Lipids in Health and Disease

REVIEW

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Long noncoding RNAs in familial hypercholesterolemia: biomarkers, therapeutics, and AI in precision medicine

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Abstract

Long noncoding RNAs (lncRNAs) have emerged as critical regulators of lipid metabolism, playing pivotal roles in cholesterol biosynthesis, transport, and efflux. Familial Hypercholesterolemia (FH), a genetic disorder characterized by excessive low-density lipoprotein cholesterol (LDL-C) levels, remains a significant contributor to premature cardiovascular disease (CVD). Traditional diagnostic methods, including lipid profiling and genetic testing, have limitations in sensitivity and accessibility, highlighting the need for novel molecular biomarkers. This review delves into the mechanistic involvement of lncRNAs in FH pathogenesis, shedding light on their potential as non-invasive biomarkers and therapeutic targets. Key lncRNAs such as LeXis, CHROME, and H19 have been implicated in cholesterol regulation and atherosclerosis progression, making them attractive candidates for precision medicine applications. Additionally, advancements in AI-driven lncRNA discovery and single-cell transcriptomics are paving the way for innovative diagnostic and therapeutic strategies. Emerging RNA-based therapeutics, including antisense oligonucleotides, small interfering RNAs (siRNAs), and CRISPR-based gene-editing tools, hold promise for modulating lncRNA function to restore lipid homeostasis. However, challenges such as biomarker validation, efficient RNA delivery, and regulatory approval must be addressed for clinical translation. The integration of lncRNA-based approaches into FH management offers new possibilities for early detection, targeted therapy, and personalized cardiovascular risk assessment, underscoring the need for continued research in this rapidly evolving field.

Keywords Familial hypercholesterolemia, Long noncoding RNAs, Lipid metabolism biomarkers, RNA-based therapeutics, Single-cell transcriptomics, AI-driven precision medicine, Cardiovascular risk

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Introduction

Familial Hypercholesterolemia (FH) is a monogenic disorder predominantly caused by mutations in LDLR, PCSK9, and APOB genes, leading to impaired clearance of LDL-C and a lifelong predisposition to atherosclerosis and cardiovascular diseases [1–3]. Despite advancements in genetic screening, many cases remain undiagnosed due to the high cost and accessibility limitations of genetic testing. Current diagnostic methods, including lipid profiling, do not always detect FH in its early stages, emphasizing the need for novel biomarkers with high specificity and sensitivity [4, 5].

LncRNAs are emerging as critical regulators of lipid metabolism, influencing cholesterol synthesis, efflux, and catabolism [1, 6–9]. Unlike protein-coding genes, lncRNAs function through diverse mechanisms, including chromatin remodeling, transcriptional regulation, and post-transcriptional modifications, making them attractive candidates for biomarker discovery and therapeutic intervention [10–14]. Several lncRNAs, such as LeXis, MeXis, CHROME, and H19, have been implicated in lipid homeostasis and cardiovascular disease pathogenesis [7, 15–18], but their specific roles in FH remain underexplored.

This review aims to consolidate current knowledge on the involvement of lncRNAs in FH pathogenesis, evaluating their potential as diagnostic biomarkers and therapeutic targets. We explore how lncRNA-based diagnostics could complement existing genetic testing and how emerging RNA-targeting therapeutics may offer novel avenues for FH management. Furthermore, we discuss recent advancements in AI-driven biomarker discovery, single-cell transcriptomics, and RNA-based therapeutics, highlighting their potential integration into precision medicine frameworks for FH treatment.

Molecular mechanisms of lncRNAs in cholesterol homeostasis

lncRNAs in cholesterol synthesis and uptake

Cholesterol synthesis is a complex process that occurs primarily in the liver, where acetyl-CoA is converted into cholesterol through the mevalonate pathway [19]. This pathway is tightly regulated by multiple transcriptional and post-transcriptional mechanisms, including the sterol regulatory element-binding proteins (SREBPs), which act as master regulators of cholesterol biosynthesis [20–22]. Low-density lipoprotein (LDL) uptake is another key mechanism in cholesterol homeostasis, mediated by the LDL receptor (LDLR), which binds circulating LDL and facilitates its clearance from the bloodstream [21, 23, 24].

Recent studies have identified several lncRNAs that modulate these processes, either by directly influencing key regulatory genes or by acting as molecular sponges for microRNAs (miRNAs) that suppress cholesterol synthesis. Here, we discuss some of the most critical lncRNAs involved in cholesterol biosynthesis and LDL uptake.

LeXis: a negative regulator of cholesterol biosynthesis

LeXis (Liver-expressed lncRNA regulating cholesterol homeostasis) has been identified as a crucial regulator of cholesterol biosynthesis [7, 25–27]. It interacts with the ribonucleoprotein RALY, which is involved in RNA processing and gene regulation, to suppress the activity of SREBP2, a master transcriptional regulator of cholesterol biosynthetic genes [19, 25, 26, 28, 29]. By inhibiting SREBP2, LeXis downregulates key enzymes in the mevalonate pathway, including HMG-CoA reductase (HMGCR) and HMG-CoA synthase 1 (HMGCS1), leading to a reduction in intracellular cholesterol synthesis [25, 26]. Moreover, studies suggest that LeXis is regulated by nuclear receptors such as Liver X Receptors (LXRs), linking it to broader lipid metabolism pathways [25].

Experimental studies in mice have demonstrated that LeXis overexpression significantly reduces plasma cholesterol levels and protects against diet-induced hypercholesterolemia [25, 30]. Conversely, LeXis knockout mice exhibit increased hepatic cholesterol synthesis and higher LDL-C levels, further confirming its role as a negative regulator of cholesterol biosynthesis [25, 30, 31]. Additionally, LeXis appears to function as a crucial link between SREBP2 and LXR-mediated pathways, coordinating lipid metabolism and cholesterol homeostasis. By suppressing the transcriptional activity of SREBP2, LeXis exerts an overarching effect on lipid metabolic networks, positioning itself as an essential checkpoint in cholesterol biosynthesis [25, 30, 31].

Notably, recent evidence has revealed a novel extracellular role for LeXis. A study demonstrated that LeXis is (along with LASER and HIF1 A-AS2) transported by high-density lipoprotein (HDL) particles in subjects with FH [32]. Importantly, HDL-bound LeXis was significantly associated with cardiovascular risk markers, showing an inverse correlation with lipoprotein(a) [Lp(a)] levels and pulse wave velocity (PWV), a surrogate marker of arterial stiffness and vascular dysfunction [32]. This suggests that LeXis may exert both intracellular and extracellular functions, with potential as a circulating biomarker for vascular damage and cardiovascular risk stratification in FH.

