Human Glycine-tRNA Ligase

Hangjia & Mariella

2019.10.08

Human Glycine--tRNA ligase

Function: ATP + glycine + $tRNA^{Gly}$ = AMP + diphosphate + glycyl-$tRNA^{Gly}$

- Catalyzes ATP-dependent ligation of glycine to the 3'-end of tRNA, via formation of intermediate (Gly-AMP)

Encoding gene: GARS located at 7p14.3

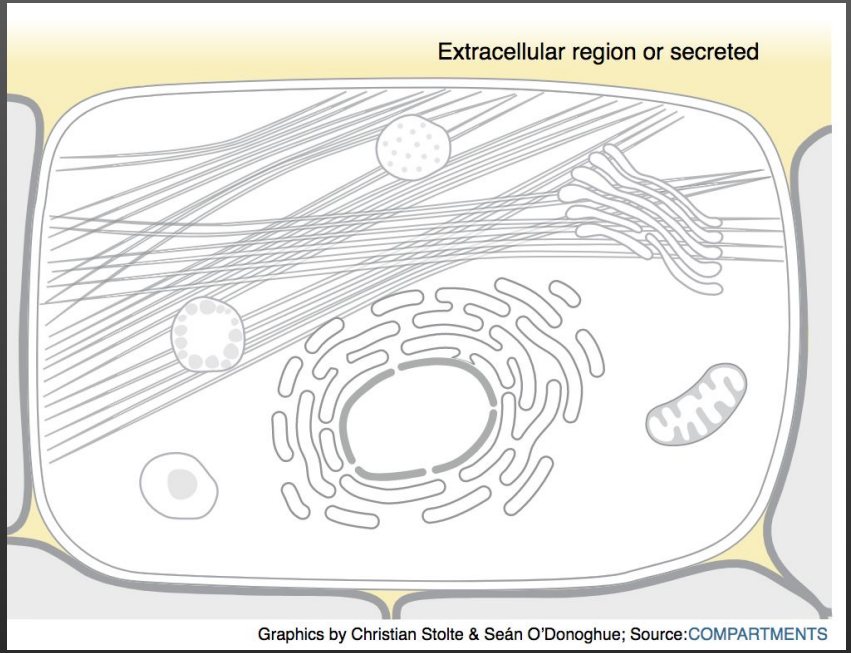
Size: 685AA, 1 polypeptide chain

https://www.ncbi.nlm.nih.gov/protein/NP_001303701.1 https://www.uniprot.org/uniprot/P41250

Cellular location

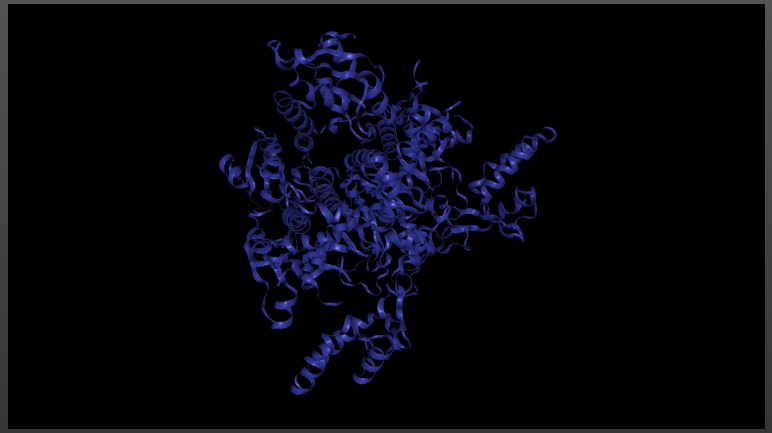
- Secreted to extracellular region
- Other locations:

  cytoplasm, mitochondria

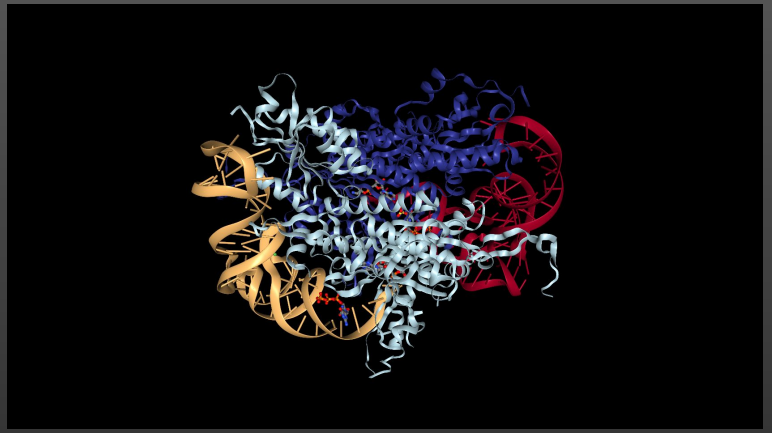


https://www.uniprot.org/uniprot/P41250#function

Structure



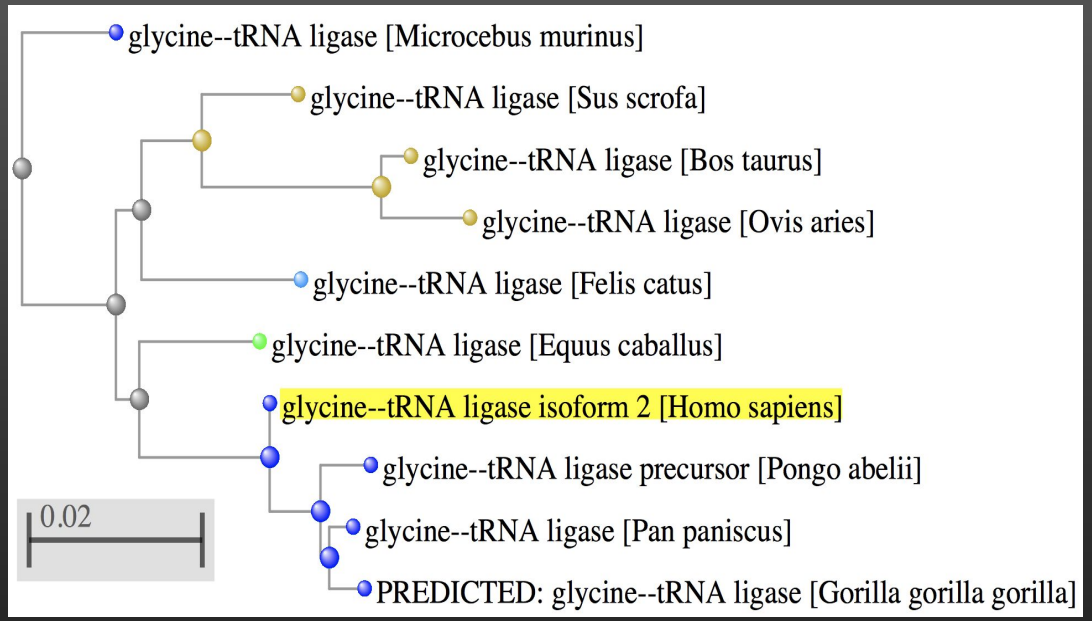
Individual glycyl-tRNA ligase



Homodimers bound with tRNAGly

https://www.rcsb.org

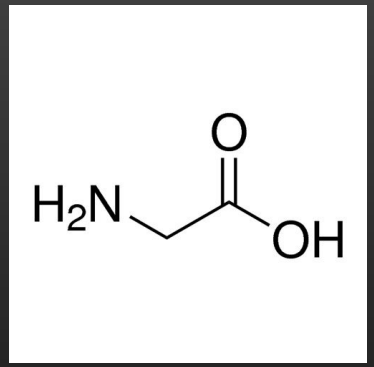
Across species → Conserved!



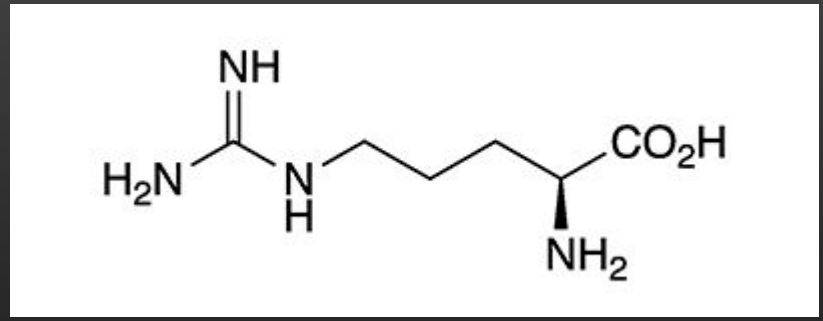
https://blast.ncbi.nlm.nih.gov/Blast.cgi

