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Review

Applications of genomic copy number variations on livestock: A review

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Genomic copy number variations (CNVs) have significantly modified genomic regions during inversions, translocations, duplications and deletions that keep shaping phenotypic variation through changes in gene dosage, regulation and transcript structure. The objective of this review was to discuss the current application of CNVs on domestication, adaptations, productions, coat colour, morphology and diseases of livestock, and also address implication of CNV on genotyping selections, limitation and in the future, directions of livestock breeding. The CNVs are a key role in generating essential variation in the livestock population and disease phenotype. The association of CNVs with phenotypic traits was utilized for the determination of feed conversion ratios in beef cattle, growth, milk production, reproduction, coat color, health, demostication and morphology. Genomic CNVs are an important type of genetic variation in livestock development in different environments. This knowledge will be extremely pertinent from a molecular perspective and practical applications of genomic CNVs in animal breeding and allowed breeders to consider genomic selection of young animals at earlier ages. However, in livestock species, there are still open questions remaining about the genome frequency of CNVs. Therefore, application of genomics CNVs in livestock breaks the bridging between breeders and livestock producers; however, there are still gaps on genotypes and overlapping genes.

Key words: Adaptation, association, production, coat color and morphology.

INTRODUCTION

A key area of research in livestock genetics is the investigation of DNA variants which highly influence the phenotype of individuals (Clop et al., 2012). Chromosomal rearrangements have significantly modified genomic regions during inversions, translocations, duplications and deletions that is constantly shaping phenotypic variation through changes in gene dosage, regulation and transcript structure (Bickhart and Liu, 2014; Clop et al., 2012). According to the reviews of Freeman et al. (2006), genomic divergence can be observed in several forms, including single nucleotide polymorphisms (SNPs), variable numbers of tandem repeats, transposable elements and structural variations such as deletions, duplications and inversions. As Dekkers (2004) report,

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genetic markers have provided opportunities to enhance the selection for economically crucial quantitative traits in beef cattle, especially for traits that are difficult to improve by conventional selections. The main goal in the application of genetic markers towards livestock breeding goals is the detection of genes which are important for quantitative traits. These are implicated in phenotypes variations and their interaction with the gene-environment or economic traits. In previous studies, genetic variation in livestock has been described using microsatellites (Curi et al., 2005) and SNPs (Utsunomiya et al., 2013). Until recently, SNPs were considered nucleotide variations detected during genome sequencing, and the most important cause of genetic variation by the livestock research community. For this reason, many studies have utilized SNP markers for genetic improvement of beef and dairy cattle (Hayes et al., 2009; Van Raden et al., 2009; Wiggans et al., 2009). For instance, the development of yak gene specific SNPs for adaptation mechanisms to hypoxia and growth, and detection of the causal mutation of polledness in yak breeds have been reported (Liang et al., 2016; Liu et al., 2014; WU Xiao-Yun et al., 2015). However, compared with SNPs, Henrichsen et al. (2009a) reported that CNVs are significant sources of genetic variation and play a major role in phenotypic diversity and evolutionary adaptation (Hou et al., 2011; Zhang et al., 2009). Also, variation in the number of gene copies in the genome (Redon et al., 2006; Zhang et al., 2009) affects the expression of genes as well as having a large-scale influence on the transcriptome (Henrichsen et al., 2009b). Gene dosage, gene interruption, generation of a fusion gene, position effects, unmasking of recessive coding region mutations, and other functional SNPs are predominant molecular mechanisms by which CNVs convey diverse phenotypes and genotype along with complex diseases (Beckmann et al., 2007; Feuk et al., 2006; Lupski and Stankiewicz, 2005; Redon et al., 2006; Reymond et al., 2007; Weischenfeldt et al., 2013; Zhang et al., 2009).

