From Dog to Human: Searching the genetic bases of hip dysplasia

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INTRODUCTION

Canine Hip Dysplasia (CHD) is an abnormality in the development of the hip joint in dogs and is homologous to the Developmental Dysplasia of the Hip (DDH) in humans. This disease is caused by excessive laxity of the joint, resulting in poor coaptation of the bones. It then leads to a deformation of the joint profiles and the development of osteoarthritis in later age.

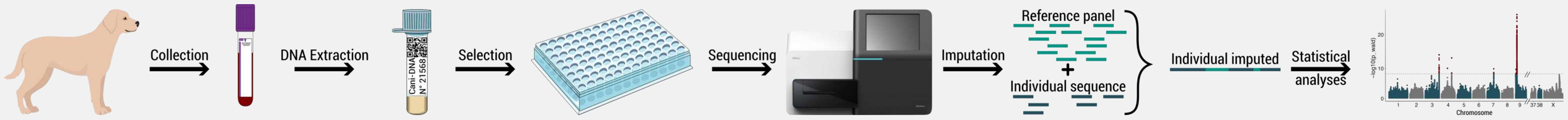
In dogs, this condition entails high costs for the organisations that train working dogs. The "Association les Chiens Guides d'Aveugles de l'O*uest"* and the Visio Foundation have therefore asked our team, with the collaboration of Prof. Jean-Pierre Genevois[1], to carry out a research project on the genetic causes of CHD.

CHD is a complex, multifactorial disease with several genes and environmental factors (e.g., nutrition, exercise) involved in its development. Multiple loci are currently under investigation, but none have yet been confirmed as involved in the canine or human disease.

Dogs are a useful orthopaedic model because they share similar environments, diseases, diagnosis and treatments with humans. Moreover, family dogs are a non experimental and natural model easier to study than humans: they have shorter generation time, their information and samples are simpler to obtain and the diseases prevalence tends to be higher due to population structure.

OBJECTIVES:

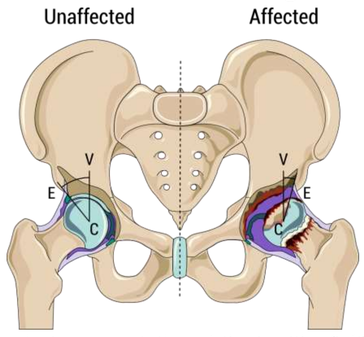
- Identify the different loci / genes associated with the disease in dogs to better understand the biological background
- One Health concept: Findings in dogs will help the veterinarian field as well as human patients



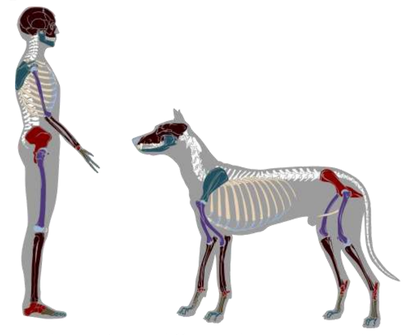
HYPOTHESES & METHODS

HYPOTHESES

- Each canine breed = genetic isolate, facilitating the identification of genetic regions involved, as the combinations of major and minor genes are different depending on the breed
- CHD and DDH are homologous ➔ genetic regions involved are similar



Anatomical representation of the healthy (left) and osteoarthritic affected (right) hip joint. The VCE angle is lower in affected joints.



