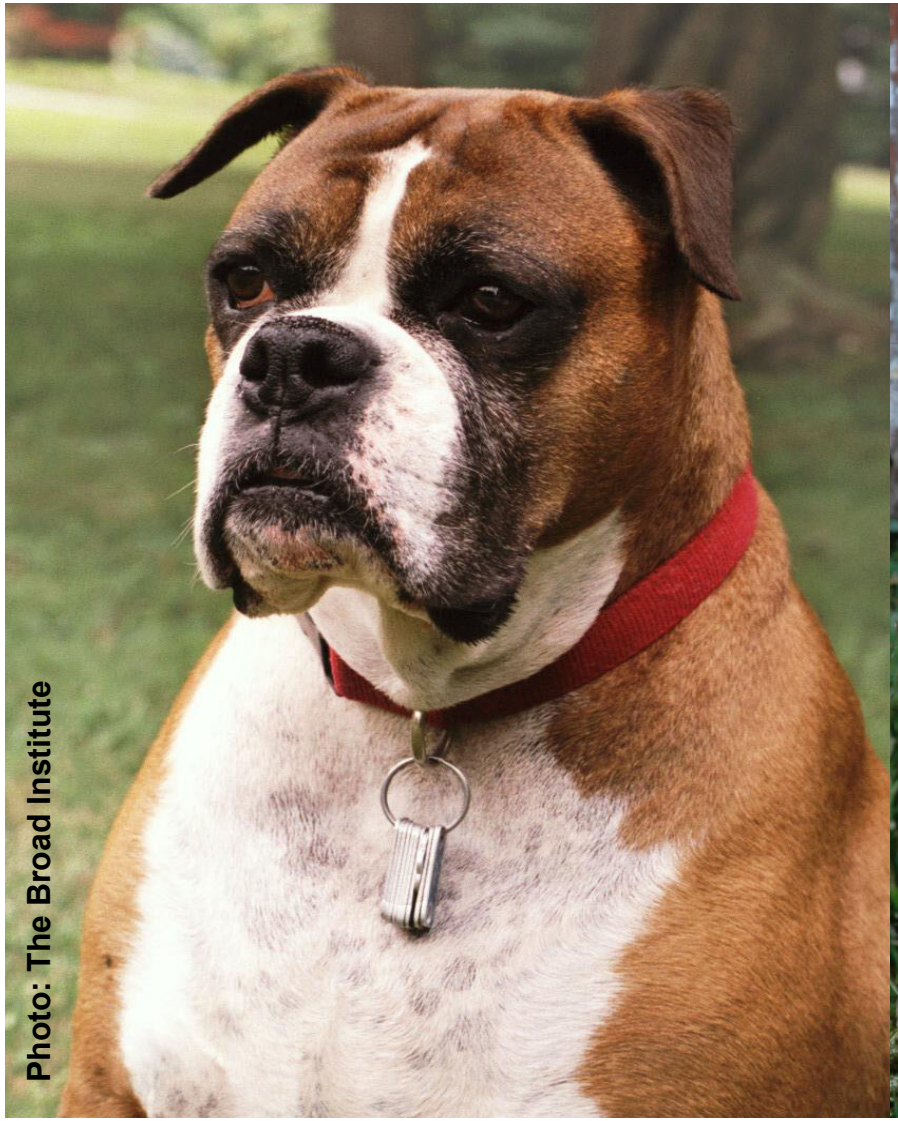
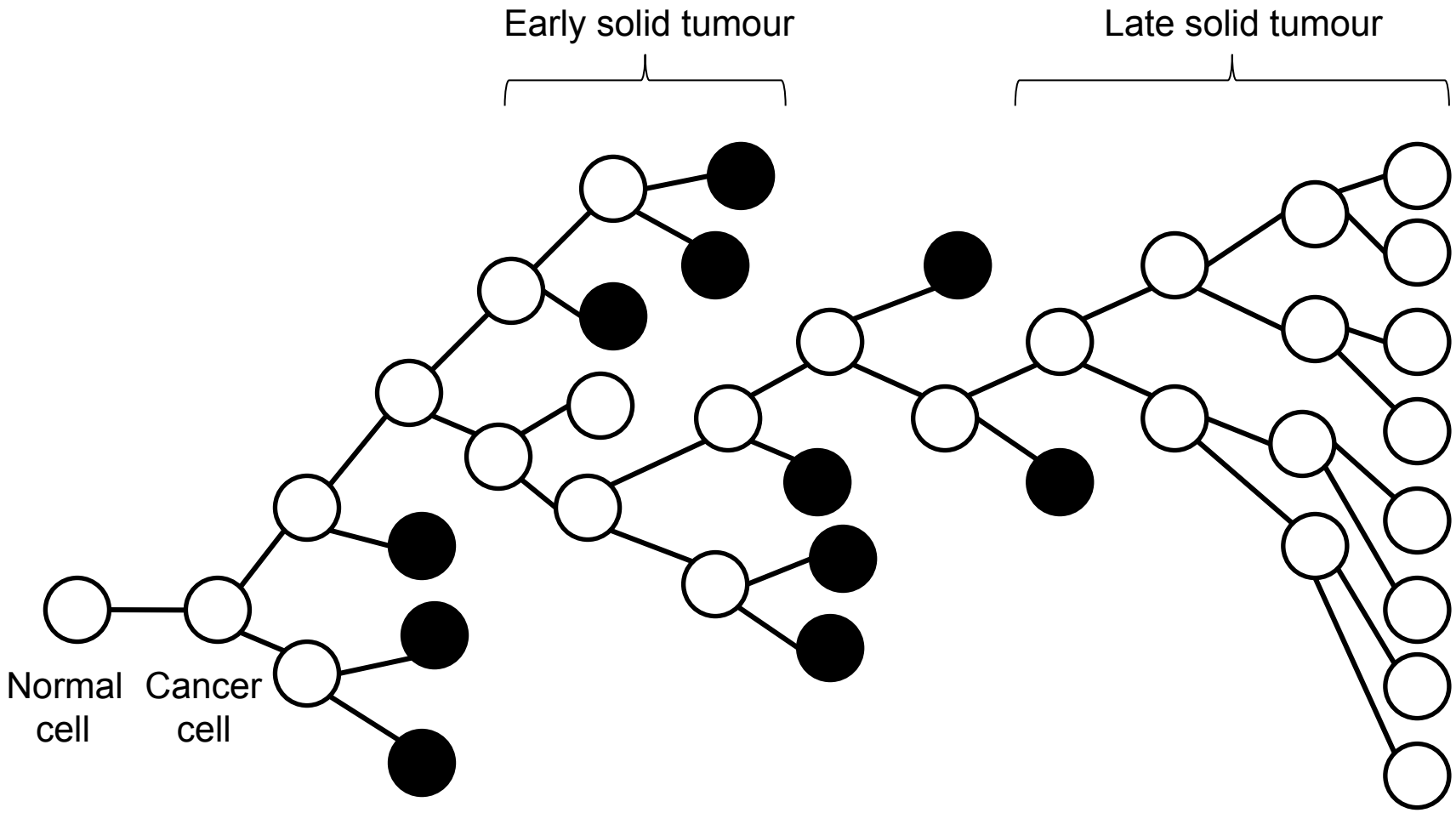
Clonally transmissible cancers in dogs and Tasmanian devils



Elizabeth Murchison, Wellcome Trust Sanger Institute, Cambridge, UK

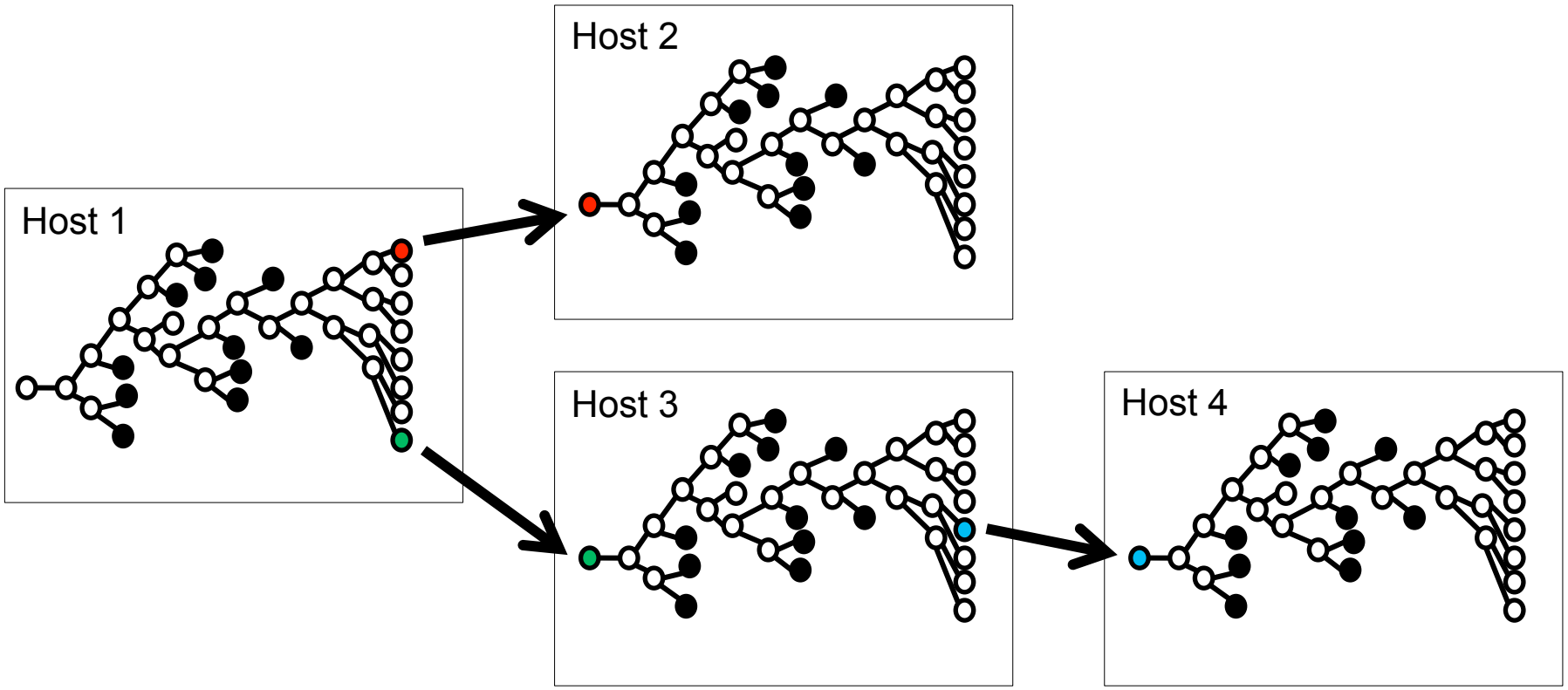
Clonal evolution of cancer



Adapted from Nowell, *Science*, 194 (4260):23-26, 1976

Clonally transmissible cancer

- Tasmanian devil facial tumour disease (DFTD)
- Canine transmissible venereal tumour (CTVT)



Transmissible cancers in devils and dogs

To use genomics to understand

- Origin
- Diversity
- History
- Evolution

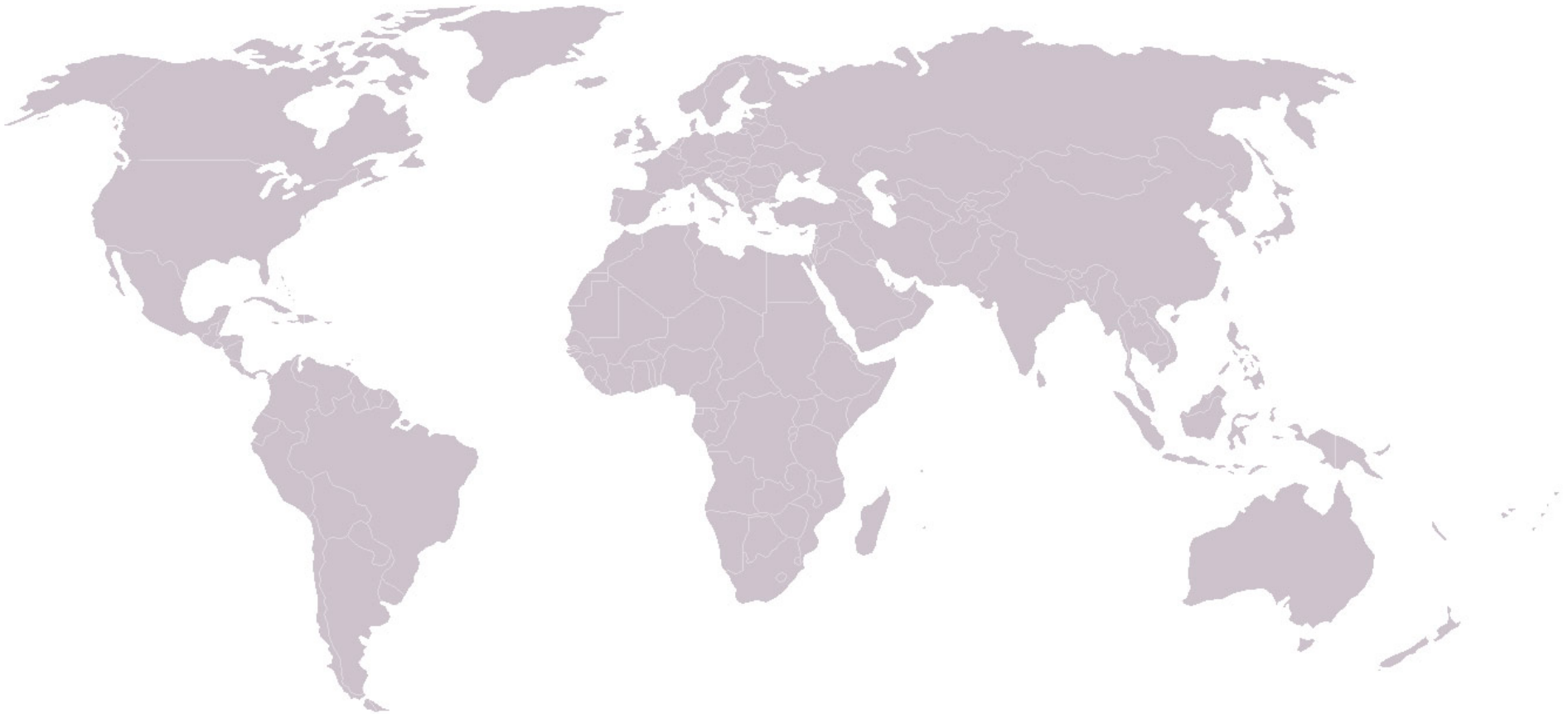
Photo: Tasmanian Devil Conservation Park

Photo: www.animalswallpaper.info

Tasmanian devil

Sarcophilus harrisii

Photo: Wayne McLean




Nick Mooney

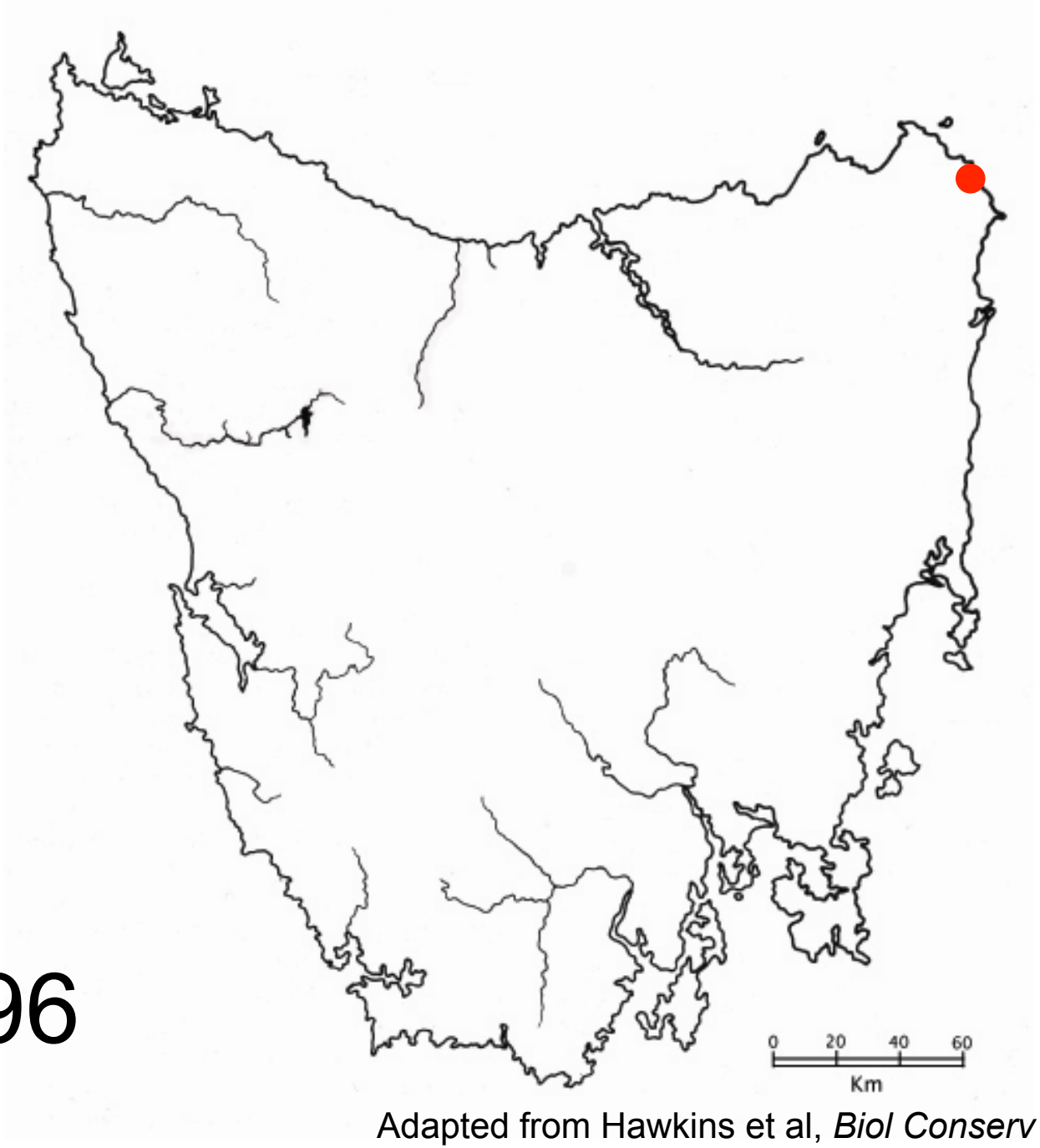

Photo: Rodrigo Hamede

Photo: Tasmanian Department of Primary Industries, Parks, Water and the Environment


Photo: Christo Baars

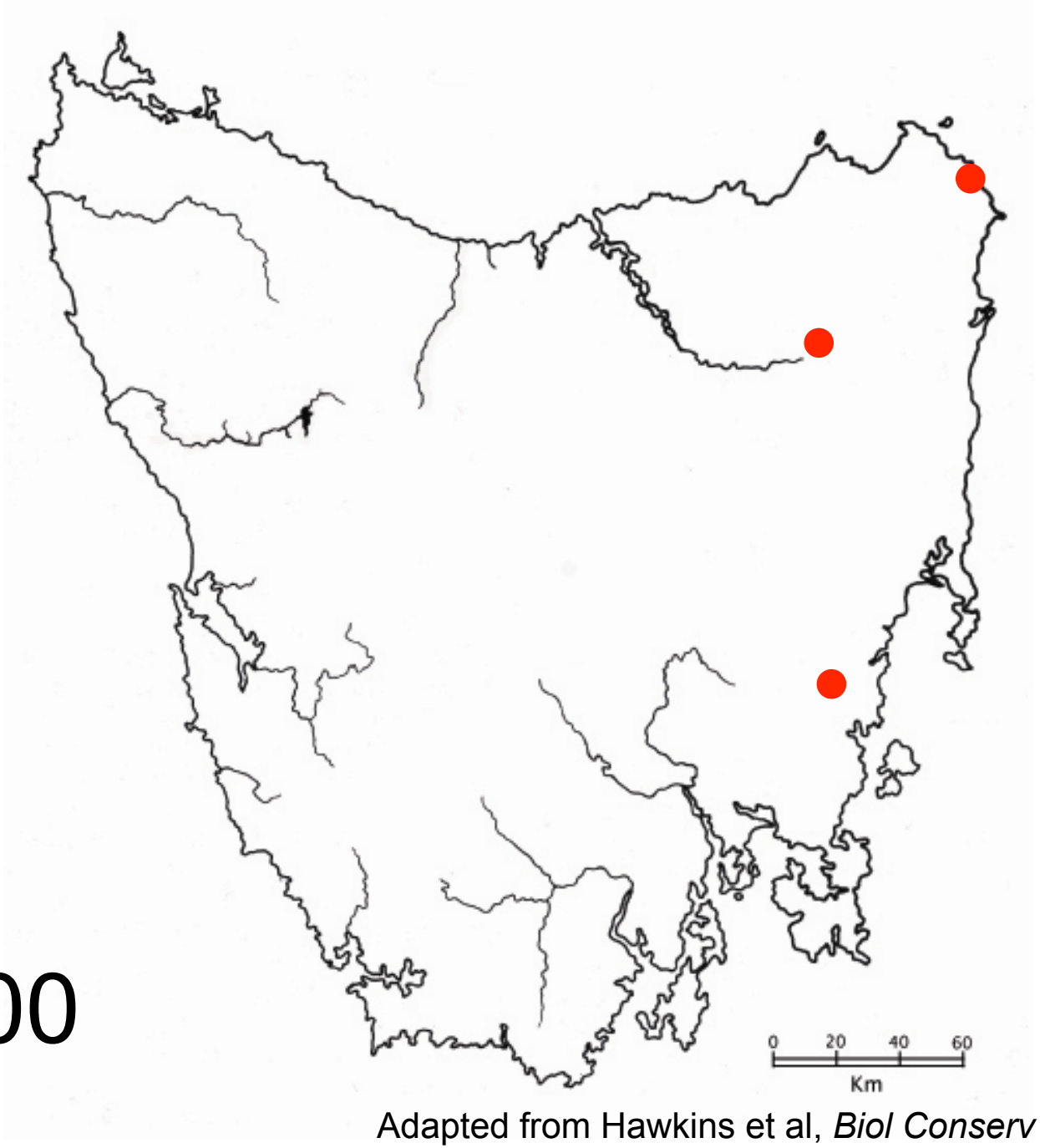
Photo: Rodrigo Hamede


Photo: Christo Baars, 1996



1996

Adapted from Hawkins et al, *Biol Conserv* 131:307-24, 2006



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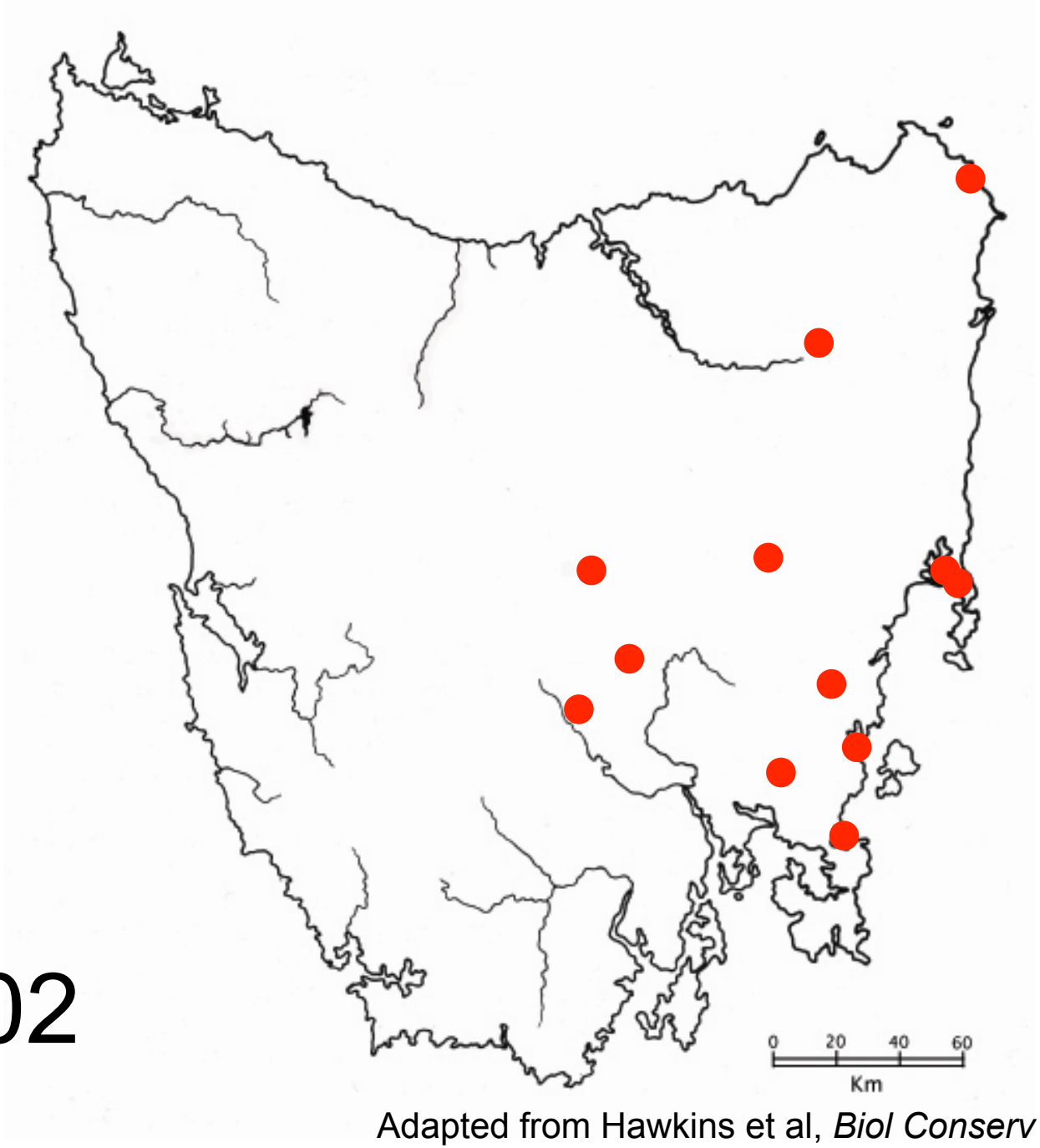

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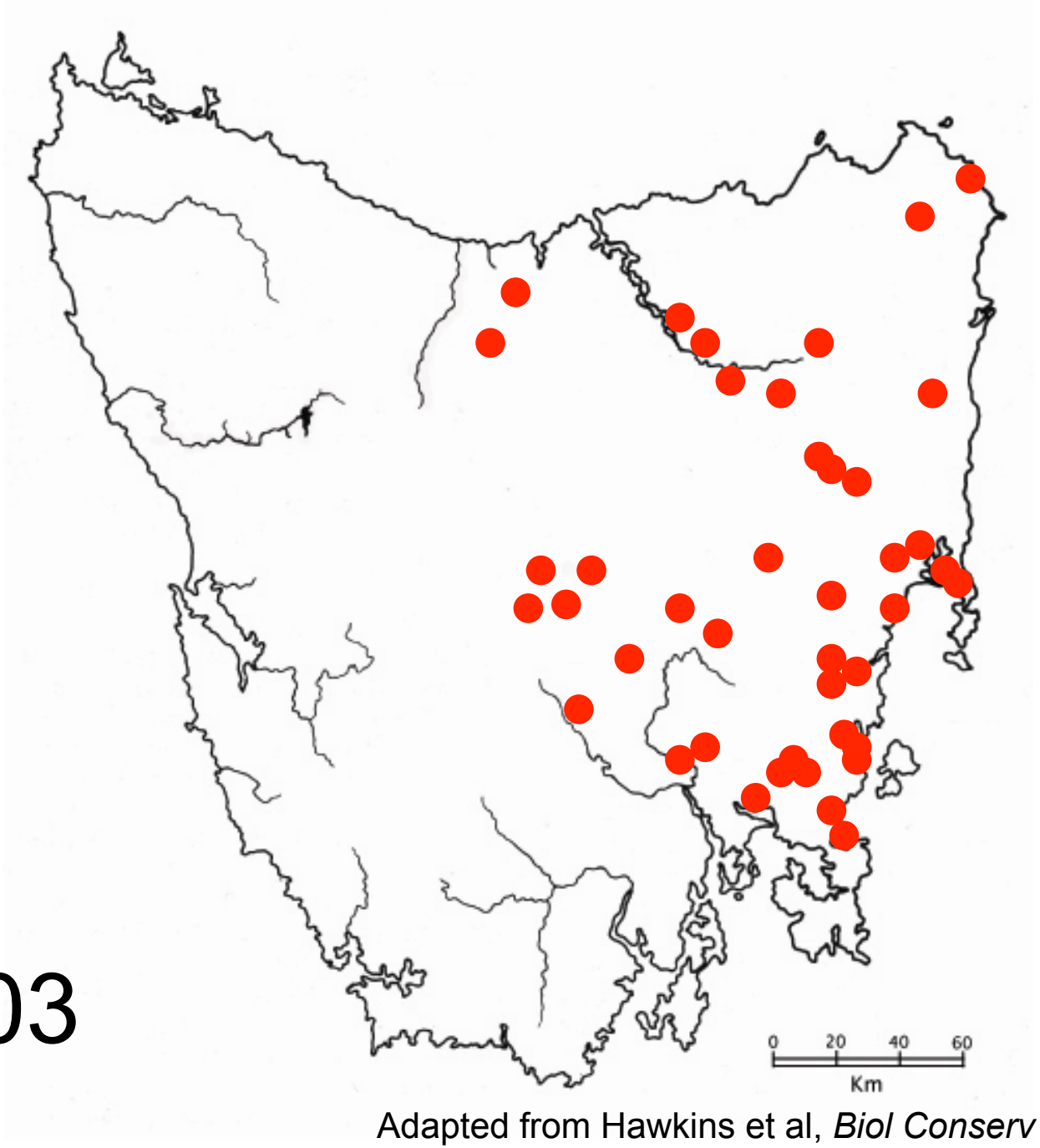
Adapted from Hawkins et al, *Biol Conserv* 131:307-24, 2006



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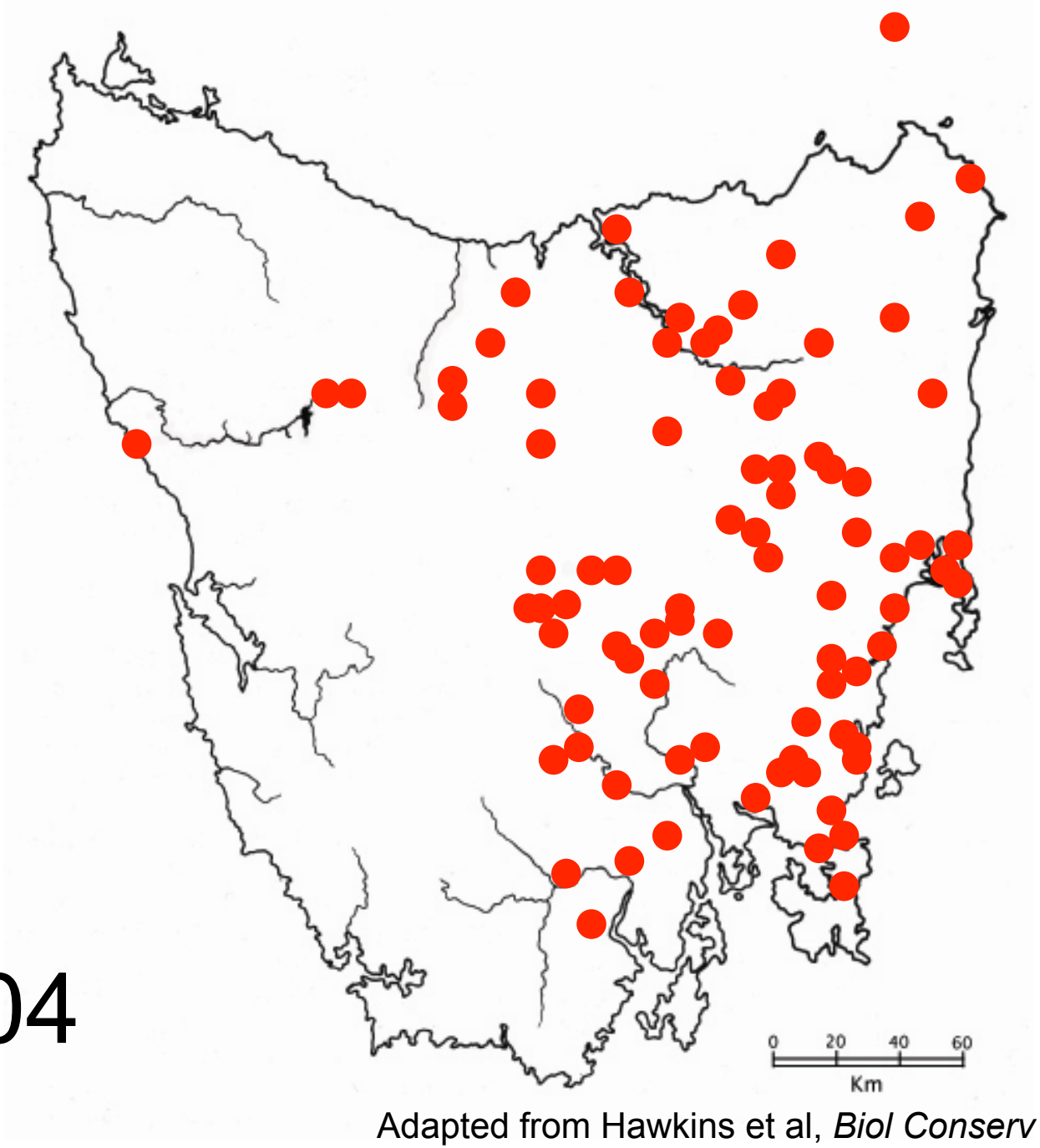

