

Identification of Candidate Genes that Control Differences in HPNS Seizure Susceptibility

Dale McCall*, James Blum, Dargan Frierson****
Departments of Anthropology*, Mathematics & Statistics**



Figure 1

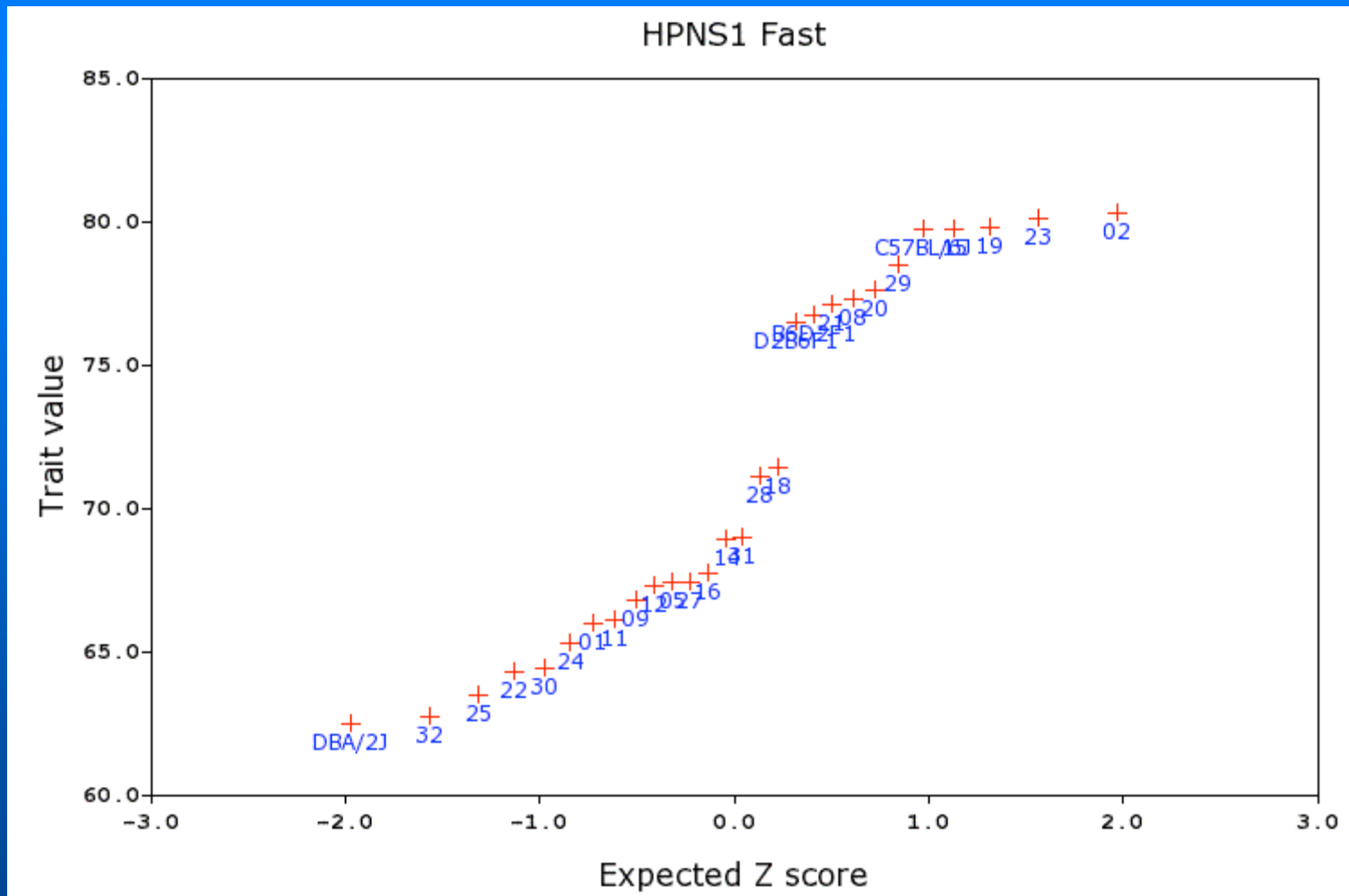


Figure 2

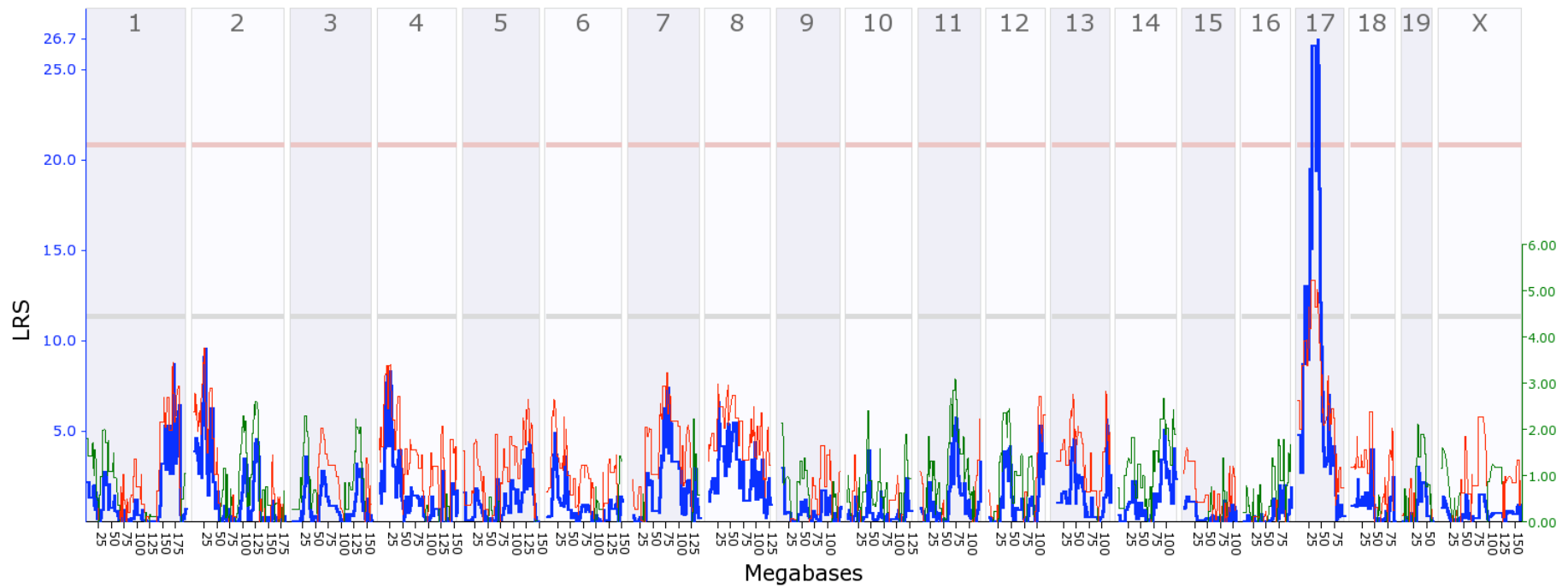


Figure 3



