Review Article

Penggunaan Hewan pada Nutrigenomik
Animal Models for Nutrigenomics

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Abstract

The development of nutrigenomic studies has brought about a number of new research tools (transcriptomics, proteomics and metabolomics), which are important in animal nutrition and food research. This review presents an overview on the application of nutrigenomics tools in animals models. The study of how genes and gene products interact with dietary chemicals to alter phenotype and, conversely, how genes and their products metabolize nutrients is called nutritional genomics or nutrigenomics. Some example studies showed the importance of nutrigenomic from animal site aspects.Application of these modern research tools, known as "omics" technologies, should yield new knowledge on the course of molecular processes in animal organisms and a more precise evaluation of the biological properties of feeds. The development research using nutrigenomic approach on animals has been delivered for the improvement of food quality and economic benefit in both livestock industry and other species.

1. Background

In 1986, Thomas Roderic, one of American scientist proposed the concept "Genomics". There were two terms, structural genomics (whole-genome sequencing) and functional genomics with (gene function identification). The completion of human genome project in2001was lead to post genomic era. Continuous research and studies are more actively to develop and explore the genomics technology (Chen and Zhao, 2013).

In 1999, Della Penna defined nutritional genomics as the general approach to gene discovery that are synthesized or accumulated by plants and other organism (Kore et al., 2008). Diet and feeding strategies play an important role in determining the basic physiological processes that influence the health and wellbeing of animals and ultimately influence the efficiency of production. Most of research concentrated on nutrient deficiencies and impairment of health (Mutch et al., 2005; Afman and Muller, 2006). However, it has often been difficult to easily evaluate the effects of specific nutrients, combinations of nutrients and nutrient interactions because of the lack of straightforward biological indicators that respond to even the simplest changes in nutrition or nutritional status. Over the last decade, advances in the biochemical technologies available for examining functional genomics have provided a number of new molecular tools for evaluating responses to nutritional strategies (Banerjee et al. 2015; Chen and Zhao, 2013).

2. Definition

Nutritional genomics (nutrigenomics) is an emerging science that studies the molecular relationships between nutrition (diet) and the response of our genes, to determine how even subtle genetic changes can affect human and animal health (Afman and Muller, 2006; Banerjee et al. 2015;Neeha and Kinth, 2012; Kaput and Rodriguez, 2004). Nutrigenomics have the potential to rapidly learn about the hidden effects of nutrition and feeding strategies on digestive processes, immunity, and reproduction.

The conceptual basis for nutrigenomicscan be builds on five premises: *1)* Common dietary chemicals act on the human genome, either directly or indirectly, to alter

gene expression or structure; *2*) Under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases; *3*) Some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases;*4*) The degree to which diet influences the balance between healthy and disease states may depend on an individual's genetic background; and*5*) Dietary intervention based on knowledge of individual's nutritional requirement, nutritional status, and genotype can be used to prevent, mitigate or cure chronic disease (Kaput and Rodriguez, 2004).

3. Rationale and aims

The basic concept is that chemical nutrients affect gene expressions in a specific mode by switching from health to an abnormal (pathophysiological) condition, or vice versa. (Kaput and Rodriguez, 2004). Aim of nutrigenomics research is to study genome-wide influences of nutrition, focus on the role of metabolic stress in the genesis of metabolic syndrome and final goal is primary on health and disease prevention (Afman and Muller, 2006). The ability to identify the markers of early phases of diet-related diseases, in order to do nutritional intervention can return the patient to a healthy state. Another aim is to demonstrate the effects of biologically active food components on health, leading to the design of functional foods that will keep individuals healthy according to their own specific needs.

Nutrients relay signals that tell a specific cell in the body about the diet. Basically, a sensory system in the cell interprets information from nutrients about the dietary environment. Once the nutrient interacts with this system, it changes gene (genomics) and protein (proteomics) expression and metabolite production (metabolomics) accordingly (Mutch et al., 2005). Therefore,different diets elicit different patterns of gene and protein expression and metabolite production. Nutrigenomics describes the patterns of these effects, which are called molecular dietary signatures (Farhud et al., 2010; Kaput and Rodriguez, 2004).

