

Human Glycine-tRNA Ligase

Hangjia & Mariella

2019.10.09

Human Glycine--tRNA ligase

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

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

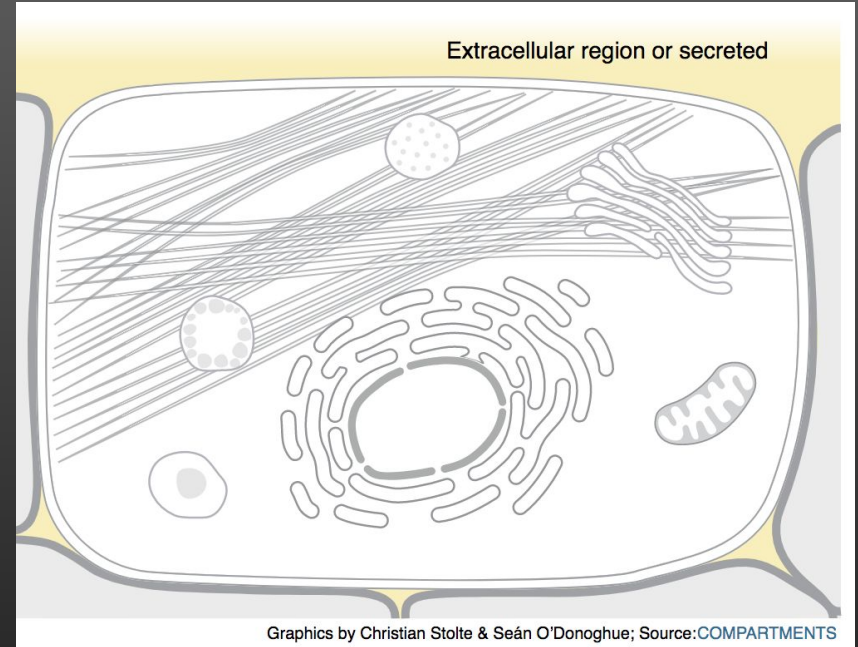
Encoding gene: GARS located at 7p14.3

Size: 685AA, 1 polypeptide chain

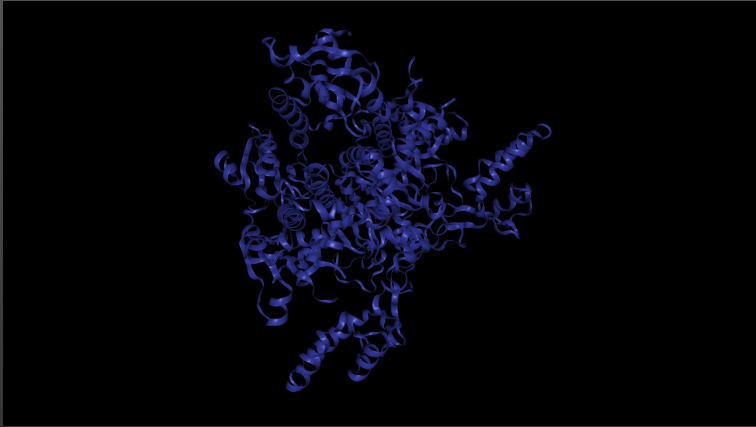


Cellular location

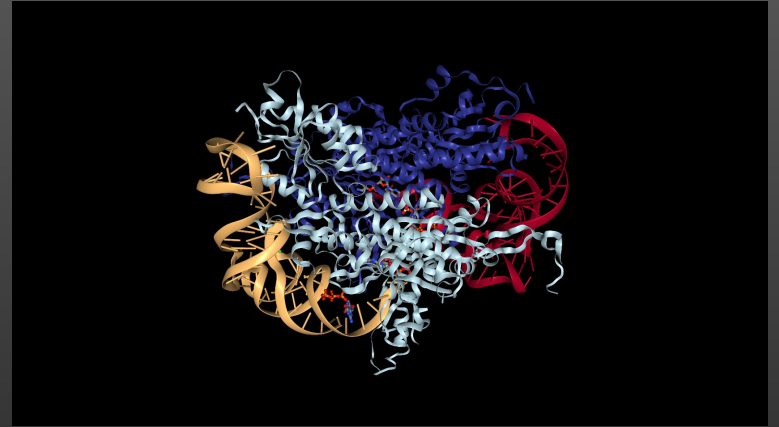
- Secreted to extracellular region
- Other locations:
cytoplasm, mitochondria



