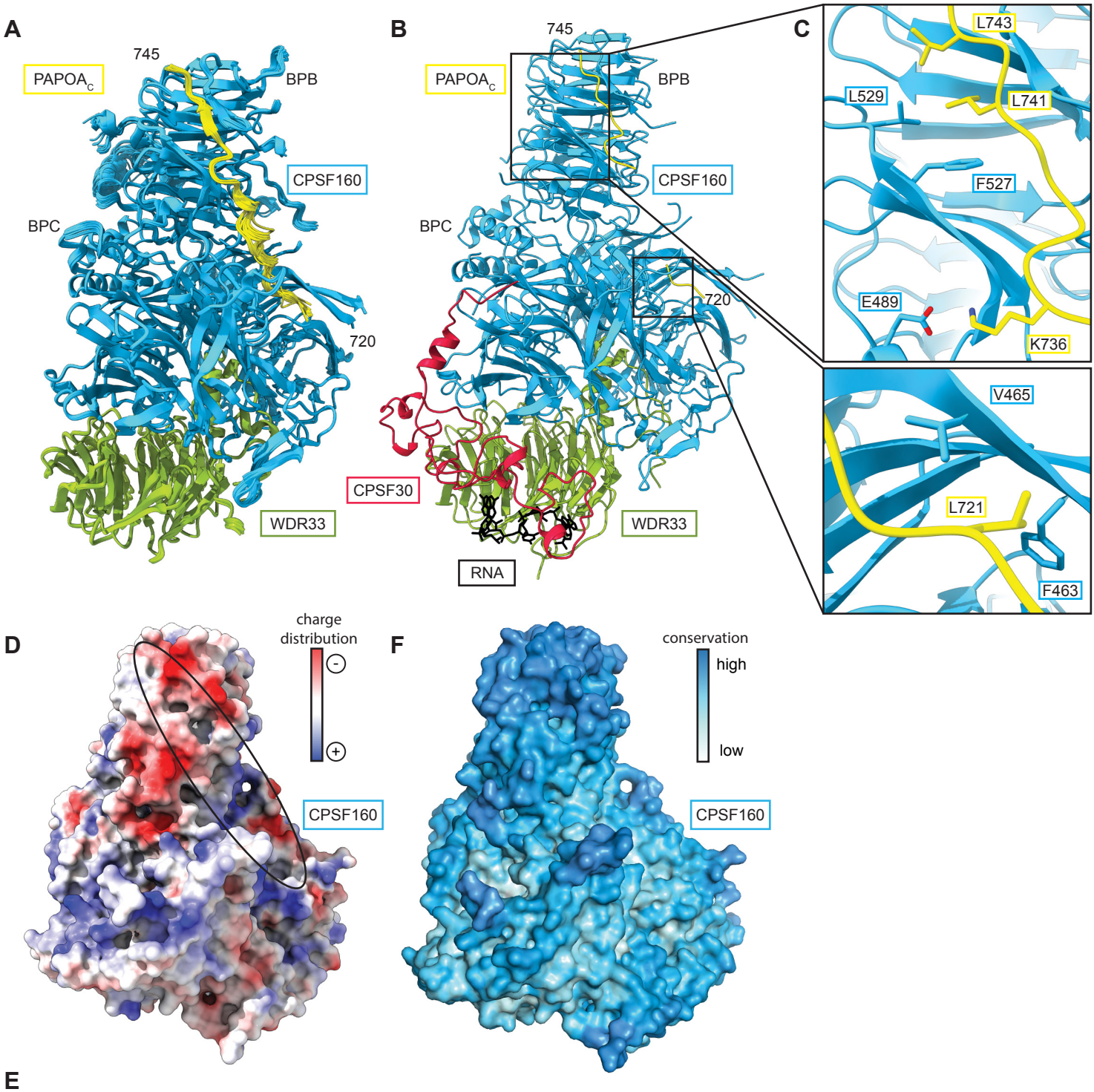


## E

### PAPOA

```
H. sapiens        648 GVKRTSSPHK-EESPKK---TKTEEDETSEDANCLALSGHDKTEAKEQLD---T-------ETSTTQSETIQTAASLLASQKTSSTDLSDIPA--LPANPIPVIKNSIKLRLNR 745
B. taurus         642 GVKRTSSPHK-EESPKK---TKTEEDETSEDANCLALSGHDKTETKEQLD---T-------ETSTTQSETIQTATSLLASQKTSSTDLSDIPA--LPANPIPVIKNSIKLRLNR 739
M. musculus       642 GVKRTSSPNK-EESPKK---TKTEEE----------------------QVD---L-------ETSAVQSETVPASASLLASQKTSSTDLSDIPA--LPANPIPVIKNSIKLRLNR 718
E. caballus       642 GVKRTSSPHK-EESPKK---TKTEEDETSEDANCLALSGHDKTETKEQLD---T-------ETSTTQSETIQTAASLLASQKTSSTDLSDIPA--LPANPIPVIKNSIKLRLNR 739
C. lupus          642 GVKRTSSPHK-EESPKK---TKTEE-----------------------------------------------KTSSTDLSDIPA--LPANPIPVIKNSIKLRLNR 693
X. tropicalis     638 GVKRTSSPSN-EESPKK---TKTEEDENDSSNS-TEVDEQNKLETEELKE---V-------L--SEAKSSSPVPGELPSSQRSSSTDLSDISV--LPATPIPVIKNSIKLRLNR 732
D. rerio          623 AVKRPASALE-NEMTKK---AKVEDLSAPEAKSSGETDGHVAPAIVEVIPSDGE------LKTETELMVEDTAEKVPLAQKTSNADLSDVPV--LPSNPIPVVKNSIKLRLSR 723
D. melanogaster   727 GHKRKQQTATSTTMISSSNIAHSNYTQHSTHNNNGGGGGSH-YNKTYYIDDDDEDNNQPLLTPNNQTQQQQKAVRIT---ATSASPATSVPVAASAAPPAPTISL--------- 827
S. pombe          ----------
S. cerevisiae     ----------
```

