Legends to Supplementary Figures and Tables

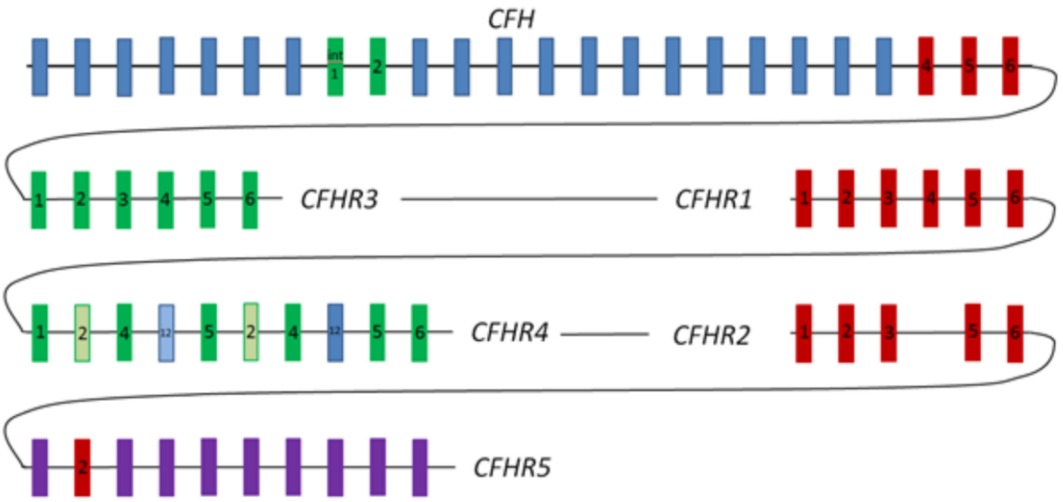

Figure S1. Schematic representation of the *CFH* region exons. These genes are located in tandem on chromosome 1. Several exons of *CFHR3* (in green), *CFHR1* (in red) and *CFH* (in blue) are duplicated in *CFH*, *CFHR4*, *CFHR2* and *CFHR5*. *CFH* exon 8 is a duplicate of *CFHR3* intron 1 and *CFH* exon 9 is a duplicate of *CFHR3* exon 2. *CFHR 1* exons 4, 5 and 6 are duplicated as the ultimate 3 exons of *CFH.* *CFHR4* is closely related to *CFHR3* and *CFHR2* is closely related to *CFHR1.*

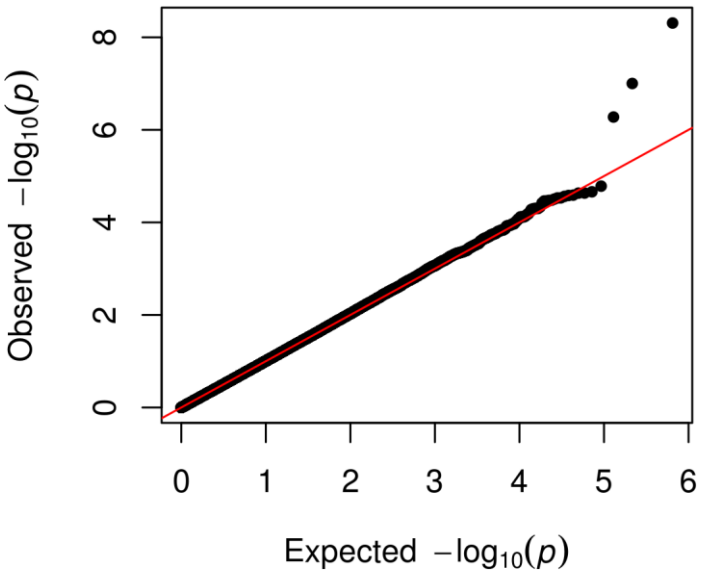

Figure S2. Q-Q plot of genome-wide case-case study of neovascular AMD compared to drusen.

