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## ADAMTS7: A Novel Therapeutic Target in Atherosclerosis

Allen Chung<sup>1</sup>, Muredach P. Reilly<sup>1,2</sup>, Robert C. Bauer<sup>1</sup>

<sup>1</sup>Cardiometabolic Genomics Program, Division of Cardiology, Department of Medicine, Columbia University, New York, NY, USA

<sup>2</sup>Irving Institute for Clinical and Translational Research, Columbia University, New York, NY, USA

### Abstract

**Purpose of Review:** Genome-wide association studies have repeatedly linked the metalloproteinase ADAMTS7 to coronary artery disease. Here we aim to highlight recent findings surrounding the human genetics of *ADAMTS7*, novel mouse models that investigate ADAMTS7 function, and potential substrates of ADAMTS7 cleavage.

**Recent Findings:** Recent genome-wide association studies in coronary artery disease have replicated the GWAS signal for *ADAMTS7* and shown that the signal holds true even across different ethnic groups. However, the direction of effect in humans remains unclear. A recent novel mouse model revealed that the proatherogenicity of ADAMTS7 is derived from its catalytic functions, while at the translational level, vaccinating mice against ADAMTS7 reduced atherosclerosis. Finally, *in vitro* proteomics approaches have identified extracellular matrix proteins as candidate substrates that may be causal for the proatherogenicity of ADAMTS7.

**Summary:** ADAMTS7 represents an enticing target for therapeutic intervention. The recent studies highlighted here have replicated prior findings, confirming the genetic link between ADAMTS7 and atherosclerosis, while providing further evidence in mice that ADAMTS7 is a targetable proatherogenic enzyme.

### Keywords

ADAMTS7; Extracellular Matrix; Smooth Muscle Cells; Atherosclerosis; Coronary Artery Disease; Genome-Wide Association Studies

### Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in The United States [1]. Despite the immense success of lipid-lowering therapies in treating coronary artery disease (CAD), there remains a great deal of residual risk, underscoring the need for identifying novel lipid-independent therapeutics. Genome-wide association studies (GWAS)

Correspondence to: Robert C. Bauer, Ph.D., 630 W. 168th Street, PS10-401, New York, New York 10032, USA. rcb36@columbia.edu.

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Human and Animal Rights

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

are an unbiased approach for identifying regions of the genome that are involved in disease pathogenesis, and CAD GWAS have identified hundreds of genomic loci that significantly associate with CAD in humans [2–5]. To date, 279 genomic loci have been associated with CAD by GWAS [2]. As expected, CAD GWAS have identified genes involved in lipid metabolism, such as *APOB* and *LDLR*, known regulators of low-density lipoprotein (LDL) cholesterol, a critical risk factor for CAD [6, 7]. However, CAD GWAS have highlighted other biological pathways that contribute to CAD risk independent of lipids. For example, inflammation-related genes such as *IL5*, *IL6R*, and *CXCL12* have been significantly associated with CAD via GWAS [6]. Inflammation is a critical component of CAD progression [8], and the therapeutic targeting of the pro-inflammatory cytokine interleukin-1 $\beta$  reduces adverse cardiovascular events [9], suggesting that CAD GWAS are identifying biological pathways that are viable therapeutic targets. Vascular remodeling has also been identified by CAD GWAS as a pathway contributing to disease progression [2, 6], and given the above examples, vascular remodeling warrants consideration as a biological pathway for therapeutic intervention.

Single nucleotide polymorphisms (SNPs) in the chromosome 15q25.1 genomic locus have been repeatedly identified as significantly associated with CAD, thus making this a proven, consistent, reproducible CAD GWAS signal [2, 3, 6, 10–13]. The signal centers around the gene *ADAMTS7* (*ADAMTS7*). *ADAMTS7* is a member of the ADAMTS family (19 members) of metzincin metalloproteinases, which are secreted proteins that degrade extracellular matrix (ECM) [14] [15]. The ADAMTS proteins have highly homologous metalloprotease domains but vary significantly in their C-terminal structure which confers substrate specificity [16]. These proteins have been previously linked to human disease. *ADAMTS13* is the metalloproteinase that cleaves Von Willebrand factor (VWF) [17], and inactivating mutations in *ADAMTS13*, or its inhibition by auto antibodies, causes the disorder thrombotic thrombocytopenic purpura (TTP), which can cause fatal cardiac events in affected individuals [18, 19]. The first family member described, *ADAMTS1*, is reported to have both pro and anti-tumorigenic properties. *ADAMTS1* can alter vascularization, inhibit angiogenesis, and increase cancer cell proliferation [20], highlighting the diverse roles of ADAMTS proteinases in human disease.

