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Genome-wide selection signal analysis of Australian Boer goat by using insertion/deletion variants

ying yuan[1], Bai-Gao Yang[1], yongmeng he[1], xinghai Duan[1], weiyi zhang[1], Ri-Su Na[2], yanguo Han[1], Yan Zeng[1], Yongfu Huang[1], Yong-Ju Zhao[3], Zhong-Quan Zhao[4], shizhi wang[1], and guangxin e[1]

[1]Southwest University
[2]Chongqing Engineering Research Centre for Herbivores Resource Protection and Utilization, Southwest University
[3]College of Animal Science and Technology, Chongqing Key Laboratory of Forage & Herbivore, Chongqing Engineering Research Centre for Herbivores Resource Protection and Utilization, Southwest University
[4]Chongqing Key Laboratory of Forage & Herbivore, Chongqing Engineering Research Centre for Herbivores Resource Protection and Utilization, Southwest University

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Abstract

Breed selection for commercial goat is needed for production efficiency, growth trait alteration, and improved livestock quality. Boer goat is famous for its stable production performance, fast growth rate, and high meat production. Detecting selective signatures in its genome can elucidate selection mechanisms for its economic and adaptive traits. In this study, 1,122,858 InDels were identified based on the whole genomes of 46 Australian Boer goats and 81 worldwide local goats. FST was used to identify the candidate selection signatures in 127 goats. A total of 11229 InDels were obtained from the top1% of all inDels, and 1239 candidate genes were annotated. A total of 1193 and 476 candidate genes were involved in 4726 GO terms and 299 KEGG pathways, respectively. Many genes were related to muscle development (MEF2C, MAPK14, TMOD1 etc.), reproduction (SRD5A1, FBXW11, DMRT1 etc.), immunity (CD200, SGK1, IL17RB etc.) and metabolism (INSR, STXBP3, H6PD etc.). The results provide novel and important insights into the genetic basis of selection in Boer goat and may be useful for goat molecular breeding.

INTRODUCTION

Boer goat, which was first domesticated in South Africa in the early 19th century, has attracted worldwide attention due to its stable production performance, fast growth rate, and high meat production (Casey et al., 1998). Owing to the extensive introduction and breeding of Boer goats in worldwide, comprehensive and detailed studies have been conducted on various characteristics of Boer goat. Many studies have successively explored their adaptability, growth performance, and hybrid improvement. Particularly, many dominant genotypes of economic traits due to long-term selection have been discovered (Yang et al., 2011; Silveira et al., 2002).

Insertion/deletion markers (InDels) are a kind of structural variation widely studied in various biology fields. For example, an 8 bp duplicated frameshift insertion in *FOXF1* is linked to alveolar capillary dysplasia associated with pulmonary vein dislocation in human (Karolak et al., 2019). A 1,423 bp InDel in the cis-regulatory region of LanFTc1 is related to the vernalization and flowering time of*Lupinus angustifolius*

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(Taylor et al., 2019). A 49 bp deletion in the 3'-untranslated region (UTR) of the *MTNA* gene is correlated to increased oxidative stress tolerance in *Drosophila* (Ramnarine et al., 2019). In domestic animals, a bounteously InDel is connected to various economic traits, such as litter size (Li et al., 2020; Akhatayeva et al., 2020;), reproduction (Chen et al., 2019), growth (Zhang et al., 2019; Wang et al., 2019; Li et al., 2020; Cui et al., 2019), milk (Ju et al., 2020). Especially in goat, abundant results have been obtained in this area. For example, 11 and 14 bp InDels within the*CSN1S1* and *CMTM2* genes are substantially associated with litter size (Kang et al., 2019; Wang et al., 2018). InDels within intron 2 of goat *IGF2BP1* and the UTRs are remarkably associated with their growth traits (Wang et al., 2020). An 11 bp InDel polymorphism within the *CSN1S1* gene is associated with milk performance and body measurement traits (Zhang et al., 2019).

As a special meat breed, Boer goat has experienced long-term artificial selection. Owing to its extremely outstanding growth performance, this domestic animal is an important natural model in studies on artificial breeding. In this work, InDel mutations from Boer goats were investigated to determine potential InDel variants by using genome re-sequencing technology. The results provide a theoretical basis for the study of genetic mechanisms and support the valuable molecular genetic markers for the economic traits and molecular breeding of goat in the future.

