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Supplemental information

Ultra-rare complement factor 8 coding variants in families with age-related macular degeneration

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Supplemental item titles and legends

Table S2 – Variants in C8A and C8B identified in the study, Related to Figure 1 and 2.

	Variant 1	**Variant 2**
Gene	*C8A*	*C8B*
Ref Transcript	NM_000562	NM_000066
Change DNA	c.G1331A	c.G1144T
Change Protein	p.R444H	p.D382Y
Genomic Position (GRCh38)	chr1:56908064	chr1:56943786
RS_ID	rs143908758	rs139498867
Ref Allele	G	G
Alt Allele	A	T
ExAC_ALL	0.004	0.0042
gnomAD	0.003971	0.006335
SIFT	deleterious	deleterious
Polyphen	probably_damaging	possibly_damaging
CADD Score	32	28.2
# of families identified	1	3

Table S3 – Protein stability calculation by FoldX, Related to Figure 3.

	C8 complex		**Individual subunit**	
Subunit protein	**ΔG kcal/mol**	**ΔΔG kcal/mol**	**ΔG,kcal/mol**	**ΔΔG, kcal/mol**
C8A, reference sequence	495.5	-	233.84	-
C8A, R444H substitution	462.3	-33.2	231.51	-2.34
C8B, reference sequence	495.5	-	230.05	-
C8B, D382Y substitution	418.6	-43.7	193.05	-37

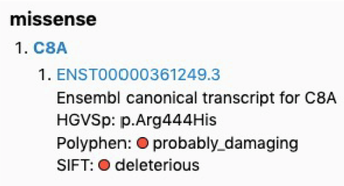
Supplementary figures and legends

Figure S1 – Pathogenicity prediction and DNA level conservation of identified variants in C8A and C8B genes, Related to Figure 2.

Pathogenicity predictions are taken from gnomAD server from Broad Institute (https://gnomad.broadinstitute.org/).

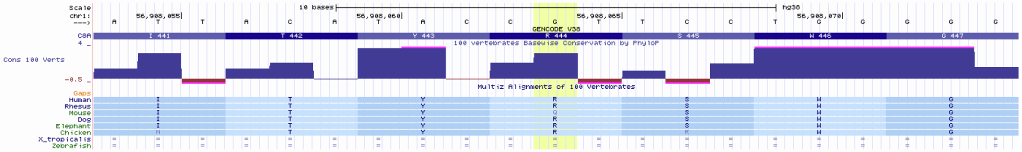
DNA level conservation is from 100 vertebrate track (PhyloP) in UCSC genome browser.

A

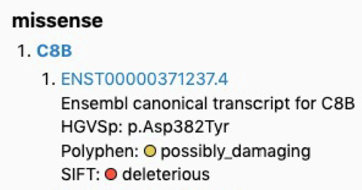


missense

1. **C8A**
   1. ENST00000361249.3
      Ensembl canonical transcript for C8A
      HGVSp: p.Arg444His
      Polyphen: ● probably_damaging
      SIFT: ● deleterious



B



missense

1. **C8B**
   1. ENST00000371237.4
      Ensembl canonical transcript for C8B
      HGVSp: p.Asp382Tyr
      Polyphen: ● possibly_damaging
      SIFT: ● deleterious

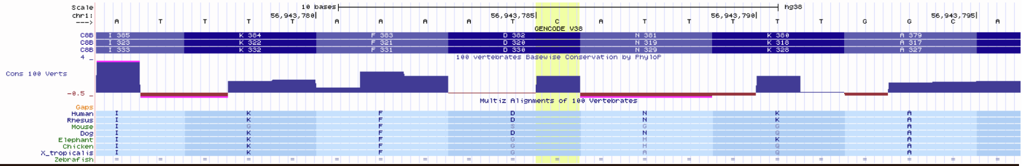
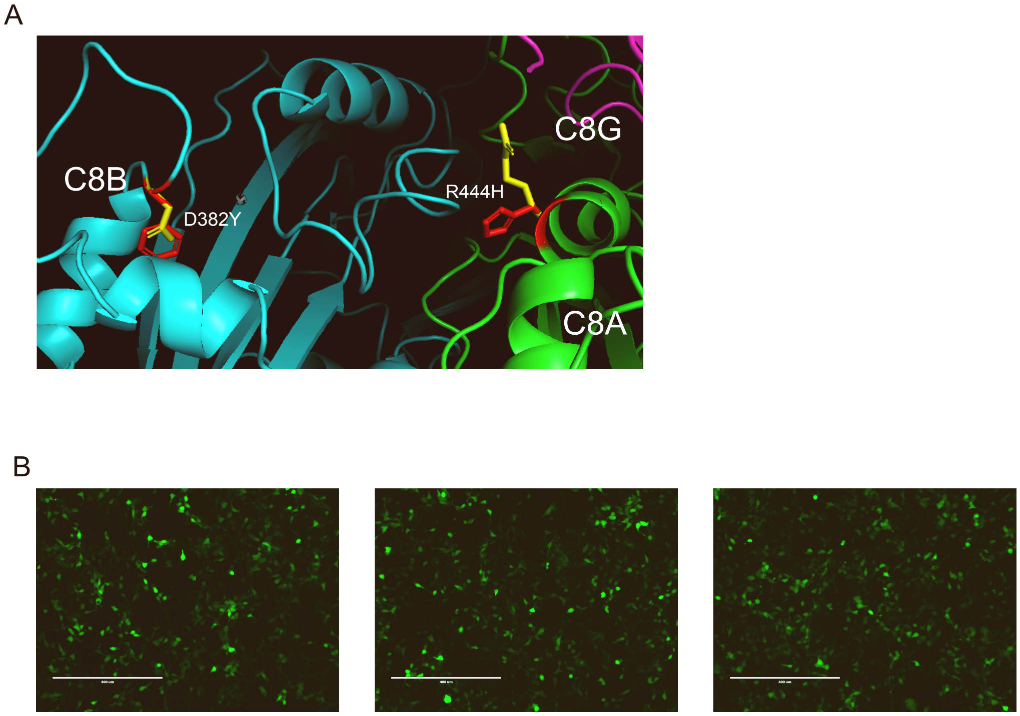


Figure S2 – Effect of variants on C8 complex subunits interaction, Related to Figure 3.



C8A_WT/C8B_WT/C8G   C8A_WT/C8B_Mut/C8G   C8A_Mut/C8B_WT/C8G

A. Snapshot of the C8 complex structure, showing both variants in red and WT residues in yellow. B. Representative images of transfection efficiency of different plasmid combinations in HEK293 cells. WT: wild type sequence; Mut: ultra-rare sequence variant.