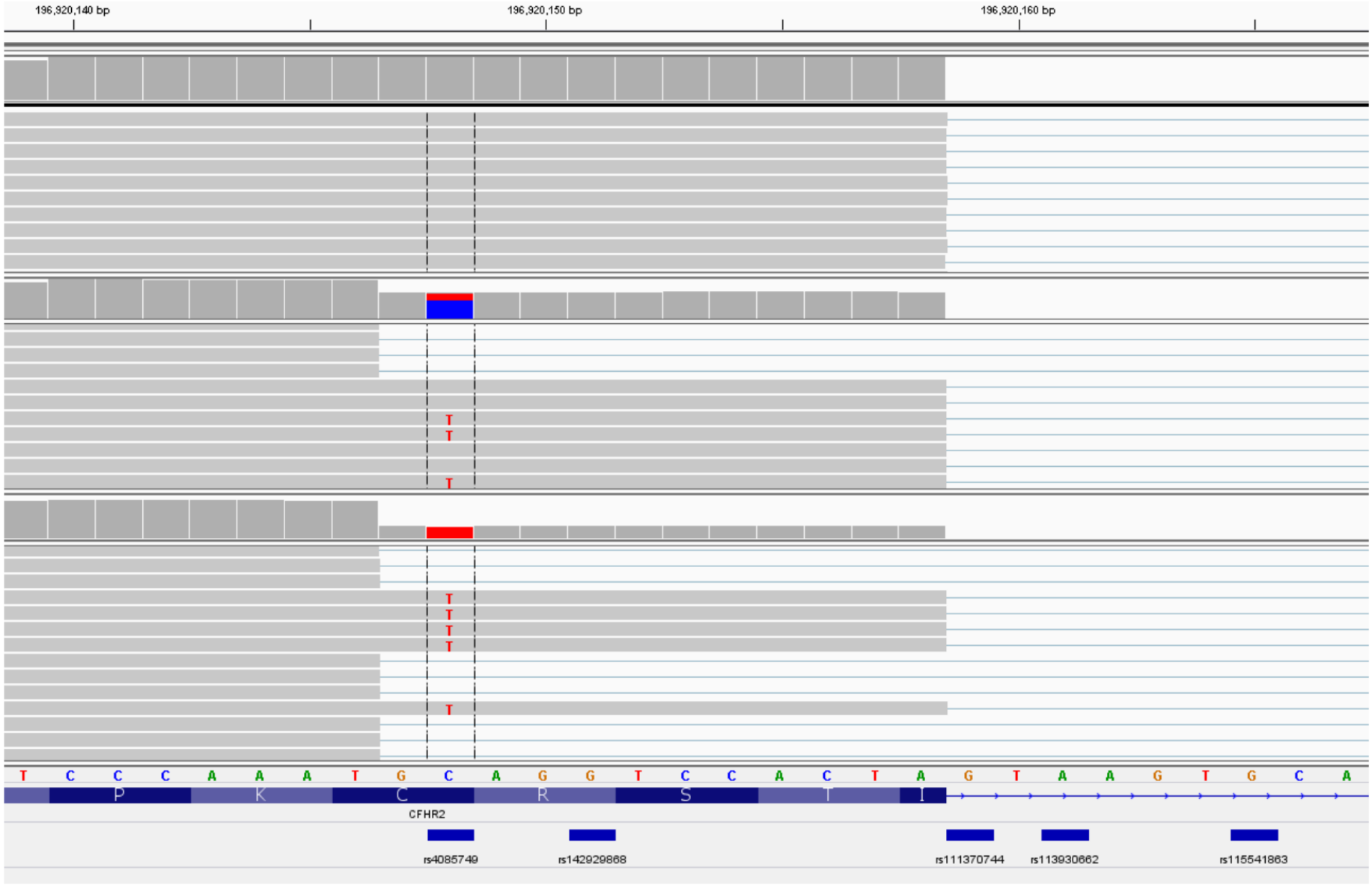
196,920,140 bp
196,920,150 bp
196,920,160 bp
T C C C A A A T G C A G G T C C A C T A G T A A G T G C A
P K C R S T I
CFHR2
rs4085749
rs142929868
rs111370744
rs113930662
rs115541863

Figure S3. *CFHR2* rs4085749 (C140C) in liver RNA-seq reads from carriers of haplotypes BD (top panel), AC (middle panel) and CC (bottom panel), carrying 0, 1 and 2 copies of the T allele, respectively. Note the reduction in read depth and early splicing associated with the majority of T allele reads (figure produced in Integrative Genomics Viewer).