### CPSF160

```
H. sapiens        327 ATFISYDK----------MVISLKGGEIYVLTLITDGMRSVRAFHF-------DKAA--ASVLTTSMVTM------EPGYLFLGSRLGNSLLLKYTEKLQEPPASAVREAADK-EEP-------PSKKK 422
B. taurus         330 AAFISYDK----------MVISLKGGEIYVLTLITDGMRSVRAFHF-------DKAA--ASVLTTSMVTM------EPGYLFLGSRLGNSLLLKYTEKLQEPPASTAREAADK-EEP-------PSKKK 425
M. musculus       327 AAFISYDK----------MVISLKGGEIYVLTLITDGMRSVRAFHF-------DKAA--ASVLTTSMVTM------EPGYLFLGSRLGNSLLLKYTEKLQEPPASSVREAADK-EEP-------PSKKK 422
E. caballus       330 AAFISYDK----------MVISLKGGEIYVLTLITDGMRSVRAFHF-------DKAA--ASVLTTSMVTM------EPGYLFLGSRLGNSLLLKYTEKLQEPPASAVREAAEK-EEP-------PSKKK 425
C. lupus          330 AAFISYDK----------MVISLKGGEIYVLTLITDGMRSVRAFHF-------DKAA--ASVLTTSMVTM------EPGYLFLGSRLGNSLLLKYTEKLQEPPASAARDAADK-EEP-------PSKKK 425
X. tropicalis     327 ATFISYDK----------MVISLKGGEIYVLTLITDGMRSVRSFHF-------DKAA--ASVLTTSMTPM------EPGYLFLGSRLGNSLLLRYTEKVQDSPAGPSKDPDKQ-DEP-------PNKKK 422
D. rerio          327 ASFITSDK----------MVISLKGGEIYVLTLITDGMRSVRAFHF-------DKAA--ASVLTTCMMTM------EPGYLFLGSRLGNSLLLRYTEKLQETPMEEGKENEEKEKQP--------PNKKK 423
D. melanogaster   338 FAFLIDVDK----------LVISLRTGDLIVLTLCVDSMRTVRNEHF-------HKAA--ASVLTSCICVL------HSEYIFLGSRLGNSLLLHFTEEDQSTVITLDEVEQQSEQQQRNLQDEDQNLEE 441
S. pombe          356 AIPLTSSKT-------ETPFVWLVHTSGQFFYLDFLLDGKS-VKGLSLQALDLEINDDF--LKSGITCAVPA------GENLVFLGSQTTDSYLLRWSRRTTNEEVRLDEGDDTL---------- 454
S. cerevisiae     344 SIWIPSSAKSKNGGSNNDETLLLM-DLKSNIYYIQMEAEGRLLIK-PDI--FKLPIVNDLLKENSNPKCITRLNATNSNKNMDLFIGFGSGNALVLRLNNLKSTIETREAHNPSSGTNSLM---------- 459

H. sapiens        423 --RVDATAGWSAAGKSVPQDEVDEIEVY----------GSEAQS-GTQLATYSFEVCDSILNIGPCANAAVGEPAFLSEE-------FQNSPEPDLEIMVCSGHGKNGALSVLQKSIRPQVVTTFELPGCY 533
B. taurus         426 --RVDATTGWSG-SKSVPQDEVDEIEVY----------GSEAQS-GTQLATYSFEVCDSILNIGPCANAAMGEPAFLSEE-------FQNSPEPDLEIMVCSGYGKNGALSVLQKSIRPQVVTTFELPGCY 535
M. musculus       423 --RVEPAVGWTG-GKTVPQDEVDEIEVY----------GSEAQS-GTQLATYSFEVCDSMLNIGPCANAAVGEPAFLSEE-------FQNSPEPDLEIMVCSGYGKNGALSVLQKSIRPQVVTTFELPGCY 532
E. caballus       426 --RVDSTVGWSG-GKSVPQDEVDEIEVY----------GSEAQS-GTQLATYSFEVCDSILNIGPCANAAMGEPAFLSEE-------FQNSPEPDLEIMVCSGYGKNGALSVLQKSIRPQVVTTFELPGCY 535