Multiple ADAMTS proteinases have described roles in atherosclerosis. One of the initiating steps of atherosclerosis is the retention of LDL within the intima of the vasculature [21], a process mediated by proteoglycans that bind LDL [22]. The catalytic cleavage of proteoglycans has been well described for *ADAMTS1*, 4, 5, 8, 9, 15, and 20 [16]; however, this cleavage activity has yielded inconsistent directions of influence on atherosclerosis. Mechanistic studies have shown that *ADAMTS5* can cleave the proteoglycans biglycan and versican, both of which have been shown to bind to LDL [23, 24]. Whole-body knockout of *ADAMTS5* causes the accumulation of proteoglycans and increased retention of LDL particles in the aorta [25, 26]. Indeed, *ADAMTS5* levels are reduced in atherosclerotic lesions in both mice and humans [25, 27], however no *in vivo* atherosclerosis studies have been performed to confirm a role for *ADAMTS5* in atherogenesis. In contrast, genetic ablation of *Adamts4* on the *ApoE*<sup>-/-</sup> background reduced atherosclerosis [28]. While both *ADAMTS4* and *ADAMTS5* can cleave proteoglycans, the loss of *ADAMTS5* is presumed to

increase atherosclerosis, whereas the loss of ADAMTS4 reduces atherosclerosis, suggesting higher level substrate specificity not yet completely elucidated. *ADAMTS3* is a GWAS hit for both CAD and LDL-C, suggesting it contributes to atherosclerosis via dyslipidemia [2, 10, 29, 30], but there are no studies investigating *ADAMTS3* and atherosclerosis. The differing directionality of atherosclerotic disease for ADAMTS4 and ADAMTS5 and the potential role of *ADAMTS3* in dyslipidemia reflect the continual need to investigate these proteinases in atherosclerosis.

Our group first identified an association between SNPs near *ADAMTS7* and CAD [10], implicating it in CAD pathophysiology. The *ADAMTS7* signal has since been replicated multiple times [2–4, 6, 11–13]. Prior to its identification in CAD GWAS, ADAMTS7 was predominantly studied in the context of osteoarthritis [14], owing to the fact that ADAMTS7 can degrade cartilage, a hallmark of the disease. One of the first studies hinting at a role for *ADAMTS7* in atherosclerosis was the *in vitro* overexpression and knockdown of *Adamts7* in rat vascular smooth muscle cells (SMCs) [31]. This study found that ADAMTS7 increases SMC migration, and *ADAMTS7* expression could be induced *in vitro* by cytokines such as TNF $\alpha$  and PDGF-BB, and *in vivo* via carotid wire injury. After its identification as a CAD locus, follow-up studies have found that *Adamts7* whole-body knockout mice had a net reduction in atherosclerosis, implicating ADAMTS7 as a pro-atherogenic metalloproteinase [32]. Importantly, there is no association between the *ADAMTS7* genomic locus and any lipid parameters [33, 34], and *Adamts7* knockout mice do not exhibit altered cholesterol levels, suggesting that its role in atherosclerosis is lipid-independent [32]. Therefore, targeting ADAMTS7 could be an effective strategy for reducing residual risk outside of lipid lowering.

### Causal SNPs at the *ADAMTS7* locus

The first CAD GWAS that implicated *ADAMTS7* was performed in patients of European ancestry who had at least 50% occlusion within at least one coronary artery [10]. The lead SNP identified in this study (rs1994016) lies in an intron of *ADAMTS7*. Given the location of this lead SNP, the locus was assigned to *ADAMTS7*. A subsequent CAD GWAS performed by the CARDIoGRAM consortium replicated the *ADAMTS7* GWAS signal, but instead identified a coding SNP (rs3825807) as the lead SNP [12]. This SNP results in a serine-to-proline substitution (S214P) within the prodomain of ADAMTS7, causing decreased secretion of ADAMTS7 in primary SMCs and presumably reduced function [12, 35]. The identification of a missense variant in ADAMTS7 that reduces ADAMTS7 function and also significantly associates with CAD via GWAS greatly increased the confidence that ADAMTS7 is the causal gene at this locus. This finding also provided directionality in humans, as the loss of function allele is associated with decreased CAD risk, implying that ADAMTS7 is proatherogenic in humans.

