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Molecular Insights into Hypertriglyceridemia-Associated Cardiovascular Disease and Pancreatitis in Pakistan: A Systematic Review

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ABSTRACT

Background: Hypertriglyceridemia (HTG), defined as fasting triglyceride levels above 150 mg/dL, is a complex lipid disorder that significantly contributes to the burden of cardiovascular disease (CVD) and acute pancreatitis worldwide. While lifestyle factors, such as poor diet, obesity, and diabetes, play a major role in its development, genetics also have a profound impact on when and how the condition manifests, as well as how patients respond to treatment. In Pakistan, where consanguineous marriages are common and dyslipidemia is on the rise, the genetic landscape of HTG offers unique insights but remains largely unexplored. This review summarizes published research on the genetics of HTG in Pakistan. **Methods:** We systematically searched PubMed and Google Scholar up to June 2025 for studies on Pakistani individuals reporting genetic data related to triglyceride metabolism, using combinations of HTG-related terms and MeSH headings. Eligible designs included case reports, case–control studies, and family studies. Data were extracted on study characteristics, genetic variants, and clinical associations. **Results:** Five studies met the inclusion criteria. Variants in *APOA5, LPL, GPIHBP1,* and *CETP* were associated with severe or moderate HTG, therapeutic responses, and CVD risk. No studies examined the genetic basis of HTG-associated pancreatitis in Pakistan. Limitations included small sample sizes, restricted gene coverage, and the absence of longitudinal follow-up. **Conclusion:** Limited evidence links both rare, high-impact and common triglyceride-related variants to HTG and CVD risk in Pakistani populations. There is an urgent need for large-scale genomic studies, especially on pancreatitis genetics, to enable precision-based interventions.

Keywords: Cardiovascular Diseases, Dyslipidemias, Genetic Variation, Hypertriglyceridemia, Pakistan, Pancreatitis

INTRODUCTION

Hypertriglyceridemia (HTG), defined as elevated fasting triglyceride (TG) levels >150mg/dL, is a multifactorial metabolic disorder associated with both cardiovascular disease (CVD) and pancreatitis. The condition is categorized as mild (150–199 mg/dL), moderate (200–499 mg/dL), severe (500–999 mg/dL), and very severe (≥1000 mg/dL) [1, 2]. Globally, the prevalence of HTG continues to rise, largely driven by the obesity epidemic, poorly balanced diets, diabetes mellitus, and secondary contributors such as alcohol and medication effects [3]. In Pakistan, the overlap of high dyslipidemia prevalence, dietary patterns rich in refined carbohydrates and fats, and a high rate of consanguineous marriages creates an environment conducive to both polygenic and monogenic forms of HTG [4]. Two main complications define HTG clinically. First is CVD - elevated TG, drives atherosclerosis through remnant cholesterol, small dense low-density lipoprotein (LDL) particles, and low high-density lipoprotein (HDL) [5-8]. Second is acute pancreatitis - severe HTG triggers pancreatic inflammation, with risk spiking when TG exceeds 1000 mg/dL [9-11]. However, no genetic studies from Pakistan have investigated the relationship between HTG and pancreatitis, making this a critical unexplored research gap despite strong global evidence for this link.

At the molecular level, pathogenic variants in genes such as LPL, APOA5, GPIHBP1, APOC2, and LMF1 can disrupt TAG hydrolysis, impair chylomicron clearance, and reduce responsiveness to fibrates, leading to severe, treatment-resistant HTG [12, 13]. Common single-nucleotide polymorphisms (SNPs) in these and other lipid-regulating genes contribute to polygenic HTG, often in synergy with environmental factors. These genetic mechanisms influence susceptibility, disease severity, and therapeutic response—key considerations for precision medicine approaches. Despite Pakistan's high HTG burden, national research remains fragmented. In contrast, neighbouring India has conducted genome-wide association studies (GWAS) and candidate gene investigations that have identified novel variants, explored gene–diet interactions, and informed region-specific risk prediction [14-16]. No whole-exome sequencing (WES) or whole-genome sequencing (WGS) studies have yet been conducted for HTG in Pakistan, and few studies have linked genetic findings to clinical outcomes such as premature CVD or pancreatitis. This review, therefore, synthesizes available evidence on genetic variants associated with HTG and CVD risk in Pakistan, highlighting the absence of pancreatitis genetics research, the lack of large-scale genomic datasets, and the limited integration of genetic data with clinical outcomes. By identifying these gaps, the review aims to guide future research priorities and lay the groundwork for precision-based interventions in this high-risk population.