Copy number variations (CNVs), a segment of DNA, that is 1 kb or larger in size and is present at a variable copy number in comparison with a reference genome, namely, deletions and duplications; as well as insertions, inversions and translocations (Feuk et al., 2006), contributes significantly to genetic and phenotypic variation among individuals of a species (Beckmann et al., 2007; Conrad et al., 2010; Feuk et al., 2006; Ghosh et al., 2014; Mills et al., 2011; Shi et al., 2016; Weischenfeldt et al., 2013). The application of CNVs animal breeding had long been held back due to the lack of reliable genotyping methods for CNVs (Zhou et al., 2016). Besides, in recent years, advances in genomic technologies have allowed the construction of maps of CNVs for cattle (Liu et al., 2010), horses (Ghosh et al., 2014), goats (Fontanesi et al., 2010), sheep (Liu et al., 2013), pigs (Paudel et al., 2013), dogs (Alvarez and Akey, 2012), chickens (Zhang et al., 2014), and yaks

(Zhang et al., 2016), using different methods including whole-genome sequencing, array-based comparative genomic hybridization (aCGH), SNP array, and next-generation sequencing (NGS) and providing a very significant resource for determining how CNVs convey economically important phenotypic traits in livestock species. The effects of CNVs on phenotype traits have been elucidated in different domestic animals. The association of CNVs with phenotypic traits was utilized for the determination of feed conversion ratios in beef cattle (de Almeida Santana et al., 2016), milk somatic cell scores in Holstein cattle (Ben Sassi et al., 2016; Durán Aguilar et al., 2016; Xu et al., 2014) and quantitative traits in a Brown Swiss population (Prinsen et al., 2017). A further study using quantitative real-time polymerase chain reaction (qPCR) in Chinese cattle revealed that CNVs in the genes MICAL-like 2 (*MICAL-L2)* (Xu et al., 2013), leptin receptor (*LEPR*) (Shi et al., 2016; Xu et al., 2017), myosin heavy chain 3 *(MYH3)* (Xu et al., 2014), potassium voltage-gated channel subfamily J member 12 (*KCNJ12)* (Zhou et al., 2016) mitogen-activated protein kinase 10 (*MAPK10*) (Liu et al., 2016), phospholipase A2 group IID (*PLA2G2D)* (Zhang et al., 2014) and cytochrome P450 family 4 subfamily A member 11 (*CYP4A11*) (Yang et al., 2017) are associated with gene expression and growth traits. On the other hand, the association of CNVs with growth traits was explored for the muscle development (Lin et al., 2018) and growth traits (Rao et al., 2016) in chickens and meat tenderness, feed conversion ratio, shear force, residual feed intake and marbling score in a Nelore Cattle (Da Silva et al., 2016a). The objective of this review was to discuss the current application CNVs on domestication, adaptations, productions, coat colour, morphology and diseases of livestock and also address implication CNV on genotyping selections, limitation and in the future directions of livestock breeding.

DOMESTICATION AND COPY NUMBER VARIATIONS

Notable changes in behavior, morphology, physiology and reproduction of the evolution of wild species into tame forms are domestication (Darwin, 1859). Domestications have shaped the genome of all living things in our globe. After domestication, human adjust animals by selecting important traits to further add to the complexity of evolution. The plants and animals domestication was one of the most prominent roles in cultural and evolutionary changes over the past 20,000 decade (Larson et al., 2014). Zebu and taurine breeds are differentiated primarily by the presence or absence of a hump, taurine are domesticated in the Fertile Crescent ~8,000–10,000 years ago and indicine are domesticated in the Indus Valley ~6,000–8,000 years ago (Larson et al., 2014; Loftus et al., 1994). Qiu et al. (2015) reported that domestication of yaks occurred approximately 7,300

