Dogs

Dogs?

Are dogs a model organism?

What can dogs teach us?

Morphology

Behavior

on in the dog. Above are shown extreme examples of brac
o right: Pug, Japanese Chin, Brussels Griffon, French Bul


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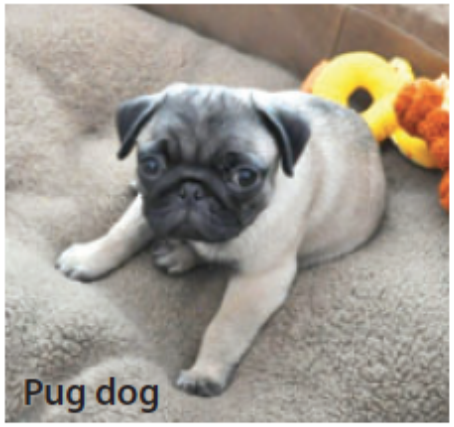
Border collie


Bernese mountain dog


Portuguese water dog


Pug dog


Foxhounds


Whippet


Alaskan sled dogs


German shorthaired pointer

What resources do we need?

Genetic map

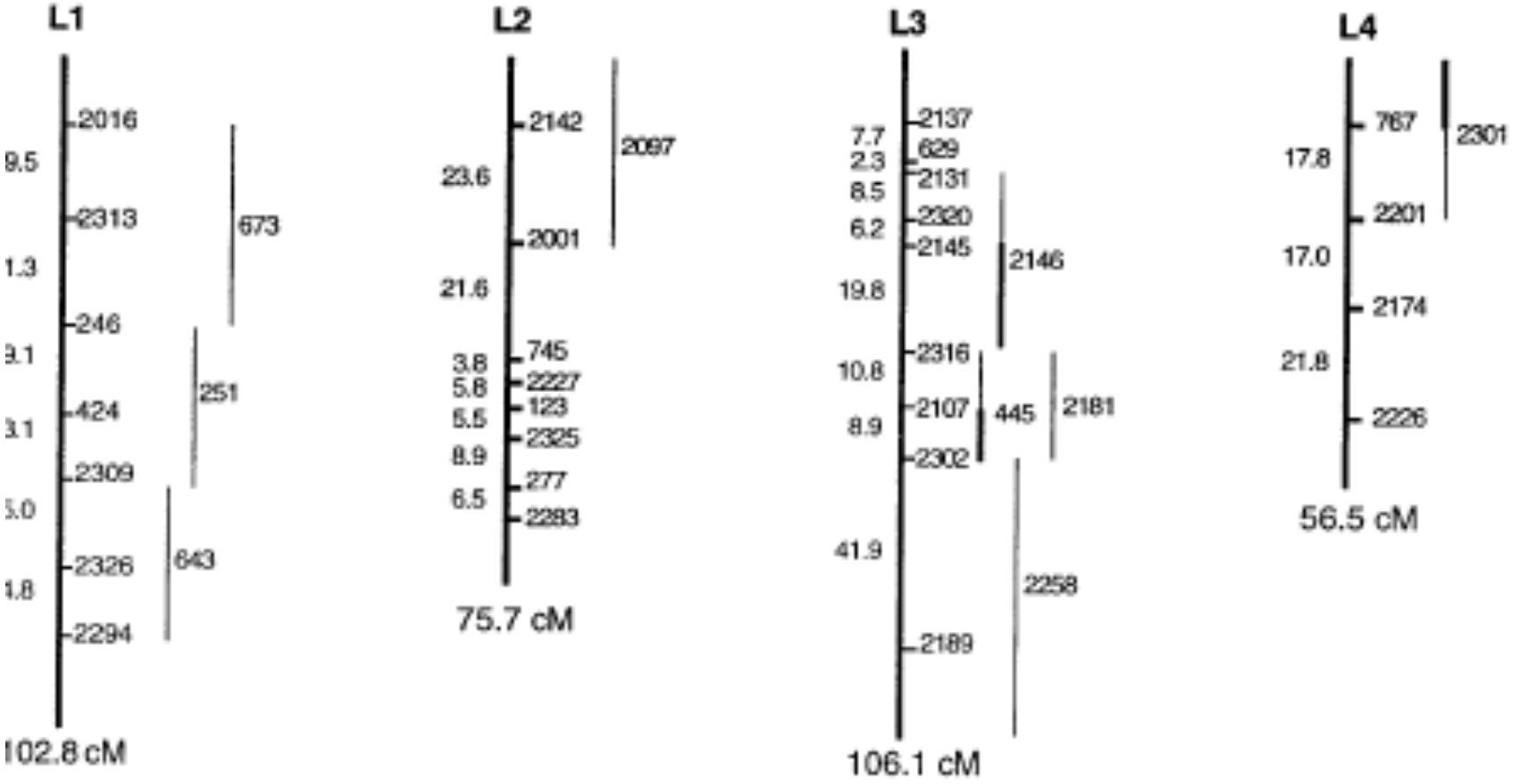
Physical map/DNA sequence

Populations with distinct phenotypes;
a segregating pedigree would be ideal

Genome-Wide Association Study (GWAS).
Look for haplotypes present in one phenotype, not the other

Dog Genetic Map

Based solely on polymorphic markers [eg, (CA)n repeats]



