Supplementary Materials I: "Gene Level Meta-analysis of Quantitative Traits by Functional Linear Models"

Appendix A. Information and Extra Results of the Eight European Cohorts

For each of the eight European cohorts, we performed analysis for four lipid traits and 22 genes. The information of the 22 genes is given in Table S.1. The sample sizes of each trait are presented in Table S.2. The results of association analysis by Hom-F and Het-F are reported in Tables S.3 and S.4.

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
Total	11440	10652	11009	11437

Table S.3: **Association Analysis of Lipid Traits in Eight European Cohorts by Homogeneous F-distributed Statistics (Hom-F), Hom-MetaSKAT-O, and Hom-MetaSKAT.** The associations that attain a threshold significance of $P < 3.1 \times 10^{-6}$ are marked by red (Liu *et al.* 2014). 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 (3), and the results of "Basis of beta-Smooth Only" were based on smoothing $\beta_\ell(t)$ only approach of model (5), the results of "Additive Model (7)" were based on the additive effect model (7), and the p-values of Hom-MetaSKAT and Hom-MetaSKAT-O were based of R package MetaSKAT. Abbreviation: GVF = Genetic Variant Function.

Traits	**Gene**	**P-values of the Hom-F**					**P-values of Hom-Meta-**	
		Basis of Both GVF and $\beta_\ell(t)$		**Basis of beta-Smooth Only**		**Additive Model (7)**		
		B-spline Basis	**Fourier Basis**	**B-spline Basis**	**Fourier Basis**		**SKAT**	**SKAT-O**
HDL	**LPL**	3.17×10^{-6}	6.72×10^{-9}	3.77×10^{-6}	7.17×10^{-7}	8.93×10^{-4}	1.08×10^{-3}	1.21×10^{-3}
LDL	**APOB**	3.63×10^{-9}	7.67×10^{-4}	6.12×10^{-8}	1.93×10^{-4}	4.29×10^{-5}	1.63×10^{-2}	2.51×10^{-2}
	APOE	1.13×10^{-85}	7.12×10^{-89}	2.38×10^{-81}	8.19×10^{-88}	5.05×10^{-87}	1.18×10^{-43}	6.67×10^{-44}
	LDLR	9.90×10^{-15}	2.10×10^{-14}	6.14×10^{-15}	1.13×10^{-13}	9.47×10^{-17}	1.03×10^{-10}	2.94×10^{-10}
	PCSK9	2.39×10^{-6}	6.04×10^{-10}	1.72×10^{-6}	1.37×10^{-7}	3.62×10^{-17}	6.18×10^{-7}	2.00×10^{-6}
TG	**APOE**	5.13×10^{-6}	6.93×10^{-6}	5.37×10^{-7}	2.01×10^{-6}	1.43×10^{-6}	1.34×10^{-3}	2.59×10^{-3}
	LPL	2.27×10^{-11}	8.93×10^{-13}	2.90×10^{-11}	5.20×10^{-14}	6.67×10^{-7}	1.78×10^{-5}	1.77×10^{-5}
CHOL	**APOB**	2.11×10^{-8}	7.97×10^{-3}	2.30×10^{-7}	1.20×10^{-4}	8.08×10^{-8}	6.17×10^{-2}	1.00×10^{-1}
	APOE	1.33×10^{-52}	2.12×10^{-52}	6.24×10^{-48}	8.37×10^{-51}	1.03×10^{-50}	9.08×10^{-23}	2.15×10^{-22}
	HNF1A	1.08×10^{-1}	1.85×10^{-2}	9.00×10^{-3}	2.99×10^{-6}	1.77×10^{-2}	1.89×10^{-1}	2.77×10^{-1}
	LDLR	8.93×10^{-11}	9.47×10^{-10}	9.32×10^{-10}	7.33×10^{-9}	2.43×10^{-12}	3.43×10^{-7}	1.15×10^{-6}

