

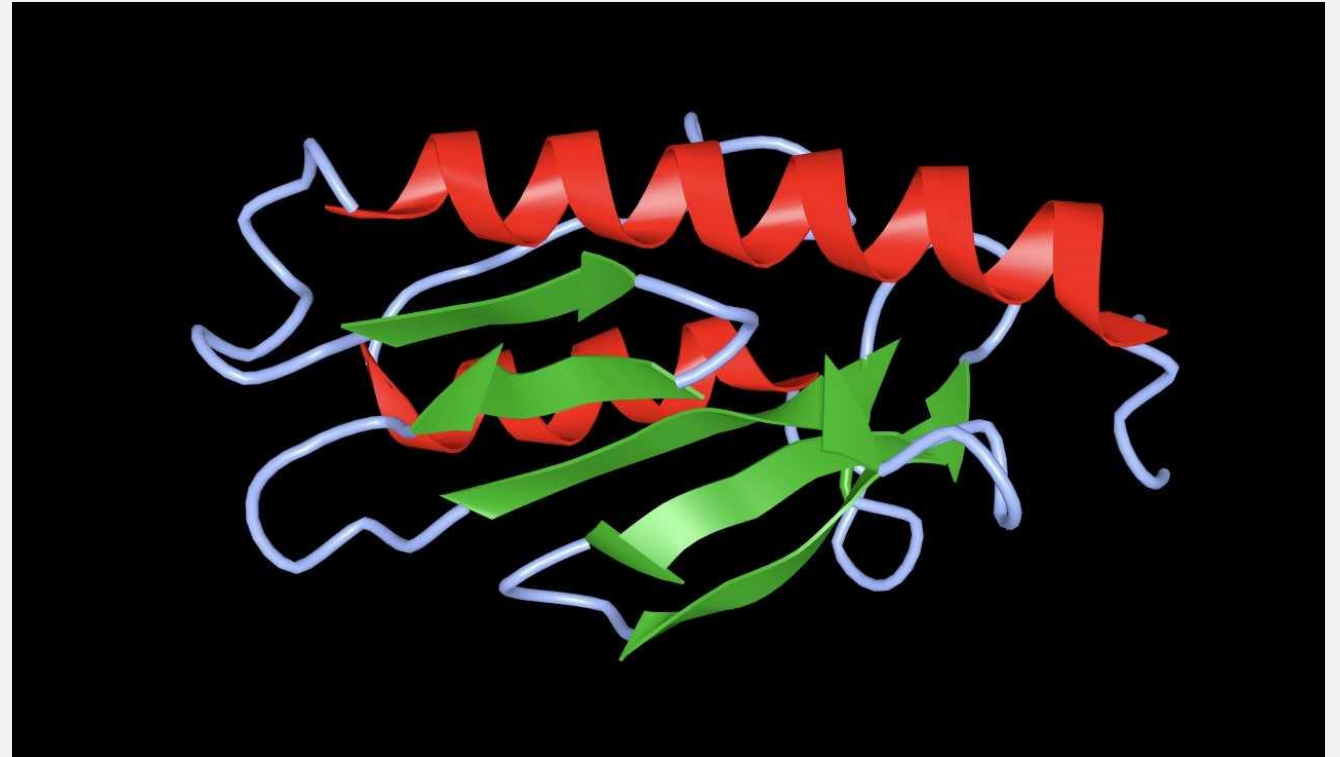
FRATAXIN

Composition of data from PDB, Uniprot, clinVar, PolyPhen etc.

by Catrina Friedrich & Sebastian Leimbacher

OVERVIEW

- Monomer
- 2 helices
- 5 beta sheets
- Sequence length: 129 aa
- Ligand interaction: Iron
- 3 isoforms



Frataxin (PDB ID: 3S4M, created with iCn3D)

Q16595	FRDA_HUMAN	1	MWTLGRRAVAGLLASPSPAQAQTLTRVPRPAELAPLCGRRGLRTDIDATCTPRRASSNQR	60
Q16595-2	FRDA_HUMAN	1	MWTLGRRAVAGLLASPSPAQAQTLTRVPRPAELAPLCGRRGLRTDIDATCTPRRASSNQR	60
Q16595-3	FRDA_HUMAN	1	MWTLGRRAVAGLLASPSPAQAQTLTRVPRPAELAPLCGRRGLRTDIDATCTPRRASSNQR	60