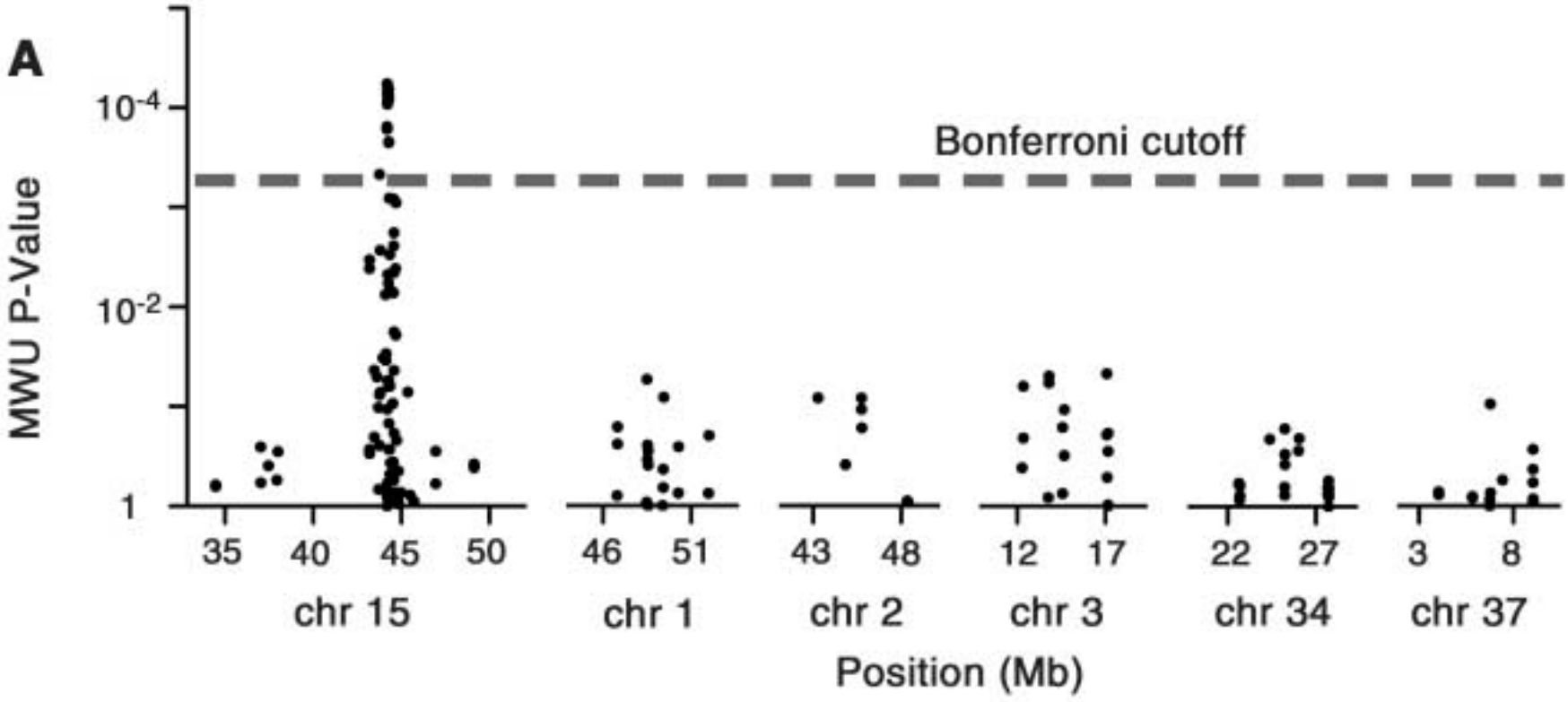
29 linkage groups plus X chromosome

Size variation

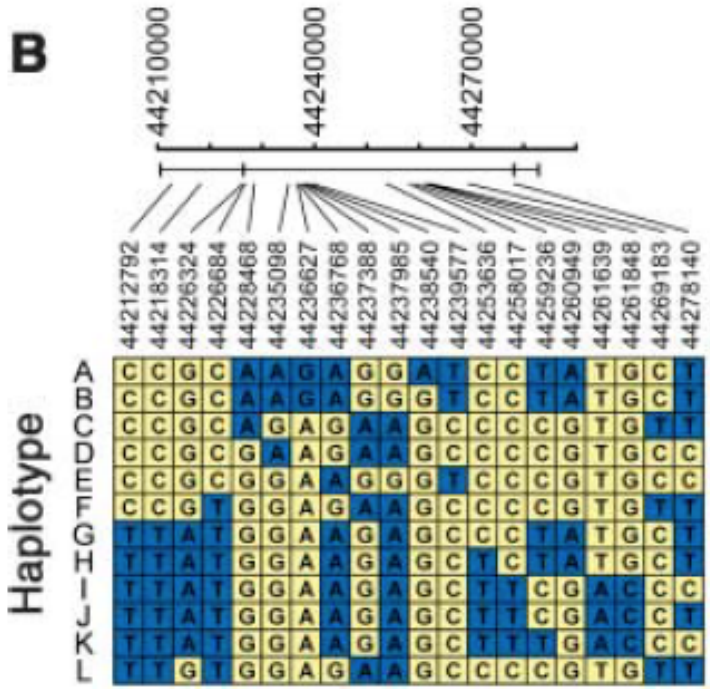
30-fold difference in mass between these two breeds

