Supplement

Supplement A – Generation of case-control data for male sub-samples

Let a be the risk and A the other allele. The penetrance α_m and the relative risk γ in males are then defined as

$$\alpha_m = P(case|A) \quad \text{and} \quad \gamma = \frac{P(case|a)}{P(case|A)}\,.$$

Analogously to Wittke-Thompson et al.[14] (App. A and B) we calculate the disease prevalence in the male population by

$$K_p = P(case) = \alpha_m \cdot p_m + \alpha_m \cdot \gamma \cdot q_m,$$

with q_m the risk allele frequency and p_m the other allele frequency in males. Hereby, the risk and other allele frequencies in male cases are given by

$$q_m(case) = P(a|case) = \frac{\alpha_m \cdot \gamma \cdot q_m}{K_p} \quad \text{and} \quad p_m(case) = 1 - q_m(case)\,.$$

The risk and other allele frequency in male controls are given by

$$q_m(control) = P(a|control) = \frac{(1 - \alpha_m \cdot \gamma_m) \cdot q_m}{1 - K_p} \quad \text{and} \quad p_m(control) = 1 - q_m(control)\,.$$

Now, these frequencies are used to simulate case-control data for male samples.

Supplement B – Results of simulation study

Supplementary Table 1: Type 1 error frequencies under departure from Hardy-Weinberg equilibrium. Minor allele frequency = 0.3. Nominal error level $\alpha = 0.05$.

ε	Z_A^2	Z_C^2	Z_{mfA}^2	Z_{mfG}^2	T_A	T_{AD}	T_{AD}^s	S_A
-0.4	0.0245	0.0501	0.0252	0.0531	0.0538	0.0480	0.0284	0.0545
-0.2	0.0344	0.0522	0.0350	0.0514	0.0487	0.0482	0.0498	0.0514
-0.05	0.0446	0.0488	0.0455	0.0484	0.0505	0.0487	0.0478	0.0492
0	0.0486	0.0478	0.0486	0.0482	0.0467	0.0469	0.0456	0.0477
0.05	0.0541	0.0520	0.0544	0.0486	0.0479	0.0513	0.0494	0.0502
0.2	0.0634	0.0483	0.0639	0.0482	0.0468	0.0448	0.0465	0.0479
0.4	0.0787	0.0505	0.0789	0.0500	0.0505	0.0493	0.0478	0.0493

Supplementary Table 2: Type one error frequencies for differences in allele frequencies between sexes under an unbalanced sample design of different numbers of males and females in total sample. Sex ratios equal in cases and controls (50 %). Nominal error level $\alpha = 0.05$.

Design[a]	$q_f - q_m$	q	Z_A^2	Z_C^2	Z_{mfA}^2	Z_{mfG}^2	T_A	T_{AD}	T_{AD}^s	S_A
250 males,	- 0.1	0.1	0.0460	0.0481	0.0494	0.0498	0.0751	0.0713	0.0161	0.048
150 females		0.5	0.0563	0.0509	0.0563	0.0536	0.0507	0.0491	0.0526	0.0521
	- 0.05	0.1	0.0497	0.0481	0.0511	0.0514	0.0647	0.0610	0.0224	0.0483
		0.5	0.0562	0.0517	0.0562	0.0511	0.0509	0.0507	0.0523	0.0517
	0.05	0.1	0.0475	0.0462	0.0498	0.0500	0.0350	0.0378	0.0342	0.0481
		0.5	0.0563	0.0534	0.0563	0.0519	0.0492	0.0504	0.0498	0.0499
	0.1	0.1	0.0450	0.0472	0.0507	0.0496	0.0202	0.0249	0.0334	0.0502
		0.5	0.0567	0.0514	0.0567	0.0519	0.0480	0.0490	0.0482	0.0499
150 males,	-0.1	0.1	0.0471	0.0499	0.0512	0.0519	0.0956	0.0915	0.0206	0.0518
250 females		0.5	0.0533	0.0492	0.0531	0.0503	0.0486	0.0491	0.0505	0.0489
	-0.05	0.1	0.0493	0.0500	0.0508	0.0496	0.0670	0.0700	0.031	0.0496
		0.5	0.0546	0.0524	0.0544	0.0508	0.0508	0.0530	0.0534	0.0513
	0.05	0.1	0.0513	0.0524	0.0527	0.0527	0.0356	0.0351	0.0389	0.0523
		0.5	0.0573	0.0552	0.0571	0.0496	0.0494	0.0511	0.0514	0.0485
	0.1	0.1	0.0461	0.0468	0.0511	0.0525	0.0234	0.0266	0.0406	0.0505
		0.5	0.0565	0.0521	0.0564	0.0513	0.0463	0.0463	0.0498	0.0492

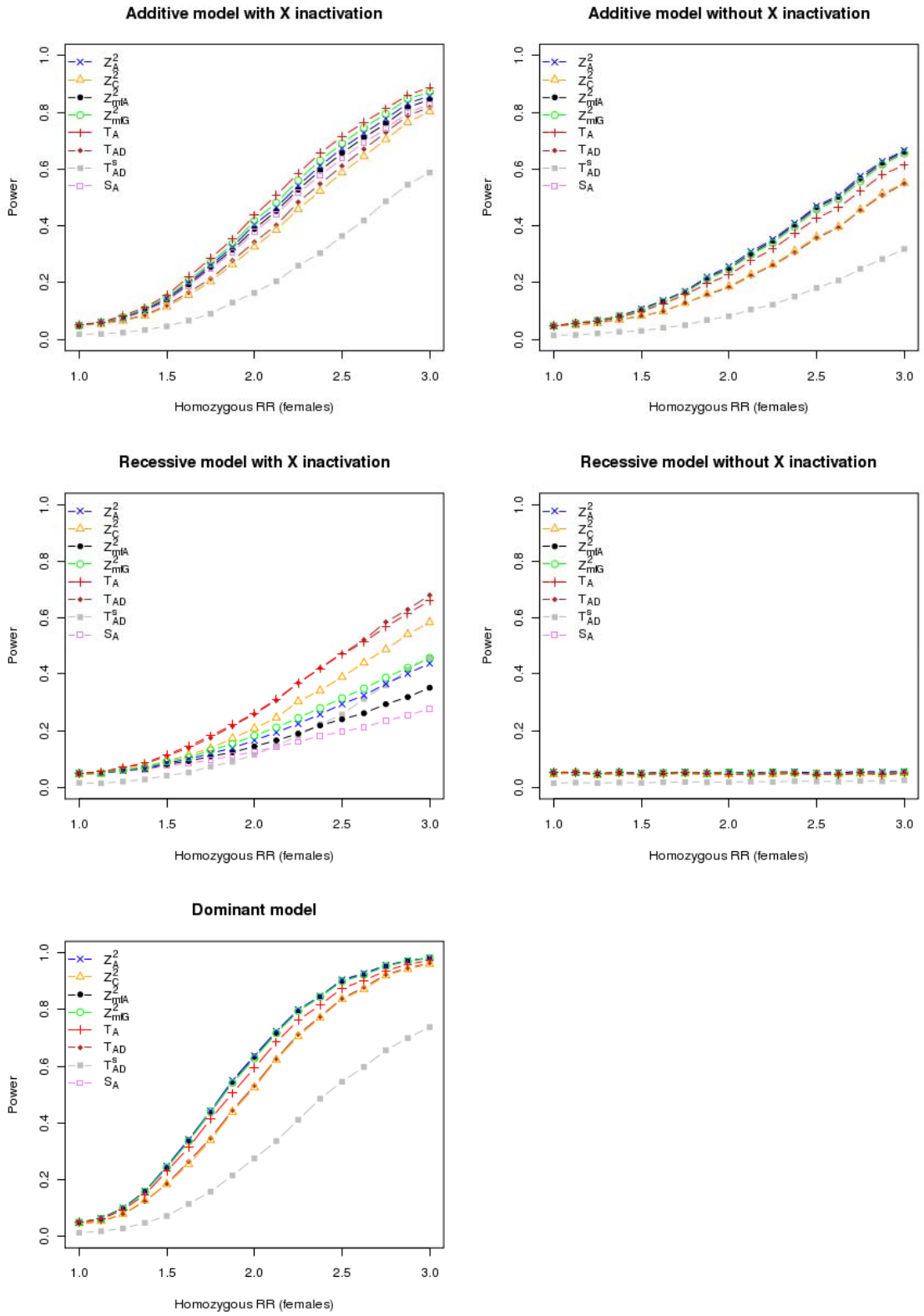
q_f: Minor allele frequency (MAF) in females; q_m: MAF in males; q: mean MAF in entire sample.

Supplementary Table 3: Type one error frequencies for differences in allele frequencies between sexes under unbalanced sample designs of 67% female cases and 33% female controls. Nominal error level $\alpha = 0.05$.

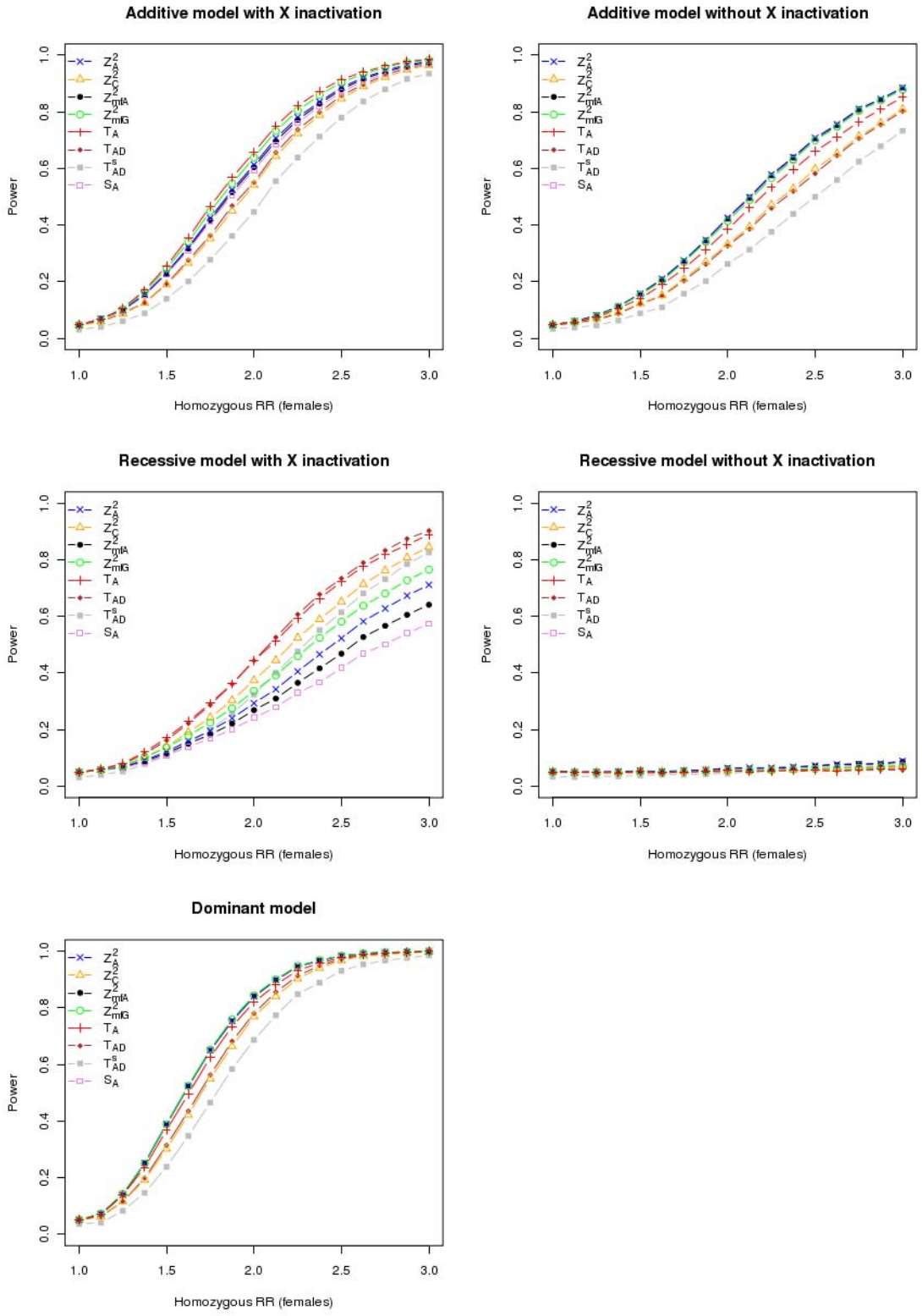
$q_f - q_m$	q	Z_A^2	Z_C^2	Z_{mfA}^2	Z_{mfG}^2	T_A	T_{AD}	T_{AD}^s	S_A
- 0.1	0.1	0.0496	0.0497	0.0505	0.0520	0.0879	0.0805	0.0170	0.0506
	0.3	0.0482	0.0489	0.0508	0.0484	0.0525	0.0523	0.0484	0.0493
	0.5	0.0522	0.0544	0.0552	0.0497	0.0477	0.0501	0.0553	0.0520
- 0.05	0.1	0.0516	0.0546	0.0513	0.0522	0.0696	0.0682	0.0279	0.0514
	0.3	0.0487	0.0515	0.0490	0.0509	0.0547	0.0506	0.0485	0.0498
	0.5	0.0516	0.0494	0.0541	0.0501	0.0485	0.0480	0.0498	0.0502
0.05	0.1	0.0457	0.0469	0.0464	0.0460	0.0295	0.0326	0.0364	0.0458
	0.3	0.0473	0.0510	0.0484	0.0484	0.0432	0.0433	0.0513	0.0486
	0.5	0.0478	0.0500	0.0500	0.0477	0.0478	0.0523	0.0528	0.0476
0.1	0.1	0.0488	0.0460	0.0503	0.0503	0.0202	0.0259	0.0383	0.0507
	0.3	0.0511	0.0515	0.0521	0.0512	0.0436	0.0446	0.0473	0.0520
	0.5	0.0521	0.0489	0.0553	0.0487	0.0465	0.0509	0.0522	0.0502
-0.05	0.1	0.1056	0.0489	0.0490	0.0485	0.1230	0.1128	0.0275	0.0493
	0.5	0.0689	0.0524	0.0581	0.0554	0.0682	0.0551	0.0494	0.0558
-0.02	0.1	0.0608	0.0513	0.0531	0.0521	0.0637	0.0541	0.0340	0.0519
	0.5	0.0510	0.0468	0.0522	0.0507	0.0526	0.0470	0.0514	0.0502
0.02	0.1	0.0560	0.0476	0.0508	0.0493	0.0499	0.0472	0.0398	0.0499
	0.5	0.0515	0.0506	0.0512	0.0508	0.0516	0.0446	0.0473	0.0496
0.05	0.1	0.0898	0.0489	0.0522	0.0505	0.0732	0.0644	0.0417	0.0509
	0.5	0.0637	0.0487	0.0497	0.0474	0.0642	0.0534	0.0476	0.0489

q_f: minor allele frequency (MAF) in females; q_m: MAF in males; q: mean MAF in entire sample.

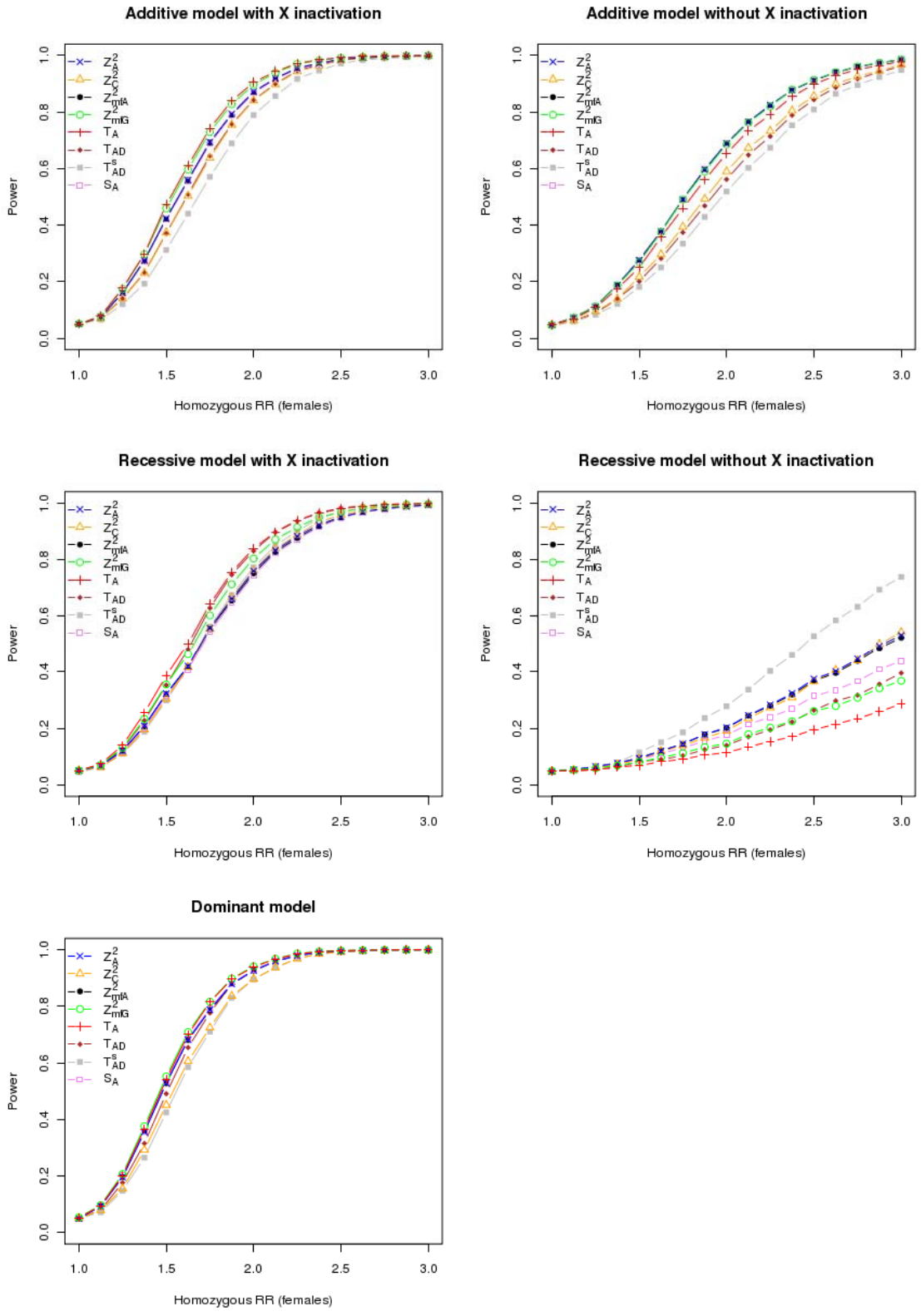
Supplementary Figure 1: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency=0.05, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



