

Supplementary Table 1: Two-locus model used in simulations.

Scénario	G_2	Penetrance function for the specific phenotype $f_S(G_1, G_2)$			Penetrance function for other phenotypes within broad $(f_B - f_S)(G_1, G_2)$			Complement of the penetrance function for the unaffected subjects $1 - f_B(G_1, G_2)$		
		G_1			G_1			G_1		
		a/a	A/a	A/A	a/a	A/a	A/A	a/a	A/a	A/A
1	a/a	0	0	0	0.02	0.52	0.52	0.98	0.48	0.48
$p_1=0.03$	A/a	0	0.89	0.89	0.02	0.02	0.02	0.98	0.09	0.09
$p_2=0.1$	A/A	0	0.89	0.89	0.02	0.02	0.02	0.98	0.09	0.09
2	a/a	0	0	0	0	0.89	0.89	1	0.11	0.11
$p_1=0.03$	A/a	0	0.89	0.89	0	0	0	1	0.11	0.11
$p_2=0.1$	A/A	0	0.89	0.89	0	0	0	1	0.11	0.11
3	a/a	1.0e-4	0.05	0.05	9e-4	0.45	0.45	0.999	0.5	0.5
$p_1=0.027$	A/a	0.5	0.5	0.5	0	0	0	0.5	0.5	0.5
$p_2=0.027$	A/A	0.5	0.5	0.5	0	0	0	0.5	0.5	0.5

G_1 : Genotype at locus 1, G_2 : Genotype at locus 2, p_1 : A allele frequency in locus 1, p_2 : A allele frequency in locus 2

Supplementary Table 2: Descriptive statistics of the simulated families.

Scenario	Specific phenotype		Other phenotype		Total broad phenotype	
	Mean	Range	Mean	Range	Mean	Range
1	5	2 – 13	2	0 – 7	7	3 – 13
2	5	2 – 13	3	0 – 9	8	3 – 15
3	3	1 – 10	3	1 – 11	6	3 – 13

Supplementary Table 3: Signal at modifier locus (locus 2) using joint modeling of a specific and a broad phenotype under simulation scenario 2.

Statistic ^a			Two epistatic genes only (100 replicate samples of 10 families)				Two epistatic genes plus heterogeneity (100 replicate samples of 40 families)			
			Mean (SD)	Mean θ (SD)	Power ^b	Power ^b (pre-select)	Mean (SD)	Mean θ (SD)	Power ^b	Power ^b (pre-select)
All families	One-locus analyses	LOD within broad (Z_w^{1L})	4.74 (1.96)	0.05 (0.04)	0.84	NA	3.40 (2.10)	0.22 (0.06)	0.60	NA
		HLOD within broad (Z_w^{H-1L})	4.92 (1.85)	0.03 (0.04)	0.88	NA	5.16 (2.08)	0.05 (0.05)	0.91	NA
	Two-locus analyses	Conditional LOD (Z^{COND})	6.28 (1.76)	0.00 (0.02)	0.97	0.97	5.44 (2.07)	0.08 (0.08)	0.95	0.96
		Sliced LOD (Z^{SLICED})	6.29 (1.76)	0.00 (0.02)	0.97	0.97	5.46 (2.08)	0.08 (0.08)	0.95	0.96
		Conditional HLOD (Z^{H-COND})	6.29 (1.76)	0.00 (0.01)	0.97	0.97	6.77 (2.17)	0.02 (0.04)	0.99	0.99
		Sliced HLOD ($Z^{H-SLICED}$)	6.29 (1.76)	0.00 (0.01)	0.97	0.97	6.44 (2.09)	0.02 (0.05)	0.99	0.99
Selected families	One-locus analyses	LOD within broad (Z_w^{1L+}) ^c	4.63 (1.94)	0.05 (0.04)	0.85	NA	6.17 (2.40)	0.11 (0.05)	0.97	NA
	Two-locus analyses	Conditional LOD (Z^{COND+})	6.03 (1.79)	0.00 (0.02)	0.95	0.97	9.10 (2.52)	0.05 (0.05)	1.00	1.00
		Sliced LOD ($Z^{SLICED+}$)	6.01 (1.79)	0.00 (0.02)	0.97	0.97	8.52 (2.47)	0.04 (0.05)	1.00	1.00

^a All statistics are maximized over the corresponding model family (one-locus or two-locus model family) with the specific phenotype prevalence set to $\pi_S = 0.01$ and the broad phenotype prevalence set to $\pi_B = 0.053$

^b Power for significance level $\alpha = 0.0017$

^c Families with $Z_i^{2L}(\tilde{\theta}_1(k), \frac{1}{2}, k) > 0$ (as in Z^{COND+})

Supplementary Table 4: Signal at modifier locus (locus 2) using joint modeling of a specific and a broad phenotype under simulation scenario 1, without requiring an unaffected pivot.