Structure

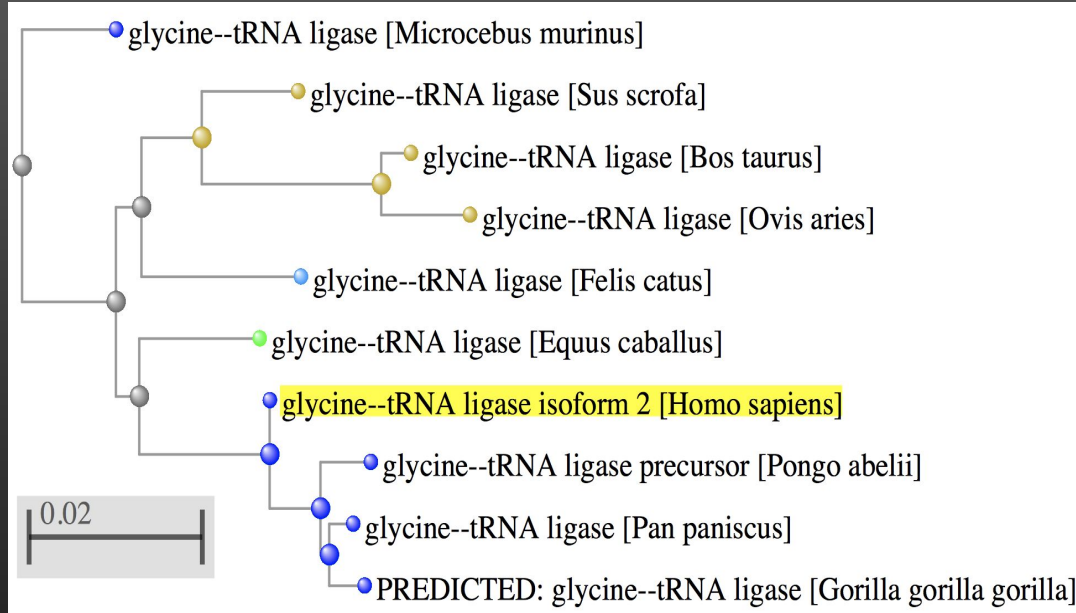


Individual glycyl-tRNA ligase

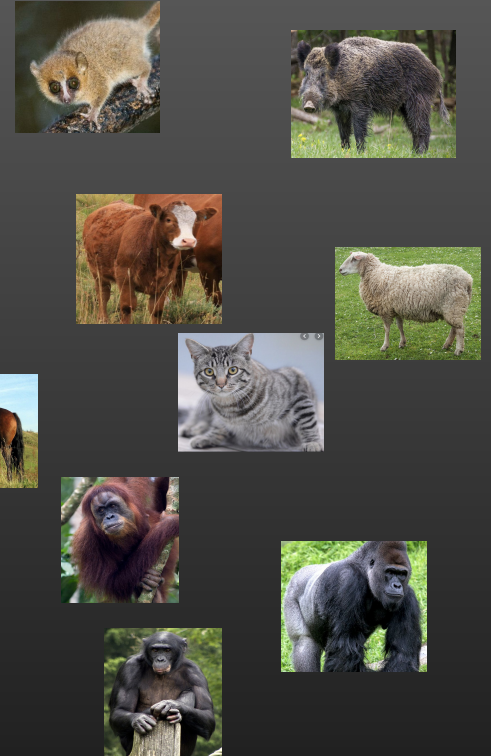


Homodimers bound with tRNA^{Gly}

Across species → Conserved!



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



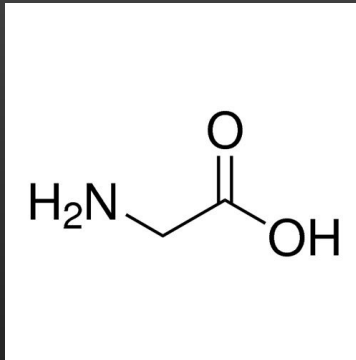
Variant of human glycine-tRNA Ligase (PDB: 2PMF)

- **DNA Level:** GARS1 Gene: chr7:30628598 (GRCh38.p12)
→ G > C (dbSNP: rs137852646)

