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Exploring Multi-Omics Approaches to Familial Hypercholesterolemia in the Middle East

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Abstract

Familial hypercholesterolemia (FH), an autosomal-dominant hereditary disorder of lipid metabolism, results in significantly elevated plasma levels of low-density cholesterol (LDL-C), significantly increasing the risk of premature cardiovascular disease (CVD). Given the high prevalence of consanguinity in Middle Eastern populations, FH is more common in the region and necessitates tailored diagnostic and therapeutic strategies. This review explores the role of multi-omics approaches—including genomics, transcriptomics, proteomics, metabolomics, lipidomics, and epigenomics—in understanding FH pathophysiology and developing precision medicine strategies tailored to Middle Eastern populations. Recent genomic studies have identified LDLR, APOB, and PCSK9 mutations contributing to a high burden of FH. Metabolomic and lipidomic analyses reveal distinct biochemical alterations, including oxidative stress markers and lipid metabolism disruptions, while transcriptomic and epigenetic findings suggest variations in gene expression and statin responsiveness. Despite these advancements, multi-omics research in the Middle East is limited by high costs, restricted access to genetic testing, and the absence of national FH registries. Multi-omics approaches provide critical insights into FH pathophysiology and treatment. To optimize FH management in the Middle East, efforts should focus on expanding genetic screening programs, integrating multi-omics data into clinical practice, and addressing financial and ethical concerns. Strengthening regional collaborations and leveraging artificial intelligence-based analytics will further enhance precision medicine for FH.

Introduction

Familial hypercholesterolemia (FH, OMIM #143890), a hereditary disorder of lipid metabolism, results in significantly elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) above 190 mg/dL [1]. It is a genetic disorder that follows either an autosomal dominant inheritance pattern, resulting from monoallelic mutations in the *LDLR, APOB, or PCSK9* genes, or an autosomal recessive inheritance pattern, caused by biallelic mutations in the *LDLRAP1* gene [2, 3].

FH presents in two primary forms: heterozygous FH (HeFH), characterized by a mutation in a single allele, leading to elevated low-density lipoprotein cholesterol (LDL-C) levels approximately 2 to 3 times higher than normal (190–390 mg/dL); and homozygous FH (HoFH), where mutations occur in both alleles, resulting in severely elevated LDL-C levels, typically 6 to 10 times above normal (650–1000 mg/dL) [4]. Long-term exposure to increased circulating LDL-C levels accelerates atherosclerotic cardiovascular disease, especially in relation to coronary heart disease (CHD). Left untreated, those with heterozygous FH (HeFH) usually develop CHD before the age of 55 in men and 60 in women [5]. A more severe variant, homozygous FH (HoFH), affects people typically developing CHD at the age of 20 and have a reduced life expectancy [6]. Crucially important to genomics, genetic testing uses cascade screening to confirm FH diagnosis and find at-risk relatives [7]. The hallmark features of the disorder elevated LDL-C levels, tendon xanthomas, corneal arcus, and a family history of premature CHD—form the basis of several diagnostic criteria, including the Simon Broome Register (SBR), the Make Early Diagnosis to Prevent Early Death (MEDPED) criteria, and the Dutch Lipid Clinic Network (DLCN) criteria [8]. The MEDPED criteria rely solely on age- and family-specific cholesterol thresholds, whereas the DLCN criteria incorporate additional clinical and genetic parameters [9, 10]. However, no universally standardized international diagnostic tool exists. So, reducing morbidity and death linked with FH-related CVD still depends on early identification [8].

According to cohort studies, HeFH accounts for most FH occurrences; this monogenic condition affects 1 in 200 to 1 in 300 persons [11-13]. HoFH is significantly less common, with a prevalence of 1 in 160,000 to 1 in 300,000 persons [14]. In the Gulf region, studies indicate a higher prevalence of FH, with HeFH affecting approximately 1 in 112 to 1 in 200 individuals [15]. HoFH patients may be compound heterozygotes with different mutations in each allele of the same gene, genuine homozygotes with identical mutations in both alleles and double heterozygotes with mutations in two different genes influencing *LDLR* function [16].