Further investigations have elucidated that LeXis functions through epigenetic modifications, influencing histone methylation patterns that modulate SREBP2 target gene expression [33, 34]. The RALY-LeXis complex dynamically interacts with the regulatory elements of cholesterol biosynthetic genes [25, 34–36], indicating that targeting LeXis pharmacologically could provide a new avenue for cholesterol-lowering therapies in FH patients.

This dual intracellular and extracellular functionality reinforces LeXis's therapeutic and diagnostic potential, linking its mechanistic roles in gene regulation to its emerging utility as a plasma-based biomarker for vascular risk.

lncARSR: a positive regulator of cholesterol synthesis

lncARSR (lncRNA Activated in Renal Cell Carcinoma with Sunitinib Resistance) has been found to modulate

cholesterol metabolism by upregulating HMGCR, the rate-limiting enzyme in cholesterol biosynthesis [37–39]. Mechanistically, lncARSR functions as a competing endogenous RNA (ceRNA) by sponging miR-30c, a microRNA known to inhibit HMGCR translation [40, 41]. By preventing miR-30c from binding to HMGCR mRNA, lncARSR enhances HMGCR expression, leading to increased cholesterol synthesis [7, 40, 42]. Studies in hypercholesterolemic models have shown that lncARSR overexpression correlates with elevated LDL-C levels and hepatic cholesterol accumulation, reinforcing its role in cholesterol dysregulation and atherosclerosis progression [18, 43, 44].

HOXC-AS1: a regulator of LDL uptake

LDL uptake is a fundamental process that regulates circulating cholesterol levels [45–47]. HOXC-AS1, an antisense lncRNA, has been implicated in the regulation of LDLR expression [48, 49]. LDLR is essential for removing LDL particles from circulation, and its activity is tightly controlled by multiple regulatory factors, including lncRNAs [7, 23, 49]. Knockdown studies have demonstrated that HOXC-AS1 depletion reduces LDLR expression, impairing LDL clearance and increasing plasma LDL-C levels, a hallmark of FH [48–50]. Mechanistically, HOXC-AS1 is thought to regulate LDLR gene expression through chromatin remodeling, suggesting that it may interact with chromatin-modifying enzymes to alter LDLR promoter accessibility [1, 38, 48, 51]. Furthermore, studies have indicated that HOXC-AS1 influences histone modifications, thereby affecting LDLR transcriptional activity [48, 52–54]. These findings highlight HOXC-AS1 as a potential target for increasing LDL uptake in FH treatment and warrant further investigation into its role in cholesterol homeostasis and gene regulation.

SRA: a transcriptional coactivator in cholesterol metabolism

SRA (Steroid Receptor RNA Activator) is a multifunctional lncRNA that has been shown to enhance cholesterol biosynthesis by acting as a transcriptional coactivator for nuclear receptors, including Liver X Receptors (LXRs) and Peroxisome Proliferator-Activated Receptors (PPARs) [36, 54–58]. These nuclear receptors regulate lipid metabolism by controlling the expression of genes involved in lipid synthesis, storage, and transport [28, 59]. Recent studies have demonstrated that SRA overexpression is associated with increased hepatic lipid accumulation, while its inhibition reduces cholesterol biosynthesis and promotes lipid clearance [29, 31, 56, 60]. Additionally, SRA has been implicated in fatty liver disease and metabolic syndrome, highlighting its broader role in lipid-related disorders [58, 60, 61].

AT102202 (LncHMGCR): a negative regulator of HMGCR expression

AT102202 is a long non-coding RNA identified in HepG2 liver cells that negatively regulates HMGCR, the rate-limiting enzyme in cholesterol biosynthesis [7, 62]. Treatment with epigallocatechin gallate (EGCG) was shown to upregulate AT102202, leading to a reduction in HMGCR mRNA expression and a subsequent decrease in cholesterol synthesis [7, 62]. Conversely, knockdown of AT102202 resulted in elevated HMGCR levels, confirming its inhibitory regulatory role [62]. While "LncHMGCR" is not a formally recognized gene symbol, we use it here as a functional label to reflect AT102202's specific role in modulating HMGCR expression. These findings highlight AT102202 as a potential therapeutic target for attenuating hepatic cholesterol production, particularly in the context of FH.

While regulating cholesterol synthesis and uptake is crucial for maintaining cellular cholesterol balance, the removal of excess cholesterol through efflux and transport mechanisms is equally vital. Several lncRNAs also prominently influence these pathways, affecting lipid homeostasis and cardiovascular risk.

lncRNAs in cholesterol efflux and transport

Cholesterol efflux and transport play crucial roles in maintaining lipid homeostasis and preventing excessive cholesterol accumulation, which is a key driver of atherosclerosis [7, 23, 63]. These processes are primarily mediated by ATP-binding cassette (ABC) transporters, such as ABCA1 and ABCG1, which facilitate cholesterol transfer to HDL for reverse cholesterol transport to the liver for excretion [64–67]. Disruptions in cholesterol efflux lead to foam cell formation, contributing to atherosclerotic plaque development and cardiovascular disease [63, 65, 68, 69]. Several lncRNAs have been identified as key regulators of these processes, influencing cholesterol metabolism at transcriptional and post-transcriptional levels.

MeXis: a key enhancer of cholesterol efflux

MeXis (Macrophage-expressed lncRNA stimulating ABCA1) has been shown to act as a transcriptional coactivator for liver X receptors (LXRs), enhancing the expression of ABCA1, which is essential for cholesterol efflux [59, 63, 70–74]. Increased expression of MeXis correlates with enhanced cholesterol clearance, improved HDL formation, and reduced foam cell formation, which are critical for preventing atherosclerosis [59, 63, 74, 75]. Conversely, MeXis-deficient mice exhibit impaired cholesterol transport and increased lipid accumulation in macrophages, leading to accelerated plaque development

[27, 76]. This highlights MeXis as a potential therapeutic target for promoting cholesterol efflux and reducing cardiovascular disease risk.

CHROME: a master regulator of cholesterol homeostasis

CHROME (Cholesterol Homeostasis Regulator of miRNA Expression) is a lncRNA that influences cholesterol efflux by regulating a set of microRNAs that target ABCA1 and ABCG1 [21, 27, 77]. CHROME acts by suppressing miRNAs (such as miR-27b, miR-33, and miR-128), which are known to downregulate genes involved in cholesterol transport [21, 27, 77, 78]. By inhibiting these miRNAs, CHROME enhances HDL formation and reverse cholesterol transport, protecting against cholesterol accumulation and atherosclerosis [21, 27, 76, 79, 80]. Reduced expression of CHROME has been linked to dyslipidemia and increased cardiovascular risk [9, 27, 81], making it a promising candidate for therapeutic intervention.