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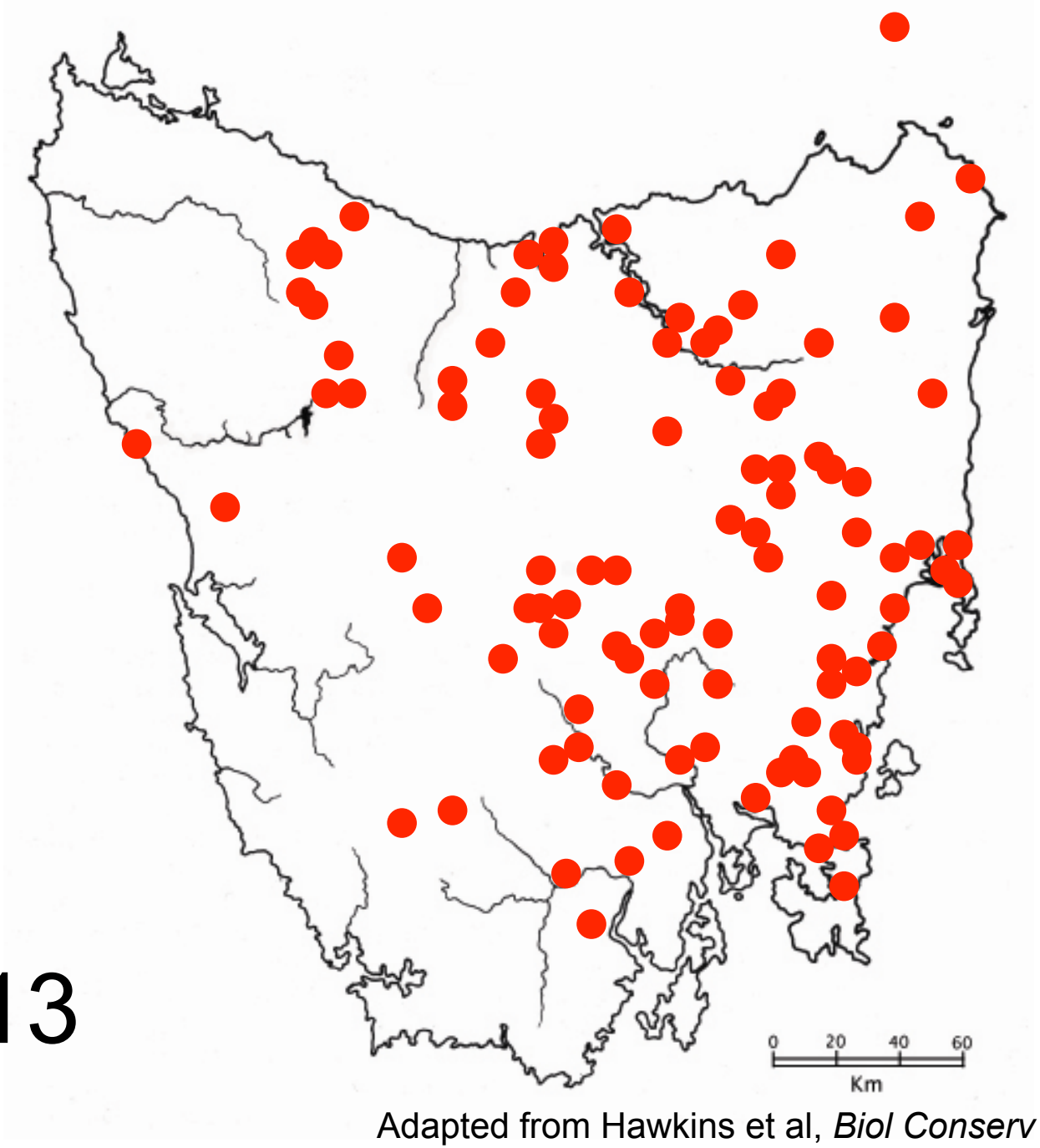

2013

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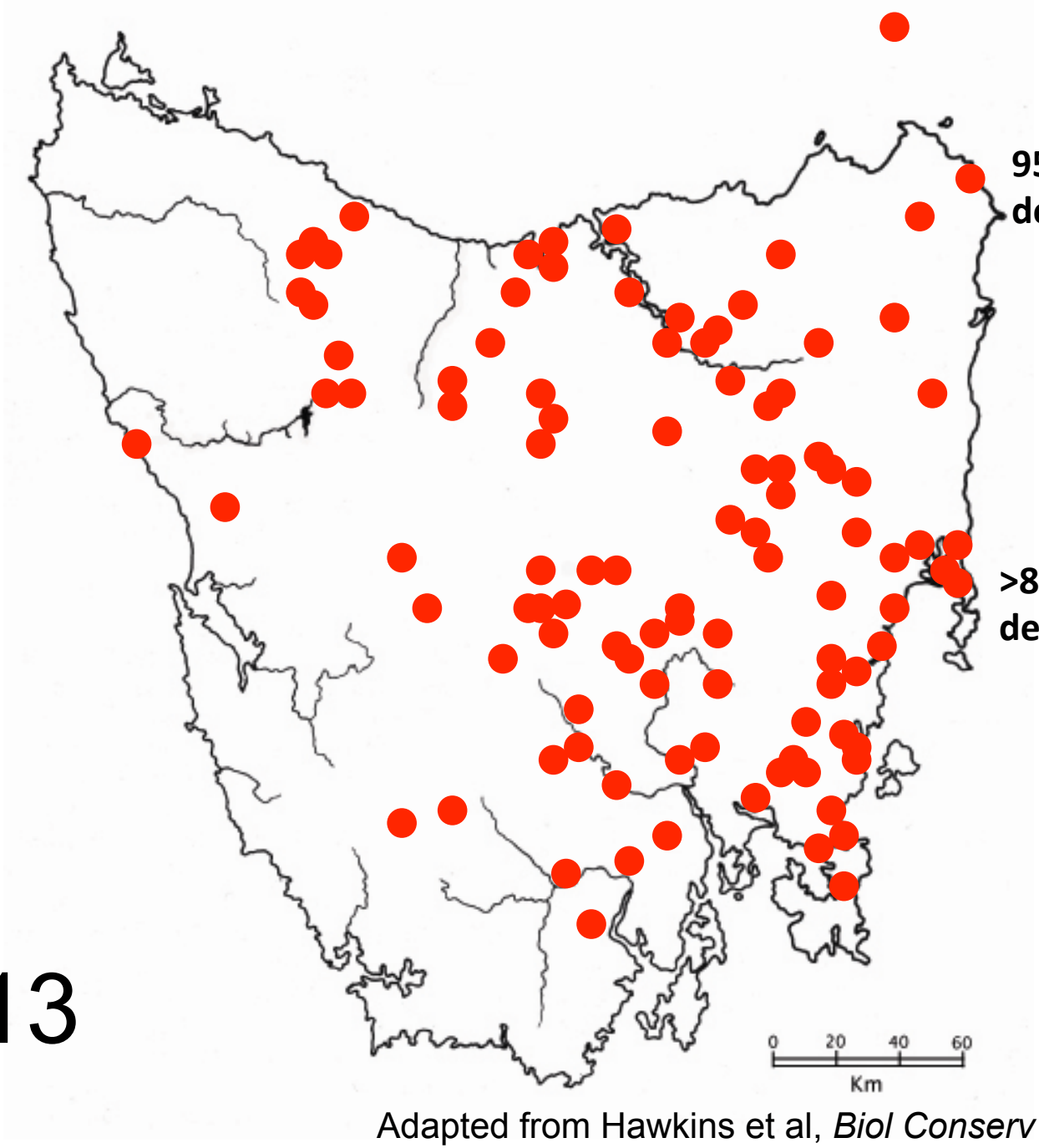
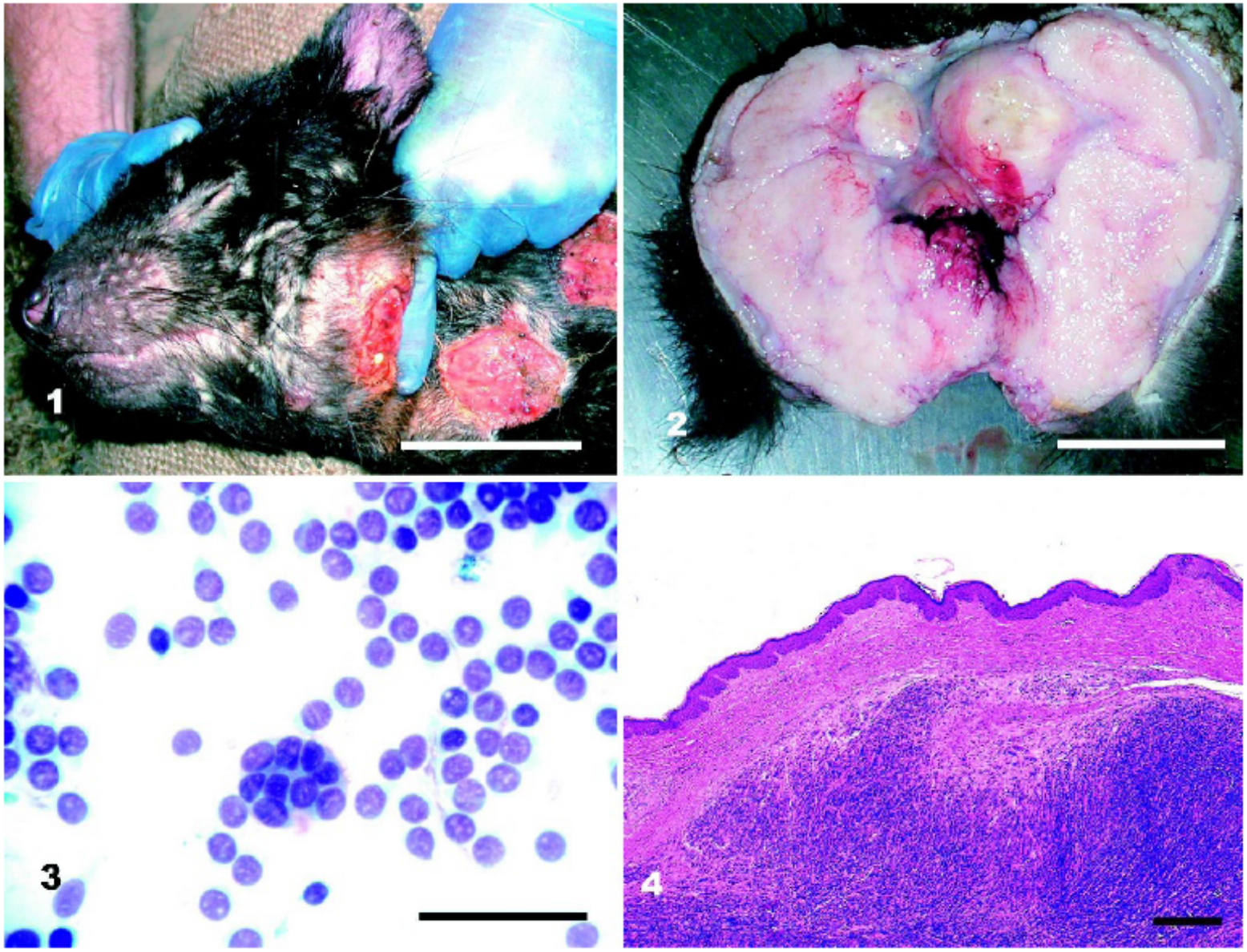


2013

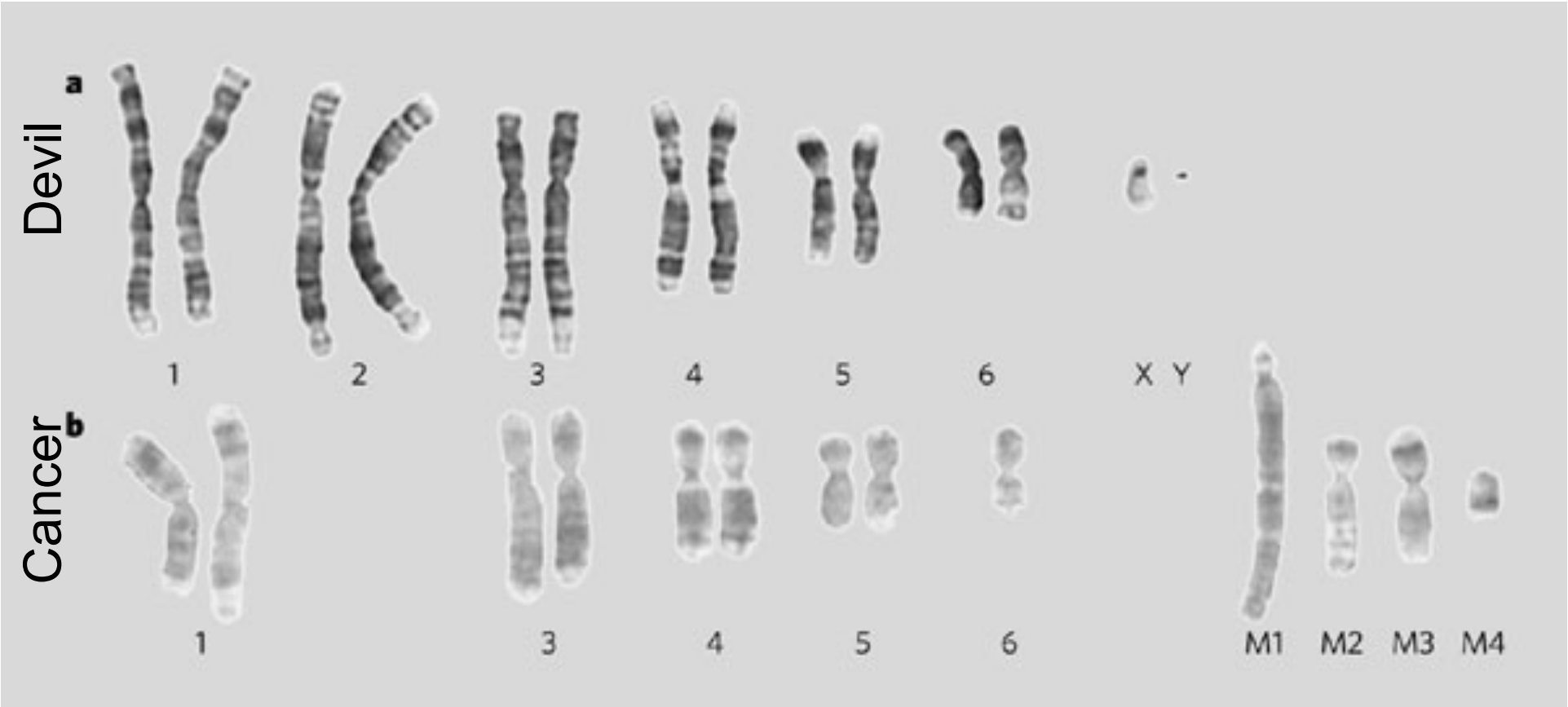
Adapted from Hawkins et al, *Biol Conserv* 131:307-24, 2006

“Tasmanian Devil Facial Tumour Disease” (DFTD)



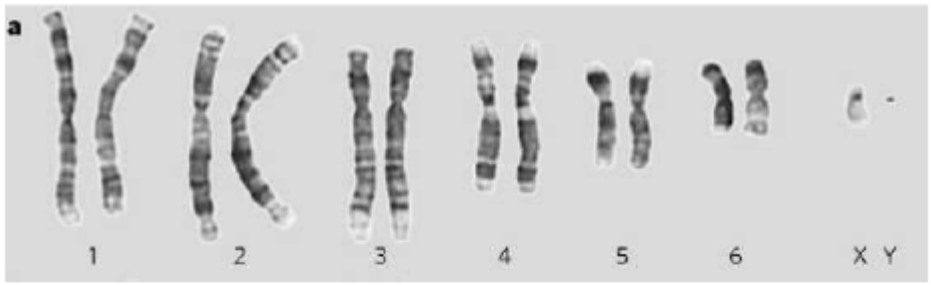
Loh et al, *Vet Pathol*, 43:890 - 895, 2006

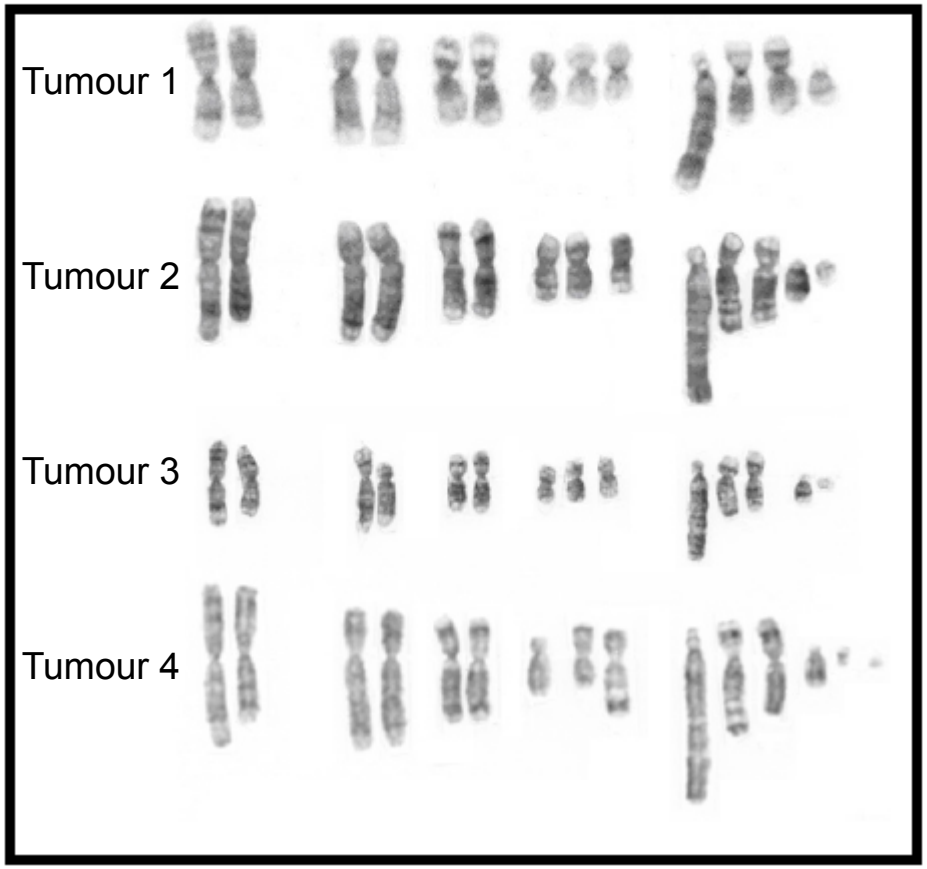
Devil cancer chromosomes



Pearse and Swift, *Nature*, 439 (7076):549, 2006

Normal devil





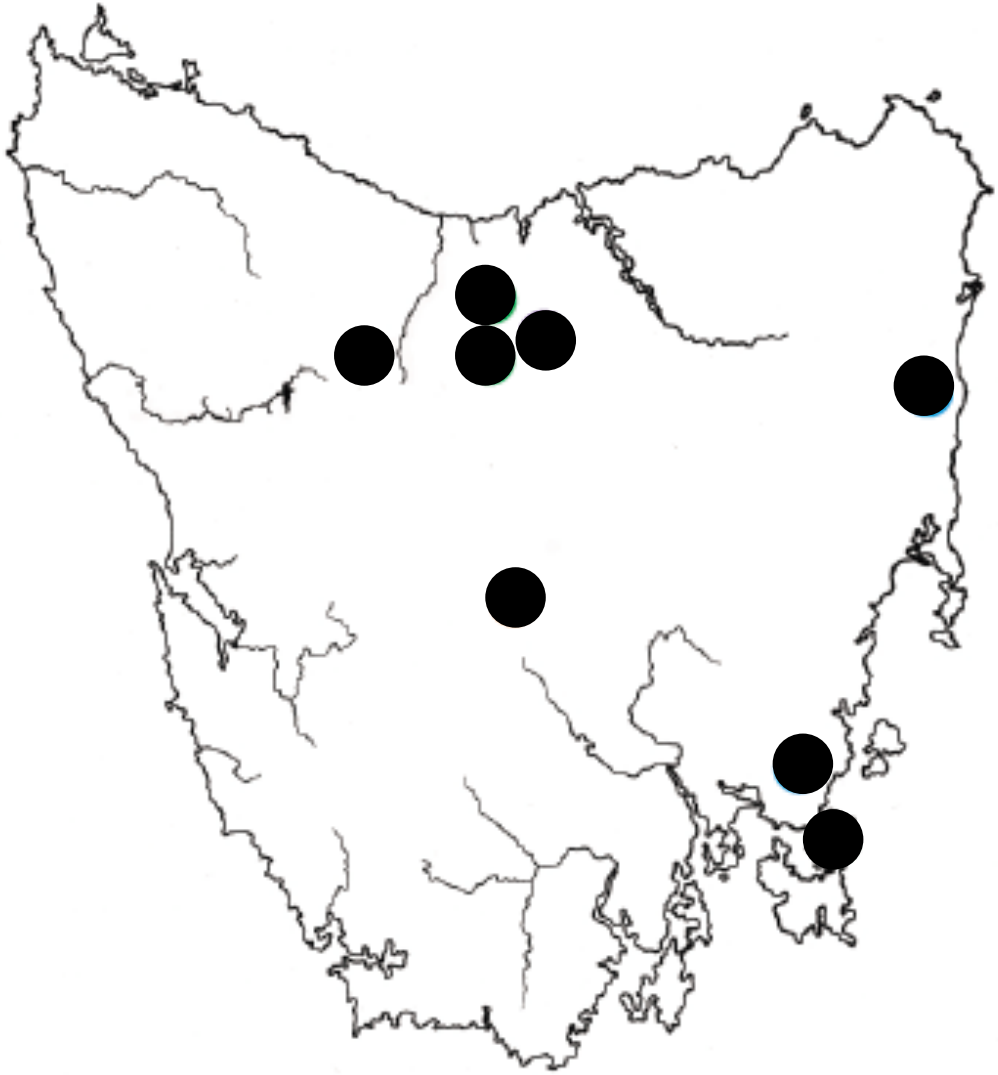
Anne-Maree Pearse, Unpublished


Photo: Christo Baars

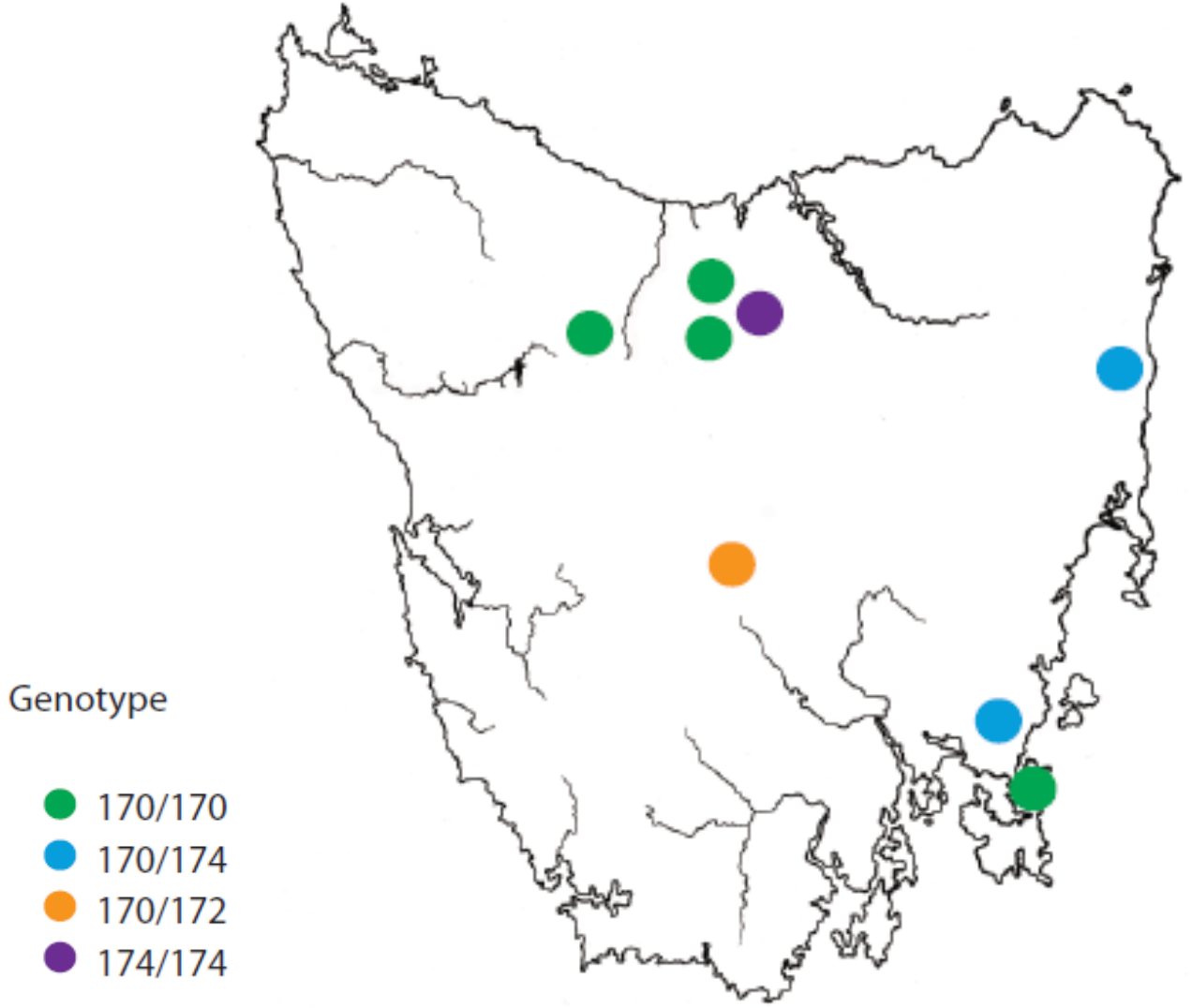
Predictions….

- If the devil's cancer is spread by living cancer cells then
  - All the cancers should be genetically identical
  - The cancers should be genetically different to their hosts

