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DJ-1

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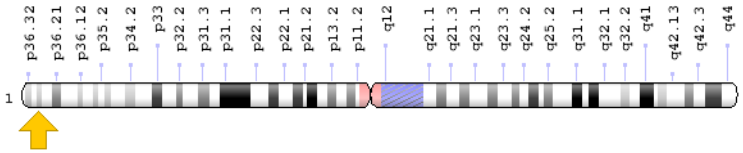
BIO 392 – Bioinformatics of Molecular Sequence Variations

HS 2019

DJ-1 in a nutshell…

- multifunctional homodimer, where each chain consists of 189 amino acids
- Mass: 19,891 Da (~ 20 kDa)
- Encoded by the PARK7 gene

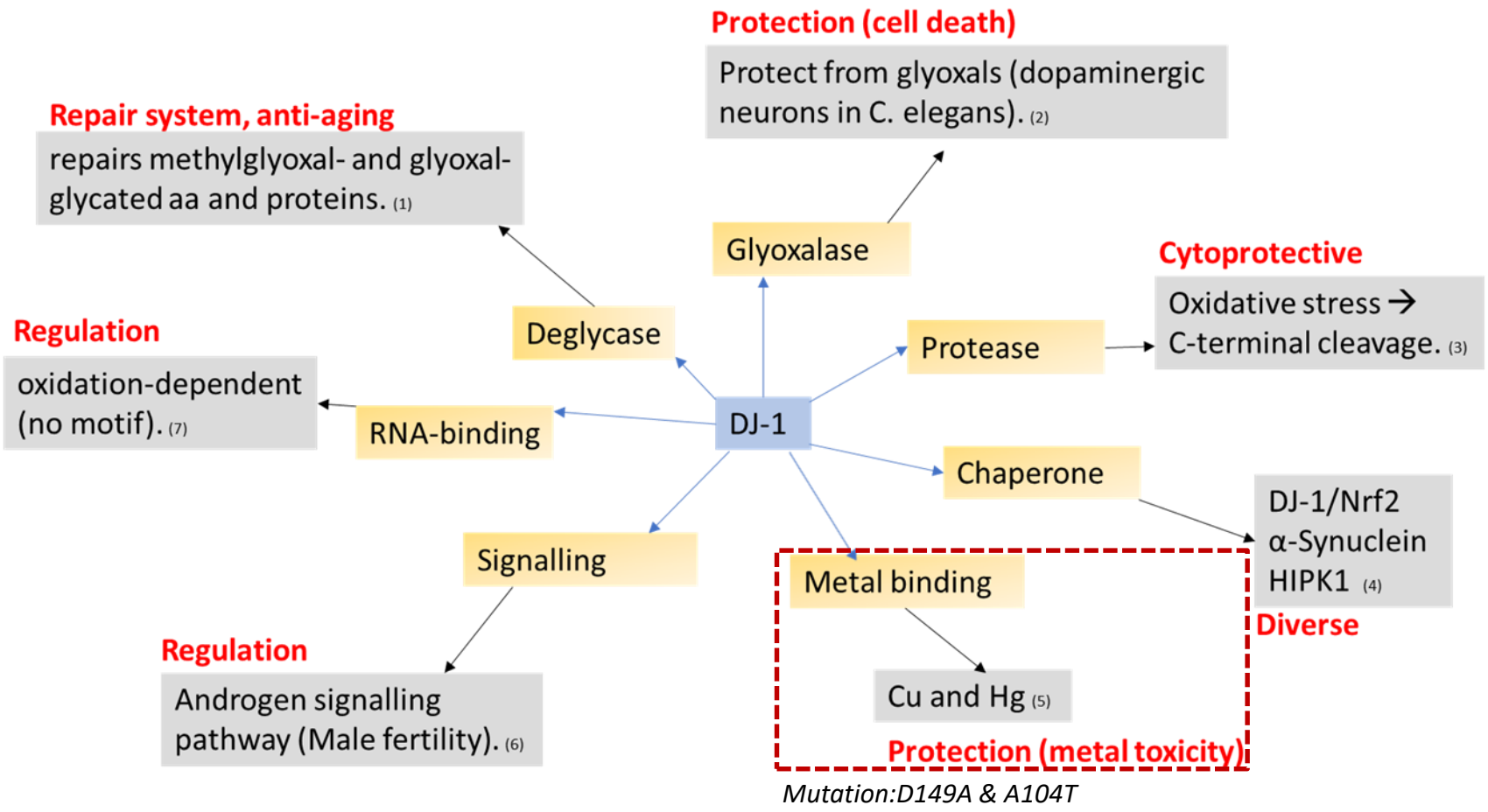


(ghr.nlm.nih.gov; reference genome: GRCh38.p13)

- predominately located in the cytoplasm
- several mutations of DJ-1 are highly associated with familial Parkinson Disease

(Unipot.org)

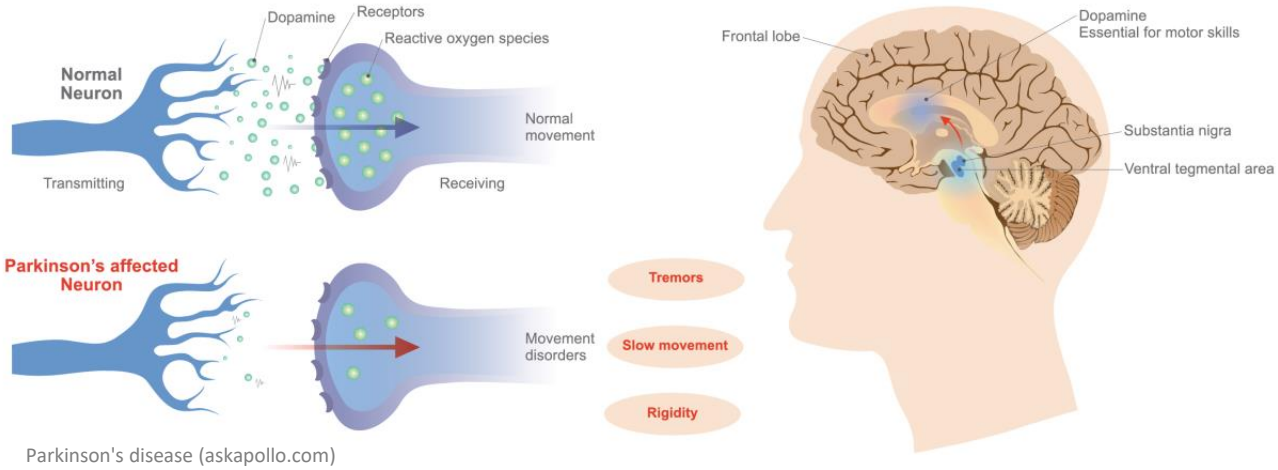
Functions:


Protection (cell death)
Protect from glyoxals (dopaminergic neurons in C. elegans). (2)
Repair system, anti-aging
repairs methylglyoxal- and glyoxal-glycated aa and proteins. (1)
Glyoxalase
Cytoprotective
Oxidative stress → C-terminal cleavage. (3)
Regulation
oxidation-dependent (no motif). (7)
Deglycase
Protease
RNA-binding
DJ-1
Chaperone
DJ-1/Nrf2
α-Synuclein
HIPK1 (4)
Diverse
Signalling
Metal binding
Regulation
Androgen signalling pathway (Male fertility). (6)
Cu and Hg (5)
Protection (metal toxicity)
Mutation:D149A & A104T

Disease involvement

- Side note: Cancer
  - Ras signalling / PTEN (Oncogene)
  - DJ-1/Nrf2 therapeutic target
  - Tumor biomarker

- Early-onset Parkinson disease



Parkinson's disease (askapollo.com)

  - Environmental factors
  - Oxidative stress
  - α-synuclein (Lewy bodies)

Structure of DJ-1

- Consist of two identical chains (homodimer)
  FASTA Format

- Secondary structure of our protein:

(Uniprot.org)

