

# International breeding programs to improve health in pedigree dogs

Shizhi Wang

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*par*

**Shizhi WANG**

**International breeding programs to improve health in pedigree dogs**

Directeur de thèse : Etienne VERRIER (AgroParisTech)

Co-encadrement de la thèse : Grégoire LEROY (AgroParisTech) et Erling STRANDBERG (Swedish University of Agricultural University)

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### Composition du jury :

- M. Laurent TIRET, Professeur, PhD, École Nationale Vétérinaire d'Alfort (France), Président
- Mme Lisa COLLINS, Professeur, PhD, University of Leeds (UK), Rapporteur
- M. Åke HEDHAMMAR, Professeur, PhD, Swedish University of Agricultural Sciences (Suède), Rapporteur
- Mme Coralie DANCHIN-BURGE, Chef de Projet, PhD, Institut de l'Élevage (France), Rapporteur
- M. Tom LEWIS, Généticien des populations, PhD, The Kennel Club (UK), Examinateur
- M. Erling STRANDBERG, Professeur, PhD, Swedish University of Agricultural Sciences (Suède), Co-directeur de thèse
- M. Grégoire LEROY, Maître de conférences, PhD, AgroParisTech (France), Co-encadrant de thèse
- M. Etienne VERRIER, Professeur, PhD, AgroParisTech (France), Directeur de thèse

### Nom de l'Unité d'accueil France

UFR Génétique, Élevage et Reproduction,  
AgroParisTech,  
Paris,  
France

### Nom de l'Unité d'accueil Etranger

Department of Animal Breeding and Genetics,  
Swedish University of Agricultural Sciences,  
Uppsala,  
Sweden



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Shizhi Wang

*Institut Agronomique, Vétérinaire et Forestier de France  
AgroParisTech  
UMR Génétique, Élevage et Reproduction  
Paris, France*

*Institut National de la Recherche Agronomique  
Département de Génétique Animale  
UMR Génétique Animale et Biologie Intégrative  
Jouy-en-Josas, France*

*Swedish University of Agricultural Sciences  
Faculty of Veterinary Medicine and Animal Sciences  
Department of Animal Breeding and Genetics  
Uppsala, Sweden*

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# International breeding programs to improve health in pedigree dogs

## Abstract

Implementation of breeding programs in order to reduce incidence of inherited disorders and their impact on welfare should be a priority for dog breeders and breeding organizations. In that respect, exchange of breeding animals between countries constitutes a critical point to be taken into account. The purpose of this thesis was to investigate management strategies to improve breed health in an international context, concerning both genetic evaluation and management of genetic variability. A survey, which was completely filled in by 15 national kennel clubs (KCs), demonstrated shared concerns among KCs about health in pedigree dogs and a shared intent of improving breeding and health status, especially among European national KCs. In addition, with data provided by the French, Swedish and British kennel clubs, including pedigree databases and phenotypic records of hip dysplasia (HD), the feasibility of joint evaluations across countries and the efficiency of international breeding programs were investigated. The benefits of exchanging breeding animals across countries were clearly shown in terms of improved genetic variability and increased genetic progress, especially for breeds in countries with small populations. Further, the efficiency of breeding programs including importation of breeding males concerning genetic improvement of complex traits and inbreeding management was tested by simulation. We concluded that international breeding programs are useful and alternative options to improving canine genetic health and their benefits will be amplified with an expected increase in exchange of breeding animals in the future. Importing male dogs could lead to higher genetic progress, however, it is necessary to have a high genetic correlation between countries and high accuracy of estimated breeding values of imported dogs.

*Keywords:* Canine, inherited disorders, hip dysplasia, survey, genetic variability, genetic evaluation, stochastic simulation, breeding program

*Author's address:* Shizhi Wang, SLU, Department of Animal Breeding and Genetics, P.O. Box 7023, 750 07 Uppsala, Sweden

# Internationella avelsprogram för att förbättra hundars hälsa

## Abstract

Att införa avelsprogram som syftar till att minska förekomsten av sjukdomar med genetisk bakgrund är ett sätt att förbättra hundars välfärd. Detta bör därför vara högprioriterat för såväl uppfödare som avelsorganisationer, t ex nationella kennelklubbar. När man utformar avelsprogram är det också viktigt att man tar hänsyn till det utbyte av avelsdjur som sker över landsgränser. Syftet med denna avhandling var att undersöka olika strategier för att förbättra hundars hälsa i ett internationellt sammanhang, med avseende på såväl avelsvärdering som genetisk variation. En enkät, som besvarats av 15 nationella kennelklubbar, visade en stark gemensam oro över hundars hälsa, men också ett starkt gemensamt intresse av att förbättra avelsarbetet för hundars hälsa, särskilt bland europeiska kennelklubbar. Med hjälp av härstamningsinformation och uppgifter om höftledsdysplasi (HD) från röntgenresultat, från Frankrike, Storbritannien och Sverige, undersöktes förutsättningarna för att genomföra en gemensam avelsvärdering av HD över landsgränser. Fördelarna med utbyte av avelsdjur mellan länder visade sig i form av ökad genetisk variation och högre genetiskt framsteg, särskilt i länder med små populationer. Dessutom användes en simulering för att studera effektiviteten för olika avelsprogram, inklusive import av hanhundar, vad gäller genetiskt framsteg i en komplex egenskap (t ex HD) och inavelsutveckling. En slutsats är att internationella avelsprogram kan vara användbara alternativ för att förbättra hundars hälsa och att fördelarna kommer att öka med ett förväntat ökat utbyte av avelsdjur i framtiden. Att importera hanhundar kan leda till högre genetisk framstegstakt men det är nödvändigt med en hög genetisk korrelation mellan länderna och en hög säkerhet för de importerade hundarnas avelsvärden.

