Supplementary Figures

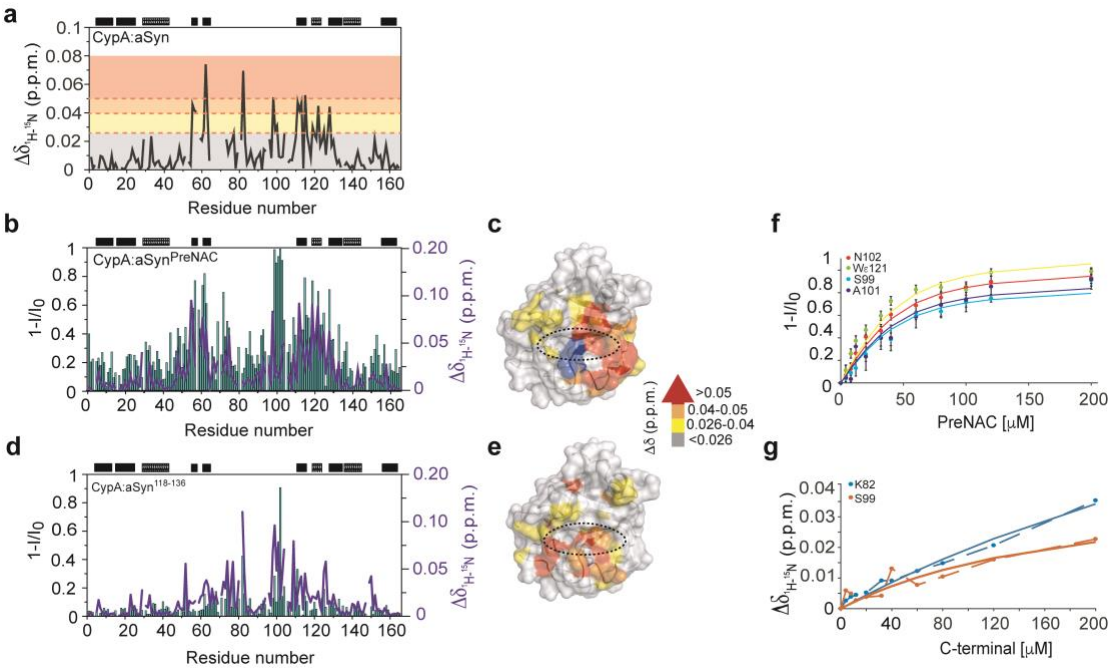


Figure S1. Residue-specific chemical shift perturbation in CypA upon binding to aSyn. **a)** Residue-specific chemical shift changes in CypA upon addition of a 5-fold excess of aSyn. Regions undergoing chemical shift changes are mapped in Fig. 2b onto the 3D structure of CypA from grey ($\Delta\delta_{^1H\text{-}^{15}N} < 0.026$ ppm) to red ($\Delta\delta_{^1H\text{-}^{15}N} > 0.05$ ppm). CypA secondary structure elements are shown on top. **b-e)** Intensity changes (green bars) and chemical shift changes $\Delta\delta_{^1H\text{-}^{15}N}$ (purple line) in $^1H\text{-}^{15}N$ HSQC spectra of CypA in presence of 8-fold molar excess of the peptides aSyn$_{PreNAC}$ (b,c) and aSyn$_{118\text{-}136}$ (d,e). CypA residues, which were broadened beyond detection in presence of aSyn$_{PreNAC}$, are shown in blue in (c). **f)** Changes in signal intensities of selected CypA residues at increasing concentrations of the peptide aSyn$_{PreNAC}$. **g)** Changes in chemical shifts of selected CypA residues at increasing concentrations of the peptide aSyn$_{118\text{-}136}$.

