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ORIGINAL ARTICLE

Intragenic *PNPLA1* duplication in Labrador retrievers with nonepidermolytic ichthyosis

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Abstract

Background: Ichthyoses represent a heterogeneous group of cornification disorders characterised by epidermal scaling.
Objectives: To describe the clinical, histopathological and genetic analysis of a Labrador retriever with nonepidermolytic ichthyosis, and the results of a population screening for a newly detected *PNPLA1* genomic duplication.
Animals: Two 7-year-old male littermates, 531 population samples.
Materials and Methods: Clinical and histopathological analysis, whole genome sequencing and digital PCR-based genotyping were performed.
Results: Generalised scaling and histological laminar orthokeratotic hyperkeratosis confirmed the ichthyosis diagnosis on Dog 1. Dog 2 showed mild clinical signs possibly associated with allergies and not ichthyosis. The genome of Dog 1 was sequenced and compared to 1469 genetically diverse control genomes. The analysis identified a 6099-bp duplication spanning three internal exons of the PNPLA1 gene, which is predicted to result in an altered C-terminal tail of the protein, NP_001277038.2:p.(E558Lfs*17). Dog 2 had a heterozygous genotype and carried one copy of the duplicated *PNPLA1* allele. Of the screened 531 additional Labrador retrievers, 491 were homozygous wild-type, 36 were heterozygous carriers and four carried the duplication in a homozygous state.
Conclusions and Clinical Relevance: Previously identified *PNPLA1* variants cause autosomal recessive ichthyosis in golden retrievers and humans. Given the well-established function of *PNPLA1*, the identified genomic duplication represents a likely candidate causal variant for the observed ichthyosis in the examined Labrador retriever. This is the first report of a new form of autosomal recessive ichthyosis in Labrador retrievers, which provides the basis for genetic testing.

KEYWORDS
dog, genetics, genodermatosis, ichthyosis

INTRODUCTION

The term ichthyosis describes a heterogeneous group of hereditary cornification disorders which affect humans and animals alike.[1] Ichthyoses are associated with skin barrier dysfunction and are clinically characterised by dry scaly skin, which is an adaptive response to repair the damaged barrier.[2] The skin barrier is formed by the following main elements: keratin and filaggrin and their degradation products; the cornified cell envelope (CE); the corneocyte lipid envelope (CLE); and the intercellular lipid layers.[3] The

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CLE connects the CE to the intercellular lipid layer and mainly comprises long-chain acylceramides.[3,4] Acylceramides are essential lipids for skin barrier formation, and alterations in the functionality of enzymes such as acyltransferase, which are involved in acylceramide production, can play a role in ichthyosis pathogenesis.[3]

Based on histological findings, ichthyoses can be subdivided into epidermolytic and nonepidermolytic forms. Epidermolytic ichthyoses are exclusively caused by defects in genes encoding keratins.[2] Nonepidermolytic ichthyoses have been clinically characterised in several dog breeds and can be caused by genetic variants in different genes.[5] To date, causative variants in three genes related to lipid metabolism have been described in dogs with ichthyosis. They comprise an indel variant in *PNPLA1* in golden retrievers (OMIA:001588–9615),[1] a frameshift deletion in *ABHD5* in golden retrievers (OMIA:002368–9615)[6] and a missense variant in *SDR9C7* in a Chihuahua (OMIA:002659–9615).[7]

Nonepidermolytic ichthyosis has been anecdotally reported in Labrador retrievers based on histological features;[2] yet no further tests have been performed. The objective of this study was to investigate the clinical, histopathological and genetic aspects of nonepidermolytic ichthyosis in a Labrador retriever, and to describe the results of a population screening for a newly detected *PNPLA1* genomic duplication, thereby providing the basis for genetic testing in this breed of dogs.

MATERIALS AND METHODS

The collection of samples from the two Labrador retriever littermates (Dog 1 and Dog 2) was performed for diagnostic and therapeutic reasons and did not constitute an animal experiment in the legal sense.

