IS THERE A ROLE FOR MITOCHONDRIAL INHERITANCE IN SHEEP BREEDING?

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Abstract. Mitochondrion is a cytoplasmic organelle of the eucaryotes. The versatile tasks of mitochondria in cell biology include the energy supply, maintenance of redox potential, production of heat and free radicals, as well as storing of calcium and modulation of calcium signals. Nuclear DNA codes many of the proteins that function in the mitochondrion, but the mitochondrion has also a genome of its own. In mammals the mitochondrial DNA (mtDNA) codes 37 genes. MtDNA has been widely employed in phylogenetic and phylogeographic studies. The distribution of mtDNA variation has shown greater degree of temporal inertia than that of nuclear genes and it seems to reflect often the primary spreading of the species rather than a secondary gene flow. In domestic sheep two divergent groups of mitochondria are found. One is found only in Europe and the other is rare in Europe, but prevails elsewhere. The new data from Northern European sheep confirms the existence of both main types in many European breeds. There are no comprehensive studies of mitochondrial effects in sheep and the characterisation of DNA variation lays ground for exploring associations of mtDNA variation with sheep phenotype variation also for breeding purposes.
Keywords: *Ovis aries*, mitochondria, genetic diversity, maternal inheritance.

AR MITOCHONDRINIS PAVELDIMUMAS TURI REIKŠMĘ AVIŲ VEISIME?

Santrauka. Naminių gyvūnų genetiniai ištekliai nyksta. Valstybės, pasirašydamos Rio de Žaneire "Biologinės įvairovės" konvensiją, įsipareigojo išsaugoti savo naminių gyvūnų genetinę įvairovę. Siekiant įvertinti avių veisles ir užtikrinti efektyvų įvairovės išsaugojimą, buvo tiriama Šiaurės Europos avių mitochondrinė įvairovė. Straipsnis apžvelgia mitochondrinio paveldimumo biologinius veiksnius ir mitochondrinės įvairovės mokslinių tyrimų galimybes. Mitochondrija yra citoplazminė organelė, kilusi iš α-rausvųjų bakterijų ir laiko bėgyje perdavusi daugumą genų chromosomose esančiai branduolinei DNR. Mitochondrija turi savo genomą, kuriame mitochondrinė DNR (mtDNR) koduoja 37 genus. Koduojanti mtDNR seka užtikrina suderinamumą tarp skirtingų audinių įvairiapusių poreikių ir audiniams specifiškos branduolinio ir mitochondrinio genomo ekspresijos. Kadangi mitochondrijų veikla yra svarbi daugeliui ląstelės metabolinių procesų, jos turėtų įtakoti ir pvz. avių produktyvumą. Su galvijais atlikti tyrimai rodo, kad egzistuoja priklausomybė tarp mtDNR ir fenotipinių požymių įvairovės, tačiau panašių tyrimų avims atlikta nėra. Populiacijose mitochondrinio paveldimumo mechanizmas skiriasi nuo branduolinio paveldimumo. Daugelyje naminių gyvūnų rūšių, dėka paveldėjimo tik iš motinos pusės, mtDNR įvairovė yra pakankamai nejautri antriniam genų nutekėjimui. Naminių avių tarpe yra aptiktos dvi viena nuo kitos besiskiriančios mitochondrijų linijos. Viena jų plačiai paplitusi Europoje, kita – aptinkama likusioje žemyno dalyje, tačiau naujausi duomenys patvirtina, kad daugelyje Europos avių veislių yra aptinkama ir reta Azijos tipo mitochondrijų linija. MtDNR tyrimai rodo, kad Europos avių veislės yra labai polimorfiškos, tačiau net 70 % šios įvairovės sudaro vidupopuliacinė įvairovė. Mitochondriniam paveldėjimui reikia išskirtinio dėmesio nes tradiciniai veisimo metodai šią sritį ignoruoja. MtDNR tyrimai ne tik suteiks informacijos apie veislių formavimąsi, bet taip pat atvers kelius šios įvairovės apsprendžiamų požymių praktiniam pritaikymui.
Raktažodžiai: *Ovis aries*, mitochondrija, genetinė įvairovė, paveldėjimas tik iš motinos pusės.