Q16595	FRDA_HUMAN	61	GLNQIWNVKKQSVYLMNLRKSGTLGHPGSLDETTYERLAEETLDSLAEFFEDLADKPYTF	120
Q16595-2	FRDA_HUMAN	61	GLNQIWNVKKQSVYLMNLRKSGTLGHPGSLDETTYERLAEETLDSLAEFFEDLADKPYTF	120
Q16595-3	FRDA_HUMAN	61	GLNQIWNVKKQSVYLMNLRKSGTLGHPGSLDETTYERLAEETLDSLAEFFEDLADKPYTF	120

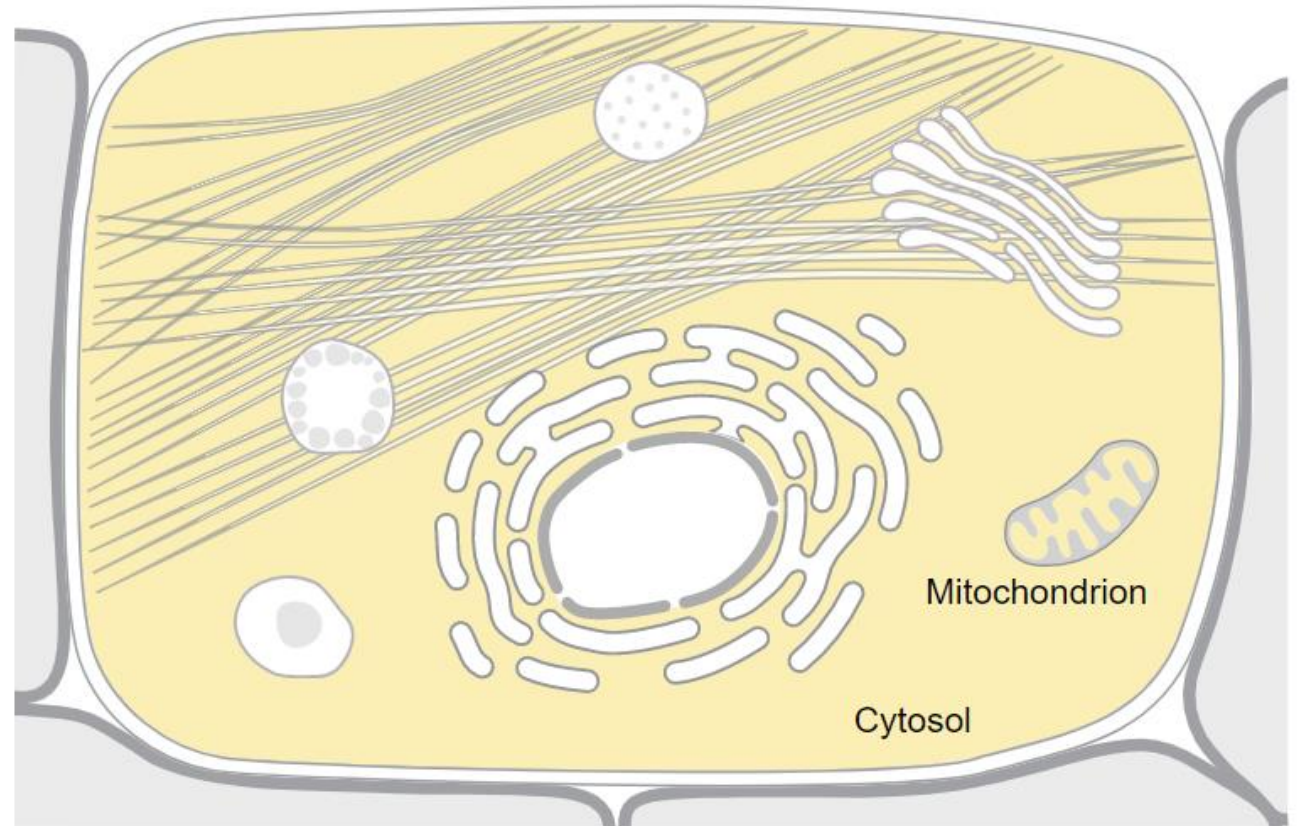
Q16595	FRDA_HUMAN	121	EDYDVSFGSGVLTIVKLGGDLGTIVINKQTPNKQIWLSSPSSGPKRYDWTGKNWVYSHDGV	180
Q16595-2	FRDA_HUMAN	121	EDYDVSFGSGVLTIVKLGGDLGTIVINKQTPNKQIWLSSPSR----LTWL--LWLFHP---	171
Q16595-3	FRDA_HUMAN	121	EDYDVSFGSGVLTIVKLGGDLGTIVINKQTPNKQIWLSSPSR----YVVD--LSVMTGLGK	174

