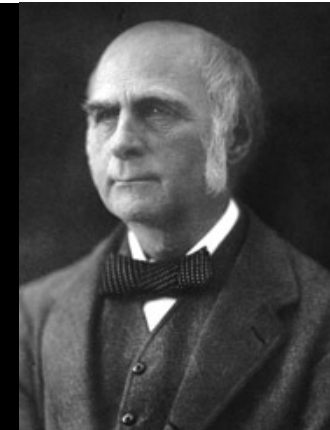




GOAL: understand the genetic underpinnings of Behavior



Genes that are necessary for:  
**Single Gene**

Genes that Contribute to:  
**Quantitative or many genes**

Historic figure

Galton

Mendel  
identify dominant & recessive  
identify single genes  
define mechanisms

define Genomic Architecture  
(#, location, interaction, specificity, linkage)  
quantify variation in a population  
describe change in gene frequency

Immediate goals

Sever disruptions  
Lab induced (white coat)

Raw Materials used

Subtle variation  
Naturally occurring (rubber boot)

Tools used

Bottom Up  
Forward  
Phenotype >>> Gene  
mutagenesis/screening  
transgenesis

Top Down (= Forward)  
Observational  
Comparative Genomics  
Association mapping (GWAS)  
Experimental  
artificial selection  
crossing (artificial or natural population)  
QTL mapping  
Recombinant inbred lines  
Association Studies

Reverse  
Gene >>> Phenotype  
Knockout  
RNAi

Type of Result

Essential genes of behavior  
(newer techniques are more subtle)

Genes that Contribute to Behavior  
Factors, epistasis, GXE, probability



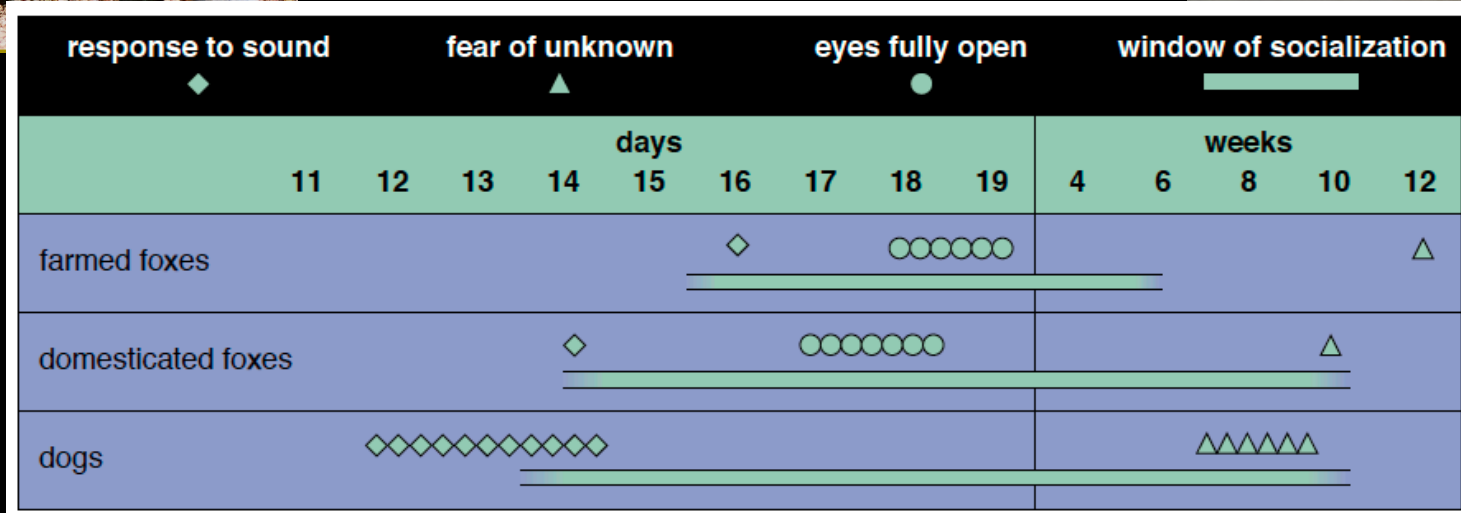
Dmitry K. Belyaev, Inst. Of Cytology and Genetics 1950s



appearance of dwarf and giant varieties	all
piebald coat color	all
wavy or curly hair	sheep, poodles, donkeys, horses, pigs goats, mice, guinea pigs
rolled tails	dogs, pigs
shortened tails, fewer vertebrae	dogs, cats, sheep
floppy ears	dogs, cats, pigs, horses, sheep, goats, cattle
changes in reproductive cycle	all except sheep



