## Comprehensive Prediction Results

| Mutation Site | | Structural Features | |
|---|---|---|---|
| Protein: | 4YZF | SS element: | Other (turns, coils, etc.) |
| Chain: | A | Solvent accessibility: | 8.17% |
| Wild type AA: | ALA | Torsion angles: | -105.6°, 2.2° |
| Residue ID: | 400 | | |

### Amino Acid Mutations

| Amino acid | Overall Stability | Torsion* | Predicted ΔΔG (kcal/mol) |
|---|---|---|---|
| GLY | Destabilising | Unfavourable | -1.22 |
| VAL | Destabilising | Unfavourable | -5.56 |
| LEU | Destabilising | Unfavourable | -3.26 |
| ILE | Destabilising | Unfavourable | -3.55 |
| MET | Destabilising | Unfavourable | -1.27 |
| PRO | Destabilising | Unfavourable | -1.82 |
| TRP | Destabilising | Unfavourable | -5.84 |
| SER | Destabilising | Favourable | -1.93 |
| THR | Destabilising | Favourable | -1.0 |
| PHE | Destabilising | Favourable | -3.23 |
| GLN | Destabilising | Favourable | -1.56 |
| LYS | Stabilising | Unfavourable | 2.42 |
| TYR | Destabilising | Favourable | -3.36 |
| ASN | Destabilising | Favourable | -2.44 |
| CYS | Destabilising | Unfavourable | -6.37 |
| GLU | Stabilising | Unfavourable | 0.45 |
| ASP | Destabilising | Favourable | -1.15 |
| ARG | Destabilising | Favourable | -0.73 |
| HIS | Stabilising | Favourable | 0.94 |

**Supplementary Figure S5. Protein stability prediction (CUPSAT) suggests a destabilizing effect of the p.Ala703Thr mutation in SLC4A2.**
The patient mutation in SLC4A2, c.503T>C, p.Ala703, was modeled on the crystal structure of the human SLC4A1 paralogue (Arakawa T Science 350:680-4, 2015).[22] Ala400 in SLC4A1 corresponds to Ala703 in SLC4A2. Thermal protein stability was predicted (http://cupsat.tu-bs.de/index.jsp) for the paralog SLC4A1. CUPSAT predicts destabilization of SLC4A2 for p.Ala703Thr.