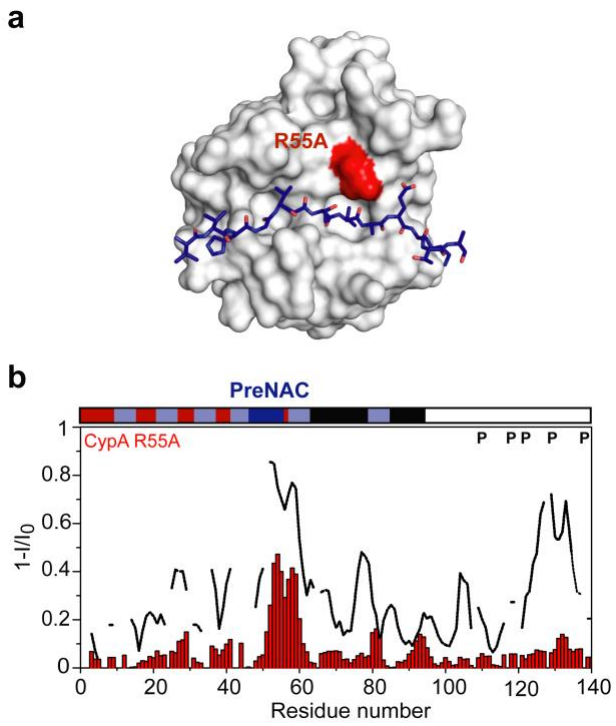


Figure S2. Mutation of the catalytic CypA residue R55 attenuates binding to aSyn. **a)** Location of the CypA mutation R55A in the 3D structure of the CypA/aSyn$_{PreNAC}$ complex. **b)** Residue-specific intensity changes in aSyn upon addition of a 5-fold excess of CypA$_{R55A}$ (red bars). I_0 and I are the intensities of ^{1}H-^{15}N HSQC cross-peaks in the absence and presence of CypA$_{R55A}$, respectively. For comparison, the black line displays the intensity broadening profile induced by wild-type CypA at the same molar ratio.

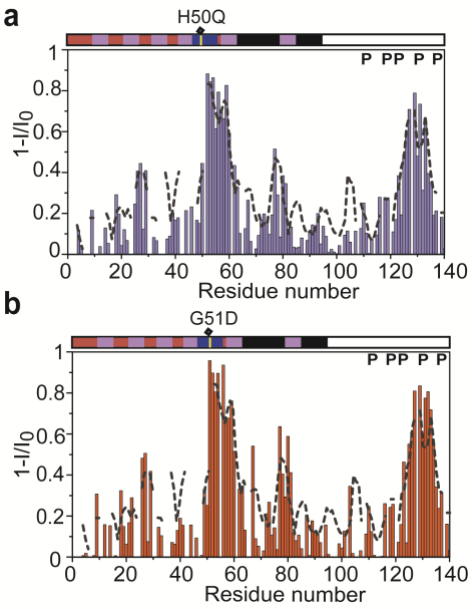


Figure S3. Binding of CypA to aSyn containing PD-associated mutations H50Q (a) and G51D (b). Residue-specific intensity changes upon addition of a 5-fold excess of CypA. The CypA-induced intensity broadening profile of wild-type aSyn is shown as dashed line.

Table S1. X-ray data collection statistics.

Data statistics	**PreNac/CypA-complex**
Wavelength	1.0 Å
Beamline	SLS-X10SA
Detector	PILATUS 6M
Space group	$P4_32_12$
a	61.034 Å
b	61.034 Å
c	129.152 Å
Resolution[a]	1.38 Å (1.40-1.38 Å)
Reflections measured	1,231,308
Unique reflections	51,144
Redundancy	24.01 (12.56)
Completeness(%)	99.7 (92.6)
Mean I/σ (I)	27.39 (1.16)
R_{rim} (%)[b]	2.92 (68.9)

[a] Values in parentheses are outer-resolution shell.

[b] $R_{rim} = \sum_{hkl}\left[N/(N-1)\right]^{1/2}\sum_{i}\left|I_i(hkl)-\langle I(hkl)\rangle\right| / \sum_{hkl}\sum_{i} I_i(hkl)$, where N is the redundancy and $I_i(hkl)$ is the ith observation of reflection hkl and $\langle I(hkl)\rangle$ is the weighted average intensity for all observations i of reflection hkl.

Table S2. X-ray structure refinement statistics CypA/αSyn$_{PreNAC}$-complex.

