Blodtypes in Ragdoll and the b-3 variant

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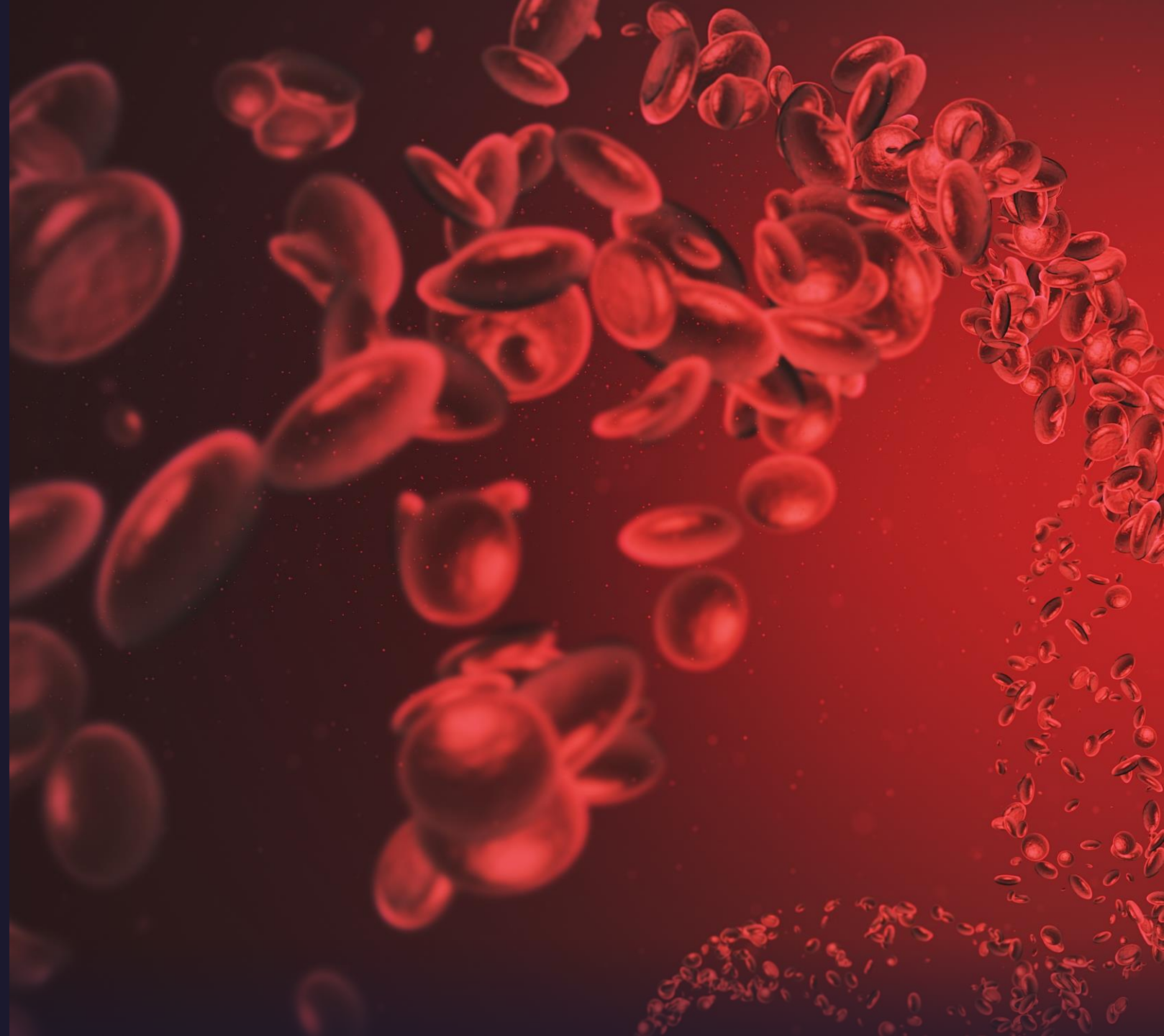
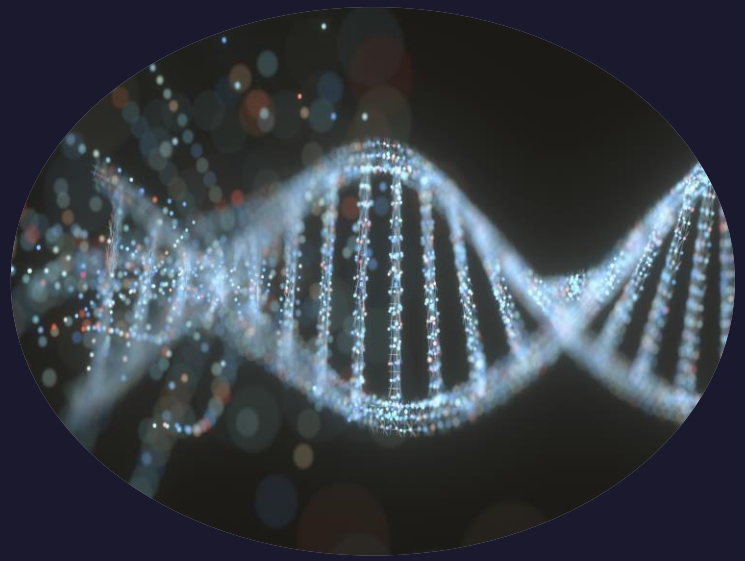
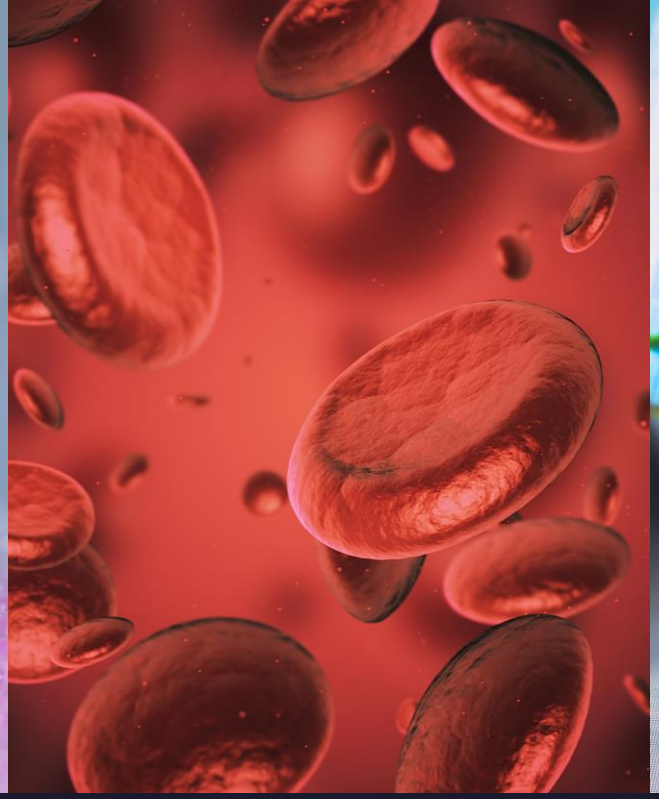


