Genome wide linkage studies identifies a novel locus for syringomyelia associated with Chiari-like malformation in the Cavalier King Charles Spaniels

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A multi-staged genome wide two-point non-parametric linkage scan for syringomyelia in LODPAL identified a locus with LOD=3.07 in our canine pedigrees. This locus was then fine-mapped by dense SNP association and haplotype analyses. One marker shows mild association for the disease (*P* value of 1.0×10^{-4}). Haplotype analysis indicates one specific 10-SNP haplotype strongly associated to unaffected dogs (*P* value = 5.35×10^{-10}). This 10-SNP window contains one validated gene with strong biological plausibility. Gene sequencing and additional fine-mapping with genetically related affected breeds are currently under way.

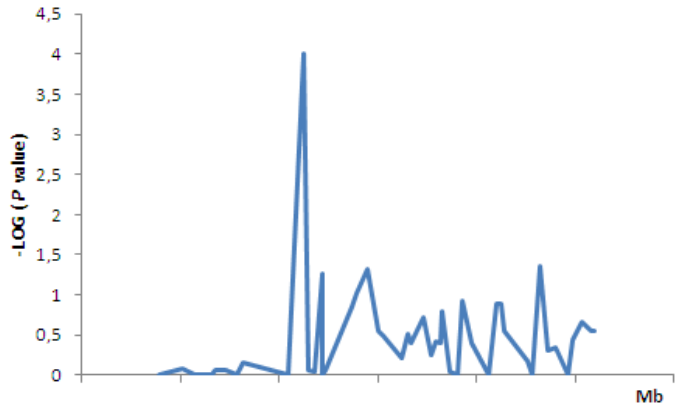
Linkage Results

3 analysis stages after two point non-parametric analysis in LODPAL from SAGE 5.20

Scan	Markers and cohorts	ARP/DSP/CUSP
Genome wide	247 microsatellites 8.47 cM density 121 pairs	6 regions with LOD > 1
1st fine-mapping	57 ***new*** microsatellites 2.38 cM density 199 pairs	1 region with LOD > 3 4 regions with LOD > 1
2nd fine-mapping and validation	15 ***total*** microsatellites 0.63 cM density 297 pairs	***LOD = 3.07***

Association Results

Below is a plot of *P* values of single marker analysis of validated SM region in PLINK v1.07 after clustering and the cluster-specific Cochran-Maenztel-Hantel test with 10,000 permutations



LD in fine-mapping has identified one haplotype from Block 1 (in blue) contains Marker 1 and shows a very significant *P* value in Haploview after 10,000 permutations.

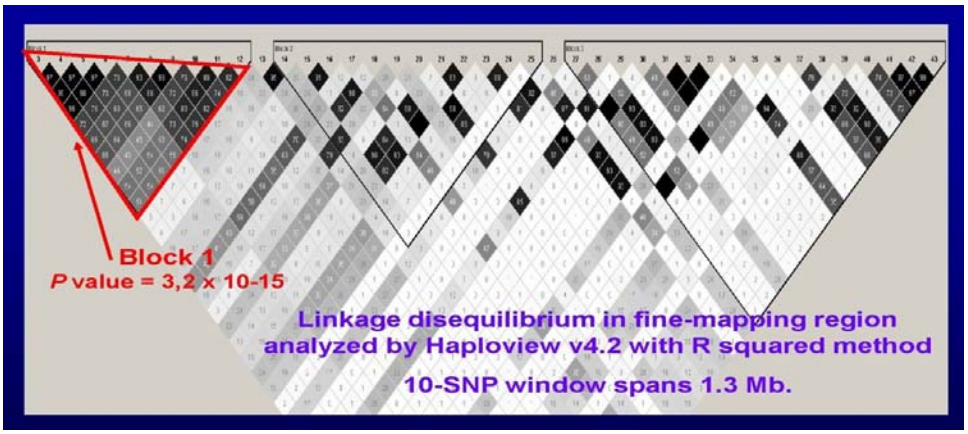


Table below shows the most frequent haplotypes of Block 1 reconstructed by PHASE v2.1.1 with its increased accuracy and its possibility to impute missing genotypes (in blue is the most significant haplotype)

Haplotype	Cohort freq (n=566)	Affected freq (n=442)	Unaff. freq (n=124)	*P* value
TCGAACTTGG	58.1%	58.4%	57.3%	0.82
GTAGGACCAT	27.2%	28.5%	22.6%	0.19
TTAGGCTTGG	6.0%	6.1%	5.6%	0.85
GTAGGACCGT	2.3%	0.2%	9.7%	$5{,}35 \times 10^{-10}$
GTAGGATTGG	1.8%	1.8%	1.6%	0.88

Current Steps

1. Wider dense SNP coverage
2. Candidate gene sequencing