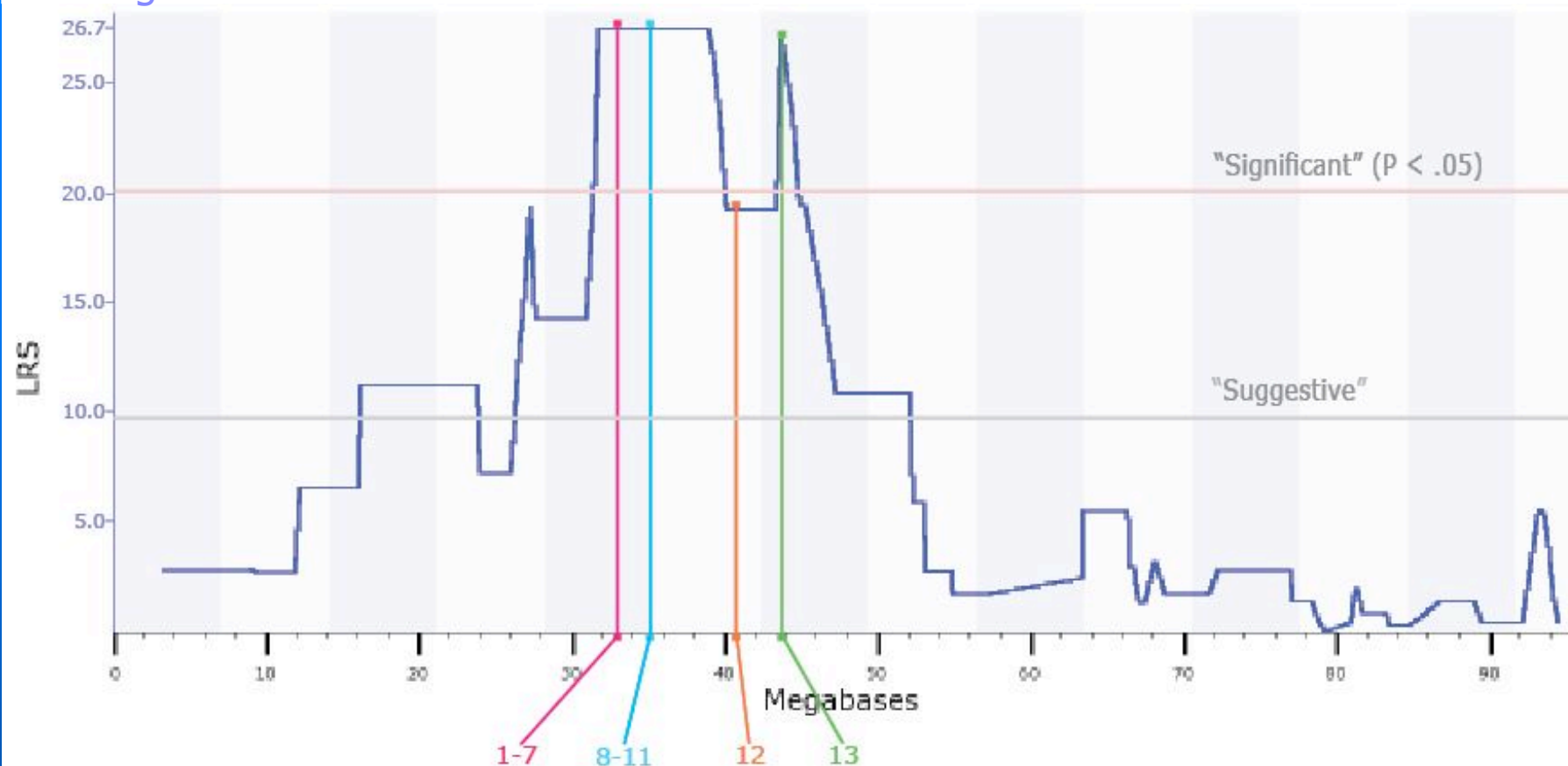
Figure 4



LRS (LOD)	SNP Locus	Gene	Probe Set	Chr 17 position (Mb)
26.384 (5.723)	rs13482963 rs6395893	Vps52	1447894_x_at	33.577317
		Ring1	1422647_at	33.631601
		H2-Ke6	1454987_a_at	33.636502
		-DMb1	1449580_s_at	33.759289
		-Ab1	1451721_a_at	33.87553
		-Aa	1452431_s_at	33.891537
		Flot1	1448559_at	35.438721
26.384	rs3672987 rs13482958 gnf17.035.152 mCV22965443 rs13482963	H2-K1	1425336_x_at	34.875152
		-T24	1422160_at	35.61401
		-T23	1449556_at	35.71728
26.384	rs6242153 rs13482948	H2-T17	1449875_s_at	35.646496
26.732 (5.799)	rs13482998 rs3677240	Enpp5	1425702_a_at	43.548812

