Golden retrievers help scientists track human disease genes

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A team of EU-funded researchers has successfully identified a gene that triggers a skin disorder in dogs - and the findings could have implications for humans who also suffer from the condition. Whether it manifests in golden retrievers or in humans, the disease ichthyosis has the same common genetic basis; therefore, any new bounds made in understanding the condition in dogs are applicable to humans too. No molecular cause for ichthyosis has previously been identified.

Humans and dogs tend to suffer from the same conditions. We live together in the same environments and the dogs' genetic make-up could hold the key to better understanding the genetic origins of cancer, epilepsy, cardiovascular diseases and diabetes.

The main aim of the LUPA project, which started in 2008 and ran until the end of 2011, was to bring together veterinary practitioners and scientists, and collect deoxyribonucleic acid (DNA) samples from large numbers of dogs suffering from a range of diseases to which humans are also susceptible. Identifying susceptibility genes for common human diseases is always tricky due to the complexity of the underlying causes, but dogs' diseases are genetically a lot simpler.

In this new study which presents the latest findings carried out with support from LUPA, the team identified an eighth gene for an ichthyosis type in humans called autosomal recessive congenital ichthyosis (ARCI). They also serve up evidence for the involvement of its gene product in the cutaneous barrier, a feat that has never been achieved before.

Writing in the journal Nature Genetics, the team outline how this ichthyosis type belonging to ARCI results in generalised scaling of the skin, diagnosed at birth. Although the disease is rare in humans, it is occurs frequently in golden retrievers due to inbreeding, and because it has not been counter-selected.

The team took advantage of the unique breeding history of dog populations to identify the genetic alterations responsible for this skin disorder in golden retrievers.. These new findings highlight a unique mutation in the PNPLA1 gene, perfectly segregating on a recessive transmission mode.

Once they had identified the gene in dogs, they analysed the corresponding human gene in selection of individuals affected by the condition. These results showed that six affected individuals belonging to two families carry distinct mutations, both affecting the catalytic domain of the protein. Further experiments involving electronic microscopy, immunolocalisation by confocal microscopy and biochemistry analyses, helped identify the precise role of the protein.

PNPLA1 lipase is located in-between the upper epidermal and the lower layers of the cornified layer, and is required for the correct keratinocyte differentiation. It belongs to the PNPLA family of proteins (PNPLA1 to PNPLA5), key elements in the lipid metabolism of the cutaneous barrier.

Previous studies supported by LUPA have identified a new epilepsy gene in Lagotto Romagnolo, a breed of dogs known for their gift for truffle hunting. This could be a new candidate gene for human childhood epilepsies characterised by seizure remission. The team also discovered a novel gene that triggers primary ciliary dyskinesia (PCD), a rare genetic respiratory disease found in both humans and dogs.

More information: Grall, A. et al., 'PNPLA1 mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans', *Nature Genetics*, 2012. doi:10.1038/ng.105

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