

**Table S1.** Computation time for gene-level tests

Gene size: 20, sample size: 3000, number of cores = 20, number of replication: 1000				
QTest <sub>1</sub>	QTest <sub>2</sub>	QTest <sub>3</sub> (including QTest <sub>1</sub> & QTest <sub>2</sub> results)	SKAT	SKAT-O
91.321s	103.139s	113.207s	100.102s	235.41s

**Table S2.** Top genes associated with liver enzymes in KARE (using rare variants).

phenotype	Gene name	Chromosome	Gene size	P-value				
				SKAT	SKAT-O	QTest <sub>1</sub>	QTest <sub>2</sub>	QTest <sub>3</sub>
ALT	KLF4	9	15	1.89E-04	1.37E-04	7.39E-05	6.24E-06	3.41E-05
AST	GPR22	16	2	9.97E-04	1.11E-04	4.52E-05	9.77E-04	2.10E-05
	PLAGL2	20	4	1.17E-03	5.23E-05	2.79E-05	5.68E-04	3.09E-05
	TRIM22	11	14	7.05E-03	2.93E-05	4.44E-02	7.14E-05	6.33E-05
GGT	CTPS	7	20	4.92E-01	6.70E-01	3.28E-02	3.02E-05	6.77E-05

Gene-Set Association Tests for Next-Generation Sequencing Data

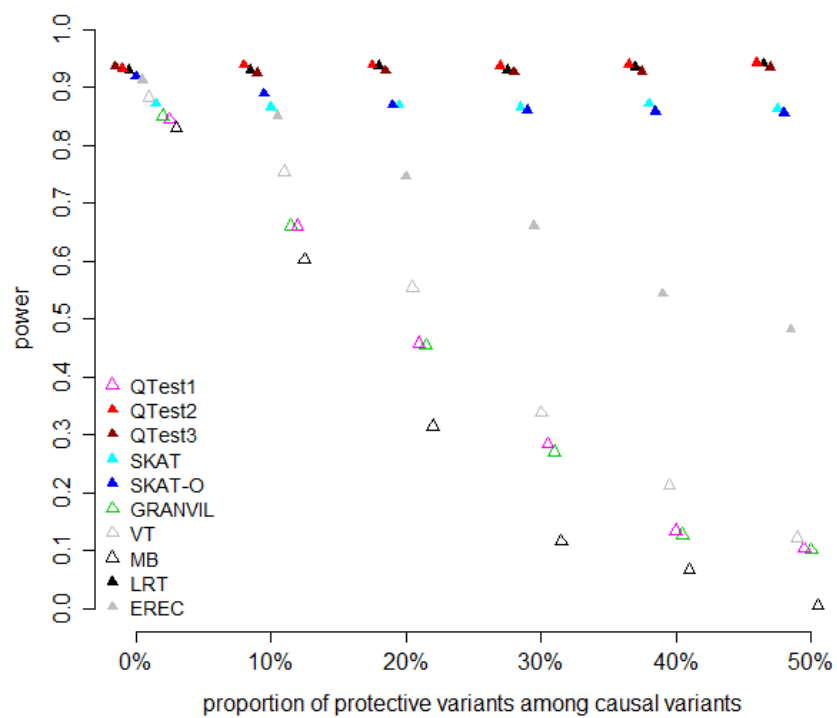
**Table S3.** Significant genes within two identified gene-sets associated with liver enzymes

