University of Veterinary Medicine
Budapest
Department and Clinic of Surgery and Ophthalmology

Enamel hypoplasia in small animals

Literature review

By
Anne Camilla Eklund Arnesen

Supervisor: Dunay Miklós Pál, DVM
Department of Surgery and Ophthalmology

Budapest, Hungary

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1. Abstract

Enamel hypoplasia (EH) represents a significant developmental anomaly affecting dental hard tissues and is attributed to a variety of etiological factors, including infectious diseases, pyrexia, trauma, and nutritional insufficiencies during the amelogenesis phase. Notably, the past decade has witnessed the identification of hereditary origins for EH in certain canine breeds such as Swedish Standard Poodles, Italian Greyhounds, and Samoyed Dogs, which are clinically referred to as amelogenesis imperfecta.

In light of the recent incidental positive selection associated with amelogenesis imperfecta within these breeds, there is a heightened need for a comprehensive exploration of EH. This thesis aims to review the pathogenesis, classification, and hereditary dimensions of EH in dogs and cats. Furthermore, it delves into an extensive analysis of the existing literature, offering insights into disease prevalence, epidemiology, and causative factors.

The clinical facets of EH are summarized to provide a valuable reference tool for veterinarians. This includes a comprehensive overview of key aspects such as case profiles, patient history, clinical manifestations, presentation characteristics, differential diagnosis, diagnostic approaches, treatment modalities, and effective management strategies. Additionally, this thesis explores the imperative areas of prevention, and breeding practices, and offers a glimpse into the future perspectives of managing EH.

2. List of Abbreviations

AI	Amelogenesis imperfecta
bp	Base pair
CDV	Canine distemper virus
DEH	Diffuse enamel hypoplasia
EH	Enamel hypoplasia
ENAM	Enamelin gene
FEH	Focal enamel hypoplasia
GWAS	Genome wide association study
PCR	Polymerase chain reaction
TR	Tooth resorption

3. Introduction

The state of dental health in small animals has garnered increasing attention, propelled by advancements in veterinary dentistry and the extended lifespans of our companion animals. Within the domain of domestic canines and felines, periodontal disease is emerging as a growing health concern, exerting profound influences on their well-being. Notably, among dogs aged three years and older, the prevalence of periodontal diseases is conservatively estimated at a minimum of 80% [1–3], while in the feline population, this figure stands at 70% [4], rendering it the predominant disease in both species. Moreover, an association has been made between these conditions and various systemic diseases, accentuating the negative consequences of compromised dental health on the overall physiological state [5–7].

Enamel hypoplasia (EH) is a dental pathology characterized by deficient, incomplete, or absent tooth enamel formation. Enamel, the outermost dental tissue, plays a multifaceted role pivotal to dental integrity. Its principal function is as a protective mantle that guards the vulnerable dentin and pulp against mechanical trauma, chemical erosion, and microbial intrusion. Noteworthy for its extraordinary hardness, enamel endures the rigors of occlusal forces during mastication, facilitating the efficient comminution of ingested foods for digestive processes. Additionally, enamel serves as an insulating layer, safeguarding the tooth against extreme thermal fluctuations while mitigating sensitivity to thermal stimuli.

In instances where amelogenesis is deficient, the unshielded dentin becomes susceptible to elevated plaque retention, manifesting as discoloration ranging from tan to dark brown, accompanied by substantial patient discomfort. Moreover, this exposed dentin further exposes the dentinal tubules, amplifying the risk of infection. The affected teeth become predisposed to heightened inflammatory responses, culminating in a heightened likelihood of eventual dental loss [8].

Enamel hypoplasia can be the consequence of trauma to the unerupted tooth, frequently associated with the extraction of the deciduous teeth.

Trauma is the most common acquired cause. Alternatively, it may arise from the hereditary condition called amelogenesis imperfecta (AI), resulting in diminished enamel matrix production during tooth development, and in such instances, nearly all surfaces of all teeth will be affected [8]. It can also be the consequence of significant pyrexia, malnutrition, toxicant or drug exposure, and infections like distemper, particularly when these occur early in life or in utero.

3.1 Enamel development

Tooth development happens inside the maxillary and mandibular bones, after which they erupt into the oral cavity. The exposed portion of the mammalian tooth is called the dental crown, while the portion buried inside the bone is called the dental root. The dental morphology of dogs and cats is classified as brachydont, describing teeth or a relatively short and sharp nature, with somewhat flattened crowns, suitable for their carnivorous diet [9]. The crown is mostly made up of vascularized dental pulp, surrounded by dentin and enamel, while the root consists of nerve and blood supply, surrounded by dentin and a cementum. In dogs and cats, the physiological enamel thickness varies from 0.1 mm to 1mm [10].

The development of brachydont molars consists of two main events: the formation of the root and the shaping of the crown. It is a highly regulated process that plays a crucial role in the overall oral health and function of the animal. The formation of the tooth bud, when the dental lamina invaginates into the cranial neural crest cells, is the first recognizable step in tooth development, after which the formation of the root can begin [11]. The dental papilla cells that develop within the tooth bud begin to differentiate into odontoblasts, which are responsible for the secretion of dentin. Dentinogenesis is a vital step in root formation, as it provides the structural foundation upon which the rest of the tooth will develop. As the odontoblasts deposit dentin, they gradually move away from the center of the tooth bud, leaving behind a pulp chamber in the center, which eventually houses the dental pulp containing nerves and blood vessels.

The shaping of the crown represents the other critical phase in tooth development. It involves the differentiation and interaction of various dental tissues, including the enamel organ, which gives rise to the enamel, and the dental follicle, which forms the supporting structures like the periodontal ligament and alveolar bone. The enamel-forming cells, known as ameloblasts, secrete enamel matrix proteins, which undergo mineralization to create the exceptionally hard and protective outer layer of the tooth. The folding and growth of the enamel organ, as well as the interactions with the underlying dentin and dental pulp, lead to the precise shape and morphology of the tooth. This series of morphological phases is named the bud, cap, and bell stages. The bell stage is of particular developmental importance, as it is during this period that the form, shape, size, and number of the crowns are determined [12]. During the bell stage, the enamel organ consists of the outer enamel epithelium, the star-shaped cells of the stellate reticulum, that connect to each other, as well as to the outer enamel epithelium and the stratum intermedium, and finally, the inner enamel epithelium, as shown in **Figure 1** [13]. Differentiation of the inner enamel epithelium will give rise to the enamel-producing ameloblasts, against which the cell layer of the dental papilla will form dentin-producing odontoblasts.

