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**GENETICS AND PHENOTYPES OF CHONDRODYSPLASIA  
(ACHODROPLASIA) ACROSS DOMESTIC ANIMALS SPECIES**

DIPLOMA WORK

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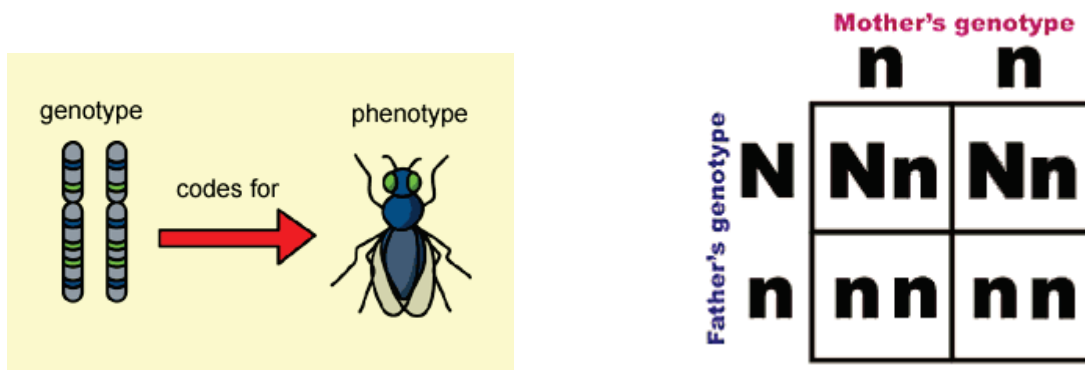
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# 1 Introduction

## 1.1 Definitions of genotype and phenotype

The genotype and phenotype of an animal are closely connected to each other as the phenotype is depending on the genotype (ZÖLDÁG, 2008). When we talk about the genotype we refer to the genetic material an animal has inherited from its parents, what makes up its genetic code. With phenotype we mean the observed properties of an animal, for example its development and configuration.



The genetic inheritance may be dominant or recessive and an animal can be heterogeneous or homogenous for a specific genetic trait. The phenotypic appearance of an animal is depending on this.

## 1.2 What is chondrodysplasia?

Chondrodysplasia means abnormal growth of cartilage and is an umbrella term used for many defects of the cartilage (KAMAN et al, 1991). These are disorders of normal growth and development of cartilage and bone, resulting in abnormal configurations (RADOSTITIS et al, 2000). It is a hereditary defect affecting the linear growth of the long bones, by affecting the chondrocytes in the growth plates of the bones, causing an abnormal ossification (KYÖSTILÄ et al, 2013). Characteristic are the disproportionally short limbs with abnormal configuration, and the condition is therefore often referred to as disproportionate dwarfism (ETTINGER and FELDMAN, 2005).

The condition of chondrodysplasia is affecting all species to a higher or lesser extent, and in some breeds of certain species it is even considered to be a breed characteristic. Except from affecting the long bones, the condition may also affect other bones of the body.

Conformational abnormalities of the limbs may cause secondary lameness or pain and lead to motoric disorders (HOULTON et al, 2006). In some cases chondrodysplasia may be accompanied by other defects, for example in the Alaskan Malamute where chondrodysplasia occur together with anemia.

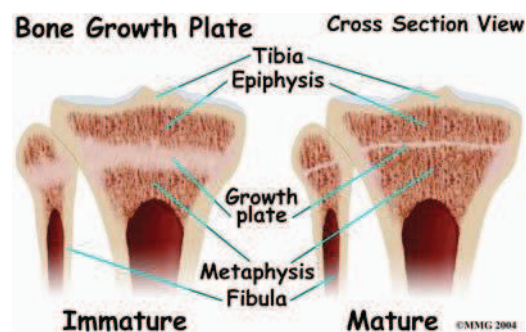
Pathological changes can be observed in the cartilage and fibrous elements of the skeleton (HOULTON et al, 2006), especially in the growth plates of the long bones. Lesions can be seen in the metaphysis and epiphysis, and the cartilage has an uneven appearance. The chondrocytes fails to form columns and have a disorganized structure. Other skeletal structures, besides the long bones, may display pathological changes, such as the skull, vertebrae, ribs and sternum.

