Supplemental Online Content

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eTable 1. Age-related macular degeneration stages according to Rotterdam classification

| Grades Rotterdam classification | Definition |
|--------------------------------|------------|
| 0                              | No signs of AMD or hard drusen (< 63 μm) only |
| 1                              | Soft indistinct drusen (≥ 63 μm) or pigmentary abnormalities |
| 2                              | Soft indistinct drusen (≥ 125 μm) or reticular drusen or soft indistinct drusen (≥ 63 μm) with pigmentary abnormalities |
| 3                              | Soft indistinct drusen (≥ 125 μm) or reticular drusen with pigmentary abnormalities |
| 4                              | Atrophic, neovascular or mixed AMD |

Table detailing the different stages of age-related macular degeneration according to Rotterdam classification. AMD = age-related macular degeneration.
eTable 2. Fifty-two AMD-associated variants included in GRS calculation

| Locus name            | Variant   | Alternative variant |
|-----------------------|-----------|---------------------|
| ABCA1                 | rs2740488 |                     |
| ACAD10/BRAP           | rs61941274| rs61941272 (R² 1.0) |
| ADAMTS9-AS2          | rs62247658|                     |
| APOE                  | rs429358  |                     |
| APOE(EXOC3L2/MARK4)   | rs73036519|                     |
| ARHGAP21              | rs12357257|                     |
| ARMS2/HTRA1           | rs3750846 |                     |
| B3GALT2              | rs9564692 |                     |
| C2/CFB/SKIV2L         | rs116503776/rs429608|           |
| C2/CFB/SKIV2L         | rs144629244/rs2746394|           |
| C2/CFB/SKIV2L (PBX2)  | rs114254831/rs204993|           |
| C20orf85              | rs201459901| rs117420707 (R² 0.99) |
| C3                    | rs2230199 |                     |
| C3                    | rs147859257|                   |
| C3 (NRTN/FUT6)        | rs12019136| rs17855739 (R² 0.95) |
| C9                    | rs62358361|                     |
| CETP                  | rs5817082 |                     |
| CETP                  | rs17231506|                     |
| CFH                   | rs10922109|                     |
| CFH                   | rs570618  |                     |
| CFH                   | rs121913059|                  |
| CFH                   | rs148553336|                    |
| CFH                   | rs187328863| rs79436252 (R² 1.0) |
| CFH                   | rs35292876|                     |
| CFH                   | rs191281603|                   |
| CFH (CFHR3/CFHR1)     | rs61818925| rs61818924 (R² 0.80) |
| CFI                   | rs10033900|                     |
| CFI                   | rs141853578|                  |
| CNN2                  | rs67538026| rs113772652 (R² 0.996) |
| COL4A3                | rs11884770|                     |
| COL8A1                | rs140647181|                  |
| COL8A1                | rs55975637|                     |
| CTRB2/CTRB1           | rs72802342| rs55993634 (R² 0.89) |
| KMT2E/SRPK2           | rs1142    |                     |
| LIPC                  | rs2043085 |                     |
| LIPC                  | rs2070895 |                     |
| MIR6130/RORB          | rs10781182|                     |
| MMP9                  | rs142450006|                  |
| NPL oc4/TSPAN10       | rs6565597 |                     |
| PIRLB/PILRA           | rs7803454 |                     |
| PRLR/SPEF2            | rs114092250| rs74767144 (R² 0.77) |
| RAD51B                | rs61985136|                     |
| RAD51B                | rs2842339 |                     |
| RDH5/CD63             | rs3138141 |                     |
| SLC16A8               | rs8135665 |                     |
| SYN3/TIMP3            | rs5754227 |                     |
| TGFBR1                | rs1626340 |                     |
| TMEM97/VTN            | rs11080055|                     |
| TNFRSF10A             | rs79037040/rs13278062|            |
| TRPM3                 | rs71507014|                     |
| VEGFA                 | rs943080  |                     |

