Biological Networking of Proteins Having Impending Role in Milk Fat Content of Bovines

Maryam Javed[1*], Masroor Ellahi Babar[2], Asif Nadeem[1], Muhammad Wasim[1], Tanveer Hussain[2], Abu Saeed Hashmi[1]

[1] Institute of Biochemistry & Biotechnology, University of Veterinary & Animal Sciences, Lahore, Pakistan, 54000
[2] Department of livestock production, University of Veterinary & Animal Sciences, Lahore, Pakistan, 54000
*Corresponding Author: maryam.javed@uvas.edu.pk

Abstract: In this era of postgenomic research, scientists are searching for biological catalogues that can assist in filling gapes in existing biological information. Intermingling of genomics, bioinformatics and computational biology is a promising approach towards advanced functional genomics and is answering many unanswered queries in science. Biological networking of macromolecules specially proteins is opening new horizons for exploring functional relations between gene products and the respective networks of such associations. Present study was planned to investigate the biological networks of three candidate genes/proteins that are involved in determining milk fat content in bovines. CYP11b1, OLR1 and SCD were selected for the purpose of analysis and meaningful results were found depicting their functional interactions in respective pathways. This study can be a first step towards the genetic and genomic screening of these genes at population level in the search of useful markers for selection of superior dairy animals.

[Maryam Javed, Masroor Ellahi Babar, Asif Nadeem, Muhammad Wasim, Tanveer Hussain, Abu Saeed Hashmi . **Biological Networking of Proteins Having Impending Role in Milk Fat Content of Bovines.** *Life Sci J* 2014;11(10s):659-663]. (ISSN:1097-8135). http://www.lifesciencesite.com. 126

Key words: Biological networking, CYP11b1, OLR1, SCD, Interactions

Introduction

With the expansion of "omics" loop (proteomics, genomics, lipidomics, and metabolomics etc) scientists are now better able to find missing links in genes, transcripts, proteins, metabolites and their inter-connections. But regulation of these entities to work together in a system is still a big challenge (Aloy and Russell, 2004). A newly emerging field in bioinformatics is Systems Biology which organizes molecular interactions as networks and characterizes information flow within networks. Most desirable use of this is the provision of insight into the protein-protein interactions (PPIs) which is considered as a strong in-silico approach towards functional genomics (Kholodenko et al. 2012). The generation of accurate cellular protein interaction networks is an ongoing process in which data is produced form Yeast2Hybrid system and mass spectroscopy. But very preliminary information is available so far (Arimura et al. 2004).

Present study was designed to find the biological interactions of three candidate proteins having key role in determining milk yield and quality in dairy animals. After the recognition of system biology, now we know that proteins don't work in isolation. One protein is affecting many others in the vicinity positively or negatively (Ashburner et al. 2000; Strogatz 2001). Genetic screening and association of candidate genes involved in production traits is very crucial area of research in animal breeding and genetics and to find the role of respective proteins in biological systems (PPIs) is also inevitable to understand the function of this protein. In this study, respective proteins for these genes were investigated for the interactions in biological systems.

Material and Methods

Selection of Candidate Proteins

For the purpose of analysis, three candidate genes were selected; CYP11b1, OLR1 and SCD. Cytochrome P-450, family1, subfamily-B, polypeptide-1 localizes to the endoplasmic reticulum and is responsible for controlling milk yield, fat %age and fat yield. This gene influences the production of cortisol, androgen function and ultimately the proliferation of milk gland cells (Barrett et al. 2005). Oxidized low density lipoprotein (lectin-like) receptor 1(LOX1) is also responsible for fat%age and fat yield (Riaz et al. 2008). Khatib et al. (2006) also identified association of this gene with milk-fat yield and percentage. Stearoyl-CoA desaturase (SCD) is also involved in milk fat%age and fat yield. (Barrett et al. 2005) and is a multifunctional complex enzyme important in the cellular biosynthesis of fatty acids.