Table S1. Study Population.

Experiment	Participants (n)	% Male	Average Age (years)	Origin
Massively parallel sequencing of *CFH* region	4	100	76	Northern Ireland, UK.
RNA-seq of eye tissues	8	63%	73.9	USA
RNA-seq of liver	3	NA	NA	NA
Secondary analyses of AMD GWAS	2157 cases 1150 controls	38% 44%	78.6 74.1	USA

Table S2. Synonymous SNPs in *CFH* and *CFH*-related genes identified from massively-parallel sequencing of genomic DNA of four homozygous individuals.

Gene	*CFH*	*CFH*	*CFH*	*CFH*	*CFHR3*	*CFHR3*	*CFHR3*	*CFHR3*	*CFHR3*	*CFHR1*	*CFHR1*	*CFHR1*	*CFHR1*	*CFHR4*	*CFHR5*	*CFHR5*
SNP	rs1061147	rs2274700	rs3753396		rs446868	rs400344	rs149352569/ rs379049	rs402372	rs390837	rs3201739	rs4230	rs414628	rs390679	rs150845796/ rs379049	rs9427662	rs10922153
Codon	A307A	A473A	Q672Q	T1046T	5'UTR	S159S	P262P*	3' UTR	3' UTR	T196T	R302R	R314R	3' UTR	P509P*	5' UTR	3' UTR
Haplotype A	A	G	A	C	C	C	A	C	G	A	G	A	C	A	T	G
Haplotype B	C	G	G	C	A	T	T>A	T	C	A	G	A	C	A>T	T	G
Haplotype C	C	A	A	C>T	C	T	A	C	G	G	T	T	A	A	T	T
Haplotype D	C	A	A	C	null	null	null	null	null	null	null	null	null	A	T/C	T

**CFHR3* P262P and *CFHR4* P509P represent the same SNP. *CFHR4* P509P is a mapping artefact.

Table S3. SNPs with association $p<5x10^{-5}$ in additive model logistic regression of 867 cases of neovascular AMD compared to 519 with drusen in a genome-wide case-case study.

SNP	Gene	Allele	Odds Ratio	P
rs932275	*HTRA1*	A	1.60	$4.91x10^{-9}$
rs2248799	*HTRA1*	C	0.66	$9.95x10^{-8}$
rs4075920	*ALK*	T	0.65	$5.28x10^{-7}$
rs931257	-	C	0.68	$1.65x10^{-5}$
rs6991827	-	A	0.67	$2.18x10^{-5}$
rs6467778	-	A	0.65	$2.32x10^{-5}$
rs6560293	*TMC1*	A	0.71	$2.33x10^{-5}$
rs4688950	-	C	0.68	$2.57x10^{-5}$

rs12076580	-	A	0.70	$2.62x10^{-5}$
rs12052880	*LRP1B*	A	0.70	$2.74x10^{-5}$
rs1544733	*TRIM24*	C	0.66	$2.95x10^{-5}$
rs9938986	-	C	0.68	$2.96x10^{-5}$
rs2280141	*PLEKHA1*	A	0.72	$3.13x10^{-5}$
rs785512	*PIK3R3*	A	0.70	$3.31x10^{-5}$
rs1709835	*KCNJ6*	T	0.73	$3.35x10^{-5}$
rs4833961	-	A	0.71	$3.43x10^{-5}$
rs4660883	*TRIM24*	A	0.70	$3.44x10^{-5}$
rs785484	*PIK3R3*	T	0.70	$3.79x10^{-5}$
rs1052748	*PLD2*	T	1.38	$4.66x10^{-5}$
rs1622208	*MAST2*	T	0.71	$4.99x10^{-5}$
rs6585827	*PLEKHA1*	G	0.72	$4.99x10^{-5}$

Table S4. Minor allele frequencies and results of additive model analyses in candidate gene study of cases with neovascular AMD, drusen and unaffected controls from the MMAP study.