Table detailing the genetic variants included for calculation of the genetic risk score. AMD = age-related macular degeneration, GRS = genetic risk score.
### eTable 3. Relevant medical conditions EODM group

| Medical condition                                                                 | No. of patients affected | Comments                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------------------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| C3 glomerulopathy (dense deposits disease [DDD] / membranoproliferative glomerulonephritis type 2 [MPGN type 2]) | 3                        | - Macular drusen can be observed in patients with C3 glomerulopathy.¹ ²  
- Mutations in the complement factor H (CFH) gene are identified in patients with C3 glomerulopathy, as well as several single nucleotide polymorphisms (SNPs) in the CFH gene.¹ ³  ⁴ ⁵  |
| Membranoproliferative glomerulonephritis type 1 (MPGN type 1)                     | 1                        | - In contrast to C3 glomerulopathy (complement-related), MPGN type 1 (immune complex related) is not associated with drusen. However, drusen are reported in 1 case report (patient with MPGN type 1).⁶                                                                                   |
| Behcet’s Disease                                                                  | 1                        | - Ocular conditions associated with Behcet’s Disease include iritis, uveitis, retinal vasculitis, vitritis and optic neuropathy. Drusen are not associated with Behcet’s Disease.                                                                                                                                                                           |
| X-linked agammaglobulinemia (XLA)                                                 | 1                        | - XLA is characterized by a lack of antibodies, resulting in increased risk of infections. In literature, drusen are not associated with XLA.                                                                                                                                                                                             |

Table detailing medical conditions reported in early-onset drusen maculopathy patients that are relevant in light of this study.
eTable 4. Patients with EODM carrying rare complement variants

| No. | Variant 1       | Source variant 1 | Variant 2       | Source variant 2 | Variant 3       | Source variant 3 |
|-----|-----------------|------------------|-----------------|------------------|-----------------|------------------|
| 1   | C9 Pro167Ser    | WES              |                 |                  |                 |                  |
| 2   | CFH c.350+6T>G  | Sanger           |                 |                  |                 |                  |
| 3   | CFH Gln408*     | WES, smMIPs      | C3 Arg735Trp    | smMIPs, exome chip, KASPar |
| 4   | CFH Gln408*     | Sanger           |                 |                  |                 |                  |
| 5   | CFH Ala301Glnfs*22 | smMIPs       |                 |                  |                 |                  |
| 6   | C3 Arg735Trp    | KASPar           |                 |                  |                 |                  |
| 7   | C9 Cys54*       | WES              |                 |                  |                 |                  |
| 8   | CFH 1697-17-8delATTTTACCTT | WES, Sanger   |                 |                  |                 |                  |
| 9   | CFH Ala161Ser   | smMIPs, Sanger   | CFH Gln950His   | smMIPs, Sanger   | C9 Met45Leu     | smMIPs           |
| 10  | CFH Gln400Lys   | smMIPs, Sanger   |                 |                  |                 |                  |
| 11  | CFH Gly255Glu   | smMIPs, Sanger   |                 |                  |                 |                  |
| 12  | CFH Ile184Leufs*33 | smMIPs, Sanger |                 |                  |                 |                  |
| 13  | CFH Gln950His   | WES, exome chip  |                 |                  |                 |                  |
| 14  | CFI Gly188Ala   | smMIPs, WES      |                 |                  |                 |                  |
| 15  | CFH Arg1078Ser  | WES              |                 |                  |                 |                  |
| 16  | CFH Arg166Trp   | smMIPs, WES      |                 |                  |                 |                  |
| 17  | CFH Trp858Arg   | smMIPs, WES      |                 |                  |                 |                  |
| 18  | C3 Lys155Gln    | smMIPs           | CFH Gln950His   | smMIPs           | C9 Pro167Ser    | smMIPs           |
| 19  | C9 Val69Ile     | smMIPs           |                 |                  |                 |                  |
| 20  | CFH Ala425Val   | smMIPs           |                 |                  |                 |                  |
| 21  | CFH Tyr243His   | smMIPs           | CFB Lys533Arg   | smMIPs           |                 |                  |
| 22  | CFH Tyr916*     | smMIPs, Sanger   |                 |                  |                 |                  |
| 23  | CFI Pro50Ala    | smMIPs, Sanger   |                 |                  |                 |                  |
| 24  | CFH Cys357Ser   | smMIPs, Sanger   |                 |                  |                 |                  |
| 25  | CFH Gln376*     | smMIPs, Sanger   |                 |                  |                 |                  |
| 26  | C9 Pro167Ser    | smMIPs           |                 |                  |                 |                  |
| 27  | CFH Gly255Glu   | smMIPs, Sanger   |                 |                  |                 |                  |
| 28  | CFH Lys204Thrfs*26 | smMIPs, Sanger |                 |                  |                 |                  |
| 29  | CFH Arg175Gln   | smMIPs, KASPar   |                 |                  |                 |                  |
| 30  | CFH Arg303Gln   | smMIPs, WES      | CFH Ser193Leu   | smMIPs, WES     |                 |                  |
| 31  | CFH Leu3Val     | WES, smMIPs      |                 |                  |                 |                  |
| No. | Variant 1       | Source variant 1     | Variant 2       | Source variant 2 | Variant 3 | Source variant 3 |
|-----|-----------------|----------------------|-----------------|------------------|-----------|------------------|
| 32  | CFH Arg303Gln   | WES, exome chip      | CFH Ser193Leu   | WES, KASPar      |           |                  |
| 33  | C3 Ser1619Arg   | smMIPs               |                 |                  |           |                  |
| 34  | CFH Gln950His   | smMIPs, WES          | C3 Arg735Trp    | smMIPs, WES      |           |                  |
| 35  | CFH Gln846Arg   | smMIPs, WES, Sanger  |                 |                  |           |                  |