The two Labrador retriever dogs went through physical and dermatological examinations, and cytological and genetic evaluations. Histopathological evaluation was performed for Dog 1. Four 8 mm punch biopsies were taken at the dorsum and base of the tail of Dog 1, and routinely processed for histopathological investigation. Haematoxylin and eosin-stained slides were reviewed by a board-certified veterinary pathologist (DJW). Ethylenediaminetetraacetic acid blood samples for DNA isolation were obtained from both dogs. The genome of Dog 1 was sequenced at ×26.7 coverage on a Novaseq 6000 instrument (Illumina). Mapping to the UU_Cfam_GSD_1.0 reference genome assembly and variant calling were performed as described previously.[8]

Genotyping assays for the *PNPLA1* duplication

Two assays were developed to determine the presence of the 6099-bp *PNPLA1* duplication and the number of copies of the *PNPLA1* in positive samples. Details of the genotyping assays can be found in Methods S1 in the Data S1.

Population screening for the *PNPLA1* duplication

Five hundred thirty-one pure-bred (owner-reported) Labrador retrievers from North America were screened for the *PNPLA1* genomic duplication using banked blood or buccal swab samples. The samples were previously submitted to the Veterinary Genetics Laboratory at the University of California for different genetic testing. A consent form was signed by each owner for the use of banked samples for research purposes.

RESULTS

Clinical investigation

Dog 1 was a 5-year-old male, neutered, black Labrador retriever that initially presented to the Dermatology service at the University of Ilinois Veterinary Teaching Hospital for evaluation of chronic interdigital furunculosis as a result of allergic dermatitis and secondary deep pyoderma. Based on medical records, the dog had experienced clinical signs of pruritus and pododermatitis for several years. At physical examination, additional generalised scaling with prominent large scales on the dorsal thorax and lumbar areas and base of the tail was observed (Figure 1). The scaling was reported to have been present for several years previously. Cytological results from the exudative erythematous lesions on the paws revealed pyogranulomatous inflammation, cocci and rod bacteria, while skin cytological results from dorsal areas with scales were unremarkable. A tapering course of glucocorticoids and antibiotics was prescribed to address the suspected allergic dermatitis and secondary pyoderma. At a subsequent recheck 2 months later, the pruritus had improved, and the bacterial infection had resolved. Ciclosporin was prescribed as a long-term maintenance treatment for allergic disease. The dog continued to have generalised scaling that now involved the face bilaterally. At a subsequent recheck 4 months later, cytological findings of areas of increased scaling on the ventral abdomen and lateral thorax were unremarkable. Owing to clinical suspicion of ichthyosis, a biopsy was taken.

Histopathological investigation

Histopathological examination revealed an expansion of the stratum corneum (SC) by laminar orthokeratotic hyperkeratosis with small clefts between keratin layers (Figure 2). The epidermis had a normal thickness, and no inflammation was present. The clinical signs, together with the histopathological findings, led to the diagnosis of nonepidermolytic ichthyosis.

Dog 2 was a 7-year-old male, neutered, black Labrador retriever, seen at the Dermatology service 2 years after the diagnosis of nonepidermolytic ichthyosis of his littermate (Dog 1). At the time of the visit, Dog 2 was presented with fine small scales most prominent along the dorsum and the base of the tail. He was also reported to have seasonal pedal pruritus that was not under management. The