Q16595	FRDA_HUMAN	181	SLHELLAAELTKALKTKLDDLSSLAYSGKDA	210
Q16595-2	FRDA_HUMAN	172	-----	171
Q16595-3	FRDA_HUMAN	175	TGCTPTTACPSMSC---WPQSSLKP-----	196



Entry	Entry name	Protein names	Organism	Gene name
Q16595	FRDA_HUMAN	Frataxin, mitochondrial	Homo sapiens (Human)	FXN FRDA, X25
Q16595-2	FRDA_HUMAN	Isoform 2 of Frataxin, mitochondria...	Homo sapiens (Human)	FXN FRDA, X25
Q16595-3	FRDA_HUMAN	Isoform 3 of Frataxin, mitochondria...	Homo sapiens (Human)	FXN FRDA, X25

Algment of isoforms of Frataxin (Aligned with Unirpot Align tool)

LOCATION

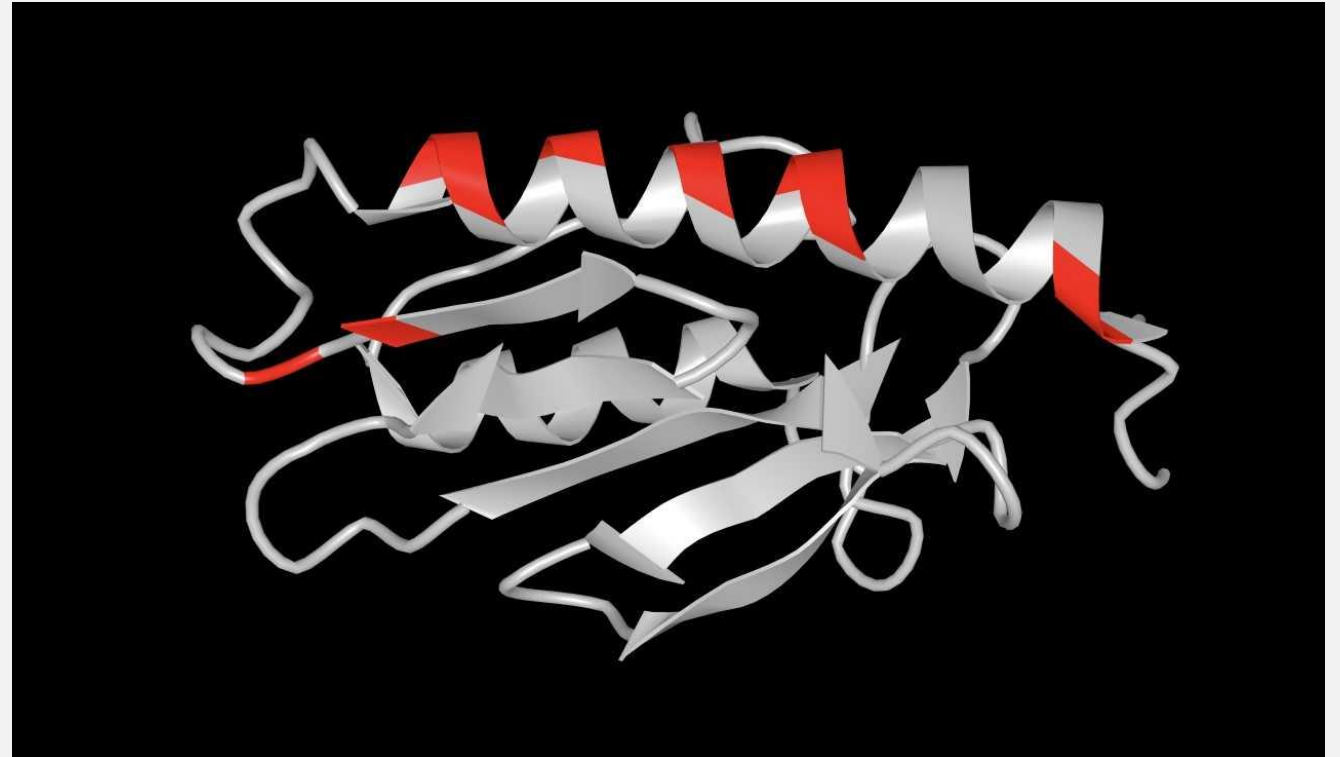


Graphics by Christian Stolte & Seán O'Donoghue; Source: [COMPARTMENTS](#)

 Manual annotation  Automatic computational assertion

KNOWN FUNCTIONS

- *Primarily in mitochondrion*
- *Ferroxidase activity:*
$$4 \text{Fe}^{2+} + 4 \text{H}^{+} + \text{O}_2 = 4 \text{Fe}^{3+} + 2 \text{H}_2\text{O}$$
- *Biosynthesis of heme proteins*
- *Assembly/repair iron-sulfur clusters*



Putative iron binding site (created with iCn3D)

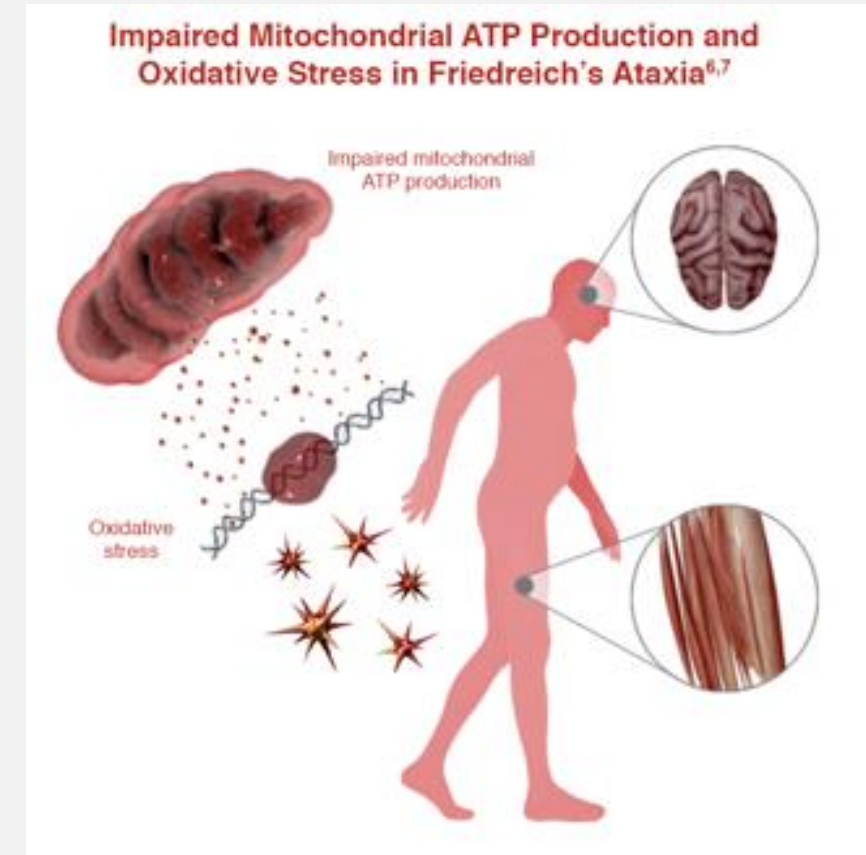
- **Report the GO terms for your protein**