Dmitry K. Belyaev, Inst. Of Cytology and Genetics 1950s



Dmitry K. Belyaev, Inst. Of Cytology and Genetics 1950s

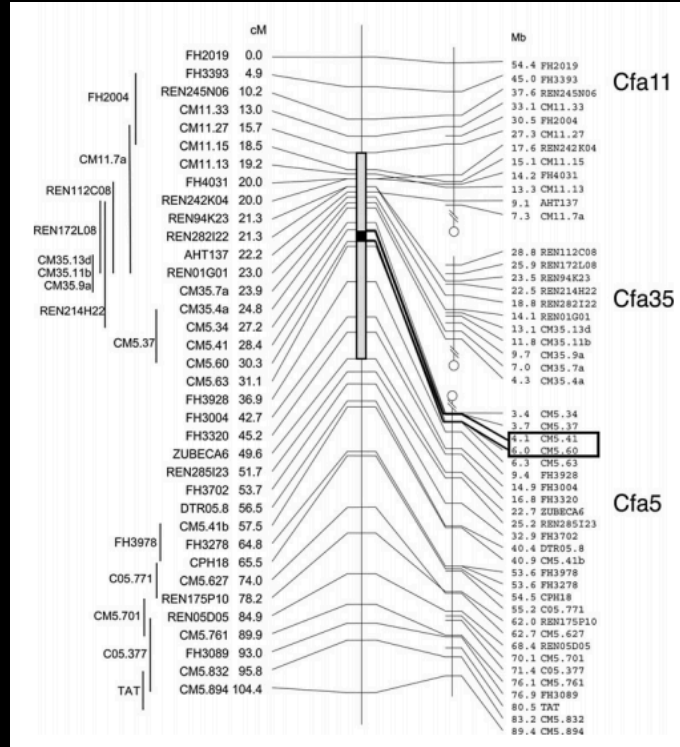


F

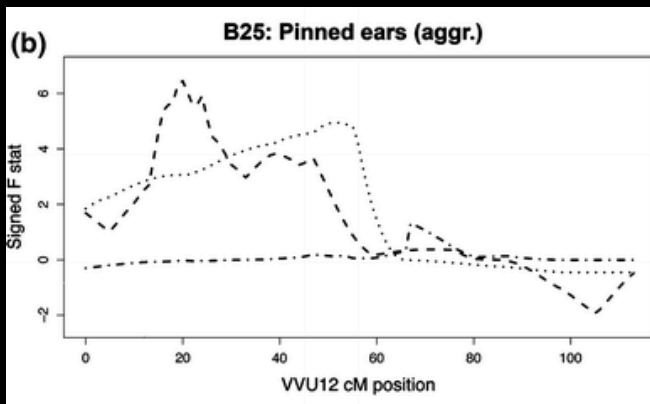
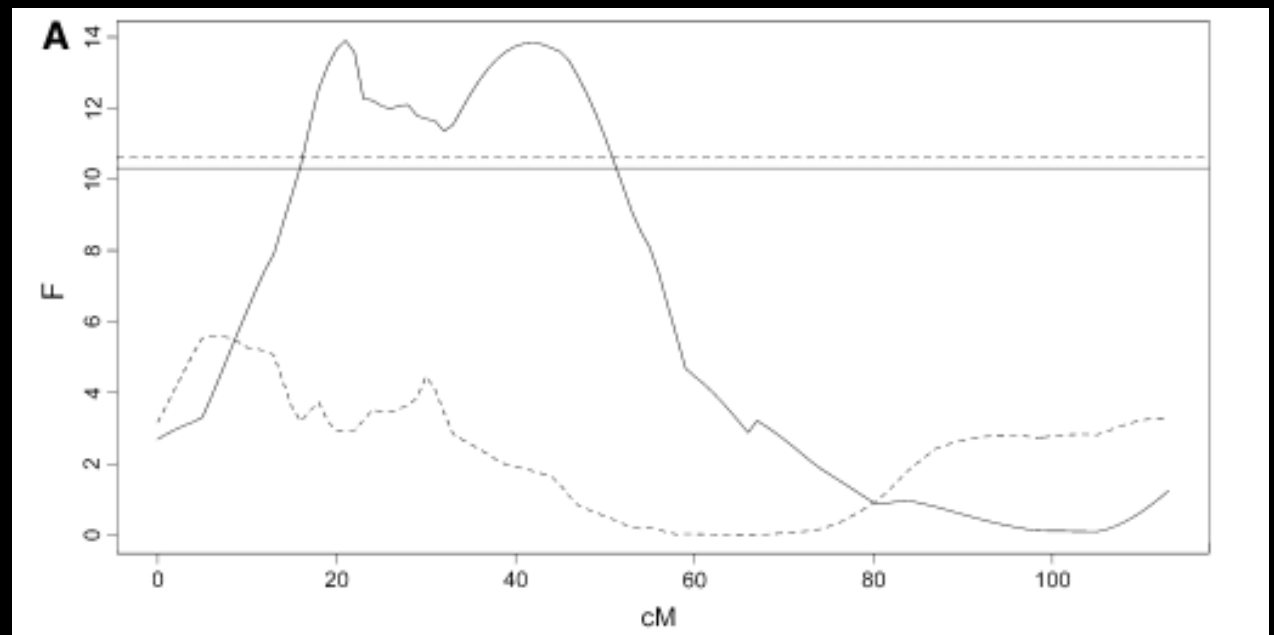
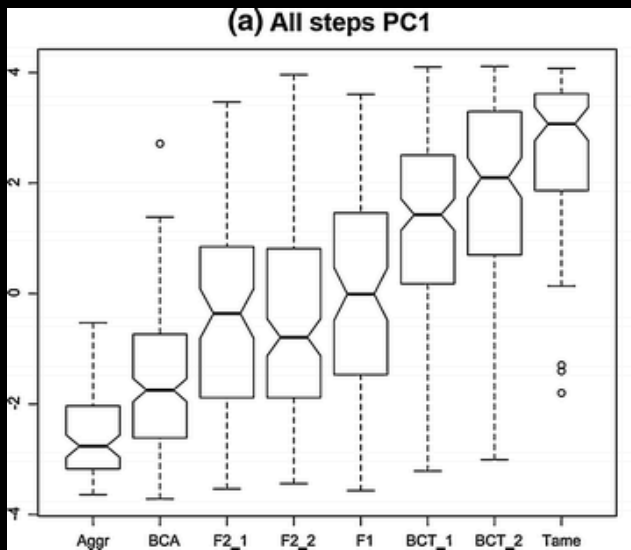