			Frequency			Drusen: Unaffected		NV AMD: Unaffected		NV AMD:Drusen	
Gene	Variant	Allele	Drusen	AMD	Controls	OR	P	OR	P	OR	P
CFH	Haplotype A	CACG	0.59	0.60	0.36	2.59	$9.06x10^{-32}$	2.75	$4.12x10^{-46}$	1.05	0.57
CFH	Haplotype B	CGTG	0.15	0.15	0.17	0.89	0.24	0.90	0.24	1.02	0.86
CFH	Haplotype C	TGCG	0.11	0.11	0.23	0.44	$2.23x10^{-13}$	0.41	$1.68x10^{-20}$	0.95	0.68

CFH	Haplotype D	CGCA	0.10	0.09	0.20	0.47	$1.75x10^{-10}$	0.41	$1.33x10^{-18}$	0.88	0.33
CFB	rs429608	A	0.08	0.08	0.16	0.48	$8.11x10^{-09}$	0.48	$4.60x10^{-12}$	1.00	0.98
HTRA1	rs932275	A	0.33	0.44	0.18	2.13	$6.94x10^{-18}$	3.36	$1.41x10^{-56}$	1.60	$4.01x10^{-9}$
C3	rs2250656	G	0.27	0.25	0.31	0.82	0.02	0.75	$5.65x10^{-5}$	0.92	0.32

NV, neovascular; AMD, age-related macular degeneration; OR, odds ratio; P, *P* value. *CFH* haplotype SNPs: rs800292, rs10801555, rs11582939, rs6677604

Table S5. RNA-Seq read depth at final base of *CFH* exon 9 or first base of exon 10a (FHL-1 expression) or 10 (FH expression), with % of FH transcription.

	Peripheral Retina				Macular Retina				Peripheral RPE/Choroid/Sclera				Macular RPE/Choroid/Sclera			
Donor	exon 9	exon 10a	exon 10	% FH	exon 9	exon 10a	exon 10	% FH	exon 9	exon 10a	exon 10	% FH	exon 9	exon 10a	exon 10	% FH
1	14	10	3	23.1	12	3	8	72.7	437	274	114	29.4	395	341	54	13.7
2	15	7	5	41.7	12	0	9	100.0	541	245	272	52.6	616	385	221	36.5
3	22	13	13	50.0	16	1	12	92.3	731	313	358	53.4	257	169	96	36.2
4	9	3	8	72.7	16	2	12	85.7	384	160	189	54.2	416	248	153	38.2
5	10	4	5	55.6	17	2	12	85.7	317	141	146	50.9	247	106	147	58.1
6	20	11	7	38.9	17	6	10	62.5	368	184	180	49.5	266	206	55	21.1
7	6	4	2	33.3	37	17	18	51.4	726	364	306	45.7	114	61	41	40.2
8	0	0	0	N/A	0	0	0	N/A	57	24	31	56.4	6	14	0	0.0

Table S6. Median of mean exonic read depths for each gene in liver RNA-seq samples from three individuals, adjusted for sequencing bias and normalised to FH†.

	Haplotype		
	AC	BD>AD*	CC
CFHR1	2.50	1.31	1.96
CFHR2	1.48	0.93	0.98
CFH†	1.00	1.00	1.00
CFHR3	0.48	0.20	0.25
CFHR4	0.10	0.17	0.10
CFHR5	0.09	0.16	0.05

*Haplotype D carries a deletion of *CFHR3* and *CFHR1*

†Restricted to exons 1-9, which are common to FH and FHL-1

Table S7. Numbers of exon-spanning RNA-seq reads of liver samples from three individuals and % of full-length *CFH* transcripts, according to haplotype.

Haplotype	BD>AD	AC	CC
FHL-1 transcripts of *CFH (*exons 9-10a)	206	523	1080
FH transcripts of *CFH* (exons 9-10)	306	432	434
% FH	60	45	29