Nyckelord: hund, genetiska sjukdomar, höftledsdysplasi, enkätstudie, genetisk variation, avelsvärdering, stokastisk simulering, avelsprogram

Författarens adress: Shizhi Wang, SLU, Institutionen för husdjursgenetik,

P.O. Box 7023, 750 07 Uppsala, Sweden

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## List of publications

This thesis is based on the work contained in the following papers, referred to by Roman numerals in the text:

- I Wang, S.\*, Laloë, D., Missant, F., Malm, S., Lewis, T., Strandberg, E., Brenda, B., Leroy, G. (2018). Breeding policies and management of pedigree dogs in 15 national kennel clubs. *The Veterinary Journal*, 234, pp.130-135.
- II Wang, S.\*, Leroy, G., Malm, S., Lewis, T., Strandberg, E. and Fikse, W.F., (2017). Merging pedigree databases to describe and compare mating practices and gene flow between pedigree dogs in France, Sweden and the UK. *Journal of Animal Breeding and Genetics*, 134(2), pp.152-161.
- III Wang, S.\*, Leroy, G., Malm, S., Lewis, T., Viklund, Å., Strandberg, E. and Fikse, W.F., (2017). Genetic correlations of hip dysplasia scores for Golden retrievers and Labrador retrievers in France, Sweden and the UK. *The Veterinary Journal*, 226, pp.51-56.
- IV Wang, S.\*, Strandberg, E., Viklund, Å., Windig, J. J., Malm, S., Lewis, T., Laloë, D., Leroy, G. Simulation on genetic improvement of canine hip dysplasia through sire selection across countries. (manuscript)

Papers I-III are reproduced with the permission of the publishers.

\* Corresponding author.



## Abbreviations

<i>BLUP</i>	Best Linear Unbiased Prediction
<i>BMA</i>	Bullmastiff
<i>BMD</i>	Bernese mountain dog
<i>BVA/KC</i>	British Veterinary Association/The Kennel club
<i>EBV</i>	Estimated breeding value
<i>ESE</i>	English setter
<i>FCI</i>	Fédération Cynologique Internationale
<i>GDR</i>	Golden retriever
<i>HD</i>	Hip dysplasia
<i>KCs</i>	National kennel clubs
<i>LBR</i>	Labrador retriever
<i>OFA</i>	Orthopaedic Foundation for Animals
<i>OMIA</i>	Online Mendelian Inheritance in Animals



# 1 Introduction

## 1.1 Dog breeding

The dog is believed to be the first domesticated species (Vilà et al. 1997). Although the exact time of domestication is still in controversy, most estimates are between 15,000 years to 35,000 years ago (Perri et al. 2016). Initially selected for a wide diversity of uses, including hunting, guarding, or shepherding, around 350 dog breeds are currently recognised by the Fédération Cynologique Internationale (FCI) and mostly used for the companionship they provide to humans.

Decision of dog breeding is mostly in the hands of individual breeders, who have diverse selection objectives, considering either specific morphologies, size, colours or behaviour. The effects of this variety have accumulated over time and contribute to that dogs today vary widely in many traits. In a survey of French dog breeders (Leroy et al., 2007), it has been shown that the main breeding goal relates to morphology in relation to breed standard, followed by behaviour; with selection for hunting skills also being prominent in pointing dogs and scent hounds. At the same time as breeding goals differ, breeding practices, such as mating between close relatives or use of artificial insemination, may also differ among breeders. Furthermore, some breeders produce litters regularly, whereas others may have only one or a few litters.

In modern society, dog breeders and owners are generally organized in associations (e.g., breed clubs) and regulated by national kennel clubs (KCs). Those national KCs play a very important role in regulating and managing dog breeding and they are generally in charge of the maintenance of breed standards, the rules behind the organization of dog shows and working trials, and the recording of genealogical information for pedigree dogs. Breed clubs maintain

breed standards and are members of or collaborate with KCs to tailor the breeding for their breed within countries.

Although the structure of breeding systems is vague among the main stakeholders (herein breeders, owners and KCs), the direction of breeding can still be adjusted by communication and cooperation between breeders, owners, breed clubs and KCs. The exact governance of dog breeding, as well as the compliance of breeders and owners to national rules and strategies may differ largely across countries (O'Neil et al. 2017). For instance, depending on country, there can be one or several clubs in charge of a given breed. It should also be underlined that in Nordic countries, there has been a culture of compliance to strong regulation in place, whereas in southern Europe, such regulatory approach could drive breeders away from their respective KCs.

Dog breeders are directly influenced by national KCs and breed clubs in their countries, while dog breeding is also influenced by international regulations (Council of Europe, 1987) and organizations (FCI, 2010). In particular, FCI is a federation of KCs from 94 countries, created in 1911 to promote cynology across the world. FCI has more than 2 million individual members in participating countries and over 2.2 million puppies are registered each year by national KCs within the FCI. FCI focuses on the rules and regulations that are relevant to breeding and genetic health of dogs, the recognition of breeds and doping rules. Recently, adopting strategies to enhance canine genetic health and activities to counteract exaggerated anatomical features have been highlighted in FCI actions (Hedhammar et al. 2011).

## 1.2 Inherited disorders in pedigree dogs

Owing to the affectional bond between dogs and humans, as well as an increasing public concern toward animal welfare, especially in Europe, dog health has become a major concern for breeders, owners, as well as the general public in many countries (APGAW, 2009). The broadcast of the documentary 'Pedigree Dogs Exposed' by BBC in 2008, exposing health and welfare issues facing pedigree dogs in the United Kingdom, has been emblematic of this concern. Given their role in the management of dog breeders, national KCs are often considered as carrying the major, if not only, responsibility for the situation.

Until early 2018, the Online Mendelian Inheritance in Animals (OMIA) reported 307 Mendelian disorders/traits in dog<sup>1</sup>. These disorders have variable prevalence across breeds, affect various functions and organs (cardio-vascular, immune, musculoskeletal, nervous-sensory, respiratory...), and have impact on welfare from anecdotal to incapacitating or even lethal (Collins et al. 2010). They have also multiple forms of inheritance, from simple single gene inheritance to more complex ones, the inheritance mode being not always known.

Two main mechanisms are considered to be responsible for the spread of inherited disorders within dog breeds. Initially, recessive alleles related to inherited disorders had already been accumulated during the creation of dog breeds or during historical genetic bottleneck events due to breeding in a small and closed population (Leroy, 2011). Particularly, breeding practice such as mating between close relatives and using popular sires were commonly used in dog breeding, which tend to increase the frequency of a disorder by chance. In addition, intensive selection on exaggerated morphological features (conformation) is considered another major reason for the increase of inherited disorders in recent decades (Rooney and Sargan, 2009). In two studies on the same group of UK dog breeds (Asher et al. 2009, Summers et al. 2010), inherited disorders in dogs were divided into 312 non-conformation linked disorders and 84 directly or indirectly related to conformation.

Prevention of single-gene disorders can be managed, once the mutation is identified, by genetic testing before reproduction. Genetic test services are commercially and widely available, e.g., Animal Genetics Laboratory of Swedish University of Agricultural Sciences in Sweden. However, increased prevalence of complex diseases and disorders (determined by multiple genes in combination with environmental influences) is more difficult to manage. In many countries, reducing the prevalence of inherited disorders was performed by forbidding dogs with severe status to reproduce, e.g., in Sweden dogs having D or E grades of hip dysplasia were not allowed to reproduce and dogs with C grade were only allowed to mate with dogs having A or B grades.

