Lack of evidence of significant homology of SARS-CoV-2 spike sequences to myocarditis-associated antigens.

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Abstract: COVID-19 mRNA vaccines have proven to be highly safe and effective. Myocarditis is an adverse event associated with mRNA vaccination, especially in young male subjects. These events are rare and, in the majority of cases, resolve quickly. As myocarditis can be driven by autoimmune responses, we wanted to determine if the SARS-CoV-2 spike protein antigen encoded in the mRNA COVID vaccines had potential cross-reactivity with auto-antigens previously associated with myocarditis. To examine this, we performed a sequence identity comparison between SARS-CoV-2 spike protein-derived peptides and myocarditis-associated antigens. We found no significant enrichment in the frequency of spike-derived peptides similar to myocarditis-associated antigens as compared to several controls. Thus, our results do not support the notion that increased occurrence of myocarditis after SARS-CoV-2-spike vaccination is mediated by a cross-reactive adaptive immune response.

Introduction

In late 2019, severe acute respiratory coronavirus 2 (SARS-CoV-2) emerged causing a global pandemic of COVID-19 disease resulting in widespread morbidity and mortality. COVID-19 typically presents as a dry cough, sore throat, fever, and loss of taste and smell[1], but more rare complications have arisen as well including heart injury[2]. Following the rapid development and approval for emergency use of several different SARS-CoV-2 vaccines, as of September 2021, over five billion COVID-19 vaccine doses have been administered worldwide[3]. Rare occurrences of myocarditis and pericarditis have been reported as associated with COVID-19 vaccination in the context of mRNA[4,5], but only extremely rarely with viral vector-based vaccines which are in turn associated with a different class of adverse event such as increased frequency of blood clots[6]. The etiology of these rare side effects is poorly understood, but the possibility of autoimmune adaptive reactions needs to be investigated. As the two currently authorized mRNA vaccines BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) are both encoding the SARS-CoV-2 spike protein as the vaccine immunogen, we set out to determine if specific sequences

contained in the spike protein could lead to a cross-reactive immune response to autoantigens associated with autoimmune myocarditis in particular[7–9].

Methods

Myocarditis associated auto-antigens (cardiac proteins)

To compile a list of myocarditis-associated antigens, we first queried the Immune Epitope Database (IEDB)[10], which includes myocarditis-associated epitopes and their respective source antigens. A search for positive assays that included disease entries of “myocarditis” (DOID: 820), “rheumatic myocarditis” (DOID: 8481), and “experimental autoimmune myocarditis” (ONTIE ID: 0003439) revealed 66 human epitopes, which were contained in eight protein antigens. In addition, we reviewed the autoimmune myocarditis literature[7–9], which provided 23 additional antigens that had known associations with myocarditis and four antigens that were mentioned for potential associations with myocarditis, but either weak or no evidence was noted. In total, we compiled this list of 35 antigens (Table 1) to use for this conservation analysis.

Table 1. Myocarditis-Associated Cardiac Antigens

Protein Name	Gene	UniProt ID	Source
Myosin-6	MYO6	Q9UM54	IEDB
Myosin-7	MYH7	P12883	IEDB
Muscarinic acetylcholine receptor M2	CHRM2	P08172	IEDB
Myosin-binding protein C - cardiac-type	MYBPC3	Q14896	IEDB
Myosin-binding protein C - fast-type	MYBPC2	Q14324	IEDB
Beta-2-glycoprotein 1	APOH	P02749	IEDB
Laminin subunit alpha-1	LAMA1	P25391	IEDB
Transmembrane protease serine 4	TMPRSS4	Q9NRS4	IEDB
Troponin I	TNNI3	P19429	Review Literature
Troponin T	TNNT2	P45379	Review Literature
Beta-1 adrenergic receptor	ADRB1	P08588	Review Literature
Actin, alpha cardiac muscle 1	ACTC1	P68032	Review Literature

