Supplementary Information

Crystal structure of the N-terminal domain of human CDC73 and its implications for the hyperparathyroidism-jaw tumor (HPT-JT) syndrome

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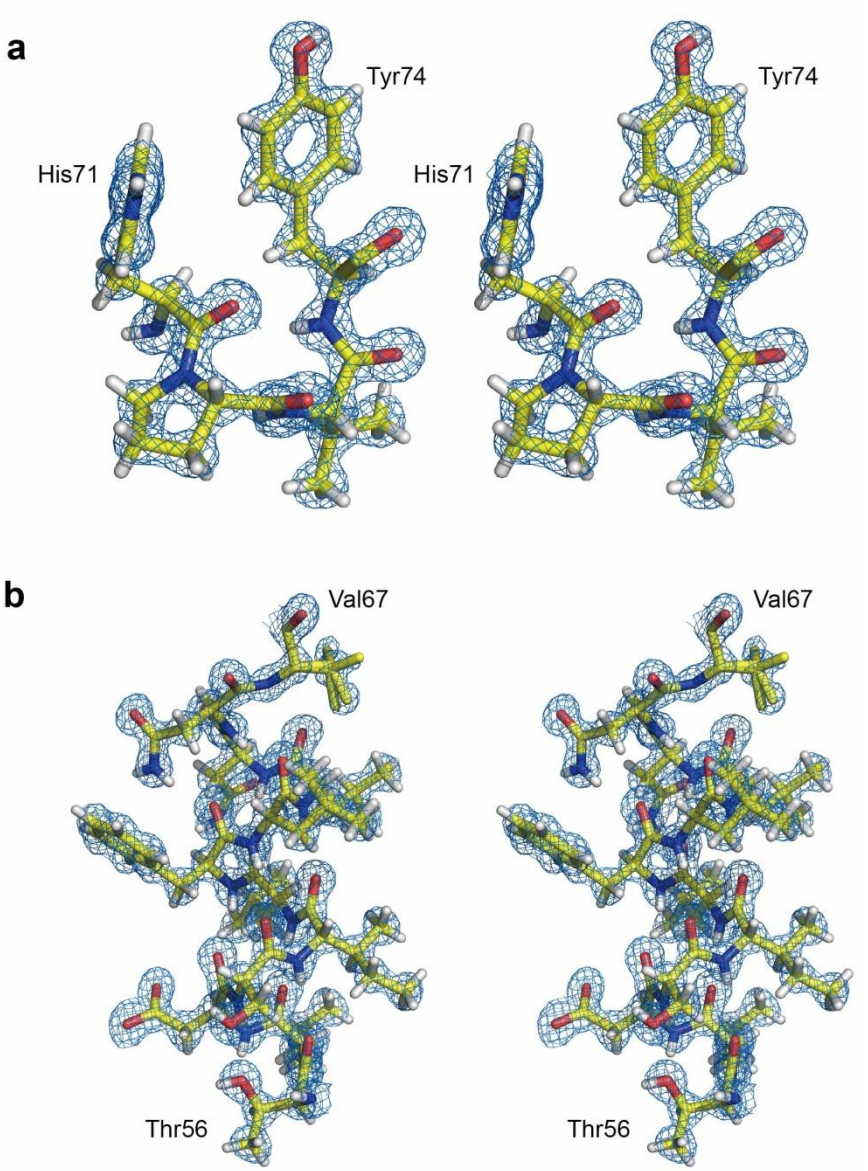
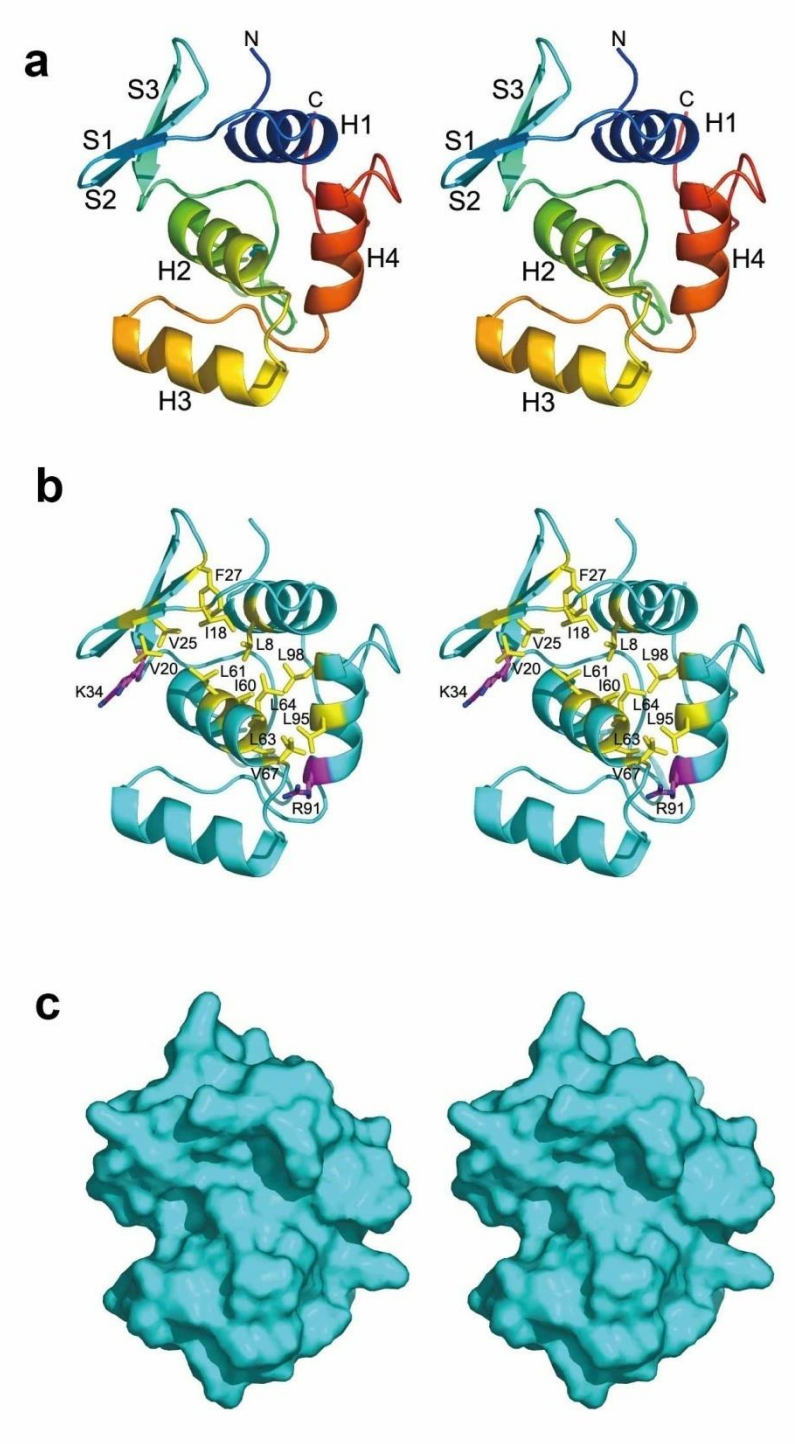
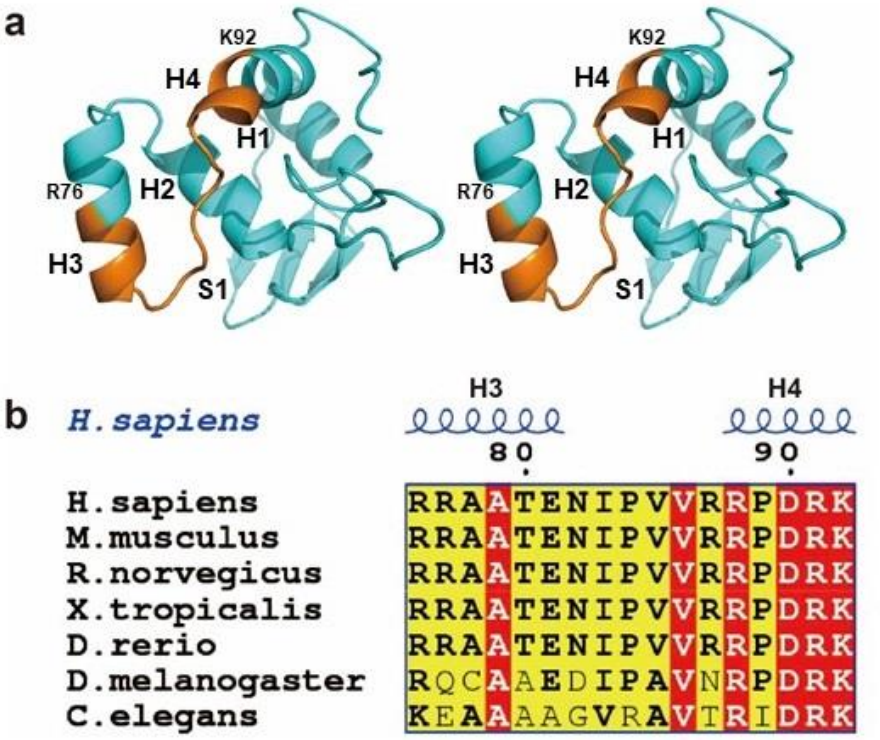


