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Araştırma Makalesi

Gene Enrichment and Pathway Analysis for Ketosis Resistance in Dairy Cattle: A GWAS-Based Approach

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ABSTRACT

Ketosis in dairy cattle is a common metabolic disorder that arises during the transition period from late gestation to early lactation. It is primarily caused by an imbalance between energy intake and expenditure, leading to an excessive accumulation of ketone bodies. This condition can significantly affect cattle health and productivity. Recent advances in genomic research, especially genome-wide association studies (GWAS), offer an opportunity to explore the genetic factors that contribute to ketosis resistance. The aim of this study is to comprehensively review and analyze existing GWAS data using gene enrichment analysis to identify potential functional candidate gene pathways associated with ketosis resistance in dairy cattle. In this study, data obtained from seven different studies were examined and 640 non-repetitive genes were obtained after filtering. Using Enrichr, an online tool for gene annotation, pathway analysis was performed with human homologs of the identified genes. Our findings highlight the acylglycerol homeostasis pathway, the regulation of triglyceride metabolism, and the role of chylomicrons in maintaining metabolic balance during ketosis. Additionally, immune response pathways were found to be linked to the genes associated with ketosis, offering insights into the intricate interplay between metabolic and immune pathways in ketosis. This study emphasizes the importance of understanding genetic factors in developing breeding strategies aimed at enhancing metabolic health and productivity in dairy cattle. Future research should focus on validating these candidate genes and exploring their mechanistic roles to facilitate targeted interventions and improve resistance to ketosis in dairy herds.

Key words: Dairy cattle ketosis, GWAS, gene enrichment

Süt Sığırlarında Ketozis Direnci için Gen Zenginleştirme ve Yolak Analizi: GWAS Tabanlı Bir Yaklaşım

ÖZ

Süt sığırlarında ketozis, geç gebelik döneminden erken laktasyon dönemine geçişte ortaya çıkan yaygın bir metabolik bozukluktur. Bu durum, enerji alımı ile harcaması arasındaki dengesizlikten kaynaklanır ve keton cisimciklerinin aşırı birikimine yol açar. Ketozis, sığır sağlığını ve verimliliğini önemli ölçüde etkileyebilir. Genom araştırmalarındaki, özellikle de genom boyu dizileme analizleri (GWAS) gibi son gelişmeler, ketozis direncine katkıda bulunan genetik faktörleri keşfetme fırsatı sunmaktadır. Bu araştırmanın amacı, süt sığırlarında ketozis direnci ile ilişkili potansiyel fonksiyonel aday gen yolaklarını belirlemek için var olan GWAS verilerini gen zenginleşmesi analizi kullanarak kapsamlı bir şekilde incelemek ve analiz etmektir. Bu çalışmada yedi farklı çalışmadan elde edilen verileri incelenmiş ve filtreleme sonrası 640 tekrarsız gen elde edilmiştir. Tanımlanan genlerin insan homologları ile Enrichr adlı çevrimiçi gen anotasyon aracı kullanılarak yolak analizi yapılmıştır. Bulgularımız, trigliserit metabolizmasının düzenlenmesini ve ketozis sırasında metabolik dengenin korunmasında şilomikronların rolünü ve asilgliserol homeostaz yolaklarını ön plana çıkarmaktadır. Ayrıca, immün yanıt yolaklarının ketozis ile ilişkili genlerle bağlantılı olduğu bulunmuştur, bu da metabolik yolaklar ve immün yolaklar arasındaki karmaşık etkileşimlere dair bilgiler sunmaktadır. Bu çalışma, süt sığırlarında metabolik sağlığı ve

verimliliği arttırmayı amaçlayan yetiştirme stratejilerinin geliştirilmesinde genetik faktörlerin anlaşılmasının önemini vurgulamaktadır. Gelecek araştırmalar, bu aday genlerin doğrulanmasına ve mekanistik rollerinin incelenmesine odaklanarak, hedefe yönelik müdahaleleri kolaylaştırmalı ve süt sürülerinde ketozis direncini artırmalıdır.