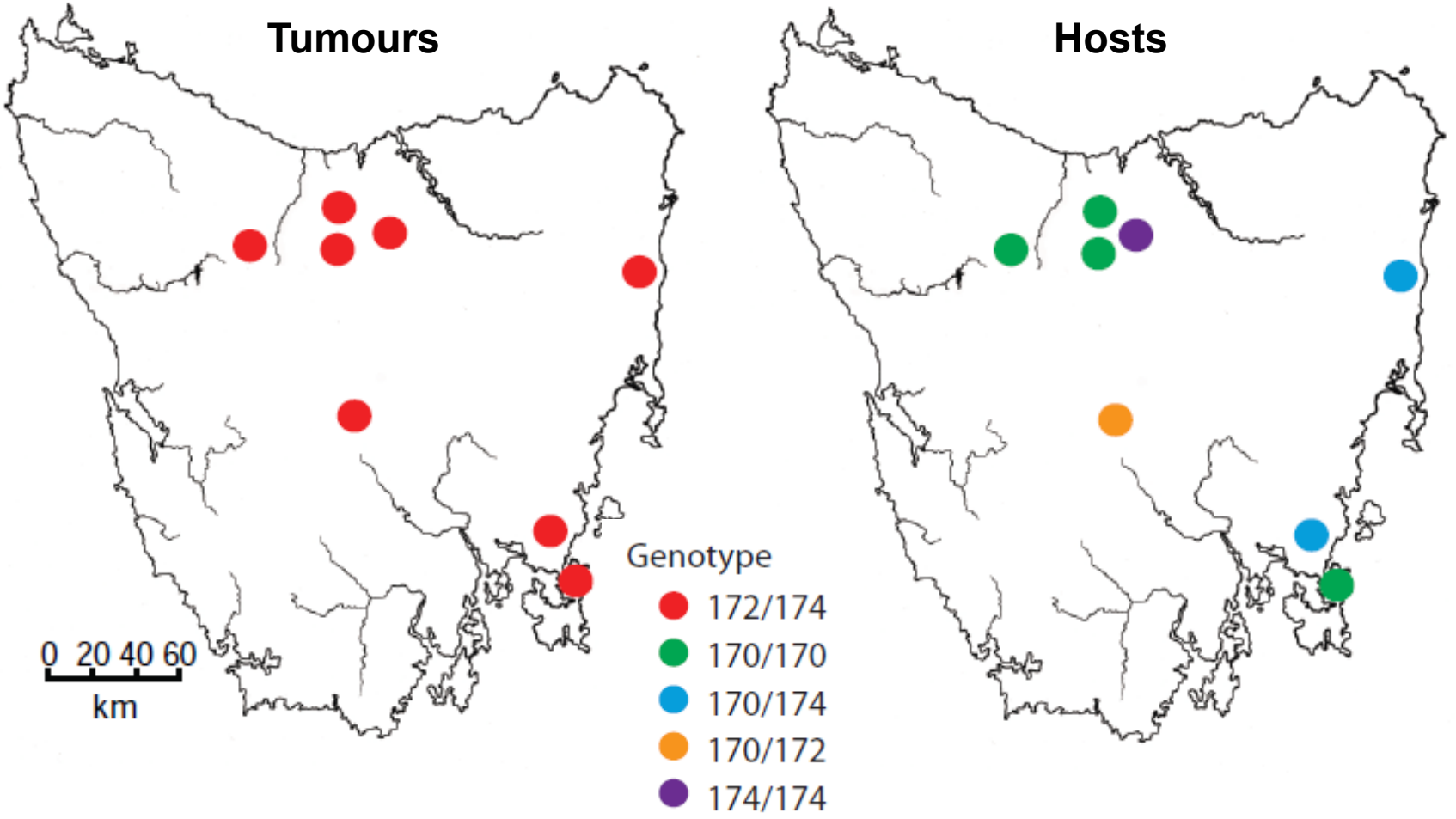
Microsatellite genotyping



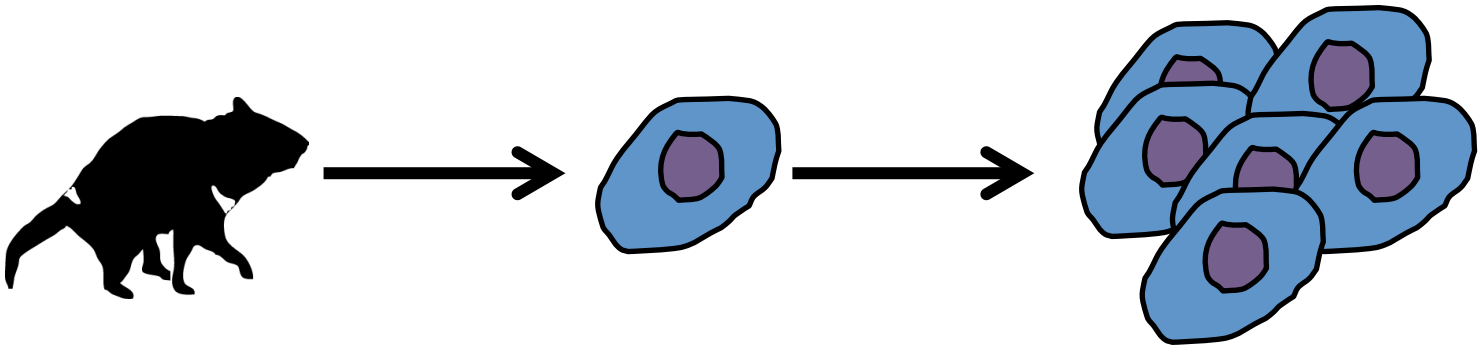
Microsatellite genotyping



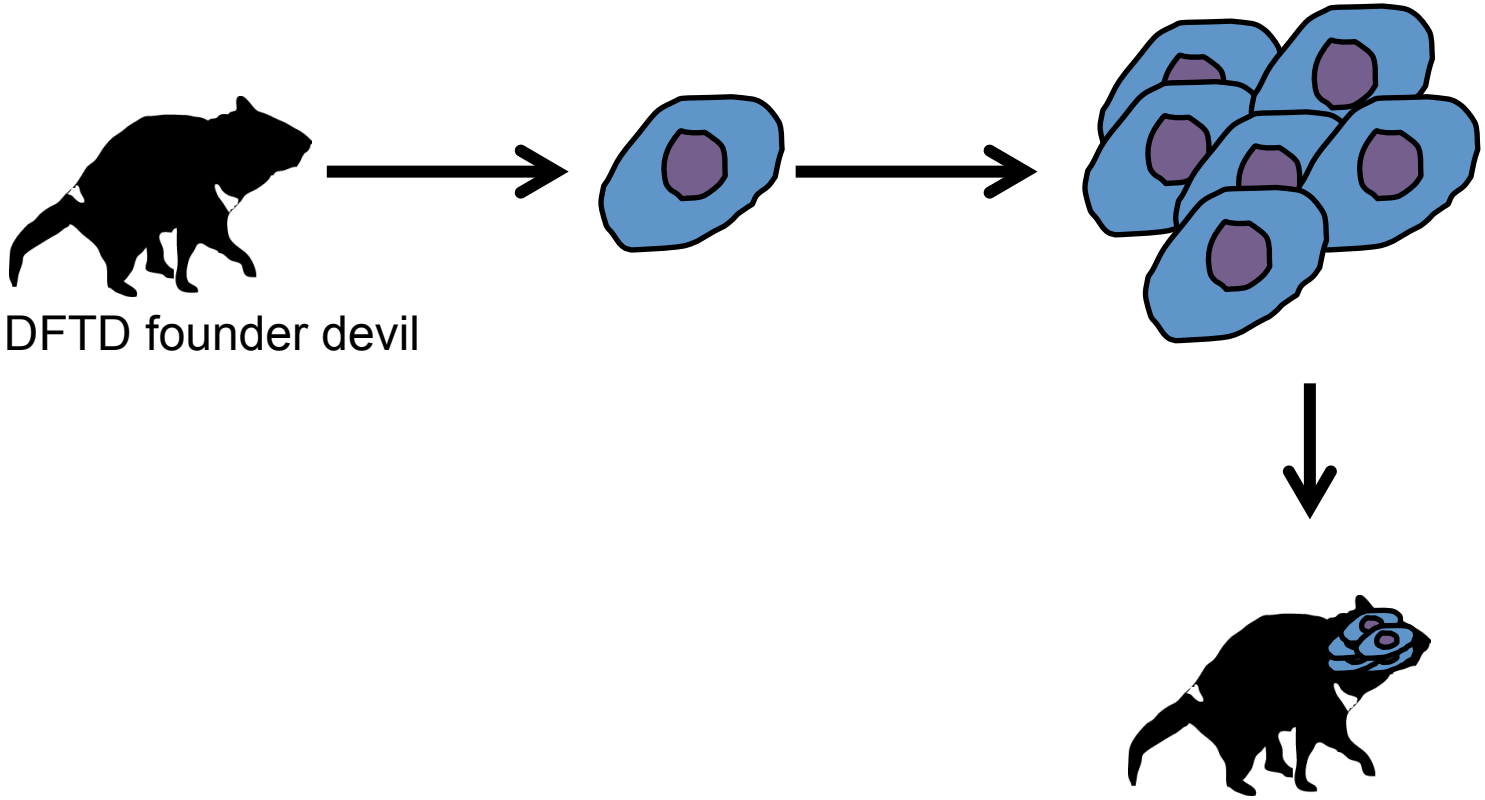
Devil tumours are genetically identical

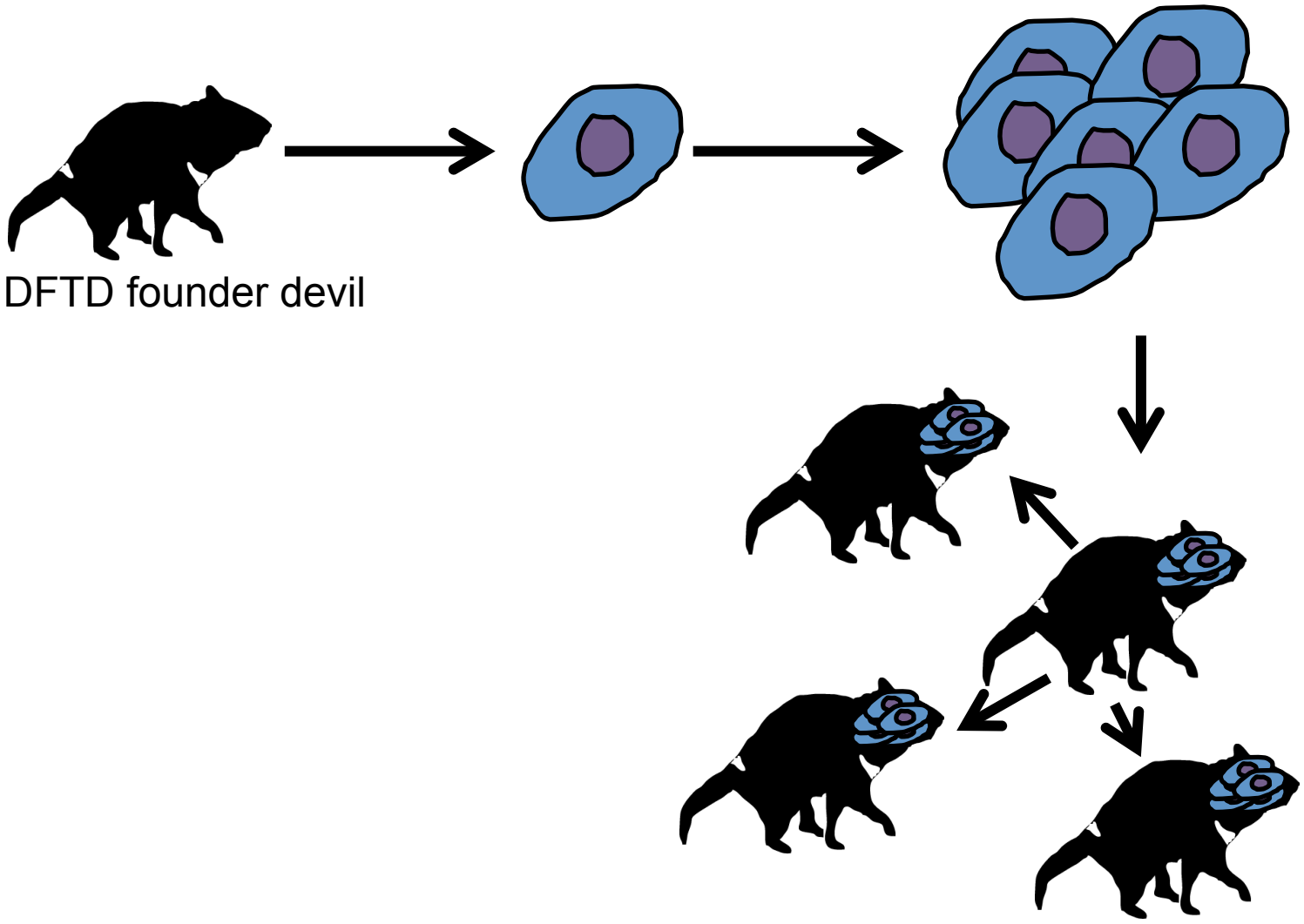


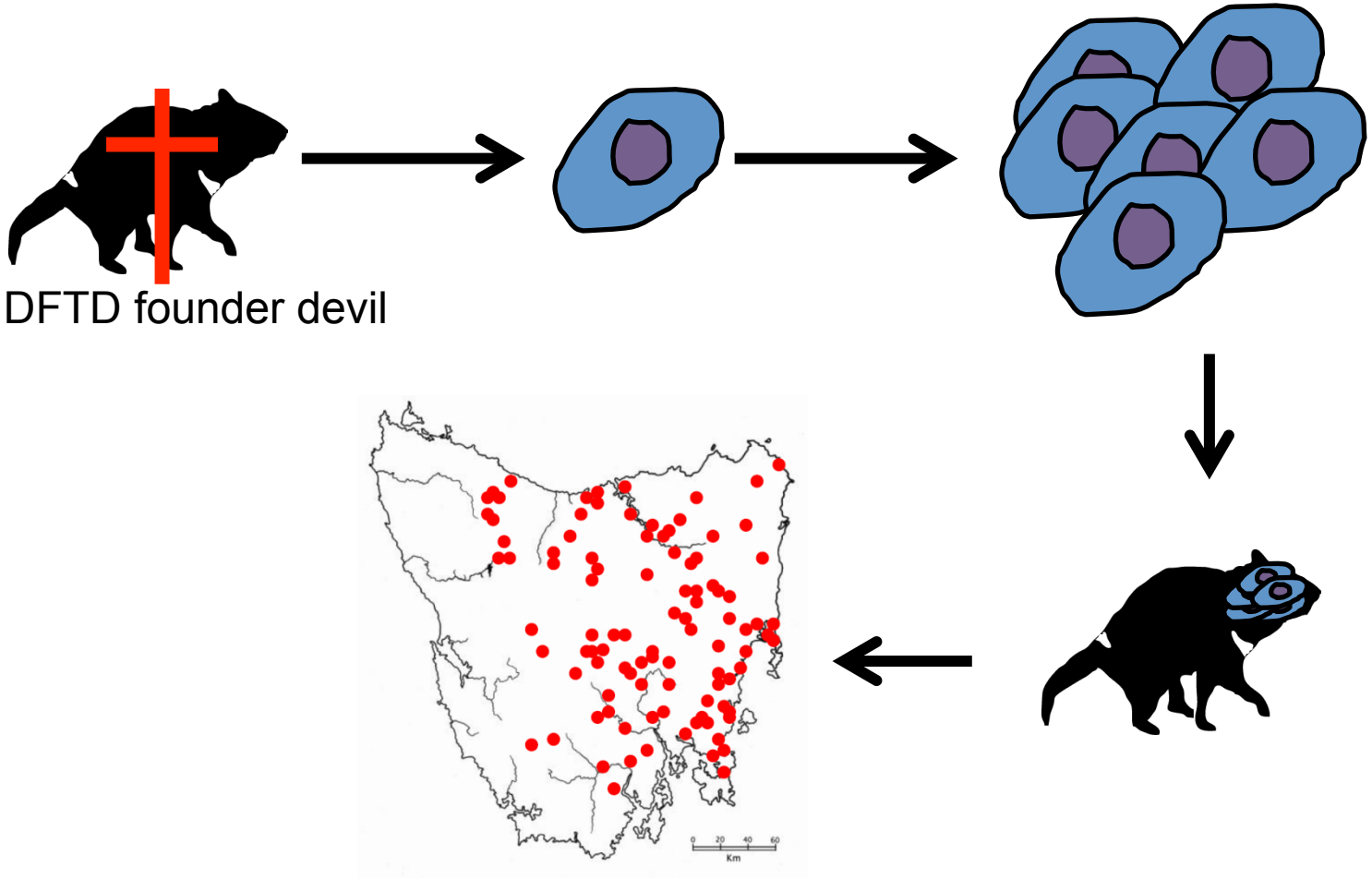
Murchison et al, *Science*, 327:84-7, 2010
Siddle et al, *PNAS*, 104 (41):16221-16226, 2007



DFTD founder devil


DFTD founder devil


DFTD founder devil


DFTD founder devil
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Km

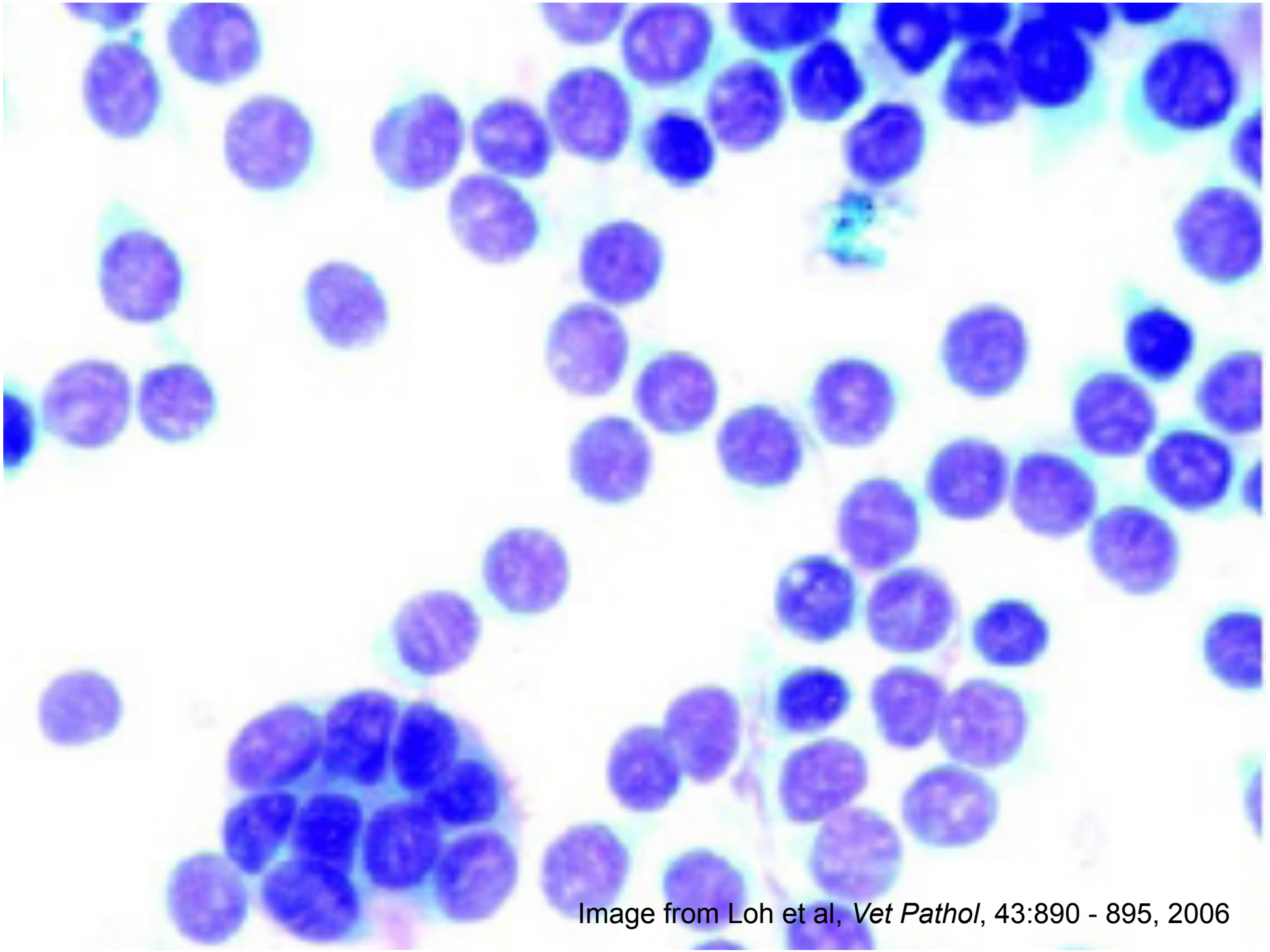


Image from Loh et al, *Vet Pathol*, 43:890 - 895, 2006


Wellcome Image Library

Tasmanian devil reference genome

Photo: Taronga Zoo

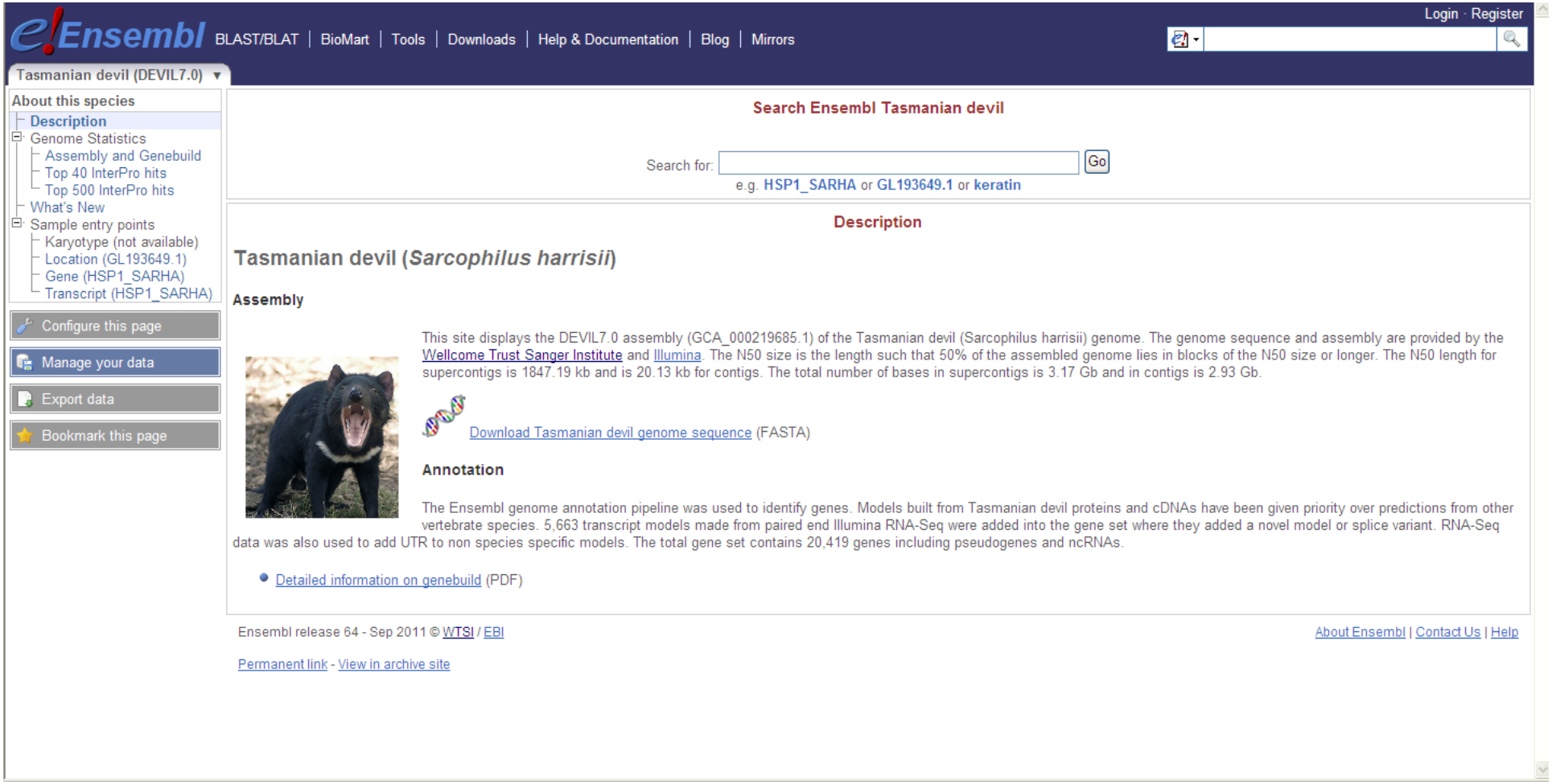
“Salem”: Female Tasmanian devil

⇩

Illumina paired end sequencing

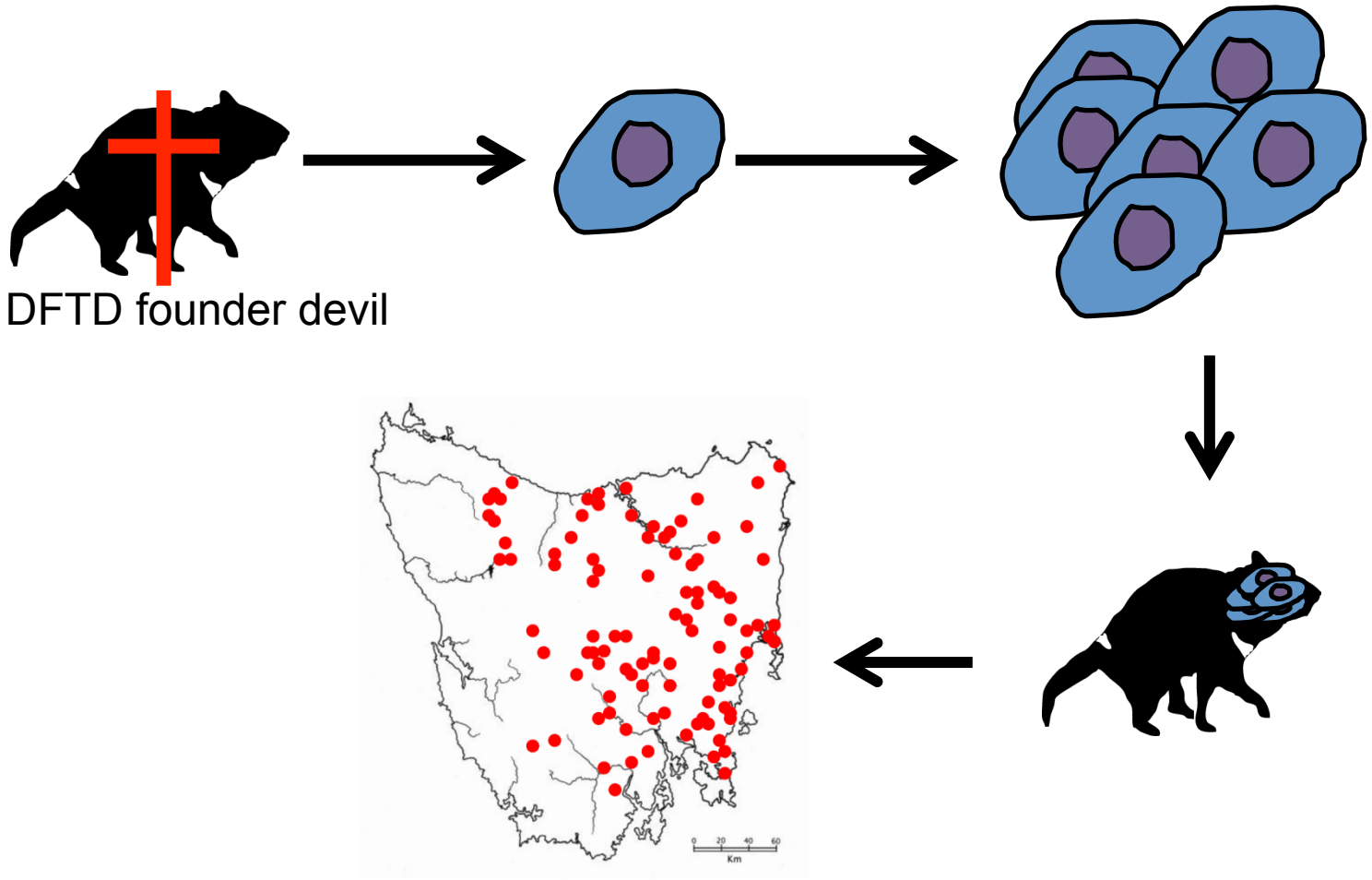
⇩

De novo assembly

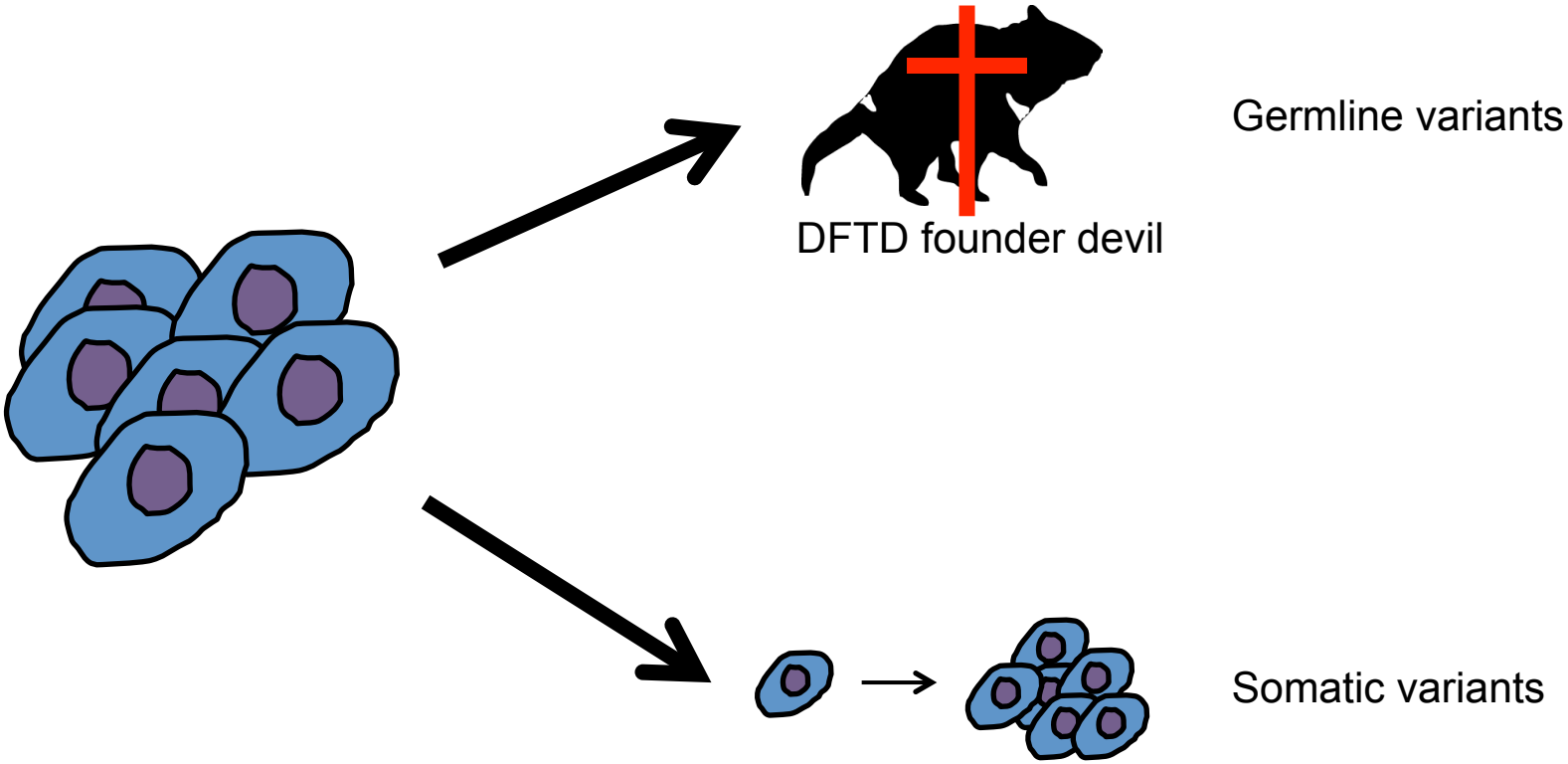


http://www.ensembl.org/Sarcophilus_harrisii

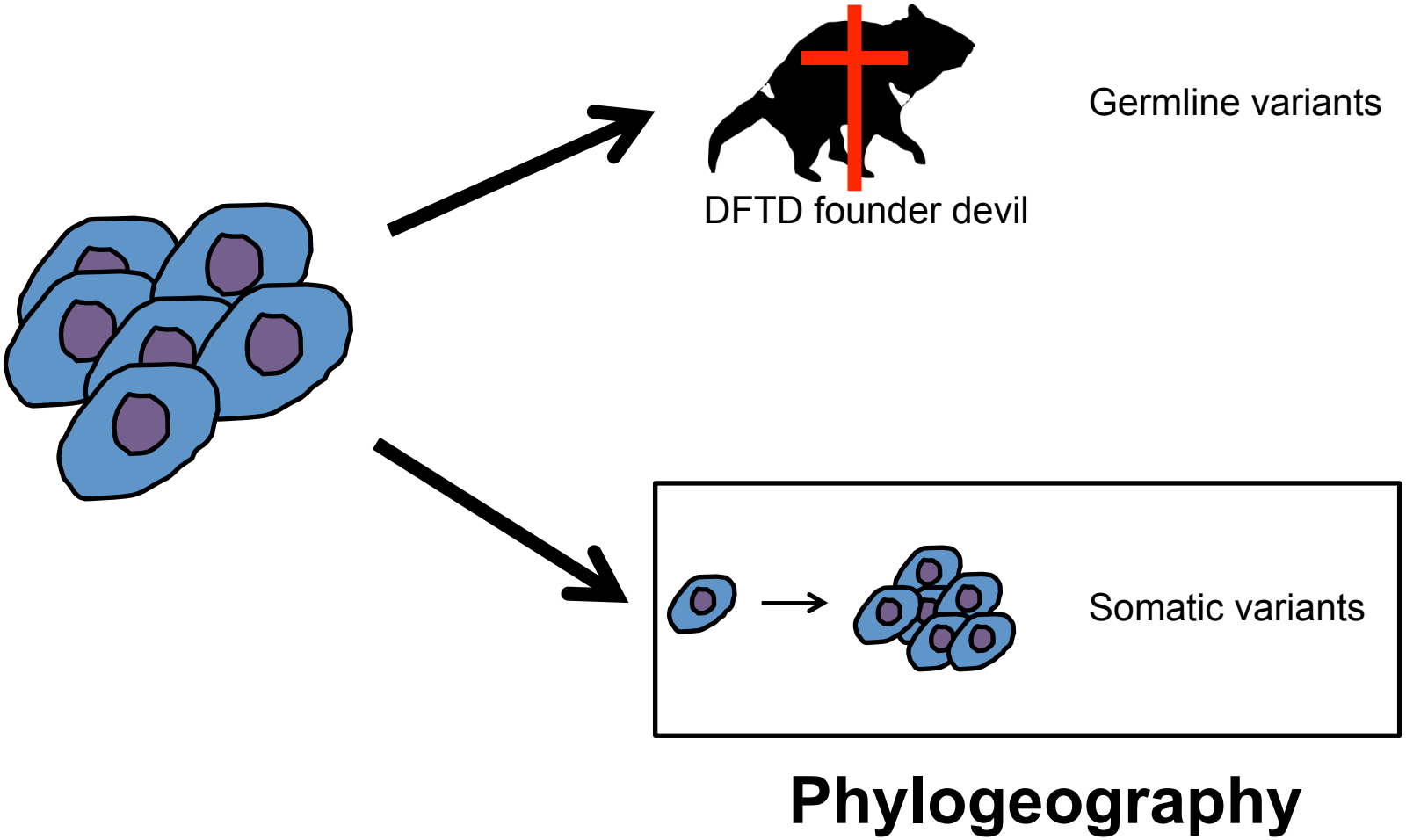
Sequencing the DFTD genome



The DFTD genome

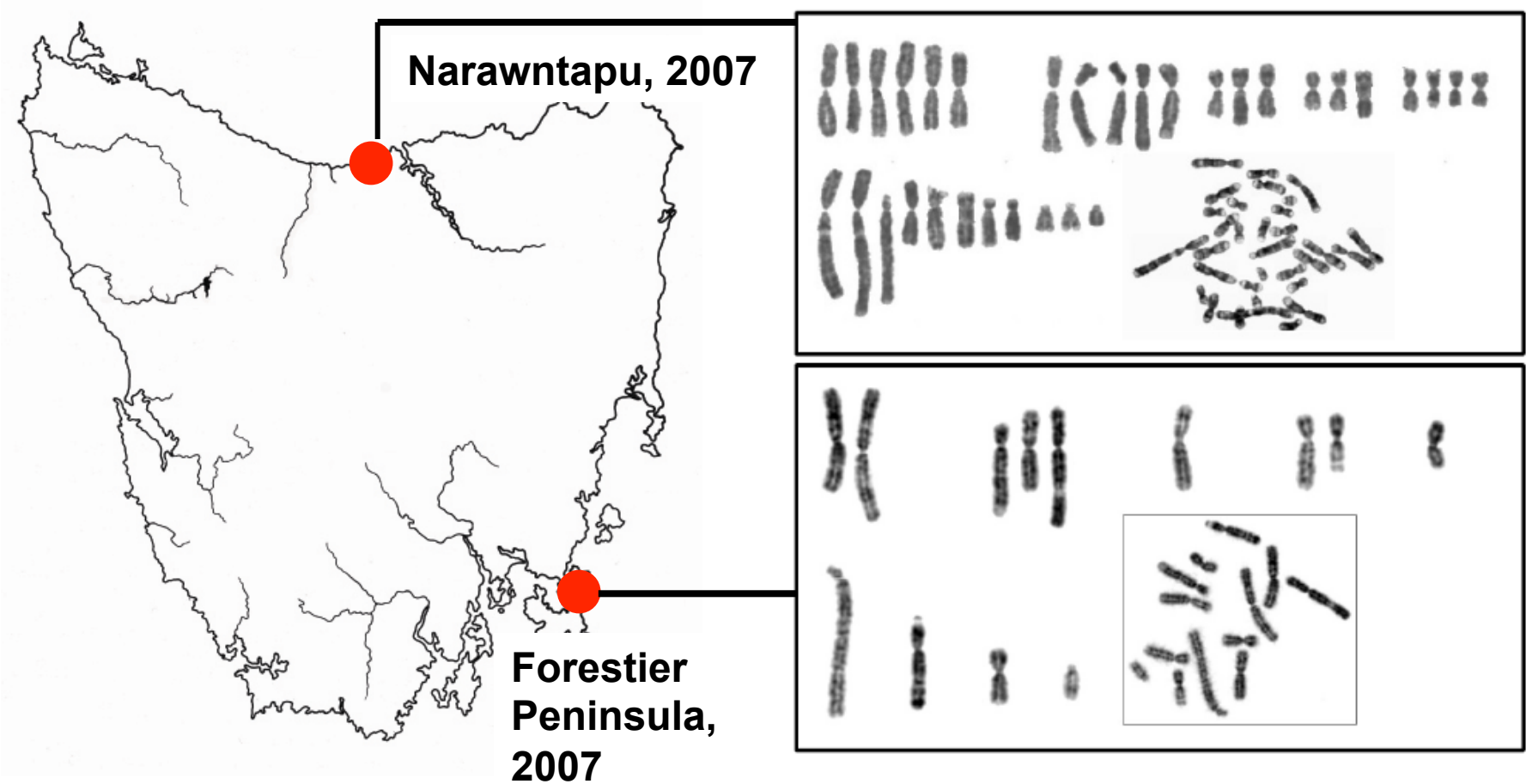


The DFTD genome



How many somatic mutations are present in DFTD?