Supplementary Figure S1. Electron density map of two typical regions of CDC73(1-111) are shown in panel a and b, respectively. The map was calculated with 2*Fo-Fc* coefficients and contoured at 1.5σ as a blue mesh.



Supplementary Figure S2. Stereo views of CDC73-NTD. **(a)** Stereo views of the overall structure. **(b)** Stereo views of the structure with K34, R91 and residues on the hydrophobic groove shown in sticks. **(c)** Stereo views of the surface. All the views are in the same orientation.



Supplementary Figure S3. A proposed nucleolar localization signal (NoLS) in CDC73-NTD. **(a)** Stereo illustration to show that the proposed NoLS forms a surface patch of CDC73-NTD. Residues corresponding to this NoLS, spanning from H3 to H4, are shown in orange. The curved CDC73-NTD hydrophobic groove, formed by the helices H1, H2, H4 and the S1 β-strand, is roughly located in the "back side" of this illustrated structure. **(b)** This proposed NoLS is conserved among species.

Supplementary Table S1. Human CDC73 variants with explicit clinical significance.

All these variants, except three missense ones (referenced), are from the ClinVar database. The abbreviations of the clinical manifestation "Condition" are as follows: HPT-JT: hyperparathyroidism-jaw tumor syndrome; FIHP: familial isolated primary hyperparathyroidism; PTC: parathyroid carcinoma; PTA: parathyroid adenoma; CC: clear cell renal carcinoma; OF: ossifying fibroma; N. P.: Not provided.

Class	Number	Variation	Condition(s)	Clinical significance
Missense	1	CDC73:c.3G>A (p.Met1Ile)	HPT-JT	Pathogenic
	2[1]	CDC73:c.100A>C (p.Lys34Gln)	CC	Pathogenic
	3[2]	CDC73:c.179T>A (p.Ile60Asn)	OF	Pathogenic
	4	CDC73:c.191T>C (p.Leu64Pro)	HPT-JT	Pathogenic
	5[3]	CDC73:c.272G>C (p.Arg91Pro)	FIHP, PTA	Pathogenic
Nonsense	1	CDC73:c.25C>T (p.Arg9Ter)	HPT-JT	Pathogenic
	2	CDC73:c.85G>T (p.Glu29Ter)	N.P.	Pathogenic
	3	CDC73:c.109A>T (p.Lys37Ter)	N.P.	Pathogenic
	4	CDC73:c.128G>A (p.Trp43Ter)	PTC	Pathogenic
	5	CDC73:c.162C>G (p.Tyr54Ter)	PTC	Pathogenic
	6	CDC73:c.226C>T (p.Arg76Ter)	N.P.	Pathogenic
	7	CDC73:c.355C>T (p.Gln119Ter)	N.P.	Pathogenic
Frameshift	1	CDC73:c.4delG (p.Ala2Argfs)	PTC	Pathogenic
	2	CDC73:c.8_10delACGinsCT (p.Asp3Alafs)	OF	Pathogenic
	3	CDC73:c.13_16delCTTA (p.Leu5Alafs)	OF	Pathogenic
	4	CDC73:c.53delT (p.Ile18Metfs)	PTA	Pathogenic
	5	CDC73:c.85delG (p.Glu29Serfs)	PTC	Pathogenic
	6	CDC73:c.245delA (p.Asn82Ilefs)	PTC	Pathogenic
	7	CDC73:c.455_456delGA (p.Arg152Ilefs)	PTC	Pathogenic
	8	CDC73:c.679_680insAG (p.Arg227Lysfs)	HPT-JT, PTC	Pathogenic
	9	CDC73:c.687_688dupAG (p.Val230Glufs)	PTC, N.P.	Pathogenic
	10	CDC73:c.723_725delAGGinsC (p.Gly242Lysfs)	N.P.	Pathogenic
	11	CDC73:c.766_767delGT (p.Val256Lysfs)	PTC	Pathogenic