Statistic ^a			Two epistatic genes only (100 replicate samples of 10 families)				Two epistatic genes plus heterogeneity (100 replicate samples of 40 families)			
			Mean (SD)	Mean θ (SD)	Power ^b	Power ^b (pre-select)	Mean (SD)	Mean θ (SD)	Power ^b	Power ^b (pre-select)
All families	One-locus analyses	LOD within broad (Z_w^{1L})	3.94 (2.20)	0.08 (0.06)	0.73	NA	2.86 (1.92)	0.22 (0.08)	0.52	NA
		HLOD within broad (Z_w^{H-1L})	4.21 (2.18)	0.01 (0.03)	0.94	NA	4.58 (2.28)	0.05 (0.06)	0.87	NA
	Two-locus analyses	Conditional LOD (Z^{COND})	5.79 (2.18)	0.01 (0.03)	0.94	0.94	5.30 (2.47)	0.09 (0.08)	0.89	0.89
		Sliced LOD (Z^{SLICED})	5.81 (2.18)	0.01 (0.03)	0.94	0.94	5.31 (2.48)	0.09 (0.08)	0.89	0.89
		Conditional HLOD (Z^{H-COND})	5.84 (2.17)	0.01 (0.03)	0.94	0.94	6.53 (2.62)	0.02 (0.04)	0.95	0.95
		Sliced HLOD ($Z^{H-SLICED}$)	5.85 (2.17)	0.01 (0.03)	0.94	0.94	6.37 (2.63)	0.02 (0.04)	0.94	0.94
Selected families	One-locus analyses	LOD within broad (Z_w^{1L+}) ^c	3.87 (2.25)	0.07 (0.07)	0.67	NA	4.91 (2.52)	0.13 (0.07)	0.85	NA
	Two-locus analyses	Conditional LOD (Z^{COND+})	5.48 (2.16)	0.01 (0.03)	0.89	0.92	8.23 (2.52)	0.06 (0.06)	0.99	0.99
		Sliced LOD ($Z^{SLICED+}$)	5.45 (2.20)	0.01 (0.03)	0.90	0.93	7.72 (2.57)	0.05 (0.05)	0.97	0.97

^a All statistics are maximized over the corresponding model family (one-locus or two-locus model family) with the specific phenotype prevalence set to $\pi_S = 0.01$ and the broad phenotype prevalence set to $\pi_B = 0.053$

^b Power for significance level $\alpha = 0.0017$

^c Families with $Z_i^{2L}(\tilde{\theta}_1(k), \frac{1}{2}, k) > 0$ (as in Z^{COND+})

Supplementary Table 5: Signal at locus 2 using joint modeling of a specific and a broad phenotype under simulation scenario 3.

		Statistic ^a	Mean (SD)	Mean θ (SD)	Power ^b	Power ^b (pre-select)
All families	One-locus analyses	LOD (Z^{1L})	4.30 (2.02)	0.04 (0.06)	0.80	NA
		HLOD (Z^{H-1L})	4.39 (1.99)	0.03 (0.05)	0.79	NA
		LOD within broad (Z_w^{1L})	4.43 (2.16)	0.05 (0.05)	0.77	NA
		HLOD within broad (Z_w^{H-1L})	4.58 (2.16)	0.03 (0.05)	0.75	NA
	Two-locus analyses	Conditional LOD (Z^{COND})	4.91 (2.20)	0.02 (0.04)	0.84	0.82
		Sliced LOD (Z^{SLICED})	4.92 (2.20)	0.02 (0.04)	0.84	0.82
		Conditional HLOD (Z^{H-COND})	4.98 (2.18)	0.01 (0.03)	0.82	0.81
		Sliced HLOD ($Z^{H-SLICED}$)	4.99 (2.19)	0.02 (0.04)	0.82	0.81
Selected families	One-locus analyses	LOD within broad (Z_w^{1L+}) ^c	2.89 (1.66)	0.05 (0.06)	0.55	NA
	Two-locus analyses	Conditional LOD (Z^{COND+})	3.10 (1.50)	0.04 (0.08)	0.51	0.51
		Sliced LOD ($Z^{SLICED+}$)	3.08 (1.57)	0.03 (0.06)	0.53	0.55