Tropomyosin alpha-1 chain	TPM1	P09493	Review Literature
Tropomyosin beta chain	TPM2	P07951	Review Literature
Tropomyosin alpha-3 chain	TPM3	P06753	Review Literature
Cytoplasmic aconitate hydratase	ACO1	P21399	Review Literature
ADP/ATP translocase 1	SLC25A4	P12235	Review Literature
Creatine kinase B-type	CKB	P12277	Review Literature
Creatine kinase S-type, mitochondrial	CKMT2	P17540	Review Literature
Creatine kinase U-type, mitochondrial	CKMT1A	P12532	Review Literature
Creatine kinase M-type	CKM	P06732	Review Literature
Desmin	DES	P17661	Review Literature
Dihydrolipoyl dehydrogenase, mitochondrial	DLD	P09622	Review Literature
60 kDa heat shock protein, mitochondrial	HSPD1	P10809	Review Literature
Heat shock 70 kDa protein 1A	HSPA1A	P0DMV8	Review Literature
Vimentin	VIM	P08670	Review Literature
E3 ubiquitin-protein ligase TRIM21	TRIM21	P19474	Review Literature
Lupus La protein	SSB	P05455	Review Literature
Pyruvate kinase	PKLR	P30613	Review Literature
Ubiquinol-cytochrome-c reductase complex assembly factor 1	UQCC1	Q9NVA1	Review Literature
Sodium/potassium-transporting ATPase subunit alpha-1	ATP1A1	P05023	Review Literature
Natriuretic peptides B	NPPB	P16860	Review Literature
Natriuretic peptides A	NPPA	P01160	Review Literature
Troponin C, slow skeletal and cardiac	TNNC1	P63316	Review Literature

muscles			
Transmembrane protein 65	TMEM65	Q6PI78	Review Literature

Randomized human protein control sets

We compiled 1,000 sets of 35 proteins each that were randomly selected from the human proteome (UniProt proteome ID: UP000005640) using custom Python scripts. These sets provide a control how human proteins not specifically selected to be associated with myocarditis compare to the set describe above.

Spike protein-derived peptides and shuffled controls

The SARS-CoV-2 spike protein (UniProtID: P0DTC2) is 1,273 amino acids in length. Since cross-reactivity at the level of either $CD8^+$ or $CD4^+$ T cells is of potential concern, we considered 9-mers and 15-mers, as these epitope sizes are associated with $CD8^+$ or $CD4^+$ T cell epitopes, respectively. To identify possible peptides of relevance, we split the spike protein sequence into all possible 9-mers, overlapping by eight amino acids, and all possible 15-mers, overlapping by 14 amino acids using custom Python scripts. In total, we compiled 1,265 9-mers and 1,259 15-mers. As a control, we also generated shuffled sequences of all peptides using the Python shuffle function.

Conservation analysis

We considered different levels of sequence identity to identify potentially relevant hits for CD4- and CD8 T cell immune responses. Previous studies[11] support the notion that 50% is a conservative identity threshold for cross-reactivity for CD4 T cells, which are typically 15 residues in length. For CD8 epitopes, which are typically 9 residues in length, more than two substitutions are in general non-cross-reactive[12]. Both the spike peptide and shuffled peptide sets were searched for matches in the cardiac proteins, as well as the 1,000 control sets, using PEPMatch, a tool developed by the IEDB (manuscript in progress; https://github.com/IEDB/PEPMatch). PEPMatch is optimized for short peptide searches, and guarantees finding complete sets of results in contrast to, for example, BLAST[13] with default settings.

Results

To evaluate the occurrence of peptides in SARS-CoV-2 spike that have high similarity to peptides in proteins associated with cardiac autoimmunity (cardiac proteins for short hereafter), we generated a set of 1,259 15-mers overlapping by 14 residues spanning the entire spike protein. 15-mer peptides were considered first, as the typical length of MHC-II restricted CD4 T cell epitopes. We compared these peptides to a set of 35 cardiac proteins associated with cardiac autoimmunity. We found zero peptides in the spike that matched any of these cardiac antigens at a sequence identity of 60% or more. Relaxing the identity threshold further, at 53% homology, we found 13 matches for peptides from the spike protein. However, we also found 14 matches from shuffled peptides, which means there is no statistically significant increased sequence identity of

actual spike peptides as compared to shuffled controls at the 53% threshold (p=1.0, OR=.928 (Table 2)).

