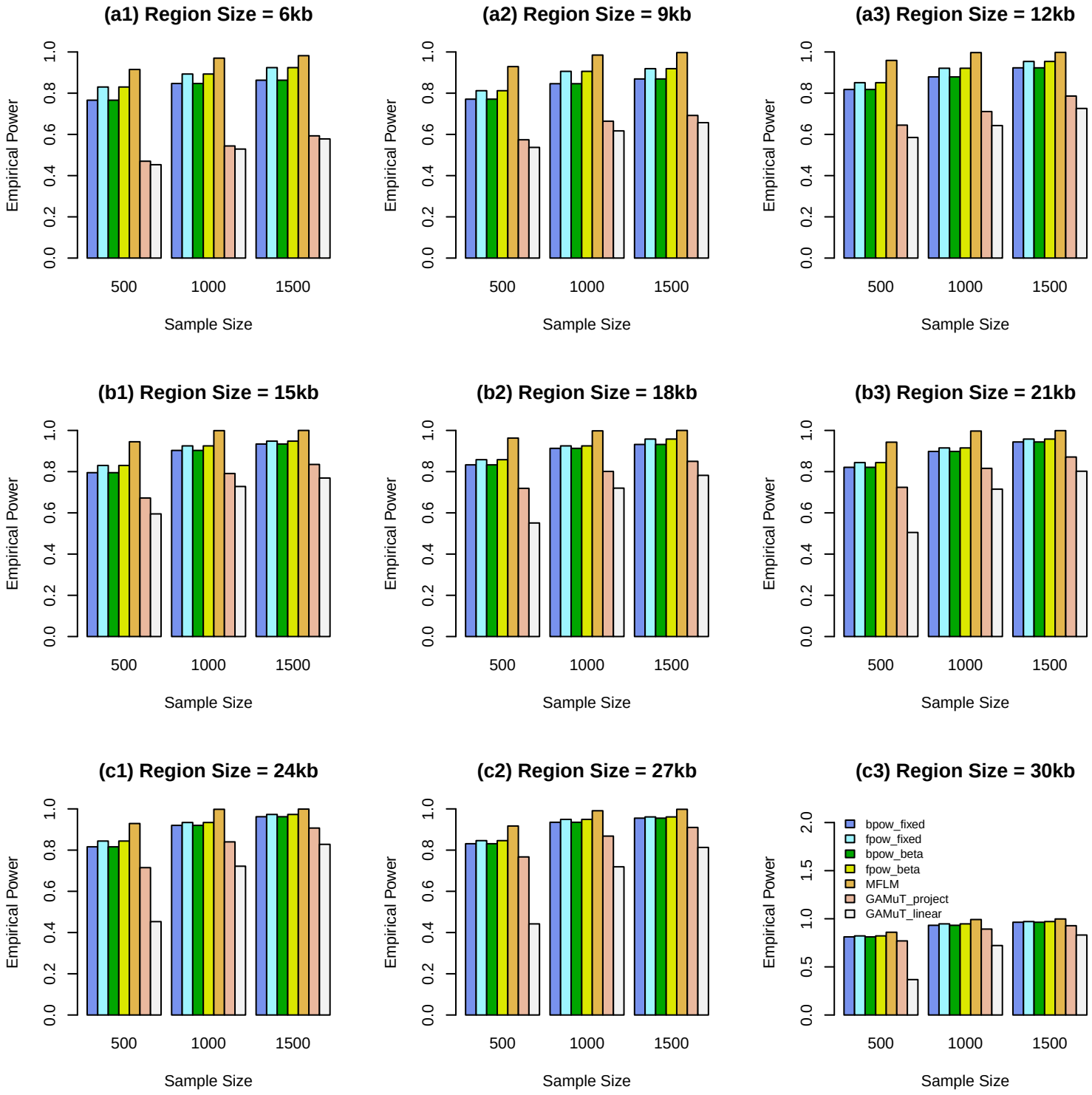

Figure S.3: **The empirical power of the approximate F-distributed tests of the additive models of MANOVA (1) and MFLM (5) and (7) based on Pillai-Bartlett trace and GAMuT at $\alpha = 2.5 \times 10^{-6}$ for six traits and high correlation, when some causal variants are rare and some are common, 20%/80% causal variants have negative/positive effects for each of six traits, and 5% variants are causal.** The order of B-spline basis was 4, the number of B-spline basis functions was $K = K_\beta = 15$, and the number of Fourier basis functions was $K = K_\beta = 21$.