Table detailing the 35 patients with early-onset drusen maculopathy carrying one or more rare variants in the complement genes CFH, CFI, CFB, C3 or C9, and the corresponding genotype platform where the variant was identified. CFH = complement factor H, CFI = complement factor I, CFB = complement factor B, C3 = complement 3, C9 = complement 9, WES = whole exome sequencing, smMIPs = single molecule molecular inversion probes; empty cells indicate no additional variants were identified.
eTable 5. Logistic regression analysis for the association of CFH rare variant carriership with EODM phenotype

| Variable                          | OR    | 95% CI     | P value |
|----------------------------------|-------|------------|---------|
| CFH rare variant carriership     |       |            |         |
| No [reference]                   | 1     | -          | -       |
| Yes                              | 7.209 | 2.657-19.562 | <.001  |
| Sex                              |       |            |         |
| Male [reference]                 | 1     | -          | -       |
| Female                           | 2.342 | 1.163-4.717 | .02    |
| Smoking status                   |       |            |         |
| Never [reference]                | 1     | -          | -       |
| Past                             | 0.376 | 0.175-0.809 | .01    |
| Current                          | 0.734 | 0.282-1.909 | .53    |

Table detailing the results of the binary logistic regression analysis for the association of CFH rare variant carriership with EODM phenotype, adjusted for sex and smoking status. CFH = complement factor H, OR = odds ratio, CI = confidence interval.
**eTable 6. Characteristics complete and incomplete data**

