

Human Glycine-tRNA Ligase

Hangjia & Mariella

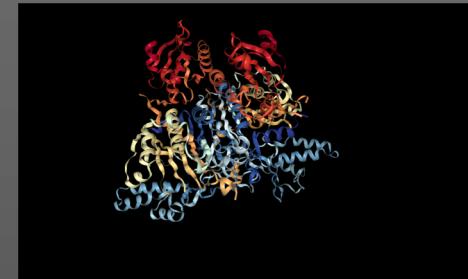
2019.10.08

Human Glycine--tRNA ligase

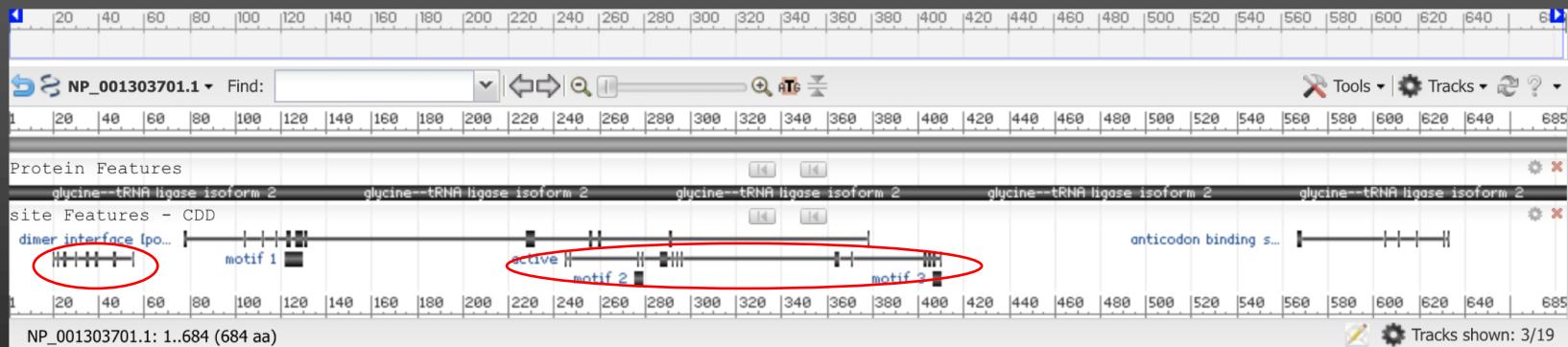
Function: ATP + glycine + tRNA^{Gly} = AMP + diphosphate + glycyl-tRNA^{Gly}