# Fox Genetic Markers

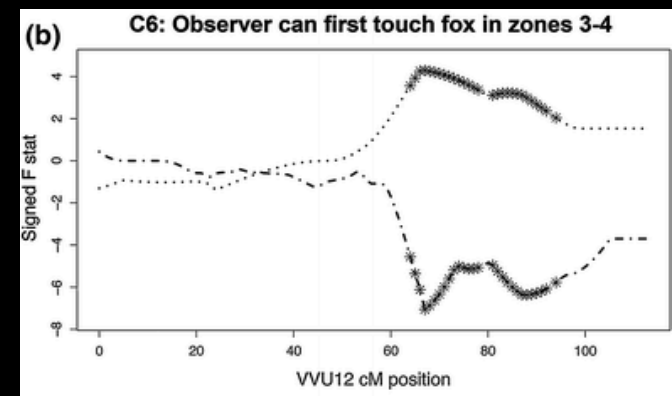
# Canine Genetic Markers



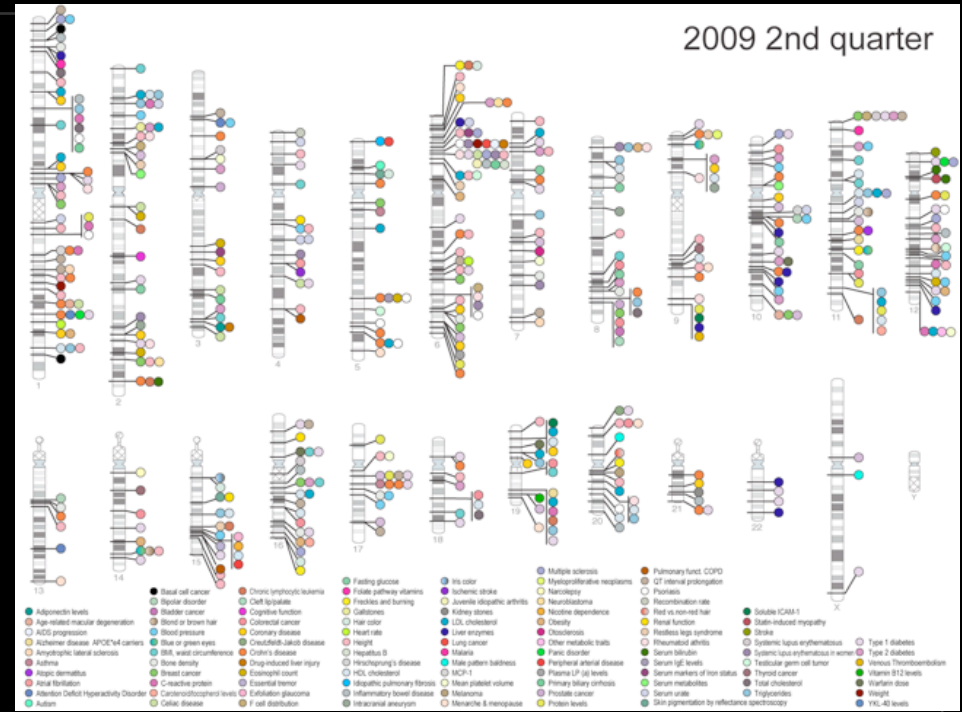
Kukekova Lab  
Univ. Illinois



↑ Aggressive  
↓ tameness



# GWAS (WGAS)

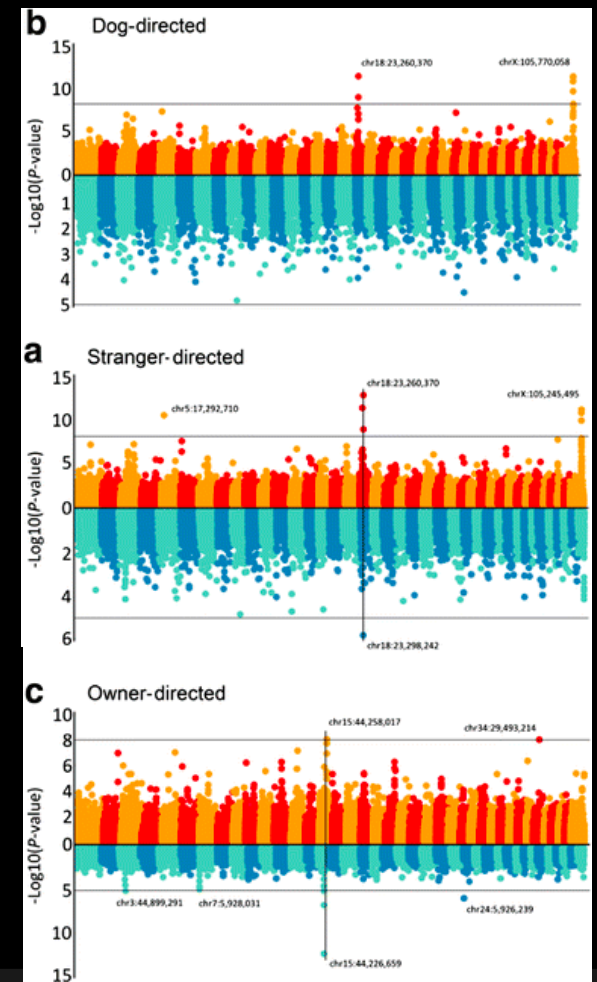
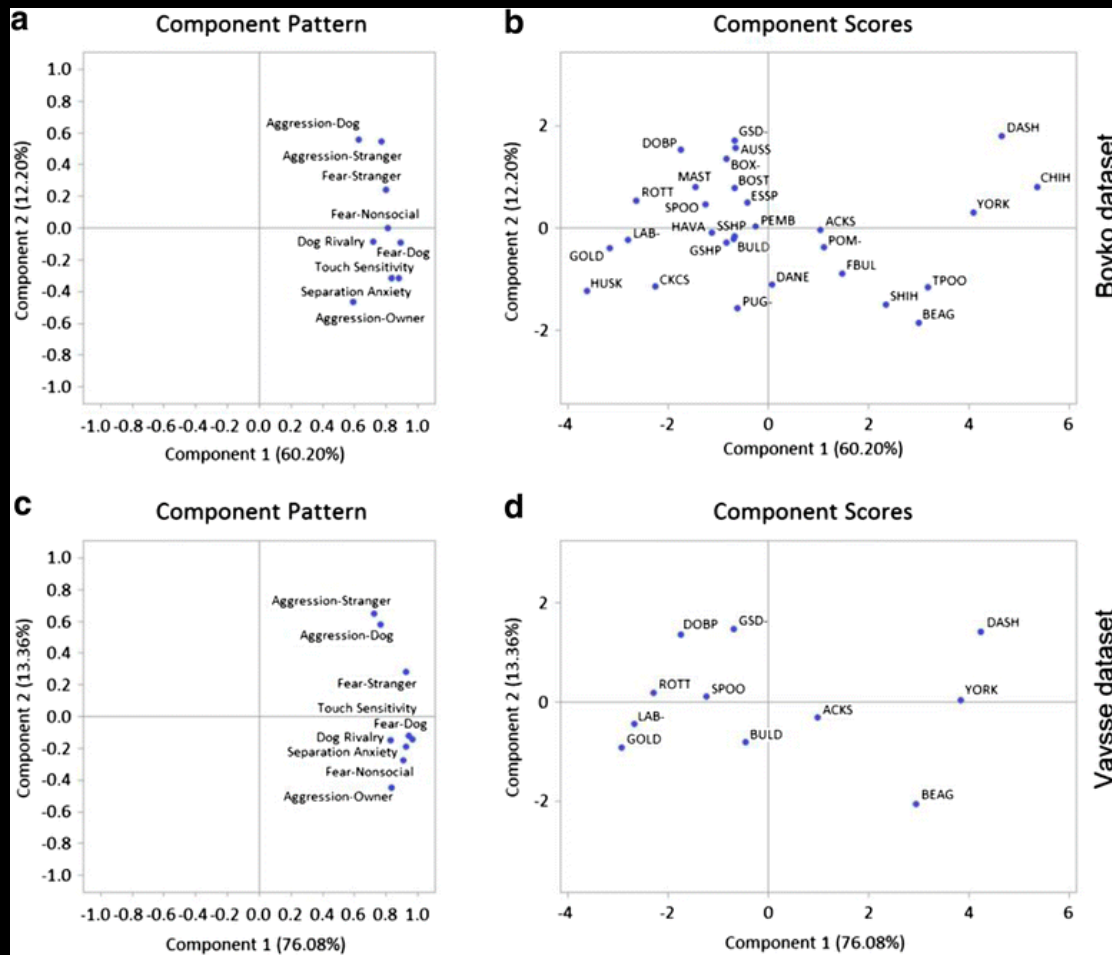


## Single Nucleotide Polymorphisms : SNPs

Requires extensive knowledge of SNPs

Requires many individuals to reach statistical significance

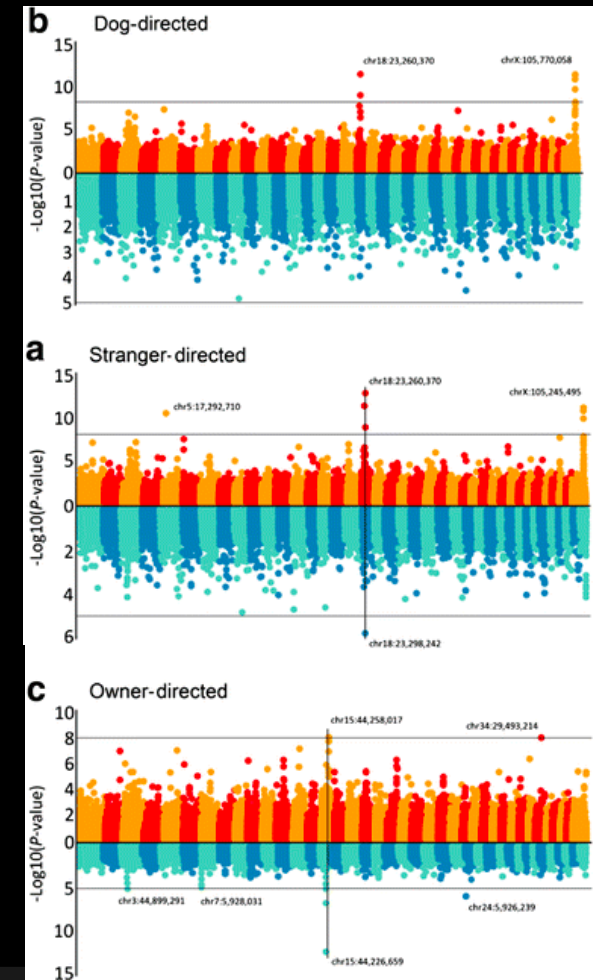
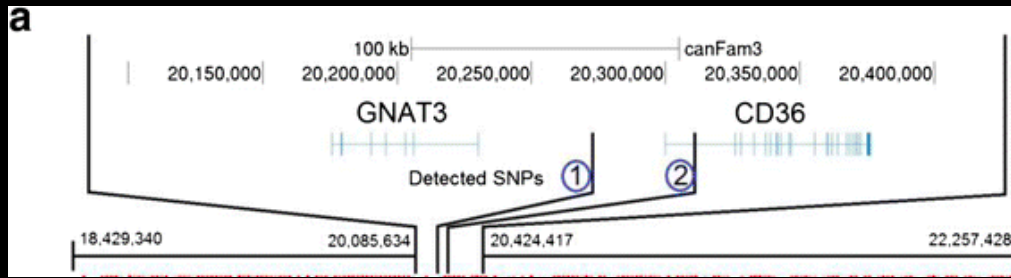
Works best with common variants, not rare ones.



