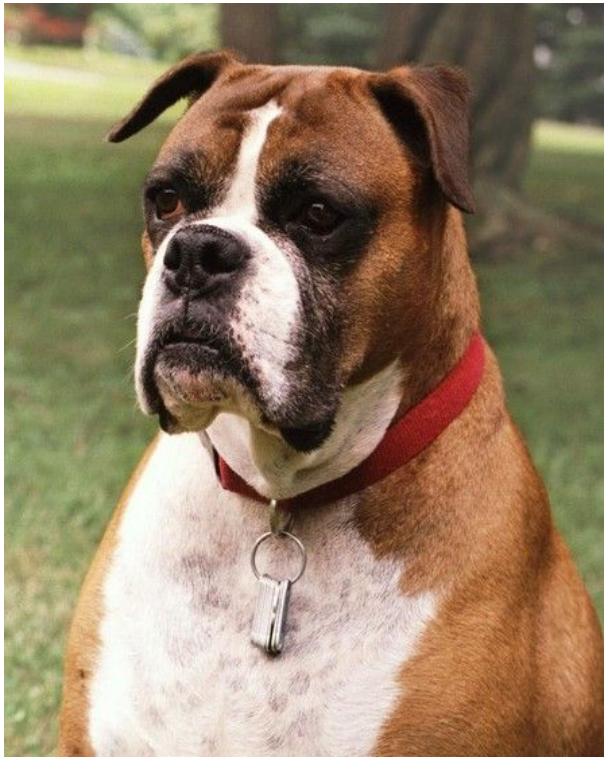
What's in a Mutt? An Intro to Dog DNA Analysis

