
Article:
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Bialellic mutations in tetratricopeptide repeat domain 7A (*TTC7A*) cause common variable immunodeficiency-like phenotype with enteropathy

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Capsule Summary

TTC7A deficiency typically causes severe gastrointestinal manifestations such as multiple intestinal atresia or early onset inflammatory bowel disease. In some cases this is associated with severe combined immunodeficiency. Partial loss-of-function mutations appear to be associated with a milder phenotype resulting in common variable immunodeficiency-like condition with enteropathy.

Key words:

TTC7A
CVID
Enteropathy

To the Editor:

Biallelic mutations in tetratricopeptide repeat domain 7A (*TTC7A*) gene have been shown to cause several overlapping clinical phenotypes. These include multiple intestinal atresia (MIA) with various degrees of combined immunodeficiency (CID) (1), severe form of very early onset inflammatory bowel disease, apoptotic enterocolitis (AE) (2) and immune deficiency–related enteropathy-lymphocytopenia-alopecia (ELA) syndrome (3). All affected individuals reported to date have presented in first few months of life and all suffered severe life-threatening gastrointestinal (GI) and/or immunological disease manifestations. In the case of MIA, surgical intervention is often necessary early in life. Disease progression and relapses of atresia and stenosis in many patients requires repeat surgeries and small bowel transplantation (4). Many patients with enteropathy required total parenteral nutrition (TPN). Immunological studies of these patients showed varying degrees of hypogammaglobulinemia and lymphopenia which in some cases was consistent with a diagnosis of severe combined immunodeficiency (SCID).

Here we report a case presenting with clinical features consistent with Common Variable Immunodeficiency (CVID) and enteropathy, but was later found to have compound heterozygous mutations in *TTC7A*. The patient presented at the age of 15 with lethargy, pallor and a low body mass index. He was found to be anaemic and had low levels of ferritin, folate, calcium and Vitamin D. He did not report any overt diarrhoea, abdominal pain or other symptoms suggestive of small bowel obstruction. He also had no prior history of recurrent or unusual infections. An oesophago-gastroduodenoscopy showed an atrophic duodenal mucosa, there was no evidence of any atresia. Histology showed variable villous atrophy and marked lymphocytosis (Fig 1, C) with absence of plasma cells. He was found to have severe panhypogammaglobulinaemia with normal T and B cell numbers but almost absent class-switched memory B cells. Further investigations showed normal proliferative T cell response to PHA and anti-CD3 stimulation and normal neutrophil function tests (Table E1). The features were consistent with diagnosis of CVID; coeliac disease could not be excluded. Gluten free diet had only a modest effect at alleviating his symptoms. Although he had no history of infections, due to the severity of his panhypogammaglobulinaeamia he was commenced on immunoglobulin replacement therapy. At the age of 17 the patient was diagnosed with type 1 diabetes mellitus

following an admission for diabetic ketoacidosis. He remains free from infections, but continues to have difficulties with malabsorption and poor weight gain.

The patient gave consent to participate in a study investigating molecular causes of primary immunodeficiencies. Two mutations in *TTC7A* were identified by whole exome sequencing (WES): rs139010200, exon 16/20 c.1817 aAg/aGg (K606R); and rs149602485, exon 17/20 c.2014 Tct/Cct (S672P). Sanger sequencing confirmed *TTC7A* variants in the proband as well as heterozygosity of A1817G paternally and T2014C maternally (Fig 1, B). No inheritance of affected alleles occurred in healthy siblings (Fig E1) (for methods please see online supplement).

These SNVs have been reported previously by Chen et al. (patient F5-A) on the maternal allele of European descent and in combination with exon 7 c.1000DAAGT on the paternal allele of French-Canadian descent (1). Samuels et al. also report this same 4-nt deletion in a number of unrelated French-Canadian patients with MIA (5). We suspect that compound heterozygous combination of K606R and S672P leads to a mild form of disease although we have not identified a clear mechanism by which this occurs. Confirmed pathogenicity of these variants will require in-depth functional analysis and reports of other similar instances.

The biological functions of TTC7A in MIA have been reviewed by L. Notarangelo (6) where this protein is suggested to act as a repressor of RhoA signalling. The administration of ROCK inhibitors is thought to ameliorate proliferative activity and epithelial architecture of the lumen and intestinal crypts. Avitzur et al. identify phosphatidylinositol 4-kinase IIIa (PI4KIIIa) as a major TTC7A-interacting protein (2). The protein EFR3 homolog B (EFR3B) tethers TTC7A to the plasma membrane thereby allowing localisation of PI4KIIIa at the cell membrane. In adult mice the inactivation of murine PI4KIIIa leads to death due to necrosis of enterocytes in the villi and intestinal crypts (7). However, the key immunological features of thymic dysplasia and lymphoid depletion in MIA-CID have not yet been explained.

The patient we presented here has a much milder clinical phenotype both in terms of his immunological and GI disease manifestations. We wondered if *TTC7A* variants found in this patient might have less detrimental effects on the function of the protein. To assess protein expression levels immunohistochemistry was performed on the patient's small intestine biopsy using rabbit polyclonal TTC7A antibody (Proteintech IL, USA). Hyperplasia is evident in comparison with healthy control (Fig

1, D and E and F). No reduction in protein expression was seen. K606R is reported in EXAC with allele frequency 0.002061 including as homozygous. Given the mild phenotype presented here it is not likely that this SNP alone produces a noticeable effect. A loss of fully functional protein may occur in combination with S672P without any visible reduction in expression. Genome, exome, and clinical panel sequencing in rare diseases generally requires filtering of common SNPs. The contribution toward disease due to mutations with allele frequency greater than 0.001 occurring in a biallelic state may be neglected in cases such as this.

Known variants associated with disease are shown in Table 1 and notated on the gene representation (Fig 1, A). This presents an updated list originally compiled by Yang et al. (8). These variants were mapped on a model of the predicted TTC7A protein structure in Fig E2. Modelling was based on the recently reported crystal structure of TTC7B (9) which has high sequence similarity to TTC7A. This reference data was combined with that of other tetratricopeptide repeat (TPR) domains found in a large number of proteins (6) (supplemental report E3 and E4). A confidence of 714 residues (81%) was modeled at >90% accuracy. The TPR domains are identified as cartoons on the ribbon structure (Fig E2).

The variants K606R and S672P have been described in patients as pathogenic but always in association with another more severe alteration. From our model, K606 and S672 lie buried on the beta-turn-beta between TPR domains 6/7 and may not be involved in major interactions resulting in a milder phenotype compared to other variants in the surrounding region.

Limited in vivo models exist for this condition but it is hopeful that models of human intestine using pluripotent stem cells could allow greater functional study of *TTC7A*. A precise mechanism shared between gut development and robust immune function is yet to be identified. Our case expands the clinical phenotype associated with biallelic *TTC7A* mutations. Enteropathy is a relatively common complication of CVID, and as we continue to use more advanced genetic techniques to study this condition, it is possible that these less severe *TTC7A* variants will be found more frequently in this patient population.

Authors have no potential conflict of interest to disclose.

References

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Fig 1. Representation of TTC7A pathogenic variants with genetic and pathological findings. (A) Representation of the *TTC7A* gene and position of mutations identified to date in apoptotic enterocolitis, multiple intestinal atresias, combined immunodeficiency, and enteropathy-lymphocytopenia-alopecia. Vertical bars: Protein changes, purple; stop codon, red; frame shift, green; exon skipping, curved arrows between orange bars; retained intron, blue. Horizontal bars: Tetratricopeptide repeat domains (1-9) 121 – 157 and 177 – 210 Red, 414 – 447 orange, 497 – 531 yellow, 533 – 565 Green, 566 – 599 Cyan, 745 – 778 Blue, 780 – 812 Purple, 813 – 846 Magenta. (B) Pedigree and mutation inheritance pattern. (C) Gastrointestinal pathology. Duodenal biopsy with subtotal villous atrophy, marked crypt hyperplasia and villous tip lymphocytosis. Goblet and Paneth cells are preserved. 20x Higher magnification – shortened villi with lymphocytosis and conspicuous lack of plasma cells within the lamina propria. (D) Immunohistochemistry of the patient's small intestine biopsy using rabbit polyclonal TTC7A antibody (Proteintech IL, USA).

Hyperplasia is evident in comparison with healthy control (E). No reduction in protein expression was seen. (F) Patient biopsy control with no primary antibody.

Fig E1. Sanger sequence electropherogram of pedigree.
Sanger sequence electropherogram of the proband II.ii for exon 16/20 c.1817 aAg/aGg (K606R) and exon 17/20 c.2014 Tct/Cct (S672P). Heterozygosity of A1817G paternally I.i and T2014C maternally I.ii. Healthy siblings II.i, II.iii and II.iv (arranged by age left to right on pedigree) show no presence of affected alleles.