Hip dysplasia (HD) has been viewed as the most common disease in many medium and large size breeds (Wilson et al. 2010). Orthopaedic Foundation for Animals (OFA) reported in 2016 that this disorder was affecting around 183 breeds, with prevalence ranging from 0 to 71.8%<sup>2</sup>. The term hip dysplasia means

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<sup>1</sup> <http://omia.org/home/>

<sup>2</sup> [http://www.ofa.org/stats\\_hip.html](http://www.ofa.org/stats_hip.html)



abnormal development of the hip joint and its development is characterised by a loose coxofemoral articulation (Brass, 1989), which leads to several clinical symptoms including gait abnormalities, difficulties in rising, walking and running, and lameness (Fry and Clark, 1992). Radiographic screening is widely used for evaluation of hip status and three major grading systems are currently in place: the FCI, the OFA, and the BVA/KC (British Veterinary Association/The Kennel Club). For instance, FCI has a five-level grading system in which A and B are normal, C is mild, D is moderate and E is severe HD. The percentage of dogs that are scored for HD vary largely according to breed and country. However, the efficiency of phenotypic selection is weak, owing to the categorical nature of affected/unaffected status of those inherited disorders, especially if the unaffected group is relatively large (Malm et al. 2008). BLUP selection is considered as the most efficient method to improve a complex trait (Wilson et al. 2011) but until now, only a limited number of countries, like Sweden and UK, have implemented genetic evaluation for some of their breeds.

### 1.3 International exchanges and collaboration

In recent years, increasing exchanges of breeding animals and semen between countries have been observed in dogs (Hedhammar et al. 2011), especially within EU. This could be important for breed and health management for several reasons. Those exchanges may indeed enlarge the pool of breeding animals, and therefore reduce inbreeding rate, which is of particular interest for breeds in countries with small and closed populations. However, it is not easy to assess the genetic quality of an imported animal, and, as different national populations of the same breed can have different prevalence of a disease, exchange of breeding animals can be either beneficial or detrimental, depending on how those exchanges are made. Also, there might be missing pedigree or health information, or incomparable evaluation results (e.g., different scales for HD) and if the imported animals are widely used, becoming thus 'popular sires', it makes the breeding management of pedigree dogs more difficult than ever before.

Therefore, operational tools (e.g., international pedigree databases, genetic evaluation routines) are needed to assist international breeding management and implement international breeding programs. Furthermore, the breeding context and breeding rules differ across countries, which will make the international breeding work become more complex, and not only a matter of technical issues.

Kennel Clubs from France, Sweden and UK have been among the first countries to consider potential international collaboration on breeding and health programmes. All three are among the founding members of the International Partnership for Dogs (IPFD), an international organization whose mission is to facilitate collaboration and sharing of resources to enhance the health, well-being and welfare of dogs worldwide. These three national KCs are among the most influential national KCs worldwide. The British Kennel Club (officially The Kennel Club), although not a member of the FCI, is the oldest recognized kennel club in the world (founded in 1873). It registers around 250,000 dogs per year. The French Kennel club (officially Société Centrale Canine) was founded in 1881. It is one of the founding members of the FCI, and registers more than 230,000 dogs per year. Also a member of the FCI and founded in 1889, the Swedish Kennel Club (officially Svenska Kennelklubben) registers about 50,000 dogs per year. It is one of the most advanced kennel clubs in terms of breeding and health strategies. Both British Kennel Club and Swedish Kennel Club have implemented a genetic evaluation of HD for some of their breeds a few years ago.

International genetic evaluation programs for dairy cattle and beef cattle were started in 1980 and 2007 based on the platform of international bull evaluation service (Interbull). Until 2018 Interbull has provided international genetic evaluation service on dairy and beef cattle to 35 countries, including two from Asia, one from Africa, three from America, and two from Oceania<sup>3</sup>. Meanwhile, the feasibilities of international genetic evaluations were also studied in warmblood sports horse in Nordic countries (Viklund et al. 2015). In dog breeding, the British and Swedish Kennel Clubs have been the first couple of national KCs starting to explore the feasibility and efficiency of joint genetic evaluation of HD, which was shown by the study of Fikse et al. (2013). By learning from the experiences of the British and Swedish KCs, the French Kennel Club is also working on the setting up national genetic evaluation routines for HD. Considering that the three countries already have a long history of HD screening and recording, it could be meaningful to study joint genetic evaluation and selection program on HD, as an example of international collaboration.

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<sup>3</sup> <http://www.interbull.org/ib/itbcreports>



## 2 Aims of the thesis

The overall aim of this project was to investigate management strategies to improve breed health in an international context, concerning both genetic evaluation and management of genetic variability. These tools are required before actually starting international breeding programs. The specific aims were to:

- Improve understanding of current concerns, strategies and tools being used by kennel clubs internationally as well as the needs and future plans for dog health and welfare (Paper I);
- Investigate evolution of inbreeding, breeding practices and gene flow over time by merging pedigree information from three countries for four breeds (Paper II);
- Estimate genetic parameters for a health trait, hip dysplasia, in three countries using a joint across-country genetic evaluation (Paper III);
- Evaluate efficiency of implementation of genetic evaluation and various strategies for importing sires with high genetic merit for hip dysplasia, by use of stochastic simulation (Paper IV).



## 3 Summary of studies

This thesis is comprised of four papers in which an online survey, statistical analysis of nationally collected phenotypes and pedigree, and a simulation study were employed to answer several technical issues needed to be finalized, before truly starting international programs to improve genetic health of pedigree dogs. In paper I, using a survey, breeding objectives were elucidated from the shared concerns of Kennel Clubs in 15 countries regarding inherited disorders in pedigree dogs. In paper II, pedigree databases of France, Sweden and the UK for four breeds (Bullmastiff (BMA), Bernese mountain dog (BMD), English setter (ESE) and Labrador retriever (LBR)) were merged. This was done both to be able to study the evolution of inbreeding, breeding practices and gene flow over time, but also as a necessary step to carry out international genetic evaluations. In paper III, for two breeds (Golden retriever (GDR) and LBR), heritabilities for and genetic correlations between HD scores across three countries (France, Sweden and the UK) and two types of HD scores (FCI and BVA/KC scales) were estimated. In paper IV, international breeding strategies were explored and possible genetic progress was predicted by computer simulation.