|                                | Complete data | Incomplete data |
|--------------------------------|---------------|-----------------|
|                                | EODM (n = 89  | AMD (n = 91     |
|                                | [178 eyes])  | [182 eyes])     |
|                                | EODM (n = 81  | AMD (n = 82     |
|                                | [162 eyes])  | [164 eyes])     |
| **Sex, No. (%)**               |               |                 |
| Male                           | 31 (34.8)     | 46 (50.5)       |
| Female                         | 58 (65.2)     | 45 (49.5)       |
| **CFH rare variant carrier, No. (%)** | 27 (30.3)     | 7 (7.7)         |
| Predominant drusen type in grid, No. of eyes (%) | 26 (32.1)     | 6 (7.3)         |
| Hard drusen                    | 1 (0.6)       | 4 (2.2)         |
| Soft drusen < C1               | 10 (5.6)      | 23 (12.6)       |
| Soft distinct drusen           | 8 (4.5)       | 29 (15.9)       |
| Soft indistinct drusen         | 154 (86.5)    | 75 (41.2)       |
| Reticular drusen               | 3 (1.7)       | 27 (14.8)       |
| Cannot grade or not applicable | 2 (1.1)       | 24 (13.2)       |
| Largest drusen size within grid, No. of eyes (%) | 2 (1.9)       | 24 (14.6)       |
| < C0 (63 μm)                   | 1 (0.6)       | 5 (2.7)         |
| < C1 (125 μm)                  | 23 (12.9)     | 24 (13.2)       |
| < C2 (250 μm)                  | 49 (27.5)     | 48 (26.4)       |
| ≥ C2 (250 μm)                  | 98 (55.1)     | 90 (55.6)       |
| Reticular                      | 4 (2.2)       | 26 (14.3)       |
| Cannot grade or not applicable | 3 (1.7)       | 26 (14.3)       |
| Small drusen in grid, No. of eyes (%) | 53 (29.8)     | 54 (29.7)       |
| Absent                         | 121 (68.0)    | 104 (57.1)      |
| Present                        | 13 (7.1)      | 107 (66.0)      |
| Cannot grade or not applicable | 9 (5.6)       | 90 (54.9)       |
| Intermediate drusen in grid, No. of eyes (%) | 9 (5.6)       | 13 (7.9)        |
| Absent                         | 165 (92.7)    | 145 (79.7)      |
| Present                        | 13 (7.1)      | 150 (92.6)      |
| Cannot grade or not applicable | 4 (2.2)       | 24 (13.2)       |
| Large drusen in grid, No. of eyes (%) | 24 (13.5)     | 24 (14.2)       |
| Absent                         | 151 (84.8)    | 124 (68.1)      |
| Present                        | 13 (7.1)      | 136 (84.0)      |
| Cannot grade or not applicable | 4 (2.2)       | 108 (65.9)      |
| Proportion of grid area covered by drusen, No. of eyes (%) | 24 (14.8)     | 32 (19.5)       |
| 0 to 10 %                      | 45 (25.3)     | 42 (25.9)       |
| 10 to 50 %                     | 103 (57.9)    | 94 (58.0)       |
| > 50 %                         | 27 (15.2)     | 24 (14.9)       |
| Cannot grade or not applicable | 3 (1.7)       | 23 (14.2)       |
| Drusen outside grid, No. of eyes (%) | 24 (13.5)     | 22 (13.6)       |
| Absent                         | 153 (86.0)    | 139 (85.2)      |
| Present                        | 13 (7.1)      | 138 (85.2)      |
| Cannot grade or not applicable | 2 (1.1)       | 2 (1.2)         |
| Increased pigment, No. of eyes (%) | 2 (1.1)       | 2 (1.2)         |