^a All statistics are maximized over the corresponding model family (one-locus or two-locus model family) with the specific phenotype prevalence set to $\pi_S = 0.01$ and the broad phenotype prevalence set to $\pi_B = 0.053$

^b Power for significance level $\alpha = 0.0017$

^c Families with $Z_i^{2L}(\tilde{\theta}_1(k), \frac{1}{2}, k) > 0$ (as in Z^{COND+})

Supplementary Table 6: prevalence of the different phenotypes

phenotype	prevalence (%)	definition and justification
SZ narrow	1.0	Schizophrenia [1,2]
SZ extended	1.2	SZ narrow + small increment to account for schizophreniform disorder and schizotypal personality
BP narrow	1.0	Type I bipolar disorder [3]
BP extended	7.0	BP narrow subjects + subjects with recurrent MDD [4-6]
Major psychosis narrow	2.3	SZ narrow subjects + BP narrow subjects + schizo-affective disorder
Major psychosis extended	8.5	SZ extended subjects + BP extended subjects + schizo-affective disorder

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3. Angst J: The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143-151.
4. Grolleau A, Cougnard A, Begaud B, Verdoux H: Congruence between diagnosis of recurrent major depressive disorder and psychotropic treatment in the general population. Acta Psychiatr Scand 2008;117:20-27.
5. Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman AT: Prevalence and predictors of recurrence of major depressive disorder in the adult population. Acta Psychiatr Scand;122:184-191.
6. Janzing JG, de Graaf R, ten Have M, Vollebergh WA, Verhagen M, Buitelaar JK: Familiality of depression in the community; associations with gender and phenotype of major depressive disorder. Soc Psychiatry Psychiatr Epidemiol 2009;44:1067-1074.

Supplementary Table 7: list of marker pairs tested in the analysis of the Eastern Quebec mixed SZ and BP kindreds

locus 1	locus 2	pheno 1	pheno 2
D2S298	D3S1579	MP-extended	SZ-narrow
	D3S3023	MP-extended	SZ-narrow
	D3S3023	MP-extended	SZ-extended
	478B14-848	MP-extended	SZ-narrow
	D8S1110	MP-extended	BP-narrow
	D8S1110	MP-extended	SZ-extended
	D8S1110	MP-extended	SZ-narrow
	D13S1233	MP-extended	BP-extended
	D13S1312	MP-extended	SZ-narrow
	D13S287	MP-extended	SZ-extended
	D13S287	MP-extended	SZ-narrow
	D13S326	MP-extended	BP-extended
	D13S788	MP-extended	SZ-extended
	D13S788	MP-extended	SZ-narrow
	D15S540	MP-extended	SZ-extended
D3S1558	478B14-848	MP-extended	SZ-narrow
	D8S1110	MP-extended	SZ-extended
	D8S1110	MP-extended	SZ-narrow
	D8S1110	MP-extended	BP-narrow
	D13S1233	MP-extended	BP-extended
	D13S1312	MP-extended	SZ-narrow
	D13S287	MP-extended	SZ-extended
	D13S287	MP-extended	SZ-narrow
	D13S326	MP-extended	BP-extended
	D13S788	MP-extended	SZ-extended
	D13S788	MP-extended	SZ-narrow
	D15S540	MP-extended	SZ-extended
D3S2418	478B14-848	MP-extended	SZ-narrow
	D8S1110	MP-extended	SZ-extended
	D8S1110	MP-extended	SZ-narrow
	D8S1110	MP-extended	BP-narrow
	D13S1233	MP-extended	BP-extended
	D13S1312	MP-extended	SZ-narrow
	D13S287	MP-extended	SZ-extended
	D13S287	MP-extended	SZ-narrow
	D13S326	MP-extended	BP-extended
	D13S788	MP-extended	SZ-narrow
	D13S788	MP-extended	SZ-extended
	D15S540	MP-extended	SZ-extended
D6S334	D3S1579	MP-extended	SZ-narrow
	D3S3023	MP-extended	SZ-narrow
	D3S3023	MP-narrow	SZ-narrow
	D3S3023	MP-extended	SZ-extended
	478B14-848	MP-extended	SZ-narrow
	D8S1110	MP-extended	SZ-narrow
	D8S1110	MP-extended	SZ-extended
	D8S1110	MP-narrow	SZ-narrow