Anahtar kelimeler: Süt sığırlarında ketozis, GWAS, Gen zenginleştirme

INTRODUCTION

Dairy cattle ketosis represents a metabolic disorder that manifests predominantly in the transition phase spanning from late gestation to early lactation. This state, inducing metabolic imbalance, significantly compromises the well-being and efficiency of livestock, distinguished by an abnormal accumulation of ketone bodies in the circulatory system (Wathes et al., 2007; Leroy et al., 2008). A swift reduction in food consumption, heightened energy demands during the lactation phase, and altered hormonal levels are multiple factors that influence the onset of ketosis (David Baird, 1982). At the onset of lactation, there is a decrease in insulin secretion alongside an elevation in glucagon production, consequently stimulating the degradation of adipose tissue and the release of fatty acids into the bloodstream. Subsequently, the liver metabolizes these fatty acids into ketones, augmenting ketone body concentrations (Zarrin et al., 2013). The primary ketone bodies produced during ketosis include acetoacetate (AcAc), beta-hydroxybutyrate (BHB), and acetone (Krebs, 1960).

Cattle in a state of ketosis experience a variety of symptoms, but they frequently include decreased appetite, lethargy, weight loss, reduced milk production, and increased susceptibility to illness (Yameogo et al., 2008). Ketosis can cause culling or death of the cow in extreme cases (Littledike et al., 1981). Early detection and timely treatment are crucial for this condition to be successfully managed (Oetzel and Mcguirk, 2008).

For the diagnosis of ketosis, blood samples are frequently used in the field, but occasionally, clinicians and farmers prefer non-invasive samples, like those from milk or urine (Faruk et al., 2020). Blood ketone tests are considered the most precise diagnostic method because they accurately measure ketone body levels in the bloodstream. However, these tests can be costly, labor-intensive, and time-consuming (Carrier et al., 2004; Faruk et al., 2020).

The common course of action for treating ketosis in cattle entails addressing the underlying metabolic imbalances as well as giving the animal supportive care to aid in its recovery (David Baird, 1982; Sakai et al., 1993). This might involve giving the animal extra food, giving them extra glucose or other energy sources, or using medications or other therapeutic substances to help control their metabolism (McSherry et al., 1960; Shpigel et al., 1996).

Identifying the genes associated with cattle ketosis can assist breeders in developing more resistant and resilient cattle and aid in creating new therapeutic interventions. Additionally, detecting gene pathways provides insight into the biological mechanisms and pathways involved in a given disease (Hasin et al., 2017). Identifying the gene pathways responsible for bovine ketosis can help us comprehend the metabolic processes that cause the disease. This knowledge can be applied to breeding plans that aim to reduce the prevalence of ketosis in cattle and develop more efficient therapeutic approaches (Pryce et al., 2016). Recent studies have shown that several genes are involved in the development of cattle ketosis (Gaddis et al., 2018; Kroezen et al., 2018; Yan et al., 2020). However, no comprehensive evaluation or gene enrichment analysis of GWAS results for resistance to ketosis in dairy cattle has been carried out to date. Therefore, the objective of this study was to conduct a systematic review and gene enrichment analysis of GWAS studies to identify possible functional candidate genes associated with resistance to ketosis-related features in dairy cattle.

MATERIALS and METHODS

In the pursuit of relevant scientific literature, a variety of online databases including Scholar Google, Web of Science, and BIOSIS, along with a comprehensive review of conference proceedings were searched. In total, the investigation yielded seven articles containing data on a total of 786 genes. Following the exclusion of duplicate entries and uncharacterized gene names, 640 genes were retained for subsequent analyses. To conduct gene enrichment and pathway analyses, Enrichr, an online resource for gene functional annotation (Evangelista et al., 2023), which encompasses the KEGG (Kyoto Encyclopedia of Genes and Genomes), GO (Gene Ontology), and Reactome platforms (http://amp.pharm.mssm.edu/Enrichr/) was used with default parameters and using human equivalents for all gene identifiers.

Table 1. List of gene identifiers used in the analyses (Table continues in the next page).

