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Comparative analysis of differentially expressed genes in breast cancer across Asian and European populations: insights into molecular pathways and biomarkers

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Abstract

Aim: Breast cancer (BC) is the most common malignancy among women and a leading cause of cancer-related mortality. Early detection and prediction are crucial for prognosis and targeted therapy selection. This study investigates differences in BC gene expression between European and Asian populations by analysing differentially expressed genes (DEGs) and identifying potential biomarkers for diagnosis and treatment.

Methods: This study analyzed gene expression datasets from the NCBI Gene Expression Omnibus (GEO), including GSE15852 (Malaysia), GSE29044 (Saudi Arabia), GSE89116 (India), GSE61304 (Singapore), GSE29431 (Spain), GSE21422 (Germany), and GSE42568 (Ireland). DEGs were identified using GEO2R, with significance thresholds set at $p < 0.05$ and logFC > 2.0. Protein-protein interaction (PPI) networks were constructed using STRING and analyzed in Cytoscape, helping in identification of highly upregulated biomarker (HUB) genes. Functional enrichment was conducted using Enrichr-KG and GeneMANIA to explore pathway associations.

Results: Two common HUB genes, cluster of differentiation 36 (*CD36*) and leptin (*LEP*), were identified across five datasets, suggesting their universal relevance in BC. Additionally, caveolin-1 (*CAV1*) and perilipin 1 (*PLIN1*) were significant in the Asian datasets, while *CAV1*, insulin-like growth factor 1 (*IGF1*), apolipoprotein B (*APOB*), and peroxisome proliferator-activated receptor gamma (*PPARG*) were HUB genes in European datasets. Functional pathway analysis revealed that these genes are primarily involved in cholesterol metabolism, adipocytokine signaling, AMP-activated protein kinase (*AMPK*) regulation, and fatty acid metabolism, highlighting their role in BC progression.

Conclusions: *CD36* and *LEP* are universal biomarkers with potential diagnostic and prognostic significance in BC. Region-specific HUB genes emphasize the need for precision medicine in treatment. Their role in cholesterol metabolism and adipocytokine signaling suggests potential therapeutic targets. *CD36* and *LEP* could be used in liquid biopsy screening, and their metabolic function supports further investigation into

CD36 inhibitors, *LEP* antagonists, and *PPARG* modulators. Future studies should focus on large-scale validation and multi-omics approaches for personalized BC management.

Keywords

Breast cancer, differentially expressed genes (DEGs), Asian, European, biomarkers, highly upregulated biomarker (HUB) genes

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and leading cause of cancer-related mortality among women globally, with over 2.3 million new cases [1]. Despite significant advances in diagnostic and therapeutic lifestyle, and environmental factors, this heterogeneity poses a challenge for developing universally effective treatments and underscores the need for region-specific studies [2].

Several factors can increase the risk of developing BC, including aging, obesity, excessive alcohol consumption, family history of BC, exposure to radiation, reproductive history (such as the age of menstruation onset and age at first pregnancy), tobacco use, and postmenopausal hormone therapy. Interestingly, around half of BC cases develop in women who have no identifiable risk factors other than being female and over 40 [2].

BC is classified based on the affected breast cells. Ductal carcinoma in situ (DCIS) is a non-invasive cancer with abnormal cells in the duct lining that haven't spread. Invasive ductal carcinoma (IDC) is the most common type, where cancer cells spread beyond the ducts into other breast tissues. Invasive lobular carcinoma (ILC) begins in the lobules and spreads to surrounding tissues. Triple-negative BC lacks estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) receptors, making it harder to treat. HER2-positive BC is characterized by high levels of the HER2 protein, which promotes cancer cell growth, but can be treated with targeted therapies [3].

Genetic biomarkers like breast cancer gene 1/2 (*BRCA1/2*), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), GATA binding protein 3 (*GATA3*), tumor protein p53 (*TP53*), mitogen-activated protein kinase (MAPK) kinase kinase 1 (*MAP3K1*), partner and localizer of *BRCA2* (*PALB2*), and *BRCA1* interacting protein C-terminal helicase 1 (*BRIP1*) genes provide insights into the origins and treatment of BC [4]. Risk factors for BC include increasing age, family history, genetic mutations [particularly in *BRCA1*, *BRCA2*, and checkpoint kinase 2 (*CHEK2*)], exposure to female hormones, early menstruation, a previous BC diagnosis, and certain non-cancerous breast conditions. Lifestyle factors such as being overweight, insufficient physical activity, and alcohol consumption can also increase risk slightly. Differential gene expression (DGE) is crucial in cancer research as it helps identify genes uniquely expressed in cancer versus normal tissues, understand tumor biology, develop targeted therapies, predict treatment responses, and uncover mechanisms of drug resistance [4, 5].

While the basic ingredients in European diet and Asian diet remain the same they differ in terms of preparation with Asian cuisine focusing more on spices and aromatics. South Asians also tend to eat fewer meals per day and later in the evening than Europeans [6]. Asian populations have lower body mass index (BMI), but have higher total and central adiposity for a given body weight when compared with a matched white population. They also have 3 to 5 percent higher total body fat compared to European populations. Obesity is a major risk factor in BC and changes in obesity patterns may provide an insight into BC risks in the two populations [7].

Materials and methods

Workflow: Figure 1. Such as Figure 1 shows the workflow followed in the paper.

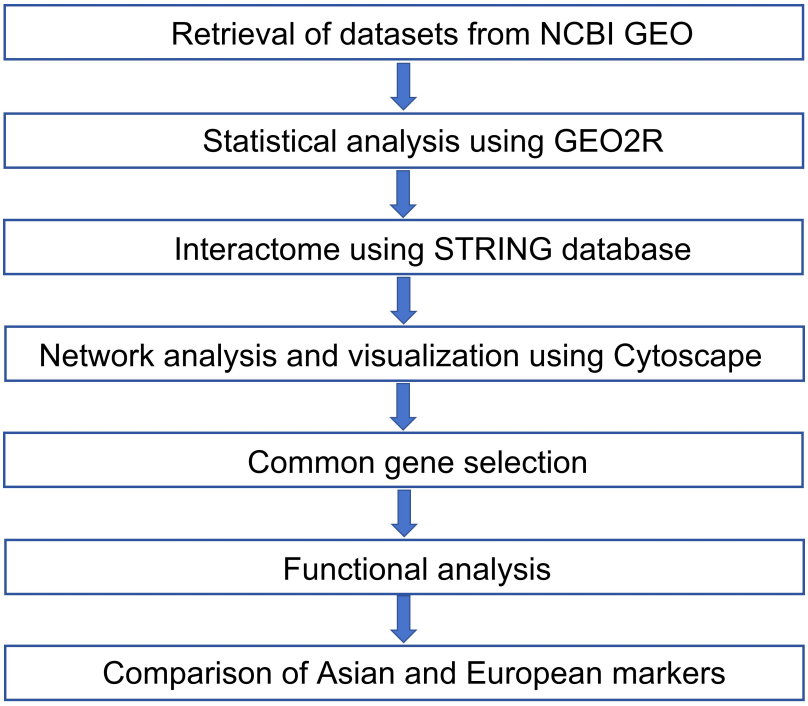

Figure 1. Workflow. GEO: Gene Expression Omnibus

Retrieval of datasets and extraction of differentially expressed genes

The NCBI-Gene Expression Omnibus (GEO) [8] is a publicly accessible database that houses microarray data. It is extensively utilized for gene expression datasets and platform records. For this BC, we obtained gene expression datasets from NCBI-GEO and analyzed them using GEO2R online tool. Differentially expressed genes (DEGs) were identified using Benjamini & Hochberg's false discovery rate (FDR), considering genes with $p < 0.05$ and logFC > 2.0 as significantly upregulated, data available in the Supplementary material.