Delins	1	CDC73:c.13_30del18 (p.Leu5_Gln10del)	PTC	Pathogenic
	2	CDC73:c.237+28_237+31delTCTA	PTC	Benign
	3	CDC73:c.729+50_729+51delAG	PTC	Benign
	4	CDC73, 4-BP DEL, 685AGAG	PTC, PTA	Pathogenic
	5	CDC73, 2-BP DEL	HPT-JT	Pathogenic
	6	CDC73, 1-BP INS, 373A	PTC	Pathogenic
	7	CDC73, 41-BP DUP/INS	HPT-JT	Pathogenic
	8	CDC73, 41-BP DUP/INS	HPT-JT	Pathogenic
Splice site	1	CDC73:c.131+1G>A	HPT-JT, PTA, N.P.	Pathogenic
	2	CDC73:c.132-2A>G	HPT-JT	Likely pathogenic
	3	CDC73:c.237+1G>C	PTC	Pathogenic
	4	CDC73:c.237+1G>T	HPT-JT, HPT-JT	Pathogenic
	5	CDC73:c.238-2A>T	N.P.	Pathogenic
	6	CDC73:c.238-1G>A	HPT-JT	Pathogenic
	7	CDC73:c.423+1G>A	N.P.	Pathogenic
	8	CDC73:c.729+1G>T	PTC	Likely pathogenic
UTR	1	CDC73:c.-95G>A	PTC, HPT-JT, FIHP	Likely benign
	2	CDC73:c.-11G>A	PTC	Benign
	3	CDC73:c.-10G>T	PTC, HPT-JT, FIHP	Benign/Likely benign
	4	CDC73:c.*12C>A	PTC, HPT-JT,FIHP	Likely benign
	5	CDC73:c.*94A>G	PTC, HPT-JT, FIHP	Likely benign
	6	CDC73:c.*518A>G	PTC, HPT-JT, FIHP	Likely benign
	7	CDC73:c.*580A>T	PTC, HPT-JT, FIHP	Likely benign
	8	CDC73:c.*1083A>T	PTC, HPT-JT, FIHP	Likely benign
	9	CDC73:c.*1251A>G	PTC, HPT-JT, FIHP	Likely benign
	10	CDC73:c.*1267A>G	PTC, HPT-JT, FIHP	Likely benign
	11	CDC73:c.*1365T>C	PTC, HPT-JT, FIHP	Likely benign
	12	CDC73:c.*1472T>G	PTC, HPT-JT, FIHP	Likely benign
	13	CDC73:c.*1499T>A	PTC, HPT-JT, FIHP	Likely benign
	14	CDC73:c.*1761T>C	PTC, HPT-JT, FIHP	Likely benign
	15	CDC73:c.*2085G>C	PTC, HPT-JT, FIHP	Likely benign
	16	CDC73:c.*2304T>G	PTC, HPT-JT, FIHP	Likely benign
	17	CDC73:c.*2420A>C	PTC, HPT-JT, FIHP	Likely benign
	18	CDC73:c.*2427T>C	PTC, HPT-JT, FIHP	Likely benign
	19	CDC73:c.*2677G>A	PTC, HPT-JT, FIHP	Likely benign
	20	CDC73:c.*2950A>G	PTC, HPT-JT, FIHP	Likely benign
	21	CDC73:c.*2962T>C	PTC, HPT-JT, FIHP	Likely benign

