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Two detrimental mutations in cattle mitogenome indicate the presence of Leber's hereditary optic neuropathy

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Abstract

While mitochondriopathies, mitochondrial diseases, caused by mutations in mitochondrial DNA (mtDNA), are well documented in humans, single pathogenic mtDNA mutation or disorders are unknown in livestock populations. In a survey of 799 complete cattle mtDNAs belonging to more than 120 breeds two mutations, one in ND1 (C4171T) and the other in ND4L (T10663C) gene were identified, that are confirmed to be pathogenic in humans causing Leber's hereditary optic neuropathy (LHON). In one Cika cow with T10663C mutation, which was in humans reported to cause an acute onset of visual loss or/and many other LHON associated clinical manifestations, an exophthalmia of the right eye that might fit to the pathogenesis of LHON was observed. This work supports the existence of potentially detrimental mtDNA mutations in cattle, while aetiology and pathogenesis need to be further documented.

Keywords: cattle, detrimental mutation, mtDNA

Introduction

Mitochondrion is a double-membrane-bounded organelle found in most eukaryotic organisms. Mitochondrial DNA (mtDNA) is maternally inherited in vertebrates and encodes 13 out of ~85 components of the oxidative phosphorylation (OXPHOS), a metabolic pathway that is crucial for aerobic respiration (Wallace, 1999). In human medicine/genetics a number of disorders caused by dysfunctional mitochondria have been identified. Mitochondrial diseases, in about 15% in humans (Dimauro and Davidzon, 2005), are caused by mutations in mtDNA. Clinical symptoms, such as poor growth, loss of muscle coordination, muscle weakness, visual and hearing problems, learning disabilities, heart disease and dementia, are mostly results of encephalopathy, myopathy, optic neuropathy or lactic acidosis. Some of the most

important diseases in humans are Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, Stroke-like symptoms (MELAS), Leber's hereditary optic neuropathy (LHON) or Leigh Syndrome (known also as a Leigh Disease, LD). LHON is one of the first and most important mitochondrial diseases discovered. LHON is a blinding disorder characterized by subacute/acute loss of central vision that most frequently affects young males. It is maternally inherited disorder associated with different mtDNA point mutations (Carelli et al., 2004; Newman, 2005; Yu-Wai-Man et al., 2011). In humans, three mutations are considered as highly prevalent and pathogenic 11778G>A, 3460G>A and 14484T>C affecting MT-ND4, MT-ND1 and MT-ND6, respectively (Torroni et al., 1997; Carelli et al., 2006; Hudson et al., 2007). In addition, there are number of less prevalent and confirmed pathogenic or just suspicious mutations (MITOMAP, 2018). While in human medicine/genetics mitochondrial diseases are well documented and large databases with plenty of complete mtDNAs are available, in veterinary medicine/genetics, information on complete mitogenomes that are deposited in GenBank (https://www.ncbi.nlm.nih.gov/genbank/) are infrequent and limited to several livestock species. There was awareness that mtDNA pathogenic mutations or mtDNA disorder are not found in livestock populations. The aim of this study was to locate detrimental mutations, present in protein coding regions, in cattle mtDNA that correspond to pathogenic mtDNA mutations in humans.

Materials and methods

A dataset of 799 complete cattle mtDNAs belonging to more than 120 breeds from mitoTAUROmics project was analyzed. Sequences were aligned using Clustal W in Mega7 software. All 11 protein coding regions from cattle mtDNA dataset: ND1-6, ATP6 and 8, COX1-3 and CYTB were retrieved. Specific positions in the reference human mtDNA sequence (GenBank accession number NC_012920), previously confirmed as pathogenic mutations in humans (MITOMAP, 2018), were marked. Then, coding region of human mtDNA with marked specific mutations was aligned using Clustal W codons to corresponding cattle sequence dataset. Specific position in human mtDNA where the confirmed pathogenic mutation was found, was compared with the same position in cattle mtDNA after aligning. All differences were recorded.

Results and discussion

Atogether 20 mutations were confirmed to be pathogenic in human mtDNA and cause LHON according to the web database MITOMAP were found. All 20 mutations were positioned in Nicotinamide dehydrogenase complex. This study revealed many differences between human and cattle mtDNA, but interestingly those specific "pathogenic" mutation sites in human and cattle mtDNA were homologous (Table 1).

Table 1. Specific pathogenic sites in human mtDNA associated with LHON[1] and corresponding mutations in cattle

Position	Gene	Disease associated	Mutation	Mutations in cattle (number of animals, breed)
3376	ND1	LHON[1]/MELAS[2]	G3376A	-
3460	ND1	LHON[1]	G3460A	-
3635	ND1	LHON[1]	G3635A	-
3697	ND1	MELAS[2]/LD[3]/LDYT[4]	G3697A	-
3700	ND1	LHON[1]	G3700A	-
3733	ND1	LHON[1]	G3733A	-
4171	ND1	LHON[1]	C4171A	2 Korean cattle,1 Kosovo Buša; 1 Croatian Buša
10197	ND3	LD[3]/Dystonia/ Stroke/LDYT[4]	G10197A	-
10663	ND4L	LHON[1]	T10663C	2 Cika cattle
11778	ND4	LHON[1]/Progressive Dystonia	G11778A	-
13042	ND5	Optic neuropathy/retinopathy/LD[3]	G13042A	-
13051	ND5	LHON[1]	G13051A	-
13094	ND5	Ataxia+PEO/MELAS[2]/LD[3]/LHON[1]/myoclonus/fatigue	T13094C	-
13513	ND5	LD[3]/MELAS[2]/LHON[1]-MELAS[2] Overlap Syndrome	G13513A	-
14459	ND6	LDYT[4]/LD[3]	G14459A	-
14482	ND6	LHON[1]	C14482A-G	-
14484	ND6	LHON[1]	T14484C	-
14495	ND6	LHON[1]	A14495G	-
14568	ND6	LHON[1]	C14568T	-

[1]Leber's hereditary optic neuropathy; [2]Mitochondrial encephalopathy, Lactic Acidosis and Stroke-like episodes; [3]Leigh disease; [4]Leber's hereditary optic neuropathy and dystonia.