C. lupus          426 --RVDCAAGWSG-GKSVPQDEVDEIEVY----------GSEAQS-GTQLATYSFEVCDSILNIGPCANAAMGEPAFLSEE-------FQNSPEPDLEIMVCSGYGKNGALSVLQKSIRPQVVTTFELPGCY 535
X. tropicalis     423 --RVDSSLARPGGSKGNMVDEIDEIEVY----------GSEMQS-GTQLSTYSFEVCDSILNIGPCATASMGEPAFLSEE-------FQESPEPDLEIMLCSGYGKNGALSVLQKSIRPQVVTTFELPGCH 533
D. rerio          424 --RVDSNWAGC-PGKGNLPDELDEIEVY----------GSEAQS-GTQLATYSFEVCDSILNIGPCASASMGEPAFLSEE-------FQTNPEPDLEVVCSGYGKNGALSVLQKSIRPQVVTTFELPGCH 533
D. melanogaster   442 IFDVDQLEMAP-TQAKSRRIEDEELEVY----------GSGAKASVLQLRKFIFEVCDSLMNVAPINYMCAGERVEFEEDGVTLRPHAESLQDLKIELVAATGHSKNGALSVFVNCINPQIITSFELDGCL 561
S. pombe          455 -------Y---GTND---AEMDDMLDIMETDES----VGSKRKI-AYENGPLRLEICDVLTNIGPITDFAVGKAGSYSY---------FPQDNHGPLELVGTAGADGAGGLVVFRRNIFPLIAGEEQFDGCE 559
S. cerevisiae     460 ----------DINDDDDEEMDDLMADEAPENGLLTTNDSKGTVETVQPFDIELLSSLRNVGPITSLTVGKVSSIDDV----VKGLPNPNKNEYSLVATSGNGSGSHLTVIQTSVQPEIELALKFISIT 572
```

**Figure S3: Characterization of the PAPOA-CPSF160 interaction**

(A) Overlay of 25 computationally predicted models of the CPSF160-WDR33-PAPOA$_C$ complex, shown in the same orientations and colors as in (**Fig. 3A**). CPSF160 flexible loops and WDR33 disordered C-terminus are not shown for clarity.

(B) Structural model of mPSF-PAPOA$_C$ shown in the same orientation and colors as in (**Fig. 3C**). The CPSF160 ß-propeller domains are indicated.

(C) Close-up of the binding interfaces of CPSF160-PAPOA$_C$. Labeled PAPOA$_C$ residues were changed to glutamic acid.

(D) Structural model of CPSF160 shown in surface representation with residues colored by electrostatic properties. The interaction pocket engaged by PAPOA$_C$ is indicated with a black ellipse.

(E) Multiple sequence alignment of PAPOA and CPSF160 from different eukaryotic organisms around the PAPOA-CPSF160 binding site, with residues colored by identity. The minimal PAPOA binding peptide is in bold and boxed, while mutated residues leading to a weakened or disrupted interaction are labeled with yellow asterisks. CPSF160 residues involved in the interaction are labeled with blue triangles.

(F) Structural model of the CPSF160 shown in surface representation with residues colored by sequence conservation, from low conservation in white to high conservation in blue.