Table S.4: **Association Analysis of Lipid Traits in Eight European Cohorts by Heterogeneous F-distributed Statistics (Het-F), Het-MetaSKAT-O, and Het-MetaSKAT.** The associations that attain a threshold significance of $P < 3.1 \times 10^{-6}$ are marked by red (Liu *et al.* 2014). 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 (3), and the results of "Basis of beta-Smooth Only" were based on smoothing $\beta_\ell(t)$ only approach of model (5), the results of "Additive Model (6)" were based on the additive effect model (6), and the p-values of Het-MetaSKAT and Het-MetaSKAT-O were based of R package MetaSKAT. Abbreviation: GVF = Genetic Variant Function.

Traits	**Gene**	P**-values of the Het-F**					P**-values of Het-Meta-**	
		Basis of Both GVF and $\beta_\ell(t)$		**Basis of beta-Smooth Only**		**Additive Model (6)**		
		B-spline Basis	**Fourier Basis**	**B-spline Basis**	**Fourier Basis**		**SKAT**	**SKAT-O**
LDL	**APOB**	7.29×10^{-11}	6.69×10^{-8}	7.29×10^{-11}	6.69×10^{-8}	5.80×10^{-6}	7.61×10^{-2}	1.40×10^{-1}
	APOE	1.90×10^{-78}	1.30×10^{-76}	1.90×10^{-78}	1.30×10^{-76}	9.51×10^{-76}	2.23×10^{-33}	1.28×10^{-38}
	CDC123	2.04×10^{-6}	4.57×10^{-8}	2.04×10^{-6}	4.57×10^{-8}	6.22×10^{-3}	2.54×10^{-1}	4.19×10^{-1}
	CDKAL1	6.11×10^{-7}	6.77×10^{-8}	6.11×10^{-7}	6.77×10^{-8}	9.21×10^{-3}	3.74×10^{-1}	5.81×10^{-1}
	CDKN2B	7.97×10^{-7}	1.20×10^{-5}	7.97×10^{-7}	1.46×10^{-5}	1.88×10^{-5}	7.46×10^{-1}	9.20×10^{-1}
	FTO	2.46×10^{-6}	1.29×10^{-5}	2.46×10^{-6}	1.29×10^{-5}	4.43×10^{-4}	1.11×10^{-2}	2.23×10^{-2}
	HNF1A	8.93×10^{-11}	7.60×10^{-8}	8.93×10^{-11}	3.26×10^{-8}	1.61×10^{-10}	1.31×10^{-1}	2.26×10^{-1}
	LDLR	7.96×10^{-9}	1.95×10^{-9}	1.12×10^{-8}	1.72×10^{-9}	3.19×10^{-9}	4.27×10^{-7}	4.93×10^{-7}
	OASL	1.41×10^{-7}	5.25×10^{-6}	1.41×10^{-7}	7.48×10^{-6}	1.11×10^{-5}	1.20×10^{-1}	8.81×10^{-2}