Subsequent CAD GWAS have continuously replicated the 15q25.1 GWAS signal [36], yet the location of the lead SNP has changed as the cohort sizes have grown larger. A recent CAD GWAS from the UK Biobank, the CARDIoGRAMplusC4D Consortium and Biobank Japan studying over 1.3 million individuals localized the lead SNP (rs7173743) at the 15q25.1 locus to a region upstream of the *ADAMTS7* gene rather than within the gene (Fig.

1). Non-coding GWAS SNPs are frequently linked to alterations in the expression of nearby genes via eQTL analysis, wherein a specific allele of a SNP is associated with increased or decreased gene expression due to altered enhancer activity, a common functional mechanism of GWAS SNPs. The non-coding location of rs7173743 implies that a similar mechanism is at play in the *ADAMTS7* locus. However, in large consortium eQTL data such as the GTEx consortium, the non-coding alleles that associate with increased risk also associate with decreased *ADAMTS7* expression in the vasculature [37], implying that *ADAMTS7* is antiatherogenic, in stark opposition to the directionality implied by the coding S214P variant.

The lack of clear directionality in humans is a major shortcoming of the genetics surrounding *ADAMTS7*. The lead non-coding SNP also has weak linkage to the S214P coding variant, making it difficult to discern which variant, if not both, is driving the genetic signal at this locus. Definitive exome sequencing to identify other loss of function *ADAMTS7* variants in humans to support causality and directionality are hampered due to the presence of five highly homologous *ADAMTS7* pseudogenes, contaminating variant calling in short-read sequencing studies [38]. Furthermore, as the vast majority of the 15q25.1 GWAS SNPs are non-coding, there remains a pressing need to conduct further functional genomic investigations into non-coding regions near *ADAMTS7* to validate any functional effects. Any attempts at therapeutic intervention will necessitate further human genetic data or functional genomic investigations that can confirm a disease directionality for *ADAMTS7* in humans.

## Candidate genes in the *ADAMTS7* locus

As stated above, recent GWAS have localized the lead SNPs in the 15q25.1 locus to the region upstream of the *ADAMTS7* transcriptional start site. The gene directly upstream of *ADAMTS7* is *MORF4L1*, which codes for the histone acetyltransferase MRG15. The location of the lead SNP (rs7173743) is within the intronic region of one transcript variant of *MORF4L1*, thus the GWAS signal is sometimes described as *MORF4L1-ADAMTS7*. Early studies of *MORF4L1* have shown that homozygous knockout of *Morf4l1* is embryonically lethal due to reduced cellular proliferation [39]. Subsequent studies of *Morf4l1* in the liver revealed its essentiality for the rhythmic regulation of lipid genes [40]. Knockout of MRG15 by CRISPR-Cas9 can reduce blood triglyceride and cholesterol, liver steatosis, and liver expression of essential lipid-related genes such as *Srebf1* and *Fasn* [40]. These in vivo data linking *MORF4L1* to lipid genes raises the possibility that *MORF4L1* contributes to the GWAS signal at 15q25.1, however this is unlikely as this locus has not been associated with plasma lipids in large-scale GWAS [34]. To date there are no investigations of *MORF4L1* in rodent models of atherosclerosis.