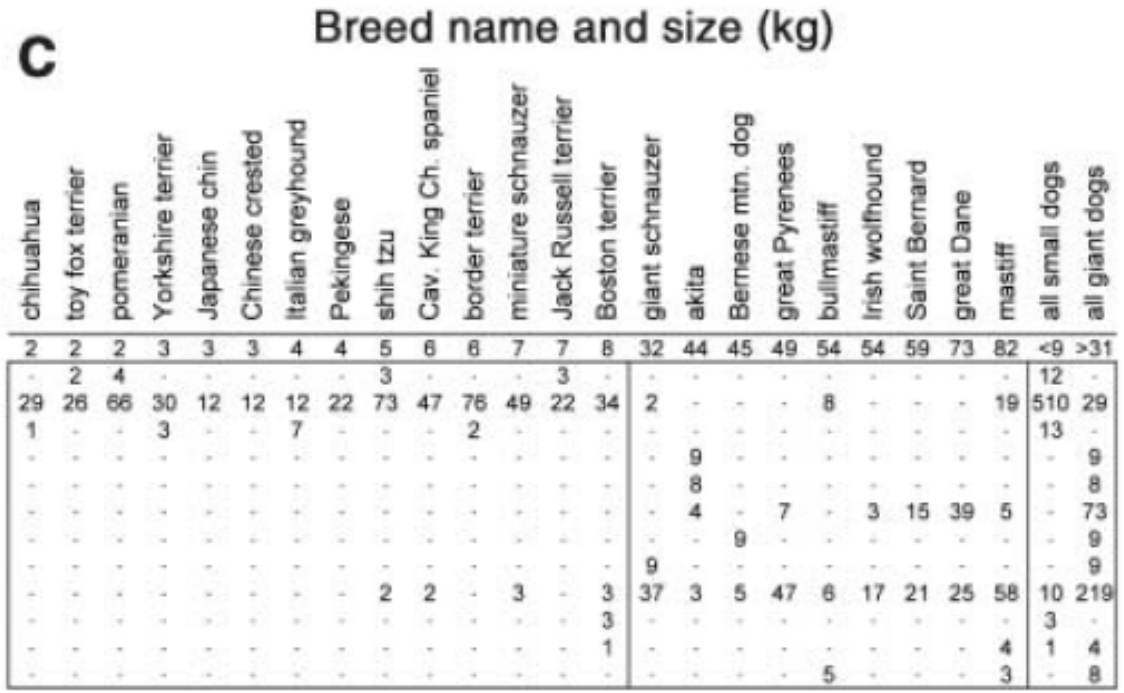
Other breeds differ in mass by 100-fold

Insulin-like Growth Factor is the major determinant of size differences among breeds



