

EDITORIAL

The underappreciated role of the “unknown” *MXRA7* gene in diseases

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Effective treatment of any disease relies on a better—ideally thorough—understanding of the various—omes of human. However, we are still far away from that point. In 2023, Rocha *et al.*¹ coined the concept of “Unknome” to refer to the unknown part of all information that all genes bear. By Unknome’s definition and criteria, a “knownness score” could be calculated for a human gene by integrating information known in all known creature species, and the theoretical maximum knownness score for any gene could reach ~220. At present, only 4% of all 19,916 human genes are known by over 10% of their knownness scores. Among the less-known genes, 2763 have a knownness score of 0, which are almost completely unknown by scientists. Matrix remodeling associated 7 (*MXRA7*) is one of such “unknown” genes, though our team had published a dozen papers based on intentional studies of *MXRA7* biology. These facts highlight the risk that current understandings of health and disease—as well as approaches to diagnosis and treatment—may be fundamentally biased or incomplete due to the exclusion of the Unknome. In other words, the Unknome holds promise for addressing unresolved medical challenges, including those related to the circulatory system.

The promise for cures of cardiovascular diseases embedded in Unknome was exemplified by recent publications mentioning *MXRA7*’s involvement in physio- or pathological processes of the heart or vessels. DeWan’s team² in Yale University integrated genome-wide, transcriptome-wide, and proteome-wide association studies (GWAS, TWAS, and PWAS, or together X-WAS) to search for possible genes responsible for the development of coronary artery disease (CAD). From materials or information derived from 181,522 CAD patients and 1,165,690 non-CAD controls, ten genes (detailed below) surfaced from assays and were further confirmed to be associated with CAD risk factors. Interestingly, except for *MXRA7*, which had a knownness score of 0 in Unknome, all other nine genes were well-characterized (knownness scores: *IL6R*, 35; *CHMP2B* 27.1; *MIF*, 24.8; *PCSK9*, 24.4; *NUDT5*, 15.1; *NME2*, 13.1; *WARS*, 12.1; *CLIC4*, 7.0; *TAGLN2*, 2.3) and had been associated with cardiovascular system-related processes in different studies (undiscussed here), strongly proposing a role of *MXRA7* in CAD as well.

Inspired by the report from DeWan’s team, we performed a retrospective investigation into earlier publications and found that *MXRA7* had been caught in other human heart diseases or disease models. Using a TWAS+PWAS plus Mendelian randomization strategy but with different patients/controls data resources, an international team led by Butterworth identified seven genes/proteins (*ABO*, *GSTT2B*, *MST1*, *MXRA7*, *PCSK9*, *PDE5A*, and *TMEM106A*) as potential causative factors of coronary heart disease.³ Again, *MXRA7* was the only one among these genes that had a knownness score of 0. Involvement or association of *MXRA7* in CAD was observed not only in tissue biopsy from the heart but also in blood samples. Yang *et al.*⁴ first utilized proteome-

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wide Mendelian randomization analysis to identify 41 circulating proteins associated with CAD, among which 12 proteins (ANGPTL4, APOB, C1R, C1S, FN1, IL6R, PCSK9, PTK7, RGMB, TAGLN2, TIMP3, and VIM) with strong support evidence and five (ANGPTL1, MGAT1, MST1, *MXRA7*, and THSD1) with medium evidence were identified through colocalization analysis. More intriguingly, in an attempt to study whether the atherosclerotic patients without standard modifiable risk factors but experiencing myocardial infarction manifested any trace of transcriptomic change in peripheral blood mononuclear cells, Mol *et al.*⁵ revealed that after multiple testing correction, *MXRA7* and *RAB20* were significantly underexpressed in patient cells while *PTK2* was overexpressed. To search for molecules underlying peripartum cardiomyopathy, Li *et al.*⁶ performed protein and metabolite profiling of left ventricular tissue samples, and their results showed that *MXRA7* ranked seventh by fold changes among all significantly upregulated proteins in the diseased tissues. Another study examined the causal effects of about 3000 circulating proteins through a combination of methods, and identified *MXRA7* as one of the 46 proteins that was significantly associated with blood pressure, with strong cis+, cis+trans Mendelian randomization and colocalization evidence.⁷ Besides “disorders,” normal functions of the heart might also be subjected to the influence of the *MXRA7* gene. In a multi-omics study, both protein and expression quantitative trait loci (pQTLs and eQTL, respectively) analyses identified *MXRA7* as one of the limited number of genes associated with resting heart rate,⁸ which is determined by sinoatrial pacemaker cells.