METHODS AND MATERIALS

Genomes (>10×depth) of 46 Australian Boer goats (case group) were obtained from our unpublished parallel projects (PRJNA671542). For the control group dataset, 81 published deeply sequenced genomes of indigenous goats (non-specialized meat) from Europe, Asia, and Africa were applied. Information on all samples is shown in S Table1.

High-quality reads (HQRs) were initially filtered by removing the adapter, low-quality raw paired reads, and reads with an N ratio greater than 10%. The number of bases with a mass value of Q[?]20 was ensured to be more than 50% of the entire read to achieve HQRs. HQRs were aligned to the goat reference genome (ASR1) using BWA (0.7.17-r1188 version). The resulting sequence alignment/map format (SAM) files were converted to Binary Alignment/Map (BAM) files by using samtools (Etherington*et al.,* 2015) and picard (2.23.6 version). InDel variant was detected with GATK (version 4.1.9.0) Unified Genotyper. The InDels were filtered for quality purposes by considering the following standards: (filter- QD < 2.0 || FS > 60.0 || MQRankSum < -12.5 || ReadPosRankSum < -8.0 || SOR > 3.0 || MQ < 40.0). The following secondary filtered standard was applied to select high-quality InDEls: –max-missing 1 –max-alleles 2 –min-alleles 2 –maf 0.05. InDels exhibiting segregation distortion or sequencing errors were discarded.

The selective sweep of each variant was quantified according to F_{ST} (Hudson et al., 1992), which was calculated for each InDel signal using VCFtools (version 0.1.16) and sweep regions with top 1% threshold used for next analysis. The annotation of each InDel physical position and attribution gene was determined by ANNOVAR (Wang et al., 2010).

KOBAS 3.0 online tool (Zeng et al., 2019) was utilized to annotate the candidate genes for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG). Hypergeometric test was conducted on significantly enriched GO and KEGG terms based on the number of enriched genes. The calculated P value underwent corrected P-value, with corrected P-value[?]0.05 set as a threshold.

RESULTS

A total of 1,122,858 InDels were obtained from the genome of127 goats. Most of these InDels were found in intergenic (63.8430%) and intron (29.7546%), and some were located in UTR3 (0.4220%), exon region (0.1584%) and UTR5 (0.0636%) (Figure 1). The InDels located in the exon region include 1,065 (59.6973%) deletion mutations, which are composed of 673 (37.72%) frameshift mutations and 392 (21.9730%) non-frameshift mutations, and 614 (34.417%) insertion mutations, which are composed of 446 (25%) frameshift mutations and 168 (9.4170%) non-frameshift mutations. A total of 105 (5.886%) InDel variants were located in the initiation/ termination code.

The F_{ST} value of 1,122,858 InDels between case and control group was obtained (Figure 2). A total of

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11,229 InDels with high signal were collected according to the top 1% threshold of F_{ST} statistical parameters (F_{ST}[?]0.623043, S Table 2).

Then 3,488 of that 11,229 InDels which distributed in the exon, intron, 3'UTRn and 5'UTR region were extracted for candidate gene annotation. Finally, 1,239 candidate genes were annotated. In addition, 1,193 candidate genes were enriched to 4,726 GO terms (S Table 3), and the top 20 significantly enriched GO terms are shown in Figure 3. The protein binding GO terms (*ZCCHC10* , *NCBP1* , *WLS* , etc.) with the largest number of genes were selected, and 791 candidate genes was enriched.