years before now, which coincides with two early human population expansions on the Qinghai-Tibet Plateau (QTP) of China during the early-Neolithic age and the late-Holocene, respectively. Guo et al. (2006) revealed that all domestic yaks may have originated from a single wild population (or gene pool); however, their divergence occurred before the domestication. Indeed, Lai et al. (2007) suggested that the Chinese yak was domesticated from two distinct matrilineal sources or from a heterogeneous pool containing both divergent lineages, with occasional gene introgression from cattle. This indicates that it is slightly later than the domestication of many livestock species (10,000-8,000 year before present) (Larson et al., 2014; Zeder, 2008). The divergence times of *Bos* and *Poephagus* (yaks) are 0.57–1.53 million years after the present (Qiu et al., 2012). Moreover, the diverged time for yak and cattle, yak and water buffalo, yak and sheep/goat were approximately 4.9, 12.2 and 20.6 million years ago, respectively (Qiu et al., 2012). However, divergence times of two cattle (*Bos taurus* and *Bos indicus*) are estimated 1.7-2.0 million years ago (Hiendleder et al., 2008). During domestication, the breeds were mostly selected based on coat colour and polled phenotypes (Bickhart et al., 2016). Therefore, bovine genomes were modified by human and livestock interaction in the surroundings environment. Ajmone-Marsan (2010) revealed that after domestication, human selected traits that enabled easy management and breeders wanted to improve production traits by using artificial selection (artificial insemination) which affects genetic variability within breeds.

In past few years, genomic changes of domestications history of the cattle and yaks breeds were identified using different markers, such as SNPs (Decker et al., 2009; McTavish et al., 2013), whole-genome resequencing (Qiu et al., 2015), mtDNA (Wang et al., 2010) and CNVs (Bickhart et al., 2012, 2016; Liu et al., 2009, 2010; Zhang et al., 2016) which are accompanied by breed specific genomic differentiation, hybridization, and introgression (Zhang et al., 2015). Qiu et al. (2015) detected signals of selection in 209 genes of domestic yaks which is associated with behaviour and tameness. Similarly, Zhang et al. (2016) revealed that CNVs was the potential contributions in the process of yak domestication, although Wang et al. (2010) identified about 38 genes related to domestication of yaks by using SNP. Moreover, Zhang et al. (2016) found that 46 CNVs genes delineate between domestic and wild yaks that is correlated with behavior, brain and nervous system development. For instance, the CNVs of the *GRIN2D, SHANK3, KCNJ14, CA11* and *NTF4* genes were associated with normal brain development, learning, working memory and behavior (Zhang et al., 2016). Thus, Carneiro et al. (2014) argued on the effect of strong selection on reducing aggressive behavior and neurological traits.

Domestication is a change reproductive efficiency of livestock breeds; for example, in yak CNVs of the *TSEG2*, *AKR1C3* and *IZUMO1* genes were associated reproductive performance traits, such as age of puberty, sperm production, ovulation rate and embryonic mortality (Zhang et al., 2016). Domestic and wild CNVs are significantly different in nutrition metabolism and mitochondrial oxidative phosphorylation (Zhang et al., 2016). Biological processes such as neurobiology, growth and metabolism, and immunobiology play significant roles in the domestication and subsequent evolution of European *Bos taurus* cattle, which is accompanied by behavioral selection and phenotypic traits (meat and milk) (Park et al., 2015). CNVs have been playing significant roles in the behavioral changes of cattle due to domestication (Shin et al., 2014). Comparative analyses of the olfactory receptor (OR) genes of cattle, pigs, humans, mice, and dogs showed that 6.0% of functional OR cattle genes were species-specific because OR gene subfamilies that are important for the survival of the species are likely to expand in the genome through evolution (Lee et al., 2013).