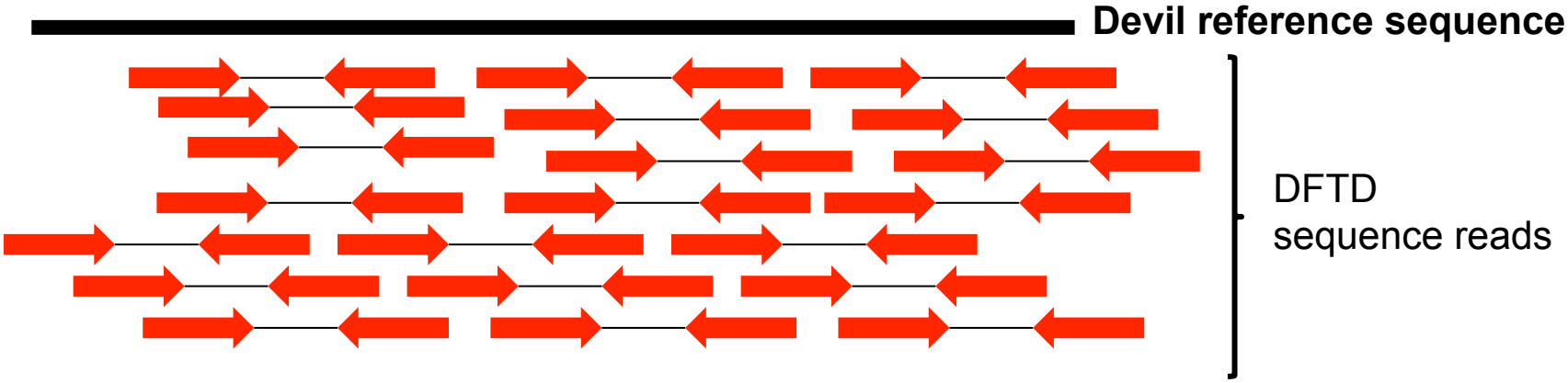
Tasmanian devil cancer genome sequencing



