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.
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.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Participants (n)</th>
<th>% Male</th>
<th>Average Age (years)</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massively parallel sequencing of CFH region</td>
<td>4</td>
<td>100</td>
<td>76</td>
<td>Northern Ireland, UK.</td>
</tr>
<tr>
<td>RNA-seq of eye tissues</td>
<td>8</td>
<td>63%</td>
<td>73.9</td>
<td>USA</td>
</tr>
<tr>
<td>RNA-seq of liver</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Secondary analyses of AMD GWAS</td>
<td>2157 cases 1150 controls</td>
<td>38% 44%</td>
<td>78.6 74.1</td>
<td>USA</td>
</tr>
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</table>
Table S2. Synonymous SNPs in CFH and CFH-related genes identified from massively-parallel sequencing of genomic DNA of four homozygous individuals.

<table>
<thead>
<tr>
<th>Gene</th>
<th>CFH</th>
<th>CFH</th>
<th>CFH</th>
<th>CFHR3</th>
<th>CFHR3</th>
<th>CFHR3</th>
<th>CFHR3</th>
<th>CFHR3</th>
<th>CFHR1</th>
<th>CFHR1</th>
<th>CFHR1</th>
<th>CFHR4</th>
<th>CFHR5</th>
<th>CFHR5</th>
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<tbody>
<tr>
<td>SNP</td>
<td>rs1061147</td>
<td>rs2274700</td>
<td>rs3753396</td>
<td>rs446868</td>
<td>rs4100344</td>
<td>rs149352569/69/69/69</td>
<td>rs402372</td>
<td>rs390837</td>
<td>rs3201739</td>
<td>rs4230</td>
<td>rs414628</td>
<td>rs390679</td>
<td>rs150845796/96/96/96</td>
<td>rs427662</td>
</tr>
<tr>
<td>Codon</td>
<td>A307A</td>
<td>A473A</td>
<td>Q672Q</td>
<td>T1046T</td>
<td>S159S</td>
<td>P262P*</td>
<td>3' UTR</td>
<td>3' UTR</td>
<td>T196T</td>
<td>R302R</td>
<td>R314R</td>
<td>3' UTR</td>
<td>5' UTR</td>
<td>3' UTR</td>
</tr>
<tr>
<td>Haplotype A</td>
<td>A</td>
<td>G</td>
<td>A</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>A</td>
<td>C</td>
<td>G</td>
<td>A</td>
<td>G</td>
<td>A</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>Haplotype B</td>
<td>C</td>
<td>G</td>
<td>G</td>
<td>C</td>
<td>A</td>
<td>T</td>
<td>T&gt;A</td>
<td>T</td>
<td>C</td>
<td>A</td>
<td>G</td>
<td>A</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>Haplotype C</td>
<td>C</td>
<td>A</td>
<td>A</td>
<td>C&gt;T</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>C</td>
<td>G</td>
<td>G</td>
<td>T</td>
<td>T</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Haplotype D</td>
<td>C</td>
<td>A</td>
<td>A</td>
<td>C</td>
<td>null</td>
<td>null</td>
<td>null</td>
<td>null</td>
<td>null</td>
<td>null</td>
<td>null</td>
<td>null</td>
<td>A</td>
<td>T/C</td>
</tr>
</tbody>
</table>