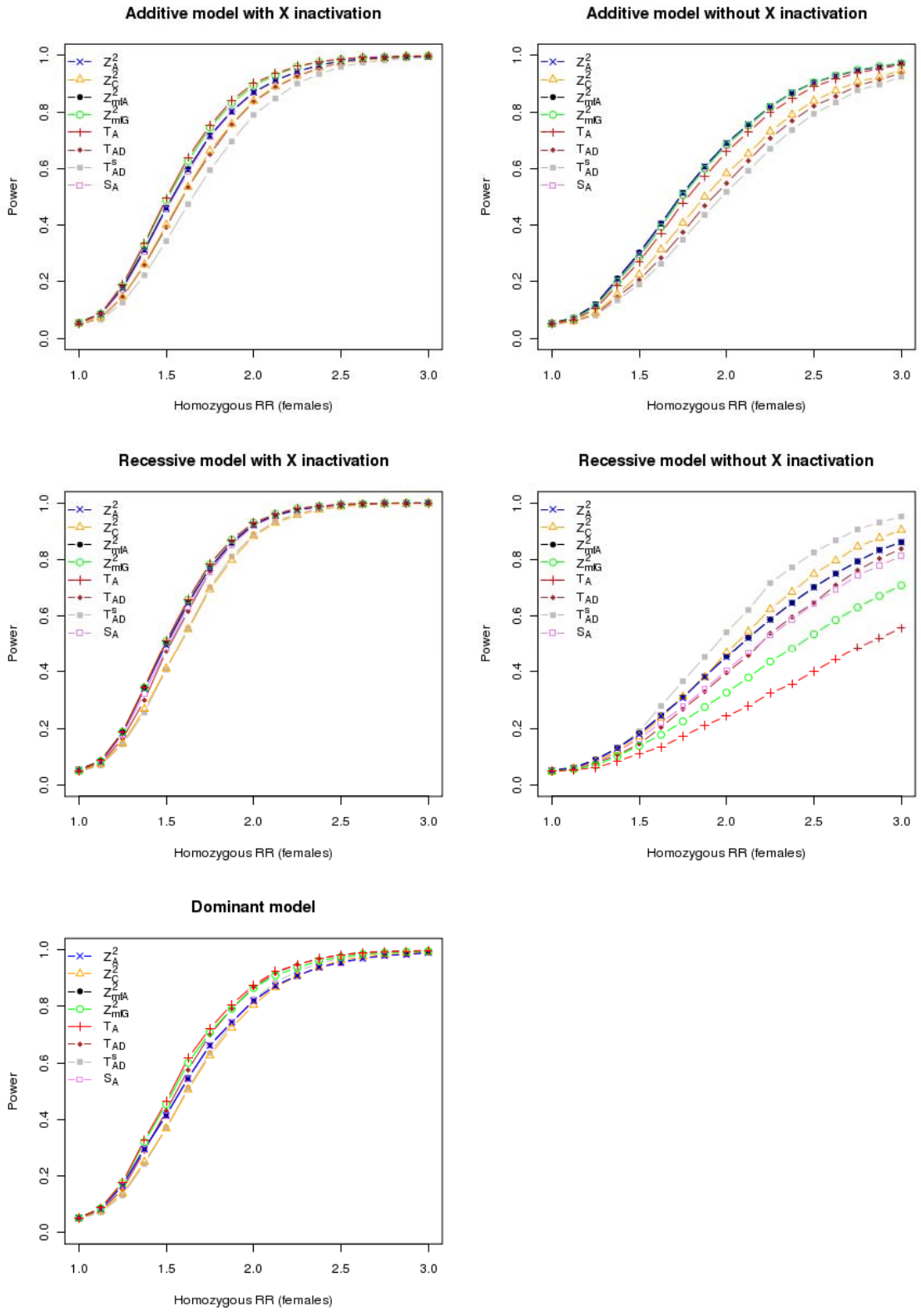
Supplementary Figure 2: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency=0.1, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



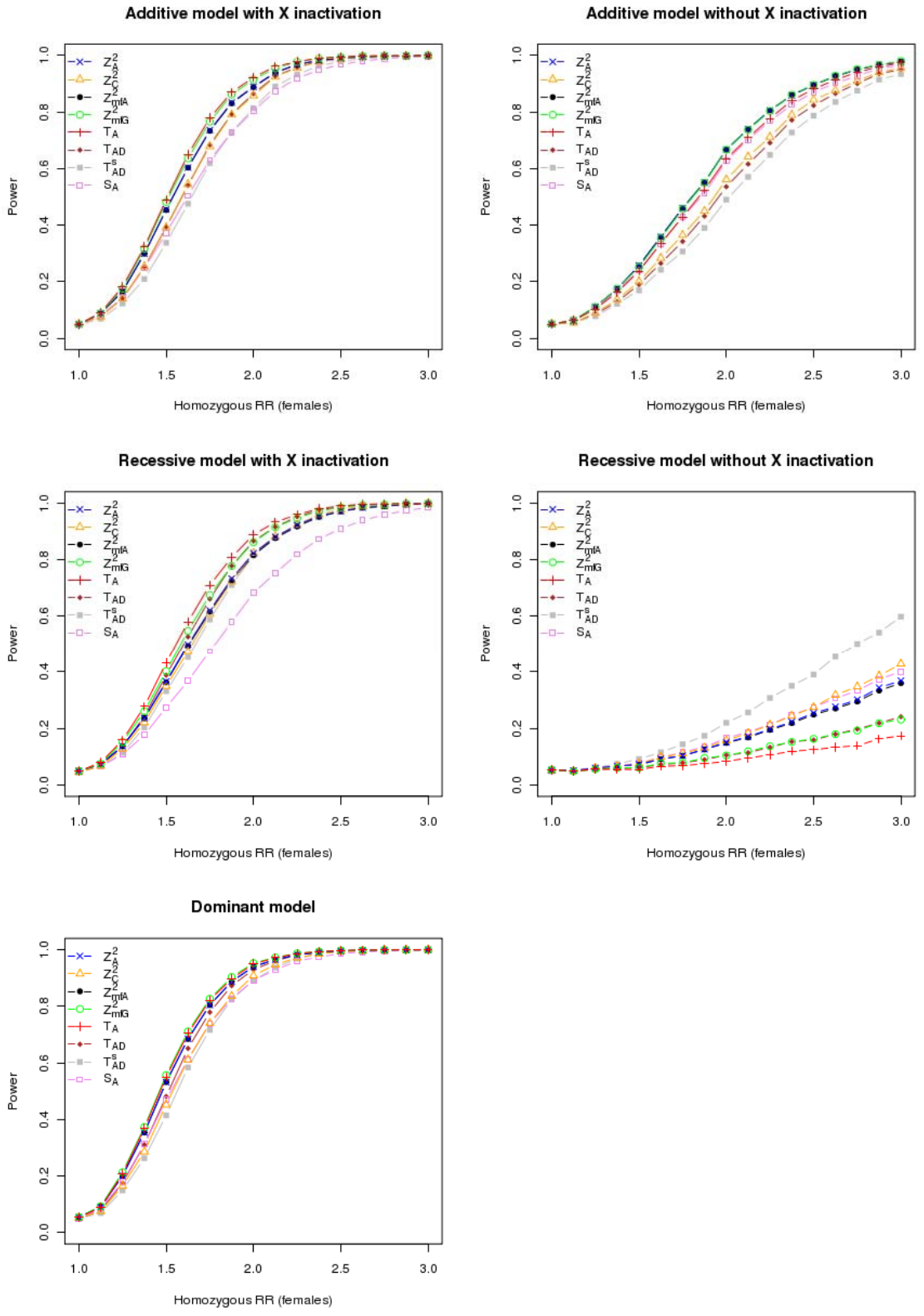
Supplementary Figure 3: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency=0.3, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



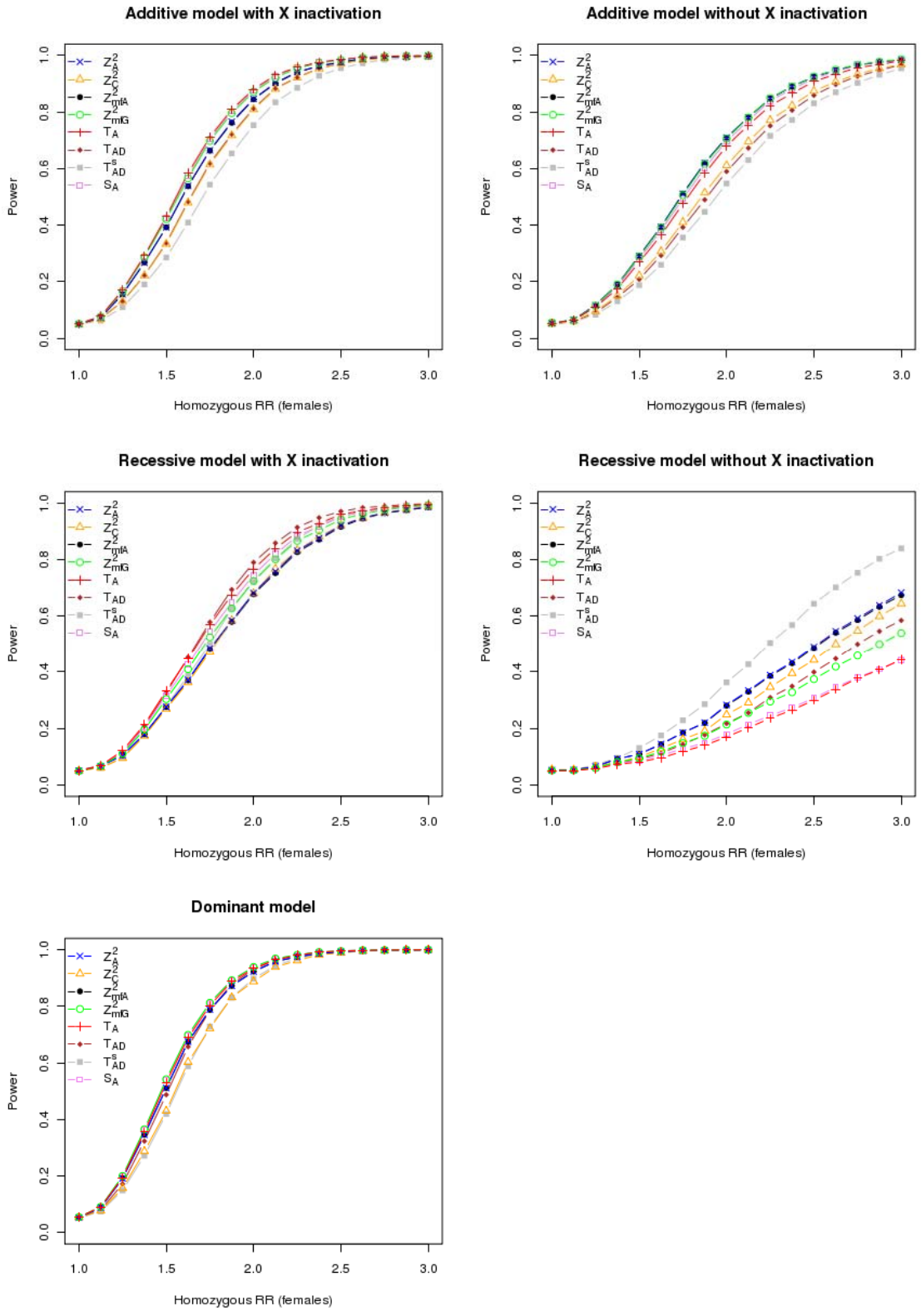
Supplementary Figure 4: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency=0.5, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



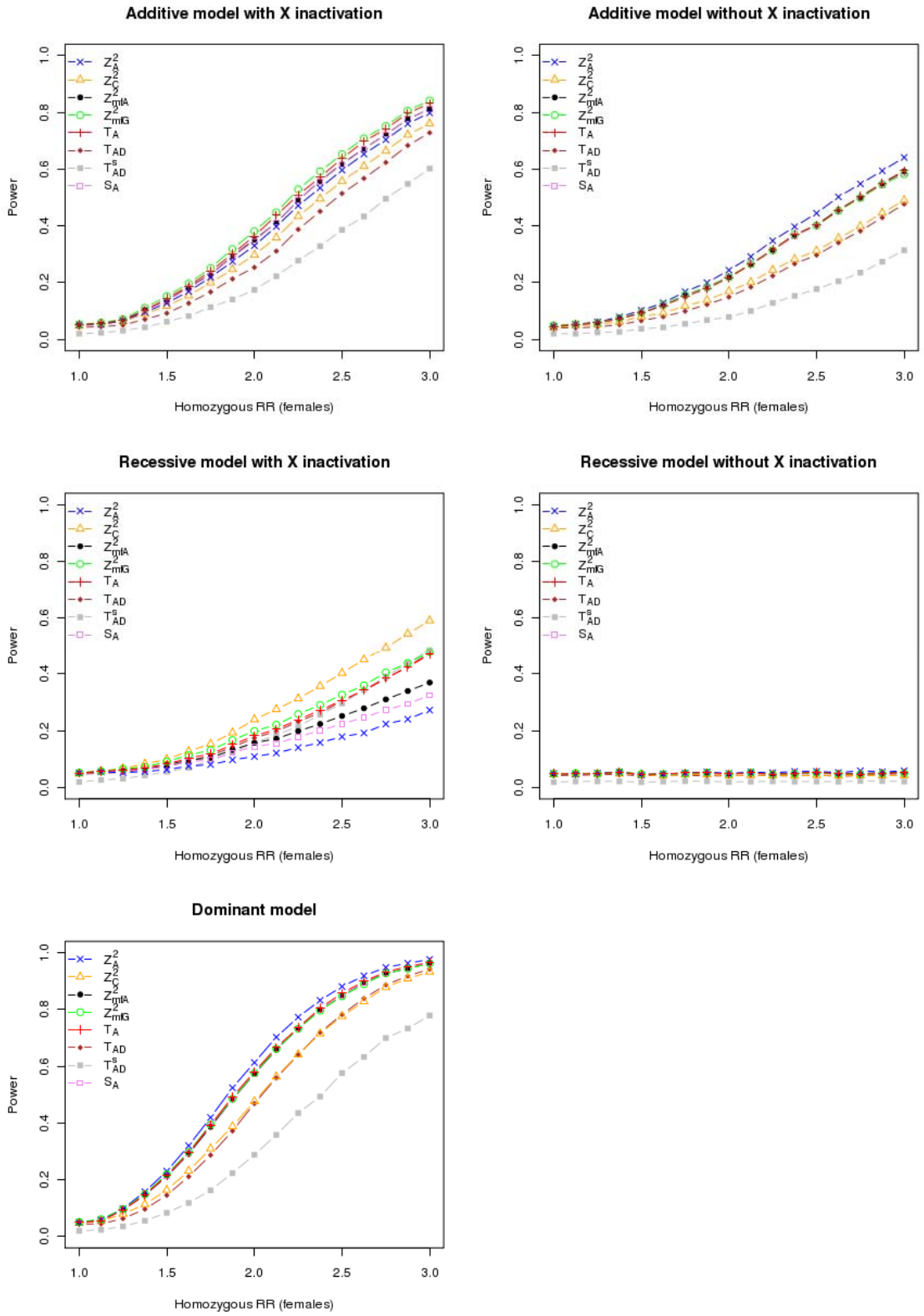
Supplementary Figure 5: Power of test statistics under different genetic models in an unbalanced sample design of 150 females and 250 males but equal sex ratios in cases and controls. Minor allele frequency=0.3, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