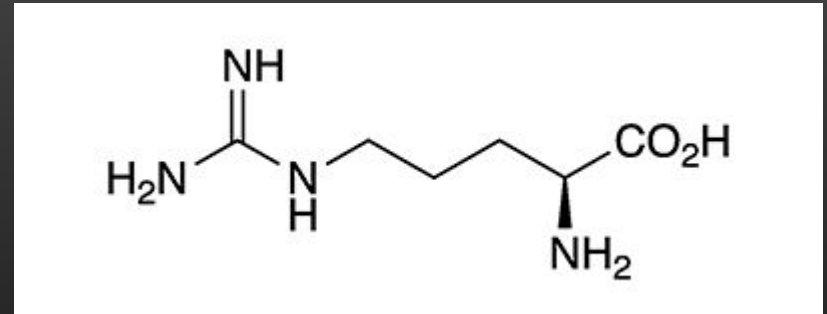
leading to missense mutation on

... **Protein Level**

- Missense Variation (G526R) at position 526: Glycine to Arginine



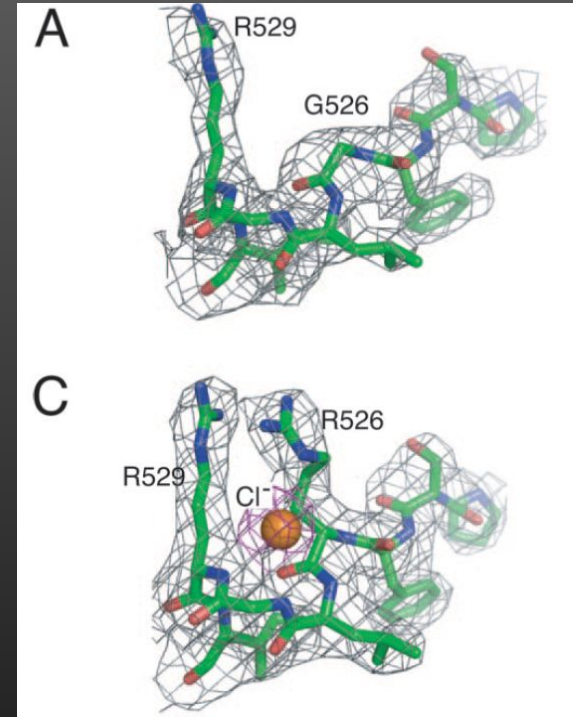
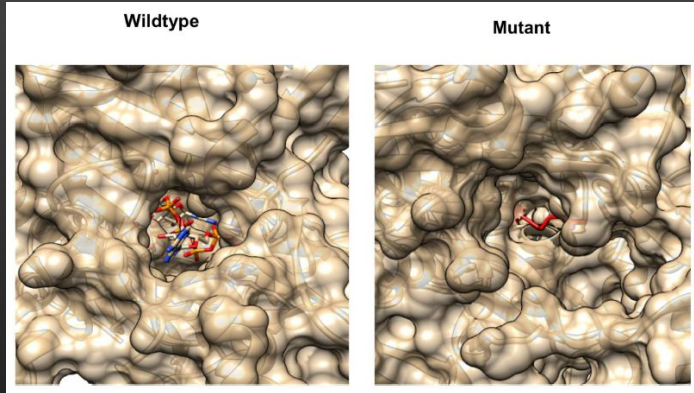
Glycine, G



Arginine, R

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



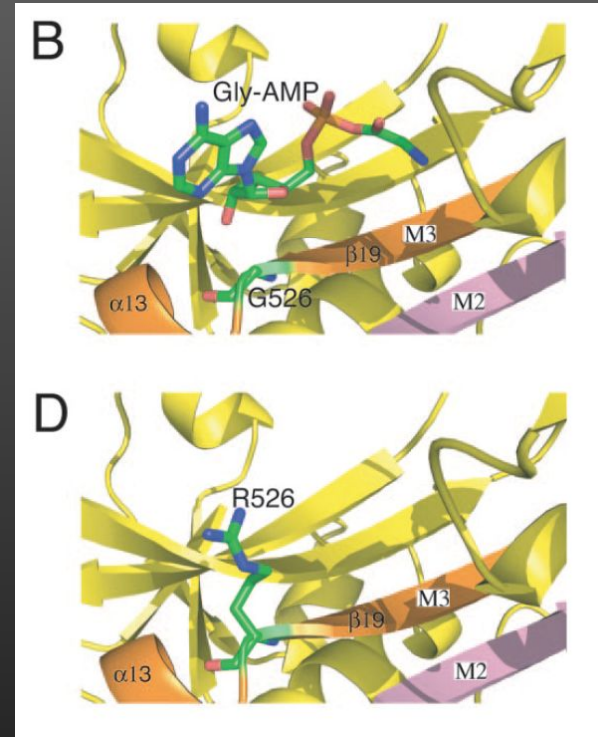
Wildtype

Mutant

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

Association with disease

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



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