Table 2. SARS-CoV-2 Spike 15-mers vs. Shuffled 15-mers (Homology >= 53%)

	Match in Cardiac Proteins	No Match in Cardiac Proteins	Total Peptides
Spike Peptides	13	1,246	1,259
Shuffled Peptides	14	1,245	1,259
Total Peptides	27	2,491	2,518

Next, we examined the homology of 9-mer peptide fragments, which is the length of typical MHC-I restricted CD8 T cell epitopes. At 78% homology or more (two substitutions), three spike peptides and one shuffled peptide were found in cardiac proteins, which is not a significant enrichment (p=0.63). At the 67% homology level, we found 77 homologous peptides from spike and 55 homologous from shuffled peptides (Table 3), which is also not a statistically significant increase (p=0.06).

While these analyses do show a trend for a higher number of 9-mer peptides in spike that match the cardiac proteins, that enrichment is not statistically significant, and thus does not support the notion that spike protein sequences are significantly enriched in peptides that are potential epitopes with significant sequence identity to human self-proteins associated with autoimmune myocarditis. Conversely, the analysis also identifies 13 15-mer and 77 9-mer peptides that could be further evaluated experimentally for their potential to mediate cross-reactive responses in individuals experiencing post-vaccination myocarditis (Supplemental Table 1).

Table 3. SARS-CoV-2 Spike 9-mers vs. Shuffled 9-mers (Homology >= 67%)

	Match in Cardiac Proteins	No Match in Cardiac Proteins	Total Peptides
Spike Peptides	77	1,188	1,265
Shuffled Peptides	55	1,210	1,265
Total Peptides	132	2,398	2,530

Finally, we repeated these analyses with sets of human proteins selected randomly, to create distributions of peptide match frequencies at each homology level. For 9-mers at the 56% homology level, 89.5% of sets were below the cardiac protein set and 10.5% were at or above it in terms of peptide match frequency. At the 67% homology level, 84.8% were below and 15.2% were at or above the cardiac protein set (Figure 1). This shows a trend for increased hits in cardiac proteins rather than in randomly selected proteins, but as before this trend is not statistically significant at the conventional p = 0.05 cutoff.

Only spike 15-mers at the 53% homology level had matches within the cardiac protein set and 48.7% of the randomly selected protein sets were below it and 51.3% were at or above it in terms of peptide match frequency (Figure 2). This is also not considered significant.

Figure 1. Spike vs shuffled 9-mers >= 67% homology match distribution of 1,000 random protein sets