Any interference in this process of odontogenesis can result in structural abnormalities of the enamel or the gross anatomy of the tooth. Particularly disturbances that occur earlier in the process of tooth development, have a heightened likelihood of resulting in abnormalities of the tooth, than disturbances that occur later, when certain aspects of tooth development have already been achieved. In the dog, the sensitive processes of dentino- and amelogenesis of all permanent teeth occur during a narrow timeframe spanning approximately 8 weeks, which starts shortly after birth [14].

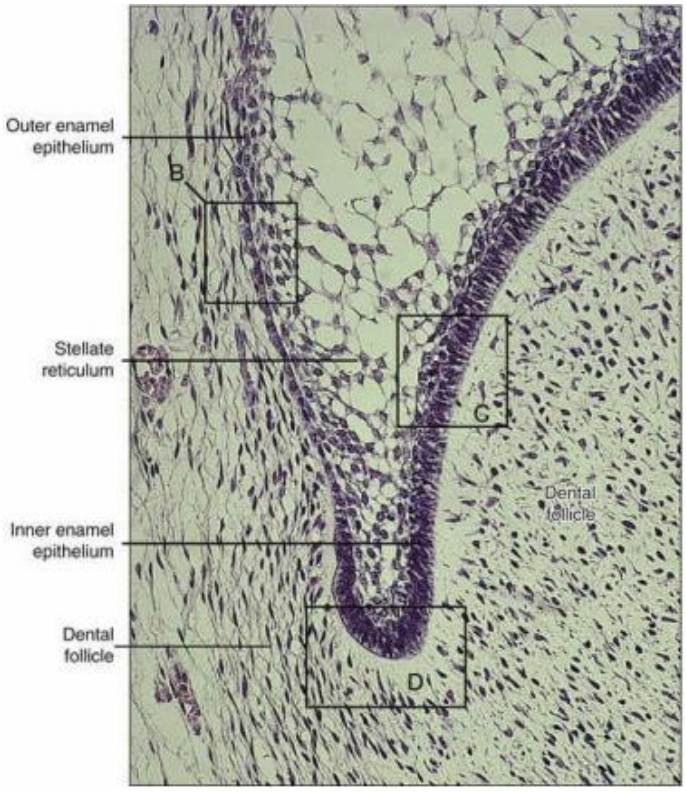

Figure 1*: The enamel organ during the early bell stage, as seen with light microscopy, taken from Nanci et al* [13].

3.2 Classification of enamel hypoplasia

Enamel hypoplasia can be classified by its pathogenesis, etiologic factors, which can be subdivided into hereditary factors and environmental factors, and the extent of the involvement of the dentition [15]. In humans, the clinical appearance of EH is classified as pits (single/multiple, shallow/deep tiny areas of enamel loss), grooves of enamel loss (<2 mm wide), or areas of partial or complete absence of enamel of the tooth crown [16].

The pathogenesis of clinical enamel hypoplasia can be broadly divided into two groups: first, EH arising from incomplete or disrupted enamel matrix production, and second, EH occurring as a secondary consequence of insufficient matrix mineralization [15]. Hypomineralized enamel typically exhibits initial presentation characteristics distinct from the type caused by incomplete matrix production, with enamel edges that are sharp and irregular where the enamel has chipped off. However, once these sharp edges are

smoothened by wear, they become indiscernible from EH resulting from inadequate matrix production [15, 17].

The hereditary cause of EH is called amelogenesis imperfecta. This hereditary disease is also present in humans, in which it has been studied more elaborately. In dogs, amelogenesis imperfecta has to date been documented in Swedish standard poodles, Italian greyhounds, and Samoyed dogs, and various recessive genetic mutations have been identified as the cause of this dental maldevelopment [18–21].

Environmental factors that can cause EH include 1). trauma, 2). infectious causes, 3). pyrexia of any origin, 4). exposure to chemicals with a toxic influence on ameloblasts (fluoride), and 5). nutritional deficiencies. Regarding trauma, the extraction of deciduous teeth or bite wounds during the first 8-10 weeks of life are frequently responsible [15]. Infection with canine distemper virus is a frequent infectious origin of EH. This paramyxovirus, which typically infects puppies during the sensitive stage of amelogenesis, divides freely in the developing tooth, causing necrosis, disorganization of the ameloblasts, multinucleate giant cells and large eosinophilic cytoplasmic viral inclusions [22].

Fluoride has a harmful effect on amelogenesis by causing an alteration to the mineralization process, that can lead to hypomineralization. The early maturation stage of enamel formation is particularly sensitive to the effect of fluoride [23]. Tetracycline antibiotics are also known to have an adverse effect on enamel development, causing maldevelopments such as a permanent yellowing of the teeth and increased susceptibility to cavities, particularly in offspring if the bitch receives these antibiotics during pregnancy [24].

Nutritional deficiencies, particularly deficiencies in vitamins A, C, D, calcium, phosphorus, and zinc, which are essential for physiologic amelogenesis, have been shown to cause enamel hypoplasia when affecting children during the development of the permanent teeth [25–27].

When classifying EH according to the extent of dentition that is affected, we can broadly describe two categories: focal enamel hypoplasia (FEH), also known as Turner's hypoplasia, and diffuse enamel hypoplasia (DEH) (**Fig. 2**). FEH is a tooth defect that can vary from a focal area of opaque white, yellow or brown discoloration to grossly abnormal tooth morphology, generally affecting only one tooth, which is referred to as a Turner's tooth [28].

This type of EH is most commonly caused by environmental factors such as localized infection, or trauma to the developing tooth germ. It can also be caused iatrogenically, following poorly performed extraction of deciduous teeth. The focal character of FEH is the result of an insult that stopped some ameloblasts from producing enamel matrix, while others were still able to fulfill their function [29]. DEH presents with similar pathological changes but involves much of the dentition, usually resulting from direct infection of the ameloblasts (by distemper virus, for example), or by systemic diseases with pyrexia. DEH can also be the clinical manifestation of the hereditary disease amelogenesis imperfecta.