Nutrients and genome interact at two levels:

- Nutrients can induce or repress gene expression altering individula phenotype;
- Single nucleotide polymorphism (SNPs) can alter the bioactivity of important metabolic pathways and mediators and influence the interaction and metabolic.
Macronutrients such as: proteins and lipids, also micronutrients such as: minerals and vitamins. (Farhud et al., 2010).

Dietary chemicals can affect gene expression directly or indirectly. At the cellular level, nutrients may: *1*) act as ligands for transcription factor receptors; *2*) be metabolized by primary or secondary metabolic pathways, thereby altering concentrations of substrates or intermediates; or *3*) positively or negatively affect signal pathways. This is shown schematically in Fig. 1.
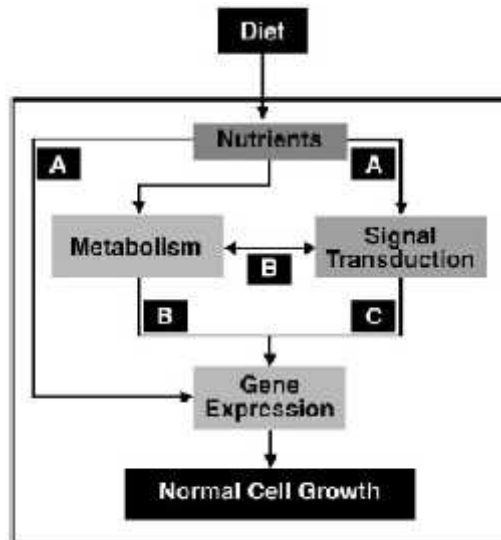
Figure 1. Fate and activities of nutrients in the cell. Nutrients may act directly as ligands for

transcription factor receptors (*pathway A*); may be metabolized by primary or secondary metabolic pathways, thereby altering concentrations of substrates or intermediates (*pathway B*) involved in gene regulation or cell signaling; or alter signal transduction pathways and signaling (*pathway C*) (source: Kaput and Rodriguez, 2004).

Transcription factors are the main agents of nutrients which can interfere with gene expression. According to Afman and Muller (2006), the human genome there are 48 members of nuclear receptor superfamily of transcription factors such as; peroxisome proliferator activator receptor- (PPAR) responding to fatty acid binding) and liver X receptor   (binding cholesterol metabolites).

4. Technology of nutrigenomics
Some technologies involved in the nutrigenomics, proteomics and metobolomics studies. Related research in genomics technologies such as DNA chip (cDNA microarray), mRNA differential display. Proteomics technology is gene expression profile responding to dietary consist of sample preparation, separation of protein and identification of separated protein. Metabolomics technology involved the endogenous small molecule metabolite as a whole and its variation for cells, tissues, or organs mechanism. Metabolomics focus on terminus in the bioreactor. Magnetic Resonance Spectroscopy (NMR) and Mass Spectrometry (MS) could be use for metobolomics analysis detection (Dawson, 2006; Chen and Zhao, 2013).
Study of gene expression in cattle using oligo-based and cDNA microarray such as (Dawson, 2006):
- Evaluation of gene expression patterns associated with pathogenic microorganism, disease chalenge and immune function;
- Evaluation of gene expression patterns associated with milk performance, muscle development, and meat quality;
- Examination of expressed gene patterns that are important in follicular development and embryo development.

There are many more research and studies related to the nutrigenomics and nutrigenetic. Microarray studies in cattle have focused on characterization of gene expression of embryo development during pregnancy and periparturient periods.

5. Nutrigenomics application in farm animal

Nutrition research is studying how dietary constituents at the molecular level can optimize and maintain cellular, tissue and organ balance to help prevent disease. A number of molecular tools are used to evaluate the effects of dietary strategies on gene expression and the flow of information from the genetic code (DNA) to biological functions and structure(Afman and Muller, 2006; Banerjee et al. 2015; Neeha and Kinth, 2013; Kaput and Rodriguez, 2004).

