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Prediction of Molecular Structure and Effects of Single Nucleotide Polymorphisms in Ovine Leptin - In Silico

Musa. S. Ibrahim

Department of Animal Science, Nasarawa State University, Keffi, Nigeria

***Corresponding Author:** Musa. S. Ibrahim, Department of Animal Science, Nasarawa State University, Keffi, Nigeria*

ABSTRACT

Leptin hormone acts as a nutritional signal that link metabolic status and neuro endocrine control of growth and reproduction. The objective of this study was to predict the molecular structure and effects of single nucleotide polymorphism in ovine leptin using computational methods. Data used for the study was obtained from database of national center for biotechnology information (GenBank). The physico chemical characteristics of ovine leptin was evaluated using Protparam server. The secondary structure was predicted using Raptor X protein structure prediction server, the analysis showed 4% alpha helix, 45% beta turns, 49% coiled and 3% disordered positions. Evaluation of solvent accessibility indicate 45% exposed, 37% medium and 17% buried. The 3D structure of leptin was predicted using Raptor X protein structure prediction server. Analysis of single nucleotide polymorphisms was done using Protein Variation Effect Analyzer (PROVEAN). The results indicate that the 2 amino acid substitutions evaluated had no effect on the functions of ovine leptin (Neutral). Investigations of the molecular structure and association studies on single nucleotide polymorphisms in ovine leptin can provide useful information for genetic selection in sheep.

Keywords: *Analysis, Molecular structure, ovine, Leptin, In silico*

INTRODUCTION

Leptin is secreted primarily by white adipose tissue and act as an endocrine indicator of energy reserve to the hypothalamus and other tissues in the regulation of appetite and metabolism with nutrient availability (Margetic *et al*., 2002). It is also reported to link nutritional status with neuro-endocrine and immune functions (Zhou *et al*., 2009). A positive correlation between serum leptin levels and muscle mass has been documented (Femendez *et al*., 2000). The primary function of the hormone leptin is regulation of adipose tissue mass through hypothalamic mediated effects on hunger and energy balance (Margetic *et al*., 2000). Leptin interacts with other hormones and energy regulators mediating the effects of insulin, glucagon, insulin like growth factor, growth hormone and glucocorticoids (Farr *et al*., 2006). It acts as a receptor in the lateral hypothalamus to inhibit hunger and the medial hypothalamus to stimulate satiety (Elmguist et al., 1999).

The neuro endocrine system translate nutritional signals detected by the central nervous system into signals that alter secretion of luteinizing hormone (LH) and growth hormone (Barb *et al*., 2001). Leptin in association with Kiss peptin is reported to play a role in regulating the onset of puberty. Exogenous leptin influenced LH and GH secretion in sheep, indicating that the fat derived hormone link nutritional status to mechanisms regulating neuro endocrine functions in ruminants (Nagatani *et al*., 2000).

Significant association has been established between genetic variation in leptin gene and milk yield in cows (Abdul et al., 2008). Positive association between single nucleotide polymerphism in ovine leptin gene and skeletal muscle growth and meat quality traits has been documented (Boucher et al., 2006).

MATERIALS AND METHODS

Protein sequence of ovine leptin (Accession number (NP_001009763.1) and data on single nucleotide polymorphisms was obtain from the data base of National center for biotechnology information (GenBank) for molecular analysis.

Determination of Physical and Chemical Properties of the Ovine Leptin

ProtParam Tool was used for the computation of various physical and chemical properties of the Ovine leptin using protein sequences. The computational parameters include molecular weight, theoretical pI (isoelectric point), amino acid composition, extinction coefficient, estimated half-life, instability index, aliphatic index and grand average of hydropathicity (GRAVY) (Gasteiger, 2005). Protparamis a tool which allows the computation of various physical and chemical parameters for a given protein stored in Swiss – Prot or TrEMBL or for a user entered protein sequence.

The secondary structure and 3D structure of ovine leptin was predicted using Raptor X protein structure prediction server. RaptorX is a protein structure prediction server developed by Xu group, excelling at predicting 3D structures for protein sequences without close homologs in the Protein Data Bank (PDB). Given an input sequence, RaptorX predicts its secondary and tertiary structures, contacts, solvent accessibility, disordered regions and binding sites (Mortein *et al*., 2012). Parameters evaluated include percentages of alpha helix, beta turns, coiled, disordered positions and solvent accessibility. The predicted 3D model of ovine leptin was also generated.