R-factor[a]	16.3%
R_{free}[b]	17.8%
Solvent	60.6%
Mean B-value (Å^2)	
chain A	24.26
chain B	32.01
waters	37.5
No. of protein residues	177
No. of water residues	248
Root mean square deviations from ideal geometry	
Bond lengths	0.019 Å
Bond angles	2.18°
Ramachandran plot (%)	
Favoured	95.1
Allowed	4.9
Outliers	0

[a] $R = \sum_{hkl} \left| |F_{obs}| - |F_{calc}| \right| / \sum_{hkl} |F_{obs}|$, where F_{obs} and F_{calc} are the observed and calculated structure factors, respectively.

[b] R_{free} was determined using 5% of the data [1].

Full wwPDB X-ray Structure Validation Report (i)

Nov 8, 2018 – 03:52 PM GMT

PDB ID	:	6I42
Title	:	Structure of the alpha-Synuclein PreNAC/Cyclophilin A-complex
Deposited on	:	2018-11-08
Resolution	:	1.38 Å(reported)

This is a Full wwPDB X-ray Structure Validation Report.

This report is produced by the wwPDB biocuration pipeline after annotation of the structure.

We welcome your comments at *validation@mail.wwpdb.org*
A user guide is available at
https://www.wwpdb.org/validation/2017/XrayValidationReportHelp
with specific help available everywhere you see the (i) symbol.

The following versions of software and data (see references (1)) were used in the production of this report:

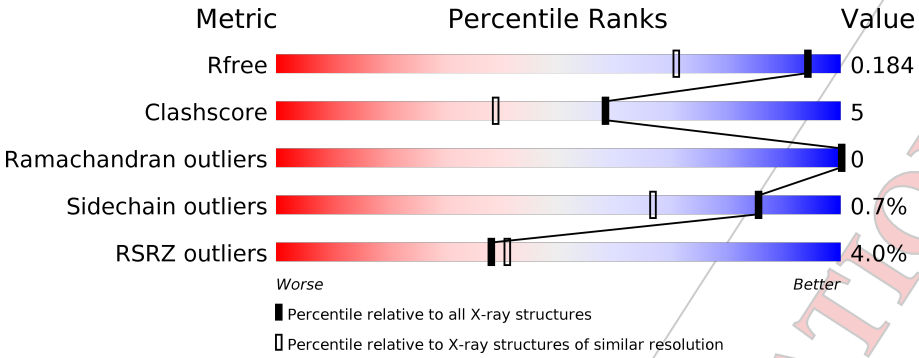
MolProbity	:	4.02b-467
Xtriage (Phenix)	:	1.13
EDS	:	rb-20031633
Percentile statistics	:	20171227.v01 (using entries in the PDB archive December 27th 2017)
Refmac	:	5.8.0158
CCP4	:	7.0 (Gargrove)
Ideal geometry (proteins)	:	Engh & Huber (2001)
Ideal geometry (DNA, RNA)	:	Parkinson et al. (1996)
Validation Pipeline (wwPDB-VP)	:	rb-20031633

1 Overall quality at a glance

The following experimental techniques were used to determine the structure:
X-RAY DIFFRACTION

The reported resolution of this entry is 1.38 Å.

Percentile scores (ranging between 0-100) for global validation metrics of the entry are shown in the following graphic. The table shows the number of entries on which the scores are based.



Metric	Whole archive (#Entries)	Similar resolution (#Entries, resolution range(Å))
R_{free}	111664	2404 (1.40-1.36)
Clashscore	122126	2520 (1.40-1.36)
Ramachandran outliers	120053	2464 (1.40-1.36)
Sidechain outliers	120020	2463 (1.40-1.36)
RSRZ outliers	108989	2346 (1.40-1.36)

The table below summarises the geometric issues observed across the polymeric chains and their fit to the electron density. The red, orange, yellow and green segments on the lower bar indicate the fraction of residues that contain outliers for >=3, 2, 1 and 0 types of geometric quality criteria. A grey segment represents the fraction of residues that are not modelled. The numeric value for each fraction is indicated below the corresponding segment, with a dot representing fractions <=5% The upper red bar (where present) indicates the fraction of residues that have poor fit to the electron density. The numeric value is given above the bar.