Chondrodysplasia is sometimes noticed at birth, but in some cases the condition becomes obvious first as the animal develops (HOULTON et al, 2006).

Although the most characteristic symptom of chondrodysplasia over species is a short stature, there is a condition, mostly described, in sheep causing an elongation of the limbs. This condition is also regarded to belong to the group of chondrodysplasias, even though it shows a completely different phenotypic appearance in the affected animals.

### 1.3 Cartilage and bone development and essential components in case of chondrodysplasia

Cartilage is formed by chondrocytes, which originate from mesenchymal cells and they are also the precursors of the bone forming cells osteocytes. Abnormal development and maturation of chondrocytes can cause disorders of cartilage and bone development. In case of chondrodysplasia they often show a disorganized pattern in the growth plates. A growth plate is a thin layer of cartilage located between the metaphysis and epiphysis, composed of a resting, a proliferating and a hypertrophic zone. The growth plate should be completely replaced by bone at the end of puberty, and then the longitudinal growth will cease (MARTÍNES et al, 2006).



Long bones are developed by endochondral ossification which is regulated by many different genes, and defective function of any of these genes may lead to chondrodysplasia. During the ossification process the chondrocytes undergo proliferation, maturation and a hypertrophic stage with strict columnar alignment (SOGAWA et al, 2007).

Proteoglycans functions as aggregates in the extracellular matrix of cartilage, one of the most essential for normal function being aggrecan (ACAN). Its chief role is to hold water in the extra cellular matrix, and mutations in this proteoglycan is known to cause dwarfism in both

humans and animals.

Fibroblast growth factor 3 (FGFR3) normally inhibits chondrocytes and thereby has a negative regulatory effect on bone growth, thus limiting skeletal elongation

([http://www.askjpc.org/vspo/show\\_page.php?id=202](http://www.askjpc.org/vspo/show_page.php?id=202),  
<http://en.wikipedia.org/wiki/Achondroplasia>).

There are many other genes that have been proven or suggested to cause chondrodysplasia, such as oligomeric matrix protein (COMP), Perlecan and several different collagens. Parathyroid hormone 1 receptor (PTH1R), responsible for chondrocyte differentiation and proliferation, and a sulphate transporter (SLC26A2), regulating sulfation of the extracellular matrix proteoglycans, are possible candidates (KYÖSTILÄ et al, 2013). The possible involvement of the COL10A1 gene has also been suggested. Collagen X is found in hypertrophic zones of growth plates and if defect it can lead to developmental defects of the skeleton (SWEETMAN et al, 1992).

#### **1.4 Differential diagnosis**

Not all forms of dwarfism are caused by gene mutations affecting cartilage and bone development directly, and it might be of importance or interest to be able to distinguish what the underlying cause might be. In general chondrodysplasia is diagnosed by its main symptoms, usually disproportionally short limbs with abnormal configuration (KAMAN et al, 1991). We are also able to use x-rays during the rapid growth phase (SCHAER, 2010), and DNA tests (<http://www.socialstyrelsen.se/ovanligadiagnoser> ) are available for identification of carriers and homozygous fetuses.

Causes of dwarfism include (HORTON and LACDRICH, 2013):

- Mutations in genes responsible for hormone production and/or recognition
- Hormonal dysfunctions
- Metabolic disturbances
- Disorders of cartilage or bone growth plate development

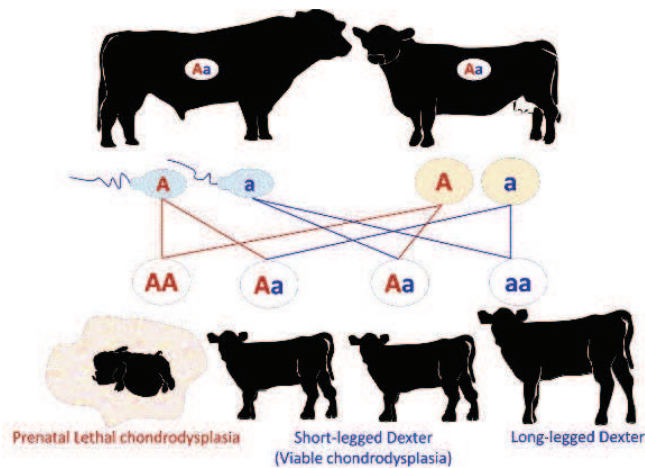
## 2 Chondrodysplasia in different animals