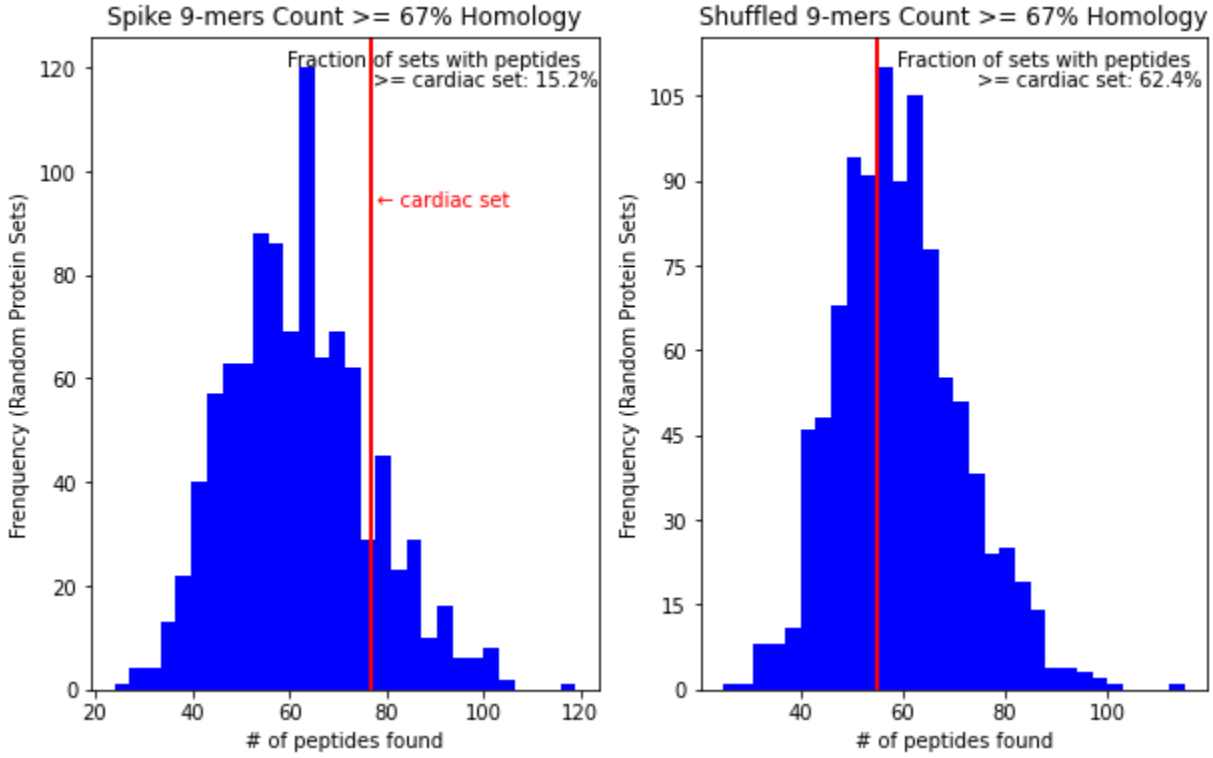
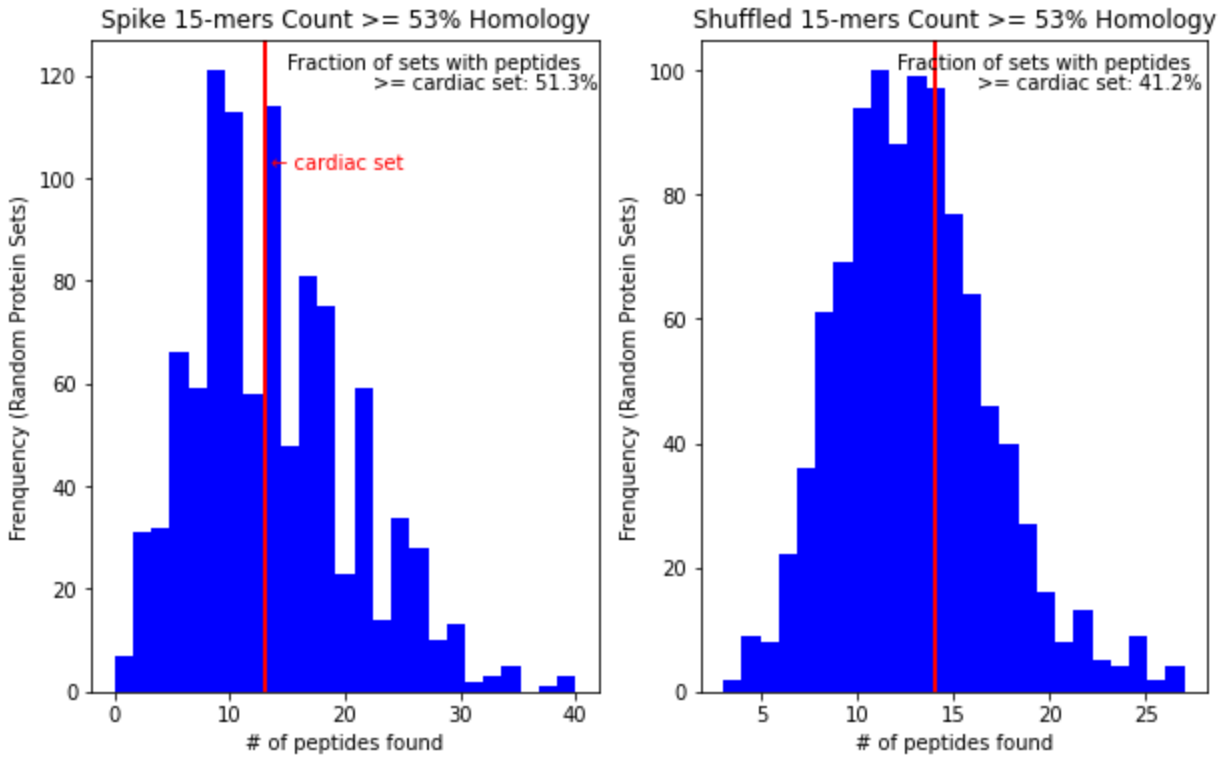


Figure 2. Spike vs shuffled 15-mers >= 53% homology match distribution of 1,000 random protein sets