Encoding gene: GARS located in 7p14.3

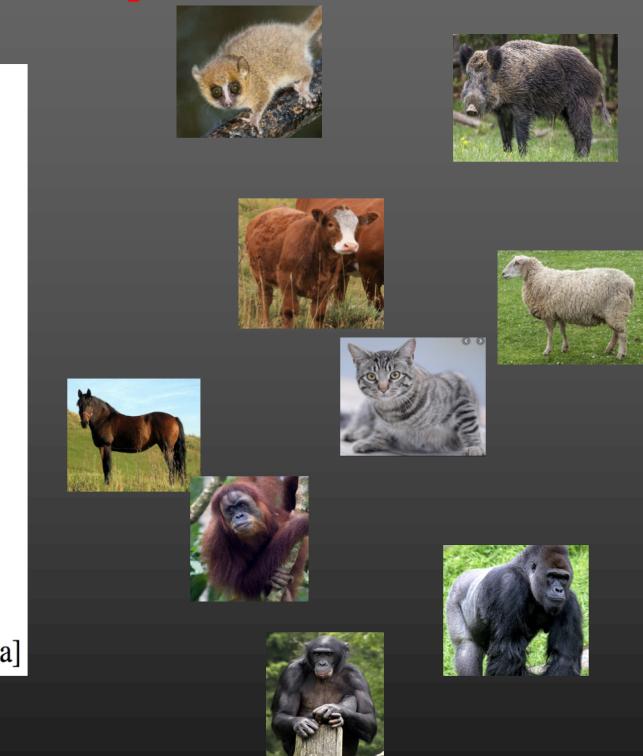
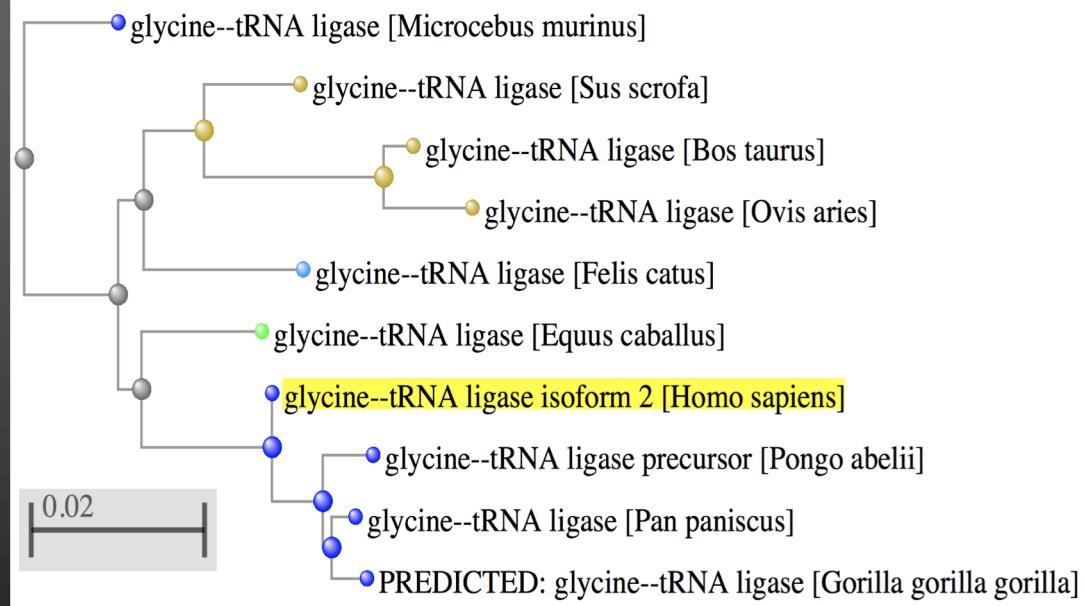
Size: 685AA, 1 polypeptide chain