	PCSK9	6.51×10^{-9}	1.70×10^{-12}	6.51×10^{-9}	3.55×10^{-11}	9.92×10^{-12}	9.03×10^{-4}	2.09×10^{-3}
	TSPAN8	8.68×10^{-9}	2.17×10^{-10}	1.06×10^{-10}	1.38×10^{-10}	2.20×10^{-10}	6.47×10^{-2}	1.22×10^{-1}
TG	**LPL**	1.43×10^{-5}	1.11×10^{-6}	1.43×10^{-5}	1.11×10^{-6}	6.70×10^{-5}	3.38×10^{-6}	6.30×10^{-6}
CHOL	**APOB**	2.09×10^{-12}	5.30×10^{-10}	2.09×10^{-12}	5.30×10^{-10}	2.93×10^{-9}	6.04×10^{-2}	1.12×10^{-1}
	APOE	9.35×10^{-54}	4.49×10^{-51}	9.35×10^{-54}	4.49×10^{-51}	5.85×10^{-51}	2.76×10^{-20}	3.08×10^{-22}
	CDC123	2.66×10^{-6}	1.79×10^{-6}	2.66×10^{-6}	1.79×10^{-6}	1.21×10^{-2}	7.13×10^{-1}	8.97×10^{-1}
	CDKAL1	5.74×10^{-8}	4.01×10^{-9}	5.74×10^{-8}	4.01×10^{-9}	2.30×10^{-4}	1.17×10^{-1}	2.06×10^{-1}
	CDKN2B	2.20×10^{-7}	1.71×10^{-6}	2.20×10^{-7}	8.20×10^{-7}	1.57×10^{-6}	8.76×10^{-1}	6.39×10^{-1}
	FTO	3.43×10^{-7}	1.88×10^{-6}	3.43×10^{-7}	1.88×10^{-6}	9.52×10^{-7}	9.84×10^{-3}	1.99×10^{-2}
	HNF1A	6.09×10^{-11}	1.29×10^{-8}	6.09×10^{-11}	1.20×10^{-8}	6.62×10^{-10}	4.33×10^{-1}	5.38×10^{-1}
	IDE	6.78×10^{-5}	1.74×10^{-6}	6.78×10^{-5}	1.74×10^{-6}	1.08×10^{-4}	2.30×10^{-1}	3.86×10^{-1}
	JAZF1	2.56×10^{-6}	4.91×10^{-6}	2.56×10^{-6}	4.91×10^{-6}	9.79×10^{-4}	9.52×10^{-2}	1.71×10^{-1}
	KIF11	1.15×10^{-6}	8.67×10^{-7}	1.15×10^{-6}	8.67×10^{-7}	1.72×10^{-5}	2.77×10^{-1}	4.40×10^{-1}
	LDLR	2.81×10^{-6}	4.98×10^{-8}	3.73×10^{-6}	4.77×10^{-8}	9.10×10^{-8}	4.77×10^{-4}	2.28×10^{-5}
	MTNR1B	8.07×10^{-7}	7.59×10^{-7}	8.07×10^{-7}	1.80×10^{-7}	7.96×10^{-7}	4.16×10^{-2}	7.48×10^{-2}
	OASL	1.36×10^{-7}	1.26×10^{-7}	1.36×10^{-7}	1.91×10^{-7}	1.51×10^{-7}	3.11×10^{-1}	5.06×10^{-2}
	PCSK9	2.11×10^{-5}	2.61×10^{-6}	2.11×10^{-5}	1.00×10^{-5}	7.69×10^{-7}	1.89×10^{-2}	3.72×10^{-2}
	TSPAN8	1.46×10^{-10}	3.38×10^{-13}	4.54×10^{-13}	4.24×10^{-13}	4.02×10^{-13}	9.43×10^{-2}	1.74×10^{-1}