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|                                | Complete data | Incomplete data |
|--------------------------------|---------------|-----------------|
| **RPE degeneration, No. of eyes (%)** | EODM (n = 89 [178 eyes]) | AMD (n = 91 [182 eyes]) | EODM (n = 81 [162 eyes]) | AMD (n = 82 [164 eyes]) |
| Absent                          | 112 (62.9)    | 142 (78.0)      | 101 (62.3)      | 130 (79.3)     |
| < C2 (250 μm)                   | 15 (6.4)      | 10 (6.5)        | 14 (8.6)        | 8 (4.9)        |
| ≥ Central grid                  | 36 (20.2)     | 22 (12.1)       | 32 (19.8)       | 21 (12.8)      |
| Cannot grade or not applicable  | 12 (6.7)      | 2 (1.1)         | 12 (7.4)        | 2 (1.2)        |
| **Geographic atrophy, No. of eyes (%)** | Absent | Present | Cannot grade or not applicable |
| Absent                          | 141 (79.2)    | 109 (59.9)      | 126 (77.8)      | 97 (59.1)      |
| Present                         | 36 (20.2)     | 72 (39.6)       | 35 (21.6)       | 66 (40.2)      |
| Cannot grade or not applicable  | 1 (0.6)       | 1 (0.5)         | 1 (0.6)         | 1 (0.6)        |
| **Choroidal neovascularization, No. of eyes (%)** | Absent | Present | Cannot grade or not applicable |
| Absent                          | 132 (74.2)    | 119 (65.4)      | 122 (75.3)      | 107 (65.2)     |
| Present                         | 41 (23.0)     | 62 (34.1)       | 35 (21.6)       | 56 (34.1)      |
| Cannot grade or not applicable  | 5 (2.8)       | 1 (0.5)         | 5 (3.1)         | 1 (0.6)        |
| **Serous detachment (if CNV), No. of eyes (%)** | Absent | Present | Cannot grade or not applicable |
| Absent                          | 11 (26.8)     | 16 (25.8)       | 11 (31.4)       | 16 (28.6)      |
| Present                         | 24 (58.5)     | 45 (72.6)       | 21 (60.0)       | 39 (69.6)      |
| Cannot grade or not applicable  | 6 (14.6)      | 1 (1.6)         | 3 (8.6)         | 1 (1.8)        |
| **Subretinal hemorrhage (if CNV), No. of eyes (%)** | Absent | Present | Cannot grade or not applicable |
| Absent                          | 35 (85.4)     | 44 (71.0)       | 31 (88.6)       | 40 (71.4)      |
| Present                         | 2 (4.9)       | 18 (25.8)       | 2 (5.7)         | 14 (25.0)      |
| Cannot grade or not applicable  | 4 (9.8)       | 2 (3.2)         | 2 (5.7)         | 2 (3.6)        |
| **Fibrous scar (if CNV), No. of eyes (%)** | Absent | Present | Cannot grade or not applicable |
| Absent                          | 13 (31.7)     | 12 (19.4)       | 9 (25.7)        | 9 (16.1)       |
| Present                         | 26 (63.4)     | 49 (79.0)       | 25 (71.4)       | 46 (82.1)      |
| Cannot grade or not applicable  | 2 (4.9)       | 1 (1.6)         | 1 (2.9)         | 1 (1.8)        |
| **Hard exsudates (if CNV), No. of eyes (%)** | Absent | Present | Cannot grade or not applicable |
| Absent                          | 33 (80.5)     | 39 (62.9)       | 29 (82.9)       | 35 (62.5)      |
| Present                         | 4 (9.8)       | 23 (37.1)       | 4 (11.4)        | 21 (37.5)      |
| Cannot grade or not applicable  | 4 (9.8)       | 0 (0.0)         | 2 (5.7)         | 0 (0.0)        |

Table detailing characteristics in the complete and incomplete dataset due to missing smoking status in 17 patients. Chi-square tests and t-tests were performed between a dummy variable for smoking (0 = missing; 1 = observed) and other variables in the dataset (category, sex, GRS, disease stage, CFH rare variant carriership). Smoking status was missing at random, as missingness on this variable was not related to the values of the other variables in the dataset (category, sex, GRS, disease stage, CFH rare variant carriership). Multiple imputation was not performed. AMD = age-related macular degeneration, EODM = early-onset drusen maculopathy, CNV = choroidal neovascularization, CFH = complement factor H.
eTable 7. Details of rare complement variants identified in patients with early-onset drusen maculopathy