94 candidate genes were enriched in 88 GO terms related to muscle development. In particular, 36 GO terms were related to skeletal muscle development, skeletal muscle cell differentiation (*MEF2C* ,*ZNF689*), and skeletal muscle tissue development (*MAPK14*); 39 GO terms were related to myocardial development and cardiac muscle cell proliferation (*TGFBR3* , *TGFB2* , and *TENM4*); and 19 GO terms were related to smooth muscle development, such as in the positive regulation of vascular associated smooth muscle cell proliferation (*GNAI3*). Enrichment was also observed in a large number of GO terms related to immune cells, such as B cell proliferation (*MEF2C* , *HSPD1* , *LEF1* , *BCL2*), T cell differentiation (*VAV1* , *RUNX2* , *PTPN22* ,*ZAP70*), and positive regulation of immune response (*TGFB2* ,*RSAD2*). Sixty-two reproductive function-relative GO terms were also enriched, such as spermatogenesis (*LRGUK*), which is related to germ cell development and differentiation, and estrogen receptor activity (*LEF1* , *ESR1*), which is related to reproductive hormones. A large number of GO terms related to metabolism were also enriched, such as the protein catabolic process (*LNPEP* ,*P2RX7* , *RNF165*), amino acid metabolism (*UCHL3*), glycerolipid metabolism (*DGKH*), and fatty acid metabolism (*LCP1)* .

KEGG results showed that 476 candidate genes were enriched to 299 KEGG signaling pathways, 98 of which were significantly enriched (corrected P <0.05, S Table 4). Information on the top 20 significant KEGG enrichment pathways is shown in Figure 4. The 29 candidate genes were significantly enriched in two signaling pathways related to muscle regulation, namely, vascular smooth muscle contraction (*ACTA2* ,*MYH11* , *PRKCB* , etc.) and cardiac muscle contraction (*RYR2* , *SLC9A, CASQ2* etc.). In addition, 45 candidate genes were enriched in 7 signaling pathways related to reproduction, such as GnRH signaling pathway (*PLCB1* , *PRKCB* , and *PLCB4*). Multiple signaling pathways related to growth and development were also enriched, such as cGMP-PKG signaling pathway (*NFATC1* ,*PLCB3* , and *PLCB4*). A large number of immune-related signaling pathways were also enriched, such as NF-kappa B signaling pathway (*TRAF6* , *IL1R1* , and *ERC1*). Many metabolism relative pathways were also enriched, such as insulin signaling pathways (*RPTOR* , *PPP1CC* , and *PRKAG2*), ether lipid metabolism (*PLA2G4A* , *PLA2G4,* and *PLA2G4E*), and beta-alanine metabolism (*EHHADH* , *HIBCH* , *CNDP1* , and *DPY*).

DISCUSSION

InDel mutations related to economic traits have been investigated in domestic animals such as pigs (Jung et al., 2020; Zhang et al., 2019), cattle (Zhou et al., 2019; Xu et al., 2018), and sheep (Wu et al., 2020; Zhao et al., 2018), indicating that InDel has a non-negligible role in animal breeding. In this study, various candidate genes for economic traits and adaptive traits of animals have been identified. In particular, 94 candidate genes were found to be related to muscle development (such as *MEF2C* , *TCF4* , *MAPK14* , and*DDX17*).

Myocyte enhancer factor 2C (*MEF2C*) is widely involved in the development of heart and skeletal muscle during the embryonic stage. The synergistic action between *MEF2C* and the *MYoD* family factors promote the development of skeletal muscle during the embryonic process, and *MEF2C* can regulate cell proliferation by acting as the endpoint of the intracellular signaling pathway regulated by various growth factors (Black et al., 1998). *MEF2C* also exhibits DNA binding activity in muscles and is highly expressed in muscle cells during embryonic formation to regulate muscle development and differentiation by interacting with muscle-derived bHLH protein, thyroid hormone receptor, *PEA3* , and *PDP1* (Pozarska et al., 2016). As a marker of muscle connective tissue fibroblasts, transcription factor 4 (*TCF4*) can regulate the development of slow and fast muscles and promote the conversion of fetuses to adult muscles (Mathew et al., 2011). Tumor protein p73 (*TP73*) is involved in the regulation of cell apoptosis (Stiewe et al., 2001), polyciliogenesis (Fujitani et

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al., 2017), germ cell maturation (Santos et al., 2018), and multiple biological processes (Nemajerova et al., 2019). Thus, *TP73* plays an important role in animal development and homeostasis maintenance.