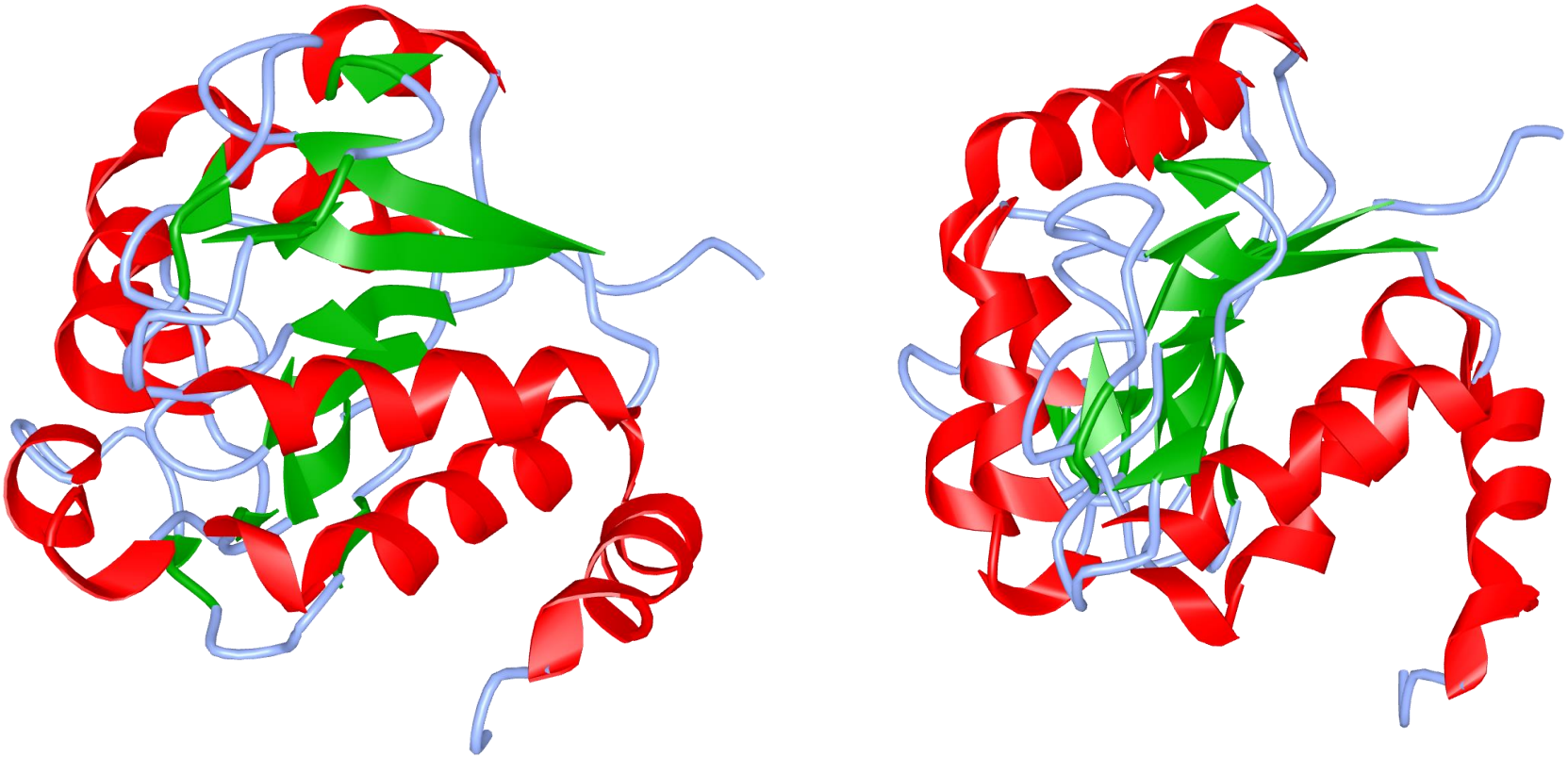
- Tertiary structure of DJ-1:

  → pictures were generated in iCn3D with the wild type structure of DJ-1

  (Huai Q. et al, 2003; PDB ID: 1Q2U)

- We found on NCBI different variants, which we marked in the protein structure
  variants

Tertiary structures

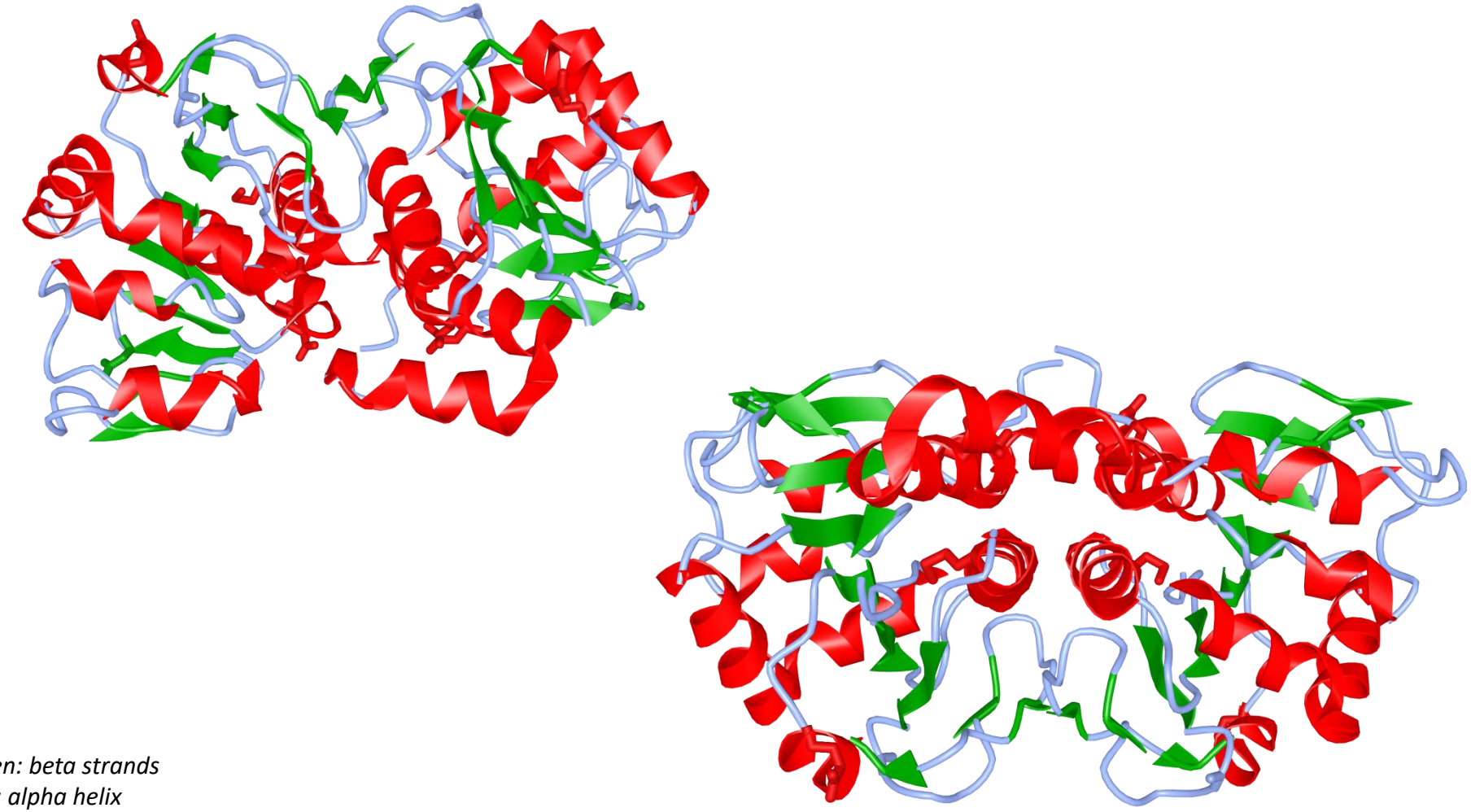


green: beta strands
Red: alpha helix
Blue: turns

Tertiary structures

