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Single Nucleotide Polymorphism Applications in Animals

Betelhem Seyoum Dersso
Ethiopian Institute of Agricultural Research
(National Agricultural Biotechnology Research Center)

Abstract
Polymorphism occurs between individuals of the same species. It can be distinguished phenotypically in production, disease resistance and tolerance, coat color, height, weight… etc and genotypically using molecular markers for instance Restriction Fragment Length Polymorphisms (RFLPs), Minisatellites or VNTRs (Variable Numbers of Tandem Repeats) Microsatellites or SSRs (Simple Sequence Repeats), large (copy number variants) and small segmental deletions/insertions/duplications, Single Nucleotide Polymorphisms (SNPs).SNPs are changes of single base to another base in a given region of the genome. It is widely accepted molecular marker due to high throughput technology and statistically sound approach. They are used to identify candidate genes, gene mapping, QTL identification, and generally applied in marker assisted breeding. It has been used in disease diagnosis and pharmacology to identify the correct medication for the individual patients. It has also advantage in food safety and quality assurance scheme. It helps to recognize the species in the meat market, which is protected from illegal substitution of high price meat with low price one and unhealthy meat. Moreover SNPs are better marker than others in its application and advanced technology that support its acceptability.Therefore, this review article illustrates the application of SNPs (single nucleotide polymorphism) markers.
Keywords: SNPs, Genomics, Breeding, Disease, Food safety

1. Introduction

Polymorphisms take place in two or more visible variations in the phenotypes and genotypes of a particular population of the same species, at the same habitats and times. Natural selection and adaptability to the specific environment play an important role for the divergence of a given population. Spatial difference, competition to resource and specialization or artificial selection to some economically important and complex trait able to create the alteration between populations. Generally the interaction of environment and genotype are influencing the organism phenotype. The genetics, environmental cues and randomly assigned during development might determine its variation (Lemair, 2005). In the recent time genetic polymorphism has been given a great emphasis to understand the diversity and functional change of an organism towards the very initial stage to improve agricultural production, animal and human medication and conservation of biodiversity. Studying genetic polymorphisms also assist to understand the evolutionary information and ancestral relationships of the organisms. Genetic and phenotypic diversity permits populations to familiarize to environmental fluctuations, making them less disposed to extermination.

In molecular biology it is described as certain types of modification in the genome of the individual organism. Genetic polymorphism is the result of nucleotide sequence deletion, insertion, and alteration at the time of DNA replication. Meiosis and mitosis similarly allow genetic variations through a process of recombination, random segregation and independent assortment of chromosomes, while the cells are dividing (science learn, 2011). A change in the gene sequence causes functional variability, in production, disease susceptibility, resistance and tolerance, adaptability to the environment and other factors. Individuals may respond differently to common environmental challenges, and the individual's genetic profile tempts to differential response. There are certain type of genetic polymorphism markers such as Restriction Fragment Length Polymorphisms (RFLPs), Minisatellites or VNTRs (Variable Numbers of Tandem Repeats) Microsatellites or SSRs (Simple Sequence Repeats), large (copy number variants) and small segmental deletions/insertions/duplications, Single Nucleotide Polymorphisms (SNPs).

Single Nucleotide Polymorphisms (SNPs) are a widely used marker nowadays. This is because of abundances in whole genome and applied in every organism. In human DNA there is 0.1% polymorphism between two individuals this means 1bp changes in 1000bp DNA sequence (Shastry., 2009). "SNPs have many advantages over more traditionally used allozymes, microsatellite loci and chain-termination (Sanger) sequencing of select loci. These include availability in high numbers, presence in coding and non-coding regions, low-scoring error rates, relative ease of calibration between different studies and conform to simple models of mutation. Furthermore, high-throughput protocols used to SNPs genotyping that allow thousands of loci to score simultaneously, even from low quality DNA samples" (Haynes and Latch 2012). Therefore, they could be found in both the coding and the regulatory regions of genes with the ability to modify the gene function or expression and they may result in undesirable or desirable conditions, like diseases or yield increment. The aim of this review article is to describe about single nucleotide polymorphism application in molecular breeding and disease diagnosis of farm animals.