Mol	Chain	Length	Quality of chain
1	A	164	2% 89% 10%
2	B	13	31% 100%

2 Entry composition

There are 3 unique types of molecules in this entry. The entry contains 1698 atoms, of which 0 are hydrogens and 0 are deuteriums.

In the tables below, the ZeroOcc column contains the number of atoms modelled with zero occupancy, the AltConf column contains the number of residues with at least one atom in alternate conformation and the Trace column contains the number of residues modelled with at most 2 atoms.

- Molecule 1 is a protein called Peptidyl-prolyl cis-trans isomerase A.

Mol	Chain	Residues	Atoms					ZeroOcc	AltConf	Trace
			Total	C	N	O	S			
1	A	164	1354	854	236	255	9	0	11	0

- Molecule 2 is a protein called VAL-VAL-HIS-GLY-VAL-ALA-THR-VAL-ALA-GLU-LYS-THR-LYS.

Mol	Chain	Residues	Atoms				ZeroOcc	AltConf	Trace
			Total	C	N	O			
2	B	13	89	56	16	17	0	0	0

- Molecule 3 is water.

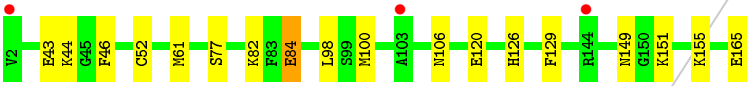
Mol	Chain	Residues	Atoms		ZeroOcc	AltConf
			Total	O		
3	A	232	238	238	0	6
3	B	16	17	17	0	1

3 Residue-property plots

These plots are drawn for all protein, RNA and DNA chains in the entry. The first graphic for a chain summarises the proportions of the various outlier classes displayed in the second graphic. The second graphic shows the sequence view annotated by issues in geometryand electron density. Residues are color-coded according to the number of geometric quality criteria for which they contain at least one outlier: green = 0, yellow = 1, orange = 2 and red = 3 or more. A red dot above a residue indicates a poor fit to the electron density (RSRZ > 2). Stretches of 2 or more consecutive residues without any outlier are shown as a green connector. Residues present in the sample, but not in the model, are shown in grey.

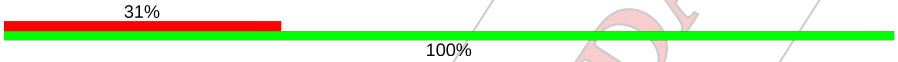
- Molecule 1: Peptidyl-prolyl cis-trans isomerase A

Chain A:



- Molecule 2: VAL-VAL-HIS-GLY-VAL-ALA-THR-VAL-ALA-GLU-LYS-THR-LYS

Chain B:



4 Data and refinement statistics (i)

Property	Value	Source
Space group	P 43 21 2	Depositor
Cell constants a, b, c, α, β, γ	61.03Å 61.03Å 129.15Å 90.00° 90.00° 90.00°	Depositor
Resolution (Å)	44.40 – 1.38 44.36 – 1.38	Depositor EDS
% Data completeness (in resolution range)	99.7 (44.40-1.38) 99.7 (44.36-1.38)	Depositor EDS
R_{merge}	0.06	Depositor
R_{sym}	(Not available)	Depositor
$< I/\sigma(I) >$ [1]	1.49 (at 1.38Å)	Xtriage
Refinement program	REFMAC 5.8.0238	Depositor
R, R_{free}	0.163 , 0.178 0.169 , 0.184	Depositor DCC
R_{free} test set	2548 reflections (4.99%)	wwPDB-VP
Wilson B-factor (Å^2)	22.7	Xtriage
Anisotropy	0.213	Xtriage
Bulk solvent k_{sol}(e/Å^3), B_{sol}(Å^2)	0.36 , 40.7	EDS
L-test for twinning[2]	$< \|L\| > = 0.50, < L^2 > = 0.33$	Xtriage
Estimated twinning fraction	No twinning to report.	Xtriage
F_o,F_c correlation	0.97	EDS
Total number of atoms	1698	wwPDB-VP
Average B, all atoms (Å^2)	26.0	wwPDB-VP

Xtriage's analysis on translational NCS is as follows: *The largest off-origin peak in the Patterson function is 7.78% of the height of the origin peak. No significant pseudotranslation is detected.*

[1] Intensities estimated from amplitudes.