Source	Gene identifiers
Huang et al., 2019	BMP4, HNF4A, APOBR, SOCS4, GCH1, ATG14, RGS6, CYP7A1, and MAPK3
Ze Yan et al., 2019	GRINA, MAF1, MAFA, C14H8orf82 and RECQL4
Freebern et al., 2020	PARP10, LOC783947, KCNT, LY6K, and DGAT1
Schmidtmann et al., 2023	CFAP221, HECW2, and GALNTL6
Gaddis et al., 2018	TTLLY, FERMT2, ARAP2, DDHD1, BMP4, NAGK, CYP26B1, EXOC6B, ATP6V1BI, CD207, CLECIF, ZNF638, XDH, SRD5A2, SPAST, SLC30A6, RASGRP3, NLRCA, PRP8, FAM98A, PRP6, CLCNT, PRP4, MAPKSIP3, SULFI, UBE21, SLCO5A1, PRP1, PTX4, and TELO2
Nayeri et al., 2019	XPO6, OPLAH, NRBP2, WDR97, ZNF34, LOC100140490, GNRHR, DNAH5, DCK, MTHFD2L, PSCA, ORAI1, OTULINL, NPFFR2, NA, SHARPIN, TONSL, EPHA5, PUF60, UGT2B10, SDAD1, UGT2A1, ZC3H3, RASSF6, ARHGAP39, FAM47E, CYHR1, GC, LY6H, LOC781988, LOC787628, SCRIB, MROH1, RNF19A, HSF1, LOC786966, MYO10, SLURP1, C14H8orf33, TTC27, GRHL2, RHPN1, CXCL8, SLC4A4, APOBR, MIR1839, FOXH1, CSN1S1, MAF1, ADAMTS3, FRAS1, LOC100138004, BIRC6, CCDC166, LY6K, CLN3, SULT1E1, IL4R, GRINA, BTC, ZNF7, FBXL7, GML, RGS22, KIAA1324, DGAT1, TRIO, IL27, ANKH, PSPH, YTHDC1, LYPD2, PTP4A3, and SMPD5.

Table 1. List of gene identifiers used in the analyses.

