Medical Research
Volume 7, Issue 1, 2025, Page 54-61
https://doi.org/10.6913/mrhk.070107

Medical Research

Gastric Xanthoma Biomarker Screening and Lipid Metabolism Mechanism Analysis as Potential Indicators for Gastric Cancer

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Abstract

The early detection of gastric cancer (GC) is critical for reducing its high mortality rates[1,2]. Gastric xanthoma (GX), a lipid-associated lesion in the gastric mucosa, has been identified as a potential precursor to various stomach malignancies[3,4]. In this study, we comprehensively profiled the gut microbiota, lipid metabolism, and amino acid metabolism to identify novel biomarkers for the early detection of GX, with potential implications for GC prevention and therapy. By employing 16S rRNA sequencing[5,6], transcriptomics[7], and gene ontology (GO) analysis[8], we revealed significant correlations between gut microbiota composition, dysregulated lipid transport, and aberrant amino acid metabolism in GX. These findings underscore the contribution of lipid metabolic dysfunction[9,10] and gut microbiota alterations[11,12] to the pathogenesis of GX, offering promising strategies for early GC detection and targeted intervention.

Keywords biomarkers; gastric xanthoma; lipid metabolism; 16S rRNA

To Cite This Article Xiaohua BAO,et al. (2025). Gastric Xanthoma Biomarker Screening and Lipid Metabolism Mechanism Analysis as Potential Indicators for Gastric Cancer. *Medical Research*, 7(1), 54-61. https://doi.org/10.6913/mrhk.070107

Medical Research, ISSN 2664-0333 (print), ISSN 2664-0341 (online), DOI 10.6913/mrhk, a bimonthly, founded on 2018, Indexed by CNKI, Google Scholar, AIRITI, Scilit, CrossRef, Elsevier PlumX, etc., published by Creative Publishing Co., Limited. Email: wtocom@gmail.com, https://mrhk.cc, https://cpcl.hk.

1 Introduction

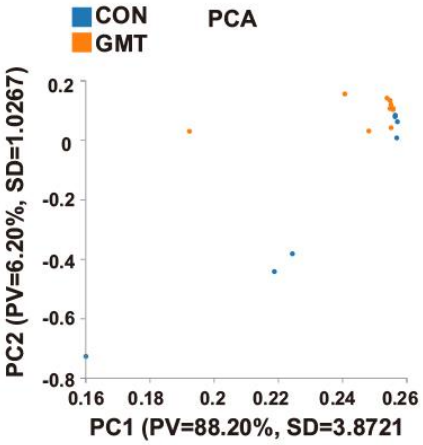
Gastric cancer (GC) remains a leading cause of cancer-related deaths globally, largely due to the challenges in its early detection[2,13]. Gastric xanthoma (GX), characterized by lipid-laden foam macrophages in the gastric mucosa, is recognized as a precursor lesion linked to precancerous conditions such as atrophic gastritis and intestinal metaplasia[3,4]. However, its progression to GC and the underlying mechanisms remain underexplored.

Emerging research highlights the significant role of the gut microbiota and its regulation of key metabolic pathways, including lipid and amino acid metabolism, in tumor progression[11,12]. Dysregulated lipid metabolism—particularly involving long-chain fatty acids (LCFAs) and oxidized low-density lipoproteins (oxLDLs)—has been implicated in creating a pro-tumorigenic environment[9,10]. Similarly, amino acids such as tryptophan and proline have been shown to modulate immune responses and metabolic processes relevant to GX[14,15].

This study integrates microbial profiling[5,6], transcriptomics[7], and functional analyses[8] to investigate GX-associated alterations in gut microbiota, lipid metabolism, and amino acid biosynthesis. Our findings aim to identify novel biomarkers for the early detection of GX and offer insights into its transition to GC, paving the way for targeted prevention and treatment strategies.

2 Methods

Ethics. All patients with gastric xanthoma (GX) were diagnosed based on endoscopy and histological confirmation. Healthy controls were recruited from asymptomatic individuals with no significant abnormalities confirmed by endoscopy. The exclusion criteria for healthy controls were consistent with those used for GX patients (see Supplementary Table S1). This study was approved by the Ethics Committee of the Chinese People's Liberation Army 964 Hospital (Approval No. 2018-Y-XH-005).