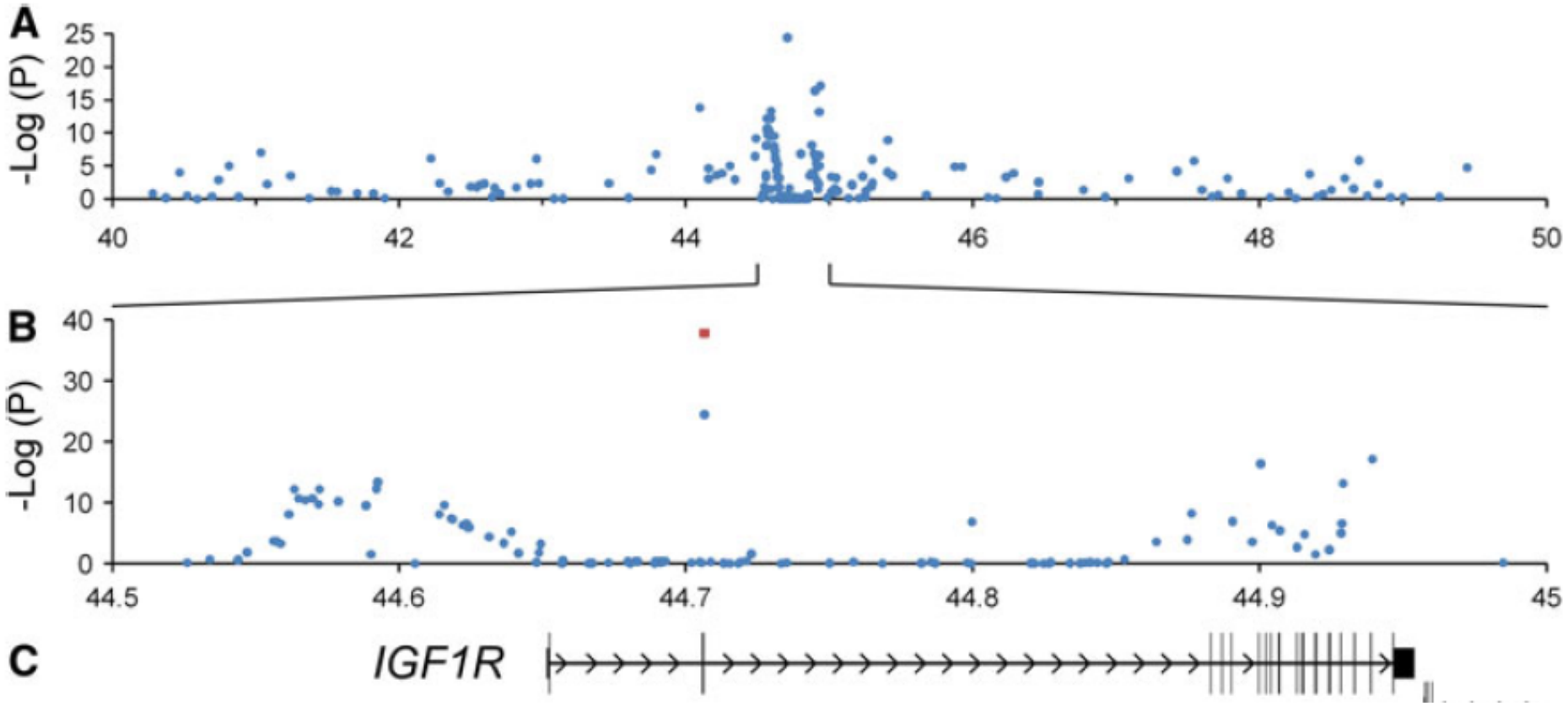
All small breeds have a single haplotype at the *IGF1* locus; large breeds have a different haplotype