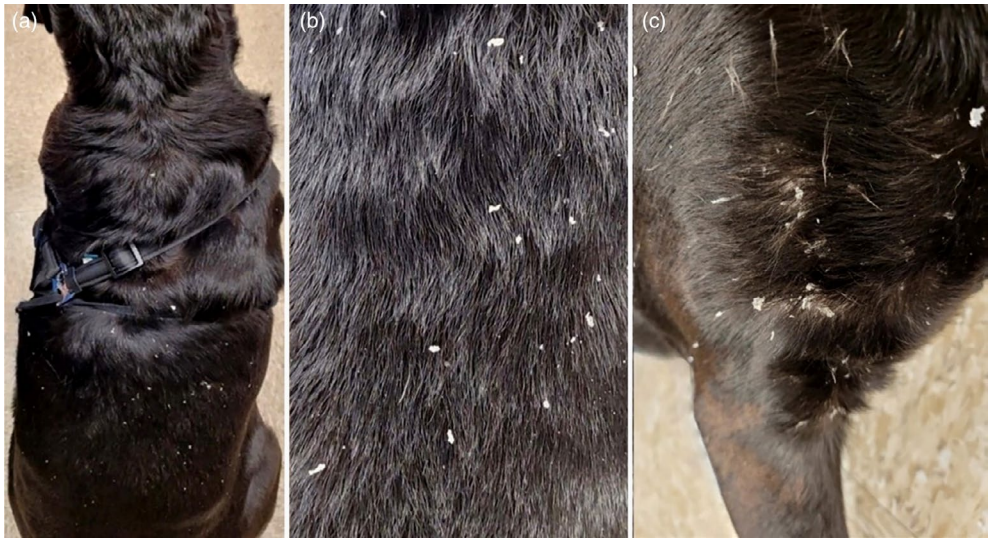

FIGURE 1 Labrador retriever (Dog 1) with nonepidermolytic ichthyosis. (a) Generalised large white scales along the dorsum, (b) closer image of large white scales at dorsum and (c) at dorsal lumbar/tail base area.

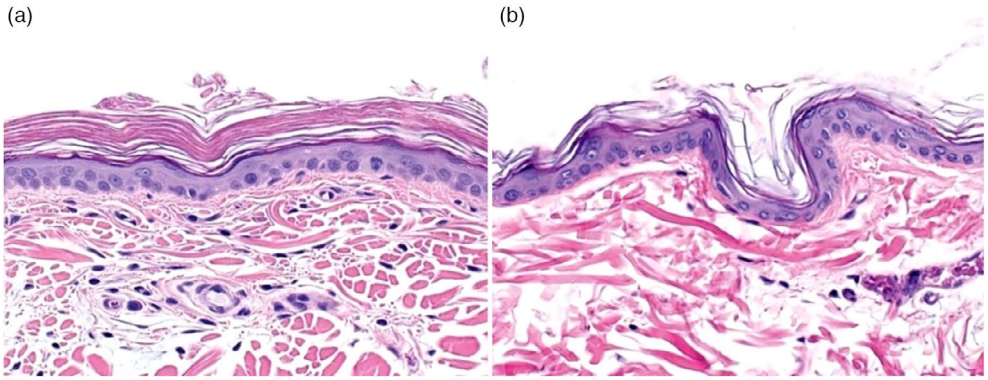

FIGURE 2 (a) Histological results of Dog 1: Lamellar, orthokeratotic hyperkeratosis. Note the small clefts between keratin layers. Haematoxylin and eosin, ×400. (b) Histological results of normal skin of a Labrador retriever: Normal thickness stratum corneum, orthokeratotic basketweave keratin. H&E, ×400.

mild generalised scaling had reportedly been present for several years. The cytological findings of the dorsal thorax and dorsal lumbar areas were unremarkable.

Genetic analysis

The whole genome of Dog 1 was sequenced and compared to 1469 control genomes. This initial analysis revealed 40 heterozygous and nonhomozygous private protein-changing variants (Tables S1 and S2). However, none of these variants occurred in a curated set of ichthyosis candidate genes (Table S3). We then inspected the whole genome sequencing data of these candidate genes using the Integrative Genomics Viewer (IGV).[9] This revealed a homozygous duplication of 6099 bp in the *PNPLA1* gene, including exons 7–9 of the gene's 1 exons (Figure 3). The variant can be designated as Chr12:5,596,853_5,602,951dup (UU_Cfam_GSD_1.0) or NM_001290109.2:c.1361_1671dup. Assuming that splicing is not altered and that the transcript is not completely degraded by nonsense-mediated decay, the duplication is predicted to replace the last eight codons of the wild-type (WT) open reading frame (ORF) protein with 16 different codons before a stop codon emerges, NP_001277038.2:p.(E558Lfs*17).[10] The presence of the duplicated allele in both affected Labrador retrievers was verified by successful PCR amplification across the junction of the two copies in the tandem duplication. Dog 2 carried the duplication in a heterozygous state.