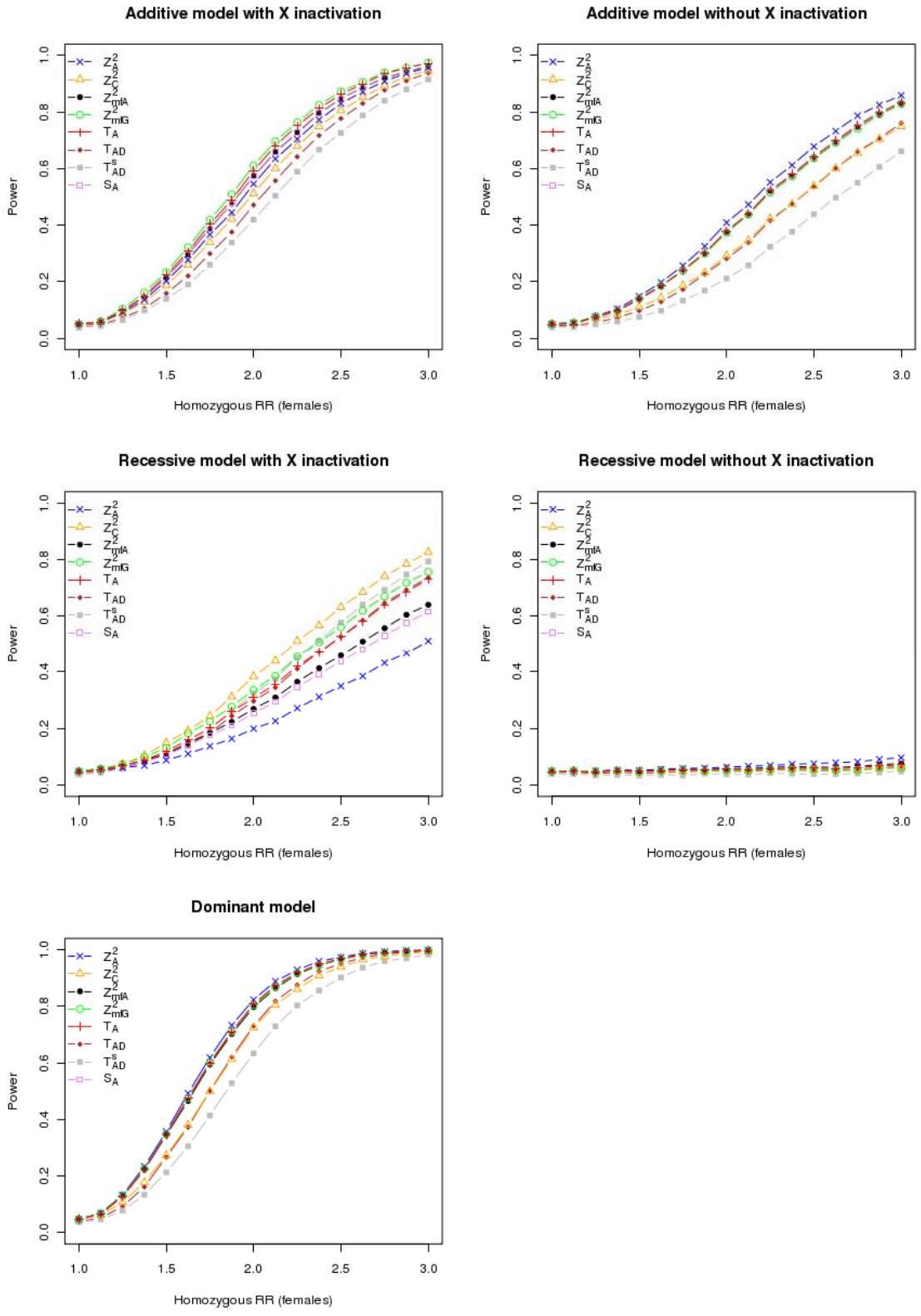
Supplementary Figure 6: Power of test statistics under different genetic models in an unbalanced sample design of 250 females and 150 males but equal sex ratios in cases and controls. Minor allele frequency=0.3, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



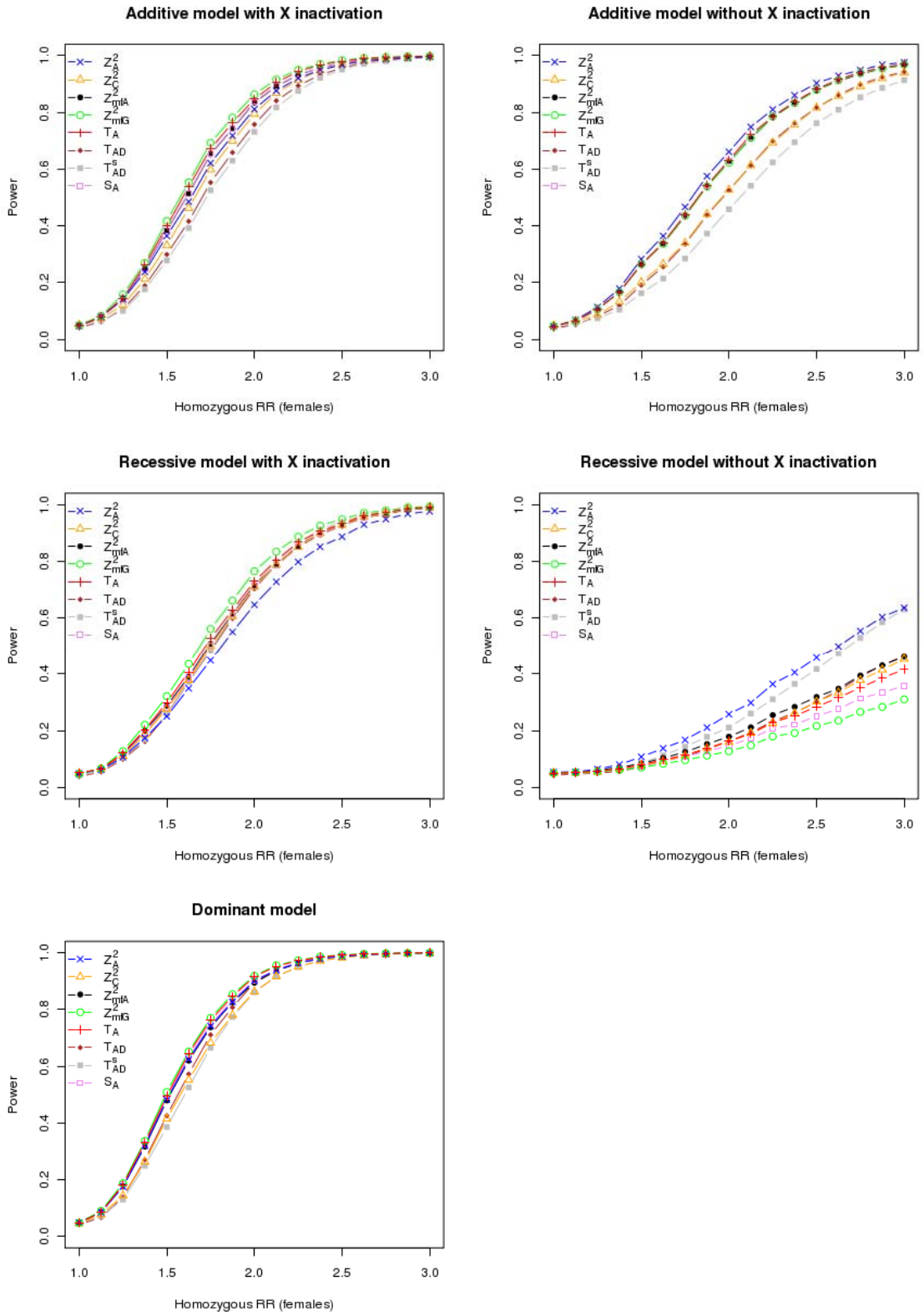
Supplementary Figure 7: Power of test statistics under different genetic models in an unbalanced sample design of 67 % female cases and 33 % female controls. Minor allele frequency =0.05, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



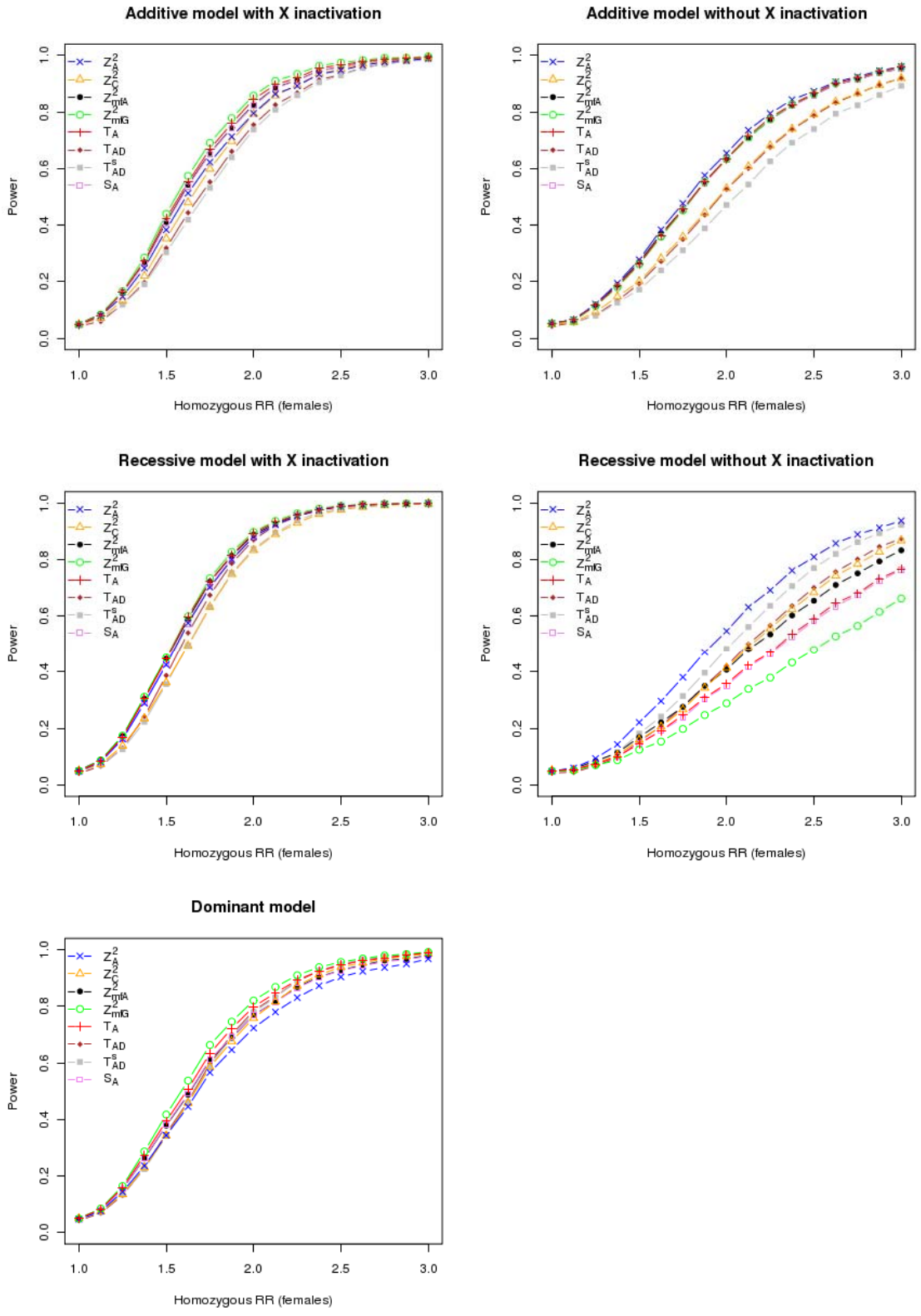
Supplementary Figure 8: Power of test statistics under different genetic models in an unbalanced sample design of 67 % female cases and 33 % female controls. Minor allele frequency =0.1, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



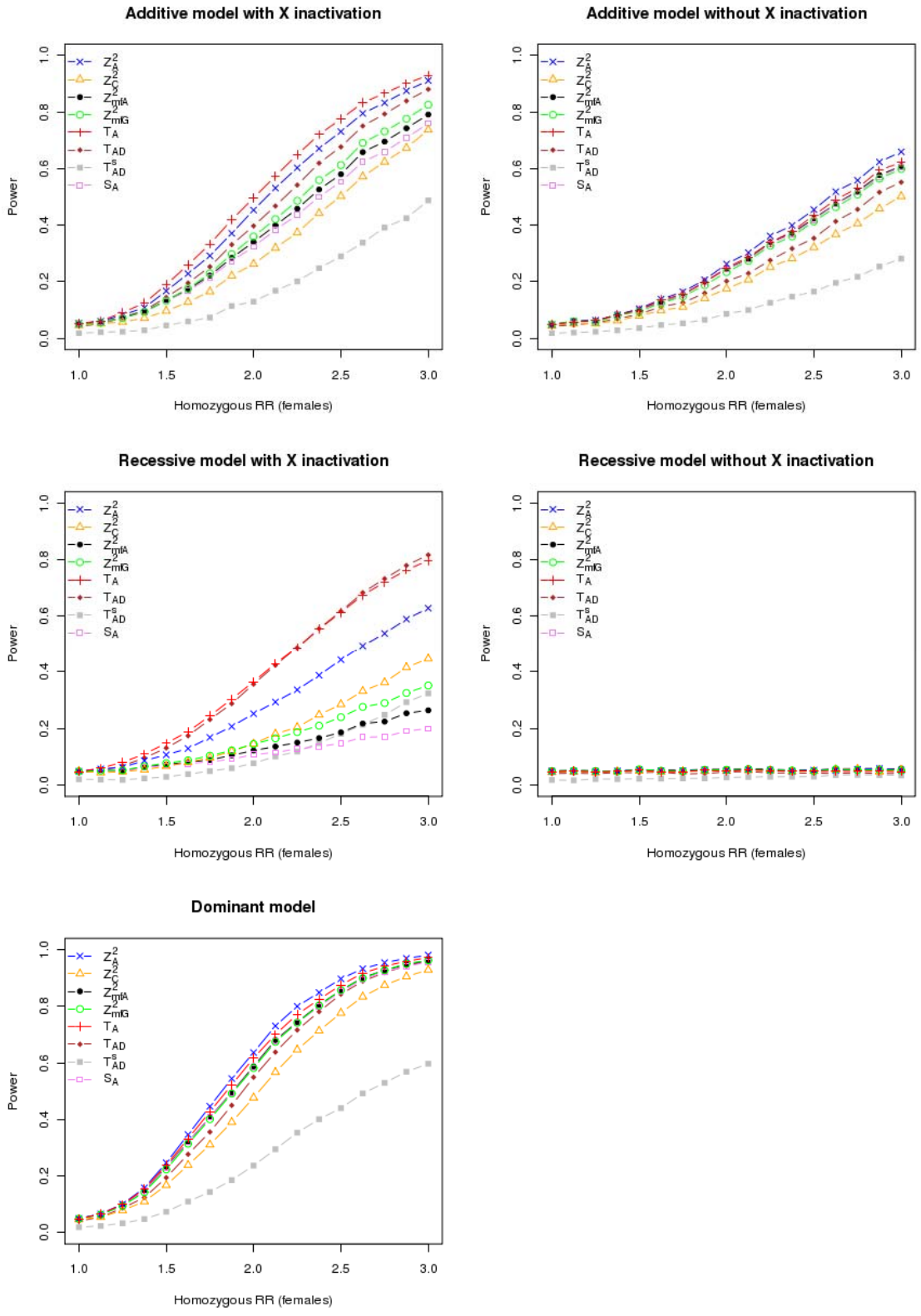
Supplementary Figure 9: Power of test statistics under different genetic models in an unbalanced sample design of 67 % female cases and 33 % female controls. Minor allele frequency =0.3, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



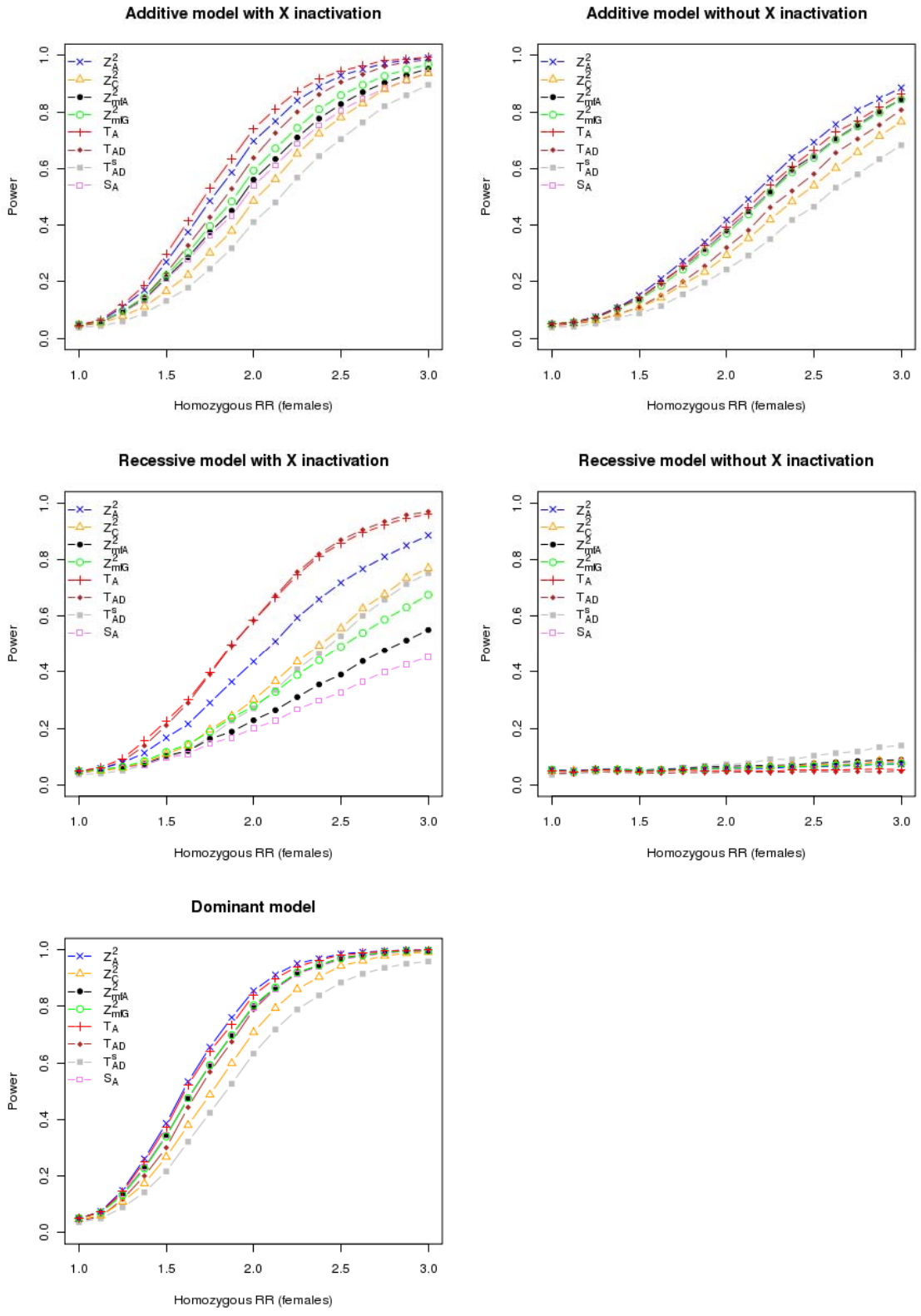
Supplementary Figure 10: Power of test statistics under different genetic models in an unbalanced sample design of 67 % female cases and 33 % female controls. Minor allele frequency =0.5, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