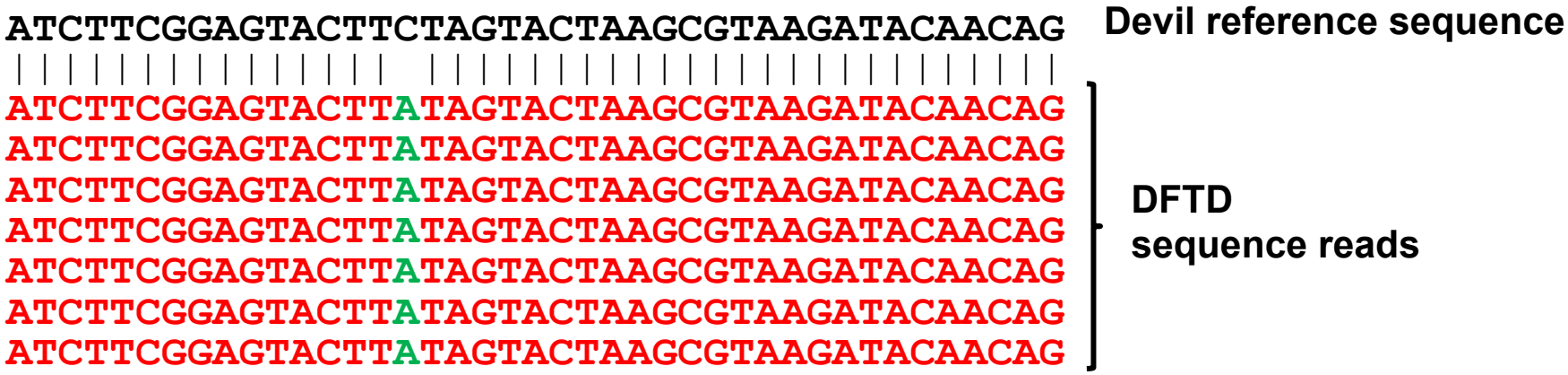
DFTD genome sequencing

~2 x 10^9 paired end sequence reads

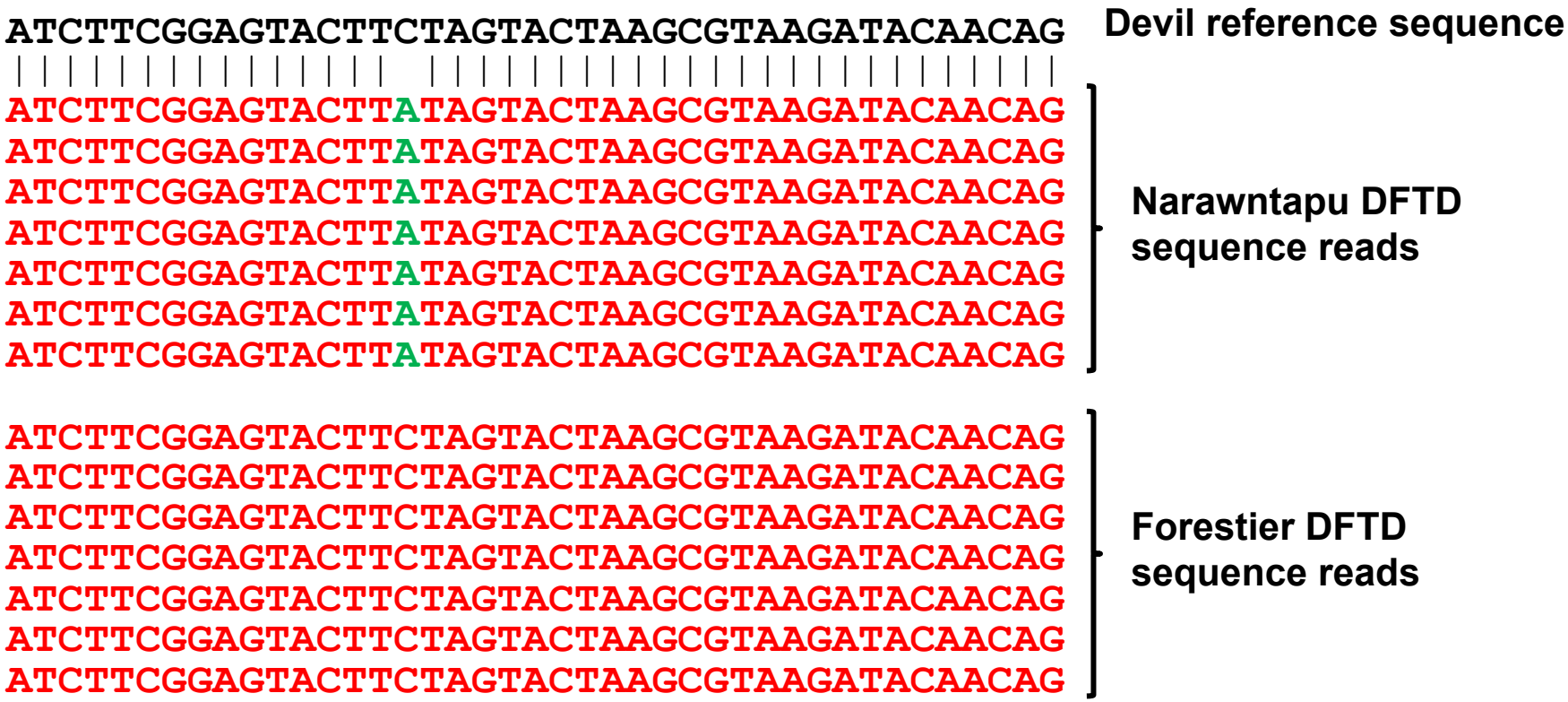
DFTD genome analysis



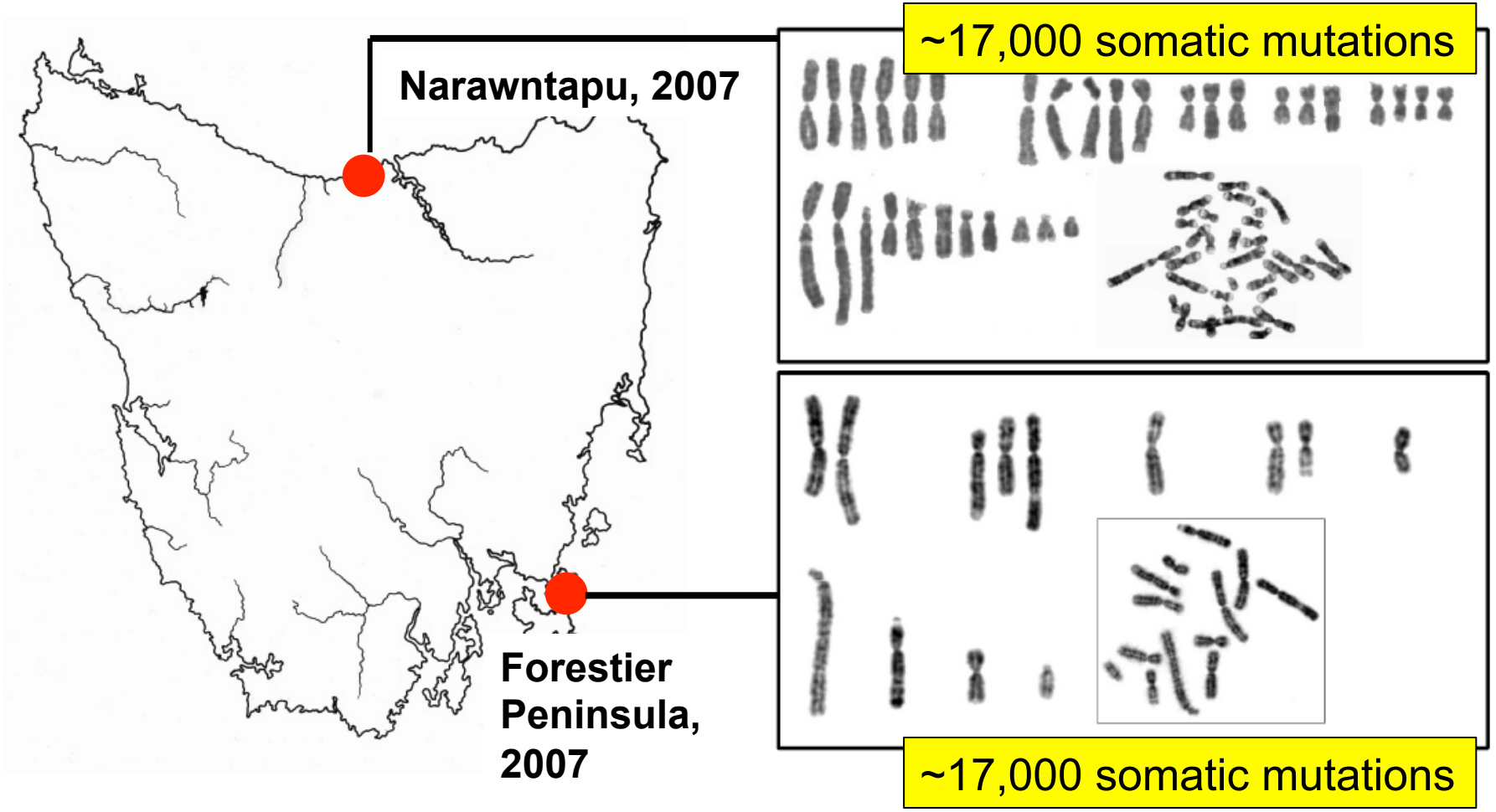
DFTD variant calling



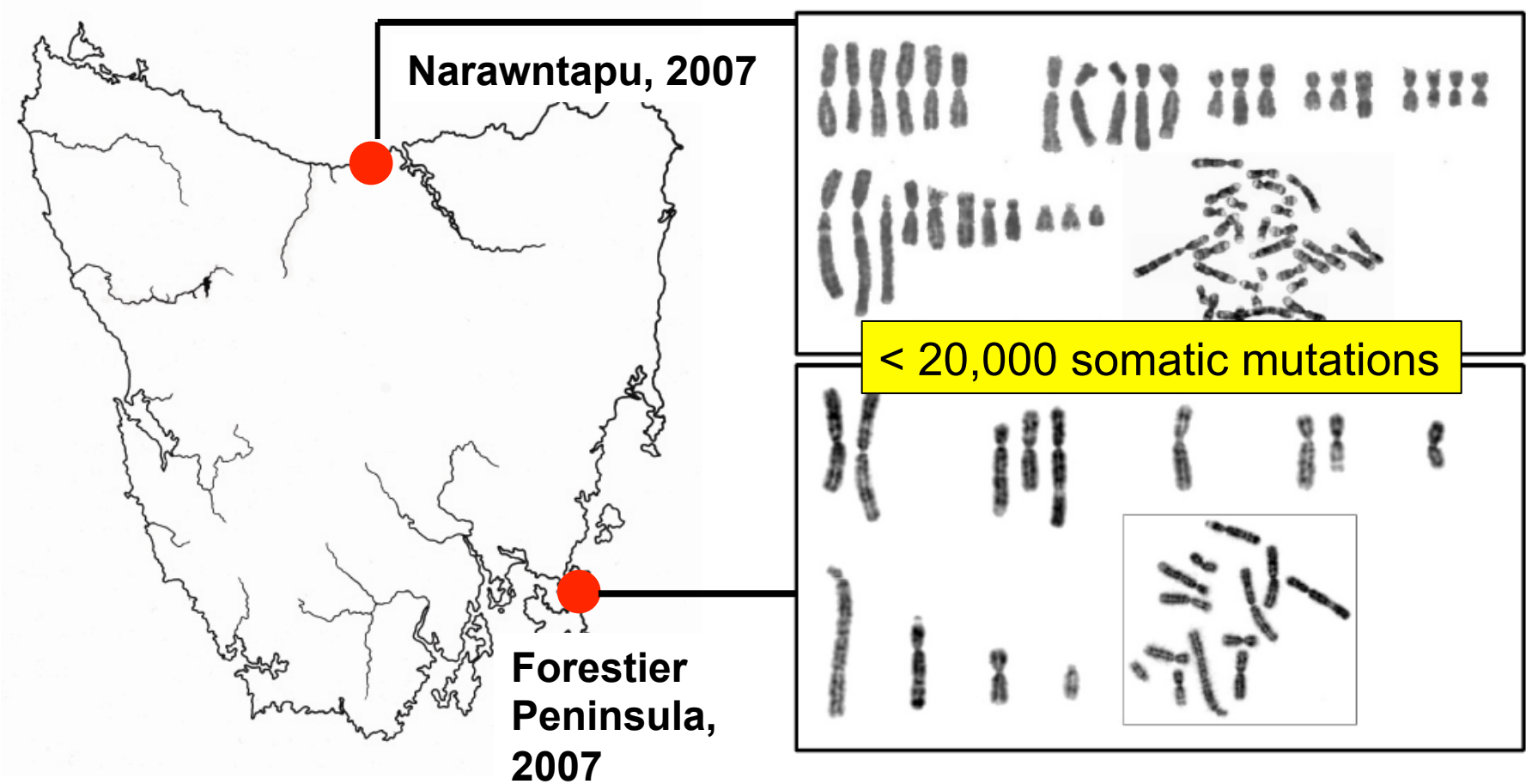
DFTD variant calling



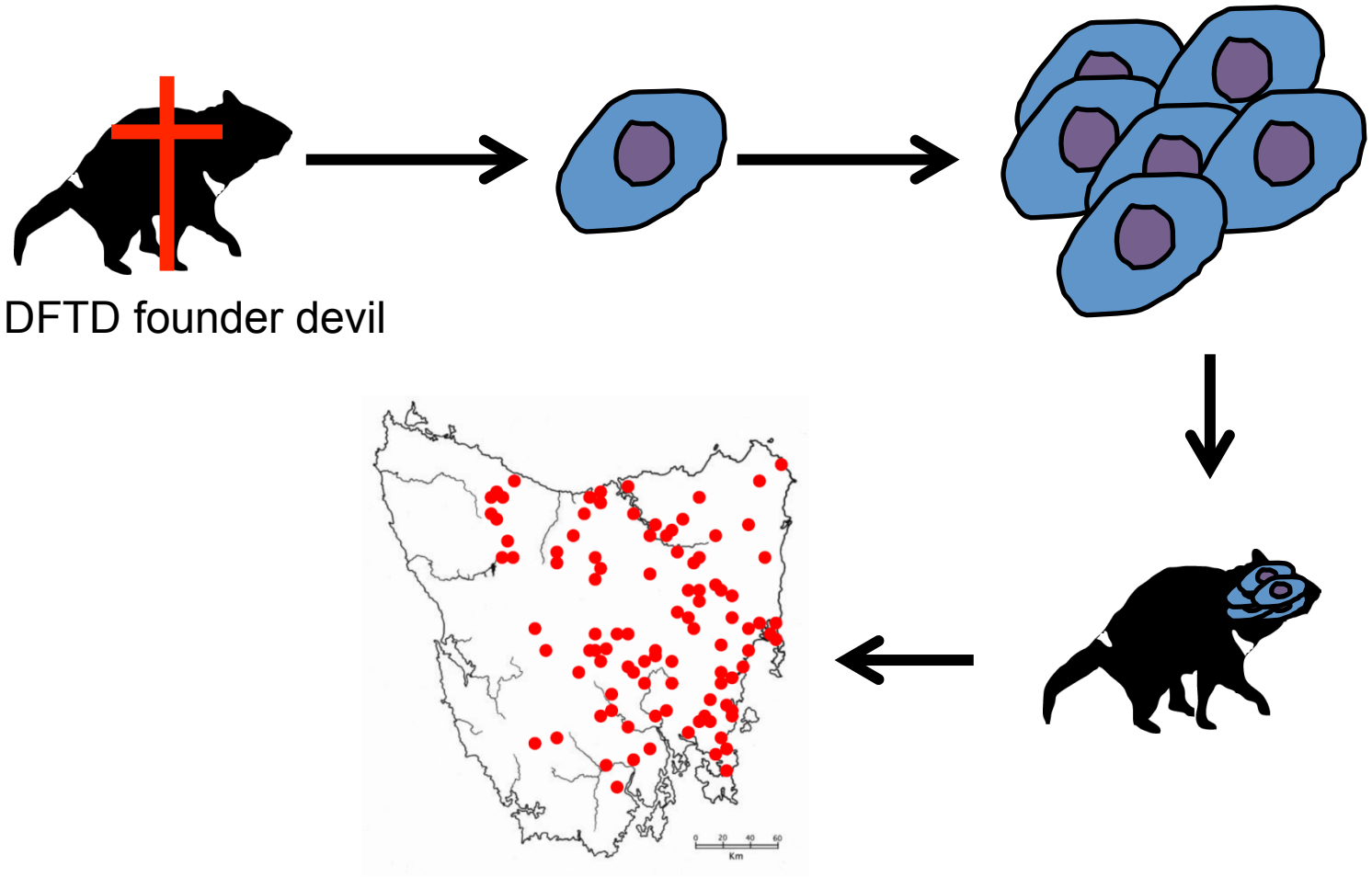
Tasmanian devil cancer genomes



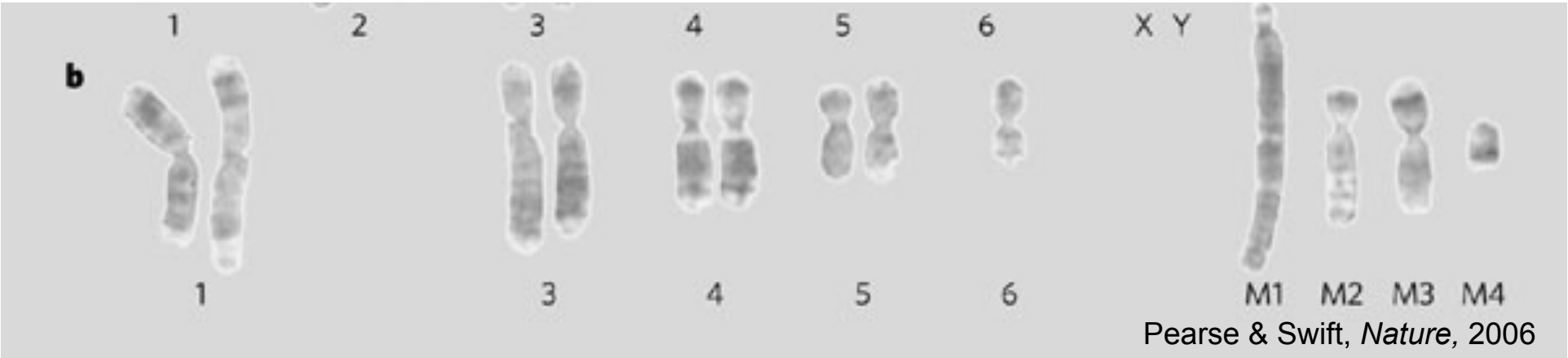
Tasmanian devil cancer genomes



DFTD founder devil

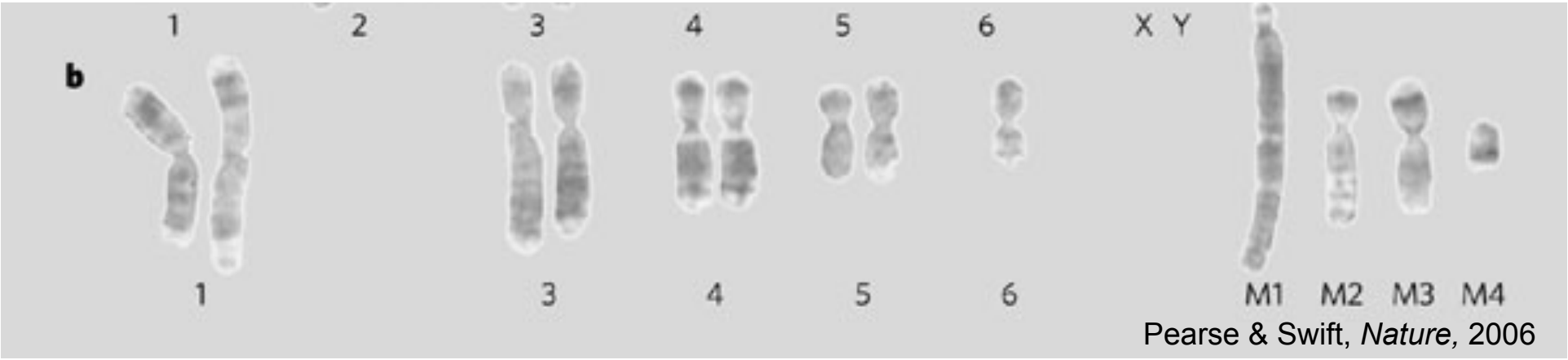


Gender of the founder devil



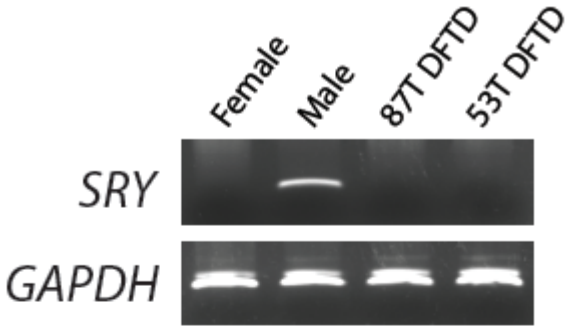
Pearse & Swift, *Nature,* 2006

Gender of the founder devil

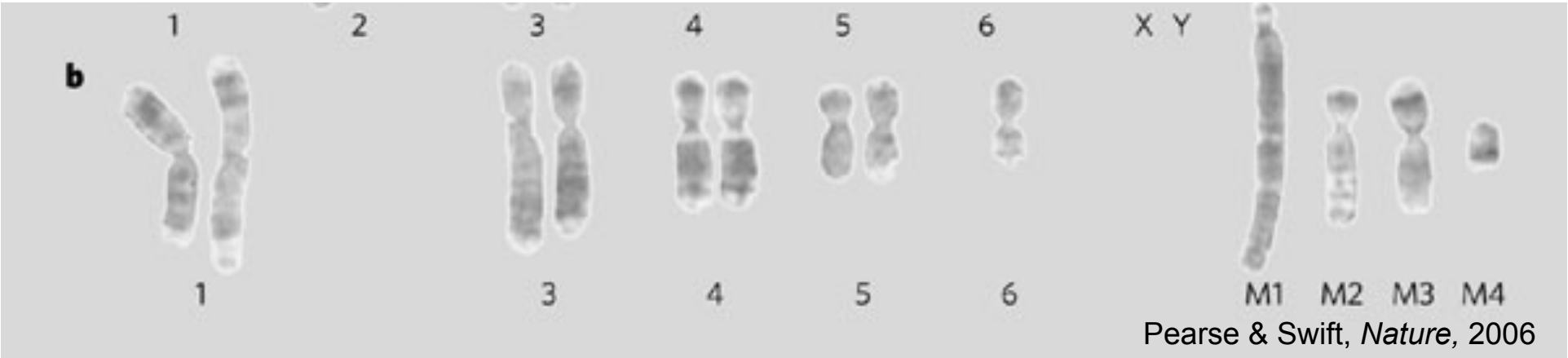


Pearse & Swift, *Nature,* 2006

Y chromosome

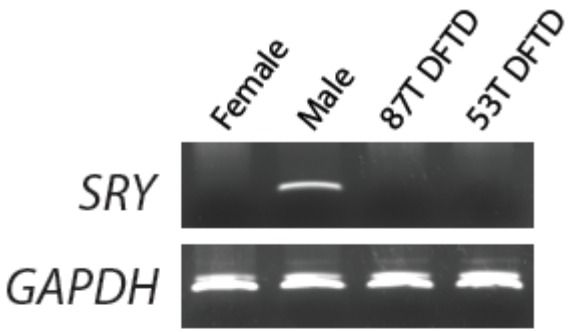


Gender of the founder devil

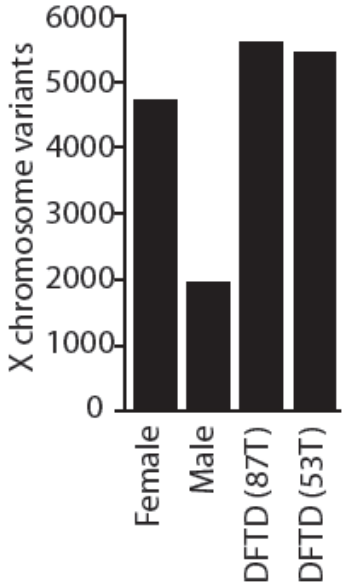


Pearse & Swift, *Nature,* 2006

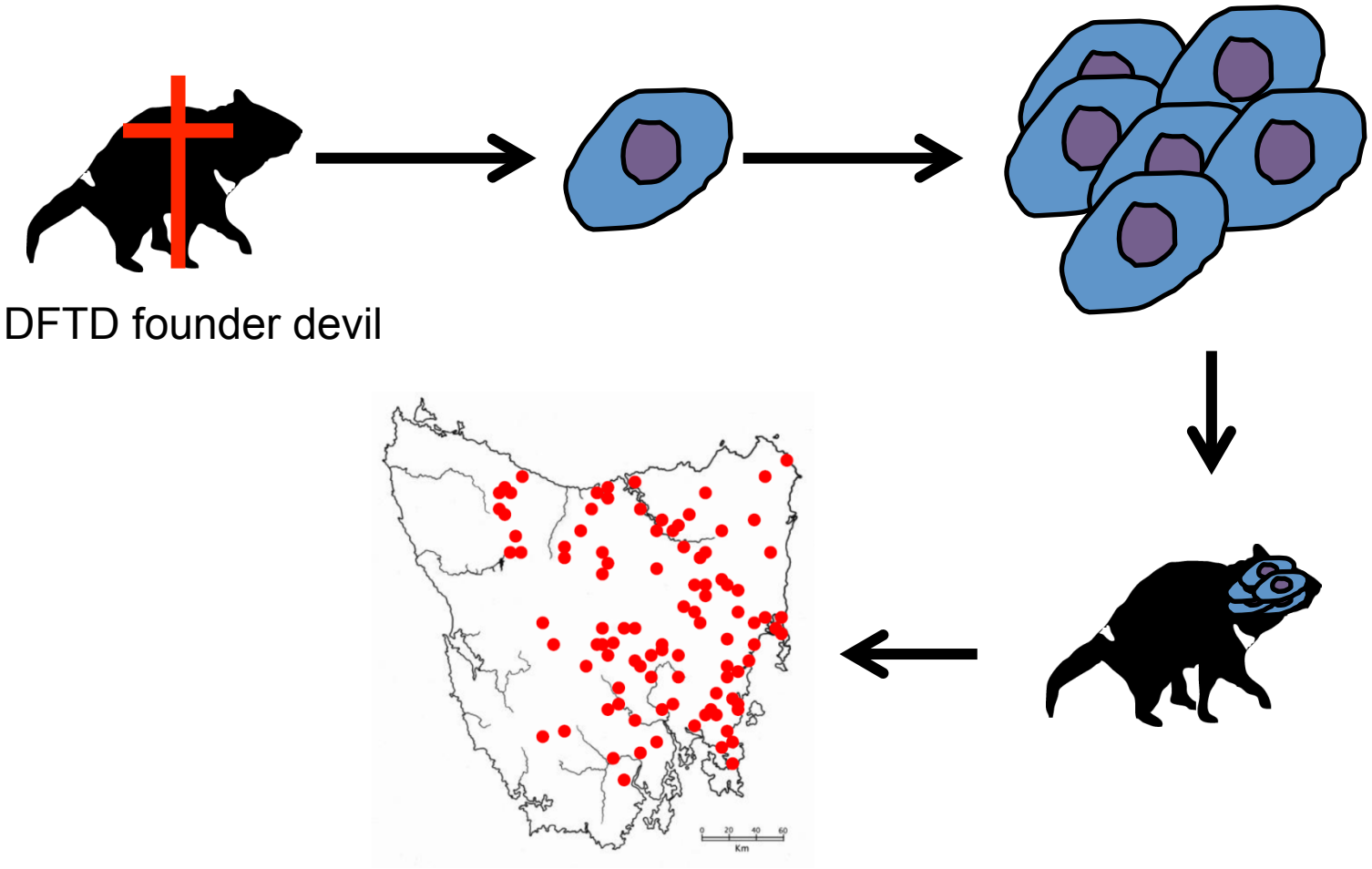
Y chromosome



X chromosome



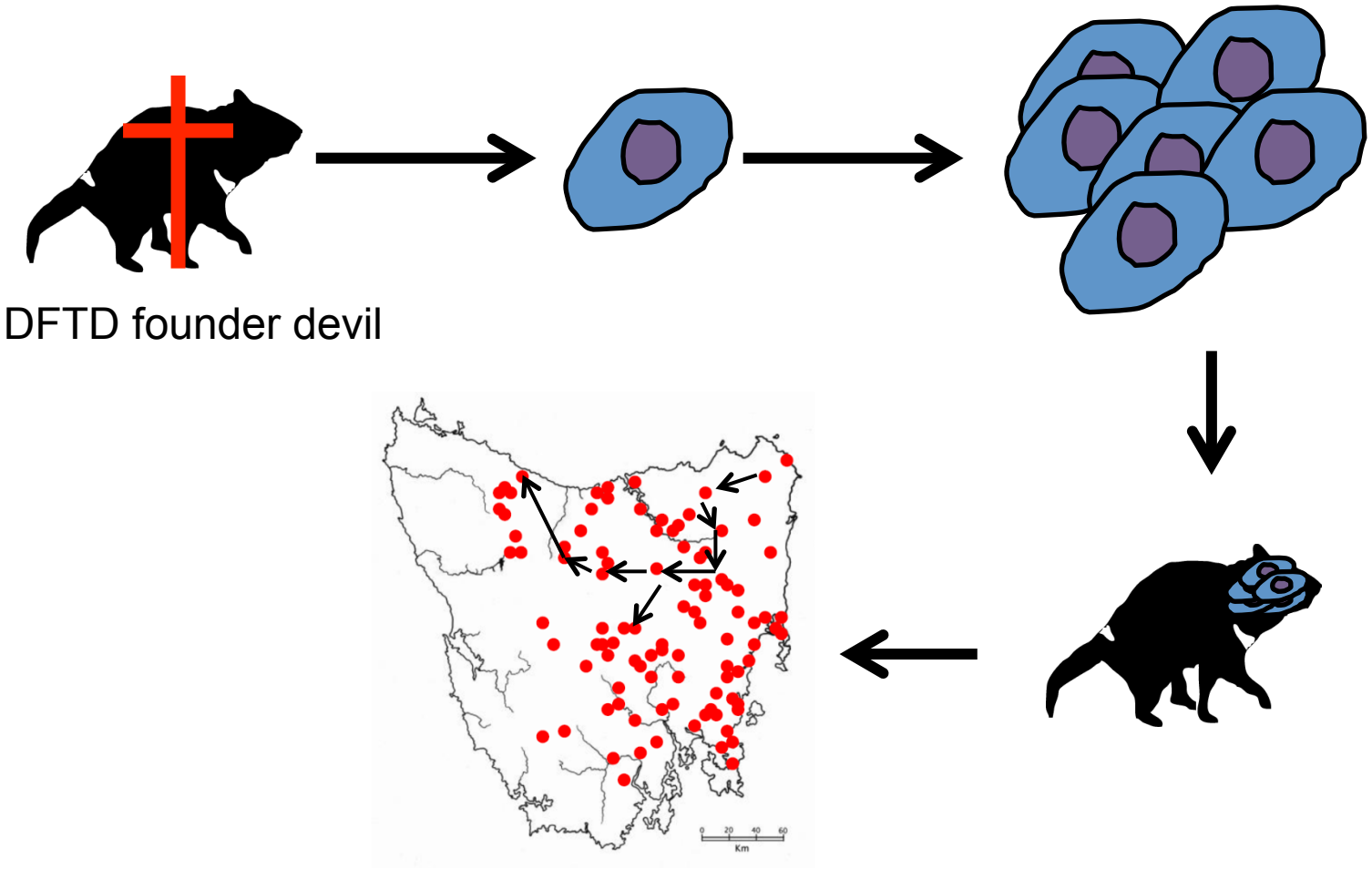
Summary



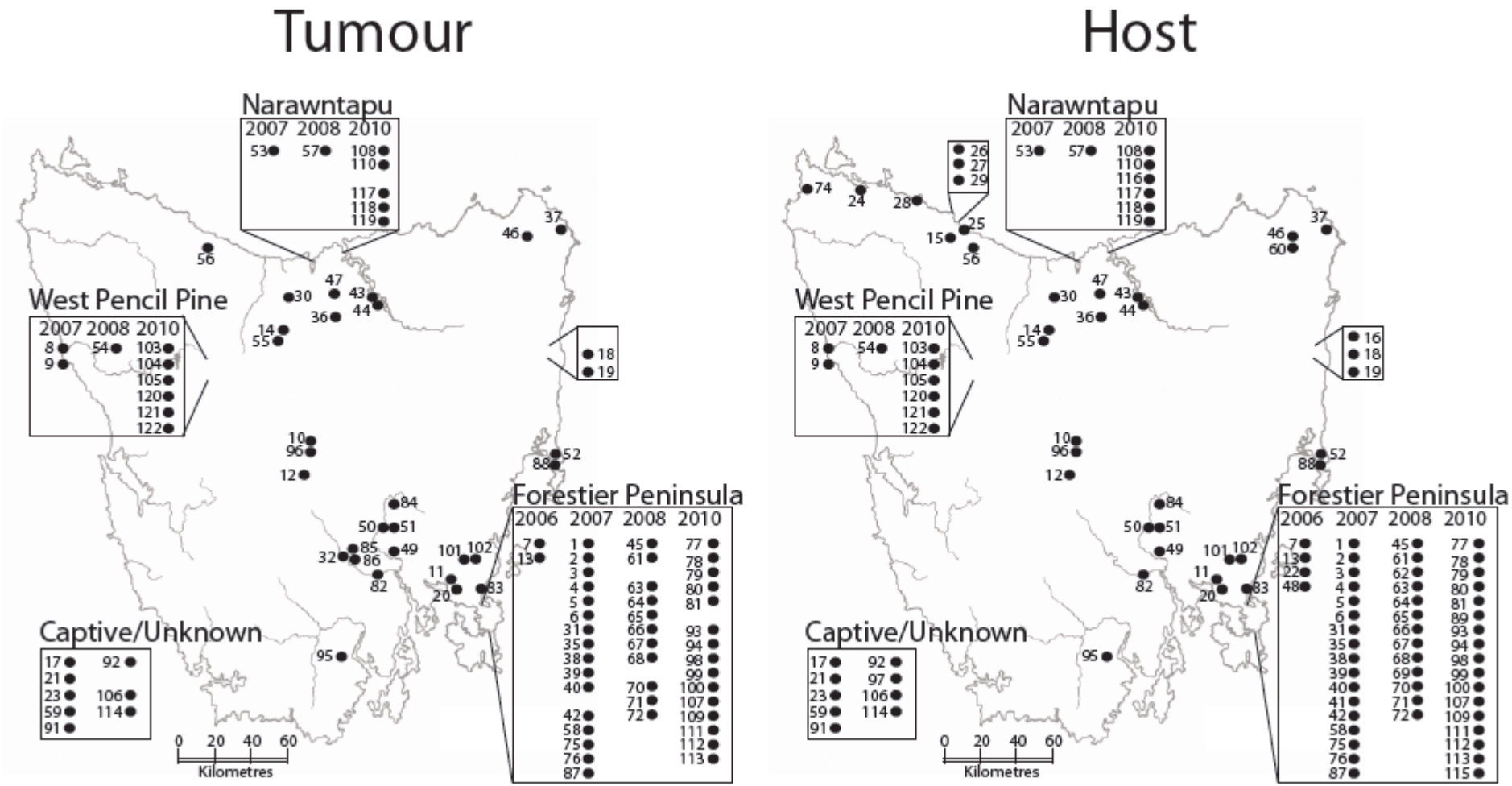
DFTD founder devil

Murchison et al *Cell* 148:1-12(2012)

Cancer phylogeography

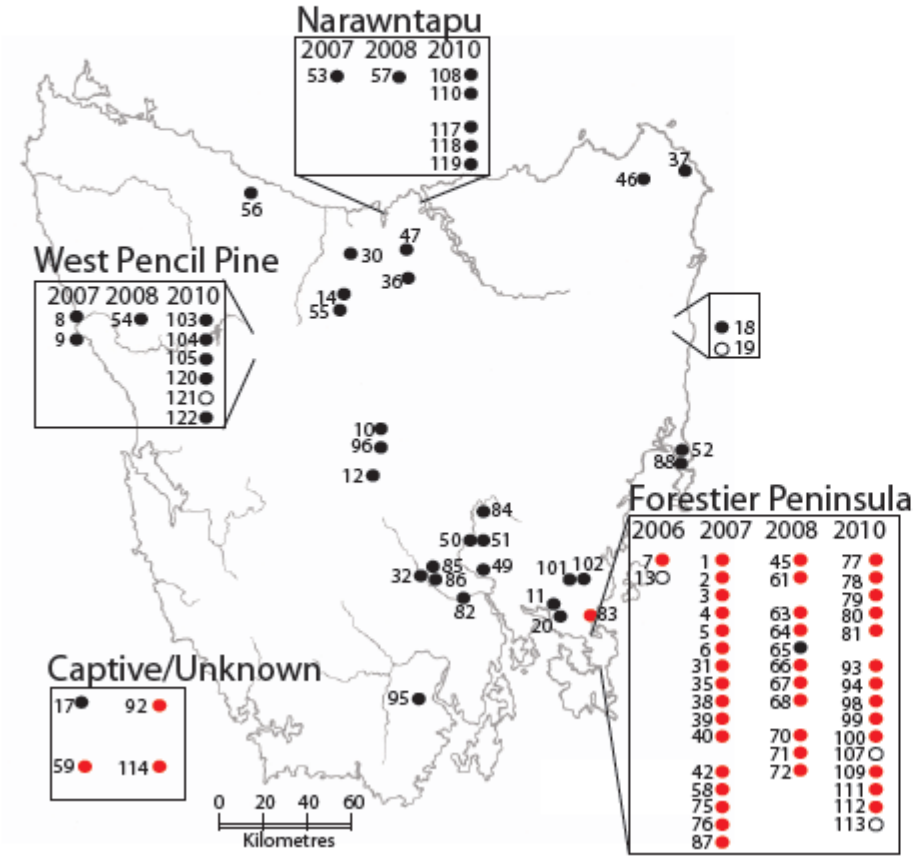


Devil samples

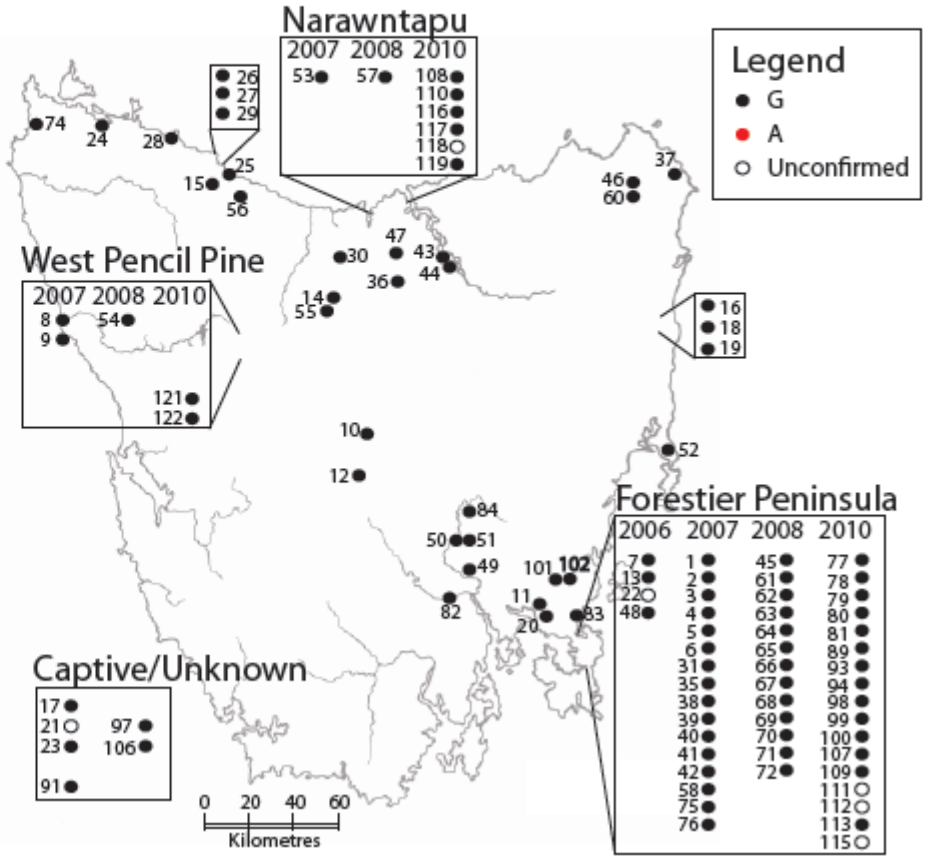


MT:3297 G>A

Tumour

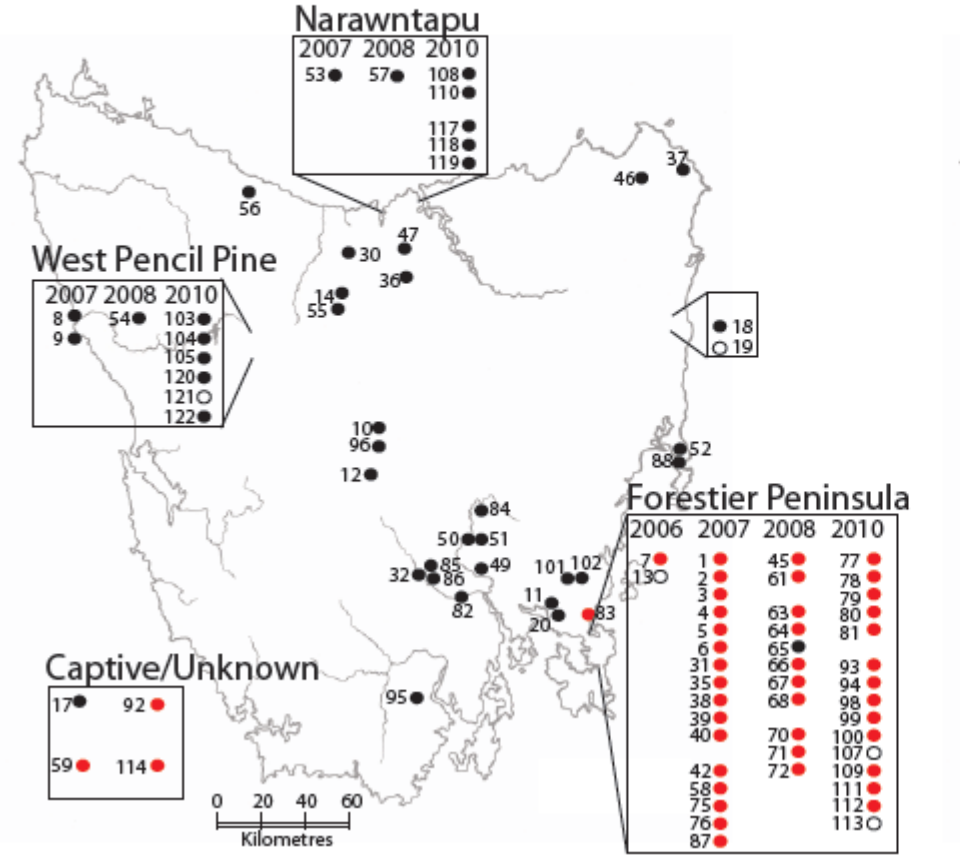


Host



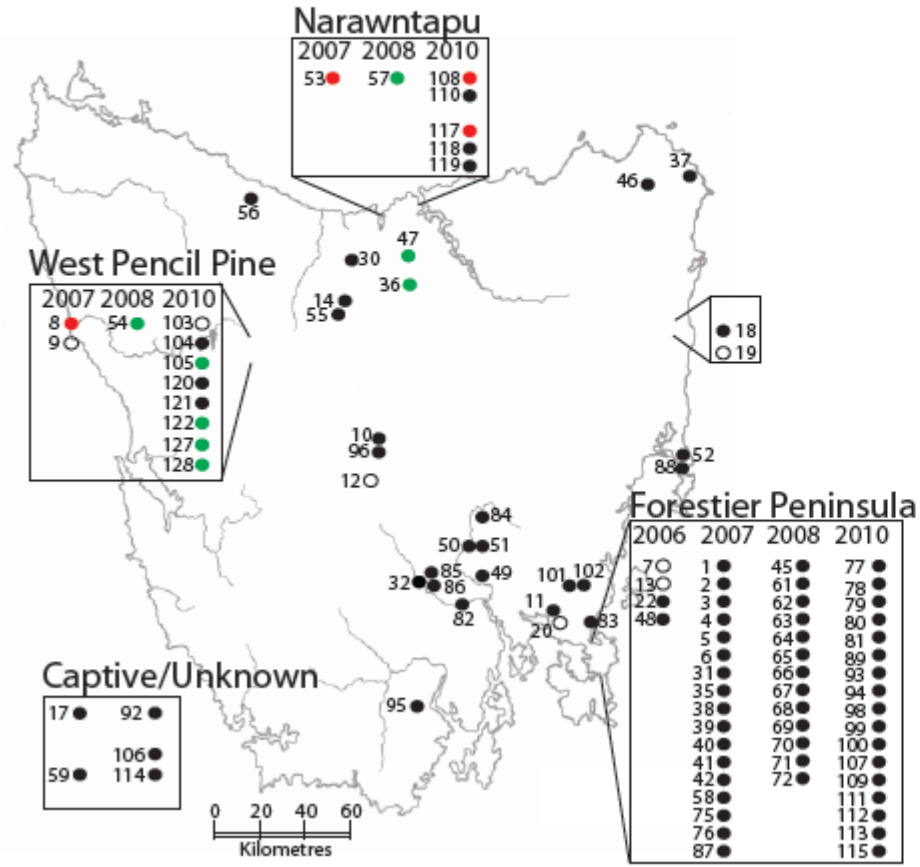
MT:3297 G>A

Tumour



Chromosome 1_supercontig_000000246:95466 T>C

Tumour



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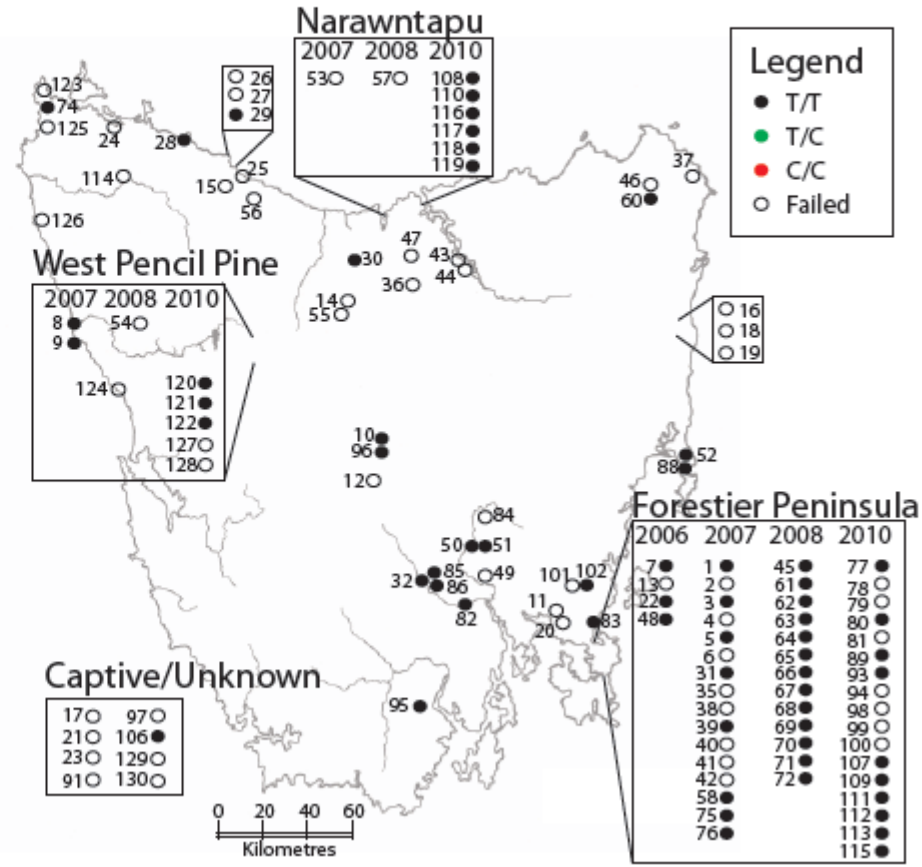
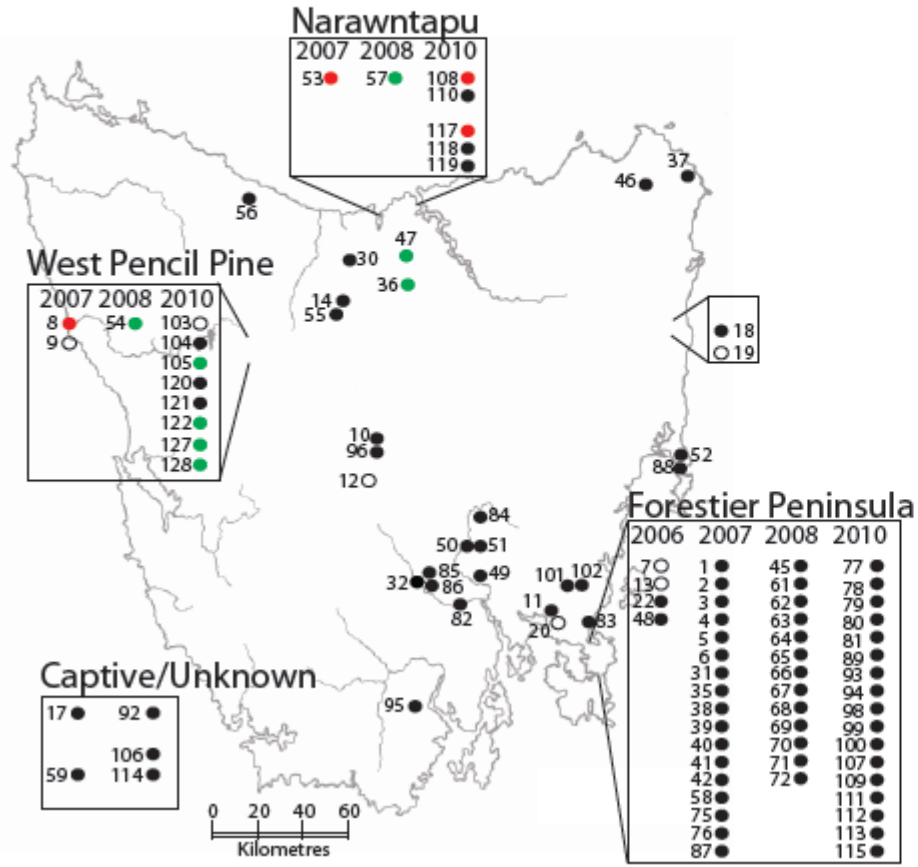
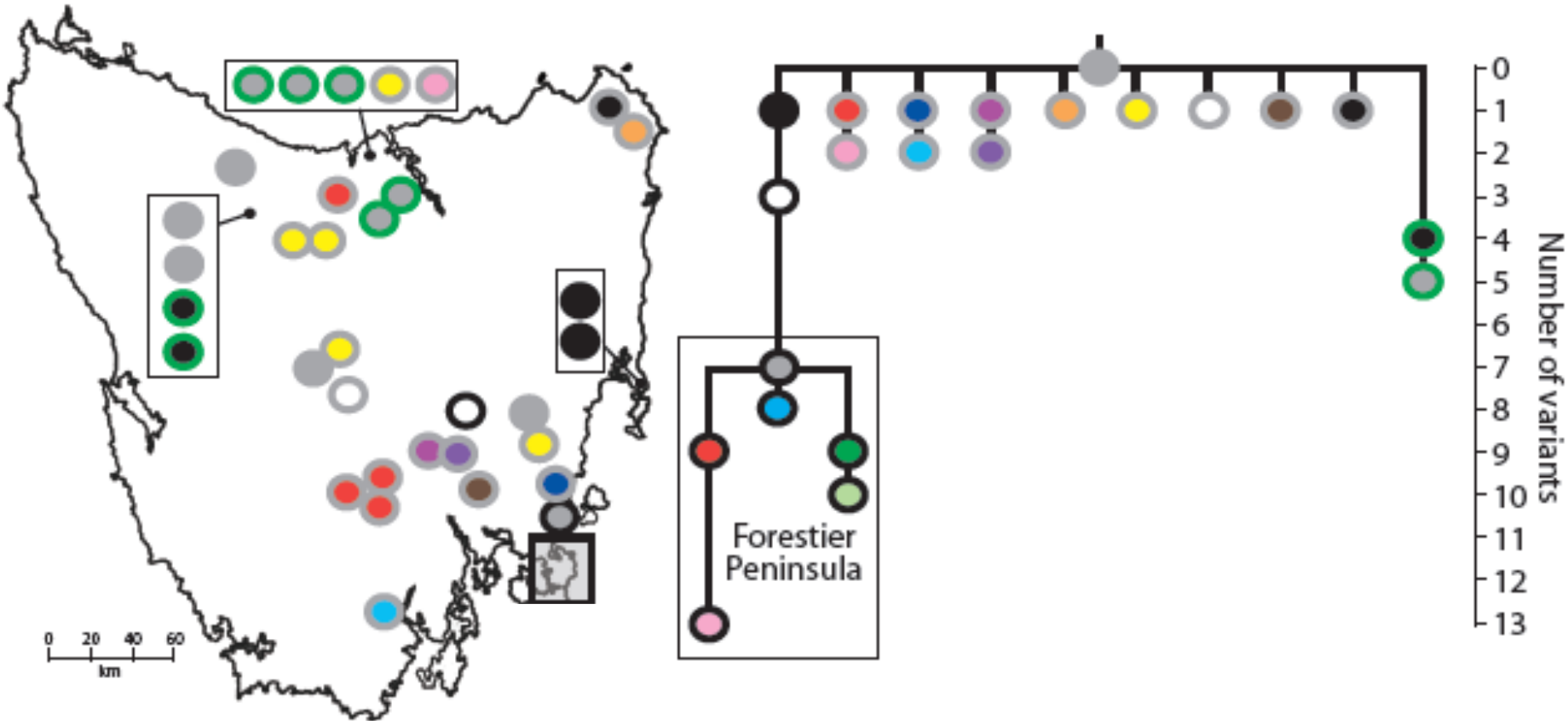
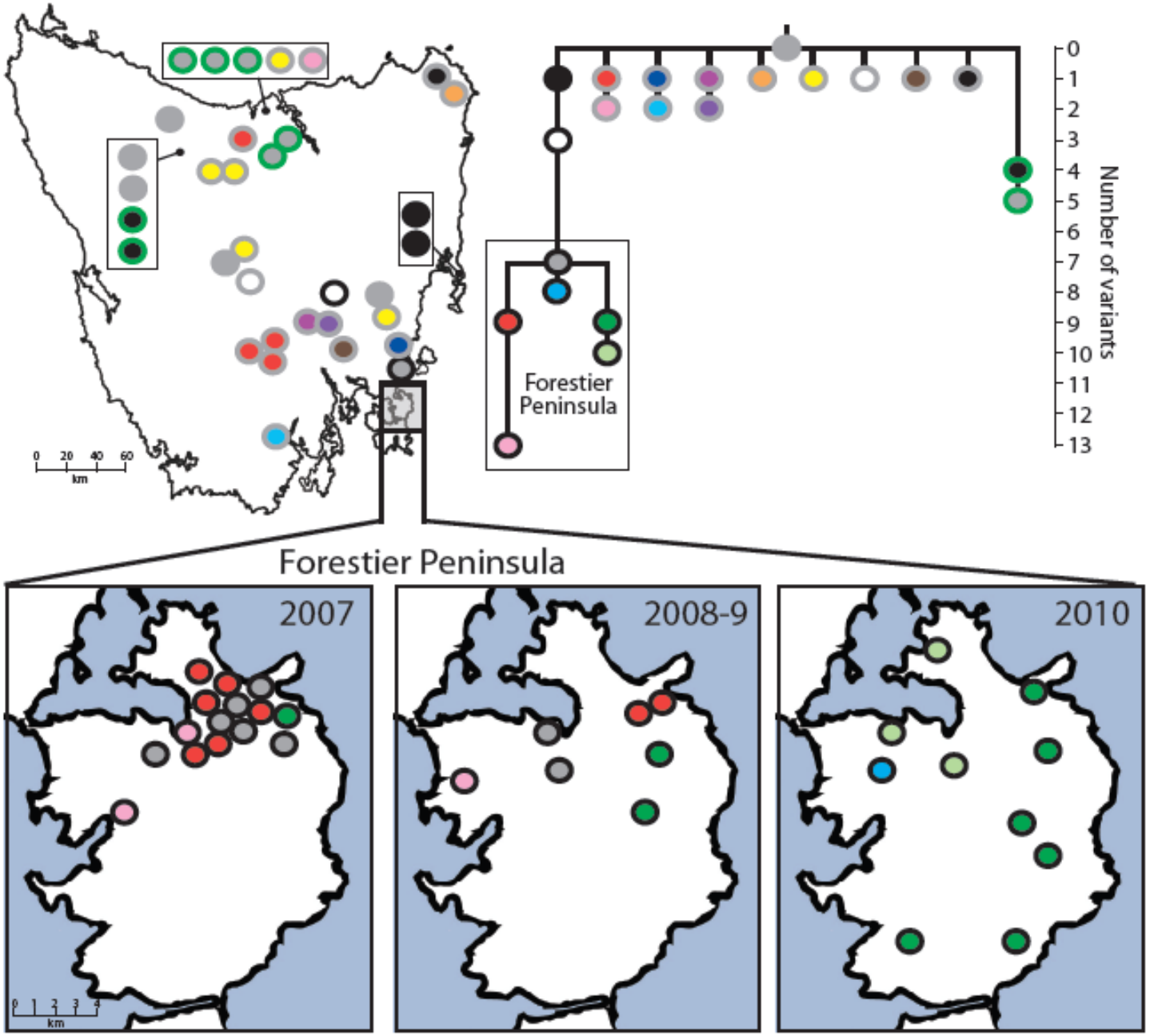


Chromosome 1_supercontig_000000246:95466 T>C
Tumour



Summary


0 20 40 60
km
Forestier Peninsula
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Number of variants


0 20 40 60
km
Forestier
Peninsula
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Number of variants
Forestier Peninsula
2007
2008-9
2010
0 1 2 3 4
km

What's next for the Tasmanian devil?

