

## Information about the Cystinuria Research in the Irish Terrier & Kromfohrländer

### What is the purpose of this study?

In some breeds cystinuria is more prevalent than in others and gene tests for particular cystinuria types in the dog and in the cat were established by the PennGen laboratory. PennGen discovered an androgen-dependent cystinuria in Irish Terriers and Kromfohrländer, for which no gene test is available yet. The androgen-dependent cystinuria may only develop in the presence of male sexual hormones, thus it exclusively occurs in intact (non-castrated) adult male dogs. Diseased dogs are prone to getting urinary tract stones (cystine stones), which can cause a life-threatening state and may have to be removed surgically or endoscopically. The mode of inheritance of this disease is not entirely clear at the moment; it seems not to be X-linked recessive, but rather complex or autosomal recessive. The research is very difficult because female dogs never show cystinuria, and male dogs have only a predisposition with increased risk for stone formation. The molecular genetic basis of the androgen-dependent form of cystinuria is largely unknown and particularly difficult to investigate.

In collaboration between the University of Bern and the University of Pennsylvania, we would like to closer investigate this disease and develop a genetic test. The aim of this genetic test is to recognize risk animals (before they show cystinuria or cystine stones formation) and carriers of the disease. We also collaborate with the laboratories of Laboklin and Biocontrol. We kindly ask owners, breeders, and veterinarians for submission of urine samples (for COLA-value determination) and blood samples (for DNA isolation and the genetic analysis).

### Which samples should I submit? How should these be taken?

We need in particular samples from male dogs suffering from cystinuria (**"cases"**) and their relatives (**parents and litter siblings**), and also from healthy non-castrated male dogs who are older than 5 years and don't have relatives affected by cystinuria (**"controls"**). For this we need your support. Below you find additional specific details regarding the required samples. If your dog is suitable for our study, we kindly ask for samples and information.

### Samples and data which are required for "cases" and their relatives:

A case is defined as a dog that has been diagnosed with cystinuria at any time during its life. The diagnosis can be either made based on urine stone analysis by a specialized laboratory (cystine stone) or based on an increased COLA-test result in a urine sample (cystine-value > 200 µmol/g creatinine or COLA-sum > 700 µmol/g creatinine). We need:

- Blood samples from cases
- Blood samples from both parents and ideally from all littermates of cases
- Urine COLA-test results from the male intact (non-castrated) relatives (father, if not castrated and male littermates, if not castrated)
- Filled questionnaire
- Copy of the pedigree

**Samples and data, which are required for “controls”:**

Control dogs are strictly non-castrated male dogs who are older than 5 years, never had problems with cystinuria and never had pathologic COLA findings. Controls must not be closely related to cystinuria affected dogs (parents, siblings, offspring). We need:

- Blood samples from male control dogs
- Urine COLA-test results from male control dogs
- Filled questionnaire
- Copy of the pedigree

If your dog is male castrated (surgical or chemical) or female, and not closely related to a case (parents or littermates), we do not necessarily need a sample from your dog for this study. However you are most welcome to still send us a blood sample for our archive, we can use for future research projects. Thank you very much!

**Information about delivery of general blood samples from Europe to the University of Bern:**

We need:

- EDTA blood sample (preferably 5 ml, at least 2 ml)
- Completed and signed consent form
- Copy of the pedigree
- Copies of stone analysis and urine-COLA-test result(s) from the case and his male intact (non-castrated) relatives (if available)

**Information about urine sample and COLA-test by Laboklin and Biocontrol:**

The COLA-test is performed by Laboklin and Biocontrol based on specifications developed by PennGen. A urine sample of 5-10 ml is needed. This should be collected cleanly in the morning before the first meal, and can be delivered in a normal sterile urine or serum tube. If the urine sample remains for more than 24 hours with you or your veterinarian, it must be frozen. The sediment should not be removed.

**How is the research coordinated between Prof. Dr. Urs Giger (University of Pennsylvania, USA) and Prof. Dr. Tosso Leeb (University of Bern)?**

Prof. Dr. Urs Giger is a veterinarian and scientist and the world's leading expert in the field of inherited metabolic diseases in domestic animals. He studied cystinuria: clinically, biochemically and genetically over many years. He defined the COLA-test threshold values and developed genetic tests for cystinuria in other breeds (PennGen). Prof. Dr. Tosso Leeb has a very high level of expertise in molecular genetics and a laboratory with the most modern equipment for DNA sequence analysis. Therefore, most genetic laboratory experiments are performed in Bern. All blood samples from Europe should be sent to Bern and will there be centrally collected. All data are regularly exchanged between the two institutions. Linda Anderegg is a doctoral student at the Institute of Genetics in Bern.

**Who can help me if I have questions about the research or sample submission?**

If you have questions or comments in relation to this study, do not hesitate to get in contact with the Institute of Genetics of the University of Bern. Direct contact person regarding sample submission: Sarah Kiener (veterinarian), Institute of Genetics, Email: [sarah.kiener@vetsuisse.unibe.ch](mailto:sarah.kiener@vetsuisse.unibe.ch), Tel. +41(0)31 684 25 24. All information will be treated confidentially.