Purpose of the work. This article aims to review special characteristics of mitochondrial inheritance and to explore motivation to study associations between mtDNA types and phenotypic variation in sheep that becomes feasible due to the characterisation of mtDNA variation in Northern European sheep.

Introduction. Genetic resources of the world are subjected to erosion, which might close breeding options available for us in the future. The erosion is caused by substitution and crossing of local breeds with common international breeds. The responsibility of maintaining biodiversity belongs to each individual country according to Convention on Biological Diversity (Rio), but international efforts also lend a hand in carrying out this task. The characterisation of existing diversity is needed in planning the maintenance of the genetic diversity efficiently. In 1999 a project "Origin and Genetic Diversity of North European Sheep Breeds" was founded by The Nordic Gene Bank Farm Animals (NGH) to characterise sheep diversity concentrating on the breeds of North Europe and Baltic countries, but also including breeds from North-western Russia, Britain and Nederland. The project has been organised through the co-operation of researchers in all the Nordic countries, including Greenland and the Faeroe Islands, together with the three Baltic countries. We have gathered information about physical characteristics, cultural aspects of breeds and we analysed microsatellite variation at DNA level according to the guidelines of The Food and Agriculture Organization (FAO) of the United Nations. Additionally,

we have analysed variation at mitochondrial control region.

Mitochondrial DNA (mtDNA) has been widely applied as an evolutionary marker to study phylogeographic and phylogenetic patterns. Since mitochondrion has a central role in many metabolic pathways, there has also been an interest to explore the effects of mitochondrial DNA variation to phenotypes; e.g. diseases and production traits.

Biology of mitochondria. Practically all the oxygen that we breathe in is used by cell organelles called mitochondria. Mitochondria are located in the cytoplasm of almost all cells of animals. Nowadays mitochondria are energy-producing organelles of eukaryotic cells, but according to a commonly accepted idea they have originated from incorporated α-purple bacteria that united either with an archaebacterium or an ancestral eukaryotic cell without mitochondria. This symbiosis resulted in eukaryotic organisms; e.g. mammals (Gray et al., 1999). The rich variation of mitochondrial structure has been reviewed in depth elsewhere (Frey and Mannella, 2000), but in principle mitochondrion is a cytoplasmic organelle with a double membrane. The outer membrane separates the mitochondrion from the cytosol and the inner membrane is invaginated to form the cristae, which protrude into and define the matrix of the organelle. Mitochondria contain their own genome, the mitochondrial DNA (mtDNA), which is located in the mitochondrial matrix. Each mitochondrion generally contains multiple identical copies of mtDNA (Michaels et al., 1982; Robin and Wong, 1988).

The structure and gene organisation of mtDNA is very conserved in mammals including sheep. The mitochondrial genome is a closed circular, double-stranded DNA molecule of about 16 500 base pairs long which contains 13 protein coding genes, 22 transfer RNA genes and 2 ribosomal genes. The molecule is very tightly organised, the genes have no introns and, except for one regulatory region, intergenic sequences are absent or limited to a few bases (Wolstenholme, 1992). Regions of mtDNA differ from each other; e.g. the substitution rate of mitochondrial genes can be between 1 and 100 times higher than the rate of nuclear genes (Pesole et al., 1999; Saccone et al., 2000) and the base composition varies among mitochondrial regions and also between species. In cattle 70 % and in sheep 64 % of bases in 5' hypervariable section of control region are A or T, whereas in the central conserved domain of control region the proportion of A and T bases is approximately equal to the proportion of C and G bases (Sbisa et al., 1997). In the complete mitochondrial genome of sheep the proportion of A and T is 61 %.