Comparison of the different bone groups between humans and dogs

METHODS

- To compare the genomes of affected dogs and unaffected dogs
- To identify the genetic alterations more frequently found in affected dogs by means of bioinformatic and statistical methods

INDIVIDUALS	100 unaffected individuals + 100 affected individuals per breed Labrador Retriever · Golden Retriever · Bernese Moutain Dog · Dogue de Bordeaux · Cane Corso Italiano
DATA	Official FCI[2] grade A (unaffected) versus D or E (affected) Low-pass Sequencing (coverage of the genome of 0.5 - 1.5 ×) Single Nucleotide Polymorphism (SNP) genotype data (700K SNP/dog)
IMPUTATION	Complete the missing genomic data by denser corresponding data from a reference panel (i.e. > 800 dogs from 158 breeds)
ANALYSES	Genome-wide Association Study (GWAS) and genetic linkage analysis

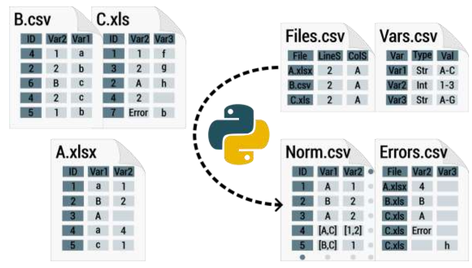
PARTICULAR EMPHASIS

- Respect the Findable, Accessible, Interoperable, Reusable (FAIR) principle
- Ethics (spontaneous and non experimental model)
- One Health concept

RESULTS

REALISATIONS

1. 10 years of sample collection = (100 affected + 100 unaffected dogs) * 5 breeds ➔ 1000 dogs collected (800 sequenced or SNP genotyped)



2. CHALLENGE: Multiple data not standardised in many files

   SOLUTION: Customisable Python application

3. CHALLENGE: Pedigree creation by hand, tedious and time consuming

   SOLUTION: R library (Kinship 2) update (filtering and GUI interface)

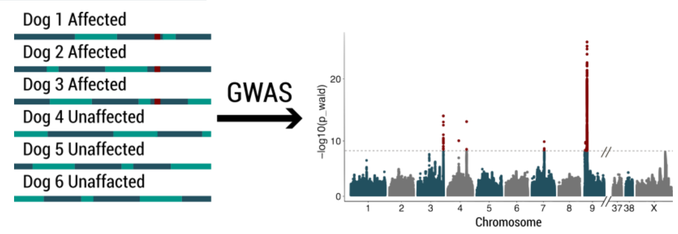
4. CHALLENGE: Imputation mostly by 1 company (not Open Science)

   SOLUTION: Sub-workflow development in nf-core (Open Science, 1st module done)

IN PROGRESS

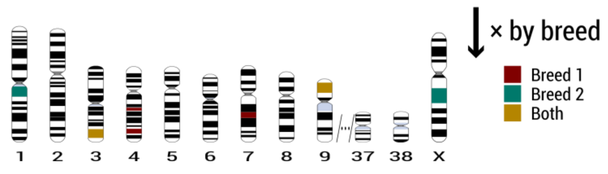
5. IMPUTATION:

   1M SNP/dog ➔ 30M SNP/dog



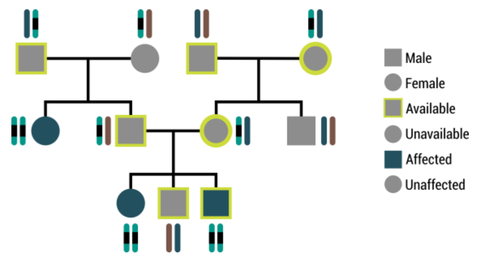
6. GWAS:

   Identification of genome regions (loci) associated with the disease unique within breeds and common between breeds



7. GENETIC LINKAGE ANALYSES:

   Identification of specific locus segregating in families, allowing the refinement of the loci identified by GWAS



CONCLUSION

- Open-science solution for multiple challenges of this project
- Multiple breeds help to understand the multigenic nature of CHD
- The dog: a natural model of hip dysplasia

PERSPECTIVES

- Highlight the genetical and biological pathways involved in hip dysplasia
- Genetic risk test to reduce the incidence of CHD in the dog breeds studied
- Translational research with human medicine

[1] Professor Jean Pierre Genevois = International veterinarian expert about CHD
[2] FCI = "Fédération Cynologique Internationale"

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With the collaboration and financial support of ACGAO and Visio:

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FONDATION VISIO L'INNOVATION NOUS GUIDE