Support for hypothetical roles of *MXRA7* in cardiology also came from studies that did not mention *MXRA7* in publications but actually generated datasets containing

information of *MXRA7* (Table 1). For example, the GSE3585 dataset contained transcriptome assay of subendocardial left ventricular tissues collected from seven patients with dilated cardiomyopathy (DCM) and five non-failing (NF) donor hearts but with palpable coronary calcifications.⁹ Domestic calculation in our dataset showed that among 10,642 mRNA species detected, *MXRA7* was ranked from 103th to 212th, placing itself above 98.6% genes on average, in all five NF hearts. In DCM tissues, *MXRA7* expression showed a modest but statistically significant increase to 1.26-fold, ranking between 71st and 139th—placing it in the top 0.8% of expressed genes (99.2 percentile). In an accompanying dataset GSE3586 obtained from septal myocardial tissues of 13 DCM patients and from 15 NF donor hearts, *MXRA7* ranked in the top 6–27% (73–94%) among all 30,499 transcripts in 15 NF hearts, with a slight yet statistically significant reduction to 0.89-fold in DCM hearts. Although the discrepancy of expression changes in *MXRA7* mRNA in the two restricted sites (*i.e.*, subendocardial left ventricle and ventricular septum) requires further confirmation or clarification, this preliminary study has highlighted that *MXRA7* was expressed at a very high mRNA level in the human heart. Correspondingly, and in the updated Human Protein Atlas (HPA)¹⁰ (by April 29, 2025), “heart muscle” expresses *MXRA7* at the first or second highest rank, in terms of mRNA level, among all studied human tissues (Figure 1). The *MXRA7* expression at the protein level was denoted as “medium” in the HPA. Simply put, it is very reasonable to believe or to propose that a gene expressed at such a high level in the heart, though still classified as “unknown,” plays roles in the cardiovascular system.

Similarly to the heart, the brain also contains tissues that express *MXRA7* at high mRNA and protein levels (Figure 1), and integrative analysis of large genome-

Table 1. Examples of cardiological studies implicating *MXRA7*'s roles

Research document	Study design	Results relating to <i>MXRA7</i>
GSE3585/GDS2205 ⁹	Subendocardial left ventricular tissues were collected from seven patients with DCM and five NF donor hearts with palpable coronary calcifications. Transcriptome microarrays were used.	<i>MXRA7</i> ranked 103 rd –212 th (average 148, above about 98.6% genes) among all 10,642 mRNA species detected in all five NF hearts, and exhibited a modest but statistically significant increase in expression, up to 1.26-fold (ranking 71 st –139 th , average 84, above 99.2% genes) in DCM hearts.
GSE3586/GDS2206 ⁹	<i>MXRA7</i> expression in septal myocardial tissues from 13 DCM patients versus 15 NF hearts was compared by means of transcriptome microarrays.	<i>MXRA7</i> ranked in the top 6–27% (73 rd –94 th percentile) in terms of mRNA expression level among all 30,499 transcripts in 15 NF hearts, with a modest yet statistically significant reduction in expression, down to 0.89-fold, in DCM hearts.
Cai <i>et al.</i> (2023) ¹¹	Cardiorespiratory fitness of 10,707 individuals in the Fenland study was assessed using the enhanced 160-SNP genetic risk score and Protein Targets by the aptamer-based technology (SomaScan®).	<i>MXRA7</i> was among the 14 proteins significantly correlated with cardiorespiratory fitness.

Abbreviations: DCM: Dilated cardiomyopathy; NF: Non-failing; SNP: Single-nucleotide polymorphism.