Lecture 6

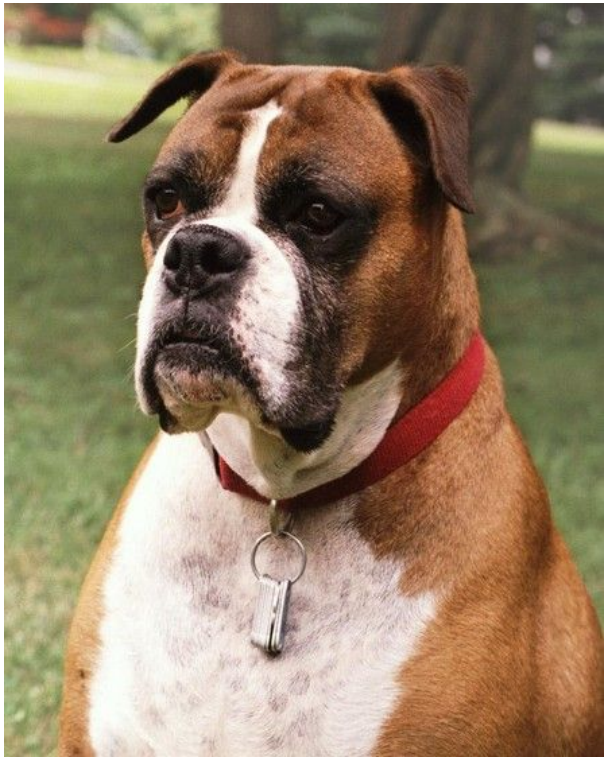
Jan 18th, 2019

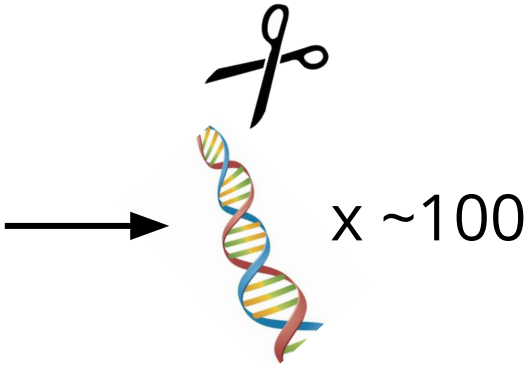
Tasha's genome



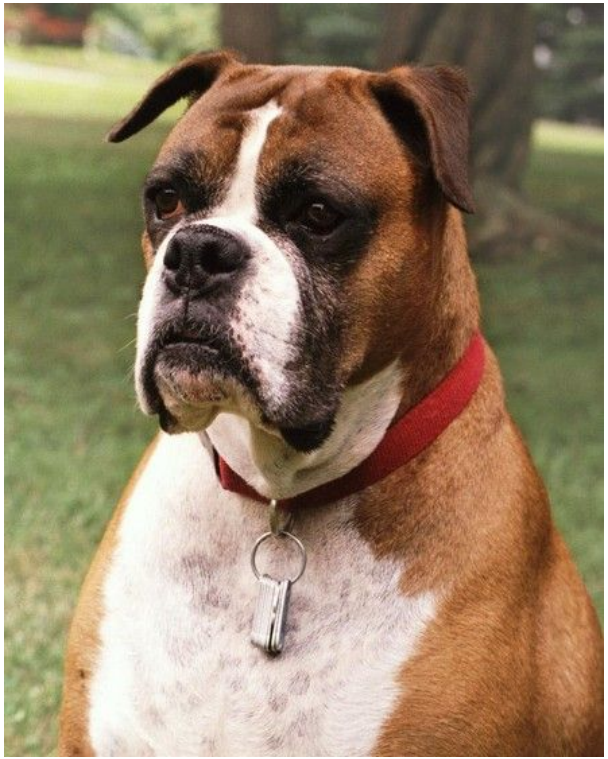
x ~100

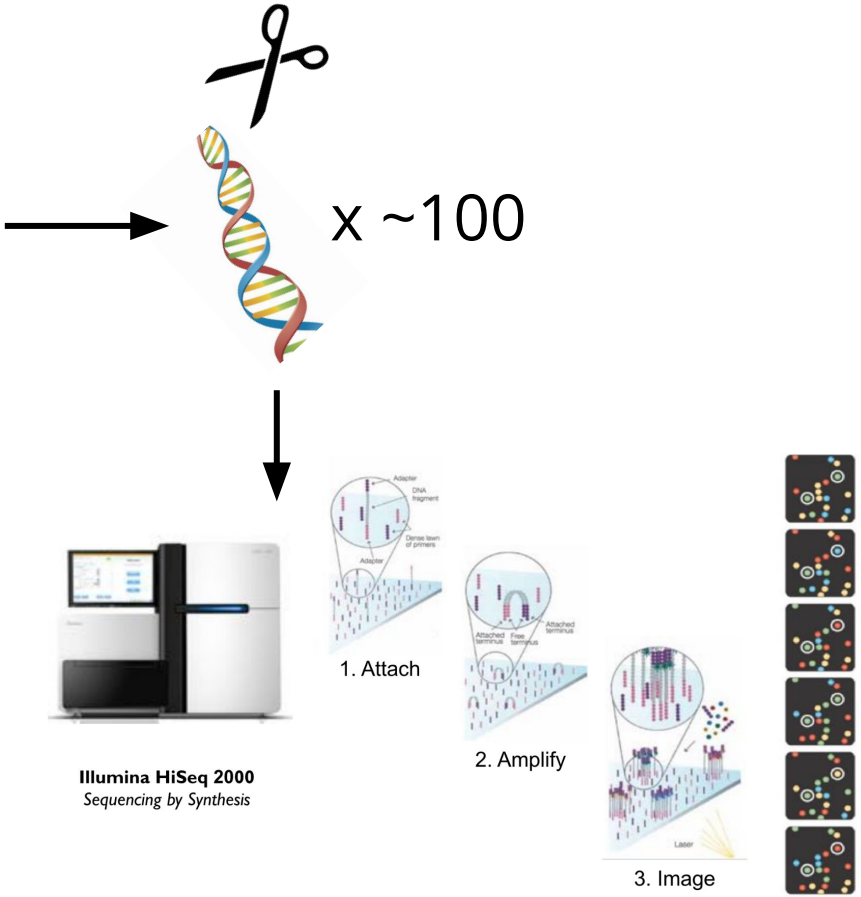
Tasha's genome



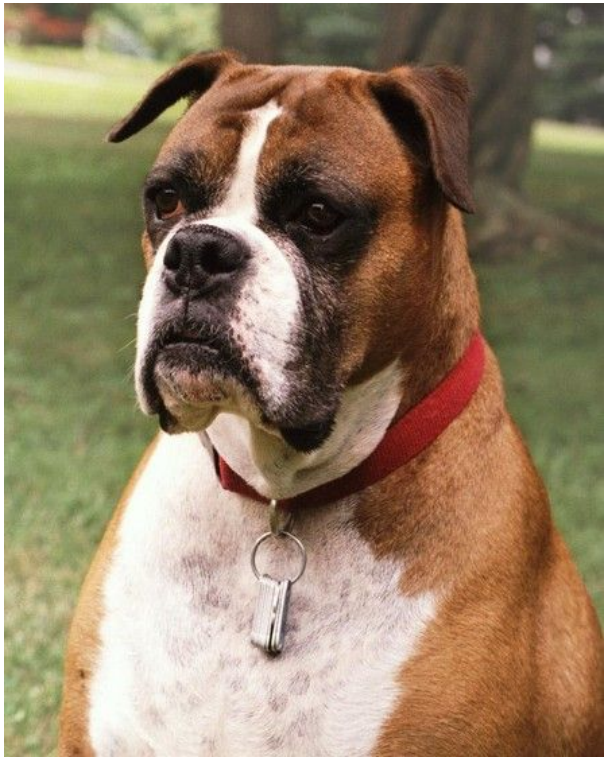


Tasha's genome





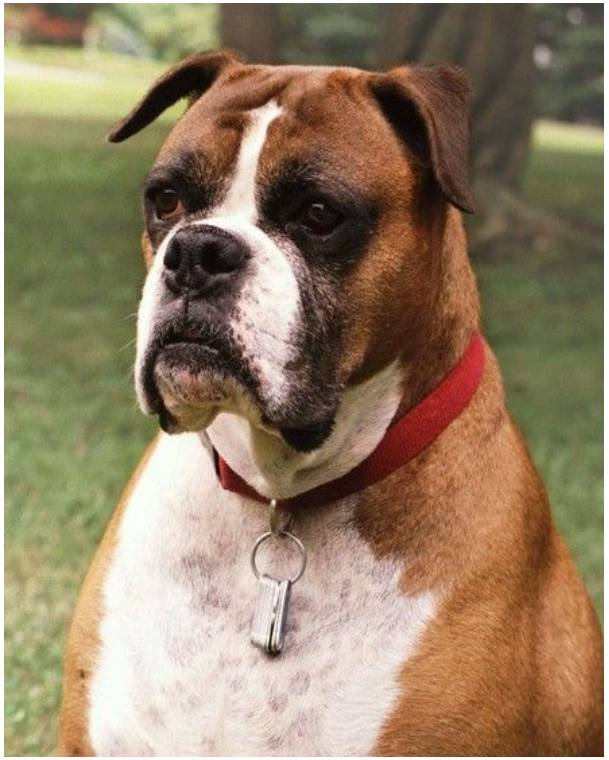
Tasha's genome

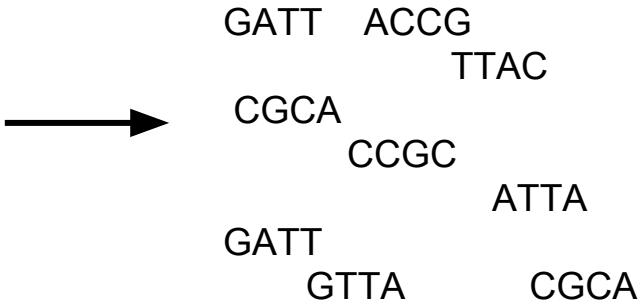


GATT ACCG
TTAC
CGCA
CCGC
ATTA
GATT
GTTA CGCA

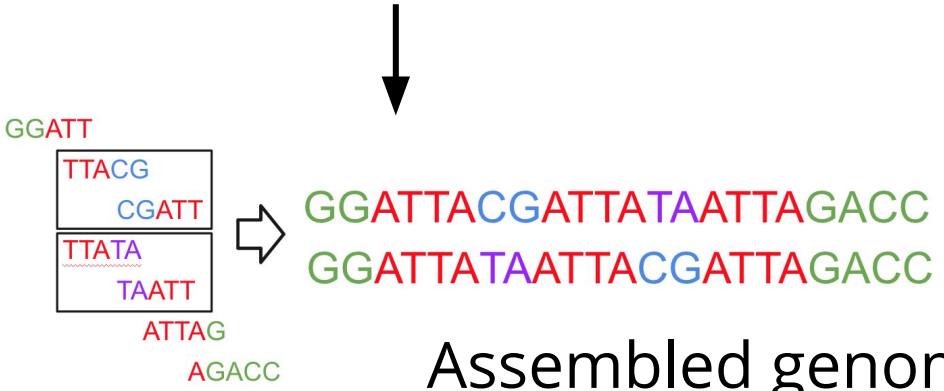
Billions of ~250 base ***reads***

Tasha's genome





Billions of ~250 base ***reads***



Assembled genome

Sequence Alignment


```
                                                                GGTATAC...
...CCATAG          TATGCGCCC          CGGAAATTT          CGGTATAC
...CCAT        CTATATGCG                  TCGGAAATT          CGGTATAC
...CCAT    GGCTATATG              CTATCGGAAA          GCGGTATA
...CCA   AGGCTATAT              CCTATCGGA          TTGCGGTA    C...
...CCA   AGGCTATAT          GCCCTATCG              TTTGCGGT    C...
...CC    AGGCTATAT          GCCCTATCG          AAATTTGC          ATAC...
...CC  TAGGCTATA        GCGCCCTA              AAATTTGC      GTATAC...
```

...CCATAGGCTATATGCGCCCTATCGGCAATTTGCGGTATAC...