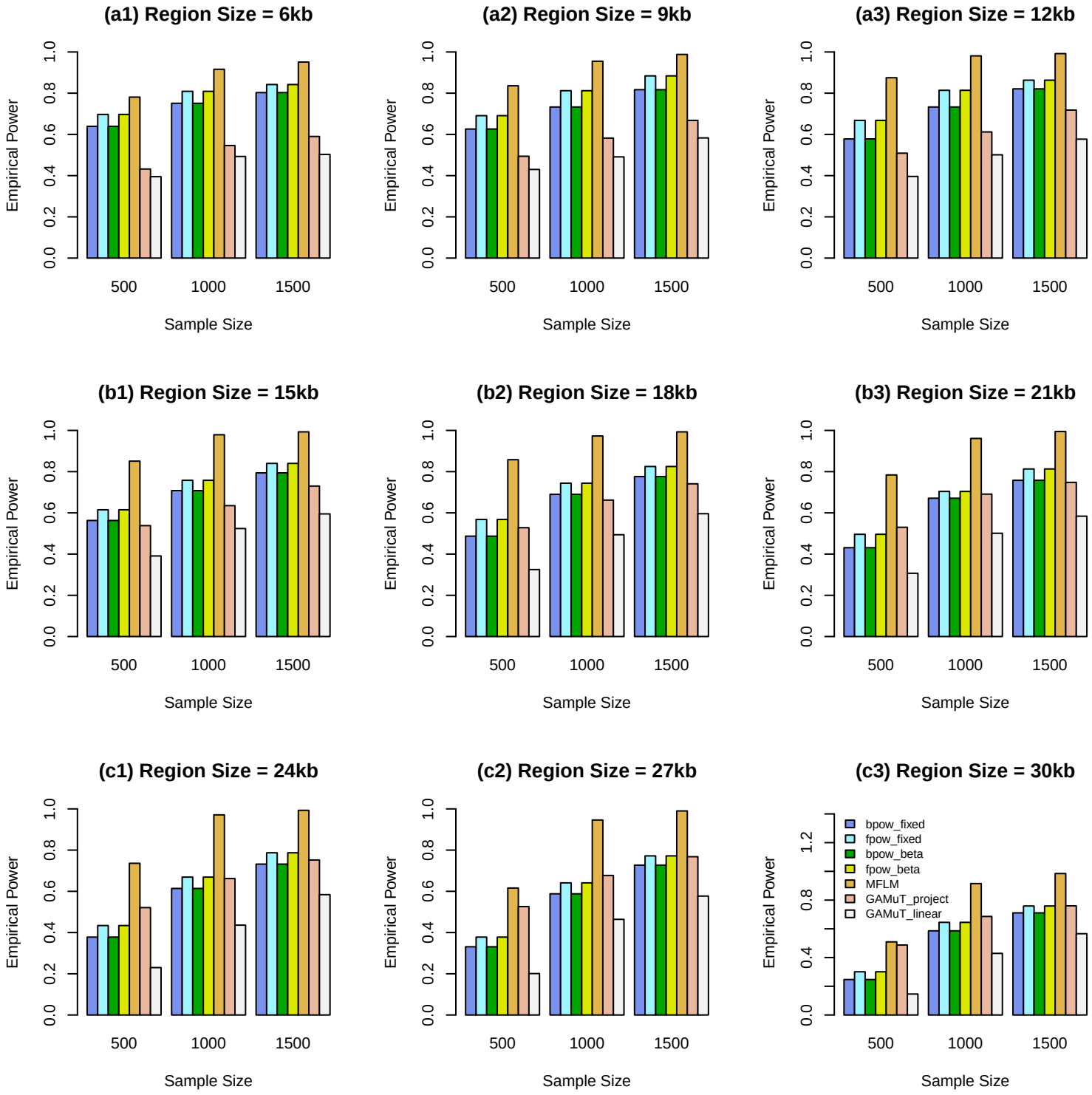

Figure S.4: **The empirical power of the approximate F-distributed tests of the additive models of MANOVA (1) and MFLM (5) and (7) based on Pillai-Bartlett trace and GAMuT at $\alpha = 2.5 \times 10^{-6}$ for six traits and high correlation, when all causal variants are rare, 20%/80% causal variants have negative/positive effects for each of six traits, and 5% variants are causal.** The order of B-spline basis was 4, the number of B-spline basis functions was $K = K_\beta = 15$, and the number of Fourier basis functions was $K = K_\beta = 21$.