Author of the original: Krunoslav Brcic-Kostic, PhD, Ruder Boskovic Institute, Zagreb
Translation to English: Jelena Brkljacic, PhD, Obsidian Snowflake kennel, Zagreb

LUA dalmatian dogs

The origin of LUA population

LUA dalmatians are the result of crossbreeding the pointer male and dalmatian female in 1973 under the supervision of Dr Robert Schalble. The main goal of that crossbreeding was to genetically map the gene responsible for increased level of uric acid, which is specific for dalmatians, but later turned into an aspiration to completely knockout the allele (gene variation) responsible for this phenotype from the future dalmatian populations. In their population this allele is fixed, which means all dogs have it. dalmatian dogs finish their purine metabolism one step earlier, so, instead of alantoin, uric acid accumulates in their urine. In other dog breeds the urate oxidase enzyme (uricase) catalyzes the oxidation of uric acid into alantoin. This is the reason why dalmatians have 10 times higher concentration of uric acid in their urine, compared to other breeds. Because uric acid does not dissolve in water as easy as alantoin, dalmatians have much higer risk of developing urate stones or stone dust. It's interesting that they have a functional gene for urate oxidase enzyme, but they have a mutation in the gene for the transporter which brings the uric acid in the contact with urate oxidase and this is the cause of described phenotype. This gene is called SLC2A9 and point mutations that cause this defect have been discovered.

We will simply label the functional and unfunctional variants of this gene (alleles) with capital and small letter **„u“**. Allele **u** (small letter is used because it is recessive) gives so called HUA (High Uric Acid) phenotype. The other breed (pointer) was chosen as forefather (sire) of new population because pointers have „normal allele“ and as the result have lower uric acid concentration which gives so called LUA (Low Uric Acid) or NUA (Normal Uric Acid) phenotype. This so called „normal“ allele is labeled with **U** (capital letter is used because it is dominant). As the result of this crossbreeding F1 (first-generation) hybrids were created and they were all heterozygous genotype **Uu** and LUA phenotype because the **U** allele is dominant over the allele **u**. These dogs were in all other characteristics true hybrids, because they were the mix of morphological phenotypes between dalmatian and pointer (they had in average 50% genes of dalmatian and 50% genes of pointer breed). Dogs from this F1 generation were further crossbred with dalmatians registrated in AKC (American Kennel Club) and for the further breeding only dogs with **U** allele, which gives LUA phenotype, were selected. In genetics this procedure is called backcross, so the project was named „The Dalmatian Backcross Project“. The procedure was continued and now we have 14th generation since the first crossbreed in 1973 (Figure 1). In the meantime the project has changed its name into „Dalmatian Low Uric Acid Project“. During this project the percentage of dalmatian genes was continuously increasing and todays dogs have in average 99.8% similarity to AKC registrated dalmatians. In 2011, with a lot of resistance, AKC has recognized and registrated LUA dalmatians. Although they are recognized only by AKC, few LUA populations were imported to some European countries were no strict controls exist, where they were already bred with European registrated dalmatians.

In further text I will bring up some reasons against the introduction of LUA population into a registrated population of dalmatian dogs. These are the high posibility they are carrying some pointer genes closely connected to SLC2A9 gene (allele U), among which are the ones highly important for the shape and quality of spots in dalmatian, posibility of introducing other adverse mutations (from pointer) and finally the well known fact from the population genetics, that recessive adverse mutations are very hard to eliminate from population.