Mutation C4171T (ND1 region), not reported to be pathogenic in humans, was observed in two animals of Korean cattle and one animal of Kosovo Buša, whereas mutation C4171A, reported as pathogenic in humans (Table 1), was observed in one animal belonging to Croatian Buša population. The most intriguing was the mutation T10663C in ND4L subunit that was found in two Slovenian Cika cows. In humans this mutation was reported to cause an acute onset of visual loss or many other clinical manifestations known as LHON. One of two animals is still alive and according to anamnesis and clinical inspection, exophthalmia (Figure 1) of the right eye was observed. In human LHON cases, the affected eye can demonstrate an oedema of the nerve fibre layer, which can result as exophthalmus (Fraser et al., 2010; Yu-Wai-Man et al., 2011). Clinical finding of exophthalmus in animal with specific mutation in position which is highly pathogenic in humans can support assumption that mitochondrial diseases, at least LHON, are present in cattle as well. Still, further analyses are needed to reveal the prevalence, pathogenesis and aetiology of this specific mutation in Slovenian Cika cattle.

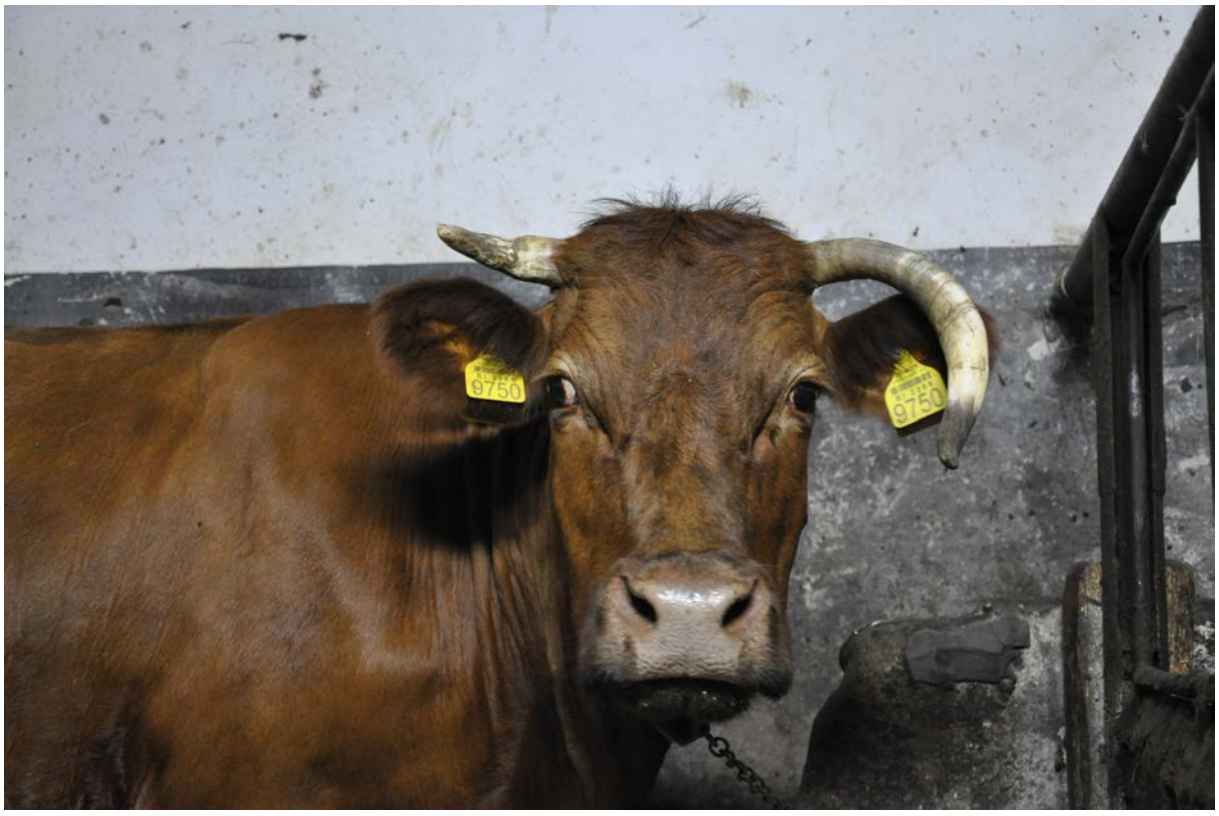

Figure 1. Exophthalmia of the right eye in Cika cow (Foto: Mojca Simcic)

Conclusions

While detrimental mtDNA mutations have not been identified in livestock populations so far, present work supports the existence of potentially detrimental mtDNA mutations in cattle as the same (homologous) mutations are causative for Leber's hereditary optic neuropathy in humans. Still, the resulting etiology and pathogenesis of those mutations need to be further investigated. At the same time, this study

provided the proof of the concept for an efficient strategy for identifying mitogenome detrimental mutations in livestock populations.

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