Network Analysis

To determine in silico networking of candidate proteins, String data base was used (string-db.org). Biological networks for CYP11b1, OLR1 and SCD proteins were predicted. Along with the networks, interaction scores were also calculated. Three dimensional protein structures were also predicted with Pdb identifiers. This information was accessible for

CYP11b1 and OLR1 but no structural information was provided for SCD.

Results

In silico prediction of protein-protein interaction was performed for three candidate proteins. Results of each protein have been given below:

CYP11b1

Analysis of CYP11b1 network provided ten functional partners; CYP11B2, CYP17A1, CYP19A1, HSD3B2, HSD17B6, HSD3B1, HSD17B3, HSD17B1 and ENSG00000232414 (Fig-1). It was a closely related network and all of associations were strong with higher score values for interaction. These values have been shown in table-1. Along with this information, three dimensional structure of CYP11b1 protein was also predicted with 34% homology. This structure has been mentioned in Fig-1.

OLR1

Analysis of OLR1 revealed a closely linked network with ten functional partners; APOB, HSPA4, NOS3, DIF, CRP, AKT1, VEGFA, CCL2, ACE and DECR1 (Fig-2). Four out of total were showing higher scores for interaction; HSPA4, APOB, NOS3 and DIF. Remaining were showing values below 0.80 (Table-2). Three dimension structure prediction was performed with 99.3% homology (Fig-2).

SCD

Analysis of SCD revealed ten functional partners; CYB5A, FADS1, FASN, UBC, NR1H4, PPARG, SREBF1, NROB2, INS and LEP (Fig-1). SREBF1, LEP, PPARG, INS and CYB5A were showing higher interaction scores while remaining were depicting lower values for interaction (Table-3). Three dimensional protein structure could not be predicted for this protein.

Discussion

Biological networking of macromolecules is essential field to completely understand the functional activities of cells (Barabasi and Oltvai, 2004). Protein interactions do have a role in defining cells ability to cope up many challenging tasks at the same time. Some proteins are responsible for core functioning in a metabolic pathway and others may have regulatory role (positive or negative). Balance of these all would define the successful happenings in the cell. Prior knowledge of protein functionality is essential before screening a gene for variations and their associations (Bork et al. 2004; Colland et al. 2004; Ge et al. 2004). In this context, present study was planned to investigate three functional attributes of milk quality trait (fat content); CYP11b1, OLR1 and SCD. Network analysis revealed no sharing of functioning pathways. All three were having own networks where these control milk fat content. CYP11b1 was mitochondrial gene, OLR1 was lipoprotein receptor and SCD was enzyme controlling biosynthesis of fatty acids. As all were different in nature so their functions were also different from each other. This information is useful in molecular characterization of these genes for the search of valid genetic markers that can enhance their function. For this scientists can target strong interactions that have direct effect on the targeted signaling pathway and which can enhance the efficiency of that reaction.