Sequence Alignment

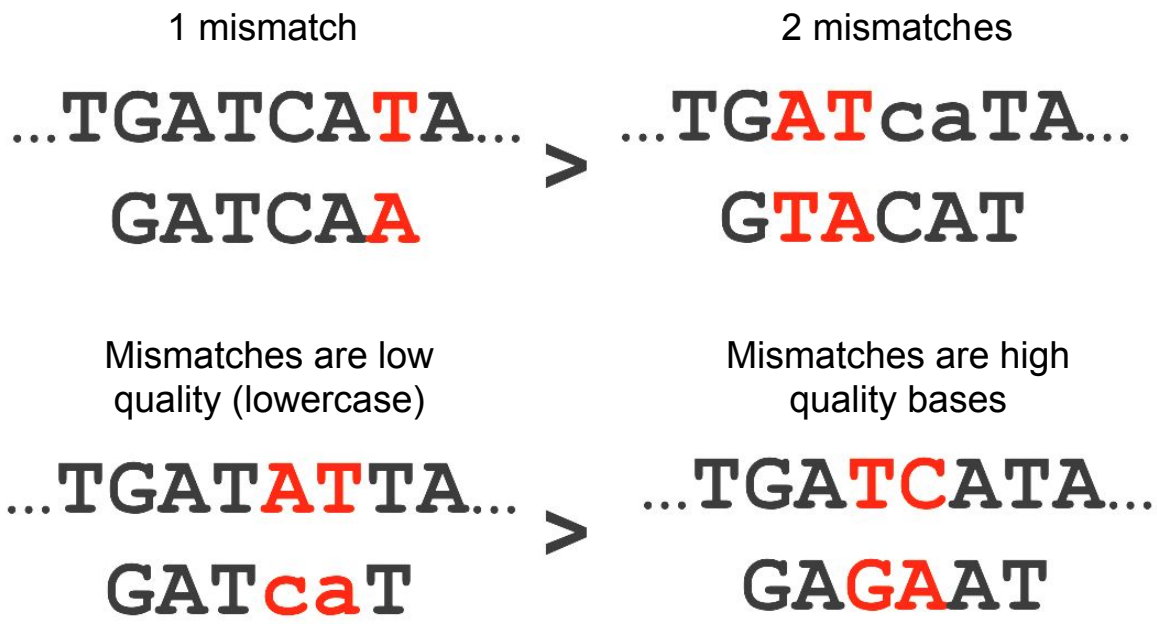
We found a SNP!

Finding the best alignment

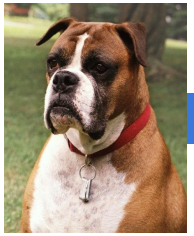
How might we tell if one alignment is better than another?

Finding the best alignment

- Number of mismatches
- Type of difference
- Base “quality”
  - Sequencer reports how confident it is in the base “call”



Alignment and phasing



Tasha (Reference)

C A T A

A G

G T

T

G G

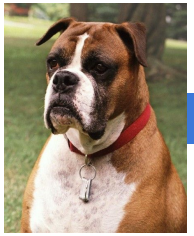
A

G G T

? ? ? ?

? ? ? ?

Alignment and phasing



Tasha (Reference)

C A T A

A G

G T

T

G G

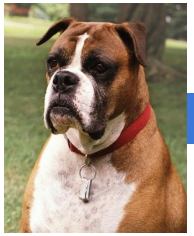
A

G G T

C G G ?

A A T ?

Alignment and phasing



Tasha (Reference)

