Bioinformatic and mutational studies of related toxin–antitoxin pairs in *M. tuberculosis* predict and identify key functional residues

Running title: Toxin-Antitoxin relationships in *M. tuberculosis*

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Keywords: Toxin-antitoxin, homology, paralogues, structure-function, *Mycobacterium tuberculosis*, genome analysis, bacteriostasis, VapBC, PIN domain, phylogeny, molecular modelling, protein evolution

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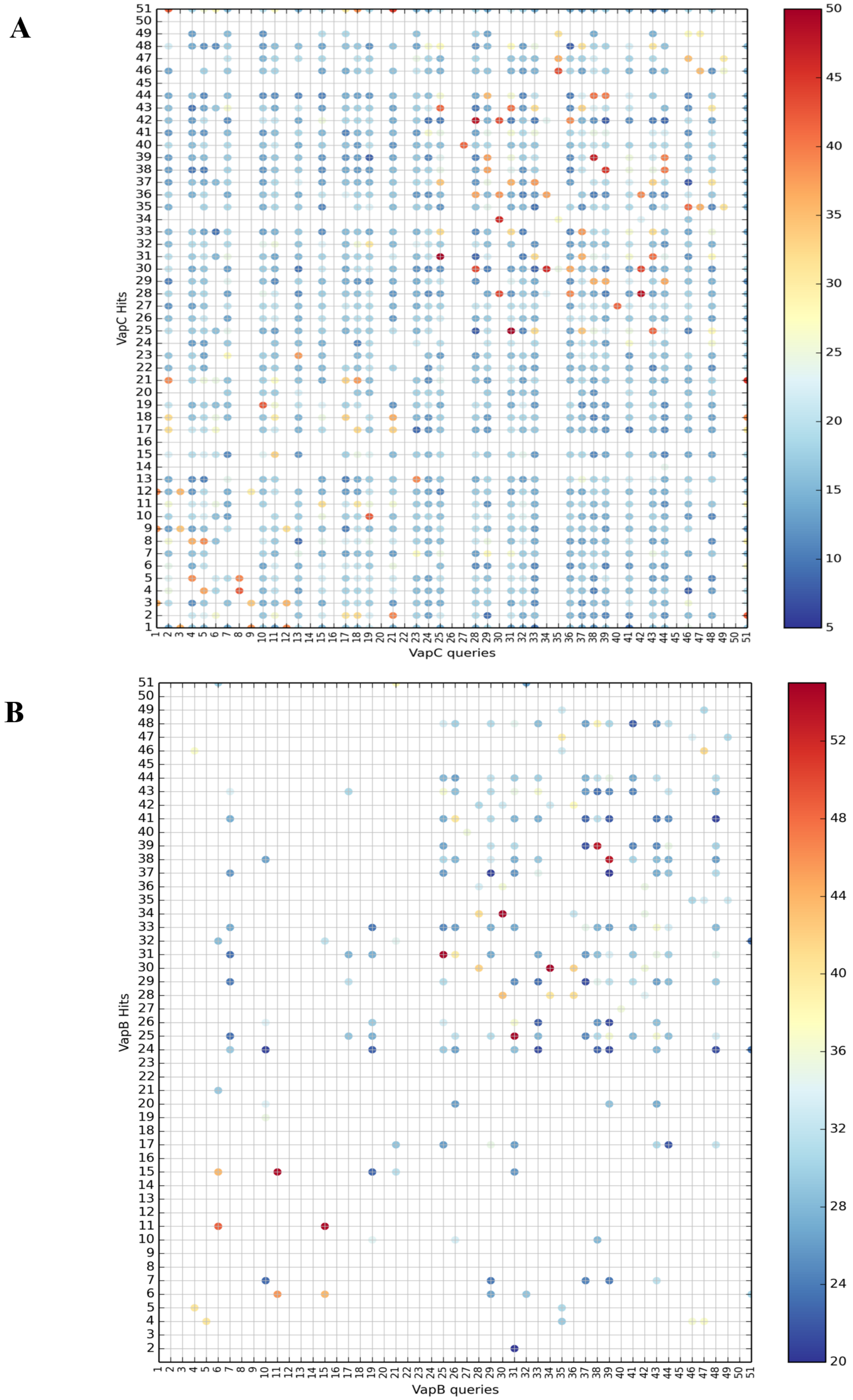


Figure S1: Paralogous VapBC TA within the *M. tuberculosis* genome: Plots show the hits for individual VapC toxin queries **(A)** and VapB antitoxin queries **(B)** in PSI-BLAST searches within the *M.tuberculosis* genome. Each dot represents a hit (on y-axis) for each query in the X-axis. For consideration as a hit, an e-value cut-off of 0.0001 was imposed in the PSI-BLAST searches. Searches were performed till convergence of the runs or a maximum of ten iterations. The color of each dot represents the percent sequence identity of a hit for the query. This ranges from blue-red depending on the sequence identity score. For the purpose of clarity, self-hits that fall along the diagonal of the plot are not reported in the figure and the sequence identity for toxins is capped at a maximum value of 50% and for antitoxins at 55%.

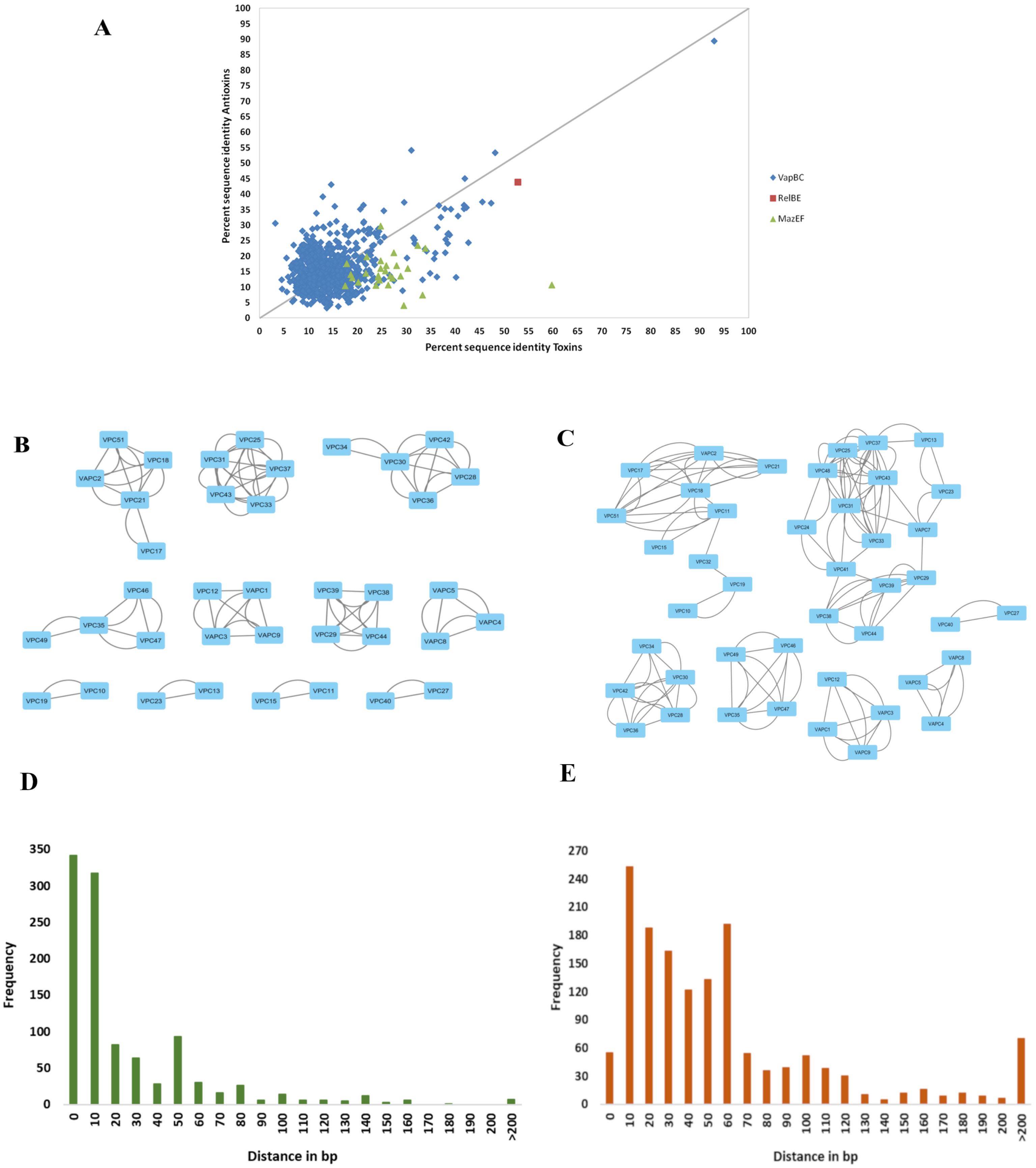


Figure S2 : **(A)** Scatter plot comparing the distribution of sequence identity between the various toxins along the X-axis and their cognate antitoxin pairs in the Y-axis. For VapBC toxins, for e.g, percentage sequence identity scores of each VapC toxin with every other VapC toxin is determined. Likewise, the sequence identity score of each VapB antitoxin with every other VapB antitoxin is determined. The points on the plot show the distribtion of scores for each such pair. VapBC scores are represented using blue diamonds, MazEF with grey triangles and RelBE with red squares. Clustering of *M. tuberculosis* VapC toxins at search thresholds of 60% query coverage and **(B)** 30% and **(C)** 25% sequence identity. 11 and 7 distinct clusters were formed separately. Histogram of distances (in bp) between the homologues of *M. tuberculosis* toxin and antitoxin detected for **(D)** mycobacteria and **(E)** other prokaryotic genomes.

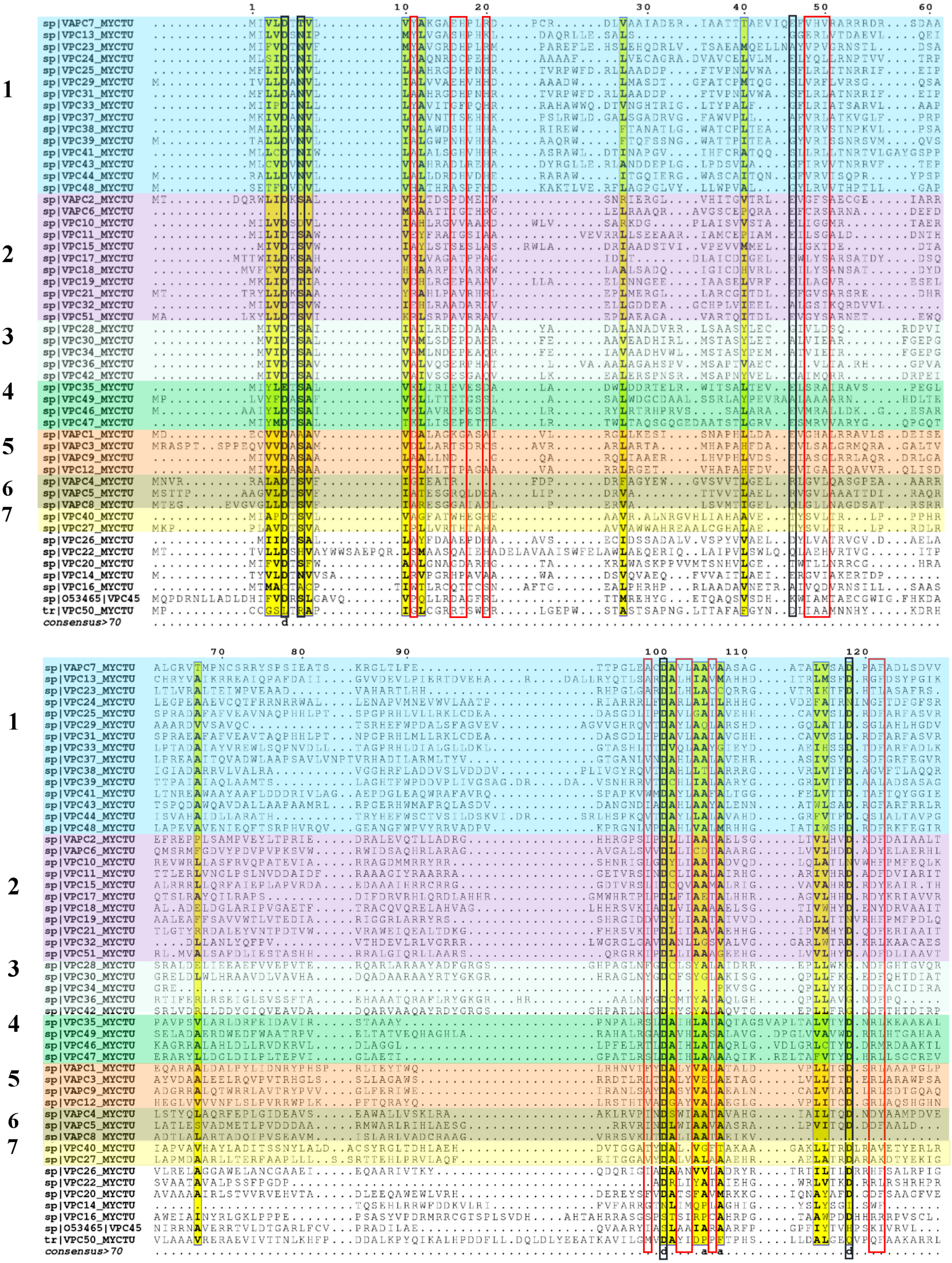
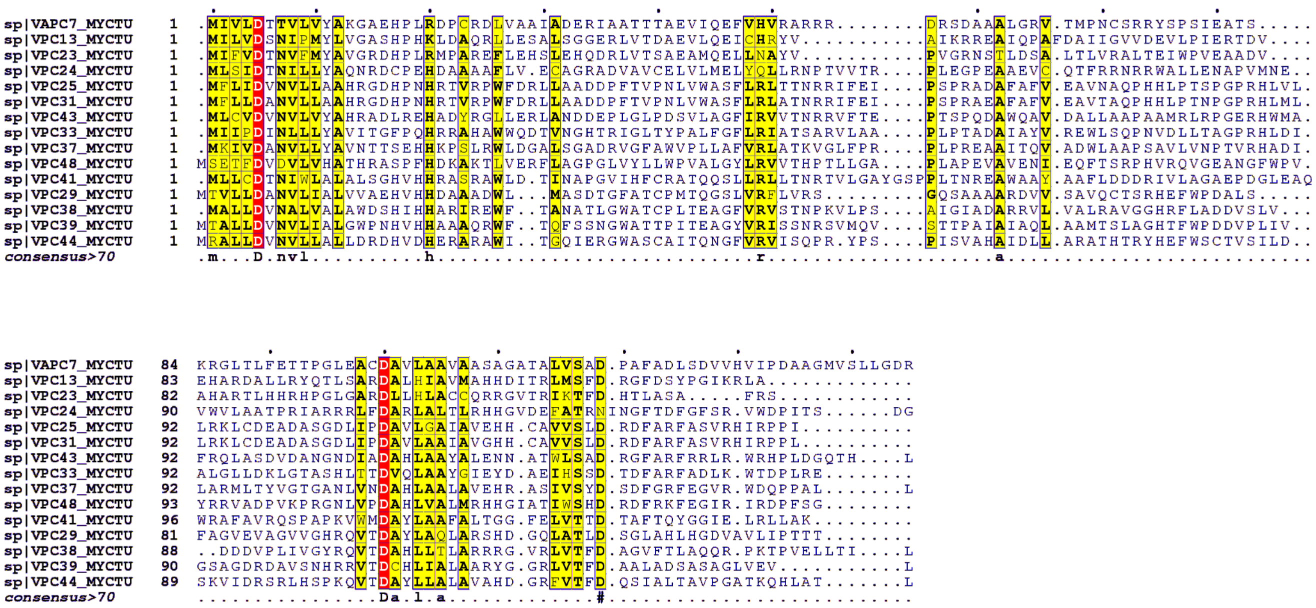


Figure S3 : Multiple sequence alignment of 51 VapC toxins of *M.tuberculosis* using MAFFT. Clusters are numbered from 1-7 and each cluster is indicated by a distinct color. The characteristic quartet of acidic residues of the PIN domain, that are well conserved across the cluster members, are shown marked in black boxes. Alignment positions, where residues that are fairly well conserved within a cluster but differ from residues in the same position in other clusters, are marked within a red box.