2. Discovery of SNPs

SNPs (single nucleotide polymorphisms) are one of the group of genetic polymorphism, which is the alteration of any single nucleotide in a DNA sequence at given locality; it accounts for almost 90% of all the known sequence variations (Collins et al., 1998) (Koopaee, and Esmailizadeh, 2015). They distributed throughout the genome and have estimated to occur at a frequency of approximately one in every 100 to 300 bp (Chorley et al., 2008). In genomic DNA such sequence is considere when it's least frequent allele is having a frequency of 1% or greater in a given population; any mutation of single nucleotide can't be considered as SNPs (vigenal et al., 2001,) otherwise it is point mutation or simple indel (insertion and deletion). SNPs having a minor allele frequency ≥20% are called "common SNPs". The bi-allelic characteristic of SNPs originates low-frequency of single base pair substitution. As Vigenal et al mentioned different studies confirm that the ratio of the two mutations are very low Therefore the of base change occur in the same position in the genome is very low (vigenal et al., 2001). Furthermore, two mechanisms of SNPs mutation are there transtion (purine-purine, pyrimiden-pyrimiden) A to G, C to T and transversion (purine-pyrimiden, pyrimiden-purine) A to C, A to T, G to C, G to T. There is a higher possibility of transitions than transversions. This is probablily as a result of molecular mechanism of the unexpected deamination of 5-methyl cytosine (5mC) to thymidine in the CpG dinucleotides (Wang et al., 1998), (Cooper et al., 1989).

Single nucleotide polymorphisms (SNPs) are stable, co-dominant markers and abundant in mammalian (Markovtsova et al. 2000; Nielsen 2000; Thomson et al., 2000). The estimation of human SNPs are approximately at 165,000 in 20,000- 25,000 genes that protein encoding regions cover, about 1.5% of the human genome (Lander et al., 2001, I.H.G.S., 2004). In the bovine genome 2.44 million SNPs are identified (Gibbs et al., 2009; Eck et al., 2009). The Bovine Genome Sequencing Consortium revealed roughly 62,000 high quality SNPs (Van Tassell et al., 2008). These SNPs have been utilized to make a whole-genome cattle SNP genotyping microarray. A novel high-density whole-genome bovine SNP Bead Chip, containing approximately 770,000 SNPs has been established by Illumina (Chorley et al., 2008,). In 2016 NCBI database shows,100,170,652 and 39,722,628 validated SNPs in Bostaurus;153, 953,962 and 100,815,862 validated SNPs in human; 54,004,408 and 28,361,713 validated SNPs in Ovis Aries; 21,303,759 and 13,010,394 validated SNPs in galus galus; 37,106,560 and 0 validated SNPs in Capra heiricus and 342 and 0 validated SNPs in Oreochromis niloticus. The drawback of these markers is the lesser informational content compared with that of a highly polymorphic microsatellite, but compensated wth the use of a higher number of markers (Werner et al. 2004, Werner et al. 2002). Therefore, their acceptance and amenability is increased time to time with the help of high throughput technology.

There are so many tools that are used to detect and discover SNPs, most of them have already been discussed by different authors including their positive and negative side. Identifying and genotyping of SNPs using a sequencing machine and microarray chip are common practice in every laboratory due to the ease of automated sequencer and microarray chip reader that reduce the cost and time consumption relative to the older techniques. Additionally, computer software and Bioinformatics have assisted a lot in the discovery and identification of single nucleotide polymorphism (SNP); markers from amplified segments of genomic DNA as well as the whole genome (Heaton et al. 2002). SNPs are considered as very amenable to high-throughput analysis, however, in vitro SNP discovery can be a lengthy and expensive process. Identifying SNPs in silico and then validating the polymorphisms in vitro provides a cost-effective method of SNPs discovery for mapping or association studies. Generally technological advancement in genotyping platform and the improvement of computational techniques to analyze these data have consequence impressive progressions in genetic association studies over the past decade. Studies that used to be restricted to a small number of candidate genes now cover the whole genome (Sauna and Kimchi, 2011), (Rasal et al., 2015).

The advent of high computational tools such as SIFT, PolyPhen, PANTHER, I-Mutant and SNPs3D is useful for predicting the effect of nsSNPs on protein (Capriotti et al., 2005; Johnson et al., 2005; Rajith and Doss, 2011). On the other hands genome wide association studies used such kind of tools; GenABEL enables the analysis of GWA data using R library. It implements effective storage and handling of GWA data, fast procedures for genetic data quality control, testing of association of single nucleotide polymorphisms with binary or quantitative traits, visualization of results (Aulchenko et al., 2007). These genome-wide association studies (GWASs) have made it achievable to recognize loci in genes that were not necessarily previously associated with the disease (Manolio et al., 2008). SCOPA Software for correlated Phenotype Analysis, MUGBAS multi species Gene-Based Association Suite so many other Bioinformatics and genetic data analysis application are there for single nucleotide polymorphism (SNPs) analysis.