[2] Theoretical values of $< |L| >$, $< L^2 >$ for acentric reflections are 0.5, 0.333 respectively for untwinned datasets, and 0.375, 0.2 for perfectly twinned datasets.

5 Model quality

5.1 Standard geometry

The Z score for a bond length (or angle) is the number of standard deviations the observed value is removed from the expected value. A bond length (or angle) with $|Z| > 5$ is considered an outlier worth inspection. RMSZ is the root-mean-square of all Z scores of the bond lengths (or angles).

Mol	Chain	Bond lengths		Bond angles	
		RMSZ	#$\|Z\|>5$	RMSZ	#$\|Z\|>5$
1	A	0.98	5/1381 (0.4%)	1.06	1/1841 (0.1%)
2	B	0.99	0/89	1.07	0/121
All	All	0.98	5/1470 (0.3%)	1.06	1/1962 (0.1%)

All (5) bond length outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(Å)	Ideal(Å)
1	A	84[A]	GLU	CD-OE2	6.43	1.32	1.25
1	A	84[B]	GLU	CD-OE2	6.43	1.32	1.25
1	A	120	GLU	CD-OE1	6.08	1.32	1.25
1	A	43	GLU	CD-OE2	6.04	1.32	1.25
1	A	77	SER	CA-CB	-5.04	1.45	1.52

All (1) bond angle outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(^{o})	Ideal(^{o})
1	A	46	PHE	CB-CG-CD1	6.07	125.05	120.80

There are no chirality outliers.

There are no planarity outliers.

5.2 Too-close contacts

In the following table, the Non-H and H(model) columns list the number of non-hydrogen atoms and hydrogen atoms in the chain respectively. The H(added) column lists the number of hydrogen atoms added and optimized by MolProbity. The Clashes column lists the number of clashes within the asymmetric unit, whereas Symm-Clashes lists symmetry related clashes.

Mol	Chain	Non-H	H(model)	H(added)	Clashes	Symm-Clashes
1	A	1354	0	1321	15	0
2	B	89	0	90	0	0

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Mol	Chain	Non-H	H(model)	H(added)	Clashes	Symm-Clashes
3	A	238	0	0	4	0
3	B	17	0	0	2	0
All	All	1698	0	1411	15	0

The all-atom clashscore is defined as the number of clashes found per 1000 atoms (including hydrogen atoms). The all-atom clashscore for this structure is 5.

All (15) close contacts within the same asymmetric unit are listed below, sorted by their clash magnitude.

Atom-1	Atom-2	Interatomic distance (Å)	Clash overlap (Å)
1:A:84[A]:GLU:HG2	3:A:261:HOH:O	1.66	0.94
1:A:52[B]:CYS:SG	1:A:155[B]:LYS:NZ	2.47	0.88
1:A:52[B]:CYS:SG	1:A:155[B]:LYS:HE3	2.39	0.62
1:A:52[B]:CYS:SG	1:A:155[B]:LYS:CE	2.88	0.61
1:A:84[A]:GLU:CD	1:A:84[A]:GLU:H	2.05	0.61
1:A:82[A]:LYS:HE3	3:B:102:HOH:O	2.03	0.56
1:A:100:MET:O	1:A:126:HIS:HD2	1.88	0.55
1:A:126:HIS:HE1	3:B:109:HOH:O	1.89	0.53
1:A:165[B]:GLU:OE1	3:A:201:HOH:O	2.19	0.53
1:A:149:ASN:ND2	1:A:151:LYS:H	2.10	0.50
1:A:44[B]:LYS:HG2	3:A:243:HOH:O	2.15	0.47
1:A:84[B]:GLU:OE2	3:A:202:HOH:O	2.20	0.47
1:A:98:LEU:HG	1:A:129:PHE:CZ	2.54	0.43

There are no symmetry-related clashes.