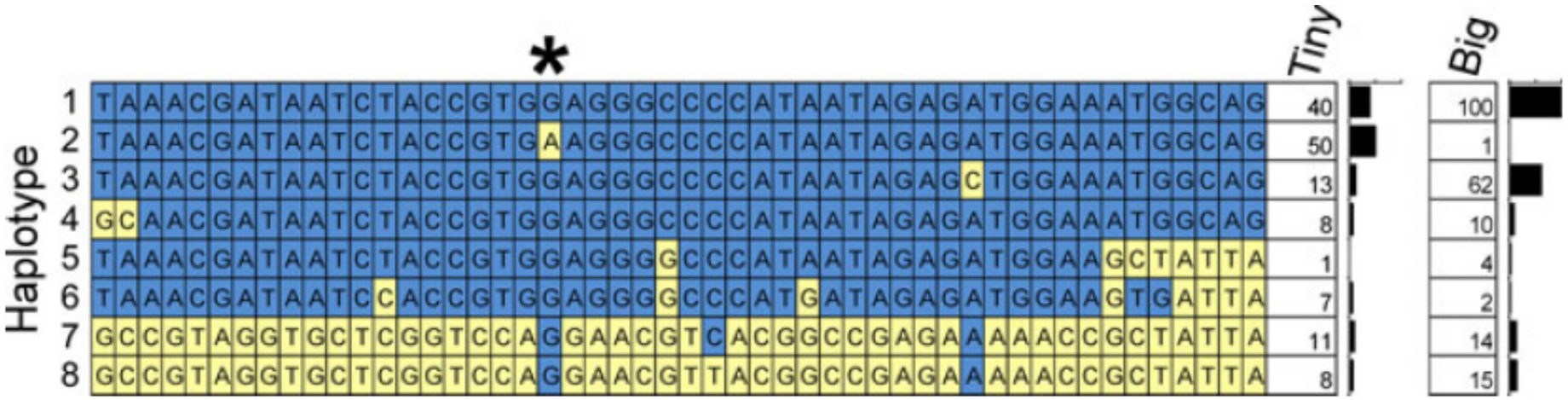


Small breeds have haplotype “B”; large breeds haplotype “I”