Gene-set	Gene	P-value											
		Discovery (KARE)					Replication (CAVAS)						
		Size	QTest <sub>1</sub>	QTest <sub>2</sub>	QTest <sub>3</sub>	SKAT	SKAT-O	Size	QTest <sub>1</sub>	QTest <sub>2</sub>	QTest <sub>3</sub>	SKAT	SKAT-O
KEGG_BETA_ALANINE_METABOLISM (#genes=20 for discovery)	ALDH2	1	9.6E-08 (9.1E-08)	9.6E-08 (9.1E-08)	9.6E-08 (9.1E-08)	1.1E-07	1.1E-07	3	8.8E-11 (0)	8.6E-01 (8.6E-01)	3.3E-07 (3.1E-07)	1.0E-01	7.2E-02
	AOC2	7	3.3E-01 (3.3E-01)	9.0E-02 (9.3E-02)	1.3E-01 (1.3E-01)	2.2E-02	3.8E-02	2	2.2E-01 (2.2E-01)	2.8E-01 (2.8E-01)	3.9E-01 (3.9E-01)	3.3E-01	2.5E-01
	ECHS1	2	5.7E-03 (5.3E-03)	1.6E-02 (1.2E-02)	1.3E-02 (1.3E-02)	1.1E-02	4.5E-03	-	-	-	-	-	-
	DPYS	5	4.9E-02 (5.2E-02)	1.2E-01 (1.2E-01)	9.9E-02 (8.9E-02)	9.3E-02	2.0E-02	3	1.3E-01 (1.4E-01)	6.2E-02 (6.3E-02)	1.3E-01 (1.7E-01)	6.6E-02	1.1E-01
	GAD1	6	1.1E-02 (1.0E-02)	9.0E-02 (8.6E-02)	2.3E-02 (1.8E-02)	3.7E-02	2.0E-02	2	6.6E-02 (6.3E-02)	8.2E-01 (8.6E-02)	1.2E-01 (1.3E-01)	1.3E-01	6.8E-02
	GAD2	3	5.2E-02 (5.2E-02)	4.6E-02 (4.2E-02)	5.1E-02 (4.1E-02)	2.7E-02	4.2E-02	-	-	-	-	-	-
	HADHA	3	1.5E-02 (1.6E-02)	4.8E-02 (4.9E-02)	3.2E-02 (2.7E-02)	2.1E-02	2.0E-02	-	-	-	-	-	-
	MLYCD	3	9.9E-01 (9.9E-01)	6.2E-01 (6.2E-01)	7.1E-01 (7.1E-01)	2.3E-01	2.8E-01	2	2.2E-02 (2.5E-02)	7.1E-02 (7.0E-02)	4.7E-02 (4.0E-02)	3.9E-01	3.0E-01
KEGG_LYSINE_DEGRADATION (#genes=33 For discovery)	AASDH	9	5.5E-01 (5.4E-01)	4.7E-02 (4.8E-02)	8.2E-02 (7.1E-02)	5.7E-02	1.1E-01	4	6.1E-01 (6.2E-01)	3.6E-02 (3.7E-02)	3.9E-02 (3.1E-02)	1.7E-02	2.9E-02
	AASS	3	6.0E-01 (6.0E-01)	3.2E-01 (3.2E-01)	3.8E-01 (3.8E-01)	3.8E-01	5.5E-01	2	9.9E-01 (9.9E-01)	6.3E-01 (6.1E-01)	3.8E-02 (3.0E-02)	6.3E-02	9.5E-02
	ALDH2	1	9.6E-08 (9.1E-08)	9.6E-08 (9.1E-08)	9.6E-08 (9.1E-08)	1.1E-07	1.1E-07	3	8.8E-11 (0)	8.6E-01 (8.6E-01)	3.3E-07 (3.1E-07)	5.5E-02	2.9E-02
	ECHS1	2	5.7E-03 (5.3E-03)	1.6E-02 (1.2E-02)	1.3E-02 (1.3E-02)	1.1E-02	4.5E-03	-	-	-	-	-	-
	EHMT2	3	7.8E-03 (6.8E-03)	6.5E-01 (6.5E-01)	1.7E-02 (1.2E-02)	7.1E-01	7.9E-01	-	-	-	-	-	-
	PLOD3	7	7.1E-01 (7.0E-01)	2.0E-03 (2.4E-03)	2.4E-03 (1.7E-03)	6.4E-03	1.2E-02	4	8.4E-01 (8.4E-01)	5.7E-01 (5.7E-01)	6.5E-01 (6.4E-01)	5.0E-01	5.5E-01
	SUV420H2	1	3.4E-02 (3.3E-02)	3.4E-02 (3.3E-02)	3.4E-02 (3.3E-02)	3.4E-02	3.4E-02	-	-	-	-	-	-