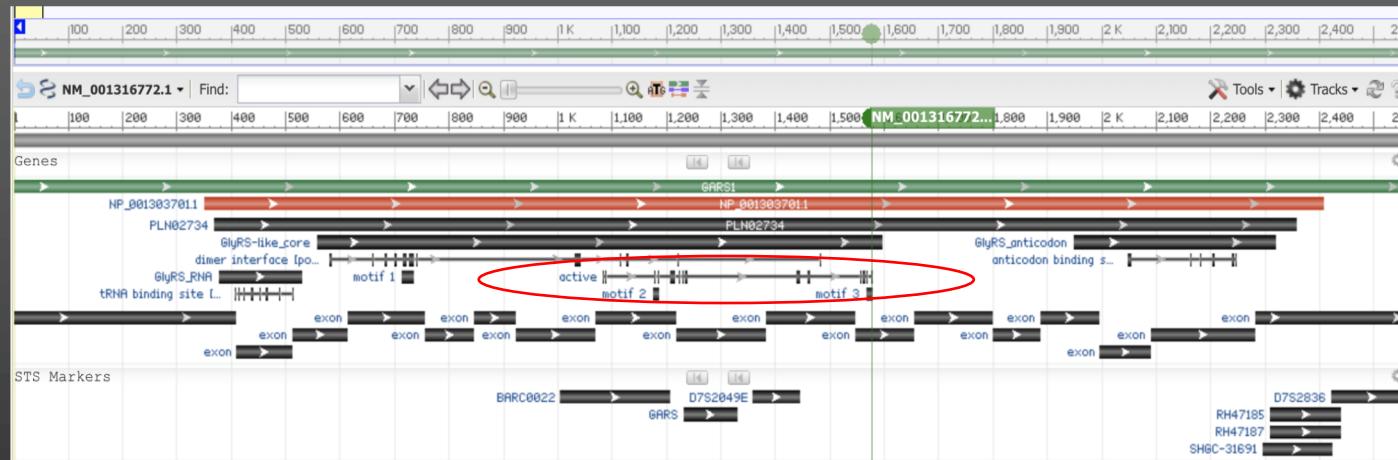
<https://www.rcsb.org/structure/2zome>



Across species

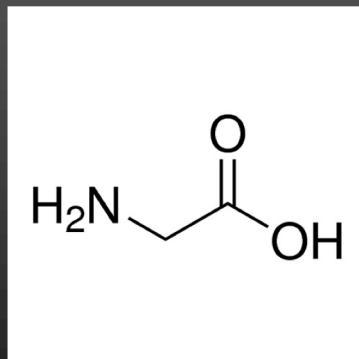


Location of the mutation G526R

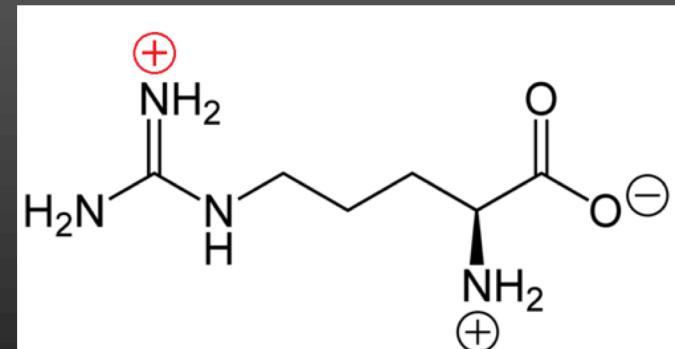
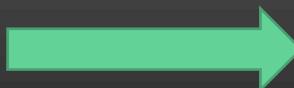


Variant of human glycine-tRNA Ligase (PDB: 2PMF)

- **DNA Level:** GARS1 Gene: chr7:30628598 (GRCh38.p12)
→ G > C (dbSNP: rs137852646) leading to missense mutation on
- ... **Protein Level (Mutant Protein PDB: 2PMF)**
- Missense Variation (G526R) at position 526: Glycine to Arginine