C A T A

A G A

G T

T

G G

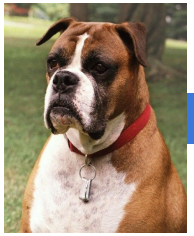
A A

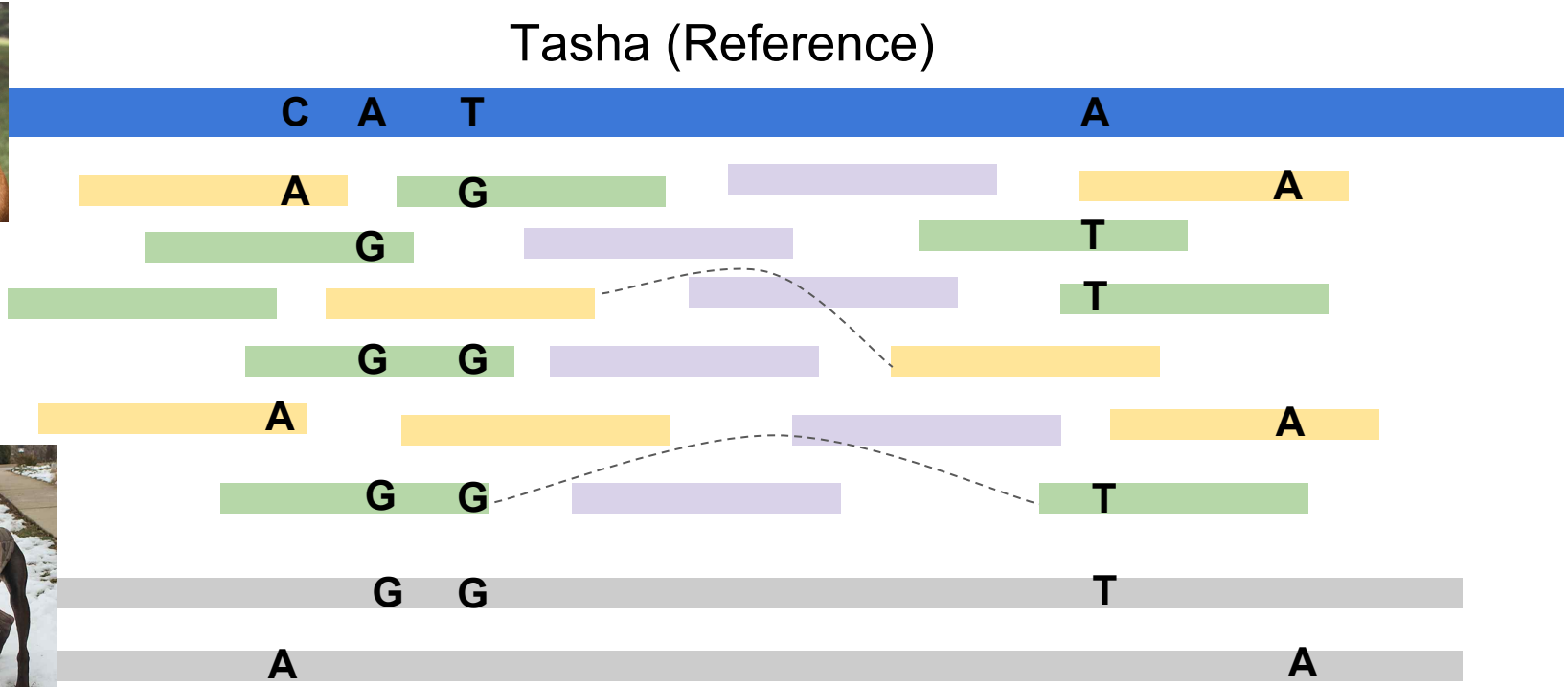
G G T

G G A

A T

Alignment and phasing





Getting to 2.5 million SNPs





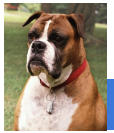









Which SNPs are interesting?



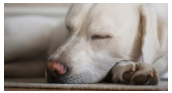
HCRTR2 gene

G

G

G

G



A

A

A

A

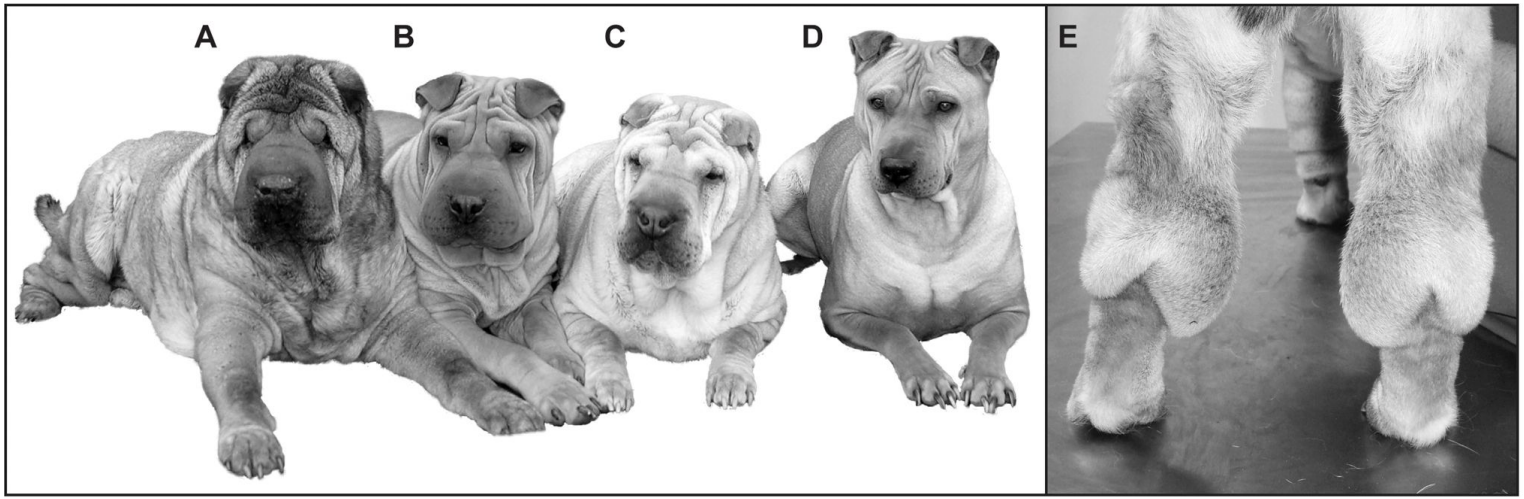
Discovering cause of fever illness in Shar-Peis