green: beta strands
red: alpha helix
blue: turns

Quartiary structure of the homodimer



green: beta strands
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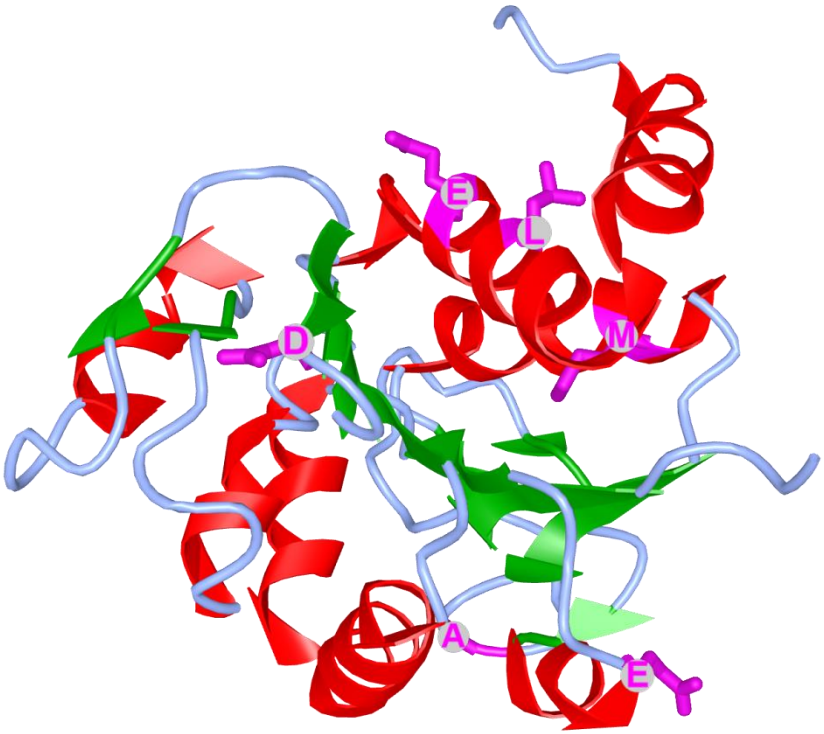
Blue: turns

Tertiary structure with the variants



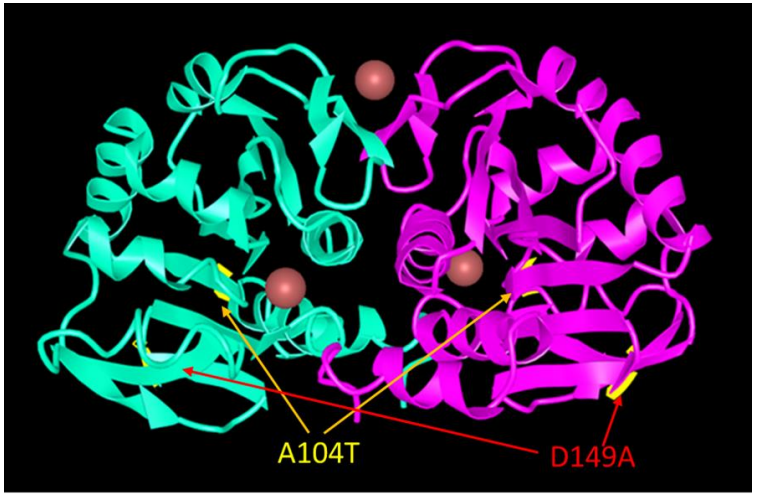
green: beta strands
Red: alpha helix
Blue: turns