ANRIL: a link between inflammation and cholesterol transport

ANRIL (Antisense Noncoding RNA in the INK4 Locus, also known as CDKN2B-AS1) plays a dual role in lipid metabolism and inflammation [82, 83]. Elevated expression of ANRIL has been associated with NF-κB-mediated inflammatory responses, which indirectly impair cholesterol efflux mechanisms [82–85]. ANRIL modulates vascular endothelial function and affects macrophage cholesterol handling, linking it to both atherosclerosis progression and impaired lipid metabolism [85–89]. Furthermore, ANRIL has been shown to regulate the expression of genes within the INK4/ARF locus, influencing cell cycle pathways that contribute to vascular remodeling and plaque stability [87–91]. Given its inflammatory role, ANRIL is emerging as a potential target for interventions aimed at both inflammation control and cholesterol homeostasis restoration.

Lnc-HC: a dual regulator of cholesterol efflux and bile acid metabolism

Lnc-HC is a hepatocyte-enriched long noncoding RNA that plays a critical inhibitory role in both cholesterol efflux and hepatic catabolism [18]. Functionally, it suppresses the expression of ATP-binding cassette transporters ABCA1 and ABCG1, thereby impairing the efflux of excess intracellular cholesterol to HDL [7, 18, 92–94]. This inhibition promotes cholesterol retention in macrophages and hepatocytes, contributing to foam cell formation and atherogenesis [92, 93]. In parallel, Lnc-HC downregulates cholesterol 7 alpha-hydroxylase (CYP7 A1), the rate-limiting enzyme in bile acid synthesis, further exacerbating hepatic cholesterol accumulation by limiting its catabolic clearance [18, 92–94]. Mechanistically, Lnc-HC is thought to exert its effects through interactions with nuclear receptors such as PPARα, influencing both transcriptional activity and downstream lipid-handling pathways [92, 93]. Knockdown of Lnc-HC has been shown to enhance ABCA1/ABCG1 expression and restore CYP7 A1-mediated bile acid production [92–94], underscoring its dual contribution to dyslipidemia in FH and its potential as a therapeutic target.

Maintaining cholesterol homeostasis not only requires effective synthesis and efflux regulation but also depends on efficient catabolic breakdown [7]. The hepatic conversion of cholesterol into bile acids represents a key mechanism for reducing intracellular lipid burden. The next section examines other lncRNAs that influence this catabolic pathway and contribute to lipid regulation in FH.

lncRNAs in cholesterol catabolism

Cholesterol catabolism is a crucial process that facilitates cholesterol homeostasis and prevents its excessive accumulation in tissues [23, 95]. The primary pathway for cholesterol breakdown involves its conversion into bile acids in the liver, which are subsequently excreted through the enterohepatic circulation [96–100]. The process is tightly regulated by nuclear receptors, transcription factors, and various epigenetic mechanisms, including lncRNAs [97, 99, 101–103]. Recent studies have identified several lncRNAs that play pivotal roles in cholesterol catabolism by modulating the expression of key enzymes involved in bile acid synthesis and lipoprotein metabolism.

RP5-833 A20.1: a modulator of lipoprotein metabolism

RP5-833 A20.1 is another lncRNA that has been implicated in cholesterol clearance through its interaction with NF1 A, a transcription factor that regulates lipoprotein metabolism [76, 104, 105]. NF1 A plays a crucial role in lipoprotein uptake and cholesterol trafficking [106]. Experimental studies have shown that RP5-833 A20.1 inhibits NF1 A activity, thereby impairing lipoprotein metabolism and reducing cholesterol clearance [76, 104, 105, 107]. Knockdown of RP5-833 A20.1 restores NF1 A function, enhancing lipoprotein metabolism and promoting cholesterol excretion [76, 105, 107], highlighting its potential role in modulating cholesterol homeostasis and bile acid metabolism.

LncRNA-DYNLRB2-2: a potential modulator of cholesterol homeostasis

LncRNA-DYNLRB2-2 has been implicated in cholesterol efflux and lipid metabolism regulation [105, 108, 109]. Specifically, its overexpression in macrophage-derived foam cells has been associated with increased expression of ATP-binding cassette transporter A1 (ABCA1) and G

protein-coupled receptor 119 (GPR119), both of which facilitate cholesterol efflux and reduce lipid accumulation [105, 108, 109]. These findings suggest that LncRNA-DYNLRB2-2 may play a role in maintaining lipid balance and preventing excessive cholesterol buildup.

Although its precise molecular mechanisms remain unclear, its involvement in cholesterol efflux highlights its potential relevance to hepatic cholesterol metabolism. Further studies are needed to explore whether LncRNA-DYNLRB2-2 could serve as a therapeutic target for enhancing cholesterol clearance in conditions such as FH. A deeper understanding of its regulatory functions may provide novel insights into cholesterol homeostasis and lipid-related disease management.

Beyond their metabolic roles, lncRNAs significantly impact inflammation and vascular processes underlying atherosclerosis. Understanding their regulatory roles provides deeper insights into FH-associated cardiovascular risk.

lncRNAs in atherosclerosis and inflammation

Atherosclerosis, the underlying cause of most cardiovascular diseases, is a chronic inflammatory disorder driven by lipid accumulation, endothelial dysfunction, and immune system activation [110, 111]. In FH, excessive low-density lipoprotein cholesterol (LDL-C) triggers inflammatory responses that accelerate plaque formation [1, 112–114]. Emerging evidence suggests that lncRNAs play significant roles in modulating inflammatory pathways, endothelial integrity, and macrophage activation, all of which contribute to atherosclerosis progression [111]. Here, we discuss key lncRNAs involved in these processes and their implications for FH and cardiovascular disease management.

H19: a pro-atherogenic lncrna enhancing endothelial dysfunction

H19 has been implicated in the pathogenesis of atherosclerosis through its effects on vascular endothelial cells and smooth muscle cells [115–120]. Studies have shown that H19 is highly expressed in human atherosclerotic plaques and injured carotid arteries in rat models, whereas its expression is minimal in normal coronary arteries [115, 116, 118, 121–125]. In patients with atherosclerosis, elevated levels of H19 have been detected in plaques, and its upregulation has been associated with increased proliferation and reduced apoptosis of vascular smooth muscle cells (VSMCs)[116, 117, 121, 123, 124]. H19 has also been reported to promote the proliferation of vascular endothelial cells in arteriosclerosis obliterans and inhibit their apoptosis via the nuclear factor kappa-B (NF-κB) pathway [126–128]. Increased H19 expression accelerates atherosclerosis by activating inflammatory pathways, while H19 silencing has been shown to suppress ex vivo adipogenesis and inflammatory responses induced by oxidized low-density lipoprotein (ox-LDL) treatment [124, 129]. Given its role in endothelial dysfunction and vascular inflammation, H19 is a promising therapeutic target for mitigating atherosclerosis, particularly in patients with FH.