A Sub-cluster 1

```
sp|VAPC7_MYCTU    1  .MIVLDTTVLVYAKGAEHPLRDPCRDLVAAIADERIAATTTAEVIQEFVHVRARRR........DRSDAAALGRV.TMPNCSRRYSPSIEATS.....
sp|VPC13_MYCTU    1  .MILVDSNIPMYLVGASHPHKLDAQRLLESALSGGERLVTDAEVLQEICHRYV...........AIKRREAIQPAFDAIIGVVDEVLPIERTDV....
sp|VPC23_MYCTU    1  .MIFVDTNVFMYAVGRDHPLRMPAREFLEHSLEHQDRLVTSAEAMQELLNAYV...........PVGRNSTLDSA.LTLVRALTEIWPVEAADV....
sp|VPC24_MYCTU    1  .MLSIDTNILLYAQNRDCPEHDAAAAFLV.ECAGRADVAVCELVLMELYQLLRNPTVVTR....PLEGPEAAEVC.QTFRRNRRWALLENAPVMNE..
sp|VPC25_MYCTU    1  .MFLIDVNVLLAAHRGDHPNHRTVRPWFDRLLAADDPFTVPNLVWASFLRLTTNRRIFEI....PSPRADAFAFV.EAVNAQPHHLPTSPGPRHLVL.
sp|VPC31_MYCTU    1  .MFLLDANVLLAAHRGDHPNHRTVRPWFDRLLAADDPFTVPNLVWASFLRLATNRRIFEI....PSPRAEAFAFV.EAVTAQPHHLPTNPGPRHLML.
sp|VPC43_MYCTU    1  .MLCVDVNVLVYAHRADLREHADYRGLLERLANDDEPLGLPDSVLAGFIRVVTNRRVFTE....PTSPQDAWQAV.DALLAAPAAMRLRPGERHWMA.
sp|VPC33_MYCTU    1  .MIIPDINLLLYAVITGFPQHRRAHAWWQDTVNGHTRIGLTYPALFGFLRIATSARVLAA....PLPTADAIAYV.REWLSQPNVDLLTAGPRHLDI.
sp|VPC37_MYCTU    1  .MKIVDANVLLYAVNTTSEHHKPSLRWLDGALSGADRVGFAWVPLLAFVRLATKVGLFPR....PLPREAAITQV.ADWLAAPSAVLVNPTVRHADI.
sp|VPC48_MYCTU    1  MSETFDVDVLVHATHRASPFHDKAKTLVERFLAGPGLVYLLWPVALGYLRVVTHPTLLGA....PLAPEVAVENI.EQFTSRPHVRQVGEANGFWPV.
sp|VPC41_MYCTU    1  .MLLCDTNIWLALALSGHVHHRASRAWLD.TINAPGVIHFCRATQQSLLRLLTNRTVLGAYGSPPLTNREAWAAY.AAFLDDDRIVLAGAEPDGLEAQ
sp|VPC29_MYCTU    1  MTVLLDANVLIALVVAEHVHHDAAADWL...MASDTGFATCPMTQGSLVRFLVRS.........GQSAAAARDVV.SAVQCTSRHEFWPDALS.....
sp|VPC38_MYCTU    1  .MALLDVNALVALAWDSHIHHARIREWF..TANATLGWATCPLTEAGFVRVSTNPKVLPS....AIGIADARRVL.VALRAVGGHRFLADDVSLV...
sp|VPC39_MYCTU    1  MTALLDVNVLIALGWPNHVHHAAAQRWF..TQFSSNGWATTPITEAGYVRISSNRSVMQV....STTPAIAIAQL.AAMTSLAGHTFWPDDVPLIV..
sp|VPC44_MYCTU    1  MRALLDVNVLLALLDRDHVDHERARAWI..TGQIERGWASCAITQNGFVRVISQPR.YPS....PISVAHAIDLL.ARATHTRYHEFWSCTVSILD..
consensus>70         .m...D.nvl..........h............................r....................a...........................

sp|VAPC7_MYCTU   84  KRGLTLFETTPGLEACDAVLAAVAASAGATALVSAD.PAFADLSDVVHVIPDAAGMVSLLGDR
sp|VPC13_MYCTU   83  EHARDALLRYQTLSARDALHIAVMAHHDITRLMSFD.RGFDSYPGIKRLA.............
sp|VPC23_MYCTU   82  AHARTLHHRHPGLGARDLLHLACCQRRGVTRIKTFD.HTLASA....FRS.............
sp|VPC24_MYCTU   90  VWVLAATPRIARRRLFDARLALTLRHHGVDEFATRNINGFTDFGFSR.VWDPITS......DG
sp|VPC25_MYCTU   92  LRKLCDEADASGDLIPDAVLGAIAVEHH.CAVVSLD.RDFARFASVRHIRPPI..........
sp|VPC31_MYCTU   92  LRKLCDEADASGDLIPDAVLAAIAVGHH.CAVVSLD.RDFARFASVRHIRPPL..........
sp|VPC43_MYCTU   92  FRQLASDVDANGNDIADAHLAAYALENN.ATWLSAD.RGFARFRRLR.WRHPLDGQTH....L
sp|VPC33_MYCTU   92  ALGLLDKLGTASHLTTDVQLAAYGIEYD.AEIHSSD.TDFARFADLK.WTDPLRE........
sp|VPC37_MYCTU   92  LARMLTYVGTGANLVNDAHLAALAVEHR.ASIVSYD.SDFGRFEGVR.WDQPPAL.......L
sp|VPC48_MYCTU   93  YRRVADPVKPRGNLVPDAHLVALMRHHGIATIWSHD.RDFRKFEGIR.IRDPFSG........
sp|VPC41_MYCTU   96  WRAFAVRQSPAPKVWMDAYLAAFALTGG.FELVTTD.TAFTQYGGIE.LRLLAK.........
sp|VPC29_MYCTU   81  FAGVEVAGVVGHRQVTDAYLAQLARSHD.GQLATLD.SGLAHLHGDVAVLIPTTT........
sp|VPC38_MYCTU   88  ..DDDVPLIVGYRQVTDAHLLTLARRRG.VRLVTFD.AGVFTLAQQR.PKTPVELLTI....L
sp|VPC39_MYCTU   90  GSAGDRDAVSNHRRVTDCHLIALAARYG.GRLVTFD.AALADSASAGLVEV...........L
sp|VPC44_MYCTU   89  SKVIDRSRLHSPKQVTDAYLLALAVAHD.GRFVTFD.QSIALTAVPGATKQHLAT.......L
consensus>70         ................Da.l.a.............#...........................
```

B Sub-cluster 4

```
sp|VPC35_MYCTU    1  ..MIYLETSALVKLIRIEVESDALADWLD.......DRTELRWITSALTEVELSRAIRAV
sp|VPC46_MYCTU    1  MAAIYLDSSAIVKLAVREPESDALRRYL.........RTRHPRVSSALARAEVMRALLDK
sp|VPC47_MYCTU    1  ..MIYMDTSALTKLLISEPETTELRTWLTA.....QSGQGEDAATSTLGRVESMRVVARY
sp|VPC49_MYCTU    1  MPLVYFDASAFVKLLTTETGSSLASALWDGCDAALSSRLAYPEVRAALAAAARNHDLTES
consensus>70         ..m!Yl#.SA.vKL...E.es..l...l.........r.....v.saL...e..r.....

sp|VPC35_MYCTU   52  S.PEGLPAVPSVLARLDRFEIDAVIRSTAAAYPNP.ALRSLDAIHLATAQTAGSVAPLTA
sp|VPC46_MYCTU   52  G.ESARKAGRRALAHLDLLRVDKRVLDLAGGLLPF.ELRTLDAIHLATAQRLG..VDLGR
sp|VPC47_MYCTU   54  GQPGQTERARYLLDGLDILPLTEPVIGLAETIGPA.TLRSLDAIHLAAAAQIK..RELTA
sp|VPC49_MYCTU   61  ELADAERDWEDFWAATRPVELTATVEQHAGHLARAHALRGADAVHLASALAVG..DPGLV
consensus>70         ............la.ld.......!...A........LR.lDA!HLA.A...g....l..

sp|VPC35_MYCTU  110  LVTYDNRLKEAAEALSLAVVAPGQAR.
sp|VPC46_MYCTU  108  LCTYDDRMRDAAKTLGMAVIAPS....
sp|VPC47_MYCTU  111  FVTYDHRLLSGCREVGFVTASPGAVR.
sp|VPC49_MYCTU  119  VAVWDRRLHTGAHAAG.CRVAPAQLDP
consensus>70         ..tyD.R$...a...g...vaP.....
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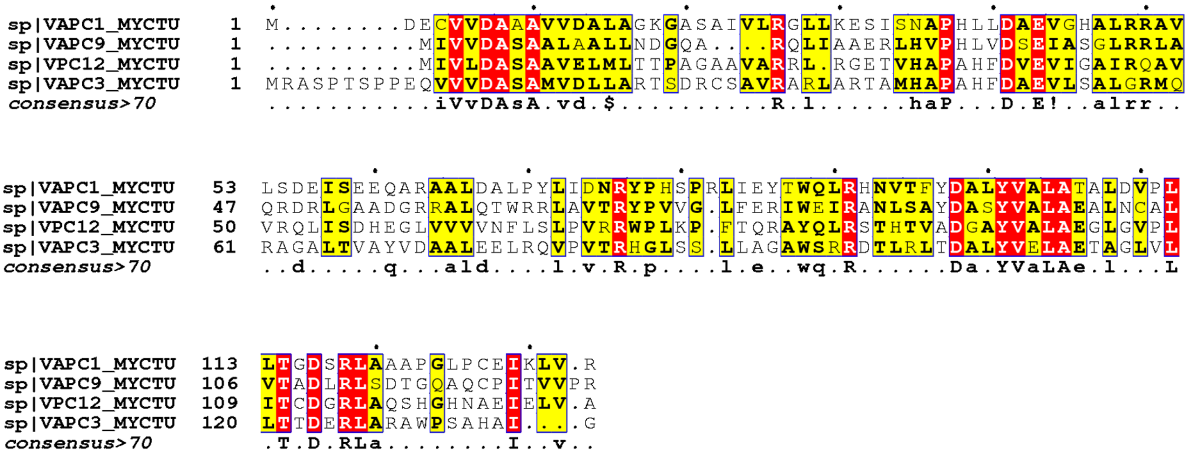


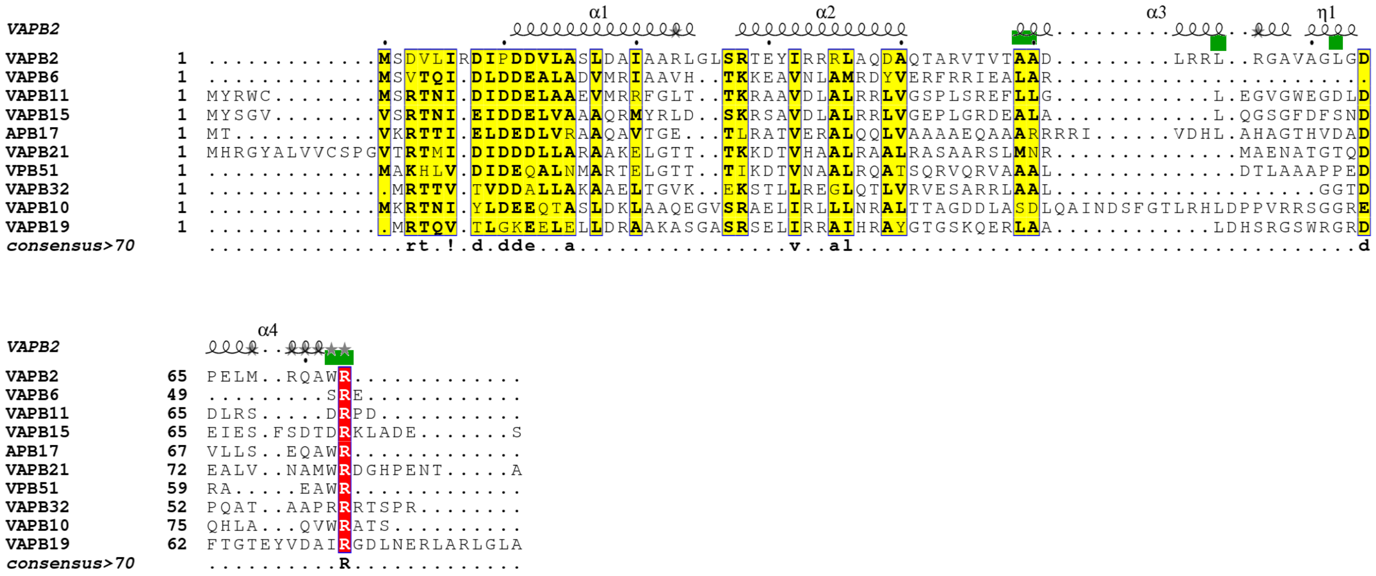
C Sub-cluster 5

```
sp|VAPC1_MYCTU    1  M........DECVVDAAAVVDALAGKGASAIVLRGLLKESISNAPHLLDAEVGHALRRAV
sp|VAPC9_MYCTU    1  ..........MIVVDASAALAALLNDGQA....RQLIAAERLHVPHLVDSEIASGLRRLA
sp|VPC12_MYCTU    1  ..........MIVLDASAAVELMLTTPAGAAVARRL.RGETVHAPAHFDVEVIGAIRQAV
sp|VAPC3_MYCTU    1  MRASPTSPPEQVVVDASAMVDLLARTSDRCSAVRARLARTAMHAPAHFDAEVLSALGRMQ
consensus>70         ...........iVvDAsA.vd.$..........R.l......haP...D.E!..alrr..

