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Transcriptional Differences Following Myocardial Infarction

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Agenda

- Introduction
- Hypothesis
- Methods
- Results
- Discussion
- Future Directions

Introduction

- Cardiovascular Disease remains the leading cause of death worldwide according to WHO [1]
- approximately 85% of these CVD deaths were attributable to either heart attack or stroke [1]
- In 2019 almost a third of patients admitted to hospitals in the UK for MI were initially misdiagnosed, this misdiagnosis at first contact was then found to be correlated with a significantly higher in-hospital and 1-year mortality rate [2]
- It is more important than ever to find reliable, expedient, and non invasive ways to detect myocardial infarctions (MI) to increase patient survival and long term prognosis
- The first step to solving this problem is travelling all the way back to the beginning of the metabolic process to identify possible candidates via transcriptional differences

Hypothesis

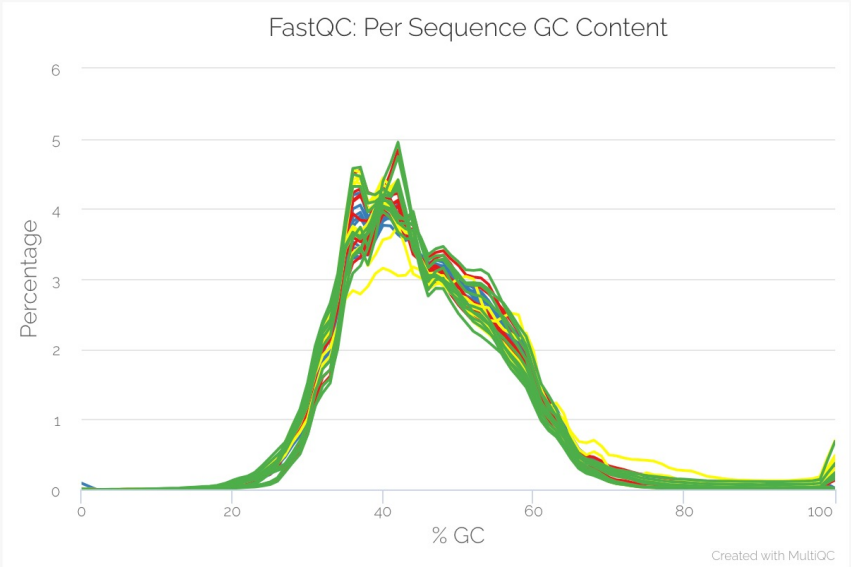
There are transcriptional differences present in cardiac tissue following a MI when compared to a control

Methods (Dataset)

- “Integrative transcriptomic analysis of tissue-specific metabolic crosstalk after myocardial infarction” by Arif et al (GEO Series GSE153485)
- Dataset chosen because it contained 4 relevant conditions with 5 biological samples for each
- The conditions for the dataset were 6 and 24 hours after an induced MI, as well as 6 and 24 hours after a sham procedure
- all samples were bulk RNA-seq data from cardiac tissue, sequenced on an Illumina NovaSeq 6000.

Methods (FastQC)

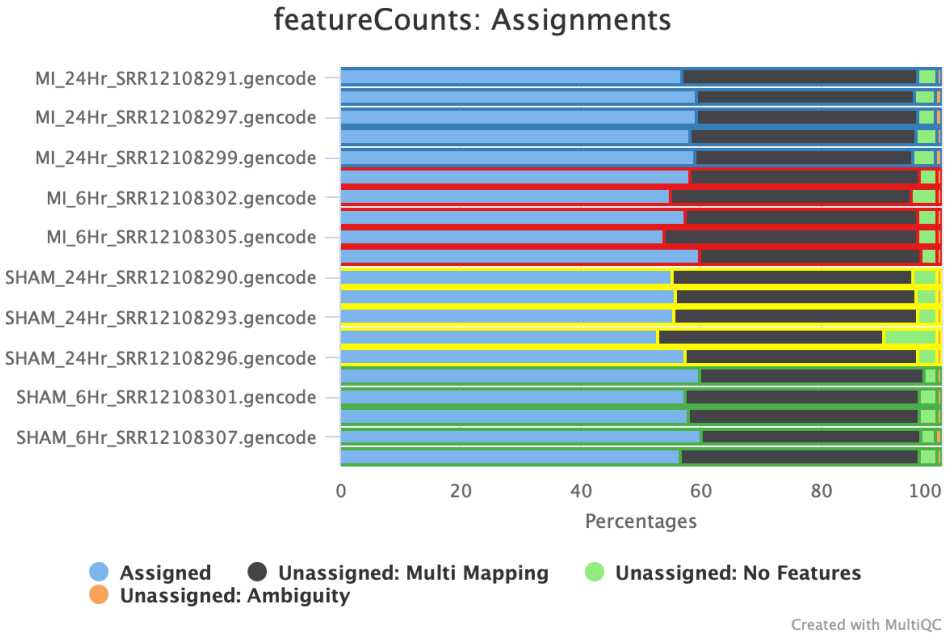
- Clear shoulder on the right side and right skewed tail
- Top 5 most overrepresented sequences were mitochondrial DNA
- Top overrepresented sequence was 40 nts of G
- Clear peak at roughly 45%, ideal for mouse genome