GAS5: an inhibitor of cholesterol efflux and macrophage foam cell formation

Growth arrest-specific 5 (GAS5) is a lncRNA known for its role in apoptosis and metabolic regulation [130, 131]. Recent findings suggest that GAS5 suppresses cholesterol efflux by inhibiting ATP-binding cassette transporter A1 (ABCA1) expression, a key regulator of cholesterol removal from macrophages [130]. Reduced ABCA1 expression leads to cholesterol accumulation in macrophages, promoting foam cell formation, a hallmark of early atherosclerotic lesions [69, 80, 130, 132, 133]. Inhibition of GAS5 has been associated with increased ABCA1 expression, enhanced cholesterol efflux, and reduced atherosclerosis burden [130, 134]. These findings suggest that targeting GAS5 may be an effective strategy for improving lipid clearance and reducing inflammation in FH-associated cardiovascular disease.

MIAT: a key regulator of vascular smooth muscle cell proliferation

Myocardial infarction-associated transcript (MIAT) is a lncRNA involved in vascular remodeling and smooth muscle cell proliferation, both of which contribute to atherosclerotic plaque stability and progression [135–142]. MIAT has been shown to activate NF-κB signaling, a major inflammatory pathway linked to atherosclerosis [143, 144]. By promoting smooth muscle cell migration and proliferation, MIAT contributes to plaque destabilization and increases the risk of cardiovascular events [144]. Inhibiting MIAT has been found to suppress NF-κB activation and attenuate inflammation in atherosclerotic models [138, 141, 144], highlighting its potential as a therapeutic target for stabilizing plaques and reducing inflammatory responses in FH.

Together, these findings highlight the diverse roles of lncRNAs in the regulation of cholesterol metabolism and vascular pathology in FH. From hepatic biosynthesis and bile acid catabolism to macrophage-driven cholesterol efflux and vascular inflammation, lncRNAs orchestrate multiple layers of lipid homeostasis. Figure 1 provides an integrated schematic of these regulatory pathways, emphasizing the key lncRNAs involved in each biological process and their mechanistic targets across relevant cell types.

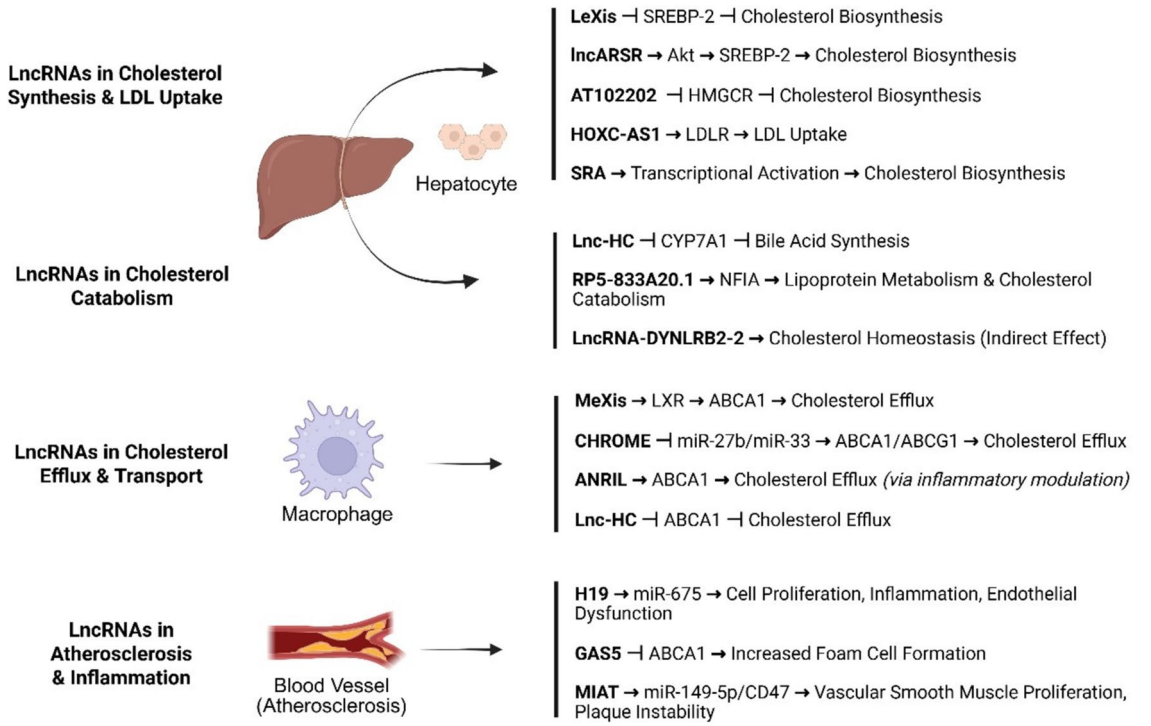

Fig. 1 Schematic overview of key lncRNAs regulating cholesterol metabolism and inflammation in familial hypercholesterolemia (FH). This schematic illustrates the functional roles of key long noncoding RNAs (lncRNAs) across major regulatory domains in FH, including cholesterol synthesis and LDL uptake, cholesterol catabolism, cholesterol efflux and transport, and atherosclerosis-related inflammation. The pathways are shown across hepatocytes, macrophages, and vascular cells. Positive regulation is indicated by solid arrows (→), and inhibition by blunt-end lines (⊣). Created in BioRender

LncRNAs as diagnostic biomarkers in FH

LncRNAs are emerging as dynamic molecular indicators in FH, given their roles in lipid regulation and atherosclerosis (Table 1). Unlike traditional lipid profiling or static genetic tests, lncRNAs reflect real-time metabolic states and can be detected in blood, offering a non-invasive means of cardiovascular risk stratification. Recent work revealed that lncRNAs such as LEXIS, LASER, and HIF1 A-AS2 are transported by HDL particles in FH patients, with HDL-bound LEXIS inversely associated with plasma levels of lipoprotein(a) and pulse wave velocity (PWV), an indicator of arterial stiffness [32]. These findings suggest that HDL-bound lncRNAs may serve not only as mechanistic regulators but also as circulating biomarkers of vascular dysfunction. Building on this insight, the following sections explore the diagnostic potential of lncRNAs, their integration into existing FH detection strategies, and the challenges that remain for clinical translation.