Source	Gene identifiers
Soares et al., 2021	RAB2A, FST, NUPR2, CCDC36, AGBL5, NARF, bta-mir-371, TACR2, F13A1, EGFLAM, WASHC3, SLIT2, ASNS, PREB, KCNQ3, RF00407, GYPC, P4HB, ZC3H3, SLC5A6, RAC3, IFI6, ANKS1A, PSAPL1, PTCD2, TNIP2, RF00156, CXCR5, TCTA, CSNK1D, FN3KRP, WRNIP1, IL20, OGFOD3, QARS, C22H3orf84, ACAT2, TSPAN15, PACSIN1, GLI3, bta-mir-2345, USP2, CENPA, PSMC5, RF00026, NOP14, E2F3, MGST3, GH1, bta-mir-2344, CELSR3, FOXR1, TGDS, CDH12, ITGAD, CCDC57, SPTLC3, RF00285, ARHGDIA, PAH, ASCL1, PCYT2, RF00100, DLX5, GPN1, RASSF5, ADYC2, bta-mir-12011, PPA1, EIF2B4, ABCG4, RF01887, RF00289, PBX1, BCKDK, LIFR, SECTM1A, BSN, SUPT7L, HHLA1, PNLDC1, HTRA4, CHD7, TFAP2E, ADRA2C, NLRX1, MRPL32, CDHR4, UIMC1, bta-mir-2346, CDKAL1, C1GALT1, IRAK1BP1, SYNPO2, PHIP, MAP3K3, SNX17, UNC5A, DPYSL5, NUP37, CCDC137, NOTUM, MAPRE3, ABLIM2, APOA1, USP19, KLHDC8B, SNRPC, COL7A1, STAT1, FABP2, ZNF513, ZNF512, FOXK2, MYOZ2, HK3, USP53, HMX1, FCMR, PRR30, bta-mir-3533, SOX21, CHCHD2, IL10, EIF2D, SMIM12, TMEM214, TCF23, IDO1, ARCN1, SCUBE3, HTRA3, LMX1A, RNF123, PSMB2, ILRUN, DDX6, VPS11, RF00001, STRADA, FGR, SMARCD2, AFAP1, GTF3C2, COX18, BAHCC1, ZNF331, SCN4A, ARL16, PSMA2, DCAF7, CENPX, TRMT44, NRN1, LRRC52, bta-mir-10173, GNPTAB, NCDN, ZMYM4, RF00003, MEI4, HGS, TACO1, PDZD3, ZNF629, PDE5A, OXLD1, ZNF346, bta-mir-2450a, MRPS17, IGF1, MIR191, HEXD, TCAM1, SEL1L2, MRPL18, ASPSCR1, RF00322, NEUROG3, ARIH2, ALYREF, NCKIPSD, SLCO3A1, NICN1, FLRT2, SLC25A20, DLGAP3, WDR45B, FCHO2, DRAM1, PSPH, DYRK3, NRCAM, NDUFC1, ST8SIA2, SH3BP2, DDX42, FGFR4, MFSD10, TM2D2, DCXR, TTC39B, PHKG1, SLC6A15, NDUFAF5, PRKAR2A, WASF2, NDUFS4, TASP1, RF00091, PYCR1, APOA5, SYTL1, SERPINB6, RF00612, LRRC45, MRPS27, bta-mir-2451, RNF26, ZNF696, MYLK4, bta-mir-2450b, ISM1, GRK4, NPB, ADAM18, CD164L2, ITGAM, ETNK1, APEH, RF02271, MRPL12, RF00398, ESF1, SPDEF, TSPAN19, ALDH9A1, RF00429, bta-mir-425, GFOD1, DCT, NUDT3, PDE6G, SFPQ, TEX2, ZNF677, SLC37A4, ADCY8, PHLDB1, VKORC1, IMPDH2, IP6K1, UPK2, FASN, TOP1MT, ACTG1, SERPINB9, BAIAP2, NAA15, FCAMR, bta-mir-2450d, MYADML2, MYO10, PACRGL, TRHDE, ZNF713, DRC1, MPV17, PMCH, MAPKAPK2, COL13A1, SH3TC1, FAM241B, P4HTM, CMAS, bta-mir-95, GCGR, BABAM2, NPFFR1, ST8SIA1, ADAM3A, LIMD2, RXRG, GMDS, PRSS53, TCP11, ADAM32, HGFAC, RF00401, STK10, DPAGT1, RF00004, GLS, PRR16, TMEM222, SUMF2, CD79B, SECTM1, RF01888, ABHD1, TYSND1, RPS10, TRAPPC4, PHACTR1, UQCRC1, TBC1D7, ATRAID, MGC139164, C22H3orf62, GPS1, TDO2, MAFG, TBCD, GPX1, bta-mir-2347, DAG1, ZMYM1, BCL7C, KAT8, CD7, MAP3K6, RFNG, TAC1, UBA7, MSANTD1, SNORD42, RNF4, B3GNTL1, PLEKHA2, IKBKE, MRPL33, ADAM2, TMEM174, TREH, APOA4, SAR1A, BUD13, LRRIQ1, KCNH6, H2AFY2, DALRD3, ZPR1, TNPO1, COL28A1, DYNLRB2, SIRT7, SDHAF3, PLB1, TCP1, KIAA0319L, BCL9L, FTSJ3, RPS25, ZMYM6, RF00066, RHPN1, AMT, ZNF366, THY1, CPZ, IL24, UCK2, TRIM72, RPTOR, TMEM171, FBXW11, CCDC71, RF00045, ACOX3, ERN1, APOC3, OTOF, ANAPC11, AHDC1, ZNF646, bta-mir-2452, SLC26A6, GMPPB, CTSO, LCA5, DNAH5, MAFA, WDR6, ZBBX, PP1R27, ACE, FAAP100, USP4, LAMB2, PNPLA8, TRIM54, RHOA, FAM193A, QRICH1, ARMC5, PIGR, UHRF1BP1, KCNIP4, MAP1B, RF01778, C1QTNF5, PARPBP, CCDC47, RF00598, LRPAP1, CCDC153, NIPSNAP2, C2CD2L, FOSL2, CBL, GPR180, SERPINB1, CYB561, NPLOC4, MCRIP1, IL19, NLRP12, C2CD5, ADAM9, AMIGO3, TAF11, NDST3, RAB40B, MST1, TSPAN10, HTT, DOK7, LRRC20, HYOU1, CHMP6, DLX6, C6H4orf3, C4H7orf25, NDUFAF3, HMBS, IP6K2, RBKS, CDYL2, GPR3, ASIC5, TMEM89, MCAM, DUS1L, COX6A2, C3H1orf216, ZNF750, CLSPN, AIFM2, TANC2, TMCO1, MBOAT1, HMGA1, KCNA2, ADD1, INKA1, FARS2, PPP1R27, EFCAB9, MGARP, EFR3A, ANKRD17, CTF1, PRSS8, TGFB1I1, CCT6A, VKORC1L1, FREM1, SLC38A10, SELENOI, MOCS2, NME8, C11H2orf16, DNAJC5G, CGREF1, SLC35F6, UBTD2, ELF2, ALB, FBXL19, PRSS36, SLC5A2, RF00414, GUSB, CER1, NDUFAF8, bta-mir-2284y-1, ITGA2, SFRP4, FNDC4, SLC30A3, KHK, KCNK3, SH3PXD2B, NOCT, AFP, ORAI3, FUS, C25H16orf58, ZDHHC21, TEPSIN, DGRF3, ITGA1, EPDR1, IFT172, CAD, EMILIN1, AFM, SETD1A, PYCARD, AHSP, NFIB, CEP131, HADHB, PELO, KRTCAP3, RASSF6, SYNP02, HSD3B7, AATK, HADHA, NRBP1, 7SK, STX1B, bta-mir-338, PPM1G, CXCL8, STX4, and ZNF668

