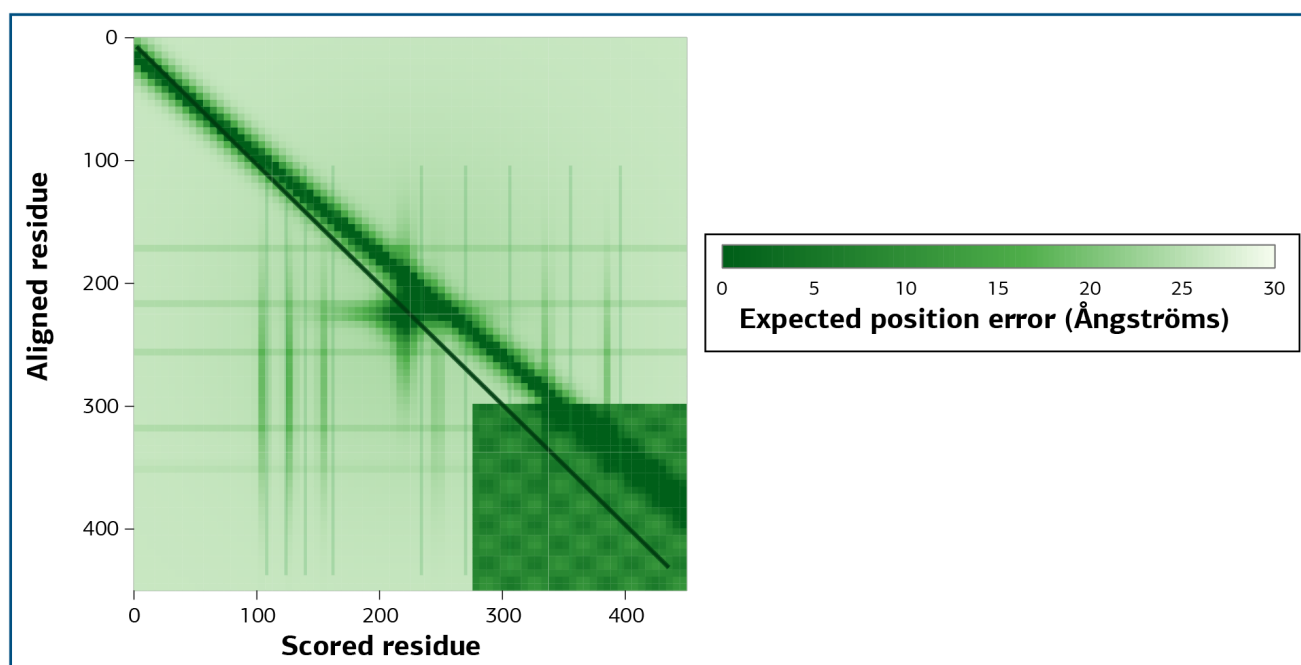
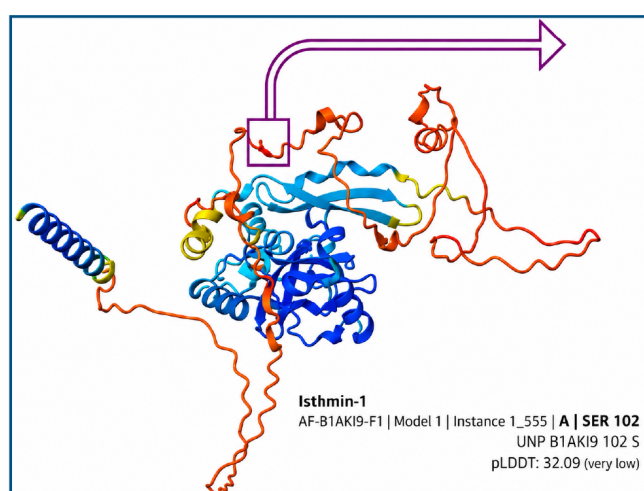
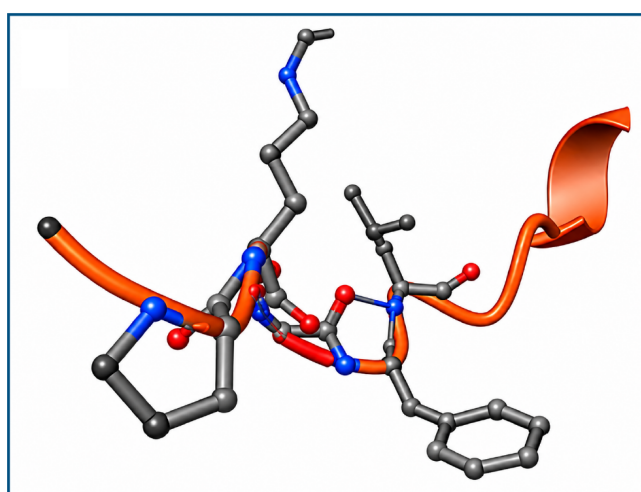




**A**



**B**



**C**

**Figure 1.** Structural context of the p.Ser102Pro substitution in Isthmin 1 predicted by AlphaFold2. A – AlphaFold predicted aligned error (PAE) heatmap; the loop harboring Ser102 shows elevated pairwise error, indicating flexible and poorly constrained geometry. B – Full-length ISM1 model (AF-B1AKI9-F1) colored by predicted local distance difference test (pLDDT); the arrow highlights the Ser102 loop (orange-red; local pLDDT  $\approx$ 32), distal to the well-resolved core (blue). C – Local environment of Ser102 (left) and the modeled Pro102 rotamer (right); the Ser→Pro substitution may rigidify the backbone and perturb nearby hydrogen bonding, although the low-confidence of this segment means that these effects should be considered hypothesis-generating. Abbreviations: ISM1 – Isthmin 1; PAE – predicted aligned error; pLDDT – predicted local distance difference test.