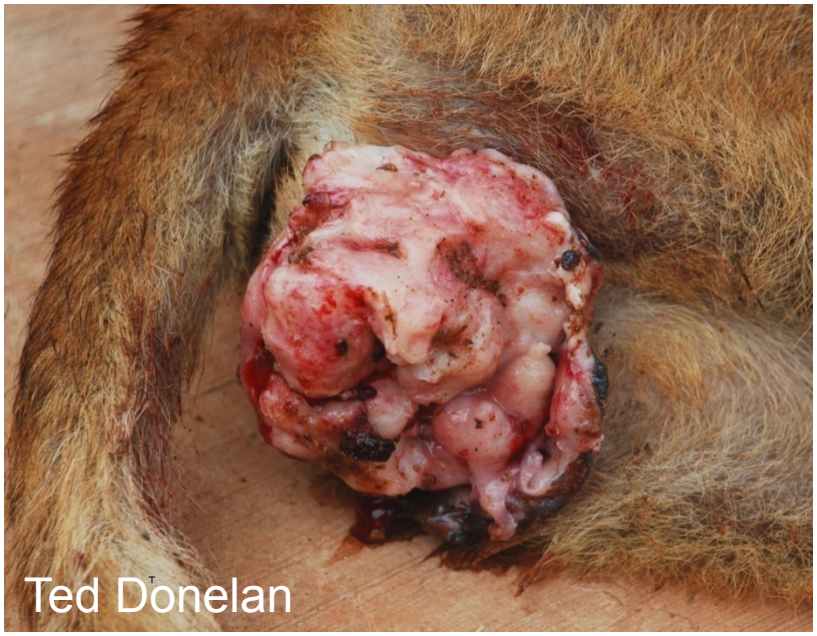
- Captive breeding programs
- Restrict disease spread in the wild
- Future research
  - Monitor DFTD genetic diversity and evolution
  - DFTD host interaction
  - DFTD vaccines and therapies

Photo: Save the Tasmanian Devil Program

Canine transmissible venereal tumour

Canine transmissible venereal tumour (CTVT)

Male



Female

CTVT worldwide distribution

Andrea Strakova

CTVT is a single somatic cell lineage with a global distribution

- Transplantation experiments
  (Nowinsky, 1876; Sticker, 1904)
- Karyotype
  (Murray et al, 1969; Oshimura et al 1973, Weber et al 1965, Wright et al, 1970)
- Genetics
  - LINE-1 insertion upstream of *MYC*
    (Katzir et al, 1987)
  - Microsatellites, MHC
    (Murgia et al, 2006; Rebbeck et al, 2009)

ON THE

DISEASES

OF

HORSES AND DOGS;

so conducted as to

ENABLE PERSONS TO PRACTISE WITH EASE AND SUCCESS

ON

THEIR OWN ANIMALS,

WITHOUT THE ASSISTANCE OF A FARRIER:

Including likewise the Natural Management, as Stabling, Feeding, Exercise, &c.: together with the Outlines of a Plan for the Establishment of Genuine Medicines for these Animals throughout the Kingdom.

BY DELABERE BLAINE,

PROFESSOR OF ANIMAL MEDICINE;

Author of "The Anatomy of the Horse;" "Outlines of the Veterinary Art;" "A Treatise on the Distemper in Dogs," &c. &c.

FOURTH EDITION,

WITH VERY LARGE ADDITIONS.

LONDON:

PRINTED FOR T. BOOSEY, 4, OLD BROAD STREET, ROYAL EXCHANGE.

1810.

habitants of mountainous countries, and has been supposed to be dependant on some particular quality of the water in those vicinities. But in dogs no such peculiarity takes place: it does not appear in them indigenous to any particular soil, but almost peculiar to some particular species of dogs, though other dogs sometimes have it, as terriers; but it is much less frequent, and in the larger tribes is hardly ever seen. It comes on generally while very young, and continues to increase to a certain size, when it becomes stationary, seldom increasing to such a degree as to prove fatal. It is however troublesome, and in some measure hurtful, from the pressure it occasions on the surrounding parts. If an ointment is made with equal parts of mercurial and blistering ointment, and the swelling rubbed with it every day, avoiding salivation, it commonly lessens and frequently wholly removes it. But it is necessary also at the same time to give internal alteratives: four, five, six, or seven grains of burnt sponge, with half the quantity of nitre given every morning, will be found useful.

CANCER.

Two parts only in dogs are subject to a cancerous affection, and both these are organs concerned in generation. The teats of bitches become at times indurated, and swelled with a schirrous indolent tumour, which more commonly remains indolent and without ulcer: but now and then, when such a tumour has increased to a very considerable size, a small ulcer bursts out, which slowly increases to a very considerable surface. In the worst of these cases there is not present the virulent and horrible spreading of the

human cancer, nor does it appear to give much pain, or to injure the health; and dogs who are suffered to remain with it, live for a great length of time without much inconvenience to themselves. This state admits of only one cure, which is the complete removal of the whole tumour. The vagina or rather the womb of bitches also frequently takes on an ulcerous state, accompanied with a fungous excrescence, which is brought on oftentimes from the horrible brutality of boys who force dogs from bitches in the act of copulation. This complaint admits of no cure, that I have witnessed. In the penis of dogs also a similar fungous excrescence sometimes forms, but it does not appear to erode the neighbouring parts much: it increases rather than diminishes the size, till its offensiveness obliges the animal to be made away with.

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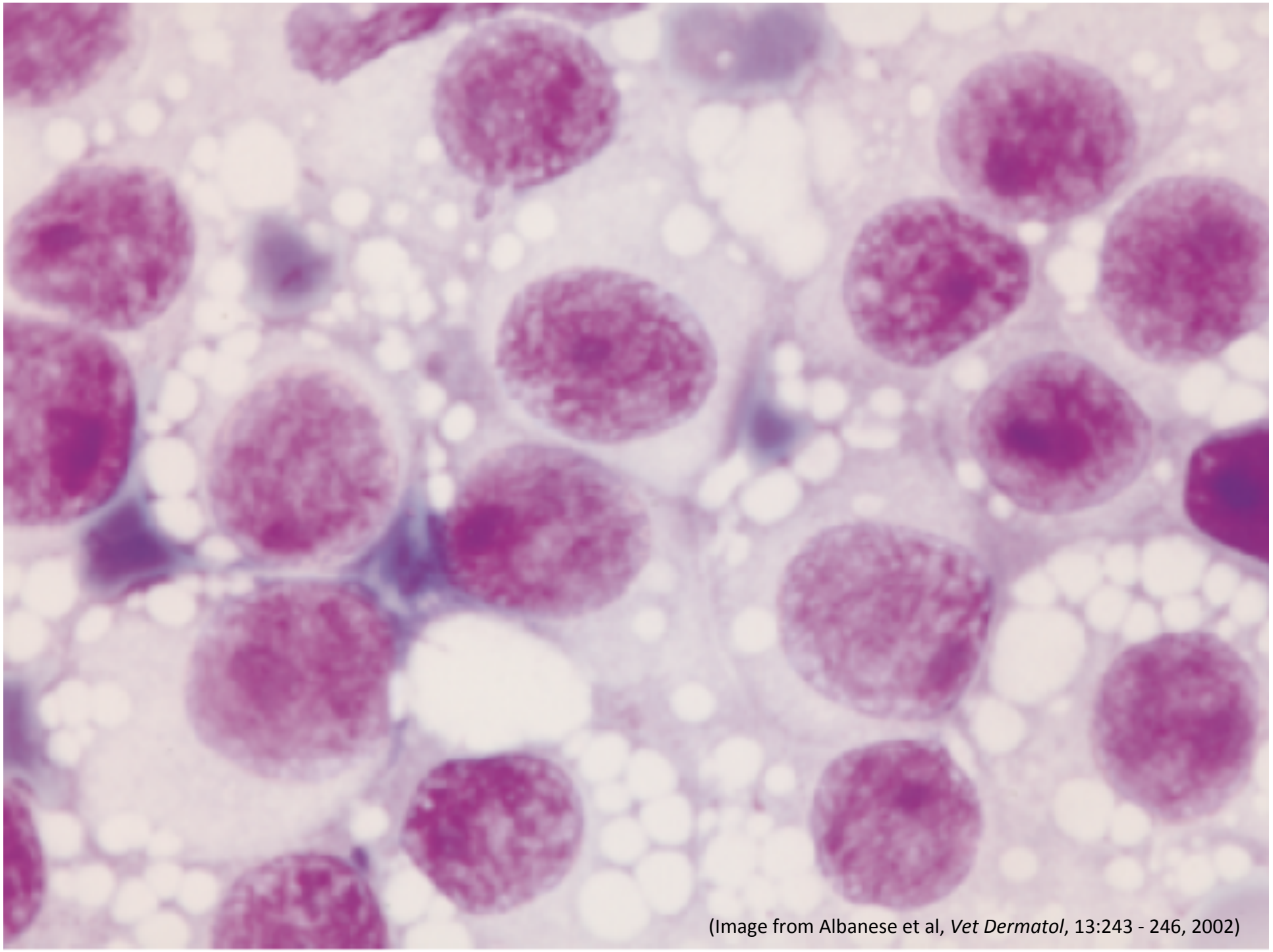
Delabere Blaine, 1810

CTVT is the oldest known mammalian somatic cell lineage

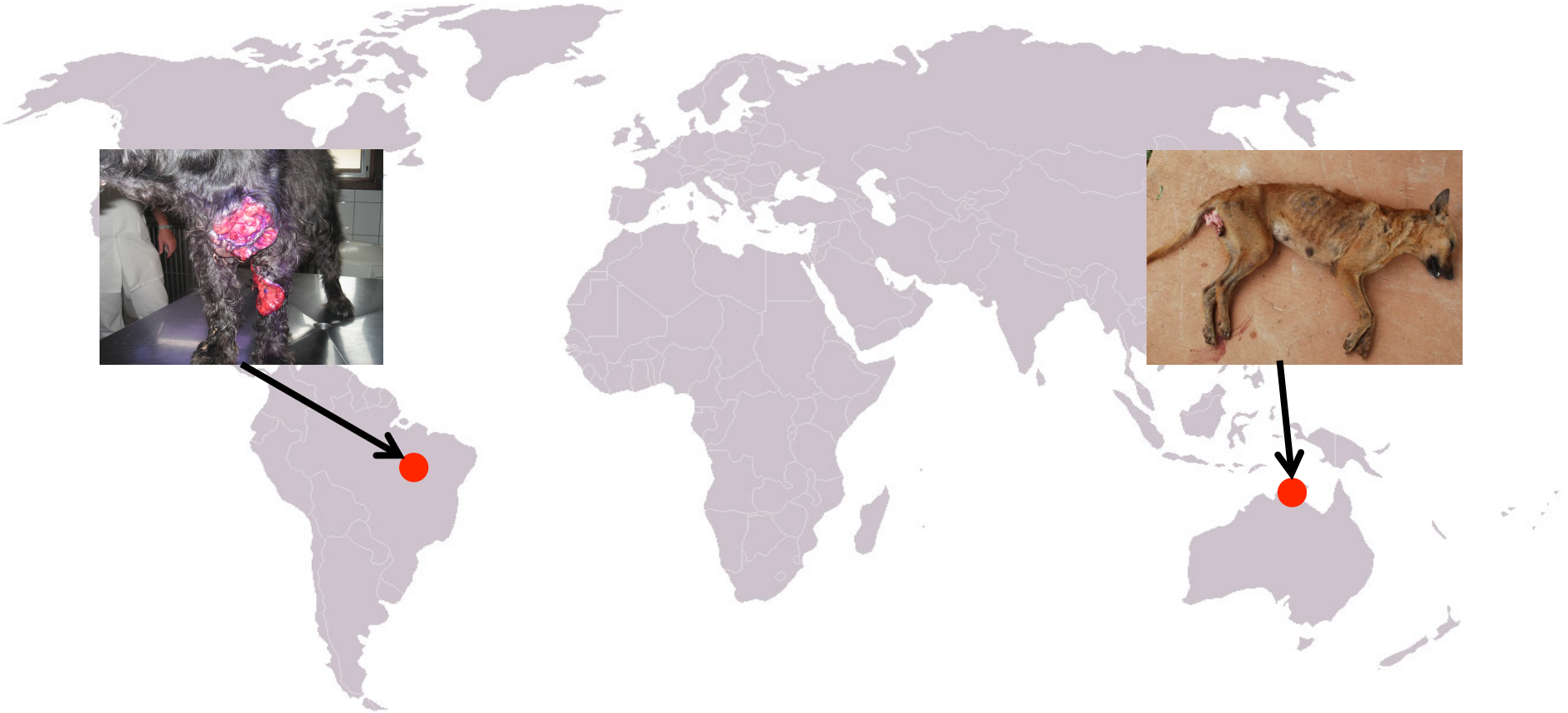
- CTVT lineage is at least 200 years old
- CTVT may be much older than this

Murgia et al, *Cell,* 126:477-87, 2006; Rebbeck et al *Evolution,* 63(9):2340-9, 2009

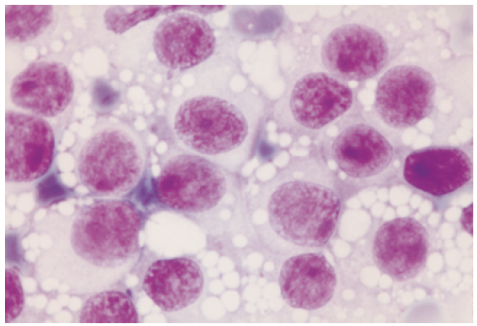


(Image from Albanese et al, *Vet Dermatol*, 13:243 - 246, 2002)

CTVT genome sequencing

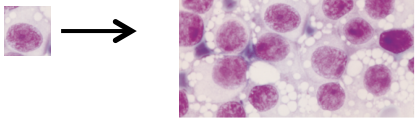


The CTVT genome



CTVT Founder animal

Germline variants

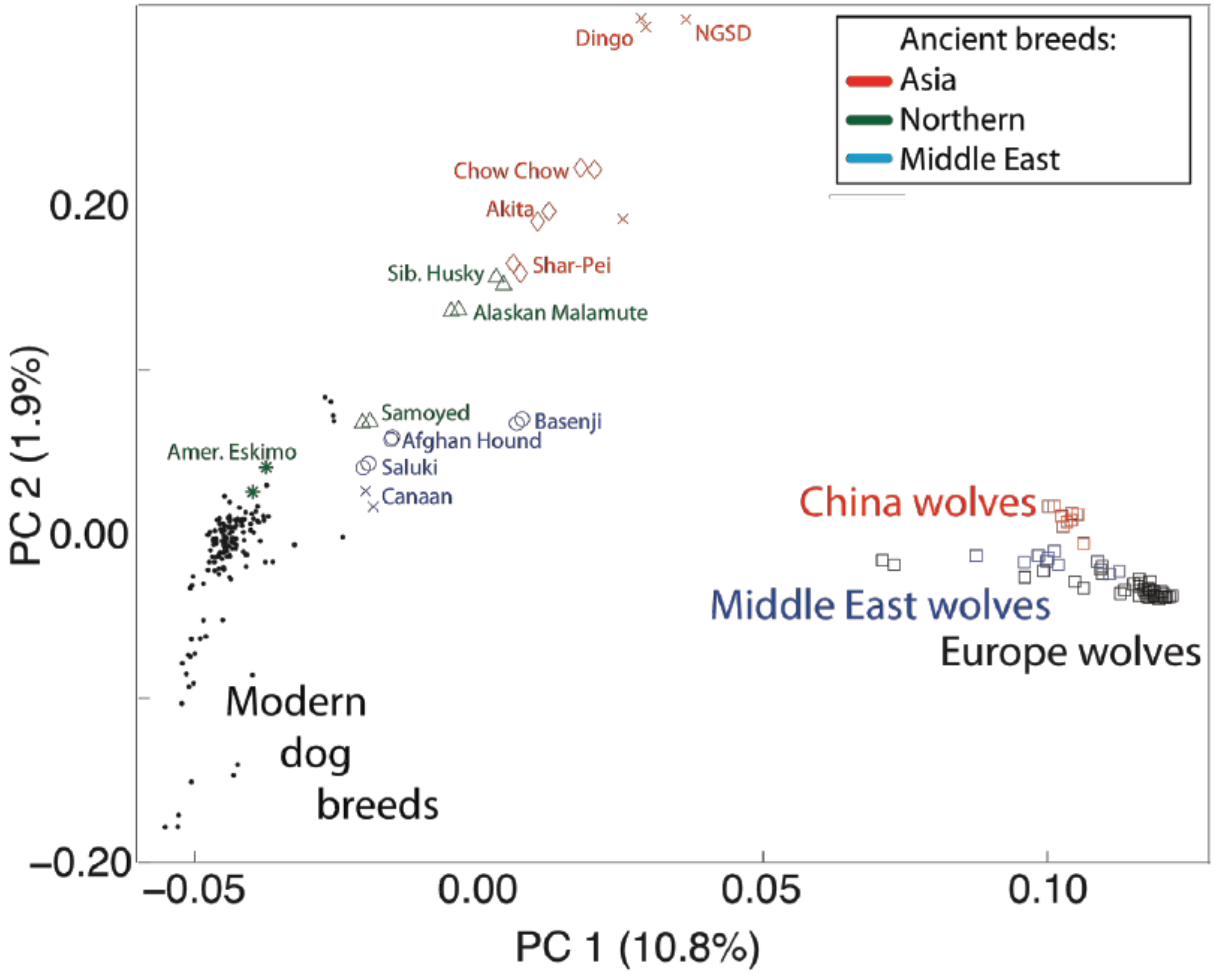


Somatic variants

(Image from Albanese et al, *Vet Dermatol*, 13:243 - 246, 2002)

Identity of the CTVT founder animal

Principal component analysis of dogs and wolves



vonHoldt et al, *Nature* 364:898 (2010)

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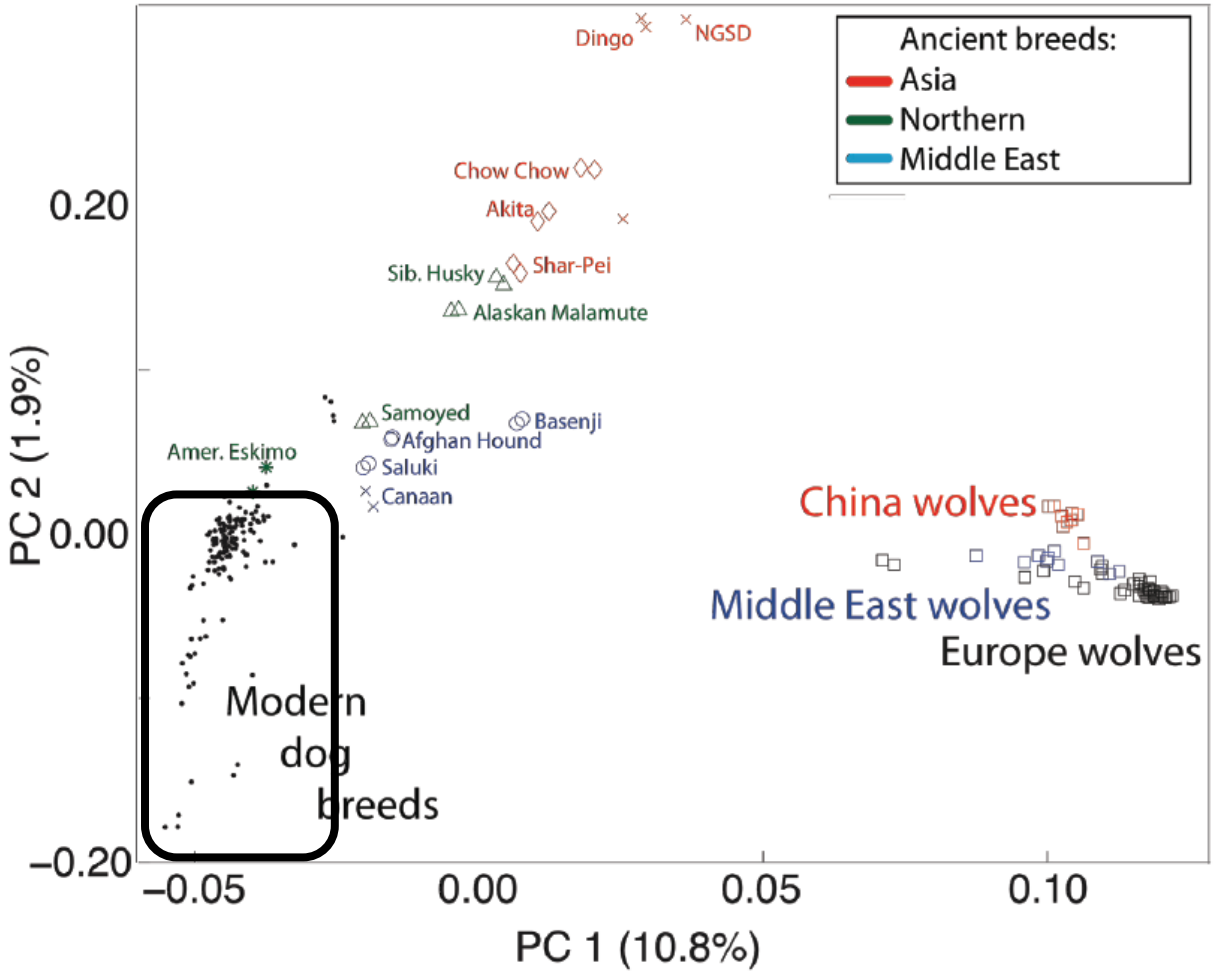

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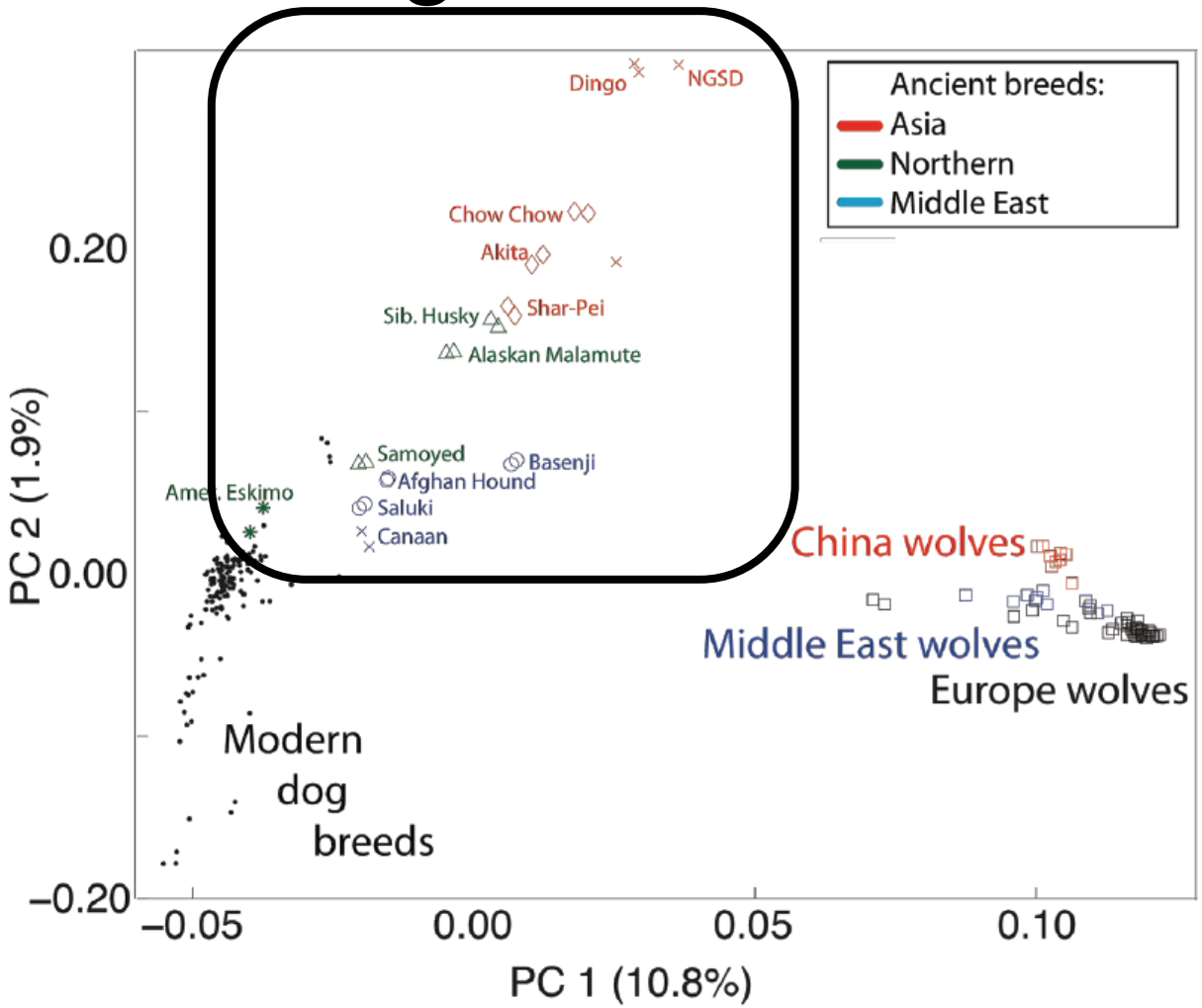

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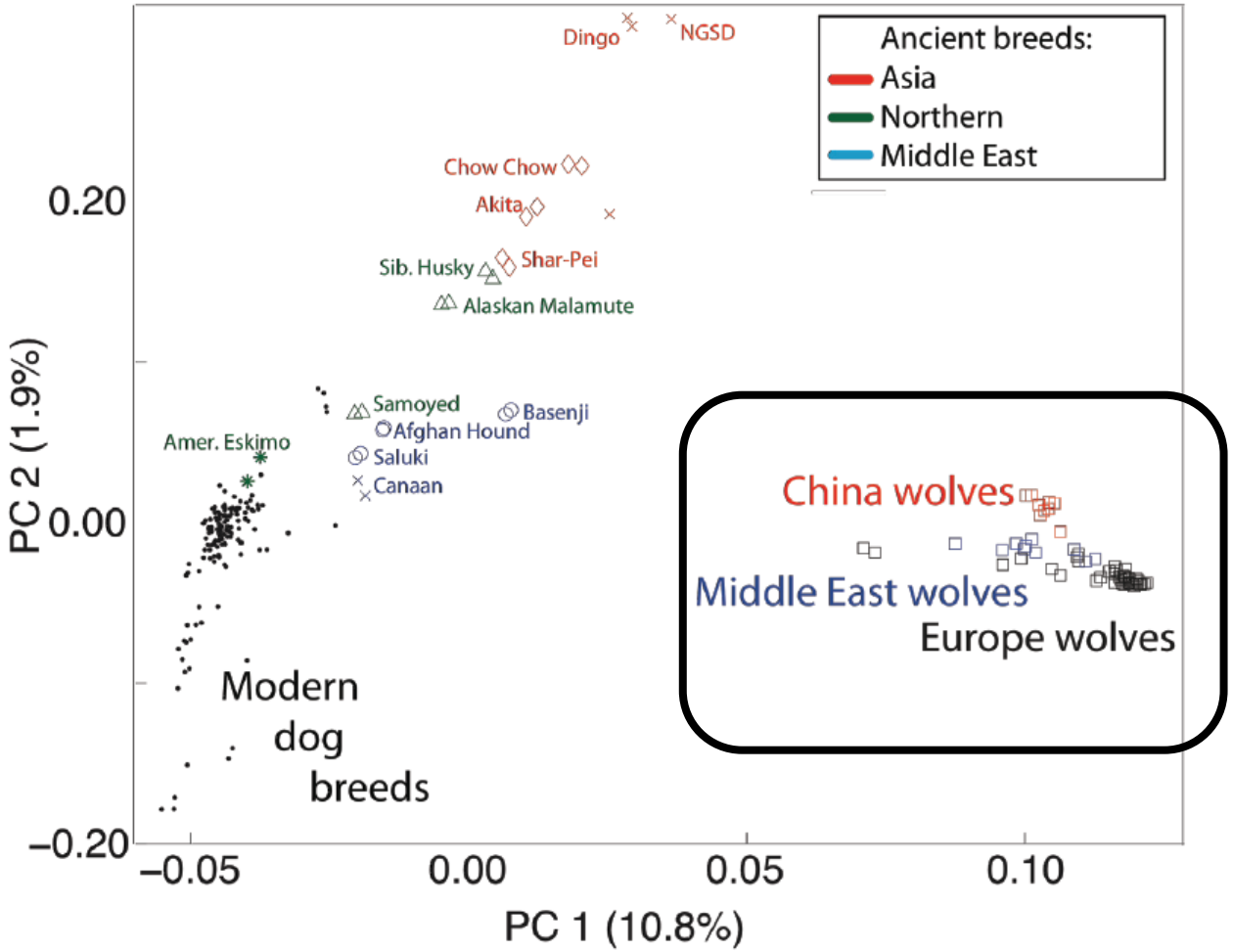
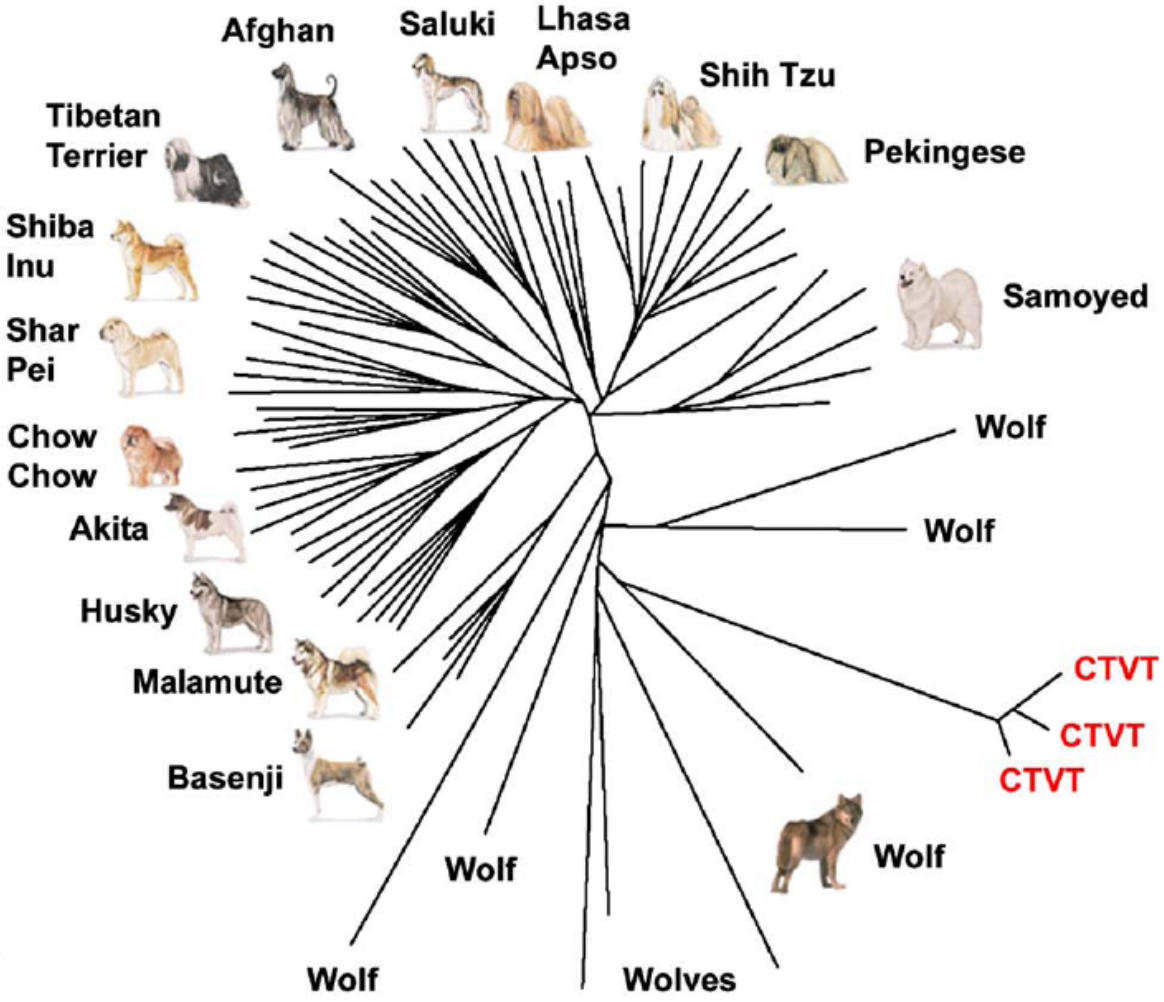


vonHoldt et al, *Nature* 364:898 (2010)