Challenges in current FH diagnosis

The diagnosis of FH remains a clinical challenge despite advancements in lipid profiling, genetic testing, and established scoring systems such as the Dutch Lipid Clinic Network (DLCN) score [4, 150]. Traditional lipid profiling, which assesses LDL-C levels, lacks specificity as cholesterol levels can be influenced by various metabolic and environmental factors, including obesity, diet, and secondary dyslipidemia [8, 151–153]. Furthermore, LDL-C levels alone are insufficient to differentiate FH from polygenic hypercholesterolemia, leading to potential misclassification [1, 154]. Genetic testing, while providing high specificity, is not without limitations. A significant proportion of clinically diagnosed FH patients do not exhibit mutations in LDLR, APOB, or PCSK9, the primary genes implicated in monogenic FH [155–160], suggesting that additional, unidentified molecular mechanisms may contribute to FH pathology. Additionally, the high cost and limited availability of genetic testing,

Table 1 Summary of key lncRNAs involved in FH

LncRNA	Function	Implicated Pathway(s)	Clinical Relevance	References
LeXis	Feedback inhibitor of hepatic cholesterol biosynthesis	LXR-induced; binds RALY to inhibit SREBP2 targets (e.g., HMGCR)	Lowers cholesterol in mice; HDL-bound in FH patients; inversely associated with Lp(a) & PWV; potential biomarker in NAFLD/NASH and FH	[25, 26, 30, 32, 84, 152]
lncARSR	Promotes hepatic cholesterol biosynthesis	Activates Akt → SREBP-2 → HMGCR (upregulates the rate-limiting HMG-CoA reductase)	Elevated in hypercholesterolemia; knockdown lowers LDL; potential therapeutic target	[43, 44, 152]
HOXC-AS1	Suppresses cholesterol accumulation in macrophages (anti-foam cell)	Upregulates HOXC6 to reduce lipid uptake	Downregulated in plaques; overexpression limits foam cell formation; anti-atherosclerotic potential	[14, 48, 50, 52, 152]
SRA	Coactivates nuclear receptors; regulates lipid & inflammatory genes	Represses PPARγ → ↓ATGL → ↓lipolysis, ↑inflammation	Promotes endothelial dysfunction & atherosclerosis; linked to fatty liver & metabolic disorders	[58, 60, 61, 153]
AT102202 (LncHMGCR)	Inhibits cholesterol synthesis	Negatively regulates HMGCR mRNA expression	Potential therapeutic target for cholesterol suppression; effect mimics statins in hepatocytes	[7, 62]
MeXis	Enhances macrophage cholesterol efflux	LXR-induced; scaffolds DDX17 at ABCA1 promoter	Promotes HDL formation; protects against atherosclerosis; potential FH target	[71, 79, 84, 127, 152]
CHROME	Enhances cholesterol efflux and HDL formatio	LXR-induced; sponges miR-27b/33/128 → ↑ABCA1/ABCG1	Upregulated in CAD; promotes HDL biogenesis; biomarker/target in dyslipidemia	[27, 86, 155–157]
ANRIL (CDKN2B-AS1)	Promotes cholesterol efflux; regulates inflammation & cell cycle	Recruits DNMT1; ↓ADAM10 → ↑ABCA1; interacts with Polycomb complexes	9p21 CAD risk locus; reduces foam cells; loss linked to plaque formation & FH complications	[7, 89, 90, 92, 93, 95, 97]
Lnc-HC	Inhibits cholesterol disposal; promotes hepatic retention	Binds hnRNPA2B1 → ↓CYP7 A1 & ↓ABCA1; sponges miR-130b-3p → ↓PPARγ	Impairs clearance; knockdown ↑bile acids & HDL; target in dyslipidemia, but with systemic effects	[7, 85, 99–101]
RP5-833 A20.1 (NFIA-AS1)	Regulates cholesterol efflux & inflammation in macrophages	Sponges miR-382-5p → ↑NFIA → ↑cholesterol efflux	Induced by oxLDL; promotes HDL, lowers LDL/VLDL; potential anti-atherosclerotic target	[7, 84, 111, 112, 114]
LncRNA-DYNLRB2-2	Promotes cholesterol efflux from macrophages	↓TLR2 → ↓NF-κB → ↑ABCA1.	Reduces foam cell formation; potential target to enhance reverse cholesterol transport	[7, 111, 112, 115, 116]
H19	Promotes lipid accumulation & atherogenesis	Inhibits miR-130a → ↑PPARγ, SREBP-1c; activates MAPK/NF-κB.	Elevated in atherosclerosis & NAFLD; silencing reduces plaque burden; potential target in metabolic syndrome & FH	[123, 124, 131, 134–136]
GAS5	Represses cholesterol efflux; promotes foam cell formation	Recruits EZH2 to ABCA1 promoter → epigenetic silencing.	Upregulated in plaques; knockdown ↑ABCA1 & reduces atherosclerosis; potential FH plaque target	[137, 138, 140, 141]
MIAT	Promotes plaque progression & instability	Sponges miR-149-5p → ↑CD47; activates PI3 K/Akt → ↑cytokines.	Elevated in CAD & hypoxic plaques; silencing stabilizes lesions; potential FH marker in high-risk cases	[143, 145–147, 149, 151]

Note: *Arrows represent molecular relationships: → = "leads to" or "activates", ↑ = "increases" or "upregulates", ↓ = "decreases" or "downregulates"*

particularly in developing regions, restrict its widespread application. Clinical scoring systems, such as the DLCN and Simon Broome criteria, rely heavily on family history and physical findings [161], both of which may be unreliable due to incomplete medical records or variable phenotypic expression among affected individuals. Moreover, these criteria may lack sensitivity in pediatric populations, where lipid levels fluctuate due to developmental factors [159, 162–165], further complicating early diagnosis. The inability of existing diagnostic modalities to consistently identify FH across diverse populations underscores the pressing need for novel, non-invasive biomarkers that are both sensitive and specific. lncRNAs have emerged as promising candidates, given their roles in cholesterol metabolism, lipid homeostasis, and cardiovascular disease progression, potentially bridging the diagnostic gap in FH.

The potential of lncrnas as biomarkers and their integration into FH diagnostic algorithms

The integration of lncRNAs into FH diagnostics presents a novel approach to overcoming limitations associated with lipid profiling, genetic testing, and clinical scoring systems. Unlike traditional diagnostic tools that rely on static measurements of LDL-C or genetic mutations, lncRNAs offer a dynamic, molecularly precise method to assess cholesterol metabolism, disease progression, and treatment response. Their ability to reflect real-time metabolic changes makes them ideal candidates for integration into FH diagnostic algorithms, particularly in cases where existing methods fail to provide conclusive results.