Overrepresented sequence	Samples	Occurrences	% of all reads
CTCGAATGTGTGATATGGTGGAGGGCAGCCATGAAGTCATTCTAAATTTG	20	1117774	0.2841%
CTCAAATTATAAAGATCATGATGAGAACAGCTGTTAGTGAAATAAATGAT	20	626166	0.1591%
CTTAGATTTATGGATAGTTGGGTAGTAGGTGTAAATGTATGTGGTAAAAG	20	361933	0.0920%
CTACTACATAGTATGTATCGTGAAGCACGATGTCAAGGGATGAGTTGGAT	20	457416	0.1163%
GTCAGTATCATGCTGCGGCTTCAAATCCGAAGTGATGTTTTGATGTGAAG	20	461569	0.1173%
CTCCGATTAGGTGTATTAATAAGTGTCCTGCAGTAATGTTAGCTGTAAGC	20	365130	0.0928%
CTTGATTTATGTGGTTTCGTTTACCTTCTATAAGGCTATGATGAGCTCAT	20	335692	0.0853%
CAAAGAATCAGAACAGATGCTGGTAGAGAATTGGGTCCCCTCCTCCAGCG	20	281272	0.0715%
GTGAAATTTTAGTTGTCGTAGTAGGCAAACAATAAGGAATGTTGATCCAA	20	224482	0.0571%
GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	20	1356461	0.3447%
CTCATGCATATCACATAGTTAATCCAAGTCCATGACCATTAACTGGAGCC	20	429563	0.1092%
GTTTAGGTTGCGGTCTGTTAGTAGTATAGTAATGCCTGCGGCTAGCACTG	19	314154	0.0798%
GTTGCAAGTCAGCTAAATACTTTGACACCGGTAGGAATTGCGATAATTAT	19	303931	0.0772%
CTCAACCAATCACAAAGATATCGGAACCCTCTATCTACTATTCGGAGCCT	19	323264	0.0822%
GTTCGATTCCTTCCTTTCTTATTTTACTTTTACATAGGTTGGTTCCTCGA	18	384978	0.0978%

Methods (featureCounts)

- consistent assignment rates across MI/SHAM and 6Hr/24Hr
- Assigned reads account for 55-60% of each library, multi-mapping reads for 20-30%, and unassigned no-features or ambiguous for < 5% (19/20 samples)
- elevated multi-mapping reflects repetitive transcripts such as the mitochondrial DNA previously found in FastQC