RESULTS and DISCUSSION

In total seven articles containing data on a total of 786 genes were found. Duplicate entries and uncharacterized gene names were removed, and 640 genes were used in the analyses. 558 genes were matched. In Enrichr platform, GO Biological Process 2021, Reactome 2022, and KEGG 2021 Human libraries were used to run pathway analyses for the matched genes. As a result, 15 pathways had a significant p-value ($p< 0.05$). Chylomicron assembly pathway was found to be significant in both GO and Reactome libraries. All significant pathways were listed in Table 2. The genes associated with the significant pathways were shown as a network analysis in Figure 1.

Table 2. List of significant pathways.

Term	Library	*p*-value
acylglycerol homeostasis (GO:0055090)	GO_Biological_Process_2021	0.0001104
Chylomicron Assembly R-HSA-8963888	Reactome_2022	0.0001151
Chylomicron Remodeling R-HSA-8963901	Reactome_2022	0.0001151
chylomicron assembly (GO:0034378)	GO_Biological_Process_2021	0.000187
regulation of intestinal lipid absorption (GO:1904729)	GO_Biological_Process_2021	0.0003108
triglyceride homeostasis (GO:0070328)	GO_Biological_Process_2021	0.0003899
negative regulation of type I interferon production (GO:0032480)	GO_Biological_Process_2021	0.0003931
Plasma Lipoprotein Remodeling R-HSA-8963899	Reactome_2022	0.0005555
Plasma Lipoprotein Assembly R-HSA-8963898	Reactome_2022	0.001391
FCGR3A-mediated Phagocytosis R-HSA-9664422	Reactome_2022	0.002951
Vitamin digestion and absorption	KEGG_2021_Human	0.006629
PPAR signaling pathway	KEGG_2021_Human	0.009387
Tryptophan metabolism	KEGG_2021_Human	0.01057
Fatty acid degradation	KEGG_2021_Human	0.01165
Fat digestion and absorption	KEGG_2021_Human	0.01165