Fig E2. Ribbon structure model of TTC7A and tetratricopeptide repeat domains. All known pathogenic variants in apoptotic enterocolitis, multiple intestinal atresias, combined immunodeficiency, and enteropathy-lymphocytopenia-alopecia are mapped. Annotation colors match that of the gene representation of Figure 1 A. Protein changes, purple; stop codon, red; frame shift, green; exon skipping causing variants, orange; retained intron, blue. Tetratricopeptide repeat domains (TPR) are identified as cartoons also corresponding to horizontal bars shown in Figure 1 A. Tetratricopeptide repeat domains (1-9) 121 – 157 and 177 – 210 Red, 414 – 447 orange, 497 – 531 yellow, 533 – 565 Green, 566 – 599 Cyan, 745 – 778 Blue, 780 – 812 Purple, 813 – 846 Magenta.

E3. Modeling report.
Detailed template report for data used with Phyre2 software indicating alignment, coverage, confidence and % i.d. Template Information 1-20 used for model construction.

E4. Sequence structure report.
Phyre2 software report of secondary structure and disorder prediction showing disorder confidence and conserved domain information.

Figure 1

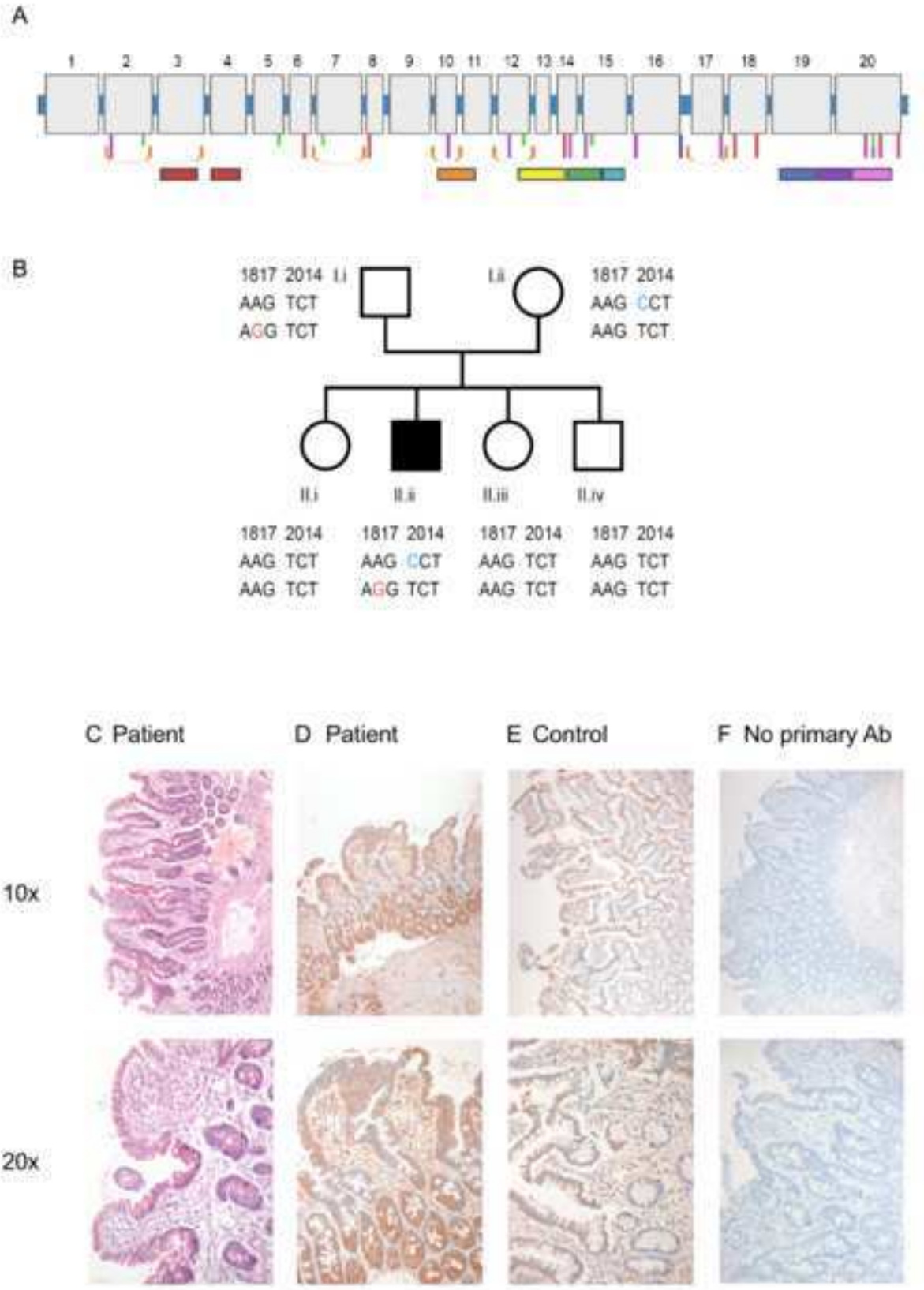

Table 1. Genetic variants related to MIA-CID, AE, or ELA reported to date.

Region	Nucleotide	Amino acid	Variant affect	Population	Phenotype	Reference	Family ID per ref	Inheritance Type
Exon 2	G214A	E71K	Missense	Caucasians /Sudanese	AE, CID, No atresia	Avitzur/Ngan*	1	CH
Exon 2	G214A	E71K	Missense	-	ELA	Lemoine	F1	Homo/consanguineous
Skipping of 2–3	del Ex2c.185_348	del D62_S116	Exon skipping	Mixed European	MIA-CID	Bigorgne	A	CH
Skipping of 2	del Ex2c.185_517	del D62_G173	Exon skipping	Mixed European	MIA-CID	Bigorgne	A	CH
Exon 2	del Ex2c.313TATC	Y105fs	Frame shift	Serbian	MIA-CID	Chen	2	Homo
Exon 2	del Ex2c.313TATC	Y105fs	Frame shift	Bosniak	MIA-CID	Chen	3	Homo/related parents
Skipping of 2–3	Unknown mutations	-	Exon skipping	Italian	MIA-CID	Chen	8	Non-consanguineous
Exon 5	AG764A	K255fs	Frame shift	-	MIA-CID	Chen	4	CH
Exon 6	C833T	Q277X	Stop	Saudi Arabia	MIA-CID	Bigorgne	B	Homo/consanguineous
Skipping of 7	844-1G>T	-	Exon skipping	Caucasians	AE, MIA-CID	Avitzur	2	CH
Exon 7	delEx7c.911T	L304fsX59	Frame shift	-	ELA	Lemoine	F2 P3	CH
Skipping of 7	del Ex7c.1000_1003AAGT	-	Exon skipping	French-Canadian and Mixed European	MIA-CID	Chen	5	CH
Skipping of 7	del Ex7c.1000_1003AAGT	-	Exon skipping	French-Canadian	MIA	Samuels	F1 F4 F6	Homo
Skipping of 7	del Ex7c.1000_1003AAGT	-	Exon skipping	French-Canadian/English	MIA-CID	Samuels	F7	CH
Skipping of 7	del Ex7c.1000_1003AAGT	-	Exon skipping	French-Canadian	MIA-CID	Fernandez	F	Homo
Skipping of 7	del Ex7c.1000_1003AAGT	-	Exon skipping	French-Canadian	MIA-CID	Fernandez	P2	CH
Exon 8	C1111G	Y337X	Stop	Mixed European	MIA-CID	Bigorgne	E	CH
Exon 9	T1198C	L400P	Missense	Italian	MIA-CID	Chen	7	Homo
Skipping of 10	Ex10c.1204-2A>G	-	Exon skipping	Caucasians	AE, MIA-CID	Avitzur	2	CH
Skipping of 12	Exon11 - 4 bp deletion	-	Exon skipping	Norway	MIA-CID	Bigorgne	D	CH
Skipping of 12	Intron12c.1510+105T-A	del L465-A504	Exon skipping	Mixed European	MIA	Bigorgne	F	CH
Exon 12	1433T>C	L478P	Missense	-	ELA	Lemoine	F2 P3	CH
Exon 12	del Ex12c.1479G	L493fsX13	Frame shift	Mixed European	MIA-CID	Bigorgne**	E	CH
Exon 14	C1576T	Q526X	Stop	Caucasians /Sudanese	AE, CID, No atresia	Avitzur/Ngan*	1	CH
Exon 14	C1616T	S539L	Missense	Norway	MIA-CID	Bigorgne	D	CH
Exon 15	1652C>A	A551D	Missense	Irish/Ashkenazi Jew	MIA-CID	Agarwal	F1	CH
Exon 15	Ins Ex15c.1673G	A558GfsX7	Frame shift	Mixed European	MIA	Bigorgne	F	CH
Ex 16 Read-through intron	del Ex16c.1919+1G>A	-	Retained intron	Arabic	MIA-CID	Chen	1	Homo/consanguineous
Exon 16	A1817G	K606R	Missense	French-Canadian and Mixed European	MIA-CID	Chen	5	CH
Exon 16	A1817G	K606R	Missense	European	CVID and enteropathy	Presented here	-	CH
Skipping of 17	1920-2A>G	-	Exon skipping	Malay	MIA-CID	Yang	F1d	CH
Exon 17	T2014C	S672P	Missense	French-Canadian and Mixed European	MIA-CID	Chen	5	CH
Exon 17	T2014C	S672P	Missense	European	CVID and enteropathy	Presented here	-	CH
Exon 18	C2033A	S678X	Stop	Italian	MIA-CID	Chen	6	CH
Exon 18	C2134T	Q712X	Stop	Italian	MIA-CID	Chen	6	CH
Exon 20	T2468C	L823P	Missense	-	MIA-CID	Chen	4	CH
Exon 20	T2468C	L823P	Missense	French-Canadian	MIA-CID	Fernandez	P2	CH
Exon 20	T2468C	L823P	Missense	French-Canadian/English	MIA-CID	Samuels	F7	CH
Exon 20	C2482T	Q828X	Stop	Irish/Ashkenazi Jew	MIA-CID	Agarwal	F1	CH
Exon 20	del 2496-2497 CG	A832fsX1	Frame shift	Sri Lanka	MIA-CID	Bigorgne**	C	Homo/likely consanguineous
Exon 20	G2494A	A832T	Missense	-	AE, No CID, No atresia	Avitzur	3	Homo
Exon 20	G2569T	E857X	Stop	Malay	MIA-CID	Yang	F1d	CH

