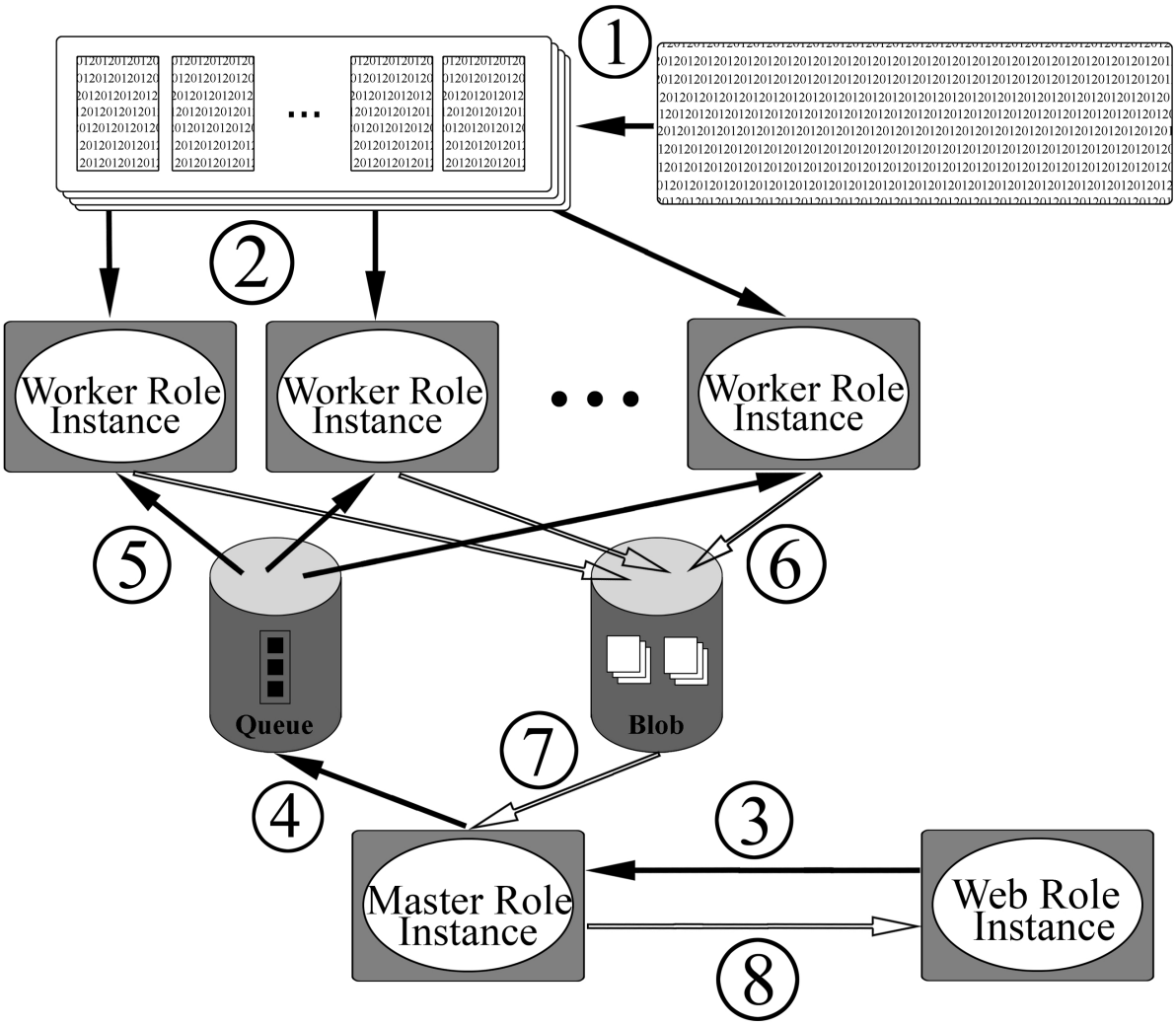
SUPPLEMENTARY MATERIALS:

Figure S1: The workflow of the cloud implementation of DCHE on Windows Azure platform.