### 3.1 Materials and methods

Initially, BMA, BMD, ESE and LBR were used in studies of both paper I and paper II. But the trivariate analysis of HD scores in France, Sweden and the UK did not converge for BMA, BMD and ESE, so GDR was added to the study on joint genetic evaluations. A summary of materials and methods are listed in Table 1.

Table 1. *Summary of materials and methods used in papers I-IV*

Study	Data	Breeds <sup>1</sup>	Countries	Methods
Paper I	Survey answers	All breeds	15 countries <sup>2</sup>	General statistical analysis
Paper II	Pedigree databases	BMA, BMD, ESE, LBR	France, Sweden and the UK	Genealogical analysis
Paper III	Merged pedigree databases, phenotypic records of HD	GDR, LBR	France, Sweden and the UK	Genetic evaluation
Paper IV	Parameters from papers II-III	Non-specific	Non-specific	Stochastic simulation

<sup>1</sup> BMA=Bullmastiff; BMD = Bernese Mountain Dog; ESE = English Setter; Labrador retriever; GDR = Golden retriever.

<sup>2</sup> 15 countries: Denmark, Austria, Latvia, France, Sweden, UK, USA, Australia, Norway, Netherlands, Uruguay, Ireland, Mexico and Germany

### 3.1.1 Kennel club survey (Paper I)

A survey on breeding and health in pedigree dogs was designed and distributed in April 2017 by email to national KCs of 37 FCI countries and three non-FCI countries. These 40 countries were all with more than 2,000 puppies registered by KCs in 2015. Questions comprised eight subjects: 1) importance of issues related to dog breeding and health for the kennel club, 2) existence of government regulations, 3) management of data, 4) information recorded, 5) information provided to breeders and owners, 6) breeding strategies implemented, 7) breeding recommendations, requirements and restrictions, and 8) implementation of specific breeding tools. The survey was completely filled in by 11 European KCs and 4 non-European KCs. Statistical analysis was performed using R software (R Core Team, 2017) including: likert score analysis and heat map analysis.

### 3.1.2 Merging pedigree databases (Paper II)

Pedigree databases of four breeds (BMA, BMD, ESE and LBR) were provided by French, Swedish and British KCs and were merged across countries through detecting and removing duplicate dog IDs. Afterwards, using a FORTRAN package PEDIG (Boichard 2002), we calculated genealogical parameters (e.g., equivalent complete generations, inbreeding and coancestry coefficients, effective population sizes) and founder contributions according to the birth

period, breed and registration country of dogs, to study underlying breeding practices and already existing gene flow between countries by breeds.

### 3.1.3 Estimation of genetic correlations (Paper III)

Pedigrees databases of GDR and LBR between France, Sweden and the UK were merged using the method of paper II. For French HD scores, the levels of HD (A, B, C, D, and E) were replaced with 1, 2, 3, 4, and 5, respectively. Data transformation of phenotypic records for Swedish and British HD scores were as in Malm et al. (2008) and Lewis et al. (2010), respectively. A trivariate analysis of HD records from the three countries was performed for each breed with mixed linear animal model using DMU software (Madsen and Jensen, 2013) and genetic parameters (e.g., heritability, genetic correlation, selection differential, accuracy of selection) were calculated. The fixed effects in the model differed somewhat across countries, but the random effects of animal (additive genetic effect) and litter were included for all countries. For Sweden, a random clinic-year effect was included as well.

### 3.1.4 Simulation of breeding strategies (Paper IV)

Specific functions needed in our study were added to the original simulation workflow of the FORTRAN program GenManSim (Windig and Oldenbroek, 2015), including generating breeding values and phenotypes for individual animals and selection on breeding values or phenotypes of HD. Eventually, we conducted a simulation study of national and international breeding programs to describe the potential changes in genetic progress in an example trait, HD, when moving from a national breeding program to an international one.

## 3.2 Main findings

### 3.2.1 Increasing concerns of stakeholders toward dog health and welfare (Paper I and II)

Although there were large differences between KCs on how they regarded breeding policies and management, the awareness to improve breeding and health for pedigree dogs was strong among the surveyed countries. Along with having different views on important issues and facing different challenges, KCs



are currently making great efforts to collect and provide information related to breeding and health, as well as providing breeding strategies and guidance in their countries. This issue is even more complex owing to the wide diversity of traits potentially of interest for breeding, which differ according to breeds and national populations, as well as the growing number of genetic variants identified and commercialized gene tests, making it difficult to identify and prioritize breeding goals. Getting a consensus, in terms of constraints and priorities for breeding, is therefore probably one of the most challenging issues for KCs on the road towards implementing effective strategies for health and welfare that would be endorsed by clubs and breeders.

In addition to ‘inherited disorders’, national KCs also ranked ‘exaggerated morphological features’ and ‘inbreeding and genetic variability’ as issues of highest priority. These concerns seem to be in line with recent evolutions of mating practices by dog breeders from France, Sweden and UK, as the results from genealogical analysis in paper II showed a decrease of the proportion of matings between close relatives over the last years in most of the national breed populations studied.

### 3.2.2. Merging pedigree databases can increase pedigree knowledge and reduce inbreeding in dogs (Paper II)

Merging pedigree databases across countries and quantifying breeding practices and gene flow for pedigree dog breeds is possible and pedigree knowledge was improved after merging pedigrees. The breeding practice of matings between close relatives varied between France, Sweden and the UK. Moreover, a clear tendency of increased gene flow between countries over time was shown for all the breeds and countries in the study. More importantly, the potential to improve genetic variability within pedigree dogs through exchanging breeding animals across countries was confirmed by an increased effective population size when merging the populations of different countries, especially for small-sized populations.

### 3.2.3. International evaluation across countries and HD measurement scales is possible (Paper III)

The possibility of performing genetic evaluations of HD across countries was confirmed by the favorable genetic correlation estimated in our study between

different measurement scales of HD in France, Sweden and the UK. The existence of connections between populations, also an important prerequisite for international evaluations, was illustrated by the number of common sires shared between countries. Enlarging the population size of selection candidates through combining data from different countries can increase the genetic progress of HD, particularly for small populations. The accuracy of selection for the most recent birth-year cohorts of male dogs was, however, only marginally improved by international evaluation compared to national evaluation.