Construction of protein-protein interaction network

We constructed protein-protein interaction (PPI) networks using STRING [9] and analyzed them in Cytoscape (v3.10.2) using Molecular Complex Detection (MCODE) and CytoHUBba plugins. We selected genes with at least three overlapping algorithms to identify highly upregulated biomarker (HUB) genes.

In total, 456 upregulated DEGs were extracted from the four datasets, and were utilized to construct the PPI network for the Asian population, and 2,950 upregulated DEGs were extracted from the three datasets, and were utilized to construct the PPI network for the European population.

Visualization and analysis of the network

Further analysis and visualization of the network were conducted using Cytoscape software (v3.10.2) [10]. Respective STRING networks were analyzed on Cytoscape using MCODE and CytoHUBba plugins. The networks were analyzed by MCODE and densely connected regions (clusters) within large PPI networks were identified. CytoHUBba was used to identify important nodes and subnetworks [11]. All 12 algorithms in cytoHUBba were used for analysis, namely: Degree Centrality, Betweenness Centrality, Closeness Centrality, Stress Centrality, Eccentricity, Radiality, BottleNeck, Edge Percolated Component (EPC), Maximum Neighborhood Component (MNC), Density of MNC (DMNC), Clustering Coefficient, and Maximal Clique Centrality (MCC).

Functional analysis

Gene set enrichment was performed using Enrichr-KG and GeneMANIA online bioinformatic tools to explore associations with known metabolic pathways, particularly cholesterol metabolism, adipocytokine signaling, and AMP-activated protein kinase (*AMPK*) regulation. Pathways with an adjusted *p*-value of less than 0.005 were considered [12, 13].

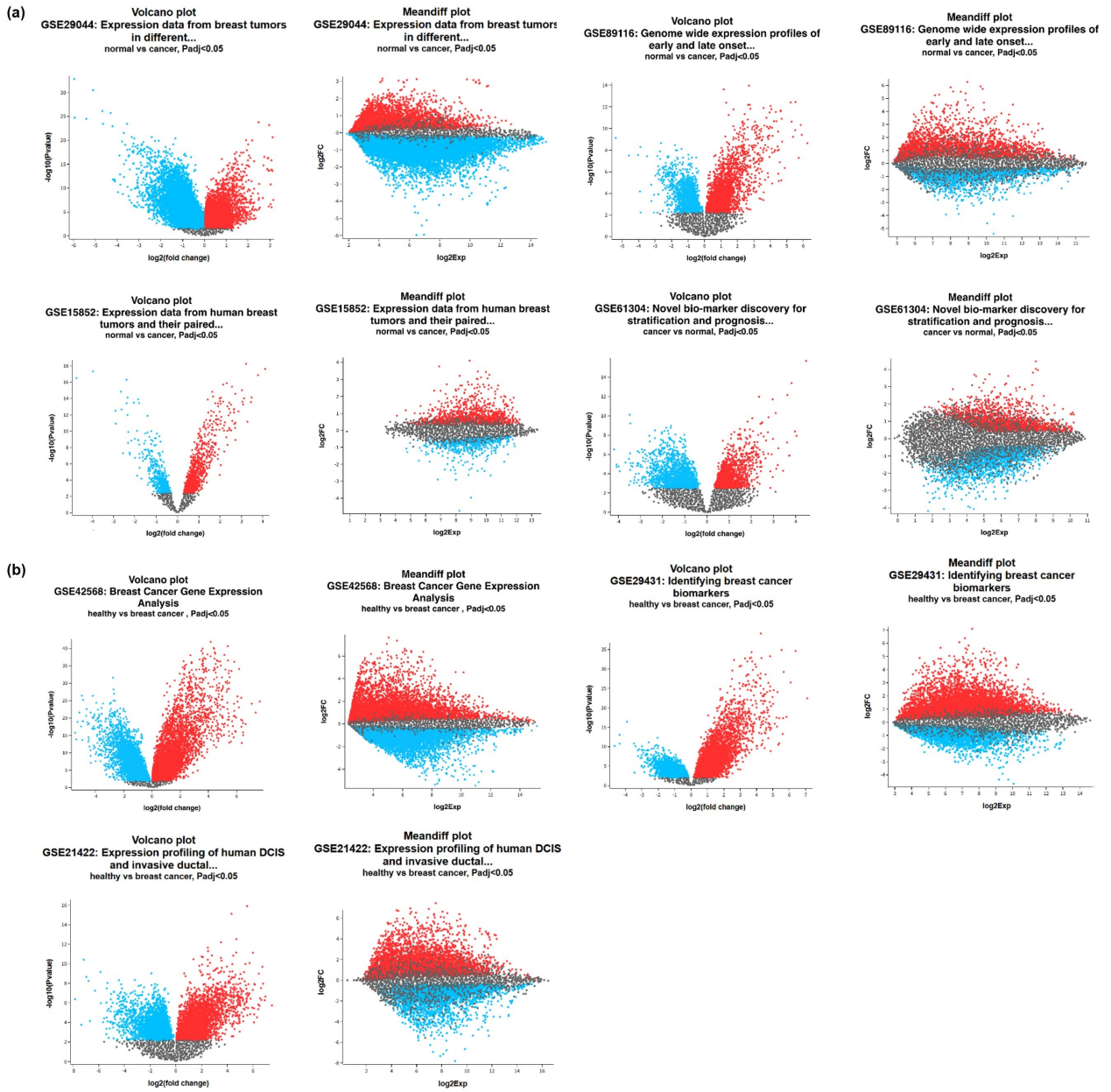

Figure 2. Graphical representation of DEGs. (**a**) Graphical representation of DEGs in Asian dataset; (**b**) graphical representation of DEGs in European dataset. DCIS: ductal carcinoma in situ; DEGs: differentially expressed genes; Exp: gene expression value; FC: fold change. Red points represent genes that are significantly upregulated in breast cancer. Blue points represent genes that are significantly upregulated in healthy tissue. Gray points represent genes that are not significantly different in expression between the two conditions

Results

GEO dataset processing to extract common DEGs

For BC, four GEO datasets with accession numbers GSE29044, GSE15852, GSE89116, and GSE61304 for the Asian population and three GEO datasets with accession numbers GSE42568, GSE21422, and GSE29431 for the European population were retrieved from the freely accessible NCBI-GEO database. GSE15852 https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE15852 (Malaysia), GSE29044 https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE29044 (Riyadh, Saudi Arabia), GSE89116 https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE89116 (New Delhi, India), and GSE61304 https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE61304 (Singapore) datasets were chosen for BC analysis of Asian population and GSE29431 https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE29431 (Barcelona, Spain), GSE21422 https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE21422 (Berlin, Germany), and GSE42568 https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE42568 (Dublin, Ireland) were chosen for the European

population. Samples were taken from patients of different age groups and at different stages of cancer progression, DGE analysis results of these datasets provide HUB genes whose expression in BC could be dependent on environmental factors, diet, genetic history, and lifestyle disorders. Set of images in Figure 2a graphical representation of DEGs in Asian datasets, and set of images in Figure 2b graphical representation of DEGs in European datasets.