CTVT founder phenotype



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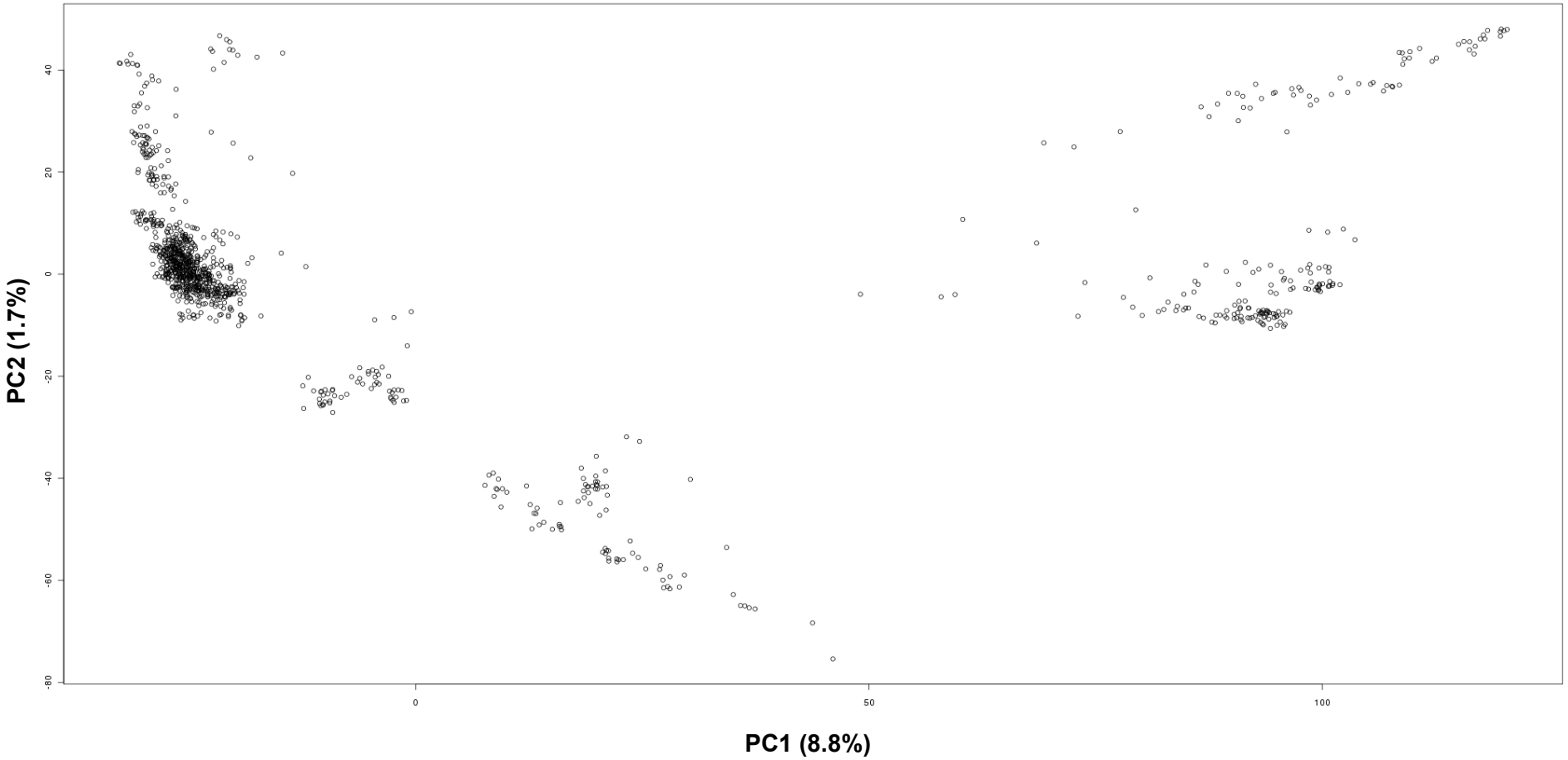
The CTVT founder



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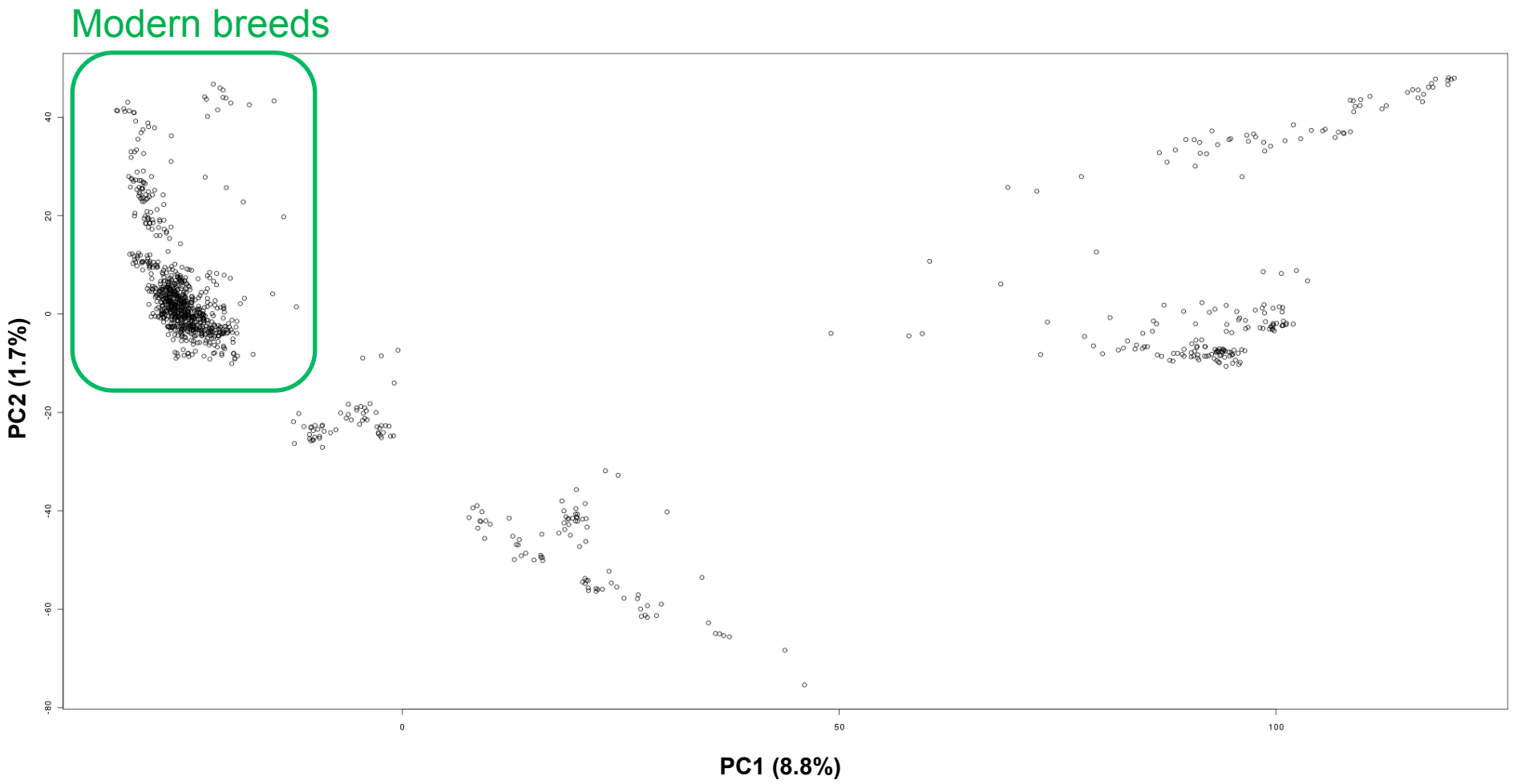
The CTVT founder



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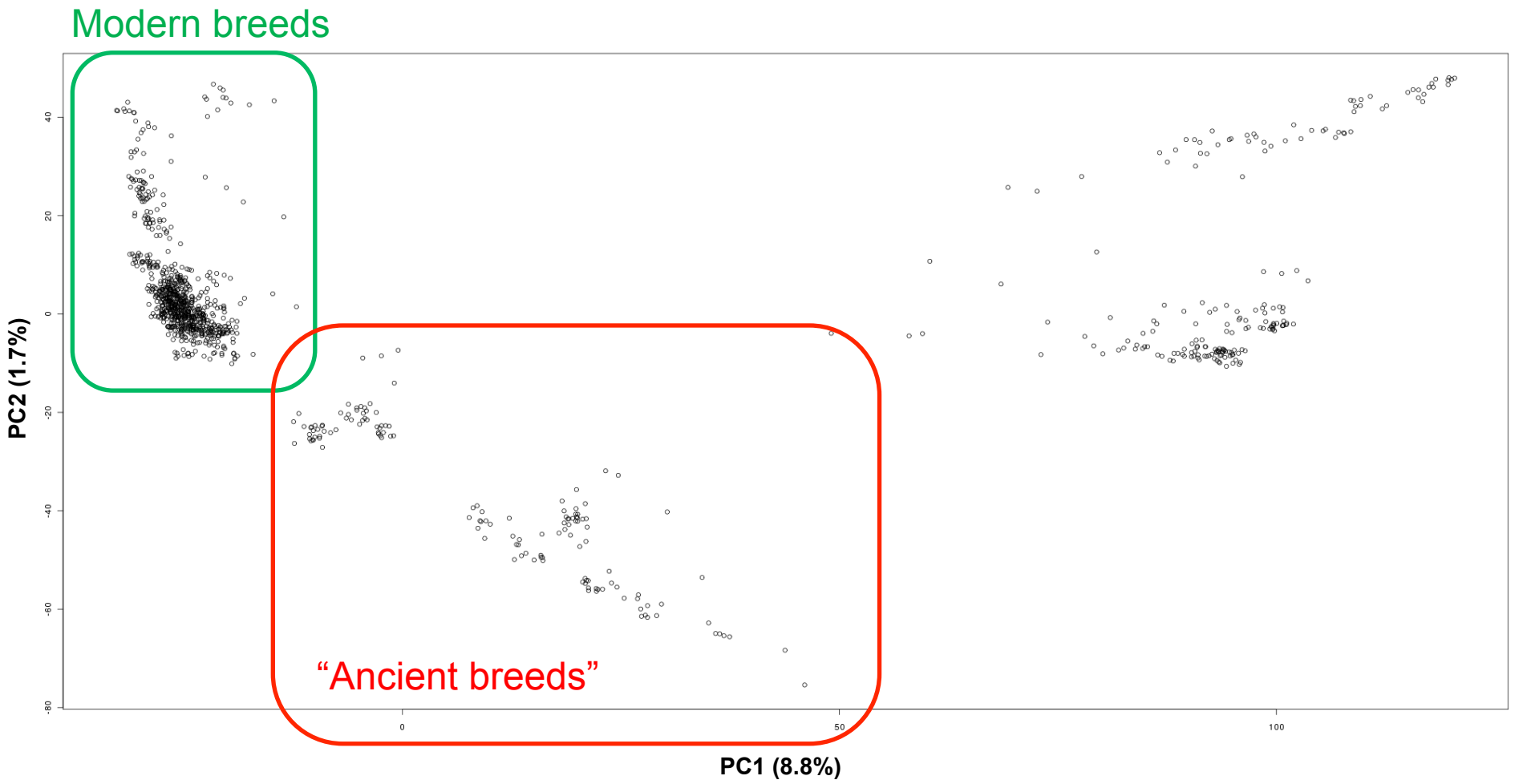

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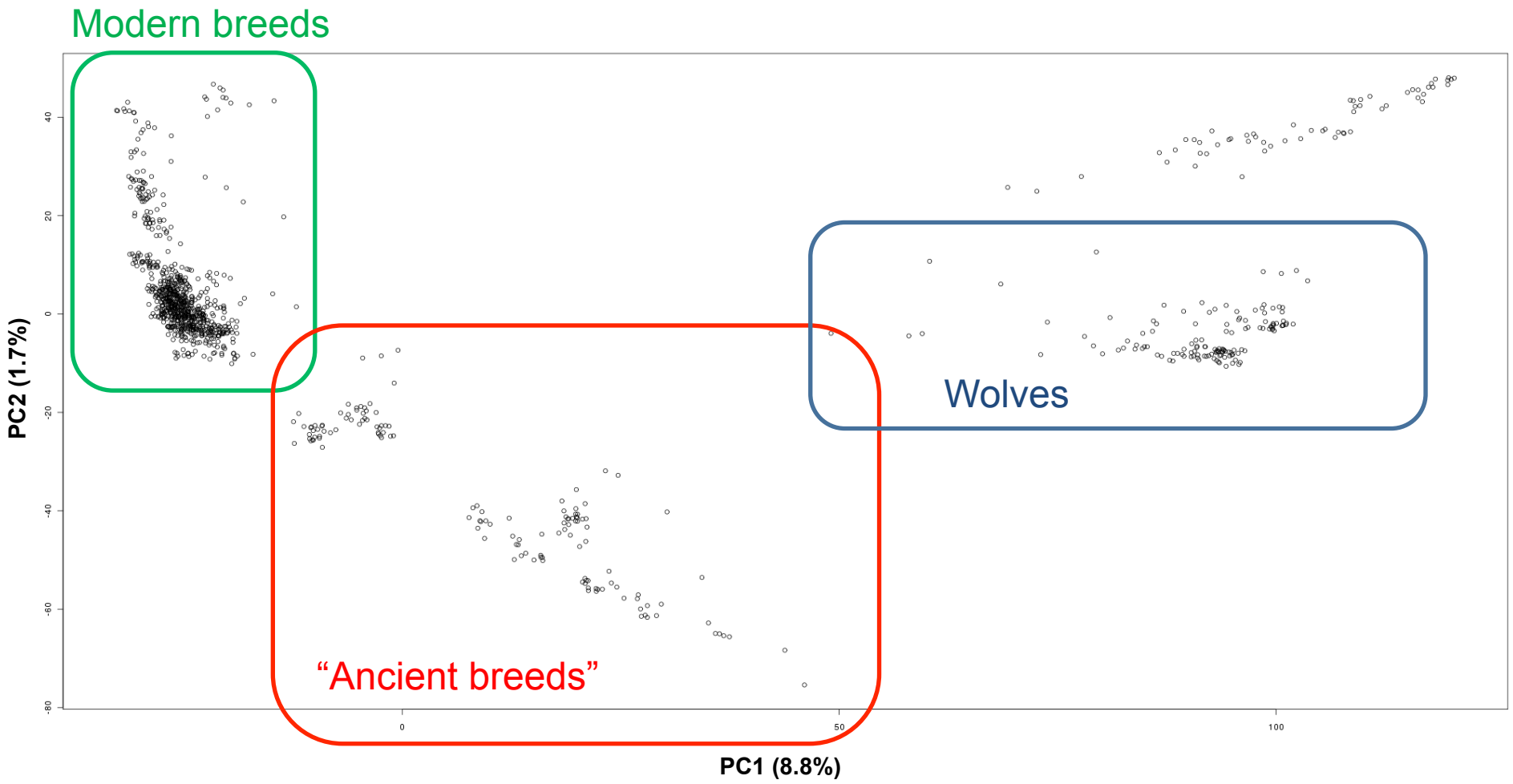

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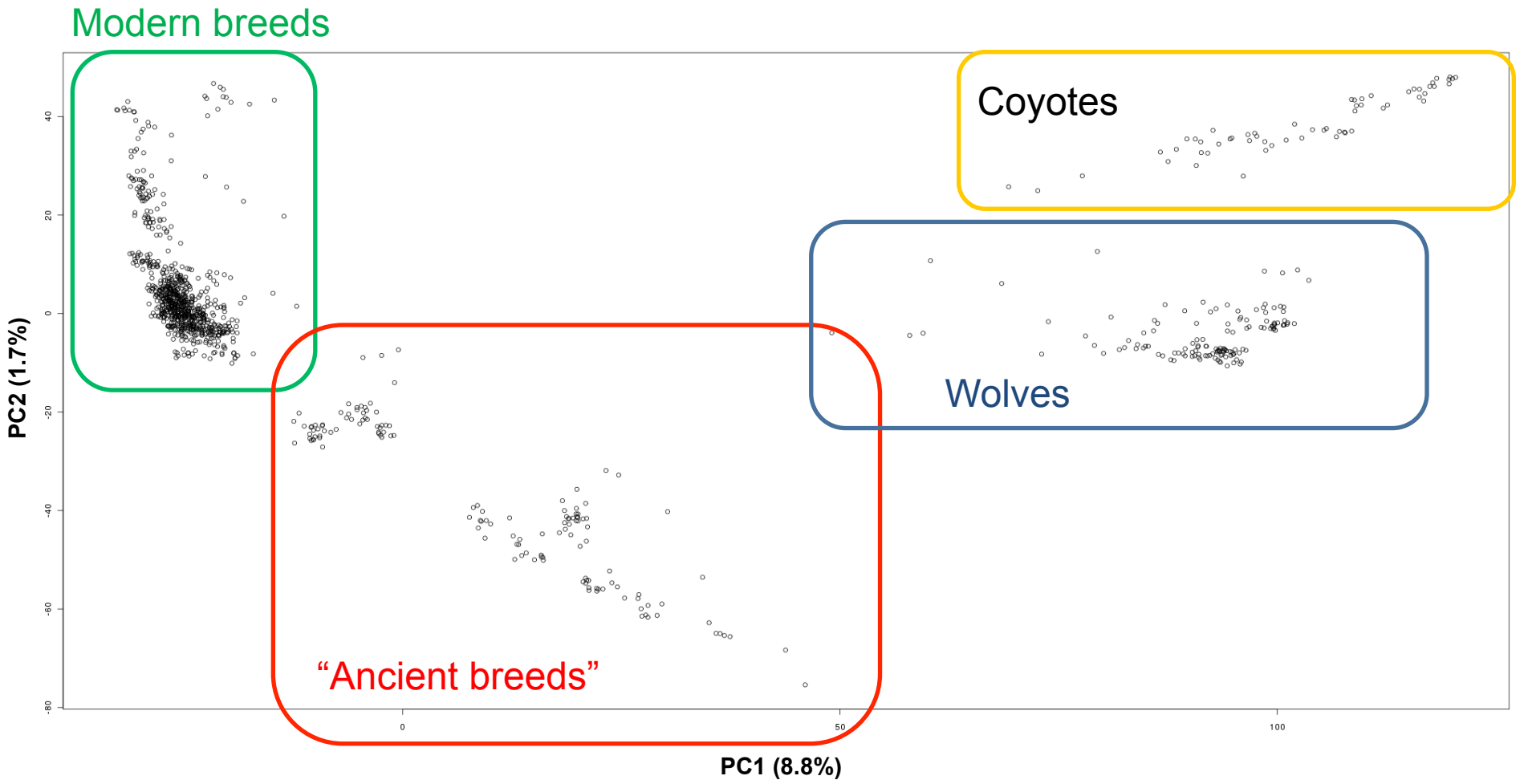

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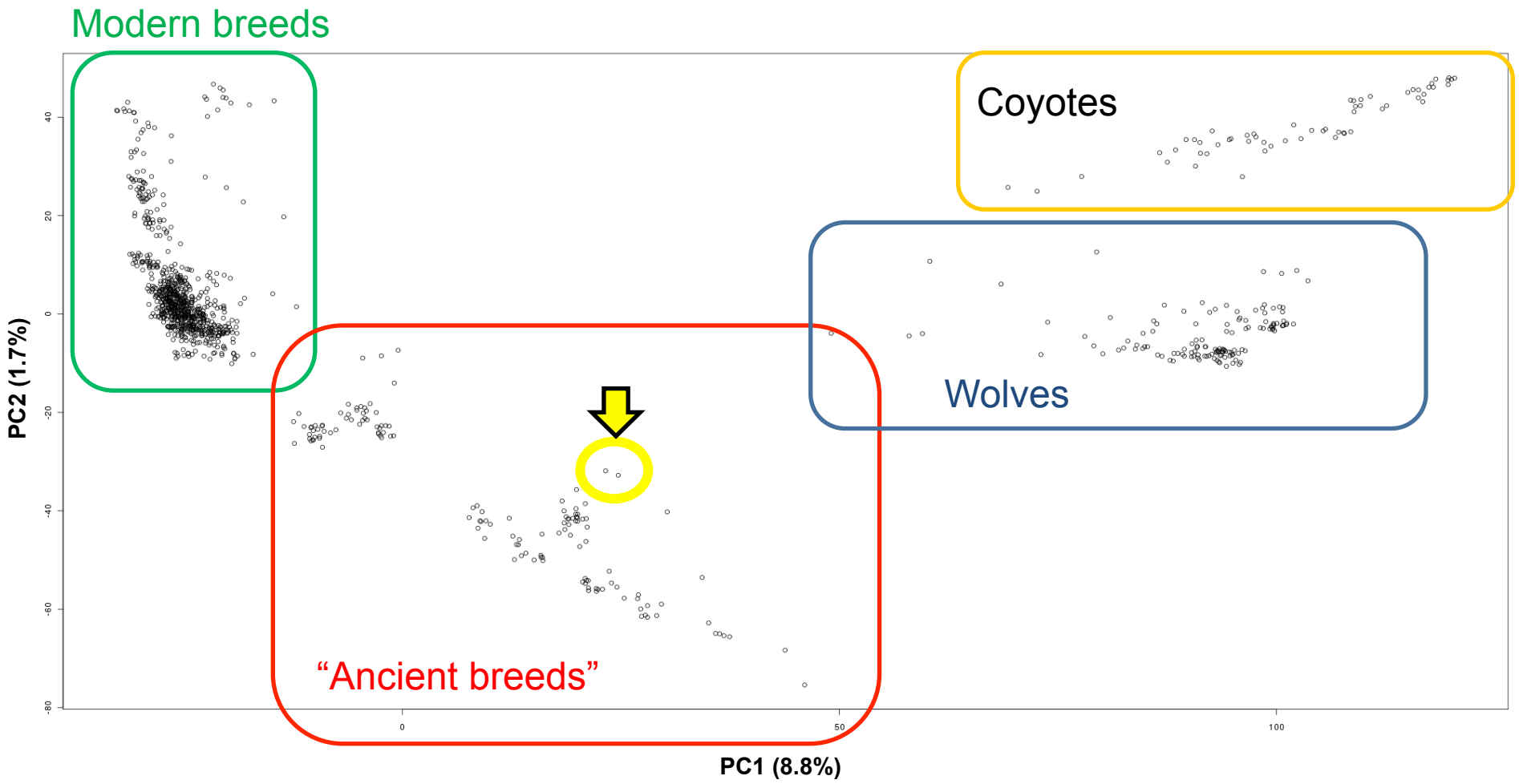
The CTVT founder was an “ancient breed” dog



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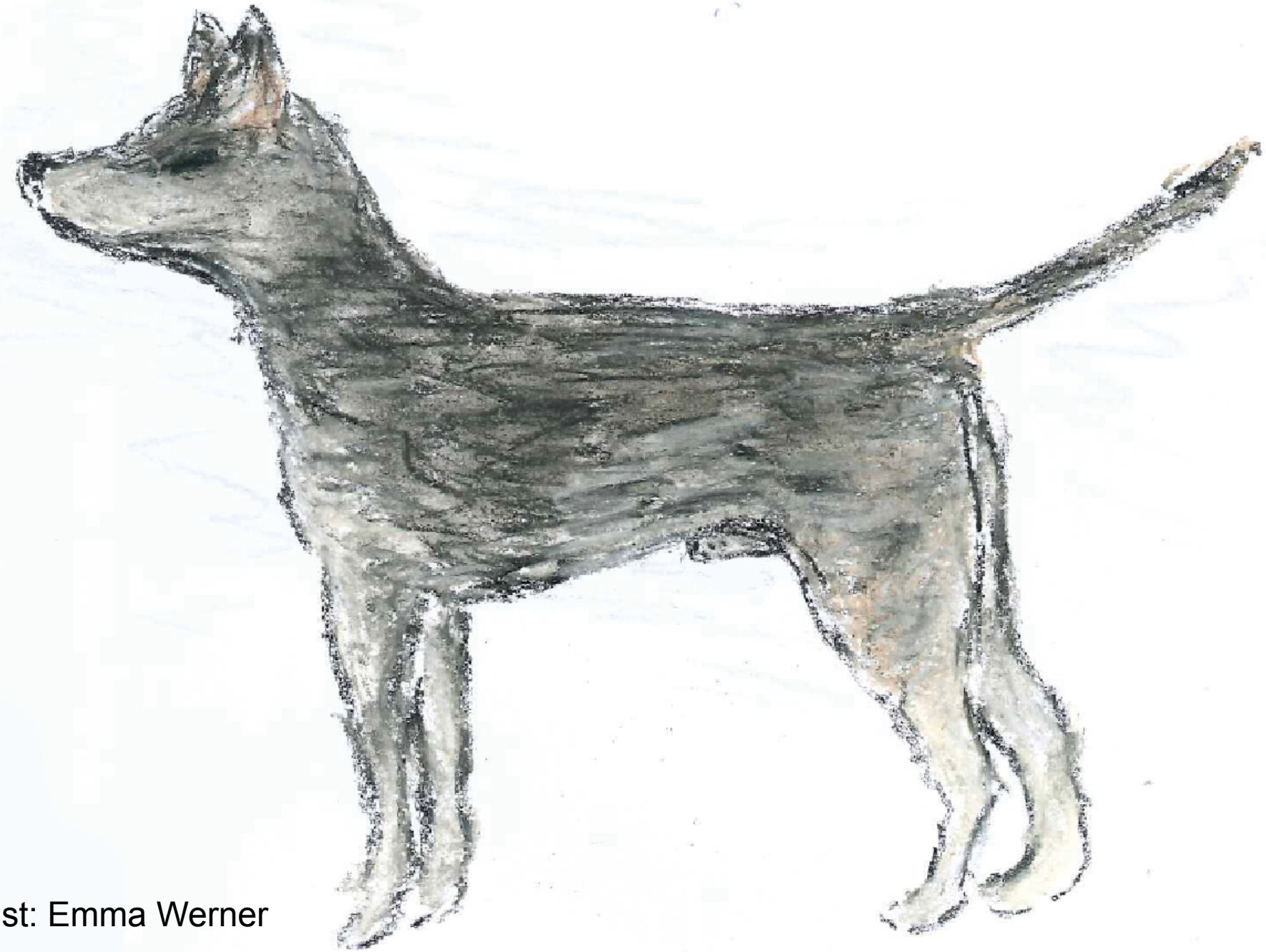
Images downloaded from www.akc.org

Founder dog phenotype

Gene	Variant	CTVT genotype	CTVT phenotype	Reference
ASIP	24:23,393,510/14TA>GG	GG/GG	Agouti coat	Schmutz et al, 2007
FGF5	32:7,473,337G>T	G/G	Short hair	Cadieu et al, 2009
KRT71	27:5,542,806C>T	C/C	Straight hair	Cadieu et al, 2009
-	10:11,072,007C>T	T/T	Prick ears	Vaysse et al, 2011
-	10:11,169,956C>T	C/C	Medium to large size	Vaysse et al, 2011
BMP3	32:8,196,098C>A	C/C	Pointy snout	Schoenebeck et al, 2012
SLC1A2	18:35,681,332G>A	G/G	Less aggressive	Takeuchi et al, 2009
CDH2	7:63,867,472	C/C	Lower risk of OCD	Dodman et al, 2010



Artist: Emma Werner

LETTER

doi:10.1038/nature11837

The genomic signature of dog domestication reveals adaptation to a starch-rich diet

Erik Axelsson[1], Abhirami Ratnakumar[1], Maja-Louise Arendt[1], Khurram Maqbool[1], Matthew T. Webster[1], Michele Perloski[2], Olof Liberg[3], Jon M. Arnemo[4,5], Åke Hedhammar[6] & Kerstin Lindblad-Toh[1,2]

MGAM chr16:10,135,196C>T V1001I

C: Adaptation to starch-rich diet
T: Meat-lover

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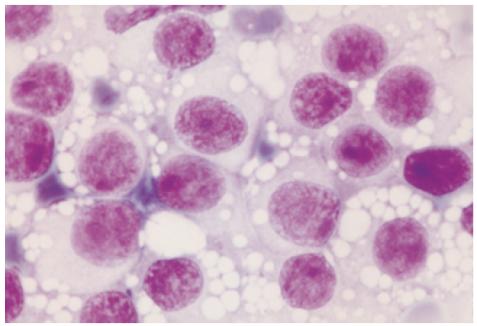
CTVT: T/T

C: Adaptation to starch-rich diet
T: Meat-lover

Artist: Emma Werner

The CTVT genome



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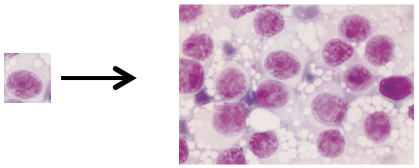
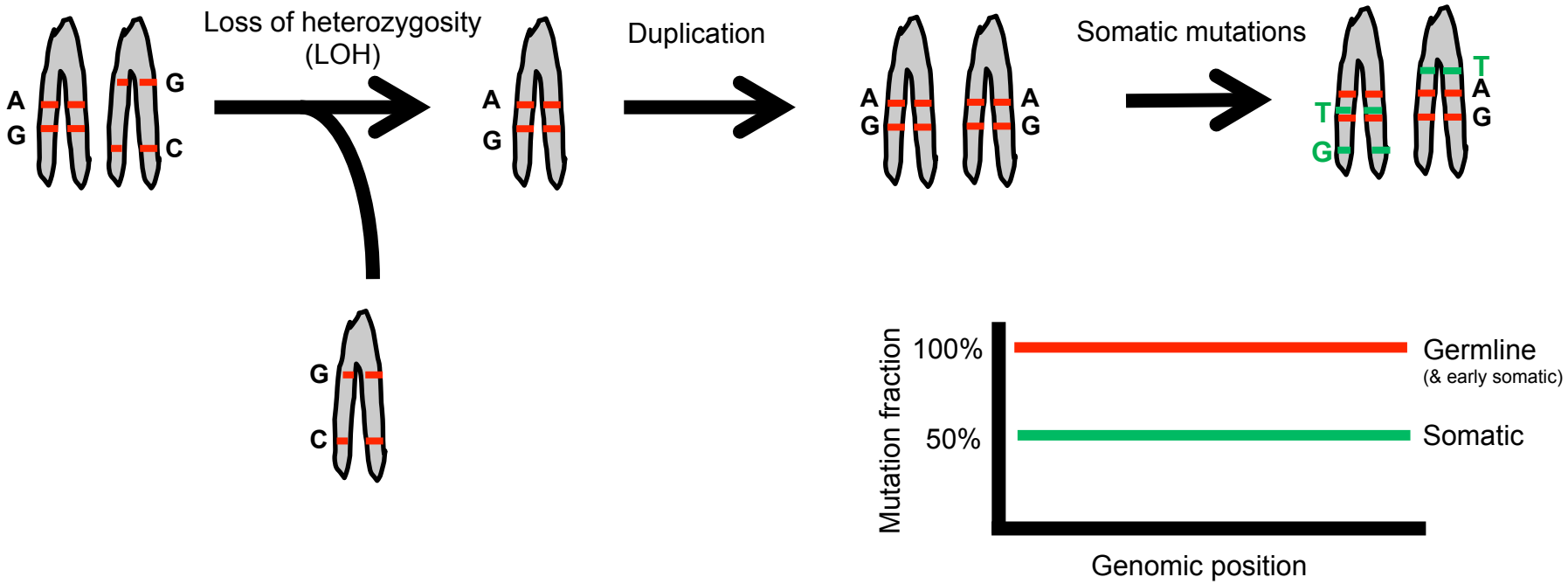


Somatic variants

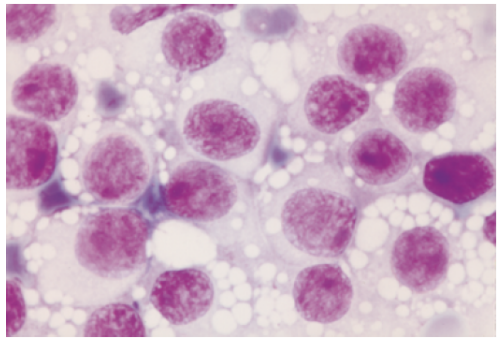
Images from Emma Werner and Albanese et al, *Vet Dermatol*, 13:243 - 246, 2002

Using Loss of Heterozygosity (LOH) to identify somatic mutations



Number of somatic mutations in CTVT

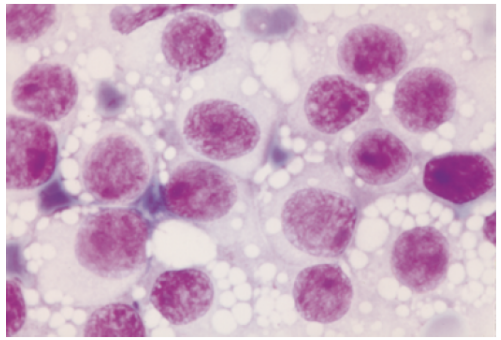
SOMATIC MUTATIONS



(Images by Emma Werner and from Albanese et al, *Vet Dermatol*, 13:243 - 246, 2002)

