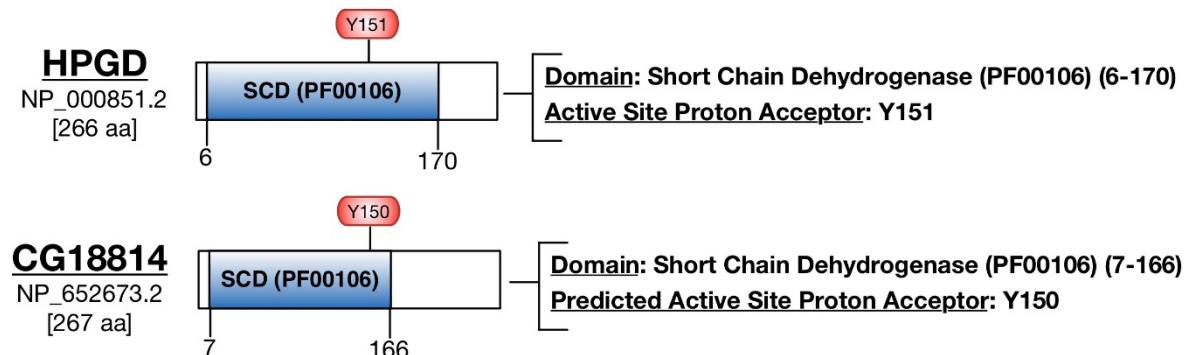
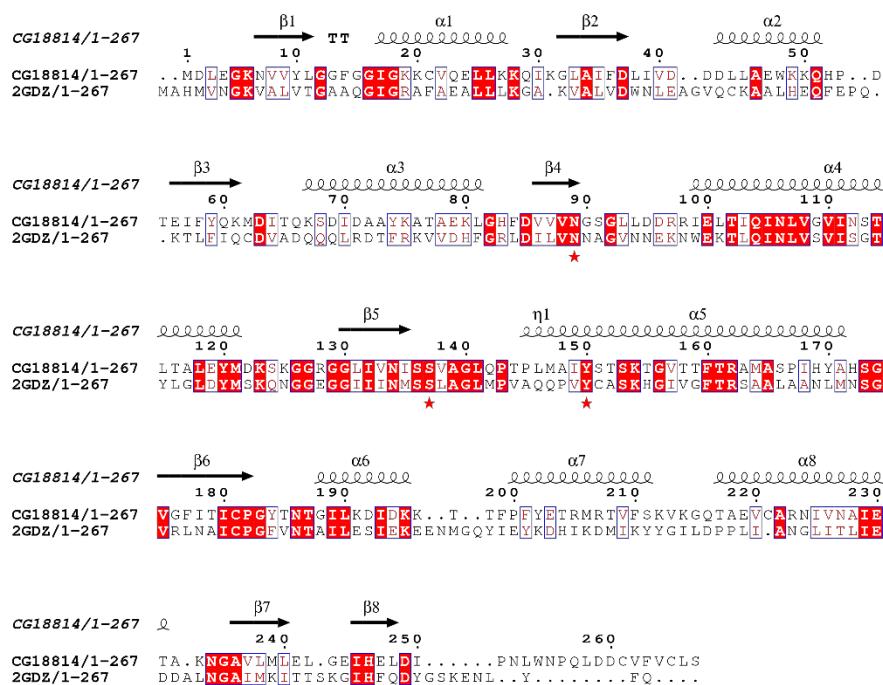


A.



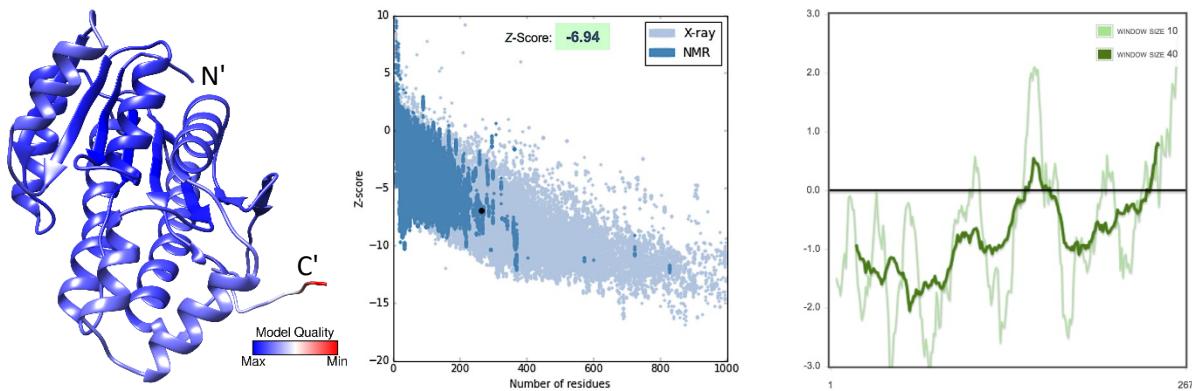
B.