Population screening for the *PNPLA1* duplication

Among 531 additionally screened Labrador retrievers, 92.47% (n=491) were homozygous WT, 6.78% (n=36) genotyped as heterozygous carriers and 0.75% (n=4) carried the duplication in a homozygous state. The allele frequency for the *PNPLA1* duplication in this sample set is 4.14%. One owner-reported Labrador retriever–unknown cross was genotyped as a heterozygous carrier for the duplication. In the absence of selective breeding, disease incidence in the population is predicted to be 1 in 585.

Medical records of two of the four homozygous Labrador retrievers were available for review. One dog was 3 years old and clinically diagnosed with ichthyosis at 8 weeks of age owing to excessive scaling. The cutaneous signs improved without treatment after

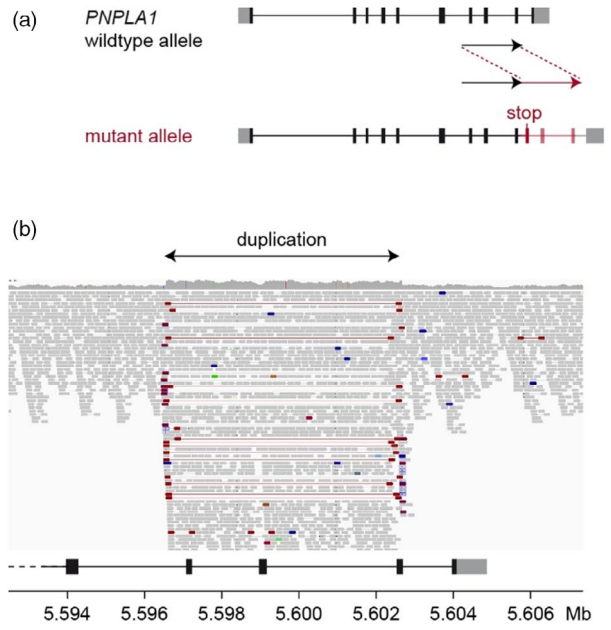

FIGURE 3 Details of the *PNPLA1* duplication. (a) Schematic illustration of the genomic organisation of the *PNPLA1* gene. The wild-type gene has 10 exons. The 6099-bp genomic duplication harbours exons 7–9 and results in a new stop codon. (b) Visual representation of the short-read alignments of the WGS data to the reference genome illustrates a twofold increased coverage of sequence reads across the duplicated region. Furthermore, read pairs with unexpected read orientations at the junction of the duplicated sequence are highlighted in red. The position on chromosome 12 is indicated at the bottom.

2 months, and no other lesions had been observed since then. The second dog was a 1-year-old male that reportedly had a normal dermatological examination since birth. His dam had been having intermittent skin lesions for the past few years; yet a definitive diagnosis had not been determined at the time of writing.

DISCUSSION

Herein we report the clinical, histopathological and genetic evaluation of a Labrador retriever with nonepidermolytic ichthyosis. Given the well-established function of *PNPLA1*, the identified intragenic genomic duplication represents a likely candidate causal variant for the observed ichthyosis in the studied dog.