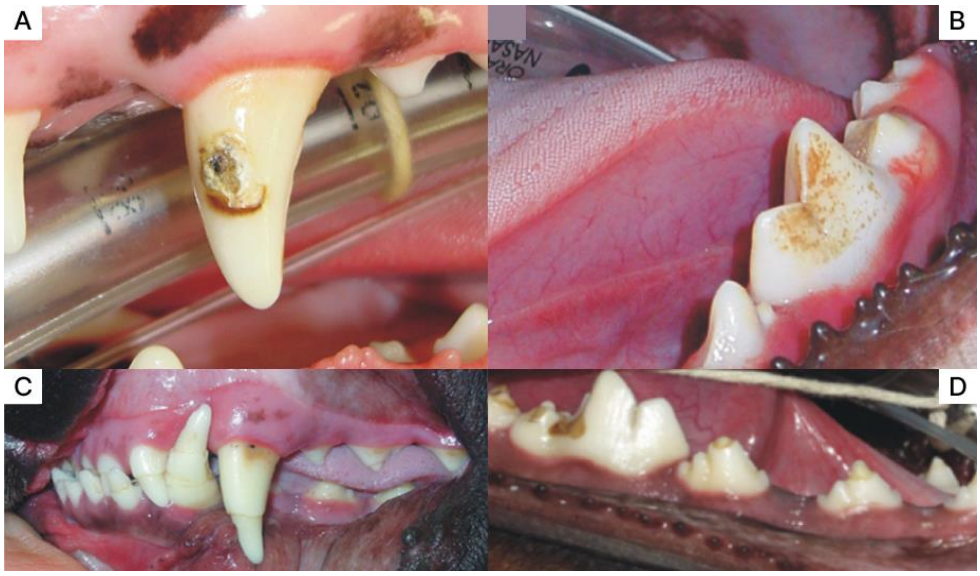

Figure 2*: A left maxillary canine (A) and left mandibular first molar (B) present with FEH, affecting the labial/buccal surfaces, respectively. In (C) and (D), DEH with circumferential hypoplastic lines is visible. There is still enamel present on the crown surfaces (C) leading to the unstained appearance. More severe EH with dentin exposure and resultant staining is visible in (D). All pictures are taken from Boy et al, 2016* [15].

3.3 Amelogenesis imperfecta

A hereditary component causing enamel hypoplasia has been identified in the Swedish Standard Poodle, the Italian Greyhound, the Samoyed Dog, the Parson Russel Terrier, and the Akita [18–20, 30]. In humans, amelogenesis imperfecta has been researched more elaborately, and three clinically distinguishable types have been described: a hypoplastic type with defective matrix secretion by ameloblasts, a hypocalcified type where the mineralization process of the matrix is defective, and a hypomature type where the enamel crystal growth during maturation is defective due to ineffective enamel protein removal [15, 31].

In dogs, amelogenesis imperfecta was first reported in the Swedish Standard Poodle in 2009, by Mannerfelt and Lindgren [30]. They performed histological studies on the suspect lesions in standard poodles and documented a defect of enamel mineralization. The affected enamel

contained a large residual amount of organic matrix, indicating that the enamel was not fully mineralized. In certain places, enamel appeared intact but still showed signs of poor mineralization. Five dogs out of twenty-seven standard poodles present at a dog show had discolored teeth. Insight into pedigree data showed examples of parents having amelogenesis imperfecta as well. In all litters from these dogs, at least one dog had discolored teeth, and two histologically confirmed cases of amelogenesis imperfecta appeared four generations later. This is strongly suggestive of the familial nature of this disorder, though no genomic studies were performed to attempt to identify the genetic culprit.

The EH lesions described in these dogs clinically and histologically resemble the hypocalcified type of amelogenesis imperfecta, though this was not genetically confirmed. Based on the documented prevalence in this admittedly small-scale study, it can be assumed that amelogenesis imperfecta is a common cause of discolored teeth in standard poodle dogs in Sweden.

In Italian greyhounds, familial enamel hypoplasia was reported in 2013, by Gandolfi et al [18]. They describe the condition as uniformly affecting deciduous and permanent teeth and manifesting through enamel roughening and thinning, accompanied by brownish mottling. Interestingly, they note that basic tooth structure is usually maintained throughout the life of the animal and that dental cavities and fractures are not as frequent of a complication as in humans. A 5-base pair (bp) deletion associated with enamel hypoplasia was identified in exon 10 of the *enamelin* (*ENAM*) gene. This genotype relates mostly to the hypoplastic type of amelogenesis imperfecta [32]. Moreover, based on genome analysis, this trait appears to be under inadvertent positive selection. The protein enamelin is an organic matrix protein that plays an important role in the development of enamel, as its interaction with the ameloblasts is essential for the formation of enamel's intricate architecture [33]. A genetic test was developed to identify this specific 5 bp deletion in the *ENAM* gene, to enable breeders to manage the trait.

In Samoyed dogs, familial enamel hypoplasia was reported in 2017, by Pedersen, Shope and Liu [19]. They looked at a total of 182 Samoyeds, out of which 14 dogs were clinically affected by lesions consistent with those caused by enamel hypoplasia. As opposed to familial EH in Italian greyhounds, which affects deciduous and adult teeth uniformly, in Samoyeds the deciduous teeth are normal, but the abnormalities of the adult teeth are apparent immediately upon eruption. Bad breath was shown to be an early indicator of the disease. The typical appearance of the teeth of a Samoyed with EH is noticeable discoloration, small, blunt teeth that are further apart than usual, and irregular tooth surfaces. Gingivitis and swelling of the gums were identified as common accompanying problems that often progress to advanced periodontal disease. A genome-wide association study (GWAS) performed on seven Samoyeds with EH-like lesions and five Samoyeds with healthy teeth, showed an extended region of homozygosity in the gene *SCL24A4* on chromosome 8, known to cause enamel hypoplasia in humans [19]. Polymerase chain reaction (PCR) was used to amplify this region, followed by sequencing, which allowed the identification of two nucleotide changes in this gene. A single base pair mutation in exon 12, cytosine to thymine, changes the amino acid coded for by that codon from proline to leucine, and a 21 bp insertion was identified in exon 17.

A test was developed to detect the 21 bp insertion in exon 17 of *SCL24A4*, which allowed the identification of dogs that did not have the mutation, as well as dogs that were heterozygous or homozygous for the mutation. Following this, the 14 dogs presumed to have enamel hypoplasia were then tested and confirmed to all be homozygous for this mutation. Twenty of the remaining 168 healthy dogs were found to be heterozygous for the mutation, and most of them were parents or known close relatives of affected dogs. The affected and carrier dogs were distributed randomly across the entire population, indicating that this defect had been present in the population for some time. The authors of the study also note that the occurrence of the disease has been increasing, suggesting that the mutation has been under recent positive selection, just like in the Italian greyhound.

The mutation might be associated with a desired trait, explaining its recent increase in occurrence.

A 2019 study by Hytönen et al [20] identified two more recessive genetic alterations that are linked to amelogenesis imperfecta in dogs. Using whole-exome sequencing, the authors identified a missense variation in exon 8 of the *ENAM* gene, in three Parson Russel terriers littermates that presented with gingivitis, dental calculus, and a lack of normal enamel. This missense variation, affecting the same gene that is affected in Italian greyhound AI, results in a proline to leucine substitution. Screening 369 Parson Russel terriers, Hytönen et al note that the three affected littermates were homozygous for this variant, and 33 dogs were heterozygous, indicating a carrier frequency of 9% in the cohort.