Agenda

- Introduction to genetics
- The different blood types, and their inheritance
- B-1, B-2 and B-3, why use a DNA-test
- The effect of blood types in breeding
- How do we proceed now?








Introduction

- A third mutation with regards to bloodtypes was recently discovered in ragdolls and closely related breeds. This new mutation is in a gene which can give blood type B and can only be detected by a DNA-test.
- This blood type is unwanted as it complicates our breeding and can lead to high mortality in newborn kittens in some cases. We have had very little B-blood in our breed until now, but this can change quickly if we don't act now.

Genetics

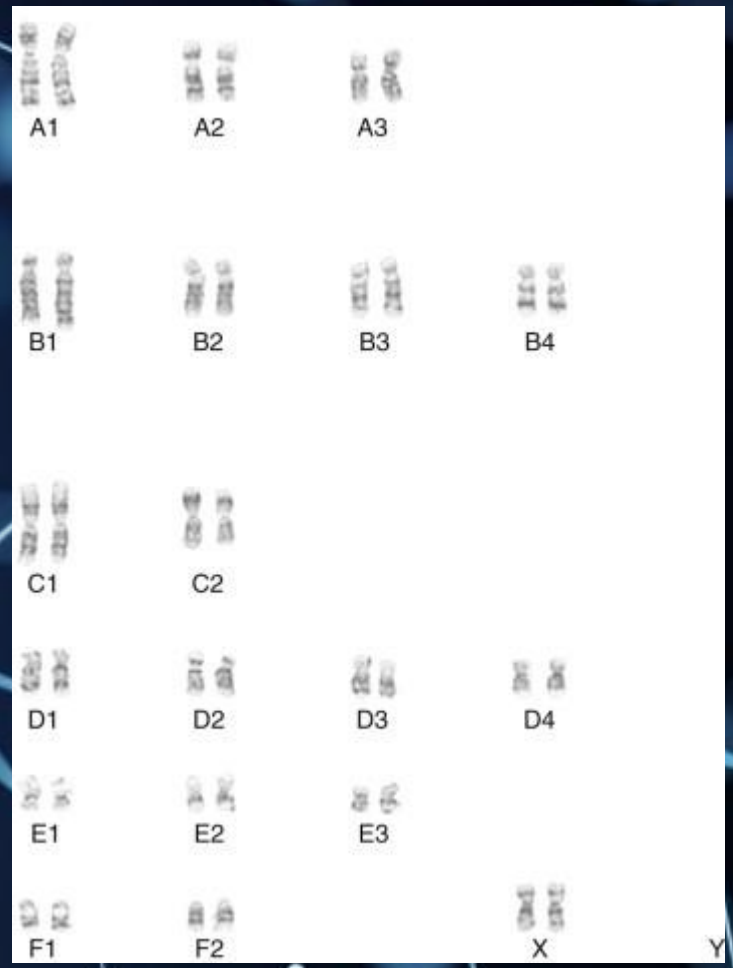
A short introduction first ☺

A cat has a total of 38 chromosomes, 19 from mom and 19 from dad. The chromosomes are made up of long threads of DNA, and sections of these threads are the genes. The chromosomes makes up pairs, with the exeption of the sex-chromosomes (X and Y).

Genes with the same functions are placed in the same location on both chromosomes in a pair. Both we and the cats therefore have two genes with the same function, one from each of our parents. Due to evolution, our genes have small differences in them. This is a result of mutations and has given us many different variants within our genes. Variants of the same gene are called alleles.

Only one of the two alleles are normally "active", and which allele that is regulated by the different strengths of the variants. We can arrange these strengths by dominant/recessive genes, where the dominant gene "shuts off" the recessive one.

Note: Polygenics, co-dominance and pleiotropic genes does not affect blood-types, and will therefore not be explained in this paper.



Courtesy Roscoe Stanyon.

Punnett square

We can use a punnet square to predict possible allele-combinations in the offspring of two individuals with known alleles.

Let's take the tabby pattern as an example:

The allele for tabby (A) is dominant, and the female in this example has one dominant gene: Aa. An individual with one dominant, and one recessive allele is "heterozygote" for this gene .We usually write the dominant gene with upper case, and the recessive gene with lower case.

The male in this example is not tabby and is therefore homozygote for the recessive gene: aa.

Mother ⇨ A / Father ⇩	**A**	**a**
a	Aa	aa
a	Aa	aa

The result of this combination is that any offspring will have a 50% possibility for being tabby (Aa) and a 50% probability for being homozygote for the recessive gene(aa)

Blodtypes in ragdoll

Cats have three main blood groups: A, B and AB.