MATERIALS AND METHODS

The scientific protocol involved in this study is outlined in the following section in a sequential method.

DATA SOURCES AND SEARCH STRATEGY

A comprehensive search was conducted in PubMed, Scopus, Web of Sciences and Google Scholar to locate studies reporting genetic variants associated with HTG in Pakistani populations. The search covered publications from January 2000 to June 2025, a timeframe selected to include both early candidate gene studies and recent genomic findings. Keywords and Medical Subject Headings (MeSH) were used in different combinations, including hypertriglyceridemia, LPL, APOA5, pancreatitis genetics, cardiovascular genetics, and Pakistan. Boolean operators were applied to expand the search, and reference lists from the selected studies were reviewed to identify additional relevant publications.

STUDY SELECTION AND ELIGIBILITY CRITERIA

Studies were included if they examined Pakistani individuals and reported original genetic data directly related to TG metabolism. Acceptable designs included case reports, family-based studies, case–control analyses, and observational cohorts. Only English-language publications were considered. Exclusion criteria were non-human or in vitro studies, articles without primary genetic results, and reports where Pakistani subgroup data could not be separated from other populations. This review differs from earlier literature surveys, which typically addressed South Asia or global trends without isolating Pakistan-specific findings [17]. The present work also highlights research gaps, such as the absence of genetic studies on HTG-associated pancreatitis in Pakistan,

the lack of national-scale whole-exome or whole-genome sequencing (WES/WGS) projects, and the limited linkage of genetic data to clinical outcomes like cardiovascular disease.

DATA EXTRACTION AND QUALITY ASSESSMENT

Information from the included studies was systematically extracted into a predefined template. This covered study type, participant details, genes and variants examined, key results, and associations with cardiovascular disease, pancreatitis, or therapeutic outcomes. The methodological rigor of each study was evaluated using adapted versions of the Newcastle–Ottawa Scale for observational studies and the CARE guidelines for case reports.

DATA SYNTHESIS

Given the limited number and diversity of eligible studies, results were summarized narratively rather than through meta-analysis. The synthesis was organized into three categories: (1) rare, high-impact variants such as frameshift or missense mutations; (2) common single-nucleotide polymorphisms (SNPs) with polygenic effects; and (3) clinical implications, including disease susceptibility, severity, and treatment response.

RESULTS

OVERVIEW OF IDENTIFIED STUDIES

A total of 164 records were identified. After removing duplicates (n = 49), titles and abstracts of 113 articles were screened, and 16 full-text articles were assessed for eligibility. Of these, 5 studies met the inclusion criteria and were included in this review (Figure 1). These studies provide insight into both rare monogenic forms and common polygenic variants contributing to HTG in Pakistan.

STUDY SUMMARIES

Table 1 summarizes the main findings of all studies included in the final review. Aslam et al. (2025) performed a case–control study involving 300 patients with HTG and 100 normolipidemic controls, focusing on two LPL polymorphisms (rs258, rs268). The study reported that these variants were significantly associated with elevated TG levels. Additionally, carriers of these variants experienced greater TG reduction after fibrate therapy, suggesting potential pharmacogenetic relevance. However, the study did not evaluate pancreatitis or CVD outcomes [18].

Table 1: Genetic Studies on Hypertriglyceridemia in Pakistani Populations

Study	Design	Sample	Genes/Variants	Main Findings	Clinical Associations	Limitations
[18]	Case–control	300 HTG patients, 100 controls	LPL (rs258 T>C, rs268A>G)	Variants significantly associated with higher TG levels; carriers had greater TG reduction after fibrate therapy.	No pancreatitis or CVD data	Limited SNP panel; cross-sectional
[19]	Case series	4 patients (1 Pakistani)	LPL (unspecified variants)	One Pakistani patient had partial LPL deficiency with severe HTG	Not associated with risk of pancreatitis and CVD	small sample
[20]	Case report (pediatric)	1 Pakistani child (5.5 years)	GPIHBP1 (c.230G>A; p. Cys77Tyr)	A homozygous missense variant caused severe HTG (TG ≈ 5,137 mg/dL); parents/siblings were heterozygous carriers.	Eruptive xanthomas, palate deposits, splenomegaly, lethargy; first GPIHBP1 mutation reported in Pakistan	Single patient; no long-term follow-up