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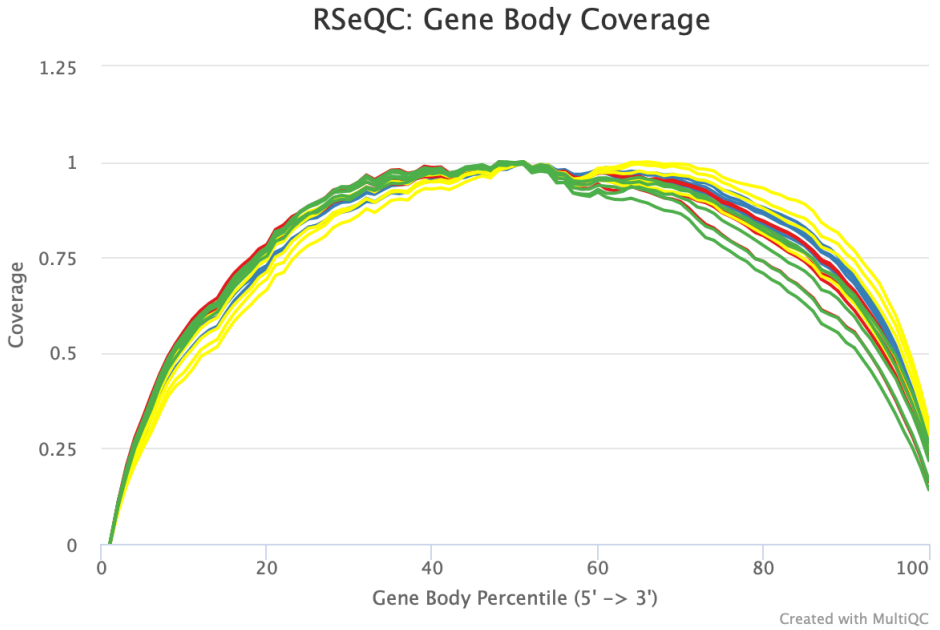
Methods (RSeQC)

- tight clustering among all samples
- no dramatic 3’ bias or 5’ drop off in any of the samples
- all curves plateau within the 40-60th percentile



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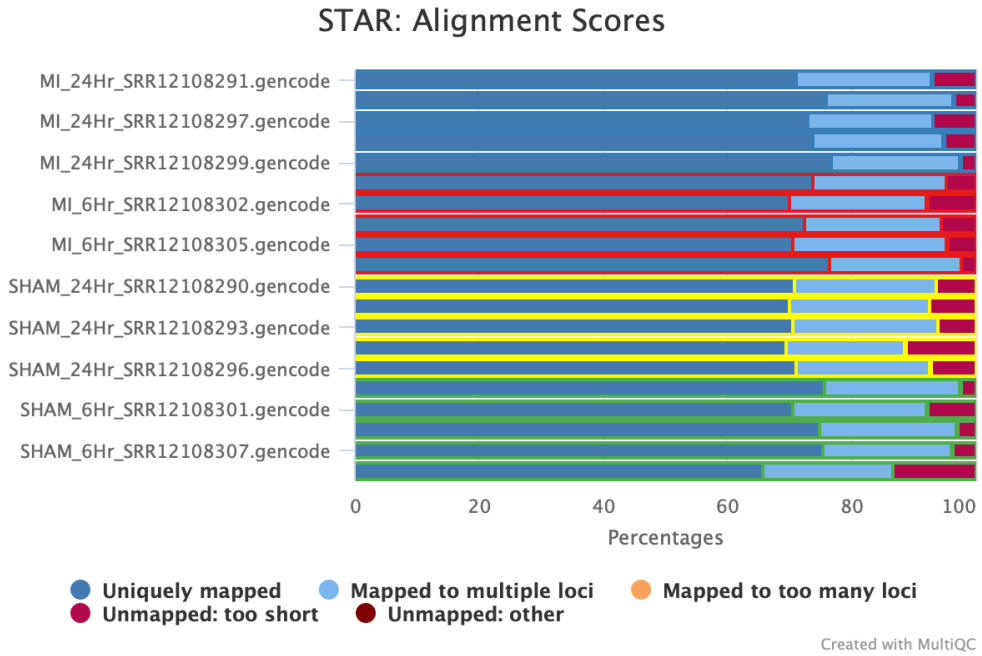
Methods (MultiQC STAR Log)

- >65% of reads were uniquely mapped for all samples
- 20-25% of reads were multimapped
- <10% of reads were unmapped due to being too short for all but 2 samples
- high mapping yields and low unmapped counts demonstrate good alignment across both conditions and timepoints