The importance of nutrigenomics on animal farm industry has lead into better understanding that proper nutrition or diet can fight againts several disease, in terms of cost production efficiency (Ghormade et al., 2011; Kaput and Rodriguez, 2004). The proper coordination between diet and omics is important key regulator in maintain animal health. These include transcriptomic tools that quantitatively evaluate the formation of m-RNA (gene expression), proteomic tools that measure the formation of specific proteins (protein expression) and metabolomic tools that measure the products from the resulting metabolic activities (metabolic profiling). Perhaps the most powerful molecular tools for examining nutrient effects at the most basic level comes from high-throughput microarrays (gene chips), that allow for the examination of the expression of thousand genes at a time(Banerjee et al., 2015; Neeha and Kinth, 2013; Kaput and Rodriguez, 2004).

Application of nutrigenomics in animal:
- To develop animal feed/ food regarding to mismatch of their genotype;
- To select nutrient fine-tune with genes of animal;
- Tounderstand the role od nutritional management in animal performance (production/ disease);
- Nutrient and gene interaction;
- To understand the mechanism of animal aging process;
- Nutrigenomics and immune system interaction and association;
- Correlation between nutrigenomics and disease.
Newer technologies have been widely applied to develop research and study to solve the puzzle above (Kaput and Rodriguez, 2004, Zdunczyk and Pareek, 2009).

6. Nutrigenomics in poultry production

Variation in genome (DNA) combined with variation in nutrition for poultry production will give variation in performance as end result. In poultry industry, development in improved of animal feed and breeding animals with the most profitable genes has greatest profit because it reduced cost of production. Some examples of nutrigenomics research based on diet related gene expression in chicken showed in Table 1 (Zuidhof et al., 2014; Banerjee et al., 2015).

Table 1. Diet related gene expression in chicken

Feed Intake	Gene Expression	References
Nicotinic acid	Lipid metabolism in Arbor Acres (AA) and Beijing You (BJY) broiler chicken, hepatic genes apolipoprotein A-I (ApoA-1) and apolipoprotein B (Apo B)	Jiang et al. (2014)
Vitamin E	Lipid oxidation and antioxidant gene expression to reduce stress and enhanced meat quality	Li et al. (2009)
Vitamin E	Immune protein againts bacterial lipopolysaccharide associated infection	Kaiser et al. (2012)
Zinc and Selenium	Zinc actively regulate transporter gene in intestine, selenium is a key regulator of gender specific gene regulation	Brennan et al. (2012)
Diet with 80%	Reduce fecal mineral excression without growth	Yuan et al. (2011)

Mintrex-Zn/ Mn	performance compromised	
Diet with immunomodulators like ascorbic acid, 1,3-1,6 -glucans and corticosterone	Cytokine gene expression (IL-1 , IL-2, toll-like recptorss 4 and 15) in spleen	Kumar et al. (2011)
Lead containing feed	Decrease regulation of sugar, peptide and amino acid transporters. Increase regulation of stress related gene	Ebrahimi et al. (2015)
Feed with mannan-oligosaccharides	Expression of 77 protein synthesis gene, including superoxide dismutase 1, lumican 2-microglobin, apolipoprotein A-1, fibronectin 1	Xiao et al. (2012)
Effect of oil by product from conjugated linoleic acid (CLA)	Lipogenic gene expression	Kim et al. (2009)

The study of the effect of commercial selection on the growth, efficiency, and yield of broiler chickens has been done. There were three strains of broiler chickens (180 per strains) took place for the experimental study. Growth rate, feed intake, and measures of feed efficiency (feed conversion ratio, residual feed intake, and residual maintenance energy requirements) characterized during 56 days period.