# Genetic mapping of canine fear and aggression

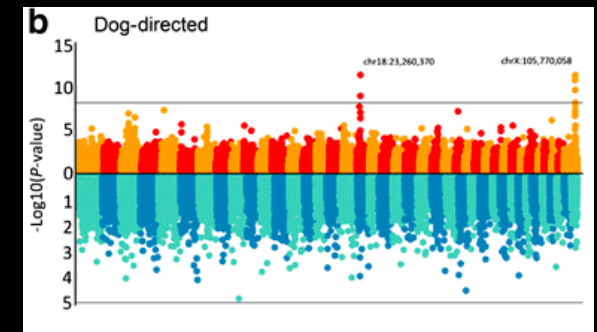
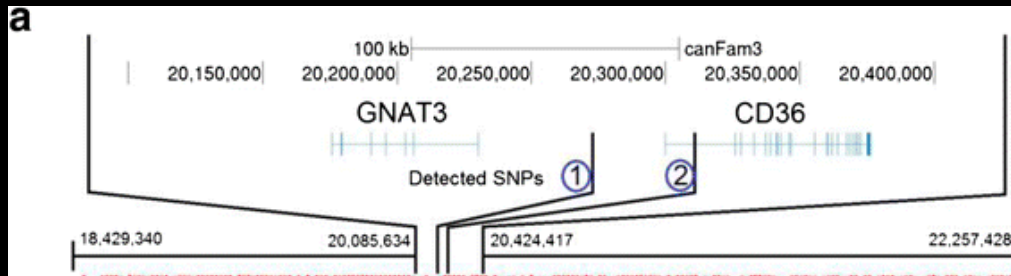
Isain Zapata, James A. Serpell and Carlos E. Alvarez ✉





# Genetic mapping of canine fear and aggression

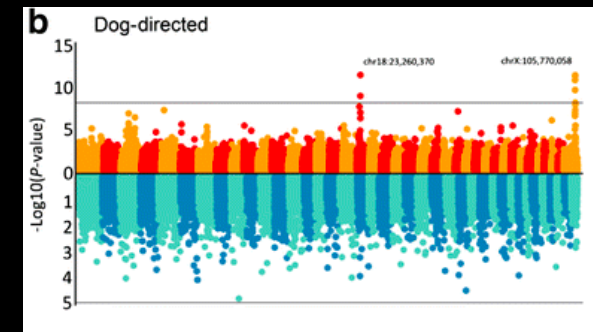
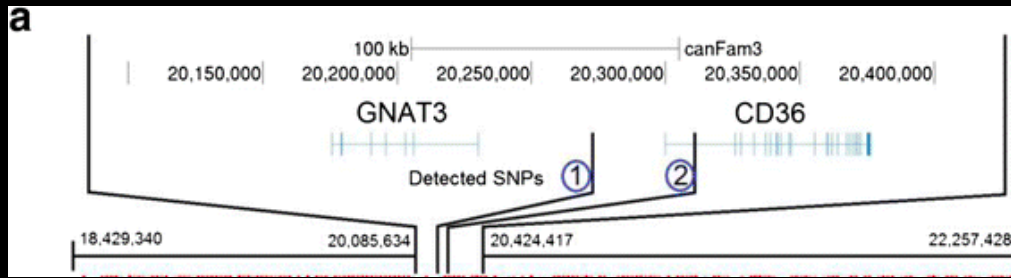
Isain Zapata, James A. Serpell and Carlos E. Alvarez ✉



*GNAT3* encodes Gustducin alpha, the G alpha subunit that transduces taste receptor signaling. Gustducin alpha also has chemosensory roles in the vomeronasal organ, airways and gastrointestinal tract [41, 42]. There are also reports that *GNAT3* is expressed in areas of the brain that include the brainstem, hypothalamus and hippocampus [43, 44, 45]. However, those studies targeted specific brain regions and we are not aware of systematic analysis of the entire brain in any mammal. We consulted the Allen Brain Atlas of *in situ* mRNA hybridization analysis [46] and found evidence that *GNAT3* is most highly expressed in the amygdala in the adult mouse, specifically in layer 2 of the Cortical Amigdalal Area (Additional file 2: Figure S2). That finding is supported by analysis of public gene expression data showing that the highest ranked expression-change of *Gnat3* mRNA in any brain region is a 3.73-fold increase in the amygdala of rats 6 h after pain exposure... the Allen Brain Atlas of the adult mouse reveals lower levels of expression in parts of the pons: Lateral reticular nucleus, Paragigantocellular reticular nucleus, lateral part, and the Facial motor nucleus

## Genetic mapping of canine fear and aggression

Isain Zapata, James A. Serpell and Carlos E. Alvarez ✉

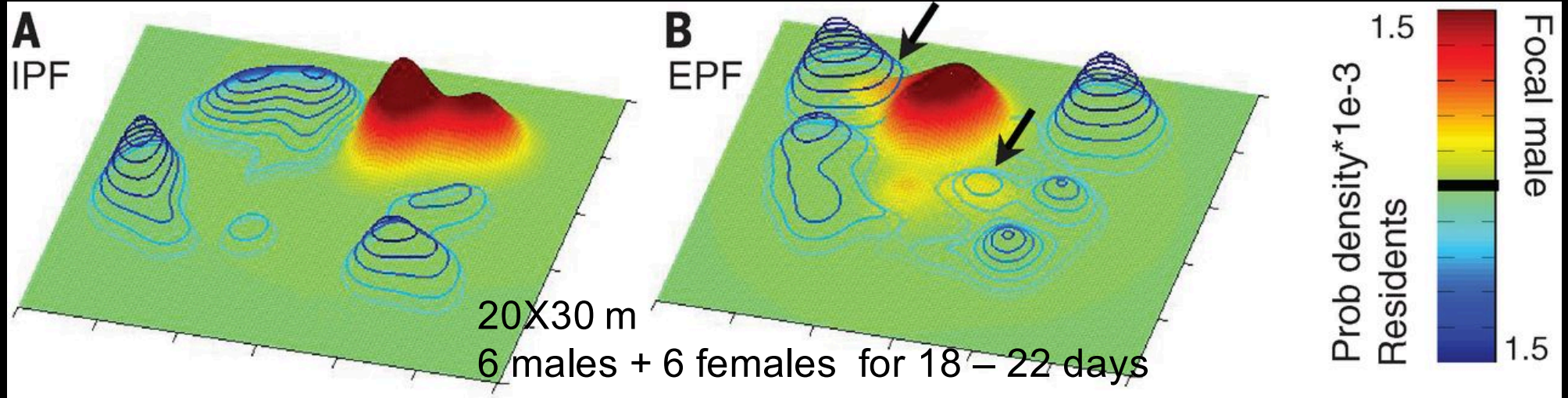


CD36 is an enigmatic protein known to be widely expressed and to have varied biological roles [49]. Its functions include chemosensory sensing and signaling (including in taste, pheromone and airway sensing), sensing and transport of fatty acids in diverse metabolic roles, high affinity binding and signaling of several molecules (including collagen and thrombospondin), and it is a subunit of cell surface scavenger receptors involved in phagocytosis. In the brain, the highest levels of *CD36* mRNA have been mapped to the Cortex-amygdala transition zone, Medial amygdaloid nucleus, posterior part, hypothalamic Premammillary nucleus, ventral part and and ependymal cells of the Central canal and Fourth ventricle; and high levels are also present in the Piriform cortex, Perirhinal cortex, Field CA1 of hippocampus, ventral, pyramidal cell layer, Basolateral amygdaloid nucleus, posterior part, Amygdalopiriform transition area, and Paraventricular thalamic nucleus, anterior [49]. Recent studies showed that *CD36*<sup>-/-</sup> mice have behavioral phenotypes that include increased anxiety, aggression and locomotor activity [50].