*Ngan et al. independently report on the same case as Avitzur et al. with further work on WGS, thymus and lung pathology. Further features relating to phenotypes may be reported in indiviual references. **The dermatological phenotypes of Patients C3 and E3 in Bigorgne et al. have also been recently reported (E). AE, Apoptotic enterocolitis; MIA, Multiple intestinal atresias; CID Combined immunodeficiency; ELA, Enteropathy-lymphocytopenia-alopecia; CH, compound heterozygous; Homo, homozygous.

Supplemental references:

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Fig E1

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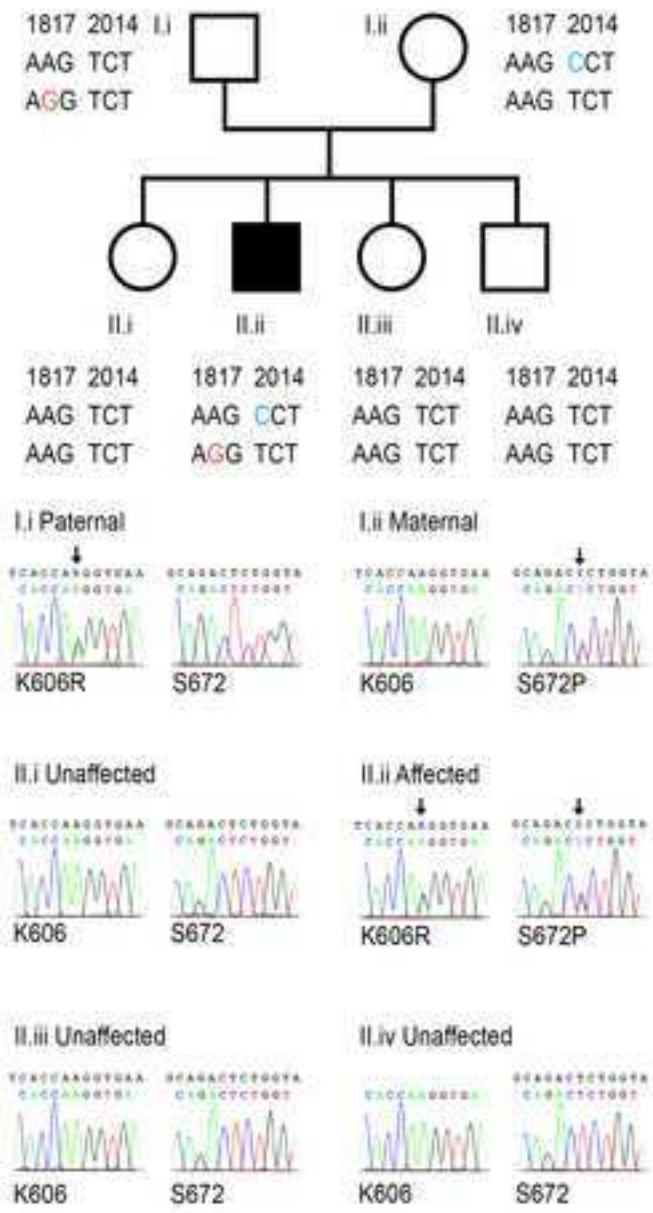

Fig E2

Click here to download Electronic Supplemental Material (ESM) Figure E2.tif

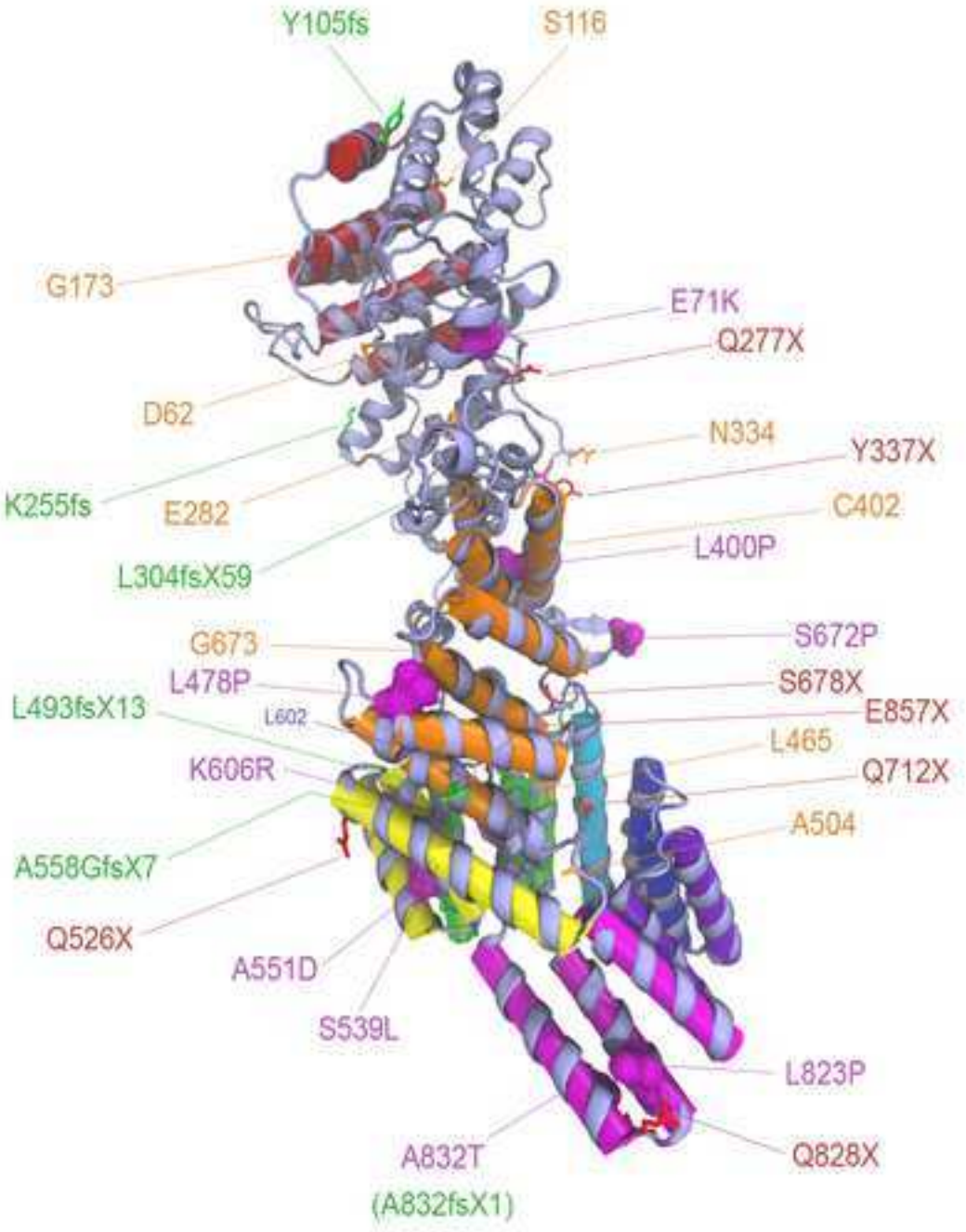

Fig E3

Click here to download Electronic Supplemental Material (ESM) Figure E3 Modelling report.pdf