Immediately downstream of *ADAMTS7* lies a cluster of nicotine receptors, *CHRNA3-A5-B4*, and data from recent GWAS show that the 15q25.1 signal overlaps these genes. Smoking is a major confounding lifestyle risk factor for CAD, and nicotine receptors are likely candidates to associate with CAD risk. A study examining genetics and smoking across 60,919 CAD patients and 80,243 controls across 29 studies found that smoker status blunts the cardioprotective effect of the 15q25.1 locus [41]. The protective allele of the

lead variant in that study (rs7178051) confers a 12% reduction in CAD. With smoking, this protection drops to 5%, equating to a 60% reduction in protection [41]. The protective allele associates with reduced *ADAMTS7* expression in human aortic endothelial cells and lymphoblastoid cell lines. Furthermore, cigarette smoke extract induced the expression of *ADAMTS7* in human coronary artery SMCs, providing further evidence of the association between smoking and *ADAMTS7* and a possible mechanism for the increased CAD associated with smoking [41]. These observations are consistent with mouse data indicating that *ADAMTS7* may be pro-atherogenic. Given the data, it is possible that the cluster of nicotine receptors represent a separate GWAS signal for CAD in this locus or are mechanistically linked to the *ADAMTS7* signal.

As one of the most reproducible GWAS signals in CAD, there is a possibility that the human genetic signal at 15q25.1 implicates *MORF4L1*, *ADAMTS7*, and the nicotine receptors. One noteworthy finding from the most recent GWAS studies is that this GWAS signal replicates in non-Europeans, including those of East Asian, Japanese [42], and Hispanic descent [3]. Thus, this locus is likely relevant to cardiovascular health across all ethnicities, underscoring the importance of further studies of the molecular mechanisms underlying this genetic association.

## Novel mouse models of ADAMTS7

Human genetics provided an impetus to investigate *ADAMTS7*; subsequent studies of *ADAMTS7* have relied heavily on mouse models to further explore both the direction of effect and mechanisms underlying the genetic association [43]. The first study involving *ADAMTS7* in the vasculature showed the upregulation of *Adamts7* in response to balloon injury in rat arteries [31]. Subsequently, our group showed that whole-body knockout of *Adamts7* reduced atherosclerosis [32]. These early rodent studies provided a directionality to the GWAS signal, indicating that *ADAMTS7* promotes neointima formation and atherosclerosis.

More recently, two other novel rodent approaches have been reported. The first is a genetic mouse model in which the catalytic activity of *ADAMTS7* was rendered inactive [44]. The second model inactivates *ADAMTS7 in vivo* through a vaccination-mediated antibody response [45]. In the first model, the investigators generated a genetically modified mouse with whole-body catalytic inactive *ADAMTS7* by substituting a glutamine for a highly conserved glutamic acid at position 373 (E373Q) within the catalytic site, rendering the protein inactive [44]. Hyperlipidemic mice harboring this inactivated form of *ADAMTS7* displayed a reduction in atherosclerosis, confirming that the pro-atherogenicity of *ADAMTS7* is conferred by its catalytic function. When compared to the previously described findings in mice with whole-body knockout of *Adamts7*, the catalytic inactive *ADAMTS7* replicated key findings including the reduction of atherosclerosis, blunted SMC migration, and reduced thrombospondin 1 (TSP1) cleavage [32, 44, 46]. These studies highlight the potential of targeting the catalytic activity of *ADAMTS7* in the therapeutic treatment of atherosclerosis.

In the second novel model to investigate ADAMTS7, a vaccine against the ADAMTS7 catalytic domain was used to immunologically inactivate ADAMTS7 [45]. This peptide vaccine was able to reduce restenosis in mice in response to wire injury, whereas for swine, vaccination against ADAMTS7 reduced stent associated intimal hyperplasia. Additionally, the vaccination against ADAMTS7 reduced atherosclerosis in mice by both en-face and aortic root measurements in both the *Ldlr*<sup>-/-</sup> and *ApoE*<sup>-/-</sup> atherosclerotic background. A critical aspect of this study involved the timing of vaccination and initiation of high fat diet feeding. For the cohort on the *ApoE*<sup>-/-</sup> background, the mice were vaccinated before high fat diet induction and subsequently given boosters throughout high fat diet feeding. Of the *Ldlr*<sup>-/-</sup> cohort, the mice were fed four weeks of high fat diet prior to any vaccination against ADAMTS7. Even with the onset of atherosclerosis, this cohort on the *Ldlr*<sup>-/-</sup> background exhibited a significant reduction in plaque burden. As prior literature indicates that *ADAMTS7* is induced in early atherogenesis [32], it would be interesting to see if vaccination against ADAMTS7 after longer durations of western diet priming would affect atherosclerosis. This study overall is an important first proof of principle that ADAMTS7 can be therapeutically targeted to reduce atherosclerosis[45].