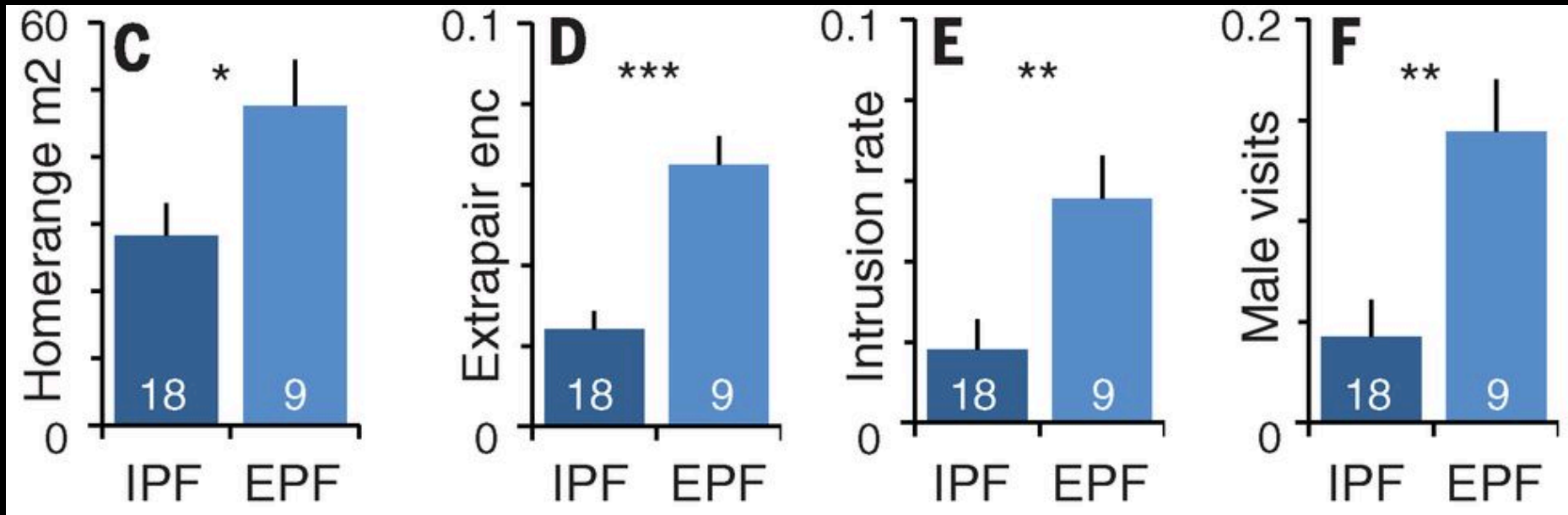
## Genetic mapping of canine fear and aggression

Isain Zapata, James A. Serpell and Carlos E. Alvarez ✉

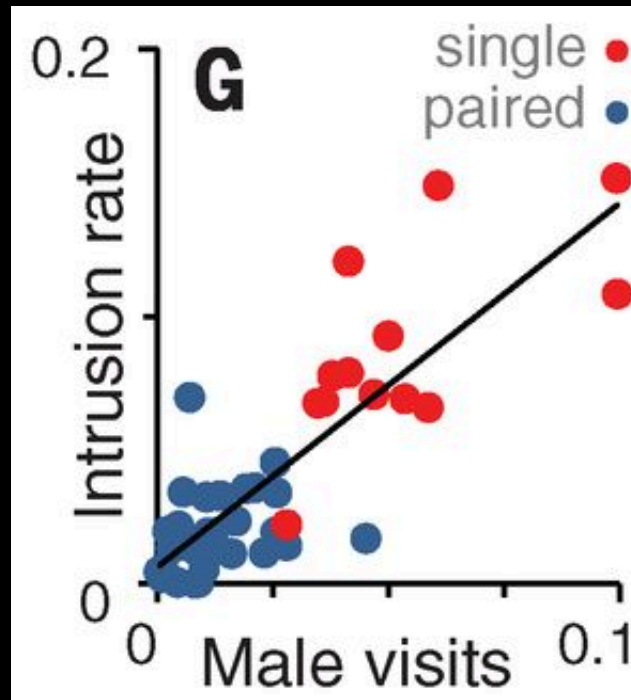




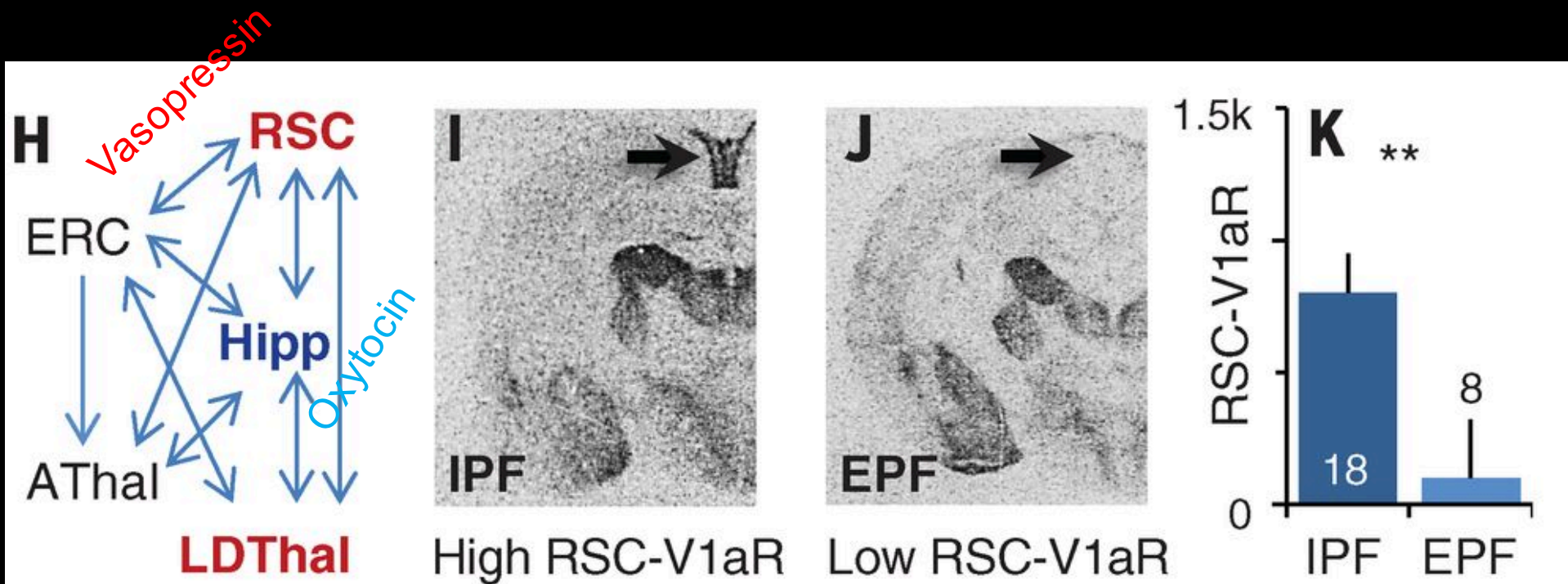
Prairie voles are socially monogamous but 25% of offspring are from EPFs. Use radio telemetry to examine the relationship between space use and sexual fidelity. Estimate how often a male encounters neighbors in own or other territory.