### 2.1 Cattle

Chondrodysplasia occur in a wide range of different cattle breeds, but might be mostly associated with the Irish breed Dexter cattle. Chondrodysplasia in cattle is an inherited genetic defect; the gene mutation differs among the affected breeds. In Dexter cattle it shows an incompletely dominant inheritance, while in other breeds the condition is recessive (PIRIPI, 2008). The phenotypic appearance between the breeds appears to be similar and is generally recognized by shortening of the limbs.

#### *Dexter cattle*

Dexter cattle carry a hereditary genetic mutation, causing short limbs in heterozygous animals (ZÖLDÁG, 2008). These are small sized cattle that can be born with long legs, short legs or as homozygous bulldog calves. The defect is caused by a mutation in the ACAN gene (HODGINS, 2010; KEMPER et al, 2012).



Homozygous calves are called bulldog calves and are usually aborted in late gestation since homozygosity is lethal (ZÖLDÁG, 2008). This severe form of dwarfism affecting Dexter cattle, but also some other breeds, is due to two mutations in the ACAN gene (HODGINS, 2010).

The bulldog calves show a severely shortened vertebral column with the tail located high up on the back, an increased amount of subcutaneous fat and abdominal hernia. The head is large and broad with a bulging forehead and usually we can observe an underbite, cleft palate and protruding tongue.



### *Other cattle breeds*

Chondrodysplasia has been seen in many other cattle breeds, showing a similar phenotype but the genetic mutations being of different origin. Bulldog calves has been described in not only Dexter cattle, but also Jersey, Holstein-Friesian and Guernsey cattle (PIRIPI, 2008).

In Hereford cattle this condition has been eliminated by genetic selection. Characteristic for Hereford chondrodysplastic calves are short limbs and faces, bulging foreheads and a large abdomen. Due to the shortness of the head these dwarfs are called brachycephalic dwarfs or snorter calves (PIRIPI, 2008).

Chondrodysplasia in Angus cattle is caused by a PRKG2 (c-GMP-dependent protein kinase type2) mutation (PIRIPI, 2008). As they are characterized by short limbs with long heads they are called doliocephalic dwarfs. In the Aberdeen-Angus has also been described a dwarfism characterized by a short, wide head and a reduced growth rate.

Also in Japanese Brown cattle and Shorthorn cattle has disproportionate dwarfism been described, in the Japanese Brown cattle the defect has been mapped to a mutation in the LIMIN gene (PIRIPI, 2008).

There is also a form of chondrodysplasia affecting some cattle breeds that show similar phenotypic appearance as the spider-lamb syndrome in sheep. These animals show excessively long and thin limbs, fragile bones, scoliosis and a shortened mandible ([http://www.askjpc.org/vspo/show\\_page.php?id=202](http://www.askjpc.org/vspo/show_page.php?id=202)).

## **2.2 Sheep**

Chondrodysplasia of sheep is a rare hereditary defect (PIR YAGCI et al, 2010). The two mostly described syndromes classified into the group of chondrodysplasias are the Ancon-dwarfism and the Spider lamb syndrome. Common for the two syndromes are their disproportional stature with abnormal leg conformation, but looking at the phenotypes they are remarkably different.

### *Ancon sheep*

Ancon sheep, or Otter sheep as they are also called, are disproportional dwarfs that were

earlier bred in the USA for their inability to jump. They are today extinct as they are no longer desired from either breeders or scientists. It is believed to have been caused by a recessive gene. These sheep were characterized by their short legs with abnormal conformation and a flattened face, but with a normal sized body.



