

**Table S1.** Basic demographic details (by gender, age at collection) for the 396 cases and 867 controls that passed all QC and were used in the GWAS analysis.

	RHD Cases	Healthy Controls
Sample size		
Males	130	353
Females	266	514
Total	396	867
Age at collection		
Males		
Mean±SD	37.41±12.80	38.21±12.84
Range	18-74	18.2-83.8
Females		
Mean±SD	37.4±12.94	39.97±13.38
Range	18.3-82.9	18-73.8
Total		
Mean±SD	37.40±12.88	39.25±13.18
Range	18-82.9	18-83.8

**Table S2.** Summary of experimentally confirmed published epitopes for (A) GAS M proteins for which there is evidence of cross-reaction with human heart-related proteins. (B) GAS M proteins for which there is evidence of non-cross-reactive T- and B-epitopes, and (C) other GAS proteins with evidence of cross-reactive epitopes.

Function/peptide name*	Position **	Peptide Studied	AA Location M5	AA Location M6	Reference
<b>(A) GAS M5 and M6 epitopes cross-reactive with human myosin and/or heart valve tissue</b>					
Valve cross-reactive	NT	AVTRGTISDPQR <del>AKEALDKY</del> ELENH	1-25	-	1-4
Myosin cross-reactive NT4	NT	GLKTENEGLKTE <del>N</del> NEGLKTE	33-51	-	5,6
Myosin cross-reactive NT5	NT	KKEHEAENDKLKQQ <del>R</del> DTL	59-76	-	5
Valve cross-reactive	NT	DKLKQQ <del>R</del> DTL <del>S</del> TQKET LKQQRDTL <del>S</del> TQKETLEREVQN STQKETLEREVQN	67-82 69-89 77-89	-	3,4,7
Myosin cross-reactive	NT	QRDTL <del>S</del> TQKETLEREVQN	72-89	-	1-3,5
Myosin cross-reactive B.6 B repeat (B1-B2)	B	TVKDKIAKEQENKETIGTLK VKDKIAKEQENKETIGTL	136-155 161-180	130-149 155-174 180-199	8 5
Myosin cross-reactive B repeat (B1-B2)	B	ETIGTLKKILD <del>E</del> TVK	149-163 174-188	143-157 168-182 193-207	4
Myosin cross-reactive B repeat (B2, B3A)	B	TIGTLKKILD <del>E</del> TVKDKIA IGTLKKILD <del>E</del> TVKDKLAK	150-167 176-193	144-162 169-88; 194-211	9 5
<b>(B) Vaccine candidates and related epitopes (not cross-reactive)</b>					
StreptInCor Vaccine	C	KGLRRDLDASREAKKQLEAEQQKLEE <del>QNKISEASRKGLRRDLDASREAKKQ</del> VEKA KGLRRDLDASREAKKQLEAEQQKLF <del>E</del> QNKISEASRKGLRRDLDASREAKKQ <del>V</del> EKA	223-242; 244-273; 258-277; 279-312	237-260 285-302	10-12
P145 minimal T epitope	C	RDLDASREAKKQ	227-238; 262-273; 298-308	246-257 288-299	13

Human responses India; C-repeat J14	C	KQAEDKVK <b>ASREAKKQVEKALE</b> QLEDRVK	231-238; 301-314	249-261 292-305	<sup>14</sup>
T cell (C1-A)	C	NKISEASRKGLRRDLDASRE	250-269 285-304	234-253 281-295	<sup>8</sup>
C-term p145	C	LRRDLDAS <b>REAKKQVEKALE</b>	224-237 295-314	243-260 286-305	<sup>13,15-18</sup>
P145 minimal B epitope	C	<b>ASREAKKQVEKALE</b>	231-238 301-314	249-260 293-305	<sup>13</sup>
J8 vaccine peptide	C	QAEDKVKQS <b>REAKKQVEKALK</b> QLEDKVQ	<b>302-313</b>	251-260 293-304	<sup>19</sup>
C-term T and B cell	C	KLTEKEKAELQAKLEAEAKA	335-354	325-345	<sup>18</sup>
<b>(C) Other GAS proteins with cross-reactive epitopes</b>					
STRP1 streptopain x vimentin		KKKLGVRLLSLLA	3-15		<sup>20</sup>
HSP70 x vimentin		AYFNDAQRQATKDA	118-131		<sup>20</sup>

**Note 1:** Bold and grey highlights indicate the region of the peptide epitope(s) that matches the AA location for the M5 (Accession Number CAM31002.1) and M6 (Accession Number AAA26920.1) protein sequences used in our epitopes mapping studies. AA locations are for the mature protein sequence (i.e. after removal of the signal peptide). \* Peptide name from the relevant publication; \*\*NT=N terminal region; B= B repeat region; C = C repeat region.

**Note 2:** Many of these epitopes have been worked on in murine and rat<sup>21</sup> models of disease, as recently reviewed,<sup>22</sup> which are not all referenced in this table.

## References

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