The explanation of steps is in the main text.

Figure S2: **Performance comparison on additive models with main effects.** For each model, we simulate data using sample size 800 and $MAF \in \{0.1, 0.2, 0.4\}$. The red, green, blue, cyan and magenta boxes show powers of DCHE, TEAM, SNPRuler, EDCF and BOOST, respectively.

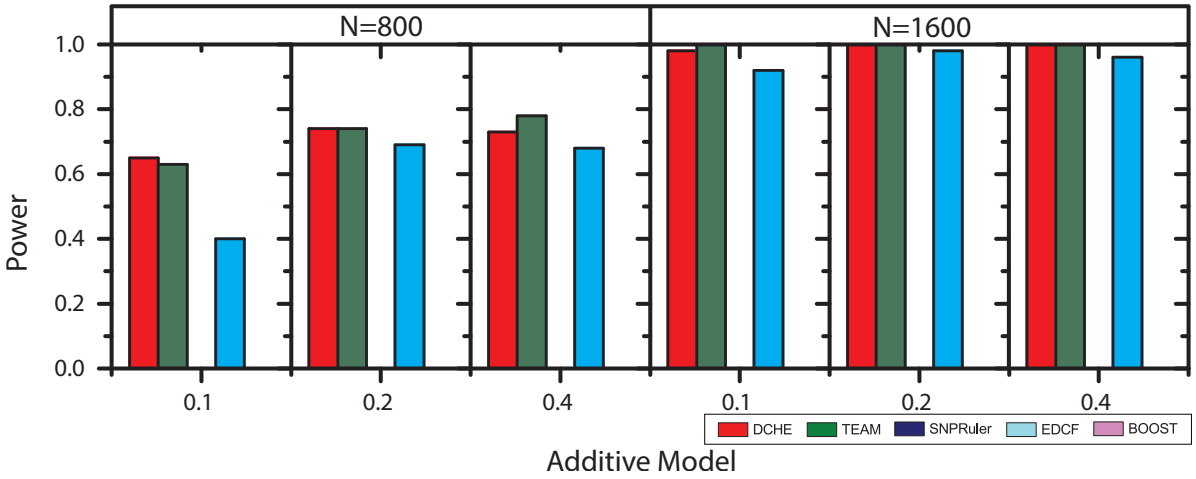


Table S1: Odds tables of epistasis models 1, 2, 3 and 4.

Model 1	BB	Bb	bb
AA	α	α	α
Aa	α	$\alpha(1+\theta)$	$\alpha(1+\theta)^2$
aa	α	$\alpha(1+\theta)^2$	$\alpha(1+\theta)^4$

Model 2	BB	Bb	bb
AA	α	$\alpha(1+\theta)$	$\alpha(1+\theta)$
Aa	$\alpha(1+\theta)$	α	α
aa	$\alpha(1+\theta)$	α	α

Model 3	BB	Bb	bb
AA	α	α	$\alpha(1+\theta)$
Aa	α	$\alpha(1+\theta)$	α
aa	$\alpha(1+\theta)$	α	α

Model 4	BB	Bb	bb
AA	α	$\alpha(1+\theta)$	α
Aa	$\alpha(1+\theta)$	α	$\alpha(1+\theta)$
aa	α	$\alpha(1+\theta)$	α

The parameters α and θ control the prevalence $p(D)$, heritability h^2 by given MAF.

Table S2: Odds table of epistasis model 5.

	BBCC	BbCC	bbCC	BBCc	BbCc	bbCc	BBcc	Bbcc	bbcc
AA	α	α	α	α	α	$\alpha(1+\theta)$	α	$\alpha(1+\theta)$	α
Aa	α	α	$\alpha(1+\theta)$	α	$\alpha(1+\beta\theta)$	α	$\alpha(1+\theta)$	α	α
aa	α	$\alpha(1+\theta)$	α	$\alpha(1+\theta)$	α	α	α	α	α

The parameters α, β and θ control the prevalence $p(D)$, heritability h^2 and marginal effect size λ of disease loci (see definitions in the main text).