An alternate genetic cause of AI was identified in Akitas by the same authors. Six Akitas were diagnosed with AI based on clinical signs and pedigree data suggesting an autosomal recessive disease. Five affected and eight unaffected dogs were genotyped, leading to the discovery of a 1 bp duplication in the *ACP4* gene, which has a known association with AI in humans. This duplication is predicted to cause a frameshift, resulting in a faulty amino acid sequence, which disrupts the transmembrane domain of the ACP4 protein, responsible for the dephosphorylation of enamel proteins [34]. All six initially identified dogs and two more littermates were homozygous for this variant of the *ACP4* gene, and 36 out of 151 other Akitas were heterozygous, indicating a carrier frequency of 18,6%. Screening of American Akitas (n = 197), Alaskan Malamutes (n = 36), Kai (n = 9), and Hokkaido (n = 3) breeds revealed one homozygote and 44 heterozygotes among American Akitas and no variants in the other related breeds.

4. Literature review
4.1 Enamel Hypoplasia in Canines
4.1.1 Prevalence studies

The earliest ever documented case of EH in canines is likely to be found among the Bonn-Oberkassel dog remains, which are estimated to be 14223 years old, the oldest domestic dog burial that we know of [35]. The Bonn-Oberkassel dog was a late juvenile, buried at approximately 27-28 weeks old, together with two adult humans and grave goods, showing its pet-like status. The lesions in the oral cavity indicate that the dog was gravely ill, and likely suffered from a canine distemper virus infection. There are visible dental lines suggestive of enamel hypoplasia at the 19-week developmental stage, the 21-week developmental stage, and the 23-week developmental stage. These changes are accompanied by severe periodontal disease, that may have been facilitated by the immunodeficiency caused by canine distemper virus infection.

In the currently published literature, four large cohort studies measure the prevalence of EH in populations of Grey Wolves, Arctic Foxes, Kit Foxes, or a combination of canids including domestic dogs. In a cohort of 207 Alaskan Grey Wolf (*Canis lupus*) skulls examined for dental and temporomandibular joint pathology, EH was present in five skulls (2.4%), affecting 8 teeth (0.1%) in total [36]. A study documenting craniomandibular trauma and tooth loss in archaeological remains of 544 dogs and wolves (*Canis lupus*) noted that the occurrence of EH was rare, with only 17 dogs and wolves (3.1%) affected, with dogs being affected slightly more often than wolves, though this was not statistically significant [37]. Mandibular canines were the most commonly affected teeth in both dogs and wolves. The macroscopic examination of 224 museum specimen Arctic fox skulls collected from Alaska, USA between 1931 and 2016, identified EH in 8 foxes (3.6%) [38]. Macroscopic examination of 559 Kit foxes (*Vulpes macrotis*) stored at the Museum of Vertebrate Zoology at the University of California, Berkeley, identified eleven foxes (2.0%) with lesions consistent with EH [39]. Comprehensive, large-scale studies documenting the prevalence of EH in dogs presented at the veterinary clinic are currently lacking in the literature,

though an excellent review article has been written about the diagnosis and treatment of developmental structural tooth defects in dogs by Boy et al [15].

4.1.2 Canine Distemper and EH

Canine distemper virus (CDV) infection has long been known to cause EH in dogs, as it has a specific tissue tropism that allows it to proliferate in the tissues of the developing tooth [22]. As mentioned earlier, a macroscopic examination of 224 Arctic Fox skulls identified 8 skulls with EH [38]. Coincidentally, all of these skulls were discovered on St. Matthew Island, Alaska, in 1963, strongly suggesting an infectious disease (likely to be canine distemper, which occasionally causes outbreaks in the area) as the cause of these lesions. Since the development and widespread implementation of vaccination as a preventative measure against canine distemper, the clinical occurrence of this disease has lowered, but eradication seems far from the horizon as not all vaccine administration results in the development of active immunity against CDV. A study that measured the response to CDV vaccination in healthy adult dogs noted that 5% of the vaccinated dogs turned out to be “humoral non-responders”, that had no antibody production against CDV after vaccination, whatsoever [40].

4.1.3 Trauma and EH

Trauma stands as another substantial contributor to EH in canids. A study examining dental abnormalities in immature dogs with a history of mandibular fractures reported that 16.1% of these dogs exhibited EH [41]. Boy et al report that in their two veterinary dental referral practices, FEH is the most common type of dog tooth abnormality, and bite wounds during the first 8-10 weeks of life are suspected to be the most common cause for FEH in their practices [15]. Veterinarians themselves might occasionally contribute to the pathogenesis of EH, as poorly performed extraction of deciduous teeth can be an iatrogenic cause of FEH. Though these appear to be the most common causes of trauma-induced EH, less acutely traumatic events such as chewing on wood are also suspected to cause FEH, as reported in a 14-month-old German Shepherd Dog with two small FEH lesions [42].

4.1.4 Nutritional Deficiencies and EH

Although relatively rare, nutritional deficiencies can lead to EH in canids. A case study involving a litter of 3-month-old Pharaoh hound puppies presented a unique example. Severe skin issues, inappetence, lethargy, and stunted growth in three out of five puppies led to a diagnosis of zinc deficiency [25]. Intravenous zinc supplementation partly alleviated their conditions, but the two surviving affected puppies continued to exhibit stunted growth and developed DEH in their permanent dentition. This case underscores the potential impact of nutritional deficiencies on dental development, an occurrence more commonly documented in humans.

4.1.5 Summarizing EH prevalence in canids

The limited epidemiological surveys that have been performed on these dental defects of dogs and other canids make it challenging to estimate the actual incidence rate of EH in these species. Based on the currently published epidemiological surveys, there is a documented 3.6% prevalence in Arctic Foxes [38], 2.4% in Alaskan Grey Wolves [36], 3.1% in a mixed cohort containing dogs and wolves [37], 2.0% in Kit Foxes [39], and 16.1% in immature dogs with a history of mandibular fracture [41], showing that this is a significant predisposing factor for the development of EH. Based on this data, it is reasonable to conclude that a 2-4% prevalence of EH is to be expected in canid populations, with a higher incidence rate in patient groups that are exposed to canine distemper infection and in those that suffer traumatic injuries to the dental regions early in life.