One of the fundamental advantages of lncRNAs as diagnostic biomarkers is their tissue specificity. Unlike LDL-C measurements, which provide only a systemic assessment of lipid levels, lncRNAs exhibit tissue-restricted expression patterns [145, 166–171], enabling more accurate molecular profiling of lipid metabolism disorders. For example, LeXis, CHROME, and Lnc-HC, which have been detailed in the Molecular Mechanisms of lncRNAs section, are known to regulate hepatic cholesterol biosynthesis and efflux, making them potential liver-specific biomarkers for FH. In addition, lncRNAs such as ANRIL and H19, which modulate vascular inflammation and endothelial function, could serve as markers of FH-related cardiovascular risk, adding another layer of clinical utility beyond lipid profiling.

Another critical feature of lncRNAs is their stability in circulation. Many lncRNAs are protected within extracellular vesicles (exosomes) or bound to RNA-binding proteins, preventing degradation in plasma and serum [172–177]. This structural stability enhances their suitability for non-invasive liquid biopsy applications, unlike messenger RNAs, which are prone to rapid degradation [178]. CHROME, for instance, is actively secreted in exosomes and regulates cholesterol efflux through miRNA interactions, highlighting its potential as a circulating biomarker for lipid dysregulation in FH patients [27].

In addition to their stability and tissue specificity, lncRNAs provide functional insights into FH pathogenesis, making them superior to genetic testing in certain contexts. While genetic screening identifies mutations in LDLR, APOB, or PCSK9, it does not account for epigenetic regulation or environmental influences on disease progression [5, 149, 179–182]. In contrast, lncRNA expression is dynamically regulated by cholesterol levels, inflammatory cytokines, and oxidative stress, making them more responsive indicators of FH severity and treatment outcomes [30, 148, 183–187]. For instance, Lnc-HC negatively regulates ABCA1 and ABCG1, impairing cholesterol efflux, and its upregulation has been associated with higher LDL-C levels in FH patients [63, 64, 69, 74, 188–190]. Similarly, ANRIL expression correlates with increased cardiovascular risk, reinforcing its potential use in FH risk stratification [82, 83].

Given these advantages, the incorporation of lncRNAs into FH diagnostic frameworks could enhance disease classification and patient stratification. This is particularly relevant for distinguishing monogenic FH from polygenic hypercholesterolemia, a long-standing challenge in clinical practice [5, 181, 191]. As monogenic FH arises from a single pathogenic mutation, whereas polygenic hypercholesterolemia results from multiple small-effect genetic variants, lncRNA-based molecular profiling could provide additional discriminatory power, guiding personalized treatment strategies.

Moreover, lncRNAs could improve FH diagnosis in pediatric populations, where current lipid-based screening lacks sensitivity [159, 163, 165, 192, 193]. Given that LDL-C levels fluctuate during childhood [163, 192], standard clinical criteria often fail to identify at-risk children early enough for effective intervention. Circulating lncRNAs with stable expression patterns could serve as early biomarkers for pediatric FH, allowing for earlier risk assessment and preventative lipid-lowering therapy initiation.

Ultimately, integrating lncRNA biomarkers into existing FH diagnostic algorithms could address critical gaps in current screening methods. Their ability to complement genetic testing, improve phenotype prediction, distinguish between FH subtypes, and facilitate early pediatric diagnosis positions them as next-generation tools for precision medicine in lipid disorders. However, further validation in large, multicenter clinical studies is necessary before lncRNAs can be formally incorporated

into routine FH screening and risk stratification protocols.

Challenges in translating lncRNAs to clinical use

Despite the promising role of lncRNAs as biomarkers in FH diagnostics, significant challenges remain before their routine clinical implementation can be realized. One of the primary obstacles is the lack of standardized detection methods. Unlike conventional lipid profiling or genetic testing, which have well-established protocols, lncRNA detection is subject to variations in RNA extraction, quantification techniques, and normalization approaches [194–196]. These inconsistencies can lead to batch effects and inter-laboratory variability, complicating the reproducibility of findings across different studies. To address this, standardized protocols for RNA isolation, sequencing, and data normalization must be developed to ensure reliability and clinical applicability.

Another key challenge is the validation of lncRNA biomarkers in large, diverse patient cohorts. While several studies have identified circulating lncRNAs as potential FH biomarkers, most have been conducted in small, single-center cohorts, limiting their generalizability [197–200]. Large-scale, multicenter validation studies are required to assess interindividual variability, ethnicity-based expression differences, and disease-stage specificity. Additionally, many lncRNAs exhibit tissue-specific expression patterns, raising concerns about whether circulating levels accurately reflect disease severity or risk in a given patient population.

The biological variability of lncRNA expression further complicates their clinical application. LncRNAs are highly responsive to metabolic and environmental factors, including dietary intake, medication use, and inflammatory status, which can introduce variability in expression levels [201, 202]. This contrasts with genetic testing, where pathogenic variants remain static throughout life. Consequently, longitudinal studies are needed to determine whether lncRNA fluctuations over time provide meaningful insights into disease progression and treatment response, or whether they introduce confounding factors that limit diagnostic accuracy.

A significant barrier to clinical translation is the lack of regulatory frameworks for lncRNA-based diagnostics. Unlike well-characterized lipid biomarkers or genetic mutations, lncRNAs represent a new category of molecular markers that require distinct validation criteria before they can be incorporated into clinical guidelines and regulatory approval pathways. The process of obtaining approval from organizations such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) involves extensive validation in prospective clinical trials, which has yet to be systematically undertaken for lncRNAs in FH diagnostics. Moreover, the cost-effectiveness of implementing lncRNA-based screening at a population level remains uncertain, particularly when compared to existing low-cost lipid profiling methods.

Despite these challenges, emerging technological advancements in RNA sequencing, liquid biopsy platforms, and machine learning algorithms offer potential solutions. The integration of high-throughput RNA sequencing with artificial intelligence-driven biomarker discovery could enhance the robustness of lncRNA-based diagnostics by identifying multi-lncRNA signatures rather than relying on single-marker approaches. Additionally, the development of cost-effective, point-of-care RNA detection assays may facilitate the adoption of lncRNA biomarkers into routine clinical practice.

In summary, while lncRNAs present a groundbreaking opportunity to revolutionize FH diagnostics, their successful clinical translation requires overcoming methodological, biological, and regulatory challenges. Future research should focus on standardizing detection protocols, conducting large-scale validation studies, addressing expression variability, and establishing clear regulatory pathways. With continued advancements, lncRNA-based diagnostics could become a cornerstone of precision medicine approaches for FH detection and risk assessment.

lncRNAs as therapeutic targets in FH

The therapeutic landscape for FH has traditionally relied on statins, PCSK9 inhibitors, and lipid-lowering agents, yet these treatments are not universally effective, particularly in patients with homozygous FH (HoFH) or those who exhibit statin intolerance [38, 203–205]. Given the central role of lncRNAs in cholesterol metabolism, recent research has explored their potential as therapeutic targets, aiming to modulate lipid homeostasis, reverse dysregulated pathways, and enable precision medicine approaches in FH treatment. Advances in RNA-based therapeutics, AI-driven biomarker discovery, and single-cell transcriptomics are now shaping the development of lncRNA-targeted interventions, offering a novel paradigm for personalized FH treatment.