Number of somatic mutations in CTVT

2 – 2.5 million
SOMATIC MUTATIONS



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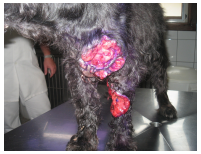
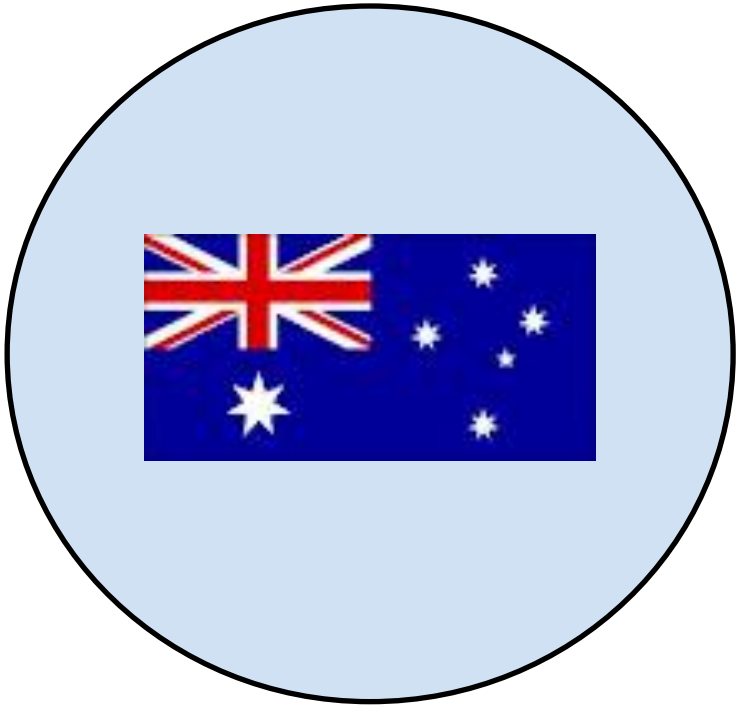
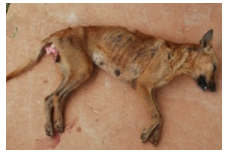
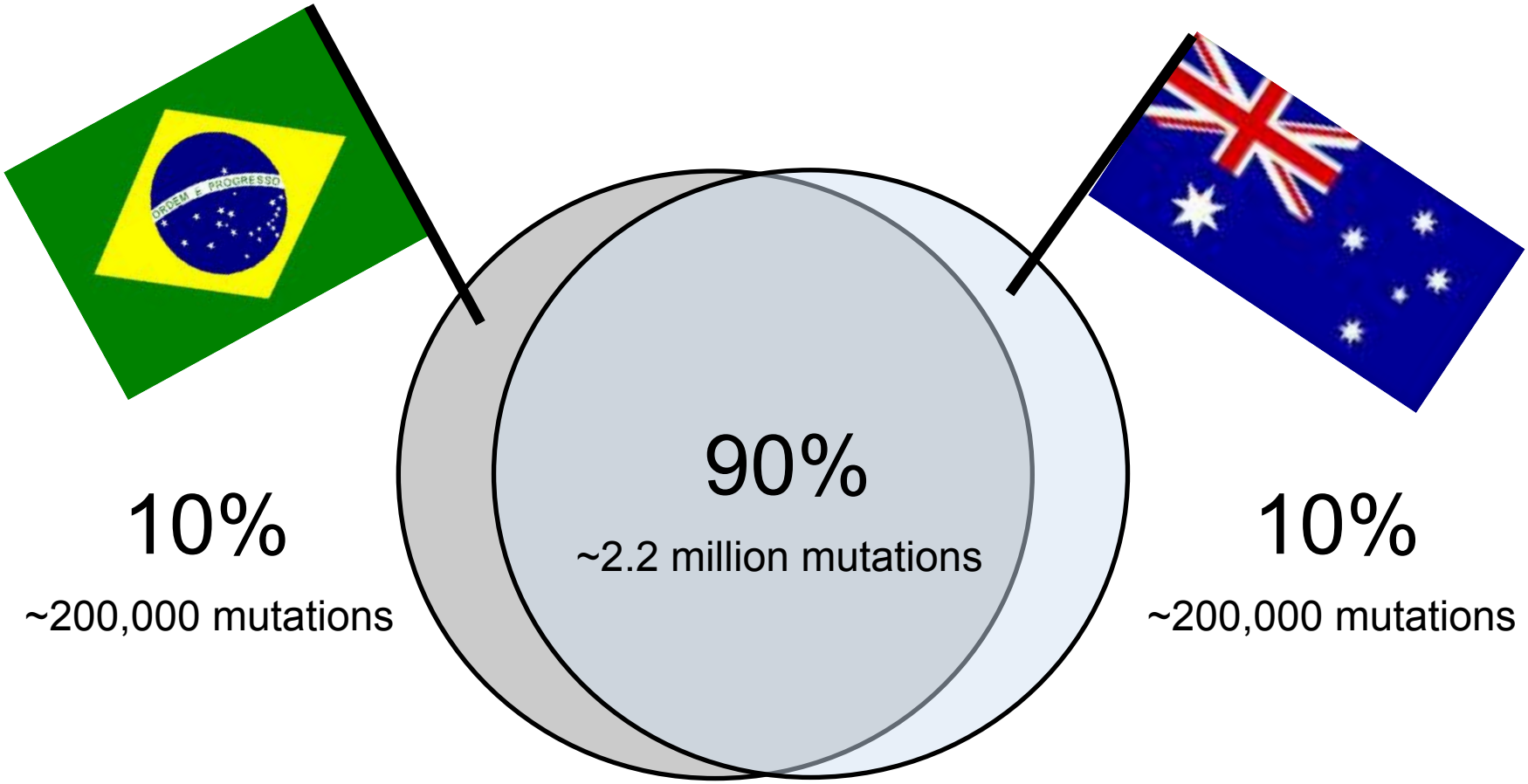
Variants in CTVT genomes





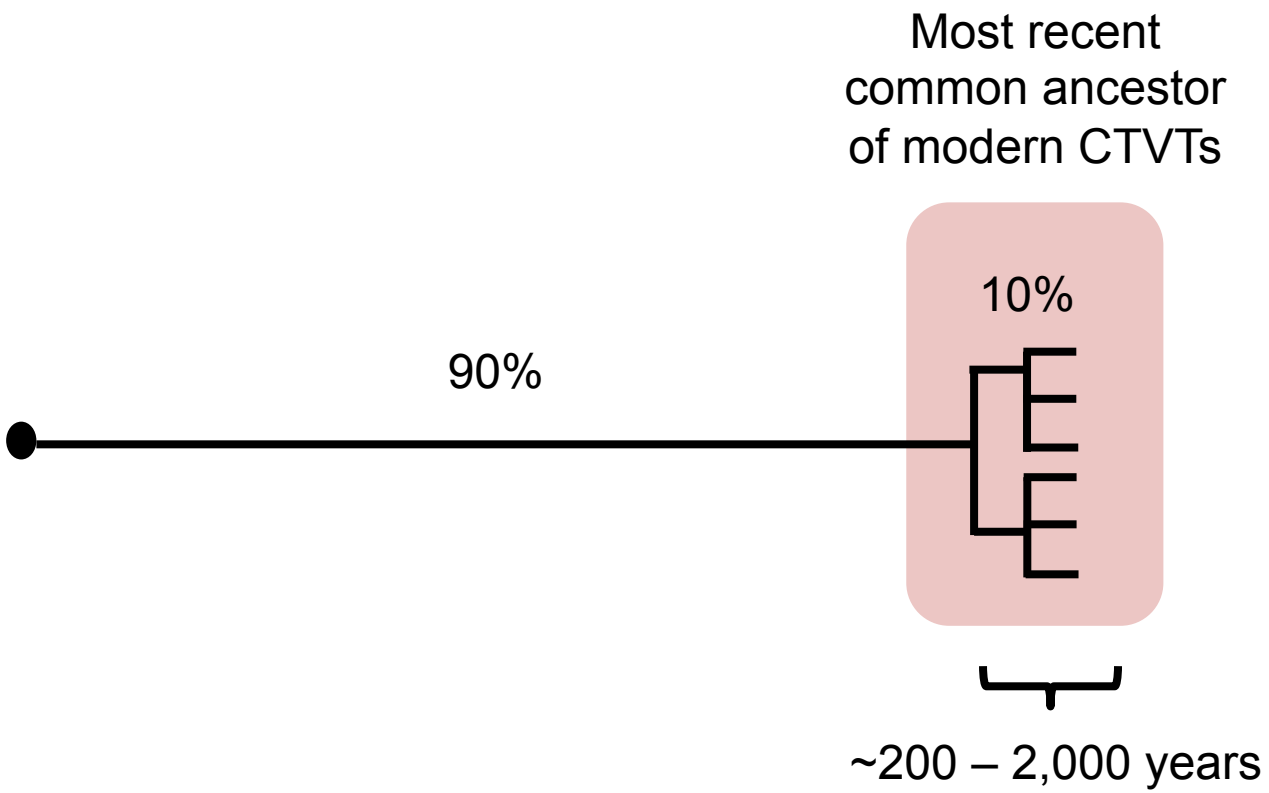


Variants in CTVT genomes



90% of mutations occurred before divergence of modern tumours

Age of CTVT

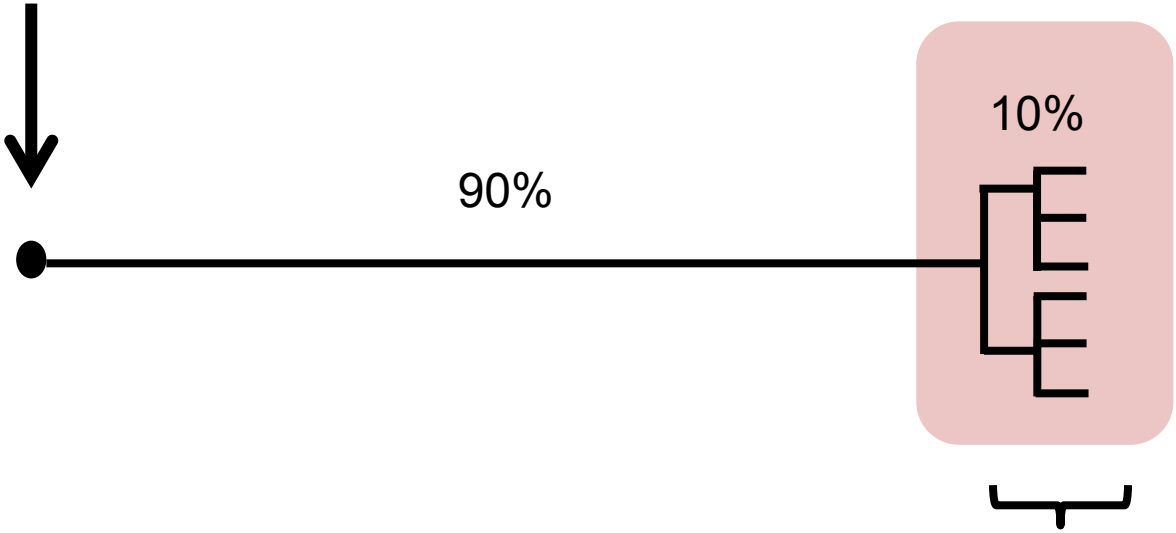


Murgia et al, *Cell,* 126:477-87, 2006; Rebbeck et al *Evolution,* 63(9):2340-9, 2009

Age of CTVT

Founder lived
2,000 to 20,000
years ago

Most recent
common ancestor
of modern CTVTs



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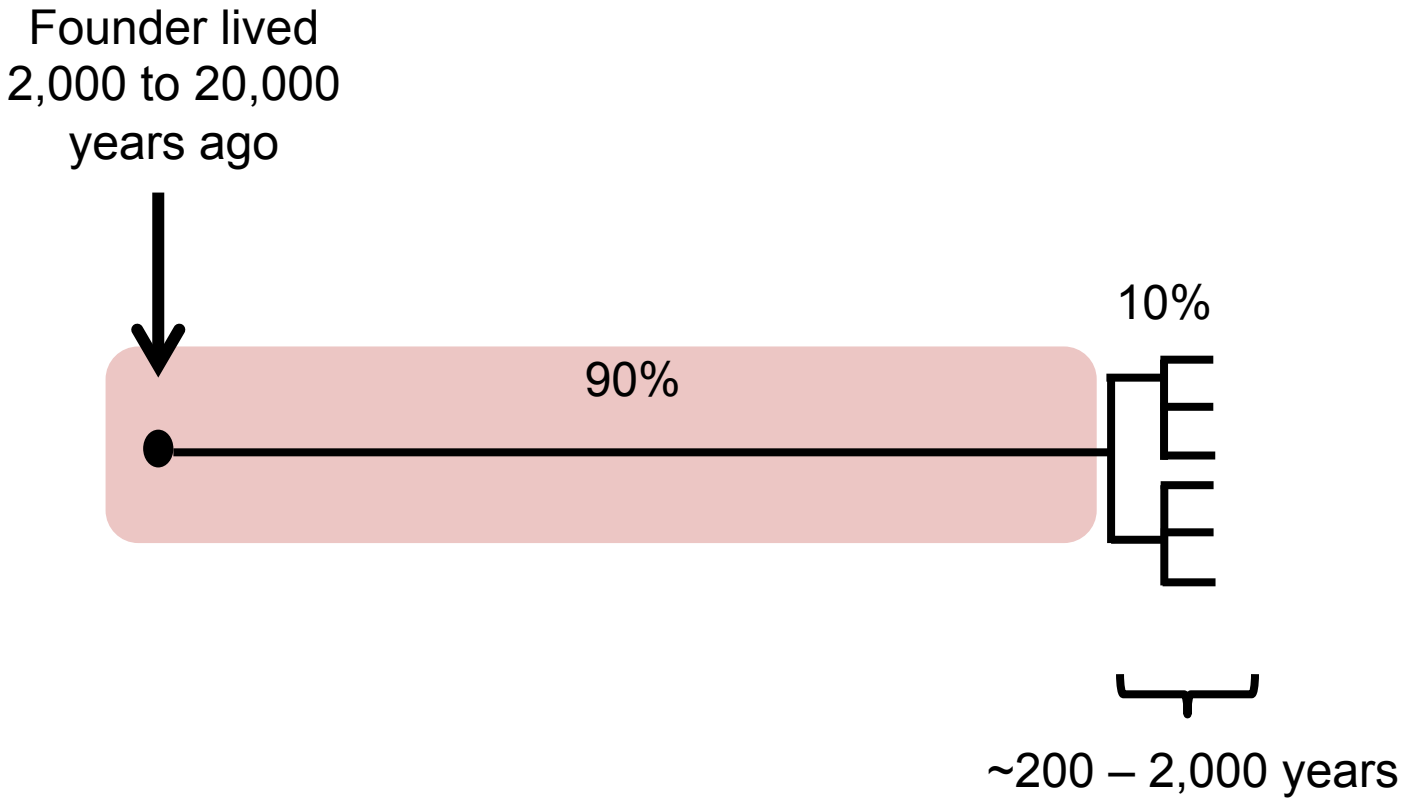
For most of its history, CTVT was probably confined to an isolated dog population



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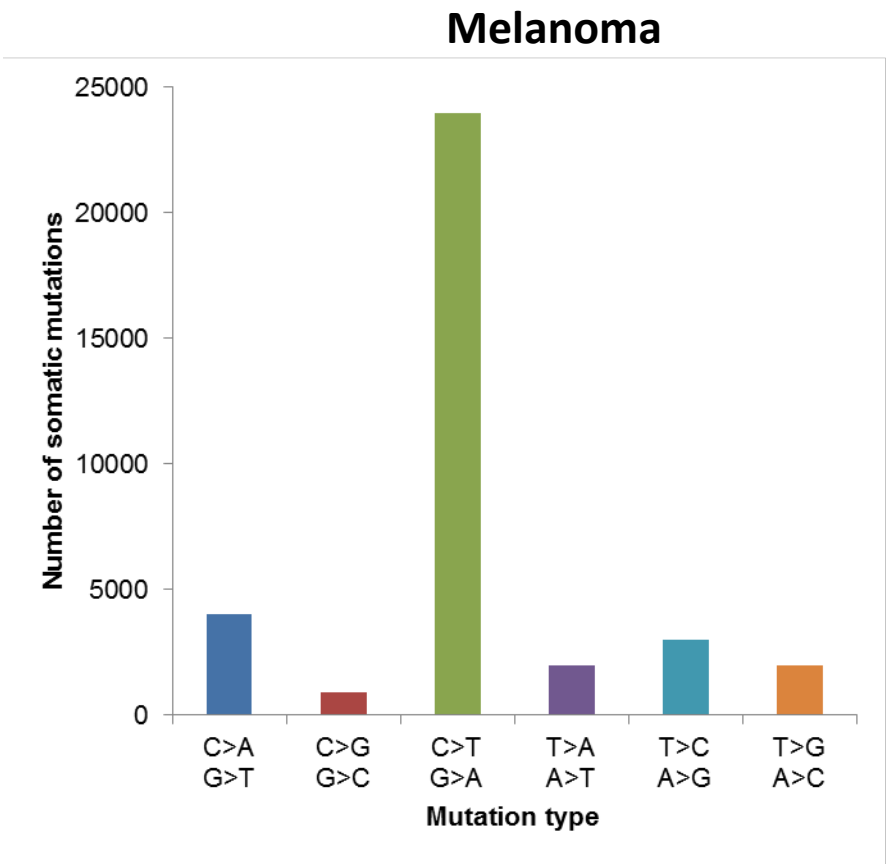
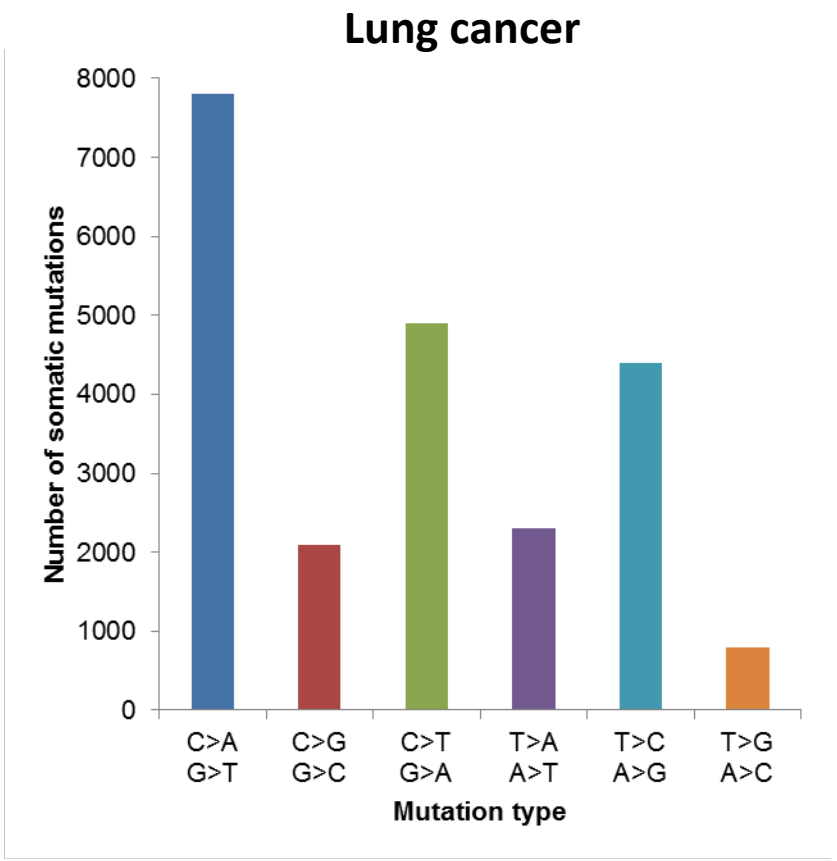
What caused the mutations in CTVT?

Mutation spectrum

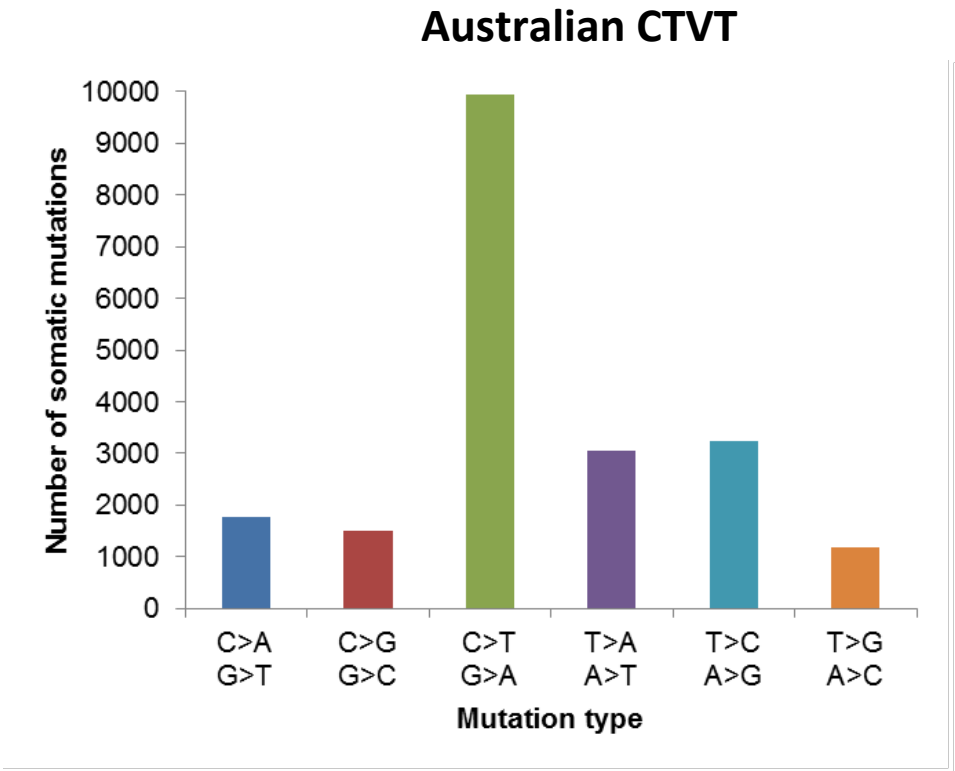
Type of mutation can give clues as to processes that caused cancer

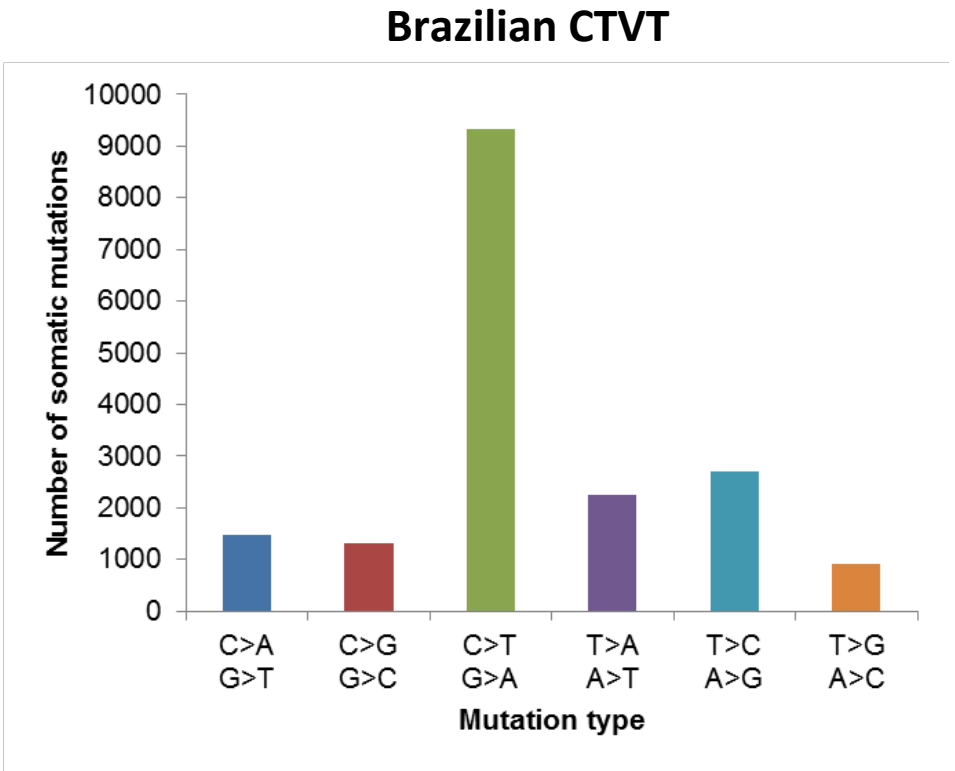




Data adapted from Pleasance et al *Nature* 463:184 (2010) and Pleasance et al *Nature* 463:191 (2010)

Mutation spectrum in CTVT





Artist: Emma Werner

Clonally transmissible cancers

DFTD

- Recent (<20years)
- Metastasis common
- Transmitted by biting
- Facial tumour
- Neural crest origin
- Unresponsive to therapy

CTVT

- Old (>1,000 years)
- Metastasis rare
- Sexually transmitted
- Genital tumour
- Histiocytic origin
- Very sensitive to therapy

Clonally transmissible cancers

Images:
Tasmanian Devil Conservation Park
www.animalswallpaper.info

Brief Report

Genetic Analysis of a Sarcoma Accidentally Transplanted from a Patient to a Surgeon

Hermine-Valeria Gärtner, M.D., Christian Seidl, M.D., Christine Luckenbach, Ph.D., Georg Schumm, M.D., Erhard Seifried, M.D., Horst Ritter, M.D., and Burkhard Bültmann, M.D.

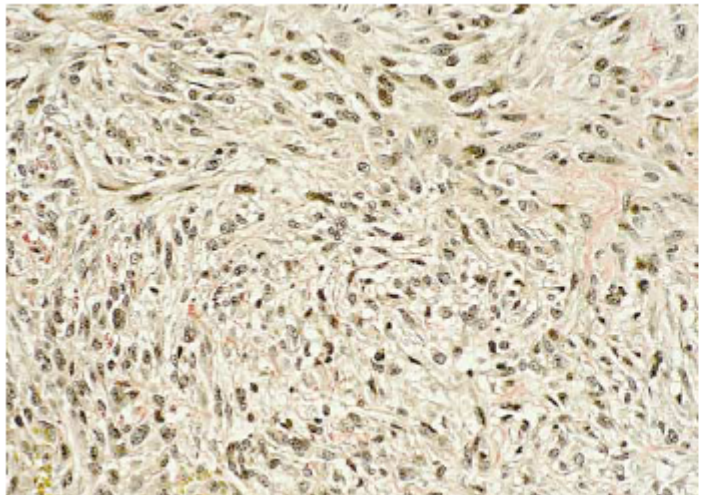
odic acid–Schiff, and van Gieson's stain. Immunostaining was performed with the avidin–biotin–peroxidase method, with antibodies against vimentin, lysozyme, alpha$_1$-antitrypsin, alpha$_1$-antichymotrypsin, keratin, endomysial antigens, S100, actin, and desmin (all antibodies were obtained from Dako, Glestrup, Denmark).

Isolation of DNA

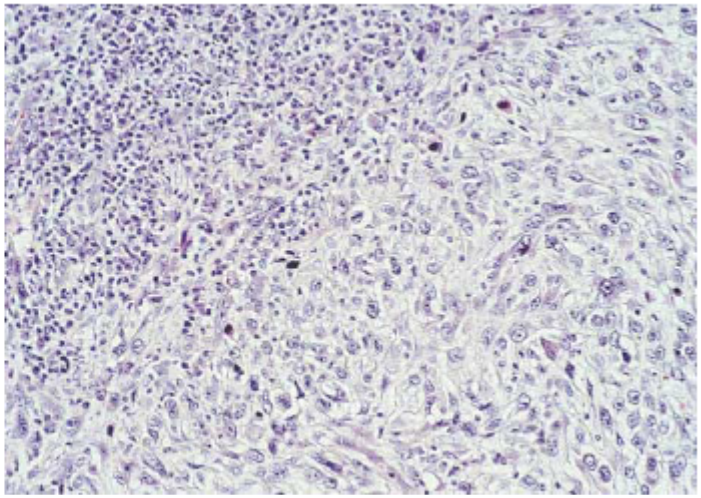
Genomic DNA from peripheral-blood samples was isolated by the "salting-out" method.[6] DNA from paraffin-embedded tumor and tissue samples was extracted according to a modification[7] of the method of Goelz et al.[8]

Analysis of Short Tandem-Repeat Polymorphisms

Short tandem-repeat polymorphisms of the loci HUMTH01, HUMCYAR04, and HUMACTBP2 were amplified by the polymerase chain reaction (PCR) with fluorescence-labeled primers. Primer sequences were chosen from published sequences.[9-11] The 5′ primer for HUMCYAR04 was labeled with 5-carboxylfluorescein, whereas



Patient's Sarcoma



Surgeon's Sarcoma

Wellcome Trust Sanger Institute

Mike Stratton
Zemin Ning
Ludmil Alexandrov
Beiyuan Fu
Zhihao Ding
Caitlin Stewart
Bee Ling Ng
Bronwen Aken
Graham Bignell
William Cheng
Tom Connor
Yong Gu
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Collaborating Organisations

Vets Beyond Borders
World Vets
SCAD Thailand
AMRRIC (Australia)
IFAW
Animal Care Association, The Gambia
St George's University, Grenada
Colorado State University
University of Messina
University of Yucatan
Bons Amigos (Cape Verde)
University of Cambridge, Vet School
European Bioinformatics Institute
Imperial College London
University College London
University of Franca
Sao Paulo State University
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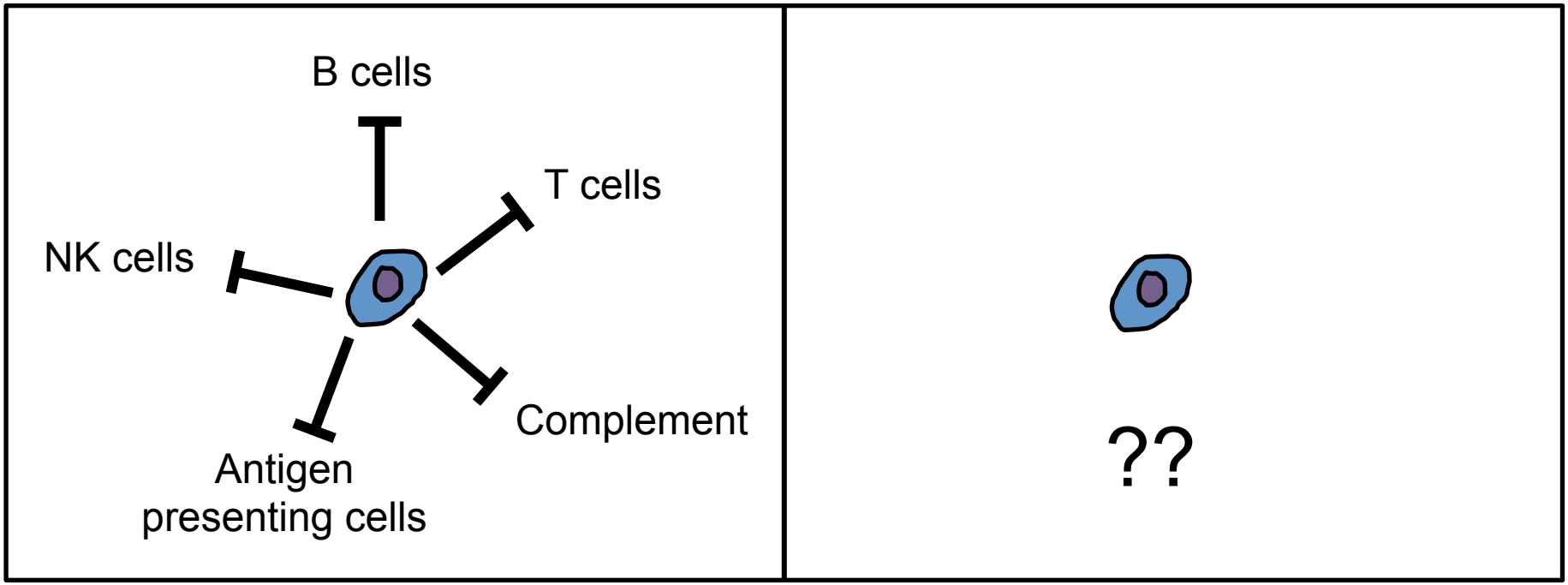
Soi Dog Foundation (Thailand)
Worldwide Veterinary Service
PAWS (Mauritius)
University of Ibidan
University of Nairobi
Usmanu Danfodiyo University
KSPCA (Kenya)
Help in Suffering (India)

Thank you!

Photo: Sarah Peck

Immune evasion



Canine transmissible venereal tumour (CTVT)

Tasmanian devil facial tumour disease (DFTD)