PPI network

In total, 2,950 upregulated DEGs were extracted from the three datasets, and were utilized to construct the PPI network for the European population and 456 upregulated DEGs were extracted from the four datasets, and were utilized to construct the PPI network for the Asian population. The PPI networks obtained from STRING [9] are shown in supplementary figures: Figures S1–7.

Common gene selection

The common genes were shortlisted using Bioinformatics & Evolutionary Genomics Venn diagram generator tool [14]. In selected BC datasets, we selected the genes which had minimum of 3 common algorithms in that particular dataset, for each (intra-dataset comparison), files are attached in the Supplementary material under CytoHUBba algorithms and CytoHUBba analysis. Followed by, every dataset's selected gene list to check for common genes within them (inter-dataset comparison) to get HUB genes. The lists are mentioned in Table 1.

Table 1. Selected gene list of all four Asian and European datasets

Asian				European		
Malaysia (GSE15852)	**New Delhi (GSE89116)**	**Riyadh (GSE29044)**	**Singapore (GSE61304)**	**Dublin (GSE42568)**	**Barcelona (GSE29431)**	**Berlin (GSE21422)**
LEP (leptin)	*PLIN1* (perilipin 1)	*LEP*	*PPM2*	*PPARG* (peroxisome proliferator-activated receptor gamma)	*PPARG*	*PPARG*
LPL (lipoprotein lipase)	*IGF1* (insulin-like growth factor 1)	*ALAS2* (5'-aminolevulinate synthase 2)	*CDK1* (cyclin-dependent kinase 1)	*EGFR* (epidermal growth factor receptor)	*IGF1*	*LEP*
CD36 (cluster of differentiation 36)	*PPARG*	*HBB* (hemoglobin subunit beta)	*AURKA* (aurora kinase A)	*LEP*	*CDH5* (cadherin-5)	*CD34*
GPD1 (glycerol-3-phosphate dehydrogenase 1)	*CD36*	*HBD* (hemoglobin subunit delta)	*NUF2*	*CCL2* [chemokine (C-C motif) ligand 2]	*LEP*	*IGF1*
ACACB (acetyl-CoA carboxylase beta)	*LEP*	*FCG3B* (Fc gamma receptor IIIb)	*EXO1* (exonuclease 1)	*IGF1*	*EGFR*	*VWF* (von willebrand factor)
PLIN1	*IL6* (interleukin 6)	*PTG2*	*TOP2A* (DNA topoisomerase II alpha)	*CAV1* (caveolin-1)	*CD36*	*FGF2* (fibroblast growth factor 2)
PCK1 (phosphoenolpyruvate carboxykinase 1)	*APOB* (apolipoprotein B)	*CD36*	*COMP* (cartilage oligomeric matrix protein)	*APOB*	*FGF2*	*CXCL12* (C-X-C motif chemokine ligand 12)
CFD (complement factor D)	*FGF2*	*HBM* (hemoglobin subunit mu)	*COL11A1* (collagen type XI alpha 1 chain)	*PTGS2* (prostaglandin-endoperoxide synthase 2)	*APOB*	*LPL*

Table 1. Selected gene list of all four Asian and European datasets (*continued*)

Asian				European		
Malaysia (GSE15852)	**New Delhi (GSE89116)**	**Riyadh (GSE29044)**	**Singapore (GSE61304)**	**Dublin (GSE42568)**	**Barcelona (GSE29431)**	**Berlin (GSE21422)**
ANGTPL4	*ADIPOQ* (adiponectin, C1Q and collagen domain containing)	*SNCA* (synuclein alpha)	*FN1* (fibronectin 1)	*TLR4* (toll-like receptor 4)	*VWF*	*APOB*
RBP4 (retinol binding protein 4)	*FABP4* (fatty acid-binding protein 4)	*PPBP* (pro-platelet basic protein)	*FOXM1* (forkhead box M1)	*CD36*	*PPARA* (peroxisome proliferator activated receptor alpha)	*FABP4*
CAV1	*CAV1*	*KLF1* [Kruppel-like factor 1 (erythroid)]	*CCNA2* (cyclin A2)	-	*FOXO1* (forkhead box protein O1)	*ADIPOQ*
TF (transferrin)	*LIPE* (hormone-sensitive lipase)	*SLC25A37* (solute carrier family 25 member 37)	*DLGAP5* (DLG associated protein 5)	-	*FABP4*	*FOXO1*
ADH1B (alcohol dehydrogenase 1B)	*KIT* (KIT proto-oncogene, receptor tyrosine kinase)	*OXTR* (oxytocin receptor)	*STAT1* (signal transducer and activator of transcription 1)	-	*CAV1*	*CAV1*
-	*PCK*	*ADRB2* (adrenoceptor beta 2)	*MMP9* (matrix metallopeptidase 9)	-	*FOS* (Fos proto-oncogene, AP-1 transcription factor subunit)	*CD36*
-	*PNPLA2* (patatin-like phospholipase domain containing 2)	-	*TPX2* (TPX2 microtubule nucleation factor)	-	-	-
-	-	-	*ANLN* (anillin actin binding protein)	-	-	-
-	-	-	*BIRC5* (baculoviral IAP repeat containing 5)	-	-	-

-: no data

Cluster of differentiation 36 (*CD36*), leptin (*LEP*) were found to be common genes among GSE29044, GSE89116, and GSE15852 datasets and Singapore consisted of cyclin-dependent kinase 1 (*CDK1*), aurora kinase A (*AURKA*), DNA topoisomerase II alpha (*TOP2A*), and baculoviral IAP repeat containing 5 (*BIRC5*) (Asian). Caveolin-1 (*CAV1*), insulin-like growth factor 1 (*IGF1*), *CD36*, apolipoprotein B (*APOB*), peroxisome proliferator-activated receptor gamma (*PPARG*), *LEP* were found to be common genes among GSE42568, GSE21422 and GSE29431 datasets (European).

Venn diagram analysis

Venn diagram of GSE29044, GSE89116, GSE15852, and GSE61304 datasets (Asian population) and Venn diagram of GSE42568, GSE21422, and GSE29431 datasets (European population) is shown in Figure 3.

Table 2 contains tabulated data of Venn diagram of Asian and European Population. From Venn diagram Asian results we observe that there are no genes common between all four Asian datasets but *CD36* and *LEP* were found as HUB genes between GSE29044, GSE89116, and GSE15852 datasets, and *CAV1* and perilipin 1 (*PLIN1*) were found as secondary HUB genes common to GSE89116 and GSE15852. The

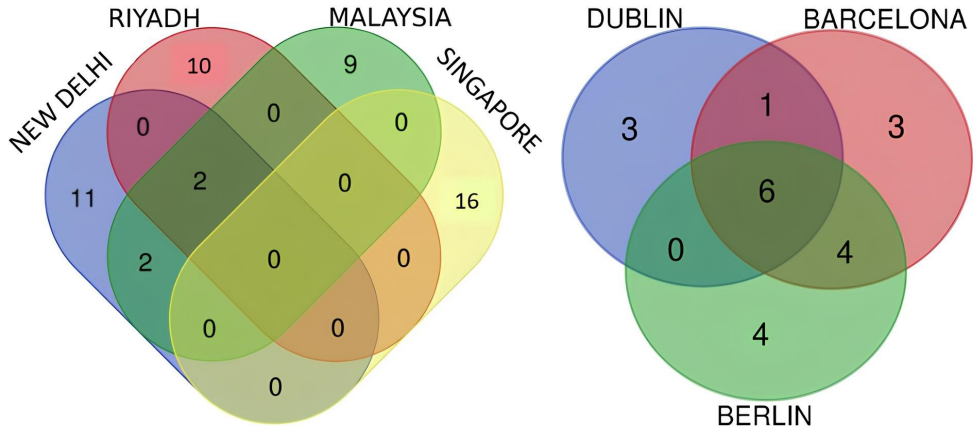

Figure 3. Venn diagram result of the HUB genes identified from each individual Asian and European datasets. HUB: highly upregulated biomarker