The role of *PNPLA1* variants causing autosomal recessive ichthyosis has been initially discovered in golden retrievers and only subsequently in human patients.[1,11] *PNPLA1* codes for a protein with the officially approved name 'patatin like phospholipase domain containing 1' that is important in the formation of the epidermal lipid barrier. The PNPLA1 protein is a transacylase catalysing the last step of the acylceramide production pathway, which involves the transfer of a linoleic acid from a triglyceride to an N-(ω-hydroxy-ultra-long-chain fatty acyl)-sphingoid base.[12] Acylceramides participate in the organisation and function of lipid lamellae in the SC as well as the formation of the CLE, and are thus essential for providing the barrier function of the skin.[13]

Golden retrievers with *PNPLA1*-related ichthyosis present with generalised scaling[2] characterised by small-to-large whitish or dark scales. The distribution may vary over different areas of the body, with the trunk area being most prominently affected.[14] Pruritus is not a feature of the disease unless secondary pyoderma or allergic skin disease develops concomitantly.[15] The mutant *PNPLA1* allele is very common in golden retrievers. Different studies found the homozygous mutant *PNPLA1* genotype in 28%–32% and a heterozygous (carrier) genotype in 48%–53% of randomly selected golden retrievers.[16–18]

Dog 1 was homozygous for the identified *PNPLA1* duplication and presented with generalised large soft white scales over the dorsum and lateral face. The clinical presentation of Dog 1 was comparable to those of golden retrievers with *PNPLA1*-related ichthyosis.[2] Pruritus and pododermatitis were present in addition to the scaling in Dog 1, and these lesions were attributed to an allergic disease with a secondary bacterial skin infection. Antibiotics and allergy treatment improved the pruritus and the pododermatitis, yet did not improve the generalised scaling. Dog 2 carried the duplication in a heterozygous state and presented with less evident clinical signs, characterised by small white scales over the dorsum. This clinical presentation, along with the historical pedal pruritus, was suspected to be associated with an allergic disease and not ichthyosis. Specific treatment to address the scaling was not pursued for both dogs.

One of the four Labrador retrievers identified in the population screening showed clinical signs of ichthyosis at a young age. The second dog had never shown signs of dermatological disease at the time of writing. These findings are consistent with those reported for golden retrievers, which can have a mild clinical presentation of ichthyosis, and some dogs with the homozygous mutant genotype can still have clinically normal skin.[5,16]

Histologically, lesions in Dog 1 were similar to the *PNPLA1*-related golden retriever ichthyosis. Perinuclear clear spaces of keratinocytes within the granular cell layer seen in the golden retriever ichthyosis[16] were not observed in the examined sections of Dog 1. However, more cases in Labrador retrievers are needed to further investigate this feature.

In conclusion, we describe a new form of mild nonepidermolytic ichthyosis in Labrador retrievers. The mode of inheritance is autosomal recessive. We identified a duplication spanning three internal exons of *PNPLA1* as the likely causative variant. To the best of our knowledge, this is the second reported pathogenic *PNPLA1* allele in dogs and the first in Labrador retrievers. Our findings enable genetic testing to confirm the diagnosis in other affected Labrador retrievers without the need to obtain skin biopsies. Disease allele frequency data suggest that this variant is currently not under negative or positive selection. Genetic testing will be important for breeders to avoid the mating of carriers, so that the unintentional breeding of further affected dogs can be avoided.

AUTHOR CONTRIBUTIONS

Stefan J. Rietmann: Conceptualization; investigation; visualization; writing – original draft; writing – review and editing. **Jennifer L. Clegg:** Conceptualization;

investigation; project administration; writing – original draft; writing – review and editing. **Vidhya Jagannathan:** Methodology; data curation; writing – review and editing. **Dominique J. Wiener:** Conceptualization; investigation; writing – review and editing. **Angelica Kallenberg:** Investigation; methodology; writing – review and editing. **Robert A. Grahn:** Investigation; methodology; writing – review and editing. **Clarissa P. Souza:** Conceptualization; funding acquisition; investigation; methodology; writing – original draft; writing – review and editing. **Tosso Leeb:** Conceptualization; funding acquisition; investigation; methodology; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

RAG and AK are employees of a commercial genetic testing laboratory. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data are freely available. Accessions for the whole genome sequence data are given in Table S1 in Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Zusammenfassung

Hintergrund: Die Ichthyose repräsentiert eine heterogene Gruppe von Verhornungsstörungen, die durch epidermale Schuppenbildung charakterisiert werden.