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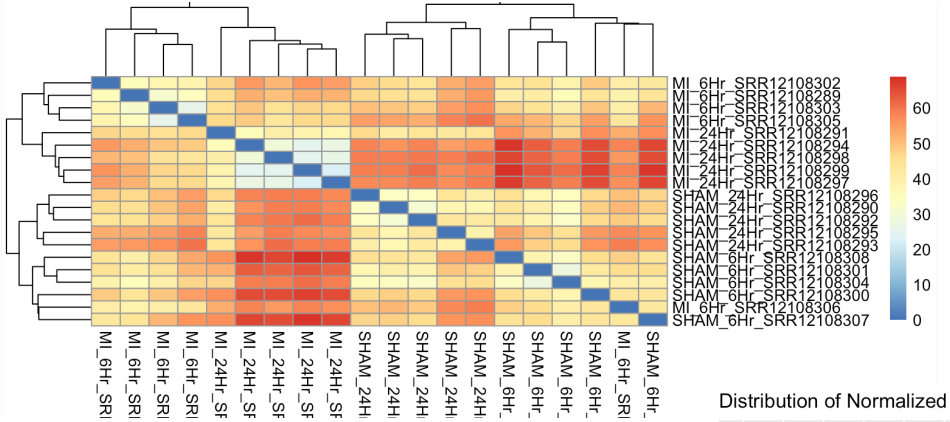
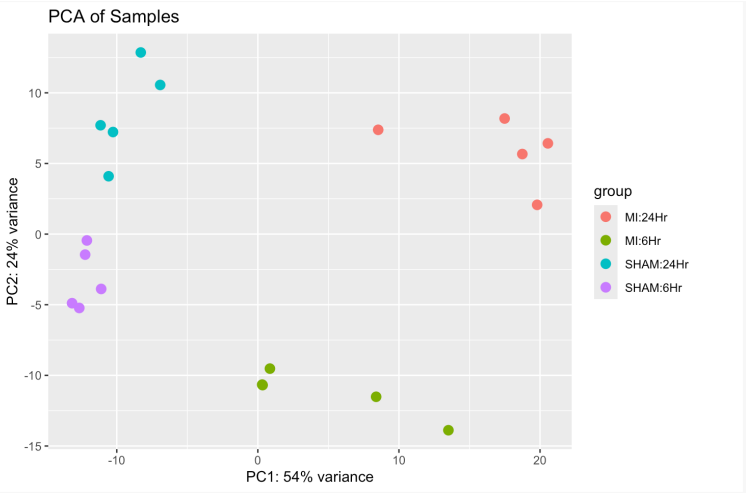
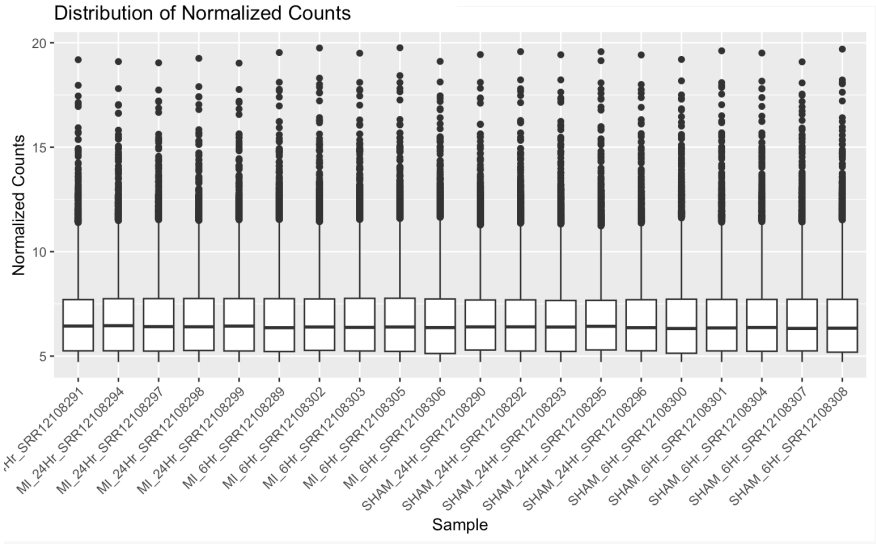
Methods (Other QC)