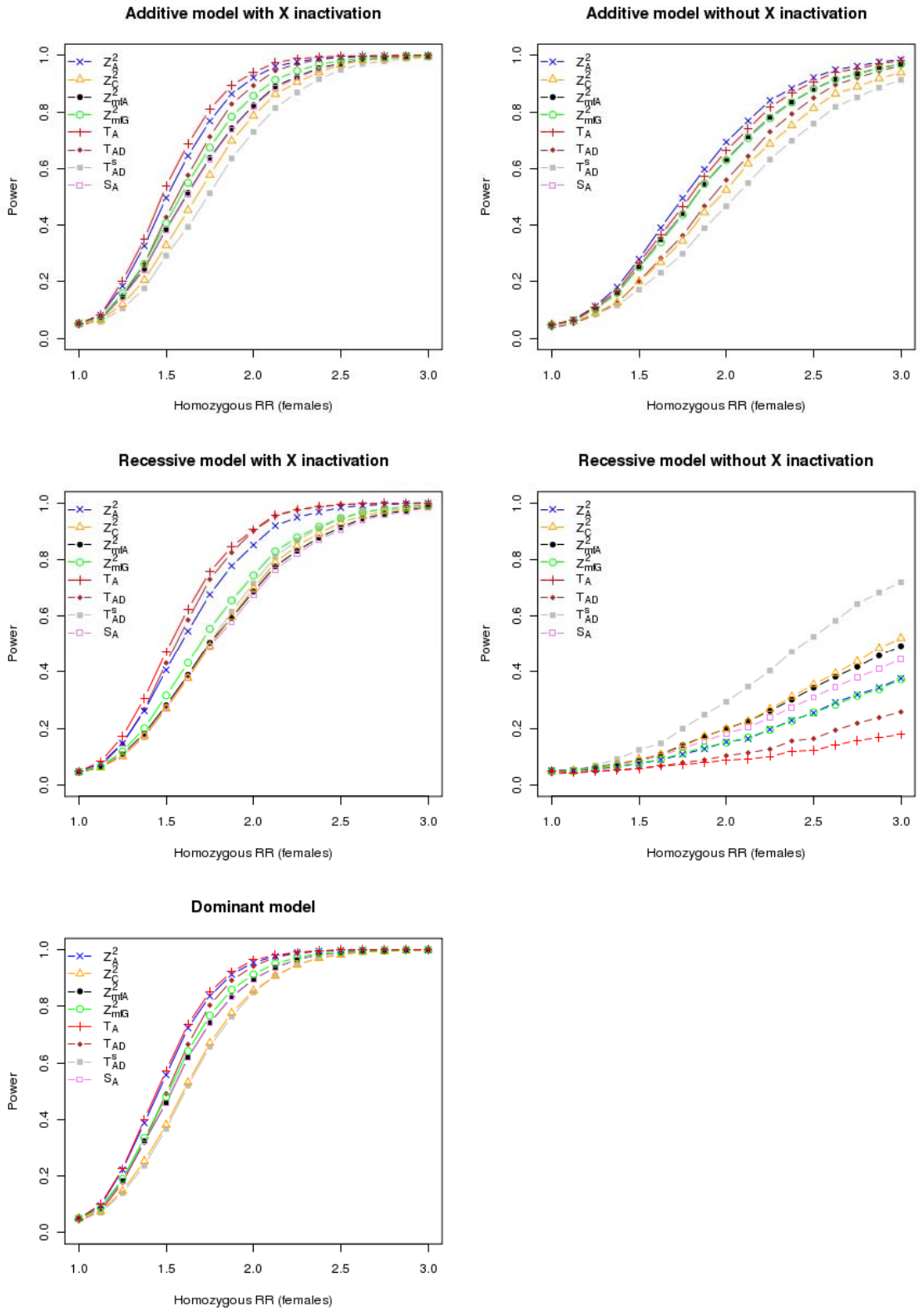
Supplementary Figure 11: Power of test statistics under different genetic models in an unbalanced sample design of 33 % female cases and 67 % female controls. Minor allele frequency =0.05, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



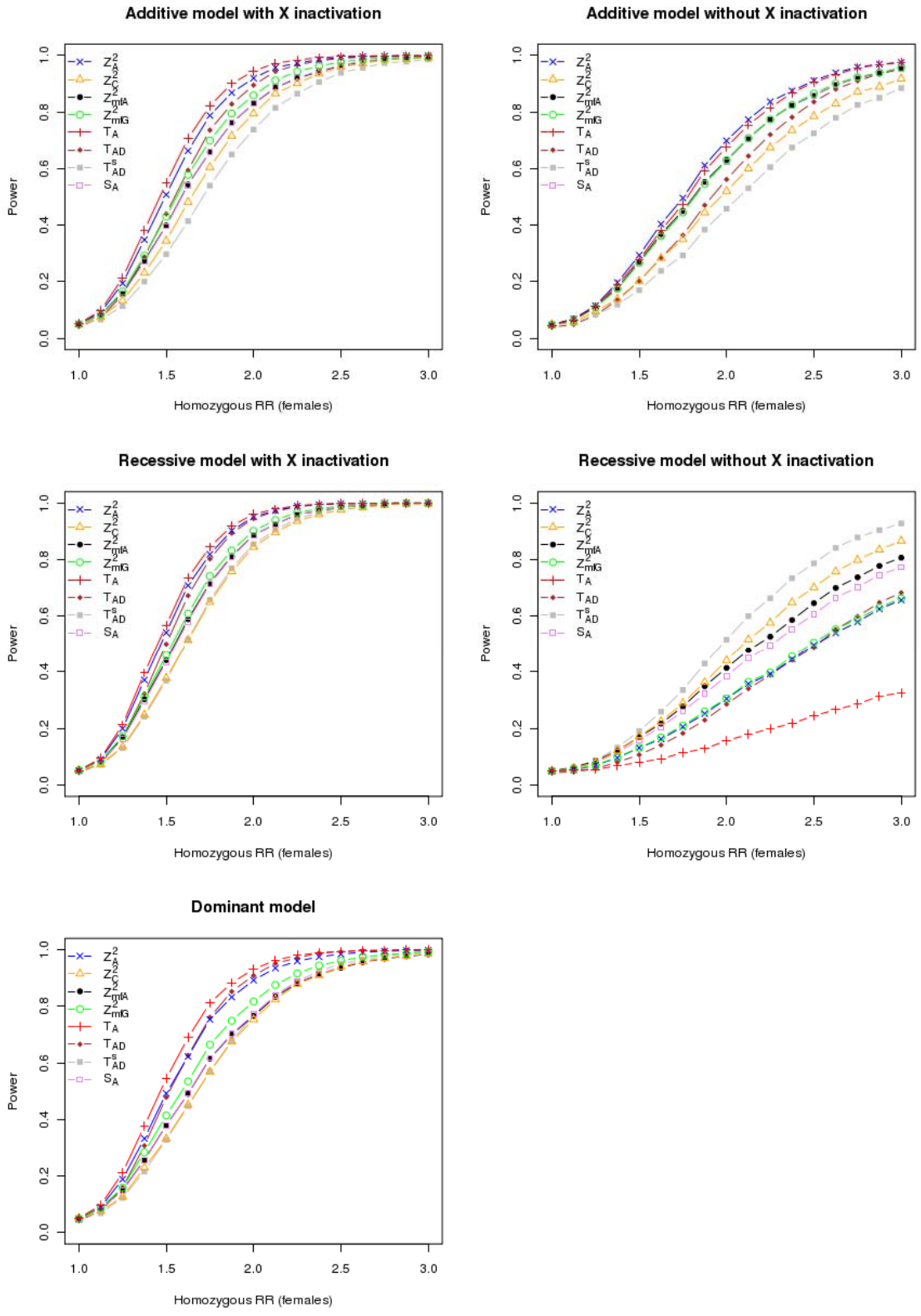
Supplementary Figure 12: Power of test statistics under different genetic models in an unbalanced sample design of 33 % female cases and 67 % female controls. Minor allele frequency =0.1, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



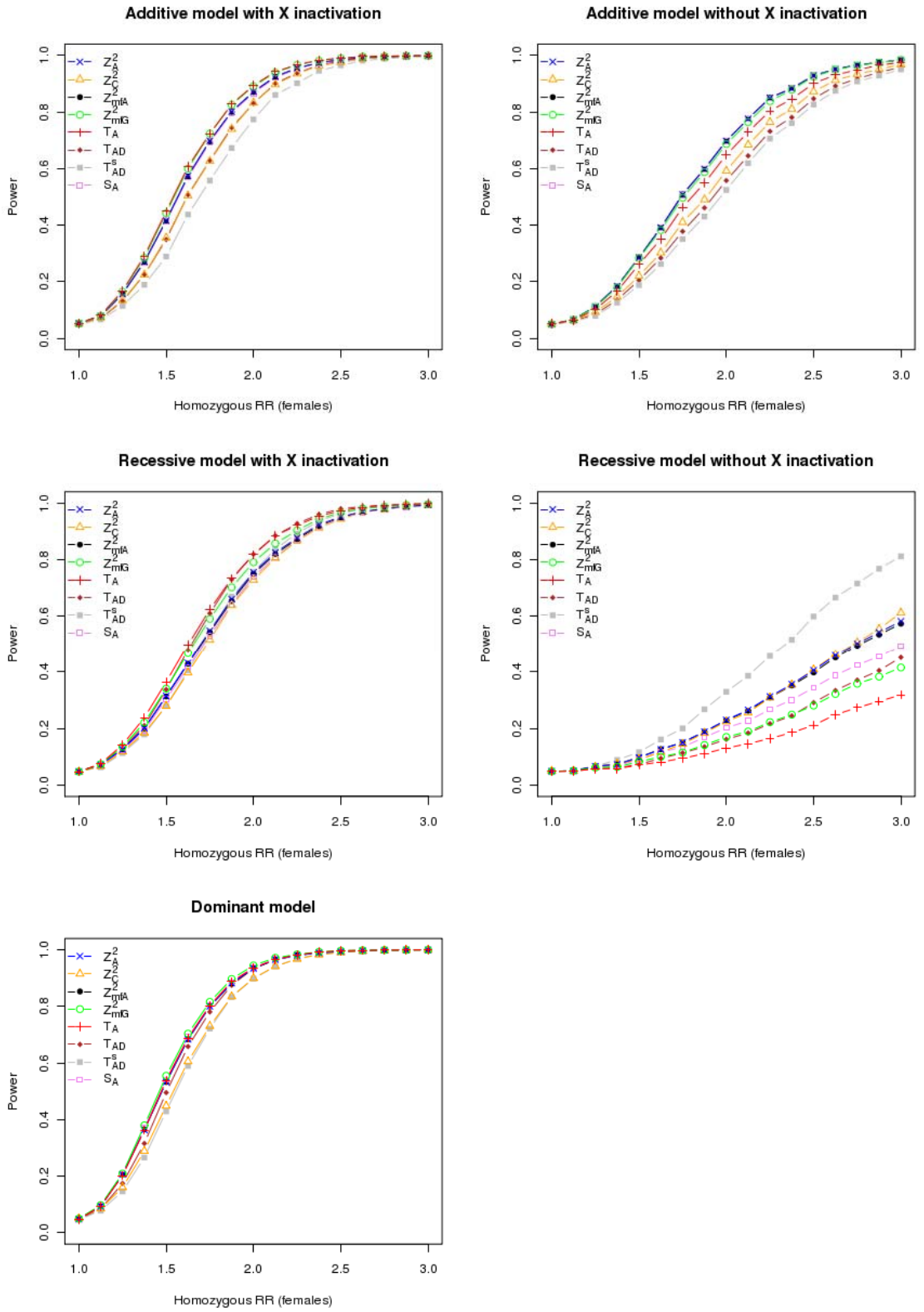
Supplementary Figure 13: Power of test statistics under different genetic models in an unbalanced sample design of 33 % female cases and 67 % female controls. Minor allele frequency =0.3, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



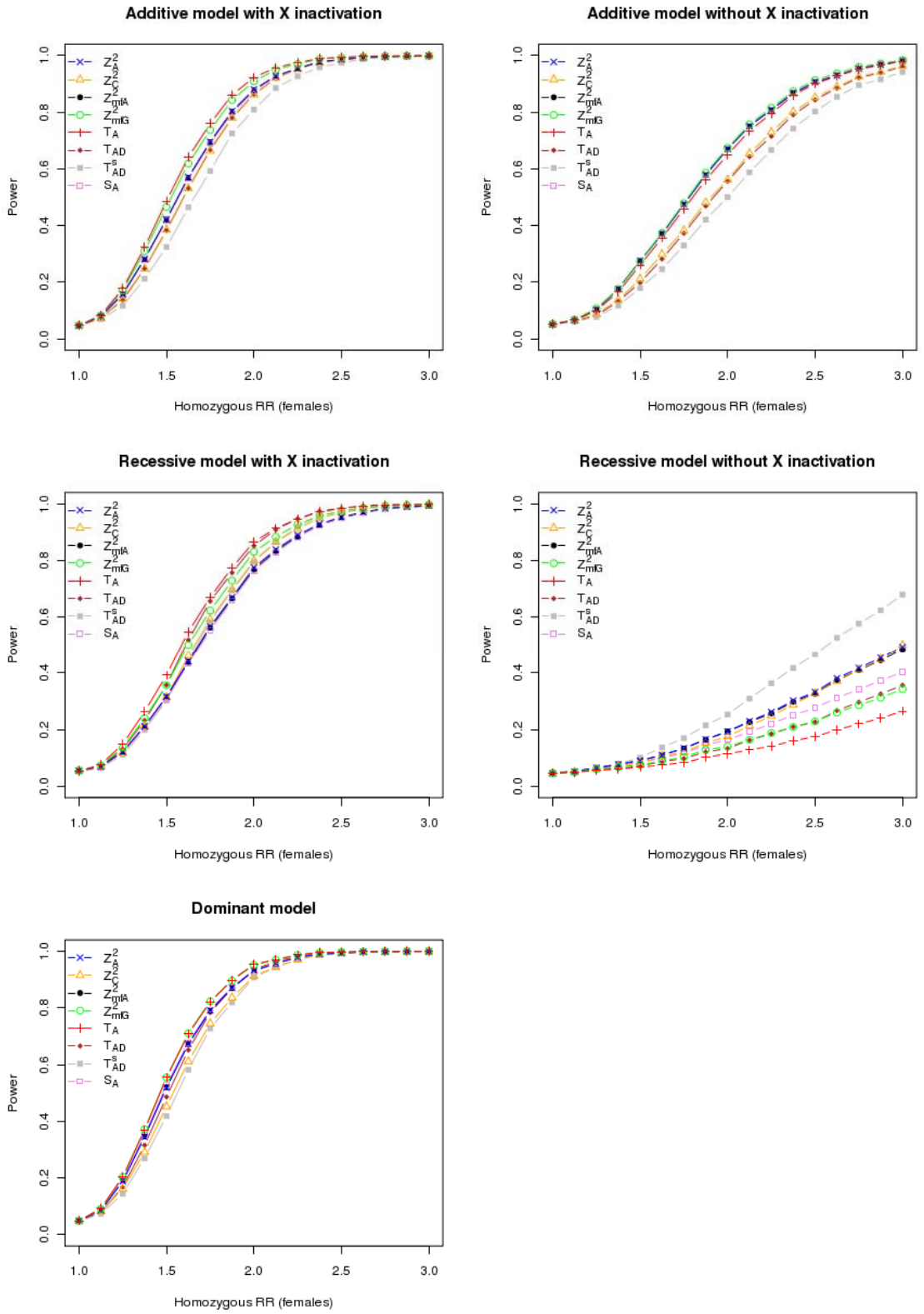
Supplementary Figure 14: Power of test statistics under different genetic models in an unbalanced sample design of 33 % female cases and 67 % female controls. Minor allele frequency =0.5, prevalence=0.1. All parameters equal in males and females. RR= relative risk.



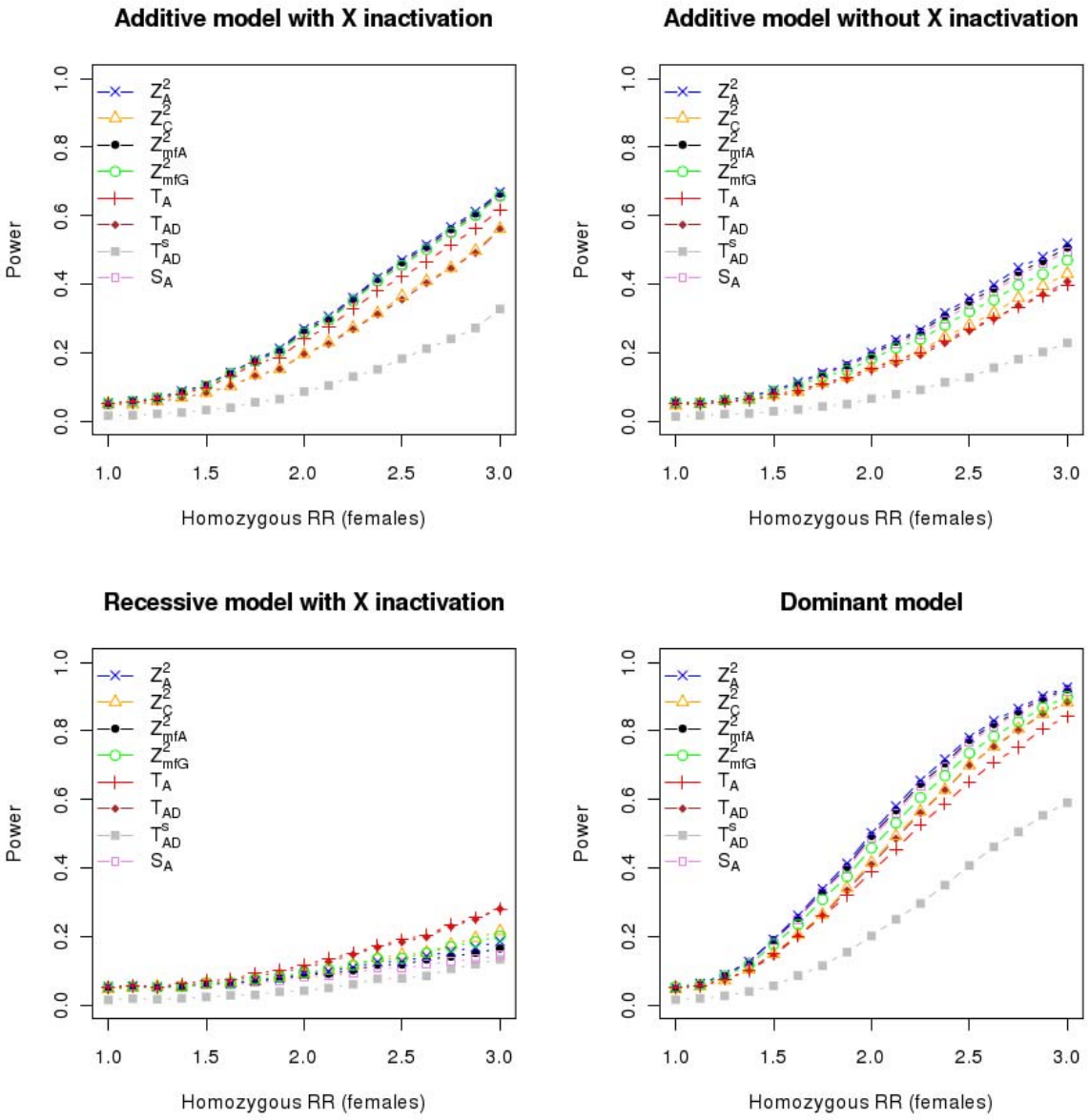
Supplementary Figure 15: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.3. Prevalence of 0.05 in males and 0.15 in females. All other parameters equal in males and females. RR= relative risk.