Phyre2

Email	umdl@leeds.ac.uk
Description	TTC7Awork
Date	Fri Apr 8 18:11:14 BST 2016
Unique Job ID	53ca2a391e73d28c

Detailed template information

#	Template	Alignment Coverage	3D Model	Confidence	% i.d.	Template Information
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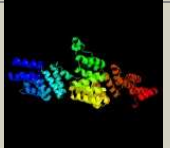
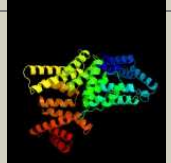
2	c5dseA_	Alignment		100.0	57	**PDB header:**protein binding **Chain:** A: **PDB Molecule:**tetratricopeptide repeat protein 7b; **PDBTitle:** crystal structure of the ttc7b/hyccin complex
3	c4bujF_	Alignment		100.0	13	**PDB header:**hydrolase **Chain:** F: **PDB Molecule:**superkiller protein 3; **PDBTitle:** crystal structure of the s. cerevisiae ski2-3-8 complex
4	c4hnxA_	Alignment		100.0	11	**PDB header:**transferase **Chain:** A: **PDB Molecule:**n-terminal acetyltransferase a complex subunit nat1; **PDBTitle:** the nata acetyltransferase complex bound to ppgpp
5	c5ganJ_	Alignment		100.0	13	**PDB header:**transcription **Chain:** J: **PDB Molecule:**pre-mrna-splicing factor 6; **PDBTitle:** the overall structure of the yeast spliceosomal u4/u6.u5 tri-snrnp at2 3.7 angstrom
6	c4kvmA_	Alignment		100.0	10	**PDB header:**transferase/transferase inhibitor **Chain:** A: **PDB Molecule:**n-terminal acetyltransferase a complex subunit nat1; **PDBTitle:** the nata (naa10p/naa15p) amino-terminal acetyltransferase complex2 bound to a bisubstrate analog
7	c2xpiA_	Alignment		100.0	13	**PDB header:**cell cycle **Chain:** A: **PDB Molecule:**anaphase-promoting complex subunit cut9; **PDBTitle:** crystal structure of apc/c hetero-tetramer cut9-hcn1
8	c4uzyA_	Alignment		100.0	12	**PDB header:**motor protein **Chain:** A: **PDB Molecule:**flagellar associated protein; **PDBTitle:** crystal structure of the chlamydomonas ift70 and ift52 complex
9	c4ui9K_	Alignment		100.0	17	**PDB header:**cell cycle **Chain:** K: **PDB Molecule:**cell division cycle protein 16 homolog; **PDBTitle:** atomic structure of the human anaphase-promoting complex
10	d1w3ba_	Alignment		100.0	18	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Tetratricopeptide repeat (TPR)
11	c4ui9C_	Alignment		100.0	12	**PDB header:**cell cycle **Chain:** C: **PDB Molecule:**cell division cycle protein 23 homolog; **PDBTitle:** atomic structure of the human anaphase-promoting complex

12	c4n5cH_	Alignment		100.0	12	**PDB header:**protein binding **Chain:** H: **PDB Molecule:**cargo-transport protein ypp1; **PDBTitle:** crystal structure of ypp1
13	c4ui9Y_	Alignment		100.0	13	**PDB header:**cell cycle **Chain:** Y: **PDB Molecule:**anaphase-promoting complex subunit 7; **PDBTitle:** atomic structure of the human anaphase-promoting complex
14	c4rg6B_	Alignment		100.0	14	**PDB header:**protein binding **Chain:** B: **PDB Molecule:**cell division cycle protein 27 homolog; **PDBTitle:** crystal structure of apc3-apc16 complex
15	c3fp4A_	Alignment		100.0	15	**PDB header:**transport protein **Chain:** A: **PDB Molecule:**tpr repeat-containing protein yhr117w; **PDBTitle:** crystal structure of tom71 complexed with ssa1 c-terminal2 fragment
16	c4hotA_	Alignment		100.0	15	**PDB header:**rna binding protein/rna **Chain:** A: **PDB Molecule:**interferon-induced protein with tetratricopeptide repeats **PDBTitle:** crystal structure of full-length human ifit5 with 5`-triphosphate2 oligoadenine
17	c4e85B_	Alignment		100.0	8	**PDB header:**structural protein **Chain:** B: **PDB Molecule:**mrna 3'-end-processing protein rna14; **PDBTitle:** crystal structure of hat domain of rna14
18	d2ooea1	Alignment		100.0	9	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**HAT/Suf repeat
19	c5aioA_	Alignment		100.0	12	**PDB header:**transcription **Chain:** A: **PDB Molecule:**transcription factor tau 131 kda subunit; **PDBTitle:** crystal structure of t131 n-terminal tpr array
20	c2y4tA_	Alignment		100.0	15	**PDB header:**chaperone **Chain:** A: **PDB Molecule:**dnaj homolog subfamily c member 3; **PDBTitle:** crystal structure of the human co-chaperone p58(ipk)
21	c2gw1A_	Alignment	not modelled	100.0	14	**PDB header:**protein transport **Chain:** A: **PDB Molecule:**mitochondrial precursor proteins import receptor; **PDBTitle:** crystal structure of the yeast tom70
22	c4ebaC_	Alignment	not modelled	100.0	9	**PDB header:**structural protein/rna binding protein **Chain:** C: **PDB Molecule:**mrna 3'-end-processing protein rna14; **PDBTitle:** crystal structure of the rna14-rna15 complex
23	c3iegB_	Alignment	not modelled	100.0	16	**PDB header:**chaperone **Chain:** B: **PDB Molecule:**dnaj homolog subfamily c member 3; **PDBTitle:** crystal structure of p58(ipk) tpr domain at 2.5 a
24	c4g1tB_	Alignment	not modelled	100.0	13	**PDB header:**antiviral protein **Chain:** B: **PDB Molecule:**interferon-induced protein with tetratricopeptide repeats **PDBTitle:** crystal structure of interferon-stimulated gene 54
25	c4m57A_	Alignment	not modelled	100.0	11	**PDB header:**rna binding protein **Chain:** A: **PDB Molecule:**chloroplast pentatricopeptide repeat protein 10; **PDBTitle:** crystal structure of the pentatricopeptide repeat protein ppr10 from2 maize
26	c4ui9O_	Alignment	not modelled	100.0	12	**PDB header:**cell cycle **Chain:** O: **PDB Molecule:**anaphase-promoting complex subunit 5; **PDBTitle:** atomic structure of the human anaphase-promoting complex
27	c3v6pA_	Alignment	not modelled	99.9	14	**PDB header:**dna binding protein **Chain:** A: **PDB Molecule:**dhax3; **PDBTitle:** crystal structure of the dna-binding domain of dhax3, a tal effector
28	c2uy1A_	Alignment	not modelled	99.9	12	**PDB header:**rna-binding protein **Chain:** A: **PDB Molecule:**cleavage stimulation factor 77; **PDBTitle:** crystal structure of cstf-77