Table S.5: **Results of Separate Association Analysis of Lipid Traits in the Individual European Studies in the Regions of *APOE* and *LDLR* Genes Using the F-distributed Statistics.** The associations that attain a threshold significance of $P < 3.1\times10^{-6}$ are marked by red (Liu *et al.* 2014). The results of "Basis of both GVF and $\beta(t)$" were based on smoothing both GVF and genetic effect functions $\beta(t)$ of fixed effect model, the results of "Basis of beta-Smooth Only" were based on beta-smooth only model (Fan *et al.* 2013), the results of "Additive Model (6)" were based on the additive effect model (6) to analyze study by study (i.e., $L = 1$), and the p-values of SKAT-O Were Based of R Package SKAT. Abbreviation: GVF = Genetic Variant Function.

Study	**Gene**	**Traits**	**P-values of the F-distributed Statistics**					**P-values of SKAT-O**
			Basis of both GVF and $\beta(t)$		**Basis of beta-Smooth Only**		**Additive Model (6)**	
			B-spline Basis	**Fourier Basis**	**B-spline Basis**	**Fourier Basis**		
D2d-2007	**APOE**	**LDL**	1.89×10^{-25}	9.02×10^{-25}	1.89×10^{-25}	9.02×10^{-25}	2.85×10^{-24}	5.87×10^{-13}
		CHOL	9.09×10^{-18}	3.01×10^{-17}	9.09×10^{-18}	3.01×10^{-17}	7.97×10^{-17}	1.72×10^{-9}
FUSION Stage 2	**APOE**	**LDL**	4.34×10^{-10}	2.24×10^{-11}	4.34×10^{-10}	2.24×10^{-11}	3.42×10^{-11}	8.61×10^{-14}
		CHOL	1.34×10^{-12}	4.92×10^{-13}	1.34×10^{-12}	4.92×10^{-13}	8.70×10^{-13}	1.64×10^{-12}
Norway	**APOE**	**LDL**	3.79×10^{-28}	1.90×10^{-27}	3.79×10^{-28}	1.90×10^{-27}	6.05×10^{-27}	6.21×10^{-6}
		CHOL	2.12×10^{-14}	6.15×10^{-14}	2.12×10^{-14}	6.15×10^{-14}	1.35×10^{-13}	3.00×10^{-3}
DIAGEN	**APOE**	**LDL**	7.84×10^{-7}	3.31×10^{-6}	7.84×10^{-7}	3.31×10^{-6}	5.76×10^{-6}	2.37×10^{-1}
METSIM	**APOE**	**LDL**	1.85×10^{-5}	1.98×10^{-5}	1.85×10^{-5}	1.98×10^{-5}	3.45×10^{-5}	1.25×10^{-4}
	LDLR	**CHOL**	3.47×10^{-4}	2.97×10^{-6}	3.47×10^{-4}	2.97×10^{-6}	5.67×10^{-6}	5.79×10^{-3}

Appendix B. Empirical Power Figures of Heterogeneous Likelihood Ratio Tests (Het-LRT)

In this section of the **Supplementary Materials I**, more empirical power results are presented based on heterogeneous likelihood ratio tests (Het-LRT).