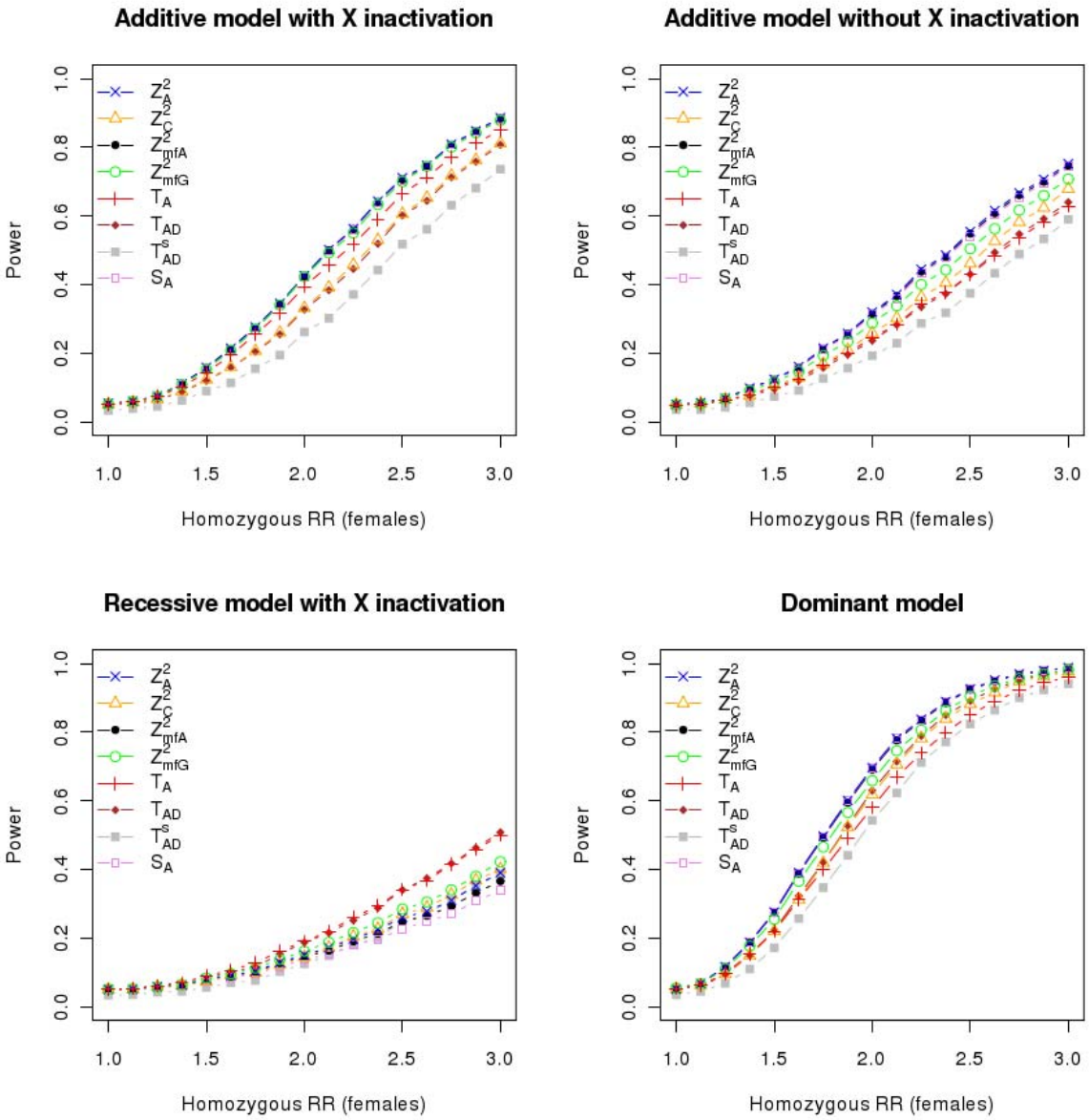
Supplementary Figure 16: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.3. Prevalence of 0.15 in males and 0.05 in females. All other parameters equal in males and females. RR= relative risk.



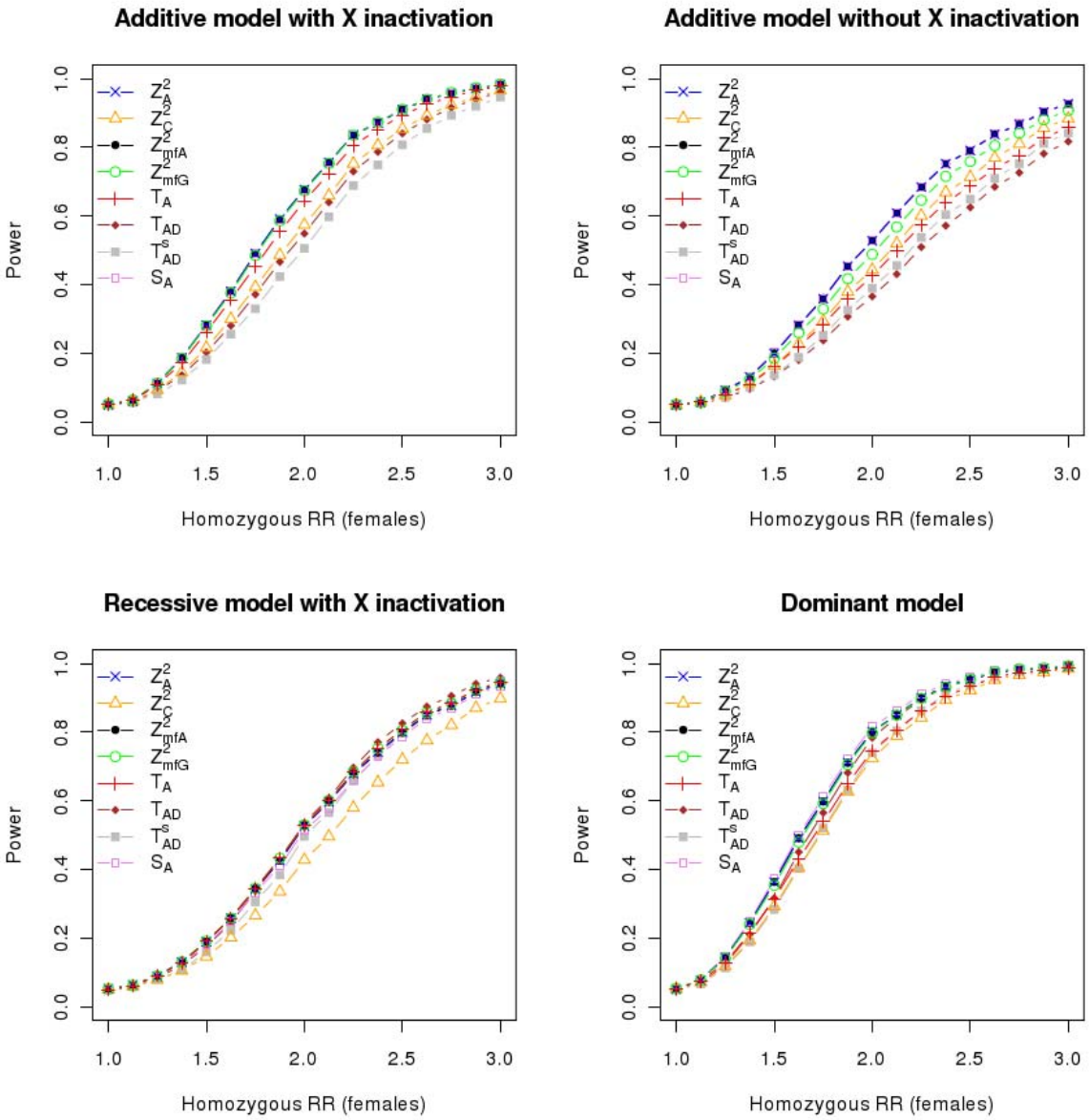
Supplementary Figure 17: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.05, prevalence=0.1. Effect sizes in males reduced by 50 %. All other parameters equal in males and females. RR= relative risk.



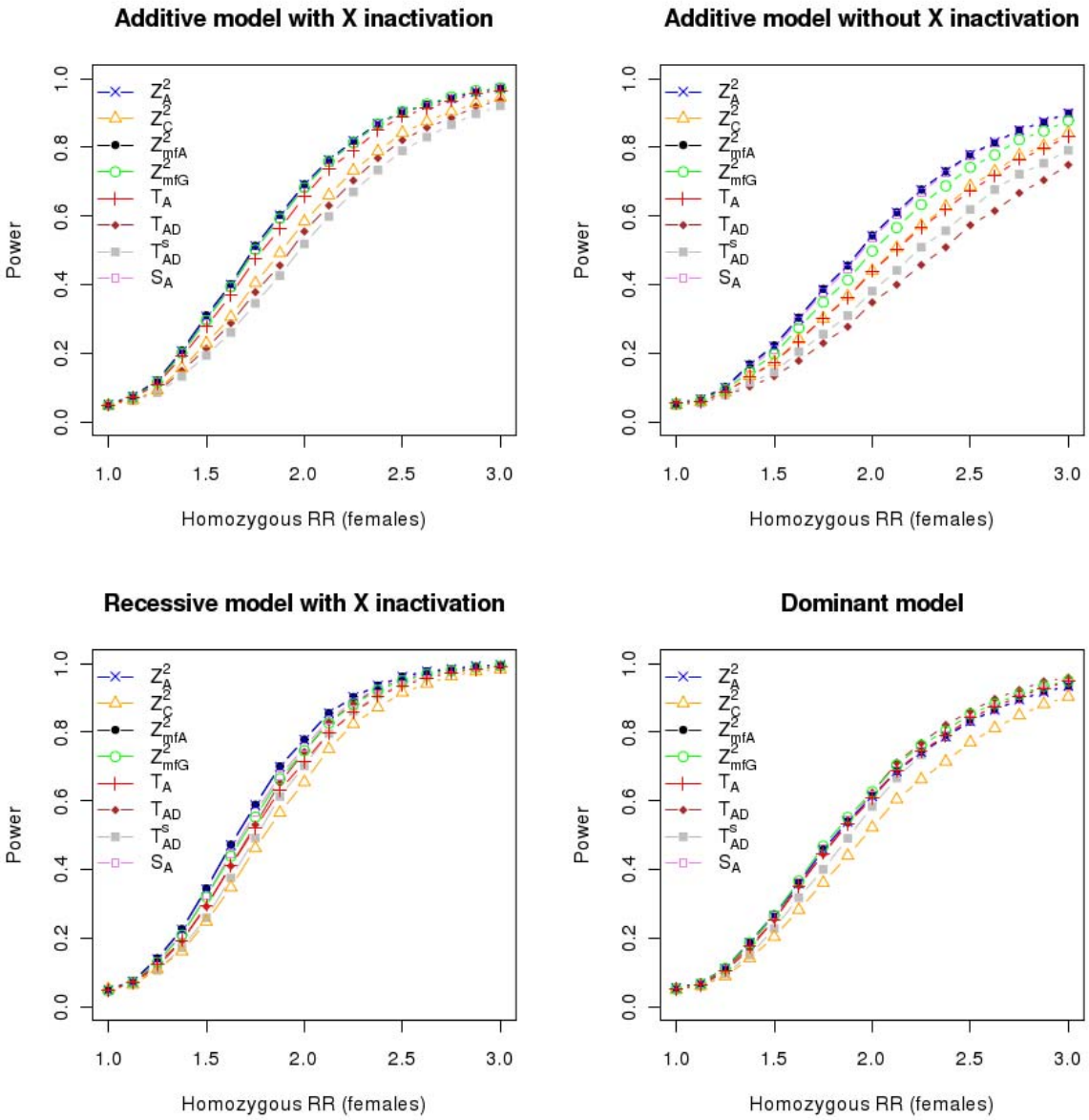
Supplementary Figure 18: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.1, prevalence=0.1. Effect sizes in males reduced by 50 %. All other parameters equal in males and females. RR= relative risk.



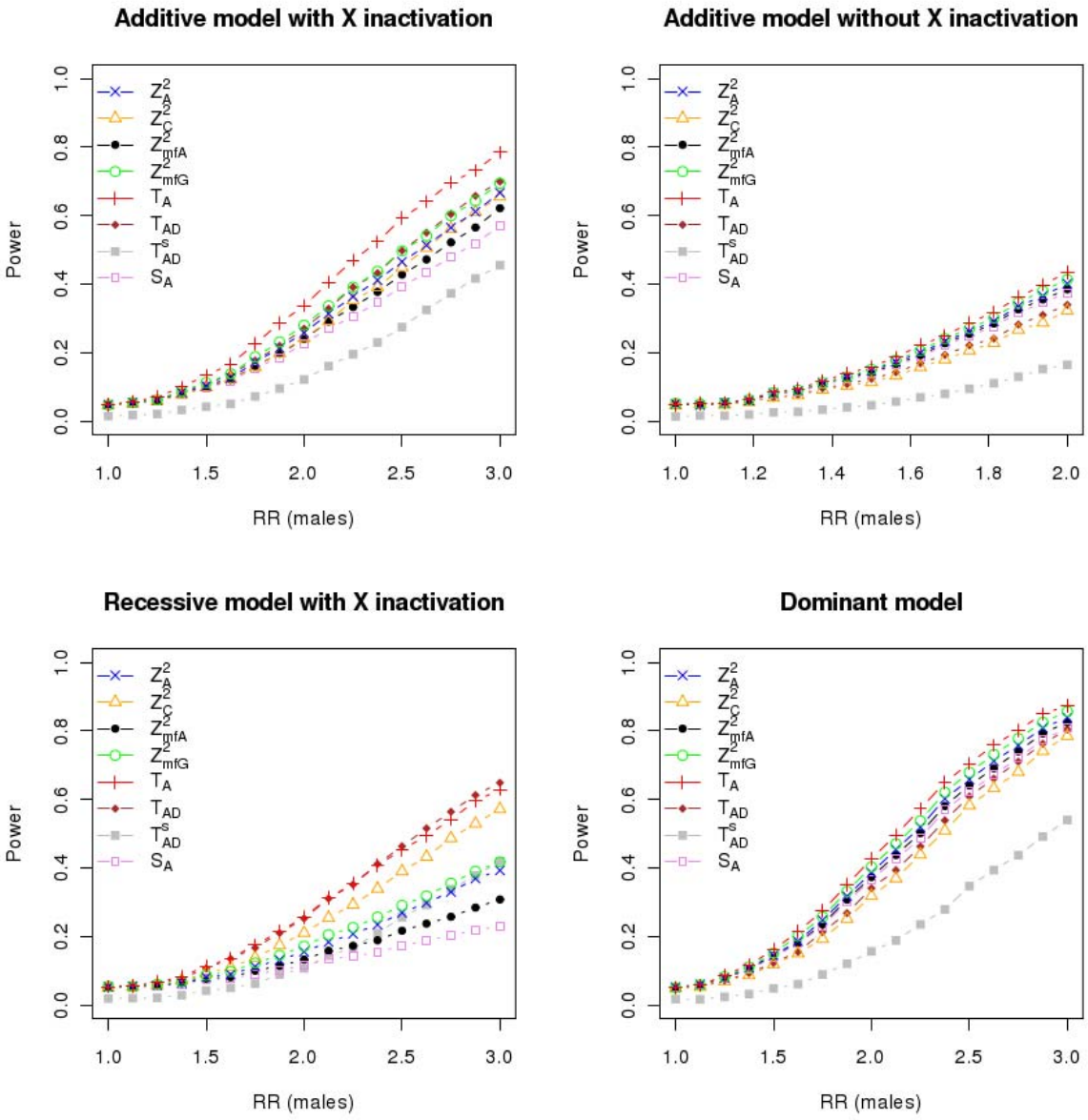
Supplementary Figure 19: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.3, prevalence=0.1. Effect sizes in males reduced by 50 %. All other parameters equal in males and females. RR= relative risk.