Discussion

Myocarditis is an inflammatory disease that affects the muscles of the heart which can be caused by an autoimmune mechanism[8]. There have been a number of cases of myocarditis occurring in humans after SARS-CoV-2 infection and with COVID-19 vaccination[4,14]. Here, we examined the potential for a cross-reactivity link based on sequence similarity of the SARS-CoV-2 spike protein encoded in mRNA COVID-19 vaccines and myocarditis-associated proteins. We did not find statistically significant overlap in terms of peptide sequence similarity between these antigens. We also did not find that the peptide conservation within these antigens was significantly higher within a distribution of randomly selected protein sets. This does not support the hypothesis that myocarditis adverse events post-mRNA COVID-19 vaccination are due to cross-reactive reactions of the adaptive immune system. This is further supported by the fact that the median onset of myocarditis incidents occurring post-vaccination was three and a half days and for those hospitalized, the median discharge was two days. By contrast, autoimmune diseases often progress over time through epitope spreading[15]. Overall, the incidents of myocarditis post-vaccination may not be T cell-mediated and perhaps are more compatible with a transient innate response.

There are several caveats to our study. First, the lack of statistical evidence of similarity between vaccine peptides and autoimmune antigens, in general, does not exclude that, in some individuals, there will be a cross-reactive response. Second, when considering epitopes recognized by antibodies, there may well be parts of proteins that are discontinuous in sequence

but form a conserved 3-dimensional pocket that is cross-reactive. Such discontinuous epitopes are not considered in our study.

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Supplementary Material

Table 4. Spike Sequences Homologous to Cardiac Proteins

Spike Peptide Sequence	Matched Peptide Sequence	Cardiac Protein	Gene	UniProt ID	Homology Level
MFVFLVLLPLVSSQC	GGVLLVLLLCVAAQC	Laminin subunit alpha-1	LAMA1	P25391	53%
FVFLVLLPLVSSQCV	GVLLVLLLCVAAQCR	Laminin subunit alpha-1	LAMA1	P25391	53%
VFLVLLPLVSSQCVN	VLLVLLLCVAAQCRQ	Laminin subunit alpha-1	LAMA1	P25391	53%
ITRFQTLLALHRSYL	GSSFQTVSALHRENL	Myosin-7	MYH7	P12883	53%
TRFQTLLALHRSYLT	SSFQTVSALHRENLN	Myosin-7	MYH7	P12883	53%
RFQTLLALHRSYLTP	SFQTVSALHRENLNK	Myosin-7	MYH7	P12883	53%
FQTLLALHRSYLTPG	FQTVSALHRENLNKL	Myosin-7	MYH7	P12883	53%
VITPGTNTSNQVAVL	AITSCTNTSNPSVML	Cytoplasmic aconitate hydratase	ACO1	P21399	53%
ITPGTNTSNQVAVLY	ITSCTNTSNPSVMLG	Cytoplasmic aconitate hydratase	ACO1	P21399	53%
SALGKLQDVVNQNAQ	EALGKAKDANNGNLQ	Lupus La protein	SSB	P05455	53%
ALGKLQDVVNQNAQA	ALGKAKDANNGNLQL	Lupus La protein	SSB	P05455	53%
LQPELDSFKEELDKY	LQKKLKGTEDELDKY	Tropomyosin alpha-1 chain	TPM1	A0A087WTJ7	53%
ISGINASVVNIQKEI	ISGDPAPTVIWQKAI	Myosin-binding protein C, cardiac-type	MYBPC3	A8MXZ9	53%