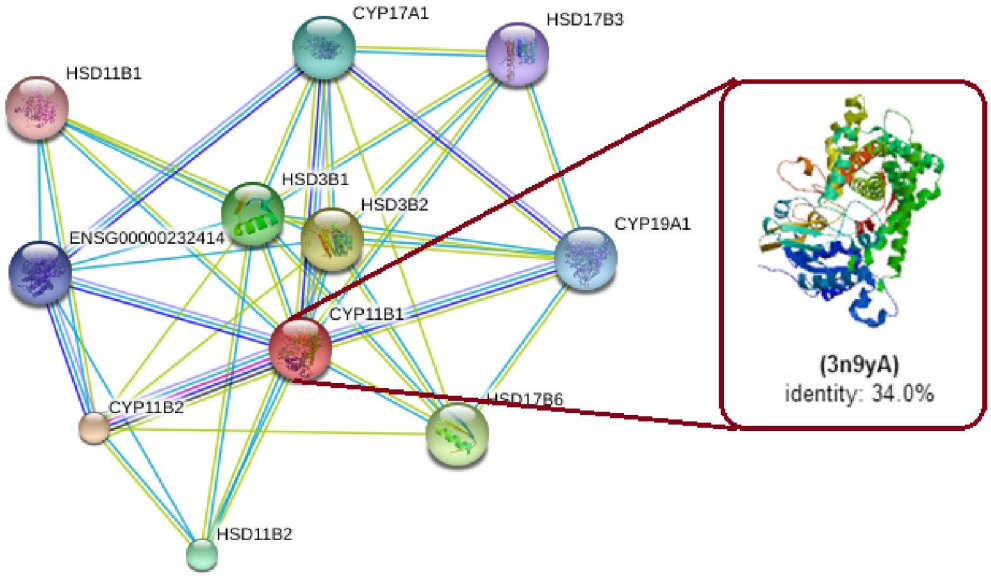

Fig-1: CYP11b1 Network View. *Network showing ten functional partners. 3D protein configuration is also predicted with 34% homology.*

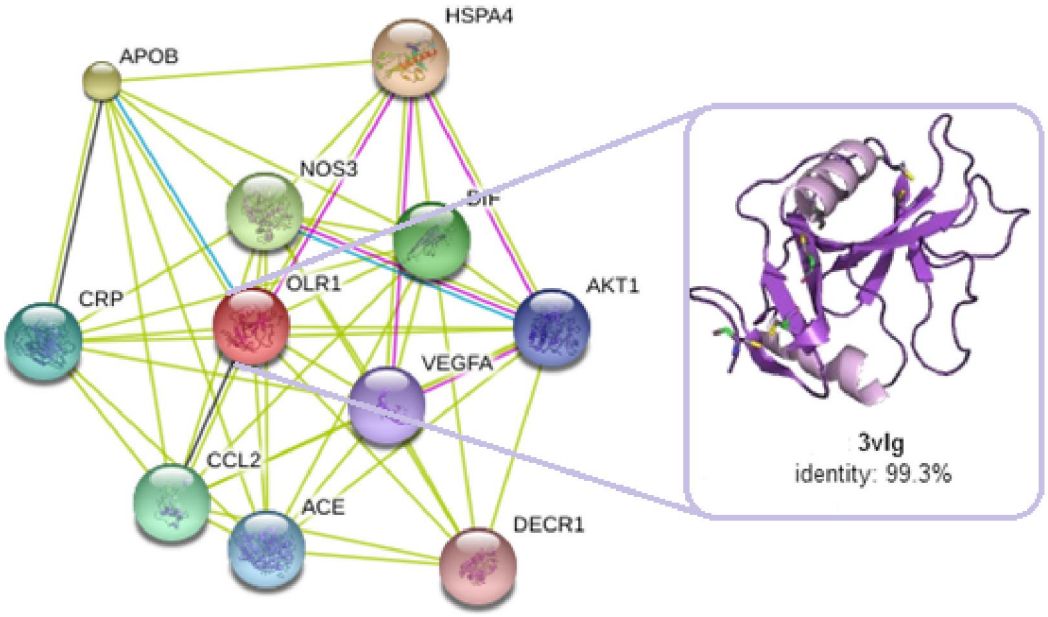

Fig-2: OLR1 Network View. *Network showing ten functional partners. 3D protein configuration is also predicted with 99.3% homology.*