It is becoming increasingly clear that the composition of a lesion plays a role in addition to lesion size. Although lesions may be the same size, lesions that are fibrous and high in SMCs are more stable and less likely to cause fatal coronary events [47]. Examination of the aortic root lesions of these mouse models has yielded no changes in lesion composition [32, 44, 45]. Regarding macrophage area, both the catalytic inactive and vaccine models reported no differences in macrophage content [44, 45]. Additionally, the original whole-body knockout model reported no change in macrophage content in plaques of the brachiocephalic artery, although macrophage content was not reported for the aortic root [32]. All three models showed no change in collagen area within the aortic root as quantified through Masson's trichrome. Although these two elements of lesion composition remain unchanged, further characterization is warranted for other aspects of lesion composition. There is still a lack of data reporting the necrotic core content, fibrous cap thickness, and SMC content of these lesions. In addition, single cell sequencing approaches (scRNA-seq) could add invaluable insight as to which cell types express *ADAMTS7* during disease progression. In summary, *Adams7* knockout reduces atherosclerosis without altering lesion morphology, highlighting that ADAMTS7 may accelerate the formation of atheroma rather than affect lesion progression.

## Cleavage substrates of ADAMTS7

The pro-atherogenicity of ADAMTS7 is derived from its metalloproteinase enzymatic function [44]. Therefore, the elucidation of specific substrates can not only add mechanistic insights on ADAMTS7 function in atherosclerosis and the vascular contribution to atherosclerotic plaque formation, but also may reveal even more novel therapeutic avenues. Cartilage oligomeric matrix protein (COMP) was the first ADAMTS7 substrate identified using a yeast two hybrid screen in the context of osteoarthritis [14]. Subsequent proteomics work showed that ADAMTS7 overexpression in SMCs causes a decrease in conditioned media TSP1 levels. ADAMTS7 was shown to cleave TSP1 in an *in vitro* cleavage assay, suggesting that TSP1 is another substrate for ADAMTS7 cleavage [46]. Since then, a



proteomics approach known as Terminal amine isotopic labeling of substrates (TAILS) has been used on three different cell types (fibroblast, endothelial cells, and SMCs) to elucidate cleavage targets of ADAMTS7 [48, 49]. TAILS is a technique that differentially labels N-termini and is used to specifically quantify cleavage products [50]. Through using this technique, TAILS has generated a rich list of candidate substrates of ADAMTS7.

The first report of TAILS and ADAMTS7 involved co-cultures of human fibroblasts and HEK293Ts transfected with ADAMTS7 cDNA [48]. This experiment identified differential cleavage in multiple components of the ECM and went the additional step of validating LTBP4 as a true cleavage target of ADAMTS7 using recombinant truncated LTBP4 with purified recombinant ADAMTS7 [48]. LTBP4 is a member of the ECM that can sequester the ligand TGFB1 and regulate its function [51]. In the context of atherosclerosis, multiple proteins in TGFB1 signaling are CAD GWAS hits, including BMP1, SMAD3, and TGFB1 itself [6]. TGFB1 has known roles in fibrosis and inflammation, two processes important for plaque formation [52]. Within the ECM, Tissue Inhibitor of Metalloproteinases (TIMPs) are endogenous inhibitors of metalloproteinases, including MMPs, ADAMs, and ADAMTSs. After validating that LTBP4 is indeed a target of ADAMTS7, the authors tested four members of the TIMP family to see if they could inhibit ADAMTS7. Of these four TIMPs, TIMP2, 3, and 4 all showed some degree of ADAMTS7 inhibition. TIMP1 had almost no inhibitory activity, while TIMP4 had the highest degree of inhibition, with 60nM of TIMP4 generating a greater than 75% inhibition of 18nM of ADAMTS7 [48]. This initial proteomics experiment provided an ADAMTS7 candidate substrate list, showed that ADAMTS7 can cleave ECM proteins, and implicated ADAMTS7 in the regulation of TGFB signaling.