LUA dalmatian and pointer genes

In average, LUA dalmatians have smaller spots (although in the limits of breed standard), and in some dogs the spots are badly shaped. The reason for the lower quality of the spots is in pointer alleles in LUA dalmatians. In the proximity of SLA2A9 gene there is one or more genes which are still not well characterized, but influence the shape and quality of spots in dalmatian. Because the lower quality of spots is present in smaller part of LUA population, we cannot be sure the dogs with normal spots are not carriers of pointer genes. This is the potential risk for furthed breeding because we don't know how these genes are regulated or if they interact with other genes alleles (epistasis). It is considered that the HUA phenotype in recognized (registrated) dalmatian population is fixed as a byproduct of selection for better spot quality (2). Similar is with alleles of genes responsible for deafness which came into the breed during the selection for recognizable colour of dalmatian dog, and are brought into connection with **S** locus (**piebald**, or **MITF** gene).
During the process of backcross, the genes of dalmatian have been entering the LUA population in two ways: free combination and recombination of alleles during meiosis. By free combination alleles were entering much faster, and on other chromosomes beside chromosome 3 where SLC2A9 gene is. This chromosome was inherited from pointer and was always selected because of LUA phenotype. In order to gradually shift the alleles of pointer with alleles of dalmatian on chromosome 3, genetic recombination or crossingover is required. We know that the crossing-over of two connected genes is very rear. The probability of crossing-over is even smaller if the genes on genetic map are closer. If they are very close to each other, they are frequently inherited together as the same haplotype, or the same allele combination (this is the reason why the allele of SLC2A9 gene responsible for HUA phenotype is also fixed in dalmatian dogs during the selection for spots quality). If, at the moment, LUA population shares 99.8% of genes with the recognized dalmatian population, it means it carries 0.2% of pointer genes. After dog (*Canis familiaris*) genome sequencing it was estimated the dog has around 25000 genes encoding for proteins. Of this number, 0.2% is 50, which means the LUA population has around 50 genes from pointer. The exchange of these genes with the ones from Dalmatiasn is going to be very slow because of the reasons stated above. The genes which are in the close proximity to SLC2A9 will probably very long, if not forever, stay together in the package as pointer alleles (among them are the genes for the spots quality). The fact that LUA population and registrated population have only around 50 different genes means nothing if the breed-specific genes are among them, and the genes for the spots quality definitely count into that group. Tha fact they will be hard or impossible to kick out of LUA population is the stronget argument not to introduce the LUA populations into the registrated dalmatian population. In the research ordered by the AKC, it was showed that, in terms of genetic polymorphisms, LUA dalmatians are the most similar to registrated dalmatian dogs, and not to pointer or any other breed. This is expected after 14 generations of backcross and this fact was the main argument for the LUA population supporters to recognize it by the AKC. However, in this research it was not confirmed if the genes in the proximity of SLC2A9 gene origin from pointer or dalmatian, and that is the key considering that the breed-specific genes are found here.

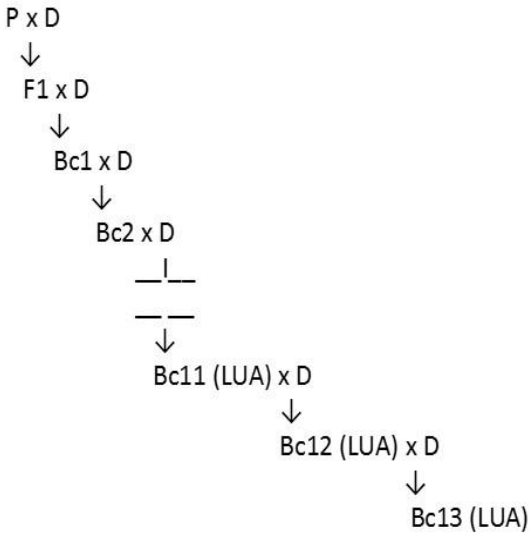

Figure 1. Sheme of bredeing in the „Low Uric Acid Priject".
D – Dalmatian; P – Pointer; F1 – first generation of progeny;
Bc – backcross generations;

Small population of LUA dalmatians

Although the internet photos promoting the LUA dalmatians show no visible difference in their appearance compared to recognized dalmatian dogs, the difference in their origin are huge. True dalmatian, as the historic breed, was created in long periods of artificial selection and was covering a big population (so called effective population size, N_e). Big population is of great importance because, during the process of breed differentiation, the genetic variability (heterozigosity) is maintained on genes that do not affect the shape, but are important for health, general physiological condition and imunitiy to diseases. That is why, from evolutionary point of view, a big population is potentially healthier than the small one. The LUA population of dalmatians has recently experienced so called „bottleneck", or dractically reduced number of individuals. The whole „Dalmatian Low Uric Acid Project" has almost experienced fiasco in 2005, when there were only few individuals left for breeding (two alive and the frozen seemen of two already passed away). From the population genetics view, the story of LUA dalmatians, or to say their todays population, starts in 2005 and not 1973 when the **U** allele from pointer was introduced. If these individuals would have some potentially adverse alleles on other genes (transferred from pointer), then they could be a problem in later generations if they would be introduced into registrated population. Even bigger potential problem exists for LUA population due to a small number of individuals. For now it is controlled through breeding with registrated dalmatian dogs of different lines, but would evoke if the mating was done exclusively inside LUA population. A similar problem, connected to a small initial population, exists in german shepards, who were selected very fast in desire to produce a dog for military puproses in the first World War in a very short period of time. In the fast selection, a small number of individuals were used, and as a consequence they have more inbreeding (homozigosity due to mating of relatives). Bad alleles are mostly recessive and if they are found in homozygous form, they reduce the fitness (adaptive value) of the individual that carries them. This was the case with german shepard, where alleles responsible for bad condition

of hips in many individuals have „smuggled“. I don't say we have the same in LUA population, but potential other risks might exist.