Ziele: Die Beschreibung der klinischen, histopathologischen und genetischen Analyse eines Labrador Retrievers mit nicht-epidermolytischer Ichthyose und die Ergebnisse eines Populations-Screenings für eine neu entdeckte *PNPLA1* genomische Duplikation.

Tiere: Zwei 7-Jahre alte Wurfgeschwister, bei eine Populationsanzahl von 531.
Materialien und Methoden: Eine klinische und histopathologische Analyse, Gesamtgenom Sequenzierung und eine digitale PCR-basierte Genotypisierung wurden durchgeführt.
Ergebnisse: Eine generalisierte Schuppen-bildende und histologisch laminäre orthokeratotische Hyperkeratose bestätigte die Diagnose einer Ichthyose bei Hund 1. Hund 2 zeigte milde klinische Zeichen, die eventuell mit Allergien und nicht mit einer Ichthyose im Zusammenhang auftraten. Das Genom des Hundes 1 wurde sequenziert und mit 1.469 genetisch unterschiedlichen Kontroll-Genomen verglichen. Die Analyse identifizierte eine Duplikation von 6.099-bp, die sich über drei interne Exons des PNPLA1 Gens ausdehnte, wodurch vorausgesagt werden kann, dass dies in einem veränderten C-Terminal Ende des Proteins NP_001277038.2:p. (E558Lfs*17) resultieren wird. Hund 2 zeigte einen heterozygoten Genotyp und trug eine Kopie des duplizierten *PNPLA1* Allels. Von den 531 zusätzlich gescreenten Labrador Retrievern trugen 491 den homozygoten Wild-Typ, 36 waren heterozygote Träger und vier trugen eine Duplikation des homozygoten Status.
Schlussfolgerungen und klinische Bedeutung: Zu früheren Zeitpunkten identifizierte *PNPLA1* Varianten verursachen autosomal rezessive Ichthyosen bei Golden Retrievern und beim Menschen. Aufgrund der gut untersuchten Funktion des *PNPLA1* repräsentiert die identifizierte genomische Duplikation aller Wahrscheinlichkeit nach einen Kandidaten, der ursächlich ist für die Variante der beobachteten Ichthyose bei dem untersuchten Labrador Retriever. Es handelt sich hierbei um den ersten Bericht einer neuen Form der autosomal rezessiven Form der Ichthyose bei Labrador Retrievern, welcher die Basis für die Gentests darstellt.

摘要
背景: 鱼鳞病是一类异质性角化疾病 , 其特征是表皮脱屑。
目的: 描述一只患有非表皮松解性鱼鳞病的拉布拉多犬的临床表现、组织病理学和遗传学分析 , 并报告一种新发现的PNPLA1基因重复突变群体的筛查结果。
动物: 两只7岁雄性同窝仔犬 , 531个群体样本。
材料与方法: 进行临床和组织病理学分析、全基因组测序以及基于数字PCR的基因分型。
结果: 犬1的全身脱屑和组织学上的层状角化过度证实了鱼鳞病的诊断。犬2出现轻微临床症状 , 可能与过敏有关 , 而非鱼鳞病。对犬1进行全基因组测序 , 并与1,469个遗传背景多样的对照基因组进行比较。分析发现PNPLA1基因的三个内含子区域存在一个6,099碱基对的重复片段 , 预计该突变会导致蛋白C端尾部结构改变 , 命名为NP_001277038.2:p.(E558Lfs*17)。犬2为杂合基因型 , 携带一份PNPLA1重复等位基因。在额外筛查的531只拉布拉多犬中 , 491只为纯合型野生型 , 36只为杂合携带者 , 4只为纯合型突变携带者。
结论及临床意义: 此前发现的 PNPLA1 基因突变导致金毛猎犬和人类患上常染色体隐性遗传鱼鳞病。鉴于 PNPLA1 的功能已得到充分证实 , 本研究中发现的基因重复突变可能是导致该拉布拉多犬患上鱼鳞病的致病突变。这是首次报告拉布拉多犬中一种新的常染色体隐性鱼鳞病 , 为后续的基因检测提供了依据。