Mitochondria are not self-supporting entities in the cell. The 13 proteins coded by mtDNA form only a part of the protein machinery working in a mitochondrion. During the evolution from ancient eubacteria form to present day organelle, the most genes of the endosymbiont were transferred to the nuclear chromosomes (Martin and Herrmann, 1998; Palmer et al., 2000). Different stages of the nuclear acquisition functioning mitochondrial genes have been documented in plants and fungi, but there are no observations of recent transfer on functional mitochondrial genes to animal nucleus (Palmer et al. 2000) and regulatory and toxic reasons might prevent the transfer of the remaining mitochondrial genes to nucleus (Sbisa et al., 1997). There is a very close cross-regulation and interaction of mitochondrial and nuclear genes and genomes (Garesse and Vallejo, 2001) and correlated evolutionary changes of the nuclear and mitochondrial genes have been observed in mammals (Adkins et al., 1996). The evolutionary co-adaptation of the genomes is complicated with tissue-specific and age-related directional selection for different mtDNA genotypes (Jenuth et al., 1997). This suggests that the coding sequence of mtDNA represents a compromise between diverse demands of different tissues and tissue-specific expression of nuclear and mitochondrial genomes.

The diseases caused by malfunctioning mitochondria are widely known, but the mtDNA variation has been reported to be associated also with more subtle effects; e.g. on carcass traits of beef cattle (Mannen et al., 1998) and milk composition, yield and health costs of dairy cattle (Boettcher et al., 1996; Schutz et al., 1993; Schutz et al., 1994). Association of mitochondrial activity and bovine sperm mobility has been reported (Chandler et al., 2000). The observations are not surprising as the organelle has several tasks in cell physiology. In addition to supplying energy to the cell, it also participates in maintaining the redox potential, produces heat (Ricquier and Bouillaud, 2000) and free radicals (Lenaz, 1998), stores an appreciable amount of calcium (Rizzuto et al., 1998), modulates calcium signals and introduces cells in apoptosis (Ichas and Mazat, 1998). They have also been proposed to play role; e.g. in aging (MacHugh et al., 1997) and in cell differentiation (Herzberg et al., 1993; Rochard et al., 2000; von Wangenheim and Peterson, 1998). There are no thorough studies about association of mtDNA polymorphisms with phenotypes in sheep yet, but the preliminary evidence implies, that they may exist (Hiendleder, 1996; Hiendleder, 1998).

Mitochondria in populations. There are several differences between the behaviour of mitochondrial and nuclear genomes in mammalian populations. The most obvious difference is that mtDNA is inherited only from the mother (Giles et al., 1980; Hayashi et al., 1978; Hutchison et al., 1974). Even if in most mammals the sperm mitochondria are transferred to the oocyte during fertilisation (Ankel-Simons and Cummins, 1996), detailed morphological studies; e.g. in cattle (Sutovsky et al., 1996) have indicated that sperm-derived mitochondria are lost early in embryogenesis and there seems to be a species specific recognition and degradation system of male derived mitochondria (Sutovsky et al., 1999). Additionally, in mammalian sperm cells, the copy number of mtDNA is low (50-75 (Hecht et al., 1984)) whereas in mammalian oocytes the copy number is extremely high ($\geq 10^5$ (Michaels et al., 1982)). Usually individuals are homoplasmic i. e. the individual has only one type of mitochondria, but some heteroplasmic individuals having

more than one type of mitochondria have also been observed; e.g. in Holstein cattle (Ashley et al., 1989). The heteroplasmic situation in Holstein was a transient phase after a new mutation in a mtDNA and in a few generations the maternal line was again homoplasmic. In population studies we can assume mtDNA to behave as a single non-recombining homoplasmic maternally inherited gene even with moderate amounts of heteroplasmy, as the maternal line becomes homoplasmic quickly compared to a loss of variation in the population (Chesser, 1998).