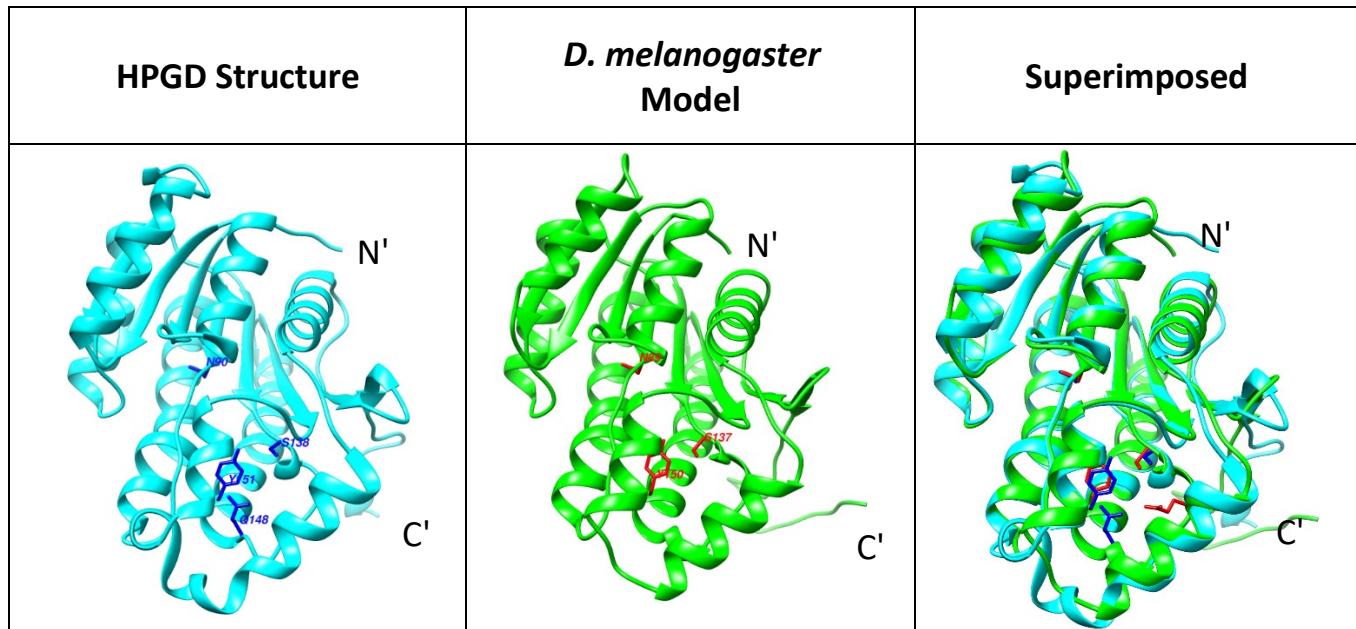
C.

Sequence alignment of CG18814/1-267, CG18814/1-267, and 2GDZ/1-267. The alignment highlights several mutations and structural features across the protein sequence.

D.



E.



| F. | Length (AA) | Domain Architecture (Pfam, range) | Functional Residues (aligned matches in <i>D. melanogaster</i>) | Sequence ID% | Structural Overlap (RMSD) |
|---|----------------|--|---|-------------------|---------------------------------|
| 15-hydroxyprostaglandin dehydrogenase NAD(+) (HPGD, NP_000851.2, PDB: 2GDZ) | 266 | Short chain dehydrogenase domain (PF00106) 6-170 | Y151 | | |
| Uncharacterized protein (CG18814, NP_652673.2) | 267 | Short chain dehydrogenase domain (PF00106) 7-166 | Y150 | 26% ID 47% SIM | 0.715 Å |

S12 Fig. Sequence and structural details of the modeled fly HPGD candidate. A. Domain architecture of HPGD and CG18814 and known/predicted functional residues B. Pairwise alignment of CG18814 and 2GDZ generated from structural superposition showing shared secondary structure elements and known/predicted functional residues (marked with red asterisks) C. Pairwise alignment of CG18814 and 2GDZ generated from structural superposition with conserved residues highlighted using the physiochemical color scheme (CLUSTALX) D. Validation of the CG18814 model: ProQ2 quality score mapped to a 3D model of CG18814 (left); ProSA global quality score ranking (middle) and per-residue quality graph (right) E. HPGD (2GDZ, cyan-blue) superimposed on the predicted structure of CG18814 (green-red) with potential matches for conserved functional residues highlighted F. Summary of features shared by HPGD and potential *D. melanogaster* ortholog CG18814.