Table S3: Penetrance table of epistasis model 6.

	BBCC	BbCC	bbCC	BBCc	BbCc	bbCc	BBcc	Bbcc	bbcc
AA	0	0	16θ	0	0	0	0	0	0
Aa	0	0	0	0	4θ	0	0	0	0
aa	0	0	0	0	0	0	16θ	0	0

With minor allele frequency $MAF = 0.5$, model 6 with this penetrance table reaches the maximum h^2 when penetrance $p \in (0; 1/16]$. There is no marginal effect of a single disease marker.

Table S4: Illustration of odds table of two-locus additive model.

	BB	Bb	bb
AA	α	$\alpha(1+\beta)$	$\alpha(1+\beta)^2$
Aa	$\alpha(1+\beta)$	$\alpha(1+\beta)^2$	$\alpha(1+\beta)^3$
aa	$\alpha(1+\beta)^2$	$\alpha(1+\beta)^3$	$\alpha(1+\beta)^4$

The parameters α, β and θ control the prevalence $p(D)$, heritability h^2 and marginal effect size λ of disease loci (see definitions in the main text).

Table S5: Odds table of two-locus additive models.

	AABB	AABb	AAbb	AaBB	AaBb	Aabb	aaBB	aaBb	aabb	MAF	pD	h^2
1	0.0743	0.1609	0.3486	0.1609	0.3486	0.7552	0.3486	0.7552	1.6359	0.1		
2	0.0603	0.1133	0.2130	0.1133	0.2130	0.7526	0.2130	0.4004	0.4004	0.2	0.1	0.03
3	0.0396	0.0698	0.1232	0.0698	0.1232	0.2175	0.1232	0.2175	0.3837	0.4		

Table S6: The contingency table of (rs1394608 and rs6847164). Here, the $p-value_{unadjusted} = 6.78 \times 10^{-10}$

Clusters	Cases	Controls	Total	Genotypes of rs1394608 and rs6847164
0	80	16	96	10, 11, 20, 22
1	15	29	44	00, 21
2	0	5	5	01, 02, 12
Total	95	46	141	

Table S7: The contingency table of (rs10487833, rs10495593, rs1740752). Here, the $p-value_{unadjusted} = 3.24 \times 10^{-18}$

Clusters	Cases	Controls	Total	Genotypes of rs10487833, rs10495593 and rs1740752
0	77	6	83	002, 010, 102, 111, 112, 122, 201, 211, 212, 220, 221, 222
1	12	15	27	001, 011, 101, 200, 210
2	0	25	25	000, 012, 100, 110, 120, 121, 202
Total	96	46	142	

Table S8: The contingency table of (rs9302001, rs10497231, rs380390, rs1940041). Here, the $p-value_{unadjusted} = 8.28 \times 10^{-28}$

Clusters	Cases	Controls	Total	Genotypes of rs9302001, rs10497231, rs380390 and rs1940041
0	77	0	77	others
1	0	44	44	0111, 0120, 0221, 1000, 1010, 1020, 1111, 1112, 1120, 1201, 1211, 1212, 1220, 1221, 2012, 2120, 2121, 2210, 2220, 2221
2	8	2	10	1100, 1200
3	3	1	4	2112
4	6	1	7	2111
5	2	2	4	2110
Total	96	50	146	

Table S9: Centre SNPs identified in top-1000 SNPs interactions on RA dataset.