Variant of human glycine-tRNA Ligase (PDB: 2PMF)

- **DNA Level:** GARS1 Gene: chr7:30628598 (GRCh38.p12)
  ➔ G > C (dbSNP: rs137852646)
  leading to missense mutation on ....
  ... Protein Level
- Missense Variation (G526R) at position 526: Glycine to Arginine

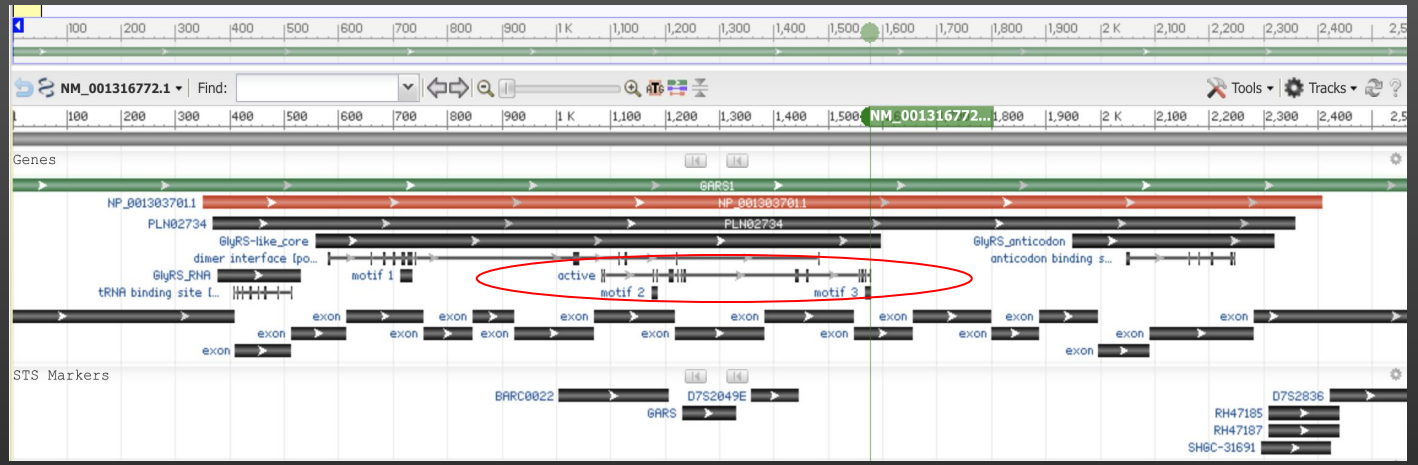


Glycine, G



Arginine, R

Location of the mutation G526R

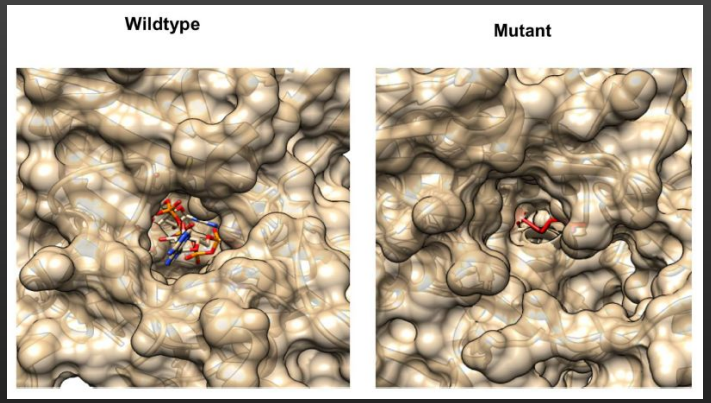


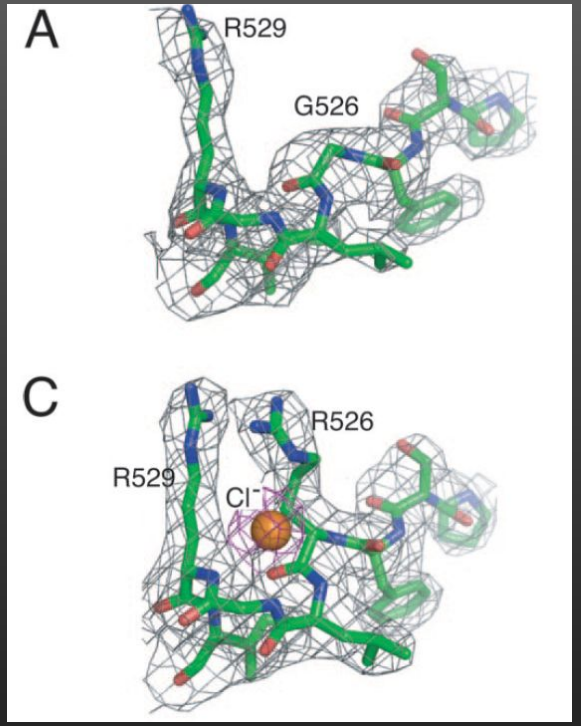
Effects of G526R mutation on Structure

- Mutant Protein almost identical to Wildtype

➜ What happens to structure?

  - AMP binding site (Pos. 583) not directly affected
  - But (bulky Arginine) sidechain of mutated residue blocks access to it





Wildtype

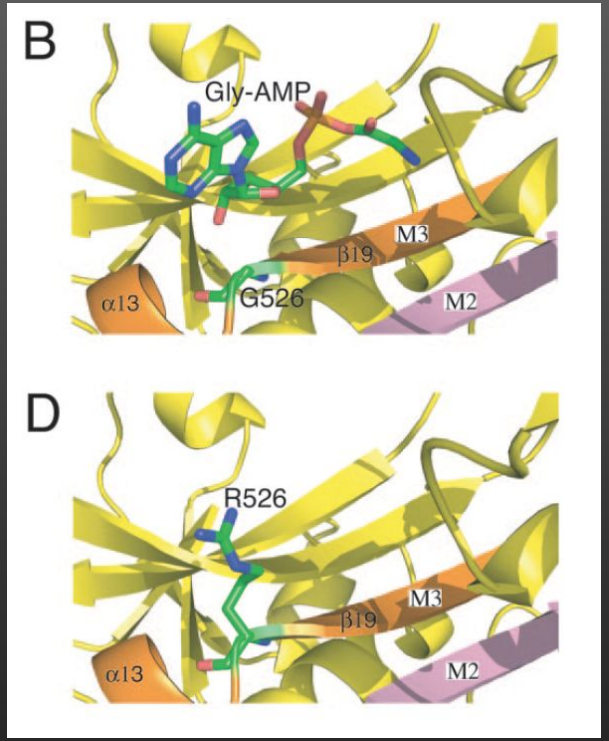
Mutant

Source: https://doi.org/10.1371/journal.pone.0171355.g004

Effects of G526R mutation on Function

- Blockage of AMP binding site leads to complete loss of enzymatic **activity**
- Mechanism?
  - Gly-AMP intermediate cannot be formed

➜ No ligation of glycine to tRNA



Wildtype

Mutant

www.pnas.orgcgidoi10.1073pnas.0703908104

Association with disease

1) Charcot-Marie-Tooth disease (CMT2D)

- One of most common heritable disorders of peripheral nervous system
- Inheritance: Autosomal, dominant
- Axonal degeneration, normal or slightly reduced nerve conduction, progressive distal muscle weakness and atrophy

https://doi.org/10.1016/S1474-4422(09)70110-3

Common disease - however….

- Exact mechanism how loss of enzymatic activity of glycine-tRNA Ligase is linked to Charcot-Marie-Tooth disorder still not known
- Suggestion: tRNA Ligase connection with the nervous system through pathways beyond aminoacylation

Reference

Xie W, Nangle LA, Zhang W, Schimmel P, Yang XL. Long-range structural effects of a Charcot-Marie-Tooth disease-causing mutation in human glycyl-tRNA synthetase. Proc Natl Acad Sci U S A. 2007;104(24):9976–9981. doi:10.1073/pnas.0703908104

Bhattacharya R, Rose PW, Burley SK, Prlić A. Impact of genetic variation on three dimensional structure and function of proteins. PLoS One. 2017;12(3):e0171355. Published 2017 Mar 15. doi:10.1371/journal.pone.0171355