4.2 Enamel Hypoplasia in Felines

Scientific resources on EH in felines are incredibly scarce, with only a handful of mentions in the literature, and even gold-standard veterinary dentistry textbooks unable to give any details on prevalence and pathogenesis. EH of felines is commonly grouped and discussed together with EH of canines, about whom more specific information is available. Due to the close taxonomical relation between these families, both of them belonging to the order of Carnivora, it is likely that many aspects of canine EH pathogenesis also account for feline EH. Clinical experience has shown feline EH to be

much less common than canine EH [43]. The one large cohort study (n=301) done on dental pathology in cats that included looking for EH, also seems to be an interesting exception to the anecdotally prevailing trend of low incidence rates of EH in felines [44]. In said study, the skulls of adult feral cats from Marion Island, a sub-Antarctic Island, were examined macroscopically for congenital, developmental, and traumatic abnormalities. EH was found in 24.6% of the cases, which the authors themselves note is exceptional since EH is rather unusual in felines. It must be taken into consideration that these skulls originated from feral cats specifically, a population that is known to suffer higher incidences of dental pathology than the average household cat, so it is likely to not be representative of populations of cats kept as pets.

5. Clinical aspects of EH

5.1 Signalment and History

Lesions caused by EH can first become apparent from the time of eruption of the permanent dentition (6 months of age) or shortly thereafter when signs of wear start to manifest. Most case reports in the scientific literature discuss puppies, or juvenile dogs up to 14-16 months of age [42, 45, 46]. One case report discusses a 14-month-old cat [47]. The veterinary patient with clinically manifesting EH is likely to be diagnosed by the practitioner during its early stage of life. In the case of EH lesions that do not cause clinical discomfort or dental pathology that requires treatment, these lesions may be found incidentally, when the patient has aged well into adulthood. This developmental pathology is more common in dogs than it is in cats, though cats can still be affected by it. It is common for puppies to present with a history of febrile illness, particularly CDV infection.

5.2 Clinical Signs and Presentation

Enamel defects manifest as irregular, pitted, or flaky enamel surfaces, often accompanied by discoloration, which can range from subtle changes to more pronounced discoloration of the diseased enamel. In some cases, these defects can lead to the potential exposure of and staining of the underlying dentin, which may appear light brown. One of the prominent clinical signs associated with enamel defects is the early or rapid accumulation of plaque and calculus on the roughened tooth surface. This heightened plaque accumulation can contribute to gingivitis and accelerated periodontal disease. Additionally, affected teeth may become more prone to fractures, making them vulnerable to damage. Another notable clinical sign is the potential development of cold sensitivity in affected animals, often observed as an aversion to outdoor water or refrigerated foods, which can cause discomfort and avoidance [43].

EH lesions often co-occur with other dental or oral cavity conditions, which may either share a common etiology with EH (like CDV infection) or result from EH itself, such as increased plaque accumulation and its subsequent effects. An interesting clinical example of this is a 10-month-old

Tanzanian mixed-breed puppy that was presented at a clinic with multiple dental developmental abnormalities, including an impacted mandibular canine, first and third premolar tooth, a partially erupted maxillary canine tooth, oligodontia of a mandibular fourth premolar tooth, as well as EH of the maxillary and mandibular canine teeth, incisors, and premolars. The puppy had clinical canine distemper at the age of two months, with no history of other systemic or generalized infection prior to the time when the dental abnormalities were observed [46]. This CDV infection is the likely cause of the DEH, as well as other dental developmental abnormalities.

A 14-month-old German Shepherd Dog was initially evaluated because of an area of gingival recession involving the right mandibular first molar [42]. It was otherwise healthy, with an unremarkable physical examination. Oral examination revealed minimal plaque, calculus, and gingivitis, apart from more moderate gingivitis and gingival recession in the area of the right mandibular first molar. Two small enamel defects consistent with FEH became apparent at the mesiobuccal aspect of the mesial cusp and the distal aspect of the central cusp of this tooth (**Fig. 3**).

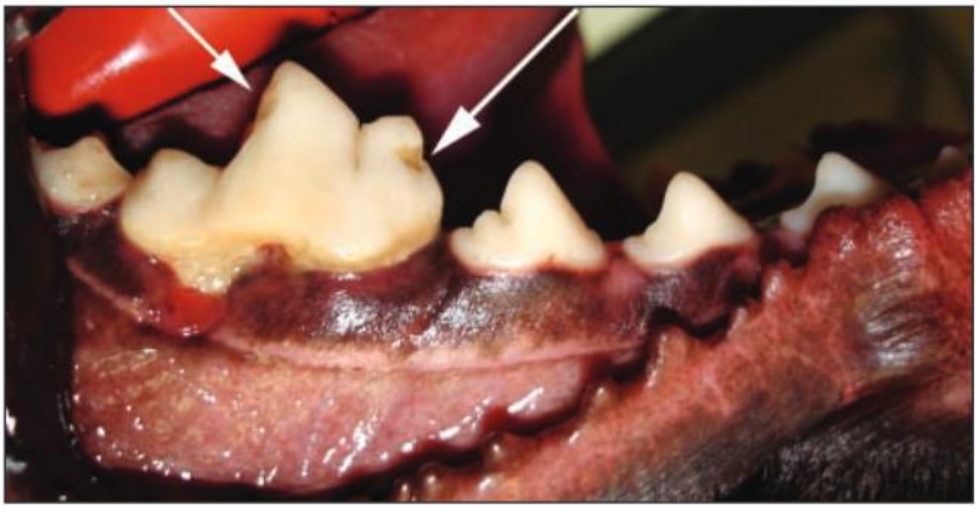

Figure 3*: The gross appearance of the right mandibular first molar in German Shepherd Dog examined because of gingival recession involving this tooth. Notice the enamel defects consistent with FEH on the mesial aspect of the mesial cusp and the distal aspect of the central cusp of this tooth (white arrows). Taken from Lommer, M. J., 2008* [42].

5.3 Diagnosis

5.3.1 Differential diagnosis

The following dental lesions can be similar in appearance to focal or diffuse EH, and must be taken into consideration while reaching a diagnosis:

- Amelogenesis imperfecta
- Enamel staining due to tetracycline therapy
- Tooth resorption
- Dental caries

Amelogenesis imperfecta (**Fig. 4a**) is a hereditary disease that leads to EH. It has been elaborately discussed in section 3.3. So far, AI has been reported in Swedish Standard Poodles, Italian Greyhounds, Samoyed dogs, the Parson Russel Terrier, and the Akita [18–20, 30]. When a patient of these breeds is affected by EH, it is of relevance to question the owner about the dentition of close ancestors and offspring, if possible. This is of particular importance in patients used for breeding.

Embryos, infants, and juveniles who receive tetracycline therapy (or who are exposed to it in the womb) are prone to developing varying degrees of permanent discoloration [15]. The likelihood and amount of discoloration are directly related to the total quantity of tetracycline absorbed during embryogenesis and tooth development. If present in the bloodstream, this drug can be deposited in the developing enamel and dentin of teeth as tetracycline-calcium-orthophosphate. This complex causes discoloration upon eruption and exposure to sunlight. Tetracycline-stained teeth can range from deep yellow to a greyish-dark discoloration, with or without banding, depending on the long- or short-term ingestion of these antibiotics [48]. This staining, though aesthetically unpleasing, does not affect the structural integrity of the dental hard tissue and does not require treatment in affected patients (**Fig. 4b**).