IGF1 Receptor variants control size in tiny dogs



Haplotype occurance



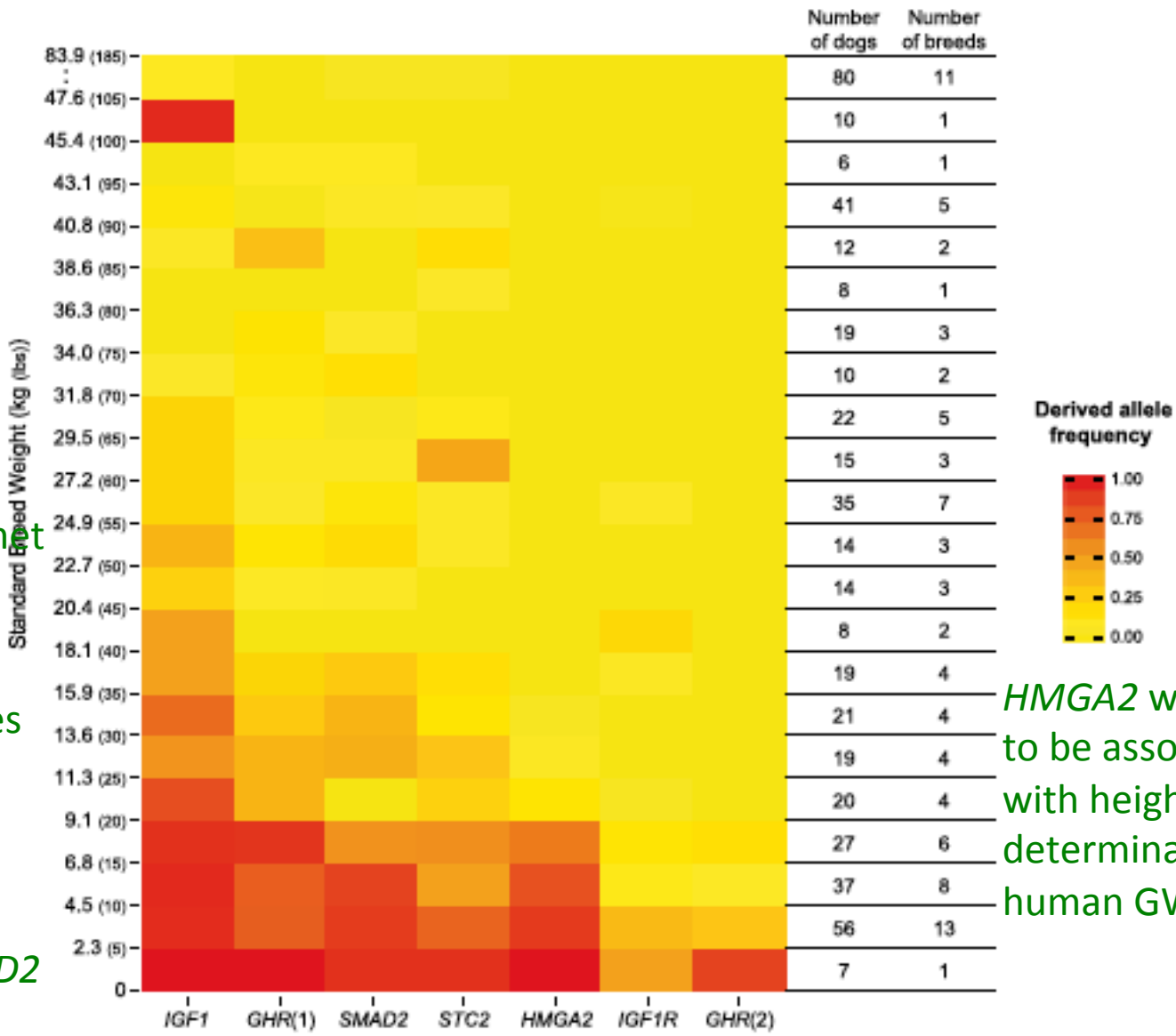
Haplotype “2” causes an R204H substitution in IGF1 receptor, a substitution that is predicted to affect ligand binding