DEAD box RNA helicase 17 (DEAD-box helicase 17, *DDX17*) regulates gene expression and transcription factor activity (Bourgeois et al., 2016). *DDX17* is an activator of *MyOD* , which regulates skeletal muscle development (Legerlotz et al., 2008). *DDX17*knockdown hinders skeletal muscle development and differentiation (Caretti et al., 2006). Mitogen-activated protein kinase 14 (*MAPK14*) belongs to the MAP kinase family and is an important factor in biological development. *MAPK14* promotes cell proliferation and activation by inhibiting the differentiation of vascular smooth muscles during vascular injury. Pro-inflammatory gene expression participates in the repair of blood vessels (Wu et al., 2019). In addition, *MAPK14* is involved in muscle atrophy by direct phosphorylating and activating Bcl-2 family member *Bax* via mitochondrial-dependent pathway, thus resulting in muscle fiber death (Wissing et al., 2014).

This work also screened many candidate genes related to germ cell development and reproductive hormone regulation, such as *SRD5A1* ,*FBXW11* , *DMRT1* , *CXADR* , and *RPTOR* . Early studies have isolated steroid 5 alpha-reductase 1 (*SRD5A1*) from rat liver and found that it is one of the three forms of steroid 5α-reductase (Russell et al., 1994). *SRD5A1* is involved in the metabolism of estrogen and androgen. The catalytic substrates of*SRD5A1* include testosterone, progesterone, androstenedione, epinephrine -T, cortisol, aldosterone, and deoxycorticosterone. This enzyme catalyzes the conversion of testosterone into stronger androgen: 5α-di hydrotestosterone (*DHT*). Therefore, *SRD5A1* plays an important role in mammalian stress, immune system regulation, and reproduction (Han et al., 2021). F-box and WD repeat domain containing 11 (*FBXW11*), a member of the F-box protein family and a part of the ubiquitin ligase complex, is important in the regulation of ubiquitin-dependent spermatogenesis. The mRNA level of *FBXW11* is positively correlated with sperm motility (Liu et al., 2021).

Double sex and mab-3 related transcription factor 1 (*DMRT1*) is involved in the sex determination of vertebrates. The functional lack of*DMRT1* in mice can lead to excessive proliferation of sertoli cells without further differentiation in the testis, leading to germ cell loss (Raymond et al., 2000). Knocking out the *DMRT1* in the sertoli cells in mice will activate *FOXL2* , which in turn causes the Sertoli cells to be reprogrammed into granular cells and the testicular tissue to transform into an ovarian-like morphology (Matson et al., 2011). As a member of the adhesion receptor tight junction protein family, CXADR Ig-like cell adhesion molecule (*CXADR*) plays an important role in embryonic development. Its absence causes embryonic development to stagnate in morula (Kwon et al., 2015). Regulatory associated protein of MTOR complex 1 (*RPTOR*) encodes the MTOR complex regulatory-related protein and is a part of the mTORC1 complex, which is important in the maintenance and renewal of mouse spermatogonia (Serra et al., 2019).

Some candidate genes related to immune regulation were also identified. CD200 molecule (*CD200*) is widely distributed on the surface of myeloid immune cells, such as thymocytes, B cells, and macrophages (Barclay et al., 1981). *CD20* 0 can combine with CD200R to participate in immune regulation. The *CD200* knockout in mice increases the activity of macrophages and cell lineage and disrupts the immune balance of body (Hoek et al., 2000). Serum/glucocorticoid regulated kinase 1 (*SGK1*) plays an important role in cellular stress response. *SGK1* mediates the regulation of glucocorticoid hormone and inhibits the proliferation of progenitor cells by increasing glucocorticoid hormone receptor phosphorylation (Anacker et al., 2013). Interleukin 17 receptor B (*IL17RB*) exhibits immunomodulatory activity, and its expression is up-regulated in patients with rhinitis (Matsumoto et al., 2011). *IL17RB* also participates in the regulation of inflammatory response by mediating NF-kappa B activation and IL8 production (Ruskin et al., 2012).