### *Spider-lamb syndrome*

This recessive genetic defect located to the ovine chromosome 6, is suggested to be caused by an inactivation of the FGFR3 gene, and primarily affect Suffolk and Hampshire sheep breeds (PIRIPI, 2008; THE MERCK VETERINARY MANUAL; PUGH, 2002).

Spider lambs are characterized by their outstretched spider-like appearance. They have disproportionally long necks and limbs, and angular deformities of the legs, e.g. valgus are common (RADOSTITIS, 2000). We can also observe skull malformations such as a roman nose, a flattened sternum (pectus excavatum), kyphosis of the spine, and muscle atrophy (PUGH, 2000; PIR YAGCI, 2010).



Elimination of the disease is difficult since carriers of the recessive gene do not show the characteristic symptoms of chondrodysplasia (THE MERCK VETERINARY MANUAL). Affected lambs show symptoms already at birth or develop them by week 6 (PUGH, 2002). Lambs suffering from severe forms of Spider lamb syndrome rarely survive more than 12 weeks after birth ([http://www.askjpc.org/vspo/show\\_page.php?id=202](http://www.askjpc.org/vspo/show_page.php?id=202)).

### *Others*

Disproportional dwarfism due to chondrodysplasia has also been described in South Down and Texel sheep (PIRIPI, 2008).



## 2.3 Horse

Chondrodysplasia is a rarely occurring hereditary defect in horses (EBERTH, 2013), but has been described in miniature horses and Friesian horses. There are two different types of chondrodysplastic dwarfism, the most common being the brachycephalic dwarf (HODGINS, 2010).

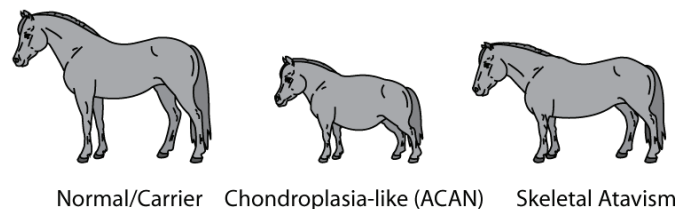
The brachycephalic dwarf is characterized by short neck and limbs, the limbs with angular deformities, but a normal body. The head has a pronounced forehead, flat nasal bridge and bulging eyes. In some individuals an overbite or underbite may be observed (EBERTH, 2013; HODGINS, 2010).

The second type of disproportional dwarfism in horses is characterized by a large head in comparison to the leg length, but the head has a normal shape (HODGINS, 2010).

### *Miniature horses*

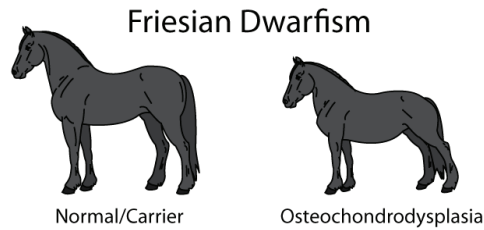
In miniature horses can be observed a chondrodysplasia-like syndrome, due to a mutation in the ACAN gene located to horse chromosome 1 (EBERTH, 2013). These horses are described as brachycephalic dwarfs. Affected horses are characterized by short necks and limbs. The skull is large with a flat face and prominent eyes. We might also observe defects of the jaws and oral cavity, e.g cleft palate, underbite and protruding tongue.

### Miniature Horse Dwarfism



### *Friesian horses*

Chondrodysplasia caused disproportional dwarfism in the Friesian horse is a hereditary recessive trait and the genetic defect is located to chromosome 14 (EBERTH, 2013). The condition is characterized by a growth disturbance in which the neck and head grows faster than the limbs. This results in horses with long necks, relatively large heads and short limbs. Affected horses have an overall smaller size than the normal Friesian horse, weighing in at approximately 50% of adult weight (HODGINS, 2010). They also have abnormal configuration of the limbs with hyperextension of the fetlock joint (SILVA et al, 2013). Despite its configuration these dwarf Friesian horses are able to move in all the normal gaits.



## 2.4 Swine

Chondrodysplasia of swine is a rare condition, but has been described in the Danish Landrace and is a dominant hereditary defect caused by a missense mutation in the COL10A1 gene (KEMPER, 2012). Affected animals are usually recognized at an age of 1-3 weeks.