- ferrous iron binding (4) + -
- mitochondrial matrix (4) + -
- protein binding (4) + -
- ferric iron binding (3) + -
- 2 iron, 2 sulfur cluster binding (2) + -
- cellular iron ion homeostasis (2) + -
- ferroxidase activity (2) + -
- iron chaperone activity (2) + -
- iron incorporation into metallo-sulfur cluster (2) + -
- mitochondrion (2) + -
- positive regulation of lyase activity (2) + -
- L-cysteine desulfurase complex (1) + -
- adult walking behavior (1) + -
- aerobic respiration (1) + -
- cellular response to hydrogen peroxide (1) + -
- cytosol (1) + -
- embryo development ending in birth or egg hatching (1) + -

- heme biosynthetic process (1) + -
- ion transport (1) + -
- iron-sulfur cluster assembly (1) + -
- mitochondrion organization (1) + -
- negative regulation of apoptotic process (1) + -
- negative regulation of multicellular organism growth (1) + -
- negative regulation of organ growth (1) + -
- negative regulation of release of cytochrome c from mitochondria (1) + -
- oxidative phosphorylation (1) + -
- positive regulation of aconitate hydratase activity (1) + -
- positive regulation of catalytic activity (1) + -
- positive regulation of cell growth (1) + -
- positive regulation of cell population proliferation (1) + -
- positive regulation of succinate dehydrogenase activity (1) + -
- proprioception (1) + -
- protein autoproccessing (1) + -
- regulation of ferrochelatase activity (1) + -
- response to iron ion (1) + -
- small molecule metabolic process

FRIEDREICH'S ATAXIA

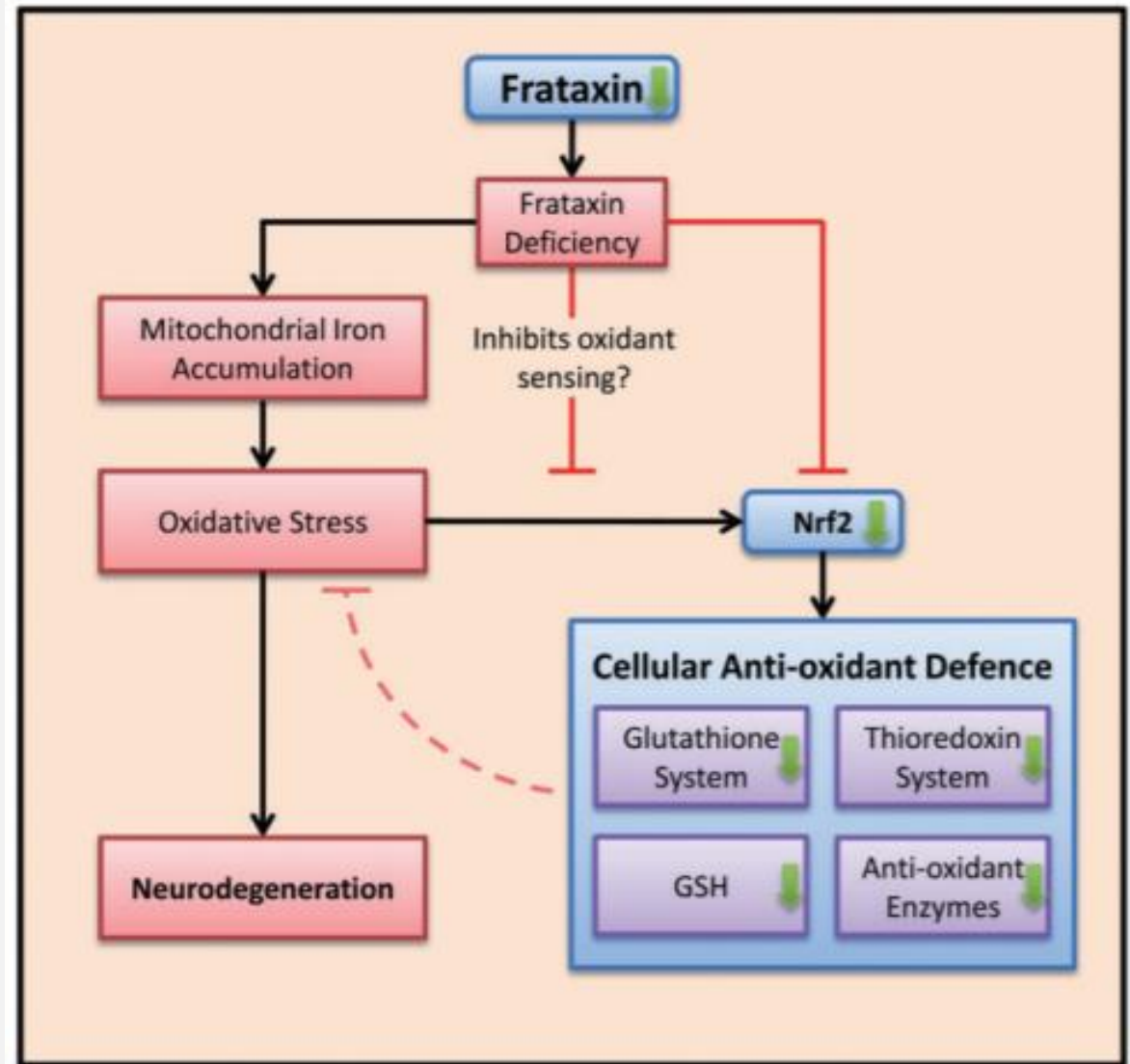
- Autosomal recessive
- Progressive (neuro-)degenerative
- Impaired balance & mobility
- Cardiomyopathy
- Speech impairment
- Scoliosis
- 1 in 50'000 individuals of European ancestry