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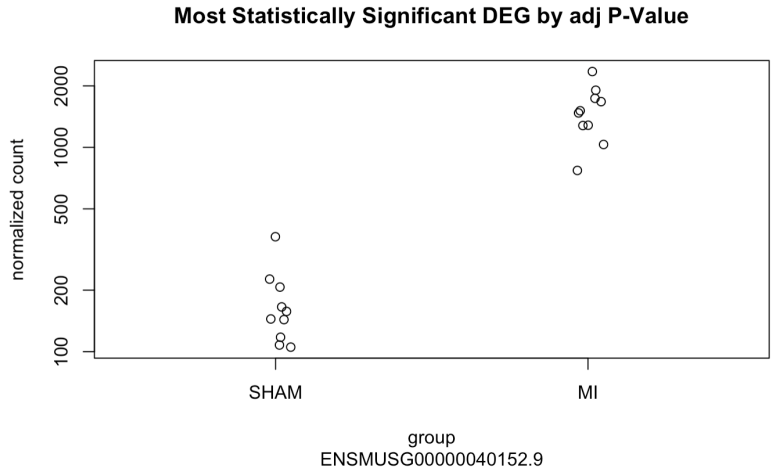
Results (DEG)

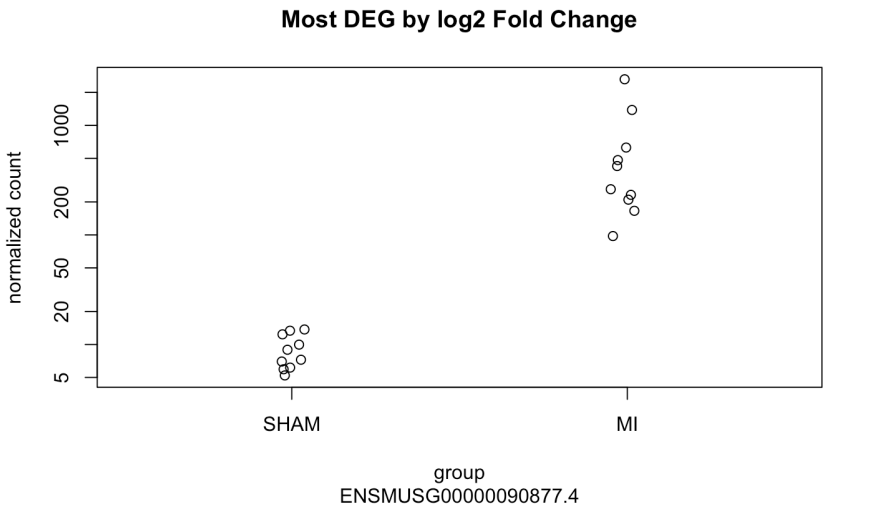
- most statistically significant gene, ENSMUSG00000040152.9 aka Thbs1 encodes a protein known to play a role in angiogenesis according to NCBI [3]
- most upregulated gene, ENSMUSG00000090877.4 aka Hspa1b is a heat shock protein described as a protein folding chaperon according to NCBI [4]

Gene ID	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
ENSMUSG00000040152.9	837.387358	3.1693	0.18957	16.71797	9.6963e-63	1.5366e-58
ENSMUSG00000024486.7	486.120552	2.9048	0.19430	14.95059	1.5438e-50	1.2232e-46
ENSMUSG00000047798.16	62.369641	3.6779	0.27910	13.17763	1.1804e-39	6.2354e-36
ENSMUSG00000026558.14	842.936737	2.0981	0.16548	12.67868	7.7633e-37	2.4605e-33
ENSMUSG00000061878.17	59.264384	2.7302	0.21511	12.69210	6.5404e-37	2.4605e-33

Gene ID	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
ENSMUSG00000090877.4	329.815534	5.8770	0.48731	12.06010	1.7158e-33	2.4718e-30
ENSMUSG00000091971.4	286.344012	5.7198	0.51201	11.17125	5.6383e-29	3.4366e-26
ENSMUSG00000000182.10	4.814779	4.9185	0.81216	6.05600	1.3954e-09	4.1961e-08
ENSMUSG00000045502.7	6.303774	4.8233	0.69309	6.95918	3.4227e-12	1.8201e-10
ENSMUSG00000004939.8	331.535885	4.7638	0.38510	12.37046	3.7767e-35	7.4812e-32

Results (DGE)