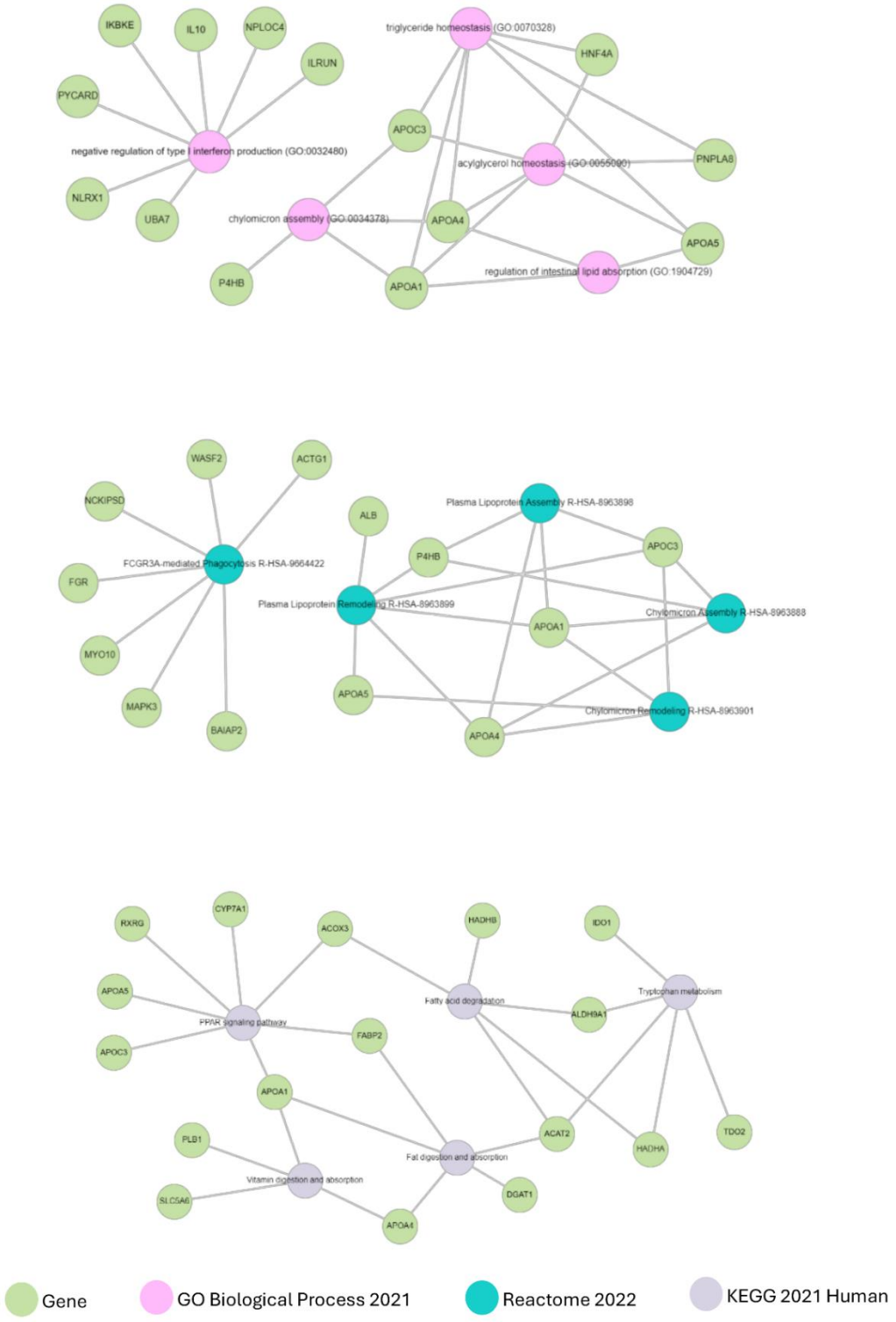

Figure 1. Interactions between genes and significant pathways

DISCUSSION

Ketosis is a metabolic state characterized by the elevated production of ketone bodies which serve as an alternative energy source when carbohydrate intake is significantly reduced. This metabolic adaptation occurs when the liver transforms fatty acids into ketone bodies through a process called beta-oxidation (Bergman, 1971; Houten and Wanders, 2010). In cows, ketosis could cause physiological changes due to decreased feed intake, increased energy requirements for milk production, and changes in hormone levels (Nielsen and Ingvartsen,

2004). This study aims to perform a systematic review and gene enrichment analysis of GWAS to identify potential functional candidate genes linked to resistance against ketosis-related traits in dairy cattle.

Among the significant pathways, acylglycerol homeostasis, which includes the regulation of triglycerides, is closely linked to ketosis. Triglycerides, the main form of stored fat in the body, are broken down into free fatty acids and glycerol during lipolysis, particularly under ketogenic conditions (McGarry and Foster, 1972; Wang et al., 2008). These fatty acids are then transported to the liver to be converted into ketone bodies (Al Odaib et al., 1998). Chylomicrons, which are lipoprotein particles that transport dietary triglycerides from the intestines to peripheral tissues, also play a crucial role in this metabolic interplay (Giammanco et al., 2015; Zhou et al., 2020). The efficient clearance and metabolism of chylomicrons are vital for maintaining triglyceride homeostasis, and any disruptions can lead to metabolic disorders such as chylomicronemia syndrome (Packard et al., 2020; Ofori, 2023). Ketone bodies, such as beta-hydroxybutyrate, produced during ketosis, may influence immune responses by modulating the production of type I interferons, which are crucial for antiviral defense and immune regulation (Zdzisińska et al., 2000; Satomura et al., 2022).

CONCLUSION

In conclusion, this study highlights the intricate metabolic adaptations associated with ketosis in dairy cattle and underscores the importance of understanding genetic factors that contribute to resistance against ketosis-related traits. Through systematic review and gene enrichment analysis of GWAS data, several potential functional candidate genes involved in key pathways such as acylglycerol homeostasis have been identified. These findings suggest that the regulation of triglyceride metabolism, particularly the role of chylomicrons and their efficient clearance, is crucial in maintaining metabolic balance during ketosis. Additionally, the influence of ketone bodies on immune function presents a novel area for further exploration, offering potential insights into how ketosis might affect disease resistance. Future research should focus on validating these candidate genes and exploring their mechanistic roles in ketosis resistance. This could pave the way for the development of targeted breeding strategies aimed at enhancing metabolic health and overall productivity in dairy cattle. Understanding these genetic underpinnings not only aids in improving cattle health but also has broader implications for livestock management and agricultural sustainability.

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