The results showed that genetic progress over 50 years has been able to reduce the amount of feed required to produce chicken meat by one-halfm and breaast meat by 67%. Modern strain chicken growing rapidly because they have tremendous genetic potential to grow (Figure 2). The broiler industries have undoubtedly proven the challenging for the high reproductive meat production (Zuidhof et al., 2014).
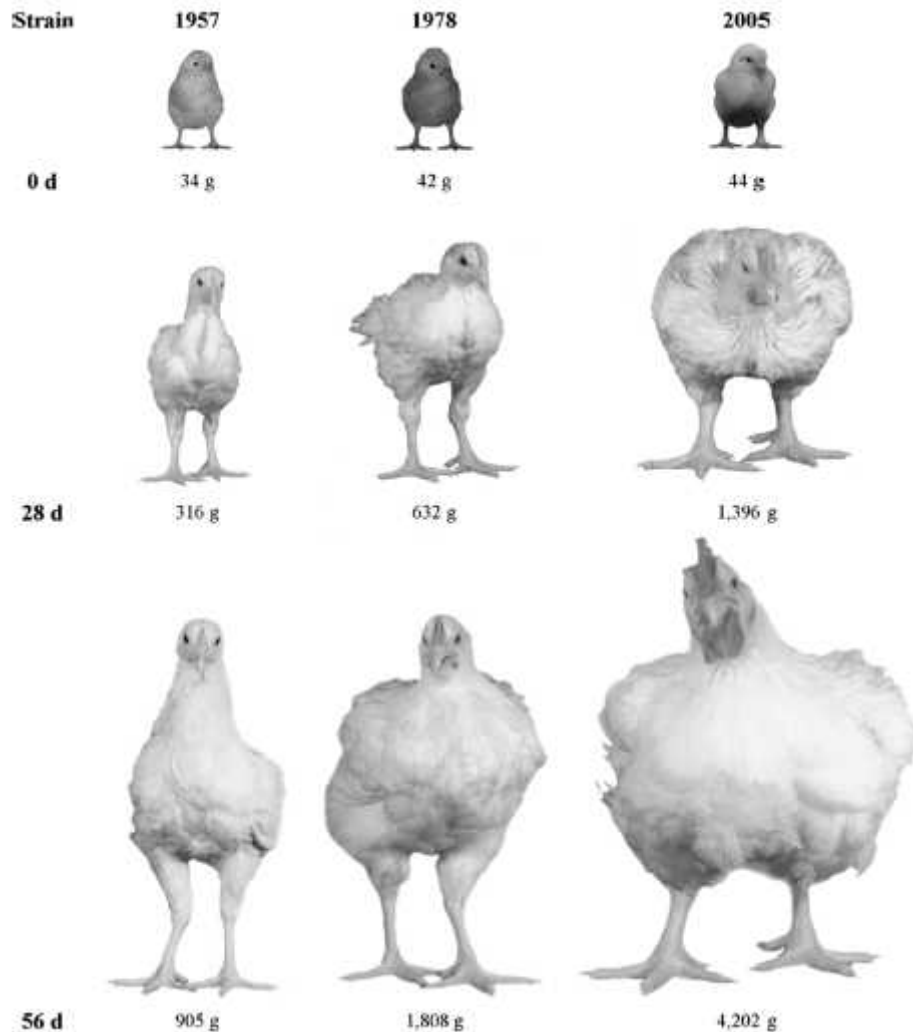
Figure 2.Age-related changes in size (mixed-sex BW and front view photos) of
University of Alberta Meat Control strains unselected since1957 and 1978,
and Ross 308 broilers (2005). Within each strain, images are of the same bird
at 0, 28, and 56 d of age (Source: Zuidhof et al., 2014).

7. Nutrigenomics in dairy cows

The sequencing of bovine genome was completed in 2003, phenotypic expression marker research using gene expression profiles increased the mechanism of reproductive function and their phenotypic expression (Berglund, 2008). Single nucleotide polymorphism (SNPs) is large array for genetic study to identify variation of base pair in the nucleic acid and genomic selection.

Genetic information of bovine carried in mitochondrial genome (16.000 bp). The bovine genome consist of 29 autosomes and two sex chromosomes, contain approximately three billion nucleic acid base pairs (Dawson, 2006). Many studies have been developing by some researchers and animal industry such as for dairy milk production. Fertility is close related to the lactation period which is the most factor that influence on the milk production (Amer et al., 2016; Berglund, 2008, Royal et al., 2002).

Genetic parameters in dairy cows have been studied to predict fertility of dairy cows (Royal et al., 2002; Veerkamp and Beerda, 2007). The genetic evaluation models showed that combination of some factors have some impacts on reproductive performance of dairy cows. The result of the study demonstrated that direct gestation

length (GL) genetic component was the most useful candidate to predict trait for fertility (Amer et al., 2016). Table 2 showed association between milk component and fertility performance in dairy cow (Bastin et al., 2016).