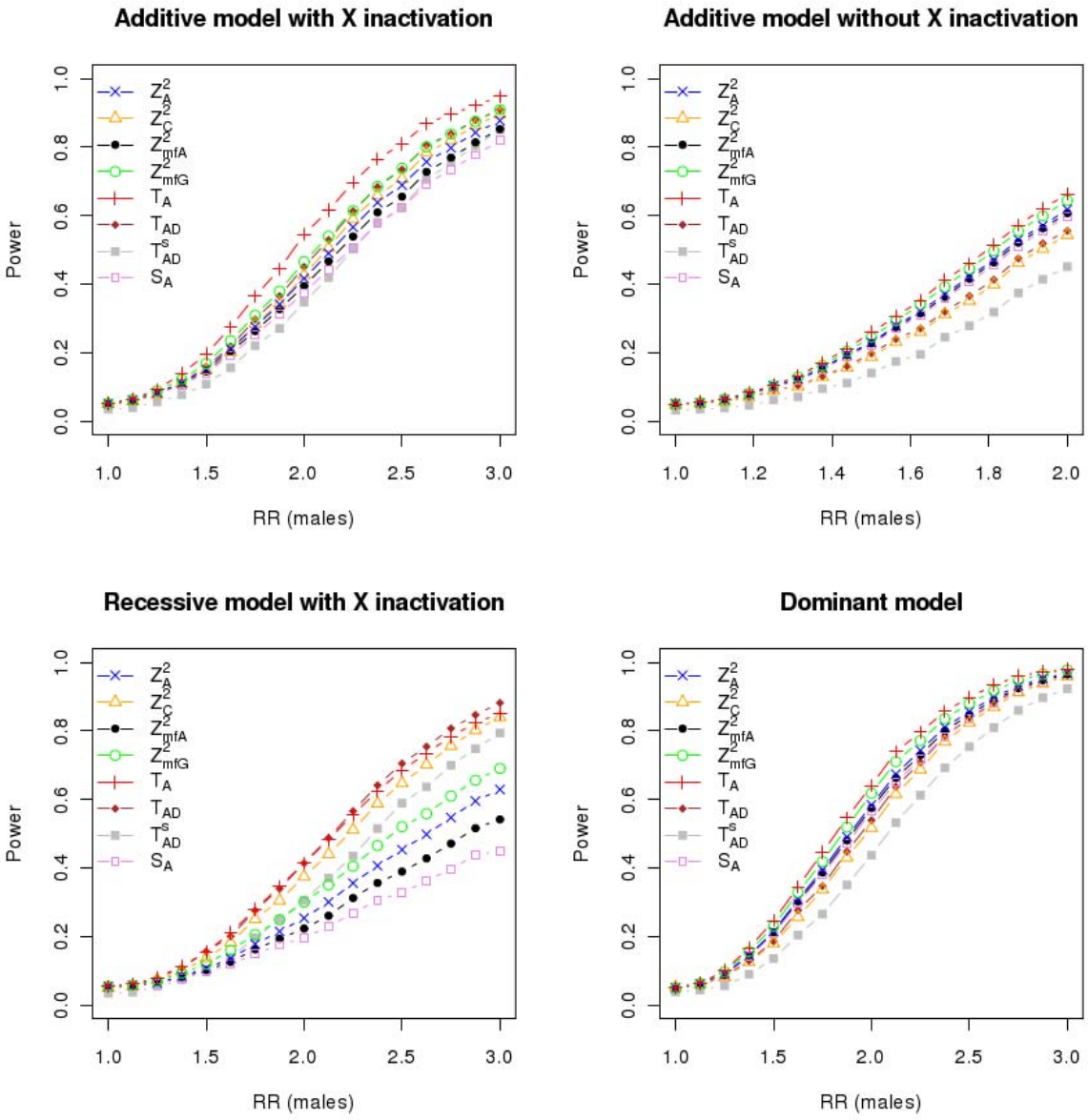
Supplementary Figure 20: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.5, prevalence=0.1. Effect sizes in males reduced by 50 %. All other parameters equal in males and females. RR= relative risk.



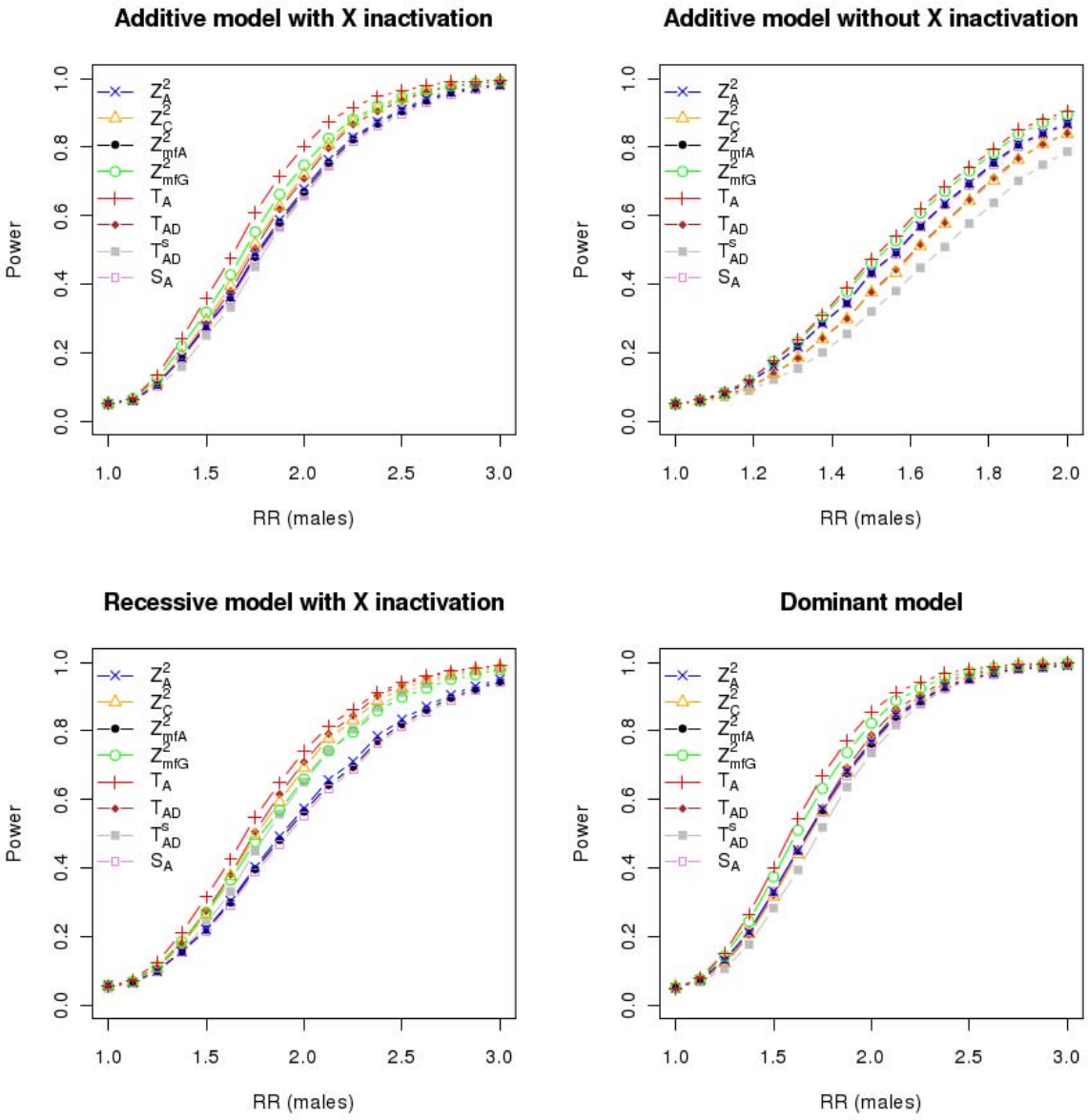
Supplementary Figure 21: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.05, prevalence=0.1. Effect sizes in females reduced by 50 %. All other parameters equal in males and females. RR= relative risk.



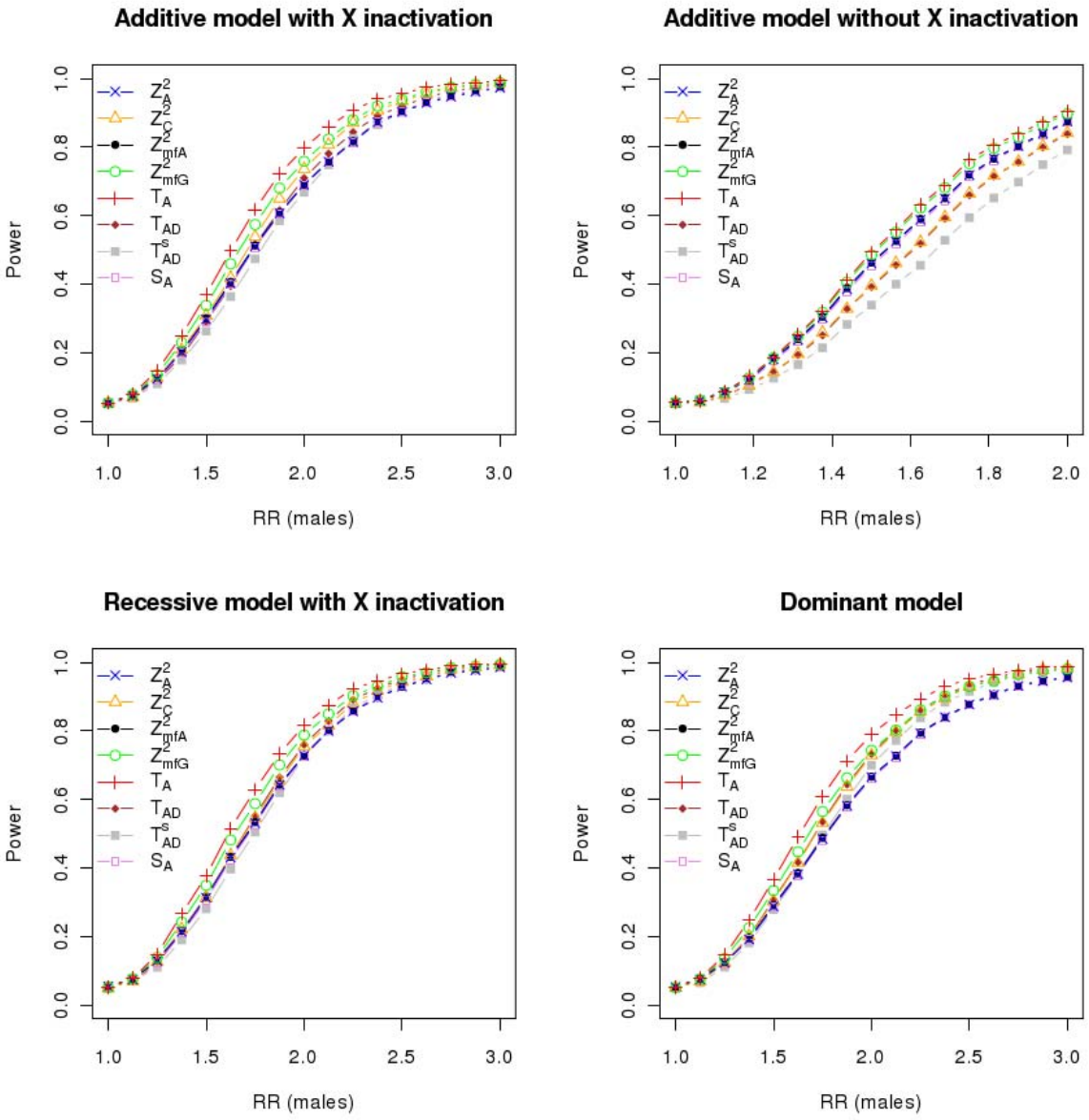
Supplementary Figure 22: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.1, prevalence=0.1. Effect sizes in females reduced by 50 %. All other parameters equal in males and females. RR= relative risk.



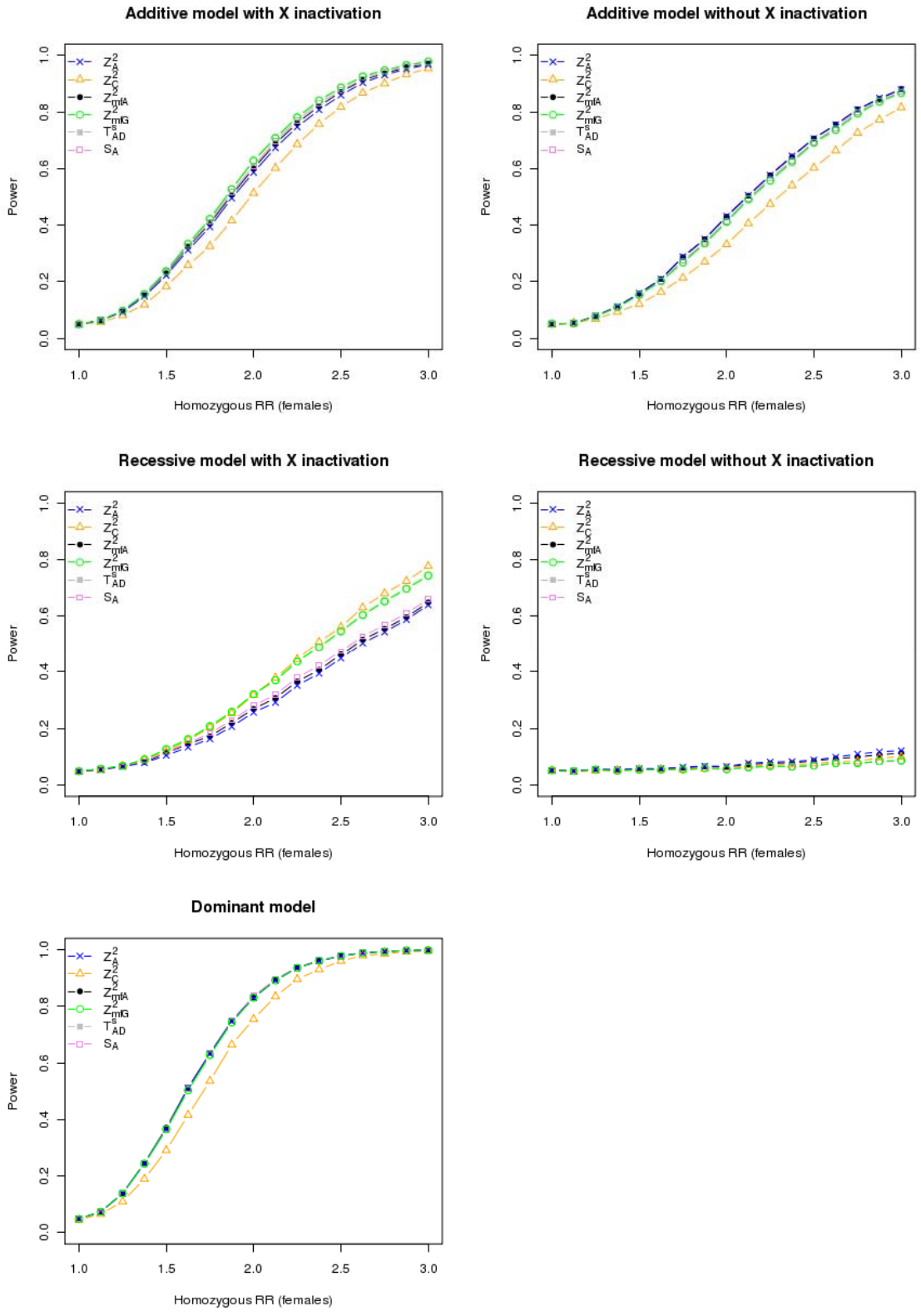
Supplementary Figure 23: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.3, prevalence=0.1. Effect sizes in females reduced by 50 %. All other parameters equal in males and females. RR= relative risk.



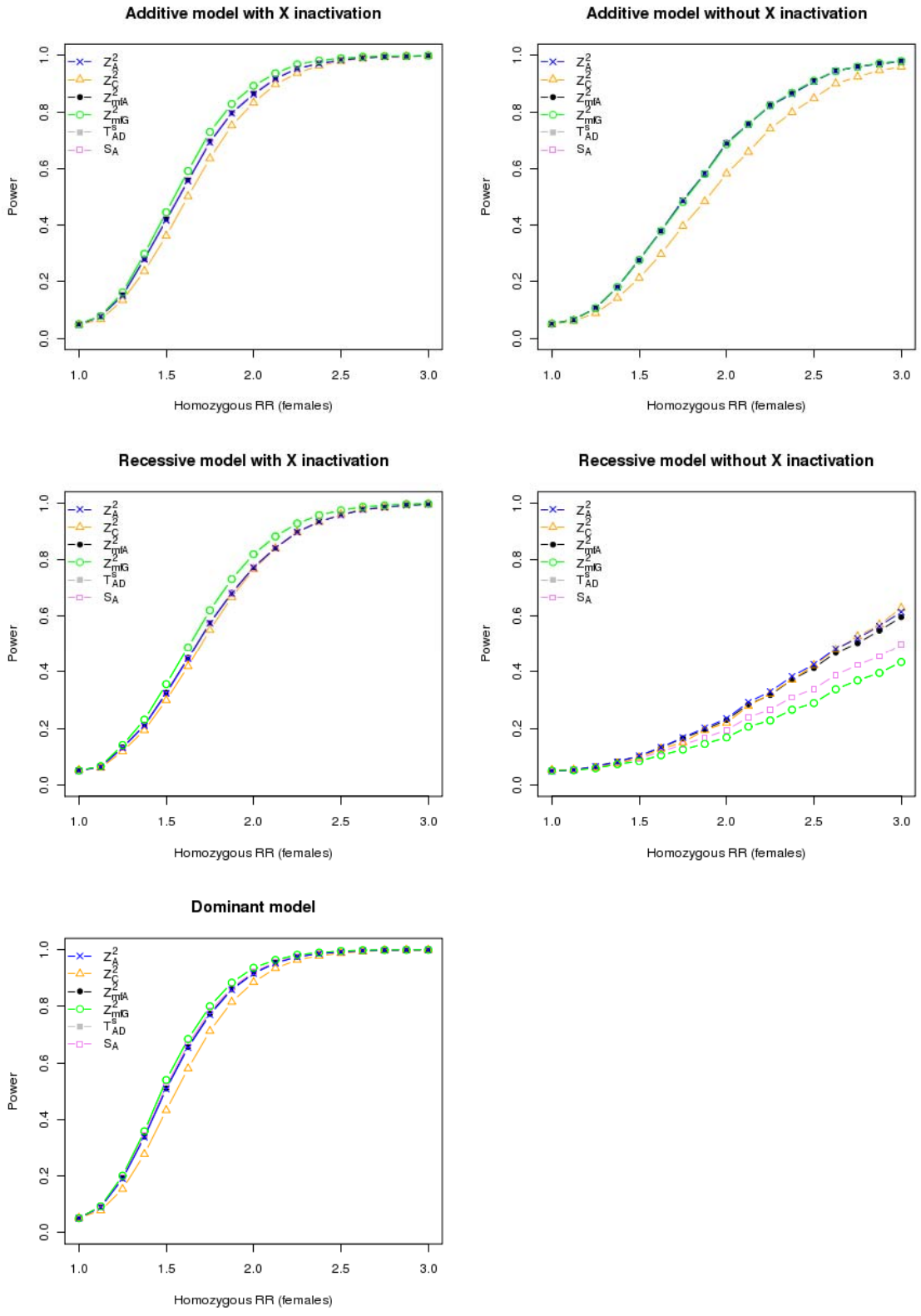
Supplementary Figure 24: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency =0.5, prevalence=0.1. Effect sizes in females reduced by 50 %. All other parameters equal in males and females. RR= relative risk.