VFLVLLPLV	VLLVLLLCV	Laminin subunit alpha-1	LAMA1	P25391.2	67%
VNLTTRTQL	VSLTTRVML	Unconventional myosin-VI (Fragment)	MYO6	A0A590UK22	67%
SKTQSLLIV	SCTVSDLIV	Myosin-binding protein C, fast-type	MYBPC2	Q14324	67%
TQSLLIVNN	TVSDLIVGN	Myosin-binding protein C, fast-type	MYBPC2	Q14324	67%
KNLREFVFK	ANLREFSDK	Laminin subunit alpha-1	LAMA1	P25391	67%
NLREFVFKN	NLREFSDKK	Laminin subunit alpha-1	LAMA1	P25391	67%
FVFKNIDGY	FVFFNWLGY	Beta-1 adrenergic receptor	ADRB1	P08588	67%
NLVRDLPQG	ILVKDLPTG	Myosin-binding protein C, cardiac-type	MYBPC3	A0A0A0MQU5	67%
LVRDLPQGF	LVKDLPTGA	Myosin-binding protein C, cardiac-type	MYBPC3	A0A0A0MQU5	67%
TRFQTLLAL	TLDQTLLEL	Tropomyosin beta chain	TPM2	Q5TCU3	67%
RFQTLLALH	SFQTVSALH	Myosin-7	MYH7	P12883	67%
FQTLLALHR	FQTVSALHR	Myosin-7	MYH7	P12883	78%
QTLLALHRS	QTVSALHRE	Myosin-7	MYH7	P12883	67%
PGDSSSGWT	PGTVSSGNT	Laminin subunit alpha-1	LAMA1	P25391	67%
SGWTAGAAA	SGMEAAAAA	Pyruvate kinase PKLR	PKLR	A0A0G2JLC7	67%
ITDAVDCAL	QTDAVQDAL	Laminin subunit alpha-1	LAMA1	P25391	67%

TDAVDCALD	TDAVQDALE	Laminin subunit alpha-1	LAMA1	P25391	67%
RGDEVRQIA	RLDEAEQIA	Myosin-7	MYH7	P12883	67%
VVVLSFELL	VAGLSQELL	Laminin subunit alpha-1	LAMA1	P25391	67%
LSFELLHAP	LRKALLHAP	Laminin subunit alpha-1	LAMA1	P25391	67%
LLHAPATVC	LLHAPTGTC	Laminin subunit alpha-1	LAMA1	P25391	67%
ADTTDAVRD	AAQTDAVQD	Laminin subunit alpha-1	LAMA1	P25391	67%
DAVRDPQTL	DYVRTPVTL	Laminin subunit alpha-1	LAMA1	P25391	67%
VITPGTNTS	AITSCTNTS	Cytoplasmic aconitate hydratase	ACO1	P21399	67%
ITPGTNTSN	ITSCTNTSN	Cytoplasmic aconitate hydratase	ACO1	P21399	78%
TPGTNTSNQ	TSCTNTSNP	Cytoplasmic aconitate hydratase	ACO1	P21399	67%
SNQVAVLYQ	SQQQAVLEQ	Unconventional myosin-VI	MYO6	Q9UM54	67%
EVPVAIHAD	EPPEAIWAD	Pyruvate kinase PKLR	PKLR	P30613	67%
TWRVYSTGS	RKRVYSFGS	Troponin T, cardiac muscle	TNNT2	A0A590UJV2	67%
WRVYSTGSN	KRVYSFGSK	Troponin T, cardiac muscle	TNNT2	A0A590UJV2	67%
RVYSTGSNV	RVYSFGSKT	Troponin T, cardiac muscle	TNNT2	A0A590UJV2	67%
NSVAYSNNS	NSTNSSNNS	Muscarinic	CHRM2	P08172	67%

		acetylcholine receptor M2			
DSTECSNLL	HSTERSCLL	Transmembrane protein 65	TMEM65	Q6PI78	67%
STECSNLLL	STERSCLLK	Transmembrane protein 65	TMEM65	Q6PI78	67%
FCTQLNRAL	FKTQLNLLL	Unconventional myosin-6	MYO6	A0A590UJ40	67%
LNRALTGIA	LSRKLPGIA	Laminin subunit alpha-1	LAMA1	P25391	67%
RALTGIAVE	RKLPGIALE	Laminin subunit alpha-1	LAMA1	P25391	67%
DKNTQEVFA	DEETYEVFA	Creatine kinase (Fragment)	CKMT1A	C9JT96	67%
QILPDPSKP	QIDVDVSKP	Vimentin	VIM	B0YJC5	67%
PSKPSKRSF	ESKPKPRSF	Troponin T, cardiac muscle (Fragment)	TNNT2	E7EPN8	67%
SKPSKRSFI	SKPKPRSFM	Troponin T cardiac isoform	TNNT2	Q7Z554	67%
LLFNKVTLA	LTINKCTLA	Myosin-binding protein C, fast-type	MYBPC2	Q14324	67%
LFNKVTLAD	TINKCTLAD	Myosin-binding protein C, fast-type	MYBPC2	Q14324	67%
FNKVTLADA	INKCTLADD	Myosin-binding protein C, fast-type	MYBPC2	Q14324	67%
NKVTLADAG	NKCTLADDA	Myosin-binding protein C, fast-type	MYBPC2	Q14324	67%
GDIAARDLI	EDIAARLNI	Sodium/potassium-transporting ATPase subunit alpha-1	ATP1A1	P05023	67%