Supplementary figure S1. Associations between differentially expressed genes (DEGs) and gastric xanthoma. PCA of relative abundance of OTUs.

Gut Microbiota Profiling. Human fecal samples were subjected to 16S rRNA gene sequenc-

ing targeting the V3 V4 region using the PacBio sequencing platform. Alpha and beta diversity metrics were calculated, and taxonomic annotation of microbial communities was conducted.

Transcriptomics Analysis. RNA sequencing (RNA-seq) was performed on gastric tissue samples from 10 GX patients and 7 healthy controls. Differentially expressed genes (DEGs) were identified, and KEGG and Gene Ontology (GO) enrichment analyses were conducted to investigate pathways related to lipid metabolism.

Real-Time PCR Validation. Quantitative real-time PCR (qPCR) was used to validate key genes associated with fatty acid transport, including *CD36*, *FABP3*, and *UCHL1*. The following primer sequences were used:

β-actin: forward 5'-GAGCACAGAGCCTCGCCTTT-3', reverse 5'-ATCCTTCTGACCC ATGCCCA-3'. CD36: forward 5'-GAACAGCAGCAACATTCAAGT-3', reverse 5'-CAGCGT CCTGGGTTACATT-3'. ETNPPL: forward 5'-GCAGAAGCCTTCAGCAGC-3', reverse 5'-AGGACAGCCAAACCAACAG-3'. FABP3: forward 5'-GGATGGAGGGAAACTTGTTC-3', reverse 5'-GTGGGTGAGTGTCAGGATGA-3'. LIPF: forward 5'-TGTGCTCCCGTGAGAT GC-3', reverse 5'-GAAGTTCCTGCTGGATTATGTG-3'.PITPNM3: forward 5'-CCAGCGT GCTAAAGGATGA-3', reverse 5'-AGTGGCGAGCCGAAGAG-3'. PPARD: forward 5'-CCTC GCCACCCTCACTG-3', reverse 5'-CCCGATGCCTTGTCCC-3'.SDS: forward 5'-TCCCTC GTGGTCATCGTC-3', reverse 5'-TGGGCAACCTATTTGTCATG-3'. UCHL1: forward 5'-CTATGAACTTGATGGACGAATG-3', reverse 5'-GAAGCGGACTTCTCCTTGC-3'.

3 Results

Gut Microbiota Dynamics in GX. Microbial diversity analyses revealed distinct gut microbiota compositions between GX patients and healthy controls (Fig. 1B J). Elevated relative abundances of *Bacteroides*, *Prevotella*, and *Enterocloster* were detected in GX patients, suggesting their role as GX-associated microbial markers (Fig. 2A E).

Transcriptomics and Functional Insights. RNA-seq identified 17,594 differentially expressed genes (DEGs) in GX, with significant upregulation of genes involved in lipid metabolism, including *CD36* and *FABP4* (Fig. 3). Gene Ontology (GO) annotation indicated enhanced long-chain fatty acid (LCFA) transport and lipid-binding activity in GX (Fig. 4B D).

Lipid Metabolism Dysregulation. Lipid metabolism in GX was significantly altered, as evidenced by KEGG-enriched pathways such as cholesterol metabolism and PPAR signaling (Fig. 5A). Dysregulated lipid transport was linked to increased LDL and oxLDL accumulation, implicating *CD36*-mediated pathways in GX pathogenesis.

Amino Acid Metabolism and Psychological Stress. Elevated levels of amino acid metabolism, particularly involving arginine and proline, were correlated with the relative abundance of *Prevotella* and *Enterobacter* (Fig. 2, Fig. 4C). These findings suggest that dietary interventions targeting amino acid metabolism may mitigate GX progression, especially under psychological stress conditions.

UCHL1-Mediated CD36 Ubiquitination. Our results revealed overexpression of *UCHL1* in GX, regulating *CD36* ubiquitination and contributing to lipid accumulation. These findings implicate *UCHL1* as a potential therapeutic target for GX management (Fig. 5).