#### 3.2.4. Importing sires with high genetic quality is beneficial to improve HD status (Paper IV)

Our simulation study demonstrated that importing sires with high genetic merit can be an efficient breeding strategy to improve the status of HD in pedigree dogs, although the outcome depends on the accuracies, genetic correlations of HD across countries, selection intensities and use of imported dogs. When considering using of foreign sires with EBV rankings among Top 50%, which is suggested by British kennel club in practice, very strong genetic correlations ( $> 0.85$ ) are necessary to guarantee the efficiency of importing sires based EBVs. While considering using sires with very high EBV rankings e.g., among Top 10%, moderate accuracies of EBVs ( $> 0.40$ ) and high level of genetic correlations ( $> 0.70$ ) are needed.



## 4 General discussion

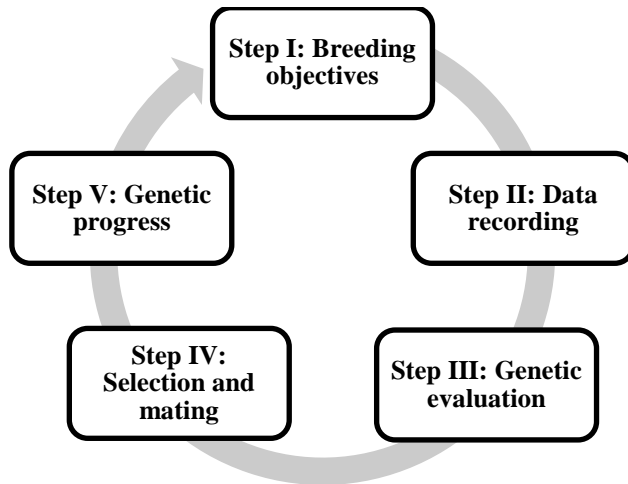
According to statistics of OMIA in 2018<sup>4</sup>, there are more than 307 disorders or disease traits reported in dogs, with various prevalence and consequences for canine health. Implementation of breeding programs in order to reduce incidence of inherited disorders and their impact on welfare should be a priority for dog breeders and breeding organizations. Efficiency of strategies in breeding programs is, however, highly dependent on several factors such as inheritance pattern, availability of efficient clinical/genetic tests and specific context conditions (e.g., prevalence, demography, existence of other disorders, and cooperation between KCs and breeders). But when settling on a breeding strategy, the fact that for many breeds the exchange of breeding animals between countries is increasing constitutes a critical point to be taken into account. Therefore, international cooperation was called for to improve genetic health in pedigree dogs (Hedhammar et al. 2011). Moreover, it has been shown that efficiency of genetic evaluation for a complex trait, such as HD, could be improved by joint evaluation across different countries (Fikse et al. 2013). However, the technical routine to combine pedigrees and health data and further to do joint evaluation under international collaboration is still unformed in dogs.

Therefore, the aim of this thesis was to investigate management strategies to improve breed health in an international context, concerning both genetic evaluation and implementation of breeding strategies. For this purpose, data were provided by the French, Swedish and British kennel clubs (KCs), including pedigree and phenotypic records of HD, to perform studies on the feasibility of international genetic evaluations and explore on the efficiency of international breeding programs. In addition, a survey was answered by 15 national KCs, which demonstrated shared concerns among KCs for health in pedigree dogs.

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<sup>4</sup> <http://www.omia.org/home/>

Combing the main findings from this study, discussion herein will mainly focus on the possibility of implementing breeding programs across countries and the involvement of national KCs in this endeavor. The content of this discussion part will follow the five-step workflow of setting up breeding programs (Figure 1) and existing and/or potential issues embraced in each step related to the results of the studies included in the thesis will be discussed.



*Figure 1.* A five-step workflow circle of breeding programs.

## 4.1 Breeding objectives

Six important issues were proposed for the future work for the improvement of dog health in the 3<sup>rd</sup> International Dog Health Workshop in 2017 (O'Neil et al. 2017), including individualized breed-specific strategies for health and breeding, extreme conformations, education and communication in relation to antimicrobial resistance, behavior and welfare, genetic testing and population-based evidence. Especially, the prevalence of inherited disorders differed between breeds and, so some KCs guided and/or helped breed clubs to make breed-specific strategies, e.g., the British KC has 'Assured Breeders Scheme' and is developing 'Breed Health & Conservation Plans' to implement breeding strategies for all breeds; the Swedish KC has 'Breed-Specific Breeding Plans' tailor-made to the conditions of the individual breeds and considering all aspects

relevant in the breeding goals. Beyond the domestic effort made by national KCs, international collaboration of breeding was called for to improve genetic health in pedigree dogs (Hedhammar et al. 2011). However, the possibilities and ambitions among the organizations responsible may differ between countries, which increase difficulty of prioritizing global breeding goals in dog world.

In paper I, we conducted an online survey to elucidate similarities and differences in breeding policies and management of pedigree dogs among national KCs and inform the development of international collaborations. It was found that most KCs consider that ‘exaggerated morphological features’, ‘inherited disorders’ and ‘inbreeding and genetic variability’ are the breeding issues with highest priority. The same concern for important breeding issues can be viewed as a ‘universal value’ among KCs to start international collaboration. Several countries emphasized that a major challenge relative to the adoption of breeding objectives and strategies lies with the difficulty to achieve consensus and compliance from breeders and clubs, underlining the need to better communicate about health issues and potential solutions.

Among the 15 countries answering the survey, ten countries indicated they have genetic evaluations of HD in place for some breeds or were planning to do so, which provides the possibilities to start joint genetic evaluations across countries. Further, the survey showed that health information of pedigree dogs is widely collected in Europe and this information is possibly available through pedigree documents or website, which is also a good foundation to expand breeding programs involving more genetic disorders.

## 4.2 Data recording

Before carrying out a genetic evaluation across countries, it is necessary to combine the data from all countries participating, and this is especially challenging for pedigree information, mainly because the same dog can appear under several aliases. Duplicate records of the same individuals are usually resulted from missing information, typographical errors or inconsistent format during pedigree registration. Therefore, we used three example countries, France, UK and Sweden, to elucidate the problems associated with merging databases in paper II, but also to use the information to study the already existing gene flow between countries for some breeds.

We detected a large number of duplicate IDs within and across countries during the procedure of merging pedigree databases by matching the four attributes of individual records: dam ID of individual, sire ID of individual, name of individual and birthdate of individual. Besides, Levenshtein distances (Levenshtein 1966) were calculated to take potential deletions, insertions and reversals of characters into account when comparing attributes. To avoid intensive workload of detecting duplicates, it is highly recommended to have a standard format of international IDs for the registration of pedigree dogs in an international context, for instance, combining a birth country code, a specific breed code/number and a unique domestic individual number together. This approach is similar to the Universal Equine Life Number (UELN) system that was proposed and used in international horse breeding (European Union, 2008).

