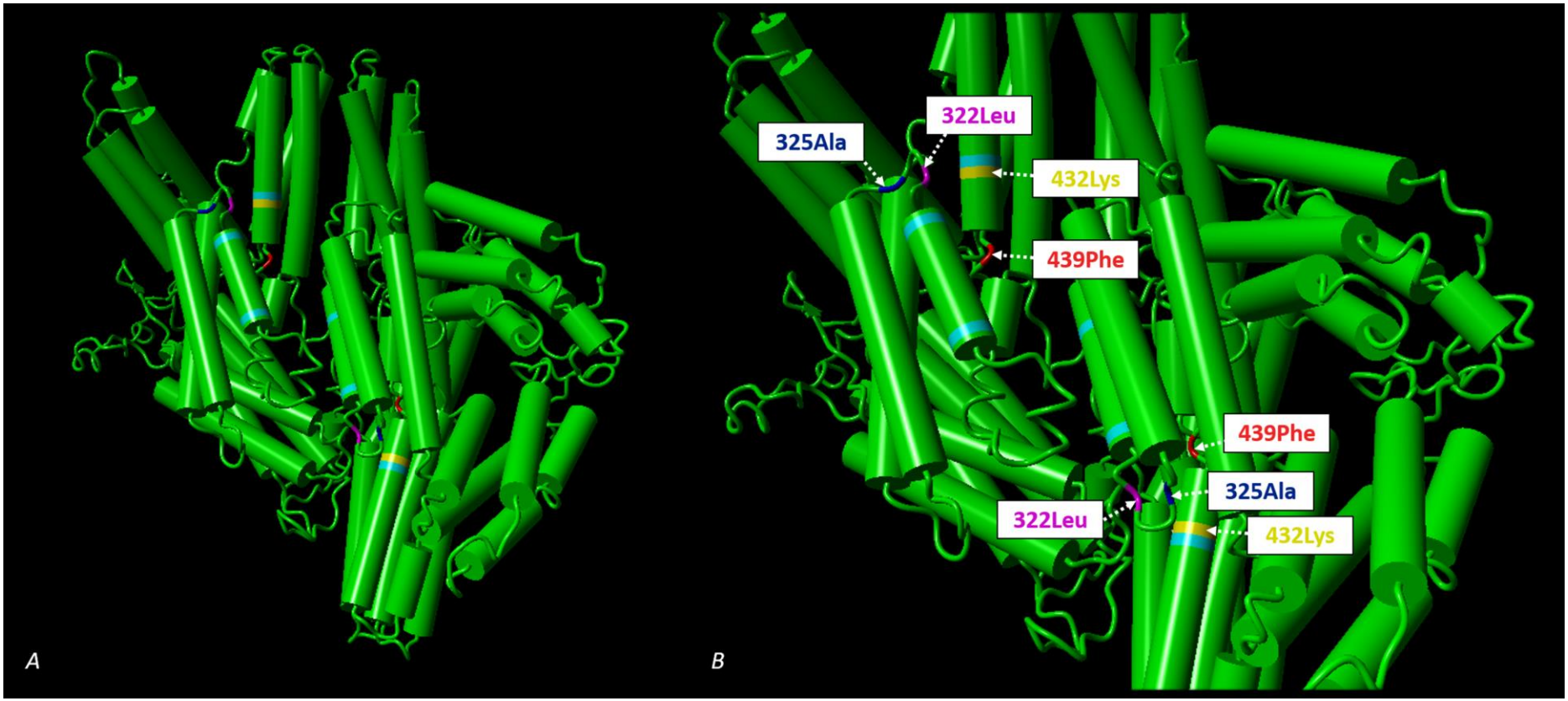

Supplementary Figure 2. Protein structure with positions of missense changes. *A*, Three-dimensional predicted protein structure with positions of previously reported changes[1] (shown in blue) as well as those reported in the current study. Three-dimensional structures were produced using online software (Protein Database 4IGG[2] and YASARA[3]). *B*, Magnified version of the region containing the changes, with amino acid changes from the current study labelled (positions 322, 325, 432 and 439; those identified in the previous study were at positions 307, 318 and 431). The c.965C>T and c.1316C>T changes result in substitution of the polar amino acid serine by leucine and phenylalanine respectively (both have hydrophobic side chains). The c. 1294G>A is predicted to change glutamate (negatively charged) to lysine (positively charged). The c.973A>G variant is predicted to change the polar amino acid

threonine to alanine (nonpolar, aliphatic). All four changes were predicted to be "probably damaging" by PolyPhen-2 and disease causing by MutationTaster. The latter predicted the variants to be evolutionarily distant and deleterious. Modelling depicts the variants on the side of the protein that interacts to form a dimer, suggesting dimerization might be compromised. Saksens et al.[1] noted that the disease-associated variants mapped in, or near to, the vinculin binding region; we speculate that the missense changes in our cohort might impact on vinculin binding as well, and lead to compromise of retinal pigment epithelium integrity.

References

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3. Krieger E, Vriend G. YASARA View—molecular graphics for all devices—from smartphones to workstations. *Bioinformatics*. 2014;30(20):2981–2982.