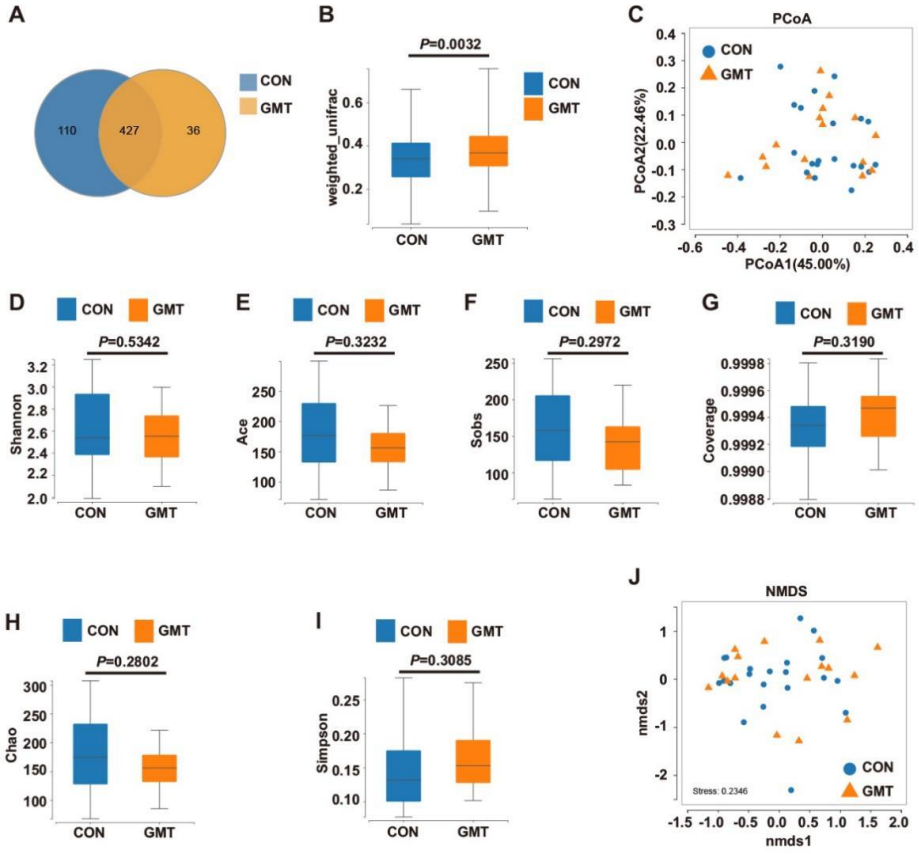


Fig. 1. Diversities of gut microbiota communities in gastric xanthoma patients. (A) Venn diagram showing the number of common and unique OTUs of the control and gastric xanthoma groups. (B) Box plot showing the gut microbial β-diversity. (C) The structure shifts (β-dive、rsity) presented by the weighted UniFrac PCoA plot based on the OTU abundance. Pr (>F) = 0.9448. (D–I) Box plots showing the gut microbial α-diversity indices of Observed species, Shannon, Ace, Sob, Coverage, Chao, and Simpson. (J) UniFrac distance-based non-metric multidimensional scaling (NMDS) analysis.

4 Discussion

Gastric xanthoma (GX) is increasingly recognized as a precursor lesion linked to gastric cancer (GC) development[1]. Our study highlights the significant interplay among gut microbiota[11,12], lipid metabolism[10], and amino acid metabolism[14,15] in the pathogenesis of GX.

Gut Microbiota and GX. We observed distinct alterations in the gut microbiota composition of GX patients, including increased abundances of *Enterocloster*, *Bacteroides*, and *Prevotella*[11,12]. These changes suggest that microbial dysbiosis may contribute to GX development. *Enterocloster*, in particular, emerged as a potential GX-specific biomarker, warranting further exploration for early detection strategies[16].

Lipid Metabolism Dysregulation. Dysregulated lipid metabolism, including enhanced long-chain fatty acid (LCFA) transport and LDL/oxLDL accumulation, was a key feature of GX[17]. Upregulation of genes such as *CD36* and *FABP4* underscores the role of lipid transport dysfunction in GX, aligning with its lipid-rich pathological characteristics[7]. These findings support the development of targeted therapies aimed at lipid metabolism in GX[18].