More efforts are required (e.g., financial source; political work) beyond the technical work to fully support a foundation of international databases. Agreement of sharing data (e.g., health status of certain disorders, genetic test results) and pedigree is a prerequisite for starting genetic evaluations across countries, which is suitable for bilateral collaboration for countries already having built databases. For multilateral collaboration, perhaps an international database holding information for genetic evaluation and inbreeding management is needed. Particularly for HD, three grading systems are widely used through the world (FCI, OFA and BVA/KC modes), which might require to have a data standard like the international organization ICAR (International Committee for Animal Recording ) have developed in milk recording.

### 4.3 Genetic evaluation

HD was the example of a complex trait in the thesis, because it is one of the most common skeletal diseases seen in pedigree dogs and has a long history of screening and data recording in many countries. For a number of breeds, selection of breeding dogs by estimated breeding values (EBVs) for hip dysplasia is implemented in several countries (Denmark, Finland, Germany, Norway, Sweden and the UK). France is preparing to introduce genetic evaluation of HD and a suitable genetic model was studied for Golden retriever and Labrador retriever in paper III. However, low proportions of D and E scores for both breeds in France may have been the reason for lower heritabilities (0.15-0.28) than those estimated for the same two breeds in Sweden and the UK (0.28-0.41). This may partly be because dogs with bad hip status are not screened or that the results are not reported. Thus, in relation to the communication challenge

underlined above, we highly suggest the French kennel club to encourage breeders and owners to screen their dogs and report scores to obtain better and more unbiased estimation.

In paper III, the feasibility of genetic evaluation was confirmed both across countries (France, Sweden and the UK) and across HD scales (FCI scores and BVA/KC scores). Meanwhile, several benefits of performing international evaluation have been confirmed or can be expected: genetic progress can be increased especially for small populations; inbreeding rate can be reduced by enlarging the pool of potential breeding animals; foreign dogs with bad genetic quality can be avoided before mating or importing by referring to EBVs.

Moreover, the genetic links, or genetic connectedness between countries, will also affect the accuracy with which a genetic evaluation can be done across countries. In paper III, we observed an inverse relation between genetic connectedness between populations and standard error of estimated genetic correlations, which means strong genetic connectedness contributes to reliable estimation of genetic correlations. With the increase of exchange of breeding animals between countries, especially in Europe, we are optimistic to have better results of international evaluation in a near future.

#### 4.4 Selection

For pedigree dog breeding, selection is decided by individual breeders and owners. Meanwhile, the ‘power’ of KCs is limited in selection and mainly concentrated on setting regulations, e.g., dog carrying one recessive allele is not allowed to mate with another dog also carrying the same recessive allele; dogs with severe HD scores are not allowed to reproduce. In other words, KCs (and breed clubs) are the organizers and promoters of breeding strategies, while individual breeders and owners are the decision makers in the dog breeding system.

Swedish and British KCs have developed online advisory mating tools allowing the computation of inbreeding coefficients for the offspring of a potential mating pair, and browsing for specific health results, respectively. Those publicly available online tools can make it convenient for breeders and owners to be informed about inbreeding coefficients and EBVs. Particularly, the online advisory tools from Swedish and British KCs already provide EBV information on HD.



It is worth noticing that too ambitious mating restrictions may risk driving breeders away from their KCs (O'Neill et al., 2017) and countries like Denmark and Belgium have experienced subsequent reductions in dog registrations following implementation of new regulations. For instance after DNA identification was made compulsory, there was a 34% reduction in the number of registrations in Belgium between 2008 and 2013. Hence the Swedish and British KCs do not require but rather recommend breeders to choose dogs with EBV above the average for breeding.

## 4.5 Genetic progress

Finally, we used a stochastic simulation study to describe the potential changes in genetic progress in HD, when moving from a national breeding program to an international one. In paper IV, importing sires with high genetic merits was shown to have the potential to be an efficient breeding strategy to improve the status of HD in pedigree dogs, particularly with more and more exchange of breeding animals in the future. Simulation studies in recent years have confirmed that breeding management (e.g., avoiding mating close relatives, equal use of sires, and limiting litter numbers) can reduce the increase in inbreeding in dog populations and decrease the expression of inherited recessive disorders (Leroy and Baumung, 2011; Windig and Oldenbroek 2015). In agreement with these studies, the simulation in paper IV suggests that KCs have further opportunities to promote health and welfare through breeding management.

Several factors were found in paper IV to affect genetic progress. Importing sires with very high EBV rankings (e.g., among Top 10% in the exporting population) is preferred to increase genetic improvement. But accuracy of selection should be at least at a moderate level, because when the precision of EBVs decreased, high EBV sires are difficult to distinguish. The same situation occurs when the genetic correlation was weak; the total genetic progress that can be achieved by importing foreign sires will get a large 'discount' by poor estimation from joint evaluations.

However, as a drawback of higher genetic progress made by EBV selection, inbreeding will increase faster than with phenotypic selection (e.g., when dogs with severe HD is not allowed to reproduce), especially in a country with a small population. From the simulation work in paper IV, when relatedness between parents is limited to less than 0.125, there was no substantial increase of

inbreeding for phenotypic selection and EBV selection during the 10 years studied. However, this might have been due to the short time period studied. Nevertheless, no matter what kind of traits and breeding strategies are eventually adopted in international breeding program, inbreeding management of imported dogs is highly recommended once the pedigree of individual dogs is available.



## 5 Conclusion and perspectives

This project studies the feasibility of initializing international breeding programs for canine inherited disorders. A shared sense of improving breeding and health status in pedigree dogs had been built among European national KCs, which is the ‘milestone’ to start international collaboration. Our results underline the need to raise awareness and communicate among the different stakeholders (breeders, breed clubs, but also show judges and veterinarians) to reach consensus on breeding objectives and strategies, as well as improving the quality and quantity of data required to achieve those objectives.

The benefits of exchanging breeding animals across countries are clearly shown from the studies, these exchanges allowing an increase in genetic variability and the rate of genetic progress, especially for small national breed populations. When considering existing systems considering international genetic evaluation in other species, implementation in dogs may be expected to be an intensive and long term task. In cattle, the formation of Interbull international evaluation service took more than ten years from initiation to practical implementation (Philipsson 2011). Financial incentives, as well as exchanges of semen (Leroy et al., 2007), are on a much lower level in dog compared to cattle which may lead to an even longer implementation period.