29	d1fcha_	Alignment	not modelled	99.9	16	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Tetratricopeptide repeat (TPR)
30	c1fchB_	Alignment	not modelled	99.9	16	**PDB header:**signaling protein **Chain:** B: **PDB Molecule:**peroxisomal targeting signal 1 receptor; **PDBTitle:** crystal structure of the pts1 complexed to the tpr region2 of human pex5
31	c3hymB_	Alignment	not modelled	99.9	11	**PDB header:**cell cycle, ligase **Chain:** B: **PDB Molecule:**cell division cycle protein 16 homolog; **PDBTitle:** insights into anaphase promoting complex tpr subdomain2 assembly from a cdc26-apc6 structure
32	c4zlhB_	Alignment	not modelled	99.9	13	**PDB header:**metal binding protein **Chain:** B: **PDB Molecule:**lipopolysaccharide assembly protein b; **PDBTitle:** structure of the lapb cytoplasmic domain at 2 angstroms
33	d1qsaa1	Alignment	not modelled	99.9	10	**Fold:**alpha-alpha superhelix **Superfamily:**Bacterial muramidases **Family:**Bacterial muramidases
34	c4r7sA_	Alignment	not modelled	99.9	11	**PDB header:**structural genomics, unknown function **Chain:** A: **PDB Molecule:**tetratricopeptide repeat protein; **PDBTitle:** crystal structure of a tetratricopeptide repeat protein (parmer_03812)2 from parabacteroides merdae atcc 43184 at 2.39 a resolution
35	c3cvpA_	Alignment	not modelled	99.9	15	**PDB header:**transport protein **Chain:** A: **PDB Molecule:**peroxisome targeting signal 1 receptor pex5; **PDBTitle:** structure of peroxisomal targeting signal 1 (pts1) binding2 domain of trypanosoma brucei peroxin 5 (tbpex5)complexed3 to pts1 peptide (10-skl)
36	c4eqfA_	Alignment	not modelled	99.9	17	**PDB header:**protein binding/transport protein **Chain:** A: **PDB Molecule:**pex5-related protein; **PDBTitle:** trip8b-1a#206-567 interacting with the carboxy-terminal seven residues2 of hcn2
37	c4jspA_	Alignment	not modelled	99.9	16	**PDB header:**transferase **Chain:** A: **PDB Molecule:**serine/threonine-protein kinase mtor; **PDBTitle:** structure of mtordeltan-mlst8-atpgammas-mg complex
38	c3pe3D_	Alignment	not modelled	99.9	18	**PDB header:**transferase **Chain:** D: **PDB Molecule:**udp-n-acetylglucosamine--peptide n- **PDBTitle:** structure of human o-glcnac transferase and its complex with a peptide2 substrate
39	c2uy1B_	Alignment	not modelled	99.9	13	**PDB header:**rna-binding protein **Chain:** B: **PDB Molecule:**cleavage stimulation factor 77; **PDBTitle:** crystal structure of cstf-77
40	c3mkrA_	Alignment	not modelled	99.9	12	**PDB header:**transport protein **Chain:** A: **PDB Molecule:**coatomer subunit epsilon; **PDBTitle:** crystal structure of yeast alpha/epsilon-cop subcomplex of the copi2 vesicular coat
41	d1dcea1	Alignment	not modelled	99.9	10	**Fold:**alpha-alpha superhelix **Superfamily:**Protein prenylyltransferase **Family:**Protein prenylyltransferase
42	c3draA_	Alignment	not modelled	99.9	10	**PDB header:**transferase **Chain:** A: **PDB Molecule:**protein **PDBTitle:** candida albicans protein geranylgeranyltransferase-i2 complexed with ggpp
43	d2h6fa1	Alignment	not modelled	99.9	12	**Fold:**alpha-alpha superhelix **Superfamily:**Protein prenylyltransferase **Family:**Protein prenylyltransferase
44	c3v6tA_	Alignment	not modelled	99.9	13	**PDB header:**dna binding protein/dna **Chain:** A: **PDB Molecule:**dhax3; **PDBTitle:** crystal structure of the dna-bound dhax3, a tal effector, at 1.852 angstrom
45	c4gpkI_	Alignment	not modelled	99.9	13	**PDB header:**transcription, peptide binding protein **Chain:** I: **PDB Molecule:**nprr; **PDBTitle:** crystal structure of nprr in complex with its cognate peptide nprx
46	c4ynvA_	Alignment	not modelled	99.9	15	**PDB header:**chaperone **Chain:** A: **PDB Molecule:**acl4; **PDBTitle:** assembly chaperone of rpl4 (acl4) (residues 28-338)
47	d1d8da_	Alignment	not modelled	99.9	13	**Fold:**alpha-alpha superhelix **Superfamily:**Protein prenylyltransferase **Family:**Protein prenylyltransferase
48	c3uq3A_	Alignment	not modelled	99.9	15	**PDB header:**chaperone **Chain:** A: **PDB Molecule:**heat shock protein sti1; **PDBTitle:** tpr2ab-domain:phsp90-complex of yeast sti1
49	c3jb9R_	Alignment	not modelled	99.9	11	**PDB header:**rna binding protein/rna **Chain:** R: **PDB Molecule:**pre-mrna-splicing factor cwf4; **PDBTitle:** cryo-em structure of the yeast spliceosome at 3.6 angstrom resolution
50	c1tnoI_	Alignment	not modelled	99.9	12	**PDB header:**transferase **Chain:** I: **PDB Molecule:**geranylgeranyltransferase type i alpha subunit; **PDBTitle:** rat protein geranylgeranyltransferase type-i complexed with2 a ggpp analog and a kkksktkcvim peptide derived from k-3 ras4b
51	d1hz4a_	Alignment	not modelled	99.9	16	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Transcription factor MalT domain III
52	c3q75A_	Alignment	not modelled	99.9	13	**PDB header:**transferase **Chain:** A: **PDB Molecule:**farnesyltransferase alpha subunit; **PDBTitle:** cryptococcus neoformans protein farnesyltransferase in complex with2 fpt-ii and tkcvvm peptide
53	c4abnA_	Alignment	not modelled	99.9	12	**PDB header:**gene regulation **Chain:** A: **PDB Molecule:**tetratricopeptide repeat protein 5; **PDBTitle:** crystal structure of full length mouse strap (ttc5)
54	c2hp1B_	Alignment	not modelled	99.8	12	**PDB header:**protein binding **Chain:** B: **PDB Molecule:**type 4 fimbrial biogenesis protein pilf;

54	c2h01B_	Alignment	not modelled	99.8	12	**PDBTitle:** functional characterization of pseudomonas aeruginosa pilf
55	c4lngA_	Alignment	not modelled	99.8	14	**PDB header:**transferase **Chain:** A: **PDB Molecule:**caax farnesyltransferase alpha subunit ram2; **PDBTitle:** aspergillus fumigatus protein farnesyltransferase complex with2 farnesyldiphosphate and tipifarnib
56	c3mv3B_	Alignment	not modelled	99.8	11	**PDB header:**protein transport **Chain:** B: **PDB Molecule:**coatomer subunit epsilon; **PDBTitle:** crystal structure of a-cop in complex with e-cop
57	d1xnfa_	Alignment	not modelled	99.8	13	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Tetratricopeptide repeat (TPR)
58	c4nrhB_	Alignment	not modelled	99.8	14	**PDB header:**chaperone/protein binding **Chain:** B: **PDB Molecule:**chaperone sycd; **PDBTitle:** copn-scc3 complex
59	c4xi0E_	Alignment	not modelled	99.8	16	**PDB header:**protein binding **Chain:** E: **PDB Molecule:**magnetosome protein mama; **PDBTitle:** mama 41-end from desulfovibrio magneticus rs-1
60	c2hyzA_	Alignment	not modelled	99.8	27	**PDB header:**de novo protein **Chain:** A: **PDB Molecule:**synthetic consensus tpr protein; **PDBTitle:** crystal structure of an 8 repeat consensus tpr superhelix2 (orthorombic crystal form)
61	c4houB_	Alignment	not modelled	99.8	20	**PDB header:**rna binding protein **Chain:** B: **PDB Molecule:**interferon-induced protein with tetratricopeptide repeats **PDBTitle:** crystal structure of n-terminal human ifit1
62	c4gyoB_	Alignment	not modelled	99.8	11	**PDB header:**hydrolase **Chain:** B: **PDB Molecule:**response regulator aspartate phosphatase j; **PDBTitle:** crystal structure of rap protein complexed with competence and2 sporulation factor
63	c3as5A_	Alignment	not modelled	99.8	16	**PDB header:**protein binding **Chain:** A: **PDB Molecule:**mama; **PDBTitle:** mama amb-1 p212121
64	c2q7fA_	Alignment	not modelled	99.8	14	**PDB header:**protein binding **Chain:** A: **PDB Molecule:**yrrb protein; **PDBTitle:** crystal structure of yrrb: a tpr protein with an unusual peptide-2 binding site
65	c3q15A_	Alignment	not modelled	99.8	13	**PDB header:**hydrolase/kinase **Chain:** A: **PDB Molecule:**response regulator aspartate phosphatase h; **PDBTitle:** crystal structure of raph complexed with spo0f
66	c1xi4D_	Alignment	not modelled	99.8	11	**PDB header:**endocytosis/exocytosis **Chain:** D: **PDB Molecule:**clathrin heavy chain; **PDBTitle:** clathrin d6 coat
67	c3vtxB_	Alignment	not modelled	99.8	16	**PDB header:**protein binding **Chain:** B: **PDB Molecule:**mama; **PDBTitle:** crystal structure of mama protein
68	c4a1sB_	Alignment	not modelled	99.8	17	**PDB header:**cell cycle **Chain:** B: **PDB Molecule:**partner of inscuteable; **PDBTitle:** crystallographic structure of the pins:insc complex
69	c4d18J_	Alignment	not modelled	99.8	12	**PDB header:**signaling protein **Chain:** J: **PDB Molecule:**cop9 signalosome complex subunit 2; **PDBTitle:** crystal structure of the cop9 signalosome
70	c4i1aB_	Alignment	not modelled	99.8	11	**PDB header:**hydrolase **Chain:** B: **PDB Molecule:**response regulator aspartate phosphatase i; **PDBTitle:** crystal structure of the apo form of rapi
71	c4f3vB_	Alignment	not modelled	99.8	17	**PDB header:**protein transport **Chain:** B: **PDB Molecule:**esx-1 secretion system protein ecca1; **PDBTitle:** crystal structure of n-terminal domain of ecca1 atpase from esx-12 secretion system of mycobacterium tuberculosis
72	c3ro2A_	Alignment	not modelled	99.8	12	**PDB header:**protein binding **Chain:** A: **PDB Molecule:**g-protein-signaling modulator 2; **PDBTitle:** structures of the lgn/numa complex
73	c3u4tA_	Alignment	not modelled	99.8	11	**PDB header:**structural genomics, unknown function **Chain:** A: **PDB Molecule:**tpr repeat-containing protein; **PDBTitle:** crystal structure of the c-terminal part of the tpr repeat-containing2 protein q11ti6_cyth3 from cytophaga hutchinsonii. northeast3 structural genomics consortium target chr11b.
74	c2vq2A_	Alignment	not modelled	99.8	10	**PDB header:**structural protein **Chain:** A: **PDB Molecule:**putative fimbrial biogenesis and twitching **PDBTitle:** crystal structure of pilw, widely conserved type iv pilus2 biogenesis factor
75	c3urzB_	Alignment	not modelled	99.8	15	**PDB header:**protein binding **Chain:** B: **PDB Molecule:**uncharacterized protein; **PDBTitle:** crystal structure of a putative protein binding protein (bacova_03105)2 from bacteroides ovatus atcc 8483 at 2.19 a resolution
76	c1wao4_	Alignment	not modelled	99.8	13	**PDB header:**hydrolase **Chain:** 4: **PDB Molecule:**serine/threonine protein phosphatase 5; **PDBTitle:** pp5 structure
77	c5djsA_	Alignment	not modelled	99.8	18	**PDB header:**transferase **Chain:** A: **PDB Molecule:**tetratricopeptide tpr_2 repeat protein; **PDBTitle:** thermobaculum terrenum o-glcnac transferase mutant - k341m
78	c4uqzA_	Alignment	not modelled	99.8	15	**PDB header:**protein transport **Chain:** A: **PDB Molecule:**hsie1; **PDBTitle:** coevolution of the atpase clpv, the tssb-tssc sheath and2 the accessory hsie protein distinguishes two type vi3 secretion classes
79	c2r5sB_	Alignment	not modelled	99.8	13	**PDB header:**structural genomics, unknown function **Chain:** B: **PDB Molecule:**uncharacterized protein vp0806; **PDBTitle:** the crystal structure of a domain of protein vp0806