Amino Acid Metabolism and Stress. Elevated amino acid metabolism—particularly of arginine, proline, and tryptophan—was correlated with microbial imbalances[14,15]. These metabolic

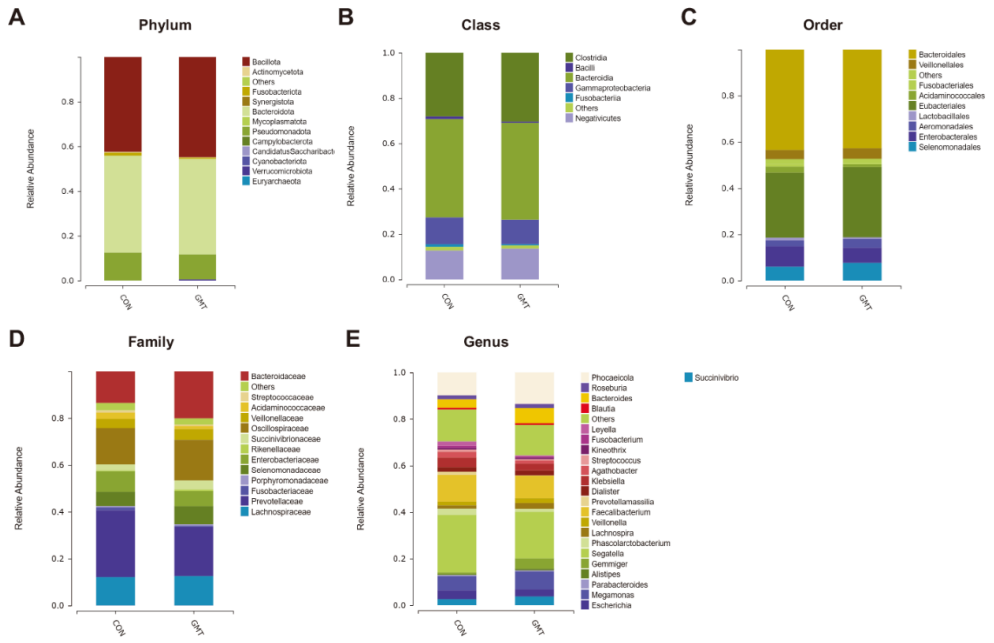


Fig. 2. Taxonomic compositions of gut microbiota communities in gastric xanthoma patients, showing the relative abundances of gut microbiota at the (A) phylum, (B) class, (C) order, (D) family, and (E) genus levels, respectively.