[21]	Case–control	500 CAD patients, 500 controls	APOA5 (rs662799), LPL (rs328, rs1801177), CETP (rs708272)	APOA5 rs662799 increased TG by ~19%; CETP C allele lowered HDL and raised TG; combined gene-score predicted TG/HDL better than individual SNPs	Not associated with higher CAD risk	No pancreatitis data; lack of longitudinal outcomes
[22]	Case report (family study)	1 consanguineous family	APOA5 (c.G425del-C, p.Arg143AlafsTer57)	A homozygous frameshift mutation caused severe HTG (~3100 mg/dL); heterozygotes had moderate HTG	Type V hyperlipoproteinemia; premature CVD features; poor fibrate response; improved with a very low-fat diet	Single-family; no functional validation

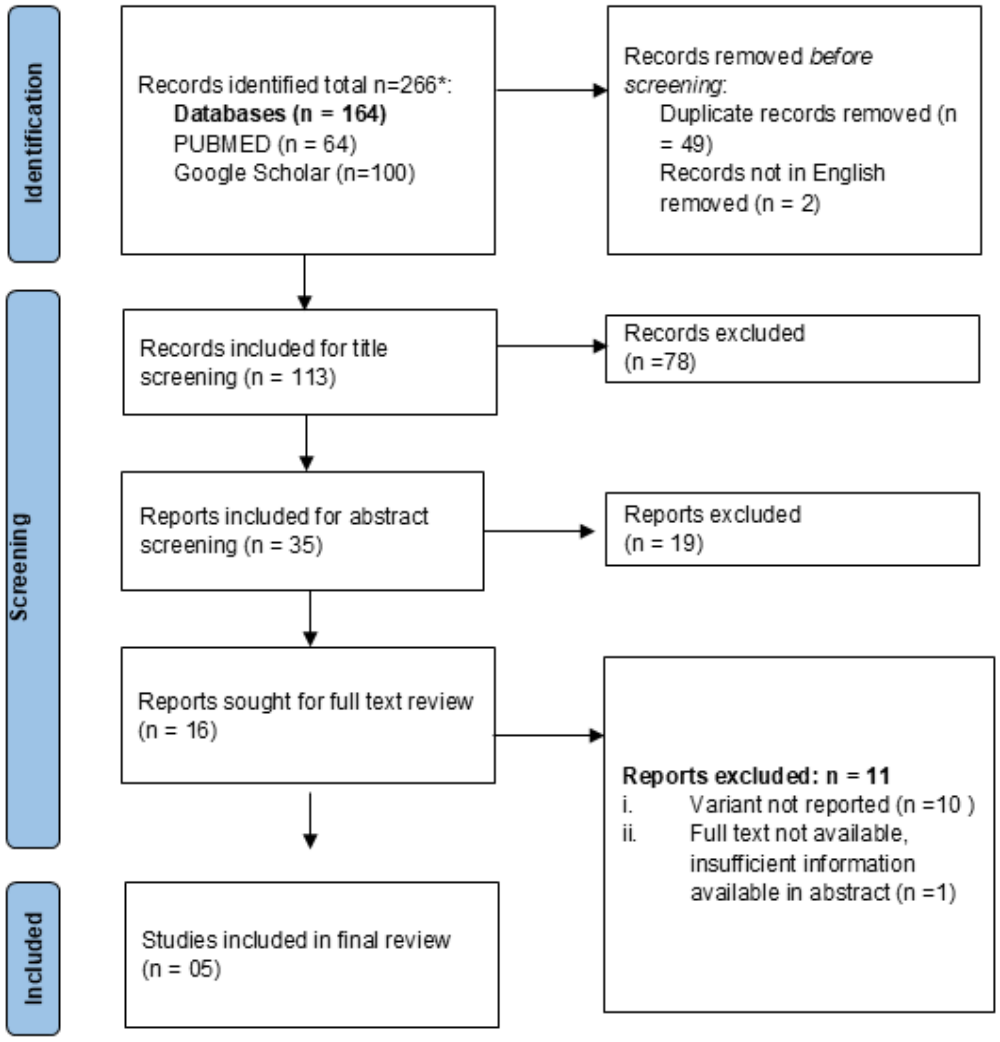

Figure 1: Showing the PRISMA FLOW Diagram of HTG Variants Reported in Pakistan

Ain et al. (2024) reported on four patients with partial LPL deficiency, including one Pakistani individual with severe HTG. Although specific variants were not disclosed, the study highlighted the role of partial LPL dysfunction in severe, treatment-resistant HTG and its association with both pancreatitis and CVD [19]. Sustar et al. (2022) described a 5.5-year-old Pakistani child with severe HTG (TG ≈ 5,137 mg/dL) caused by a homozygous missense variant in GPIHBP1 (c.230G>A; p. Cys77Tyr). The patient exhibited eruptive xanthomas, palate cholesterol deposits, splenomegaly, and lethargy, while parents and siblings were heterozygous carriers. This represents the first reported GPIHBP1 mutation in a Pakistani individual and illustrates the role of rare, high-impact variants in severe paediatric HTG [23]. Shahid et al. (2017) explored the contribution of TG-modulating gene variants to coronary artery disease (CAD) in 500 CAD patients and 500 controls. They examined polymorphisms in APOA5 (rs662799), LPL (rs328, rs1801177), and CETP (rs708272). The APOA5 rs662799 variant was associated with a ~19% increase in TG levels, while the CETP C allele correlated with lower HDL and higher TG levels. Interestingly, a multi-locus gene score combining these variants predicted TG and HDL levels more effectively than single variants alone. These findings directly linked genetic variation in TG-related genes with increased CAD risk in a Pakistani cohort [24]. Thériault et al. (2016) investigated a consanguineous Pakistani family with severe HTG (TG > 3000 mg/dL). Through Sanger sequencing, the authors identified a homozygous frameshift mutation in the APOA5 gene (c. G425delC, p. Arg143AlafsTer57). Homozygous individuals exhibited very severe HTG and features of type V hyperlipoproteinemia, while heterozygotes presented moderate elevations in TG levels. Notably, affected family members showed poor response to fibrates but demonstrated improvement on a very low-fat diet, underscoring the therapeutic implications of genetic diagnosis [22].