3. Application of SNPs

Single nucleotide polymorphisms (SNPs) are essential for identifying the genetic mechanisms of complex traits. They are used as a molecular marker that are effective in the study of multifactorial disease diagnosis and Pharmacogenomics, parentage, forensic to pinpoint criminals, mapping and genome wide association studies for

complex traits, to predict specific genetic trait, to study evolutionary relationship of different species additionally it is applied in food safety and food quality assurance.

SNPs are tremendously useful in agriculture to investigate association, gene mapping and phylogenetic. They provide genomic markers of past events that shaping individuals, breeds and species. SNPs are used to identify regions influencing important economic traits in farm animals and crops,. Single nucleotide polymorphisms have also been shown responsibility for a number of economically desirable phenotypes in farm animals, such as the muscle hypertrophy phenotype callipyge and fertility phenotype Inverdalein sheep breed (Lee et al 2006), the fertility of sire that have good semen quality for a better conception rate in beef cattle (de Camargo et al., 2015).

3.1 In the breeding program and Genetic Diversity Assessment

The genetic improvement of livestock species is required to enhance their economical important trait such as milk, meat, egg, wool production, disease tolerance and resistance, etc. The conventional way of breeding program now a day is not as such productive as compared to marker assisted selection (MAS). This is because of the important traits which are controlled by multiple gene and quantitative inheritance. They are influenced by environment and different factors since they are subjected to allelic interaction like epistasis and polietrophy. Sometimes they do not show the correct picture of the animal genotype. It is time-consuming, labor intensive and costs; these drawbacks limit the effectiveness of phenotypic selection. Immeasurable trait or difficult to record like sex-linked or measured later in life are impossible to manage in this category. Marker assisted selection is advantageous and thriving the breeding program effectively. It can minimize the generation interval, cost and increase accuracy. As a result of this technique GEBV for production traits are often 70% or greater in North American Holsteins which is twice the level of reliability associated with traditional parent averages computed from pedigrees (Kharrati and Esmailizadeh, 2014).

They are one of the markers that are applied in marker assisted selection (MAS) which are highly informative and relatively precise. In a number of reasons, the application of SNPs markers are used as a replacement of pedigree information for artificial selection and used genetic diversity assessment; especially in the case of poor and unavailable pedigree information. The traditional genetic breeding value estimation is minimal in advantage as a result of no usage of the markers as well as do not trace alleles of individuals (Baumung and Solkner, 2003; Fernandez et al., 2005; Oliehoek et al., 2006; VanRaden., 2008). However SNPs are high density markers that hold over 10,000 markers. Therefore, SNPs markers are more accurate in breeding value estimation than microsatellite and other markers. Breeding value is estimated by combining pedigree and SNPs marker data or by using SNP markers alone (Bömcke, 2011). The best opportunity of SNPs as markers are they are mostly found in the coding area of DNA so that they affect directly function of protein and stable inheritance than other markers. The other advantage of SNP markers is that it is helpful for Mendelian inheritance and non Mendelian inheritance identification, which makes it promising to detect from which parent allele is inherited.

SNPs can be used to identify regions influencing important economic traits. They have also been shown to be responsible for a number of economically desirable phenotypes in sheep, cattle, goat, chicken and other farm animals. In sheep, the muscle hypertrophy phenotype callipyge and the fertility phenotype (Galloway et al., 2000, Freking et al., 2002). In cattle, SNPs associated with fertility trait located in X chromosome genes with male fertility traits validates the QTL and it became good candidate genes to apply in genetic evaluation without influencing female fertility traits (de Camargo et al., 2015). In the poultry sector, there is also the key issue that marekes disease is very important. Identification of the genes responsible for this disease resistance would be economically significant so that Cheng et al. (2012) identify these regions by genotyping SNPs with high throughput method. Therefor SNPs can support to detect QTL regions and candidate genes that have contributed to economically important trait. The combination of QTL mapping and SNP analysis is an effective approach for identifying candidate genes. The approach can reduce the list of candidate genes down in QTL as a sort out tool for further investigation and study (Yan et al. 2004) and these are examples of their application of in animal breeding.

Additionally, this marker helps to identify the genetic diversity of specific positions in the genome. This allows observing the lowest diversification of a population, where the initial step of polymorphism originated. They provide genomic landmarks of past events shaping individuals, breeds and species. SNPs markers enable the estimation of the complete genetic diversity, with the independence of a random population base. They are preferred for analyses of population genetic diversity, speciation and historical demography. These are as a result of lower variations in comparison with microsatellite marker and their abundance throughout the genome. At the same time the innovative techniques, automated screening, haplotype inference and statistical analysis play a greater role in the acceptance of SNPs. On the other hand complication to SNP analysis is a bias towards analyzing only the most variable loci, an artifact that is usually introduced by the limited number of individuals used to screen initially for polymorphisms yet it can be corrected using high number of samples. The drawback

of these markers is the biallelic nature of that there only two alleles in a population therefor, the information, content pre SNP marker will be very low than other marker like microsatellite. That means five SNP markers hold the comparable information to a single microsatellite marker (Beuzen et al., 2000). Further more, so many studies were there on Genetic diversity, population structure and relationships. Indigenous cattle populations of Ethiopia and Korean Hanwoo breeds using SNP markers (Edea et al., 2013), Ethiopian sheep population (Edea et al., 2017) and Horo and Jarsso chicken ecotype (Psifidi et al., 2013) studies are some example of diversity assessment.