Tooth resorption (TR) is a disease of felines, defined by the resorption of dental hard tissues by odontoclasts. Resorption can be classified as external or internal in origin and has many different causes, including periapical

disease after pulpal inflammation or infection, trauma, iatrogenic irritation or infection of the pulp, and more [43]. In cats, the disease ranges in prevalence from 25 to 75%, and in dogs, it is rarely reported. Patients affected by TR might have fractured crowns, “red spots” at the cervical portion of the teeth, or missing teeth (**Fig**. **4c**). Gingiva is frequently bulgy in appearance, inflamed, and friable in areas of missing teeth.

Dental caries is the decay of dental hard tissues due to the effect of oral bacteria on the fermentable carbohydrates on the tooth surface. It is not common in domestic dogs but does occur, with a reported 5.3% of dogs one year or older having one or more caries lesions in a study that reviewed the dental records of 435 dogs [49]. A clinical caries appears as a structural defect on the surface of the crown or root, frequently filled with or lined by dark, soft, necrotic dentin. This dentin can be removed with a dental excavator (**Fig. 4d**).

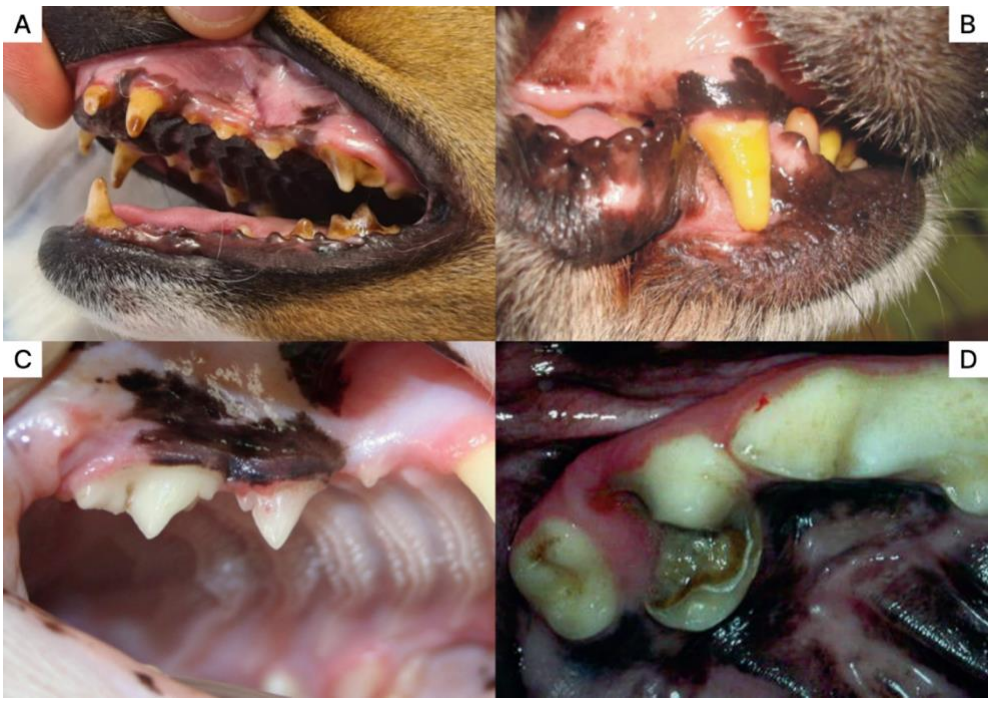

Figure 4*: Enamel hypoplasia and its main differentials. A Danish-Swedish Farm dog affected by diffuse enamel hypoplasia (A) with a suspected hereditary component, picture taken by the author of this thesis. The bright-yellow discoloration of the teeth (B) in a patient that was on confirmed tetracycline treatment as a puppy, and had no structural defects of the enamel on clinical examination, taken from Boy et al* [15]*. Loss of dental hard substance and "red spots" (C) on tooth 107 of a cat affected by tooth resorption, taken from Blackwell's five-minute Veterinary Consult Clinical Companion small animal Dentistry* [43]*. A large carious lesion (D) of the right maxillary first molar tooth of a dog, with much of the crown missing already, taken from Blackwell's five-minute Veterinary Consult Clinical Companion small animal Dentistry* [43].

5.3.2 Diagnostics

The experienced veterinary practitioner may be able to identify dental lesions suspicious for EH through visual inspection. A thorough and complete oral examination is essential to notice the current state of the dentition, as well as any pathologies possibly affecting the teeth. This comprehensive examination should go beyond detecting lesions suspicious for EH; it might reveal other comorbidities affecting the teeth and oral cavity, such as periodontal disease, tooth fractures, or tumors. By carefully evaluating the entire oral cavity, the

veterinarian can gather crucial diagnostic clues, helping in the process of narrowing down the list of differentials and ultimately achieving an accurate diagnosis. Furthermore, early detection of these additional dental issues can lead to timely intervention and improved patient outcomes.

Additional diagnostics such as a complete blood count, biochemistry, and urinalysis can play important roles in ruling out systemic disease and providing beneficial information to base a diagnosis on. Routine preoperative diagnostics must also not be left out if the patient will be put under general anesthesia.

Imaging plays an essential role in determining the course of treatment for patients with EH. Prior to therapy, dental radiographs must be taken to evaluate whether tooth non-vitality or root malformation is present. In case of extensive root dysplasia (**Fig**. **5**), malformation, or non-vitality, restorative treatment will no longer be effective, and extraction of the affected tooth might be the recommended course of action.