						(unknown function)2 from vibrio parahaemolyticus rimd 2210633
80	d1hh8a_	Alignment	not modelled	99.8	15	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Tetratricopeptide repeat (TPR)
81	c3sf4B_	Alignment	not modelled	99.8	13	**PDB header:**signaling protein/protein binding **Chain:** B: **PDB Molecule:**g-protein-signaling modulator 2; **PDBTitle:** crystal structure of the complex between the conserved cell polarity2 proteins inscuteable and lgn
82	c3u64A_	Alignment	not modelled	99.8	17	**PDB header:**transport protein **Chain:** A: **PDB Molecule:**protein tp_0956; **PDBTitle:** the crystal structure of tat-t (tp0956)
83	c3ulqA_	Alignment	not modelled	99.8	9	**PDB header:**gene regulation/transcription activator **Chain:** A: **PDB Molecule:**response regulator aspartate phosphatase f; **PDBTitle:** crystal structure of the anti-activator rapf complexed with the2 response regulator coma dna binding domain
84	d2c2la1	Alignment	not modelled	99.7	14	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Tetratricopeptide repeat (TPR)
85	c2e2eA_	Alignment	not modelled	99.7	12	**PDB header:**lyase **Chain:** A: **PDB Molecule:**formate-dependent nitrite reductase complex nrfg subunit; **PDBTitle:** tpr domain of nrfg mediates the complex formation between heme lyase2 and formate-dependent nitrite reductase in escherichia coli o157:h7
86	c5efrA_	Alignment	not modelled	99.7	10	**PDB header:**cell adhesion **Chain:** A: **PDB Molecule:**bama-bamd fusion protein; **PDBTitle:** crystal structure of a bama-bamd fusion
87	c5a6cB_	Alignment	not modelled	99.7	12	**PDB header:**cell adhesion **Chain:** B: **PDB Molecule:**g-protein-signaling modulator 2, afadin; **PDBTitle:** concomitant binding of afadin to lgn and f-actin directs2 planar spindle orientation
88	c3sz7A_	Alignment	not modelled	99.7	16	**PDB header:**chaperone regulator **Chain:** A: **PDB Molecule:**hsc70 cochaperone (sgt); **PDBTitle:** crystal structure of the sgt2 tpr domain from aspergillus fumigatus
89	c4i2wA_	Alignment	not modelled	99.7	19	**PDB header:**chaperone/protein binding **Chain:** A: **PDB Molecule:**protein unc-45; **PDBTitle:** crystal structure of the myosin chaperone unc-45 from c.elegans in2 complex with a hsp70 peptide
90	c2xcbA_	Alignment	not modelled	99.7	19	**PDB header:**protein binding **Chain:** A: **PDB Molecule:**regulatory protein pcrh; **PDBTitle:** crystal structure of pcrh in complex with the chaperone2 binding region of popd
91	c4i17A_	Alignment	not modelled	99.7	17	**PDB header:**structural genomics, unknown function **Chain:** A: **PDB Molecule:**hypothetical protein; **PDBTitle:** crystal structure of a tpr repeats protein (bf2334) from bacteroides2 fragilis nctc 9343 at 1.50 a resolution
92	c2pl2A_	Alignment	not modelled	99.7	18	**PDB header:**protein binding **Chain:** A: **PDB Molecule:**hypothetical conserved protein ttc0263; **PDBTitle:** crystal structure of ttc0263: a thermophilic tpr protein in thermus2 thermophilus hb27
93	c3zpjA_	Alignment	not modelled	99.7	12	**PDB header:**unknown function **Chain:** A: **PDB Molecule:**ton_1535; **PDBTitle:** crystal structure of ton1535 from thermococcus onnurineus na1
94	d1a17a_	Alignment	not modelled	99.7	13	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Tetratricopeptide repeat (TPR)
95	c4ga0A_	Alignment	not modelled	99.7	14	**PDB header:**transport protein **Chain:** A: **PDB Molecule:**e3 sumo-protein ligase ranbp2; **PDBTitle:** structure of the n-terminal domain of nup358
96	c4cgvA_	Alignment	not modelled	99.7	15	**PDB header:**chaperone **Chain:** A: **PDB Molecule:**rna polymerase ii-associated protein 3; **PDBTitle:** first tpr of spaghetti (rpap3) bound to hsp90 peptide srmeevd
97	c3zn3A_	Alignment	not modelled	99.7	8	**PDB header:**cell cycle **Chain:** A: **PDB Molecule:**anaphase-promoting complex subunit 8; **PDBTitle:** n-terminal domain of s. pombe cdc23 apc subunit
98	c2vyiA_	Alignment	not modelled	99.7	16	**PDB header:**chaperone **Chain:** A: **PDB Molecule:**sgta protein; **PDBTitle:** crystal structure of the tpr domain of human sgt
99	c3gyzB_	Alignment	not modelled	99.7	12	**PDB header:**chaperone **Chain:** B: **PDB Molecule:**chaperone protein ipgc; **PDBTitle:** crystal structure of ipgc from shigella flexneri
100	c2c2lD_	Alignment	not modelled	99.7	21	**PDB header:**chaperone **Chain:** D: **PDB Molecule:**carboxy terminus of hsp70-interacting protein; **PDBTitle:** crystal structure of the chip u-box e3 ubiquitin ligase
101	c3ly8A_	Alignment	not modelled	99.7	16	**PDB header:**signaling protein **Chain:** A: **PDB Molecule:**transcriptional activator cadc; **PDBTitle:** crystal structure of mutant d471e of the periplasmic domain of cadc
102	c4cr3Q_	Alignment	not modelled	99.7	12	**PDB header:**hydrolase **Chain:** Q: **PDB Molecule:**26s proteasome regulatory subunit rpn6; **PDBTitle:** deep classification of a large cryo-em dataset defines the2 conformational landscape of the 26s proteasome
103	c4gcoA_	Alignment	not modelled	99.7	16	**PDB header:**protein binding **Chain:** A: **PDB Molecule:**protein sti-1; **PDBTitle:** central domain of stress-induced protein-1 (sti-1) from c.elegans
104	c2kckA_	Alignment	not modelled	99.7	16	**PDB header:**structural genomics, unknown function **Chain:** A: **PDB Molecule:**tpr repeat; **PDBTitle:** nmr solution structure of the northeast structural genomics2 consortium (nesg) target mrr121a
						PDB header:chaperone