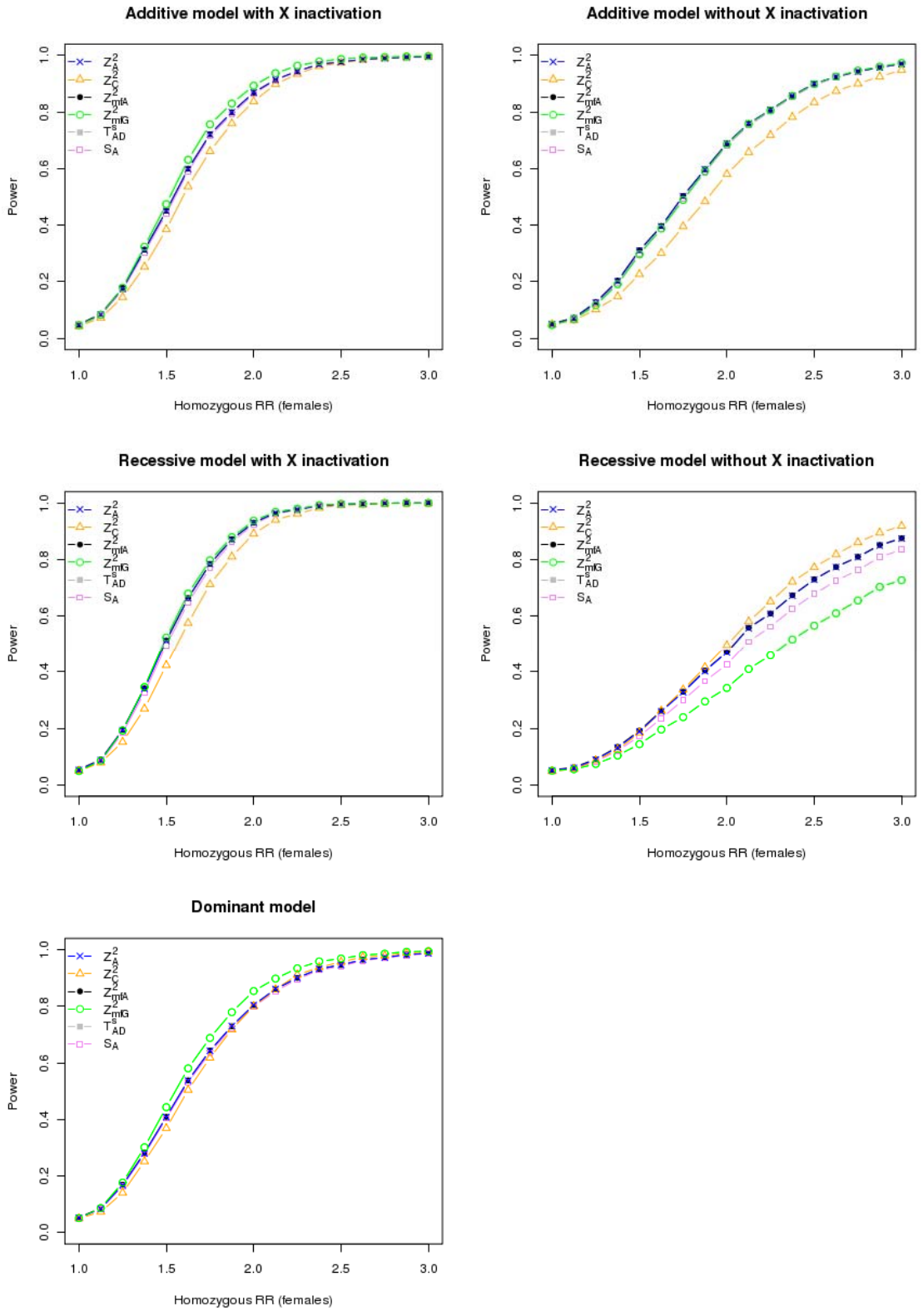
Supplementary Figure 25: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency (MAF) in males 0.075, MAF in females 0.125. Prevalence=0.1. All other parameters equal in males and females. RR= relative risk.



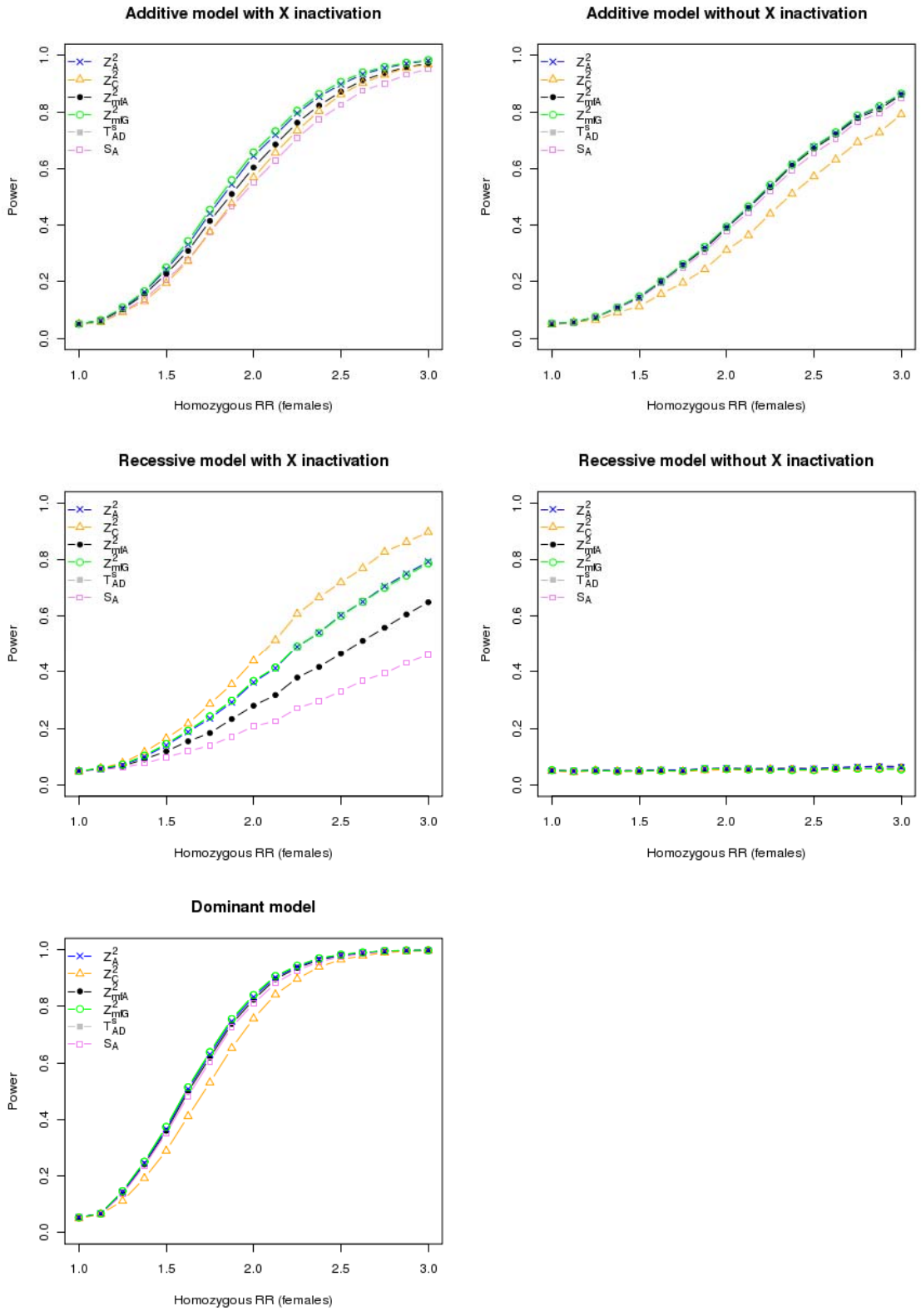
Supplementary Figure 26: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency (MAF) in males 0.275, MAF in females 0.325. Prevalence=0.1. All other parameters equal in males and females. RR= relative risk.



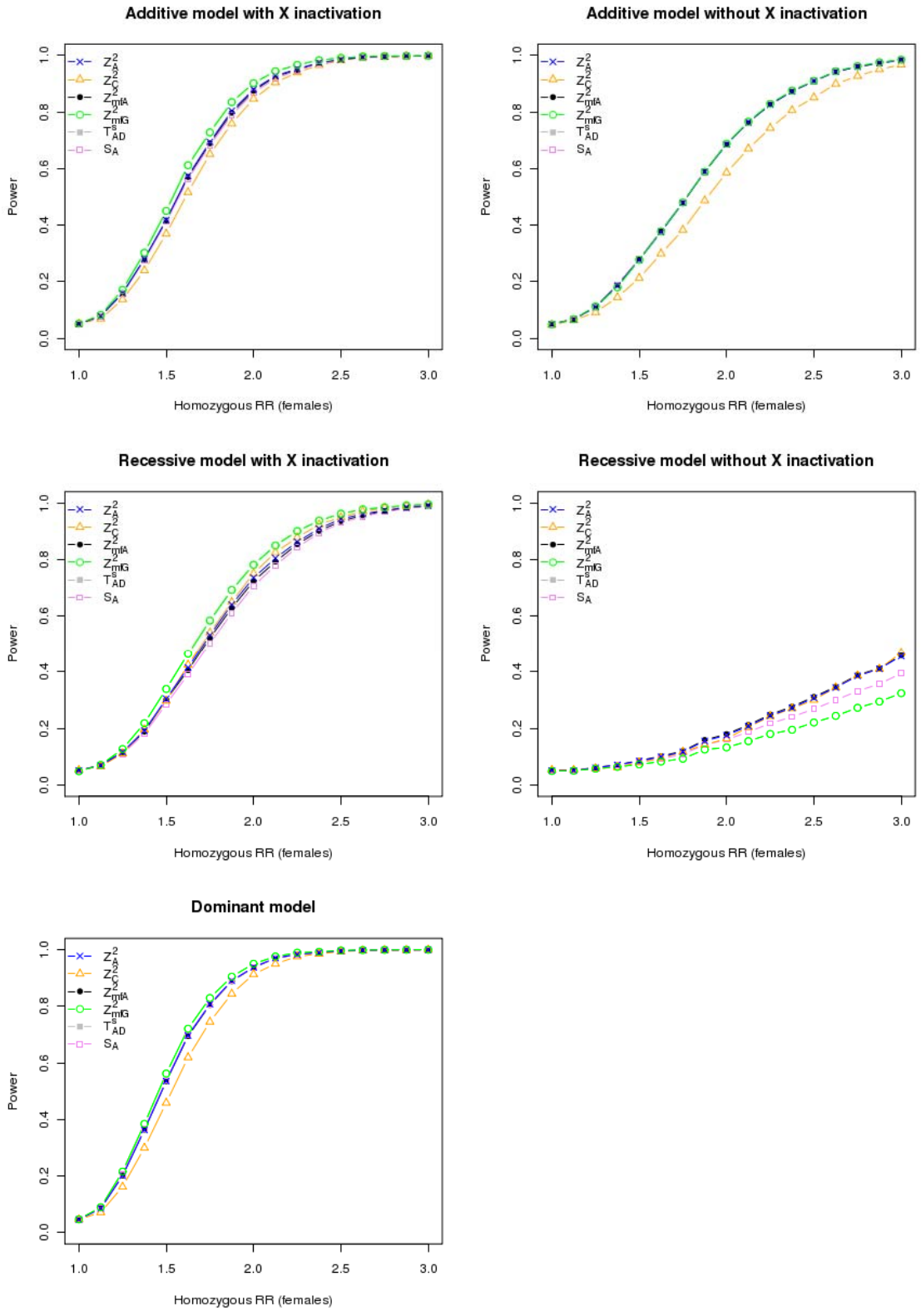
Supplementary Figure 27: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency (MAF) in males 0.475, MAF in females 0.525. Prevalence=0.1. All other parameters equal in males and females. RR= relative risk.



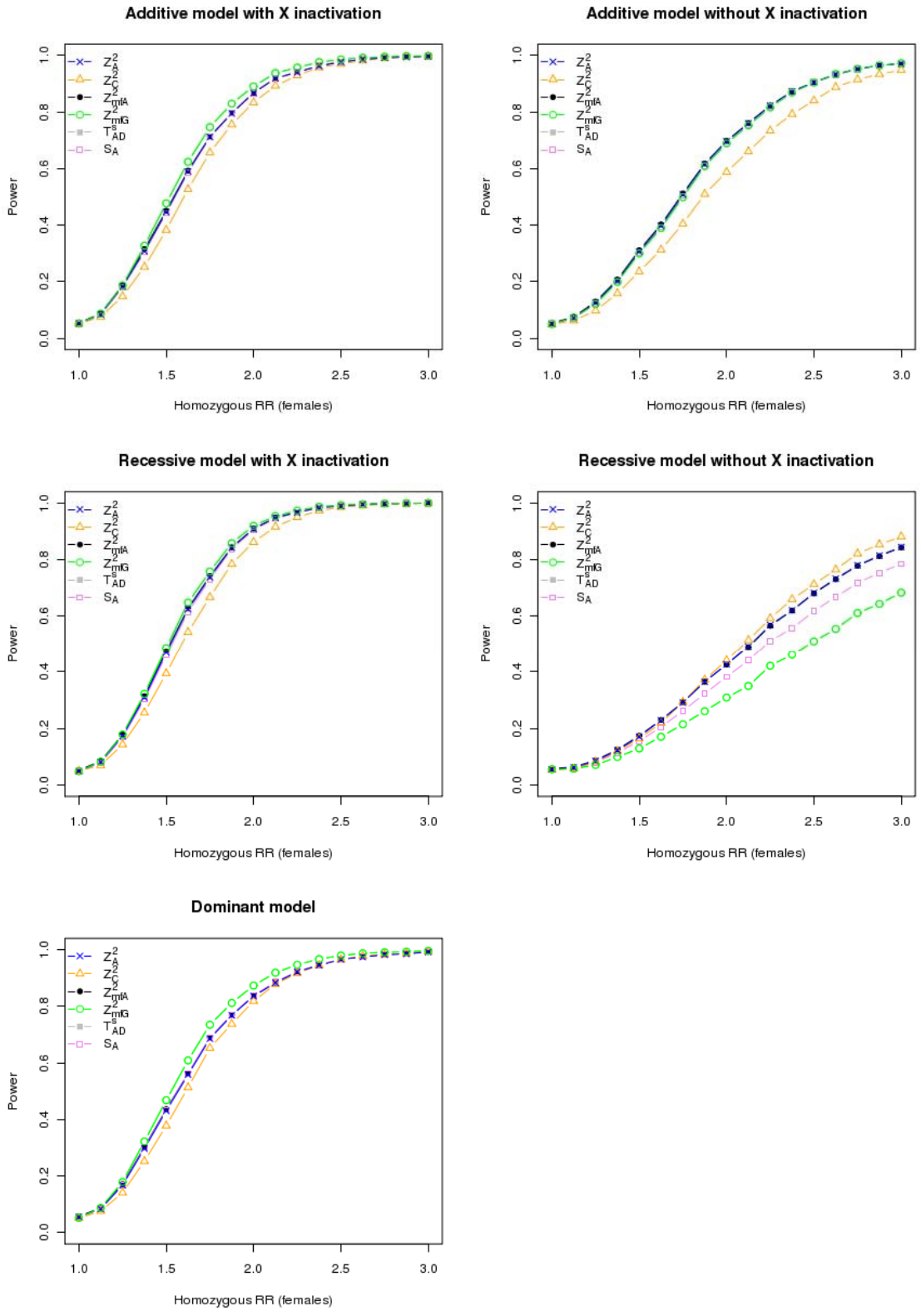
Supplementary Figure 28: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency (MAF) in males 0.125, MAF in females 0.075. Prevalence=0.1. All other parameters equal in males and females. RR= relative risk.



Supplementary Figure 29: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency (MAF) in males 0.325, MAF in females 0.275. Prevalence=0.1. All other parameters equal in males and females. RR= relative risk.