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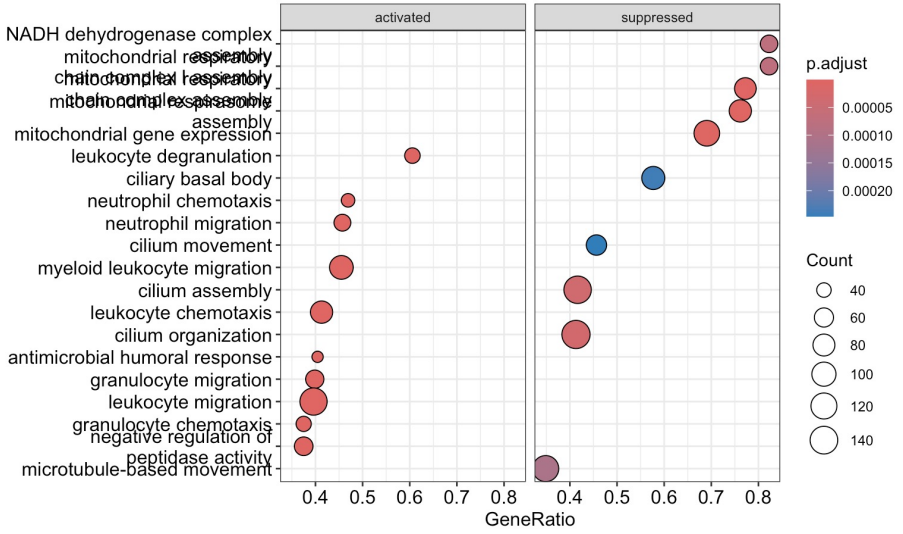
Results (GSE)

- top category for all ontologies involves the actin complex
- actin combines with myosin to form the contractile element of muscle cells
- positive regulation of cell migration because following an MI there would be a typical inflammation response

Ontology	GO ID	Description	p.adjust	Count
BP	GO:0030036	actin cytoskeleton organization	4.905592e-64	336
BP	GO:0030335	positive regulation of cell migration	2.961962e-54	283
BP	GO:2000147	positive regulation of cell motility	1.074501e-52	289
BP	GO:0040017	positive regulation of locomotion	1.130994e-51	292
BP	GO:0007015	actin filament organization	1.227639e-44	222



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Discussion

- Primary objective was to determine whether MI induces a transcriptional change in cardiac tissue.
- QC supported the integrity of the dataset overall.
- The most significant gene by adj p-value, Thbs1 (Thrombospondin-1), encodes a protein that promotes angiogenesis and is rapidly activated in infarcted cardiac tissue.
- The largest positive log2 fold-change belonged to Hspa1b, a heat-shock protein essential for cardiomyocyte survival during ischemia and reperfusion.
- DESeq2 analysis identified 5,508 genes with an adj p-value < 0.05, of which 2,902 were up-regulated and 2,606 down-regulated in MI vs SHAM
- Gene ontology over representation analysis provided context into the activated pathways.
- All three ontologies showed actin cytoskeleton rearrangement and the positive regulation of cell migration.

Future Directions

- Screen the upregulated genes for those which produce proteins and enzymes which may circulate in the blood.
- Further screen these for those which can be detected from blood panels
- Identify potential biomarker candidates for identifying when a MI has occurred.

- Conduct the study again but induce strokes instead of MIs.
- Investigate if there is an upregulation in similar genes due to the similar mechanism of action, even though they effect two different organ systems.

Questions?

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References

1. World Health Organization. Cardiovascular diseases (CVDs) [Internet]. Geneva: World Health Organization; 11 June 2021 [cited 2025 Apr 20]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

2. Gale CP, Dondo TB, West RM, Hemingway H, Timmis A, Metcalfe C, et al. Impact of initial hospital diagnosis on mortality for acute myocardial infarction: a national cohort study. Eur Heart J Acute Cardiovasc Care. 2018;7(3):204–211.

3. National Center for Biotechnology Information. Gene ID: 21825 [Internet]. Bethesda (MD): National Library of Medicine (US); [cited 2025 Apr 22]. Available from: https://www.ncbi.nlm.nih.gov/gene/21825

4. National Center for Biotechnology Information. Gene ID: 15511 [Internet]. Bethesda (MD): National Library of Medicine (US); [cited 2025 Apr 22]. Available from: https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=15511

Thank you

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