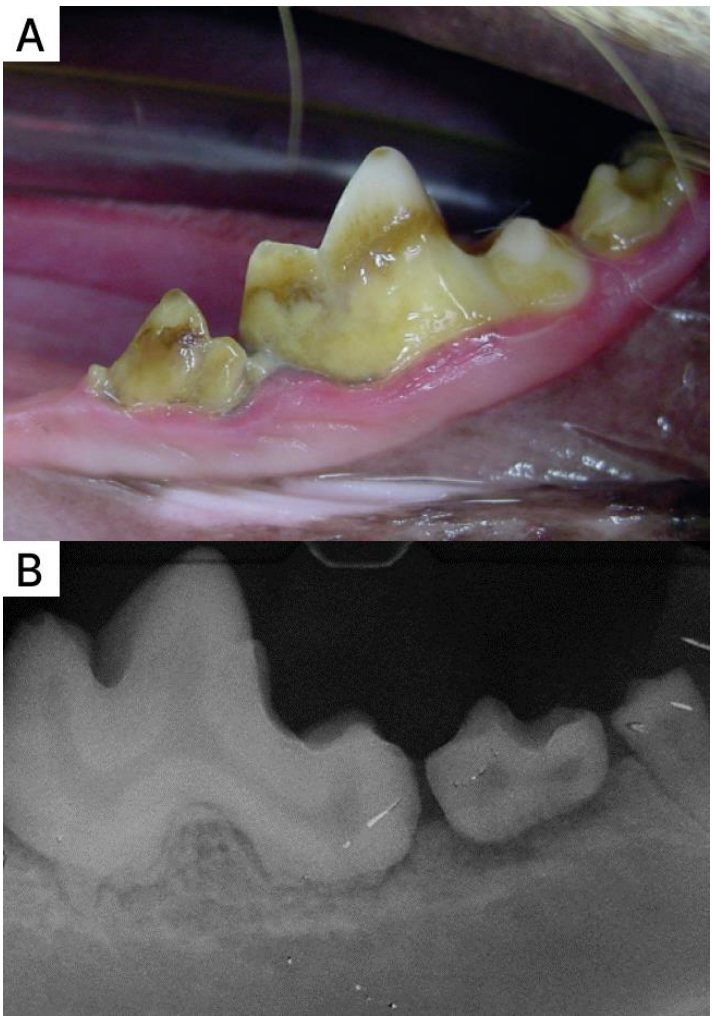

Figure 5*: Generalized hypomineralized EH (A) of the mandibular teeth of a dog. A radiograph of the same teeth (B) showing extensive root dysplasia. Pictures taken from Blackwell's five-minute Veterinary Consult Clinical Companion small animal Dentistry* [43].

5.4 Treatment and Management

The treatment of EH is dependent on the extent of the lesions and the available equipment and materials. If the patient is exhibiting the clinical signs discussed in section 5.2, prompt therapy is critical to the health of the patient. The treatment goals for a patient with EH include removing the sensitivity of the affected area, removing endodontic infection by occluding the dentinal tubules, and smoothening the tooth to decrease plaque accumulation, prioritizing giving the affected area the smoothest possible surface [8].

There are four treatment options:

1. Composite restoration.
2. Crown therapy.
3. Smoothing and bonded sealant application.
4. Extraction.

Composite restoration is the most effective way to achieve the treatment goals and has the added benefit of improving tooth appearance. This treatment can be applied mainly to focal defects. It requires appropriate skill levels and a light curing unit, which might not be available in some first-line veterinary practices. It is also not guaranteed that this treatment will hold up over the lifetime of the patient, so repeated treatments may be required.

Sittijrajusub et al have written an excellent case report on a dog with diffuse EH that was treated with composite restoration and reexamined for 6- and 20-month follow-ups [50]. The patient, a one-year-old, spayed female Welsh Corgi dog, was diagnosed with DEH, with no evidence of endodontic disease or malformation of the tooth root (**Fig**. **6a**). A restorative procedure with nanohybrid composite resin was performed. First, supragingival calculus was removed by a Magnetostrictive ultrasonic scaler, followed by hand scaling and curette to ensure complete removal. After that, subgingival scaling was applied, using a subgingival curette that was gently inserted into the pocket to remove calculus. Next, the teeth were polished to smooth the surface, with a prophy cup with a slow-speed handpiece. The restoration process was then initiated by delimination of the tooth irregularities with a

high-speed dental handpiece using a round diamond bur. Etching was then performed to demineralize the enamel and promote attachment of the bonding agents to the surface areas. A single-component adhesive system was used on the dentin and enamel, air blown, and light cured for 20 seconds. Following this bonding agent, a nano-hybrid composite shade A2 was used to fill the defect and light cured for 20 seconds. The contour was defined using a sanding disc and final polishing was performed (**Fig**. **6b**) [50].

No evidence of pain or discomfort was detected in the patient a day after the restoration. During a 6-month follow-up, most of the restorative material was still in place, with a few exceptions. There was dental tartar accumulation with mild gingivitis, even though the owner brushed the dog's teeth every day and fed it with dry food (**Fig**. **6c**). At the 20-month follow-up, there was dental tartar accumulation with mild gingivitis and mild halitosis. Dental scaling and polishing were repeated. Most of the restorative material had stayed in place (**Fig. 6d**).

Crown therapy, through the application of a cast metal crown, can be performed if damage to the tooth is severe and a permanent correction is sought after.

Though considered a suboptimal treatment, smoothing and bonded sealant application can be performed in those cases with limited financial means, or to treat lesions that are minor or affecting nonstrategic teeth. The bonding agent is used to seal exposed dentinal tubules and protect the surface of the tooth. This treatment of often used to resolve sensitivity, block infection, improve aesthetics, and smooth the tooth in case of an uncomplicated crown fracture. First, the tooth is scaled and polished. Any damaged enamel is removed with a fine diamond bur or white stone [51].

The area is then smoothened to prepare for bonding. Acid etching with 37% phosphoric acid is done to remove impurities from the tooth surface and to slightly demineralize it. This will lead to increased surface area for bonding. One- or two-step bonding agents can be used and should be applied in a very thin layer. It is light cured for 10 seconds. A layer of unfilled resin

can be applied over one-step bonding agents to add strength and smoothness to the restoration. This resin layer should also be light-cured [51].

Extraction of affected teeth is an option, though it is generally not recommended, unless the root is significantly malformed or if the tooth is radiographically nonvital (**Fig**. **5**) [43].

It is important to inform owners of a patient affected by EH that further degeneration of the remaining enamel can occur, and that additional therapy might be a necessity in the future. Affected teeth can also become non-vital over time, requiring root canal therapy or extraction. Regular professional dental cleaning and a routine home care program are recommended to these owners, including weekly application of stannous fluoride at home. Owners must be reminded to minimize the ingestion of this fluoride, because of its toxicity. Owners must also be advised to prevent their pets from chewing on hard objects [43].