AI-driven biomarker discovery for targeting lncRNAs in FH therapy

Machine learning (ML) and artificial intelligence (AI) have revolutionized biomarker discovery, paving the way for lncRNA-targeted therapies in FH. AI-based models have demonstrated the ability to identify key molecular regulators of cholesterol metabolism by integrating multi-omics datasets, single-cell transcriptomics, and electronic health records (EHRs) [206–216]. For instance,

generative AI algorithms have been used to optimize biomarker selection, increasing the predictive power of lncRNA signatures linked to lipid homeostasis [217–221]. This approach could allow for the personalized selection of lncRNA-based therapeutic targets tailored to individual genetic and metabolic profiles.

Additionally, network medicine approaches, such as weighted gene co-expression network analysis (WGCNA), have identified lncRNA-miRNA interactions as well as several hub genes and potential biomarkers for atherosclerosis, such as EGR1, PTGS2, and TNF, which are linked to inflammatory pathways and could serve as targets for early diagnosis and intervention [222]. Gene network analysis has also pinpointed influential genes and miRNAs, such as AGT, LPL, and miR-26 [223], which play roles in the pathogenesis of atherosclerosis and could be targeted to mitigate disease progression. Such models could be applied to FH therapy to determine which lncRNAs, as well as these other key genetic elements, should be silenced (e.g., Lnc-HC, which inhibits cholesterol efflux) versus those that should be activated (e.g., LeXis, which suppresses hepatic cholesterol biosynthesis), thereby enhancing the precision of personalized lncRNA-targeted interventions.

Despite its promise, the clinical implementation of AI in lncRNA biomarker discovery faces several challenges. A major limitation is the availability of large, high-quality, and well-annotated datasets, which are essential for training robust and generalizable models. Inconsistencies in data collection methods, lack of standardization across studies, and underrepresentation of diverse populations can introduce bias and reduce model validity. Additionally, integrating heterogeneous multi-omics datasets remains a computational challenge, particularly when combining transcriptomic, proteomic, and clinical data [224]. Another concern is the'black box'nature of some deep learning algorithms, which can limit interpretability and clinician trust [225]. Regulatory uncertainties further complicate the deployment of AI-driven tools in clinical settings, as validation standards and approval pathways are still evolving. Finally, few AI-predicted lncRNA biomarkers have been prospectively validated in multicenter trials, which limits their current translational readiness. Addressing these limitations will be critical to realizing the full potential of AI in precision medicine for FH.

Single-cell transcriptomics and the identification of lncRNA therapeutic targets

Recent advancements in single-cell RNA sequencing have provided unprecedented resolution, enabling the identification of cell-type-specific lncRNA expression patterns relevant to FH pathology [226–229]. Unlike traditional transcriptomic analyses that rely on bulk RNA sequencing, which can mask cellular heterogeneity, advanced single-cell RNA sequencing (scRNA-seq) techniques have been successfully applied to pinpoint cholesterol-regulating lncRNAs at the individual cell level [229–233]. This is particularly important for understanding the roles of lncRNAs in hepatic and arterial macrophage populations, where they modulate cholesterol efflux, foam cell formation, and lipid accumulation. For instance, the application of scRNA-seq in FH models could elucidate the precise functions of lncRNAs such as CHROME in HDL metabolism and Lnc-HC in suppressing ABCA1-mediated cholesterol efflux, leading to the development of targeted RNA-based therapies.

RNA-based therapeutics for lncRNA Modulation in FH

RNA-based therapeutics represent a transformative approach to FH treatment, allowing for the precise modulation of lncRNA expression through antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), and CRISPR-based gene editing technologies.

Antisense oligonucleotides (ASOs) for lncRNA silencing

ASOs have been widely investigated for their ability to suppress disease-associated lncRNAs. For instance, Mipomersen, an ASO targeting Apolipoprotein B mRNA, has demonstrated a significant reduction in LDL-C levels in clinical trials [234]. A systematic review and meta-analysis reported a mean LDL-C reduction of approximately 25% in patients with homozygous FH [235]. This success has paved the way for ASO-based lncRNA-targeting therapies. Specifically, ASOs targeting Lnc-HC, which represses cholesterol efflux by inhibiting ABCA1 and ABCG1, could be explored to restore lipid clearance mechanisms in FH patients.

siRNA therapies for lncRNA inhibition

Small interfering RNAs (siRNAs) have demonstrated high specificity in targeting lncRNA transcripts, leading to their degradation via RNA-induced silencing complex (RISC) mechanisms [12, 236, 237]. In the context of FH, siRNAs targeting Lnc-HC or ANRIL could be used to suppress their pro-atherogenic effects, thereby reducing LDL retention and vascular inflammation. Recent studies have shown that siRNA-based PCSK9 inhibitors significantly lower LDL-C levels by increasing LDL receptor activity [238–241]. This suggests that similar siRNA-based approaches could be applied to lncRNAs involved in cholesterol metabolism.

CRISPR-based gene editing for lncRNA modulation

CRISPR-based gene editing has emerged as a powerful tool for precise genetic modifications, including the activation or suppression of lncRNAs involved in lipid

metabolism [242–244]. In FH, AAV-mediated CRISPR-Cas9 targeting of LDLR mutations has successfully restored LDL receptor function in preclinical models [245–247]. A similar approach could be employed to permanently suppress pathogenic lncRNAs such as Lnc-HC while activating protective lncRNAs such as LeXis, which enhances cholesterol clearance.

Integration into precision medicine frameworks

The combination of AI-driven biomarker discovery, RNA-based therapeutics, and single-cell transcriptomics provides a foundation for precision medicine in FH [248, 249]. Machine learning models have demonstrated the ability to forecast FH patient responsiveness to statin therapy, and a comparable approach could be employed to stratify patients based on their lncRNA expression profiles [249–251]. Additionally, AI-driven predictive analytics have successfully identified cardiovascular disease risk through RNA-sequencing and personalized dietary interventions [218, 248, 252–255]. Applying these technologies to lncRNA-based FH therapy could ensure that RNA-targeted treatments are tailored to individual metabolic profiles, thereby enhancing efficacy and reducing adverse effects.