- EPF males have larger home ranges
- EPF males encounter females more often
- EPF males intrude on other territories more often
- EPF males are intruded on more often



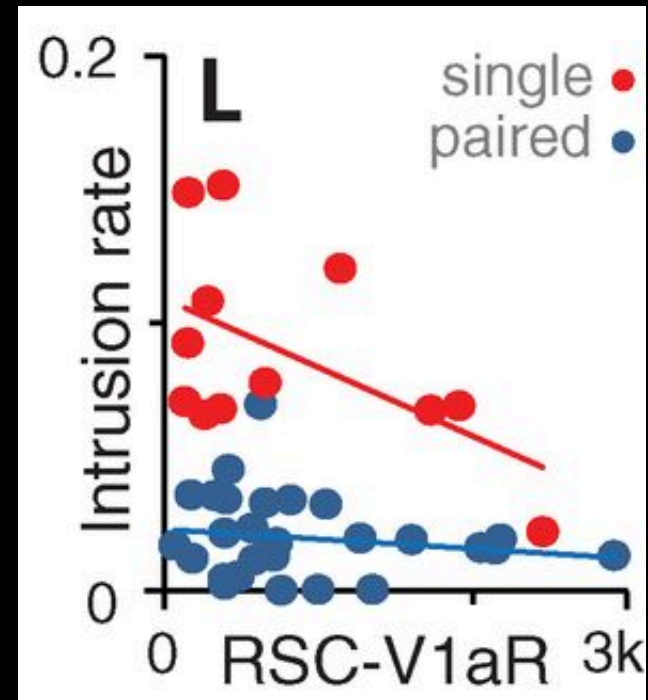
The rate at which a male intrudes on a neighbor's territory is correlated with the rate at which he encounters extra pair females, but also with the rate at which he is intruded. In other words, increasing encounter rate with females comes at the risk of being cuckolded.



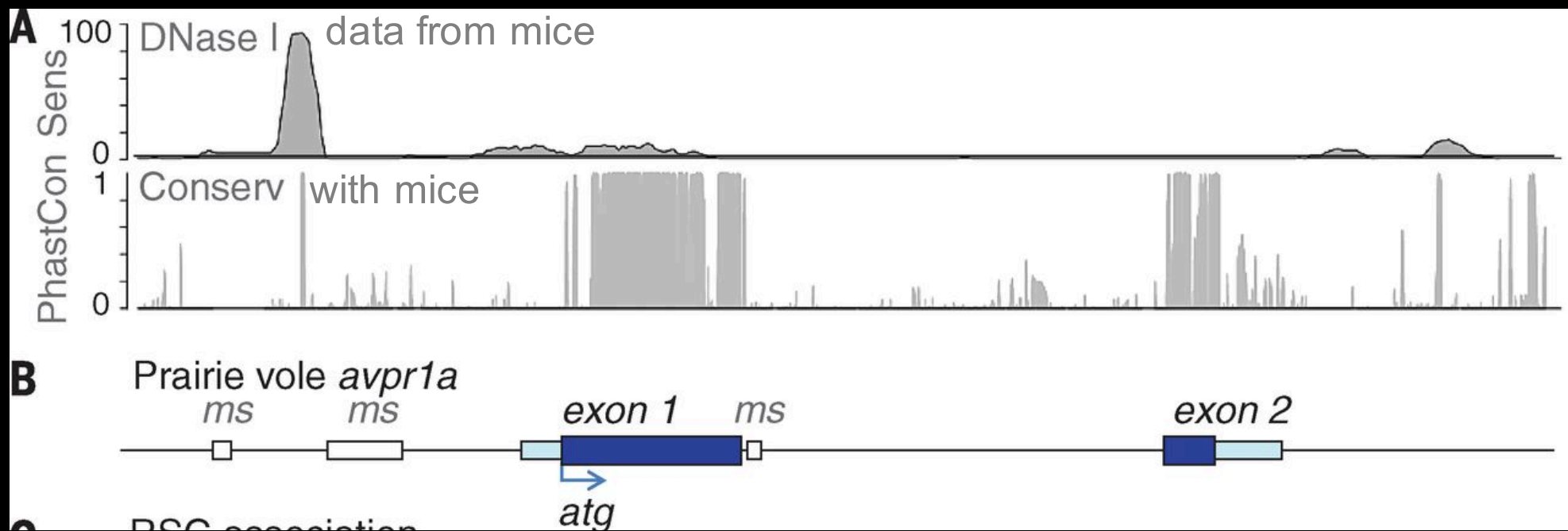
spatial memory  
 circuit

Variation in neuropeptide receptor is known in spatial memory circuit.  
 V1aR in RSC is thought to positively correlate with spatial memory.  
 By autoradiography, IPF males have higher V1aR in RSC.

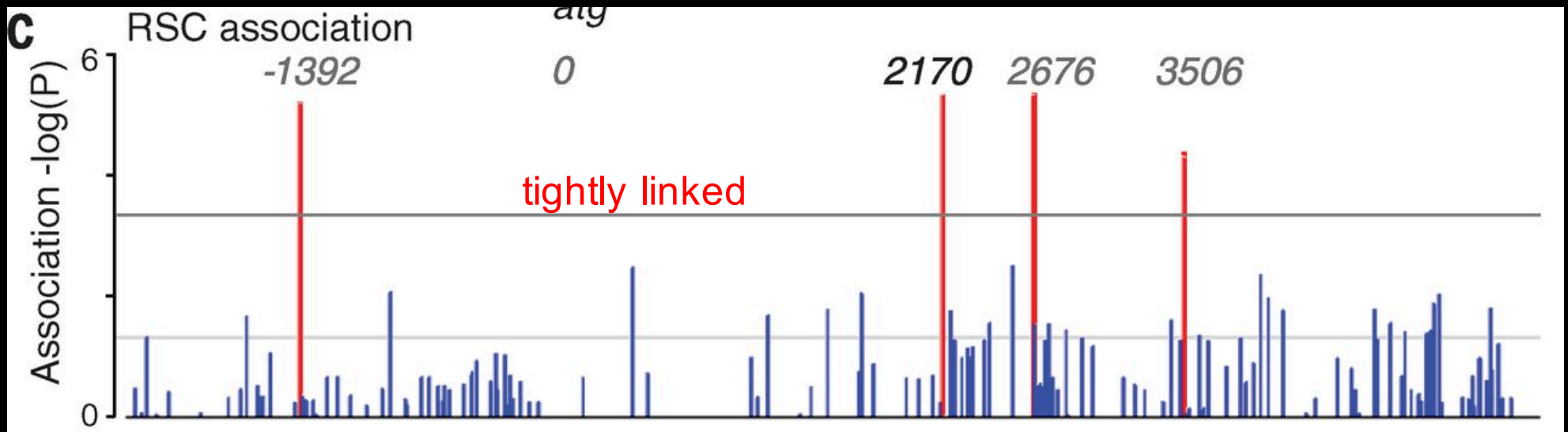




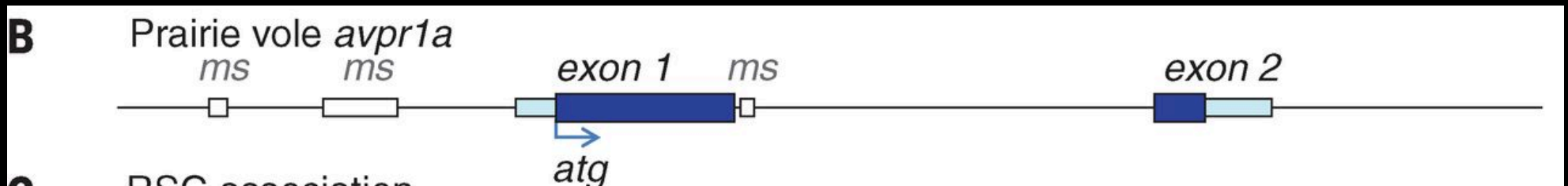
RSC-V1aR is negatively correlated with intrusion rate.  
(why don't they show EPF and IPF males differently in these plots?)  
is this "heritable"? (i.e. a genetic basis?)