In this study, many genes related to metabolism were observed (e.g.,*INSR, STXBP3, H6PD,* and *APOE*). Insulin regulates the body's glucose, protein, and fat homeostasis. As the insulin receptor,*INSR* participates in insulin signaling pathway (Mukherjee et al., 2009). When the *INSR* gene is knocked down, insulin cannot perform function normally in the liver of mice, thus leading to the gradual deterioration of liver function (Okamoto et al., 2005). Variations in*INSR* cause insulin resistance syndrome and Donohue syndrome in multiple species (Reaven et al., 2005). The combination between*STXBP3* (syntaxin binding protein 3) and syntaxin 4 regulates insulin in peripheral tissues (Jewell et al., 2010). Mice with*STXBP3* homozygous knock-

out cannot survive, whereas those with*STXBP3* heterozygous knockout exhibit reduced insulin secretion and gradually become glucose intolerant when fed with a high-calorie diet rich in fat and carbohydrates (Oh et al. 2005). Hexose-6-phosphate dehydrogenase/glucose 1-dehydrogenase (*H6PD*) is involved in cell biochemical reactions and can mediate the regeneration of glucocorticoids (Zhang et al., 2009). *H6PD* knockout in mice reduces their sensitivity to glucocorticoids, which in turn increases insulin sensitivity and glucose uptake in muscles, thus eventually leading to severe skeletal myopathy (Lavery et al., 2008). Apolipoprotein E (*APOE*) encodes apolipoprotein and is one of the transport carriers of chylomicrons. *APOE* mediates lipoprotein catabolism and promotes the hydrolysis and clearance of soluble Aβ protein (Jiang et al., 2008). Its abnormalities lead to endothelial cell atherosclerosis (Nakashima et al., 1998) and central nervous system defects (Masliah et al., 1995).

CONCLUSION

A total of 1,122,858 InDels were detected based on the whole genome resequencing data of 46 Australian Boer goats and 81 local goats. Among which, 11,229 candidate InDels with top 1% high signal were screened, and 1,239 candidate genes were annotated. Gene enrichment experiment identified important genes from muscle development, reproduction, immunity, and metabolism. The results provide a theoretical basis for the study of related genetic mechanisms in goats and valuable foundation for molecular breeding in goats.

Data Availability Statement

Sequencing data generated in this study were obtained from our unpublished parallel projects (PRJNA671542).

COMPETING INTERESTS

The authors declare that they have no competing interests.

Author Contributions

Conceptualization, Ying Yuan and Guangxin E; Data curation, Ying Yuan and Baigao Yang; Formal analysis, Ying Yuan and Yongmeng He; Investigation, Ying Yuan, Xinhai Duan and Weiyi Zhang; Methodology, Ri-Su Na ,Yanguo Han, Yan Zeng, Guangxin E; Project administration, Yongju Zhao and Zhong-Quan Zhao; Resources, Yong-Fu Huang; Software, Ying Yuan; Writing – original draft, Ying Yuan and Baigao Yang; Writing – review & editing, shizhi wang and Guangxin E. All authors read and approved the manuscript.

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Institutional Review Board Statement

The experimental conditions of this study were approved by the Committee on the Ethics of Animal Experiments of Southwest University (No. [2007] 3) and the Animal Protection Law of China.

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Figure legends

Figure1. Information for annotation distribution of 1,122,858 InDels from 46 Australian Boer goats and 81 local goats' genome in the present study.

Figure 2. Genome-wide scan for a positively selected chromosome SNP in Boer goats using pairwise fixation index (F_{ST}) based on InDel data. A dashed horizontal line indicates the cut-off threshold (F_{ST}[?]0.623043).

Figure 3. Information for top 20 Gene Ontology (GO) terms with significant enrichment of candidate genes based on InDel data of 127 goats' genome in the present study.

Figure 4. Information for top 20 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways with significant enrichment of candidate genes based on InDel data of 127 goats' genome in the present study.

Supporting information

Table S1. Basic information and data reads-depth of 127 individuals.

Table S2. The top 1% threshold of Fst statistical parameters based on InDels of 127 goat individuals.

Table S3. The list of 1143 candidate genes Gene Ontology (GO) terms with significant enrichment based on top 1% Fst statistical parameters of 127 goats' genome.