ADAPTATION AND COPY NUMBER VARIATIONS

In modern livestock breeds across the world, genetics adaptations have been affected by selective (natural and human-imposed) and non-selective forces (demographic events and introgression) (Bickhart et al., 2016). Selection pressures from environment and handlers influences a nuanced evolutionary history of livestock species (Bickhart and Liu, 2014). Compared with cattle, yaks graze throughout the year on diverse natural grasslands and have evolved morphological characteristics enabling them to consume a wide variety of plant species, thereby making them better adapt to the typically harsh characteristics of their pastures (Shao et al., 2010). Lower methane emissions from yak can be compared with cattle in rumen simulation technique (RUSITEC) fermenters (Mi et al., 2017) because the yaks have a unique rumen microbial ecosystem that is significantly different from that of cattle and has great potential as an "energy-saving" animal as many researchers around the world aim to find "low carbon" livestock (Huang et al., 2012). Qiu et al. (2012) reported that 81 genes detected in yak were related to the hypoxia response and energy metabolism. Hypoxia-inducible factors (HIF-1α and HIF-2α) expressions were higher in yak tissues than in cattle which indicated involvement of HIF-1α and HIF-2α genes in oxygen homeostasis in response to hypoxia (Xiong et al., 2015). The *PGM1*, *PKLR*, *ATP5F1*, and *NDUFA10* genes were under positive selection in hypoxia-tolerant Tibetan yak (Tian et al., 2017). Lan et al. (2018) detected that 339 genes which are related to physiological rhythm and histones, provided a basis for the evolution, molecular origin, and unique traits of Jinchuan yak. Recent studies (Xiao-Yun et al., 2015) indicated that *EPAS1* was

identified as a selective target gene and contribute to the hypoxia adaptation at high altitudes of Tibetan mastiffs (Li et al., 2014), indigenous dogs (Gou et al., 2014), Tibetan sheep (Wei et al., 2016) and yaks (Xiao-Yun et al., 2015). Yang et al. (2016) suggested that energy metabolism is a possible adaptive mechanism for ruminants that inhabit the plateau environments. For instance in yak, Zhang et al. (2016) revealed that CNVs of the *MOGAT2, GYS1, DHDH, HSD17B14, CPT1B*, *BCAT2* and *MIOX* genes are involved in metabolism of sugars, lipid, amino acid and carbohydrate during adaptation. The CNVs of *MRP4, DCC* and *DEXI* genes are associated with the hypoxia response in high and low altitude domestic yak (Zhang et al., 2016).

On the other hand, genomic differences between zebu and taurine cattle are due to their original geographic distribution. Taurine cattle are more adapted to temperate climate, while zebu cattle are better adapted to tropical environments; therefore, differences between these two cattle could be linked to genomic adaptation to the environment (Porto-Neto et al., 2013). CNVs of the *SCP2, IFNT, ULBP2* and ORs genes were related to adaptation of cattle (Hou et al., 2011; Liu et al., 2010). CNV genes are ORs that play an important role in food foraging and mate recognition in pig (Paudel et al., 2015) as well as detection of volatile chemicals in the environment (Bickhart and Liu, 2014), which provides rapid adaptation to different environments. In addition, gene families involved in sensory perception are usually fast evolving due to their importance in the organism responding to rapid changes in the environment (Zhang et al., 2016). The ORs are critical for transmitting the effects of odorants, contributing to the sense of smell, and have been implicated in participating in appetite regulation (Zhou et al., 2018). However, comparative genome study has revealed that gene families related to sensory perception were significantly expanded in yak compared to other mammals (Qiu et al., 2012). Animal genomes display enrichment of CNVs in genes which is associated to immune response and environmental interaction such as sensory perceptions of smell and chemical stimuli (Bickhart et al., 2012, 2016; Keel et al., 2016; Liu et al., 2010; Upadhyay et al., 2017; Xu et al., 2016, 2017; Yang et al., 2017; Zhang et al., 2016). Regarding Qinghai-Tibet plateau in north-western China, Yang et al. (2017) observed that CNVs of the *MRVI1, ABO, GLRB* and *EPHA3* genes were associated with adaptation of the arid environment exhibiting dry, hypoxia, and low air pressure.