Creature Feature: Shar-Pei dog

By Alice McCarthy

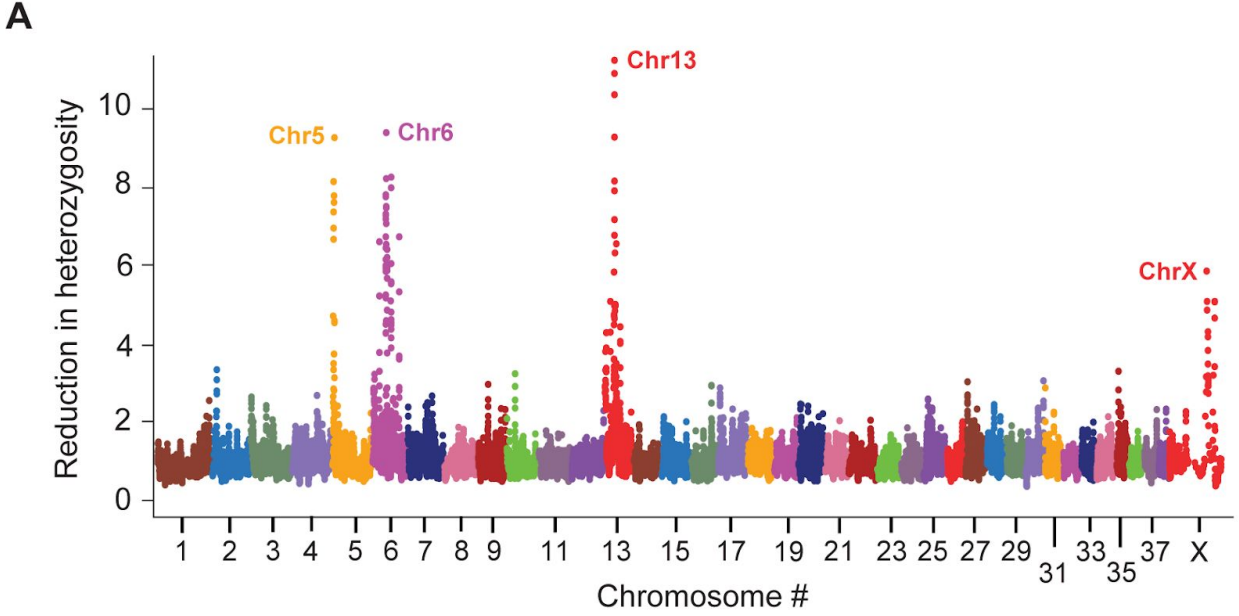
Scientists at the Broad Institute and Uppsala University in Sweden have made a discovery in the Shar-Pei dog breed that may help explain the cause of repetitive human fever illnesses. In a recent paper , the team published that a genetic regulatory gene mutation causes the dogs to develop Familial...

Genome wide association study (GWAS)



Following strong selection for the “wrinkled” skin phenotype, Shar-Pei dogs in the western world most commonly present as the meatmouth type (A–C). The traditional type of Shar-Pei (D) is the ancestral version and is still common in China. The characteristic skin is a result of a deposition of mucin, mainly hyaluronic acid (HA), in the upper dermis of the skin. The deposit collects in certain areas of Shar-Pei skin and often as “socks” around the hocks (E). The meatmouth Shar-Pei (A–C) is also predisposed to a breed-specific periodic fever syndrome called Familial Shar-Pei Fever (FSF). (Olsson *et al*, 2011).