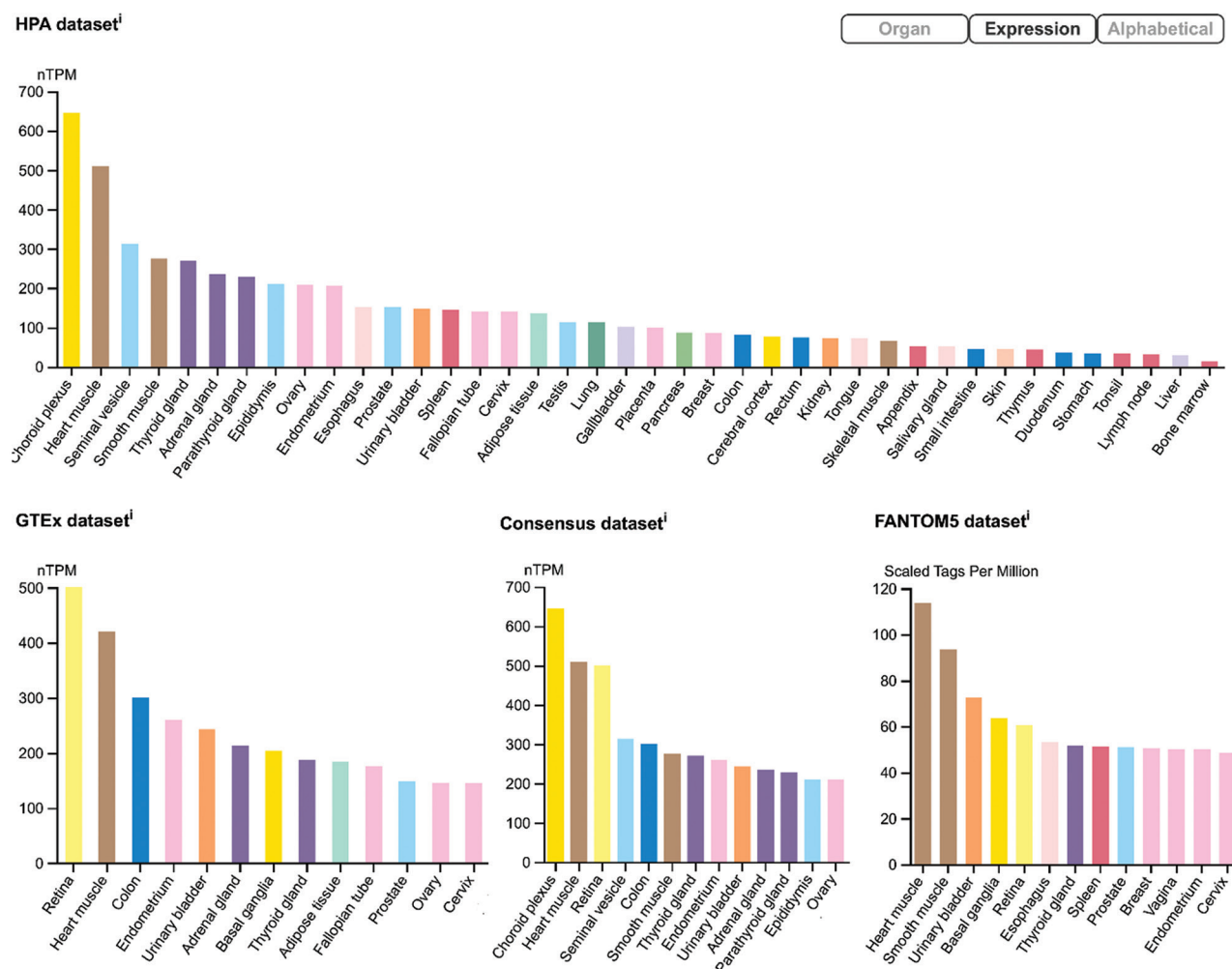


Figure 1. Expression levels of *MXRA7* across human tissues in multiple datasets. The bar graphs represent data obtained from the Human Protein Atlas (HPA), GTEx, Consensus, and FANTOM5 datasets. The upper panel (HPA dataset) shows the full range of tissues ranked by expression level, while the lower panel displays selected tissues with relatively higher expression levels, excluding those with low expression for clarity. All graphs are directly downloaded from the HPA website (<https://www.proteinatlas.org/ENSG00000182534-MXRA7/tissue>) without modification to the underlying data or scientific interpretation.

wide association studies disclosed *MXRA7* as one of four plasma proteins that correlated with rest state fluctuation amplitudes of the brain at rest.¹² *MXRA7* was also revealed to be among the biomarkers related with functional alterations of the brain in response to exogenous stimuli. In one such case, *MXRA7* was one of six biomarkers whose protein levels in cerebrospinal fluids predict a (non) responsiveness to shunt in patients with idiopathic normal-pressure hydrocephalus.¹³ Similarly, physio- or pathological status of the lung also correlates with certain omic features. For example, in patients with long COVID, namely, those recovered from acute COVID-19 but with lasting impaired lung diffusion capacity, transcriptomic and proteomic assays disclosed *MXRA7* as one of six upregulated genes in patients' peripheral blood.¹⁴ In another cohort of children

with infectious pneumonia, transcriptomic profiling performed with peripheral blood samples uncovered an *MXRA7*-inclusive five-transcript signature that could effectively differentiate bacterial from viral infections.¹⁵ In addition, HPA proposed that the prognostic capacity of *MXRA7* expression level for brain or lung cancers depends not only on cancer types (e.g., glioma, lung adenocarcinoma, lung squamous cell carcinoma) but also on features (e.g., TCGA, validation) or origins of datasets.