ASSOCIATION OF CNVs WITH REPRODUCTION AND PRODUCTION TRAITS

The association between CNVs and economically important phenotypic traits had been investigated in different breeds of domesticated animals (Chen et al., 2012; Shi et al., 2016; Xu et al., 2015; Zhang et al., 2014). Recent studies (da Silva et al., 2016; Zhang et al., 2014) underlined that CNVs are associated with health, meat, milk production and reproduction. CNVs of *PLA2G2D* gene play significant roles in lipid metabolism, fat deposition and gonadotropin-releasing hormone signalling in Back Angus cattle (Stothard et al., 2011). Also, CNV of the *PHLDA2* gene is essential for normal embryo development during early development and pre-implantation embryos (da Silva et al., 2016a). A further study using NGS in dairy cattle revealed that CNVs in *INS, IGF2, FOXO3, TH, SCD5, GALNT18, GALNT16, ART3, SNCA,* and *WNT7A* genes are potentially associated with milk protein and fat traits (Gao et al., 2017). In the works of Xu et al. (2014), Ben Sassi et al. (2016), Jiang et al. (2016) and Upadhyay et al. (2017), CNVs were significantly associated with milk production traits. In addition, CNVs of the genes are associated with reproduction and milk phenotype in cattle (Durán Aguilar et al., 2017; Da Silva et al., 2016b; McCarthy et al., 2012; Prinsen et al., 2017; Sermyagin et al., 2016; Shin et al., 2014; Xu et al., 2016; Yue et al., 2013; Zhou et al., 2018). In chickens, novel CNV of the *TGFβ3* gene is associated with duration of fertility traits (Gu et al., 2017). The study of Sasaki et al. (2016) identified a deleted-type CNV encompassing *ANXA10* in cows that was associated with embryonic mortality at 30–60 days after artificial insemination.

In past several studies, bovine CNVs of the *LEPR* (Shi et al., 2016; Xu et al., 2017), *GBP2* (Zhang et al., 2018), *MYH3* (Xu et al., 2013) and *MAPK10* (Liu et al., 2016) genes have been reportedly associated with growth traits of cattle. Indeed, Shin et al. (2014) showed that CNVs of the *TTN, HDAC4*, *TSHR*, and *CCDC141* genes were associated with meat production and were strongly related to muscle in Hanwoo cattle (Shin et al., 2014) and marbling in Japanese Black beef cattle (Yamada et al., 2009). Copy number variable regions (CNVRs) existing in a QTL is related to meat quality, feed conversion ratio, shear force, residual feed intake and marbling score in Nelore Cattle (Da Silva et al., 2016b). In addition, genome CNVs are associated with meat tenderness in Nellore Cattle (Da Silva et al., 2016b). Xu et al. (2017) suggested that the CNV of the *LEPR* gene contributed to fat deposition in muscles and desirable trait for meat production in Qinchuan cattle breeds. CNV of the *ABCA12* gene was associated with growth and development in Holstein and Jersey cattle breeds (Mesbah-Uddin et al., 2018).

On the other hand, Zhang et al. (2018) indicated that gain CNV type of the *GBP2* gene has high growth traits in body height and body length than loss/median CNV types in Pinan cattle, whereas the median CNV type of the *GBP2* showed better body length in Jian and Chaidamu cattle and yak (Zhang et al., 2018). In Jiaxian cattle, gain CNV type of the *CYP4A11* gene had higher adult hucklebone width than loss types, while in Qinchuan and

Jinnan cattle gain CNV type of the *CYP4A11* gene had higher adult heart girth, chest depth and body weight than loss types (Yang et al., 2017). The *MICAL-L2* CNVs were significantly associated with body weight, height, and length in Nanyang cattle at 6 and 12 months old (Xu et al., 2013). The individuals with copy number gain of the *MYH3* gene showed better growth trait than the loss and/or median copy number types in Chinese cattle (Xu et al., 2014). The gain/normal CNV type of the *LEPR* gene performed better in traits of body weight, height and length than the loss type in Nanyang (Shi et al., 2016). Similarly, the gain CNV type of the *MAPK10* gene performed better in traits of body weight, body height and chest girth than the loss type in Nanyang (Liu et al., 2016). Further, Bouwman et al. (2018) found that missense variant of *LCOR* (ligand-dependent co-repressor) is associated with variation in height and body size in mammalian.