Analysis of the effects of single nucleotide polymorphisms (62 Arg>Cys and 84 Arg>Gln)

in ovine leptin was done using Protein Variation Effect Analyser (PROVEAN). clustering of

BLAST hits is performed with a parameter of 75% global sequence identity. The top 30 **clusters** of closely related sequences form the **supporting sequence set**, which will be used to generate the prediction. (Choi et al., 2012) . The scores are then averaged within and across clusters to generate the final PROVEAN score. If the PROVEAN score is equal to or below a predefined threshold (e.g. -2.5), the protein variant is predicted to have a "deleterious" effect. If the PROVEAN score is above the threshold, the variant is predicted to have a "neutral" effect.

RESULTS AND DISCUSSION

The physico chemical properties of ovine leptin is presented in table 1. The result showed 895 amino acid sequences with a net positive charge. The instability index indicate an unstable protein.

Table1. *Physico-chemical characteristics of Ovine leptin predicted by ProtParam*

Parameters	Values
No of Amino Acid	895
Molecular Weight (kDa)	102208. 95
TheoriticalIsoelectric point	8. 10
No of negative charges	82
No of positive charges	87
Half Life	30 hours
Aliphatic index	92.80
Instability index	45. 31
Grand average of hydropathicity	-0. 11

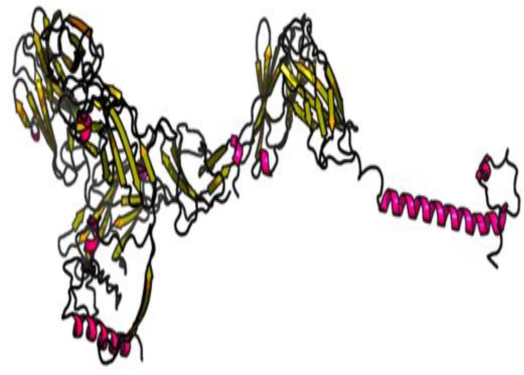
The secondary structure of ovine leptin is presented in table 2. Some single nucleotide polymorphism could disrupt protein – protein interaction thereby altering protein functions, while other SNPS are neutral to protein functions.

Table2. *Prediction of secondary structures of Ovine leptin*

Parameters	(%)
Alpha helix	4
Random coil	49
Beta turn	45

Single nucleotide polymorphisms have been documented in the leptin gene of sheep. Significant association between genetic variability in leptin and some carcass traits of sheep have also been reported (Roohalah *et al*., 2009). Similarly, leptin SNPs have been associated with amount of fat deposition in body tissues. Strong association between some variants of leptin have been associated with the onset of puberty in sheep (Halder *et al*., 2014). The age at onset of puberty is known to be influenced by genetic factors with moderate heritability (Toe et al., 2000). Higher leptin concentrations were associated with earlier age at first estrus in merino sheep (Rosales *et al*., 2013). Body size and fat composition also influence the onset of puberty) Halder et *al*., 2014). Leptin concentrations increase during pubertal development and play a significant role in regulating body fat mass. SNPs have been associated with back fat thickness and carcass fatness in cattle (Buccanan *et al*., 2002). The 3D structure of ovine leptin is presented in fiqure 1.

3D Structure of ovine leptin predicted using Raptor X Protein Prediction Server.



Fiqure1. *3 D Structure of ovine leptin*

Table3. *Prediction of effects of Single Nucleotide Polymorphism in Ovine leptin using PROVEAN*

Variants	PRVEAN score	Prediction (Cut off -2-5)
R 62 C	-1.447	NEUTRAL
R 84 Q	-0.022	NEUTRAL

CONCLUSION

Non synonymous SNPs can result in modification of protein activity. The deleterious effects of SNPs are generally attributed to their impact on protein structure and functions. Single nucleotide polymorphism may be neutral as observed in this study, in other instances it can result in structural and functional changes in a protein. Studies of molecular structure and effects of single nucleotide polymorphisms can provide useful information for selective breeding of sheep carrying desirable mutations so as to improve productivity.

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