SYNTHESIS OF FINDINGS

Collectively, these studies confirm that rare, high-impact variants (e.g., APOA5 frameshift mutations) and common polymorphisms (e.g., APOA5 rs662799, LPL, and CETP SNPs) contribute to HTG in Pakistani populations. They also suggest potential implications for therapy response (e.g., fibrate sensitivity) and cardiovascular risk stratification. However, no study to date has systematically assessed the genetic drivers of pancreatitis in Pakistan, and sample sizes remain small.

QUALITY OF INCLUDED STUDIES

Assessment using the Newcastle–Ottawa Scale indicated that the two case–control studies met basic criteria for selection and comparability but scored lower in outcome assessment due to limited follow-up and incomplete adjustment for confounders [25]. The three case reports/series, evaluated against the CARE guidelines, provided adequate patient descriptions and variant details but often lacked comprehensive clinical timelines and long-term monitoring. Across all included studies, methodological limitations were evident: most were single-centre with small sample sizes, no study employed whole-exome or whole-genome sequencing, and phenotypic characterization was inconsistent.

DISCUSSION

This review reveals a striking gap between the high prevalence of HTG in Pakistan and the limited understanding of its genetic determinants. HTG is highly prevalent in the country, mainly due to dietary habits, rich in refined carbohydrates and fats, high rates of metabolic syndrome, and sedentary lifestyles [2, 26]. These environmental pressures interact with underlying genetic susceptibility, creating a uniquely high-risk profile for both CVD and acute pancreatitis [9, 12, 27]. Despite its huge burden, few genetic studies on HTG in Pakistan exist, and these are primarily restricted to small, single-centre efforts. The findings from these studies, though limited, offer valuable insights. Variants in APOA5, GPIHBP1 & LPL, two key regulators of TG metabolism, have emerged as major contributors to severe & moderate forms of HTG [22, 28-32]. The discovery of a homozygous frameshift mutation in APOA5 within a consanguineous Pakistani family shows how rare, high-impact variants can appear in this population, especially given the high prevalence of consanguineous marriages [21]. This reflects findings from global cohorts where rare mutations in TG-regulating genes cause FCS [13, 33]. However, the absence of comprehensive functional validation & outcome data connecting these variants to pancreatitis or CVD restricts their immediate clinical utility.