Alleles at 7 genes determines half the body size difference in dog breeds

IGF1 and *IGF1R* we've already met

GHR participates in IGF pathway

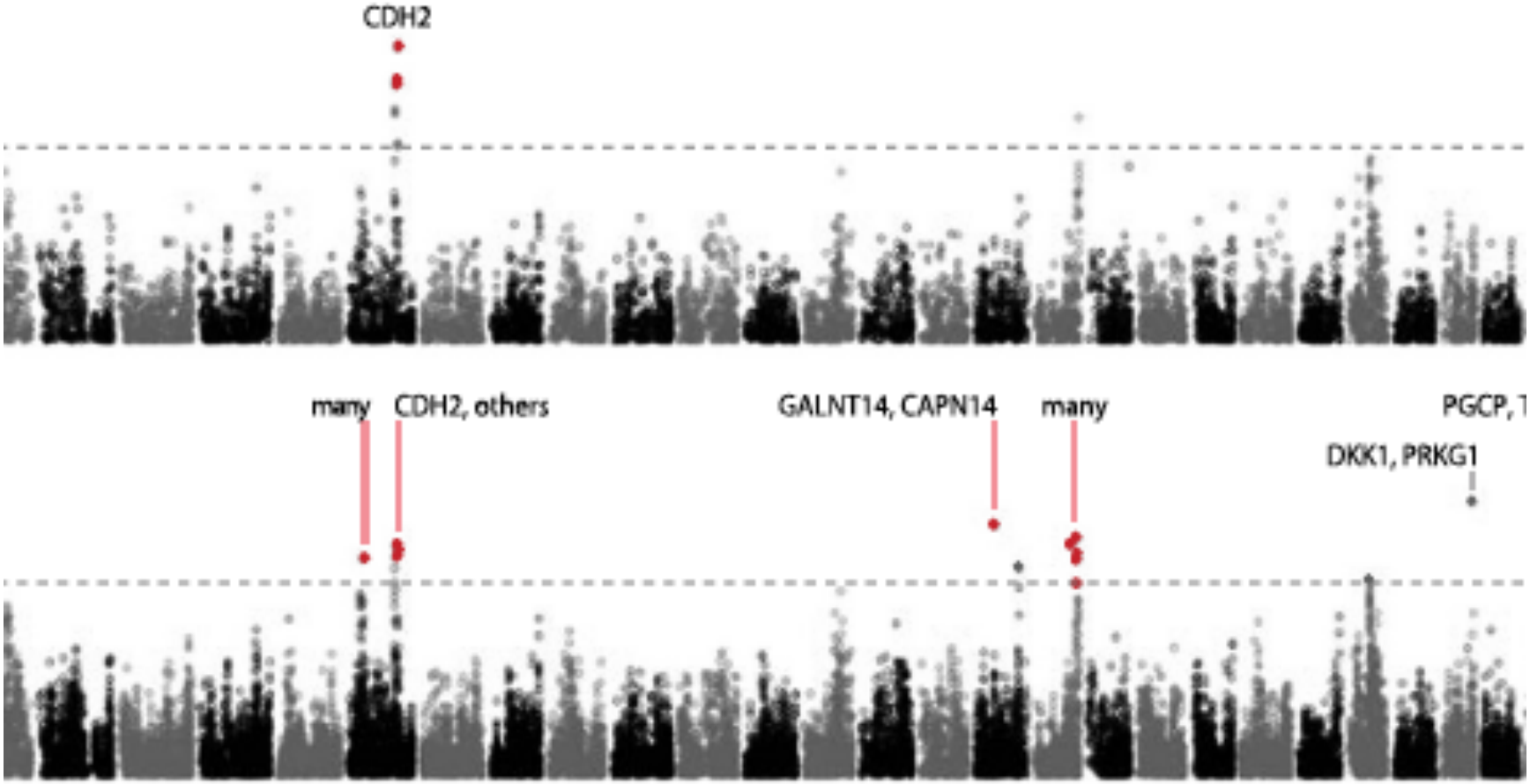
STC2 and *SMAD2* are new

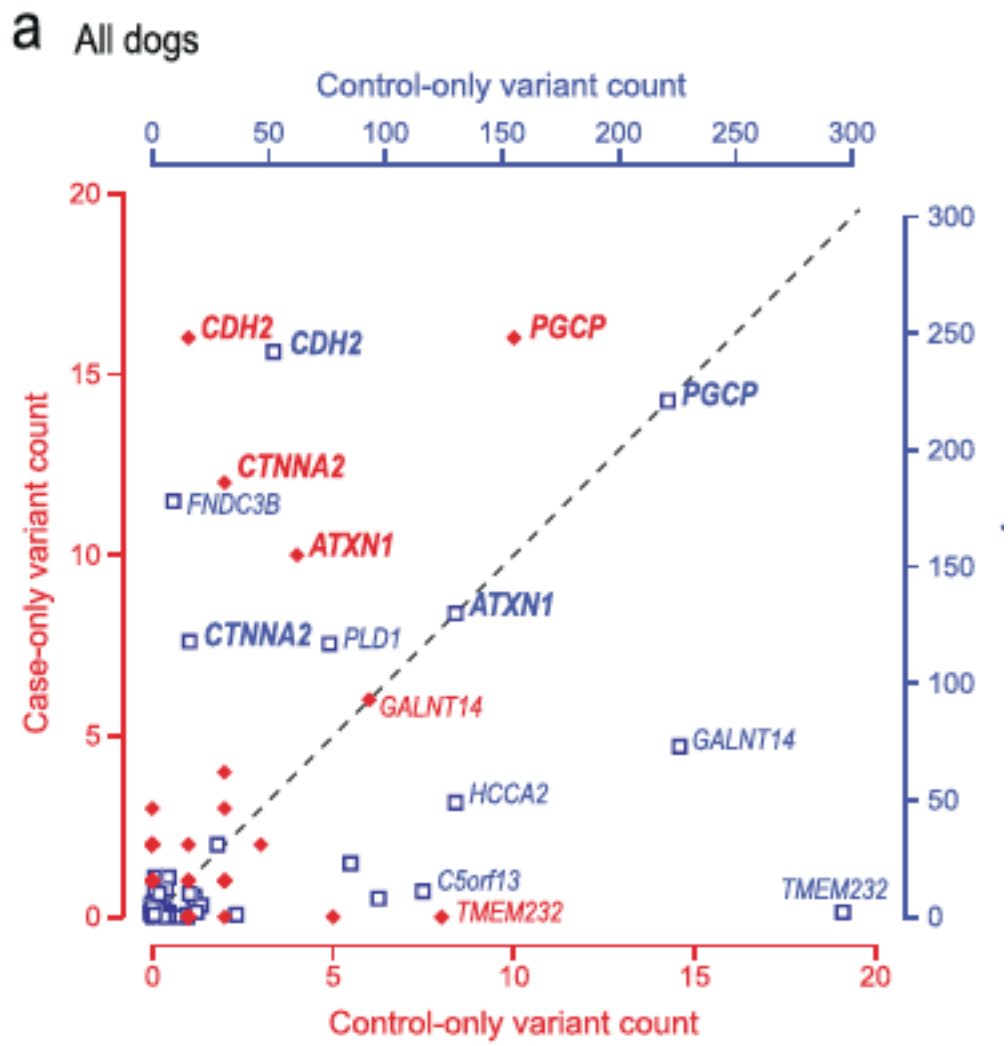


HMGA2 was found to be associated with height determination in human GWAS studies

Obsessive Compulsive Disorder (OCD)

GWAS of OCD using Doberman Pinschers, Bull Terriers, and German Shepherds




a
All dogs
Control-only variant count
0
50
100
150
200
250
300
20
15
10
5
0
Case-only variant count
CDH2
CDH2
PGCP
PGCP
CTNNA2
FNDC3B
ATXN1
ATXN1
CTNNA2
PLD1
GALNT14
GALNT14
HCCA2
C5orf13
TMEM232
TMEM232
0
5
10
15
20
Control-only variant count

Candidate genes have Intriguing connections to neural fxn and to human schizophrenia

By comparing the sequence data using gene-based tests, we confirmed one gene (*CDH2*) and identified three novel ones (*CTNNA2*, *ATXN1*, and *PGCP*) strongly implicated for involvement in disease.

CDH2, a neural cadherin, encodes a calcium dependent cell-cell adhesion glycoprotein important for synapse assembly, where it mediates presynaptic to postsynaptic adhesions [34]. Disrupting expression of CDH2 in cultured mouse neurons causes synapse dysfunction, synapse elimination and axon retraction [35].

CTNNA2 encodes a neuronal-specific catenin protein that links cadherins to the cytoskeleton [34,36] and is associated with bipolar disorder [37], schizophrenia [38], attention deficit hyperactivity disorder [38] and excitement-seeking [39]. Mice with a deletion of *CTNNA2*

ATXN1 encodes a chromatin binding protein that regulates the Notch pathway [42], a developmental pathway also active in the adult brain, where it mediates neuronal migration, morphology and synaptic plasticity [43]. Mice

Intriguingly, the three genes appear to have functional connections to the top SNPs (association $P < 10^{-5}$) in a recent human OCD GWAS, which found no single associations reaching genome-wide significance, but implicated glutamatergic signaling pathways [4] (Figure S6 in