3.2 In disease and pharmacogenomics

The focus on the health problem study in animal is the prospect of increasing productivity of human gain or using such as models for human disease research. The attention now is also being directed at the way to breeding of disease resistance. Diseases controlled by monogenic loci tend to be eliminated through years of breeding from the population. The Knowledge of the genes in this regard is very important that mutations, and interactions with other factors for effective exploitation of disease-resistant livestock or complete elimination of diseased livestock. On the other hand, some of the most economically important diseases of livestock are controlled by numerous genes and the interaction of host, pathogen and environment interactions. Exposing the genetic basis of such diseases has been most challenging and research efforts are intensifying in this respect. Different common disease like cancer, diabetes, cardiovascular disease, psychiatric issues and others emerged by the incidence of SNPs in multiple loci and environmental factors which make them most difficult to study relatively from the single locus disease or Mendelian disease (Hunt et al 2009). However the good news is association studies have revel SNPs linked with disease traits which are mostly located in non-coding region of genomic and they may have contribution in transcriptional regulation (Ameur et al. 2009).

Previous study of cattle on Toll-like receptor-2 (TLR2) and caspase recruitment domain 15 (CARD15), they are important pattern recognition receptors that play a role in the initiation of the inflammatory and subsequent immune response. They identifies a total of four SNPs, including one in intron 10 (c.2886-14A>G) and three in exon 12 (c.3020A>T, c.4500A>C and c.4950C>T) were identified in CARD15; none were identified in TLR2 (Pant et al., 2008). African black footed cats of two unaffected parents and one affected offspring vision problems were diagnosed using Whole genome sequencing and resulted 50 candidate variants that segregated concordantly progressive retinal atrophy phenotype. Other affected cat confirms two base pair deletion within IQ calmodulin-binding motif-containing protein-1 (IQCB1), the gene that encodes for nephrocystin-5 (NPHP5), had vision loss (Oh, A. et al.,2017). This kind of diagnosis will help to avoid of mating between carriers. There should be concern for the species survival for confined management. SNPs are the most appreciated marker to identifying disease resistant candidate gene, QTL and used as a diagnostic kit to investigate disease (dodsworth, 2017).

On the other hand, there is an effort to identify, catalog and study of small genetic change among human and animals that will guide to precise and successful medication. Comparing the number of SNPs in an individual; most of them have little impact on human and animal health, there is adequate evidence that certain variants cause a countless of phenotypic deviation and give a particular strong relation with disease susceptibility (Sachidanandam et al., 2001).Validated SNPs could provide as a diagnostic marker that can help to make decision about the features of medical treatment together with drug efficacy, particular diseases and unpleasant reaction to specific medicine. Pharmacogenomics/ pharmacogenetics and development of personalized medicine are advanced by the discovery of SNPs which are the main actor of drug response and disease susceptibility variation among individuals. This technique could save time, cost, and suffering for patients through accurate diagnoses and matching patients with suitable medicines. Personalized medicine and Personal genomics link genotype to phenotype and offer the understanding of the particular disease. Pharmacogenomics and pharmacogenetics connects genotype to patient-specific treatment, however in traditional medicine, the pathological states and clinical observations needed to assess and prescribe treatments.

Pharmacogenetics is responsible for specific SNPs in different genes with recognized functions that are connected to drug response. Whereas, Pharmacogenomics involve in identifying the whole genome to find single-nucleotide polymorphisms (SNPs) that might be related to drug response without necessarily knowing the specific function of the SNPs. The GWAS approaches in this area are not complete enough. They have limitations such as insufficient sample size, selection biases for genetic variants, environmental interactions that may affect the outcome measures and multiple gene–gene interactions that may underlie unexplained effects (Motsinger-Reif et al., 2010). As mentioned by (Ventola., 2013) genetic variations have been identified in cytochrome P450 (CYP) enzymes and drug receptors, transporters, and targets. These alterations can significantly affect pharmacokinetics, dosage requirements, and other aspects that interchange therapeutic outcomes. The University of Missouri, Veterinary Health Center used genome sequencing to test the feasibility of a precision medicine approach in domestic cats for the diagnosis of neurological disease in cats. The cat DNA variations were compared to the DNA variation from the database produced by the 99 Lives Cat Genome