	D8S1110	MP-extended	BP-narrow
	D8S1110	MP-narrow	BP-narrow
	D13S1233	MP-extended	BP-extended
	D13S1312	MP-extended	SZ-narrow
	D13S287	MP-extended	SZ-narrow
	D13S287	MP-extended	SZ-extended
	D13S326	MP-extended	BP-extended
	D13S788	MP-extended	SZ-narrow
	D13S788	MP-extended	SZ-extended
	D15S540	MP-extended	SZ-extended
	D18S1145	MP-narrow	SZ-narrow
	D18S472	MP-narrow	SZ-narrow
	D18S72	MP-narrow	SZ-narrow
	D18S851	MP-narrow	BP-narrow
	D18S851	MP-narrow	SZ-narrow
D10S245	D3S1579	MP-extended	SZ-narrow
	D3S3023	MP-extended	SZ-narrow
	D3S3023	MP-extended	SZ-extended
	478B14-848	MP-extended	SZ-narrow
	D8S1110	MP-extended	BP-narrow
	D8S1110	MP-extended	SZ-extended
	D8S1110	MP-extended	SZ-narrow
	D13S1233	MP-extended	BP-extended
	D13S1312	MP-extended	SZ-narrow
	D13S287	MP-extended	SZ-narrow
	D13S287	MP-extended	SZ-extended
	D13S326	MP-extended	BP-extended
	D13S788	MP-extended	SZ-extended
	D13S788	MP-extended	SZ-narrow
	D15S540	MP-extended	SZ-extended
D15S540	D3S1579	MP-extended	SZ-narrow
	D3S3023	MP-extended	SZ-narrow
	D3S3023	MP-extended	SZ-extended
	478B14-848	MP-extended	SZ-narrow
	D8S1110	MP-extended	SZ-extended
	D8S1110	MP-extended	SZ-narrow
	D8S1110	MP-extended	BP-narrow
	D13S1233	MP-extended	BP-extended
	D13S1312	MP-extended	SZ-narrow
	D13S287	MP-extended	SZ-extended
	D13S287	MP-extended	SZ-narrow
	D13S326	MP-extended	BP-extended
	D13S788	MP-extended	SZ-extended
	D13S788	MP-extended	SZ-narrow
GABRA5	D3S1579	MP-extended	SZ-narrow
	D3S3023	MP-extended	SZ-narrow
	D3S3023	MP-extended	SZ-extended
	478B14-848	MP-extended	SZ-narrow
	D8S1110	MP-extended	SZ-extended
	D8S1110	MP-extended	SZ-narrow

D8S1110	MP-extended	BP-narrow
D13S1233	MP-extended	BP-extended
D13S1312	MP-extended	SZ-narrow
D13S287	MP-extended	SZ-narrow
D13S287	MP-extended	SZ-extended
D13S326	MP-extended	BP-extended
D13S788	MP-extended	SZ-narrow
D13S788	MP-extended	SZ-extended

Supplementary Table 8: Two-locus model maximizing the conditional LOD score for marker pairs with the strongest signals.

		Penetrance function for the specific phenotype $f_S(G_1, G_2)$			Penetrance function for other phenotypes within broad $(f_B - f_S)(G_1, G_2)$			Complement of the penetrance function for the unaffected subjects $1 - f_B(G_1, G_2)$		
	G_2	G_1			G_1			G_1		
		a/a	A/a	A/A	a/a	A/a	A/A	a/a	A/a	A/A
D10S245-	a/a	0	0	0	0	0	0.1	1	1	0.9
D8S1110	A/a	0	0	0.9	0	0	0.00001	1	1	0.09999
(MPe-BPn)	A/A	0	0	0.9	0	0	0.00001	1	1	0.09999
D3S2418-	a/a	0	0	0	0.0365	0.7365	0.7365	0.9635	0.2635	0.2635
D8S1110	A/a	0	0.7	0.7	0.0365	0.03651	0.03651	0.9635	0.26349	0.26349
(MPe-SZe)	A/A	0	0.7	0.7	0.0365	0.03651	0.03651	0.9635	0.26349	0.26349

G_1 : Genotype at locus 1, G_2 : Genotype at locus 2.