Table 2. Tabulated data of Venn diagram of Asian and European Population

Asian		**European**		
Name	**Genes**	**Names**	**Total**	**Elements**
Malaysia, New Delhi, Riyadh	*CD36* (cluster of differentiation 36), *LEP* (leptin)	Barcelona, Berlin, and Dublin	6	*CAV1* (caveolin-1), *IGF1* (insulin-like growth factor 1), *CD36*, *APOB* (apolipoprotein B), *PPARG* (peroxisome proliferator-activated receptor gamma), *LEP*
Malaysia, New Delhi	*CAV1*, *PLIN1* (perilipin 1)	Barcelona, Dublin	1	*EGFR* (epidermal growth factor receptor)
New Delhi	*KIT* (KIT proto-oncogene, receptor tyrosine kinase), *FABP4* (fatty acid-binding protein 4), *PPARG*, *PNPLA2* (patatin-like phospholipase domain containing 2), *LIPE* (hormone-sensitive lipase), *PCK* (phosphoenolpyruvate carboxykinase), *IGF1*, *FGF2* (fibroblast growth factor 2), *APOB*, *IL6* (interleukin 6), *ADIPOQ* (adiponectin, C1Q and collagen domain containing)	Barcelona, Berlin	4	*FABP4*, *FGF2*, *VWF* (von Willebrand factor), *FOXO1* (forkhead box protein O1)
Riyadh	*ALAS2* (5'-aminolevulinate synthase 2), *HBD* (hemoglobin subunit delta), *SLC25A37* (solute carrier family 25 member 37), *HBM* (hemoglobin subunit mu), *FCG3B* (Fc gamma receptor IIIb), *KLF1* [Kruppel-like factor 1 (erythroid)], *SNCA* (synuclein alpha), *PPBP* (pro-platelet basic protein), *OXTR* (oxytocin receptor), *ADRB2* (adrenoceptor beta 2)	Dublin	3	*CCL2* [chemokine (C-C motif) ligand 2], *TLR4* (toll-like receptor 4), *PTGS2* (prostaglandin-endoperoxide synthase 2)
Malaysia	*TF* (transferrin), *PCK1*, *RBP4* (retinol binding protein 4), *ACACB* (acetyl-CoA carboxylase beta), *ADH1B* (alcohol dehydrogenase 1B), *LPL* (lipoprotein lipase), *CFD* (complement factor D), *ANGPTL4* (angiopoietin like 4), *GPD1* (glycerol-3-phosphate dehydrogenase 1)	Barcelona	3	*PPARA* (peroxisome proliferator activated receptor alpha), *FOS* (Fos proto-oncogene, AP-1 transcription factor subunit), *CDH5* (cadherin-5)
Singapore	*RRM2* (ribonucleotide reductase regulatory subunit M2), *CDK1* (cyclin-dependent kinase 1), *AURKA* (aurora kinase A), *EXO1* (exonuclease 1), *TOP2A* (DNA topoisomerase II alpha), *COMP* (cartilage oligomeric matrix protein), *COL11A1* (collagen type XI alpha 1 chain), *FN1* (fibronectin 1), *FOXM1* (forkhead box M1), *CCNA2* (cyclin A2), *DLGAP5* (DLG associated protein 5), *STAT1* (signal transducer and activator of transcription 1), *MMP9* (matrix metallopeptidase 9), *TPX2* (TPX2 microtubule nucleation factor), *ANLN* (anillin actin binding protein), *BIRC5* (baculoviral IAP repeat containing 5)	Berlin	4	*LPL*, *CD34*, *CXCL12* (C-X-C motif chemokine ligand 12), *ADIPOQ*

Singapore data set consisting specifically of breast adenocarcinoma did not have any common HUB gene, with the other selected datasets as the other datasets were not inclusive only of breast adenocarcinoma. From Venn diagram European results we observe that *CAV1*, *IGF1*, *CD36*, *APOB*, *PPARG*, and *LEP* are common HUB genes found in European population.

CD36 and *LEP* were found to be common HUB genes in both populations, while *CAV1* and *PLIN1* were prevalent in Asian datasets, and *CAV1*, *IGF1*, *APOB*, and *PPARG* were identified in European datasets (Table 1).

Functional enrichment analysis

Functional analysis by Enrichr-KG of Asian population

HUB genes common to GSE29044, GSE89116, and GSE15852 were found to be *CD36* and *LEP* from the Venn diagram results. The *CD36*, *LEP*, *CAV1*, and *PLIN1* genes were inputted in Enrichr-KG to obtain the following results shown in Figure 4. Table 3 represents gene table of Enrichr-KG pathways of Asian datasets.

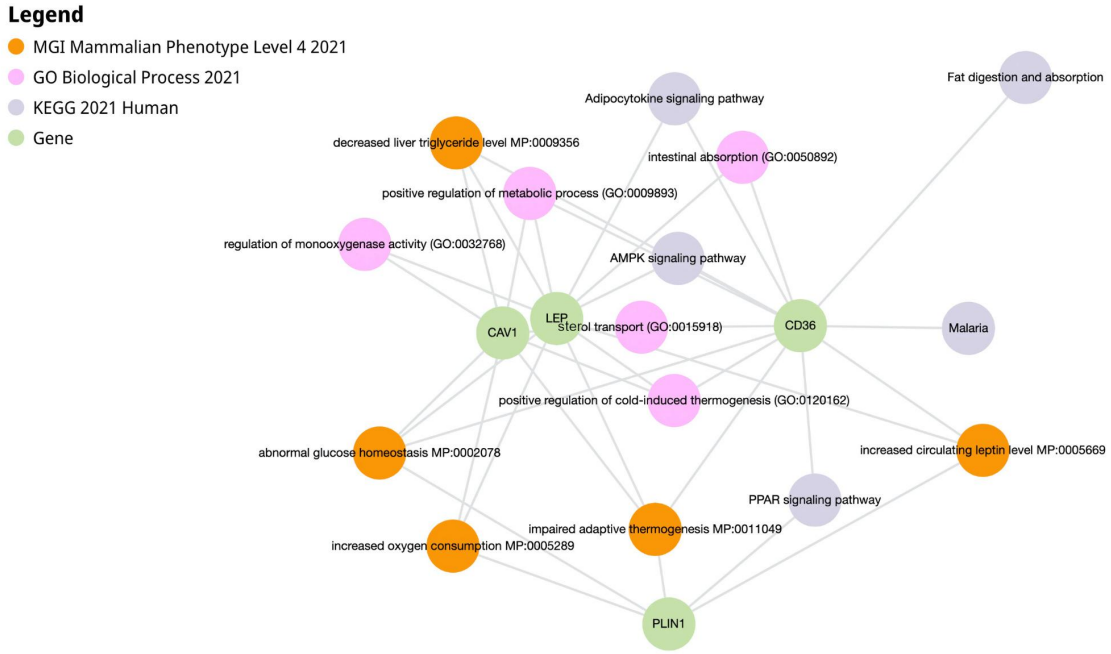

Figure 4. Enrichr-KG results of *CD36*, *LEP*, *CAV1*, and *PLIN1*. *AMPK*: AMP-activated protein kinase; *CAV1*: caveolin-1; *CD36*: cluster of differentiation 36; *LEP*: leptin; *PLIN1*: perilipin 1; *PPAR*: peroxisome proliferator-activated receptor