A multi-omics approach integrating genomics, transcriptomics, proteomics, metabolomics, lipidomics, computational biology, and epigenomics provides a comprehensive framework for understanding familial hypercholesterolemia. This strategy facilitates the investigation of genetic mutations, gene expression, protein interactions, metabolic pathways, lipid profiles, and gene-environment interactions, enhancing the identification of pathogenic variants, disease mechanisms, and potential biomarkers for diagnosis and therapy [17]. Studying FH in Middle Eastern populations is essential due to its high prevalence, nearly three times the global estimate, largely attributed to consanguinity [15] which the consanguinity prevalence across the region varies widely (10.6%–67.7%) [18].Unique genetic variations and metabolic profiles in these populations may influence FH development and treatment response, emphasizing the need for region specific therapeutic strategies [19]. Despite these insights, the global detection rate of FH remains alarmingly low, with less than 1% of affected individuals identified in many countries [19, 20]. In the Middle East, the high FH prevalence, coupled with distinct genetic and metabolic characteristics, underscores the urgent need for targeted research and treatment approaches [21]. However, limited multi-omics studies have been conducted in these populations, necessitating a review to consolidate existing evidence, identify knowledge gaps, and propose precision medicine strategies tailored to Middle Eastern FH patients.

This review aims to evaluate the application of multi-omics approaches in familial hypercholesterolemia research, with a focus on Middle Eastern populations, including Saudi Arabia. By synthesizing findings from genomics, transcriptomics, proteomics, metabolomics, lipidomics, and epigenomics, this review seeks to advance the understanding of FH pathophysiology, enhance diagnostic accuracy, and guide personalized therapeutic interventions for high-risk populations.

Methods

Literature search strategy and selection criteria

This review followed PRISMA principles, performing an extensive literature search throughout PubMed, Web of Science, and SCOPUS, along with Google Scholar and ResearchGate...A structured search strategy incorporating MeSH terms ("familial hypercholesterolemia," "multi-omics," "genomics," "proteomics," "transcriptomics," "metabolomics," "lipidomics," "epigenetics," Saudi Arabia" and "Middle East") was developed to target studies on multi-omics approaches in familial hypercholesterolemia within Middle Eastern populations, including Saudi Arabia.

Studies were included if they met the following criteria: observational studies (cohort, case-control, and cross-sectional), systematic reviews, and meta-analyses evaluating multi-omics modifications in FH; studies focusing on Middle Eastern populations or providing region-specific data on FH; and those reporting on genetic variants, molecular pathways, disease biomarkers, and therapeutic targets relevant to FH.

Studies were excluded if they focused primarily on clinical trials evaluating FH treatments rather than multi-omics insights, or if they involved animal models or in vitro studies without direct human relevance. The publication data involving study characteristics, participant characteristics, multi-omics insights, genetic variants, and biomarkers was retained for writing this review.

Discussion

Genomic Insights into FH in the Middle East

Familial hypercholesterolemia can result from mutations in several genes, most commonly LDL-R, which accounts for 52-76% of cases, followed by APOB (2-10%), and PCSK9 (up to 2%) [22], and *LDLRAP1* (~ 1%) [10]. Around 15% of FH cases may be due to polygenic mutations or underdiagnosed and rare monogenic mutations, such as those in the *APOE, APOB, SREBP2, CYP7A1, LIPA, ABCG5, ABCG8,* and *STAP1* genes [22-25].