In the broader South Asian context, Pakistan lags neighbouring countries in advancing research in this domain. India, for instance, has undertaken several genome-wide association studies (GWAS) and candidate gene investigations, identifying novel TG-related variants in APOA5, APOC3, and ANGPTL4 among its populations [34, 35]. These studies have also examined gene–diet interactions, demonstrating how traditional South Asian dietary practices can amplify genetic susceptibility to HTG. Likewise,

research efforts in Bangladesh have started to elucidate the genetic underpinnings of dyslipidemia in high-risk groups, with a notable emphasis on APOA1 and CETP variants [35]. In contrast, Pakistan's research remains limited and largely uncoordinated, with no genome-wide or large-scale multicentre studies conducted so far. This gap is particularly significant given that unique variants may exist within Pakistani populations, influenced by founder effects and prevalent consanguineous practices.

Severe forms of monogenic HTG present significant challenges for clinical care and public health. These cases often show limited response to standard therapies, which makes strict dietary management a key part of treatment. Detecting such patients early through genetic screening can enable personalized care plans and allow screening of family members who may also be at risk [36, 37]. Moreover, identifying common genetic variants that influence TG levels could improve cardiovascular risk prediction in Pakistani populations, complementing traditional risk assessment methods. However, these potential benefits cannot be achieved without strengthening genetic research in the country and integrating it into routine healthcare practice.

To address these gaps, large multi-centre studies using whole exome or whole genome sequencing are needed to capture both common and rare variants across Pakistan's diverse populations. Building prospective cohorts that link genetic findings with clinical outcomes, such as pancreatitis and early-onset cardiovascular disease, will be essential for applying these insights in practice. Exploring how genetic factors interact with cultural and dietary habits could also help design more effective, locally tailored prevention strategies. Collectively, these efforts will create a foundation for precision medicine approaches to HTG, ultimately reducing its burden and complications in Pakistan.

LIMITATIONS AND RECOMMENDATIONS

This review is constrained by the very limited number of available studies on HTG genetics in Pakistan. Most reports are single-centre investigations or isolated case descriptions, which restricts generalizability to the broader population. Sample sizes are generally small, and gene coverage is often limited to a few candidate loci, leaving much of the TG regulatory pathway unexplored. No studies employed whole-exome or whole-genome sequencing, and functional validation of identified variants was largely absent. Furthermore, none of the included studies examined the genetic determinants of HTG-associated pancreatitis in Pakistani cohorts. The heterogeneity in study design, variant reporting, and clinical outcome measurement also precluded any form of quantitative synthesis, and the possibility of publication bias cannot be ruled out.

Addressing these gaps will require coordinated, large-scale genomic research in Pakistan. Multi-centre studies utilizing whole-exome or whole-genome sequencing should be prioritized to capture both rare, high-impact variants and common polymorphisms across diverse ethnic groups. Establishing a national registry for lipid disorders, including standardized phenotyping and long-term follow-up, would facilitate linkage between genetic findings and clinical outcomes such as cardiovascular disease and acute pancreatitis. Family-based genetic screening in high-risk cases, particularly in consanguineous populations, could enable early diagnosis and targeted intervention. Functional studies are needed to confirm the pathogenicity of identified variants and to explore gene–environment interactions, especially regarding traditional dietary patterns and metabolic risk factors. Finally, research into the genetic basis of HTG-associated pancreatitis in Pakistan should be considered a priority, given its potential to improve prevention strategies and guide personalized treatment approaches.

CONCLUSION

HTG remains a significant yet underrecognized contributor to cardiovascular disease and acute pancreatitis in Pakistan. While lifestyle factors such as poor dietary patterns, physical inactivity, and the growing prevalence of metabolic disorders play a central role, the contribution of genetic factors is equally critical, particularly in a population with high consanguinity rates and unique genetic backgrounds. Evidence from limited Pakistani studies reveals that both rare, high-impact mutations in genes like APOA5 and GPIHBP1 and more common variants in APOA5, LPL, and CETP influence TG levels, therapeutic responses, and likely overall disease risk. However, these findings are derived from small, single-centre investigations, leaving major gaps in understanding how genetic variations translate into clinical outcomes such as pancreatitis or premature cardiovascular events. To bridge these gaps, there is a pressing need for well-designed, large-scale genomic studies that incorporate diverse Pakistani populations, integrate clinical data, and examine gene–environment interactions. Such efforts will not only improve diagnosis and risk

stratification but also pave the way for precision-based interventions, ultimately reducing the burden of HTG and its complications across the country.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTION

Q.A. conceptualized and designed the study, drafted the manuscript, and coordinated the overall project. F.J. and H.H. contributed to data collection, literature review, and manuscript preparation. M.A.Y. and I.K. assisted with data analysis and interpretation. M.R. provided critical revisions and intellectual input. All authors reviewed and approved the final manuscript.

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