Subsequent experiments expanded the list of ADAMTS7 candidate substrates by performing TAILS on the secretome of SMCs and endothelial cells [49]. These TAILS experiments employed an adenovirus to overexpress *Adamts7* and identified 91 unique cleavage sites in 48 different proteins. Of these 48 proteins, 16 were found in all datasets reported in this study. Interestingly, ADAMTS7 could cleave fibronectin at 12 different locations, the most unique target sites of any protein identified. Of these 16 proteins identified, EFEMP1 was further validated as a cleavage target of ADAMTS7. ADAMTS3, MMP3, and MMP7 were previously reported to cleave EFEMP1 and ADAMTS7 displayed the same cleavage site preference as these metalloproteinases [44, 53, 54]. The authors used a novel modification of ADAMTS7 in performing these experiments, where the serine amino acids within the SGSGS site of the mucin domain of ADAMTS7 were replaced with alanines. Without this modification, the hydrophobicity of the mucin site renders ADAMTS7's purification nearly impossible. These mutations allowed for the recombinant purification of ADAMTS7 for downstream assays, a technique that will be incredibly useful for the study of ADAMTS7. Using endogenous and HA-tagged EFEMP1, the authors validated cleavage of EFEMP1 ADAMTS7 via western blotting. This set of experiments replicated the finding that ADAMTS7 acts on the level of the ECM while both generating additional candidate substrates and validating one specific candidate substrate as a cleavage target of ADAMTS7. Both TAILS studies also identified autocleavage of ADAMTS7. Within the TAILS study of fibroblasts, the authors found that ADAMTS7 auto-cleaves within the spacer domain [48]. The SMC and endothelial cell TAILS dataset detected autocleavage within the

prodomain and mucin domain [49]. Whether the by-products of the autocleavage result in meaningful downstream effects or is some form of negative feedback regulatory mechanism is still unknown.

The described TAILS experiments all clearly show that ADAMTS7 cleaves ECM proteins. Comparison across fibroblasts, SMCs, and endothelial cells identifies only six proteins found in every experiment: BMP6, LTBP1, LTBP3, NID1, FN1 and COL18A1, all of which are ECM proteins. Surprisingly, neither COMP nor TSP1 were strong hits within the TAILS datasets [48, 49]. However, the identification of these six substrates and no others may owe to the tissue specific expression of these six proteins within the three cell types tested. For example, TAGLN was detected as a cleaved protein with the SMCs datasets but not in the other two cell types [49]. TAGLN is a well-described SMC-associated gene, and it is not surprising that fibroblasts and endothelial cells do not have high expression of TAGLN [55]. TAILS experiments are performed *in vitro* and cannot capture the entire secretome of the many cell types that make up the vasculature. Although these three cell types cover the vast majority of the secretome of the cells of the vasculature, if, for example, a substrate only produced by macrophages was causal, the reported TAILS experiments would not be able to capture that target substrate. As such, the definitive identification of a causal cleavage target of ADAMTS7 needs to be verified *in vivo* through an atherosclerosis study.

## Conclusion

Since its identification by GWAS as a gene of interest for CAD, much work has been done to decipher the role of ADAMTS7 in atherosclerosis. Multiple mouse models have corroborated that ADAMTS7 is pro-atherogenic, and the pro-atherogenicity is derived from its catalytic function [32, 44]. As ADAMTS7 co-stains with SMCs within human plaques, the causal cell type is highly suggestive of being SMCs [32]. A clear future direction would be the employment of conditional knockout mice to definitively show that SMCs are the causal cell type. At the cellular level, ADAMTS7 can increase the rate of migration of vascular cells. However, the link between this increase in migration and an increase in atherosclerosis is still unresolved (Fig. 2).

Furthermore, the vast majority of the SNPS that point towards *ADAMTS7* as a gene of interest lie within the non-coding region of the loci. Is the coding variant truly causative, or is there another atherogenic mechanism conferred by the non-coding region? In addition, definitive evidence of ADAMTS7 being proatherogenic in humans is still lacking. More work is needed to show the directionality of disease in humans. The identification of true *ADAMTS7* loss of function variants would aid to address this knowledge gap. The current literature also indicates that *ADAMTS7* is induced rather than constitutively expressed [32, 44]. This aspect as to when *ADAMTS7* is induced in humans requires further research. In mice, ADAMTS7 is seen in early lesions but not late advanced lesion. As the onset of atherosclerosis can occur in childhood, if the therapeutic window for ADAMTS7 intervention lies within this time, the therapeutic efficacy of ADAMTS7 is greatly diminished.