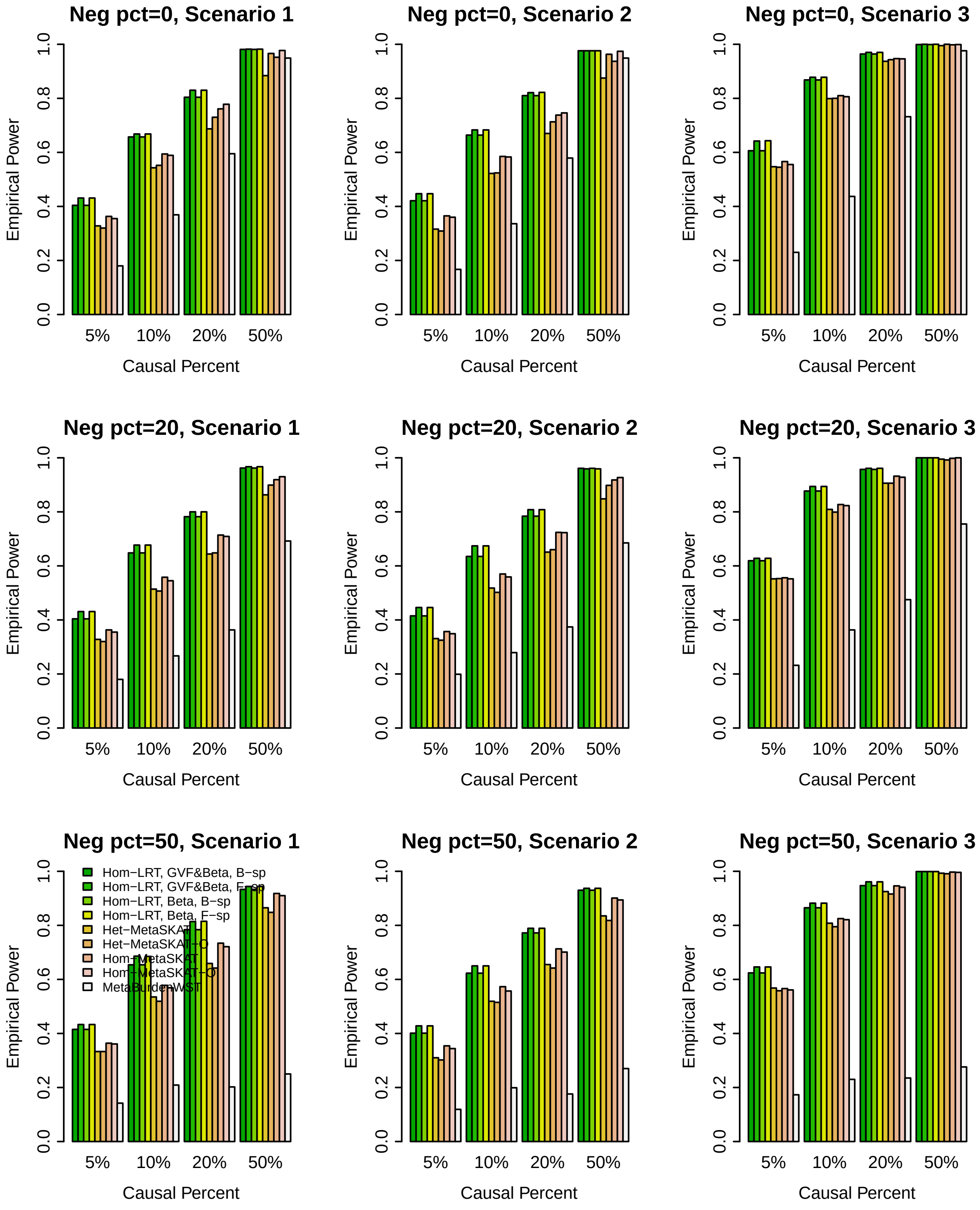

Figure S.1: **The Empirical Power of the Heterogeneous LRT Statistics (Het-LRT) of the Models (3) and (5), MetaSKAT, and MetaBurdenWST at $\alpha = 0.0001$, When Causal Variants Were Both Rare and Common and the Genetic Effect is Simulated as Homogeneous.** When Neg pct = 0, All Causal Variants Had Positive Effects; When Neg pct = 20, 20%/80% Causal Variants Had Negative/Positive Effects; When Neg pct = 50, 50%/50% Causal Variants Had Negative/Positive Effects.