In the Danish Landrace swine suffering from chondrodysplasia a normal sized head and trunk can be observed (KAMAN et al, 1991). The limbs are disproportionally short with conformational defects, e.g. lateral deviation of the femur, and an increased joint motility. As a result of the limb defects motility problems (KAMAN et al, 1991) and progressive joint disease (DJD) may be observed.

This form of disproportional dwarfism in swine, caused by type X collagen, can be used as an animal model for the human syndrome called Schmid metaphyseal chondrodysplasia (PIRIPI, 2008).

## 2.5 Dog

Chondrodysplasia in dogs is an inherited defect that causes disproportionate dwarfism. The condition may affect almost any breed of dogs but in some breeds, e.g. Dachshund and Basset hound it is a fixed, breed-defining trait, while in other breeds it is an unwanted genetic defect. The FGF4 retrogene (KEMPER et al, 2012; HODGINS, 2010), located to canine chromosome 18 is one of many genes suggested to cause chondrodysplastic syndromes in dogs ([http://www.askjpc.org/vspo/show\\_page.php?id=202](http://www.askjpc.org/vspo/show_page.php?id=202)), all mutations showing similar phenotypic appearance. Depending on the gene mutation different forms of chondrodysplasia may occur, with slight differences in configuration and some forms are accompanied by other defects.



Chondrodysplastic dogs are characterized by their short limbs, not uncommonly with carpal valgus, cubital varus and an external rotation of the feet. Due to this abnormal limb conformation lameness and motoric problems may occur in both the forelimbs and hindlimbs. The head might be larger than normal and have an abnormal conformation. If the eyes are affected we might observe microphthalmia, lens detachment, retinal defects, cataracts and glaucoma (HODGINS, 2010). The spine may also be affected, showing deviations from the normal.



Not all forms of chondrodysplasia are recognized at birth, in some cases the condition is not recognized in the new born puppies, but will be seen as they develop. Before the age of 4-5 months, affected animals are usually recognized (HOULTON et al, 2006).

In the Alaskan Malamute disproportional dwarfism is accompanied with hemolytic anemia (ETTINGER and FELDMAN, 1999; HOULTON et al, 2006). This recessive disorder can be seen from approximately 5-6 weeks of age (PIRIPI, 2008).

In the Labrador Retriever can be seen an oculo-skeletal dysplasia caused by COL9A3 gene (KYÖSTILÄ et al, 2013), where shortened curved limbs often affected by DJD, and ocular abnormalities can be observed, e.g. retinal defects and cataract (HOULTON et al, 2006). This ocular defect that accompanies chondrodysplasia can also be seen in Samoyed dogs affected by chondrodysplasia (ETTINGER and FELDMAN, 1999). In the Samoyed dog oculo-skeletal dysplasia is caused by COL11A2 gene (KYÖSTILÄ et al, 2013) and this defect may or may not be accompanied with hemolytic abnormalities (RUVINSKY and SAMPSON; 2001).

In case of the Norwegian Elkhound chondrodysplasia may be associated with glucosuria (HOULTON et al, 2006; ETTINGER and FELDMAN, 2005).

## 2.6 Cat

Chondrodysplastic cats are characterized by a small body, domed skull with a flattened face, protruding tongue and short bowed limbs.

Chondrodysplasia is a breed character in the Munchkin cat, also called the “Dachshund cat”, and is caused a dominant genetic defect ([http://en.wikipedia.org/wiki/Munchkin\\_cat](http://en.wikipedia.org/wiki/Munchkin_cat)). Individuals that are homozygous for the defect die in the womb due to gene lethality (HARTWELL, 2008-2013), while heterozygous cats will have short limbs.

The Munchkin cats are characterized by short, slightly bowed limbs, and the hindlimbs being somewhat longer than the frontlimbs. The shortness of their legs does not seem to interfere with their running and jumping abilities, although they cannot jump as high as a normal cat (THE ROYAL CANIN CAT ENCYCLOPAEDIA) and some cats may exhibit joint problems or pain. Chondrodysplasia in the Munchkin cat is associated with lordosis (excessive curvature of the spine) and pectum excavatum (flattened ribcage) (HARTWELL, 2008-2013).