A is the most common one, and is dominant over both B and AB. AB is dominant over B.

AB is quite rare, and we are still a bit unsure as to how it inherits. Research has shown that it most likely came from a mutation in the same gene that A and B originates from, and not as a result of an A to B mating as first thought.

The blood types genetically

A cat with blood type A can have severall different combinations of alleles:
- A/A (homozygote). The combination we want the most of.
- A/c (carrier of AB-blood). There are no know issues with AB-blood, so this combination is also wanted.
-A/b (carrier of B-blood). We do not want carriers of B-blood, so we should work towards getting rid of these.

A cat with blood type AB can have two different allele-combinations:
- c/c (homozygote) No problems associated with this.
- c/b (carrier of B-blood) same issue as with A/b.

A cat with B-blood can only be homozygote for b-alleles:
- b/b (not a combination we want) This can be any combination of the different variants: B1, B2 and B3:
  - For example: B1/B2, B3/B3 and B1/B3.

Antibodies:

- A blood makes a small amount of antibodies against B-blood
- B blood on the other hand produces a lot of antibodies against A-blood
- AB does not make any antibodies.

The genetic results of some matings:

Mother → / Father ↓	**A**	**A**
A	AA	AA
b	Ab	Ab

50% A/A (A-blood)

50% A/b (carrier of B-blood)

Mother → / Father ↓	**A**	**b**
A	AA	Ab
b	Ab	bb

25% A/A (A-blood)

50% A/b (carrier of B-blood)

25% b/b (B-blood)

Mother → / Father ↓	**b**	**b**
A	Ab	Ab
A	Ab	Ab

100% A/b (carrier of B-blood)

Mother → / Father ↓	**c**	**b**
b	cb	bb
b	cb	bb

50% c/b (carrier of B-blood)

50% b/b (B-blood)

The different b-variants

Both the alleles for B blood and the alleles for AB blood are mutations of the original gene for A blood, the CMAH gene. We look at these mutations as unwanted.

We have so far found 3 different variations which can give B blood: B1, B2 and B3.