sp|VAPC1_MYCTU   53  LSDEISEEQARAALDALPYLIDNRYPHSPRLIEYTWQLRHNVTFYDALYVALATALDVPL
sp|VAPC9_MYCTU   47  QRDRLGAADGRRALQTWRRLAVTRYPVVG.LFERIWEIRANLSAYDASYVALAEALNCAL
sp|VPC12_MYCTU   50  VRQLISDHEGLVVVVNFLSLPVRRWPLKP.FTQRAYQLRSTHTVADGAYVALAEGLGVPL
sp|VAPC3_MYCTU   61  RAGALTVAYVDAALEELRQVPVTRHGLSS.LLAGAWSRRDTLRLTDALYVELAETAGLVL
consensus>70         ..d.....q...ald....l.v.R.p....l.e..wq.R......Da.YVaLAe.l...L

sp|VAPC1_MYCTU  113  LTGDSRLAAAPGLPCEIKLV.R
sp|VAPC9_MYCTU  106  VTADLRLSDTGQAQCPITVVPR
sp|VPC12_MYCTU  109  ITCDGRLAQSHGHNAEIELV.A
sp|VAPC3_MYCTU  120  LTTDERLARAWPSAHAI....G
consensus>70         .T.D.RLa........I..v..
```

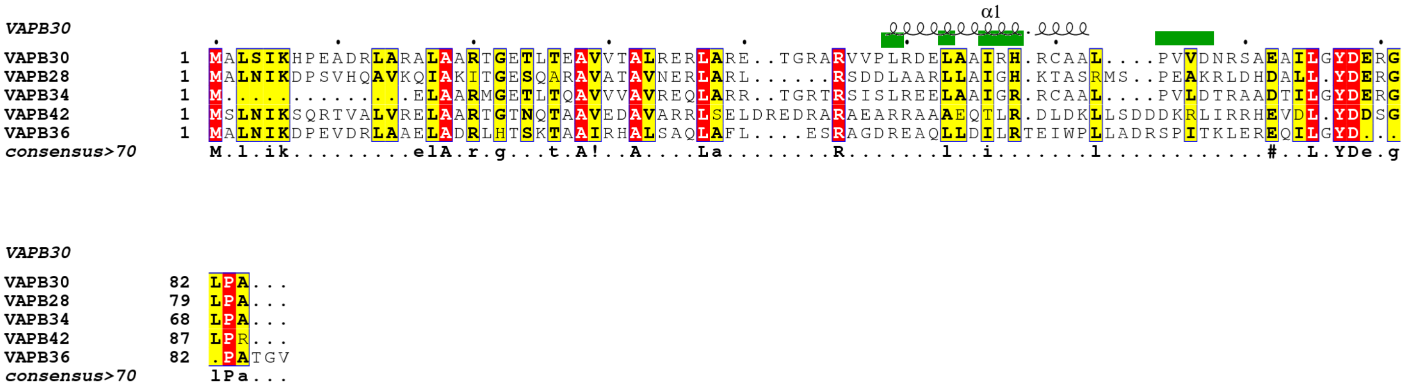
D Sub-cluster 2 (Antitoxin)



```
VAPB2
VAPB2         1 .............MSDVLIRDIPDDVLASLDAIAARLGLSRTEYIRRRLAQDAQTARVTVTAAD.........LRRL..RGAVAGLGD
VAPB6         1 .............MSVTQI.DLDDEALADVMRIAAVH..TKKEAVNLAMRDYVERFRRIEALAR........................
VAPB11        1 MYRWC........MSRTNI.DIDDELAAEVMRRFGLT..TKRAAVDLALRRLVGSPLSREFLLG............L.EGVGWEGDLD
VAPB15        1 MYSGV........VSRTNI.EIDDELVAAAQRMYRLD..SKRSAVDLALRRLVGEPLGRDEALA............L.QGSGFDFSND
APB17         1 MT...........VKRTTI.ELDEDLVRAAQAVTGE...TLRATVERALQQLVAAAAEQAAARRRRI......VDHL.AHAGTHVDAD
VAPB21        1 MHRGYALVVCSPGVTRTMI.DIDDDLLARAAKELGTT..TKKDTVHAALRAALRASAARSLMNR..............MAENATGTQD
VPB51         1 .............MAKHLV.DIDEQALNMARTELGTT..TIKDTVNAALRQATSQRVQRVAAAL..............DTLAAAPPED
VAPB32        1 ..............MRTTV.TVDDALLAKAAELTGVK..EKSTLLREGLQTLVRVESARRLAAL....................GGTD
VAPB10        1 .............MKRTNI.YLDEEQTASLDKLAAQEGVSRAELIRLLLNRALTTAGDDLASDLQAINDSFGTLRHLDPPVRRSGGRE
VAPB19        1 ..............MRTQV.TLGKEELELLDRAAKASGASRSELIRRAIHRAYGTGSKQERLAA............LDHSRGSWRGRD
consensus>70    ...............rt.!.d.dde..a................v..al......................................d

VAPB2
VAPB2        65 PELM..RQAWR.............
VAPB6        49 .........SRE............
VAPB11       65 DLRS.....DRPD...........
VAPB15       65 EIES.FSDTDRKLADE.......S
APB17        67 VLLS..EQAWR.............
VAPB21       72 EALV..NAMWRDGHPENT.....A
VPB51        59 RA.....EAWR.............
VAPB32       52 PQAT..AAPRRRTSPR........
VAPB10       75 QHLA...QVWRATS..........
VAPB19       62 FTGTEYVDAIRGDLNERLARLGLA
consensus>70    ..........R.............
```

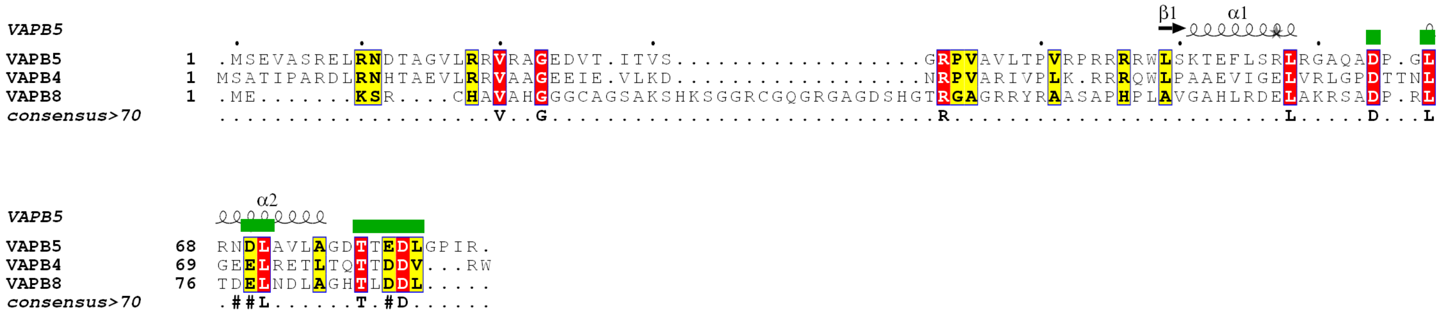
E Sub-cluster 3 (Antitoxin)



```
VAPB30
VAPB30        1 MALSIKHPEADRLARALAARTGETLTEAVVTALRERLARE..TGRARVVPLRDELAAIRH.RCAAL....PVVDNRSAEAILGYDERG
VAPB28        1 MALNIKDPSVHQAVKQIAKITGESQARAVATAVNERLARL......RSDDLAARLLAIGH.KTASRMS..PEAKRLDHDALL.YDERG
VAPB34        1 M..............ELAARMGETLTQAVVVAVREQLARR..TGRTRSISLREELAAIGR.RCAAL....PVLDTRAADTILGYDERG
VAPB42        1 MSLNIKSQRTVALVRELAARTGTNQTAAVEDAVARRLSELDREDRARAEARRAAAEQTLR.DLDKLLSDDDKRLIRRHEVDL.YDDSG
VAPB36        1 MALNIKDPEVDRLAAELADRLHTSKTAAIRHALSAQLAFL....ESRAGDREAQLLDILRTEIWPLLADRSPITKLEREQILGYD...
consensus>70    M.l.ik.........elA.r.g...t.A!..A....La........R.......l..i.......l............#..L.YDe.g

VAPB30
VAPB30       82 LPA...
VAPB28       79 LPA...
VAPB34       68 LPA...
VAPB42       87 LPR...
VAPB36       82 .PATGV
consensus>70    lPa...
```

F Sub-cluster 6 (Antitoxin)



```
VAPB5
VAPB5         1 .MSEVASRELRNDTAGVLRRVRAGEDVT.ITVS..................GRPVAVLTPVRPRRRRWLSKTEFLSRLRGAQADP.GL
VAPB4         1 MSATIPARDLRNHTAEVLRRVAAGEEIE.VLKD..................NRPVARIVPLK.RRRQWLPAAEVIGELVRLGPDTTNL
VAPB8         1 .ME.......KSR....CHAVAHGGGCAGSAKSHKSGGRCGQGRGAGDSHGTRGAGRRYRAASAPHPLAVGAHLRDELAKRSADP.RL
consensus>70    ....................V..G............................R........................L.....D...L