5.3 Torsion angles

5.3.1 Protein backbone

In the following table, the Percentiles column shows the percent Ramachandran outliers of the chain as a percentile score with respect to all X-ray entries followed by that with respect to entries of similar resolution.

The Analysed column shows the number of residues for which the backbone conformation was analysed, and the total number of residues.

Mol	Chain	Analysed	Favoured	Allowed	Outliers	Percentiles	
1	A	172/164 (105%)	169 (98%)	3 (2%)	0	100	100
2	B	11/13 (85%)	11 (100%)	0	0	100	100

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Mol	Chain	Analysed	Favoured	Allowed	Outliers	Percentiles
All	All	183/177 (103%)	180 (98%)	3 (2%)	0	100 100

There are no Ramachandran outliers to report.

5.3.2 Protein sidechains (i)

In the following table, the Percentiles column shows the percent sidechain outliers of the chain as a percentile score with respect to all X-ray entries followed by that with respect to entries of similar resolution.

The Analysed column shows the number of residues for which the sidechain conformation was analysed, and the total number of residues.

Mol	Chain	Analysed	Rotameric	Outliers	Percentiles
1	A	143/132 (108%)	142 (99%)	1 (1%)	85 67
2	B	9/10 (90%)	9 (100%)	0	100 100
All	All	152/142 (107%)	151 (99%)	1 (1%)	85 67

All (1) residues with a non-rotameric sidechain are listed below:

Mol	Chain	Res	Type
1	A	61	MET

Some sidechains can be flipped to improve hydrogen bonding and reduce clashes. All (4) such sidechains are listed below:

Mol	Chain	Res	Type
1	A	70	HIS
1	A	106	ASN
1	A	126	HIS
1	A	149	ASN

5.3.3 RNA (i)

There are no RNA molecules in this entry.

5.4 Non-standard residues in protein, DNA, RNA chains (i)

There are no non-standard protein/DNA/RNA residues in this entry.

5.5 Carbohydrates (i)

There are no carbohydrates in this entry.

5.6 Ligand geometry (i)

There are no ligands in this entry.

5.7 Other polymers (i)

There are no such residues in this entry.

5.8 Polymer linkage issues (i)

There are no chain breaks in this entry.

6 Fit of model and data

6.1 Protein, DNA and RNA chains

In the following table, the column labelled '#RSRZ> 2' contains the number (and percentage) of RSRZ outliers, followed by percent RSRZ outliers for the chain as percentile scores relative to all X-ray entries and entries of similar resolution. The OWAB column contains the minimum, median, 95^{th} percentile and maximum values of the occupancy-weighted average B-factor per residue. The column labelled 'Q< 0.9' lists the number of (and percentage) of residues with an average occupancy less than 0.9.

Mol	Chain	Analysed	<RSRZ>	#RSRZ>2	OWAB(Å^2)	Q<0.9
1	A	164/164 (100%)	0.03	3 (1%) 68 72	17, 23, 33, 54	0
2	B	13/13 (100%)	1.25	4 (30%) 0 0	19, 22, 46, 56	0
All	All	177/177 (100%)	0.12	7 (3%) 38 41	17, 23, 36, 56	0

All (7) RSRZ outliers are listed below:

Mol	Chain	Res	Type	RSRZ
1	A	2	VAL	5.6
2	B	60	LYS	3.8
2	B	49	VAL	2.9
1	A	144	ARG	2.8
2	B	48	VAL	2.7
1	A	103	ALA	2.4
2	B	59	THR	2.2

6.2 Non-standard residues in protein, DNA, RNA chains

There are no non-standard protein/DNA/RNA residues in this entry.

6.3 Carbohydrates

There are no carbohydrates in this entry.

6.4 Ligands

There are no ligands in this entry.

6.5 Other polymers (i)

There are no such residues in this entry.