Although the individuals with copy number gain in *LEPR* gene has high body weight, hucklebone width and rump length than loss or median (Xu et al., 2017), heart girth and body length are significantly associated with CNV types in CNVR (Zhang et al., 2014) in Chinese cattle. According to the finding of Liang et al. (2010), it was indicated that genotype *IGF1R* gene is associated with body weight, body height and body slanting length in yak breeds. Consistently, gain and normal copy number types has high heart girth, body length, weight and height at cattle ages of 12, 18 and 24 months (Shi et al., 2016; Xu et al., 2013); Conversely, no significant association was found at CNVs *LEPR* locus with growth traits of cattle age of 2 years (Shi et al., 2016), maybe due to breed differences and/or relatively small numbers of samples (Xu et al., 2013). Significant difference in CNV of the *LEPR* gene was determined in the Nanyang and Qinchuan cattle breeds in China (Xu et al., 2017). CNVs of the *PLA2G2D* and *MYH3* genes are significantly associated with body height, body length, heart girth, hucklebone width, and body weight (Zhang et al., 2014). Zhou et al. (2016) detected 17 CNVs overlapped with QTLs that were significantly associated with seven growth traits and one of the CNV may be involved in growth traits through *KCNJ12*. In yak, CNVs of the *KLF6, CHKB, GPC1* and *CHRM3* are associated with growth traits (Zhang et al., 2016).

ASSOCIATION OF CNVs WITH COAT COLOR

In farm animal breeds, coat colour is one of the most significant characters that can be used to distinguish them. This is influenced by different genes that are involved in determining the presence, distribution and biochemical activities of the melanocytes (Fontanesi et al., 2010). The *ASIP*, *TYR*, *TYRP1*, *KIT*, *KITLG*, *PMEL*, *MC1R,* and *MIT* genes play major roles in determining coat colour variation in livestock breeds (Brenig et al.,

2013; Fontanesi et al., 2010, 2012; Fontanesi and Russo, 2013). On the other hand, CNVRs covering the *MC1R* gene has been involved in coat color of Black Angus cattle (Hou et al., 2012).

Coat colours in sheep and goat breeds are determined by duplication CNVs of the *ASIP* gene (Fontanesi et al., 2009, 2011; Han et al., 2015; Norris and Whan, 2008, Figure 1). Similarly, Norris and Whan (2008) reported that tandem duplication of a 190-kb portion of the ovine genome is responsible for the dominant white coat color ($A^{w/t}$) allele of domestic sheep. The duplication of *ASIP* is linked to the typical white coat colour sheep species (Bickhart and Liu, 2014), because the white coats are favoured in sheep for wool production that is easily dyed. Moreover, the duplications of the *KIT* gene in the pigs are determined by the dominant white locus (Pielberg et al., 2002; Rubin et al., 2012). Moreover, Brenig et al. (2013) identified three major duplication *KIT* locus variations in White Galloway and White Park cattle that could represent the fundamental mutation for dominant white, patch and belts phenotypes. However, colour sidedness in cattle is determined by a first allele on chromosome29 (Cs29), which results from the translocation of a 492-kilobase chromosome 6 segment encompassing *KIT* to chromosome 29 through a process of micro homology mediated end joining, and a second allele on chromosome 6 (Cs6), derived from the first by repatriation of fused 575-kilobase chromosome 6 and 29 sequences to the *KIT* locus via non-allelic homologous recombination (NAHR) in several Brown Swiss and Belgian Blue cattle (Durkin et al., 2012). In White Galloway and White Park cattle, the effects of the modified *KIT* locus result in mottled markings rather than color sidedness (Brenig et al., 2013). Additionally, Durkin et al. (2012) found that colour sided Dutch witrik and Ethiopian Fogera cattle were shown to carry chromosome 29 allele; Austrian pstertaler sprinzen, Czech red-spotted cattle and French vosgienne the brown Swiss carry chromosome 6 allele; and Irish moiled, Swedish mountain and domestic yak carried both the chromosome 29 and 6 alleles. Similarly, the coloured side and white color of yak breeds are caused by the sequential translations of *KIT* chromosome 6 and 29 alleles (Zhang et al., 2014), due to introgression in yak after domestication via well-documented hybridization of *Bos taurus* and *Bos grunniens* (Durkin et al., 2012; Medugorac et al., 2017).