VAPB5
VAPB5        68 RNDLAVLAGDTTEDLGPIR.
VAPB4        69 GEELRETLTQTTDDV...RW
VAPB8        76 TDELNDLAGHTLDDL.....
consensus>70    .##L......T.#D......
```

Figure S4: Multiple sequence alignments of VapC toxins from 4 of the 7 clusters shown in Figure 1 are shown in panels **(A)** to **(C)**. Conserved residues are highlghted in red while conservatively substituted residues are highlighted in yellow and in bold font. **(D)** to **(F)** show the alignment of VapB antitoxins as suggested by Figure 1, with toxin-binding residues indicated in green.

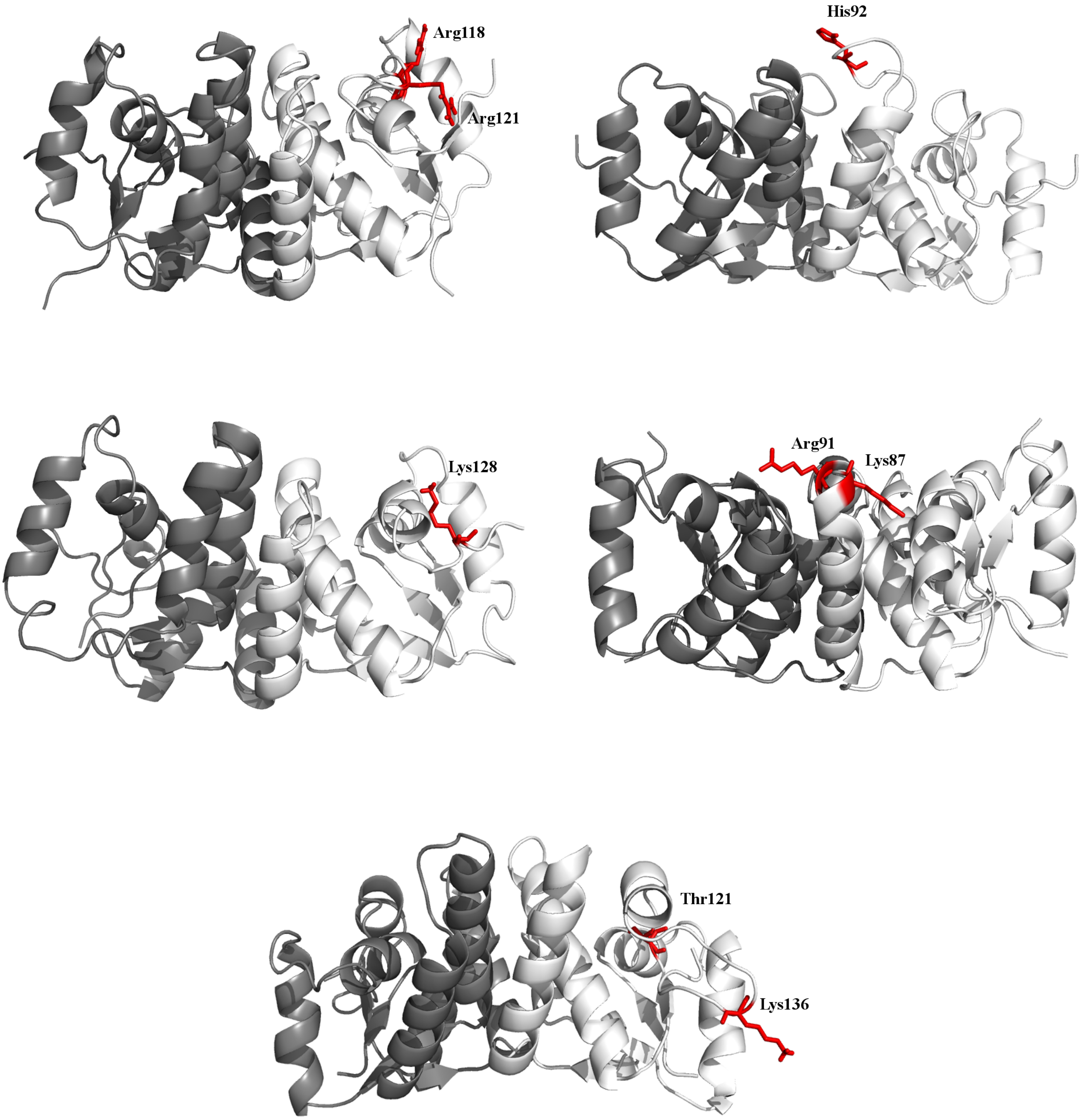


Figure S5: Structural models for various toxins used for computational alanine scanning. The models for Rv0528c, Rv0609, Rv1838c and Rv3320c were generated by modeller v9.14 using templates identified by Phyre2. The structure for Rv2757c was obtained from PDB (5sv2). The residues predicted to be important for toxin funciton that were mutated in experiments are shown in red sticks.

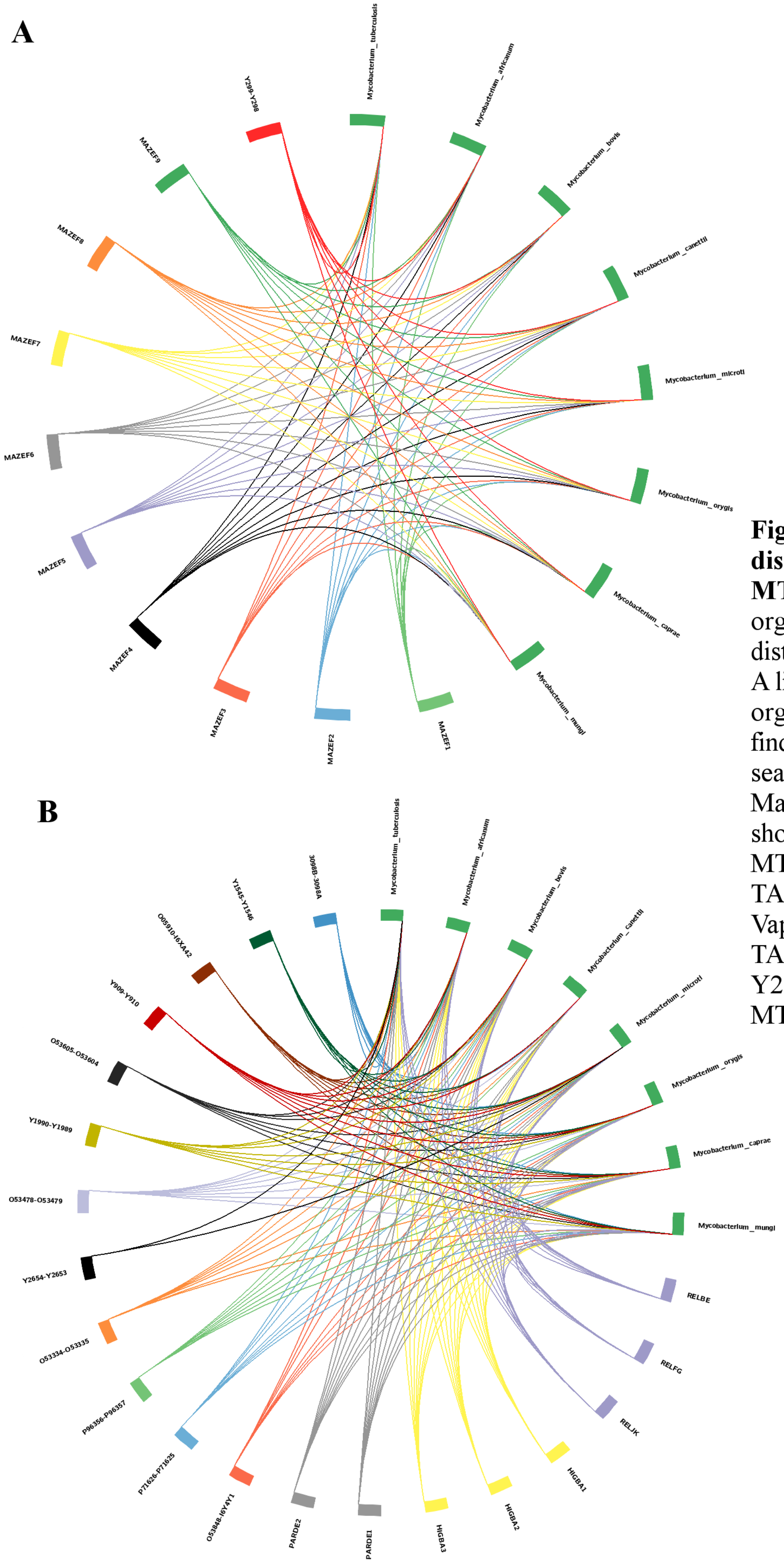


Figure S6: Circos plots showing the distribution of *M. tuberculosis* TA pairs in MTBC. In the plots, the nodes represent organism names and TA types that are grouped distinctly to facilitate interpretation of the figures. A line is drawn between a TA node and that of an organism if both the toxin and antitoxin query find a homologue in PSI-BLAST and TBLASTN searches. **(A)** shows the distribution of 10 MazEFs in the 8 MTBC of this study. The plots show that these TA are well-conserved in the MTBC (Table S6). **(B)** shows the distribution of TA systems in MTBC for query types other than VapBC and MazEF. As shown here, not all such TA are conserved as TA pairs in MTBC. E.g. Y2654-Y2653 is conserved only in 2 of the 8 MTBC in the dataset.

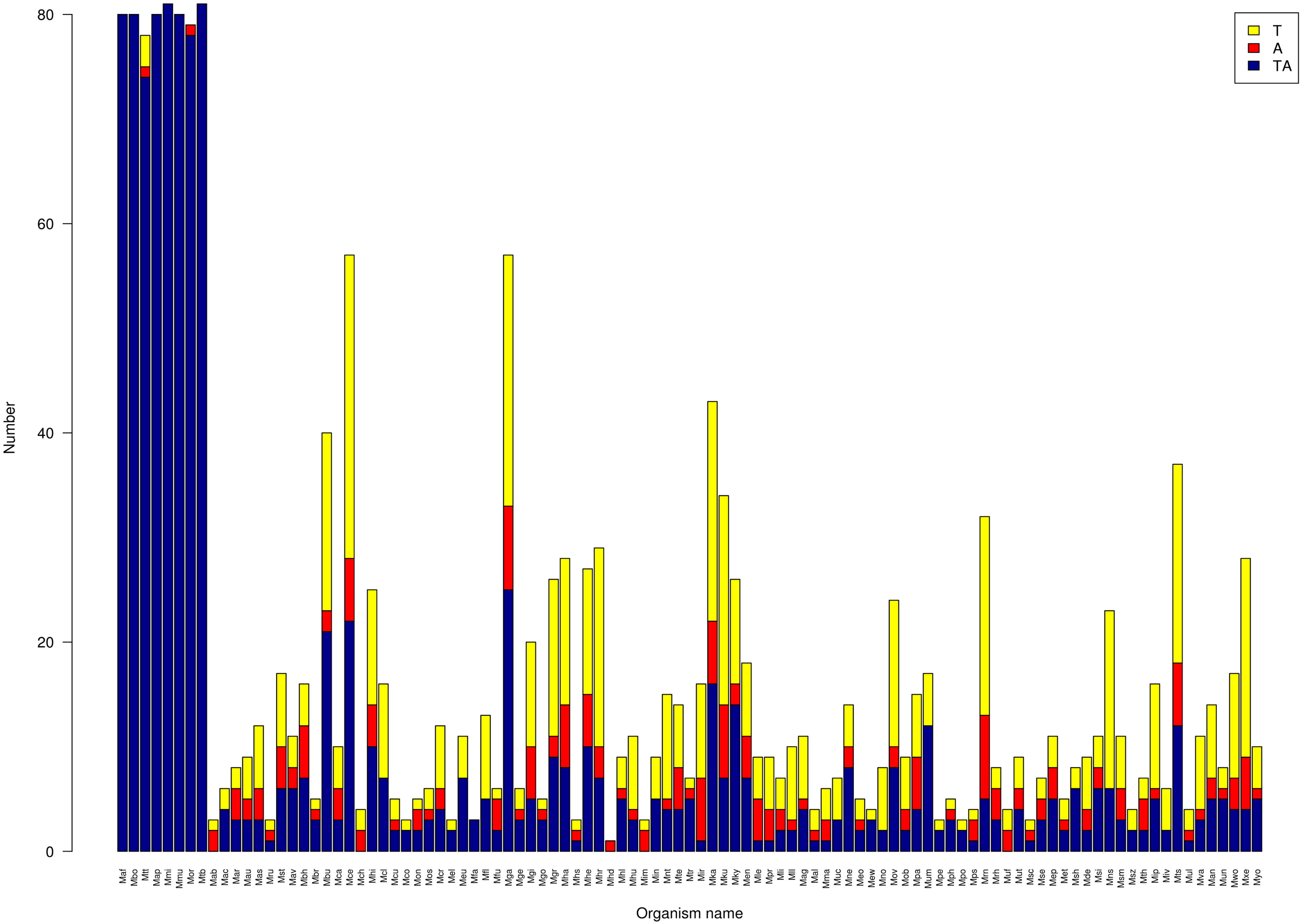
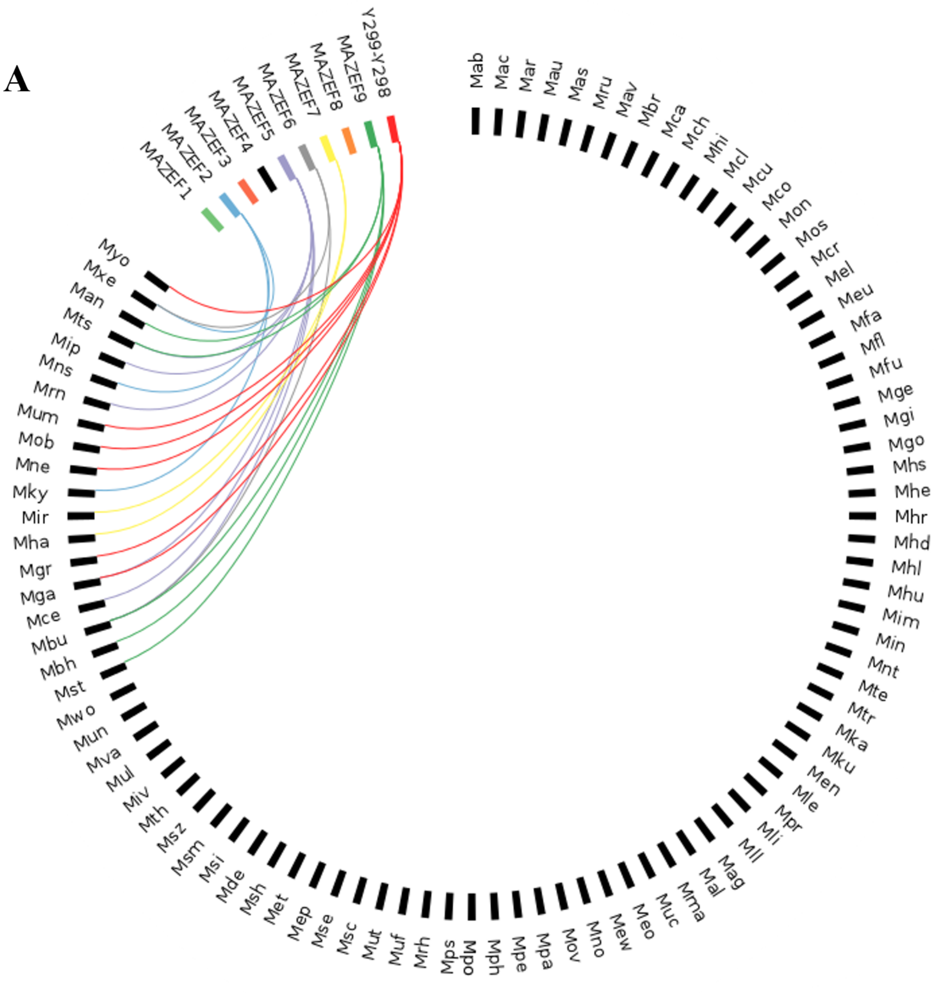


Figure S7: Plot showing the distribution of *M.tuberculosis* TA in the genus Mycobacterium. Relative abundance of the toxin and antitoxin homologues in the genus Mycobacterium. The Mycobacteria species employed in this study are listed on the X-axis using three letter codes to designate the organism (Mapping file of the code to organism name is in Table S7). The Y-axis shows the number of toxin/antitoxin/ TA pairs that were detected in the PSI-BLAST searches performed in the various genomes. Members of the MTBC complex are listed first.

A



B

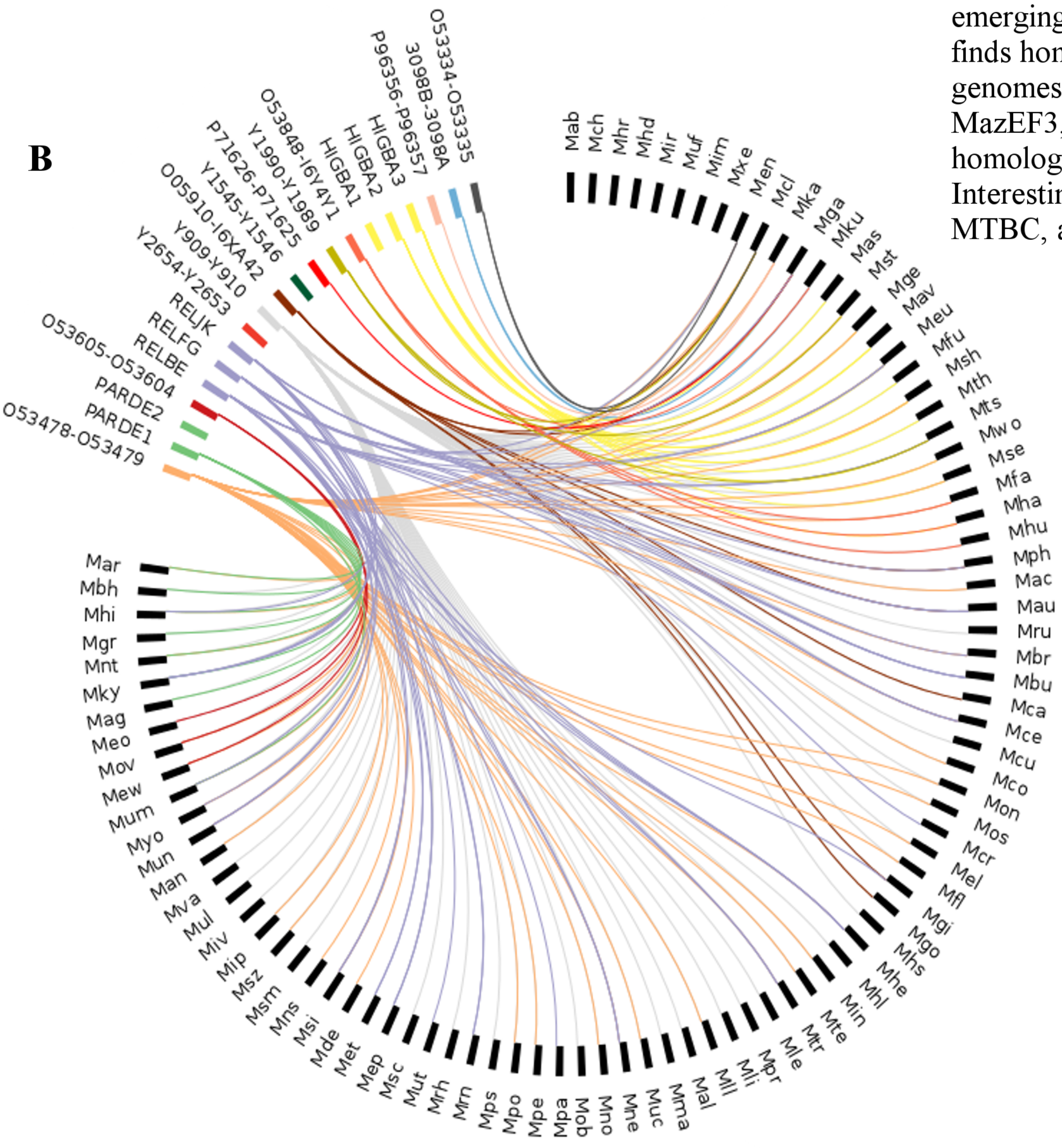


Figure S8: Circos plots showing the distribution of MazEF *M. tuberculosis* TA pairs in 93 Mycobacterial genomes excluding MTBC in **(A)** and the distribution of, all other TA in other prokaryotic genomes is shown in **(B)**.Organism names are indicated with three-letter codes as listed in Table S7. The graphs are useful to visually appreciate the spread of homologues in the various genomes studied here. For example, in (A), dense lines emerging from MazEF9 show that this TA finds homologues in a few mycobacterial genomes surveyed here. In contrast, MazEF3, MazEF8 and others do not find homologues in any of the organisms. Interestingly, all queries find homologues in MTBC, as shown in Figure S6.

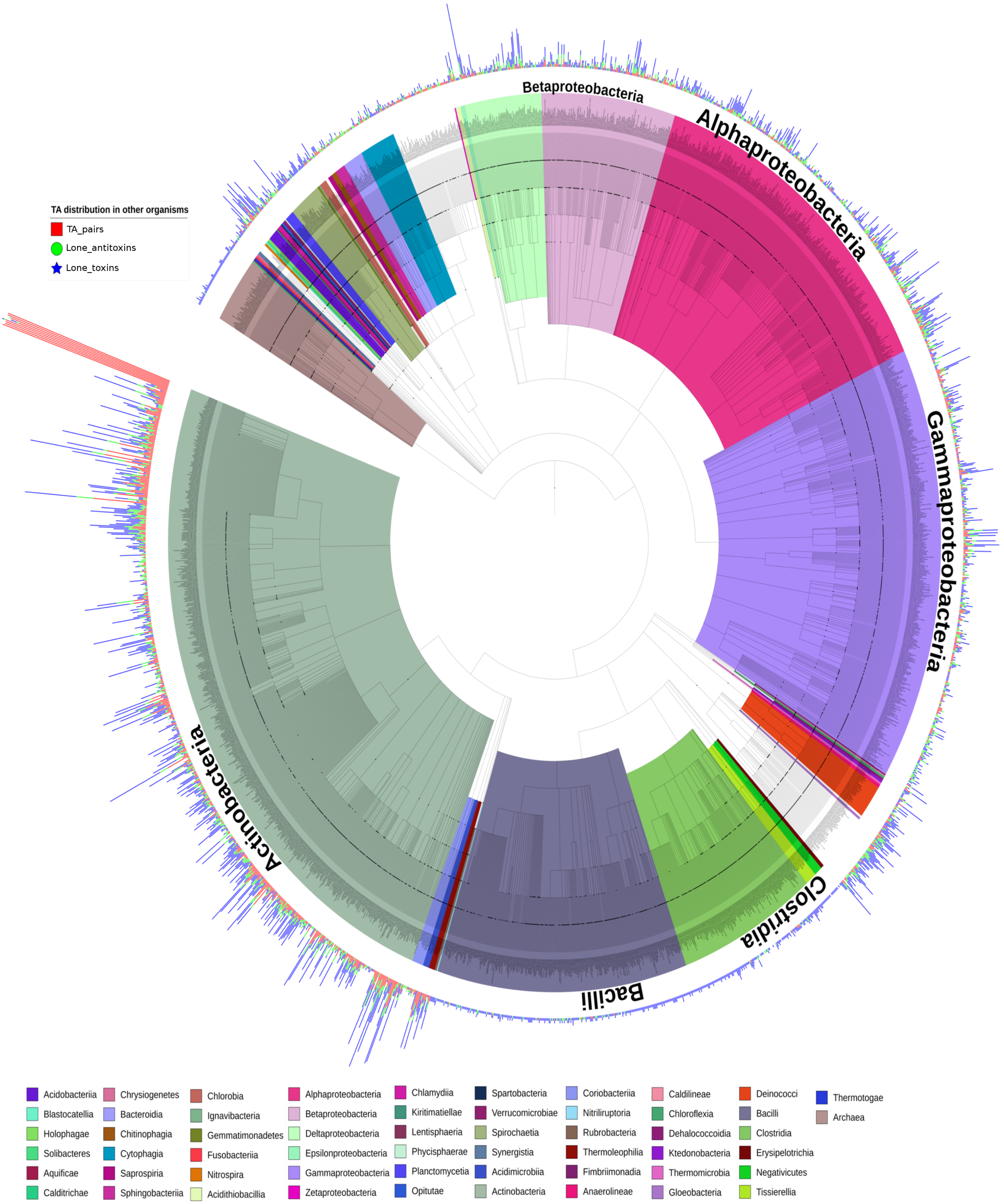


Figure S9: Phylogenetic tree showing distribution of *M.tuberculosis* TA across prokaryotic taxa. 2220 genomes containing homologues of TAs have been grouped into 54 classes shown in different colors. The organisms that are not shown in color have not been assigned a class according to NCBI taxonomy database. Outer bar-plot shows the number of *M.tuberculosis* TA homologs found in these organisms. An interactive link to this tree can be accessed at https://itol.embl.de/tree/1413912822138041518174018 where the user can hover over the tree branches for detailed data visualization. For best visibility, users are advised to visualize the tree in Firefox browser.

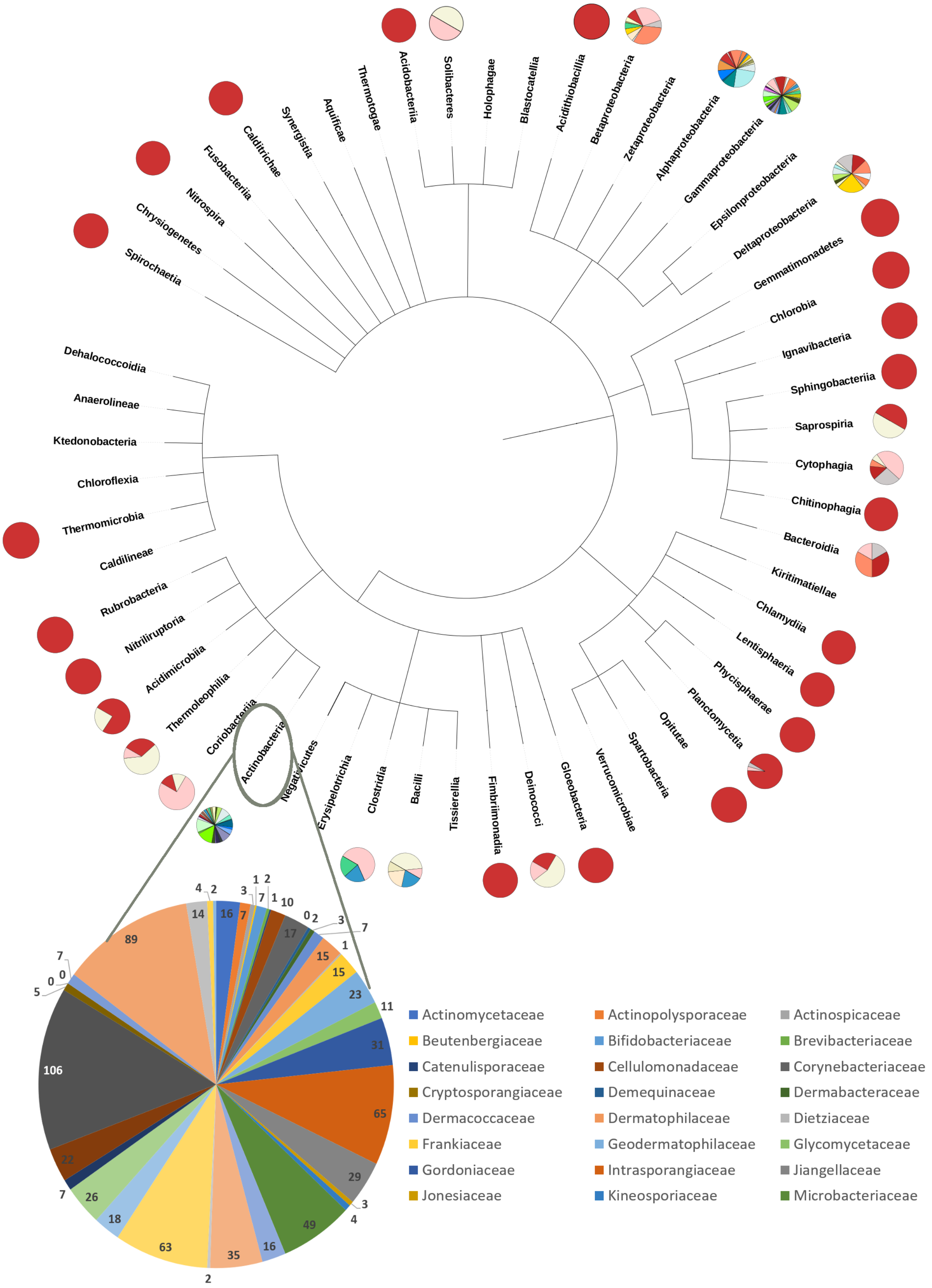
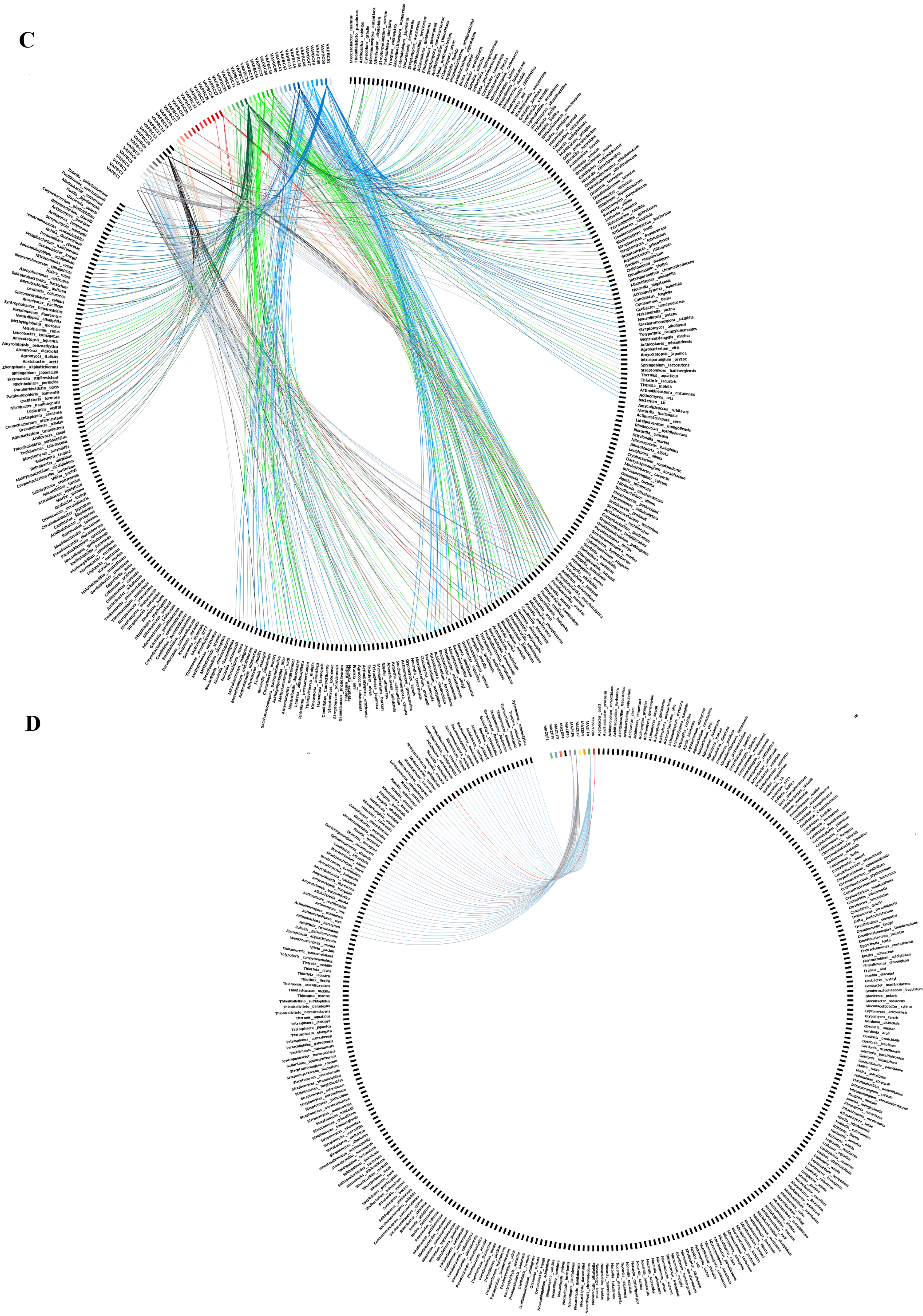