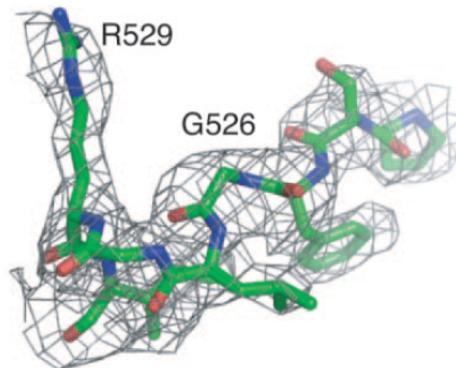
Glycine, G



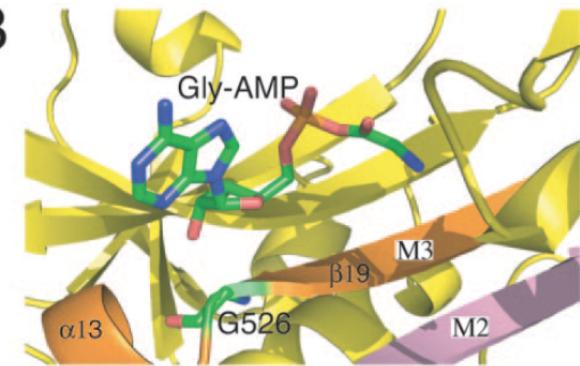
Arginine, R

Wildtype

A

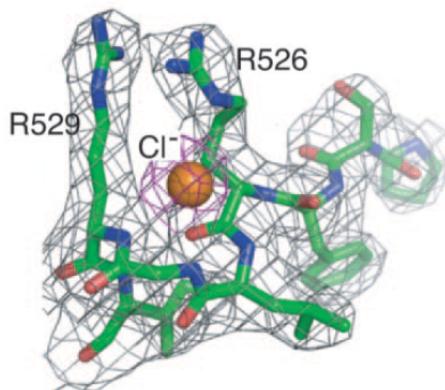


B

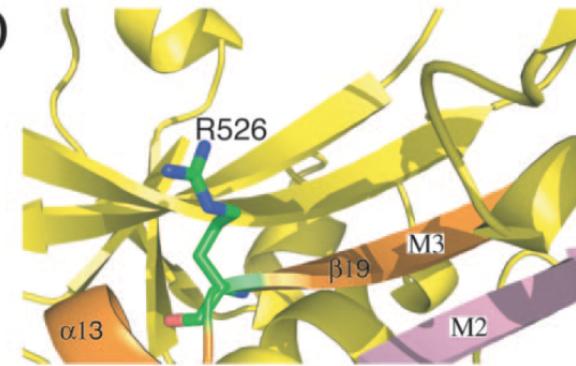


Mutant

C

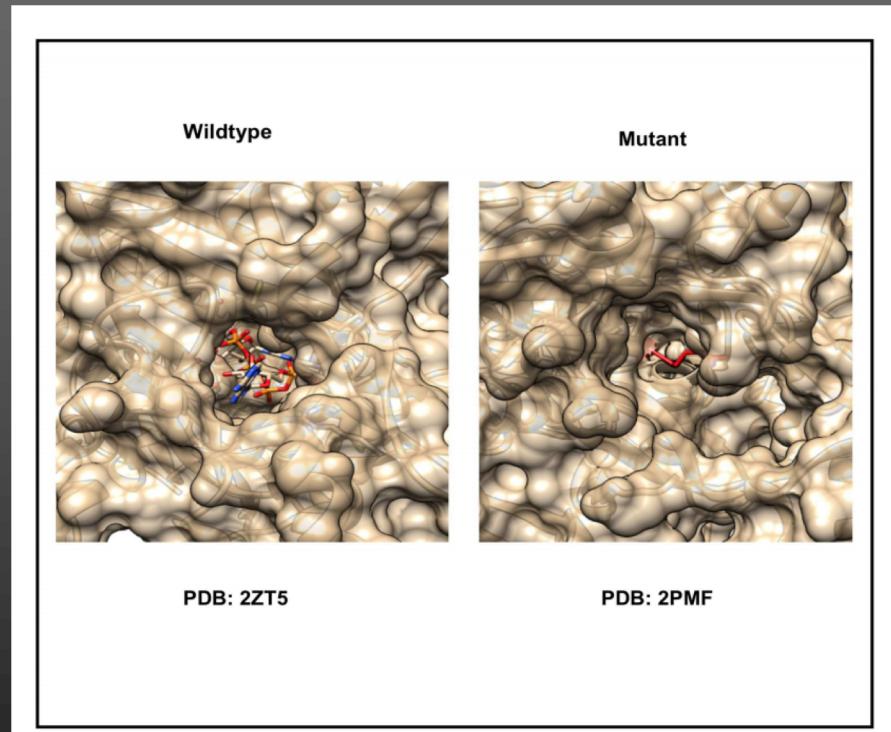


D



Effects of G526R mutation on Structure & Function

- Mutant Protein (PDB: 2PMF) is almost identical to Wildtype
- Human glycyl-tRNA synthetase loses enzymatic **activity** completely
- What happens to structure? How does it lead to complete knock-out of enzymatic activity?
 - AMP binding site (Pos. 583) is not directly affected, but the sidechain of the mutated residue blocks access to the binding site of AMP
 - As a consequence Gly-AMP intermediate cannot be formed → inactivation of enzyme function!
 - In addition, study suggests also that the mutation leads to a tighter dimer formation



1) Charcot-Marie-Tooth disease (CMT2D)

- Neuropathy, inherited in an autosomal dominant fashion
- Axonal degeneration in the absence of obvious myelin alterations, normal or slightly reduced nerve conduction, progressive distal muscle weakness and atrophy.

2) Neuropathy, Distal Hereditary Motor, Type V

- Disorder characterized by distal muscular atrophy mainly affecting the upper extremities
- Caused by selective degeneration of motor neurons

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