Mutations

Variant ID	Mutation	Mutation type	PDB ID	Location in protein (active site 106 & 126)	Polyphen 2 score	Prediction about impact?
rs74315351	Met26Ile	Bothe are non-polar (hydrophobic) but Met has Sulfid (cant make bond)	2RK4	in alpha helix	0.007	BENIGN
rs137853051	Ala39Ser	Non-polar (hydrophobic) --> polar (hydrophilic)	x	in a turn	0.000	BENIGN
rs74315353	Glu64Asp	bothe (-) charge (acidic)	x	loop	0.000	BENIGN
rs74315352	Asp149Ala	(-) charged (acidic) --> nonpolar (hydrophobic)	x	in a beta strand	0.992	Probably Damaging
rs74315354	Glu163Lys	(-) charged (acidic) --> (+) charged (basic)	2RK6 and(3B3A +other mut	in alpha helix	0.389	Probably Damaging
rs28938172	Leu166Pro	Non-polar (hydrophobic) but Proline aromatic	x	in alpha helix	1.000	Probably Damaging

Adapted from ncbi.nlm.nih.gov/variation/view/

D149A & A104T lost metal cytotoxicity protection



4MNT DJ-1 with Cu ligand. (ncbi.nlm.nih.gov)

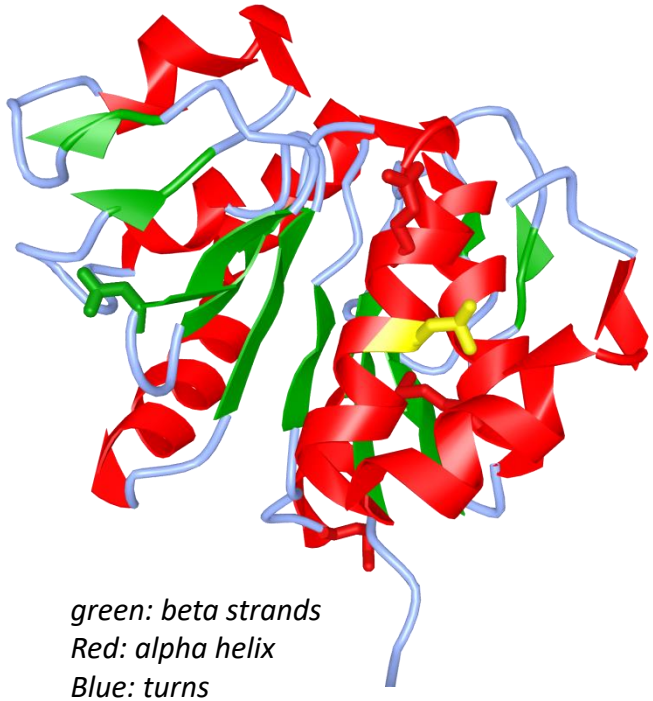
- Both:
  - Missense
  - On beta strand
  - Thermostability → influence on Secondary structure (Björkblom et al., 2013)

- **Asp149Ala**:
  Acidic →Hydrophobic
  - dbSNP:rs74315352
  - Polyphen 2 score: 0.992
  - 750 white, 160 Ashkenazi
    40 Afro-Caribbean
  - exon 7 (Abou et al.,2003)

- **Ala104Thr**:
  hydrophobic →Hydrophilic (polar uncharged)
  - dbSNP:rs774005786
  - Polyphen 2 score: 1
  - Near active site 106Cys
  - Found in 2 patients
  - exon–intron junction (exon 5) (Clark et al., 2004)

Variation L166P (dbSNP:rs28938172)

- Missense mutation where Lysine 166 is replaced by a Proline.
- Lower steady-state level of DJ-1
  - Reduced protein stability by enhancing the proteasomal degradation by 20S/26S proteasome
  - Reduced stability due to miss folding of the protein
- only appears in monomeric form
  - L166P impairs the ability to oligomerize which leads to loss of normal functions
- The loss of function due to L166P may underlies the progress of early-onset Parkinson disease.