Source: Reatapharma.com

FRATAXIN & FRIEDREICH'S ATAXIA

- Frataxin deficient cells
- Iron accumulation in mitochondria
- Increased oxidative stress
- Inhibition of antioxidant defences
- Impaired mitochondrial ATP production

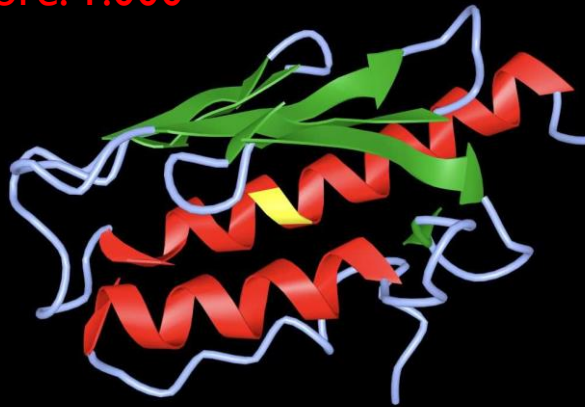


Scheme of frataxin's effect (source: Fixing frataxin: 'ironing out' the metabolic defect in Friedreich's ataxia)



Putative iron binding site (red)

Score: 1.000



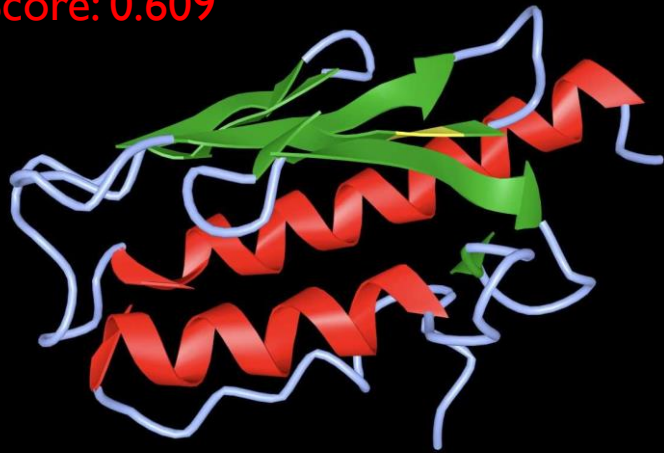
Leu > Ser or Termination (yellow)