Figure S10: Distribution of *M. tuberculosis* TA in various prokaryotes, organized in a class-specific manner. Unrooted tree with class-specific pie-charts on the nodes provide the number of TA pairs in each constituent family. As an example, inset shows the number of TA pairs in various families of class Actinobacteria. An interactive link to this tree can be accessed at https://itol.embl.de/tree/1413912822265121518597108 where user can hover over the pie-charts for families in various classes. For best visibility, users are advised to visualize the tree in Firefox browser, setting the font style to 70.


C
D

E

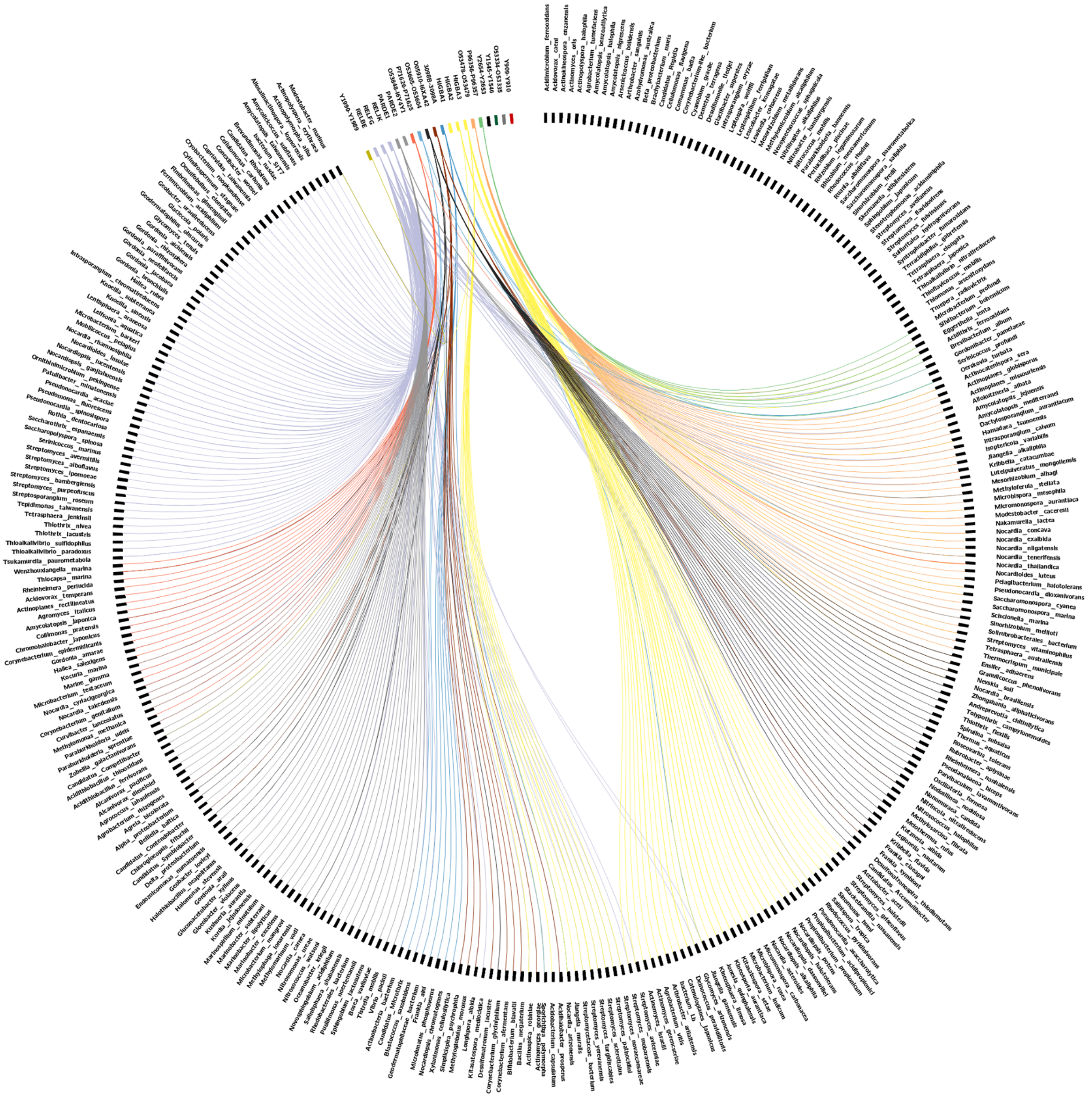


Figure S11: Circos plots showing the distribution of *M. tuberculosis* TA pairs in all 2220 prokaryotes. (A-C) show the distribution of VapBC, MazEF and other TA respectively. Plots help infer that some TA such as VapBC32 are extensively well conserved in many of the prokaryotes surveyed here. The number of homologues of MazEF TA system in the various prokaryotes is far fewer as shown in **(B)**. As shown here, Rv0909-Rv0910 is the only TA although universally present in mycobacteria is absent in prokaryotes **(C)**.

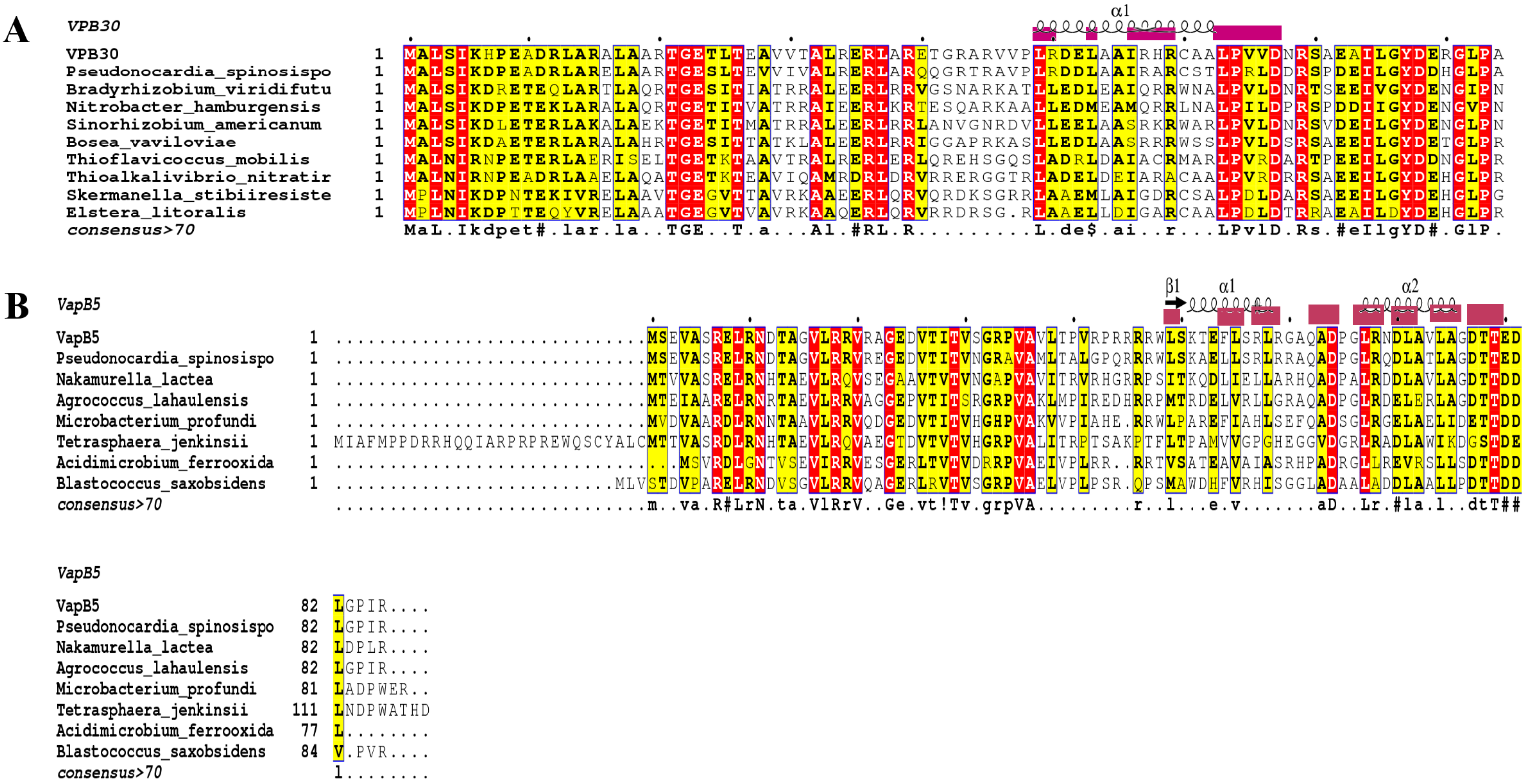


Figure S12: Multiple sequence alignment of *M.tuberculosis* **(A)** VapB30 (4xgq) with top 10 orthologues from the prokaryotic genomes. **(B)** VapB5 (3dbo) with top 10 orthologues from the prokaryotic genomes. The columns shaded dark red show conserved residues while columns shaded yellow show conservatively substituted residues. Secondary structure elements of the reference structures are depicted on top of each alignment. Pink colored boxes on top of the alignment are the toxin-binding residues in the reference structures. Consensus sequence (at a threshold > 70%) for the alignment is shown at the bottom of the alignment.

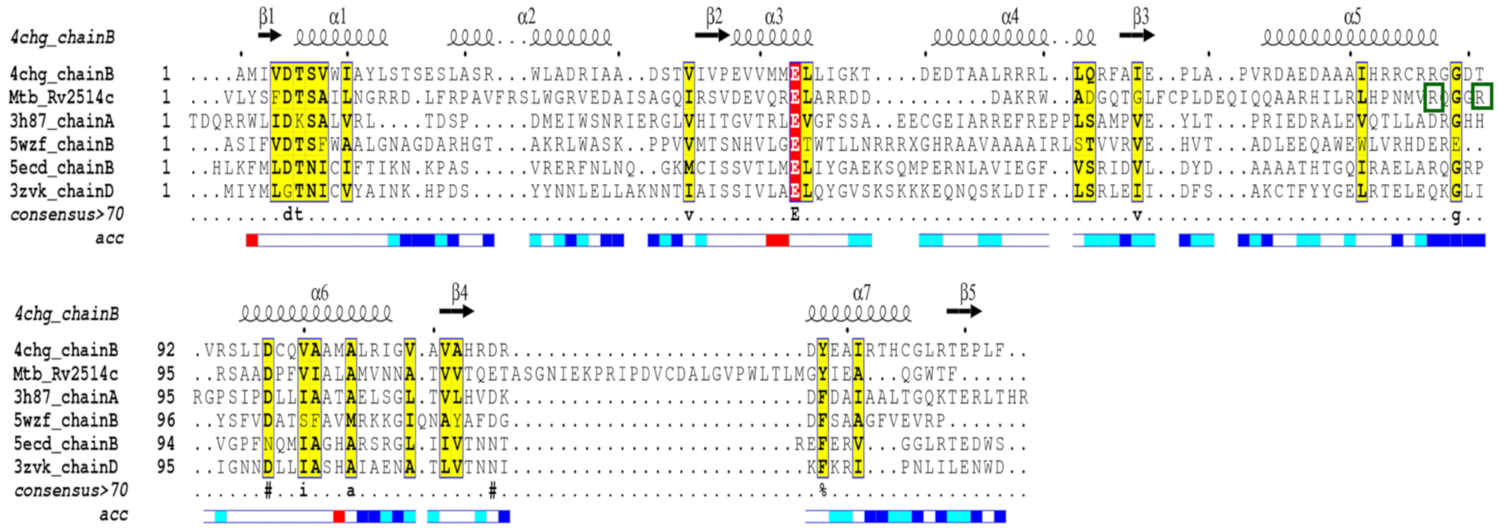
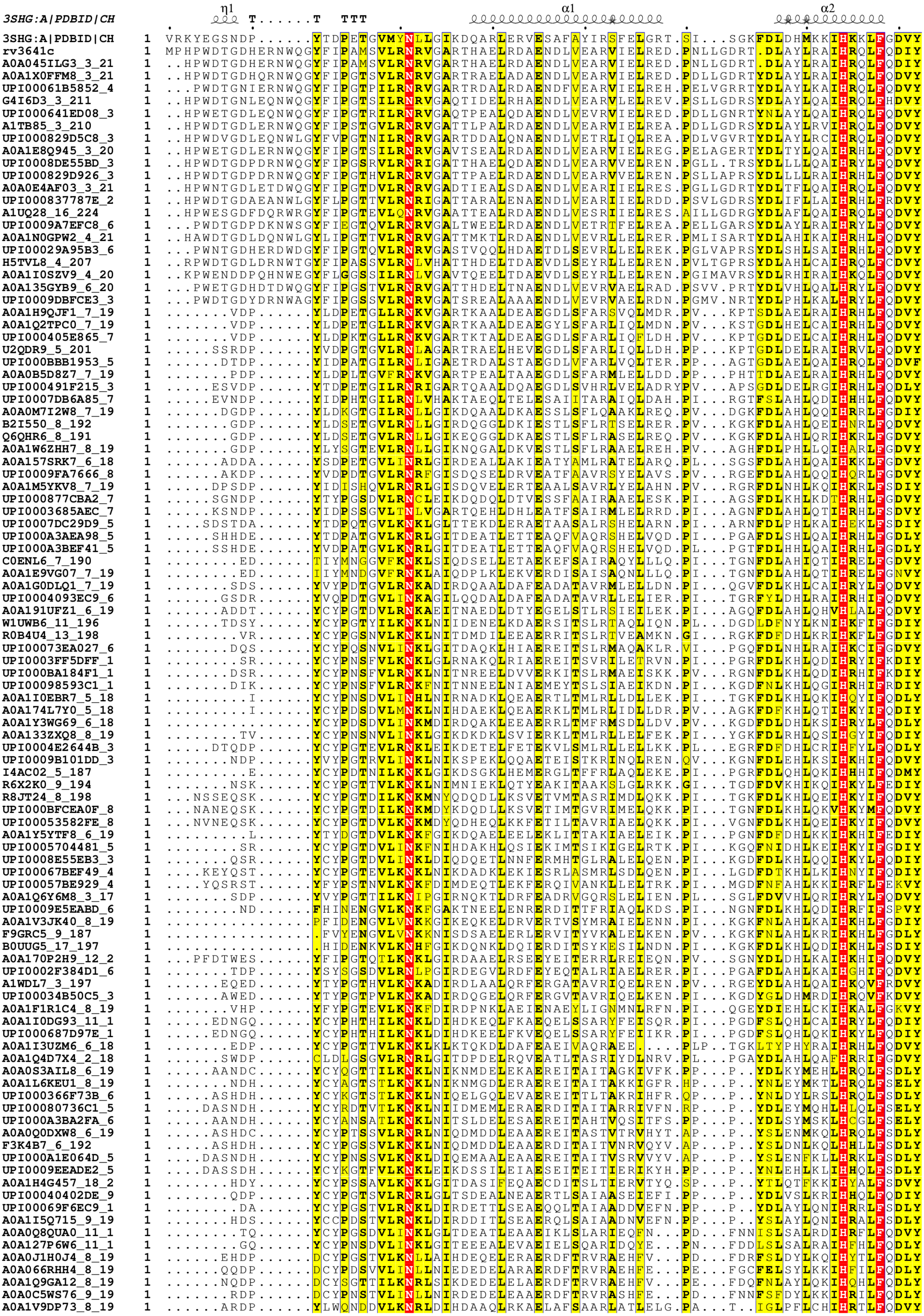
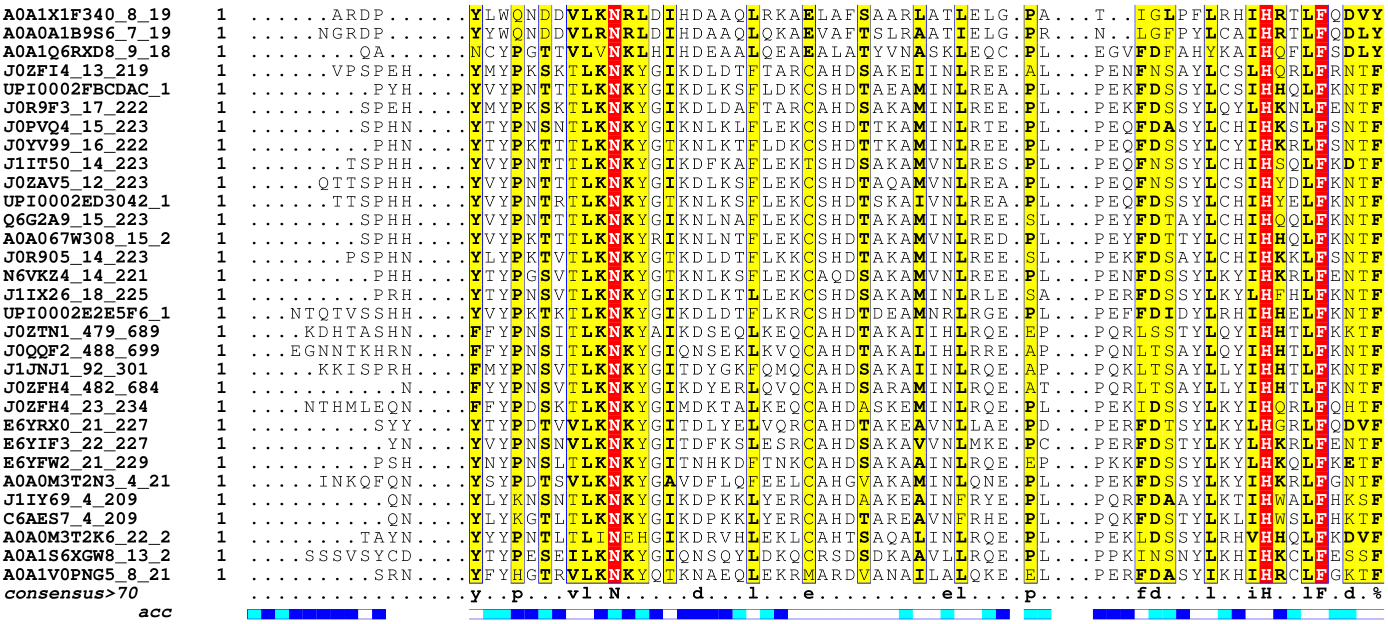


Figure S13: Alignment of Rv2514c with homologous VapC toxins from various organisms. The columns shaded dark red show conserved residues while columns shaded yellow show conservatively substituted residues. The two residues chosen for mutations are marked in green boxes. Consensus sequence (at a threshold > 70%) is shown at the bottom of the alignment. Solvent accessibility of the reference structure, shown using the Espript colour convention with dark blue indicating exposed residues, cyan showing partially exposed residues and white for buried residues (and red for residues for which this value could not be determined), is shown at the bottom of the alignment.

A





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acc
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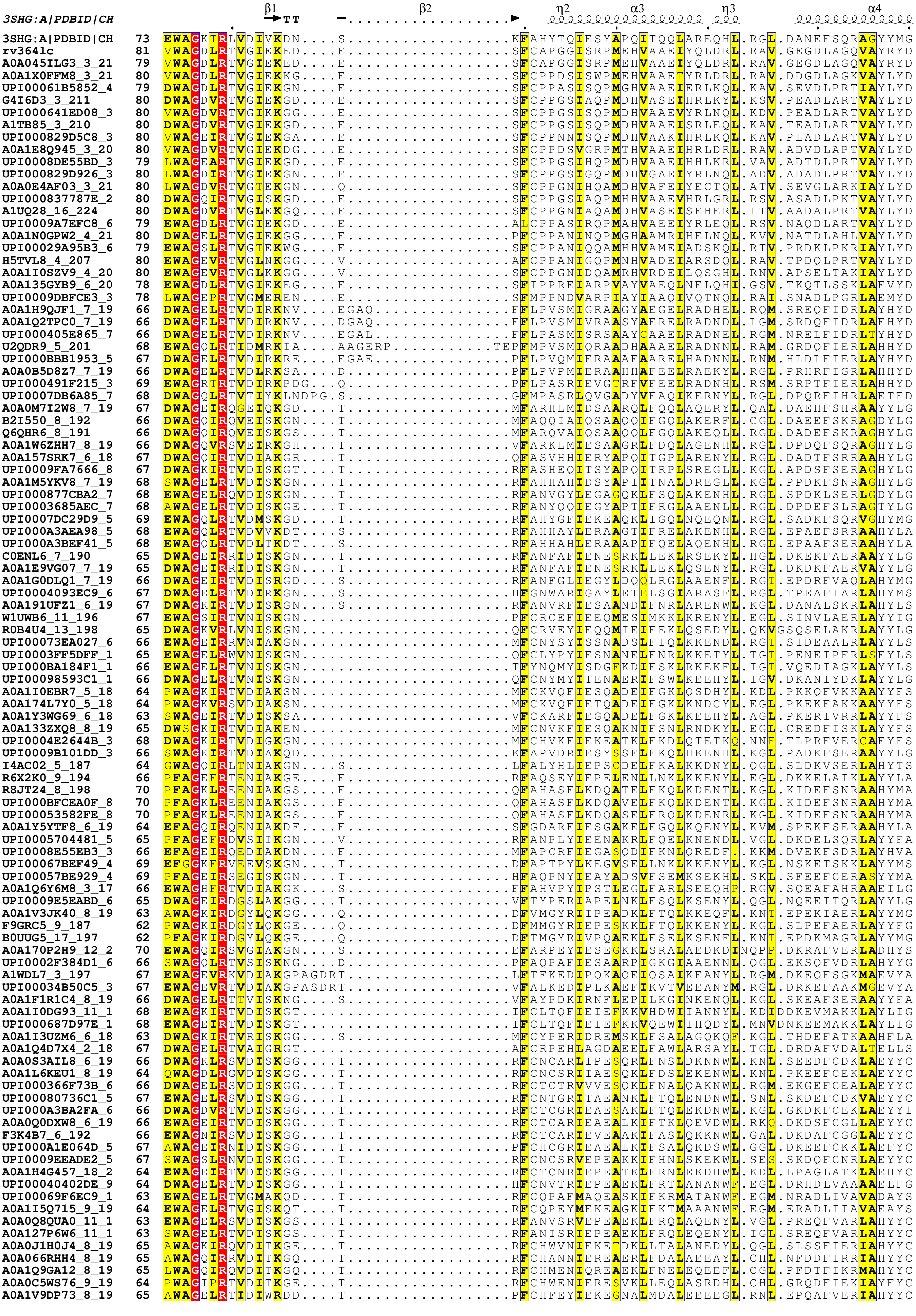

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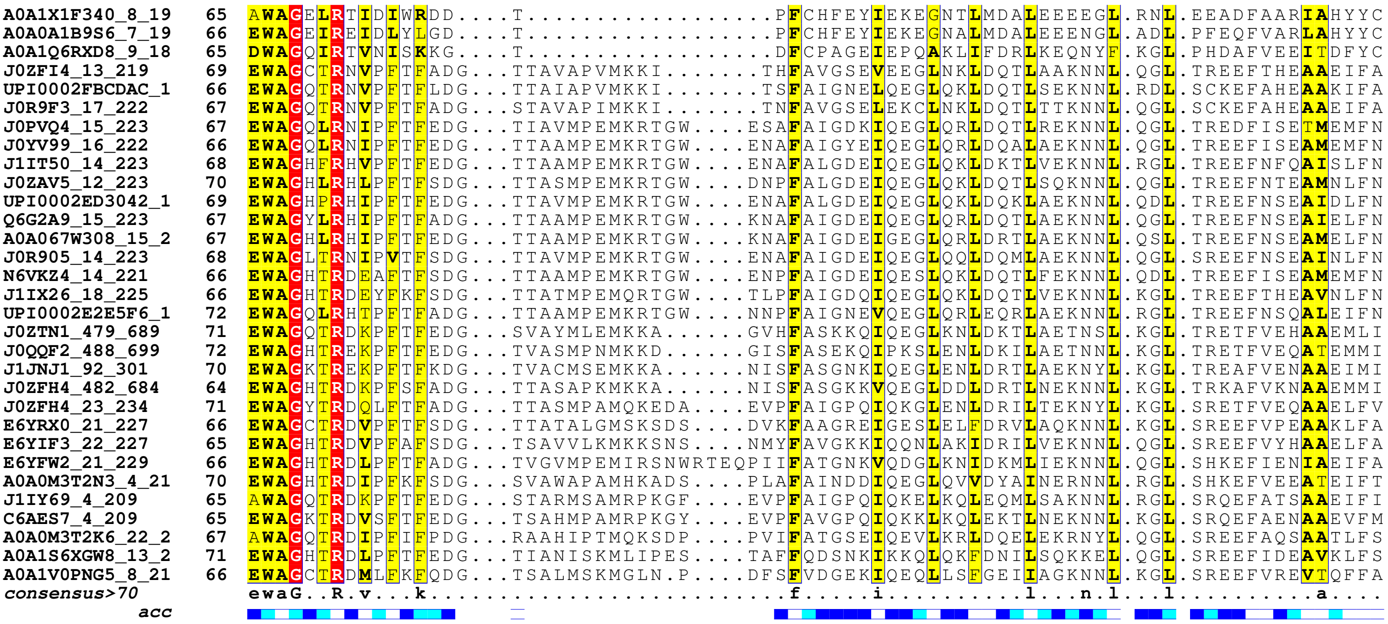

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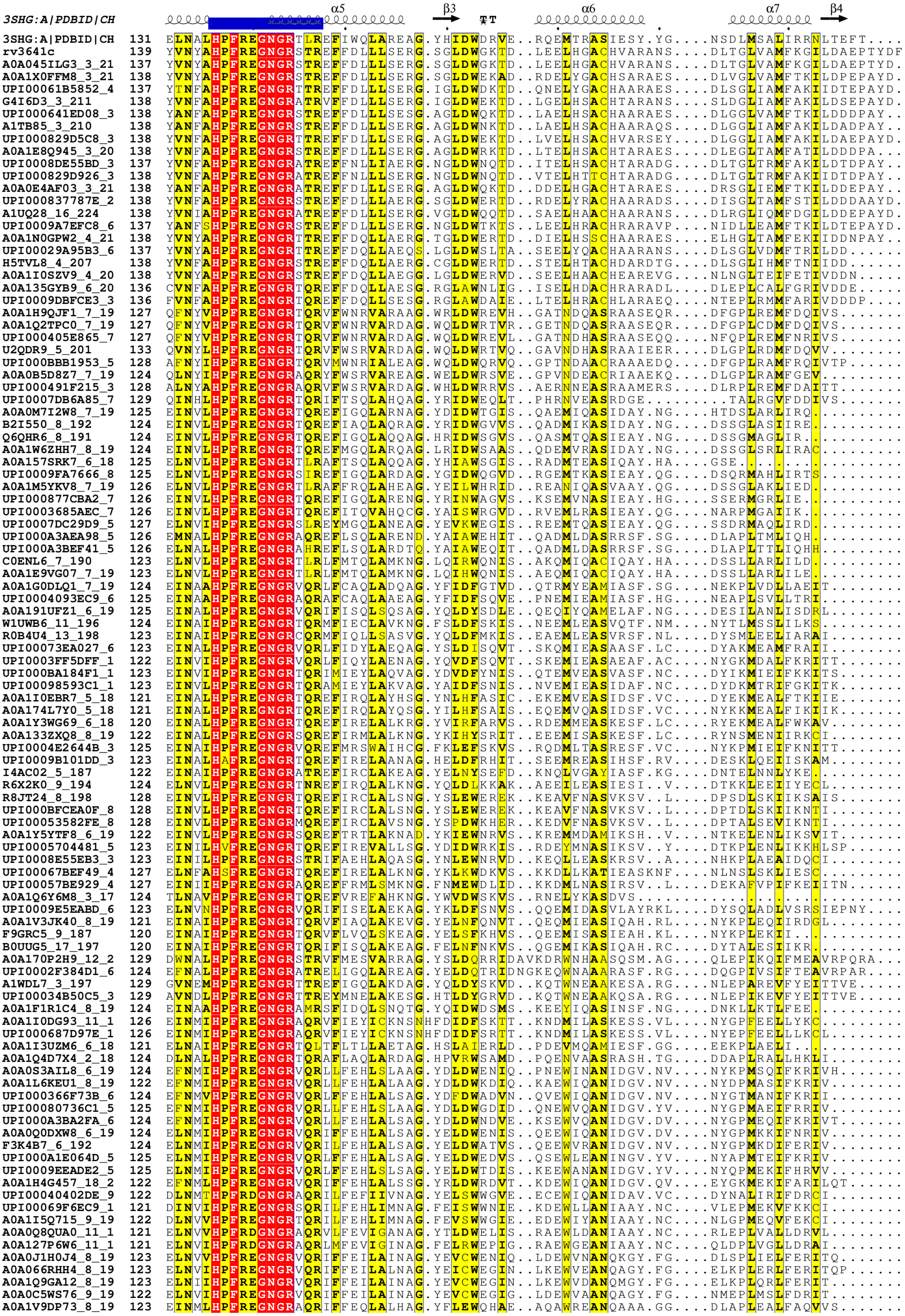

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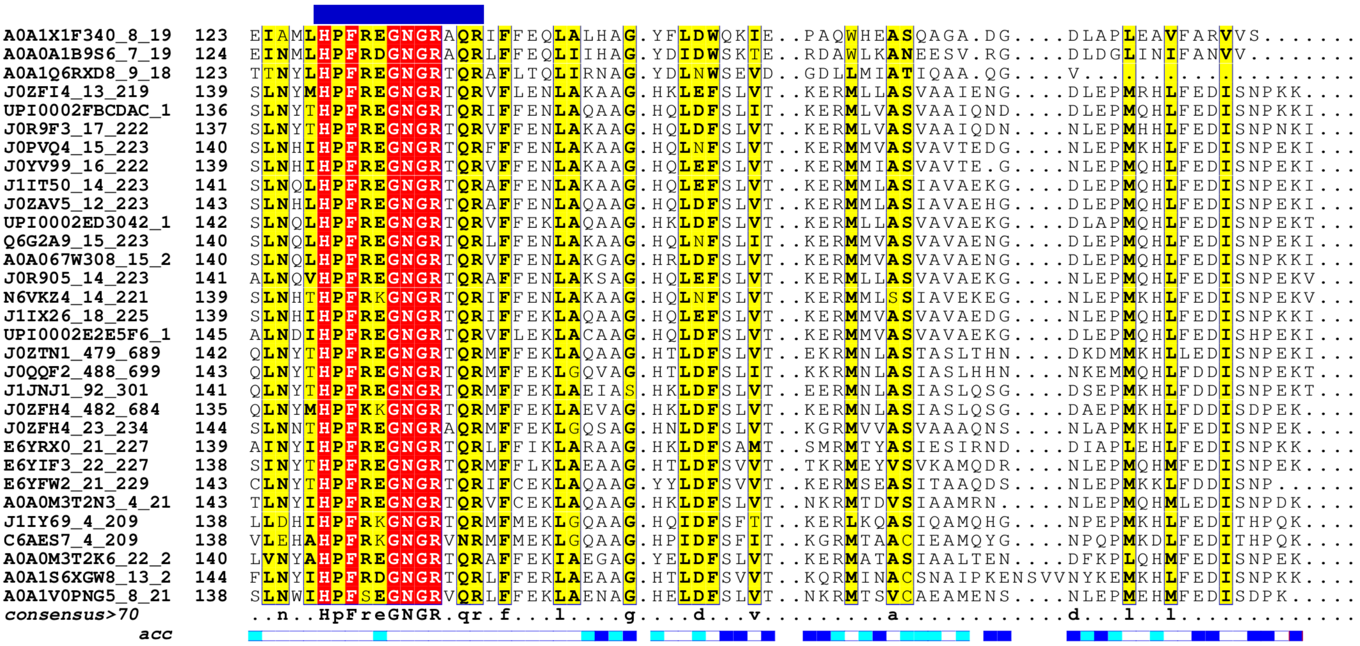

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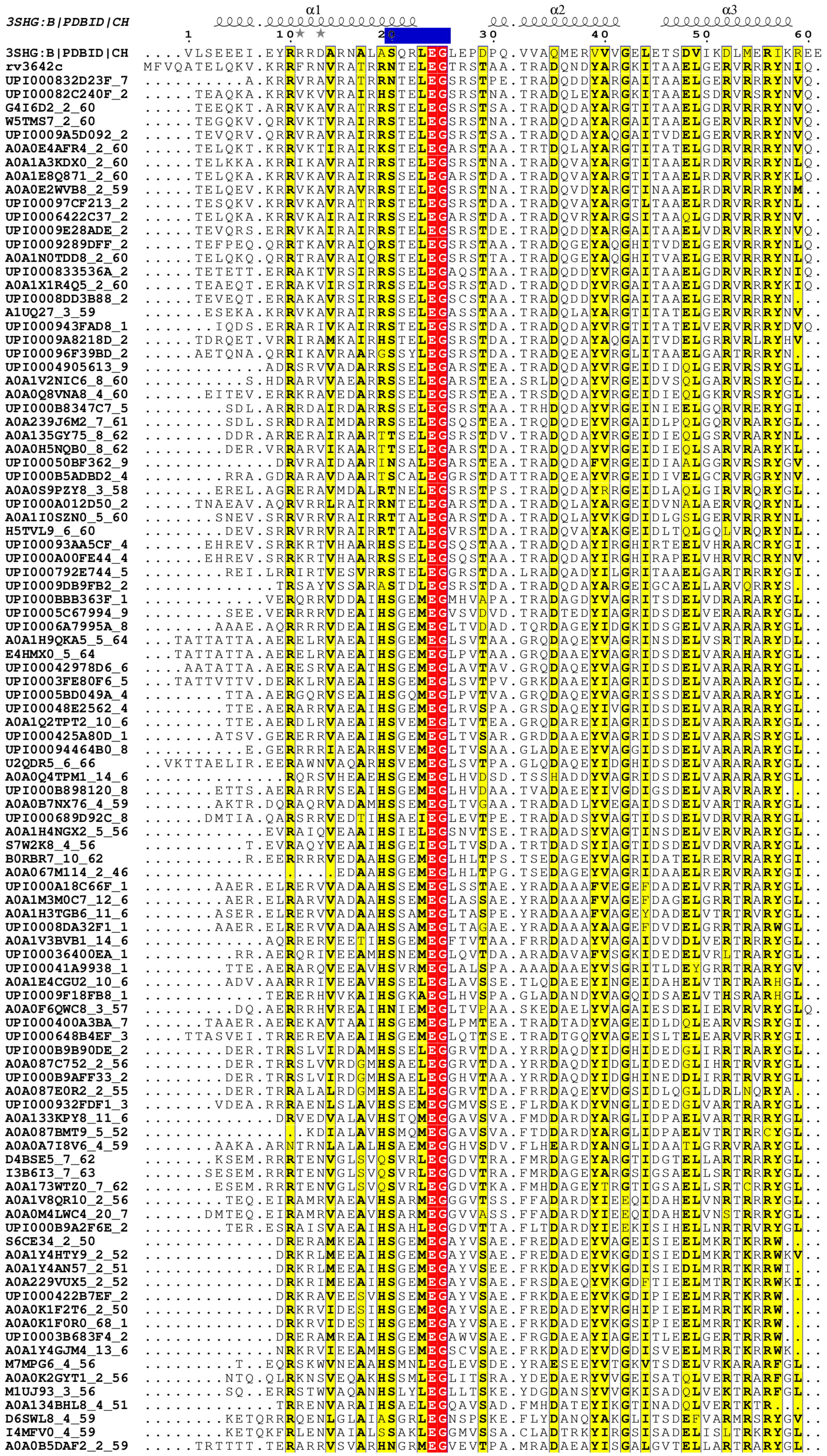

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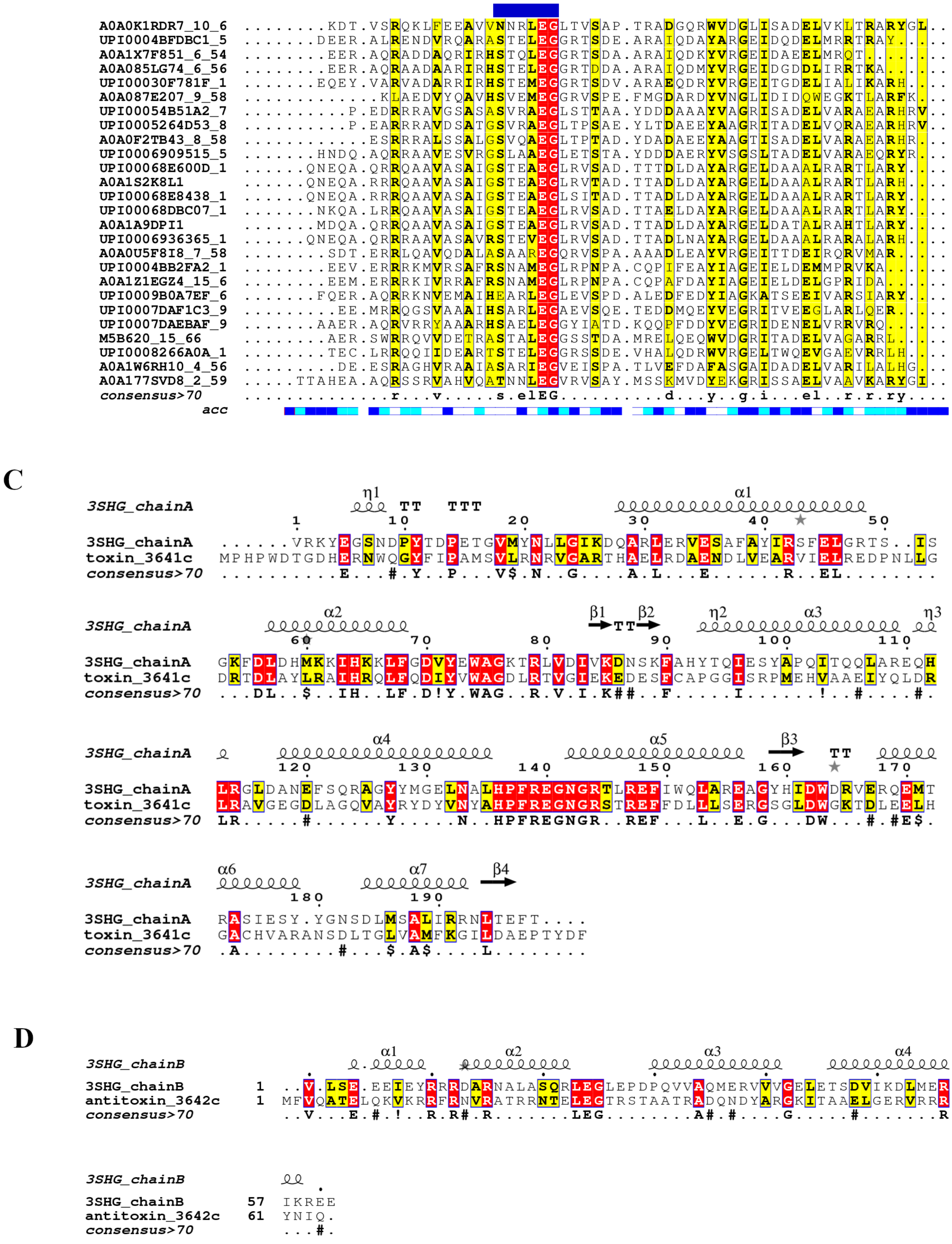

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A0A1A9DPI1         .......MDQA.QRRQAAVASAIGSTEAEGLRVSAD.TTADLDAYARGELDATALRAHTLARY....
UPI0006936365_1    ......QNEQA.QRRRAAVASAVRSTEVEGLRVSAD.TTADLNAYARGELDAAALRARALARH....
A0A0U5F8I8_7_58    ........SDT.ERRLQAVQDALASAAREGQRVSPA.AAADLEAYVRGEITTDEIRQRVMAR.....
UPI0004BB2FA2_1    ........EEV.ERRRKMVRSAFRSNAMEGLRPNPA.CQPIFEAYIAGEIELDEMMPRVKA......
A0A1Z1EGZ4_15_6    ........EEM.ERRRKIVRRAFRSNAMEGLRPNPA.CQPAFDAYIAGEIELDELGPRIDA......
UPI0009B0A7EF_6    .......FQER.AQRRKNVEMAIHEARLEGLEVSPD.ALEDFEDYIAGKATSEEIVARSIARY....
UPI0007DAF1C3_9    .........EE.MRRQGSVAAAIHSARLEGAEVSQE.TEDDMQEYVEGRITVEEGLARLQER.....
UPI0007DAEBAF_9    .......AAER.AQRVRRYAAARHSAELEGGYIATD.KQQPFDDYVEGRIDENELVRRVRQ......
M5B620_15_66       ........AER.SWRRQVVDETRASTALEGGSSTDA.MRELQEQWVDGRITADELVAGARRL.....
UPI0008266A0A_1    ........TEC.LRRQQIIDEARTSTELEGGRSSDE.VHALQDRWVRGELTWQEVGAEVRRLH....
A0A1W6RH10_4_56    .........DE.ESRAGHVRAAIASARIEGVEISPA.TLVEFDAFASGAIDADELVARILALHG...
A0A177SVD8_2_59    .....TTAHEA.AQRSSRVAHVQATNNLEGVRVSAY.MSSKMVDYEKGRISSAELVAAVKARYGI..
consensus>70       ..............r...v.....s.elEG..........d...y..g.i...el..r.r.ry....
```