105	c4cgwA_	Alignment	not modelled	99.7	18	**Chain:** A: **PDB Molecule:**rna polymerase ii-associated protein 3; **PDBTitle:** second tpr of spaghetti (rpap3) bound to hsp90 peptide srmeevd
106	d1elwa_	Alignment	not modelled	99.7	15	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Tetratricopeptide repeat (TPR)
107	c2vsnB_	Alignment	not modelled	99.7	18	**PDB header:**transferase **Chain:** B: **PDB Molecule:**xcogt; **PDBTitle:** structure and topological arrangement of an o-glcnac2 transferase homolog: insight into molecular control of3 intracellular glycosylation
108	d1zu2a1	Alignment	not modelled	99.7	17	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Tetratricopeptide repeat (TPR)
109	c3gw4B_	Alignment	not modelled	99.7	15	**PDB header:**structural genomics, unknown function **Chain:** B: **PDB Molecule:**uncharacterized protein; **PDBTitle:** crystal structure of uncharacterized protein from deinococcus2 radiodurans. northeast structural genomics consortium target drr162b.
110	c4i1aA_	Alignment	not modelled	99.7	11	**PDB header:**hydrolase **Chain:** A: **PDB Molecule:**response regulator aspartate phosphatase i; **PDBTitle:** crystal structure of the apo form of rapi
111	c2lniA_	Alignment	not modelled	99.7	15	**PDB header:**chaperone **Chain:** A: **PDB Molecule:**stress-induced-phosphoprotein 1; **PDBTitle:** solution nmr structure of stress-induced-phosphoprotein 1 sti1 from2 homo sapiens, northeast structural genomics consortium target hr4403e
112	c4j8dC_	Alignment	not modelled	99.6	18	**PDB header:**chaperone **Chain:** C: **PDB Molecule:**hsc70-interacting protein; **PDBTitle:** middle domain of hsc70-interacting protein, crystal form ii
113	c3q49B_	Alignment	not modelled	99.6	21	**PDB header:**ligase/chaperone **Chain:** B: **PDB Molecule:**stip1 homology and u box-containing protein 1; **PDBTitle:** crystal structure of the tpr domain of chip complexed with hsp70-c2 peptide
114	d2onda1	Alignment	not modelled	99.6	17	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**HAT/Suf repeat
115	c3upvA_	Alignment	not modelled	99.6	13	**PDB header:**peptide binding protein **Chain:** A: **PDB Molecule:**heat shock protein sti1; **PDBTitle:** tpr2b-domain:phsp70-complex of yeast sti1
116	c2ifuA_	Alignment	not modelled	99.6	15	**PDB header:**endocytosis/exocytosis **Chain:** A: **PDB Molecule:**gamma-snap; **PDBTitle:** crystal structure of a gamma-snap from danio rerio
117	c3qdnA_	Alignment	not modelled	99.6	14	**PDB header:**oxidoreductase **Chain:** A: **PDB Molecule:**putative thioredoxin protein; **PDBTitle:** putative thioredoxin protein from salmonella typhimurium
118	c4aifA_	Alignment	not modelled	99.6	13	**PDB header:**signaling protein/peptide **Chain:** A: **PDB Molecule:**ah receptor-interacting protein; **PDBTitle:** aip tpr domain in complex with human hsp90 peptide
119	c4bt8B_	Alignment	not modelled	99.6	12	**PDB header:**oxidoreductase **Chain:** B: **PDB Molecule:**prolyl 4-hydroxylase subunit alpha-1; **PDBTitle:** crystal structure of the apo form of n-terminal domain and2 peptide substrate binding domain of prolyl-4 hydroxylase3 type i from human
120	d1kt1a1	Alignment	not modelled	99.6	10	**Fold:**alpha-alpha superhelix **Superfamily:**TPR-like **Family:**Tetratricopeptide repeat (TPR)

Fig E4

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Phyre2

Email	umdl@leeds.ac.uk
Description	TTC7A-002_Intensive
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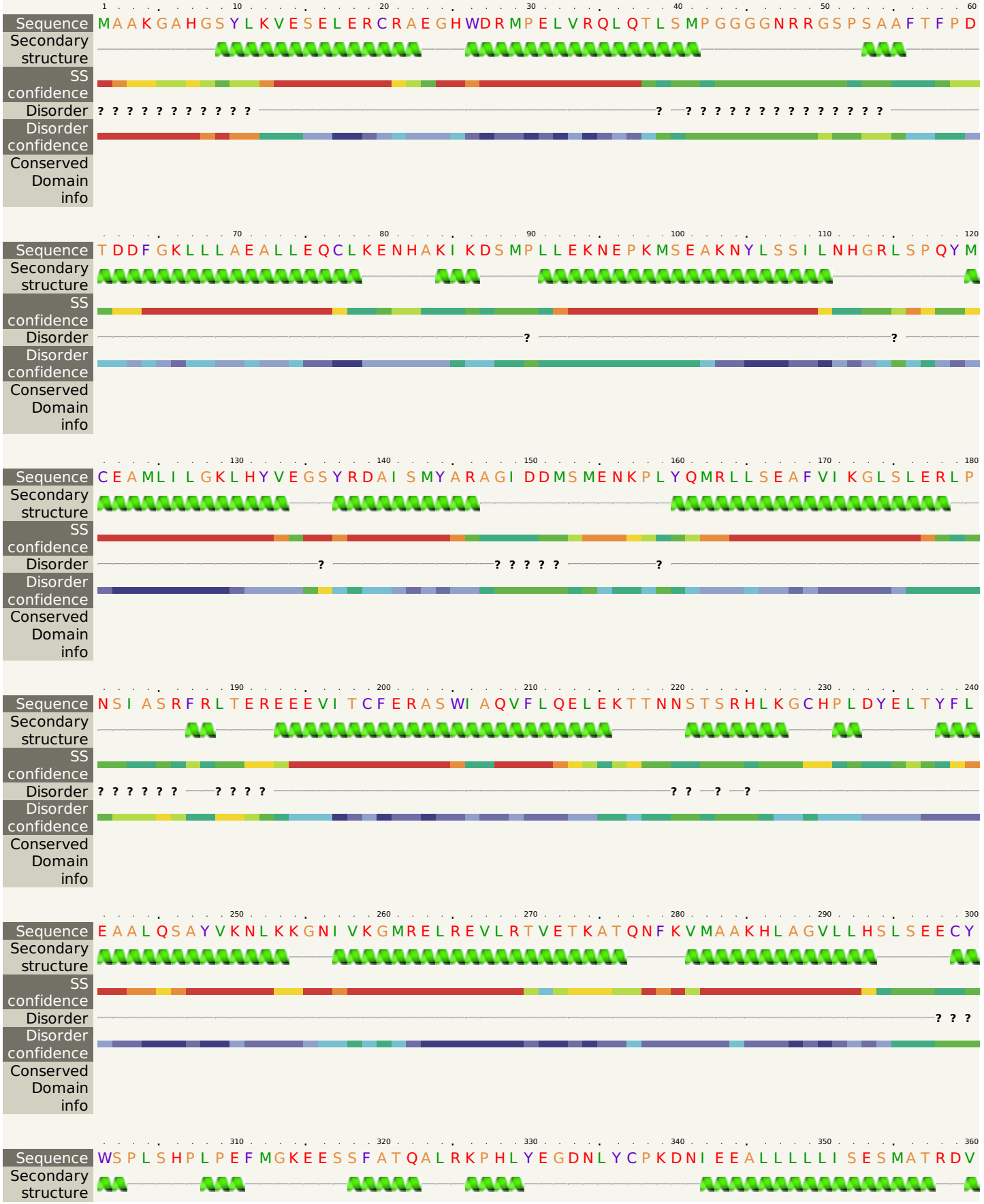
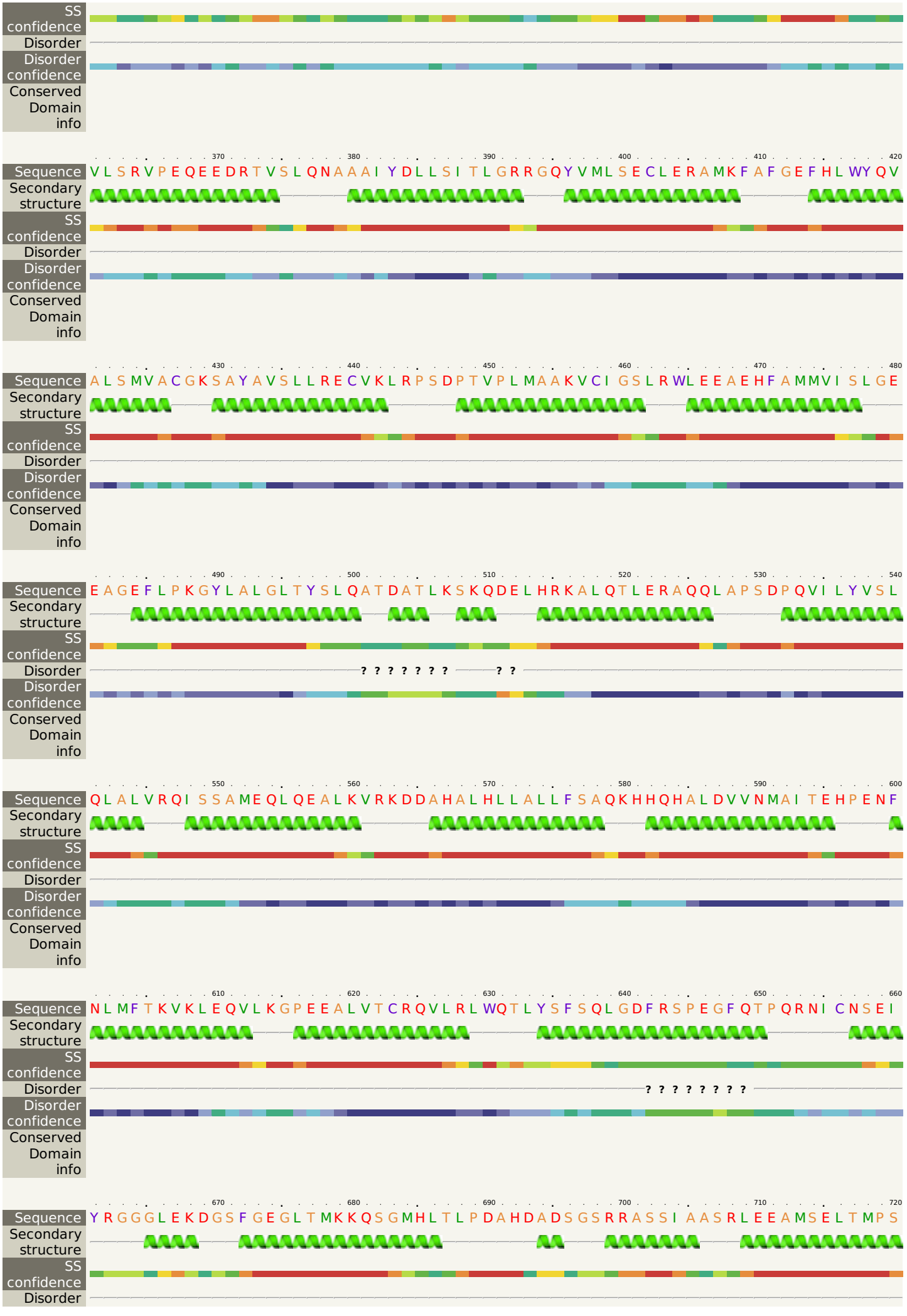
Unique Job ID	2fb079ebb0afd496