Genomics involves the comprehensive analysis of all genes, their variations, interactions, and their influence on traits and diseases [26]. Advances in genomic technologies, such as Whole Exome Sequencing (WES), SNP Arrays, and targeted gene panels using Next Generation Sequencing (NGS), have significantly enhanced our ability to examine genetic variations and their clinical implications [27-29]. For familial hypercholesterolemia, targeted genetic testing via NGS-based gene panels enables the identification of known pathogenic variants in key FH-associated genes, including *LDLR, APOB, PCSK9,* and *LDLRAP1*[30, 31]. Large deletions and duplications in the LDLR gene that are not typically detected by next-generation sequencing (NGS) can be found with multiplex ligation-dependent probe amplification (MLPA). According to studies, MLPA is crucial for a thorough genetic diagnosis in impacted families since it can identify up to 10% of instances of familial hypercholesterolemia linked to LDLR that include copy number variants (CNVs) [32, 33]. Furthermore, by finding both known and unknown variations in FH-associated genes, Whole Exome Sequencing (WES) provides a more comprehensive approach. It is especially helpful when an unusual FH phenotype indicates the involvement of other genes related to lipid metabolism or when gene panel testing fails to provide a conclusive diagnosis [34].

Beyond identifying monogenic causes, sequencing technologies have also facilitated the discovery of polygenic risk factors contributing to FH. Polygenic risk scores, derived from genome-wide association studies (GWAS), help assess the cumulative effect of multiple genetic variants, improving risk stratification and personalized treatment approaches [35]. A systematic review and related studies summarize the most common genetic variants reported in the Middle East up to 2018 [36, 37].

Common mutations in *LDLR, APOB, and PCSK9* genes help to particularly affect its frequency in the Middle East from a genetic standpoint [38]. The *LDLR* gene, responsible for approximately 95% of monogenic FH cases worldwide, harbors frequent missense and nonsense mutations in Middle Eastern countries, i.e., Saudi Arabia [39]. Studies in Lebanon reveal that LDLR p.C681X accounts for nearly 60% of FH cases [40]. The Qatar Biobank study identified 16 pathogenic *LDLR* mutations, with rs1064793799 (c.313+3A>C) and rs771019366 (p.Asp90Gly) being the most common [41]. In Saudi Arabia, limited findings related to the LDLR gene are presented in in **Table 1**. This table presents the spectrum of mutations in the *LDLR* gene reported in Saudi FH patients, including frameshift, missense, nonsense, synonymous, and silent mutations. The nucleotide and protein changes are listed alongside their respective reference sources. These mutations contribute to disrupted LDL receptor function, leading to elevated LDL-C levels and increased cardiovascular risk. Identification of such mutations highlights the genetic diversity and potential founder effects in the region, underscoring the importance of targeted genetic screening in the Saudi population.

The second gene implicated in FH is *APOB*, a critical ligand for the LDL receptor. The p. Arg490Trp variant in the *APOB* gene has been identified through WES in polygenic FH cases within Saudi and Lebanese cohorts [42]. In Saudi Arabia, the limited findings related to the *APOB* gene, as presented in **Table 2**. This table summarizes reported mutations in the APOB gene, highlighting the genetic heterogeneity of FH in the Saudi population including missense and frameshift mutations. Variants in APOB can impair this interaction, contributing to elevated LDL-C levels and the development of FH. The *PCSK9* gene, though responsible for only ~1% of FH cases globally, exhibits a higher prevalence of pathogenic variants in Middle Eastern populations [43]. Recent studies have identified novel pathogenic variants in the *PCSK9* gene among Middle Eastern populations [35]. These findings suggest potential region-specific mechanisms

influencing LDL-C metabolism and highlight the need for targeted genetic screening and personalized treatment strategies in these populations [43]. Mutations in *PCSK9* can significantly alter its function: gain-of-function mutations increase PCSK9 activity, leading to autosomal dominant hypercholesterolemia by promoting *LDLR* degradation and elevating LDL-C levels, while loss-of-function mutations enhance *LDLR* availability, reducing LDL-C levels. Whole-genome sequencing from the Qatar Biobank has identified rare *LDLR* and *PCSK9* variants, including a 1.03 Mb *PCSK9* duplication linked to severe hypercholesterolemia [41] [44]. Table 3 presents the genetic variants in Saudi Arabia. This table lists missense, synonymous, frameshift, and nonsense mutations in the PCSK9 gene reported in Saudi FH cases. *PCSK9* plays a critical role in LDL receptor degradation; gain of function mutations lead to reduced *LDLR* availability and increased LDL-C levels. The reported variants demonstrate the potential regional enrichment of specific *PCSK9* mutations, informing personalised treatment strategies such as PCSK9 inhibitor therapy.

