

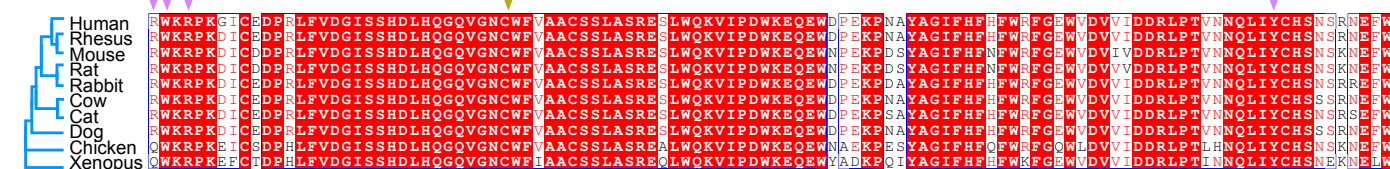
## Supplemental Figure Legends

**Figure S1. Alignments of CAPN5 in vertebrates shows high homology.** **A.** Human amino acid sequences from the domain IIa (DIIa), **B.** the C2L-domain (DIII), and **C.** the C2-domain (DIV) were aligned to 9 specific vertebrates: Rhesus, Mouse, Rat, Rabbit, Cow, Cat, Dog, Chicken, and Xenopus. CAPN5 loss of function (LOF) variants (purple) were found in highly conserved regions alongside published Autosomal Dominant Neovascular Inflammatory Vitreoretinopathy (ADNIV)-disease causing gain of function (GOF) variants (blue).

**Figure S2. ConSurf conservation analysis using our structural model of CAPN5.** Comparison to 150 closest homologues including both invertebrates and vertebrates. ConSurf conservation scores were mapped onto our full structural model of CAPN5 containing all protein domains. Variants with high conservation, magenta; variants with low conservation, cyan.

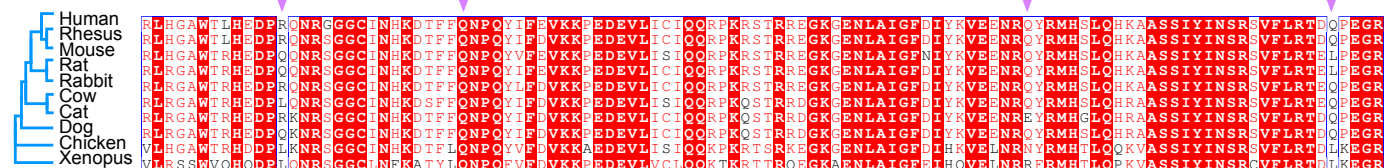
## A Domain IIa

LOF Variants



## B Domain III

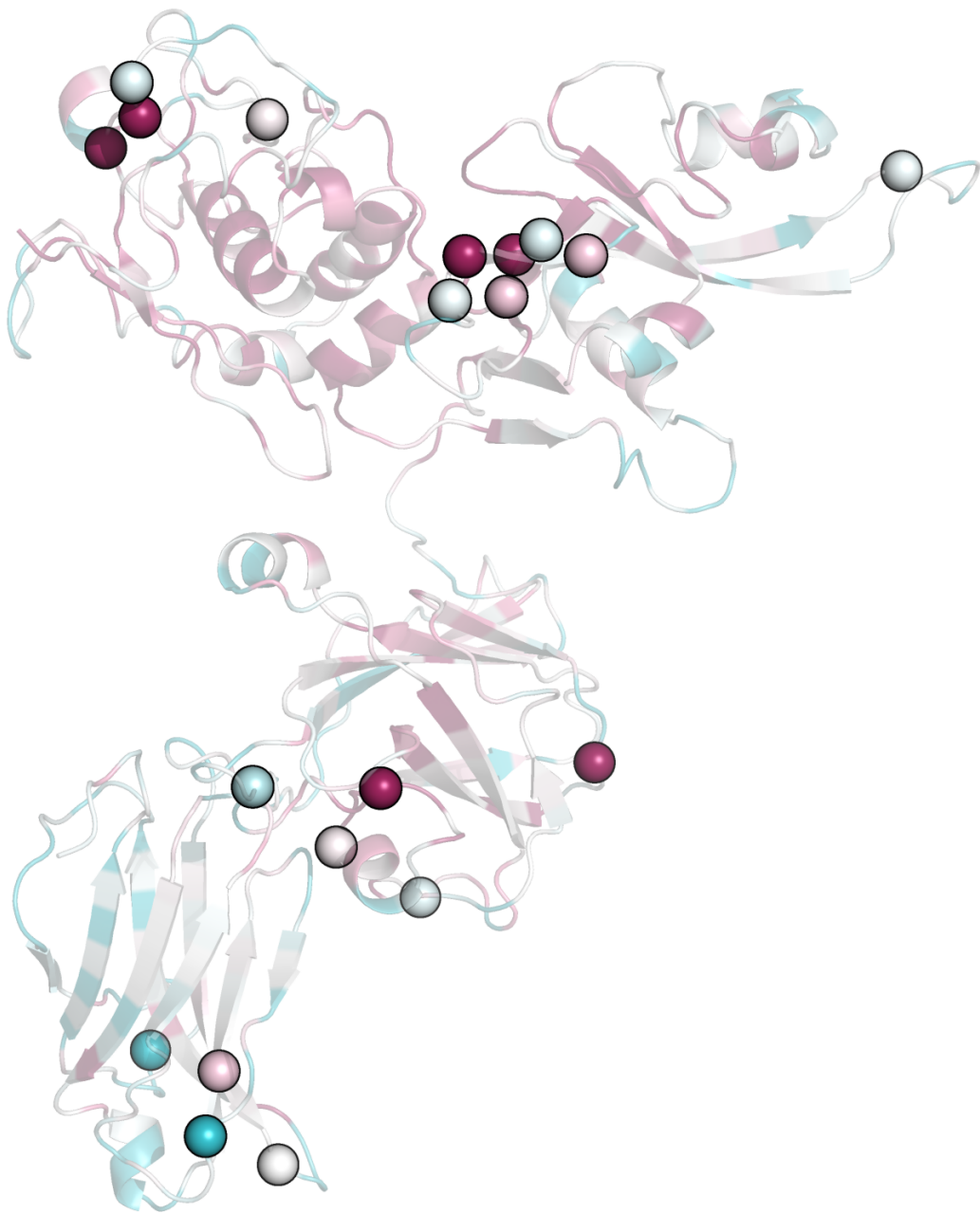
LOF Variants



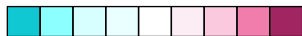
## C Domain IV

LOF Variants





Conservation



Variable

Conserved