Second difference between nuclear and mitochondrial inheritance is a lack of intermolecular homologous recombination at mtDNA. Obviously, if there is only one lineage of mitochondria in an individual, there cannot be recombination among lineages. The no-recombination assumption was challenged by a pattern of decaying linkage disequilibrium as a function of distance (Awadalla et al., 1999; Eyre-Walker et al., 1999). Conclusions about recombination based on this indirect evidence were heavily criticised (Jorde and Bamshad, 2000; Kivisild and Villems, 2000) and heterogenous substitution processes or lineage-specific selection was presented to lay behind the pattern (Ballard, 2000; Yang et al., 2000) and no recombination between lineages is thought to happen.

In sheep as well as in many other domestic mammals (reviewed in McHugh and Bradley, 2001) the distribution of mitochondrial variation has a geographical structure and the mitochondrial variation shows significant temporal inertia. This is a result of smaller reproductive variance of females than that of males and foreign genetic material being preferentially introgressed to breed through introduced males (e.g. MacHugh et al., 1997). The mode of inheritance means that immigrating males do not contribute to the pool of mitochondrial forming the next generation and even migrating females bring only one copy of mitochondrial genome (haploid) whereas they bring two copies of nuclear genome (diploid).

Sheep in Northern Europe have ancient origins. Sheep husbandry spread to British Isles, Scandinavia and Russia already 6 000 years ago (Ryder, 1991) and the Northern short-tailed sheep have been recognized as a breed group for a long time. Once it was even thought to be a species of its own. Our new study (Tapio et al., 2002) is the first description of mtDNA variation of sheep in Northern areas. It has been discovered earlier (Hiendleder et al., 1998), that the domestic sheep mtDNA haplotypes can be divided into two divergent lineages, which diverged from each other approximately 375 000 to 750 000 years ago. Therefore, the maternal roots of domestic sheep lay in at least two subspecies of wild sheep. One of the mitochondrion types was found only in European domestic sheep, while the other type is uncommon in Europe, but common elsewhere. The European type was similar to the type found in European mouflon, but for the other mtDNA haplogroup there were no corresponding mitochondria found either in mouflon or in urial and argali sheep. The initial observation (Hiendleder et al., 1998) of existence of both main mitochondrion types in European breeds was done in populations located in New Zealand and undocumented hybridisation with native Asian breeds might have happened, but our new data (Tapio et al., 2002) from 32 breeds of Northern European sheep confirmed the existence of Asian mtDNA haplogroup in Europe. The Asian type was rare in Europe, but it was most common in Atlantic long-tailed sheep breeds and in short-tailed breeds in the Baltic Sea region. It was very rare in Atlantic short-tailed sheep and absent in the sample of Baltic Sea region long-tailed sheep. The mtDNA variation seems to be geographically structured, but the variation in sheep breeds is abundant. 70 % of the observed mtDNA variation was within-population variation and 30 % was variation between the populations (Tapio et al., 2002).

Conclusion. There is emerging knowledge about mitochondrial variation in the Northern European sheep breeds and the results indicate rich variation within the breeds. There are several mitochondrial variants, but they can be grouped into two main types. It has been shown that at least some differences between main mitochondrial groups affect the products of the genes (Hiendleder, 1998) and there is preliminary evidence for mitochondrial effects on sheep phenotypes (Hiendleder, 1996), but this has not been fully studied yet. Mitochondrial inheritance might need and deserve special attention as normal breeding and conservation practices ignore it. Mitochondrial DNA could be the prime candidate for studies of genetic effects of environmental pollutants and irradiation. Another interesting question is if there are compatibility problems among nuclear and mitochondrial genes. The main goal of our mtDNA study is to clear up the processes leading to our present day breeds, but the work also makes it easier to plan studies exploring the phenotypic effects in the characterised breeds.

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