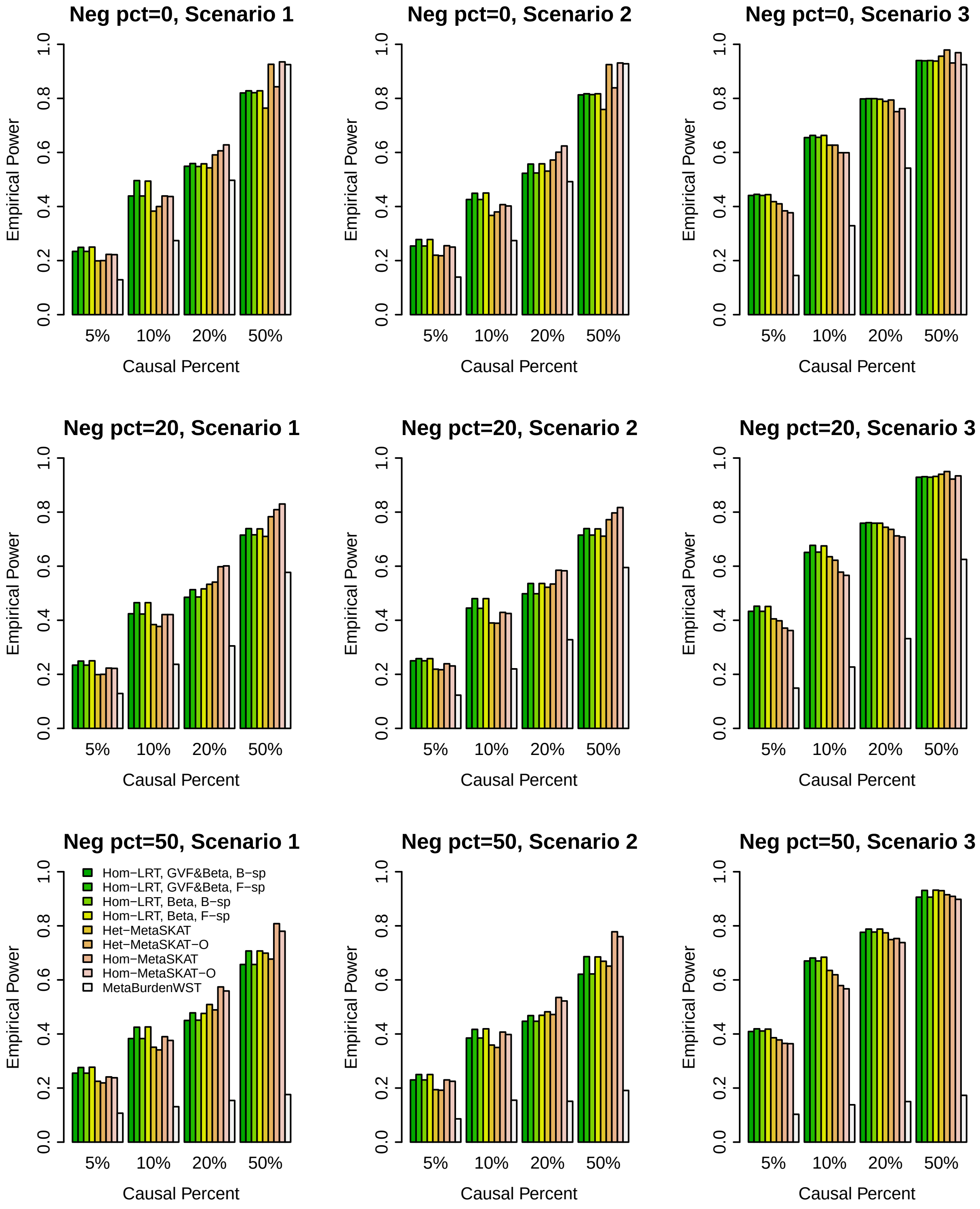

Figure S.2: **The Empirical Power of the Heterogeneous LRT Statistics (Het-LRT) of the Models (3) and (5), MetaSKAT, and MetaBurdenWST at** $\alpha = 0.0001$**, When Causal Variants Were Only Rare and the Genetic Effect is Simulated as Homogeneous.** When Neg pct = 0, All Causal Variants Had Positive Effects; When Neg pct = 20, 20%/80% Causal Variants Had Negative/Positive Effects; When Neg pct = 50, 50%/50% Causal Variants Had Negative/Positive Effects.