SNP-based LDL-C risk scores have confirmed polygenic FH cases, emphasizing the necessity of comprehensive genetic screening beyond monogenic testing [45]. Additionally, the first cases of biallelic *LDLRAP1* mutations leading to autosomal recessive hypercholesterolemia (ARH) were identified in Lebanese families [46] [47]. In a Saudi cohort, they were identified as double-heterozygous for *LDLR* and *LDLRAP1* mutations, specifically the novel p.(Y419D) variant in *LDLR* and p.(S202Tfs∗2) variant in *LDLRAP1* [48]. Another study reported a Lebanese family with familial hypercholesterolemia exhibiting double heterozygosity [48]. The different zygosity in *LDLRAP1* mutations included a p.(Q136∗) variant along with either heterozygous or homozygous p.(C681∗) mutations in the *LDLR* gene. Additionally, one patient had heterozygous mutations in the *LDLR* gene, including p.(C681∗), p.(H327fsX5), p.(A391T), and p.(I451T) [48].

Gene Name	Type of mutation	Nucleotide	Protein	Reference
LDLR	Frameshift Mutation	c.608delG	p. Pro203fs	[49]
		c.1706- 1715del.AT CTCCTCAG)	p. Asp569 Valfs*93	[50]
		c.335_336insCGAG	p. F114Rfs*17	[51]
		c.666_670dup	p. Asp224Alafs*43	[52]
		c.2027delG	p. Gly676Alafs*33	[53] [54]
		c.2026delG	p. G676Afs*33	[49] [55]
	Missense Mutations	c.1429G>A	p. D477N	[51]
		c.1474G>A	p. D492N	[51]
		c.2374G>A	p. Glu792Lys	[56]
		c.622G>A	p. Glu208Lys	[51]
		c.1255T>C	p. Tyr419His	[46] [57]
		c.1731G>T	p. W577C	[58]
	Nonsense Mutations	c.1332dup	p. Asp445*	[59]
		c.2230C>T	p.R744*	[59]
		c.693C>A	p.C231*	[60]
		c.2043C>A	p. Cys681*	[61]
	Silent Mutation	c.1413A>G	p. Arg471=	[58]
		c.1725G>A	p. L575=	[58]

Table 1: LDLR gene variants identified in FH patients in Saudi Arabia include coding mutation that contribute to disrupted LDL receptor function, leading to elevated LDL-C levels.

Gene Name	Type of mutation	Nucleotide	Protein	References
APOB	Missense Mutation	c.5066G>A	p. Arg1689His	[62]
		c.9109G>C	p. Leu3037Val	[49]
		c.1853C>T	p. Ala618Val	[63]
		c.13013G>A	p. Ser4338Asn	[63]
	Frameshift Mutation	c.6027delA	p. Leu2009fs	[49]
		c.3961delG	p. Leu1321fs	[49]
		c.702delG	p. Pro234fs	[49]
		c.671delG	p. Pro224fs	[49]

Table 2: Summarizes reported APOB gene variants identified in FH patients in Saudi Arabia, including missense and frameshift mutations.

Gene Name	Type of mutation	Nucleotide	Protein	References
PCSK9	Missense Mutation	c.1486C>T	p. Arg496Trp	[7]
		c.2009G>A	p. Gly670Glu	[49]
		c.1420G>A	p. Val474Ile	[49]
		c.158 T > C	p. Ala53Val	[64]
	Synonymous	c.1026A>G	p. Gln342=	[49]
		c.1380A>G	p. Val460=	[49]
	Frameshift Mutation	c.517delC	Pro173fs	[49]
		c.1935delG	Leu645fs	[49]

Table 3: PCSK9 gene variants identified in Saudi population.