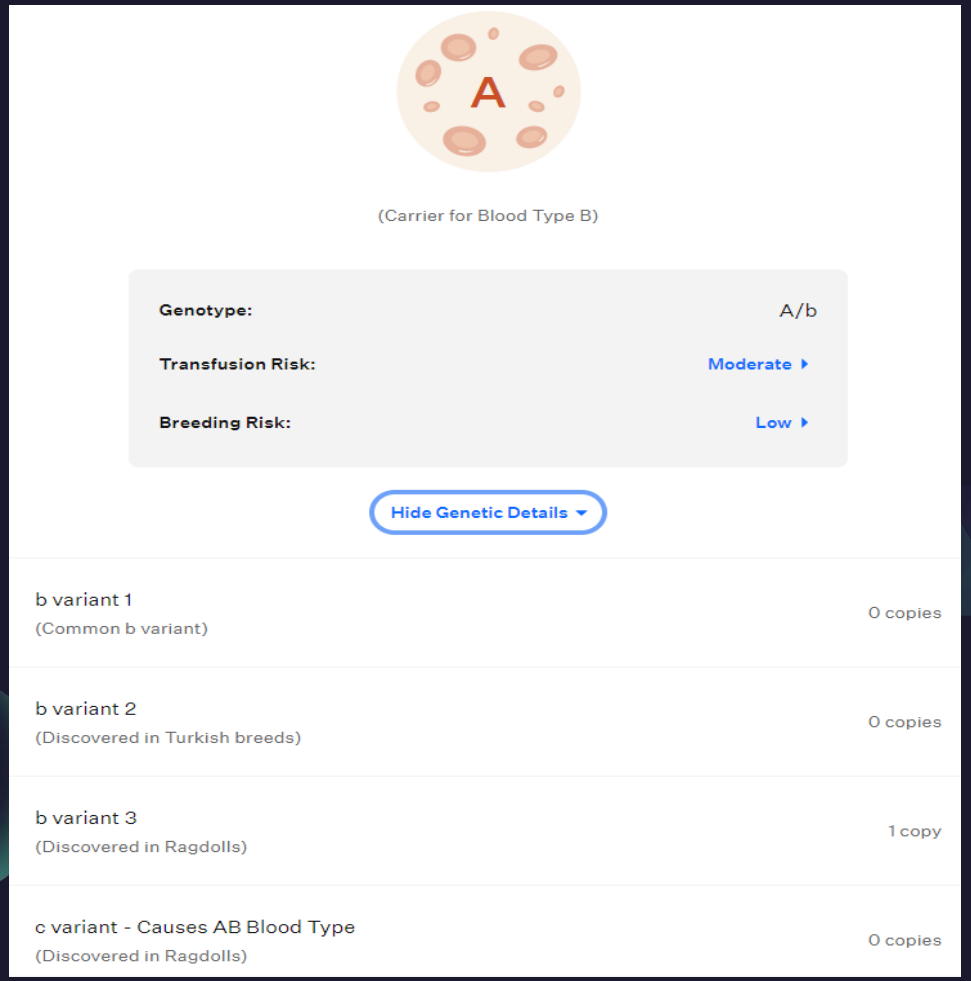
B1, B2 and B3

B1 and B2 are variants that we have know about for a while.
B1 is the most common variant across all the breeds.
B2 is less common, but has been observed in ragdolls.

B3 is the new variant which was just discovered, and is most common in ragdolls. Since we have not know about until recently, we have not been able to test for it either. Both Langford and Wisdom Panel (mycatDNA) included a analysis for this gene recently. Cats DNA tested earlier might have a void result on their blood test.

<u>None of these b-variants will be detected by a serological test (blood test), unless the cat has b-blood.</u>

It is therefore important that we only use DNA-test to determine the blood types of our breeding cats. If you have used wisdom panel, it is easy to check if you cat was tested for B3. If it says «-1 copy» the cat has not been tested for this variant.



If you want to analyse blood type through Langford it seems that you have to ask specifically for the B3 analysis. The results from them will not show you which variants they have tested for, so be sure to ask them if you are unsure.

It is also possible to ask Langford to reanalyse your test if its not too long ago since they got your samples.

Wisdom panel does not give you the possibility to test for blood types alone, this analysis is only a part of a bigger package.

Is this new variant more dangerous than B1 and B2?

Not really, the problem is that it might have been in our breed for a long time before it was detected.

We will therefore have many cats which has previously been tested to have A-blood (A/A), but who in reality is A/b or b/b. This is because the analysis does not target the alleles for A-blood, so a test that does not show the known alleles for B or AB blood will automatically be considered to be A/A. Langford estimates that 35% of cats previously thought to be A/A or A/b is actually b/b, a very scary number of cats if you ask me.

The effect of blood types in breeding

The biggest problem with blood types in breeding is when you have a female with B-blood.

As previously mentioned, a cat with B-blood will produce a lot of antibodies against A-blood. If the kittens after a B-blood mom has any other blood type than B, the result can be devastating.

Neonatal isoeryhtrolysis

Newborn kittens are not able to break down the proteins they eat, but rather absorbs these proteins whole. The antibodies in moms milk will therefore be absorbed into the kittens bloodstream where they break down the kittens own blood. This can then lead to anaemia and death. This effect is called neonatal isoeryhtrolysis and is presumed to be one of the causes to fading kitten syndrome.

Kittens to a B-mom without B-blood must therefore be kept from drinking moms milk when they are newborns, and be handfed.

The kittens will eventually be able to break down the proteins they eat, and they are then able to destroy the antibodies from mom. The timing at which they obtain this ability differs slightly between kittens, but most are able to do this when they are about 48h old.

The level of antibodies in mom is possible to chech by the help of a titrer test. If the mom has not had any litters before, she might have a low enought level for the kittens to drink from her from the start.