The Scottish Fold is carrying a gene mutation causing osteochondrodysplasia, which show dominant inheritance (ETTINGER and FELDMAN, 2005). The breed is primarily characterized by its folded ears, but other skeletal defects occur as well, although uncommon in heterozygous animals. Kittens are born with normal ears, and in those who carry the gene mutation the ears starts to fold around 2-3 weeks of age. The condition is associated with deafness (HOULTON et al, 2006). Homozygosity for the gene mutation is lethal and in these cases severe skeletal deformities can be observed.



## 2.7 Human

Chondrodysplasia in humans can be caused by more than 200 different gene mutations affecting skeletal growth and development (KEMPER et al, 2012; KYÖSTILÄ et al, 2013).

### *FGFR3 gene*

*Achondrodysplasia* is the most common form of disproportionate dwarfism in humans (KEMPER et al, 2013; MARTÍNES et al, 2006), and about 5 of 100 000 children are affected (<http://www.socialstyrelsen.se/ovanligadiagnoser> ). The condition is caused by mutations in the FGFR3 gene, located on chromosome 4, and has a dominant inheritance (PIRIPI, 2008). Homozygosity for the defect result in severe skeletal disorders, and homozygous children are unlikely to survive for more than a few months (SWEETMAN et al, 1992).



Humans affected by the condition have short limbs, the legs showing conformational deformities such as varus or valgus (<http://en.wikipedia.org/wiki/Achondroplasia>) causing a characteristic waddling gate, and a normal sized trunk. The head is relatively large with a flattened face and a prominent forehead (<http://www.socialstyrelsen.se/ovanligadiagnoser>). It is common with joint hyperextensibility and spinal kyphosis or lordosis.

The height for women is between 115 to 135 cm, and for men 121 to 145 cm (<http://www.socialstyrelsen.se/ovanligadiagnoser>)

*Hypochondroplasia* is dominant inherited skeletal defect caused by a mutation in the FGFR3 gene (PIRIPI, 2008). Affected humans will show a short stature with shortened limbs, enlarged head and lumbar lordosis. Hypochondrodysplasia has similar clinical signs as achondrodysplasia, but is less pronounced (SWEETMAN et al, 1992).

*Thanatophoric dysplasia type 1* is a dominant, lethal defect caused by a FGFR3 gene mutation. Affected humans have extremely short limbs, large heads with the eyes wide apart and a narrow chest (PIRIPI, 2008).

### *ACAN gene*

*Osteochondritis dissecans* is a dominant genetic defect caused by a mutation in the ACAN gene. It causes a short, disproportionate stature in the affected persons. It is characterized by an early onset of osteoarthritis (OD) with multiple lesions in the knee, hip and elbow joints.

*Spondyloepimetaphyseal dysplasia, Aggrecan type* is caused by an ACAN gene mutation and show a recessive inheritance. Humans affected by the mutation will show a severely short stature with mild lumbar lordosis, short neck and midface hypoplasia.

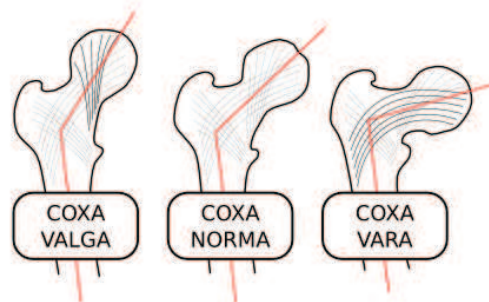
*Spondyloepiphyseal dysplasia, Kimerley type* is caused by a mutation in the ACAN gene and shows a dominant way of inheritance. In this condition we can observe persons suffering proportional dwarfism with progressive osteoarthropathy of the weight-bearing joints.



### *COL10A1 gene*

*Schmid metaphyseal chondrodysplasia* has been suggested to be due to a point mutation in the COL10A1 gene (CHAN et al, 1998) localized to chromosome 6 (SWEETMAN et al, 1992). It shows a dominant form of inheritance and is lethal for homozygous individuals. This is the most common type of metaphyseal chondrodysplasia.