We concluded that although consensus among stakeholders (herein dog breeders, owners and KCs) on the strategy to reduce inherited disorders is always needed in dog breeding, international breeding programs are useful and alternative options to improve canine genetic health, their benefits being amplified with increased exchanges of breeding animals. Importing male dogs could lead to higher genetic progress, however, it is necessary to have a high

genetic correlation between countries and high accuracy of estimated breeding values of imported dogs.

Simulation work in this thesis focused on a situation with one breeding trait, while in practice, real breeding programs in most breeds often have several traits related to health or other breeding goals. O'Neil et al. (2017) underlined the need to develop holistic methods to prioritize and combine different breeding goals in one breeding strategy. For instance, approaches could be proposed to combine a diversity of morphological, health or even behavior traits with different evaluation (phenotypic assessment, genetic test, quantitative genetic or genomic evaluation) and different priorities into synthetic index, based on experience from other species. Further simulation development could help to assess the efficiency of these different breeding strategies in terms of genetic progress and impact on genetic variability.

In that respect, the recent development of genomic tools offers opportunities to the improvement of canine genetic health. In particular there has been an increasing number of single-gene disorders with corresponding genetic tests developed, which can be useful for dog breeding (Donner et al. 2018). In parallel, variants related to risk of expressing more complex deleterious phenotype have been also identified with increasing concern on the adequate interpretation and use of corresponding test for dog breeding (Moses et al. 2018), underlining urgent needs in standardization and regulation in this area. When considering complex traits such as hip dysplasia, genomic information offers the possibility of developing accurate prediction of genetic merit both between and within full-sib families before selection decisions for breeding need to be made (Sánchez-Molano et al. 2015). Genomic prediction of HD-related traits was performed in the UK Labrador retriever (Sánchez-Molano et al. 2015) and joint genomic evaluation of HD between UK and US Labrador retriever was also studied (Edward et al. 2018), which could be the basis for future improvement of HD with faster genetic progress. In a perspective of international genetic selection, dogs without pedigree records can be included into a relationship matrix. Compared to the amount of production animals that can be genotyped by livestock breeding companies, purchase of genotyping service by individual dog breeders and owners could accumulate a larger genomic dataset on a world-wide scale, which means the accuracy of genomic selection can be firmly guaranteed if joint genomic evaluation can be performed. It is expected that here also, further standardization work, in terms of choice of methodologies, marker set, reference population definition and protocol for data exchange will be required.

Our work has identified national KCs as major decision makers in the dog breeding process. In the future, it is worth asking, to what extent the general governance of dog world will be affected by a growing importance of genomic tools, with laboratories becoming important stakeholders in the breeding decision process.

Future research could focus more on systematic designing of breeding programs, which could be studied by simulation software such as GenManSim, e.g., to simulate genetic progress considering the removal of recessive alleles and selection of complex traits at the same time as well as considering the willingness of breeders to follow breeding guidance and restrictions. In summary, with the increasing public concern for canine health and welfare, it is time for involved stakeholders (e.g., breeders, clubs, veterinarians) to work together to promote the genetic health of pedigree dogs using new advanced cutting-edge technologies.



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## Popular science summary

Pedigree dogs' health and inherited disorders are a growing concern for dog breeders, owners, as well as the general public. In 2018, more than 300 Mendelian disorders or disease traits in dog breeds were reported in the Online Mendelian Inheritance in Animals (OMIA), a global database of inherited diseases. Disorders may affect various function or organs and involve single or multiple genes. Thankfully, all diseases do not occur in all breeds, rather there seem to be more or less breed-specific mutations that lead to a certain disorder. One possible reason for this could be that many breeds were founded by very few animals, and that those founders happened to carry certain defective alleles. This has then been exacerbated by using extensively specific reproducers, as well as closing the genepool to breed or even national breed populations. This has led to inbreeding phenomena, involving higher probability of two defective alleles coming together in one individual.

However, disorders due to recessive defects are not the only problem in dog breeding. The BBC documentary 'Pedigree Dogs Exposed' in 2008 highlighted disorders resulting from selection for exaggerated morphologies in pedigree dogs in the United Kingdom. Because national kennel clubs are those responsible for maintaining breed standards, they were largely blamed for these problems, although the actual selection of breeding animals is the result of the combined decisions of all individual dog breeders.

In light of this, exchange of breeding animals across countries is an alternative option to improve the genetic health of pedigree dogs by enlarging the pool of available breeding candidates. This could both help in increasing the genetic variability and avoiding issues with recessive disorders. Furthermore, it opens up for selecting breeding animals of higher genetic merit than are available within your own country, animals that also are less related to the national population.

The aim of this project was to investigate various methods to improve dog health in an international context, concerning both management of genetic variability and genetic evaluation of potential breeding animals to ensure the selection of dogs of high genetic merit. Because national kennel clubs play a crucial role in dog breeding, it is important to better understand the current concerns, strategies and tools being used by these organizations, as well as the needs and future plans for dog health and welfare they foresee. Therefore, a survey was sent out, which was answered by 11 European and four non-European national kennel clubs. The answers demonstrated shared concerns for breeding priorities related to exaggerated morphologies, inherited disorders, as well as inbreeding and genetic variation. In the same time, there is a heterogeneity in term of information recorded and tools used by countries to manage the health of their breeds.

We then used pedigree databases and screening records of hip dysplasia provided by three national kennel clubs in France, Sweden and the UK. Our results show a common trends toward better management of inbreeding within national population. We also found that by combining all information from the three countries genetic variability could be increased, gene flow across countries could be better monitored, and international genetic selection of breeding animals could be performed. Using a computer simulation, we could also show that importing sires with high genetic merits could be beneficial, especially if the traits evaluated in both countries were genetically almost identical. Finally, we concluded that international collaboration on evaluation and selection of breeding animals is a feasible and useful strategy to improve canine genetic health.

## Populärvetenskaplig sammanfattning

Enligt en global databas över sjukdomar hos djur, finns det över 300 sjukdomar med genetisk bakgrund hos hund. Som tur är drabbas inte alla raser av alla sjukdomar. Snarare är det ofta så att en viss sjukdom bara drabbar en eller ett fåtal raser. En anledning till detta kan vara att raserna skapades baserat på ett fåtal individer och dessa råkade bära på vissa felaktiga genvarianter. Detta har sen förvärrats genom att man har stängt rasen och inte tillåter hundar utanför rasen att användas i aveln. Dessutom har hundaveln huvudsakligen skett med avelsdjur inom respektive land. Allt detta har lett till en större sannolikhet att två defektalleler hamnar tillsammans i samma hund, vilket leder till problem.