	22	CDC73:c.*3266A>G	PTC, HPT-JT, FIHP	Likely benign
	23	CDC73:c.*3419T>A	PTC, HPT-JT, FIHP	Likely benign
	24	CDC73:c.*3507G>T	PTC, HPT-JT, FIHP	Likely benign
	25	CDC73:c.*3524A>G	PTC, HPT-JT, FIHP	Likely benign
	26	CDC73:c.*3641G>A	PTC, HPT-JT, FIHP	Likely benign
	27	CDC73:c.*3786T>C	PTC, HPT-JT, FIHP	Likely benign
	28	CDC73:c.*3786T>A	PTC, HPT-JT, FIHP	Benign
	29	CDC73:c.*3811_*3813delTTG	PTC, HPT-JT, FIHP	Likely benign

References for Table S1:

1. Zhao, J. et al. Sporadic human renal tumors display frequent allelic imbalances and novel mutations of the HRPT2 gene. *Oncogene* **26,** 3440-3449 (2007).
2. Masi, G. et al. Characterization of a new CDC73 missense mutation that impairs Parafibromin expression and nucleolar localization. *PLoS One* **9,** e97994 (2014).
3. Cetani, F. et al. Different somatic alterations of the HRPT2 gene in a patient with recurrent sporadic primary hyperparathyroidism carrying an HRPT2 germline mutation. *Endocr Relat Cancer* **14,** 493-499 (2007).

Supplementary Table S2. Closest structural fold of CDC73-NTD from DALI search. Only the first 25 hits are shown.

No.	Chain ID	Z score	r.m.s.d.	Description
1	4yrd-A	3.9	3.7	Capsular polysaccharide synthesis enzyme CAP5F
2	3st7-A	3.6	3.6	Capsular polysaccharide synthesis enzyme CAP5F
3	4yrd-B	3.6	3.7	Capsular polysaccharide synthesis enzyme CAP5F
4	3vhr-A	3.3	3.7	Capsular polysaccharide synthesis enzyme CAP5F
5	4xvn-A	2.8	1.9	Small terminase
6	4fcy-B	2.8	2.3	Transposase
7	2fu4-A	2.5	3.7	Ferric uptake regulation protein
8	4xvn-D	2.5	2.1	Small terminase
9	4fcy-A	2.5	2.3	Transposase
10	2m45-A	2.5	3.3	Minichromosome maintenance protein MCM
11	2w57-A	2.3	3.8	Ferric uptake regulation Protein
12	3ehe-A	2.3	3.5	UDP-glucose 4-epimerase
13	3c46-A	2.3	4.3	Virion RNA polymerase
14	2y9z-A	2.2	4.1	Imitation switch protein 1
15	1pdn-C	2.2	1.9	DNA-paired domain complex
16	4iof-A	2.2	2.9	Insulin-degrading enzyme
17	3dpl-C	2.2	4.9	Cullin-5
18	4bkx-A	2.2	4.2	Metastasis-associated protein MTA1
19	3elk-A	2.2	2.9	Putative transcriptional regulator TA0346
20	4j2o-C	2.1	3.6	UDP-N-acetylglucosamine 4,6- dehydratase/5-epimerase
21	6pax-A	2.1	2.6	Homeobox protein PAX-6
22	3hm5-A	2.1	3.0	DNA methyltransferase 1-associated protein 1
23	1mwk-A	2.1	3.2	PARM
24	3c3w-A	2.1	3.5	Two component transcriptional regulatory protein
25	2hyt-A	2.1	3.0	TETR-family transcriptional regulator