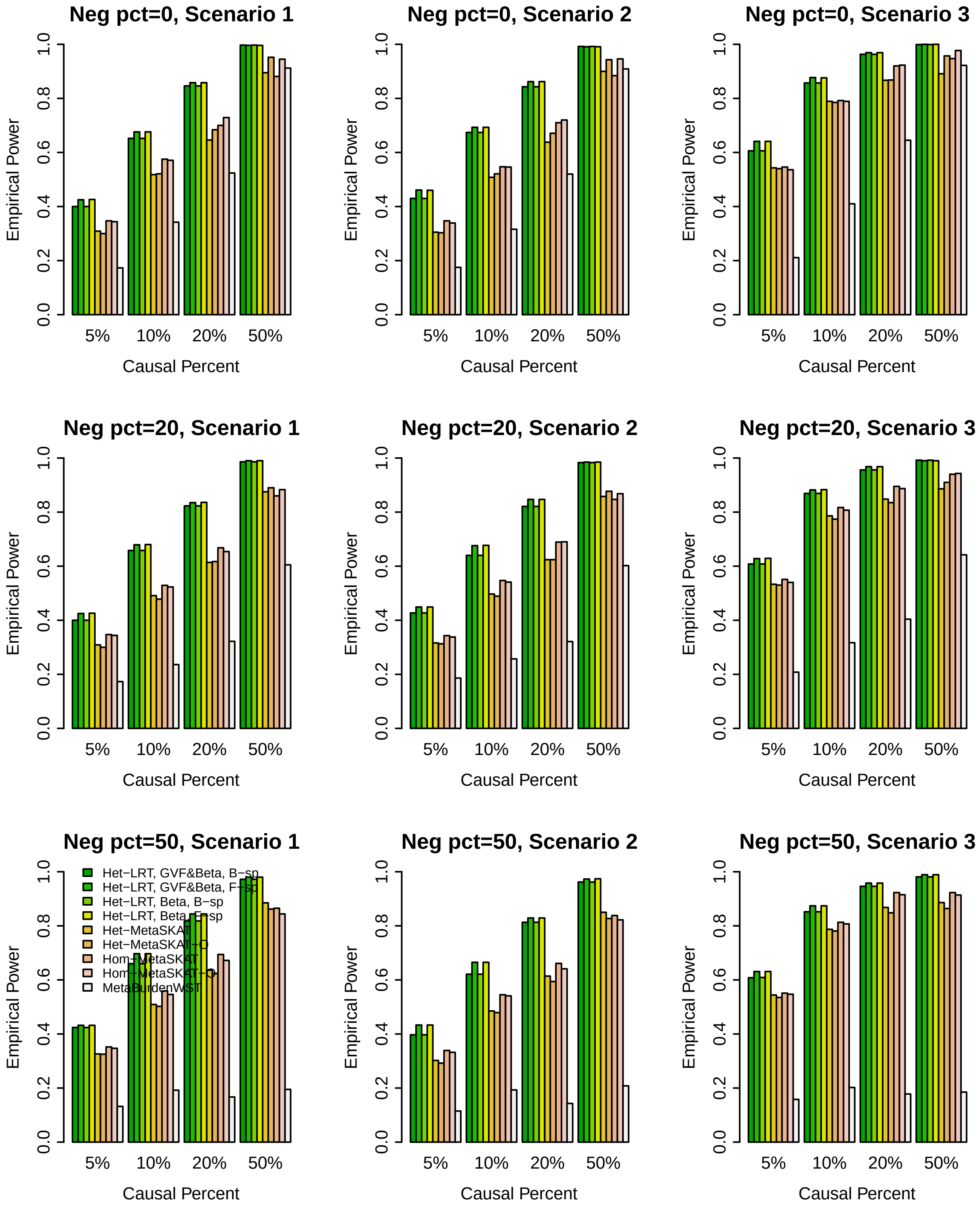

Figure S.3: **The Empirical Power of the Heterogeneous LRT Statistics (Het-LRT) of the Models (3) and (5), MetaSKAT, and MetaBurdenWST at $\alpha = 0.0001$, When Causal Variants Were Both Rare and Common and the Genetic Effect is Simulated as Heterogeneous.** When Neg pct $= 0$, All Causal Variants Had Positive Effects; When Neg pct $= 20$, 20%/80% Causal Variants Had Negative/Positive Effects; When Neg pct $= 50$, 50%/50% Causal Variants Had Negative/Positive Effects.