Transcriptomics, Proteomics, and Epigenetic Modifications in FH

Research on transcriptomics and epigenetic modifications in familial hypercholesterolemia remains underexplored in the Middle East. Globally, studies have identified differentially expressed genes and epigenetic changes linked to lipid metabolism.

Multi-omics studies, including transcriptomics, proteomics, and epigenetics, have provided insights into how genetic mutations in FH disrupt cholesterol metabolism, contributing to atherosclerosis [65]. Epigenetic modifications play a crucial role in lipid metabolism and cardiovascular risk, as highlighted by Sayols-Baixeras *et al.*, [66]. Additionally, gene expression profiling in elderly FH patients has revealed distinct molecular signatures associated with coronary heart disease, further emphasizing the impact of oxidative stress and inflammation in FH pathophysiology [67].

Epigenetic processes such as DNA methylation, histone modifications, and microRNA (miRNA) regulation are crucial for the development of FH and its reaction to lipid-lowering therapies [68]. Studies reveal that miR-33 and miR-122 regulate cholesterol metabolism and target genes involved in lipid homeostasis; their dysregulation may impact the effectiveness of statins in patients with FH [69]. Moreover, hypermethylation of LDLR gene promoter regions is associated with decreased expression of LDL receptors, which may contribute to the explanation of statin resistance [70]. The severity of the condition and the effectiveness of treatment are impacted by histone modifications such as acetylation and methylation, which also regulate the transcription of genes involved in the creation of cholesterol [71]. However, our knowledge of possible ethnic differences in FH pathophysiology is hampered by the paucity of epigenetic studies specifically focused on the Middle Eastern population.

Proteomic studies on FH patients in this region are limited. However, silico proteomics, including computational modeling, network analysis, and PPI studies, provide key insights into FH pathophysiology.

These methods help identify biomarkers and therapeutic targets by predicting protein expression patterns, structural changes, and pathway disruptions. Building on this, a study investigated coding region mutations in the LDLRAP1 gene associated with FH. Several missense mutations were analyzed for their impact on protein structure and function. Among these, the p. Glu42Lys mutation was identified as particularly significant. This mutation was predicted to induce structural changes in LDLRAP1, altering its flexibility and stability, potentially disrupting its interaction with LDLR and impairing cholesterol metabolism [72]. Further exploring this, a protein-protein docking study explored interactions between LDLR and APOB, identifying novel mutations that negatively impact binding affinity. Among these, APOB (Arg3527Trp) and LDLR (Cys318Arg) were the most significant, exhibiting low binding affinity and altered hydrogen bonding, leading to a detrimental effect on protein function [73]. Another study combining genomics and in silico protein analysis revealed that the PCSK9 R496W mutation destabilizes protein structure, increasing its binding affinity to LDLR and promoting LDLR degradation. Molecular dynamics simulations indicated heightened protein instability, while docking analysis confirmed stronger PCSK9-LDLR interactions. Functional predictions further validated its deleterious impact, reinforcing PCSK9 as a key therapeutic target for cholesterol regulation [74].

Metabolomics and Lipidomics in FH Patients

Global metabolic alterations in biological systems are examined using metabolomics, a thorough analytical method that offers important insights into illness causes, the identification of biomarkers, and treatment outcomes [75]. It includes two primary approaches: focused metabolomics, which measures predetermined metabolites linked to particular pathways, and untargeted metabolomics, which finds a wide variety of metabolites to identify unforeseen biochemical changes [76]. High sensitivity and reproducibility in detecting metabolic perturbations are made possible by advanced techniques like nuclear magnetic resonance

(NMR) spectroscopy, liquid chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), and ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS), which have improved metabolomic profiling [77].

A few studies in the Middle East have concentrated on other risk factors linked to hypercholesterolemia, despite the paucity of research on the condition. One study examined coronary heart disease (CHD) patients using untargeted metabolomics and found notable metabolic changes. Glycolysis, branched-chain fatty acid oxidation, sphingolipid metabolism, and D-arginine and D-ornithine metabolism were all disrupted, according to pathway enrichment analysis [78].