Dessvärre är inte problem med recessiva defekter det enda problemet inom hundaveln. BBC-dokumentären "Pedigree Dogs Exposed" som sändes 2008 påvisade stora problem orsakade av selektion för överdriven exteriör inom vissa raser i Storbritannien. Eftersom nationella kennelklubbar är ansvariga för att upprätthålla de s.k. rasstandarder som finns för varje ras, har en stor del av skulden för denna felaktiga selektion hamnat på dessa, även om den faktiska selektionen sker som ett samlat resultat av alla beslut som enskilda uppfödare gör.

Med allt detta i åtanke, kan utbyte av avelsdjur över landsgränserna vara ett sätt att genetiskt förbättra hälsan hos våra hundar. Genom att utöka gruppen av möjliga avelsdjur kan man dels öka den genetiska variationen och undvika inavelsproblem och problem med recessiva defekter. Dessutom öppnar det upp för att selektera genetiskt sett bättre avelsdjurs än vad som finns inom landet, djur som dessutom är mindre besläktade med de egna hundarna.

Syftet med detta projekt var att studera olika metoder för att förbättra hundars hälsa i ett internationellt perspektiv, både vad gäller bevarande av genetisk

variation och avelsvärdering av tänkbara avelsdjur för kunna välja de absolut bästa att bli föräldrar.

Eftersom nationella kennelklubbar har en viktig roll inom hundaveln, är det viktigt att förstå vilka utmaningar de ser, vilka strategier och verktyg som de har samt vilka framtida behov och planer de ser för att förbättra hundars hälsa och välfärd. Därför skickades en enkät ut till olika kennelklubbar. Denna besvarades av 15 klubbar, varav 11 fanns i Europa. Svaren visade en gemensam problembild vad gäller avelsprioriteringar mot såväl överdriven exteriöravel som genetiska sjukdomar men även frågor om inavel och genetisk variation sågs som viktiga.

Vi använde oss av härstammingsinformation och röntgenresultat för höftledsdysplasi från kennelklubbarna i Frankrike, Storbritannien och Sverige. Vi fann att genom att kombinera informationen från alla länderna kunde vi öka den genetiska variationen och få en bättre överblick över flödet av avelsdjur över gränserna. Dessutom skapades ett underlag för att kunna selektera avelsdjur från vilket land som helst. Med hjälp av en datorsimulering kunde vi också visa att det kan vara gynnsamt att importera genetiskt bra avelshundar, särskilt om egenskapen man är intresserad av att förbättra är genetiskt sett densamma i båda länderna, vilket kan antas för t ex höftledsdysplasi. Slutsatsen är alltså att internationellt samarbete för gemensam avelsvärdering som ger möjlighet till selektion av avelsdjur över landsgränser är en praktiskt användbar strategi för att förbättra hundars hälsa och välfärd.

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**Title :** International breeding programs to improve health in pedigree dogs

**Keywords :** Canine, inherited disorders, hip dysplasia, survey, genetic variability, genetic evaluation, stochastic simulation, breeding program

**Abstract :** Implementation of breeding programs in order to reduce incidence of inherited disorders and their impact on welfare should be a priority for dog breeders and breeding organizations. In that extent, exchanges of breeding animals between countries constitutes a critical point to be taken into account. The purpose of this thesis was to investigate management strategies to improve breed health in an international context, concerning both genetic evaluation and management of genetic variability. For this purpose, a survey was completely filled in by 15 national KCs, which demonstrated shared concerns among KCs for health in pedigree dogs. Shared sense of improving breeding and health status in pedigree dogs had been built among European national KCs. In addition, with data provided by the French, Swedish and British kennel clubs (KCs), including pedigree databases and phenotypic records of hip dysplasia (HD), the feasibility of joint evaluations across countries and the efficiency of international breeding programs were investigated. The benefits of exchanging breeding animals across countries are clearly showed in term of improved genetic variability and increased genetic progress, especially for breeds in countries with small populations. Besides, exact efficiency of breeding programs concerning genetic improvement of complex traits and inbreeding management together was tested by simulation. Therefore, we concluded international breeding programs are useful and alternative options to improve canine genetic health and their benefits will be amplified with the increase exchange of breeding animal in the near future. Importing male dogs could lead to higher genetic progress, however, it is necessary to have a high genetic correlation between countries and high accuracy of estimated breeding values of imported dogs.

**Titre :** Programmes d'élevage internationaux pour améliorer la santé des chiens de race

**Mots-clés :** Troubles canins, héréditaire, dysplasie de la hanche, enquête, variabilité génétique, évaluation génétique, simulation stochastique, programme d'élevage

**Résumé :** La question du bien-être et de la santé des races canines est devenue une préoccupation croissante du public et des acteurs de la cynophilie. De ce fait, la mise en œuvre de programmes de sélection visant à réduire l'incidence des maladies héréditaires et leur impact sur le bien-être devrait être une priorité pour les éleveurs de chiens et les organisations raciales et nationales. Dans cette perspective, il est important de prendre en compte la dimension internationale qui existe dans la sélection des races canines, notamment vis-à-vis des échanges de reproducteurs. L'objectif de cette thèse était d'étudier les stratégies de gestion pour améliorer la santé des races dans un contexte international, concernant à la fois l'évaluation génétique et la gestion de la variabilité génétique. Une enquête a été lancée auprès des organisations canines nationales, 15 pays ayant répondu à celle-ci, dont 11 en Europe. Les affections héréditaires, la question des hypertypes ainsi que la consanguinité et diversité génétique ont été classés comme les enjeux les plus préoccupants. Une analyse généalogique a été mise en place à partir des données fournies par trois organisations nationales, le Kennel Club (Royaume-Uni), la Société Centrale Canine (France), et le Svenska Kennelklubben (Suède). Sur la base des généalogies fournies pour les Labrador et Golden retriever, une analyse a été effectuée pour étudier la faisabilité d'évaluations conjointes entre pays pour dysplasie de la hanche. Finalement, le potentiel d'amélioration génétique pour un caractère complexe en fonction de différentes stratégies (sélection phénotypique, évaluation génétique, échanges de reproducteurs entre pays) a été testé à partir de simulations. A ce titre, les bénéfices de l'échange d'animaux reproducteurs entre les pays sont clairement démontrés par les études, ces échanges permettant d'augmenter les variabilités génétiques et d'améliorer le progrès génétique, en particulier pour les petites populations nationales.