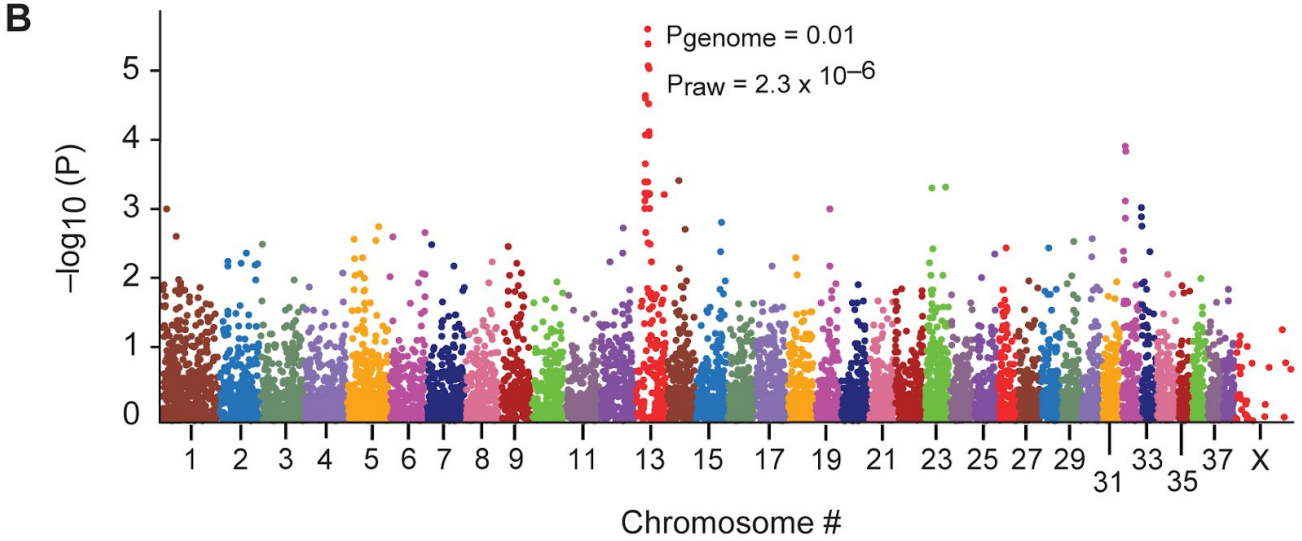
Genome wide association study (GWAS)



Regions with high homozygosity, when comparing 50 shar-peis to 24 other breeds (230 dogs). Regions of chromosome 13 in shar-peis have 10-fold less heterozygosity than other breeds.

Olsson *et al,* 2011

Genome wide association study (GWAS)



Genome wide SNP associations with Familiar Shar-Pei Fever. Strongest (and only statistically significant) association is on chromosome 13.

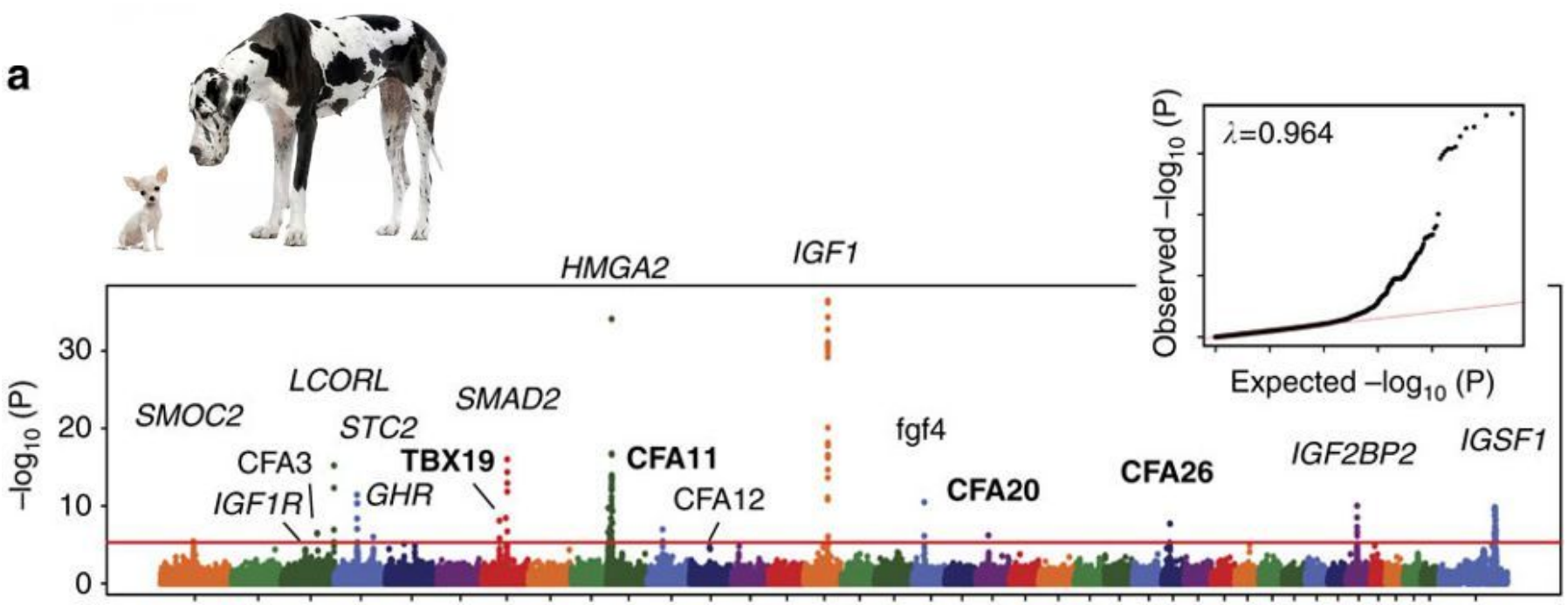
Manhattan plot: x-axis plots all SNPs as a point, ordered by chromosome position. *y*-axis plots *p*-value of significance (log scaled).