Score: 0.997



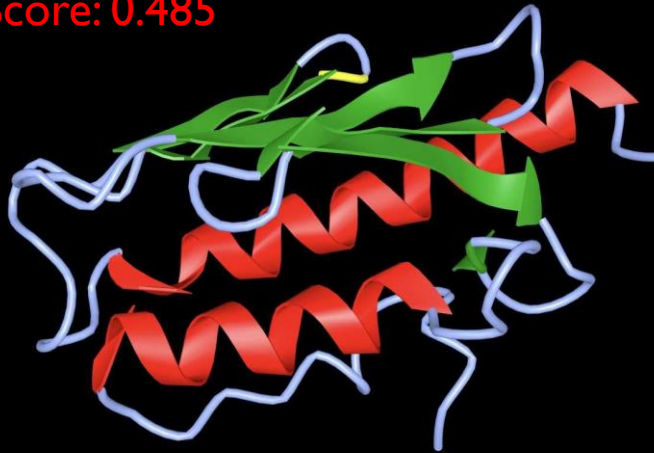
Asn > Lys (yellow)

Score: 0.609



Ile > Val or Phe (yellow)

Score: 0.485

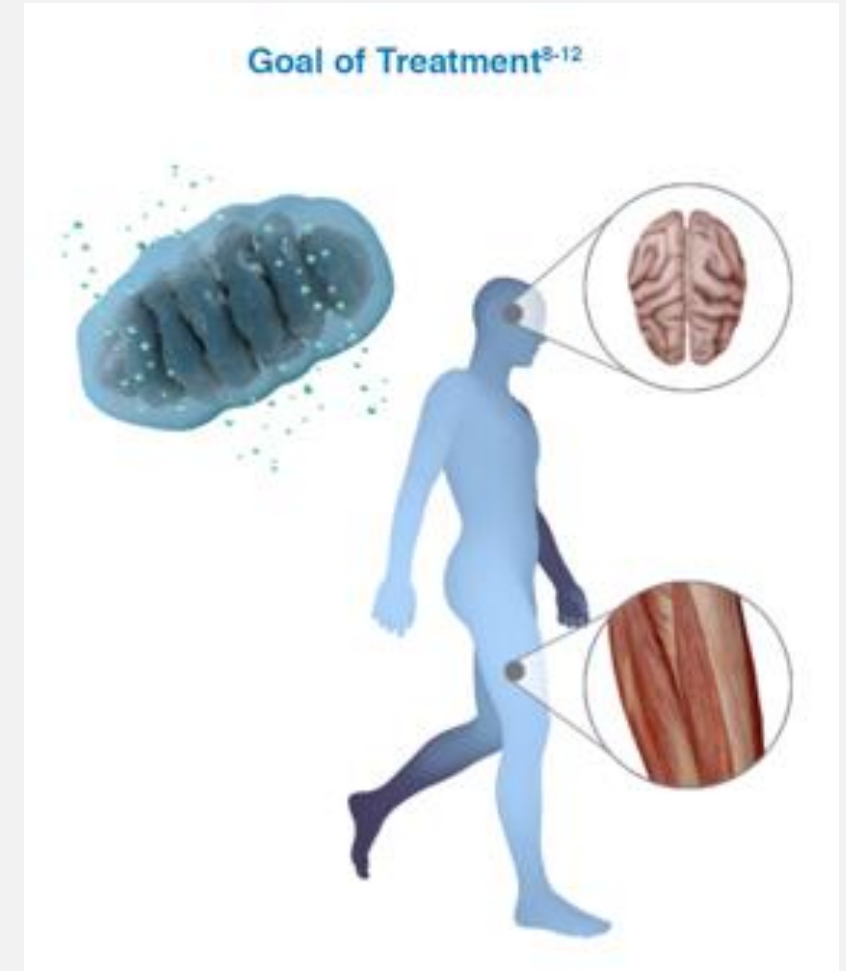


Gly > Ala or Val (yellow)

Met > Ile

TREATMENT

- Conventional cardiac treatments
- Surgery
- Clinical development: Omaveloxolone (activation of NRF2)



Source: Reatapharma.com

REFERENCES

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- NCBI Variation Viewer, <https://www.ncbi.nlm.nih.gov/variation/view/?q=BRCA1>, 04.10.2019

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- Structure-function analysis of Friedreich's ataxia mutants reveals determinants of frataxin binding and activation of the Fe-S assembly complex, 2011, Department of Chemistry, Texas A&M University, College Station, Texas 77842, USA.
- Fixing frataxin: 'ironing out' the metabolic defect in Friedreich's ataxia, 2014, A Anzovino et al.