#SNPs per interaction	Centre SNPs from analyses of complete SNP set	
	Centre SNPs (Genomic position)	#Interacting SNPs
2	**rs2395175 (Chr6: 32405026)**	880
	rs660895 (Chr6: 32577380)	53
	rs6910071 (Chr6: 32282854)	17
	rs2395163 (Chr6: 32387809)	17
	rs3763309 (Chr6: 32375973)	14
	rs3763312 (Chr6: 32376348)	14
	rs7745656 (Chr6: 32680970)	7
	rs9275595 (Chr6: 32681355)	7
	rs9275374 (Chr6: 32668526)	6
	rs9275388 (Chr6: 32669084)	6
3	rs2395175 (Chr6: 32405026)	866
	rs660895 (Chr6: 32577380)	134
	rs9275595 (Chr6: 32681355)	127
	rs9275439 (Chr6: 32671521)	109
	rs9275427 (Chr6: 32670915)	103
	rs9275418 (Chr6: 32670244)	102
	rs9275425 (Chr6: 32670874)	100
	rs9275555 (Chr6: 32677088)	99
	rs9275428 (Chr6: 32670978)	98
	rs9275393 (Chr6: 32669439)	86
4	rs2395175 (Chr6: 32405026)	999
	rs9275595 (Chr6: 32681355)	998
	rs888206 (Chr17: 53468213)	100
	rs1359679 (Chr9: 121597614)	99
	rs2817763 (Chr6: 110972494)	42
	rs7227652 (Chr18: 46223842)	41
	rs2025324 (Chr9: 7102389)	39
	rs6577430 (Chr1: 7324468)	37
	rs4238618 (Chr16: 12946129)	34
	rs3802400 (Chr9: 7119141)	29

Table S10: The disease association of DCHE selected genes from gene-only SNP analyses.

#SNPs per interaction	# DCHE genes in top 1000 SNP pairs	Reported in HuGE Navigator database	
		#Analyzed genes	#DCHE genes
2	631	793	77
3	440		40
4	719		59

Table S11: Centre genes identified in top-1000 SNPs interactions on RA dataset.

#SNPs per interaction	Centre genes from gene-only SNP analyses	
	Centre genes	#Interacting genes
2	**HLA-DRA: major histocompatibility complex, class II, DR alpha**	890
	HLA-DQB1: major histocompatibility complex, class II, DQ beta 1	101
	BTNL2: butyrophilin-like 2 (MHC class II associated)	65
	HLA-DQA1: major histocompatibility complex, class II, DQ alpha 1	56
	C6orf10: chromosome 6 open reading frame 10	33
	HLA-DQA2: major histocompatibility complex, class II, DQ alpha 2	29
	HLA-DRB1: major histocompatibility complex, class II, DR beta 1	10
	HLA-DRB9: major histocompatibility complex, class II, DR beta 9 (pseudogene)	6
	OR4X1: olfactory receptor, family 4, subfamily X, member 1	6
	FSTL5: follistatin-like 5	5
3	HLA-DRA: major histocompatibility complex, class II, DR alpha	866
	HLA-DQB1: major histocompatibility complex, class II, DQ beta 1	780
	HLA-DQA2: major histocompatibility complex, class II, DQ alpha 2	227
	HLA-DQA1: major histocompatibility complex, class II, DQ alpha 1	134
	PTPRJ: protein tyrosine phosphatase, receptor type, J	14
	FAM84B: family with sequence similarity 84, member B	13
	HSD17B8: hydroxysteroid (17-beta) dehydrogenase 8	11
	C6orf10: chromosome 6 open reading frame 10	10
	SNX16: sorting nexin 16	10
	SNX13: sorting nexin 13	9
4	HLA-DRA: major histocompatibility complex, class II, DR alpha	999
	HLA-DQA2: major histocompatibility complex, class II, DQ alpha 2	998
	CCAR2: cell cycle and apoptosis regulator 2	100
	MMD: monocyte to macrophage differentiation-associated	100
	KDM4C: lysine (K)-specific demethylase 4C	72
	CDK19: cyclin-dependent kinase 19	42
	CTIF: CBP80/20-dependent translation initiation factor	41
	CAMTA1: calmodulin binding transcription activator 1	37
	CPPED1: calcineurin-like phosphoesterase domain containing 1	34
	PPHLN1: periphilin 1	32

Figure S3: **Overlap of results from DCHE on ones from BOOST.** The yellow bar is the overlap rate, i.e. what percentage of the top rated modules yielded by BOOST has been detected by DCHE.(A) The overlap percentage on 4 simulated models embedded epistatic interaction demonstrating both main effect and interaction effect. (B) The overlap percentage on 50 models embedded epistatic interaction demonstrating weak main effect, but strong interaction effect.