*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.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Allele</th>
<th>Odds Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs932275</td>
<td>HTRA1</td>
<td>A</td>
<td>1.60</td>
<td>4.91x10^-9</td>
</tr>
<tr>
<td>rs2248799</td>
<td>HTRA1</td>
<td>C</td>
<td>0.66</td>
<td>9.95x10^-8</td>
</tr>
<tr>
<td>rs4075920</td>
<td>ALK</td>
<td>T</td>
<td>0.65</td>
<td>5.28x10^-7</td>
</tr>
<tr>
<td>rs931257</td>
<td>-</td>
<td>C</td>
<td>0.68</td>
<td>1.65x10^-5</td>
</tr>
<tr>
<td>rs6991827</td>
<td>-</td>
<td>A</td>
<td>0.67</td>
<td>2.18x10^-5</td>
</tr>
<tr>
<td>rs6467778</td>
<td>-</td>
<td>A</td>
<td>0.65</td>
<td>2.32x10^-5</td>
</tr>
<tr>
<td>rs6560293</td>
<td>TMC1</td>
<td>A</td>
<td>0.71</td>
<td>2.33x10^-5</td>
</tr>
<tr>
<td>rs4688950</td>
<td>-</td>
<td>C</td>
<td>0.68</td>
<td>2.57x10^-5</td>
</tr>
<tr>
<td>Gene</td>
<td>Variant</td>
<td>Allele</td>
<td>Frequency</td>
<td>Drusen: Unaffected</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>--------</td>
<td>-----------</td>
<td>--------------------</td>
</tr>
<tr>
<td>CFH</td>
<td>Haplotype A</td>
<td>CACG</td>
<td>0.59</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>CFH</td>
<td>Haplotype B</td>
<td>CGTG</td>
<td>0.15</td>
<td>0.15</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFH</td>
<td>Haplotype C</td>
<td>TGCG</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

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.
<p>| | | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>Haplotype D</td>
<td>CGCA</td>
<td>0.10</td>
<td>0.09</td>
<td>0.20</td>
<td>0.47</td>
<td>1.75\times10^{-10}</td>
<td>0.41</td>
<td>1.33\times10^{-18}</td>
<td>0.88</td>
<td>0.33</td>
</tr>
<tr>
<td>CFB</td>
<td>rs429608</td>
<td>A</td>
<td>0.08</td>
<td>0.08</td>
<td>0.16</td>
<td>0.48</td>
<td>8.11\times10^{-09}</td>
<td>0.48</td>
<td>4.60\times10^{-12}</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>HTRA1</td>
<td>rs932275</td>
<td>A</td>
<td>0.33</td>
<td>0.44</td>
<td>0.18</td>
<td>2.13</td>
<td>6.94\times10^{-18}</td>
<td>3.36</td>
<td>1.41\times10^{-56}</td>
<td>1.60</td>
<td>4.01\times10^{-9}</td>
</tr>
<tr>
<td>C3</td>
<td>rs2250656</td>
<td>G</td>
<td>0.27</td>
<td>0.25</td>
<td>0.31</td>
<td>0.82</td>
<td>0.02</td>
<td>0.75</td>
<td>5.65\times10^{-5}</td>
<td>0.92</td>
<td>0.32</td>
</tr>
</tbody>
</table>

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.
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.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Haplotype</th>
<th>AC</th>
<th>BD&gt;AD*</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFHR1</td>
<td></td>
<td>2.50</td>
<td>1.31</td>
<td>1.96</td>
</tr>
<tr>
<td>CFHR2</td>
<td></td>
<td>1.48</td>
<td>0.93</td>
<td>0.98</td>
</tr>
<tr>
<td>CFH</td>
<td>†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>CFHR3</td>
<td></td>
<td>0.48</td>
<td>0.20</td>
<td>0.25</td>
</tr>
<tr>
<td>CFHR4</td>
<td></td>
<td>0.10</td>
<td>0.17</td>
<td>0.10</td>
</tr>
<tr>
<td>CFHR5</td>
<td></td>
<td>0.09</td>
<td>0.16</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*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.

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>BD&gt;AD</th>
<th>AC</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHL-1 transcripts of CFH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(exons 9-10a)</td>
<td>206</td>
<td>523</td>
<td>1080</td>
</tr>
<tr>
<td>FH transcripts of CFH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(exons 9-10)</td>
<td>306</td>
<td>432</td>
<td>434</td>
</tr>
<tr>
<td>% FH</td>
<td></td>
<td>45</td>
<td>29</td>
</tr>
</tbody>
</table>