Table 3. Enrichr-KG pathways and associated gene table (Asian)

Pathway	Associated genes	Role in breast cancer (BC)
Cholesterol metabolism	*CD36* (cluster of differentiation 36), *LEP* (leptin)	Influences BC progression, aggressiveness, and drug resistance
Impaired adaptive thermogenesis	*CAV1* (caveolin-1), *LEP*, *CD36*, *PLIN1* (perilipin 1)	Promote cancer cell survival and growth
Adipocytokine signaling pathway	*LEP*, *CD36*	Influence BC cell survival, growth, invasion, and metastasis
Positive regulation of mitogen-activated protein kinase (MAPK) cascade	*LEP*, *CD36*	Key in cell proliferation and death
AMP-activated protein kinase (*AMPK*) signaling pathway	*CD36*, *LEP*	Functions as a tumor suppressor
Increased oxygen consumption	*CAV1*, *LEP*, *PLIN1*	Increase tumor proliferation
Abnormal glucose homeostasis	*CAV1*, *LEP*, *PLIN1*, *CD36*	Increases the proliferation of BC cells

GeneMANIA results of *CD36*, *LEP*, *CAV1*, and *PLIN1* are shown in Figure 5. *LEP* receptor (*LEPR*), hydroxysteroid 11-beta dehydrogenase 1 (*HSD11B1*), fatty acid-binding protein 4 (*FABP4*), *PLIN1*, *PLIN2*, *PLIN4*, *PLIN5*, abhydrolase domain containing 5 (also known as CGI-58) (*ABHD5*), scavenger receptor class B member 2 (*SCARB2*), histone deacetylase 6 (*HDAC6*), *CAV2*, low-density lipoprotein receptor-related protein 6 (*LRP6*), nitric oxide synthase 3 (*NOS3*), *NOS* trafficking (*NOSTRIN*), and potassium voltage-gated channel subfamily H member 2 (*KCNH2*) are associated genes that play roles in BC as biomarkers, inhibitors and promoters in Asian datasets based on GeneMANIA results.

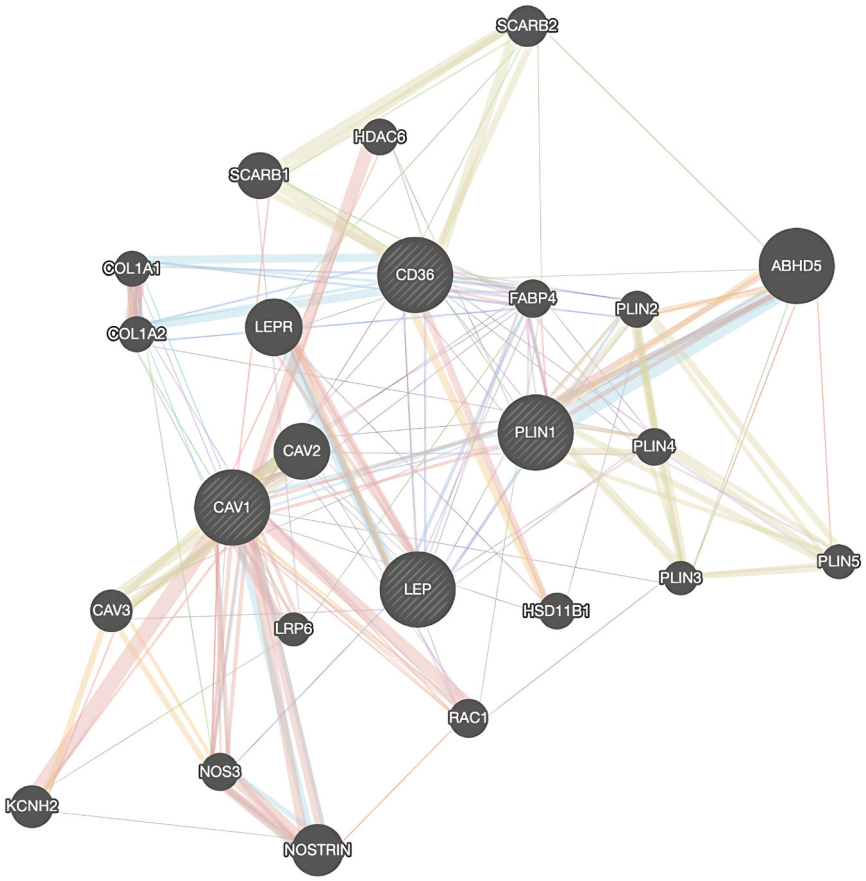

Figure 5. GeneMANIA results of *CD36*, *LEP*, *CAV1*, and *PLIN1*. *ABHD5*: abhydrolase domain containing 5; *CAV1*: caveolin-1; *CD36*: cluster of differentiation 36; *COL1A1*: collagen type I alpha 1 chain; *FABP4*: fatty acid-binding protein 4; *HDAC6*: histone deacetylase 6; *HSD11B1*: hydroxysteroid 11-beta dehydrogenase 1; *KCNH2*: potassium voltage-gated channel subfamily H member 2; *LEP*: leptin; *LEPR*: leptin receptor; *LRP6*: low-density lipoprotein receptor-related protein 6; *NOS3*: nitric oxide synthase 3; *NOSTRIN*: nitric oxide synthase trafficking; *PLIN2*: perilipin 2; *RAC1*: Rac family small GTPase 1; *SCARB2*: scavenger receptor class B member 2

Functional analysis by Enrichr-KG of European population

HUB genes common to GSE42568, GSE21422, and GSE29431 were found to be *CAV1*, *IGF1*, *CD36*, *APOB*, *PPARG*, and *LEP* from the Venn diagram results. The six genes were inputted in Enrichr-KG to obtain the following results shown in Figure 6. Table 4 represents gene table of Enrichr-KG pathways of European datasets.

GeneMANIA results of *CAV1*, *IGF1*, *CD36*, *APOB*, *PPARG*, and *LEP* are shown in Figure 7. *HSD11B1*, *CAV2*, *FABP4*, *IGF* binding protein 2 (*IGFBP2*), *APOB*, aquaporin 7 (*AQP7*), *PLIN4*, *APOA1*, *PLIN1*, cell death inducing DFFA like effector a (*CIDEA*), glycerol-3-phosphate dehydrogenase 1 (*GPD1*), hormone-sensitive lipase (*LIPE*), adiponectin, C1Q and collagen domain containing (*ADIPOQ*), early B-cell factor 1 (*EBF1*), *CIDEC*, *EBF3*, palmdelphin (*PALMD*), semaphorin 3G (*SEMA3G*), *IGFBP6*, oxidized low-density lipoprotein receptor 1 (*OLR1*), solute carrier family 19 member 3 (*SLC19A3*) are associated genes that play roles in BC based on GeneMANIA results for European datasets.

Comparison of gene expression across all seven datasets

A collective HUB gene analysis across all datasets reinforced the significance of *CD36*, *LEP*, and *PPARG* as key molecular regulators in BC progression.