Secondary structure and disorder prediction

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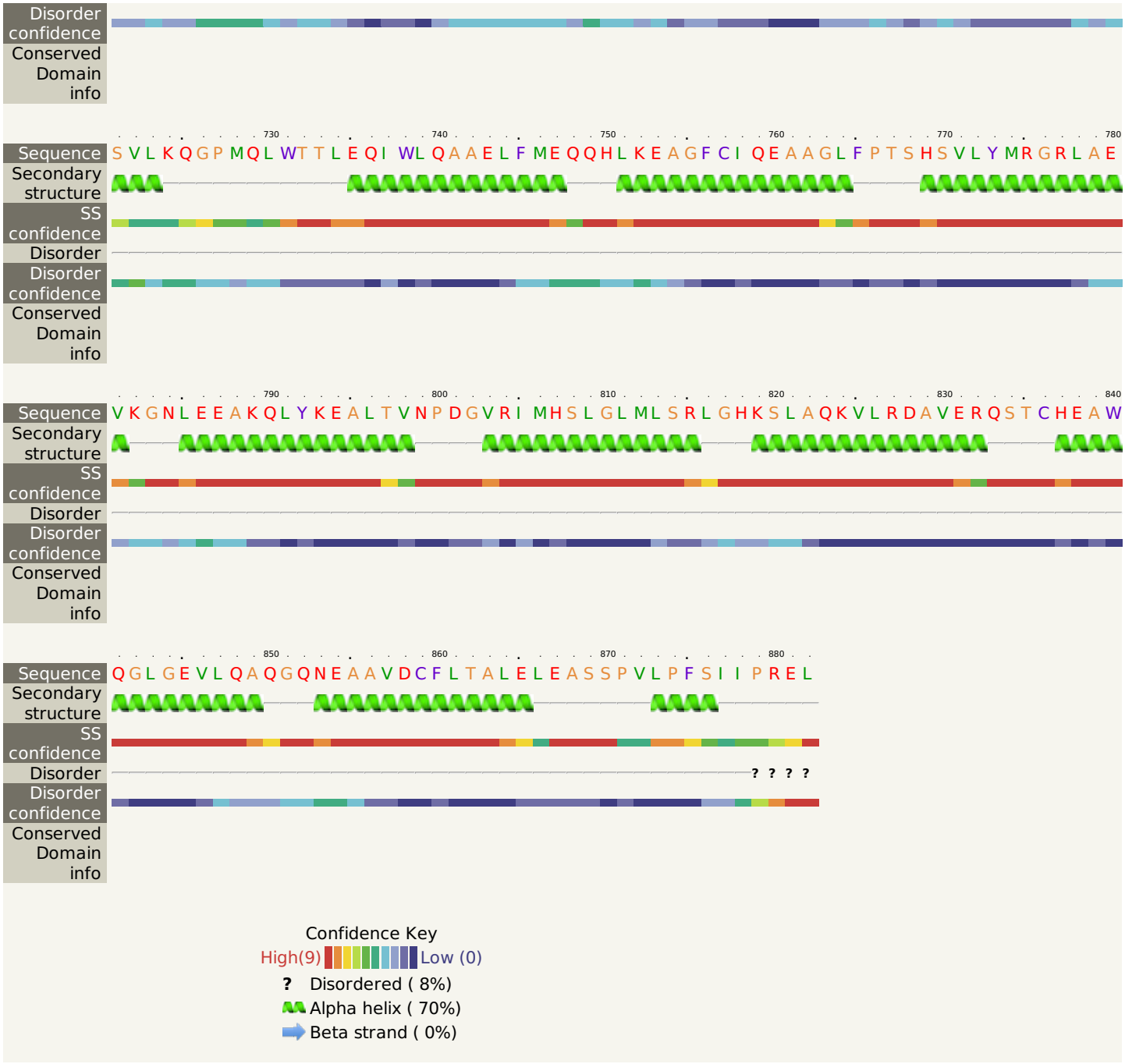
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Secondary structure
SS confidence
Disorder
Disorder confidence
Conserved Domain info
790
800
810
820
830
840
Sequence
V K G N L E E A K Q L Y K E A L T V N P D G V R I M H S L G L M L S R L G H K S L A Q K V L R D A V E R Q S T C H E A W
Secondary structure
SS confidence
Disorder
Disorder confidence
Conserved Domain info
850
860
870
880
Sequence
Q G L G E V L Q A Q G Q N E A A V D C F L T A L E L E A S S P V L P F S I I P R E L
Secondary structure
SS confidence
Disorder
? ? ? ?
Disorder confidence
Conserved Domain info
Confidence Key
High(9)
Low (0)
? Disordered (8%)
Alpha helix (70%)
Beta strand (0%)

Table 1 Immunological assessments

Tests	2012	2016	Normal ranges
IgG (g/l)	2.9	5.4 (on IVIG)	5.4-16.1
IgA (g/l)	0.07	<0.06	0.8-2.80
IgM (g/l)	0.18	0.16	0.5-1.90
IgE ku/l	<2.0		0.5-120
Pneumococcal Ab µg/ml	4.1		Adequate >30
Total lymphocytes (cells/µl)	1930	1897	1000-2800
CD3+ Lymphocytes (cells/µl)	1170	1286	800-3500
CD4+ T cells (cells/µl)	677	664	300-1400
CD8+ T cells (cells/µl)	420	540	200-900 cells/µl
NK cells CD56+ (cells/µ)l	97	163	90-600 cells/µl
B cells (CD19+) cells/µl	570	379	100-500 cells/µl
ratio	1.61	1.23	1.07-1.87
Marginal zone B cells CD19+ CD27+ IgD+ (% of CD19+)	5		0.5-8%*
Class switched memory B cells CD19+ CD27+ IgD- (% of CD19+)	1		3-18%*
PHA induced lymphocyte proliferation		Normal	N/A
Anti-CD3 induced lymphocyte proliferation		Normal	N/A
Neutrophil function test		Normal	N/A
Autoimmune screen [ANA, AMA, ACPA, Endomysial Ab (IgG and IgA)]	Negative		N/A

PHA: phytohaemagglutinin; ANA: antinuclear antibodies; AMA: antimitochondrial antibodies; ACPA: anticitrulinated protein antibodies

* Schatorje EJ, et al. Age-matched reference values for B-lymphocyte subpopulations and CVID classifications in children. Scand J Immunol 2011;74:502-10