Lipidomic studies have provided crucial insights into lipid abnormalities associated with FH in Middle Eastern populations. A study highlighted significantly elevated lipoprotein(a) levels in Middle Eastern FH patients, suggesting a greater predisposition to atherosclerosis compared to Western cohorts [15]. Moreover, shotgun lipidomics demonstrated increased levels of pro-atherogenic sphingolipids and phospholipids in homozygous FH (HoFH) patients, which correlated strongly with coronary artery disease severity [15].

Multi-omics in FH Treatment and Management

Lowering LDL-C levels is the primary goal of familial hypercholesterolemia treatment. Key therapeutic options include statins, ezetimibe, bile acid sequestrants, PCSK9 inhibitors, and Inclisiran, which target different pathways to reduce LDL-C and manage cardiovascular risk effectively [79].

The integration of multi-omics approaches, including genomics, transcriptomics, proteomics, metabolomics, lipidomics, and epigenomics, has significantly enhanced the treatment and management of FH. Metabolomics and lipidomics provide insights into lipid metabolism and oxidative stress, allowing for precision medicine approaches in selecting lipid-lowering agents such as statins and ezetimibe [80] [81].Transcriptomics and proteomics reveal gene expression patterns and protein interactions, aiding in the development of targeted therapies like PCSK9 inhibitors [82] [83]. Despite these advancements, the Gulf FH study found that only 12% of patients at high ASCVD risk reached the target LDL-C level of less than 100 mg/dL, and only 3% of patients at very high ASCVD risk achieved the more stringent target of less than 70 mg/dL [84]. Of most FH patients registered in the Gulf study, 86.8% were treated with statins, and only 62% were given high-intensity doses. Additionally, 33% were administered ezetimibe, 2.8% underwent LDL apheresis, and 1.4% received PCSK9 inhibitors [15]. Furthermore, Inclisiran, a long-acting small interfering RNA (siRNA) therapeutic, has shown promise in cholesterol reduction. The first report on Inclisiran use in the Middle East demonstrated a 54.1% LDL-C reduction and a 15.3% decrease in triglycerides [15]. By integrating multi-omics data, clinicians can develop personalized treatment plans, improve early diagnosis, and optimize therapeutic efficacy, ultimately enhancing FH management and reducing mortality [85, 86].

Conclusion

Multi-omics technologies have revolutionized our understanding of FH, particularly in Middle Eastern populations, where unique genetic, environmental, and lifestyle factors contribute to disease prevalence and treatment variability. These approaches have uncovered region-specific genetic mutations, metabolic biomarkers, and molecular pathways, improved diagnostic precision and enabling the development of personalized treatment strategies. However, despite these advancements, most research has focused primarily on genomics, with limited integration of transcriptomics, proteomics, metabolomics, and epigenomics. This gap restricts a comprehensive understanding of FH pathophysiology and hinders the development of precision medicine approaches tailored to this population. Several challenges persist, including limited access to advanced sequencing technologies, financial constraints, insufficient insurance coverage, and the lack of national FH registries incorporating multi-omics data. Ethical and cultural considerations surrounding genetic testing further complicate the widespread adoption of personalized medicine approaches. Addressing these challenges requires a coordinated effort among researchers, healthcare institutions, and policymakers to establish region-specific multi-omics frameworks. Expanding genetic and lipidomic screening programs, integrating multi-omics data into routine clinical workflows, and leveraging artificial intelligence-driven analytics will be essential to bridging the gap between research and clinical practice. By implementing these strategies, the Middle East can enhance FH management, reduce cardiovascular disease burden, and advance precision medicine tailored to its population.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Author Contributions

Conceptualization: Zuhier Awan; Literature Review and Data Curation: Hussam Daghistani, Hadiah Bassam Al Mahdi, Sherif Edris; Writing – Original Draft Preparation: Hadiah Bassam Al Mahdi, Sherif Edris; Writing – Review and Editing: Hussam Daghistani, Zuhier Awan; Supervision: Hussam Daghistani, Zuhier Awan. All authors have read and approved the final manuscript.

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