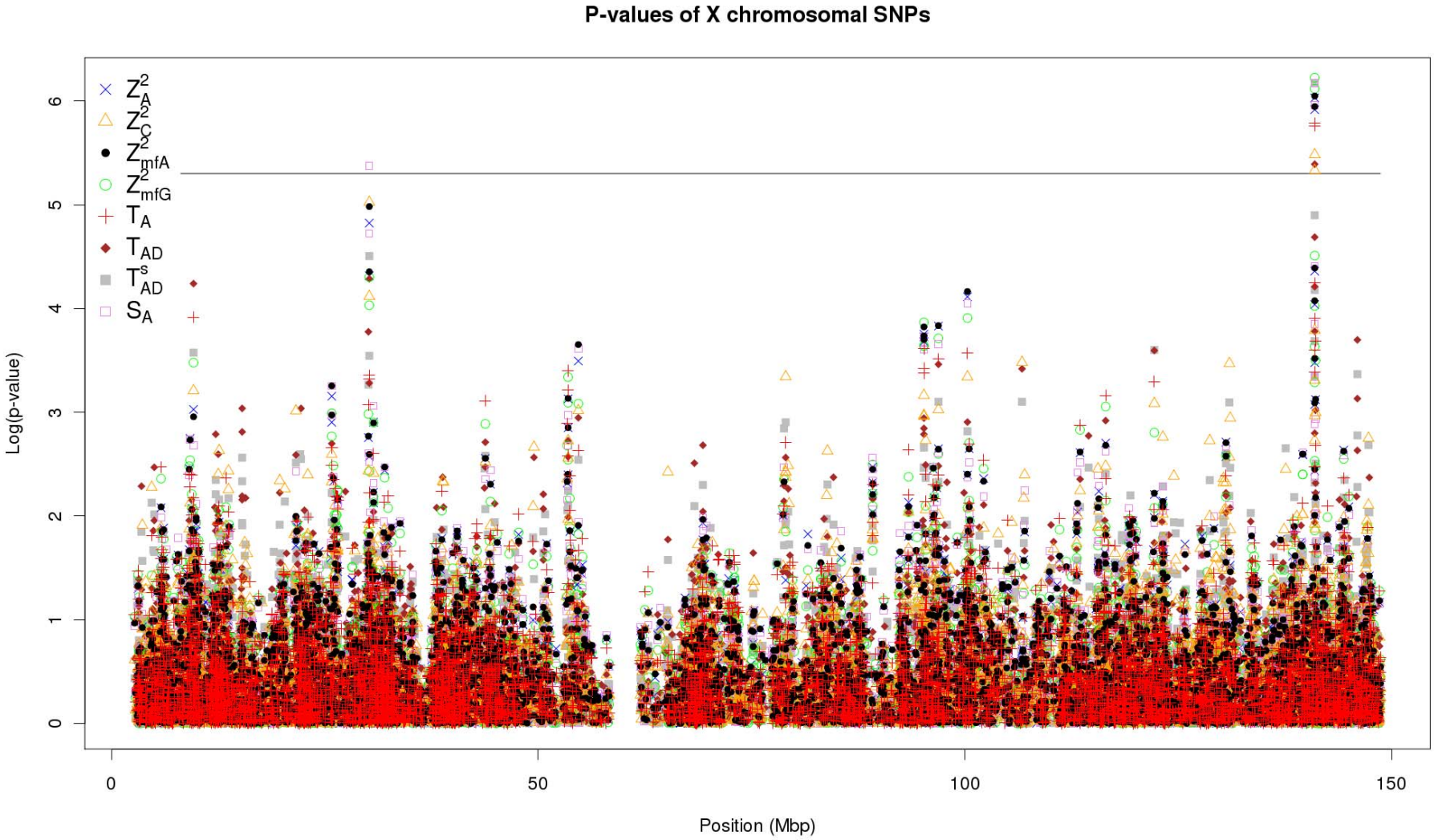


Supplementary Figure 30: Power of test statistics under different genetic models in a balanced sample design. Minor allele frequency (MAF) in males 0.525, MAF in females 0.475. Prevalence=0.1. All other parameters equal in males and females. RR= relative risk.

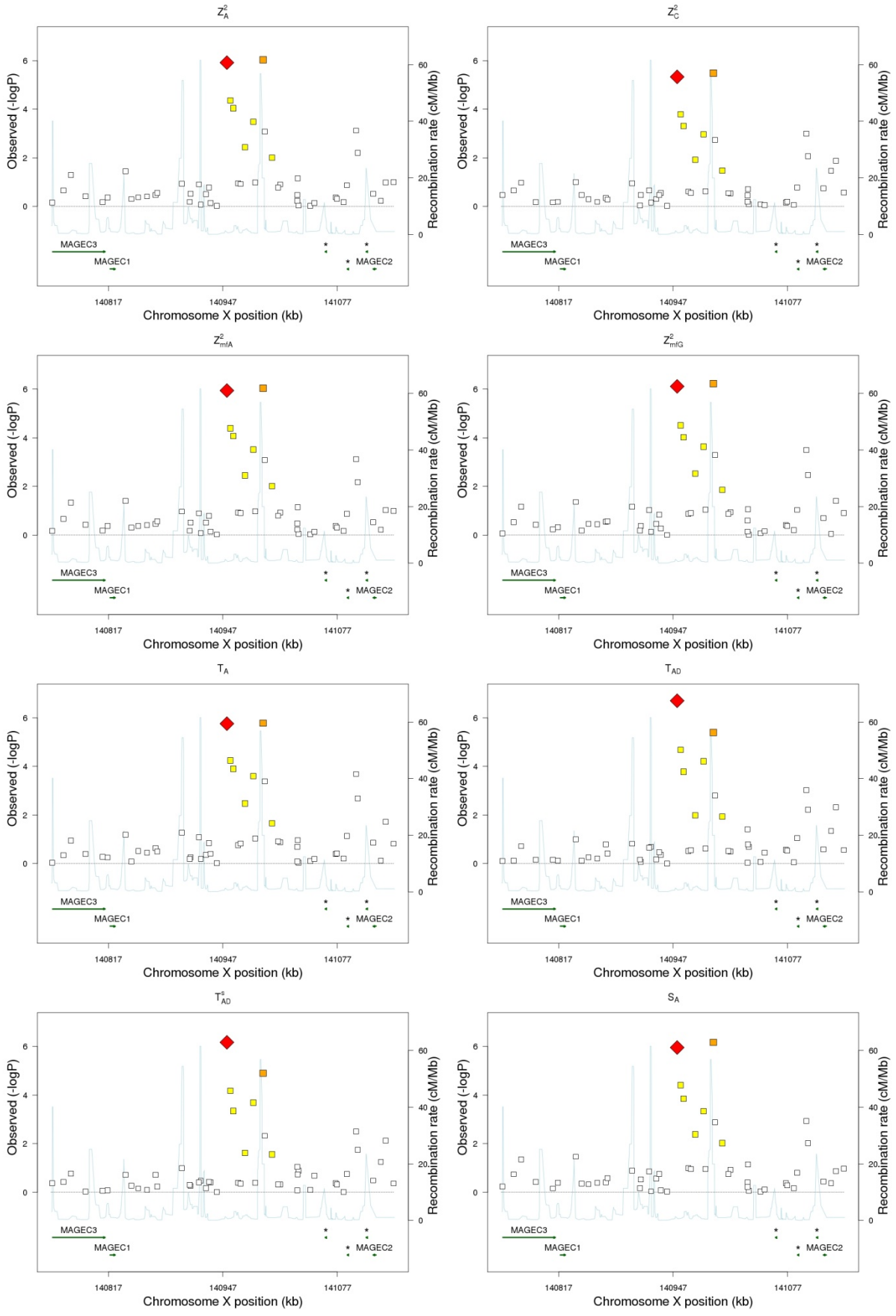


Supplement C – Results of real data analysis on Crohn's disease

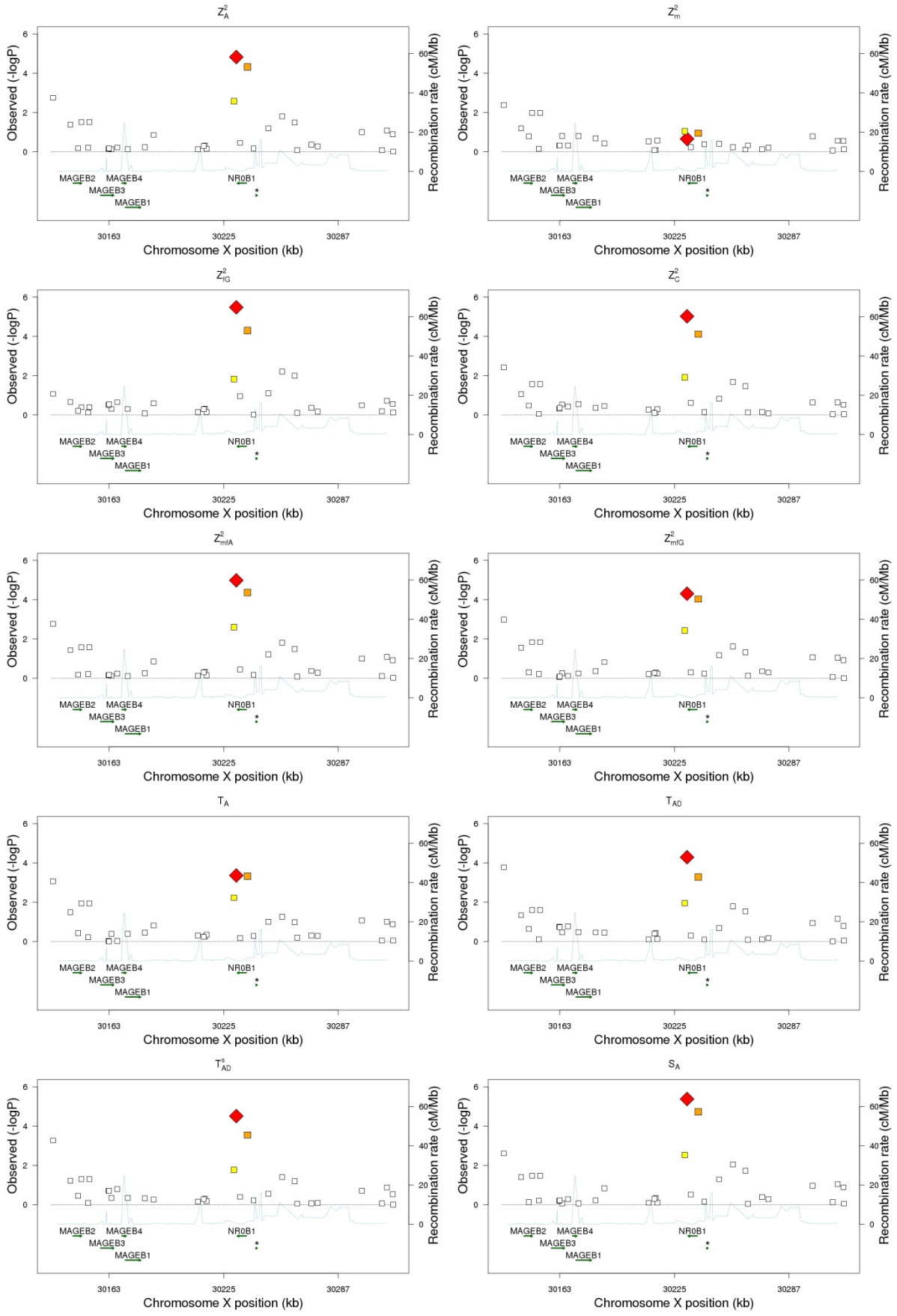
Supplementary Figure 31: Crohn's disease association results for all single-nucleotide polymorphisms (SNPs) on the X chromosome left after Quality control. For each SNP logarithmic p-values of all test statistics are presented. Position in mega base pairs (Mbp).


P-values of X chromosomal SNPs
Z^2_A
Z^2_C
Z^2_{mfA}
Z^2_{mfG}
T_A
T_{AD}
T^s_{AD}
S_A
Log(p-value)
0
1
2
3
4
5
6
0
50
100
150
Position (Mbp)

Supplementary Figure 32: Crohn's Disease association results for single nucleotide polymorphisms (SNPs) in 200 kilo base pair enviroment of rs2038265. From top left to bottom right, p-values of test statistics Z_A^2, Z_C^2, Z_{mfA}^2, Z_{mfG}^2, T_A, T_{AD}, T_{AD}^s and S_A, respectively, are shown. Each SNP represented as a square, lead SNP (rs2038265) represented as a diamond. Magnitude of linkage disequilibrium (LD) to SNP rs2038265 represented by red (high LD), orange (medium LD), yellow (low LD) and white (no LD) color.


Z_A^2
Z_C^2
Z_{mfA}^2
Z_{mfG}^2
T_A
T_{AD}
T_{AD}^s
S_A
Observed (-logP)
Recombination rate (cM/Mb)
MAGEC3
MAGEC1
MAGEC2
140817
140947
141077
Chromosome X position (kb)

Supplementary Figure 33: Crohn's Disease association results for single-nucleotide polymorphisms (SNPs) in 200 kilo base pair enviroment of rs4829424. From top left to bottom right, logarithmic p-values of test statistics Z_A^2, Z_m^2, Z_{fG}^2 Z_C^2, Z_{mfA}^2, Z_{mfG}^2, T_A, T_{AD}, T_{AD}^s and S_A, respectively. Each SNP represented as a square, lead SNP (rs4829424) represented as a diamond. Magnitude of linkage disequilibrium (LD) to SNP rs4829424 represented by red (high LD), orange (medium LD), yellow (low LD) and white (no LD) color.


Z^2_A
Z^2_m
Z^2_{fG}
Z^2_C
Z^2_{mfA}
Z^2_{mfG}
T_A
T_{AD}
T^*_{AD}
S_A
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome X position (kb)
30163
30225
30287
MAGEB2
MAGEB4
MAGEB3
MAGEB1
NR0B1

Supplementary Table 4: Association results of the Crohn's disease case-control data for the top single-nucleotide polymorphisms (SNPs) in regions Xq21.2 and Xq27.3.

SNP	position[b]	MAF[a]		p-values									
		females	males	Z_A^2	Z_m^2	Z_{fG}^2	Z_C^2	Z_{mfA}^2	Z_{mfG}^2	T_A	T_{AD}	T_{AD}^s	S_A
Xq21.2													
rs4828253	83,452,245	0.42	0.44	0.3636	0.0868	0.8618	0.2274	0.3687	0.2538	0.1829	0.0419	0.0374	0.4138
rs4828255	83,495,007	0.45	0.45	0.2391	0.1354	0.7398	0.3104	0.2390	0.1862	0.1539	0.0107	0.0199	0.2677
rs830239	83,770,551	0.19	0.20	0.4402	0.0071	0.2972	0.0156	0.4382	0.2035	0.1014	0.2313	0.0223	0.5131
rs1831116	83,811,301	0.10	0.08	0.4982	0.0035	0.2098	0.0063	0.4290	0.1936	0.1021	0.0610	0.0107	0.5054
rs2176383	84,036,853	0.07	0.10	0.2870	0.3849	0.0209	0.0477	0.2198	0.3562	0.7382	0.0449	0.8602	0.1074
rs6653047	84,351,765	0.16	0.17	0.6550	0.0777	0.0526	0.0322	0.6334	0.9842	0.6592	0.1154	0.0751	0.5039
rs12556305	84,662,951	0.34	0.35	0.1778	0.3518	0.0181	0.0396	0.1754	0.3625	0.5966	0.7468	0.0355	0.1474
Xq27.3													
rs5904945	145,984,829	0.26	0.25	0.3633	0.7749	0.1729	0.3793	0.3698	0.4752	0.6094	0.0023	0.0053	0.3270
rs930631	146,004,852	0.26	0.26	0.2296	0.8601	0.0946	0.2435	0.2335	0.3183	0.4486	2.0E-04	4.3E-04	0.1911
rs5951926	146,005,592	0.27	0.25	0.1485	0.8677	0.0882	0.2305	0.1525	0.2008	0.2835	7.4E-04	0.0017	0.1298

[a] MAF=minor allele frequency; [b] position=physical position in base pairs.

Supplementary Table 5: Genotype frequencies for top single-nucleotide polymorphisms (SNPs) in regions Xp21.2, Xq21.2, Xq27.2 and Xq27.3.

	Alleles		Female cases			Female controls			Male cases		Male controls	
SNP	A[a]	B[b]	AA	AB	BB	AA	AB	BB	A	B	A	B
Xp21.2												
rs6526959	C	A	0.23	0.39	0.38	0.22	0.54	0.24	0.37	0.63	0.51	0.49
rs4829424	G	A	0.49	0.45	0.07	0.73	0.25	0.02	0.72	0.28	0.78	0.22
rs4829169	T	G	0.46	0.47	0.07	0.67	0.31	0.02	0.71	0.29	0.78	0.22
Xq21.2												
rs4828253	C	T	0.38	0.38	0.24	0.33	0.50	0.17	0.61	0.39	0.52	0.48
rs4828255	G	A	0.37	0.38	0.25	0.28	0.53	0.18	0.60	0.40	0.52	0.48
rs830239	G	A	0.68	0.29	0.03	0.65	0.28	0.07	0.74	0.26	0.85	0.15
rs1831116	C	T	0.83	0.17	0.00	0.79	0.19	0.02	0.87	0.13	0.95	0.05
rs2176383	T	C	0.80	0.20	0.00	0.89	0.11	0.00	0.92	0.08	0.89	0.11
rs6653047	T	G	0.65	0.31	0.04	0.75	0.23	0.02	0.87	0.13	0.80	0.20
rs12556305	C	T	0.40	0.41	0.19	0.48	0.44	0.09	0.67	0.33	0.63	0.37
rs12156835	A	G	0.34	0.53	0.12	0.25	0.50	0.25	0.56	0.44	0.58	0.42
Xq27.2												
rs2038265	C	T	0.68	0.26	0.06	0.44	0.50	0.06	0.85	0.15	0.69	0.31
rs2207272	T	G	0.46	0.41	0.13	0.27	0.57	0.16	0.71	0.29	0.56	0.44
rs5908101	G	A	0.35	0.41	0.24	0.20	0.50	0.31	0.62	0.38	0.47	0.53
rs2144096	G	A	0.41	0.38	0.21	0.24	0.53	0.23	0.67	0.33	0.52	0.48
rs7889974	G	A	0.73	0.25	0.01	0.53	0.43	0.05	0.88	0.12	0.74	0.26
rs7056485	T	C	0.28	0.45	0.27	0.20	0.47	0.33	0.57	0.43	0.41	0.59
rs5908216	A	G	0.48	0.43	0.09	0.56	0.38	0.05	0.63	0.37	0.78	0.22
Xq27.3												
rs5904945	A	G	0.46	0.50	0.04	0.60	0.31	0.08	0.76	0.24	0.74	0.26
rs930631	C	T	0.44	0.53	0.03	0.61	0.31	0.08	0.75	0.25	0.74	0.26
rs5951926	A	G	0.44	0.53	0.04	0.60	0.32	0.08	0.74	0.26	0.75	0.25

[a]Major allele in entire sample; [b]minor allele in entire sample.