MOLECULAR GENETICS OF RESIDUAL FEED INTAKE AND MITOCHONDRIAL FUNCTION IN CATTLE

By

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TABLE OF CONTENTS

INDEX OF FIGURES

INDEX OF TABLES

INDEX OF APPENDICES

ABSTRACT

Residual feed intake (RFI) is a measure of net feed efficiency, an economically important trait in livestock. RFI is affected by many factors including genetics and diet although residual feed intake is usually independent of diet as it is calculated for a group of animals on a standard feed test. The RFI of an animal depends on the ability of the animal to consume less feed than expected based on their weight gain and weight maintained during the feed testing period. Those that eat less than expected have a negative RFI and are deemed more efficient. Recent work has implicated mitochondrial function as being involved in the feed efficiency of livestock including cattle, sheep, pigs and poultry.

The objectives of this study were to identify genes involved in mitochondrial function that may affect net feed efficiency in cattle and to examine the enzyme activities in the mitochondria of high and low residual feed intake animals. Several quantitative trait loci (QTL) affecting feed efficiency were previously mapped in Jersey x Limousin double backcross progeny in three sire families. Based on the QTL mapping results, ten candidate genes related to mitochondrial function and energy metabolism were identified: *aldolase B (ALDOB)*, *adenylate kinase 1 (AK1)*, *catalase (CAT)*, *ghrelin (GHRL)*, *hydroxyacyl CoA dehydrogenase beta subunit (HADHB)*, *NADH dehydrogenase alpha subcomplex 8*, *19kDa (NDUFA8)*, *NADH dehydrogenase beta subcomplex 5*, *16kDa (NDUFB5)*, *superoxide dismutase 1, soluble (SOD1)*, *superoxide dismutase 2 (SOD2)*, and *succinyl Co-A synthetase (SUCLG1)*.

All ten genes were sequenced in the three Jersey x Limousin sire families in order to locate DNA variants in the genes for association studies. A total of 58 DNA variants were discovered, which included six insertion/deletions (in/dels) and 52 single

nucleotide polymorphisms (SNPs). Of the 52 SNPs, 34 SNPs were located in introns, 9 in exons and 9 in the untranslated regions (UTR).

Fourteen SNPs were selected for genotyping in the 366 progeny from the three sire families. Genotyping results were analysed to observe the effect of the SNPs with 27 RFI related traits and specific fat depot traits, including residual feed intake and daily feed intake. The F94L *myostatin* (*MSTN*) genotype was included in some of the models as this variant was known to be segregating in the progeny and has a major effect on body composition.

Only 4 SNPs in the candidate genes were associated with residual feed intake, 3 of which were in the *HADHB* gene. The haplotype of *HADHB* from these 3 SNPs explained 8.5% of the variation in RFI. The other SNP was in the *SOD1* gene, which had a p-value <0.001 for residual feed intake and explained another 3% of the variation in this trait. The gene with a significant haplotype effect was *NDUFB5*, which had a significant effect on residual feed intake ($p = 0.005$) and explained 5% of the variation.

To examine potential epistatic effects, interactions between the genes were also analysed. The analysis of the SNP interactions between genes revealed that residual feed intake was affected by 10 SNP interactions. A SNP in the *NADH dehydrogenase alpha subcomplex 8, 19kDa* gene (ND5SNP5') had the most interactions. Four SNP interactions (between *NDUFB5* and *SOD1*, between *NDUFA8* and *SUCLG1*, between *ALDOB* and *NDUFB5,* and between *HADHB and SOD1)* explained 21% of the RFI variation. Thus, the results indicate that DNA variants in genes involved in mitochondrial function and energy metabolism can influence RFI.

Mitochondria from animals differing in residual feed intake were measured for function by assaying major mitochondrial electron transport complexes and the reactive oxygen species. The liver mitochondrial assays included Complex I, III and IV enzyme activities as well as the protein carbonyl assay to measure the reactive oxygen species. The results indicated that Complex I and Complex III enzyme activities and the ROS concentration were significantly different between the high and low residual feed intake groups. The mitochondria from low RFI animals had higher Complex I and Complex III enzyme activity and more ROS.

The outcomes of this study contribute to the knowledge of net feed efficiency at the molecular level. The results indicate the mitochondria may indeed play a role in residual feed intake in animals and that genes involved in energy metabolism may have variants that affect efficiency. The role of mitochondria was shown both at the genetic and biochemical level. The results imply that residual feed intake is not entirely a function of body composition and/or appetite.

The DNA variants discovered in the candidate genes could potentially be used as genetic markers for selection although their size of effect was not large. Future studies would need to be conducted using different populations of cattle to verify the effects of the DNA variants identified herein on feed efficiency. It is also important to repeat the mitochondrial assays in different cattle populations that has not been selected for net feed efficiency or body composition in order to validate the relationship between residual feed intake, mitochondrial function and cellular efficiency.

DECLARATION

I declare that this thesis is a record of original work and contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Nadiatur Akmar Zulkifli. To the best of my knowledge and belief, this thesis contains no material previously published or written by any other person, except where due reference is made in the text.

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DEDICATION

For the past, present and future.