Figure 5

Chromosome 17

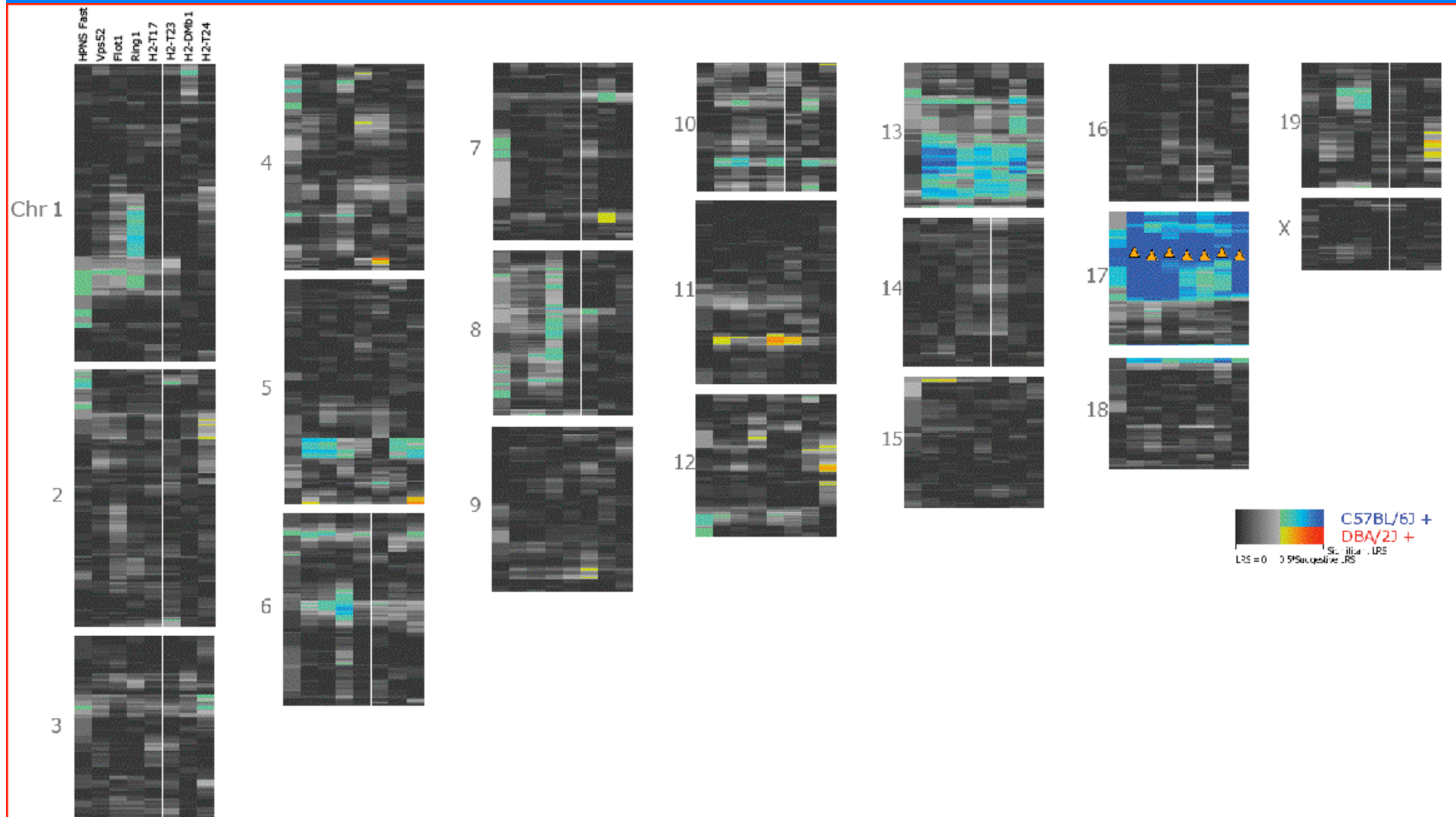


	Gene Symbol	Gene Name	Position Chr 17 (Mb)	Gene Length (Kb)	BXD SNP			
					Density (SNP/Kb)	Count	Non-redundant	Informative
1	Vps52	vacuolar sorting protein 52	33.566266	11.399	2.775	31	30	8
2	H2-K1	K1, K region	33.606474	4.237	0.003	11	2	1
3	Ring1	ring finger protein 1	33.631538	3.557	3.374	12	5	0
4	H2-Ke6	K region expressed gene 6	33.636488	2.118	2.470	5	4	1
5	H2-DMb1	class II, locus Mb1	33.746125	14.580	3.018	44	44	0
6	H2-Ab1	class II antigen A, beta 1	33.871432	6.153	0.486	3	3	2
7	H2-Aa	class II antigen, alpha	33.891095	5.020	7.570	38	38	12
8	Flot1	flotillin 1	35.431400	9.434	1.378	13	8	0
9	H2-T24	T region, locus 24	35.614707	13.857	0.000	0	0	0
10	H2-T23	T region, locus 23	35.638029	2.723	0.733	2	2	1
11	H2-T17	T region, locus 17	35.646496	4.275	0.001	3	3	1
12	Mut	methylmalonyl-coenzyme A mutase	40.398191	24.606	0.691	17	0	0
13	Enpp5	ectonucleotide pyrophosphatase/ phosphodiesterase 5	43.541924	7.769	0.910	7	5	2
Total						178	154	28