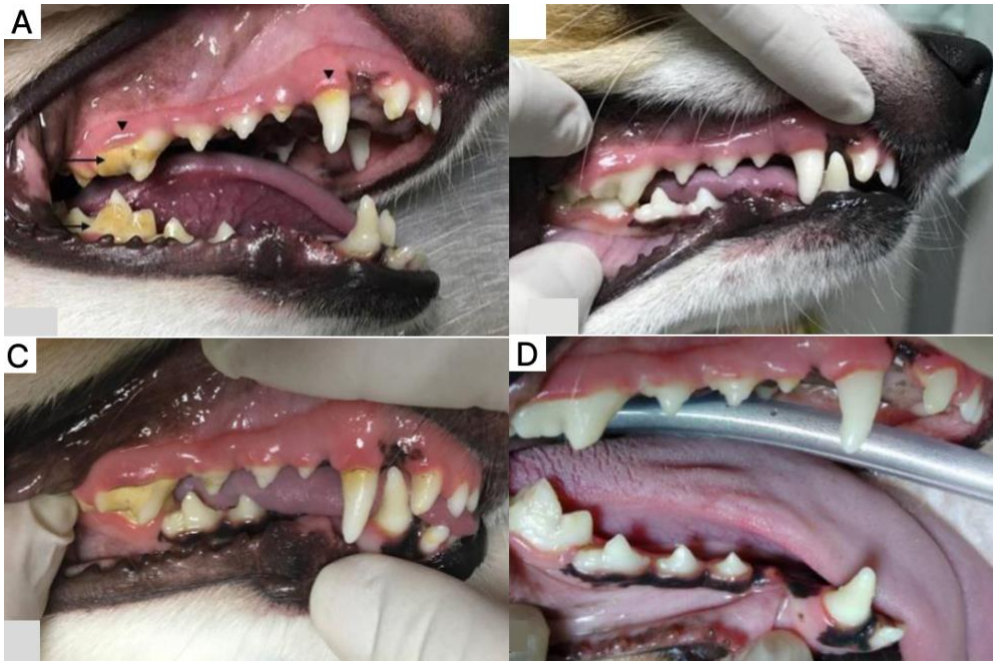

***Figure 6**: Oral examination of a 1-year-old Welsh Corgi (A) in left lateral recumbency, showing diffuse lesions of pits, irregular surface, plaque, and accumulation on the crowns, as well as gingival hyperemia on the right side of the mouth before treatment. A week after treatment (B) smoother tooth surfaces are visible on the right side of the mouth. Six months after treatment (C) the oral examination showed smooth tooth surfaces, with some dental tartar accumulation and gingivitis. Twenty months after treatment (D) dental scaling and polishing were repeated and most restorative material remains intact. All pictures are taken from Sittijrajusub et al* [50].

5.5 Prevention, breeding practices

Since EH can have a range of acquired causes, several things can be done to prevent the development of this dental pathology. First off, to minimize EH from an infectious and pyretic origin, it is essential to vaccinate puppies of the appropriate age against CDV, a common infectious cause of EH. The limitations of this preventative strategy should be known. Though vaccinated individuals are better protected against the disease, they are not fully immune, and might still suffer infection. Other infectious pathogens that affect puppies during the sensitive stage of amelogenesis and can cause high fevers, such as canine parvoviruses and enteric and respiratory canine coronaviruses, must also be avoided. Vaccinations are available against canine parvovirus, though these do not confer complete immunity. Vaccinations are also available against the enteric as well as the respiratory canine coronavirus, though these do not provide cross-protection against each other. Taking into consideration the limitations of preventative vaccination, it is prudent to keep dogs below the age of 12 weeks away from unknown dogs, dog parks, and kennels.

Since the development of the dental hard tissues happens during the first few weeks of life, and trauma to these tissues in this period can cause lifelong developmental defects, it is advisable to not allow dogs in this age group to chew on hard objects. A bite to the oral region by another dog was noted as a common traumatic cause for FEH by Boy et al [15]. Though any dog owner would be wise to avoid interactions between their pet and aggressively behaving dogs, it bears mentioning here.

The prevention of the hereditary version of EH, amelogenesis imperfecta, is another matter altogether. Due to the hereditary nature of this disease, breeding practices must be altered to avoid including individuals affected by EH, particularly those affected by DEH, in the breeding roster. In Standard Poodles, Italian Greyhounds, Samoyed Dogs, Parson Russel Terriers, and Akitas, a hereditary cause for DEH should be considered by the veterinarian upon diagnosis. There are suspected to be additional dog breeds affected by amelogenesis imperfecta, so breeders owning dogs of other breeds

affected by DEH should be encouraged to investigate their breeding records for related individuals affected by similar lesions. In Italian Greyhounds, the exact 5 bp deletion responsible for causing the disease was identified and a genetic test was developed to enable breeders to identify and manage the trait [18]. A test was developed to identify the 21 bp insertion causing AI in Samoyed Dogs as well as the mutations in Parson Russel Terriers and Akitas, though the authors do not mention whether this test will be made available for breeders [19]. In the Swedish Standard Poodle, no attempt was made to identify the genetic culprit.

5.6 Future perspectives

The prevalence of amelogenesis imperfecta, which appears to have been under unintentional selection in Italian Greyhounds and Samoyed dogs over the last few decades, can be kept at a low through diligent breeding practices with veterinary involvement. Now that a hereditary component has been confirmed in these breeds, as well as in the Swedish Standard Poodle, Parson Russel Terrier, and Akitas, breeders of these dogs should be educated about the hereditary defect. Aiding the breeders in recognizing the hereditary nature of the disease is half of the work. Veterinarians should be made knowledgeable about the hereditary etiology of AI and encourage investigation in breeding dogs affected by DEH. If sufficient awareness is spread, a strong increase in individuals affected by AI should not be expected.

There is a suspicion that additional dog breeds are affected by hereditary EH. Investigation and identification into the hereditary aspect of clusters of related individuals affected by EH could be of high value in identifying other breeds in which a genetic etiology can be recognized.

With veterinary care in general, and veterinary dentistry in particular on the rise, the author of this thesis expects the quality and quantity of veterinary dental care to go up in the coming decades. There are currently a variety of treatment options available for patients affected by EH, and future developments are expected to make these treatments more effective and affordable. The emphasis on dental care in veterinary studies and the number

of veterinary practitioners who dedicate their careers to veterinary dental care is growing.

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I could not have done it without you all.

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Thesis progress report for veterinary students

Name of student:	**Anne Camilla Eklund Arnesen**
Neptun code of the student:	MYSWLH
Name and title of the supervisor:	Dr. habil. Miklós Pál Dunay, DVM, PhD, Assoc. Prof.
Department:	Department and Clinic of Surgery and Ophthalmology
Thesis title:	**Enamel hypoplasia in small animals – literature review**

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022	09	16	Choosing the topic	
2.	2023	03	05	References and outline	
3.	2023	03	20	Checking progress	
4.	2023	06	13	Checking progress	
5.	2023	06	21	Assessing progress	

Thesis progress grade achieved at the end of the first semester: 5

Consultation – 2nd semester

Timing				Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	10	08	Checking progress	
2.	2023	10	15	Proofreading	
3.	2023	10	30	Checking draft	
4.	2023	11	01	Checking final draft	
5.	2023	11	03	Submitting thesis	

Thesis defence grade achieved at the end of the second semester: 5

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

ÁLLATORVOSTUDOMÁNYI EGYETEM Sebészeti és Szemészeti Tanszék és Klinika BUDAPEST

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis: 03.11.2023