Discussion

Comparing DEGs between European and Asian BC datasets provides crucial insights into population-specific molecular mechanisms and pathways. These comparisons highlight genetic diversity and reveal unique tumor biology shaped by distinct genetic backgrounds and environmental influences. Universal

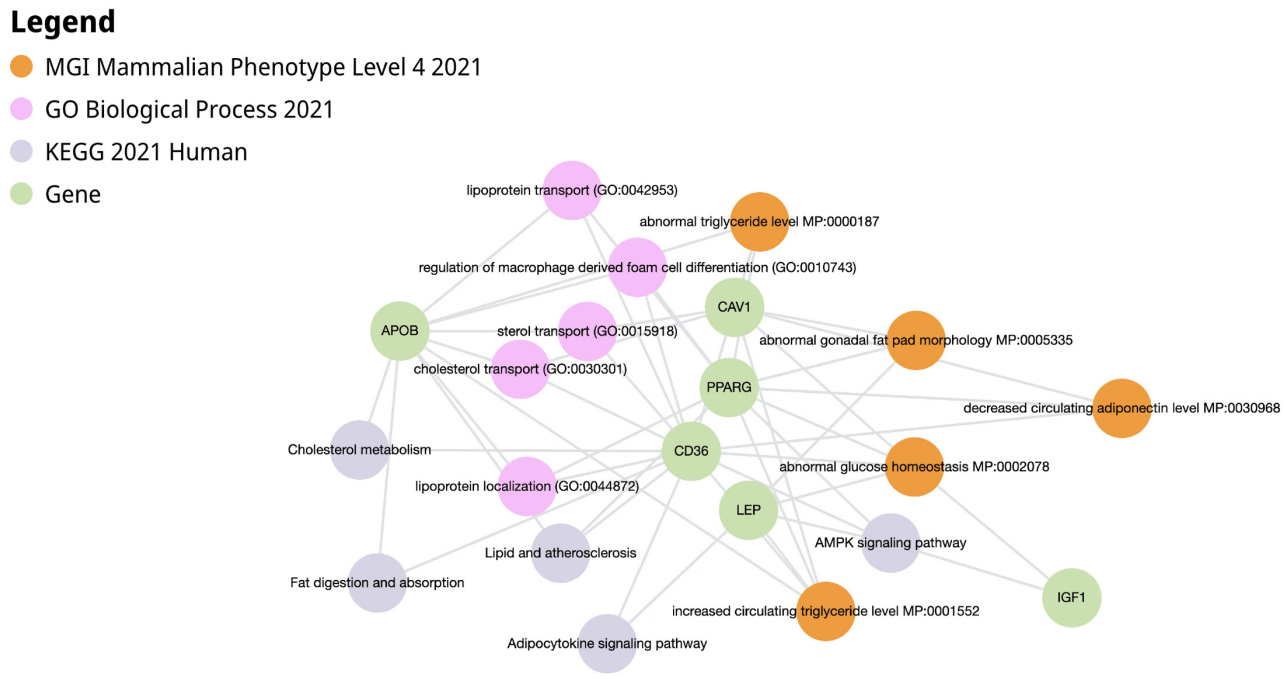

Figure 6. Enrichr-KG results of *CAV1*, *IGF1*, *CD36*, *APOB*, *PPARG*, and *LEP*. *AMPK*: AMP-activated protein kinase; *APOB*: apolipoprotein B; *CAV1*: caveolin-1; *CD36*: cluster of differentiation 36; *IGF1*: insulin-like growth factor 1; *LEP*: leptin; *PPARG*: peroxisome proliferator-activated receptor gamma

Table 4. Enrichr-KG pathways and associated gene table (European)

Pathway	Associated genes	Role in breast cancer (BC)
Cholesterol metabolism	*CD36* (cluster of differentiation 36), *APOB* (apolipoprotein B)	Influences BC progression, aggressiveness, and drug resistance
Decreased circulating adiponectin level	*CAV1* (caveolin-1), *CD36*, *PPARG* (peroxisome proliferator-activated receptor gamma)	Contribute to breast tumor development and progression
Adipocytokine signaling pathway	*LEP*, *CD36*	Influence BC cell survival, growth, invasion, and metastasis
AMP-activated protein kinase (*AMPK*) signaling pathway	*CD36*, *LEP*, *PPARG*, *IGF1* (insulin-like growth factor 1)	Functions as a tumor suppressor
Increased circulating triglyceride level	*CAV1*, *LEP*, *PPARG*, *APOB*, *CD36*	Influence cancer cell growth and survival
Abnormal glucose homeostasis	*CAV1*, *LEP*, *IGF1*, *CD36*, *PPARG*	Increases the proliferation of BC cells

biomarkers such as *CD36* and *LEP* emerge as common elements across populations, while region-specific genes like *CAV1* and *PLIN1* in Asian cohorts or *IGF1* and *APOB* in European cohorts underline molecular differences that can inform tailored diagnostic and therapeutic strategies. In volcano plot and mean difference plot: red points represent genes that are significantly upregulated in BC compared to healthy tissue. Blue points represent genes that are significantly downregulated in BC compared to healthy tissue. Gray points represent genes that are not significantly different in expression between the two conditions. In Asian datasets: GSE29044: a larger number of blue points in comparison to red points indicates that the number of downregulated genes is higher than that of upregulated genes. GSE89116: a larger number of red points in comparison to blue points indicates that the number of upregulated genes is higher than that of downregulated genes. GSE15852: An almost equal number of blue and red points are observed indicating that the number of upregulated and downregulated genes are around the same. GSE61304: the number of grey points is higher than that of both blue and red points indicating that these genes are not different in expression to that of healthy tissues and downregulated and upregulated genes are around the same number. In European datasets: GSE21422, GSE29431, and GSE42568 a larger number of red points were observed in comparison to blue points indicating that the number of upregulated genes is higher than that of downregulated genes. This comparative approach enhances our understanding of BC heterogeneity and supports the advancement of personalized medicine.