In summary, human genetic data heavily implicates ADAMTS7 as a gene involved in CAD [10]. Furthermore, basic research has subsequently elucidated ADAMTS7 to be a secreted proatherogenic proteinase [44]. There remains a need to identify the precise cleavage substrate that leads to the conferred proatherogenicity. Only recently has it been shown in model systems that therapeutic blockade of ADAMTS7 reduce atherosclerosis [45]. For ADAMTS7 based therapeutics to be translated into the clinic, the directionality of disease conferred by ADAMTS7 in humans needs to be resolved. Nonetheless, this recent publication showing a therapeutic efficacy targeting ADAMTS7 opens the doors to the development of a new class of therapeutics for CAD.

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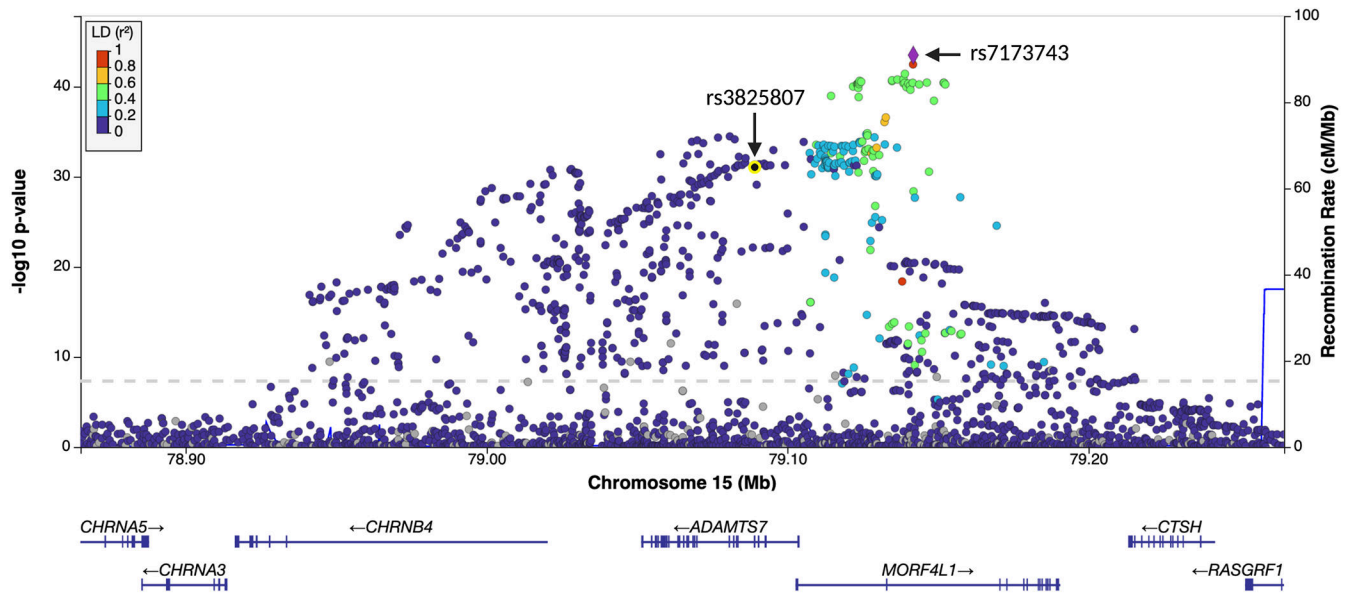
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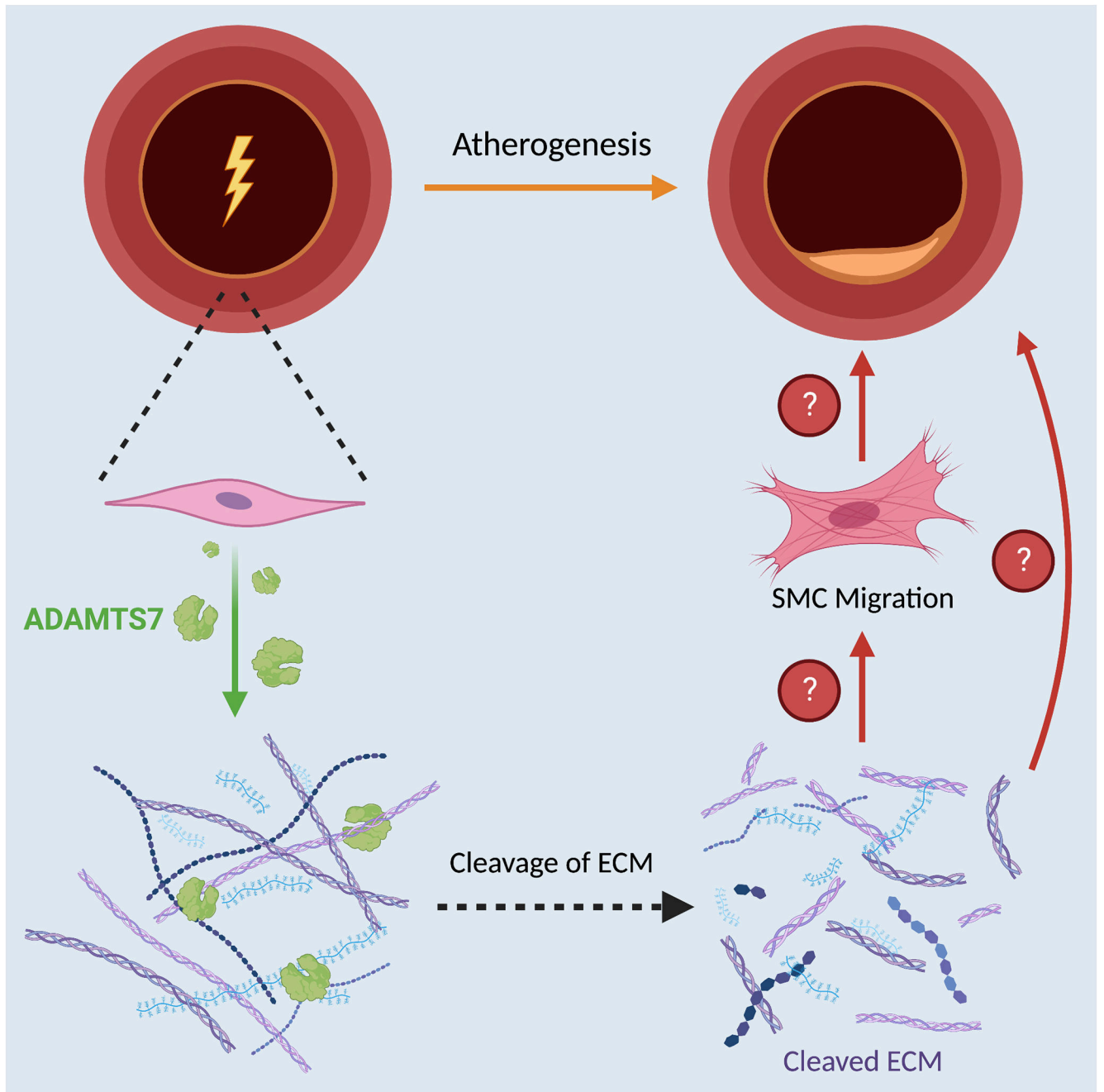
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**Fig. 1.** LocusZoom plot of the 15q25.1 GWAS signal in CAD within people of European ancestry [2]. The GWAS signal centers around *ADAMTS7*, with the histone acetyltransferase *MORF4L1* lying immediately upstream of the gene. Downstream of *ADAMTS7* lies a cluster of three nicotine receptors *CHRNA3-A5-B4*. Linkage disequilibrium is referenced to the lead SNP rs7173743. The coding S214P SNP (rs3825807) is highlighted in yellow. This figure was created using LocusZoom [56].



**Fig. 2.** Proposed model for the mechanistic effect of ADAMTS7 on the vasculature. *ADAMTS7* is induced in response to vascular injury. *ADAMTS7* cleaves components of the ECM. This cleavage activity, in turn, leads to an increase in SMC migration through a yet unknown mechanism. It is unknown whether the elevated SMC migration or the cleaved ECM itself is causal for the associated increase in atherosclerosis. Created with [BioRender.com](https://www.biorender.com)