COPY NUMBER VARIATIONS AND MORPHOLOGY

The feather growth and comb shape are the defining morphological traits of the chicken and are caused by CNVs. Dominant mutation in pea comb of chickens significantly reduces the size of the comb and wattles (Wright et al., 2009; Figure 2). Chickens dissipate up to 15% of their body heat through the comb and wattles due
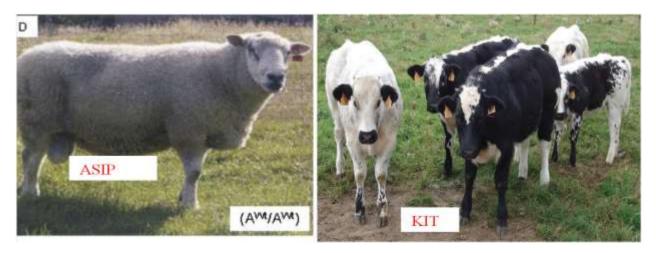
Figure 1. Copy number variation of the *ASIP* (Sheep) and *KIT* (cattle) genes contribute to phenotype (coat colours). Sources: Durkin et al. (2012), and Norris and Whan (2008).

to lack of sweat (Whittow, 2000); therefore, chicken reduce heat loss through pea comb phenotype to adaptive cold environments (Wright et al., 2009). Bickhart and Liu (2014) reported that important genes identified in chickens that have been modified by CNVs are the pea comb phenotype. Duplication of the first intron of the *SOX5* gene in male and female chickens of pea comb phenotype keeps reducing the size of combs (Wright et al., 2009). In developing countries like Ethiopia, farmers' selects indigenous chicken for breeding and marketing purpose based on comb and wattle types (Bekele et al., 2016). For instance, the market price of double comb (Pea-comb) is more than single comb (Wild-type) of chickens (Bekele et al., 2016). A sex-linked late feathering allele K containing two copies of *PRLR* has been introduced to commercial flocks and used widely for sexing hatchlings (Wang et al., 2010). The late feathering locus has been linked to a CNV positioned at the *Z* chromosome, where duplication of partial copies *PRLR* and *SPEF2* genes show mutant K alleles (Wang et al., 2010). This mutation causes reduced fertility and retarded development of fly feathers. Recent work indicated that *PRLR* expression in the skin of one-day old early feathering and late feathering chicks did not show significant difference, whilst *SPEF2* expression in the skin of one-day old displayed a significant difference between early feathering and late feathering chicks (Zhao et al., 2016), suggesting that *SPEF2* gene is good candidate genes for chicken feathering, but PRLR is not.

ASSOCIATION OF CNV WITH DISEASES

In the history of livestock evolution, CNVs of the genes is associated with immune system in different environments. Bickhart et al. (2016) found that CNVs duplication of the *KRTAP9-1* gene paralog of *KRTAP9-2* involved tick resistance in indicine cattle. Similarly, the CNVs of the

ULBP17 gene encoded was related to the immune system in yak (Zhang et al., 2016) as well as pathogen and parasite resistance in cattle (Alvarez and Akey, 2012; Bickhart et al., 2012; da Silva et al., 2016a). Although CNVRs of the *BoLA-DQA2, BoLA-DQA3* and *BoLA-DQB* genes are associated with immune response in yak (Zhang et al., 2016), the CNVR of *TICAM1* is candidate gene for response to *Trypanosome congolense* infection (Noyes et al., 2011). The *MFGE8, COL13A1, CFTR, BDKRB1, PTGS2, MR1, PECAM1,* and *LRFN5* genes are involved in immune system response of South African Nguni cattle (Wang et al., 2015). Genomic CNVs are an important type of genetic variation in livestock immune development in different environments.