C

```
                   1         10        20        30        40        50
3SHG_chainA        ......VRKYEGSNDPYTDPETGVMYNLLGIKDQARLERVESAFAYIRSFELGRTS..IS
toxin_3641c        MPHPWDTGDHERNWQGYFIPAMSVLRNRVGARTHAELRDAENDLVEARVIELREDPNLLG
consensus>70       ..........E...#.Y..P...V$.N..G....A.L...E......R..EL........

                    60        70        80        90        100       110
3SHG_chainA        GKFDLDHMKKIHKKLFGDVYEWAGKTRLVDIVKDNSKFAHYTQIESYAPQITQQLAREQH
toxin_3641c        DRTDLAYLRAIHRQLFQDIYVWAGDLRTVGIEKEDESFCAPGGISRPMEHVAAEIYQLDR
consensus>70       ...DL..$..IH..LF.D!Y.WAG..R.V.I.K##..F.....I......!..#....#.

                      120       130       140       150       160       170
3SHG_chainA        LRGLDANEFSQRAGYYMGELNALHPFREGNGRTLREFIWQLAREAGYHIDWDRVERQEMT
toxin_3641c        LRAVGEGDLAGQVAYRYDYVNYAHPFREGNGRSTREFFDLLLSERGSGLDWGKTDLEELH
consensus>70       LR.....#......Y.....N..HPFREGNGR..REF...L..E.G...DW...#.#E$.

                          180       190
3SHG_chainA        RASIESY.YGNSDLMSALIRRNLTEFT....
toxin_3641c        GACHVARANSDLTGLVAMFKGILDAEPTYDF
consensus>70       .A........#...$.A$....L........
```