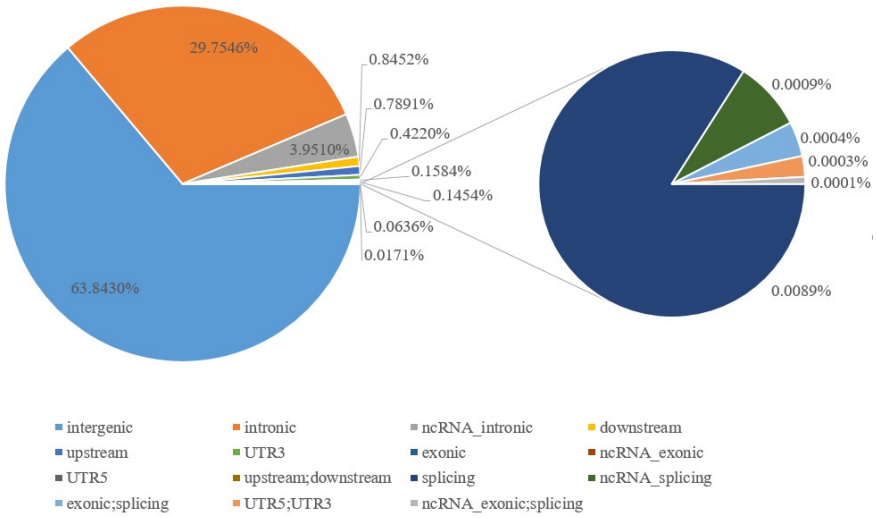
Table S4. Information for Gene Ontology (GO) terms with significant enrichment of candidate genes based on top 1% Fst statistical parameters of 127 goats' genome.

Table S5. The list of 94 candidate genes related to muscle development by Gene Ontology (GO).

Table S6. Information for Gene Ontology (GO) terms with significant enrichment of candidate genes related to muscle development based on top 1% Fst statistical parameters of 127 goats' genome.

Table S7. Information for the list of 476 candidate genes with Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways with significant enrichment of based on top 1% Fst statistical parameters of 127 goats' genome.

Table S8. Information for Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways with significant enrichment of candidate genes based on top 1% Fst statistical parameters of 127 goats' genome.



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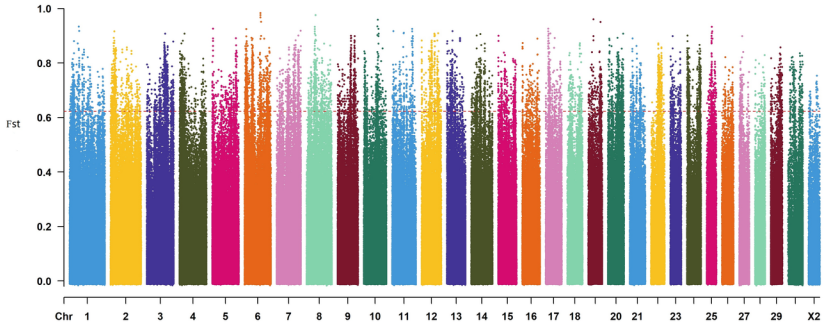

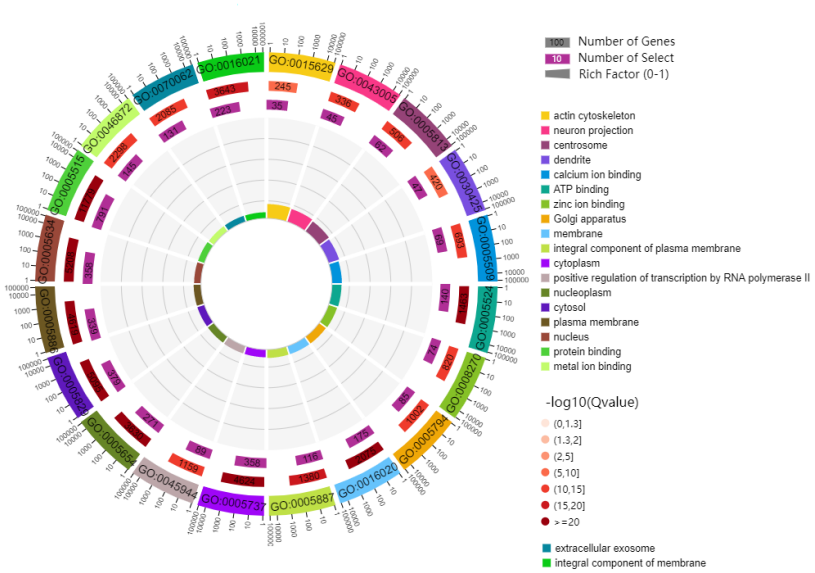

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