要約
背景: 魚鱗癬は、表皮の鱗屑を特徴とする多様な角化疾患のグループである。
目的: 本研究の目的は、 非表皮融解性魚鱗癬を有するラブラドール・レトリーバーの臨床的、病理組織学的および遺伝学的解析、ならびに新たに検出されたPNPLA1ゲノム重複についての集団スクリーニングの結果について述べることであった。
供試動物: 7歳の雄の同腹仔2頭、531の集団サンプル。
材料と方法: 臨床的および病理組織学的解析、全ゲノムシークエンシング、デジタルPCRによる遺伝子型解析を行った。
結果: 犬1では汎発性の鱗屑および組織学的な層状正角化性過角化症により魚鱗癬と診断された。犬2は魚鱗癬ではなく、アレルギーに関連した可能性のある軽度の臨床症状を示した。犬1のゲノムシークエンスにより、1,469の遺伝的に多様な対照ゲノムと比較した。解析の結果、PNPLA1遺伝子の3つのエクソンにまたがる6,099bpの重複が同定され、その結果、タンパク質のC末端(NP_001277038.2:p.(E558Lfs*17))の変異につながると予測された。犬2はヘテロ接合の遺伝子型を持ち、重複したPNPLA1対立遺伝子を1コピー保有していた。さらにスクリーニングされた531頭のラブラドール・レトリーバーのうち、491頭がホモ接合野生型、36頭がヘテロ接合型キャリア、4頭がホモ接合型で重複キャリアであった。
結論と臨床的意義: 以前に同定されたPNPLA1の変異体は、ゴールデン・レトリバーおよびヒトにおいて常染色体劣性魚鱗癬を引き起こす。PNPLA1の機能が確立されていることから、今回同定されたゲノム重複は、ラブラドール・レトリバーで観察された魚鱗癬の原因変異体候補であると考えられた。これはラブラドール・レトリバーにおける常染色体劣性魚鱗癬の新しい型の最初の報告であり、遺伝子検査の基礎を提供するものである。

Resumo
Contexto: As ictioses representam um grupo heterogêneo de distúrbios de queratinização caracterizados por descamação epidérmica.
Objetivos: Descrever a análise clínica, histopatológica e genética de um labrador retriever com ictiose não epidermolítica e os resultados de uma triagem populacional para uma duplicação genômica *PNPLA1* recém-detectada.
Animais: Dois machos de 7 anos de idade, da mesma ninhada e 531 amostras populacionais.
Materiais e Métodos: Foram realizadas análises clínica e histopatológica, sequenciamento do genoma completo e genotipagem digital baseada em PCR.
Resultados: A descamação generalizada e a hiperqueratose ortoqueratótica laminar histológica confirmaram o diagnóstico de ictiose no Cão 1. O Cão 2 apresentou sinais clínicos leves, possivelmente associados a alergias e não à ictiose. O genoma do Cão 1 foi sequenciado e comparado com 1.469 genomas de controle geneticamente diversos. A

análise identificou uma duplicação de 6.099 pb abrangendo três éxons internos do gene *PNPLA1*, que parece resultar em uma cauda C-terminal alterada da proteína, NP_001277038.2:p.(E558Lfs*17). O cão 2 tinha um genótipo heterozigoto e carregava uma cópia do alelo *PNPLA1* duplicado. Dos 531 labradores adicionais rastreados, 491 eram homozigotos do tipo selvagem, 36 eram portadores heterozigotos e quatro carregavam a duplicação em estado homozigoto.
Conclusões e Relevância Clínica: Variantes de *PNPLA1* previamente identificadas causam ictiose autossômica recessiva em golden retrievers e humanos. Devido à função bem estabelecida de *PNPLA1*, a duplicação genômica identificada representa uma provável variante causal candidata para a ictiose observada no Labrador avaliado. Este é o primeiro relato de uma nova forma de ictiose autossômica recessiva em Labrador retrievers, que fornece a base para testes genéticos.