Table 2. Association of milk component and fertility performance in dairy cow

Milk Component	Association with fertility	References
Fat content	Unfavorable	Kristula et al. (1995); Madouasse et al. (2010); de Vries and Veerkamp (2000)
Protein content	Favorable	Madouasse et al. (2010), Podpecan et al. (2008)
Urea content	Unfavorable	Rajala-Schultz et al. (2001), Butler et al. (1996), Konig et al. (2008)
Acetone content	Unfavorable	Reksen et al. (2002)

Fertility in dairy cows could be predicted by progesterone profiles (Tenghe et al., 2015; Tenghe et al., 2016). Genomic study of endocrine fertility traits indicated the presence of several potential candidate genes underlying in the target regions (Tenghe et al., 2015). Genetic parameters (luteal activity to first service, first luteal phase length, length of first interluteal interval, and length of first interovulatory interval) were used to define endocrine fertility traits from in-line milk progesterone profiles. The result of the study indicated that in-line progesterone records ca be used to define and explore several heritable endocrine fertility traits (Tenghe et al., 2016).

Other studies mentioned about the phenotype using mid-infrared (MIR) predicted trait correlation to disease traits (clinical ketosis, displaced abomasum, milk fever, metabolisc disorder, claw and leg disease). It was concluded that some indicator traits should be considered in the selection index toward improvement into the fertility and health of dairy cows (Bastin et al., 2016; Bionaz, 2014).

8. Nutrigenomics in pork industry

The increasing demand of pig meat of world wide has great attention for the industry. Nutrigenomics approach is the only possible way to achieve the reduction of raw material consumption for maximum benefit. Some studies like feed combination using special diet based on microarray study have been applied. Table 3 showed diet related gene expression studies in pig which could be considered for pork industry to improve their performance in meat quality and production (Banerjee et al., 2015).

Table 3. Diet related gene expression in pig

Feed Intake	Gene Expression	References
Olive oil	Insulin pathway related genes, cAMP-dependent regulatory, protein kinase type II alpha (PRKAR2A), catalytic sub unit of protein phosphatase 1, beta isoform (PPP1CB)	Park et al. (2012)
Soy Protein	Organic anion transporter polypeptide 2, calnexin, glutathione-S-transferase, peptide methionine sulfoxidereductase	Schwerin et al. (2002)
Camelina sativa	Hepatic gene expression of cytochrome 8b1 (CYP8B1), aldehyde dehydrogenase 2 (Aldh2) and thiosulfate transferase (TST)	Meadus et al. (2014)
Wheat bran based diet	Cationic AA tranxporters and myosin	Garcia et al. (2015)
Maternal dietary protein	Mycostatin gene	Liu et al. (2011)

Diet with high (18%) and low (14%) protein	The expression of acetyl CoA carboxulase (ACC), Fatty acid synthase (FAS) and sterol regulatory element binding protein 1c. The expression of lipoprotein lipase (LPL), carmitine palmtoyltransferase-1B (CPT-1B), peroxisome proliferator-activated receptor (PPAR) and adipocyte-fatty acid binding proteins	Zhao et al. (2010)
Diet with high cholesterol	Hepatic gene expression	Cai et al. (2015)
High (26%) and low (18%) protein diet with or without fermentable carbohydrate	Lower expression of monocarboxylate transporter 1 and higher expression of TNF-a and IL-8 with high protein diet	Tudela et al. (2015)
Diet with high and low energy content	High energy content diet up-regulated the expression of NADH dehydrogenase ubiquinone 1 beta 9, pyruvate kinase, enolase 3, muscle creatine kinase and isocitrate dehydrogenase 3	Dal Monego et al. (2007)

9. Nutrigenomics in other species

Study of nutrigenomics in animal application indicated rapid progress into wide-ranging species such as marine mammals, particularly seals and sea lions. Spitz et al. (2014) has developed biomarkers to detect physiological responses (disease, nutrition and other stressor). The study was used four Steller sea lions and took 70-day trials time. Environmental and stressor factors was divided into three stages (preliminary, acute and chronic). Sample collected during each stage and processed completely by molecular techniques. Eight different primer (for eight specific genes) were used for the molecular study.