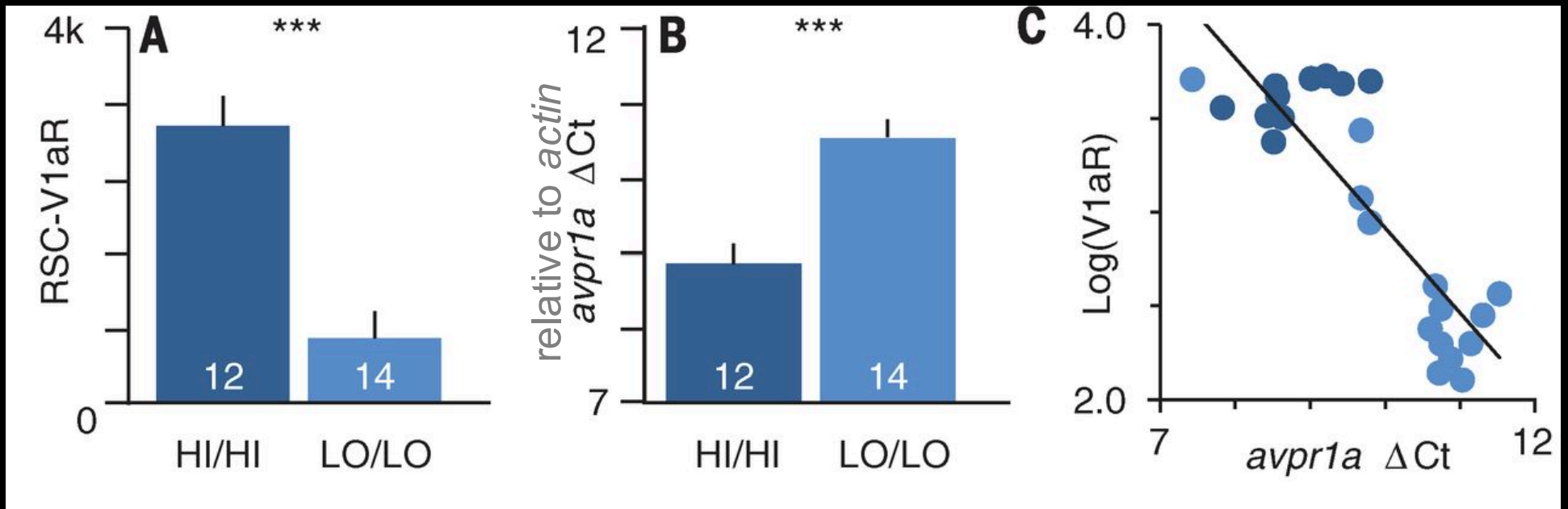
Sequenced 8kb of V1aR gene



note lab and wife samples

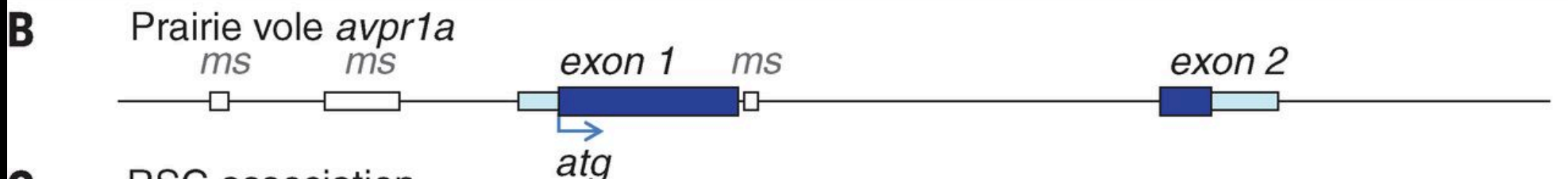
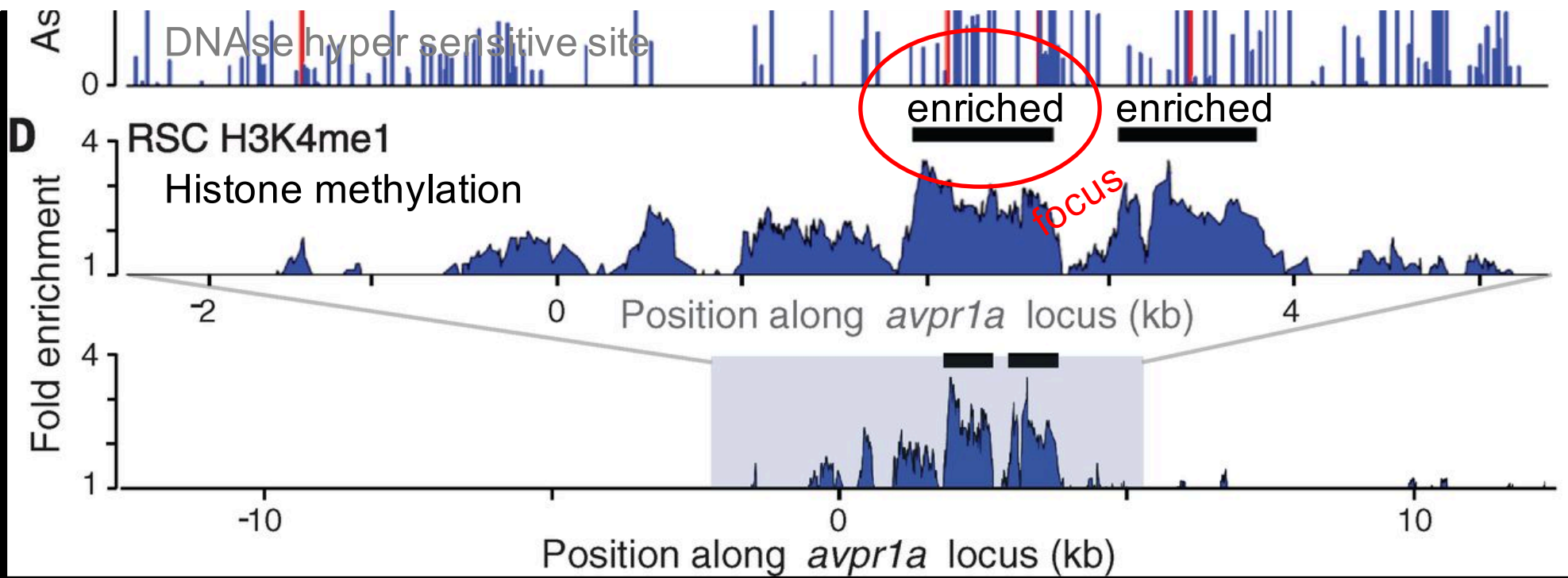


Found 151 SNPs 4 of which predict expression level in RSC.