RESUMEN
Introducción: Las ictiosis representan un grupo heterogéneo de trastornos de la cornificación caracterizados por descamación epidérmica.
Objetivos: Describir el análisis clínico, histopatológico y genético de un labrador retriever con ictiosis no epidermolítica, así como los resultados de un cribado poblacional para la detección de una duplicación genómica de PNPLA1.
Animales: Dos hermanos de camada machos de 7 años, 531 muestras poblacionales.
Materiales y métodos: Se realizaron análisis clínico e histopatológico, secuenciación del genoma completo y genotipado digital por PCR.
Resultados: La descamación generalizada y la hiperqueratosis ortoqueratósica laminar histológica confirmaron el diagnóstico de ictiosis en el perro 1. El perro 2 mostró signos clínicos leves, posiblemente asociados con alergias y no con ictiosis. Se secuenció el genoma del perro 1 y se comparó con 1469 genomas control genéticamente diversos. El análisis identificó una duplicación de 6099 pb que abarca tres exones internos del gen PNPLA1, la cual se prevé que resulte en una alteración de la cola C-terminal de la proteína, NP_001277038.2:p.(E558Lfs*17). El perro 2 presentó un genotipo heterocigoto y portó una copia del alelo PNPLA1 duplicado. De los 531 labradores retrievers adicionales examinados, 491 eran homocigotos de tipo silvestre, 36 eran portadores heterocigotos y cuatro portaban la duplicación en estado homocigoto.
Conclusiones y relevancia clínica: Las variantes de PNPLA1 previamente identificadas causan ictiosis autosómica recesiva en golden retrievers y humanos. Dada la función bien establecida de PNPLA1, la duplicación genómica identificada representa una posible variante causal de la ictiosis observada en el labrador retriever examinado. Este es el primer informe de una nueva forma de ictiosis autosómica recesiva en perros labradores que proporciona la base para las pruebas genéticas.

Résumé
Contexte: Les ichtyoses représentent un groupe hétérogène de troubles de la kératinisation caractérisés par une desquamation de l'épiderme.
Objectifs: Décrire l'analyse clinique, histopathologique et génétique d'un Labrador retriever atteint d'ichtyose non épidermolytique, ainsi que les résultats d'un dépistage dans la population d'une duplication génomique PNPLA1 récemment détectée.
Animaux: Deux mâles de 7 ans, 531 échantillons de population.
Matériels et méthodes: Analyse clinique et histopathologique, séquençage du génome entier et génotypage par PCR numérique.
Résultats: Une desquamation généralisée et une hyperkératose orthokératosique laminaire histologique ont confirmé le diagnostic d'ichtyose chez le chien 1. Le chien 2 présentait des signes cliniques légers pouvant être associés à des allergies et non à une ichtyose. Le génome du chien 1 a été séquencé et comparé à 1 469 génomes de contrôle génétiquement différents. L'analyse a identifié une duplication de 6 099 pb couvrant trois exons internes du gène PNPLA1 qui devrait entraîner une altération de la queue C-terminale de la protéine, NP_001277038.2:p.(E558Lfs*17). Le chien 2 avait un génotype hétérozygote et portait une copie de l'allèle PNPLA1 dupliqué. Sur les 531 Labrador retrievers supplémentaires dépistés, 491 étaient homozygotes de type sauvage, 36 étaient porteurs hétérozygotes et quatre portaient la duplication à l'état homozygote.
Conclusions et pertinence clinique: Des variantes de PNPLA1 précédemment identifiées sont à l'origine d'une ichtyose autosomique récessive chez les golden retrievers et les humains. Compte tenu de la fonction bien établie de PNPLA1, la duplication génomique identifiée représente un candidat variant causal probable pour l'ichtyose observée chez le Labrador retriever examiné. Il s'agit du premier rapport d'une nouvelle forme d'ichtyose autosomique récessive chez le Labrador retriever, qui constitue la base d'un test génétique.