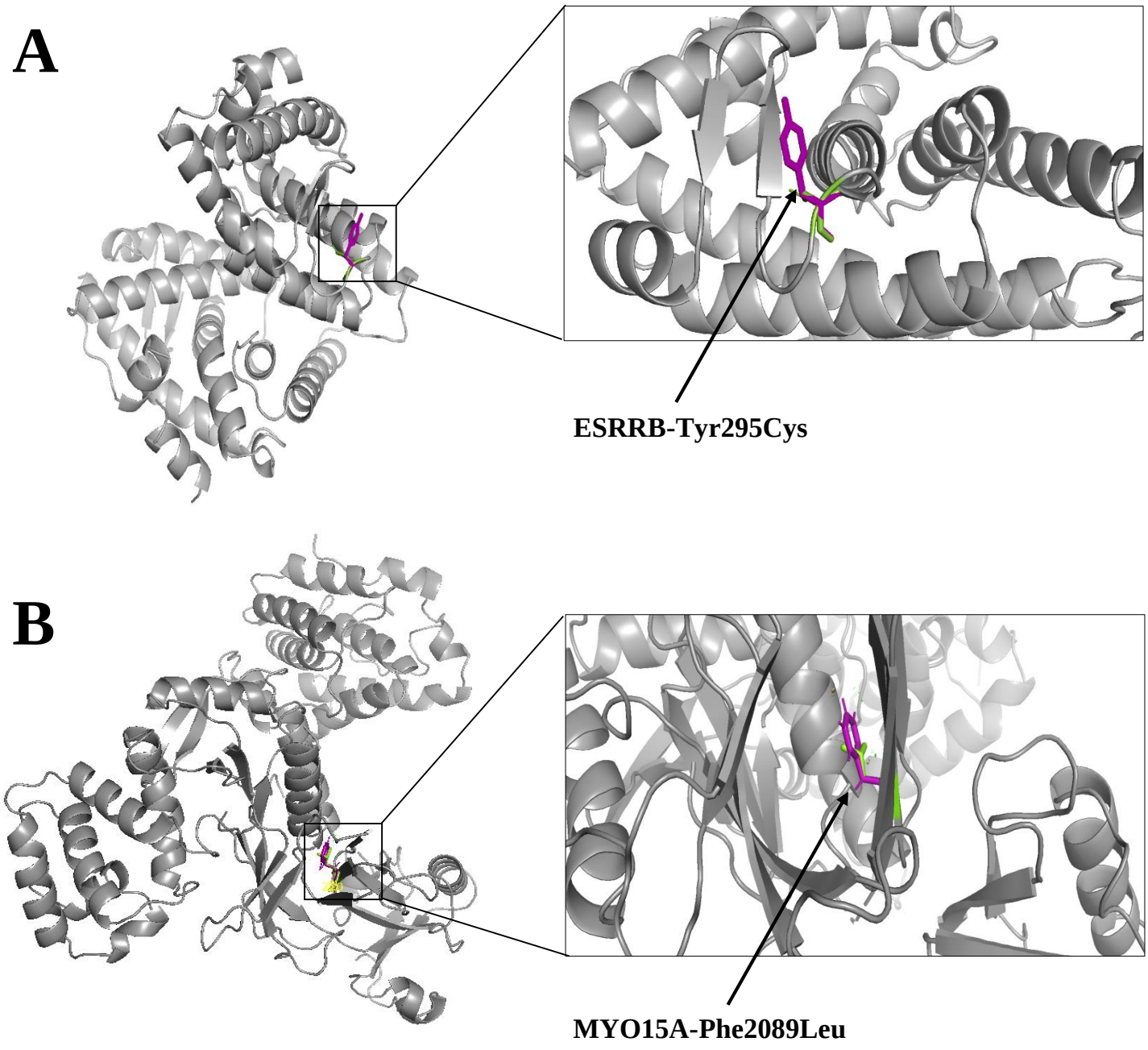
A
ESRRB-Tyr295Cys
B
MYO15A-Phe2089Leu
C
His533
Asn455
MYO7A-TYR560CYS

Figure.S2 Structural modelling and functional analysis for ESRRB-Tyr295Cys, MYO15A-Phe2089Leu and MYO7A-Tyr560Cys missense mutations.

The wild-type residues are depicted in magenta, while the mutant residues are shown in green. (A) 3D graphic representation for the predicted effect of the ESRRB-Tyr295Cys mutation. ESRRB-Tyr295Cys is located in a loop region, known as patternless regions, which connect two regular secondary structures. The substitution of the aromatic amino acid Tyr, located on the ESRRB solvent exposed areas within the protein's surface, with Cys amino acid may cause loss of hydrogen bonds in protein core and/or disturbing correct folding. (B) 3D graphic representation for the predicted effect of the MYO15A-Phe2089Leu variant. Phe2089 is located in a beta sheet and its substitution with Leu in this position may disturb the secondary rigid structure. (C) 3D graphic representation for the predicted effect of the MYO7A-Tyr560Cys mutation. Yellow lines represent hydrogen bonds. The MYO7A-Tyr560Cys variant is located in the Myosin motor domain. This mutation is located in a non-structured region. Tyrosine560 is a highly conserved amino acid which establishes two hydrogen bonds with both His553 and Asp455. The former His aa belongs to the same strand while the latter Asp aa lies upstream of the relay in the HP helix. These two residues, as well as the two hydrogen bonds, are conserved in all myosin motor domains. Replacement with cysteine will disrupt those hydrogen bonds and would probably affect the Myosin head motor domain stability. Moreover, this substitution is likely to prevent phosphorylation as this highly conserved Tyr residue is located in the surface and it is therefore totally exposed to the solvent.