| Chr | Position   | Gene | Nucleotide change | Protein change | PhyloP | CADD_Phred | Grantham Score | Functional effect                                                                 |
|-----|------------|------|-------------------|----------------|--------|------------|----------------|-----------------------------------------------------------------------------------|
| 1   | 196621254  | CFH  | 7C>G              | Leu3Val        | 0.004  | 11.9       | 32             | Unknown                                                                         |
| 1   | 196643098  | CFH  | 350+6T>G          | -              | 2.744  | 20.4       | 0              | Noncoding splice site variant, predicted to severely affect splicing⁷             |
| 1   | 196646659  | CFH  | 481G>T            | Ala161Ser      | -0.839 | 12.1       | 99             | Normal FH levels⁸                                                               |
| 1   | 196646674  | CFH  | 496C>T            | Arg166Trp      | -0.047 | 22.2       | 101            | Unknown                                                                         |
| 1   | 196646702  | CFH  | 524G>A            | Arg175Gln      | -0.059 | 0.019      | 43             | Reduced ability to degrade C3b⁹                                                 |
| 1   | 196646728  | CFH  | 550delA           | Ile184Leufs*33 | -100   | 15.04      | 0              | Frameshift variant                                                              |
| 1   | 196646756  | CFH  | 578C>T            | Ser193Leu      | 1.024  | 23.1       | 145            | Reduced ability to degrade C3b⁹                                                 |
| 1   | 196646782  | CFH  | 607 610dup        | Lys204Thrfs*26 | 0.193  | 33         | 1000           | Frameshift variant                                                              |
| 1   | 196648860  | CFH  | 727T>C            | Tyr243His      | 0.141  | 11.72      | 83             | Unknown                                                                         |
| 1   | 196648897  | CFH  | 764G>A            | Gly255Glu      | 3.912  | 23.9       | 98             | Unknown                                                                         |
| 1   | 196654304  | CFH  | 901delG           | Ala301Glnfs*22 | -100   | 11.31      | 0              | Frameshift variant                                                              |
| 1   | 196654311  | CFH  | 908G>A            | Arg303Gln      | -1.875 | 0.229      | 43             | Normal FH, FI and C3 plasma levels¹⁰                                             |
| 1   | 196658654  | CFH  | 1069T>A           | Cys357Ser      | 3.961  | 23.3       | 112            | Unknown                                                                         |
| 1   | 196658711  | CFH  | 1126C>T           | Gln376*        | -1.265 | 34         | 1000           | Protein-truncating variant                                                     |
| 1   | 196659231  | CFH  | 1198C>A           | Gln400Lys      | -2.435 | 0.015      | 53             | Lower FH levels⁴                                                                |
| 1   | 196659255  | CFH  | 1222C>T           | Gln408*        | 0.317  | 34         | 1000           | Protein-truncating variant                                                     |
| 1   | 196659307  | CFH  | 1274C>T           | Ala425Val      | -1.015 | 0.001      | 64             | Unknown                                                                         |
| 1   | 196694235  | CFH  | 1697-17del        | 0              | 2.065  | 4.57       | 0              | Noncoding splice site variant, predicted to affect splicing⁹                    |
| 1   | 196706077  | CFH  | 2537A>G           | Gln846Arg      | 0.403  | 10.67      | 43             | Unknown                                                                         |
| 1   | 196706112  | CFH  | 2572T>A           | Trp858Arg      | 4.743  | 24.9       | 101            | Unknown                                                                         |
| 1   | 196706756  | CFH  | 2748C>G           | Tyr916*        | -0.619 | 35         | 1000           | Protein-truncating variant                                                     |
| 1   | 196709816  | CFH  | 2850G>T           | Gln950His      | -0.273 | 14.41      | 24             | Normal FH levels, normal cofactor binding for FI¹¹                               |
| 1   | 196712682  | CFH  | 3234G>T           | Arg1078Ser     | -6.447 | 1.728      | 110            | Unknown                                                                         |
| 4   | 110687890  | CFI  | 148C>G            | Pro50Ala       | 5.75   | 24.8       | 27             | Reduced FI levels¹²                                                            |
| 4   | 110682768  | CFI  | 563G>C            | Gly188Ala      | 5.386  | 24.3       | 60             | Reduced FI levels; reduced ability to degrade C3b¹³                               |
| 5   | 39342243   | C9   | 133A>T            | Met45Leu       | 0.44   | 15.22      | 15             | Elevated C9 levels, but normal TCC levels¹⁴                                     |
| 5   | 39342214   | C9   | 162C>A            | Cys54*         | 1.273  | 35         | 1000           | Protein-truncating variant                                                     |
| 5   | 39341781   | C9   | 205G>A            | Val69Ile       | 0.028  | 11.24      | 29             | Unknown                                                                         |
| 5   | 39331894   | C9   | 499C>T            | Pro167Ser      | 3.414  | 23.9       | 74             | Elevated C9 levels¹⁴                                                            |