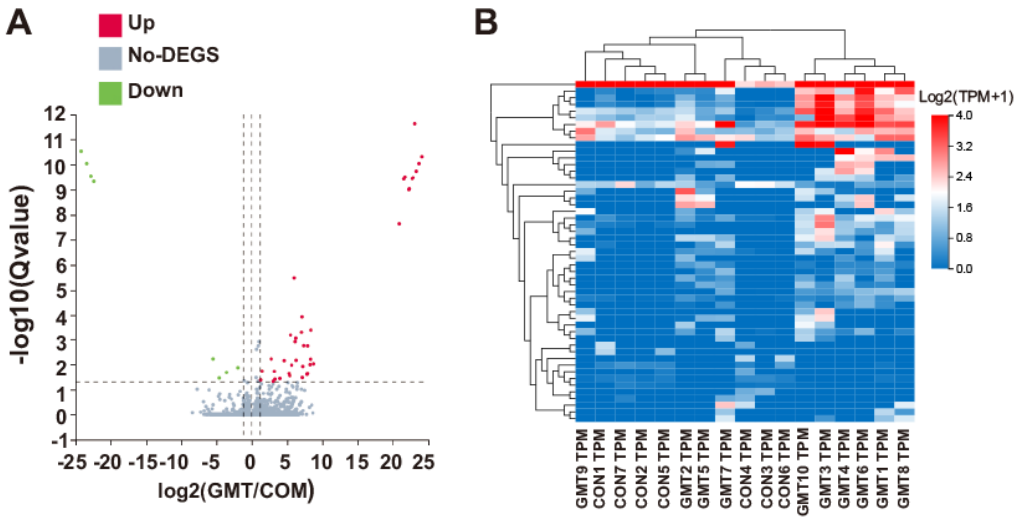


Fig. 3. Identification of differentially expressed genes (DEGs) in gastric xanthoma. (A) The differentially expressed mRNAs based on volcano plots of both control and gastric xanthoma groups. Significantly differential proteins are colored in red (up-regulated) and blue (down-regulated), while proteins showing no significant difference are highlighted in gray. (B) Hierarchical clustering heatmap of 51 DEGs between the control and gastric xanthoma groups. In the color bar, high and low expressions are presented in red and blue, respectively.

shifts may be influenced by psychological stress, which is known to affect gut microbiota composition and host metabolism[19]. The microbiota gut brain axis thus represents a promising avenue for understanding and mitigating GX progression[15].

UCHL1-Mediated Lipid Accumulation. The upregulation of *UCHL1* and its role in *CD36* ubiquitination further implicate lipid metabolism dysregulation in GX[18]. These findings suggest *UCHL1* as a potential therapeutic target, reinforcing its function in lipid transport and accumulation[1,19].

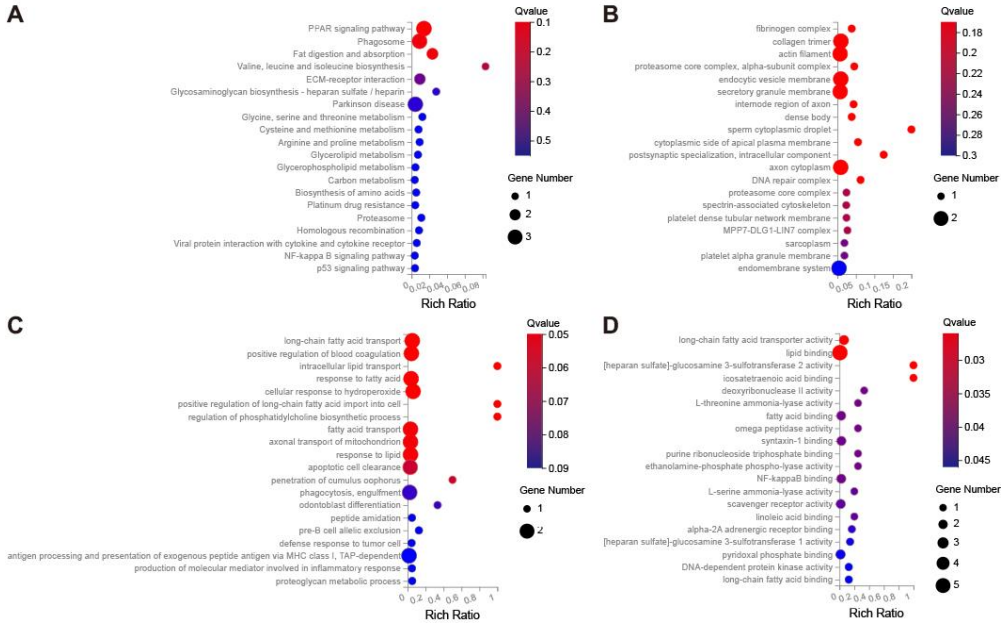


Fig. 4. Functional classification and enrichment analyses of differentially expressed genes in gastric xanthoma, showing (A) the top KEGG pathways, (B) the top GO terms in the category of cellular component, (C) the top GO terms in the category of biological process, and (D) the top GO terms in the category of cellular function.