green: beta strands
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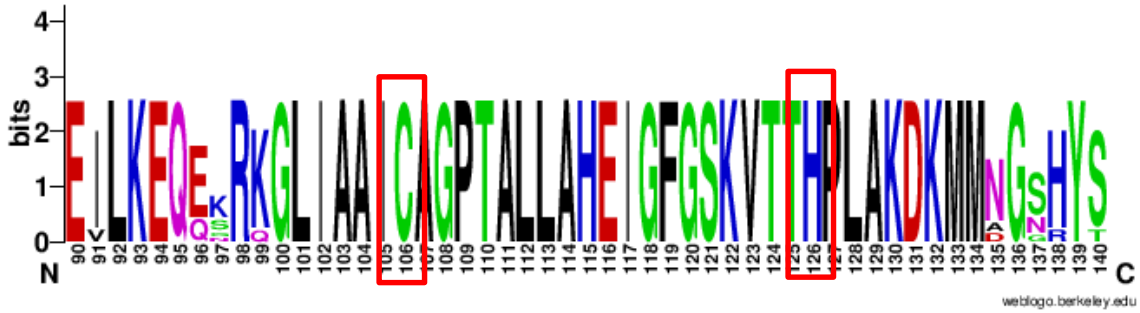
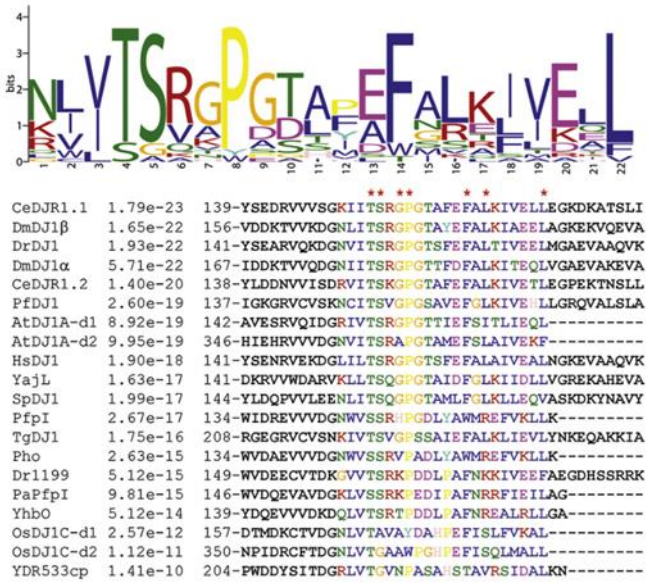
(Daren J. Moore et al, 2003
Miller D. W et al, 2003)

DJ-1 is conserved across species



Logo plot for 8 different species, witch active site in red (weblogo.berkeley.edu)



sequences corresponding to the motif DJSM (Nair et al., 2018)

- Conservation might indicates importance
- DJ-1/ThiJ/PfpI superfamily
  - DJSM (TSXGPX5FXLX5L) motif
  - Anti-oxidative activity
  - Critical for deglycase activity

Questions?

References

- https://www.uniprot.org/uniprot/Q99497#structure
- https://ghr.nlm.nih.gov/gene/PARK7#location
- https://www.ncbi.nlm.nih.gov/protein/BAB71782.1?report=fasta
- https://www.uniprot.org/uniprot/Q99497/protvista
- https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1471-4159.2003.02265.x
- https://www.ncbi.nlm.nih.gov/pubmed/12851414
- https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html?&mmdbid=118034&bu=1&showanno=1
- https://www.ncbi.nlm.nih.gov/variation/view/ dbSNP, pathogenic, missense)
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FASTA format:

>sp|Q99497|PARK7_HUMAN Protein/nucleic acid deglycase DJ-1 OS=Homo sapiens OX=9606 GN=PARK7 PE=1 SV=2

MASKRALVILAKGAEEMETVIPVDVMRRAGIKVTVAGLAGKDPVQCSRDVVICPDASLED

AKKEGPYDVVVLPGGNLGAQNLSESAAVKEILKEQENRKGLIAAI**C**AGPTALLAHEIGFG

SKVTT**H**PLAKDKMMNGGHYTYSENRVEKDGLILTSRGPGTSFEFALAIVEALNGKEVAAQ

VKAPLVLKD

(Uniprot.org)

- Active sites in red
- at position 106 and 126
- Active site 106 is on a turn; 126 is on a loop

back