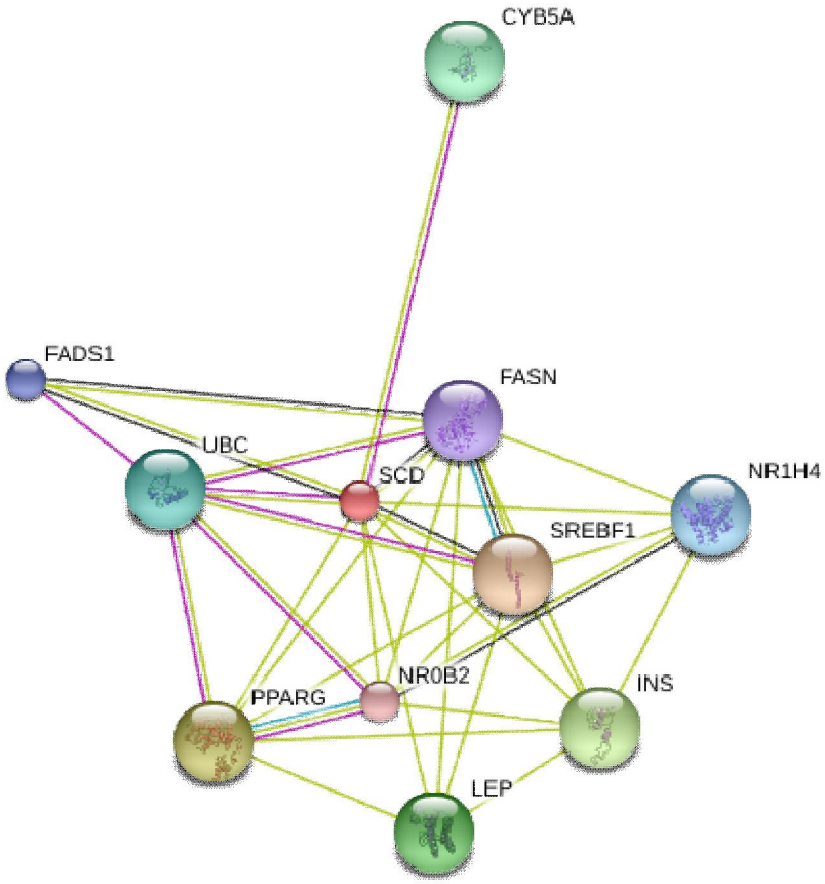

Fig-3: SCD Network View. *Network showing ten functional partners.*

Table-1: Predicted Functional Partners of CYP11b1

		Score
CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2; Preferentially catalyzes the conversion [...] (503 aa)	0.965
HSD3B2	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2; 3-beta-HSD is a b [...] (372 aa)	0.952
HSD17B6	hydroxysteroid (17-beta) dehydrogenase 6 homolog (mouse); NAD-dependent oxidoreductase with bro [...] (317 aa)	0.951
HSD3B1	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1; 3-beta-HSD is a b [...] (373 aa)	0.937
HSD11B2	hydroxysteroid (11-beta) dehydrogenase 2; Catalyzes the conversion of cortisol to the inactive [...] (405 aa)	0.932
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1; Conversion of pregnenolone and progeste [...] (508 aa)	0.929
CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1; Catalyzes the formation of aromatic C18 [...] (503 aa)	0.928
ENSG00000232414	cytochrome P450, family 21, subfamily A, polypeptide 2 isoform a (495 aa)	0.918
HSD17B3	hydroxysteroid (17-beta) dehydrogenase 3; Favors the reduction of androstenedione to testostero [...] (310 aa)	0.917
HSD11B1	hydroxysteroid (11-beta) dehydrogenase 1; Catalyzes reversibly the conversion of cortisol to th [...] (292 aa)	0.916

Table-2: Predicted Functional Partners of OLR1

		Score
HSPA4	heat shock 70kDa protein 4 (840 aa)	0.945
APOB	apolipoprotein B (including Ag(x) antigen); Apolipoprotein B is a major protein constituent of [...] (4563 aa)	0.939
NOS3	nitric oxide synthase 3 (endothelial cell); Produces nitric oxide (NO) which is implicated in v [...] (1203 aa)	0.902
DIF	Tumor necrosis factor Precursor (TNF-alpha)(Tumor necrosis factor ligand superfamily member 2)([...] (233 aa)	0.901
CCL2	chemokine (C-C motif) ligand 2; Chemotactic factor that attracts monocytes and basophils but no [...] (99 aa)	0.892
CRP	C-reactive protein, pentraxin-related; Displays several functions associated with host defense- [...] (224 aa)	0.886
ACE	angiotensin I converting enzyme (peptidyl-dipeptidase A) 1; Converts angiotensin I to angiotens [...] (1306 aa)	0.878
AKT1	v-akt murine thymoma viral oncogene homolog 1; General protein kinase capable of phosphorylatin [...] (480 aa)	0.865
VEGFA	vascular endothelial growth factor A; Growth factor active in angiogenesis, vasculogenesis and [...] (412 aa)	0.859
DECR1	2,4-dienoyl CoA reductase 1, mitochondrial; Auxiliary enzyme of beta-oxidation. It participates [...] (335 aa)	0.859