The condition is characterized by disproportionate short stature with bowed legs and lumbar lordosis. In affected people we can observe a waddling gait due to coxa vara or varus (PIRIPI, 2008; CHAN et al, 1998).



### *PTHR1 gene*

*Blomstrand chondrodysplasia* is a rare, lethal disorder (YOUNG et al, 1993) caused by a mutation in the PTHR1 gene. Characteristics for the disorder are shortened limbs with bowed arms and a long, narrow thorax. Also observed is that the eyes are widely spaced and protruding, the nasal bridge is depressed, and we can observe severe micrognathia (PIRIPI, 2008).

*Jansen metaphyseal chondrodysplasia* is also caused by a mutation in the PTHR1 gene, and show similar clinical symptoms as Blomstrand chondrodysplasia, but is unlike the Blomstrand chondrodysplasia, a dominant disorder (PIRIPI, 2008).

*Chondrodysplasia punctata, bound to the X-chromosome*

This genetic disorder can be inherited both recessively and dominantly. The recessive form is usually only seen in men, and is caused by a mutation in the ARSE gene located on the X-chromosome. The dominant form is usually only seen in women, as male fetuses are either aborted or born as healthy, non-carriers. Dominant chondrodysplasia punctata is caused by a mutation in the EBP gene located on the X-chromosome. Both causes disproportional dwarfism and scoliosis (<http://www.socialstyrelsen.se/ovanligadiagnoser>).

### **3 Materials and Methods**

This is a literature study with material gathered from both books and scientific articles. Data has been collected from many different internet sources, the major ones being PubMed and Google, and also from books found in the library and clinics I have been at during the 11th semester practice. Pictures were courtesy of the reviewed articles and internet sources.

It has been a difficult and challenging, but interesting, task to collect the material for this diploma work and put it together. The research is much more extensive when it comes to chondrodysplasia in humans than in animals, and within the different animals the information supply varies. Although it has been easier to find research material about human chondrodysplasia, it has been divided in so many different forms of the condition it has been hard to choose which is relevant and which to use. The same is valid for the animals as well, but to a much lesser extent as the information has been less all together.

### **4 Results**

As can be seen chondrodysplasia is a highly complex disorder that can be caused by a wide range of different genetic mutations. Even though we generally can see a similar phenotypic appearance of animals affected by chondrodysplasia, the genetic mutation varies both between species and within a species.



## 5 Discussion and conclusions

Chondrodysplasias are rare genetic disorders in both animals and humans, affecting all species to a higher or lesser extent. It is a complex and heterogeneous condition caused by different gene mutations, generally resulting in similar phenotypes in both animals and humans. It is difficult to compare the frequency of occurrence between species as the degree of research differs between them. Most research is put into the human conditions of chondrodysplasia, and therefore there is more material available and more syndromes classified into the group of chondrodysplasias compared to animals.

An autosomal way of inheritance has seemed to be to most common, but in humans a form of chondrodysplasia has been described where the mutation is located on the X-chromosome. Spontaneous mutations may also occur and cause chondrodysplasia, and the offspring of these animals can then inherit the genetic mutation to become carriers or clinically affected. The condition may be recessive or dominant, but this varies greatly between and within species. In one breed chondrodysplasia can be inherited as a dominant trait, while in another it can be recessive although they both belong to the same species. An animal carrying a dominant gene is easier to recognize than the carrier of a recessive gene, and is therefore easier to exclude or include in breeding depending on if the trait is desirable or not. It is important to identify carrier animals to be able to remove them from the breeding stock if the defect is undesirable. The elimination of unwanted individuals from breeding can be done by removing chondrodysplastic animals, parents with affected offspring or by detecting carriers with DNA-testing.

Generally chondrodysplasia does not seem to be a desired trait in breeding, and affected animals are considered to be defect. In some breeds, of certain species, chondrodysplasia is considered to be a characteristic trait of the breed and is a part of its breed standard. Animals carrying a genetic mutation causing chondrodysplasia can be selectively bred to create new miniature breeds. In breeding the phenotype characteristic of chondrodysplasia seems to be a more desired trait in our companion animals than in the production animals, even if a few of our production animals are also bred for the typical appearance.