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| Chr | Position | Gene | Nucleotide change | Protein change | PhyloP  | CADD_Phred | Grantham Score | Functional effect |
|-----|----------|------|-------------------|----------------|---------|------------|----------------|--------------------|
| Chr 6 | 31918154 | CFB  | 1598A>G           | Lys533Arg      | 3.242   | 15.95      | 26             | Unknown            |
| Chr 19 | 6718146 | C3   | 463A>C            | Lys155Gln      | -0.429  | 14.8       | 53             | Decreased binding of C3b to CFH<sup>15</sup> |
| Chr 19 | 6707129 | C3   | 2203C>T           | Arg735Trp      | 0.721   | 23.1       | 101            | Normal MCP binding, FI cofactor activity, FB and FH binding<sup>16</sup> |
| Chr 19 | 6678030 | C3   | 4855A>C           | Ser1619Arg     | 0.671   | 22.5       | 110            | Unknown            |

Table detailing the annotation, prediction scores and functional effects of the identified rare complement variants. Chr = chromosome, CADD = combined annotation dependent depletion, CFH = complement factor H, CFI = complement factor I, CFB = complement factor B, C3 = complement 3, C9 = complement 9, FH = factor H, FI = factor I, FB = factor B, MCP = membrane cofactor protein.
eFigure 1. Patients with EODM with large colloid drusen and temporal drusen

Figure detailing three examples of EODM patients with large colloid drusen and two examples of patients with drusen located temporal to the macula. Panel A: color fundus photographs of all three patients showed large yellow lesions. The location of the lesions varied from predominantly outside the vascular arcades (panel A3), to predominantly temporal to the macula (panel A2) and spread across the whole posterior pole (panel A1). Fundus autofluorescence images showed hyperautofluorescent lesions surrounded by hypoautofluorescent halos. Infrared reflectance images showed white round lesions surrounded by dark halos. Optical coherence tomography scans showed dome-shaped sub-retinal pigment epithelium deposits (panels A1 and A2; in panel A3 the central macula was dominated by atrophy). The patient in panel A2 is carrier of rare variants in the complement factor H (CFH) gene (Gln950His) and in the Complement 3 (C3) gene (Arg735Trp). Panel B1: color fundus photographs of a 47-year-old female with drusen located temporal to the fovea. Panel B2: color fundus photographs of a 41-year-old female with drusen isolated temporal to the fovea. Numbers in the right upper corner of each panel represent the age of the patient. The genetic risk score (GRS) is depicted in the right bottom corner of each panel.

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eFigure 2. Genetic risk score distribution in EODM and AMD cohorts

Panel A: all disease stages (RC 1-4)
- EODM (n = 72)
  - GRS, Mdn (IQR): 1.03 (0.16 - 1.94)
- AMD (n = 87)
  - GRS, Mdn (IQR): 1.50 (0.84 - 2.94)

Panel B: early and intermediate (RC 1-3) disease stages
- EODM (n = 36)
  - GRS, Mdn (IQR): 0.53 (0.14 - 1.95)
- AMD (n = 15)
  - GRS, Mdn (IQR): 1.42 (0.48 - 2.06)

Panel C: late (RC 4) disease stages
- EODM (n = 34)
  - GRS, Mdn (IQR): 1.34 (0.18 - 2.09)
- AMD (n = 72)
  - GRS, Mdn (IQR): 1.87 (1.03 - 2.84)

Figure detailing the distribution of the genetic risk score between patients with early onset drusen maculopathy and age-related macular degeneration. Panel A: all disease stages (RC 1-4), Panel B: only early and intermediate (RC 1-3) disease stages, Panel C: only late (RC 4) disease stages. Red dotted lines represent the median GRS. EODM = early onset drusen maculopathy, AMD = age-related macular degeneration, GRS = genetic risk score, RC = Rotterdam classification, Mdn = median, IQR = interquartile range.
Figure detailing a 48-year-old female primarily diagnosed with early onset drusen maculopathy. Panel A: color fundus photographs showed small yellow deposits and retinal pigment epithelium alterations in the fovea. Optical coherence tomography images showing small elevations of the retinal pigment epithelium in and around the fovea. Panel B: follow-up images of the same patient after two years. Optical coherence tomography images showed a serous detachment in the fovea in both eyes. Numbers in the right upper corner of each panel indicate the age of the patient. The genetic risk score is depicted in the right bottom corner of panel A. GRS = genetic risk score.
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