To summarize, with the accelerating accumulation of biomedical data, a growing wealth of evidence concerning *MXRA7* biology is being generated, although no further investigative attempts were made to validate the findings.¹⁶ Despite that *MXRA7* was not a target of research in these

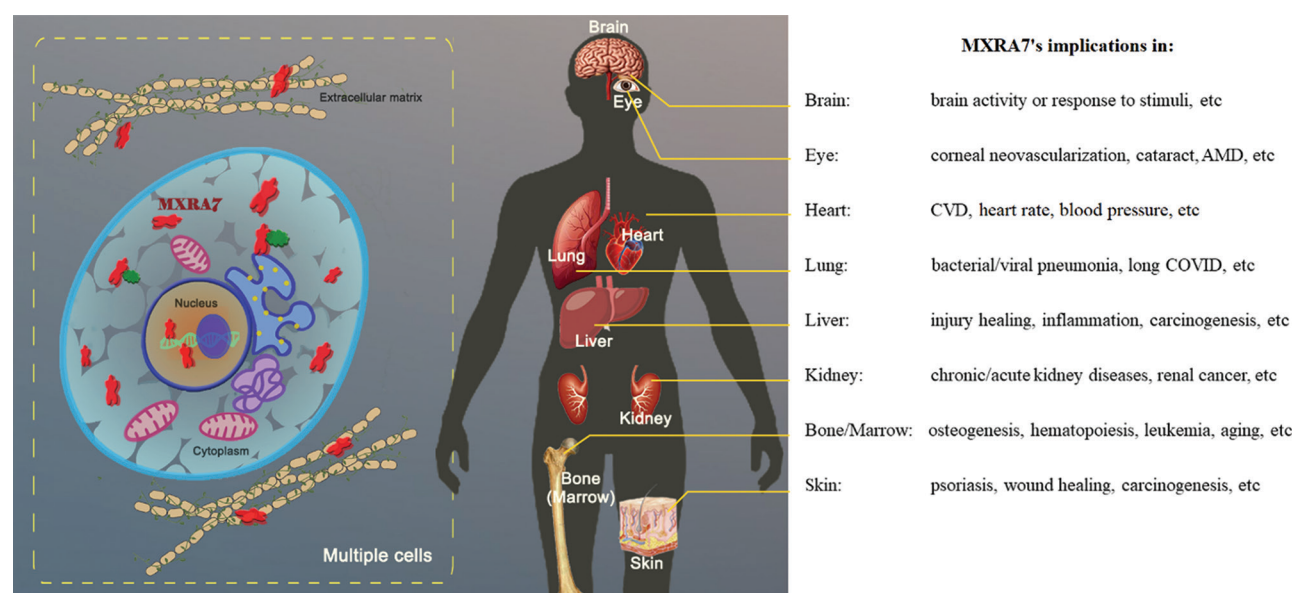


Figure 2. Distribution of MXRA7 proteins in various cells and tissues, and their presumed physio- or pathological roles in major organs. The schematic diagram on the left panel was adapted from Wang *et al.* (2020)¹⁶ with permission. Copyright © 2020 *Chin J Biochem Mol Biol*.

studies, such findings did strongly and uniformly suggest important roles of MXRA7 in almost all critical physio- and pathological processes. In fact, our dedicated research works on MXRA7 functions in pathophysiology of diseases related to eye,¹⁷ liver,¹⁸ skin¹⁹ and bone (including marrow),²⁰ as well as cancer,²¹ such as leukemia,²² have prompted us to believe that the *MXRA7* gene or its protein products participate in other critical clinical disorders, such as cardiovascular diseases, respiratory diseases, and neural diseases. We also observed that both natural and recombinant MXRA7 proteins have apparently different molecular weights, with the largest ones double their theoretical molecular weights. Virtual analysis revealed potential phosphorylation, glycosylation, and ubiquitination sites on MXRA7 protein sequences. Thus, similar to the call for greater efforts to unveil “hidden” cancer driver genes,²³ increased attentions and extensive investigations are warranted to substantiate the proposed roles of the so-called unknown gene *MXRA7* across all tissues/organs (Figure 2), whether as a key regulator or as a downstream effector. Primary consideration should center around the molecular features of the *MXRA7* gene and its protein products, including the regulation of gene expression, mechanisms underlying the generation of alternative transcripts or protein isoforms, the types and functional impacts of post-translational modifications, subcellular and extracellular distribution patterns of the proteins, and protein-protein interaction networks (interactomes). Specifically, glycomedicine²⁴ and ubiquitinomic approaches²⁵ might provide quick tools for such a purpose. Addressing these fundamental questions through research will expand our knowledge about this

least-studied gene, and ultimately reveal the significance of *MXRA7* as a target in managing human diseases.

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Conflict of interest

Yiqiang Wang is an Editorial Board Member of this journal, and declared that he has no known competing financial interests or personal relationships that could have influenced the work reported in this paper. The other author declares no conflict of interest.

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