Because of the canine genome, human genetic diseases better understood

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A dog is mankind's best friend: the old saying has once again been borne out through a medical discovery concerning the genetic origins of primary ciliary dyskinesia (PCD). In using dogs as a research model in the framework of the European LUPA project, a team from the University of Liege's GIGA-Research Unit has been able to bring to light new mutations in a specific gene responsible for the development of the disease in human beings.

Primary ciliary dyskinesia (PCD) is a rare genetic disease which affects one person in 20,000. The disease is characterised by motility defects in cellular micro-cilia. The flapping of these micro-cilia allows micro-organisms contained in the air to be expelled. PCD hinders this flapping and is at the root of chronic respiratory infections.

Several mutations in some dozen or so genes are responsible for the development of this disease, but they do not explain 60% of the cases in human beings. To try and resolve these cases the researchers brought their investigations to bear on...dogs.

In effect dogs and humans suffer from numerous diseases in common which very probably have the same genetic origin (cardiac disorders, epilepsy, cancer, diabetes, etc.). A recent trend in biomedical research is to use dogs which are ill as a subject for study in order to detect the genes which could also be involved in the same disease occurring in human beings.

The researchers at the GIGA-ULg Unit and their international colleagues followed this very logic in investigating PCD.

Several Old English Sheepdog (bobtail) puppies suffering from chronic bronchitis were examined in 2007 at the ULg's Faculty of Veterinary Medicine. The frequency of this complaint in this breed suggested a genetic origin and raised suspicions of a PCD, a conviction which was strengthened by the fact that one of the dogs had a situs inversus, in other words a reversal of the heart's normal position in the thoracic cage. During the embryo stage it is one of the functions of some hair cells to create a flow which enables organs to be correctly positioned; if this flow does not take place there is a risk that an organ's normal position will be reversed.

The researchers analysed the DNA of five ill bobtails brought in for consultation at the veterinary clinic and compared it to that of 15 other healthy bobtails. The analysis of this DNA, with the help of 40,000 genetic markers, enabled the identification of a region of canine chromosome 34 linked to the disease, and more particularly a mutation within gene CDC39.

"We were thus able to identify 15 different mutations of this disease," explains Anne-Christine Merveille, a researcher in Professor Michel Georges team at the GIGA-ULg Unit. "These mutations explain half of the cases analysed, or close to 5% of the patients throughout the world who are suffering from this disease."

The study illustrates well the usefulness of dogs for a rapid decrypting of complex human genetic diseases. ‘The demonstration of this gene's responsibility in this pathology will enable the families affected to be better advised,' adds Doctor Anne-Sophie Lequarré, in charge of the LUPA project.

More information: CCDC39 is required for assembly of inner dynein arms and the dynein regulatory complex and for normal ciliary motility in humans and dogs", *Nature Genetics*, Advance Online Publication, 05/12/2010. www.nature.com/ng/journal/vaop … ent/full/ng.726.html

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