In some animals the chondrodysplastic phenotype fills a function, e.g. in the Dachshund that benefits from its short stature when chasing foxes out of their borrows, and the Ancon sheep that was desired for their inability to jump fences. But most of the chondrodysplastic breeds are bred for their physical appearance, rather than to fill a specific function. Some breeders mean that these miniature breeds creates diversity to the species, and apparently the exterior appeals too many. Will the function of the animal be more beneficial for us, than the negative health aspects will be for the animal? This is difficult question to answer as many animals bred for the chondrodysplastic phenotype lives seemingly normal lives, and even if certain problems are associated with the condition they are not always expressed.

Chondrodysplasia is generally characterized by disproportionally short limbs with abnormal conformation. The phenotypic appearance depends on the gene mutation, the properties of inheritance and if the animal is heterozygous or homozygous for the condition. The severity

of chondrodysplasia varies with the gene mutation and the properties of inheritance. Generally homozygotes for the condition seem to be more severely affected than those animals being heterozygous. Homogeneity for the defect often appears to be lethal. There are a few documented cases where chondrodysplasia does not cause a shortening of the limbs, but instead the limbs will be long with abnormal conformation, e.g. in case of the spider-lamb syndrome in sheep.

Due to the abnormal conformation of the limbs it is not uncommon for affected animals to have motoric problems and joint pains. In some breeds chondrodysplasia may be accompanied or is even associated with other problems, e.g. in the Alaskan Malamute where the condition is associated with anemia, and in Labrador Retrievers and Samoyeds where it is associated with ocular problems.

When comparing the different species with each other, there seems to be no common denominator for what causes the phenotypic appearance of disproportionate dwarfism. The gene mutation seems to vary both between and within species, and does not seem to follow any specific pattern. Some animals can be used as models trying to understand chondrodysplasia in man. One of the most common and useful animals for research studies are mice, so also in the case of investigating possible gene mutations causing chondrodysplasia (SOGAWA et al, 2007). In case of the human condition Schmid metaphyseal chondrodysplasia, caused by a mutation in the COL10A1 gene, Danish Landrace pigs suffering from disproportional dwarfism can be used as an animal model for research, as it is caused by a mutation in the same gene.

Chondrodysplasias caused by mutations in the ACAN gene can be seen in Dexter cattle, miniature horses and in man. In the cases described the mutation causes a disproportional dwarfism, except in the human condition Kimerley type spondyloepiphyseal dysplasia in which it causes a proportional dwarfism.

Mutations in the FGFR3 gene cause chondrodysplasia in humans and sheep, but with very different phenotypic appearance. While the mutation results in several conditions of disproportional dwarfism in man, it will cause an outstretched spider-like appearance in sheep.

In general, with only a few exceptions, animals affected by chondrodysplasia show a similar phenotypic appearance even though the gene mutations responsible for the conditions vary greatly. In one species a certain gene mutation will cause chondrodysplasia while a mutation in the same gene in another species may be involved in completely different disorder. As an example can be mentioned mutations in the FGFR4 gene that in dogs cause chondrodysplasia, but in human can be involved in some forms of cancer.

As can be seen the genetic defect causing chondrodysplasia is generally not a desired trait. There are many health problems arising secondary to the defect, often undesired even in animals bred for the phenotypic appearance. We should ask ourselves if it is defensible to breed animals for extreme phenotypes accompanied with health hazards just for our own pleasure.

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## **7 Summary**

This diploma work is dedicated to the condition of disproportionate dwarfism in animals called chondrodysplasia, the genetics behind it and the phenotypic appearance of the animals suffering from it. I have shortly described several domestic animal species separately, what the characteristics are and, if known, the genetic mutation causing it. Focus has been put on the comparison between the species and also between breeds within a species. The phenotypes generally show similarities while the gene mutations differ between and within species. In many of the cases the etiology behind the gene mutation seems to be still unclear.

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