D

```
3SHG_chainB        1   ..V.LSE.EEIEYRRRDARNALASQRLEGLEPDPQVVAQMERVVVGELETSDVIKDLMER
antitoxin_3642c    1   MFVQATELQKVKRRFRNVRATRRNTELEGTRSTAATRADQNDYARGKITAAELGERVRRR
consensus>70           ..V...E.#.!..R.R#.R.......LEG........A#.#....G.....#.......R

3SHG_chainB        57  IKREE
antitoxin_3642c    61  YNIQ.
consensus>70           ...#.
```

Figure S14: Multiple sequence alignment of VbhT sequences from PFAM (PF02661) with Rv3641c in **(A)** and VbhA with Rv3642c in **(B)** shows the conservation of signature motifs characteristic of these two proteins. VbhT (3shg) from *Bartonella Schoenbuchensis* serves as the reference structure in the alignment that was generated using Promals3D. Signature motifs in the two alignments are marked with a blue box on top of the alignment. Consensus sequence (at a threshold > 70%) is shown at the bottom of the alignment. Solvent accessibility of the reference structure, shown using the Esprit colour convention with dark blue indicating exposed residues, cyan showing partially exposed residues and white for buried residues (and red for residues for which this value could not be determined), is shown at the bottom of the alignment. In **(C)** and **(D)** are shown the alignments for the toxin (Rv3641c) and antitoxin (Rv3642c) with template 3shg. This alignment was employed to model the protein.