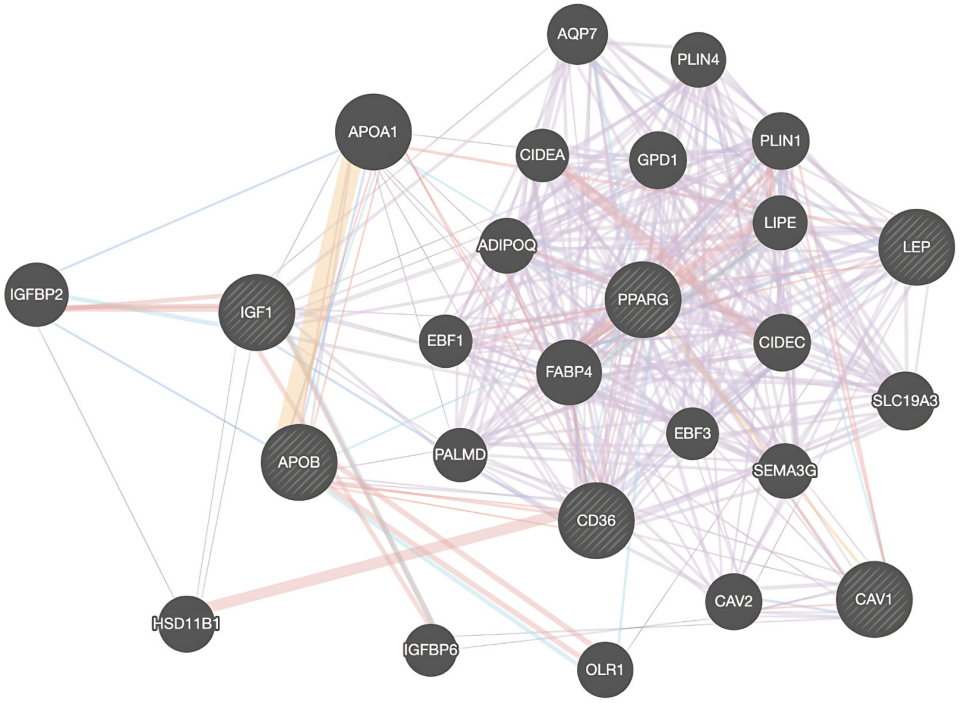

Figure 7. GeneMANIA results of *CAV1*, *IGF1*, *CD36*, *APOB*, *PPARG*, and *LEP*. *ADIPOQ*: adiponectin, C1Q and collagen domain containing; *APOA1*: apolipoprotein A1; *AQP7*: aquaporin 7; *CAV2*: caveolin-2; *CD36*: cluster of differentiation 36; *CIDEA*: cell death inducing DFFA like effector a; *EBF1*: early B-cell factor 1; *FABP4*: fatty acid-binding protein 4; *GPD*: glycerol-3-phosphate dehydrogenase; *HSD11B1*: hydroxysteroid 11-beta dehydrogenase 1; *IGF1*: insulin-like growth factor 1; *IGFBP2*: insulin-like growth factor binding protein 2; *LEP*: leptin; *LIPE*: hormone-sensitive lipase; *OLR1*: oxidized low-density lipoprotein receptor 1; *PALMD*: palmdelphin; *PLIN4*: perilipin 4; *PPARG*: peroxisome proliferator-activated receptor gamma; *SEMA3G*: semaphorin 3G; *SLC19A3*: solute carrier family 19 member 3

Lifestyle and environmental factors, such as dietary habits and adiposity patterns, significantly influence key pathways like cholesterol metabolism and adipocytokine signaling [15]. Aberrant cholesterol metabolism can trigger carcinogenic pathways, such as the Hedgehog signaling system, which aids in tumor growth and the survival of cancer stem cells [16]. The development of BC is significantly influenced by adipocytokine signaling, especially when obesity is present. While lower levels of protective adipokines like adiponectin may raise the risk of developing cancer, higher levels of specific adipocytokines, such as *LEP*, can encourage tumor growth, invasion, and metastasis [17]. Dysregulated fatty acid metabolism sustains BC cell proliferation and survival by providing essential bioenergetic and biosynthetic resources. Enhanced lipogenesis, fatty acid uptake, and altered β-oxidation support membrane synthesis, energy production, and redox balance. Additionally, lipid signaling influences oncogenic pathways, promoting cell cycle progression, apoptosis resistance, and metastasis [18].

The development of BC is significantly influenced by adipocytokine signaling, especially when obesity is present. While lower levels of protective adipokines like adiponectin may raise the risk of developing cancer, higher levels of specific adipocytokines, such as *LEP*, can encourage tumor growth, invasion, and metastasis. Asian populations exhibit higher central adiposity despite lower BMI, while European cohorts show different lipid profiles influenced by dietary fat consumption [19]. These differences impact DEGs and associated pathways, emphasizing the need for region-specific prevention and treatment strategies. By bridging knowledge gaps in global BC research, this study ensures inclusivity for underrepresented populations and contributes to identifying robust biomarkers for precision diagnostics and targeted therapies.

Gene ontology

Gene ontology for Asian populations

The datasets GSE29044 (Riyadh), GSE15852 (Malaysia), GSE89116 (New Delhi), and GSE61304 (Singapore) consist of breast carcinoma and healthy tissue samples. HUB genes identified include *CAV1*, *CD36*, *LEP*, and *PLIN1*, with additional key proteins such as *LEPR*, *PTPN1*, *SOC3*, *HSD11B1*, *CEBPA*, *PTK2*, *FABP4*, integrin

alpha-6 (*ITGA6*), clusterin (*CLU*), cartilage oligomeric matrix protein (*COMP*), ghrelin and obestatin prepropeptide (*GHRL*), *PPARG*, and *SCARB2*. These genes play significant roles as potential biomarkers and therapeutic targets.

ABHD5 suppresses cancer cell proliferation via the *ABHD5*/*ATGL* pathway, while *KCNH2* promotes epithelial-mesenchymal transition (EMT), facilitating metastasis [20]. Elevated *SCARB2* levels are linked to advanced cancer stages and poor prognosis, and overexpression of *HDAC6* enhances metastasis through heat shock factor 1 (HSF1) activation [21]. *CAV1* regulates critical signaling pathways, including estrogen receptor (ER), epidermal growth factor receptor (*EGFR*), and transforming growth factor beta (TGF-β), while *LRP6* is a biomarker for poor prognosis via Wnt signaling pathway/β-catenin activation [22]. *LEP* and its receptor *LEPR* drive proliferation and angiogenesis through janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) and Extracellular signal-Regulated Kinase (ERK) pathways [23]. Suppressor of cytokine signaling 2 (*SOCS2*) and *SOCS3* regulate STAT pathways, influencing proliferation and angiogenesis [24]. *FABP4* and *ITGA6* enhance invasive properties and establish a link between obesity and cancer risk [25]. *COMP*, identified in the Singapore cohort, is associated with cancer stem cell properties [26]. These findings underscore the roles of lipid metabolism, signaling pathways, and the tumor microenvironment in BC progression, with *CD36*, *LEP*, and *PPARG* highlighted as key therapeutic targets.

Gene ontology for European populations

The datasets GSE42568 (Dublin), GSE21422 (Berlin), and GSE29431 (Barcelona) include breast carcinoma and healthy tissue samples. HUB genes identified include *CAV1*, *IGF1*, *CD36*, *APOB*, *PPARG*, and *LEP*. Additional genes such as *IGFBP2*, *APOB*, *HSD11B1*, *AQP7*, *APOA1*, *GPD1*, *ADIPOQ*, *PPARG*, *EBF3*, *PALMD*, *SEMA3G*, *IGFBP6*, *OLR1*, and *SLC19A3* serve as biomarkers, inhibitors, or promoters in BC. *IGFBP2* promotes tumor proliferation, migration, and angiogenesis, while *APOB* mutations are linked to aggressive BC, especially in postmenopausal women [27]. *HSD11B1* induces EMT, enhancing metastasis, and *AQP7* correlates with better survival [28]. *APOA1* suppresses apoptosis and supports tumor growth [29], and *GPD1* inhibits proliferation via the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway [30]. *ADIPOQ* polymorphisms influence serum adiponectin levels and BC risk [31]. *PPARG* regulates angiogenesis and apoptosis in ER + BC and is a potential target for natural treatments like quercetin [32]. *EBF3* induces cell cycle arrest, and *PALMD* inhibits tumor growth by blocking the PI3K/AKT pathway [33]. *SEMA3G* promotes angiogenesis and metastasis, while *IGFBP6* downregulation increases metastasis risk [34]. *OLR1* upregulation indicates poor prognosis due to immune evasion [35]. *LIPE* promotes lipolysis, providing metabolic substrates for tumor growth.

Common gene ontology across populations

CD36 and *LEP* were common HUB genes identified in both European and Asian datasets, with *FABP4*, *HSD11B1*, and *PLIN* family genes emerging as associated genes. *CD36* enhances fatty acid uptake, lipid metabolism, cancer proliferation, and EMT, marking it as a potential cancer stem cell marker [36]. *LEP* activates pathways like MAPK, PI3K/AKT, and JAK2/STAT, driving proliferation, migration, and angiogenesis across BC subtypes [5]. *PLIN1* regulates lipid droplets in aggressive tumors, while *FABP4* links obesity to BC by promoting lipolysis and inflammation [37]. *HSD11B1* induces EMT, facilitating metastasis. Upregulated genes such as *LIPE*, *AQP7*, *CD36*, and *PLIN1* in epithelial and stromal compartments highlight enhanced fatty acid metabolism and transport, supporting tumor growth [28].