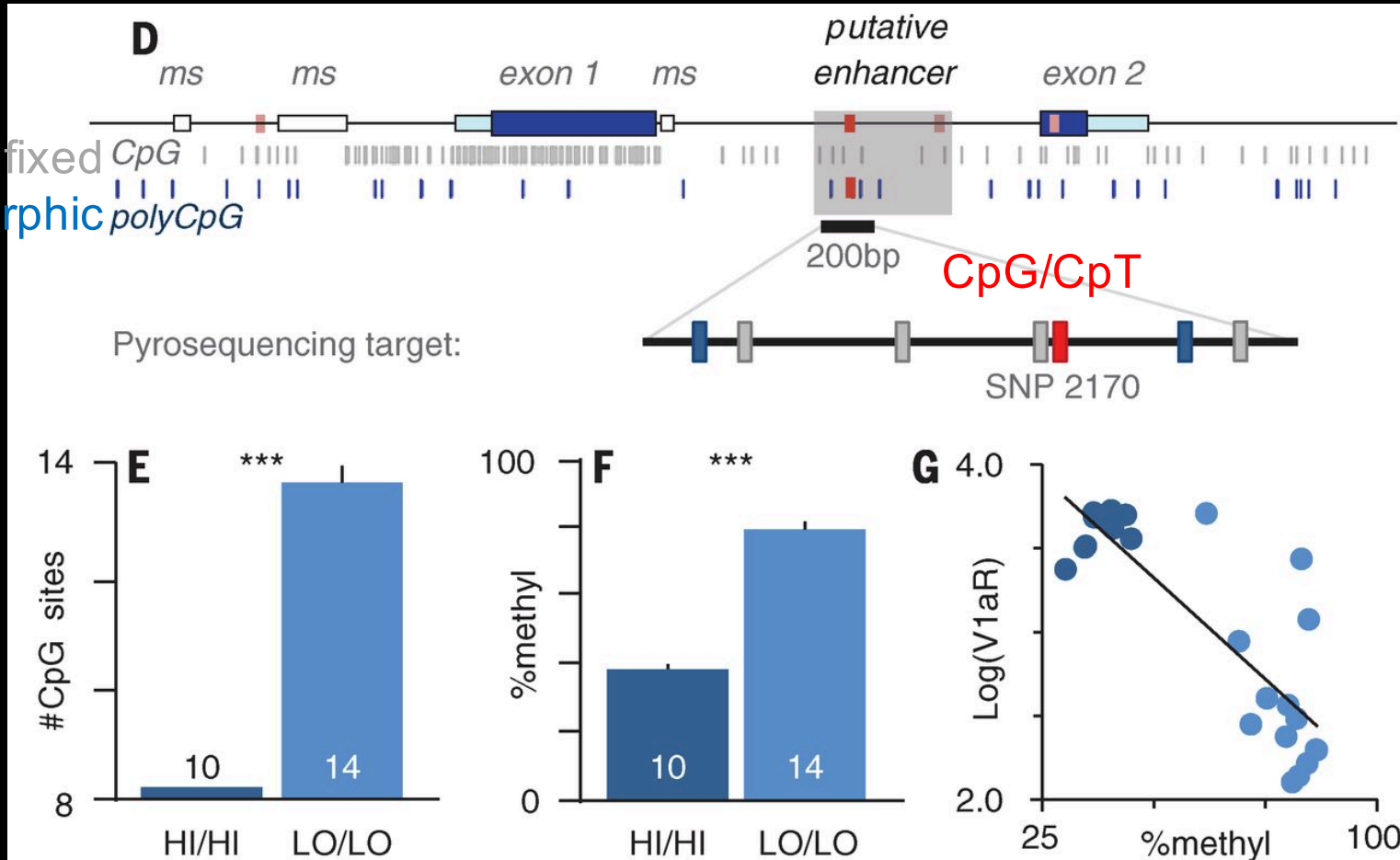
Using new animals, Hi/Lo heterozygous animals were crossed to get Hi/Hi and Lo/Lo. Hi/Hi homozygotes had higher V1aR expression in RSC by autoradiography  
 Hi/Hi homozygotes had lower Ct value for qPCR on V1aR gene expression in RSC.  
 (looks backwards cuz its delta Ct)

For the most part, there is strong correlation between qPCR results and autoradiography  
 (is this true within allele?)



ChiP sequencing of histone modification for K3K4me1 (known to mark enhancers). Retrieved sequence enriched in 2 recios

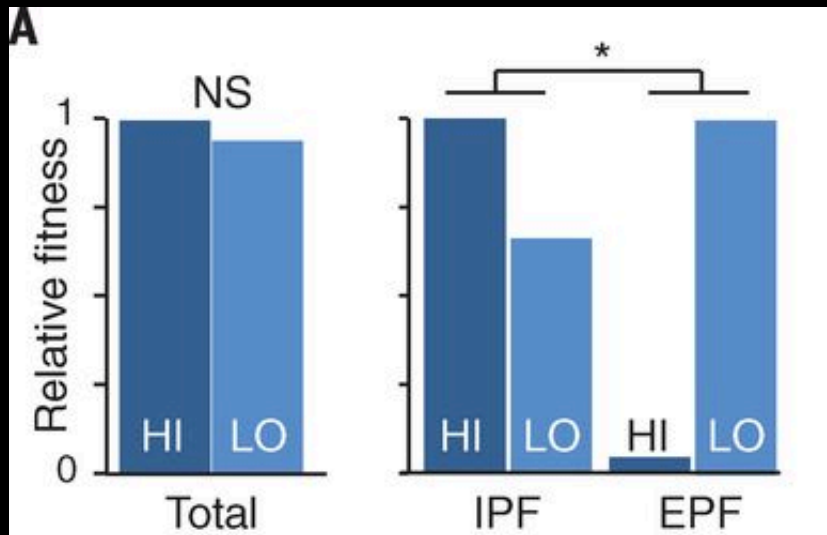
fixed  
polymorphic



Identification of CpG sites in Hi and Lo Alleles.

Hi alleles have more CpG

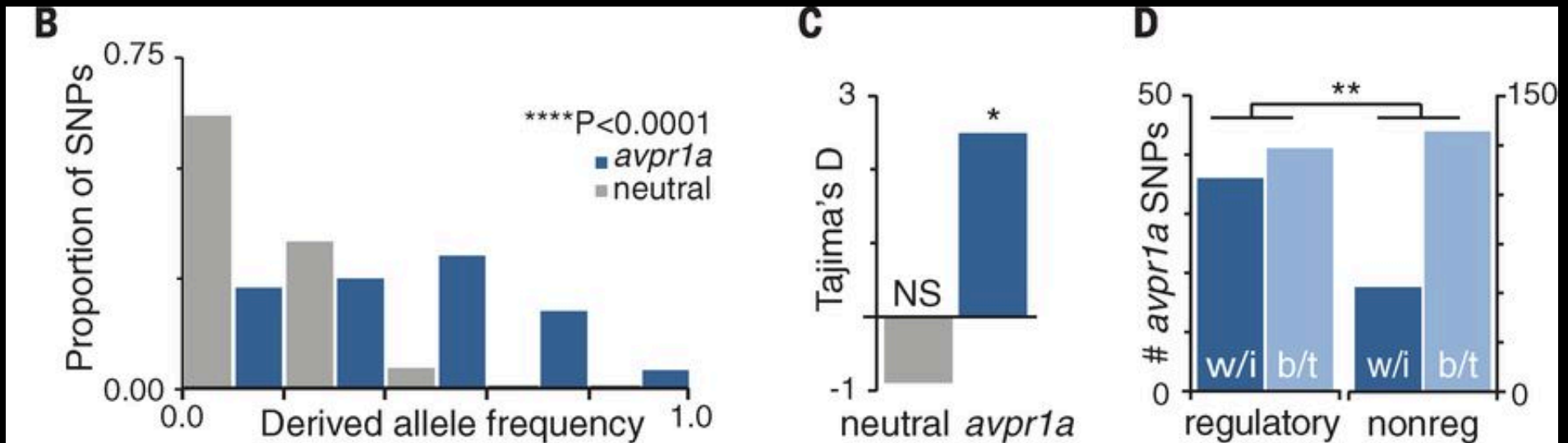
In Hi/Hi homozygotes a lower percent of the fixed CpGs were methylated



How are both alleles maintained in a population?

Hi/Hi males have higher average fitness than Lo/Los males when acting as IPF males  
 Lo/Lo males have higher average fitness than Hi/Hi males when acting as EPF males

(population density could influence this)



## Population genetics

an excess of intermediate frequency alleles for V1aR (balancing selection)

positive Tajima's D (the difference between the mean number of pairwise differences and the total number of polymorphic sites in a population)

Excess of variation (#SNPS) within regulatory region (Hudson Kreitman Guade test).