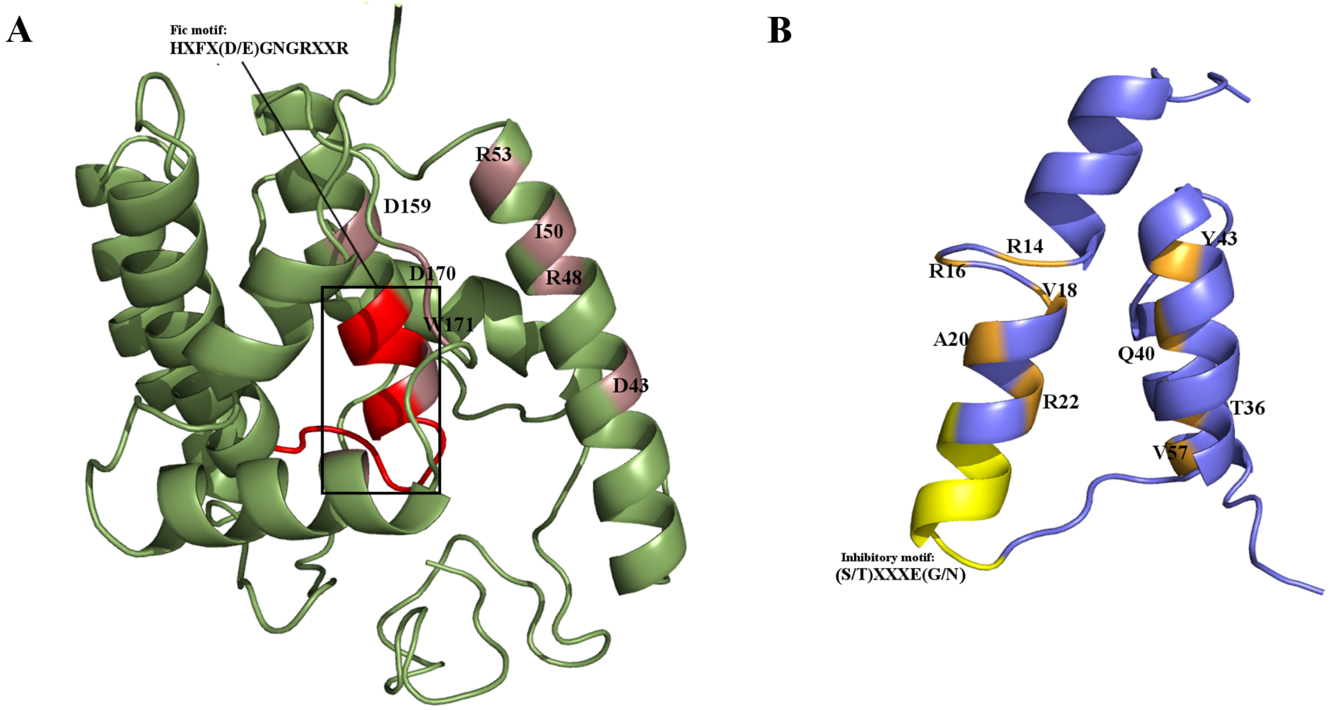

Figure S15: Structural model of putative VbhTA in *M. tuberculosis*. Cartoon representation of the comparative models of Rv3641c in green **(A)** and Rv3642c in blue **(B)** were derived using the template VbhTA (3shg) from *Bartonella schoenbuchensis*. Predicted Fic motif and inhibitory motif are shown in red and yellow respectively. Residues predicted to form the interaction interface between Rv3641c-Rv3642c are shown and colored in pink on the toxin and orange on the antitoxin.