Pathways and gene function in BC

Asian populations

CD36-mediated signaling pathways involving Src-family kinases, MAPKs, and the ERK-1/2 pathway regulate cell proliferation and survival in BC [38]. Elevated MAPK activity is observed in approximately half of breast tumors [39]. *LEP*, *CD36*, and *CAV1* contribute to thermogenesis, fostering a pro-tumor immune microenvironment by reducing cytotoxic T-cell activity and increasing immunosuppressive cells. Enhanced oxygen consumption by *LEP*, *CAV1*, and *PLIN1* creates hypoxic conditions that promote tumor progression and therapy resistance [40].

European populations

CD36 and *APOB* drive oncogenic activity through scavenger receptors like Scavenger Receptor Class B Type 1 (SR-BI), promoting tumor proliferation and migration via MAPK and PI3K pathways [36]. *IGF1*, *CD36*, *CAV1*, and *APOB* regulate hemostatic pathways, contributing to tumor progression by enhancing coagulation and angiogenesis. Toll-like receptor (TLR) signaling, influenced by *CD36* and *APOB*, promotes chronic inflammation and chemoresistance [41]. *LEP*, *PPARG*, and *CD36* modulate white adipocyte differentiation, creating cancer-associated adipocytes (CAAs) that support tumor aggressiveness.

Common pathways across populations

CD36 and *LEP* regulate cholesterol metabolism, influencing fatty acid uptake, lipid storage, and inflammation. *LEP* drives tumor proliferation and migration via *MAPK* and JAK2/STAT pathways, while *CD36* interacts with *AMPK* to suppress tumorigenic metabolism and induce cell-cycle arrest. *AMPK* plays a pivotal role in regulating metabolic pathways essential for tumorigenesis and cancer progression. It influences key cellular processes that govern cancer cell growth, survival, and proliferation while also modulating pathways involved in glucose, lipid, and protein metabolism [42]. Enhanced lipid metabolism, driven by *APOB*, *FABP4*, and *PPARG*, supports tumor growth and immune evasion [43]. Elevated triglyceride levels and dysregulated lipid metabolism are crucial for tumor proliferation, migration, and resistance to therapy [44].

AMPK and *PPAR* pathways, activated by adiponectin, provide metabolic regulation, while salt-inducible kinase 2 (SIK2) suppresses tumor progression by inhibiting the PI3K/AKT and Ras/ERK pathways [45]. Collectively, these pathways underscore the metabolic reprogramming central to BC progression.

Future directions

This study highlights *CD36* and *LEP* as promising therapeutic targets, warranting further wet lab validation and clinical trials. Additionally, integrating multi-omics approaches and AI-driven predictive models could refine precision oncology frameworks.

Conclusion

BC exhibits significant molecular heterogeneity influenced by genetic, dietary, environmental, and epigenetic factors. This study identified *CD36* and *LEP* as universal HUB genes consistently upregulated across both Asian and European BC datasets, indicating their potential as global diagnostic and prognostic biomarkers. Additionally, *CAV1*, *IGF1*, *APOB*, and *PPARG* were identified as key regulatory genes in European populations, while *PLIN1* and *CAV1* were prominent in Asian populations, suggesting region-specific molecular variations that may influence tumor progression and therapeutic response.

Functional enrichment analysis highlighted the involvement of these genes in critical pathways, including cholesterol metabolism, adipocytokine signaling, *AMPK* regulation, and lipid metabolism, emphasizing their role in BC pathophysiology. The observed differences in gene expression patterns underscore the necessity for personalized medicine approaches, incorporating molecular profiling to optimize early detection, risk stratification, and targeted treatment strategies.

Clinically, *CD36* and *LEP* may serve as potential biomarkers for non-invasive liquid biopsy screening, enabling early detection and tumor stratification. Their role in metabolic regulation also suggests potential therapeutic applications, with *CD36* inhibitors and *LEP* antagonists warranting further exploration in obesity-associated BC. Furthermore, *PPARG* agonists and lipid metabolism modulators may serve as promising candidates for targeted interventions, particularly in hormone receptor-positive BC subtypes. Given the ethnic and regional variations in HUB gene expression, incorporating population-specific molecular profiling into treatment regimens could enhance therapeutic efficacy and minimize adverse effects.

Future research should focus on large-scale cohort validation and experimental studies to confirm the clinical utility of these biomarkers and evaluate their therapeutic potential. Additionally, the integration of

multi-omics approaches, AI-driven predictive models, and metabolic interventions could refine precision oncology strategies, ensuring more effective, patient-centered treatment paradigms. *CD36* and *LEP* emerge as promising targets for advancing BC diagnostics, prognostics, and therapeutics, paving the way for more precise and individualized management strategies in breast oncology.

Abbreviations

ABHD5: abhydrolase domain containing 5

ADIPOQ: adiponectin, C1Q and collagen domain containing

AMPK: AMP-activated protein kinase

APOB: apolipoprotein B

AQP7: aquaporin 7

BC: breast cancer

BMI: body mass index

BRCA1/2: breast cancer gene 1/2

CAV1: caveolin-1

CD36: cluster of differentiation 36

COMP: cartilage oligomeric matrix protein

DEGs: differentially expressed genes

DGE: differential gene expression

EBF1: early B-cell factor 1

EMT: epithelial-mesenchymal transition

ER: estrogen receptor

ERK: Extracellular signal-Regulated Kinase

FABP4: fatty acid-binding protein 4

GEO: Gene Expression Omnibus

GPD1: glycerol-3-phosphate dehydrogenase 1

HDAC6: histone deacetylase 6

HER2: human epidermal growth factor receptor 2

HSD11B1: hydroxysteroid 11-beta dehydrogenase 1

HUB: highly upregulated biomarker

IGF1: insulin-like growth factor 1

IGFBP2: insulin-like growth factor binding protein 2

ITGA6: integrin alpha-6

JAK2: janus kinase 2

KCNH2: potassium voltage-gated channel subfamily H member 2

LEP: leptin

LEPR: leptin receptor

LIPE: hormone-sensitive lipase

LRP6: low-density lipoprotein receptor-related protein 6

MAPK: mitogen-activated protein kinase

MCODE: Molecular Complex Detection

MNC: Maximum Neighborhood Component

OLR1: oxidized low-density lipoprotein receptor 1

PALMD: palmdelphin

PI3K/AKT: phosphatidylinositol 3-kinase/protein kinase B

PLIN1: perilipin 1

PPARG: peroxisome proliferator-activated receptor gamma

PPI: protein-protein interaction

SCARB2: scavenger receptor class B member 2

SEMA3G: semaphorin 3G

SLC19A3: solute carrier family 19 member 3

SOCS2: suppressor of cytokine signaling 2

STAT1: signal transducer and activator of transcription 1

Supplementary materials

The supplementary figures for this article are available at: https://www.explorationpub.com/uploads/Article/file/1001320_sup_1.pdf. Other supplementary material for this article is available at: https://www.explorationpub.com/uploads/Article/file/1001320_sup_2.xlsx.

Declarations

Author contributions

PM: Project administration, Conceptualization, Validation, Supervision, Writing—review & editing. SS: Conceptualization, Validation, Data curation, Methodology, Writing—review & editing. SR: Data curation, Methodology, Writing—original draft.

Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

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