Olsson *et al,* 2011

GWAS in Shar-Peis; summary

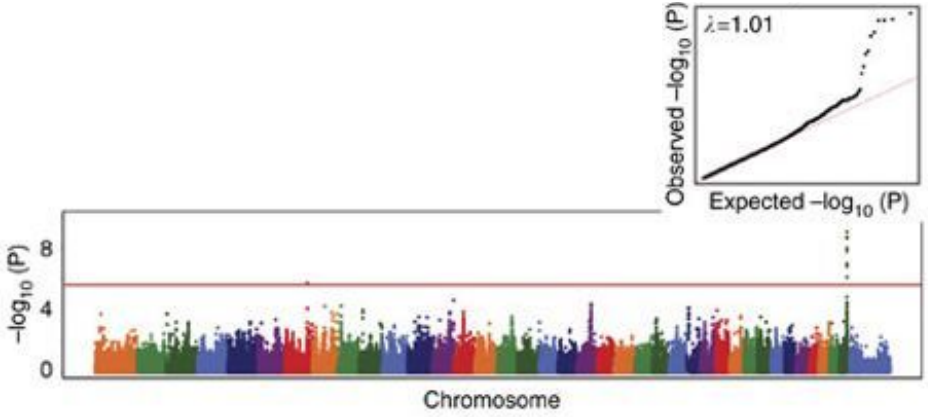
"Shar-Pei dogs have two unique features: a breed defining "wrinkled" skin phenotype and a genetic disorder called Familial Shar-Pei Fever (FSF). The wrinkled phenotype is strongly selected for and is the result of excessive hyaluronan (HA) deposited in the skin. … FSF is characterized by unprovoked episodes of fever and/or inflammation and resembles several human autoinflammatory syndromes. Here we show that the two features are connected and have the same genetic origin, a regulatory mutation located close to a HA synthesizing gene (*HAS2*). … ***HAS2* was previously not known to associate with autoinflammatory disease, and this finding is of wide interest since approximately 60% of human patients with periodic fever syndrome remain genetically unexplained.**" (Olsson *et al* 2011)

Genome wide association study (GWAS)

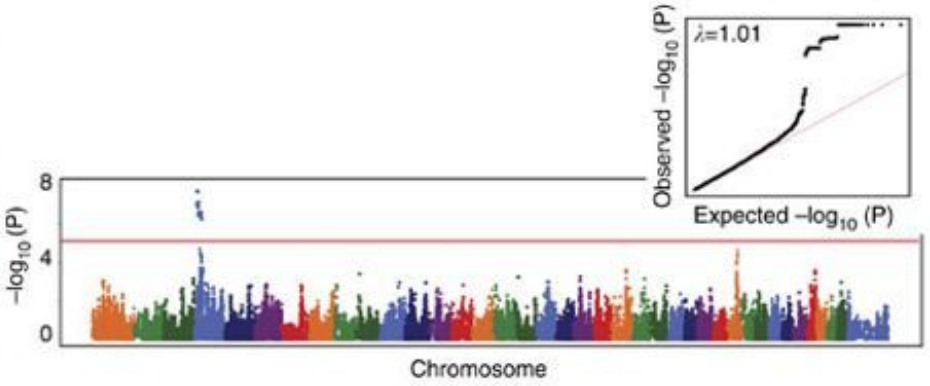


SNP associations with dog body weight, Hayward *et al* 2016.

Genome wide association study (GWAS)



Associations with granulomatous colitis in boxers and bulldogs, Hayward *et al* 2016.



Associations with idiopathic epilepsy in Irish wolfhounds, Hayward *et al* 2016.