Sequencing Consortium. A predicted p.H441P missense mutation was identified in the NPC1, the gene causing Niemann-Pick type C1 on cat chromosome D3.47456793 caused by an adenine-to-cytosine transversion, c.1322A>C. The live cat was homozygous for the variant, then additional different cat breeds were genotyped. However the variation was not identified in any of the breeds. Therefor, the study suggests precision medicine for cats can be achievable. This technique can be used for the treatment of other animals (Mauler et al., 2017). The clinical application of such pharmacogenetic findings holds great promise in improving drug efficacy and safety.

3.3 Food safety

An adulterated, altered or replaced genuine product in the food chain with the aim of maximizing profit is a common action in a market. Food traceability and authentication is a main concern for the recognition of inappropriate labeling and adulteration of processed food and feed. There are international rules and regulations to protect consumers against poor quality and impure product. Based on the regulations and rules tools are developed to validate food product like protein, metabolite and DNA marker analysis. The protein base method used immunological, electrophoretic and chromatographic assay, while the metabolite used HPLC, NMR spectrometry and mass spectrometry (Scarano and Rao, 2014). However, these techniques are not reliable due to producer procedures as well as an environmental effect either in the farm or in the industry. Therefore, DNA marker analysis is the best and influential tool to take in hand the confirmation of food quality, certification and traceability.

In the food safety, quality assurance processes any kind of DNA markers (RFLP, RAPD, AFLP, SSR, DNA Barcoding and SNPs) can be used for the analysis of food product. For example RFLP is used for authentication of seafood product (Arahishi, 2005) even if it is expensive, labor intensive and time-consuming. Other markers also used for this purpose as they can reveal species and paternity relationships. They have also the ability to trace what kind of meat is present in the whole food chain (Arana et al., 2002) and identifying genetic variations among different breed and species. DNA analysis is currently being conducted across Europe on meat, both in the supply chain and in existing products to verify for the existence of horse-meat (Hot Source, 2013). Horse meat may contain the drug residue of phenylbutazone, which is used as a sedative for domestic and sporting horses and harmful to human health therefore, it has a food safety issue if it is consumed. There is an illegal substitution of high-priced meats with low-priced ones has become unfortunately common, being driven by strong financial incentives According to The guardian in UK beef burger and meat in supermarket trace with horse DNA up to 100%. Different companies switch to another supplier and suspended their work with those who provide horse meat criminally.

Genomics used to increase consumer confidence in food and feed product. 12 SSRs recommended by the ISAG (International Society of Animal Genetics) and two SNPS were analyzed for bovine genetic identification, they were the same statistically significant discrimination power of one SSR (Scarano and Rao, 2014). SNPs is less affected by blood- relationships and population structure than SSRs. They have high levels of precision underlining the opportunity to associate an individual portion of meat with the animal breed. By the use of the Sequenom's MaSSaRRaY@ system, 80 SNPs for pig empathy were successfully tested and are now available for pig breed identification (Rohrer et al., 2007) The accessibility of SNP chips for many livestock species essentially provide a novel and powerful tool for genetic identification assays designed for quality assurance purposes. For instance the PorcineSNP60 bead-chip and its derivative that allow to identify mislabeling, providing a tool for food forensics (Ramos et al., 2009), (Wilkinson et al ., 2012). Bovine, Chicken, ovine and caprine SNP bead-chip also allows the same application as procineSNP bead\-chip. By the approach of SNPs profiles, we can unambiguously trace meat product to individual animals on a particular farm, rather than dependent on the information provided in the package. Besides, this system necessitates the development of SNP databases that profile each animal at slaughter. In 2013, Ontario cattle feed association (OFCA) joined with Loblaw Companies Ltd. and the Irish company IdentiGEN. These companies set up a DNA traceability program into the supply chain. The OFCA members provide DNA samples to this company and create a database of SNP profiles from every slaughtered animal. These ensure the traceability of any piece of meat labeled as Ontario Corn-Fed Beef using SNP profile (SMCC, 2013). This is because; SNPs has comparatively low mutation rates, functionally significant, high abundance, and provide quicker and highly automated genotyping. Developments in the effectiveness of high-throughput genotyping technology, genome-wide screens of high density SNPs are becoming more suitable for the studies of large samples of individuals. Generally SNPs and other markers have enormous prospects to develop the level of genetic progress as well as authentication of food products.

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