A decimal in parenthesis refers to a permutation p-value

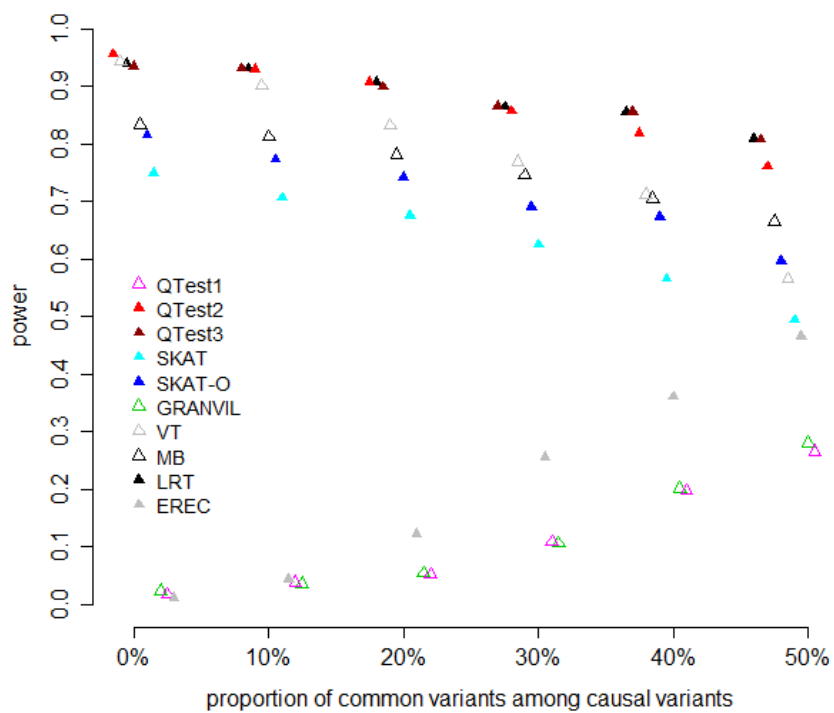
# Gene-Set Association Tests for Next-Generation Sequencing Data

**Fig. S1.** Power of gene-level tests for varying proportion of protective variants



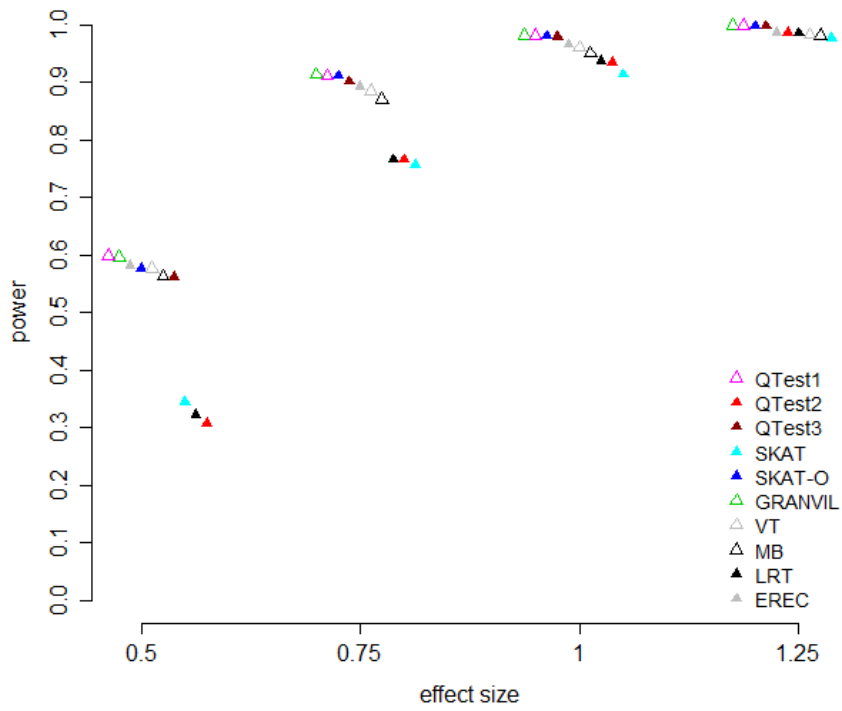
# Gene-Set Association Tests for Next-Generation Sequencing Data

**Fig. S2.** Power of gene-level tests for varying proportion of common variants



# Gene-Set Association Tests for Next-Generation Sequencing Data

**Fig. S3.** Power of gene-set-level tests for varying proportion of causal variants (for effect size 0.75).



# Gene-Set Association Tests for Next-Generation Sequencing Data

**Fig. S4.** Distribution of  $t (= \beta/se(\beta))$  in some significant gene sets