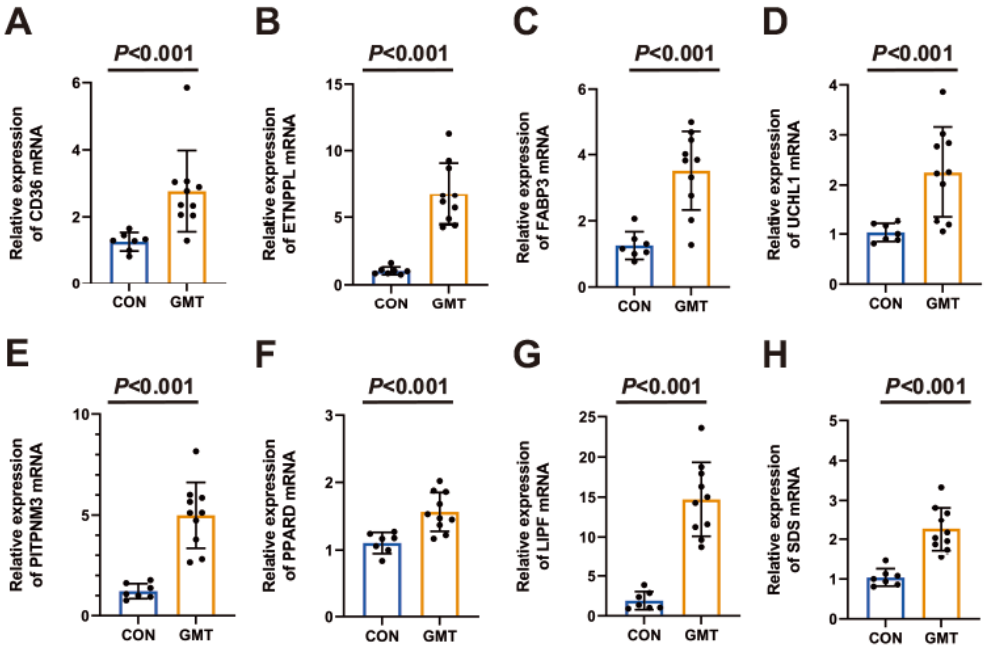


Fig. 5. Differential gene expression analysis of GMT. RT-qPCR analysis relative CD36 (A), ETNPPL (B), FABP3 (C), UCHL1 (D), PITPNM3 (E), PPARD (F), LIFP (G) and SDS (H) mRNA amounts in CON and GMT group. Actin transcripts served as an internal control for normalization. Data were analyzed by unpaired two-sided Student's t test.

5 Conclusions

Our study underscores the importance of gut microbiota and lipid metabolism in GX pathogenesis[1], providing novel biomarkers for early GX detection. The interplay between microbial dysbiosis and metabolic alterations presents opportunities for therapeutic interventions targeting

lipid metabolism and gut microbiota[14,15]. These findings lay the groundwork for future investigations into the molecular mechanisms underlying GX and its transition to GC, with implications for precision medicine approaches to GC prevention and treatment[18].

List of Abbreviations

LCFA	long-chain fatty acid
SRA	Sequence Read Archive
OTU	operational taxonomic unit
KEGG	Kyoto Encyclopedia of Genes and Genomes
GO	Gene Ontology
PCoA	principal coordinates analysis
DEGs	differentially expressed genes
PCA	principal component analysis
LDL	low density lipoprotein
oxLDL	oxidized LDL
FABPs	fatty acid-binding proteins

Author Contributions Xiaohua Bao and Zhandong Li designed the research and provided supervision. Xiaohua Bao and Runhua Li collected clinical data. Yingqi Liu, Xianjun Liu, Yue Liu, Lili Yang, Yong Yang, Wen Xu, Fengjie Sun, Hao Li, and Ying Zhu performed the experiments and wrote the manuscript. Yingqi Liu, Xiaohua Bao, Xianjun Liu, Yong Yang, Wen Xu, Fengjie Sun, Hao Li, Ying Zhu, and Zhandong Li contributed to data analysis and figure preparation. All authors reviewed and approved the final manuscript.

Availability of Data and Materials The raw sequencing data have been deposited in the NCBI Sequence Read Archive (SRA) under accession number **PRJNA1158013**. Further information, requests for materials, and access to code should be directed to Zhandong LI at lizd591@jlenu.edu.cn.

Funds This research was supported by the Department of Science and Technology of Jilin Province, China (20210101220JC) and the Centrally Guided Local Projects of Linzhi City, China (ZYYD DF2024-04).

Article History

Received: January 12, 2024 **Accepted:** January 28, 2025 **Published:** March 31, 2025

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