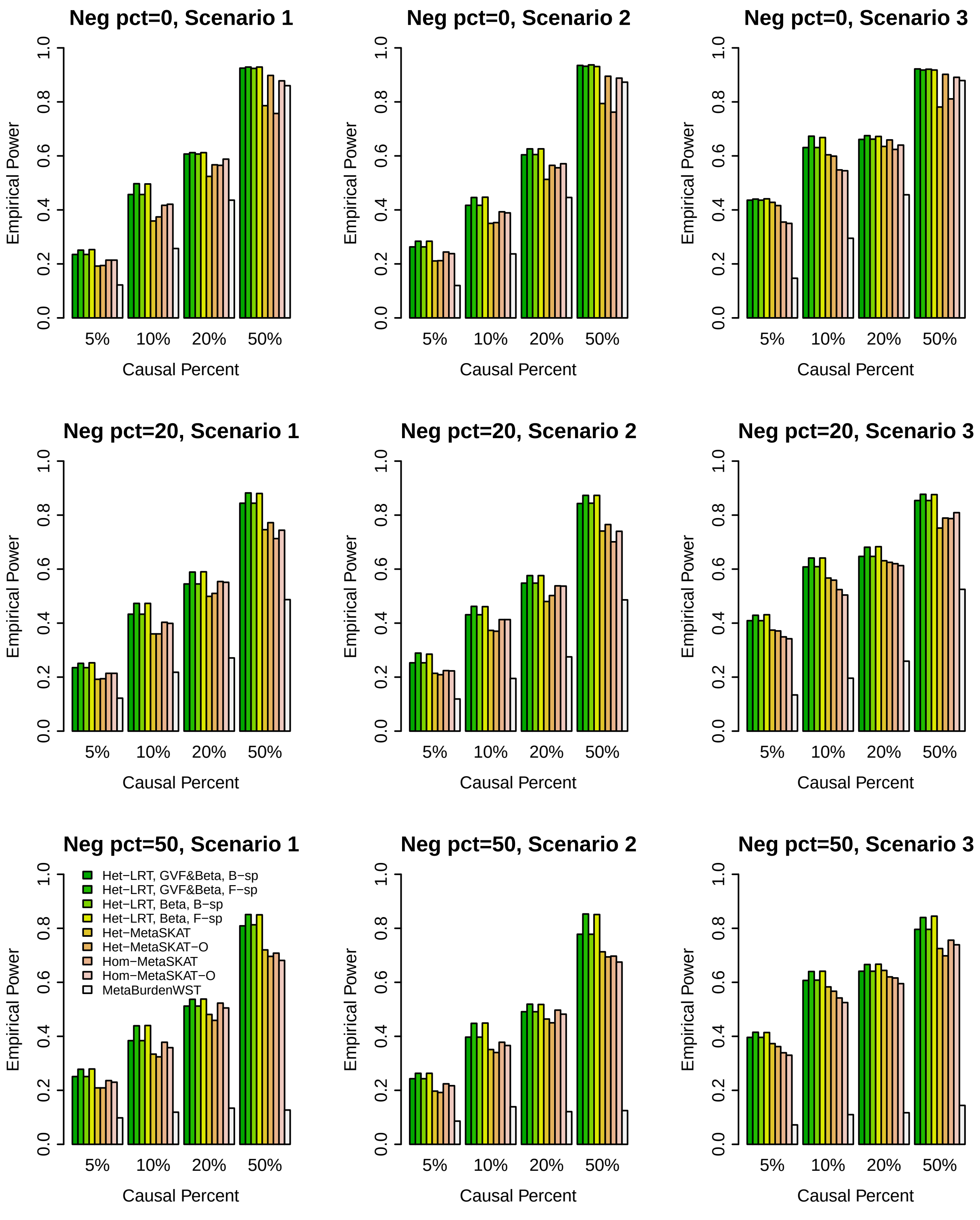

Figure S.4: **The Empirical Power of the Heterogeneous LRT Statistics (Het-LRT) of the Models (3) and (5), MetaSKAT, and MetaBurdenWST at** $\alpha = 0.0001$**, When Causal Variants Were Only Rare and the Genetic Effect is Simulated as Heterogeneous.** When Neg pct = 0, All Causal Variants Had Positive Effects; When Neg pct = 20, 20%/80% Causal Variants Had Negative/Positive Effects; When Neg pct = 50, 50%/50% Causal Variants Had Negative/Positive Effects.