Challenges and future directions in lncRNA-based FH therapies

Despite the promising potential of lncRNA-targeted therapies in FH, several challenges must be addressed before their widespread clinical adoption. One of the foremost barriers is efficient in vivo delivery, as ensuring that ASOs, siRNAs, and CRISPR-based gene editing tools reach their target tissues with high specificity remains a technical hurdle. The rapid degradation of RNA molecules in circulation limits their stability, requiring the development of nanoparticle-based delivery systems or lipid-based carriers to enhance biodistribution and cellular uptake. Additionally, off-target effects remain a critical concern, as RNA-based therapeutics can unintentionally silence genes beyond their intended targets. The application of AI-driven optimization techniques to refine lncRNA targeting specificity may provide a solution, yet these methods require further validation in preclinical and clinical settings.

Beyond technical challenges, the regulatory landscape for RNA-based therapeutics is still evolving. Unlike small-molecule drugs and monoclonal antibodies, lncRNA-targeting therapies require new frameworks for approval by regulatory agencies such as the FDA and EMA. The necessity of long-term clinical trials to assess efficacy, durability, and safety will significantly impact the timeline for translation into clinical practice. Furthermore, the high cost of RNA-based drug development and gene-editing technologies raises concerns about affordability and accessibility, particularly in low-resource healthcare settings.

The ethical implications of gene-editing therapies targeting lncRNAs must also be considered, particularly given the potential for heritable modifications when CRISPR-based interventions are applied. Ensuring that RNA-based therapeutics align with ethical and safety guidelines is essential before they can be implemented as standard treatments.

Despite these obstacles, lncRNA-based therapies remain at the forefront of precision medicine innovations. Continued advancements in AI-driven biomarker discovery, high-throughput transcriptomics, and gene therapy delivery systems hold the potential to bridge the gap between experimental research and clinical applications. Future research efforts should focus on optimizing therapeutic efficacy, minimizing off-target risks, and establishing robust validation frameworks to bring lncRNA-based interventions closer to real-world clinical integration.

Conclusion

LnRNAs have emerged as crucial regulators of lipid metabolism, offering promise as biomarkers and therapeutic targets in FH. AI-driven analytics and single-cell transcriptomics enhance the potential for precise lncRNA-based diagnostics and treatment. While challenges such as regulatory approval and clinical translation remain, integrating these technologies could revolutionize FH management. Future efforts should prioritize large-scale validation studies and AI-enhanced biomarker discovery to advance lncRNA applications in precision medicine.

Beyond their role in diagnostics, lncRNAs offer potential for targeted RNA-based therapeutics, such as antisense oligonucleotides, siRNAs, and CRISPR-mediated gene modulation. Research into lncRNAs like LeXis, CHROME, and Lnc-HC has shown promising preclinical results in regulating cholesterol homeostasis, LDL uptake, and atherosclerosis progression. Further translational research is necessary to refine delivery methods, enhance therapeutic efficacy, and minimize off-target effects. Integrating lncRNA-based interventions into clinical practice will require collaboration between bioinformaticians, molecular biologists, and clinicians to develop robust protocols and regulatory frameworks.

Moreover, the role of lncRNAs in inflammatory responses and vascular remodeling should be further investigated, as inflammation is a major contributor to FH-related cardiovascular risk. The application of AI-driven multi-omics approaches could help identify additional lncRNA candidates for intervention, leading to

more personalized, predictive, and preventative therapeutic strategies.

By addressing the limitations of current diagnostic approaches and therapeutic interventions, lncRNA-based strategies could significantly impact the early detection and treatment of FH, ultimately reducing the burden of cardiovascular disease and improving patient outcomes. The integration of AI, single-cell transcriptomics, and RNA-based therapies represents a transformative step toward precision medicine-driven cardiovascular care.

Abbreviations

AI	Artificial Intelligence
ABCA1	ATP-binding cassette transporter A1
ABCG1	ATP-binding cassette transporter G1
APOB	Apolipoprotein B
ANRIL	Antisense Noncoding RNA in the INK4 Locus
ASO	Antisense Oligonucleotide
CVD	Cardiovascular Disease
CHROME	Cholesterol Homeostasis Regulator of miRNA Expression
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
ceRNA	Competing Endogenous RNA
DLCN	Dutch Lipid Clinic Network
DLCNS	Dutch Lipid Clinic Network Score
EGR1	Early Growth Response 1
EMA	European Medicines Agency
EHR	Electronic Health Record
FH	Familial Hypercholesterolemia
FDA	Food and Drug Administration
GAS5	Growth Arrest-Specific 5
GPR119	G Protein-Coupled Receptor 119
HMGCR	3-Hydroxy-3-Methylglutaryl-CoA Reductase
HMGCS1	3-Hydroxy-3-Methylglutaryl-CoA Synthase 1
HDL	High-Density Lipoprotein
HoFH	Homozygous Familial Hypercholesterolemia
H19	Long Noncoding RNA H19
LDL	Low-Density Lipoprotein
LDLR	Low-Density Lipoprotein Receptor
LDL-C	Low-Density Lipoprotein Cholesterol
lncARSR	Long Noncoding RNA Activated in Renal Cell Carcinoma with Sunitinib Resistance
lncHMGCR	Long Noncoding RNA Regulating HMGCR Stability
Lnc-HC	Long Noncoding RNA HC
lncRNA	Long Noncoding RNA
LeXis	Liver-Expressed Long Noncoding RNA Regulating Cholesterol Homeostasis
LXR	Liver X Receptor
MeXis	Macrophage-Expressed Long Noncoding RNA Stimulating ABCA1
MIAT	Myocardial Infarction-Associated Transcript
ML	Machine Learning
miRNA	MicroRNA
NF1 A	Nuclear Factor 1 A
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
ox-LDL	Oxidized Low-Density Lipoprotein
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PPAR	Peroxisome Proliferator-Activated Receptor
RALY	RNA-Binding Protein Raly
RNA	Ribonucleic Acid
RP5-833 A20.1	Long Noncoding RNA RP5-833A20.1
RISC	RNA-Induced Silencing Complex
SRA	Steroid Receptor RNA Activator
scRNA-seq	Single-Cell RNA Sequencing
siRNA	Small Interfering RNA
SREBP	Sterol Regulatory Element-Binding Protein
SREBP2	Sterol Regulatory Element-Binding Protein 2
TRL	Technology Readiness Level
TNF	Tumor Necrosis Factor
VSMC	Vascular Smooth Muscle Cell
WGCNA	Weighted Gene Co-Expression Network Analysis

Authors' Contributions

S.N., A.A., and M.A. wrote the main manuscript. H.D. and T.S. assisted in the writing and reviewed the manuscript. Dr. J.H. and H.J. conceptualized the topic and conducted an in-depth review of the article. M.M. contributed important sections to the discussion and reviewed the manuscript. D.A. reviewed the article in depth, checked the references, handled editing and formatting, and submitted the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable, as this is a review article and does not involve human participants, animals, or clinical trial data.

Consent for publication

Not applicable, as no individual patient data is included in this manuscript.

Competing interests

The authors declare no competing interests.

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