DIAARDLIC	DIAARLNIP	Sodium/potassium-transporting ATPase subunit alpha-1	ATP1A1	P05023	67%
FGAGAALQI	AGAGAVLKI	Laminin subunit alpha-1	LAMA1	A0A1W2PQN4	67%
GAGAALQIP	GAGAVLKIR	Laminin subunit alpha-1	LAMA1	A0A1W2PQN4	67%
NGIGVTQNV	SGDGVTHNV	Actin, alpha cardiac muscle 1	ACTC1	P68032	67%
GIGVTQNVL	GDGVTHNVP	Actin, alpha cardiac muscle 1	ACTC1	P68032	67%
FNSAIGKIQ	FNSAVGHEQ	Laminin subunit alpha-1	LAMA1	P25391	67%
SSTASALGK	SSDRSALLK	Natriuretic peptides A	NPPA	P01160	67%
SALGKLQDV	SALELLQEV	E3 ubiquitin-protein ligase TRIM21	TRIM21	P19474	67%
AQALNTLVK	DQPLNSLVK	Transmembrane protease serine 4	TMPRSS4	A0A087WTU6	67%
QALNTLVKQ	QPLNSLVKV	Transmembrane protease serine 4	TMPRSS4	A0A087WTU6	67%
RLITGRLQS	RLCCCRLQS	Troponin I, cardiac muscle (Fragment)	TNNI3	K7EJP0	67%
LITGRLQSL	LLTGRNASL	Creatine kinase S-type, mitochondrial	CKMT2	P17540	67%
YVTQQLIRA	NVTHLLIRA	Laminin subunit alpha-1	LAMA1	P25391	67%
VTQQLIRAA	VTHLLIRAN	Laminin subunit alpha-	LAMA1	P25391	67%

		1			
LIRAAEIRA	SARAAEILA	Sodium/potassium-transporting ATPase subunit alpha-1	ATP1A1	P05023	67%
IRAAEIRAS	ARAAEILAR	Sodium/potassium-transporting ATPase subunit alpha-1	ATP1A1	P05023	67%
RAAEIRASA	RAAEILARD	Sodium/potassium-transporting ATPase subunit alpha-1	ATP1A1	P05023	67%
HVTYVPAQE	KVEYVPKQE	Myosin-binding protein C, fast-type	MYBPC2	Q14324	67%
VTYVPAQEK	VEYVPKQEP	Myosin-binding protein C, fast-type	MYBPC2	Q14324	67%
NGTHWFVTQ	NILHWNVTQ	Cytoplasmic aconitate hydratase	ACO1	P21399	67%
FYEPQIITT	FYLPVIIMT	Muscarinic acetylcholine receptor M2	CHRM2	P08172	67%
QIITTDNTF	QIIMLFNTF	Laminin subunit alpha-1	LAMA1	P25391	67%
NIQKEIDRL	QIQKEYDAL	Unconventional myosin-6	MYO6	A0A590UJ40	67%
IQKEIDRLN	IQKEYDALV	Unconventional myosin-VI	MYO6	Q9UM54	67%
QKEIDRLNE	QKNKDPLNE	Myosin-7	MYH7	P12883	67%
DLQELGKYE	QLQELEKDE	E3 ubiquitin-protein ligase TRIM21	TRIM21	P19474	67%
LQELGKYEQ	LQELEKDER	E3 ubiquitin-protein ligase	TRIM21	P19474	67%

		TRIM21			
CMTSCCSCL	TGTSCESCL	Laminin subunit alpha-1	LAMA1	P25391	67%
MTSCCSCLK	GTSCESCLS	Laminin subunit alpha-1	LAMA1	P25391	67%
TSCCSCLKG	TSCESCLSG	Laminin subunit alpha-1	LAMA1	P25391	78%
SCCSCLKGC	SCESCLSGY	Laminin subunit alpha-1	LAMA1	P25391	67%