Recessive bad alleles are difficult to remove - genetic population overload

LUA dalmatians do not represent some superior population which would be immune to other deficiencies. It should be emphasized that no population of any wild breed is ideal in the meaning of health and overall fitness. Natural selection removes inferior variants (or just reduces its frequences in the population). If it's not a big deficiency, than these rare genotypes might, in some changed future conditions, be superior, and then would have a selection advantage. This is the reason why it's important to have a genetic variability in the population, and it is the function of population size. Considering that even populations of wild breeds, which are under natural selection, are not ideal because of bearing some genetic burden (elimination of recessive genetic mutations by natural selection is very difficult), it is unrealistical to expect this in domestic animals. Populations of domestic animals are in average less healthy and have smaller fitness compared to wild populatoins due to medicine and technology impact (without veterinary interventios, many species would be eliminated due to natural selection). Despite the „problem“ of purine metabolism, dalmatians are relatively healthy dogs with a big reservoar of good alleles on many genes. Dalmatian dog breed was not established in 1973 nor in 2005, but it's a historical breed which is mentioned in the distant past, and that is to be respected. The price is already paid for its origin and it manifests through genetic overload considering deafness and uric acid metabolism. That was the only option or there would be no dalmatian dog! It's interesting that, besides the dalmatian, a similar problem with the purine metabolism is found in primates, although the genetic cause for this phenotype is different (mutation in the gene for urate oxidase). The question arrises, if we should intervent in human to remove this deficiency? Of course it's absurd and impossible! Even today human population hasn't got rid off many bad recessive alleles, although there even were attempts in history. These eugenic measures were supported by a great geneticist and statistician Roland A. Fisher (1890-1962), but later he understood this was a mistake. On the other hand, even with this dissadvantage, the primates live freely in nature and resist strong natural selection.

There is one more reason why it would be apsurd to introduce the LUA population into the registrated dalmatian population. This reason includes the very purpose of their breeding. LUA dalmatians were created with the purpose to throw out (or to reduce) the recessive allele. If their breeders succeeded in that (or are close to this goal), it would be illogical to breed them now with the registrated dogs who exclusively have the recessive allele. Through their crossbreed the same „problem“, which was the reason for initiating the LUA population breeding, arrises again. For the benefit of resolving the „problem“ of **u** allele, the only logical option is to leave LUA dalmatians where they are, to be recognized only by their associations, and that would not keep their breeders from showing them at dog shows they organize on their own. Only then their breeders would be able to achieve their goal and get rid off the recessive allele or put it under control. Also, it should be emphasized that in the process of selection against **u** allele many exceptional exhibition specimens (possible champions) would be lost only because of HUA phenotype, despite the fact that most of them would never get sick!

Conclusion

I personally think that, because of the reasons mentioned here, and primarily because of the huge dificulties or impossibilities to remove the pointer genes in the proximity of SLC2A9, LUA dalmatians should not be introduced into the registrated (recognized) dalmatian population. Anyway, the final answer to this question will be given in the future when the genes in the

proximity of SLC2A9 gene (responsible for the spot quality) are characterized and when it's determined which alleles are present in LUA population.

Literature

1. Schaible R, 1976, Linkage of pigmentary trait with a high level of uric acid excretion in the Dalmatian dog. Genetics 83: S68
2. Bannasch D, Safra N, Young A, Karmi N, Schaible RS, Ling GV., 2008, Mutations in the SLC2A9 gene cause hyperuricosuria and hyperuricemia in the dog. PLoS Genet. 4:e1000246
3. www.luadalmatians.com
4. Schmutz DS, Berryere TG, 2007, Genes affecting coat color and pattern in domestic dogs: a review. Anim Genet 38:539-549.
5. American Kennel Club Health and Welfare Advisory Panel, 2010, Report to AKC Board of Directors (Molecular genetic analysis of backcross Dalmatians compared to AKC Dalmatians, UK Dalmatians, Pointers and other breeds).
6. Halliburton R, 2004, Introduction to population genetics. Pearson Education Inc.
7. Falconer DS, Mackay TFC, 1996, Introduction to quantitative genetics. Longman, Essex.