IMPLICATION OF GENOMIC CNV ON LIVESTOCK

Livestock genomics and marker-assisted selection enhances genetic progress through increased genetic variation, accurate predictions of breeding values, high intensities of selection and shorter generation intervals (Pryce and Daetwyler, 2011). For instance, with genomic selection, the generation interval of dairy cattle from five years could be reduced to two years (Pryce and Daetwyler, 2011). This indicates the vital roles of genomic selection dairy industries worldwide (Hayes et al., 2013). Molecular genetics research began in livestock nearly 33 years have been passed, nevertheless, the livestock breeder have been focused on gene sequencing of all the major livestock species (Rothschild and Plastow, 2014). Recent advances in genomics studies use new genotyping tools that allowed breeders to identify specific genomic segments (Bickhart and Liu, 2014). Consequently, human population grew from an estimated 7.52 billion people to approximately 9.73 billion people in 2050

Figure 2. Copy number variation of the *SOX5* gene contributes to phenotype (pea-comb chickens) (A) Wild-type male, (B) wild-type female, (C) pea-comb male and (D) pea-comb female. Source: Wright et al. (2009).

(http://www.world-ometers.info/world-population).   Thus, this is an opportunity for animal's breeders to apply genomics selection in livestock in response to demand for livestock products, especially those that have high nutrition (meat and milk). In addition, the development of the Illumina BovineHD BeadChip (Wu et al., 2015; Durán Aguilar et al., 2016; Prinsen et al., 2016; Xu et al., 2016), the Illumina BovineSNP50 BeadChip (Ben Sassi et al., 2016), next-generation sequencing (Bickhart et al., 2012; Keel et al., 2016; Zhang et al., 2016) and whole genome sequence (Keel et al., 2016) have allowed breeders to apply genomic in livestock selection by low cost genotyping (Van Raden et al., 2009). As a result, this genotyping array gives breeders an opportunity to consider young bulls at earlier ages (Bickhart and Liu, 2014).

CONCLUSIONS AND LIMITATION

Copy number variations (CNVs) can cause radical changes in phenotype variation, gene expression, and evolutionary adaptation, through gene dosage effects, disruption of transcript arrangement, and regulatory polymorphisms. The CNV distributed within and among livestock could be modified by mutation, selection, domestication and demographic history. Several studies revealed that copy number variable regions (CNVRs) could be potentially associated with growth (*LEPR, MICAL-L2, KCNJ12 CHKB, KLF6* and *MYH*3), milk production (*PLA2G2D, NIBP, DGAT1,* and *VPS28)*, reproduction (*TSEG2, AKR1C3* and *IZUMO1)*, coat color (*ASIP, TYR, TYRP1, KIT, KITLG, PMEL, MC1R* and *MIT)*, morphology (*SOX5, SPEF2)* and health (*TICAM1, ULBP17, MHC*) in livestock. This knowledge will be extremely pertinent from a molecular perspective and practical applications of genomic CNVs in animal breeding.

Several studies have investigated CNV in the livestock genome by using comparative genomic hybridization arrays, the Illumina BovineHD BeadChip, the Illumina BovineSNP50 Bead Chip, whole genome sequence and next-generation sequencing. However, in previous studies, CNVRs comprise ~2–7% of the cattle genome (Keel et

al., 2016). Therefore, in livestock species, questions remain about the genome frequency of CNVs. In addition, in most of livestock species, the extent to which CNV affect production, reproduction, health, coat color and morphology is not well characterized such as, sizes, and locations, chromosomal properties, along with evolutionary processes. Most importantly, there is little or no works on genomic CNVs of tropically adapted livestock, particularly those adapted to hot climate (Camel, goats), survival under low feed (East African Boran cattle), and disease resistance (Sheko, NDama cattle breeds). Therefore, application of genomics CNVs in livestock break the bridging between breeders and livestock producer, however, there are still gaps on genotypes and overlapping genes.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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