Effects of mutations in the NMDA receptor GluN1 subunit on binding and dynamics: a computational approach.

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Background

- N-methyl-D-aspartate receptors (NMDARs) are ligand gated ion channels which are central to diseases such as schizophrenia.
- Recent advances in sequencing has identified novel mutations within the GluN1 ligand binding domain which affects agonist EC_{50}.
- We carried out docking and subsequent molecular dynamics simulations on the docked poses to study the effects of the Ser688Tyr mutation on an atomic level.
- Output from these simulations demonstrate a fundamental change in ligand dynamics and surrounding environment which contributes to understanding of mutations in the NMDAR.

Methods

Docking

↓

μS MD simulation

↓

Randomly-seeded MD simulation

$\Delta G_{binding}$ calculations

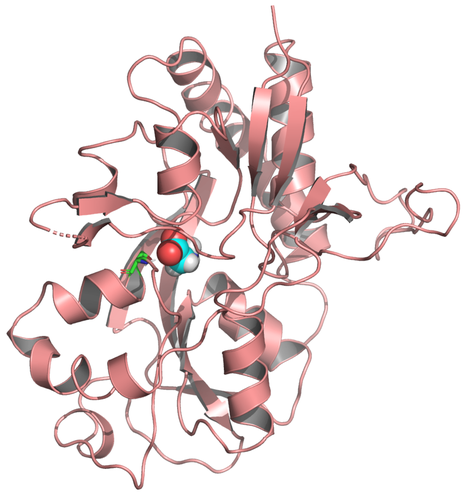
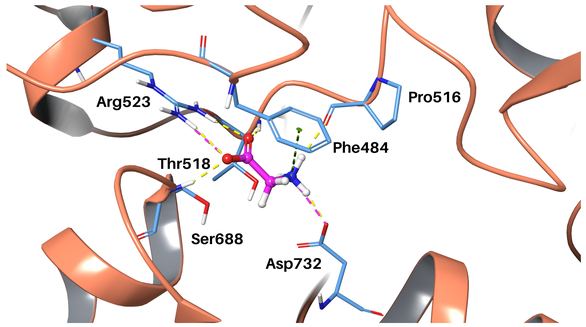


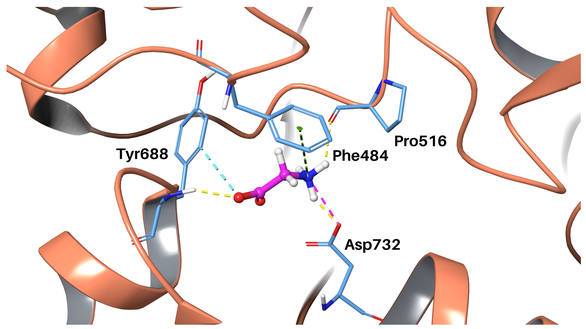
Fig.1 GluN1 ligand binding domain. Glycine ligand is shown in cyan and serine is shown in green.

Docking results and $\Delta G_{binding}$ values



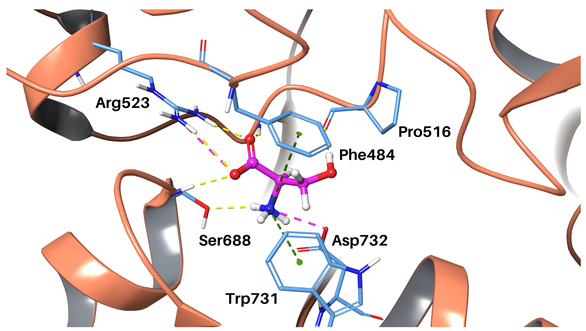
Wild type + glycine

-30.0 kcal/mol



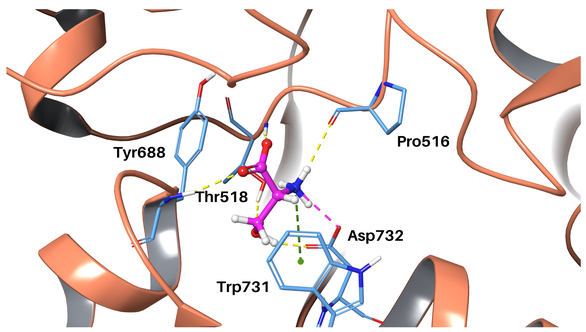
S688Y + glycine

-26.3 kcal/mol



Wild type + D-serine

-34.6 kcal/mol



S688Y + D-serine

-22.7 kcal/mol

Fig.2 Ligand interactions

Molecular dynamics

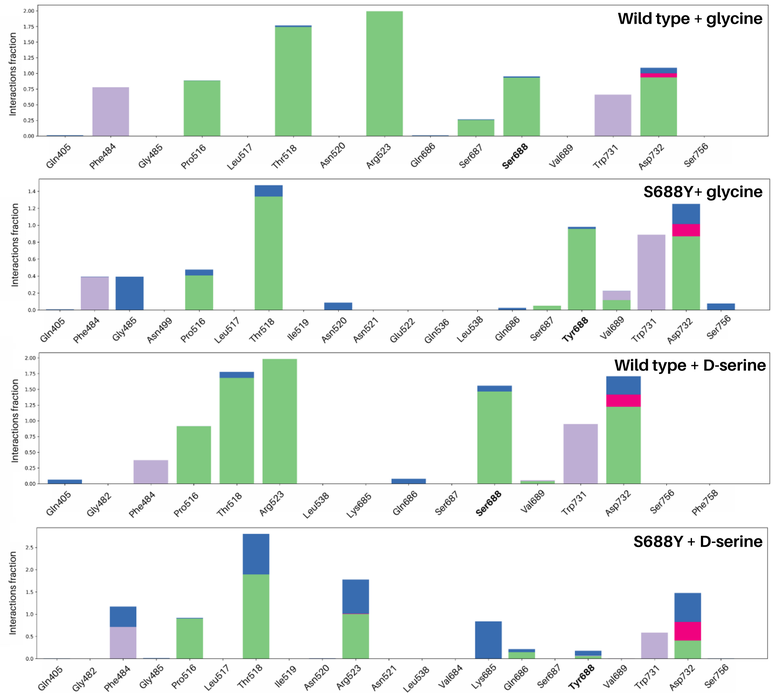


Fig.3 μS MD simulation interactions

Discussion

- Docking poses demonstrate a loss of the key Arg523 interaction with the ligand.
- There is an increase in the amount of water bridges formed around the ligand in the mutated subunit compared to the wild type subunit.
- The $\Delta G_{binding}$ values increased significantly following mutation which confirms the hypothesis that correct ligand binding is disrupted in the mutated subunit.

Further studies may involve simulation of the full NMDAR receptor as opposed to only the ligand binding domain as the mutation may also result in movement elsewhere in the protein.

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