Figure 6



Figure 7



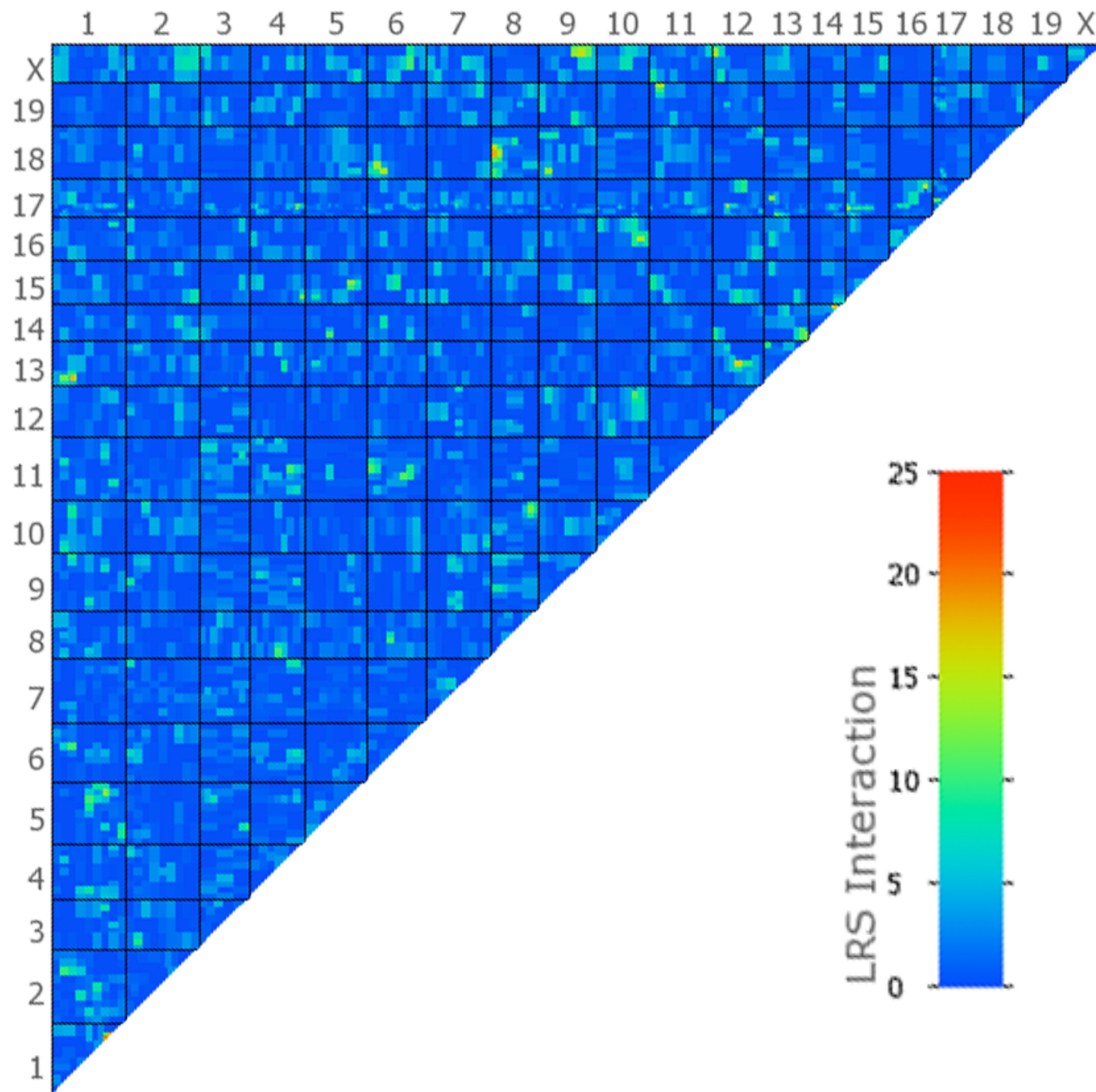


Figure 8

CONCLUSIONS:

- 1 – Heritable difference in susceptibility to the HPNS seizure under fast compression in heliox among BXD mouse strains is associated with a QTL on Chr 17.
- 2 - The QTL is located in a ~12 Mb region (31.5 - 43.5 Mb) that contains about 180 positional candidate genes. Congruent expression of genes in the QTL region and genes in the hippocampus of BXD mice reduces the number of candidate genes to 13, human homologues of which localize to a region of human chromosome 6.
- 3 - The region containing the QTL appears on the basis of SNP analysis to be strongly conserved. Only 2 of the candidate genes (Vps52 and H2-Aa) may be sufficiently polymorphic for parental B6 and D2 alleles to be associated with seizure threshold differences.
- 4 - Vps52 and H2-Aa appear to be cisQTLs, meaning that each is closely linked to the gene whose transcript is the measured trait.
- 5 - Vps52 may be a high priority candidate in respect of strength of correlation with the HPNS Fast trait and activity profile of genes in the hippocampus of BXD strains.

Caveat: These conclusions must be viewed as preliminary owing to the relatively small size of the sample of BXD strains for which HPNS seizure threshold data exist presently.