Blood hematology profile measurement compared based on each phase of the experiment. Expressions of all target genes were significantly modulated during each phase (dietary manipulation). The study showed that Steller sea lions that had different nutritional stress of stage expressed pertinent (specific) of biomarkers. Further study considering other factors (age, sex, reproductive or immune status and environmental conditions) may influence and need to be tested Spitz et al. (2014).

10. Animal as Agrimedical Model for Pediatric Nutrition and Metabolism

Agriculture and Medical or Agrimedical model used neonatal piglet as the premier model for pediatric nutrition, metabolism, and toxicological studies. Piglet model is commonly used rather than other model (such as rat) because of the similarities between piglets and infants (represent human). Piglet models have contributed to some studies and development such as: long-chain polyunsaturated fatty acid, pre and probiotics for the optimum of intestinal health, pathology of necrotizing enterocolitis, parenteral nutriton, protein synthesis of low-birth weight infants and neuroscience and brain development (Odle, et al., 2014).

Important key attributes using piglet model for pediatric nutrition shown in Table 4 (Odle, et al., 2014). Although some attributes differ between piglet/ sow compare to human/ infant, the piglet model has significant contribution of pediatric nutrition's understanding.

Table 4. Some comparative attributes between piglets and human

| Attributes	Piglets/ Sow	Infant/ Human
Mature milk macronutrient composition and consentration Ca and P ratio	Higher (fat, protein, Ca and P) except carbohydrate ± 1,5	Lower ± 1,5
Intestinal anatomy and physiology (intestinal size, histology, microbiota)	Digestive tract exceeds threefold, other almost similar and need further study.	
Precocious and rapid growth rate (Figure 3.)	30% higher than infant	Lower than piglet
Lipid nutrition and metabolism **- Fatty acid oxidation for energy** **- Bioactive lipids and epigenetic effect on development (Eicosanoids and docosanoids: prostaglandins, prostacyclins, thromboxanes, leukotrines, resolvins and protectins)**	Similar Metabolized by the liver and reesterified with -oxidative flux Synthesis of cerebral prostaglandins related to cerebral homodynamic	 Glucose from maternal ciculation Prostaglandin production related to cerebral
Carbohydrate nutrition and metabolism: **- Carbohydrate composition in milk** **- Carbohydrate digestion** **- Monosaccharide absorption in intestinal membrane** **- Glycogen metabolism** **- Gluconeogenesis**	Lower Higher pancreatic amylase secretion around weaning Present in neonatal pig Liver provides ~15% of glycogen Very high (~15 g/kg body weight per day)	Higher (10 – 100 times greater concentration of milk oligosaccharides). Higher pancreatic amylase secretion at birth Present in infant at birth Liver provides ~40% of glycogen Lower
Protein and Amino acid nutrition and metabolism **- Content of amino acid** **- Absorption of colostralimmunoglobulins in neonatal pigs**	Similar, but different proportion Transfer IgG using epitheliochoreal placenta	 Transfer IgG using hemochorial placenta
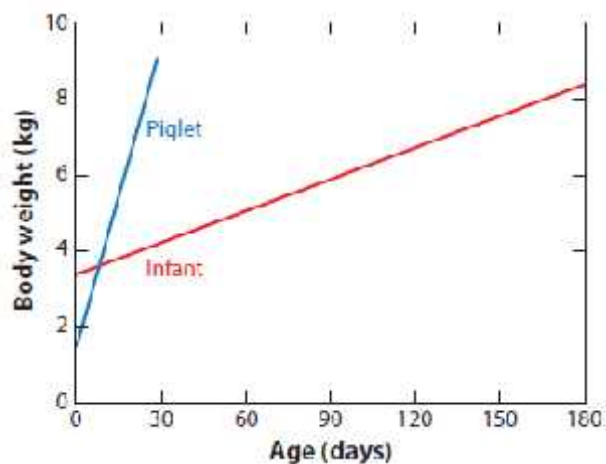
Figure 3. Comparative growth rates of newborn pigs and human infants during their respective suckling age ranges (Source: Odle et al., 2014).

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