Table-3: Predicted Functional Partners of SCD

		Score
SREBF1	sterol regulatory element binding transcription factor 1; Transcriptional activator required fo [...] (1177 aa)	0.952
PPARG	peroxisome proliferator-activated receptor gamma; Receptor that binds peroxisome proliferators [...] (505 aa)	0.926
INS	insulin; Insulin decreases blood glucose concentration. It increases cell permeability to monos [...] (200 aa)	0.917
LEP	leptin; May function as part of a signaling pathway that acts to regulate the size of the body [...] (167 aa)	0.917
CYB5A	cytochrome b5 type A (microsomal); Cytochrome b5 is a membrane bound hemoprotein which function [...] (134 aa)	0.901
UBC	ubiquitin C (685 aa)	0.886
NR1H4	nuclear receptor subfamily 1, group H, member 4; Receptor for bile acids such as chenodeoxychol [...] (472 aa)	0.878
FADS1	fatty acid desaturase 1; Component of a lipid metabolic pathway that catalyzes biosynthesis of [...] (501 aa)	0.865
FASN	fatty acid synthase; Fatty acid synthetase catalyzes the formation of long- chain fatty acids f [...] (2511 aa)	0.861
NR0B2	nuclear receptor subfamily 0, group B, member 2; Acts as a negative regulator of receptor-depen [...] (257 aa)	0.847

References

1. A.L. Barabasi, Z.N. Oltvai. 2004. Network biology: understanding the cell's functional organization. Nat. Rev. Genet. 5: 101–113.
2. Aloy P, Russell RB. 2004. Ten thousand interactions for the molecular biologist. Nature Biotechnol. 22:1317–1321.
3. B. Kholodenko, M. B. Yaffe, and W. Kolch. 2012. Computational Approaches for Analyzing Information Flow in Biological Networks. Sci. Signal. 5, re1.
4. Barrett JC, Fry B, Maller J, Daly MJ. 2005. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics. 21(2): 263-265.
5. F. Colland, X. Jacq, V. Trouplin, C. Mougin, C. Groizeleau, A. Hamburger, A. Meil, J. Wojcik, P. Legrain, J.M. Gauthier. 2004. Functional proteomics mapping of a human signaling pathway Genome Res. 14: 1324–1332.
6. H. Ge, A.J. Walhout, M. Vidal. 2003. Integrating 'omic' information: a bridge between genomics and systems biology. Trends Genet. 19: 551–560.

7. Khatib, H.; S.D. Leonard, V. Schutzkus, W. Luo, Y.M. Chang (2006). Association of the OLR1 Gene with Milk Composition in Holstein. Dairy Cattle. J. Dairy Sci. 89:1753–1760.
8. M. Ashburner, C.A. Ball, J.A. Blake, D. Botstein, H. Butler, J.M. Cherry, A.P. Davis, K. Dolinski, S.S. Dwight, J.T. Eppig. 2000. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat. Genet., 25: 25–29.
9. M. N. Riaz, n. A. Malik, f. Nasreen and j. A. Qureshi. Molecular marker assisted study of kappa-casein gene in Nili-Ravi (buffalo) breed of Pakistan . Pakistan Vet. J., 2008, 28(3): 103-106.
10. N. Arimura, C. Menager, Y. Fukata, K. Kaibuchi. 2004. Role of CRMP-2 in neuronal polarity. J. Neurobiol., 58: 34–47.
11. P. Bork, L.J. Jensen, C. von Mering, A.K. Ramani, I. Lee, E.M. Marcotte. 2004. Protein interaction networks from yeast to human. Curr. Opin. Struct. Biol. 14: 292–299.
12. S.H. Strogatz. 2001. Exploring complex networks. Nature. 410: 268–276.

9/25/2014