The antibody-level in a B-blood mom usually increases a lot after she has had a litter with non B-blood kittens. This is because her boy reacts to the small levels of unknown blood she ingest while cleaning the kittens.

The effect of neonatal isoeryhtrolysis is due to this increase often much stronger with the next litter. Thats why some breeders does not know that their female has B-blood until litter number 2 with an A male.

How do we proceed now?

- We have to DNA-test all the cats we use for breeding, so we know what we are working with. Be sure that B3 is included in the analysis.
- Should we take any cats out of breeding?

  No! We do not have to get rid of other vice good genes, but we do have to make good and informed choices when choosing mating's.
- **Our main goal is to not make any more cats with B-blood!**

What do I do if my cat has the result A/b or c/b?

Since we do not want to make any more B-blood, cats with these results should only be mated to: A/A, A/c or c/c.

A carrier of B-blood should never be mated to another carrier or a cat with B-blood.

If you do have to mate to carriers, please try to avoid using any offspring with blood type B in breeding.

How about a female with B-blood?

Many will think that the easiest thing to do is just to find a male with B-blood. But you would then create a lot of new cats with B-blood.
In Sweden you are not allowed to mate a B-female to a A-male, but there is an exception! You are allowed to do such a mating if a titre-test before mating shows a low enough number of antibodies.

I would therefore recommend that you do this test and use either an A-male or AB-male in those cases where this is possible.

That way we do not have to make any more B-cats that strictly necessary.

Mother → / Father ↓	A/A	A/b	A/c	b/b	c/c	c/b
A/A	✓	✓	✓	✓	✓	✓
A/b	✓	✗	✓	✗	✓	✗
A/c	✓	✓	✓	✓	✓	✓
b/b	✓	✗	✓	✗	✓	✗
c/c	✓	✓	✓	✓	✓	✓
c/b	✓	✗	✓	✗	✓	✗

This table shows what mating we can do, and which matings we should try to avoid in order to reduce the amount of B-blood in our breed.

An example on how we can use a B-blood female:

We start with a female with B-blood (b/b) who has a low enought number of antibodies to be mated to a male with A-blood (A/A).

Mor ➡ Far ⬇	b	b
A	A/b	A/b
A	A/b	A/b

All of the offspring in this mating will have A-blood, but be carriers of B-blood

In the next generation we should still use a mate with A-blood, but not a carrier (A/A):

Mor ➡ Far ⬇	A	b
A	A/A	A/b
A	A/A	A/b

Again, all of the offsprings has A-blood, and 50% of them carries B-blood. We have reduced the amunt of carriers by half.

So if we all makes good choices we can reduce the amount of B-blood in our breed, without reducing the genepool☺

Sources

- Omi T, Nakazawa S, Udagawa C, Tada N, Ochiai K, Chong YH, Kato Y, Mitsui H, Gin A, Oda H, Azakami D, Tamura K, Sako T, Inagaki T, Sakamoto A, Tsutsui T, Bonkobara M, Tsuchida S, Ikemoto S. Molecular Characterization of the Cytidine Monophosphate-N-Acetylneuraminic Acid Hydroxylase (CMAH) Gene Associated with the Feline AB Blood Group System. PLoS One. 2016 Oct 18;11(10):e0165000. doi: 10.1371/journal.pone.0165000. PMID: 27755584; PMCID: PMC5068781.
- Haldane S, Roberts J, Marks S, et al. Transfusion medicine. Comp Contin Edu Pract Vet 2004;26:502-518
- Giger U, Bucheler J. Transfusion of type-A and type-B blood to cats. J Amer Vet Med Assoc 1991;198:411-418
- Bucheler J. Fading kitten syndrome and neonatal isoerythrolysis. Vet Clin North Am Small Anim Pract 1999;29:853-870
- https://www.langfordvets.co.uk/media/1728/feline-blood-type.pdf